

## Hydrophobic Concave Surfaces and Cavities by Combination of Calix[4]arenes and Resorcin[4]arenes

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**Abstract:** Coupling reactions of calix[4]arenes and modified resorcin[4]arenes have been investigated. Reaction of mono-(chloroacetamido)calix[4]arene **4** with tetrahydroxycavitand **9** gave the 1:1 coupled product **13** in 61% yield. Combination of upper-rim 1,3-difunctionalized calix[4]arene **5** with **9** afforded predominantly the 2:1 calix-resorcinarene **18** in 47% yield. Reaction of 1,2-difunctionalized calix[4]arene **6** with **9** gave five products, namely, *endo* 1:1 (**19**), *exo* 1:1 (**20**), *endo-endo* 2:1 (**21**), *endo-exo* 2:1 (**22**), and *exo-exo* 2:1 (**23**) in ratios that depend on the reaction conditions. The stereochemistry of the different products was determined with NOESY experiments. The structures of **21a** and **23b** were calculated by using molecular mechanics, which revealed that intramolecular hy-

drogen bonds are only present in the former. Reaction of 1,2-bis(chloroacetamido)calix[4]arene **26**, which has two additional nitro groups at the remaining aromatic rings, with **9** yielded three different products, namely, *endo* 1:1 (**28**), *endo-endo* 2:1 (**30**), and *endo-exo* 2:1 (**32**) in ratios that depend on the reaction conditions. There is a preference for the *endo* orientation in the formation of the 1:1 coupled product, probably owing to an interaction of the nitro groups with the cavitand in the transition state. After con-

version of the nitro groups in **28** into chloroacetamido moieties, reaction with  $\text{Cs}_2\text{CO}_3$  in DMF under high-dilution conditions afforded holand **33** in 26% yield together with calix[4]arene-based carceplex **34** with an encapsulated DMF molecule (27% yield). Holand **33** was obtained in 33% yield by reaction of the tetrakis(chloroacetamide) *endo-endo* 2:1 isomer **31** with tetrahydroxycavitand **9**. Holand **33** contains a cavity of nanosize dimensions. Molecular mechanics simulations indicate that holand **33** adopts a conformation with eight hydrogen bonds and a large, preorganized cavity with two entrances of smaller dimensions. Molecular dynamics simulations of holand **33** in both  $\text{CHCl}_3$  and THF showed that four solvent molecules can be accommodated in the cavity at well-defined positions.

### Keywords

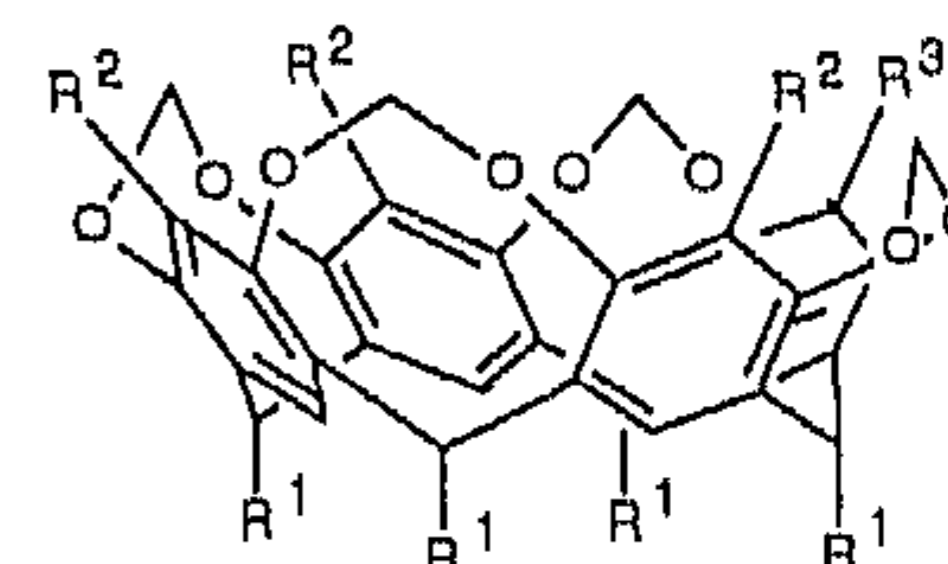
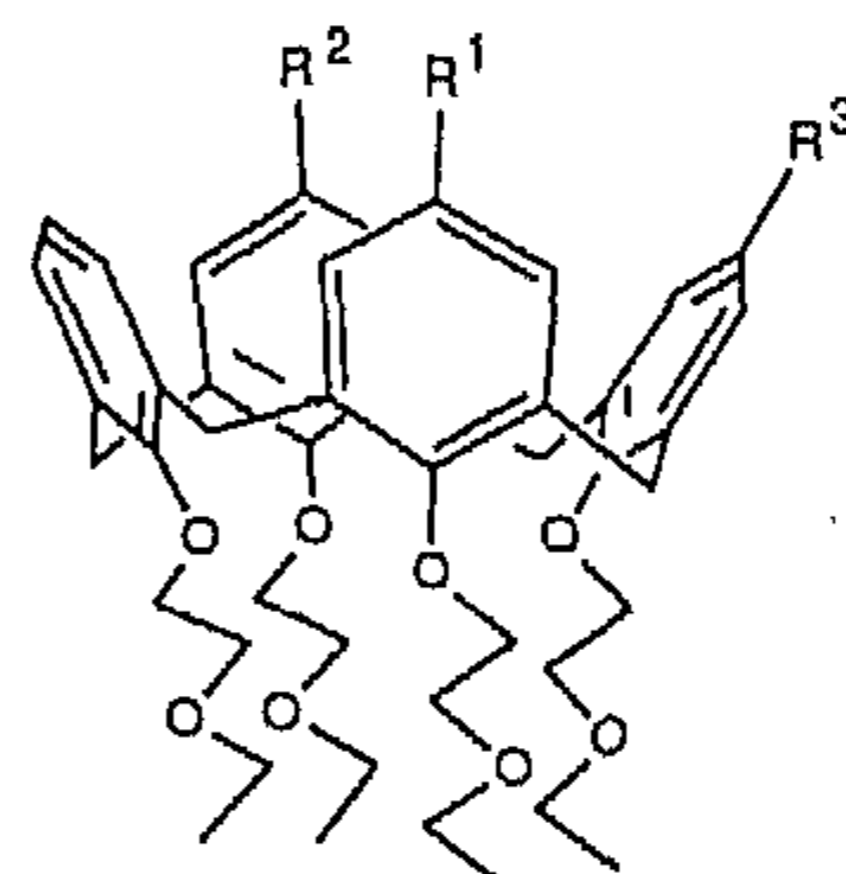
calixarenes · cavitands · molecular modeling · resorcinarenes · supramolecular chemistry

### Introduction

Among the different building blocks that have been studied for the synthesis of artificial receptor molecules, calixarenes,<sup>[1]</sup> cyclodextrins,<sup>[2]</sup> and resorcinol-based cavitands<sup>[3]</sup> are particularly useful.<sup>[4-5]</sup> Several years ago we started our work on combinations of different types of these building blocks for the synthesis of receptors,<sup>[6]</sup> inspired by the way nature constructs many different (macromolecular) receptors by combining only limited sets of building blocks. In this paper we report our results on the combination of calix[4]arenes and resorcin[4]arene-based cavitands.<sup>[7]</sup> The two major questions that we have addressed are the stereochemistry of the coupling products (*endo* vs. *exo*) and the formation of 1:1 vs. 2:1 reaction products. Further chemical modification of the coupling products (both 1:1 and 2:1) provides the starting materials for the cyclization to give either carceplexes or molecules with rigid nanosize cavities.

### Results and Discussion

First we investigated the regiospecificity of the reaction between upper-rim mono- and difunctionalized calix[4]arenes **4-6** and tetrahydroxycavitand **9**. The chloroacetamido-substituted calix[4]arenes **4-6** were synthesized in three steps from tetrakis(2-ethoxyethoxy)calix[4]arene.<sup>[8]</sup> The mononitro- and 1,3-dinitro-



- 1  $\text{R}^1=\text{NO}_2$ ,  $\text{R}^2=\text{R}^3=\text{H}$
- 2  $\text{R}^1=\text{R}^2=\text{NO}_2$ ,  $\text{R}^3=\text{H}$
- 3  $\text{R}^1=\text{R}^3=\text{NO}_2$ ,  $\text{R}^2=\text{H}$
- 4  $\text{R}^1=\text{NHC(O)CH}_2\text{Cl}$ ,  $\text{R}^2=\text{R}^3=\text{H}$
- 5  $\text{R}^1=\text{R}^2=\text{NHC(O)CH}_2\text{Cl}$ ,  $\text{R}^3=\text{H}$
- 6  $\text{R}^1=\text{R}^3=\text{NHC(O)CH}_2\text{Cl}$ ,  $\text{R}^2=\text{H}$

- 7  $\text{R}^1=\text{C}_{11}\text{H}_{23}$ ,  $\text{R}^2=\text{R}^3=\text{Br}$
- 8  $\text{R}^1=\text{CH}_3$ ,  $\text{R}^2=\text{R}^3=\text{Br}$
- 9  $\text{R}^1=\text{C}_{11}\text{H}_{23}$ ,  $\text{R}^2=\text{R}^3=\text{OH}$
- 10  $\text{R}^1=\text{CH}_3$ ,  $\text{R}^2=\text{R}^3=\text{OH}$
- 11  $\text{R}^1=\text{C}_{11}\text{H}_{23}$ ,  $\text{R}^2=\text{OH}$ ,  $\text{R}^3=\text{H}$
- 12  $\text{R}^1=\text{CH}_3$ ,  $\text{R}^2=\text{OH}$ ,  $\text{R}^3=\text{H}$

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calixarene derivatives **1** and **2** were obtained in 20% and 30–40% yield, respectively, as was reported by van Loon et al.<sup>[9]</sup> Reinvestigation of the nitration reaction revealed that considerable amounts of 1,2-dinitrocalix[4]arene **3** were present in the mother liquor after recrystallization of the 1,3-dinitro derivative **2** from MeOH. The 1,2-dinitrocalix[4]arene **3** could not be separated from the 1,3-isomer and was therefore used in further reactions as a 2:1 mixture with 1,3-dinitro derivative **2**. Reduction of the mono- and 1,3-dinitrocalix[4]arenes **1** and **2** with hydrazine/Raney Ni<sup>[9]</sup> followed by reaction with ClC(O)CH<sub>2</sub>Cl gave the corresponding chloroacetamidocalix[4]arenes **4** and **5**, respectively, in almost quantitative yield. Conversion of the mixture of **2** and **3** in a similar way gave pure 1,2-bis(chloroacetamido)calix[4]arene **6** after chromatographic separation in 74% yield (based on the amount of **3** present in the mixture).

Tetrahydroxycavitand **9** (R<sup>1</sup> = C<sub>11</sub>H<sub>23</sub>) was synthesized according to the procedure of Cram et al.<sup>[10]</sup> Treatment of tetrabromide **7** with 10 equivalents of *n*BuLi in THF at –70 °C followed by quenching with B(OMe)<sub>3</sub> and oxidative workup gave tetrahydroxycavitand **9** in 92% yield together with 7% of triol **11**. Tetrahydroxycavitand **9** is very soluble in DMF and THF, soluble in CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub>, but essentially insoluble in CH<sub>3</sub>CN and MeOH. Tetrahydroxycavitand **10** (R<sup>1</sup> = CH<sub>3</sub>) was synthesized in an analogous procedure starting from tetrabromide **8**<sup>[3a]</sup> in an overall yield of 47%. Reaction of mono(chloroacetamido)calix[4]arene **4** with 8 equivalents of tetrahydroxycavitand **9** gave 1:1 reaction product **13** in 61% yield. The <sup>1</sup>H NMR spectrum of **13** shows a downfield shift of more than 1.0 ppm of the amide-proton signal compared to that for the corresponding calix[4]arene derivative **4**. This might be due to the formation of an intramolecular hydrogen bond between the amide hydrogen and (one of) the surrounding ether oxygen atoms. This is supported by the broadening of the amide resonance in the IR spectrum compared to that of **4**. The broadening also indicates that more than one type of amide bond is present.

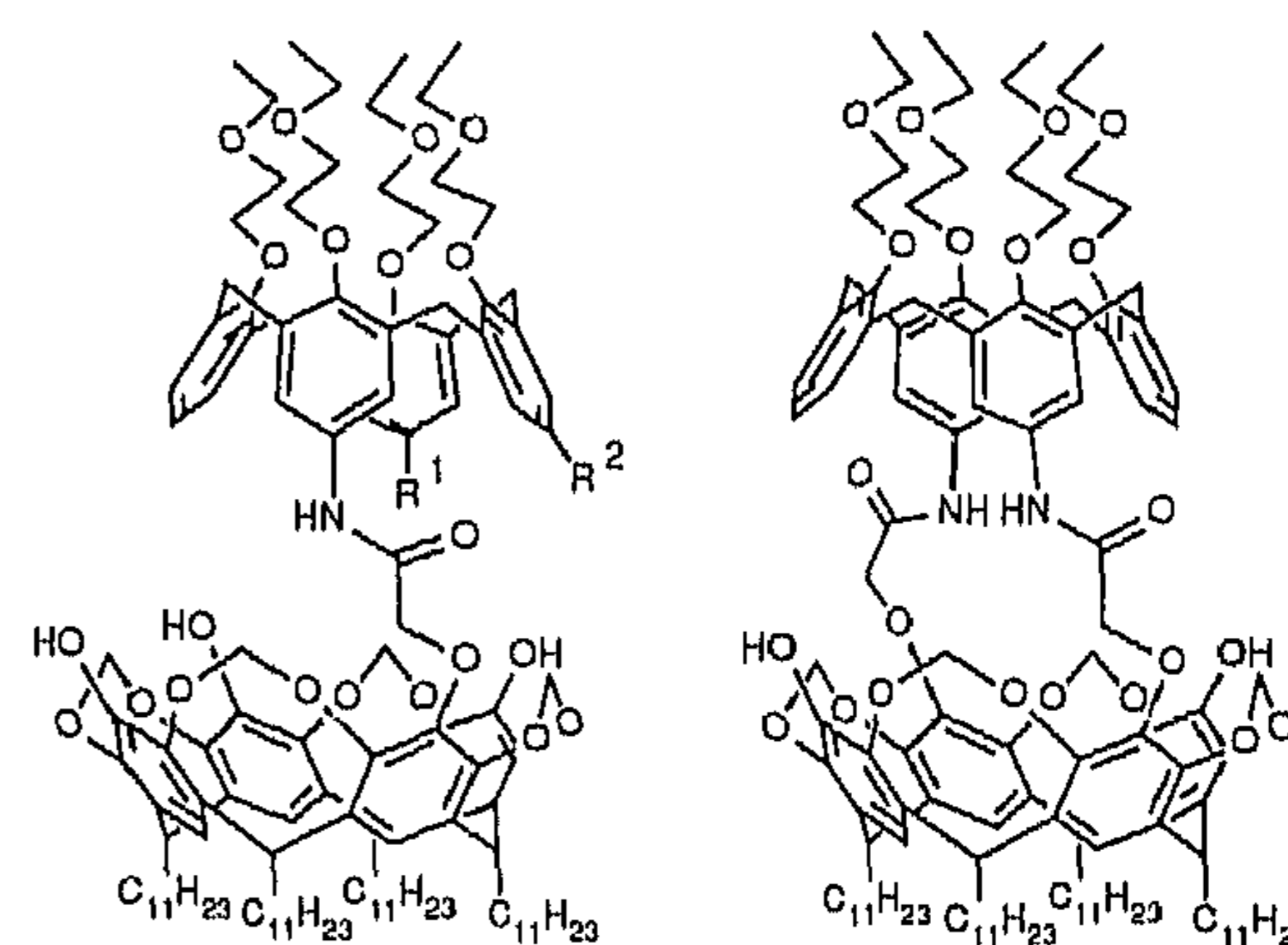


**Editorial Board Member:**<sup>[\*]</sup> *Professor David N. Reinhoudt was born in 1942 in the Netherlands. He studied Chemical Technology at the Delft University of Technology and graduated in chemistry in 1969 with Professor H. C. Beijerman. In 1970 he started the crown ether research program at Shell; he also worked on the physical organic chemistry of crown ether complexation. In 1975 he was appointed as a part-time professor (extraordinarius) at Twente University. His appointment as a full professor followed in 1978. The major part of his research deals with areas of supramolecular chemistry, such as the synthesis of calixarenes and metallamacrocycles, complexation studies with cations, anions, and neutral guest molecules, and the application of supramolecular chemistry in membrane transport, in the field of electronic and optical sensor systems, catalysis, and molecular (NLO) materials. He is the author of more than 380 scientific publications, patents, and review articles and has written a book on the chemistry of macrocycles.*

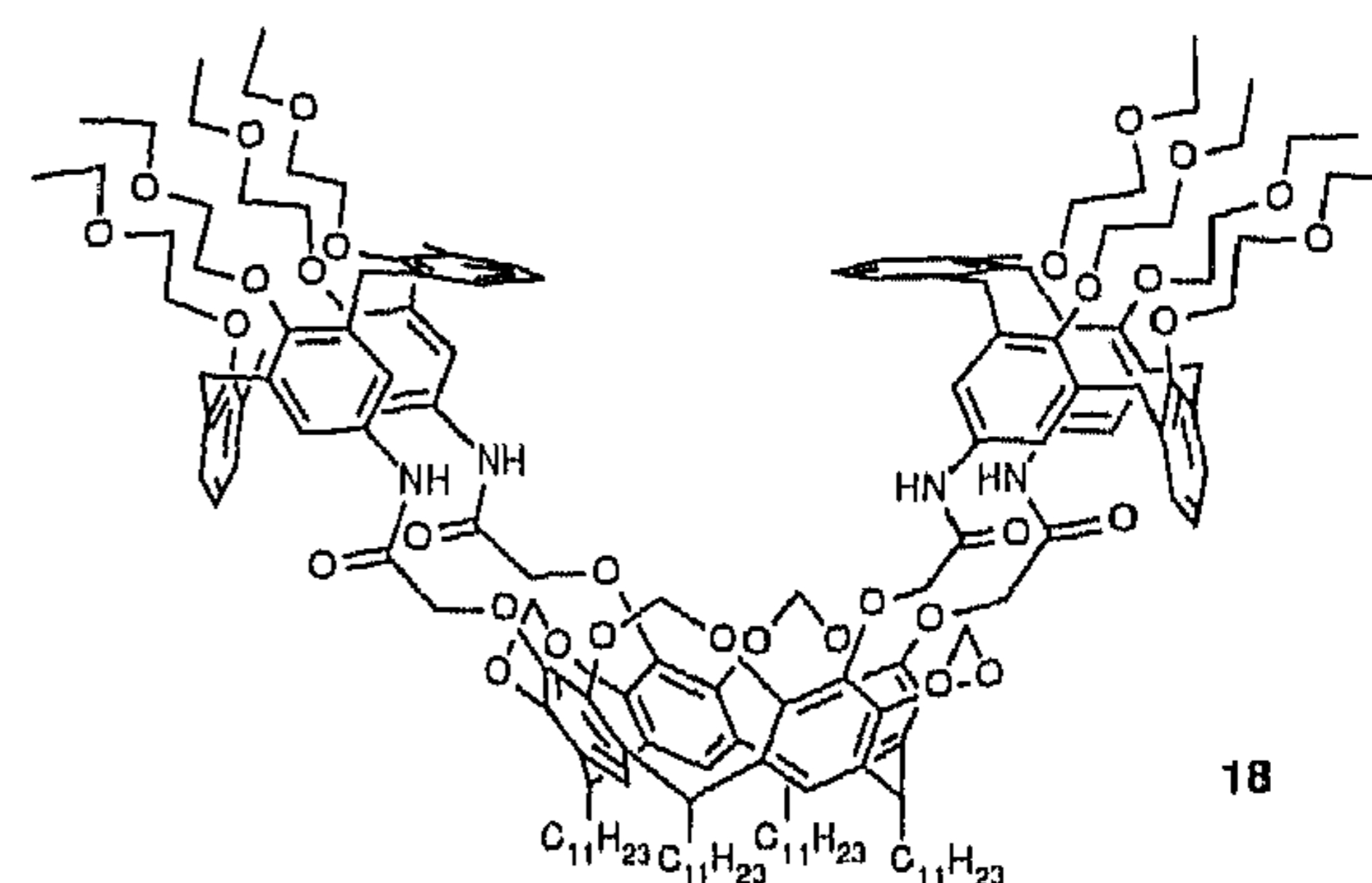
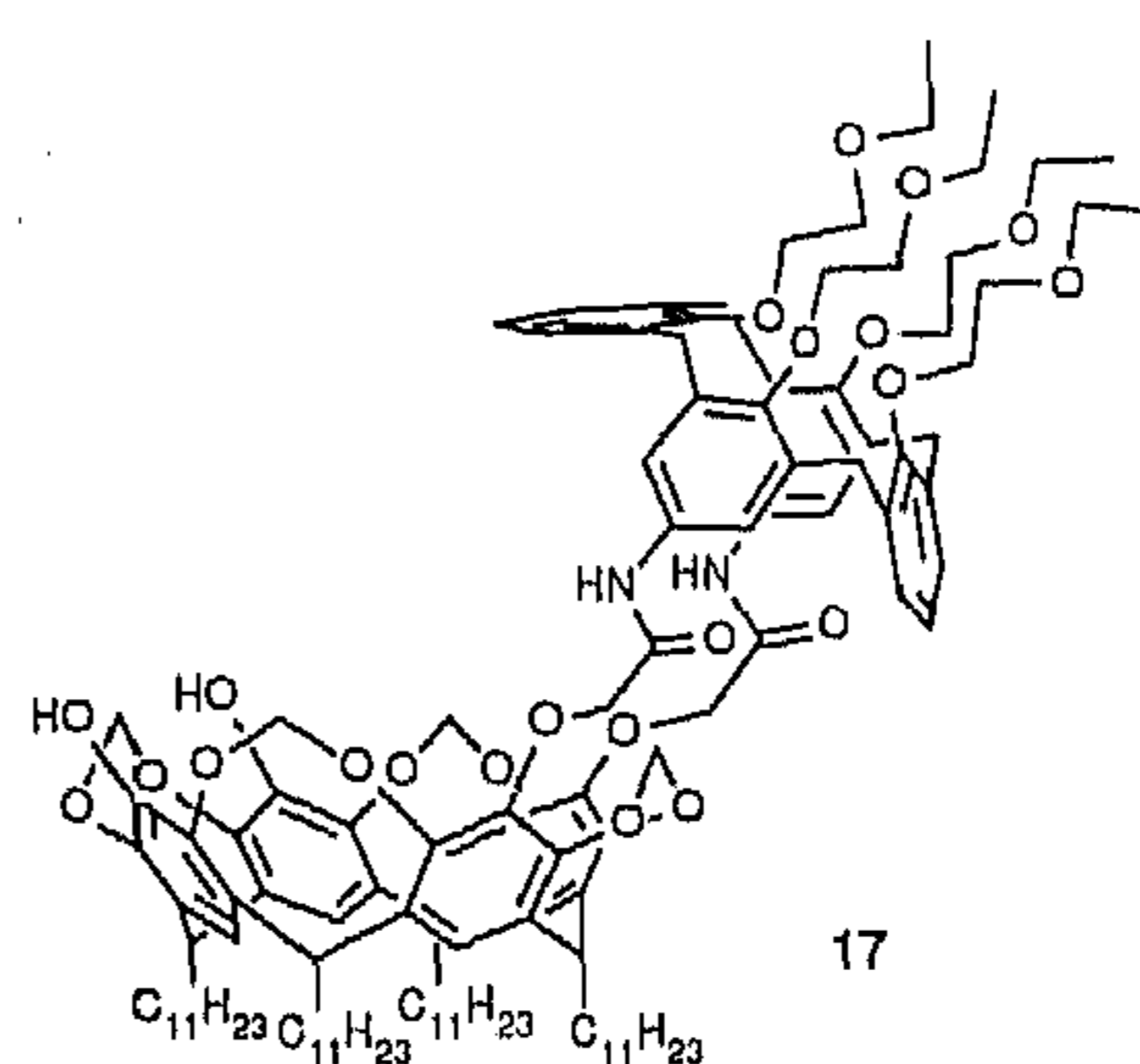
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In principle the reaction between 1,3-bis(chloroacetamido)calix[4]arene **5** and tetrahydroxycavitand **9** can give two isomeric products (**16** and **17**): the chloroacetamido group in the initially formed **14** can react either with the hydroxyl group opposite it to form compound **16**, or with one in the adjacent positions to yield compound **17**. Both **16** and **17** have two remaining free hydroxyl groups, which are able to react with a second equivalent of **5**. In the case of **16** polymerization ensued; **17** reacted to give the 2:1 product **18**. When the reaction was carried out with a 1:1 ratio of **5** and **9**, only 2:1 product **18** could



**13** R<sup>1</sup>=R<sup>2</sup>=H  
**14** R<sup>1</sup>=NHC(O)CH<sub>2</sub>Cl, R<sup>2</sup>=H  
**15** R<sup>1</sup>=H, R<sup>2</sup>=NHC(O)CH<sub>2</sub>Cl



be isolated in 35% yield. Although FAB-MS strongly suggested the presence of 1:1 products (**16** and/or **17**), they could not be isolated. The yield of **18** improved to 47% when the reaction was performed with a 2:1 ratio of **5** and **9**. The <sup>1</sup>H NMR spectrum of **18** shows a single resonance at δ = 8.3 for the four amide protons. The aromatic protons *ortho* to the amide spacer give rise to a single resonance at δ = 6.5; this indicates that rotation about the C(arene)–N bond is fast on the <sup>1</sup>H NMR time scale. Apparently the spacers do not have a well-defined orientation, and the molecule is thus rather flexible. Two of the four outer protons of the methylenedioxy bridges are consider-

Table 1. Total yields and isolated yields of products 19–23a in the reactions between 6 and 9 under several different reaction conditions.

Entry	Ratio 6/9	Solvent	Base	[6] mM	Total yield (%)	Isolated yields (%)				
						<i>endo</i> 1:1 19	<i>exo</i> 1:1 20	<i>endo-endo</i> 2:1 21a	<i>endo-exo</i> 2:1 22a	<i>exo-exo</i> 2:1 23a
1	1.1	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	2.6	103	19	32	13	39	[a]
2	2.2	CH <sub>3</sub> CN	Cs <sub>2</sub> CO <sub>3</sub>	4.8	65	–	–	12	33	20
3	2.2	DMF	Cs <sub>2</sub> CO <sub>3</sub>	4.5	66	–	–	13	34	19
4	2.2	CH <sub>3</sub> CN	K <sub>2</sub> CO <sub>3</sub>	4.7	61	–	–	16	27	19
5	1.0	DMF	K <sub>2</sub> CO <sub>3</sub>	2.8	87	13	21	11	26	16
6	2.1	DMSO	Cs <sub>2</sub> CO <sub>3</sub>	4.3	49 [b]	–	–	8	21	20

[a] Compound was formed according to TLC, but could not be isolated. [b] Decreased yield due to difficult workup.

ably shielded owing to the presence of the two calix moieties; this can be concluded from the fact that their signals are shifted 0.75 ppm upfield. Tetraalkylated calix[4]arenes are flexible and not fixed in a symmetrical cone conformation.<sup>[11]</sup> Obviously, rapid interconversion between two pinched cone conformations<sup>[12]</sup> disfavors the formation of 1:1 product 16.

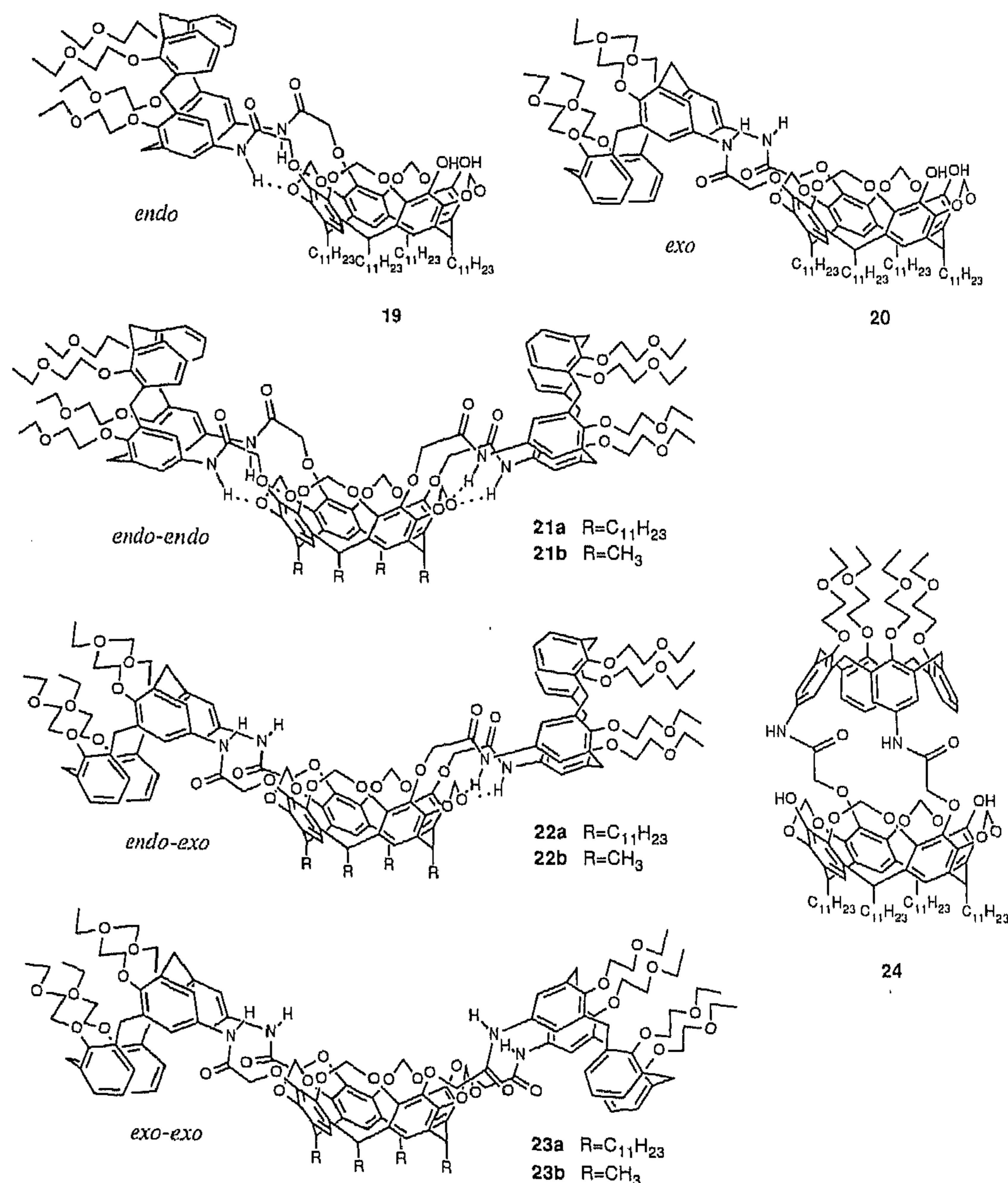
Reaction of 1,2-difunctionalized calix[4]arene 6 with tetrahydroxycavitand 9 can lead to 6 different products. When the reaction was carried out under high-dilution conditions, five different products were isolated by systematically varying the concentrations, solvent, and base. Only the 1:1 reaction product 24, formed by reaction of two opposing hydroxyl groups, could not be detected. The results are summarized in Table 1.

In contrast to the reaction between 1,3-difunctionalized calix[4]arene 5 and tetrahydroxycavitand 9, that between 1,2-difunctionalized calix[4]arene 6 and 9 gave considerable amounts of 1:1 products when the reaction was carried out with a 1:1 ratio of reactants (Entries 1 and 5). However, with a 2:1 ratio, only 2:1 products were formed (Entries 2–4 and 6).<sup>[14]</sup> It should be emphasized that the stereochemistry of 1:1 products is established only with the formation of the second bond between 6 and 9, since the initially formed product 15 can give both the *endo* isomer 19 and the *exo* isomer 20. The preference for an *endo* or *exo* orientation of the calix[4]arene moiety is therefore determined exclusively by intramolecular interactions. In contrast, the stereochemistry of the 2:1 products is established with the formation of the first bond to the second calix[4]arene moiety and therefore solely determined by intermolecular interactions.

Entries 1 and 5 show that, of the two possible 1:1 isomers 19 and 20, *exo* 1:1 isomer 20 was isolated in a slightly higher yield. The yields of these 1:1 products may reflect their rate of formation, but the higher reactivity of *endo* 1:1 isomer 19 in further reactions might also cause the lower isolated yield. Thus, when the reaction was run in CH<sub>3</sub>CN (Entry 1) *exo* 1:1 isomer 20 was apparently formed in preference, but the formation of 13% of the *endo-endo* 2:1 isomer

21a and no *exo-exo* 2:1 isomer 23a indicates that *endo* 1:1 isomer 19 is more reactive under the conditions used. When the reaction was carried out in DMF (Entry 5), both 1:1 products seemed to have comparable reactivities. In this case, *exo* 1:1 isomer 20 is presumably formed in slight preference to *endo* 1:1 isomer 19.

The reactions between 6 and 9 in a 2:1 ratio gave only 2:1 products. In these cases it is difficult to draw definite conclusions about reactivities and preferential formation of certain products, since the major product 22a (*endo-exo* 2:1 isomer) can be formed either via *endo* 1:1 isomer 19 or via *exo* 1:1 isomer 20. The only conclusion that can be drawn is that in all reactions *exo-exo* 2:1 isomer 23a is formed in slight preference



over *endo-endo* 2:1 isomer **21a**. In DMSO this preference is more pronounced than in the other solvents studied (DMF and CH<sub>3</sub>CN).

It seems that the well-known “cesium effect”<sup>[15]</sup> is not applicable in the reactions studied here (Entries 2 and 4). Apparently, the building blocks are fairly well preorganized to give, even in the absence of Cs<sup>+</sup> as a template, satisfactory yields. In a similar way compounds **21b–23b** were synthesized starting from tetrahydrocavitand **10**.

The mode of coupling of 1,2-difunctionalized calix[4]arene **6** with cavitand **9** (*endo* or *exo*) gives the resulting products **19–23a** strikingly different properties. The differences in polarity mean that all five products are easily separable by chromatography. Their <sup>1</sup>H NMR spectra show numerous dissimilarities, the most characteristic of which is the chemical shift difference of 0.6 ppm between the amide protons corresponding to an *endo*- and an *exo*-coupled calix unit. Figure 1 shows the <sup>1</sup>H NMR spectra of *endo-endo* 2:1 isomer **21b** and *exo-exo* 2:1 isomer

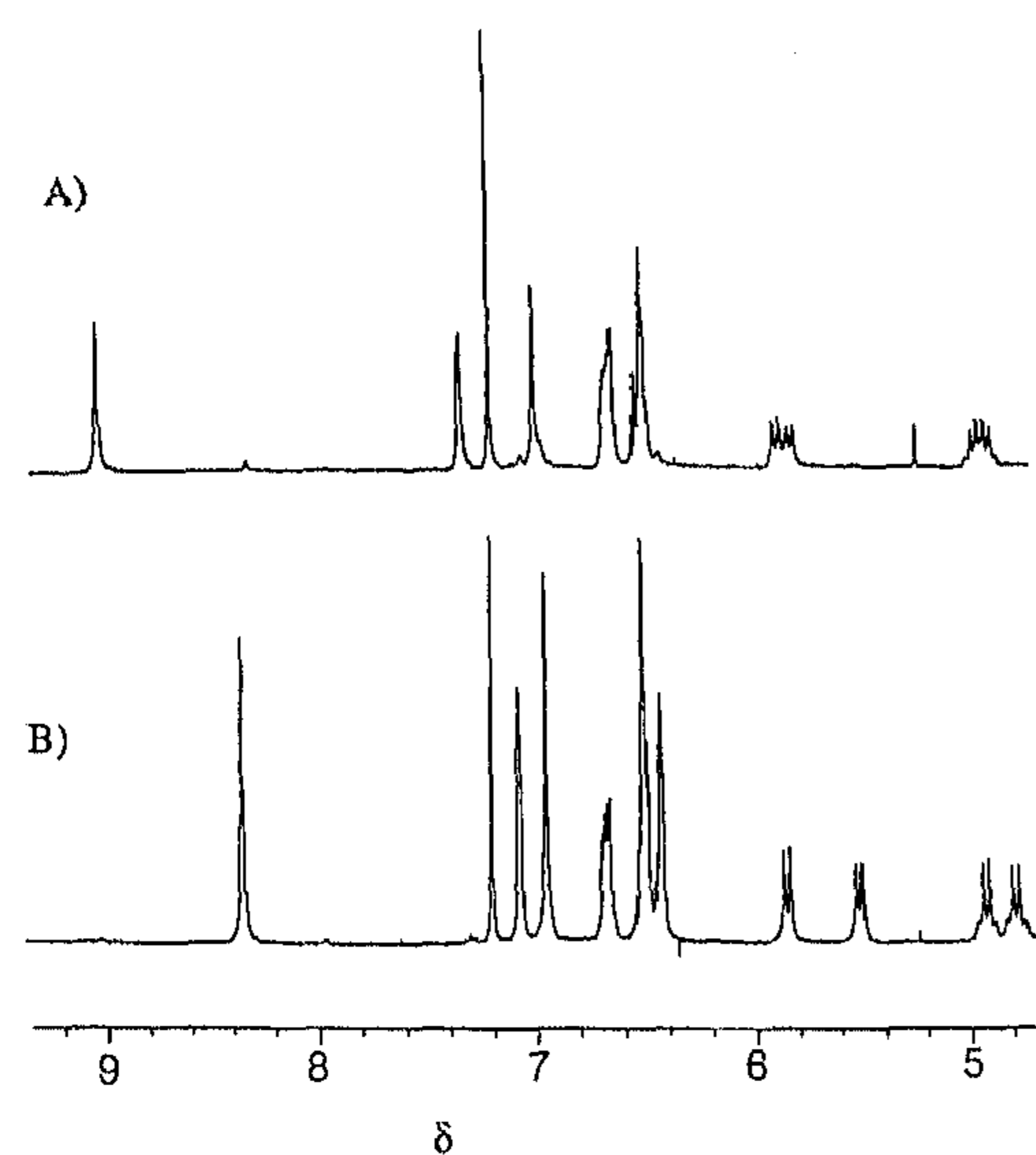


Fig. 1. <sup>1</sup>H NMR spectrum of A) *endo-endo* 2:1 **21b** and B) *exo-exo* 2:1 **23b**.

**23b**. Spectrum A, with the amide protons resonating at lowest field, shows two partly overlapping quartets around  $\delta = 4.9$  for two pairs of methine protons positioned at the bridges carrying the methyl groups. In spectrum B one of these quartets is shifted upfield to about  $\delta = 4.8$ . This points to the *exo-exo* 2:1 stereoisomer **23b**, since in this structure two of the four methine protons are located in close proximity to the unsubstituted aromatic rings of the calix[4]arene moiety. Conclusive evidence for the stereochemistry of the different products was obtained from a NOESY experiment with 2:1 isomers **21b** and **23b**. The NOE spectrum corresponding to spectrum B shows a connectivity between the upfield-shifted methine quartet and the protons of the unsubstituted aromatic rings. In the NOE spectrum corresponding to spectrum A such connectivity was not observed. This provides definite proof for the fact that spectrum A corresponds to *endo-endo* 2:1 isomer **21b** and spectrum B to *exo-exo* 2:1 isomer **23b**. Following this assignment, it can be concluded that, in compounds **19–23b**, an amide proton resonating at  $\delta = 9.0$  belongs to an *endo*-coupled calix moiety, whereas an *exo*-coupled amide gives rise to a signal at  $\delta = 8.4$ . Based on this knowledge the relative stereochemistry could be easily determined for all coupled products **19–23b**.

The large chemical shift difference between the amide protons in *endo-endo* isomer **21b** and *exo-exo* isomer **23b** stems from a different orientation of the amide spacers in these molecules. From the corresponding <sup>1</sup>H NMR spectra (Fig. 1) it can be seen that the aromatic protons *ortho* to the amide groups (*o*-NHArH) are chemically nonequivalent; this indicates that the amide moieties have a strong preference for a specific orientation. The distances between protons of less than 4 Å were determined quantitatively with NOE spectroscopy by using the initial rate approximation.<sup>[13]</sup> The most relevant distances are shown in Figure 2. In both isomers the amide protons are located closer to H<sub>a</sub> than to H<sub>b</sub>. In the *endo-endo* 2:1 isomer **21b** the difference is somewhat larger than in the *exo-exo* 2:1 isomer **23b**; this is in agreement with the somewhat larger chemical shift difference in case of an *endo*-coupled calix moiety.

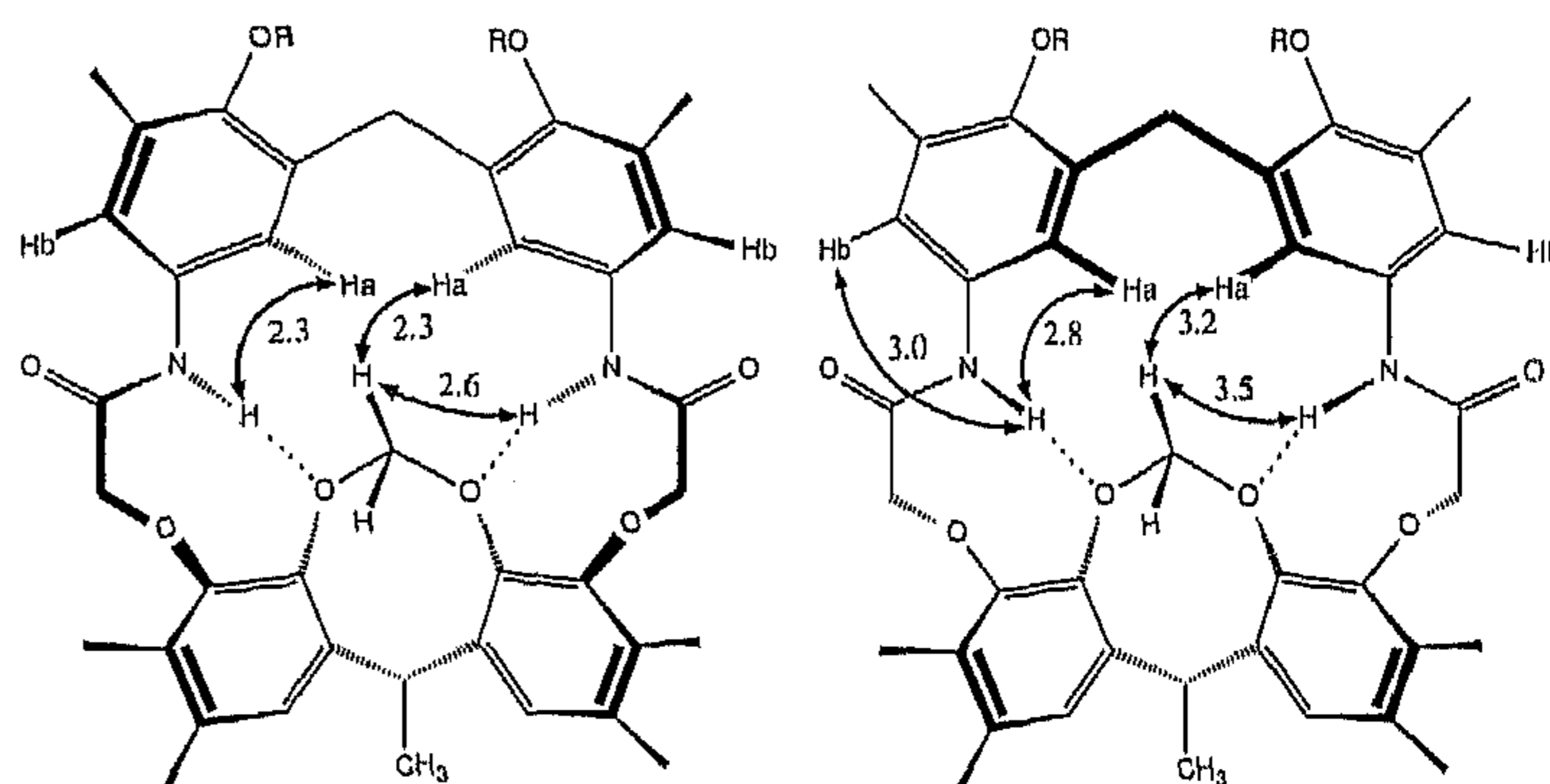


Fig. 2. Intramolecular distances in Å ( $\pm 0.2$  Å) in *endo-endo* 2:1 **21b** (left) and *exo-exo* 2:1 **23b** (right), as determined by NOESY (only parts of the structure are shown for clarity).

Molecular mechanics simulations were carried out using the experimentally determined distances as constraints (Fig. 3). In the energy-minimized structure of *endo-endo* isomer **21a** the amide moieties are parallel to the attached aromatic rings; this enables the amide protons to form intramolecular hydrogen bonds with the oxygen atoms of the methylenedioxy bridges. In *exo-exo* 2:1 isomer **23b** the aromatic rings carrying the amide spacers have been rotated by about 90°, and in this orientation

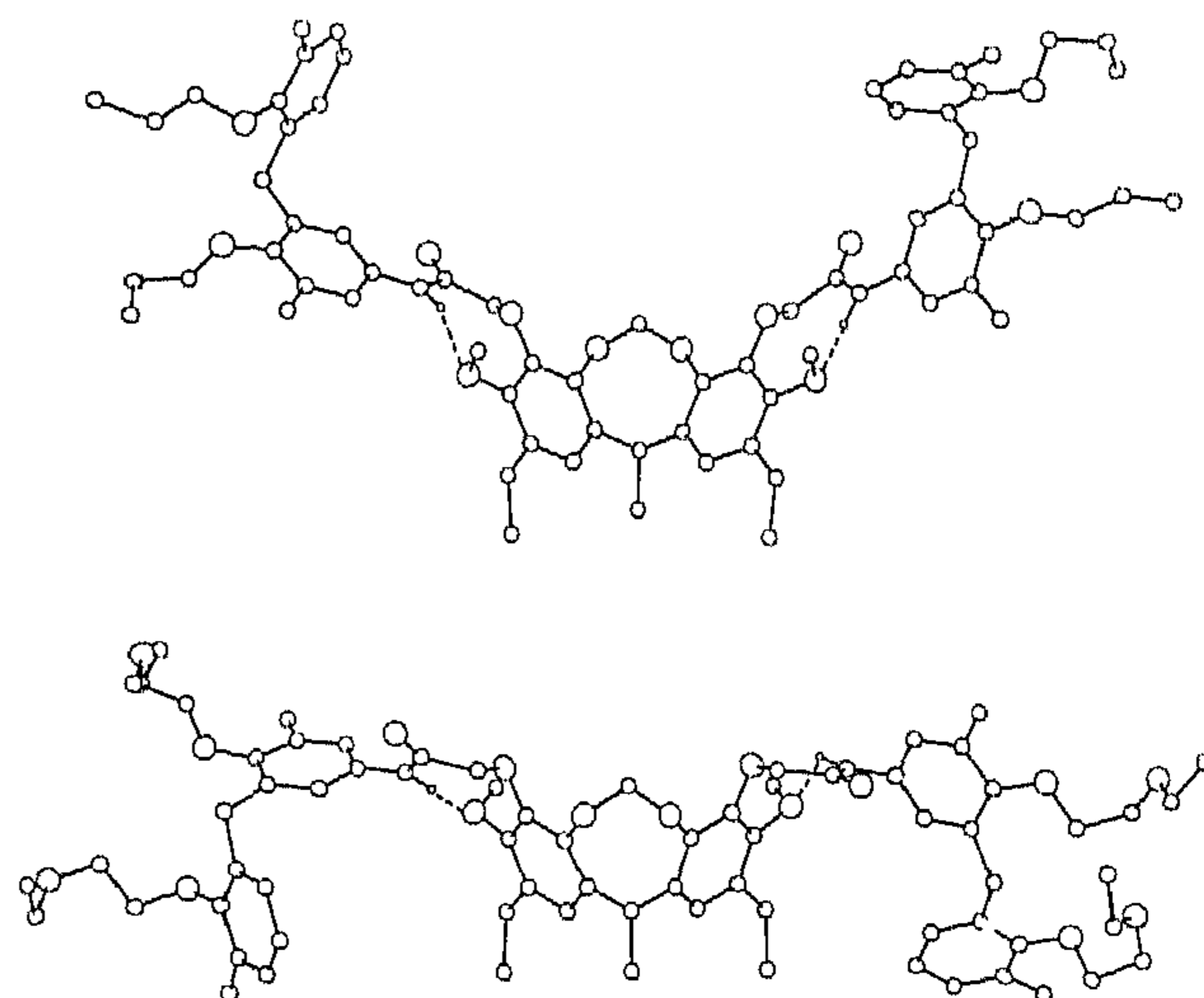
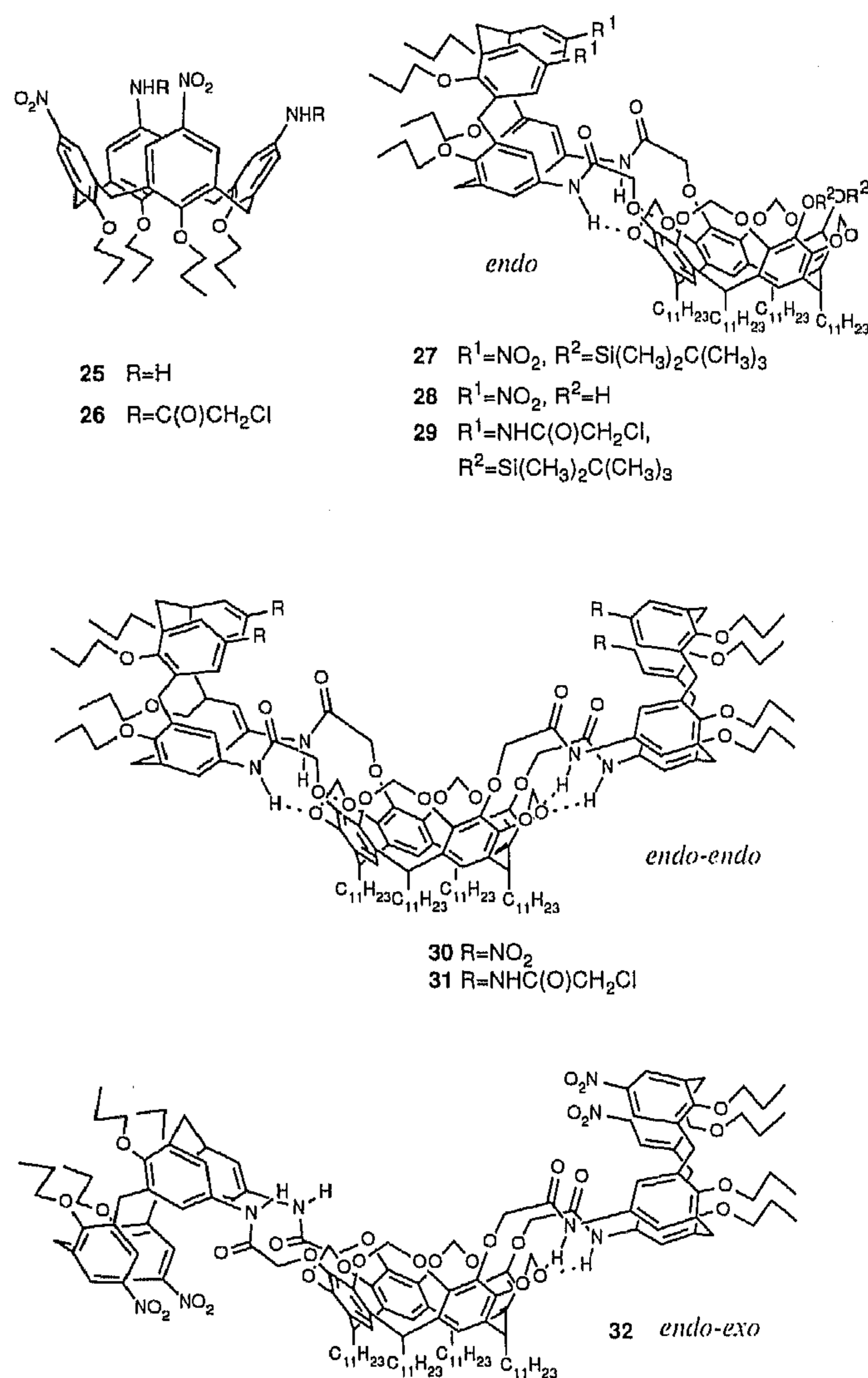


Fig. 3. Energy-minimized structures of *endo-endo* 2:1 **21b** (top) and *exo-exo* 2:1 **23b** (bottom) using the experimentally determined distances (see Fig. 2) as constraints (only parts of the structure are shown for clarity).

the intramolecular hydrogen bonds cannot be formed. Therefore, the orientation of the amide moieties in *exo-exo* 2:1 isomer **23b** can be regarded as being determined by an optimum compromise between conjugation of the C–N bond with the aromatic rings and formation of linear hydrogen bonds with the ether oxygens of the methylenedioxy bridges. Consequently, the amide moieties are rotated out of the plane of the aromatic rings and the average N–H···O arrangements are slightly bent. This indicates that the hydrogen bonds in *exo-exo* 2:1 isomer **23b** should be weaker than those in *endo-endo* 2:1 isomer **21b**. IR data support this difference in the strength of hydrogen bonding: the value of  $\tilde{\nu}$  for the stretching vibration is  $12\text{ cm}^{-1}$  lower for *endo*-coupled amide protons. An exchange experiment with *endo-exo* 2:1 isomer **22a**, which contains both *endo*- and *exo*-coupled calix[4]arene fragments, in  $\text{CDCl}_3$  with  $\text{NEt}_3$  and  $\text{D}_2\text{O}$  indicated that the *exo*-amide protons are kinetically more labile than the corresponding *endo*-amide protons.

In order to study the effect of substituents in the calixarene on the product distribution in the reaction between 1,2-difunctionalized calix[4]arenes and cavitands, we synthesized bis(chloroacetamido) calix[4]arene **26**, carrying two nitro groups at the residual aromatic rings. Compound **26** was obtained quantitatively by a nitro-group reduction<sup>[16]</sup> to give **25**, followed by reaction with 2 equivalents of  $\alpha$ -chloroacetyl chloride. The reaction between calix[4]arene **26** and tetrahydroxycavitand **9** was also carried out under different reaction conditions. The results are summarized in Table 2. In all reactions studied only three of the six possible products could be isolated, namely, the *endo* 1:1 product **28**, the *endo-endo* 2:1 product **30**, and the *endo-exo* 2:1 isomer **32**. Because of its instability, **28** was isolated as **27** after silylation of the free hydroxyl groups with *tert*-butyldimethylsilyl chloride. The result of the reaction between **26** and **9** depends on the reaction conditions. Reactions of **26** and **9** in a 1:1 ratio in  $\text{CH}_3\text{CN}$  (Entries 1, 2, and 4) generally gave a high yield of *endo* 1:1 **28**, probably as a result of precipitation during the reaction. Even in the presence of 2 equivalents of **26** (Entry 3) the *endo* 1:1 **28** was not fully consumed after 20 h of reflux; this underlines the low reactivity of this compound in further reactions. In polar solvents like DMF and DMSO in which **28** is fairly soluble, its reactivity seemed to be not much higher.<sup>[17]</sup>

The absence of both the *exo* 1:1 and the *exo-exo* 2:1 products can be related to a strong preference for an *endo* orientation in the coupling reaction between the bis(chloroacetamide calix[4]arene) **26** and cavitand **9**. This preference is determined exclusively by intramolecular interactions during formation of the second bond (vide supra). The exclusive formation of the *endo* 1:1 product might be attributed to a favorable interaction of the nitro groups with the cavitand stabilizing the transition state (Fig. 4). In the reaction leading to the *exo* 1:1 isomer the



nitro groups are too remote from the cavitand to interact. Dipole–dipole interactions, which are known to be of importance in the complexation behavior of cavitands,<sup>[3a]</sup> may play an important role, because of the polar character of both the nitro and the hydroxyl groups. Hydrogen bonding between nitro and phenolic hydroxyl groups has only been observed in the solid state and is rather weak.<sup>[18]</sup>

In all reactions the ratio of 2:1 reaction products **30** and **32** was approximately the same; this emphasizes the fact that there is no preference for an *endo* or *exo* orientation in reaction of **28** with a second equivalent of **26**. This is not surprising, since the

Table 2. Total yield and product distribution of the reaction between **26** and **9** under several different reaction conditions.

Entry	Ratio 26/9	Solvent	Base	[26] mM	Reaction time (h) [a]	Total yield (%)	Yield (%)		
							<i>endo</i> 1:1 27	<i>endo-endo</i> 2:1 30	<i>endo-exo</i> 2:1 32
1	1.0	$\text{CH}_3\text{CN}$	$\text{Cs}_2\text{CO}_3$	2.0	8 + 13	78	42	20	16
2	1.0	$\text{CH}_3\text{CN}$	$\text{Cs}_2\text{CO}_3$	6.5	8 + 9.5	54	28	13	13
3	2.0	$\text{CH}_3\text{CN}$	$\text{Cs}_2\text{CO}_3$	6.5	8 + 12	34 [b]	16	10	8
4	1.0	$\text{CH}_3\text{CN}$	$\text{K}_2\text{CO}_3$	2.8	8 + 21	53	23	14	16
5	1.0	DMF	$\text{Cs}_2\text{CO}_3$	2.0	8 + 13.5	56	28	14	14
6	1.0	DMSO	$\text{Cs}_2\text{CO}_3$	4.0	8 + 13	40	[c]	19	21
7	2.0	DMSO	$\text{Cs}_2\text{CO}_3$	7.7	8 + 13	28	[c]	14	14
8	2.0	DMSO	$\text{Cs}_2\text{CO}_3$	7.7	8 + 20.5	19	[c]	9	10

[a] Time used for addition of **26** + additional reaction time. [b] Unreacted **26** was present according to TLC, but was not isolated. [c] According to TLC, *endo* 1:1 product **28** was hardly present and therefore not isolated as *endo* 1:1 **27**.

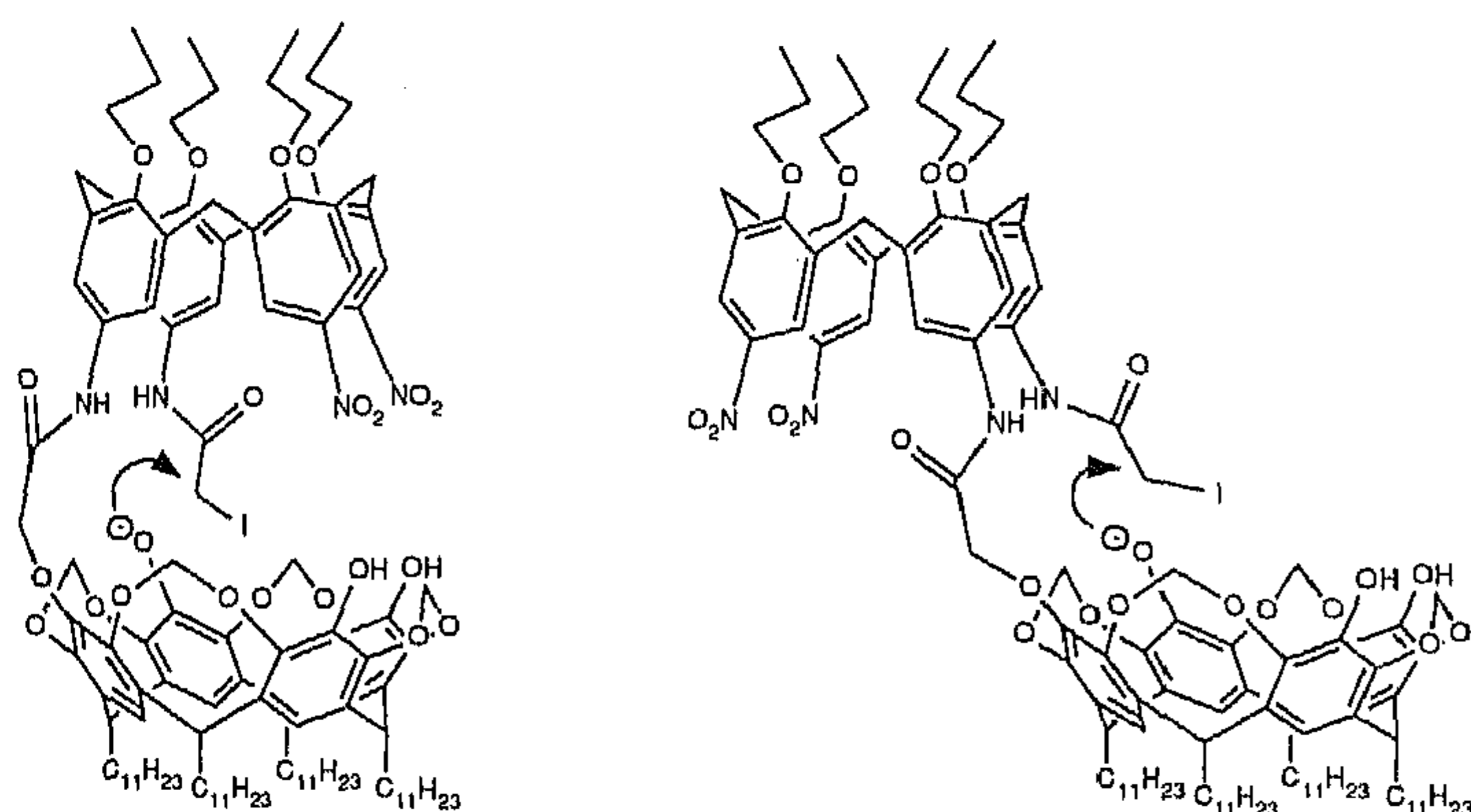


Fig. 4. Factors governing the selective formation of *endo* 1:1 product **28**: In the conformation leading to the *endo* 1:1 product (left), there are favorable intramolecular interactions of the cavitand with the nitro groups, which are absent in the conformation leading to the *exo* 1:1 product (right).

stereochemistry of the 2:1 products is determined in the formation of the first bond to the second calix[4]arene unit, which means that selectivity is largely governed by intermolecular interactions.

The nitro groups in **27** could be easily reduced to amino groups with hydrazine/Raney Ni.<sup>[9]</sup> After reaction with  $\alpha$ -chloroacetyl chloride, the bis(chloroacetamide) derivative **29** was isolated in quantitative yield. When a 5 mM solution of **29** was desilylated with CsF in DMF at 80 °C and subsequently stirred at this temperature for 48 hours in the presence of

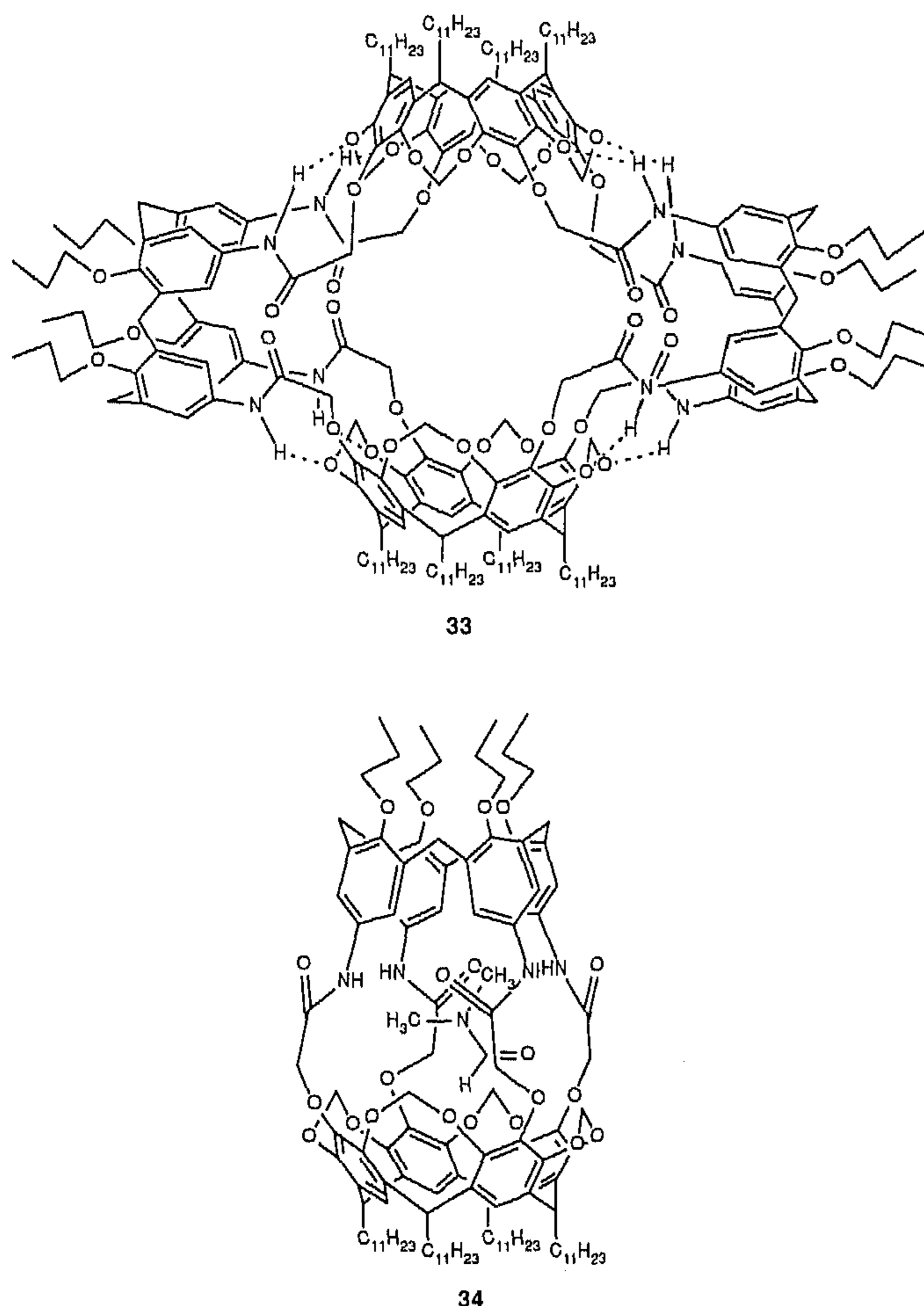


Fig. 5. Holand **33** and carceplex **34**.

Cs<sub>2</sub>CO<sub>3</sub> and KI, holand **33**<sup>[19]</sup> was isolated in 26% yield, together with calix[4]arene-based carceplex **34** (Fig. 5),<sup>[20]</sup> which carries one molecule of DMF in its interior, in 27% yield. When compound **29** was reacted at a concentration of 11 mM, the yields decreased to 12% of both **33** and **34**. Apparently, polymerization predominates at this concentration. Compound **33** could also be synthesized by a different route in slightly higher yield. The nitro groups in **30** were reduced with hydrazine/Raney Ni,<sup>[9]</sup> and subsequent reaction with  $\alpha$ -chloroacetyl chloride gave the corresponding tetrakis(chloroacetamide) derivative **31** in essentially quantitative yield. Dropwise addition of an equimolar solution of tetrakis(chloroacetamide) **31** and tetrahydrocavitand **9** in DMF to a suspension of Cs<sub>2</sub>CO<sub>3</sub> and KI in DMF gave holand **33** in 30% yield.

FAB-MS unambiguously proves the 2:2 structure of **33** [ $M_{\text{obs}} = 4084$  ( $M + \text{Na}^+$ , 100%)], and the <sup>1</sup>H NMR spectrum (Fig. 6) reflects the high degree of symmetry expected for **33**.

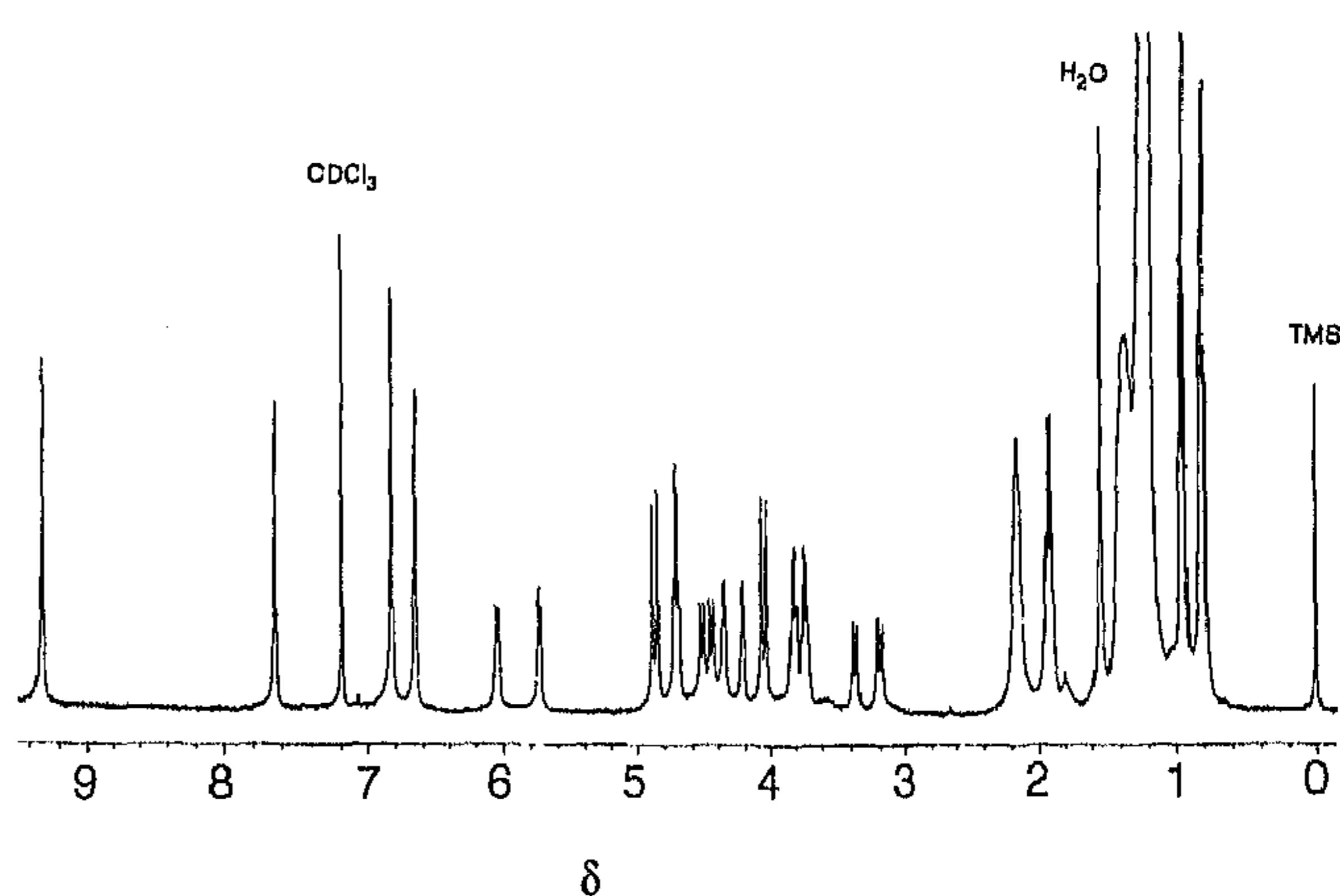


Fig. 6. <sup>1</sup>H NMR spectrum (400 MHz) of holand **33** in CDCl<sub>3</sub> at room temperature.

For its size, the molecule is extremely rigid. The calix[4]arene and cavitand fragments, which are intrinsically rigid, are connected through four highly organized spacers. This becomes evident when the <sup>1</sup>H NMR spectrum of **33** is compared with that of 1,2-bis(chloroacetamido) calix[4]arene **6** and that of *endo-endo* 2:1 isomer **21a**, two compounds in which part of the structures are identical to that of **33**, but which are much less organized. The aromatic protons *ortho* to the amide (*o*-NHArH) in **6** differ in chemical shift by only 0.08 ppm as a result of the almost free rotation about the C(arene)–N bond. However, in **21a** chemical shifts of the *o*-NHArH's differ to a much greater extent, because two of these calix[4]arene fragments are coupled with the cavitand. The 0.85 ppm chemical shift difference illustrates the rigidity of the amide spacers in **21a**. In holand **33** the mobility of the calixarene fragments is further reduced to give a  $\Delta\delta$  of 1.0. The rigidity of **33** is even better exemplified when the chemical shift difference between the two methylene protons in the spacers of **6** and **21a** is compared with that in **33**. Whereas these protons in **6** appear as a singlet, an AB quartet is observed for **21a** with  $\Delta\delta = 0.4$ . The motion of the calix fragments still present in **21a** mainly takes place by rotation about the O–CH<sub>2</sub> bond in the spacer. When this motion is finally frozen completely in **33**, the  $\Delta\delta$  value between the two AB doublets is 0.85.

The rigidity of **33** is partly a result of the hydrogen bonds between the amide hydrogens and the oxygens in the methylenedioxy bridge (indicated in Fig. 5 with dashed lines). This type of hydrogen bonding is very similar to that in *endo-endo* 2:1 iso-

mer **21 a** (vide supra). The amide protons in **33** have shifted downfield by 0.3 ppm compared to those in **21 a**, and they also vibrate at a slightly lower wavenumber in the IR spectrum ( $3358\text{ cm}^{-1}$  for **33** and  $3362\text{ cm}^{-1}$  for **21 a**). These data indicate that the hydrogen bonds in **33** are somewhat stronger than those in **21 a**, probably as a result of the greater extent of organization in holand **33**. The exact distances between protons of less than  $3\text{ \AA}$  were determined quantitatively with NOESY by using the initial rate approximation.<sup>[13]</sup> The relevant distances are shown in Figure 7.

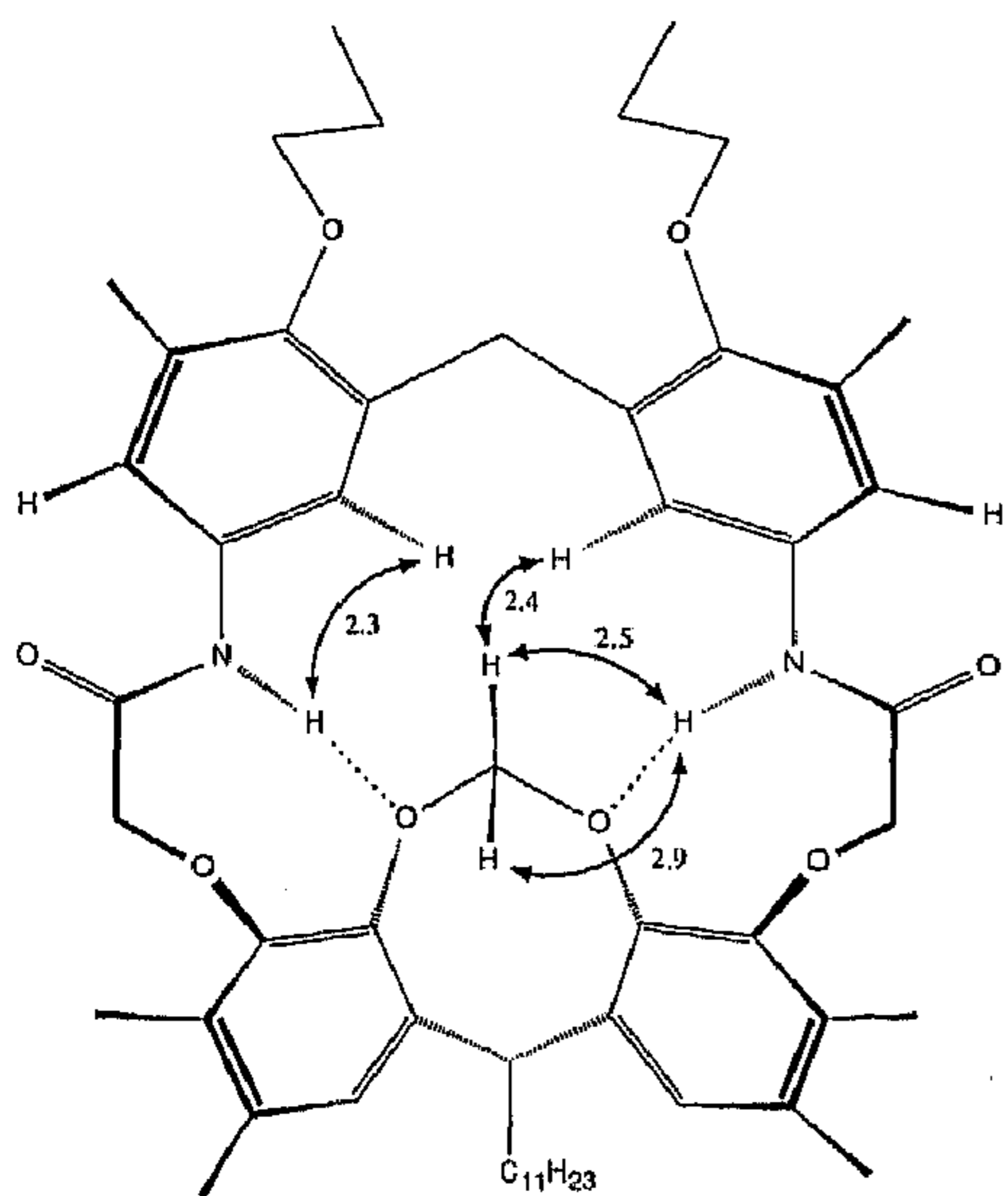


Fig. 7. Intramolecular distances in  $\text{\AA}$  ( $\pm 0.2\text{ \AA}$ ) in holand **33** as determined by NOESY (only part of the structure is shown for clarity).

Holand **33** contains a cavity of nanosize dimensions. The axes are about 1.5 and 2.0 nm long. The calculated internal volume is approximately  $1.0\text{ nm}^3$  ( $1000\text{ \AA}^3$ ). Therefore, holand **33** should be able to accommodate large organic guest molecules.<sup>[21]</sup>

### Molecular Dynamics Simulations

In order to investigate the rigidity of holand **33**, two 200 ps Molecular Dynamics simulations were performed at 300 K in  $\text{CHCl}_3$  and THF, respectively. During both simulation runs, the organization of the amide spacers as a result of the hydrogen bonds between the amide protons and the oxygens of the methylenedioxy bridges was clearly observed. Although the hydrogen bonds were sometimes broken, they reformed after a short period of time. Rotation about the C(arene)–N bond was not observed. In both simulations remarkable solvation phenomena were observed.

**$\text{CHCl}_3$  simulation:** During this simulation four  $\text{CHCl}_3$  molecules resided in the cavity of **33**. This caused only a small expansion of the cavity, which became somewhat more spherically-shaped compared to the slightly flattened cavity of the energy-minimized structure in vacuo. At the start of the simulation one  $\text{CHCl}_3$  molecule was located in the cavity of **33**. During the heating and equilibration phases, the other three  $\text{CHCl}_3$  molecules slipped into the cavity. Their positioning inside the cavity of **33** is quite remarkable. In the beginning all four  $\text{CHCl}_3$  molecules moved more or less randomly through the cavity, but after 5 ps one  $\text{CHCl}_3$  molecule was located in each of the cal-

ix[4]arene cavities with the hydrogen atom inside the cavity.<sup>[25]</sup> The other two molecules still moved around randomly through the cavity, but after a further 25 ps both molecules were positioned in the cavities of the resorcinarene fragments, one in each, with one of the chloro atoms inside the cavity (Fig. 8).

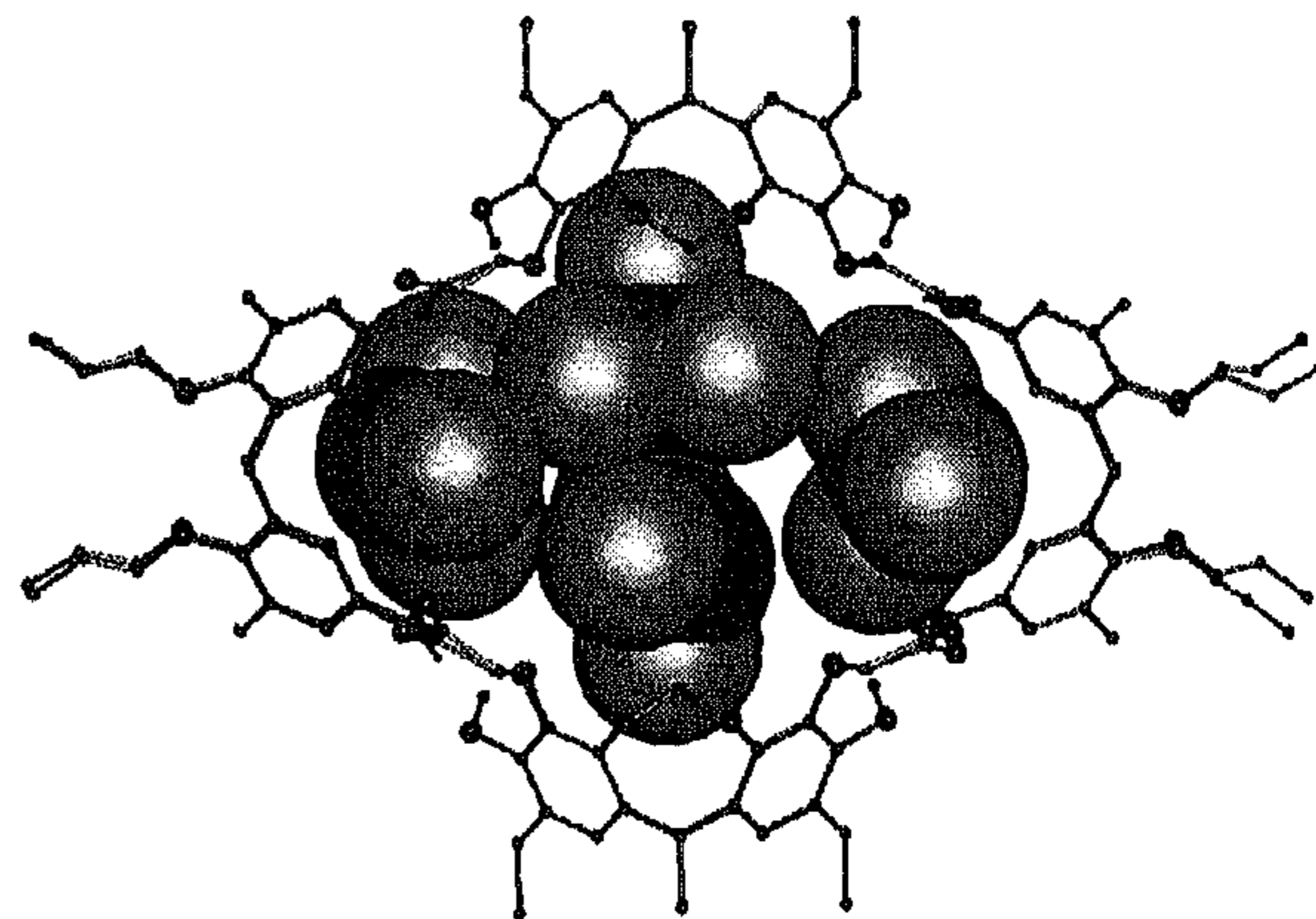


Fig. 8. Time-averaged structure of holand **33** (hydrogens not shown for clarity) and a snapshot of typical  $\text{CHCl}_3$  positions in the MD simulation (orientation as in Fig. 5).

This situation did not alter during the next 170 ps. None of the  $\text{CHCl}_3$  molecules exchanged their position with one of the other three molecules or with a  $\text{CHCl}_3$  in the remaining solvent box. Occasionally, the  $\text{CHCl}_3$  molecules located in the resorcinarene cavities exchanged the chloro atom in the cavity for one of the other two. On a few occasions, the  $\text{CHCl}_3$  in the calix[4]arene cavity changed its orientation so that it was analogous to that in the resorcin[4]arene cavity (i.e., the chloro atom was in the cavity instead of CH). This leads to a less favorable binding energy, which can clearly be seen in Figure 9 (at 175 ps).

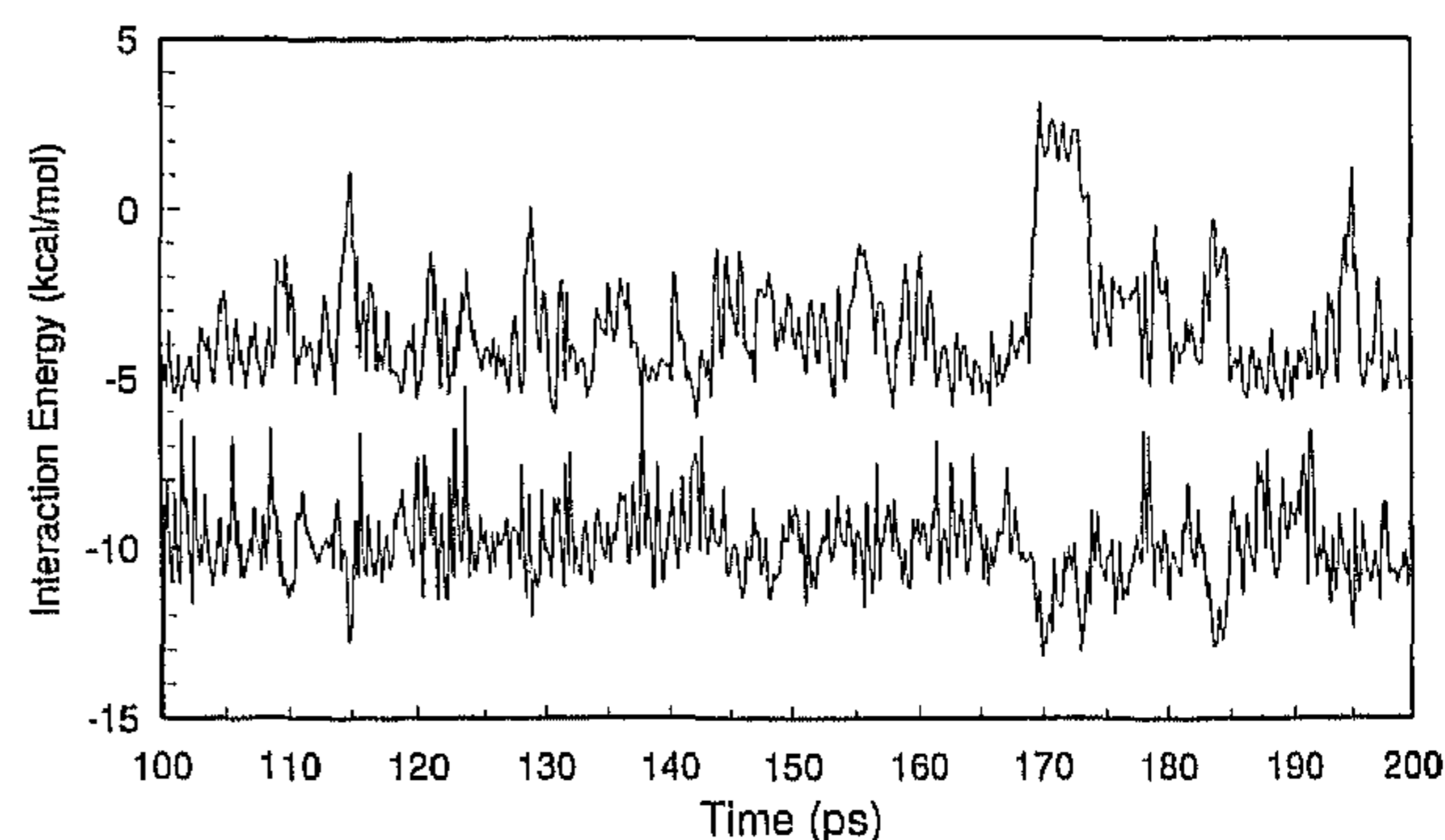


Fig. 9. Electrostatic (upper trace) and van der Waals interaction (lower trace, both in  $\text{kcal mol}^{-1}$ ) between holand **33** and the  $\text{CHCl}_3$  molecule in one of the calix[4]arene cavities as a function of simulation time. Clearly visible is the unfavorable electrostatic interaction at  $t = 170\text{--}175\text{ ps}$  as the  $\text{CHCl}_3$  moves into a resorcin[4]arene binding mode.

**THF simulation:** When a similar dynamics simulation run was performed in THF, a comparable positioning of solvent molecules inside the cavity of **33** was observed. The main differences with the simulation run in  $\text{CHCl}_3$  were the somewhat delayed entry of the final THF molecule (only after 65 ps) and the faster positioning of the two molecules in the calix[4]arene cavities (already after equilibration). These two THF molecules seemed to have a strong preference for an orientation in which their oxygen atoms point to the center of the cavity of **33**, while the

two other THF molecules, which were located in the resorcin[4]arene cavities, did not show any preference for a specific orientation (Fig. 10). Like in the simulation run in  $\text{CHCl}_3$ , the four THF molecules did not exchange with one of the other molecules nor with THF molecules from the solvent box. Hydrogen bonding of THF molecules with the amide protons was frequently observed both in- and outside the cavity.

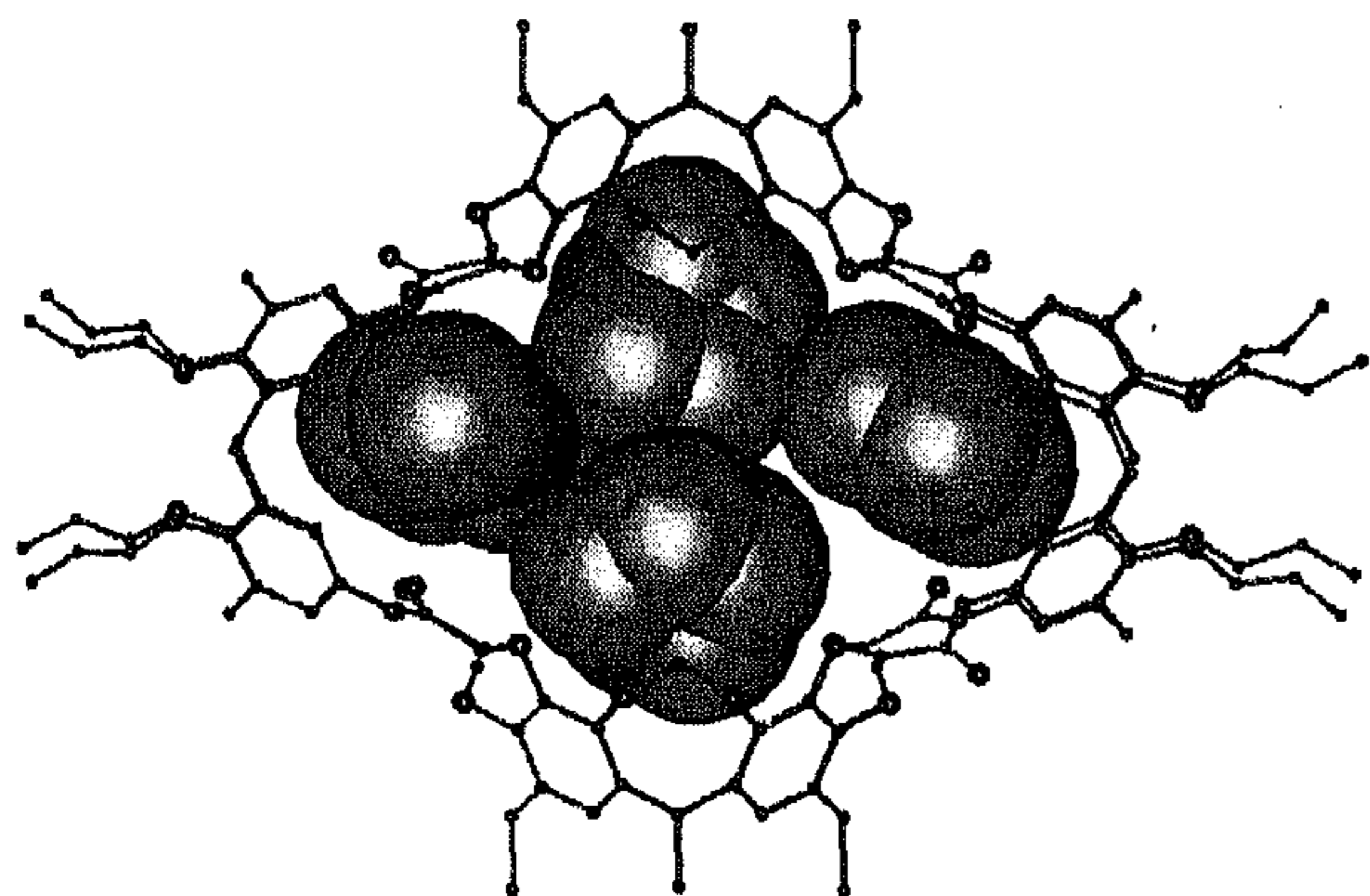


Fig. 10. Time-averaged structure of holand 33 (hydrogens not shown for clarity) and a snapshot of typical THF positions in the MD simulation (orientation as in Fig. 5).

**Analysis of solvent binding:** The nature of the binding of the solvent molecules was investigated by calculating the mean van der Waals and electrostatic interactions between the four bound solvent molecules and holand 33 (Table 3). For both solvents the electrostatic interaction energy is larger in the calix[4]arene cavities than in the resorcin[4]arene cavities. The difference in solvent interaction energy between both types of cavities is for the larger part due to the electrostatic interaction. The long-range electrostatic interaction probably accounts for the much faster and more oriented positioning of the solvent in the calix[4]arene cavities than in the resorcin[4]arene cavities. The van der Waals interaction is about  $-10 \text{ kcal mol}^{-1}$  in all cases, except for THF molecules in the resorcin[4]arene cavities ( $\approx -8 \text{ kcal mol}^{-1}$ ). The four methylene bridges of each resorcin[4]arene residue stick into the cavity, thereby reducing its size (Fig. 11). The THF molecules are larger than the  $\text{CHCl}_3$  molecules, and the fit of THF in the resorcin[4]arene cavity is less optimal. In general the THF molecules have less freedom than the  $\text{CHCl}_3$  molecules; this can be seen in the root mean square deviation from the time-averaged structure: 2.0 and 1.6 Å for  $\text{CHCl}_3$  and THF, respectively. The larger freedom of the  $\text{CHCl}_3$  molecules can also be seen from the standard deviations of the interaction energies in Table 3. Specific orientations of solvent molecules in the cavity of cavitands has been observed experimentally in the X-ray crystal structure of several resorcinol-based cavitands.<sup>[3a]</sup> While a cavitand with four bromo atoms at

Table 3. Mean interaction energies of the four included solvent molecules in holand 33 calculated from the last 100 ps of the MD simulations ( $\text{kcal mol}^{-1}$ ) [a].

Cavity	$\text{CHCl}_3$		THF	
	electrostatic	van der Waals	electrostatic	van der Waals
Calix1	-3.5 (1.7)	-9.9 (1.2)	-4.3 (1.4)	-10.7 (1.0)
Calix2	-3.3 (1.8)	-10.1 (1.2)	-4.8 (1.3)	-10.4 (1.0)
Resorcin1	-0.5 (0.7)	-9.8 (1.4)	-1.8 (1.0)	-8.0 (1.1)
Resorcin2	-0.6 (0.6)	-9.7 (1.4)	-2.0 (1.0)	-8.2 (1.1)
Total	-7.9 (2.9)	-39.5 (2.8)	-12.8 (2.5)	-37.3 (2.3)

[a] Standard deviation in parentheses.

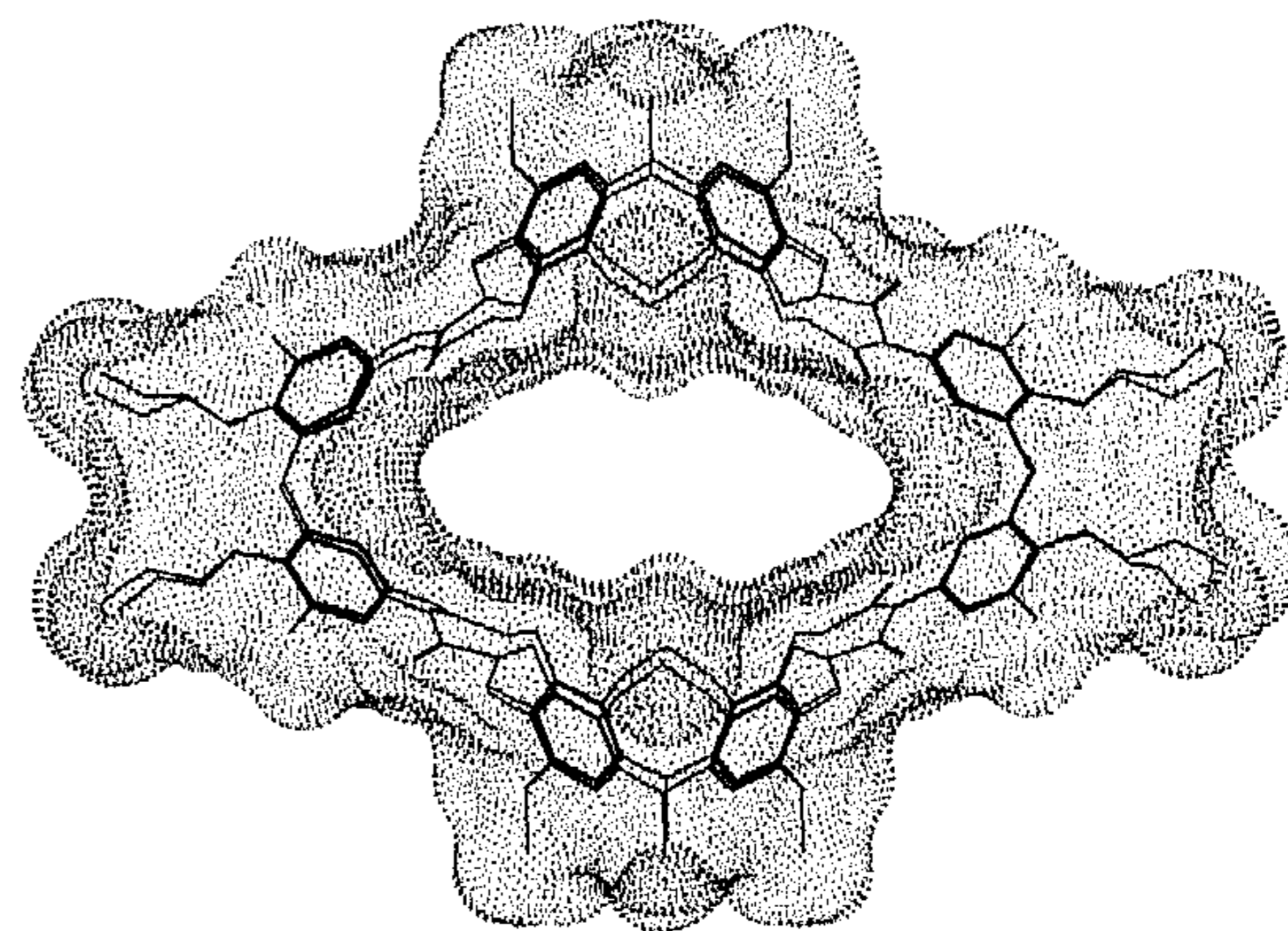


Fig. 11. Time-averaged structure of holand 33 (hydrogens not shown for clarity) from the THF simulation showing the molecular surface (orientation as in Fig. 5).

the upper-rim crystallizes from  $\text{CH}_2\text{Cl}_2$  with one of the chloro atoms of the guest molecule inside the cavity, the cavitand without bromo atoms crystallizes with one of the hydrogens of  $\text{CH}_2\text{Cl}_2$  inside the cavity.

The specific orientation of solvent molecules as observed in the computer simulations is important information for the selection of potential guest molecules. The large favorable interaction energy between holand 33 and solvent molecules ( $-47.4$  and  $-50.1 \text{ kcal mol}^{-1}$  for  $\text{CHCl}_3$  and THF, respectively) can explain why no guests have hitherto been found.<sup>[21]</sup> A Monte Carlo study by Blake and Jorgensen<sup>[26]</sup> revealed that favorable interactions between a molecular tweezer and  $\text{CHCl}_3$  can compete with the binding of a guest. Chapman and Still<sup>[27]</sup> pointed out that the binding of a guest molecule can be greatly enhanced when a solvent is used that is too large to solvate the binding site. Holand 33 has a very large binding site; the binding of solvent is thus enhanced (which competes with binding of a guest). Whitlock and Whitlock<sup>[28]</sup> recently found that the solvent size not only affects the association constant, but also the kinetic stability. This effect may also play a role in 33, because the entrance of the holand cavity is smaller than the cavity itself. A guest that fits perfectly in the holand cavity will experience large steric hindrance when entering (Fig. 11).<sup>[29]</sup> However, binding of a guest molecule in 33 will most likely be entropically favored owing to the release of four solvent molecules from the binding site and to the release of the solvent shell of the guest. The binding energy of a guest molecule may therefore be less than the interaction energy of the four solvent molecules. The solvation of 33 can be diminished by using a solvent that is too large to fit in either calix[4]- and resorcin[4]arene cavities.

## Conclusion

Modeling has revealed that a favorable interaction exists between holand 33 and  $\text{CHCl}_3$  and THF, which can explain the difficulty in finding a guest molecule. The size and rigidity of the holand makes it the organic equivalent of zeolites, molecules with great potential, because the framework can selectively be functionalized.<sup>[32]</sup>

## Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker (250 MHz) or Varian (400 MHz) instruments in  $\text{CDCl}_3$  at room temperature with  $\text{Me}_4\text{Si}$  as internal standard (unless stated otherwise). Fast atom bombardment (FAB) mass spec-



tra were recorded with a Finnigan MAT90 spectrometer using *m*-nitrobenzyl alcohol as a matrix. THF was freshly distilled from Na/benzophenone ketyl, hexane (referring to the petroleum ether fraction with b.p. 60–80 °C), CH<sub>2</sub>Cl<sub>2</sub>, and EtOAc were distilled from K<sub>2</sub>CO<sub>3</sub>. DMF and CH<sub>3</sub>CN were dried over molecular sieves (4 and 3 Å, respectively) for at least 3 days before use. *n*BuLi was used as a commercially available solution in hexane (1.5 M). Other chemicals were of reagent grade and were used without further purification. Flash column chromatography was performed with silica gel 60 (0.040–0.063 mm, 230–400 mesh) or, in case of incomplete separation, with silica gel 60H (0.005–0.040 mm). All reactions were carried out in an argon atmosphere. Dropwise addition over a period of several hours was always carried out with a perfusor. In the standard workup, the (combined) organic layers were washed with H<sub>2</sub>O (3 ×) and brine (1 ×) and dried on Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under reduced pressure. Compounds 1 [2], 2 [2], 5 [33], 7 [34], 8 [4], and 25 [16], were synthesized according to literature procedures.

**5-(2-Chloroacetamido)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (4):** A suspension of mononitro compound 1 (1.0 g, 1.3 mmol), H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O (1.0 mL), and a catalytic amount of Raney Ni in MeOH (50 mL) was refluxed for 2 h. The reaction mixture was filtered over Celite and the solvent was evaporated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and after standard workup the solvent was partially removed until the volume was approximately 10 mL. To this solution were added NEt<sub>3</sub> (0.46 mL, 3.3 mmol) and ClC(O)CH<sub>2</sub>Cl (0.10 mL, 1.2 mmol), and the solution was stirred for 5 min at room temperature (RT). It was then quenched with H<sub>2</sub>O (10 mL). CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was added, and the organic layer was successively washed with 1 N HCl (25 mL), H<sub>2</sub>O (25 mL), and 1 N NaOH (25 mL), and further treated according to standard workup procedures to give pure 4 as an oil in quantitative yield; <sup>1</sup>H NMR: δ = 7.78 (s, 1H; NH), 7.8–7.5 (m, 11H; ArH), 4.50, 3.14 (2d, <sup>2</sup>J(H,H) = 13.4 and 13.6 Hz, 8H; ArCH<sub>2</sub>Ar), 4.2–4.0 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 4.05 (s, 2H; CH<sub>2</sub>Cl), 3.9–3.8 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.7–3.5 (m, 8H; OCH<sub>2</sub>CH<sub>3</sub>), 1.3–1.2 (m, 12H; OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 163.6 (s, C=O), 156.6, 156.3 (s, ArCOR), 153.9 (s, *p*-NHArCOR), 130.7 (s, ArCNH), 128.5–128.1 (d, *m*-ORArCH), 122.4–120.7 (d, *o*-NHArCH + *p*-ORArCH), 42.9 (t, CH<sub>2</sub>Cl), 30.9 (t, ArCH<sub>2</sub>Ar); MS (EI, high resolution): *m/z*: 803.381 [*M*<sup>+</sup>, calcd for C<sub>46</sub>H<sub>58</sub>ClNO<sub>9</sub>, 803.380].

**5,11-Bis(2-chloroacetamido)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (6):** The reaction was carried out according to the procedure described for 4 with 1,2-dinitro 3 (2.17 g of a 2:1 mixture of 3 and 1,3-dinitro 2, 1.67 mmol of 3, 1.03 mmol of 2), H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O (2.2 mL), a catalytic amount of Raney Ni, MeOH (180 mL), NEt<sub>3</sub> (0.96 mL, 6.9 mmol), and ClC(O)CH<sub>2</sub>Cl (0.58 mL, 7.3 mmol) to give 1,2-bis(chloroacetamide) 6 after column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 40:60) in 64% yield. M.p. 74–75 °C; <sup>1</sup>H NMR: δ = 7.91 (s, 2H; NH), 6.79, 6.71 (2d, <sup>4</sup>J(H,H) = 2.4 and 2.5 Hz, 4H; *o*-NHArH), 6.7–6.5 (m, 6H; ArH), 4.48, 3.14 (2d, <sup>2</sup>J(H,H) = 13.5 and 13.6 Hz, 8H; ArCH<sub>2</sub>Ar), 4.08 (s, 4H; CH<sub>2</sub>Cl), 4.2–4.0 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.8 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.53 (q, <sup>3</sup>J(H,H) = 7.0 Hz, 8H; OCH<sub>2</sub>CH<sub>3</sub>), 1.19 (t, <sup>3</sup>J(H,H) = 7.0 Hz, 12H; OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 163.5 (s, C=O), 156.5 (s, ArCOR), 154.0 (s, *p*-NHArCOR), 130.7 (s, ArCNH), 128.4, 128.2 (d, *m*-ORArCH), 122.0–120.5 (d, *o*-NHArCH + *p*-ORArCH), 42.9 (t, CH<sub>2</sub>Cl), 30.9 (t, ArCH<sub>2</sub>Ar); MS (FAB): *m/z* (%): 894 (100) [*M*<sup>+</sup>]; C<sub>48</sub>H<sub>60</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>10</sub>·0.4H<sub>2</sub>O (895.9): calcd C 63.83, H 6.70, N 3.10; found C 63.44, H 6.98, N 2.96; Karl-Fischer titration for 0.4H<sub>2</sub>O: calcd 0.79; found 0.82.

**1,21,23,25-Tetraundecyl-2,20:3,19-dimetheno-1H,21H,23H,25H-bis[1,3]dioxocino-[5,4-*i*:5',4'-*i'*]benzo[1,2-*d*:5,4-*d'*]bis[1,3]benzodioxocin-7,11,15,28-tetrahydroxycavitand (9):** Prior to lithiation, tetrabromide 7 (8.5 g, 5.8 mmol) was dissolved in THF (100 mL), evaporated to dryness, and dried at 80 °C and 5 × 10<sup>-2</sup> Torr for 1 h. The reaction vessel was then brought to atmospheric pressure by flushing it with argon. After repeating this process three times, the dried residue was dissolved in THF (750 mL), cooled to -70 °C, and 1.5 M *n*BuLi (40 mL, 60 mmol) was quickly added. The resulting viscous solution was stirred for 15 min at -70 °C and subsequently quenched with B(OMe)<sub>3</sub> (10 mL, 87 mmol). The solution was warmed to RT and stirred for 1 h. After cooling the reaction mixture again to -70 °C, a 15% solution of H<sub>2</sub>O<sub>2</sub> in 1.5 M NaOH (30 mL, 145 mmol) was added. The mixture was allowed to warm to RT, and stirred overnight. Excess H<sub>2</sub>O<sub>2</sub> was destroyed by adding Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (13.3 g, 70 mmol) to the solution. The THF was removed in vacuo, H<sub>2</sub>O (100 mL) was added, the precipitated solid was filtered off, and washed with H<sub>2</sub>O (3 × 50 mL). After drying the solid at 80 °C and 5 × 10<sup>-2</sup> Torr for 3 h, it was dissolved in THF (100 mL), silica gel (20 g) was added, and the solution was evaporated to dryness. The crude product, absorbed on silica gel, was purified by flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 60:40) to give, in addition to a small amount of triol 11 (7%), tetrahydroxycavitand 9 in 92% yield. M.p. 195–196 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 6.62 (s, 4H; ArH), 5.96 (d, <sup>2</sup>J(H,H) = 6.9 Hz, 4H; outer OCH<sub>2</sub>O), 5.31 (s, 4H; OH), 4.68 (t, <sup>3</sup>J(H,H) = 8.1 Hz, 4H; CHCH<sub>2</sub>), 4.43 (d, <sup>2</sup>J(H,H) = 6.9 Hz, 4H; inner OCH<sub>2</sub>O), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.5–1.2 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.87 (t, <sup>3</sup>J(H,H) = 6.6 Hz, 12H; CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 142.0 (s, ArCOCH<sub>2</sub>O), 140.8 (s, ArCOH), 110.2 (d, ArCH), 99.8 (t, OCH<sub>2</sub>O), 36.8 (d, ArCHRAr); MS (FAB): *m/z* (%): 1217 (100) [*M*<sup>+</sup>]; C<sub>76</sub>H<sub>112</sub>O<sub>12</sub>·2H<sub>2</sub>O (1217.7): calcd C 72.81, H 9.33; found C 73.00, H 9.27; Karl-Fischer for 2H<sub>2</sub>O: calcd 2.87; found 2.81.

Triol 11: M.p. 152–154 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 7.08 (s, 1H; *m*-OCH<sub>2</sub>OArH), 6.63 (s, 3H; *p*-OArH), 6.51 (s, 1H; *o*-OCH<sub>2</sub>OArH), 5.95, 5.85 (2d,

<sup>2</sup>J(H,H) = 6.9 and 7.0 Hz, 4H; outer OCH<sub>2</sub>O), 5.31, 5.30 (2s, 3H; OH), 4.70, 4.68 (2t, <sup>3</sup>J(H,H) = 8.1 Hz, 4H; CHCH<sub>2</sub>), 4.54 (d, <sup>2</sup>J(H,H) = 7.0 Hz, 4H; inner OCH<sub>2</sub>O), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.5–1.2 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.88 (t, <sup>3</sup>J(H,H) = 6.6 Hz, 12H; CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 154.8, 142.1 (s, ArCOCH<sub>2</sub>O), 140.9 (s, ArCOH), 121.1, 116.5 (d, ArCH), 109.8 (d, *p*-OHArCH), 99.9 (t, OCH<sub>2</sub>O), 36.8, 36.6 (d, ArCHRAr); MS (FAB): *m/z* (%): 1201 (100) [*M*<sup>+</sup>]; C<sub>76</sub>H<sub>112</sub>O<sub>11</sub>·0.75H<sub>2</sub>O (1201.7): calcd C 75.11, H 9.41; found C 74.81, H 9.46; Karl-Fischer titration calcd for 0.75H<sub>2</sub>O: 1.11. Found: 1.12.

**1,21,23,25-Tetramethyl-2,20:3,19-dimetheno-1H,21H,23H,25H-bis[1,3]dioxocino-[5,4-*i*:5',4'-*i'*]benzo[1,2-*d*:5,4-*d'*]bis[1,3]benzodioxocin-7,11,15,28-tetrahydroxycavitand (10):** The reaction was carried out as described for tetrahydroxycavitand 9 with tetrabromide 8 (4.88 g, 4.64 mmol), 1.5 M *n*BuLi (30 mL, 46 mmol), B(OMe)<sub>3</sub> (7.8 mL, 69 mmol), 15% H<sub>2</sub>O<sub>2</sub> in 1.5 M NaOH (23 mL, 115 mmol), and Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (10.5 g, 55 mmol) in THF (500 mL). Repeated flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 75:25) yielded 1.5 g of a mixture of triol 12 and tetrol 10 together with 26% of pure tetrol. The triol/tetrol mixture was suspended in acetic anhydride (25 mL), pyridine (1 mL) was added, and the suspension was refluxed for 30 min, during which time a white solid precipitated. The precipitate was filtered off, thoroughly washed with acetic anhydride, and dried at 80 °C under high vacuum. It was dissolved in THF (50 mL), 2 N NaOH (10 mL) was added, and the solution was refluxed for 3 h. After cooling the reaction mixture to RT, dilute HCl was added until pH < 7. Removal of the solvent under vacuum yielded a white precipitate, which was filtered off, washed several times with H<sub>2</sub>O, and dried at 80 °C under high vacuum to give pure tetrahydroxycavitand 10 in a total yield of 46%. M.p. > 300 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 6.75 (s, 4H; ArH), 5.97 (d, <sup>2</sup>J(H,H) = 6.8 Hz, 4H; outer OCH<sub>2</sub>O), 5.38 (s, 4H; OH), 4.92 (q, <sup>3</sup>J(H,H) = 7.4 Hz, 4H; CHCH<sub>2</sub>), 4.44 (d, <sup>2</sup>J(H,H) = 6.8 Hz, 4H; inner OCH<sub>2</sub>O), 1.72 (d, <sup>3</sup>J(H,H) = 7.4 Hz, 12H; CH<sub>3</sub>); <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO): δ = 142.1 (s, ArCOCH<sub>2</sub>O), 141.6 (s, ArCOH), 109.5 (d, ArCH), 99.3 (t, OCH<sub>2</sub>O), 15.7 (q, CH<sub>3</sub>); MS (FAB): *m/z* (%): 657 (100) [*M*<sup>+</sup>]; C<sub>36</sub>H<sub>32</sub>O<sub>12</sub>·0.5H<sub>2</sub>O (656.6): calcd C 64.95, H 5.00; found C 64.56, H 5.26; Karl-Fischer titration for 0.5H<sub>2</sub>O: calcd 1.37; found 1.41.

**General Procedure for the Coupling Reactions between 4–6 and 9 or 10:** To a suspension of 9 or 10, M<sub>2</sub>CO<sub>3</sub> (M = Cs<sup>+</sup> or K<sup>+</sup>), and KI in CH<sub>3</sub>CN, DMF, or DMSO (40–100 mL) at 80–85 °C was added a solution of 4–6 in CH<sub>3</sub>CN, DMF, or DMSO (10–50 mL) over 5–6 h, and the reaction mixture was subsequently stirred for 13–26 h at this temperature ([4–6] in reaction mixture 2.6–4.9 mm). The solvent was removed in vacuo and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The solution was washed with 1 N HCl (25 mL) and subsequently treated according to the standard workup procedure to give products 13, 18, and 19–23 b.

***N*-[25,26,27,28-Tetrakis(2-ethoxyethoxy)pentacyclo[19.3.1.1<sup>3,7</sup>.1<sup>9,13</sup>.1<sup>15,19</sup>]octacosan-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-5-yl]-2-[(11,15,28-trihydroxy-1,21,23,25-tetraundecyl-2,20:3,19-dimetheno-1H,21H,23H,25H-bis[1,3]dioxocino[5,4-*i*:5',4'-*i'*]benzo[1,2-*d*:5,4-*d'*]bis[1,3]benzodioxocin-7-yl)oxyl]-acetamide (13):** The reaction was carried out with 4 (0.10 g, 0.12 mmol), 9 (1.23 g, 1.01 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.19 g, 3.66 mmol), and a catalytic amount of KI in CH<sub>3</sub>CN (40 + 10 mL) to give 13 after flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 50:50) in 61% yield. M.p. 120–121 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 8.81 (s, 1H; NH), 6.9–6.6 (m, 12H; ArH), 6.5–6.3 (m, 3H; ArH), 5.96, 5.76 (2d, <sup>2</sup>J(H,H) = 6.9 and 6.8 Hz, 4H; outer OCH<sub>2</sub>O), 5.37, 5.32 (2s, 3H; OH), 4.8–4.6 (m, 4H; CHCH<sub>2</sub>), 4.6–4.4 [m, 10H; OCH<sub>2</sub>C(O) + ArCH<sub>2</sub>Ar + inner OCH<sub>2</sub>O], 4.2–4.0 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.55, 3.52 (2q, <sup>3</sup>J(H,H) = 7.0 Hz, 8H; OCH<sub>2</sub>CH<sub>3</sub>), 3.16, 3.14 (2d, <sup>2</sup>J(H,H) = 13.6 and 13.5 Hz, 4H; ArCH<sub>2</sub>Ar), 2.3–2.0 (m, 8H; CHCH<sub>2</sub>), 1.5–1.1 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 1.18 (t, <sup>3</sup>J(H,H) = 7.0 Hz, 12H; OCH<sub>2</sub>CH<sub>3</sub>), 0.87 [t, <sup>3</sup>J(H,H) = 6.3 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 167.0 (s, C=O), 156.9, 156.0, 153.0 (s, ArCOEt), 32.0 (t, ArCH<sub>2</sub>Ar); MS (FAB): *m/z* (%): 1986 (100) [*M*<sup>+</sup> + H]; C<sub>122</sub>H<sub>169</sub>NO<sub>21</sub>·1.25H<sub>2</sub>O (1985.6): calcd C 72.96, H 8.61, N 0.70; found C 72.82, H 8.66, N 0.69; Karl-Fischer titration for 1.25H<sub>2</sub>O: calcd 1.12; found 1.12.

**12,22,40,50,82,88,93,99-Octakis(2-ethoxyethoxy)-67,73,74,75-tetraundecyl-14H,20H,26H,42H,48H,54H-4,58-(epoxymethanoxy)-1,69:3,59:61,65-trimethano-11,23:39,51-bis(methano[1,3]benzenomethano)-9,13:15,19:21,25:37,41:43,47:49,53-hexametheno-6H,34H,67H-dibenzo[*d,d'*][1,3]dioxocino[4,5-*f*:8,7-*f'*]bis[1,3,6,30,9,27]benzotetraoxadiazacyclodotriacontine-7,27,35,55(8H,28H,26H,56H)-tetrone (18):** The reaction was carried out with 5 (0.31 g, 0.35 mmol), 9 (0.19 g, 0.16 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.50 g, 1.53 mmol), and a catalytic amount of KI in CH<sub>3</sub>CN (50 + 20 mL) to give 18 after flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 50:50) in 47% yield. M.p. 167–169 °C (EtOH); <sup>1</sup>H NMR: δ = 8.30 (s, 4H; NH), 7.14 (d, <sup>3</sup>J(H,H) = 7.4 Hz, 8H; *m*-OEtArH), 6.92 (t, <sup>3</sup>J(H,H) = 7.4 Hz, 4H; *p*-OEtArH), 6.85 (s, 4H; *p*-OCH<sub>2</sub>OArH), 6.6–6.5 (m, 8H; *o*-NHArH), 5.85, 5.11 (2d, <sup>2</sup>J(H,H) = 7.0 Hz, 4H; outer OCH<sub>2</sub>O), 4.67, 4.65 (2t, <sup>3</sup>J(H,H) = 7.8 Hz, 4H; CHCH<sub>2</sub>), 4.56, 3.21 (2d, <sup>2</sup>J(H,H) = 12.8 Hz, 16H; ArCH<sub>2</sub>Ar), 4.5–4.3 [m, 18H; OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O + OCH<sub>2</sub>CH<sub>2</sub>], 4.16 (d, <sup>2</sup>J(H,H) = 7.0 Hz, 2H; inner OCH<sub>2</sub>O), 4.1–3.9 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.8–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.7–3.5 (m, 16H; OCH<sub>2</sub>CH<sub>3</sub>), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.5–1.1 [m, 96H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub> + OCH<sub>2</sub>CH<sub>3</sub>], 0.88 [t, <sup>3</sup>J(H,H) = 6.5 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 167.0 (s, C=O), 157.0, 152.7 (s, ArCOEt), 31.9 (t, ArCH<sub>2</sub>Ar); MS (FAB): *m/z* (%): 2862 (100) [*M*<sup>+</sup>]; C<sub>172</sub>H<sub>228</sub>N<sub>4</sub>O<sub>32</sub>·4.5H<sub>2</sub>O (2863.6): calcd C

70.15, H 8.11, N 1.90; found C 70.48, H 8.29, N 1.81; Karl-Fischer titration for 4.5 H<sub>2</sub>O: calcd 2.75; found 2.73.

**14,30,62,63-Tetrakis(2-ethoxyethoxy)-41,59-dihydroxy-1,47,49,57-tetraundecyl-16H,22H,28H,34H-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1H,8H,47H,49H-[1,3]benzodioxocino[9',8':4,5][1,3]benzodioxocino[9,10-d][1,3]dioxocino[4,5-I][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10H,36H)-dione (endo 1:1, 19)** was isolated from reactions 1 and 5 (Table 1) after flash column chromatography (SiO<sub>2</sub> 60H, EtOAc/hexane, 40:60–45:55) in 19% and 13% yield, respectively. M.p. 272–273 °C (EtOH); <sup>1</sup>H NMR: δ = 8.96 (s, 2H; NH), 7.33 (d, <sup>4</sup>J(H,H) = 2.4 Hz, 2H; *o*-NHArH), 6.84, 6.56 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 6.7–6.4 (m, 8H; ArH), 5.9–5.7 (m, 4H; outer OCH<sub>2</sub>O), 4.7–4.3 [m, 14H; CHCH<sub>2</sub> + inner OCH<sub>2</sub>O + OCH<sub>2</sub>C(O) + ArCH<sub>2</sub>Ar], 4.21 [d, <sup>2</sup>J(H,H) = 15.7 Hz, 2H; OCH<sub>2</sub>C(O)], 4.1–4.0 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.8–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.48, 3.49 (2q, <sup>3</sup>J(H,H) = 7.0 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.2–3.0 (m, 4H; ArCH<sub>2</sub>Ar), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.4–1.1 [m, 84H; OCH<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.9–0.7 [m, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.3 (s, C=O), 156.1 (s, *p*-HArCOEt), 153.2 (s, *p*-NHArCOEt); MS (FAB): *m/z* (%): 2041 (100) [*M*<sup>+</sup>]; C<sub>124</sub>H<sub>170</sub>N<sub>2</sub>O<sub>22</sub>·1.5 H<sub>2</sub>O (2040.6): calcd C 72.03, H 8.43, N 1.36; found C 71.90, H 8.62, N 1.52; Karl-Fischer titration for 1.5 H<sub>2</sub>O: calcd 1.31; found 1.38.

**exo 1:1 (20)** was isolated from reactions 1 and 5 (Table 1) after flash column chromatography (SiO<sub>2</sub> 60H, EtOAc/hexane, 55:45–60:40) in 32% and 21% yield, respectively. M.p. 144–148 °C (EtOH); <sup>1</sup>H NMR: δ = 8.40 (bs, 2H; NH), 6.96 (bs, 2H; *o*-NHArH), 6.80, 6.54 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 6.7–6.4 (m, 8H; ArH), 5.84, 5.42 (2d, <sup>2</sup>J(H,H) = 6.7 Hz, 4H (3:1); outer OCH<sub>2</sub>O), 5.8 (bs, 2H; OH), 4.64, 4.61 (2t, <sup>3</sup>J(H,H) = 7.5 Hz, 4H; CHCH<sub>2</sub>), 4.6–4.2 [m, 12H; inner OCH<sub>2</sub>O + OCH<sub>2</sub>C(O) + ArCH<sub>2</sub>Ar], 4.1–3.9 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.8–3.6 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.5–3.3 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.2–3.0 (m, 4H; ArCH<sub>2</sub>Ar), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.4–1.0 [m, 84H; OCH<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.81 [t, <sup>3</sup>J(H,H) = 6.0 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; MS (FAB): *m/z* (%): 2041 (100) [*M*<sup>+</sup> + H]; C<sub>124</sub>H<sub>170</sub>N<sub>2</sub>O<sub>22</sub>·0.5 H<sub>2</sub>O (2040.6): calcd C 72.66, H 8.44, N 1.37; found C 72.51, H 8.78, N 1.37; Karl-Fischer titration for 0.5 H<sub>2</sub>O: calcd 0.44; found 0.39.

**12,28,46,62,93,94,98,99-Octakis(2-ethoxyethoxy)-79,85,86,87-tetraundecyl-14H,20H,26H,32H,48H,54H,60H,66H-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-6H,40H,79H-dibenzo[*d,d'*][1,3]dioxocino[4,5-I;8,7-I']bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8H,34H,42H,68H)-tetrone (endo-endo 2:1, 21a)** was isolated from reactions 1–6 (Table 1) after flash column chromatography (SiO<sub>2</sub> 60H, EtOAc/hexane, 35:65–40:60) in yields varying from 8–16%. M.p. 156–159 °C (EtOH); <sup>1</sup>H NMR: δ = 8.98 (s, 4H; NH), 7.37, 6.52 (2d, <sup>4</sup>J(H,H) = 2.4 Hz, 8H; *o*-NHArH), 6.91 (s, 4H; *m*-OCH<sub>2</sub>OArH), 6.69 (d, <sup>3</sup>J(H,H) = 6.9 Hz, 8H; *m*-OEtArH), 6.54 (t, <sup>3</sup>J(H,H) = 7.4 Hz, 4H; *p*-OEtArH), 5.92, 5.86 (2d, <sup>2</sup>J(H,H) = 7.1 and 7.3 Hz, 4H; outer OCH<sub>2</sub>O), 4.77, 4.68 (2t, <sup>3</sup>J(H,H) = 7.8 Hz, 4H; CHCH<sub>2</sub>), 4.66, 4.26 [2d, <sup>2</sup>J(H,H) = 15.7 Hz, 8H; OCH<sub>2</sub>C(O)], 4.6–4.4 (m, 12H; ArCH<sub>2</sub>Ar + inner OCH<sub>2</sub>O), 4.2–4.0 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.55, 3.54 (2q, <sup>3</sup>J(H,H) = 7.0 Hz, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.1 (m, 8H; ArCH<sub>2</sub>Ar), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.5–1.1 [m, 96H; OCH<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.87 [t, <sup>3</sup>J(H,H) = 5.9 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.1 (s, C=O), 156.1 (s, *p*-HArCOEt), 153.2 (s, *p*-NHArCOEt); MS (FAB): *m/z* (%): 2863 (100) [*M*<sup>+</sup> – H]; C<sub>172</sub>H<sub>228</sub>N<sub>4</sub>O<sub>32</sub>·1.25 H<sub>2</sub>O (2863.6): calcd C 71.57, H 8.05, N 1.94; found C 71.81, H 8.13, N 1.86; Karl-Fischer titration for 1.25 H<sub>2</sub>O: calcd 0.78; found 0.77.

**endo-exo 2:1 (22a)** was isolated from reactions 1–6 (Table 1) after flash column chromatography (SiO<sub>2</sub> 60H, EtOAc/hexane, 40–60) in yields varying from 21 to 39%. M.p. 151–155 °C (EtOH); <sup>1</sup>H NMR: δ = 8.90, 8.34 (2s, 4H; NH), 7.36 (d, <sup>4</sup>J(H,H) = 2.0 Hz, 2H; *o*-NHArH), 7.07 (bs, 2H; *o*-NHArH), 6.90, 6.88 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 6.8–6.5 (m, 16H; *o*-NHArH + ArH), 5.9–5.8 (m, 3H; outer OCH<sub>2</sub>O), 5.53 (d, <sup>2</sup>J(H,H) = 6.9 Hz, 1H; outer OCH<sub>2</sub>O), 4.77 (t, <sup>3</sup>J(H,H) = 7.8 Hz, 2H; CHCH<sub>2</sub>), 4.68 [d, <sup>2</sup>J(H,H) = 7.8 Hz, 2H; OCH<sub>2</sub>C(O)], 4.7–4.4 [m, 14H; CHCH<sub>2</sub> + OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar], 4.41 (d, <sup>2</sup>J(H,H) = 7.1 Hz, 2H; inner OCH<sub>2</sub>O), 4.29, 4.26 [2d, <sup>2</sup>J(H,H) = 15.3 and 15.7 Hz, 4H; OCH<sub>2</sub>C(O)], 4.2–4.0 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.6–3.5 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.0 (m, 8H; ArCH<sub>2</sub>Ar), 2.3–2.0 [m, 8H; CHCH<sub>2</sub>], 1.5–1.1 [m, 96H; OCH<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.88 [t, <sup>3</sup>J(H,H) = 6.0 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.4 (s, C=O); MS (FAB): *m/z* (%): 2863 (100) [*M*<sup>+</sup> – H]; C<sub>172</sub>H<sub>228</sub>N<sub>4</sub>O<sub>32</sub>·2.25 H<sub>2</sub>O (2863.6): calcd C 71.13, H 8.07, N 1.93; found C 71.56, H 8.25, N 1.89; Karl-Fischer titration for 2.25 H<sub>2</sub>O: calcd 1.40; found 1.43.

**exo-exo 2:1 (23a)** was isolated in reactions 2–6 (Table 1) after flash column chromatography (SiO<sub>2</sub> 60H, EtOAc/hexane, 50:50–55:45) in yields varying from 16 to 20%. M.p. 135–137 °C (EtOH); <sup>1</sup>H NMR: δ = 8.37 (s, 4H; NH), 7.12, 6.49 (2d, <sup>4</sup>J(H,H) = 2.4 Hz, 8H; *o*-NHArH), 6.87 (s, 4H; *m*-OCH<sub>2</sub>OArH), 6.8–6.7 (m, 4H; *p*-OEtArH), 6.6–6.5 (m, 8H; *m*-OEtArH), 5.90, 5.54 (2d, <sup>2</sup>J(H,H) = 7.0 and 6.6 Hz, 4H; outer OCH<sub>2</sub>O), 4.75, 4.61 (2t, <sup>3</sup>J(H,H) = 8.1 Hz, 4H; CHCH<sub>2</sub>), 4.6–4.4 [m, 16H; ArCH<sub>2</sub>Ar + OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O], 4.28 [d, <sup>2</sup>J(H,H) = 15.3 Hz, 4H; OCH<sub>2</sub>C(O)], 4.2–4.0 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.55, 3.54 (2q, <sup>3</sup>J(H,H) = 7.0 Hz, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.0 (m, 8H; ArCH<sub>2</sub>Ar), 2.3–2.0 (m, 8H; CHCH<sub>2</sub>), 1.5–1.1 [m, 96H; OCH<sub>2</sub>CH<sub>3</sub> +

(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.88 [t, <sup>3</sup>J(H,H) = 7.0 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.6 (s, C=O), 156.3 (s, *p*-HArCOEt), 153.5 (s, *p*-NHArCOEt); MS (FAB): *m/z* (%): 2864 (100) [*M*<sup>+</sup>]; C<sub>172</sub>H<sub>228</sub>N<sub>4</sub>O<sub>32</sub>·H<sub>2</sub>O (2863.6): calcd C 71.68, H 8.05, N 1.94; found C 71.76, H 8.36, N 1.79; Karl-Fischer titration for 1 H<sub>2</sub>O: calcd 0.63; found 0.60.

**12,28,46,62,93,94,98,99-Octakis(2-ethoxyethoxy)-79,85,86,87-tetramethyl-14H,20H,26H,32H,48H,54H,60H,66H-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-6H,40H,79H-dibenzo[*d,d'*][1,3]dioxocino[4,5-I;8,7-I']bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8H,34H,42H,68H)-tetrone (endo-endo 2:1, 21b)** was synthesized with 6 (0.56 g, 0.63 mmol), 10 (0.25 g, 0.31 mmol), K<sub>2</sub>CO<sub>3</sub> (0.56 g, 4.1 mmol), and a catalytic amount of KI in DMF (100 + 50 mL) to give 21b after flash column chromatography (SiO<sub>2</sub>, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 35:65) in 8% yield. M.p. >290 °C (THF/EtOH); <sup>1</sup>H NMR: δ = 9.01 (s, 4H; NH), 7.33 (d, <sup>4</sup>J(H,H) = 1.7 Hz, 4H; *o*-NHArH), 6.99 (s, 4H; *m*-OCH<sub>2</sub>OArH), 6.7–6.6 (m, 8H; *m*-OEtArH), 6.5–6.4 (m, 8H; *o*-NHArH + *p*-OEtArH), 5.87, 5.81 (2d, <sup>2</sup>J(H,H) = 6.3 and 5.5 Hz, 4H; outer OCH<sub>2</sub>O), 4.95, 4.89 (2q, <sup>3</sup>J(H,H) = 7.3 and 7.4 Hz, 4H; CHCH<sub>2</sub>), 4.61, 4.17 [2d, <sup>2</sup>J(H,H) = 15.7 Hz, 8H; OCH<sub>2</sub>C(O)], 4.5–4.3 (m, 12H; ArCH<sub>2</sub>Ar + inner OCH<sub>2</sub>O), 4.1–4.0 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.48 (2q, <sup>3</sup>J(H,H) = 7.0 Hz, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.2–3.0 (m, 8H; ArCH<sub>2</sub>Ar), 1.8–1.6 (m, 12H; CHCH<sub>2</sub>), 1.15, 1.14 (2t, <sup>3</sup>J(H,H) = 7.1 Hz, 24H; OCH<sub>2</sub>CH<sub>3</sub>); MS (FAB): *m/z* (%): 2301 (100) [*M*<sup>+</sup> – H]; C<sub>132</sub>H<sub>148</sub>N<sub>4</sub>O<sub>32</sub>·3.5 H<sub>2</sub>O (2302.5): calcd C 67.01, H 6.60, N 2.37; found C 66.73, H 6.64, N 2.68; Karl-Fischer titration for 3.5 H<sub>2</sub>O: calcd 2.67; found 2.60.

**endo-exo 2:1 (22b)** was isolated in the reaction described for 21b after flash column chromatography (SiO<sub>2</sub>, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 40:60) in 11% yield. M.p. >290 °C (THF/EtOH); <sup>1</sup>H NMR: δ = 9.02, 8.37 (2s, 4H; NH), 7.38, 7.12, 6.48 (3d, <sup>4</sup>J(H,H) = 2.4 Hz, 6H; *o*-NHArH), 7.05, 7.02 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 6.8–6.7 (m, 6H; *o*-NHArH + *p*-OEtArH), 6.6–6.5 (m, 8H; *m*-OEtArH), 5.93, 5.89, 5.57 (3d, <sup>2</sup>J(H,H) = 7.1 and 6.8 Hz, 4H; outer OCH<sub>2</sub>O), 5.01, 4.85, 4.96 (3q, <sup>3</sup>J(H,H) = 7.4 Hz, 4H; CHCH<sub>2</sub>), 4.68 [d, <sup>2</sup>J(H,H) = 15.7 Hz, 2H; OCH<sub>2</sub>C(O)], 4.7–4.4 [m, 14H; OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar], 4.26, 4.23 [2d, <sup>2</sup>J(H,H) = 15.3 and 15.7 Hz, 4H; OCH<sub>2</sub>C(O)], 4.2–4.0 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.9–3.8 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.6–3.5 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.0 (m, 8H; ArCH<sub>2</sub>Ar), 1.77, 1.74, 1.68 (3d, <sup>3</sup>J(H,H) = 7.3 and 7.4 Hz, 12H; CHCH<sub>2</sub>), 1.3–1.1 (m, 12H; OCH<sub>2</sub>CH<sub>3</sub>); MS (FAB): *m/z* (%): 2302 (100) [*M*<sup>+</sup> – H]; C<sub>132</sub>H<sub>148</sub>N<sub>4</sub>O<sub>32</sub>·3.25 H<sub>2</sub>O (2302.5): calcd C 67.14, H 6.60, N 2.37; found C 66.85, H 6.82, N 2.81; Karl-Fischer titration for 3.25 H<sub>2</sub>O: calcd 2.48; found 2.49.

**exo-exo 2:1 (23b)** was isolated in the reaction described for 21b after flash column chromatography (SiO<sub>2</sub>, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 50:50) in 10% yield. M.p. >290 °C (CHCl<sub>3</sub>/EtOH); <sup>1</sup>H NMR: δ = 8.37 (s, 4H; NH), 7.07, 6.48 (2d, <sup>4</sup>J(H,H) = 2.3 Hz, 8H; *o*-NHArH), 6.94 (s, 4H; *m*-OCH<sub>2</sub>OArH), 6.7–6.6 (m, 4H; *p*-OEtArH), 6.5–6.4 (m, 8H; *m*-OEtArH), 5.83, 5.50 (2d, <sup>2</sup>J(H,H) = 7.1 and 6.9 Hz, 4H; outer OCH<sub>2</sub>O), 4.91, 4.78 (2q, <sup>3</sup>J(H,H) = 7.4 Hz, 4H; CHCH<sub>2</sub>), 4.5–4.3 [m, 16H; OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar], 4.17 [d, <sup>2</sup>J(H,H) = 15.2 Hz, 4H; OCH<sub>2</sub>C(O)], 4.1–3.9 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.8–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.6–3.4 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.2–2.9 (m, 8H; ArCH<sub>2</sub>Ar), 1.67, 1.61 (2d, <sup>3</sup>J(H,H) = 7.3 Hz, 12H; CHCH<sub>2</sub>), 1.2–1.1 (m, 12H; OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 166.1 (s, C=O), 156.3 (s, *p*-HArCOEt), 153.5 (s, *p*-NHArCOEt); MS (FAB): *m/z* (%): 2302 (100) [*M*<sup>+</sup>]; C<sub>132</sub>H<sub>148</sub>N<sub>4</sub>O<sub>32</sub>·3.5 H<sub>2</sub>O (2302.5): calcd C 67.01, H 6.60, N 2.37; found C 66.70, H 6.33, N 2.34; Karl-Fischer titration for 3.5 H<sub>2</sub>O: calcd 2.67; found 2.73.

**5,11-Bis(2-chloroacetamido)-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (26)**: To a solution of 1,2-diamine 25 (0.50 g, 0.70 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added successively NEt<sub>3</sub> (0.25 mL, 1.75 mmol) and ClC(O)CH<sub>2</sub>Cl (0.17 mL, 2.1 mmol). After stirring the reaction mixture for 5 min, it was quenched with H<sub>2</sub>O (10 mL) and subsequently washed with 1 N HCl (10 mL), H<sub>2</sub>O (10 mL), and 1 N NaOH (10 mL), followed by standard workup to give pure 26 in quantitative yield. M.p. 159–161 °C; <sup>1</sup>H NMR: δ = 7.84 (s, 2H; NH), 7.54, 7.50 (2d, <sup>4</sup>J(H,H) = 2.6 Hz, 4H; *o*-NO<sub>2</sub>ArH), 6.9–6.8 (m, 4H; *o*-NHArH), 4.52, 3.34 (2d, <sup>2</sup>J(H,H) = 14.2 Hz, 2H; ArCH<sub>2</sub>Ar), 4.46, 3.26 (2d, <sup>2</sup>J(H,H) = 14.0 Hz, 4H; ArCH<sub>2</sub>Ar), 4.39, 3.16 (2d, <sup>2</sup>J(H,H) = 13.7 Hz, 2H; ArCH<sub>2</sub>Ar), 4.17 (s, 4H; CH<sub>2</sub>Cl), 4.1–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.87 (septet, <sup>3</sup>J(H,H) = 7.5 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.00, 0.97 (2t, <sup>3</sup>J(H,H) = 7.0 Hz, 12H; CH<sub>3</sub>); <sup>13</sup>C NMR: δ = 164.4 (s, C=O), 162.3 (s, *p*-NO<sub>2</sub>ArCOR), 153.7 (s, *p*-NHArCOR), 142.3 (s, ArCNO<sub>2</sub>), 131.5 (s, ArCNH), 124.3, 123.5 (d, *o*-NO<sub>2</sub>ArCH), 120.7, 120.0 (d, *o*-NHArCH), 77.4 [t, CH<sub>2</sub>C(O)], 31.1 (t, ArCH<sub>2</sub>Ar); MS (FAB): *m/z* (%): 866 (100) [*M*<sup>+</sup>]; C<sub>44</sub>H<sub>50</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>10</sub> (865.8): calcd C 61.04, H 5.82, N 6.47; found C 61.23, H 5.91, N 6.22.

**General Procedure for the Reactions between Bis(chloroacetamide) 26 and Tetrahydroxycavitand 9**: To a suspension of tetrahydroxycavitand 9, M<sub>2</sub>CO<sub>3</sub> (M = Cs<sup>+</sup> or K<sup>+</sup>, 10 equiv), and a catalytic amount of KI in CH<sub>3</sub>CN, DMF, or DMSO (50–100 mL) at 70–85 °C was added a solution of bis(chloroacetamide) 26 in CH<sub>3</sub>CN, DMF, or DMSO (25–50 mL, [26] in reaction mixture 2.0–7.7 mM) over 8 h, and the reaction mixture was subsequently stirred for an additional 9.5–21 h (Table 2) at this temperature. The solvent was removed in vacuo and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), washed with 1 N HCl (25 mL), and further treated according to standard workup. The crude product (from reactions 1–5) was dissolved in

CH<sub>2</sub>Cl<sub>2</sub> (50 mL); *tert*-butyldimethylsilyl chloride (20 equiv), NEt<sub>3</sub> (20 equiv), and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added, and the resulting solution was stirred at RT for 24 h. The reaction mixture was washed with 1 N HCl (25 mL) followed by standard workup to give products **27**, **30**, and **32** after column chromatography.

**41,59-Bis((1,1-dimethylethyl)dimethylsilyloxy)-19,25-dinitro-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16H,22H,28H,34H-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1H,8H,47H,49H-[1,3]benzodioxocino[9',8':4,5][1,3]benzodioxocino[9,10-d][1,3]dioxocino[4,5-l][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10H,36H)-dione (endo 1:1, 27)** was isolated in reactions 1–5 (Table 2) after flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10:90) in yields varying from 16–42%. M.p. 220–222 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 9.01 (s, 2H; NH), 7.57, 7.49 (2d, <sup>4</sup>J(H,H) = 2.7 Hz, 4H; *o*-NO<sub>2</sub>ArH), 7.36, 6.52 (2d, <sup>4</sup>J(H,H) = 2.4 Hz, 4H; *o*-NHArH), 6.87, 6.67 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 5.84, 5.68 (2d, <sup>2</sup>J(H,H) = 7.2 and 7.1 Hz, 4H; outer OCH<sub>2</sub>O), 4.8–4.2 [m, 16H; CHCH<sub>2</sub> + ArCH<sub>2</sub>Ar + OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O], 4.1–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.4–3.2 (m, 4H; ArCH<sub>2</sub>Ar), 2.3–2.1 [m, 8H; CHCH<sub>2</sub>], 1.88 (q, <sup>3</sup>J(H,H) = 7.2 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.5–1.2 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 1.01, 0.99 [2t, <sup>3</sup>J(H,H) = 7.4 Hz, 12H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 0.94 [s, 18H; Si(CH<sub>3</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 0.9–0.8 [m, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>], 0.15, 0.14 [2s, 12H; Si(CH<sub>3</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR: δ = 167.0 (s, C=O), 161.9 (s, *p*-NO<sub>2</sub>ArCOR), 153.2 (s, *p*-NHArCOR), 115.3 (d, *p*-OCH<sub>2</sub>ArCH), 111.5 (d, *p*-OSiR<sub>3</sub>ArCH); MS (FAB): *m/z* (%): 2240 (100) [*M*<sup>+</sup> + H]; C<sub>132</sub>H<sub>188</sub>N<sub>4</sub>Si<sub>2</sub>O<sub>22</sub> (2239.0); calcd C 70.81, H 8.46, N 2.50; found C 70.87, H 8.80, N 2.43.

**41,59-Dihydroxy-19,25-dinitro-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16H,22H,28H,34H-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1H,8H,47H,49H-[1,3]benzodioxocino[9',8':4,5][1,3]benzodioxocino[9,10-d][1,3]dioxocino[4,5-l][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10H,36H)-dione (endo 1:1, 28)**: To a solution of **27** (42 mg, 18 μmol) in a 1:1 mixture of MeOH/THF (20 mL) was added CsF (55 mg, 0.36 mmol), and the mixture was refluxed for 5 h. After evaporation of the solvent the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 1 N HCl (10 mL) followed by standard workup to give pure **28** as a sticky solid in quantitative yield; <sup>1</sup>H NMR: δ = 8.85 (s, 2H; NH), 7.51, 7.44 (2d, <sup>4</sup>J(H,H) = 2.4 Hz, 4H; *o*-NO<sub>2</sub>ArH), 7.31, 6.42 (2bs, 4H; *o*-NHArH), 6.81 (s, 2H; *p*-OCH<sub>2</sub>ArH), 6.53 (s, 2H; *p*-OHArH), 5.95 (bs, 2H; OH), 5.88, 5.79, 5.76 (3d, <sup>2</sup>J(H,H) = 7.0, 6.0, and 6.5 Hz, 4H; outer OCH<sub>2</sub>O), 4.7–4.2 [m, 16H; CHCH<sub>2</sub> + ArCH<sub>2</sub>Ar + OCH<sub>2</sub>C(O) + inner OCH<sub>2</sub>O], 4.0–3.6 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.1 (m, 4H; ArCH<sub>2</sub>Ar), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.9–1.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.4–1.1 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.95, 0.93 [2t, <sup>3</sup>J(H,H) = 7.3 and 7.4 Hz, 12H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 0.9–0.7 [m, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.8 (s, C=O), 162.0 (s, *p*-NO<sub>2</sub>ArCOR), 153.3 (s, *p*-NHArCOR), 115.2 (d, *p*-OCH<sub>2</sub>ArCH), 109.7 (d, *p*-OHArCH); MS (FAB): *m/z* (%): 2011 (100) [*M*<sup>+</sup> + H].

**17,23,51,57-Tetranitro-12,28,46,62,93,94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14H,20H,26H,32H,48H,54H,60H,66H-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-6H,40H,79H-dibenzo[*d,d'*][1,3]dioxocino[4,5-*l*:8,7-*l'*][bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8H,34H,42H,68H)-tetrone (endo-endo 2:1, 30)** was isolated in reactions 1–7 (see Table 2) after flash column chromatography (SiO<sub>2</sub> 60 H, EtOAc/hexane, 22.5:77.5) in yields varying from 9–20%. M.p. 248–252 °C (EtOAc/hexane); <sup>1</sup>H NMR: δ = 8.86 (s, 4H; NH), 7.56, 7.48 (2d, <sup>4</sup>J(H,H) = 2.5 Hz, 8H; *o*-NO<sub>2</sub>ArH), 7.29, 6.52 (2d, <sup>4</sup>J(H,H) = 2.2 Hz, 8H; *o*-NHArH), 6.90 (s, 4H; *p*-OCH<sub>2</sub>ArH), 5.99, 5.82 (2d, <sup>2</sup>J(H,H) = 7.2 and 7.4 Hz, 4H; outer OCH<sub>2</sub>O), 4.8–4.6 (m, 4H; CHCH<sub>2</sub>), 4.71, 4.26 [2d, <sup>2</sup>J(H,H) = 15.6 Hz, 8H; OCH<sub>2</sub>C(O)], 4.58 (d, <sup>2</sup>J(H,H) = 7.2 Hz, 2H; inner OCH<sub>2</sub>O), 4.6–4.4 (m, 10H; inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar), 4.1–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.4–3.1 (m, 8H; ArCH<sub>2</sub>Ar), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.87 (sextet, <sup>3</sup>J(H,H) = 7.3 Hz, 16H; OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.5–1.1 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 1.01, 0.98 [2t, <sup>3</sup>J(H,H) = 7.3 Hz, 24H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 0.9–0.8 [m, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.8 (s, C=O), 161.9 (s, *p*-NO<sub>2</sub>ArCOR), 153.3 (s, *p*-NHArCOR); MS (FAB): *m/z* (%): 2804 (100) [*M*<sup>+</sup> + H]; C<sub>164</sub>H<sub>208</sub>N<sub>8</sub>O<sub>32</sub>·0.67 EtOAc·2H<sub>2</sub>O (2803.4); calcd C 69.05, H 7.58, N 3.87; found C 68.63, H 7.45, N 3.82; Karl-Fischer titration for 2H<sub>2</sub>O: calcd 1.27; found 1.29.

**endo-exo 2:1 (32)** was isolated in reactions 1–7 (Table 2) after flash column chromatography (SiO<sub>2</sub> 60 H, EtOAc/hexane, 25:75) in yields varying from 8–21%. M.p. 245–250 °C (THF/MeOH); <sup>1</sup>H NMR: δ = 8.76, 7.76 (2s, 4H; NH), 7.49, 7.44, 7.34 (3d, <sup>4</sup>J(H,H) = 2.7 Hz, 8H; *o*-NO<sub>2</sub>ArH), 7.30, 7.25 (2d, <sup>4</sup>J(H,H) = 2.4 Hz, 4H; *o*-NHArH), 6.75 (s, 4H; *p*-OCH<sub>2</sub>ArH), 6.33, 5.97 (2d, <sup>4</sup>J(H,H) = 2.5 Hz, 4H; *o*-NHArH), 5.75, 5.71 (2d, <sup>2</sup>J(H,H) = 7.2 and 6.5 Hz, 4H; outer OCH<sub>2</sub>O), 4.7–4.6 (m, 4H; CHCH<sub>2</sub>), 4.6–4.1 [m, 20H; inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar + OCH<sub>2</sub>C(O)], 3.9–3.5 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.0 (m, 7H; ArCH<sub>2</sub>Ar), 2.8 (d, <sup>2</sup>J(H,H) = 13.2 Hz, 1H; ArCH<sub>2</sub>Ar), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.9–1.6 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 1.4–1.0 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.9–0.7 [m, 36H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.8, 166.0 (s, C=O), 162.0, 161.8 (s, *p*-NO<sub>2</sub>ArCOR), 153.3, 153.1 (s, *p*-NHArCOR); MS (FAB): *m/z* (%): 2803 (100) [*M*<sup>+</sup>]; C<sub>164</sub>H<sub>208</sub>N<sub>8</sub>O<sub>32</sub>·2H<sub>2</sub>O (2803.4); calcd C 69.37, H 7.53, N 3.95; found C 69.34, H 7.65, N 3.74; Karl-Fischer titration for 2H<sub>2</sub>O: calcd 1.27; found 1.23.

**General Procedure for the Preparation of 29 and 31**: A solution of **28** or **30** (250 mg), hydrazine monohydrate (0.25 mL), and a catalytic amount of Raney Ni in a 1:1 mixture of MeOH/THF (20 mL) was refluxed for 2 h. After cooling the reaction mixture to RT, the Raney Ni was filtered off over Hyflo, and the resulting solution was evaporated to dryness. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and after standard workup (no removal of the solvent) NEt<sub>3</sub> and ClC(O)CH<sub>2</sub>Cl (2.5 equiv of each per amino group) were successively added. After stirring the reaction mixture for 5 min it was washed with 1 N HCl (10 mL) and further treatment according to standard workup gave pure **29** or **31**.

**19,25-Bis(2-chloroacetamido)-41,59-bis((1,1-dimethylethyl)dimethylsilyloxy)-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16H,22H,28H,34H-13,31:51,55-dimethano-46:3,45:11,15:17,21:23,27:29,33-hexametheno-1H,8H,47H,49H-[1,3]benzodioxocino[9',8':4,5][1,3]benzodioxocino[9,10-d][1,3]dioxocino[4,5-l][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10H,36H)-dione (endo 1:1, 29)**: yield quantitative. M.p. 173–176 °C; <sup>1</sup>H NMR: δ = 9.27 [s, 2H; NHC(O)CH<sub>2</sub>O], 7.85 [s, 2H; NHC(O)CH<sub>2</sub>Cl], 7.37, 6.46 [2d, <sup>4</sup>J(H,H) = 2.5 Hz, 4H; *o*-OCH<sub>2</sub>C(O)-NHArH], 6.97, 6.57 [2d, <sup>4</sup>J(H,H) = 2.5 Hz, 4H; *o*-ClCH<sub>2</sub>C(O)NHArH], 6.82, 6.62 (2s, 4H; *m*-OCH<sub>2</sub>OArH), 5.98, 5.73, 5.65 [3d, <sup>2</sup>J(H,H) = 7.1, 7.1, and 7.3 Hz, 4H; outer OCH<sub>2</sub>O], 4.7–4.1 [m, 16H; CHCH<sub>2</sub> + ArCH<sub>2</sub>Ar + OCH<sub>2</sub>C(O)NH + inner OCH<sub>2</sub>O], 4.0, 3.9 [2d, <sup>2</sup>J(H,H) = 15.1 and 15.0 Hz, 4H; ClCH<sub>2</sub>C(O)NH], 3.8–3.7 (m, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 3.2–3.0 (m, 4H; ArCH<sub>2</sub>Ar), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.8 (q, <sup>3</sup>J(H,H) = 7.4 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.4–1.1 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.93, 0.91 (2t, <sup>3</sup>J(H,H) = 7.3 and 7.2 Hz, 12H; OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.88 [s, 18H; Si(CH<sub>3</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 0.9–0.8 [m, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>], 0.09, 0.07 [2s, 12H; Si(CH<sub>3</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.8, 163.2 (s, C=O), 153.7 (s, *p*-NHArCOR); MS (FAB): *m/z* (%): 2332 (100) [*M*<sup>+</sup>]; C<sub>136</sub>H<sub>194</sub>Cl<sub>2</sub>N<sub>4</sub>Si<sub>2</sub>O<sub>20</sub>·0.75H<sub>2</sub>O (2333.1); calcd C 69.63, H 8.40, N 2.39; found C 69.80, H 8.65, N 2.26; Karl-Fischer titration for 0.75H<sub>2</sub>O: calcd 0.58; found 0.60.

**17,23,51,57-Tetrakis(2-chloroacetamido)-12,28,46,62,93,94,98,99-octapropoxy-79,85,86,87-tetraundecyl-14H,20H,26H,32H,48H,54H,60H,66H-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-6H,40H,79H-dibenzo[*d,d'*][1,3]dioxocino[4,5-*l*:8,7-*l'*][bis[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-7,33,41,67(8H,34H,42H,68H)-tetrone (endo-endo 2:1, 31)**: yield 88%. M.p. > 290 °C; <sup>1</sup>H NMR: δ = 9.32 [s, 4H; OCH<sub>2</sub>C(O)NH], 7.83 [s, 4H; ClCH<sub>2</sub>C(O)NH], 7.35 (s, 4H; *o*-NHArH), 6.99 (d, <sup>4</sup>J(H,H) = 2.4 Hz, 4H; *o*-NHArH), 6.91 (s, 4H; *m*-OCH<sub>2</sub>OArH), 6.60, 6.56 (2s, 8H; *o*-NHArH), 6.16, 5.92 (2d, <sup>2</sup>J(H,H) = 7.9 and 6.8 Hz, 4H; outer OCH<sub>2</sub>O), 4.9–4.7 (m, 4H; CHCH<sub>2</sub>), 4.77, 4.20 [2d, <sup>2</sup>J(H,H) = 15.7 Hz, 8H; OCH<sub>2</sub>C(O)], 4.6–4.4 (m, 12H; inner OCH<sub>2</sub>O + ArCH<sub>2</sub>Ar), 4.1–4.0 [m, 8H; ClCH<sub>2</sub>C(O)], 3.9–3.7 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 3.3–3.1 (m, 8H; ArCH<sub>2</sub>Ar), 2.3–2.1 (m, 8H; CHCH<sub>2</sub>), 1.90 (sextet, <sup>3</sup>J(H,H) = 7.2 Hz, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 1.5–1.2 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 1.1–0.8 [m, 36H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub> + (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.6, 163.2 (s, C=O), 153.8 (s, *p*-NHArC), 69.1, 63.4 [t, CH<sub>2</sub>C(O)]; MS (FAB): *m/z* (%): 2989 (100) [*M*<sup>+</sup>]; a satisfactory elemental analysis could not be obtained.

**19,23,57,61,87,91,109,113-Octapropoxy-40,130,131,132,143,144,145,148-octaundecyl-21H,27H,59H,65H,89H,95H,111H,117H-1,79:11,69:31,49-tris(epoxymethanoxy)-2,78:4,8:10,70:18,62:24,56:32,48:34,38:42,46:72,76:86,114:92,108-undecamethano-16,20:22,26:54,58:60,64:84,88:90,94:106,110:112,116-octametheno-13H,40H,51H,81H,103H-hexabenzo[*d,d'*,*y,y'*,*d*<sub>1</sub>,*d'*<sub>1</sub>][1,3]dioxocino[4,5-*z*:8,7-*z'*][bis[1,3,6,24,27,29,32,50,9,21,35,47]benzoctaaxatetraazacyclodopentacontine-14,28,52,66,82,96,104,118(15H,29H,53H,67H,83H,97H,105H,119H)-octone (33)**: **Method A**: A solution of **29** (58 mg, 25 μmol) and CsF (75 mg, 0.5 mmol) in freshly distilled DMF (5 mL) was stirred for 2 h at 80 °C. Cs<sub>2</sub>CO<sub>3</sub> (150 mg, 0.5 mmol) and KI (5 mg, 33 μmol) were then added, and the resulting solution was stirred for another 48 h at this temperature. After removal of the solvent, the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 1 N HCl (10 mL) followed by standard workup to give **33** (26%) and **34** (27%) after flash column chromatography (SiO<sub>2</sub>, THF/CH<sub>2</sub>Cl<sub>2</sub>, 5:95).

**Method B**: To a solution of Cs<sub>2</sub>CO<sub>3</sub> (0.22 g, 0.66 mmol) and a catalytic amount of KI (5 mg, 33 μmol) in freshly distilled DMF (25 mL) at 70 °C was added a solution of **9** (46 mg, 33 μmol) and **31** (100 mg, 33 μmol) in DMF (25 mL) over 8 h. The resulting solution was stirred for an additional 24 h at this temperature. The solvent was removed in vacuo and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 1 N HCl (10 mL) and further treated according to standard workup to give pure **32** in 30% yield after preparative TLC (SiO<sub>2</sub>, EtOAc/hexane, 50:50) and subsequent trituration with MeOH. M.p. > 300 °C (CH<sub>2</sub>Cl<sub>2</sub>/MeOH); <sup>1</sup>H NMR: δ = 9.32 (s, 8H; NH), 7.64, 6.65 (2d, <sup>4</sup>J(H,H) = 2.1 Hz, 16H; *o*-NHArH), 6.83 (s, 8H; *m*-OCH<sub>2</sub>OArH), 6.04, 5.73 (2d, <sup>2</sup>J(H,H) = 7.3 and 7.1 Hz, 8H; outer OCH<sub>2</sub>O), 4.87, 4.04 [2d, <sup>2</sup>J(H,H) = 15.7 Hz, 16H; OCH<sub>2</sub>C(O)], 4.71 (t, <sup>3</sup>J(H,H) = 7.9 Hz, 8H; CHCH<sub>2</sub>), 4.52, 4.45, 3.37, 3.20 (4d, <sup>2</sup>J(H,H) = 12.0 Hz, 16H; ArCH<sub>2</sub>Ar), 4.35, 4.21 (2d, <sup>2</sup>J(H,H) = 7.3 and 7.1 Hz, 8H; inner OCH<sub>2</sub>O), 4.4–4.2 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 2.3–2.1 (m, 16H; CHCH<sub>2</sub>), 2.0–1.8 (m, 16H; OCH<sub>2</sub>CH<sub>2</sub>), 1.5–1.1 [m, 144H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.94 [t, <sup>3</sup>J(H,H) = 7.5 Hz, 24H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 0.81 [t, <sup>3</sup>J(H,H) = 6.2 Hz, 24H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]; <sup>13</sup>C NMR: δ = 166.3 (s, C=O), 153.0 (s, *p*-NHArC), 147.7, 146.6, 144.7 (s, ArCOCH<sub>2</sub>), 132.1 (s, ArCNH), 120.8, 118.6 (d, *o*-NHArCH), 115.2 (d, *m*-OCH<sub>2</sub>OArCH); MS (FAB): *m/z* (%): 4084 (100) [*M*<sup>+</sup> + Na]; C<sub>248</sub>H<sub>328</sub>N<sub>8</sub>O<sub>40</sub>·7.5H<sub>2</sub>O (4061.2); calcd C 70.98, H 8.24, N 2.67; found C 70.57, H 8.01, N 2.70; Karl-Fischer titration for 7.5H<sub>2</sub>O: calcd 3.22; found 2.69.

**15,31,66,67-Tetrapropoxy-46,54,55,56-tetraundecyl-17H,23H,29H,35H-4,20:42,26-bis(epoxyethanimino)-3,43-(epoxymethoxy)-2,44:14,32:48,52-trimethano-12,16:18,22:24,28:30,34-tetrametheno-9H,46H,54H-bisbenzo[4,5][1,3]benzodioxocino[9,10-d:10',9'-l][1,3,6,36,9,13]tetraoxadiazacyclooctatriacotene-10,36,62,69-(11H,37H)-tetrone + DMF (34):** yield 27%. M.p. > 300 °C (CH<sub>2</sub>Cl<sub>2</sub>/MeOH); <sup>1</sup>H NMR: δ = 7.67 (s, 4H; NH), 6.96 (s, 8H; *o*-NHArH), 6.75 (s, 4H; *m*-OCH<sub>2</sub>OArH), 5.75 (d, <sup>2</sup>J(H,H) = 7.0 Hz, 4H; outer OCH<sub>2</sub>O), 4.84 [s, 1H; (CH<sub>3</sub>)<sub>2</sub>NC(O)H], 4.81 [s, 8H; OCH<sub>2</sub>C(O)], 4.63 (t, <sup>3</sup>J(H,H) = 8.0 Hz, 4H; CHCH<sub>2</sub>), 4.43, 3.18 (2d, <sup>2</sup>J(H,H) = 12.0 Hz, 8H; ArCH<sub>2</sub>Ar), 3.99 (d, <sup>2</sup>J(H,H) = 7.0 Hz, 4H; inner OCH<sub>2</sub>O), 3.74 (t, <sup>3</sup>J(H,H) = 7.5 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 2.2–2.0 (m, 8H; CHCH<sub>2</sub>), 1.88 (sextet, <sup>3</sup>J(H,H) = 7.6 Hz, 8H; OCH<sub>2</sub>CH<sub>2</sub>), 1.4–1.1 [m, 72H; (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>], 0.98 [t, <sup>3</sup>J(H,H) = 7.5 Hz, 12H; O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 0.82 [t, <sup>3</sup>J(H,H) = 6.5 Hz, 12H; (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>], 0.66 (s, 3H; CH<sub>3</sub> *trans* to carbonyl), –0.86 (s, 3H; CH<sub>3</sub> *cis* to carbonyl); <sup>13</sup>C NMR: δ = 166.7 (s, C=O), 152.9 (s, *p*-NHArCOR), 145.4 (s, ArCOCH<sub>2</sub>O), 141.4 [s, ArCOCH<sub>2</sub>C(O)], 130.7 (s, ArCNH), 121.4 (d, *o*-NHArCH), 113.5 (d, *p*-CH<sub>2</sub>OArCH), 99.4 (t, OCH<sub>2</sub>O), 70.5 [t, OCH<sub>2</sub>C(O)]; MS (FAB): *m/z* (%): 2126 (100) [*M*<sup>+</sup> + DMF + Na]; C<sub>127</sub>H<sub>171</sub>N<sub>5</sub>O<sub>21</sub> · 1.5H<sub>2</sub>O (2103.7); calcd C 71.58, H 8.23, N 3.29; found C 71.38, H 8.16, N 3.25; Karl-Fischer titration for 1.5H<sub>2</sub>O: calcd 1.27; found 1.20.

**Molecular Mechanics of 21a and 23b:** All simulations were performed with CHARMM22 [35] as implemented in Quanta 3.3 [36]. The all-atom Quanta 3.3 parameter set was used with charges assigned by the Quanta charge-templates method. Residual charge was smoothed on carbon and nonpolar hydrogen atoms. A distance-dependent dielectric constant was applied with ε = 1. No cut-offs on the nonbonded interactions were used. Energy minimizations were performed with the Steepest Descent and Adopted Basis Newton Raphson methods until the root mean square of the energy gradient was < 0.001 kcal mol<sup>-1</sup> Å<sup>-1</sup>.

**Molecular Dynamics of Holand 33:** A model for 33 was used with C<sub>2</sub>H<sub>5</sub> moieties attached to the resorcin[4]arene residues instead of C<sub>11</sub>H<sub>23</sub>. The solvent models of Jorgensen were used for THF [37] and CHCl<sub>3</sub> [38]. The all-atom Quanta 3.3 parameter set was used for 33 with charges assigned by the Quanta charge-templates method. Residual charge was smoothed on carbon and nonpolar hydrogen atoms. The nonbonded interactions were calculated with a list-based cut-off of 8 Å. The electrostatic interaction was smoothed using the shift function, the van der Waals interaction with a switch function between 6 and 8 Å. The nonbonded list was updated every 20 energy evaluations with a nonbonded list cut-off of 9 Å. A dielectric constant ε = 1 was used. Periodic boundary conditions were used for simulating a continuous solution. SHAKE [39] constraints were applied on all bonds with hydrogen atoms, allowing a time integration step of 1 fs.

The starting structures for the molecular dynamics runs were created by centering 33 in a 46 Å cubic box of solvent molecules. Overlapping solvent molecules were removed (i.e., any solvent molecule containing a heavy atom within 2.1 Å of any heavy atom of the holand was removed). The solvated holand was then energy-minimized. In both simulations, one solvent molecule was present in the starting structure. The Molecular Dynamics started with a 5 ps heating phase in which the system was heated to 300 K, followed by 10 ps equilibration during which velocity scaling was applied if the temperature was outside the 300 ± 10 K window. Finally, a 200 ps production run was carried out without velocity scaling. The temperature did not systematically deviate from 300 K. Coordinates were saved every 200 time steps. Averages were calculated on the last 100 ps of the production run.

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