Synthesis and Structural Properties of 5,17-Bis(*N*-methyl-*N*-arylaminocarbonyl)calix[4]arenes. Directing the Substituents toward the Cavity by Use of the Cis-Generating Property of the *N*-Methylaminocarbonyl Linker

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A series of cone 5,17-bis(*N*-arylaminocarbonyl)calix[4]arenes were synthesized and N-methylated using an easy and high-yielding methylation procedure. The structures of the cone 5,17-bis(*N*-methyl-*N*-arylaminocarbonyl)calix[4]arenes were studied in solution by NMR spectroscopy and in the solid state by X-ray structural resolution. The use of the *N*-methylaminocarbonyl linker between the calix[4]arene and the aromatic substituent was found to have a dominant influence on the molecular structure, forcing the substituent toward the cavity of the calix[4]arene regardless of the size of the substituent. The linker may be a very useful structure generator when considering the design of molecular receptors.

Introduction

The calixarene system has been the subject of numerous studies of widely different natures.[1,2] Apart from the very appealing molecular structure of this macrocyclic system, it has found great use in supramolecular chemistry because of the ease of preparation.[3] Furthermore, if properly designed, the calixarene system can be used as the fundamental building block in molecular receptors using the simple concept of *host* and *guest*.[4] In this way, receptors for anions,[5−8] cations,[9−11] and neutral molecules[12−14] have been prepared. Common to all these host/guest systems is that the size of the guest is relatively small. This problem can be solved by attaching substituents to the calixarene system so as to increase the apparent size of the cavity in the host molecule, thus making room for a larger guest molecule. A myriad of reports on how to substitute the calixarene moiety with various aromatic systems is found in the literature.[15−22] Earlier studies[23] on 5,17-disubstituted calix[4]arenes have shown that the substituent is generally pointing away from the cavity or when the conformation is dependent upon the solvent conditions the substituents associate, in both cases making interaction with a guest molecule difficult.

While N−H amides are found almost exclusively in the trans conformation in solution and in the solid state, the N−Me amides are found almost exclusively in the cis conformation. N-Methylation of an N−H amide can thus be used to seriously alter the conformation and thereby in many instances the function of the system in concern.[24−37]

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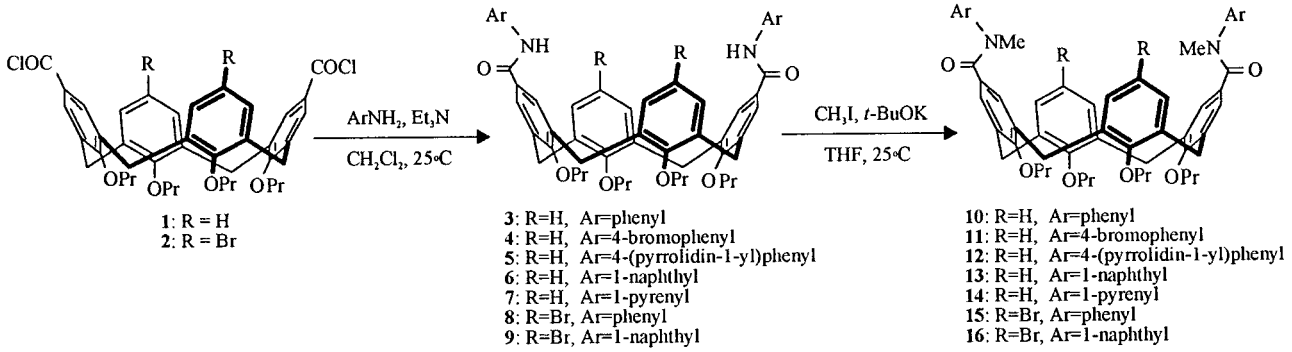
Scheme 1



1: R = H
2: R = Br

3: R=H, Ar=phenyl
4: R=H, Ar=4-bromophenyl
5: R=H, Ar=4-(pyrrolidin-1-yl)phenyl
6: R=H, Ar=1-naphthyl
7: R=H, Ar=1-pyrenyl
8: R=Br, Ar=phenyl
9: R=Br, Ar=1-naphthyl

10: R=H, Ar=phenyl
11: R=H, Ar=4-bromophenyl
12: R=H, Ar=4-(pyrrolidin-1-yl)phenyl
13: R=H, Ar=1-naphthyl
14: R=H, Ar=1-pyrenyl
15: R=Br, Ar=phenyl
16: R=Br, Ar=1-naphthyl

In this paper we present the synthesis of various 5,-17-disubstituted calix[4]arenes and 5,17-disubstituted 11,23-dibromocalix[4]arenes, where phenyl, naphthyl, and pyrenyl substituents have been linked to the calixarene unit via the *N*-methylaminocarbonyl linker. The crystal structures were solved for both the H−amide structures and the N−Me structures, which all conformed with the above conformational rule. The conformational rule was further substantiated by searching the Cambridge Crystallographic Data Centre database (CCDC) for aryl-N−H amides and aryl-N−Me amides followed by statistical analysis.

Studies in solution, using NMR spectroscopy, showed two different isomers of equal amounts (for compounds **13**−**16**), both cis with respect to the amide linker but with one isomer having a conformation similar to that observed in the crystal structure (anti) and the other isomer having both aryl substituents pointing in the same direction (syn). At elevated temperatures, however, dynamic isomerization effects were observed. The energy barrier for rotation around the bond linking the aryl substituent to the N−Me group was thus determined. The result of this study is that the *N*-methylaminocarbonyl linker is a very rigid structure generator that in this case has been used to direct a substituent group toward the cavity of the calix[4]arene unit, which may be a very desirable property when considering the design of molecular receptors based on calix[4]arenes.

Results and Discussion

The synthesis of compounds **3**−**9** was accomplished by reaction of the acid chloride, **1** or **2**, with the appropriate amine. Yields were generally high. Subsequent reaction with *t*-BuOK in dry THF followed by addition of methyliodide to yield **10**−**16** was found to be an efficient, very fast, and clean way of achieving the conversion from the N−H amide to the *N*-methylamide (Scheme 1).

It is a generally known property of calixarenes that they often find difficulty in growing crystals, and when they do, the crystals are often of a poor quality because of solvent molecules and their flexible nature. *R*-values in excess of 0.10 and certainly above 0.05 are thus not uncommon in the realm of calixarene crystallography.[38−45] It was found that of the compounds **3**−**9**, only **8** formed crystals. These, however, were not of perfect quality. Conventional sources of X-ray radiation proved insufficient to obtain data for which the structure could be solved. It was found necessary to use synchrotron radiation in order to obtain a crystal structure of the N−H amide **8** (Table 1). This was achieved, and it clearly shows that the N−H amide is in the trans conformation with a molecular structure that resembles the solution structure as shown by NMR in this paper and as shown earlier[23] (Figure 1). The methylated amides, however,

Table 1. Crystallographic Data for 11,23-Dibromo-5,17-bis(*N*-phenylaminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (Compound 8)

formula	$C_{54}H_{56}O_6Br_2N_2 \cdot 0.5H_2O$
formula wt	997.63
crystal system	monoclinic
space group	$P2_1/n$
Z	8
a, Å	16.0246(7)
b, Å	29.1394(6)
c, Å	20.8201(18)
α, deg	90
β, deg	90.916(6)
γ, deg	90
V, Å^3	9720.6(10)
ρ, g cm^3	1.360
crystal dimensions, mm	0.41 × 0.13 × 0.10
type of radiation	SR,[a] λ = 0.710 00 Å
μ, mm^{-1}	1.72
T, K	100(2)
number of reflections	20 322
unique reflections (with $I > 2\sigma$)	2574
R_{int}	0.2468
$R(F)$, $R_w(F^2)$ all data	0.1246, 0.3810

[a] SR = synchrotron radiation.

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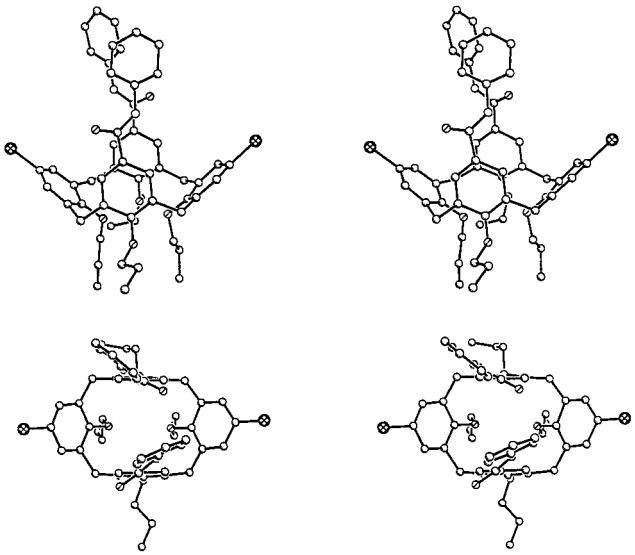

Figure 1. Stereoviews of compound **8**. One of the two molecules in the asymmetric unit is shown from the side (top) and from above (bottom). Hydrogen atoms have been omitted for clarity. The aryl groups linked by the amide linkages are clearly trans with respect to each other.

show a much greater propensity toward forming crystals of sufficient quality to allow for structural resolution using conventional methods.

Crystallographic data for compounds **13**−**16** are shown in Table 2. The data obtained, however, were not of high quality. In some of the cases this was due to disorder. In other cases, solvent molecules in the crystal were lost not only when the crystals were exposed to the atmosphere during the mounting of crystals on the diffractometer but also when crystallinity was poor. All four compounds show similar structural features. The *N*-methylation clearly causes the aromatic substituents to point toward each other. The angles between the planes defined by the phenyl ring on the calix[4]arene bearing the *N*-methylamide linker and the aromatic substituent attached to the *N*-methylamide linker were found to be in the range 61.6−72.2°. The angles defining the pinched cone (the angle between the planes defined by the unsubstituted phenyl rings of the calix[4]arene) were found to be in the range −9.7 to −13.8°. For compound **13**, the 1-naphthyl substituents are pointing inward over the cavity (Figure 2). When the larger 1-pyrenyl substituents are present, as in compound **14**, they point outward away from the cavity. This is ascribed to steric reasons as it would be impossible to place the large substituents inward. Substitution of the 11,23 positions with bromine has some bearing on the molecular structure where the steric effect of the moderately sized bromine atoms is observed. The substituents are further away from each other as seen in compound **15** (Figure 3). The effect is more drastic for compound **16** where the 1-naphthyl substituents are forced away from the cavity of the calixarene with the H2−H3 end of the naphthyl group pointing inward as opposed to the conformation observed for the similar compound **13** (Figure 4) where the H2−H3 end of the naphthyl group is pointing outward.

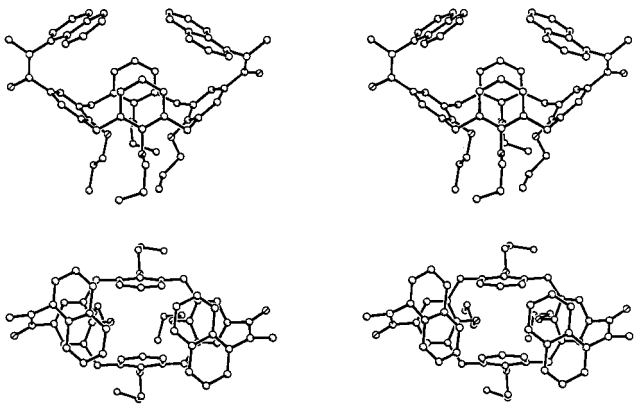

Figure 2. Stereoviews of compound **13** from the side (top) and from above (bottom). The DMSO solvent molecule and the hydrogen atoms have been omitted for clarity. The carbonyl oxygen and the *N*-methyl group of the amide linkages are cis with respect to each other. Furthermore, the naphthalene groups are in an anti conformation but close to the cavity.

Crystal structures 151 aryl-H-amide and 32 aryl-N-Me (Figure 5) are currently found in the CCDC database. These were analyzed using the program VISTA, with respect to the cis/trans conformation around the amide bond and nearly all were found to conform to the above principles. Exceptions to the above observations are

Table 2. Crystallographic Data for the 5,17-Bis(*N*-methyl-*N*-arylaminocarbonyl)Calix[4]arenes (Compounds 13−16)

	13	**14**	**15**	**16**
formula	$C_{64}H_{66}O_6N_2$·DMSO	$C_{76}H_{70}O_6N_4$·2MeCN	$C_{56}H_{60}O_6Br_2N_2$·MeCN	$C_{64}H_{64}O_6Br_2N_2$
formula wt	1037.32	1189.45	1057.93	1116.99
crystal system	triclinic	monoclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P2_1/n$	$P2/n$	$P\bar{1}$
Z	2	4	4	2
a, Å	13.316(3)	15.562(3)	14.162(3)	13.1255(6)
b, Å	13.814(3)	17.247(3)	24.243(5)	14.7386(7)
c, Å	17.661(4)	24.489(5)	16.253(3)	16.8425(8)
α, deg	78.57(3)	90.00	90	103.7090(10)
β, deg	78.51(3)	98.85(3)	110.67(3)	93.1480(10)
γ, deg	61.54(3)	90.00	90	114.1740(10)
V, Å^3	2778.7(10)	6495(2)	5220.9(18)	2845.0(2)
ρ, g cm^3	1.240	1.216	1.346	1.304
crystal dimensions, mm	0.47 × 0.25 × 0.05	0.32 × 0.27 × 0.10	0.39 × 0.18 × 0.13	0.27 × 0.15 × 0.05
type of radiation	MoKα	MoKα	MoKα	MoKα
μ, mm^{-1}	0.115	0.076	1.606	1.477
T, K	120(2)	120(2)	120(2)	120(2)
number of reflections	29 594	67 395	55 536	30 306
unique reflections (with $I > 2\sigma$)	4468	5505	7957	4127
R_{int}	0.1373	0.1649	0.0595	0.2316
$R(F)$, $R_w(F^2)$ all data	0.1267, 0.4132	0.1166, 0.3920	0.0391, 0.0940	0.1134, 0.3466

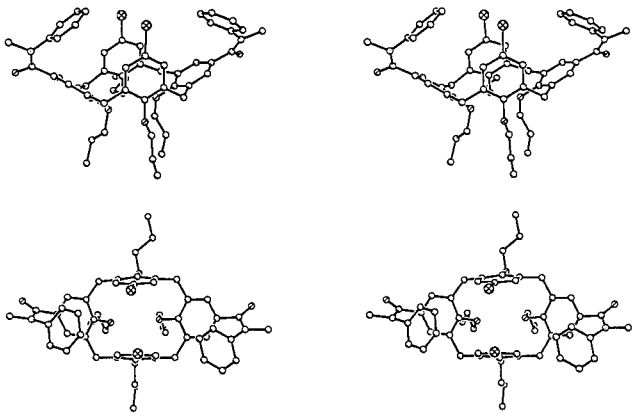

Figure 3. Stereoviews of compound **15** from the side (top) and from above (bottom). The acetonitrile solvent molecule and the hydrogen atoms have been omitted for clarity. The carbonyl oxygen and the *N*-methyl group of the amide linkages are cis with respect to each other.

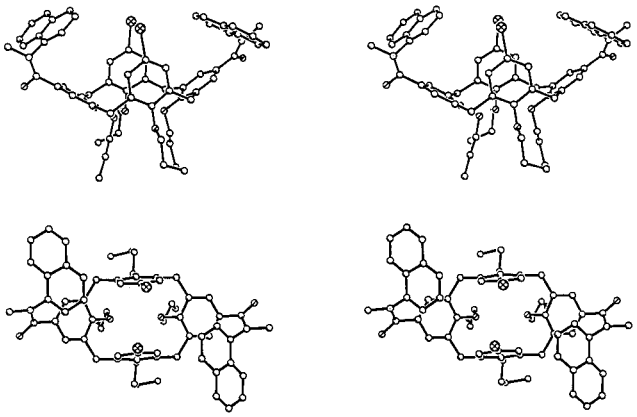

Figure 4. Stereoviews of compound **16** from the side (top) and from above (bottom). The hydrogen atoms have been omitted for clarity. The carbonyl oxygen and the *N*-methyl group of the amide linkages are cis with respect to each other. Furthermore, the naphthalene groups are in an anti conformation.

found when the molecule is constrained for steric reasons or in cases where the molecular structure implies a conformation opposite to the generally observed conformation.

Proton NMR analysis of calix[4]arenes is essential as a tool for deducing the conformational details of these compounds in solution. Calix[4]arenes, which have been fixed in the cone conformation by suitable etherification at the lower rim, exist in two rapidly interchanging pinched cone conformations.[46] In a previous study, it was shown that in one example of a 5,17-bis-*N*-phenylcarboxamide the equilibrium can be influenced by the choice of solvent.[23] In nonpolar $CDCl_3$, the *N*-phenylcarboxamide substituents prefer a coplanar arrangement with substantial $\pi-\pi$ overlap which is also found in the crystal structure of compound **8**. In the polar solvent DMSO-d_6, the calixarene−biscarboxamide instead adopts the other pinched cone conformation with the amide groups pointing away from each other. This was deduced from NOE effects between the H_{eq}/H_a and H_{eq}/H_d protons. The

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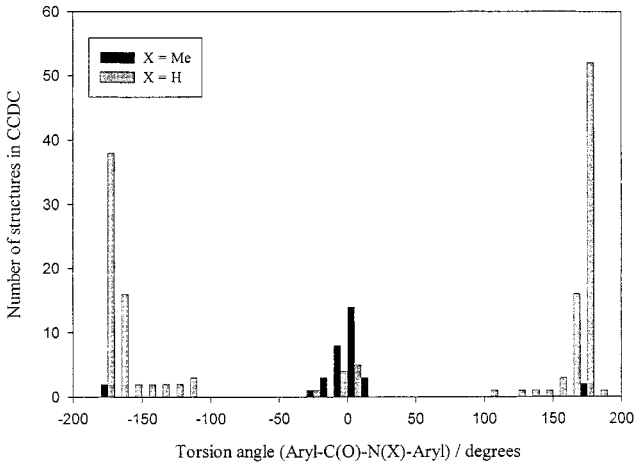


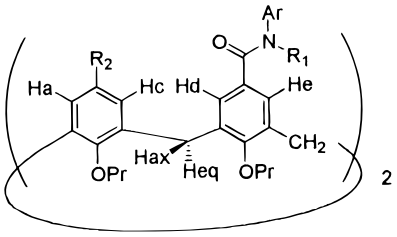
Figure 5. VISTA plot of the torsion angle for all of the aryl-C(O)-N(H)-aryl and aryl-C(O)-N(CH_3)-aryl found in the Cambridge Crystallographic Data Centre database. Nearly all of the N−H amides are in the trans conformation (±170−180°) except for a few cases where the stereochemistry does not permit the N−H amides to adopt the trans conformation. Nearly all of the N−Me amides are in the cis conformation (±0−5°) except for a few cases where the stereochemistry does not permit the N−Me amides to adopt the cis conformation.

protons on the rings that are parallel are magnetically shielded by the opposite ring, leading to an upfield shift of about 0.5−1 ppm. Similar behavior is observed for the 5,17-bis-*N*-arylcarboxamides **3**−**9**, which are all secondary amides. (See Table 3.)

Methylation of the amides changes the ^1H NMR dramatically. The ^1H NMR spectra of the tertiary bisamides **10**−**16** are rather insensitive to the solvent polarity, indicating that only one type of pinched cone is preferred in these compounds. The most remarkable feature is the high degree of shielding observed for the protons on the calixarene aryl groups not bearing the amide substituents. The fact that all of the protons ortho to the carboxamide group on the calixarene skeleton appear not to be shielded together with a smaller NOE effect of these protons on the H_{eq} protons compared to the effect from the H_a protons indicates that the conformation in solution is the pinched cone with the amide groups pointing outward and the other two aryl rings parallel. This assignment is in agreement with the solid-state structure determined for compounds **13**−**16**. The seemingly trivial substitution of a hydrogen atom for a methyl group has thus frozen out one pinched cone conformer.

The most interesting feature shown by the X-ray crystallographic work is the conformation around the amide bonds, the methyl group and the oxygen atom being cis to each other and out of plane with the aryl groups. The *N*-aryl substituents form lids over the calixarene cavity, and this explains the unusual high degree of shielding observed for some of the protons as mentioned earlier. This can be exemplified by compound **10** where the A_2B system (H_a, H_b, H_c) has moved to 6.03 and 5.50 ppm. In the N−H amide compound **3** (in DMSO-d_6) where the same type of pinched cone is preferred, these protons occur at 6.37 ppm. The extra shielding from the phenyl groups of the lids thus amounts to 0.3−0.9 ppm. This is in accordance with upfield shifts caused by ring current effects and is estimated numerically by using distances and angles obtained from the

Table 3. Selected ^{1}H NMR Data for the NH Amides (3−9) and the N−CH$_3$ Amides (10−16)[a]



R_1 = H or CH_3; R_2 = Hb or Br

	H_a/H_c	H_b	H_d/H_e	N−H	N−CH_3	H_{ax}	H_{eq}	Ar
3	6.83	6.73	7.02	7.65		4.49	3.23	Ph
3 (DMSO-d_6)	6.37		7.87	10.17		4.52	3.41	Ph
4	7.00	6.86	6.80	7.47		4.48	3.21	4-Br−Ph
6	6.80−6.72		7.25	7.93		4.54	3.29	1-naphthyl
8	7.13		6.91	7.63		4.45	3.20	Ph
9	7.30		6.93	8.00		4.49	3.25	1-naphthyl
10	5.50	6.03	7.05		3.51	4.26	2.92	Ph
11	5.54	6.27	7.02		3.49	4.29	2.95	4-Br-Ph
13	5.70/5.58/5.46	4.82/4.56	7.04/6.98		3.64	4.10/4.05	2.74/2.68	1-naphthyl
14	4.2−4.7	4.51/4.32/4.15	7.03/6.93		3.71	3.30/3.28	2.54	1-pyrenyl
	4.58/4.44					3.25/3.23		
15	7.06		5.84		3.51	4.23	2.90	Ph
16	5.05/5.08		6.59/6.67/7.31/7.56		3.57	3.91−3.99	2.30−2.36	1-naphthyl
	5.85/5.89					4.12−4.20	2.92	

[a] Values are in ppm relative to TMS and recorded in $CDCl_3$ unless otherwise stated.

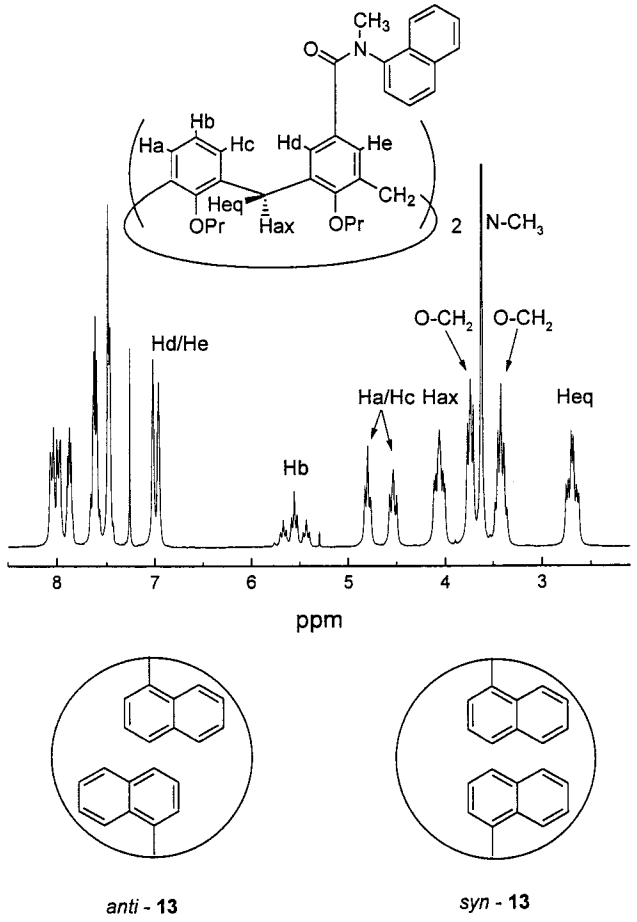
Table 4. Selected Distances Computed from NOE Diff and X-ray Data

	$r(H_{eq}-H_a/H_c)$ (Å)		$r(H_{eq}-H_d/H_e)$ (Å)	
compound	NOE diff	X-ray	NOE diff	X-ray
10	3.0	2.9	2.6	2.4
13	2.7	2.8	2.5	2.4

X-ray structure.[47] Assuming isotropic tumbling and comparable relaxation rates for the protons, NOE diff experiments can be used to calculate approximate distances in the molecules. Selected values are given in Table 4 and are in accordance with the solid-state structures.

All N-methylated amides, **10**−**16**, showed only one *N*-methyl signal, even on cooling to 223 K, corresponding to the presence of only one conformer which was previously shown to be the cis amide. This is consistent with the cis conformation being much more stable than the trans conformation observed for N−H amides, also shown previously by Azumaya et al.[48] in simpler systems. Disregarding the first part of the FIDs, thus revealing the slowly relaxing methyl protons that could be hidden under other signals, gave only one methyl signal as well.

The ^{1}H NMR spectra of the naphthyl *N*-methylamides **13** and **16** and the pyrenyl *N*-methylamide **14** show additional features that elucidate further structural details. The low-field region of the ^{1}H NMR spectrum of **13** is shown in Figure 6. Although the spectrum is rather complicated, the signals are well separated and could be assigned using COSY spectra. The H_b protons give rise to three triplets centered at 5.58 ppm with the ratio 1:2:1, while the H_a/H_c pair is seen in $CDCl_3$ as two triplets at 4.56 and 4.82 ppm. These signals are separated better in DMSO-d_6 as two sets of two doublets (4.20, 4.28, 4.54, and 4.58 ppm). Selective decoupling experiments revealed that the single H_b center triplet with intensity 2 is coupled to the doublets at 4.28 and 4.54 ppm, whereas the two remaining H_b signals, each of intensity 1, are coupled to the doublets at 4.20 and 4.58 ppm. The splitting of these signals can be explained if compound



anti - **13** *syn* - **13**

Figure 6. Low-field portion of the ^{1}H NMR spectrum of compound **13** in $CDCl_3$ (250 MHz).

(47) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.
(48) Azumaya, I.; et al. *Tetrahedron* **1995**, *51*, 5277.

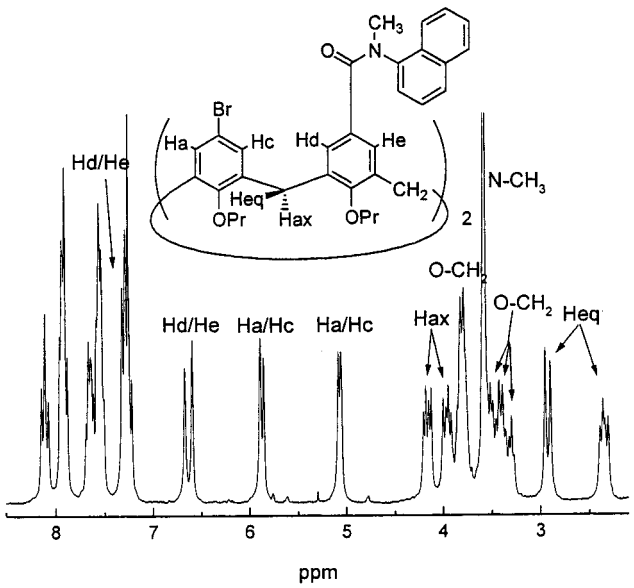


Figure 7. Low-field portion of the ^{1}H NMR spectrum of compound **16** in $CDCl_3$ (250 MHz).

13 exists as an equal mixture of the two conformers shown in Figure 6. The conformers differ in the orientation of the naphthalene substituents that are either syn or anti with respect to each other. The syn conformer has a mirror plane bisecting the calixarene through the H_b protons. This makes the two H_b protons chemically different and gives rise to the two triplets with intensity 1. The anti conformer has a C_2 axis through the center of the calixarene making the two H_b protons equivalent, which therefore gives rise to only one triplet with intensity 2. The H_a and H_c protons on the same ring become equivalent in the syn conformer but differ from the opposite ring that gives rise to the two doublets at 4.20 and 4.58 ppm, each with intensity 2, the upfield signal being assigned to the H_a/H_c pair closest to the naphthyl substituents. In the anti conformer, the H_a and H_c protons are nonequivalent but are related by symmetry to the protons on the opposite ring that gives rise to the two doublets at 4.28 and 4.54 ppm. The syn and anti forms also cause the H_{ax} and H_{eq} signals to split into a set of four doublets each and the H_d/H_e pair to split into two pairs of singlets that are almost similar in chemical shift.

The coalescence temperature of the Ha/Hc signals was found to be 399 K in DMSO-d_6, corresponding to an energy barrier of $\Delta G^{\ddagger} = 18.9$ kcal/mol for the conversion between the syn and anti forms.[49]

The ^{1}H NMR spectrum of **16** (Figure 7) though rather different can also be explained by an equal mixture of syn and anti conformers. Both the H_a/H_c and H_d/H_e signals split up into two sets of singlets each (see Table 3). The magnetic shielding of one set of H_d/H_e protons is much larger in this case than that in **13** as is also the case for the H_{ax} and H_{eq} protons and for one set of $O-CH_2$. In the solid-state structure of **16**, the naphthyl groups are twisted away from the center of the calixarene in an anti conformation. This explains the observed shielding effects since the naphthalene rings will be much closer to one set of protons and bend downward, thus shielding two sets of H_{ax}/H_{eq} more. In this case, a coalescence temperature of 374 K was measured, and the energy barrier was calculated to be $\Delta G^{\ddagger} = 17.7$ kcal/mol. As no difference in the syn/anti ratio is observed in the spectra recorded immediately after mixing, the energy barrier must have been exceeded during synthesis when an equal amount of the two conformers was formed. When converting between the two conformers, the naphthyl substituents have to rotate around the *N*-aryl bond and are likely to enter the cavity in the process. The steric hindrance imposed on the system in this process could be the reason for the relatively high energy barrier observed for these compounds. Further, it assumes absolute rigidity of the *N*-methylaminocarbonyl linker. In compound **14**, the pyrene substituents are so large that they are twisted out over the rim of the cavity. The ^{1}H NMR spectrum shows the same features as those of the naphthalene-substituted compound **13** but with an even higher degree of shielding; i.e., the A_2B system of the calixarene has moved upfield to around 4.5 ppm. The H_{eq} protons of the methylene bridge are also shielded substantially as one would expect from the structure.

Conclusion

The structure-generating properties of the *N*-methylaminocarbonyl linker were investigated in the context of calixarene macrocycles. The linker was found to have a dominant influence on the resulting molecular structure, forcing aryl substituents of varying size toward the cavity of the calixarene. In all the cases studied here, the *N*-methylaminocarbonyl group was found in the cis conformation as established earlier. This observation was further substantiated by a statistical survey of the conformations for N−H and N−Me amides found in the CCDC database, and currently all observations are found to conform to the conformational rule associated with N−H and N−Me amides.

Experimental Section

Synthetic Methods and Materials. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 250 MHz instrument and a 400 MHz instrument with TMS as internal reference at 300 K. All of the NMR spectra were recorded in $CDCl_3$ unless otherwise stated. All the reagents used were reagent grade and were used without further purification, except THF which was freshly distilled from sodium/benzophenone ketyl. Compound **1** was prepared by a method described previously.[23] Compound **2** was prepared from the corresponding acid[50] by complete analogy. The temperatures given are internal temperatures. Chromatographic separations were performed on silica gel 60 (SiO_2, 0.040−0.063 mm, 230−240 mesh). TLC was carried out on SiO_2 with *n*-hexane/EtOAc (2:1, v/v) as eluent. The crystals used for X-ray crystallography were obtained from HPLC-grade solvents. Elemental analyses (C, H, N) were performed at DB Lab, Odense M, Denmark. The samples were dried in a vacuum oven at 80 °C for 24 h prior the analysis. It is a well-known fact that calixarenes often give rise to poor elemental analyses[51,52] because of solvent that is lost from the crystals. Further X-ray structural resolution, where appropriate, and mass spectral analyses were used to establish the identity of the compounds. FAB mass spectra were recorded on a Kratos MS50 RF instrument with 3-nitrobenzoyl alcohol

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(50) Larsen, M.; Jørgensen, M. *J. Org. Chem.* **1996**, *61*, 6651−6655.
(51) Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790.
(52) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527.

as a matrix and 9 keV Xe atoms. Significant protonated molecular ions $(M + H)^+$ as well as peaks corresponding to sodiated molecular ions $(M + Na)^+$ were present in all of the spectra because of trace amounts of sodium salts in the samples. In addition, molecular ions (M^+) were present with varying intensities for the different compounds. The elemental compositions were thus confirmed by the correct isotopic patterns, in particular for the bromine-containing compounds.

General Procedure for Synthesis of Compounds 3−9. To a solution of the acid chloride (**1** or **2**) (2.0 mmol) in CH_2Cl_2 (30 mL) and Et_3N (3 mL) was added a solution of the aromatic amine (5.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 25 °C for 1 h. The mixture was then poured onto ice-cold 2 M hydrochloric acid (100 mL). The organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo, yielding the crude amide.

5,17-Bis(*N*-phenylaminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (3). Recrystallization from MeCN gave **3** as colorless flakes in 71% yield: mp 255−257 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.17 (s, 2H), 7.95−7.80 (m, 8H), 7.46 (t, 4H, J = 7.7 Hz), 7.19 (t, 2H, J = 7.3 Hz), 6.37 (s, broad, 6H), 4.52 (d, 4H, J = 13.0 Hz), 4.19 (t, 4H, J = 7.8 Hz), 3.77 (t, 4H, J = 6.4 Hz), 3.41 (d, 4H, J = 13.0 Hz), 2.15−1.85 (m, 8H), 1.20 (t, 6H, J = 7.3 Hz), 1.02 (t, 6H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.3, 161.1, 155.7, 140.3, 137.0, 133.3, 129.4, 129.3, 128.5, 124.3, 122.8, 121.3, 77.7, 77.0, 31.1, 23.9, 23.6, 11.5, 10.7; MS (FAB+) 830 *m*/*z*. Anal. Calcd for $C_{54}H_{58}N_2O_6$: C, 78.04; H, 7.03; N, 3.37. Found: C, 76.85; H, 7.05; N, 3.41.

5,17-Bis(*N*-(4-bromophenyl)aminocarbonyl)-25,26,27,-28-tetrapropoxycalix[4]arene (4). The crude product was dissolved in a minimum of hot CH_2Cl_2, and MeOH (3 vol) was added. Compound **4** crystallizes as colorless needles in 74% yield: mp 278−280 °C; ^{1}H NMR δ 7.47 (s, 2H), 7.30−7.12 (m, 8H), 7.00 (d, 4H, J = 7.3 Hz), 6.90−6.78 (s, 6H), 4.48 (d, 4H, J = 13.4 Hz), 4.00 (t, 4H, J = 7.8 Hz), 3.76 (t, 4H, J = 7.0 Hz), 3.21 (d, 4H, J = 13.4 Hz), 2.05−1.80 (m, 8H), 1.08 (t, 6H, J = 7.4 Hz), 0.94 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 165.7, 159.1, 157.1, 137.0, 135.8, 134.7, 131.4, 129.0, 128.4, 126.7, 122.6, 121.6, 116.4, 77.2, 76.7, 31.0, 23.4, 23.0, 10.6, 9.9; MS (FAB+) 986 *m*/*z*. Anal. Calcd for $C_{54}H_{56}N_2Br_2O_6$: C, 65.59; H, 5.71; N, 2.83. Found: C, 65.56; H, 5.95; N, 2.94.

5,17-Bis(*N*-(4-(pyrrolidin-1-yl)phenyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (5). The crude product was dissolved in a minimum of hot CH_2Cl_2, and MeCN (3 vol) was added. Compound **5** crystallizes in 85% yield as colorless crystals: mp 299−302 °C (dec); ^{1}H NMR δ 7.56 (s, 2H), 7.34 (d, 4H, J = 8.6 Hz), 7.26 (s, 4H), 6.54 (s, 6H), 6.44 (d, 4H, J = 8.7 Hz), 4.48 (d, 4H, J = 13.3 Hz), 3.92 (t, 4H, J = 7.5 Hz), 3.84 (t, 4H, J = 7.3 Hz), 3.35−3.10 (m, 12H), 2.10−1.80 (m, 16H), 1.02 (t, 6H, J = 7.4 Hz), 0.98 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 166.3, 160.2, 156.5, 145.7, 136.2, 134.5, 129.6, 128.8, 127.7, 127.4, 122.9, 122.8, 112.1, 77.32, 77.27, 48.2, 31.5, 25.8, 23.7, 23.6, 10.8, 10.6; MS (FAB+) 968 *m*/*z*. Anal. Calcd for $C_{62}H_{72}N_4O_6$: C, 76.83; H, 7.49; N, 5.78. Found: C, 75.46; H, 7.43; N, 5.67.

5,17-Bis(*N*-(1-naphthyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (6). Recrystallization from MeCN gave **6** in 77% yield as colorless crystals: mp 288−290 °C; ^{1}H NMR δ 7.93 (s, 2H), 7.79 (d, 2H, J = 7.8 Hz), 7.67 (t, 4H, J = 7.0 Hz), 7.60−7.41 (m, 6H), 7.25 (s, 4H), 7.22 (t, 2H, J = 7.8 Hz), 6.80−6.72 (A_2B system, 6H), 4.54 (d, 4H, J = 13.4 Hz), 4.00−3.88 (m, 8H), 3.29 (d, 4H, J = 13.4 Hz), 2.00−1.85 (m, 8H), 1.08−1.00 (m, 12H); ^{13}C NMR δ 166.4, 160.1, 157.0, 136.0, 135.2, 134.4, 133.0, 129.4, 129.0, 127.7, 127.2, 126.4, 126.2, 126.1, 125.4, 123.0, 120.9, 120.4, 77.5, 76.9, 31.3, 23.8, 23.7, 10.8, 10.7; MS (FAB+) 930 *m*/*z*. Anal. Calcd for $C_{62}H_{62}N_2O_6$: C, 79.97; H, 6.71; N, 3.00. Found: C, 79.22; H, 6.86; N, 3.09.

5,17-Bis(*N*-(pyren-1-yl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (7). Trituration with MeOH gave **7** in 87% yield as colorless crystals: mp > 300 °C. The compound was too insoluble in standard NMR solvents; MS (FAB+) 1078 *m*/*z*. Anal. Calcd for $C_{74}H_{66}N_2O_6$: C, 82.35; H, 6.16; N, 2.59. Found: C, 80.35; H, 6.11; N, 2.99.

11,23-Dibromo-5,17-bis(N-phenylaminocarbonyl)-25,-26,27,28-tetrapropoxycalix[4]arene (8). Recrystallization from MeCN (5% H_2O) gave **8** in 74% yield as colorless crystals: mp 274−276 °C; ^{1}H NMR δ 7.63 (s, 2H), 7.48 (d, 4H, J = 7.8 Hz), 7.25−7.19 (m, 4H), 7.13 (s, 4H), 7.05 (t, 2H, J = 7.3 Hz), 6.91 (s, 4H), 4.45 (d, 4H, J = 13.5 Hz), 3.93−3.80 (m, 8H), 3.20 (t, 4H, J = 13.5 Hz), 2.00−1.85 (m, 8H), 1.05−0.95 (m, 12H); ^{13}C NMR δ 165.6, 159.4, 155.7, 138.0, 136.8, 134.8, 131.2, 129.5, 128.8, 127.3, 124.0, 120.2, 115.5, 77.2, 77.0, 30.9, 23.2, 23.1, 10.3, 10.2; MS (FAB+) 986 *m*/*z*. Anal. Calcd for $C_{54}H_{56}N_2Br_2O_6$: C, 65.59; H, 5.71; N, 2.83. Found: C, 63.60; H, 5.93; N, 2.93.

11,23-Dibromo-5,17-bis(*N*-(1-naphthyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (9). Recrystallization from MeCN gave **9** in 55% yield as colorless crystals: mp 177−183 °C; ^{1}H NMR δ 8.00 (s, 2H), 7.85−7.65 (m, 8H), 7.63−7.58 (m, 4H), 7.47 (t, 2H, J = 7.5 Hz), 7.30 (s, 4H), 6.93 (s, 4H), 4.49 (d, 4H, J = 13.4 Hz), 4.00−3.80 (m, 8H), 3.25 (t, 4H, J = 13.4 Hz), 2.00−1.85 (m, 8H), 1.08−0.95 (m, 12H); ^{13}C NMR δ 165.8, 159.6, 155.6, 136.7, 135.1, 134.0, 132.4, 131.2, 129.4, 128.6, 127.5, 127.0, 126.4, 125.8, 125.7, 120.5, 120.3, 115.3, 77.2, 77.1, 31.0, 23.2, 23.1, 10.3, 10.2; MS (FAB+) 1086 *m*/*z*. Anal. Calcd for $C_{62}H_{60}N_2Br_2O_6$: C, 68.38; H, 5.55; N, 2.57. Found: C, 67.02; H, 5.68; N, 2.71.

General Procedure for Synthesis of Compounds 10−16. To a solution of the amide (**3**−**9**) (1.0 mmol) in THF (50 mL) was added *t*-BuOK (1.12 g, 10 mmol), and the mixture was stirred for 5 min at 25 °C. The solution changed from colorless to yellow. Methyliodide (1.42 g, 10 mmol) was added. A white precipitate was formed almost immediately, and it changed from yellow to colorless. After being stirred for 10 min, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), the organic layer was washed with 1 M hydrochloric acid (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by column chromatography using *n*-hexane/EtOAc (2:1, v/v) as eluent.

5,17-Bis(*N*-methyl-*N*-phenylaminocarbonyl)-25,26,27,-28-tetrapropoxycalix[4]arene (10). Recrystallization from *n*-hexane gave **10** in 90% yield as colorless crystals: mp 152−154 °C; ^{1}H NMR δ 7.35−7.15 (m, 10H), 7.05 (s, 4H), 6.03 (t, 2H, J = 7.6 Hz), 5.50 (d, 4H, J = 7.6 Hz), 4.26 (d, 4H, J = 13.4 Hz), 3.90 (t, 4H, J = 7.6 Hz), 3.55 (t, 4H, J = 7.5 Hz), 3.51 (s, 6H), 2.92 (d, 4H, J = 13.4 Hz), 2.05−1.75 (m, 8H), 1.03 (t, 4H, J = 7.4 Hz), 0.81 (t, 4H, J = 7.4 Hz); ^{13}C NMR δ 171.4, 158.9, 154.8, 145.6, 136.5, 132.3, 129.4, 129.3, 129.0, 127.3, 127.1, 125.9, 121.6, 76.7, 76.2, 38.2, 30.5, 23.3, 22.8, 10.6, 9.7; MS (FAB+) 858 *m*/*z*. Anal. Calcd for $C_{56}H_{62}N_2O_6$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.22; H, 7.39; N, 3.31.

5,17-Bis(*N*-methyl-*N*-(4-bromophenyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (11). Recrystallization from MeCN gave **11** in 90% yield as colorless flakes: mp 167−170 °C; ^{1}H NMR δ 7.44 (d, 4H, J = 8.5 Hz), 7.06 (d, 4H, J = 8.5 Hz), 7.02 (s, 4H), 6.27 (t, 2H, J = 7.6 Hz), 5.54 (d, 4H, J = 7.6 Hz), 4.29 (d, 4H, J = 13.4 Hz), 3.92 (t, 4H, J = 7.8 Hz), 3.56 (t, 4H, J = 6.7 Hz), 3.49 (s, 6H), 2.95 (d, 4H, J = 13.4 Hz), 1.90−1.75 (m, 8H), 1.04 (t, 4H, J = 7.4 Hz), 0.82 (t, 4H, J = 7.4 Hz); ^{13}C NMR δ 171.5, 159.2, 154.9, 144.8, 136.9, 132.4, 132.3, 129.3, 129.2, 128.8, 127.3, 122.2, 119.7, 77.3, 76.9, 38.2, 30.7, 23.4, 22.9, 10.7, 9.8; MS (FAB+) 1014 *m*/*z*. Anal. Calcd for $C_{56}H_{60}N_2Br_2O_6$: C, 66.14; H, 5.94; N, 2.75. Found: C, 67.44; H, 6.99; N, 3.09.

5,17-Bis(*N*-methyl-*N*-(4-(pyrrolidin-1-yl)phenyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (12). Recrystallization from MeCN gave **12** in 79% yield as slightly yellow crystals: mp 169−172 °C; ^{1}H NMR δ 7.08 (s, 4H), 6.99 (d, 4H, J = 8.7 Hz), 6.41 (d, 4H, J = 8.7 Hz), 5.89 (t, 2H, J = 7.6 Hz), 5.61 (d, 4H, J = 7.5 Hz), 4.25 (d, 4H, J = 13.3 Hz), 3.9 (t, 4H, J = 8.0 Hz), 3.54 (t, 4H, J = 6.7 Hz), 3.45 (s, 6H), 3.24 (t, 8H, J = 6.2 Hz), 2.93 (d, 4H, J = 13.4 Hz), 2.00 (t, 8H, J = 7.6 Hz), 1.90−1.65 (m, 8H), 1.03 (t, 6H, J = 7.4 Hz), 0.79 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 172.1, 159.2, 155.3, 146.6, 136.7, 134.2, 132.9, 130.4, 129.8, 128.4, 128.0, 122.0, 112.0, 77.2, 76.6, 48.0, 31.1, 25.9, 23.9, 23.3, 11.2, 10.2; MS (FAB+) 996 *m*/*z*.

Anal. Calcd for $C_{64}H_{76}N_4O_6$: C, 77.07; H, 7.68; N, 5.62. Found: C, 75.85; H, 7.80; N, 5.83.

5,17-Bis(*N*-methyl-*N*-(1-naphthyl)aminocarbonyl)-25,-26,27,28-tetrapropoxycalix[4]arene (13). Recrystallization from hexane gave **13** in 78% yield as a white powder: mp 142−145 °C; ^{1}H NMR δ 8.15−7.85 (m, 6H), 7.75−7.65 (m, 4H), 7.55−7.4 (m, 4H), 7.04 (s, 2H), 6.98 (s, 2H), 5.8−5.3 (3 × t, 2H), 4.82 (2 × t, 2H, J = 7.5 Hz), 4.55 (2 × d, 2H, J = 9.6 Hz), 4.20−4.00 (m, 4H), 3.76 (t, 4H, J = 7.9 Hz), 3.64 (s, 6H), 3.55−3.35 (m, 4H), 2.8−2.6 (m, 4H), 1.9−1.6 (m, 8H), 1.1−0.85 (m, 6H), 6.22 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 172.9, 159.4, 155.0, 154.9, 154.8, 142.4, 137.1, 137.0, 136.3, 135.1, 132.7, 132.6, 132.5, 130.7, 130.0, 129.1, 128.9, 128.2, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 126.1, 123.4, 122.0, 121.8, 121.7, 77.1, 76.6, 38.9, 30.9, 23.7, 23.3, 11.1, 10.2; MS (FAB+) 958 *m*/*z*. Anal. Calcd for $C_{64}H_{66}N_2O_6$: C, 80.14; H, 6.94; N, 2.92. Found: C, 79.47; H, 7.09; N, 2.98.

5,17-Bis(*N*-methyl-*N*-(pyren-1-yl)aminocarbonyl)-25,-26,27,28-tetrapropoxycalix[4]arene (14). Recrystallization from MeCN gave **14** in 82% yield as slightly pink crystals: mp 218−225 °C; ^{1}H NMR δ 8.35−7.75 (m, 18H), 7.03 (s, 2H), 6.93 (s, 2H), 4.75−4.20 (m, 6H), 4.00−3.80 (m, 4H), 3.70 (s, 6H), 3.59 (t, 4H, J = 7.5 Hz), 3.25 (t, 4H, J = 6.7 Hz), 2.65−2.40 (m, 4H), 1.70−1.40 (m, 8H), 0.85 (t, 6H, J = 7.1 Hz), 0.57 (t, 6H, J = 7.2 Hz); ^{13}C NMR δ 173.2, 173.0, 159.6, 159.5, 154.8, 154.7, 154.6, 139.6, 136.8, 136.4, 136.3, 132.3, 132.1, 131.6, 131.5, 131.3, 130.9, 129.7, 129.5, 129.4, 129.3, 129.2, 128.3, 127.8, 127.6, 127.1, 127.0, 126.9, 126.4, 126.2, 126.0, 125.9, 125.5, 125.0, 122.3, 121.9, 121.8, 121.7, 76.9, 76.4, 39.5, 39.4, 30.9, 30.8, 23.6, 23.1, 11.0, 10.0; MS (FAB+) 1106 *m*/*z*. Anal. Calcd for $C_{76}H_{70}N_2O_6$: C, 82.43; H, 6.37; N, 2.53. Found: C, 81.25; H, 6.50; N, 2.61.

11,23-Dibromo-5,17-bis(*N*-methyl-*N*-phenylaminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (15). Recrystallization from MeCN gave **15** as colorless flakes in 74% yield: mp 231−233 °C; ^{1}H NMR δ 7.55−7.15 (m, 10H), 7.06 (s, 4H), 5.84 (s, 4H), 4.23 (d, 4H, J = 13.5 Hz), 3.91 (t, 4H, J = 7.4 Hz), 3.60−3.45 (m, 10H), 2.90 (d, 4H, J = 13.5 Hz), 1.90−1.65 (m, 8H), 1.02 (t, 6H, J = 7.4 Hz), 0.77 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 170.6, 159.0, 154.4, 145.2, 135.8, 134.8, 130.0, 129.8, 129.8, 127.5, 126.7, 125.9, 115.3, 77.2, 76.4, 38.4, 30.9, 23.3, 22.6, 10.6, 9.6; MS (FAB+) 1014 *m*/*z*. Anal. Calcd for $C_{56}H_{60}N_2Br_2O_6$: C, 66.14; H, 5.94; N, 2.75. Found: C, 65.86; H, 6.01; N, 2.82.

11,23-Dibromo-5,17-bis(*N*-methyl-*N*-(1-naphthyl)aminocarbonyl)-25,26,27,28-tetrapropoxycalix[4]arene (16). Recrystallization from MeCN gave **16** in 85% yield as colorless crystals: mp 234−236 °C; ^{1}H NMR δ 8.13 (t, 2H, J = 9.1 Hz), 8.00−7.88 (m, 4H), 7.73−7.51 (m, 6H), 7.36−7.23 (m, 4H), 6.69 (s, 1H), 6.61 (s, 1H), 5.91 (s, 1H), 5.87 (s, 1H), 5.10 (s, 1H), 5.08 (s, 1H), 4.17 (2 × d, 2H, J = 13.5 Hz), 3.97 (2 × d, 2H, J = 13.2 Hz), 3.89−3.73 (m, 4H), 3.60 (s, 6H), 3.57−3.27 (m, 4H), 2.92 (d, 2H, J = 13.8 Hz), 2.35 (2 × d, 2H, J = 13.8 Hz), 1.83−1.58 (m, 10H), 0.97 (2 × t, 6H, J = 6.9 Hz), 0.72 (t, 6H, 7.5 Hz); ^{13}C NMR δ 172.3, 172.1, 159.4, 154.6, 141.9, 136.5, 136.3, 135.4, 135.3, 135.1, 134.9, 134.8, 134.7, 133.7, 131.3, 130.8, 130.3, 130.2, 130.0, 129.9, 129.6, 129.47, 128.8, 128.6, 127.6, 127.0, 126.9, 126.6, 123.1, 123.0, 115.7, 77.6, 76.7, 38.9, 38.8, 31.2, 31.1, 23.7, 23.6, 22.9, 11.0, 10.9, 10.8, 9.9; MS (FAB+) 1114 *m*/*z*. Anal. Calcd for $C_{64}H_{64}N_2Br_2O_6$: C, 68.82; H, 5.77; N, 2.51. Found: C, 68.63; H, 6.10; N, 2.67.

Crystallographic Methods. Crystals of **13**−**16** were drawn from the mother liquor, coated with a thin layer of oil, mounted on glass capillaries with grease, and transferred quickly to the cold-nitrogen stream on the diffractometer. Data were collected on a Siemens SMART platform diffractometer with a CCD area sensitive detector. The crystals of **8** were mounted as described above, and data were collected on Beamline D3 at the synchrotron facility DORIS III at HASYLAB. (X-ray crystallographic data were collected in part at the synchrotron facility DORIS III at HASYLAB, Notkestrasse 85, D-22603 Hamburg, Germany, and in part at the Department of Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark.) Absorption corrections were made for compounds **8** and **13**−**16** using SADABS.[53] Direct methods for the structure solution and full-matrix least-squares refinements were used for all compounds. For all compounds, hydrogen atoms were included in calculated positions. For compound **8**, only the bromine atoms were treated anistropically with respect to the thermal parameter. One large Fourier peak was found close to the amide links in one of the molecules in the asymmetric unit. This was ascribed to a water molecule. The hydrogens were, however, not introduced. The programs used were SMART, SAINT, and SHELXTL from Siemens.[54,55] For compound **13**, the DMSO solvent molecule was found to be disordered. This was modeled as a composite of two possible conformations for the DMSO solvent molecule. Each conformation was refined with respect to the sof. One of the two conformers was dominant with a sof of 0.629 (the second conformer had a sof of 0.371). For compound **14**, two of the propoxy groups and one of the acetonitrile solvent molecules were found to be disordered. This was modeled as a composite of two possible conformations for the propoxy groups and as two independent mutually exclusive molecules for the acetonitrile molecule. Each conformation was refined with respect to the sof. One of the two conformers was dominant with sof's of 0.803 and 0.809 for the two different propoxy groups (the second set of conformers had sof's of 0.197 and 0.191, respectively). For the disordered acetonitrile molecule the sof's is 0.500. All structures were checked for overlooked symmetry using MISSYM and for voids in PLATON.[56]

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Supporting Information Available: Copies of proton and carbon NMR spectra and tables of X-ray crystallographic data (99 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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