Aggregates of calix[4]arenes based on the 2,6-diaminotriazine · imide system

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Abstract. The synthesis of several calix[4]arenes functionalized with uracil or diaminotriazine moieties is described. The association between these complementary calix[4]arenes is strongly influenced by processes related to the position and directionality of the hydrogen-bonding moieties. In the case of bis(uracil)calix[4]arene (**4**), self-association is observed ($K = 3.4 \cdot 10^3 \text{ M}^{-1}$ in CDCl_3) whereas, in the case of bis(diamidotriazine)calix[4]arene (**16**), it was concluded from $^1\text{H-NMR}$ studies that intermolecular association is hampered by the formation of intramolecular hydrogen bonds. Due to the divergent orientation of the hydrogen-bonding groups of bis(diaminotriazine)calix[4]arene (**15b**), it forms hydrogen-bonded strands through interaction with 5-ethyl-5-phenylbarbituric acid (**17**), resulting in the formation of a gel in chloroform.

Introduction ^a

One of the fields in supramolecular chemistry which is receiving increasing interest is that of noncovalent assembly of single components into well-defined aggregates¹. The formation of these aggregates may result in products with specific macroscopic properties.

Calix[4]arenes have proven to be very easily functionalizable molecular building blocks which have found widespread use in different applications². Although calix[4]arenes seem to meet the prerequisites for a molecule of interest in the construction of well-defined aggregates, very little effort has been devoted to the behavior of calix[4]arenes in noncovalent aggregation processes³.

One of the first steps in the development of calixarenes that are able to form well-defined hydrogen-bonded aggregates, is the investigation of calix[4]arenes that can form well-characterizable hydrogen-bonded 1:1 adducts. Such complexes may provide valuable information on the conformational and associative behavior of calix[4]arenes functionalized with moieties with hydrogen-bonding capacity. These calix[4]arenes should not only give insight into how the calix[4]arene skeleton and the preorganization of its functionalizable positions may be used as a structural component in the synthesis of supramolecular structures, but also on any unfavorable phenomena which may exist and must be taken into account.

For sufficiently strong aggregates to be obtained it is neces-

sary to provide the calix[4]arene with multiple-hydrogen-bonding sites. Further, a predictable directionality of the hydrogen bonds at these sites should contribute to the formation of an aggregate of a designed structure. One way to achieve both goals is to attach complementary hydrogen-bonding moieties to the calix[4]arene platform via short, well-structured linkages. This ensures optimal exploitation of the preorganization already present to a large degree in calix[4]arenes.

In an earlier attempt, a calix[4]arene fixed in the cone conformation was substituted with a self-complementary pyridone moiety⁴. This molecule dimerizes in chloroform with a dimerization constant of 100 M^{-1} , comparable to that of simple pyridones^{5,6}. However, attaching a second pyridone moiety to the calix[4]arene did not result in well-defined dimers; instead a mixture of oligomers was obtained. The group of Shinkai⁷ and our group⁸ have reported hydrogen-bonded duplexes formed through interaction between a calix[4]arene with four carboxyl groups and a calix[4]arene with four stilbazole and pyridine moieties, respectively. The formation of a hydrogen-bonded calix[4]arene dimer based on the self-complementarity of carboxylic acids has recently been described by Pochini et al.⁹. Very recently, we reported the formation of large, self-assembled boxes based on calix[4]arene double rosettes as a result of hydrogen bonding between melamine moieties and barbituric or cyanuric acid derivatives¹⁰.

An example of a hydrogen-bonding system which combines weak self-association with strong cross-association is the well-documented 2,6-diamidopyridine · imide combination. The system is characterized by the formation of three strong $\text{NH} \cdots \text{O}$ hydrogen bonds with alternating hydrogen-bond donors and acceptors on the individual components; the association constant for this system is generally in the order of $100\text{--}500 \text{ M}^{-1}$ (Ref. 11-13).

Since the hydrogen-bonding pattern of diaminotriazines is similar to that of diamidopyridine, the former has also been used in the molecular recognition of imides¹⁴.

Like other imides¹⁵, thymine and uracil have a very low

^a Abbreviations and nomenclaturebarbituric acid = pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trionecyanuric acid = 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trionecytosine = 4-aminopyrimidin-2(1*H*)-one

dicyanodiamide = cyanoguanidine

melamine = 1,3,5-triazine-2,4,6-triamine

orotic acid = 1,2,3,4-tetrahydro-2,6-dioxypyrimidine-4-carboxylic acid

stilbazole = 2-(2-phenylethenyl)pyridine

thymine = 5-methylpyrimidine-2,4(1*H*,3*H*)-dioneuracil = pyrimidine-2,4(1*H*,3*H*)-dione

tendency towards self-association; their K_a values of 3.2 M^{-1} and 6.1 M^{-1} , respectively^{16,17}, are an order of magnitude smaller than those determined for the self-association of cytosine ($28\text{--}51 \text{ M}^{-1}$)^{18,19}, even though in both cases two hydrogen bonds are formed. This difference can be explained by taking the secondary interactions into account¹⁷. In cytosine, there are two attractive and two repulsive secondary interactions, while in uracil or thymine all four secondary interactions are repulsive.

Even though the association between imides and diamidopyridines is not among the strongest for systems involving three hydrogen bonds, the weak self-association of the two components, in combination with the good cross-association, makes this system a very interesting candidate for application in well-defined hydrogen-bonded aggregates of calix[4]arenes. In this paper we report the synthesis and hydrogen-bonding behavior of several calix[4]arene derivatives bearing uracil and diaminotriazine substituents on either the upper or the lower rim.

Results and discussion

Synthesis of uracil- and diaminotriazine-functionalized calix[4]arenes

The lower-rim-substituted bis(uracil)calix[4]arenes **3** and **4** were synthesized in 90% and 74% yield, respectively, from the corresponding calix[4]arenes (**1**, **2**) by alkylation with the commercially available 6-(chloromethyl)uracil in acetonitrile or acetone under conditions that are known to yield diametrically substituted products²⁰. The tetrahexylcalix[4]arene was prepared by a Friedel–Crafts acylation of the upper rim with hexanoyl chloride and subsequent reduction of the obtained tetraketone with triethylsilane, both according to literature procedures²¹. The reason for making the tetrahexyl derivative **4** was the low solubility of **3** in apolar solvents.

The synthesis of upper-rim-substituted bisuracil **8** started with the tetraalkylation of the lower rim of calix[4]arene **1** using dodecyl bromide and sodium hydride in DMF, to give **5** in 80% yield. The long aliphatic chains ensured the solubility of the resulting product. Nitration of two diametrical para positions of tetradodecylcalix[4]arene **5** proceeded in 32% yield^{14e}. Subsequently, the resulting dinitro derivative **6** was quantitatively reduced to diamine **7**. Finally, a coupling reaction was executed with orotic acid in DMF using carbonyldiimidazole as a catalyst to give bisuracil **8** in 16% yield, which was well soluble in chloroform.

The complementary bis(diaminopyrimidine)calix[4]arene **10**

was synthesized in two steps from bisuracil **3**. By refluxing **3** in phosphoryl chloride²² the corresponding tetrachloro derivative **9** was obtained in 59% yield. This could be easily converted into target compound **10** by reaction with *n*-butylamine in refluxing dioxane^{14e} and, after purification, was obtained as a soluble crystalline product in 44% yield.

Figure 1. ¹H-NMR dilution curve of **4** in CDCl₃ (25°C); ● = N(1)H; ◇ = N(3)H; = calculated for $K = 3.2 \cdot 10^3 \text{ M}^{-1}$.

In the synthesis of triazine-substituted calix[4]arenes **15** and **16** the selective functionalization of the two diametrical para positions is achieved making use of the greater tendency of phenols to be brominated compared to phenolic ethers²⁰. Thus, after selective 1,3 alkylation of the lower rim with propyl iodide or dodecyl bromide, the dialkoxy derivative **11** was selectively brominated on the free phenols using bromine in dichloromethane. The alkylation proceeds better for the propoxy derivative than for the dodecyloxy derivative (95% vs. 51%), whereas the bromination is quantitative in both cases. The remaining phenolic groups of **12** were then also alkylated and the dibromo derivative **13** was converted into the dicyanocalix[4]arene **14** with copper(II) cyanide under Rosenmund–von-Braun conditions²³. The latter two reactions proceed with comparable efficiency for the two derivatives: 90% and 85% yields for the propoxy vs. 91% and 75% yields for the dodecyloxy derivative. The base-catalyzed condensation of dicyanocalix[4]arenes **14a** and **14b** with dicyanodia-

Figure 2. Hydrogen-bonded association of a bisuracil (I) and a bispyridone (II) through a combination of intra- and intermolecular hydrogen bonding.

vide²⁴, to give the diaminotriazine-substituted calix[4]arenes **15a** and **15b**, required a very large excess of dicyanodiamide (50 equiv) to prevent side-reactions such as the hydrolysis of the cyano group²⁵. Under the conditions applied, a substantial amount of melamine is formed, but this can be easily removed by treatment with hot water. Compound **15a**, which was obtained in 68% yield, has a very limited solubility in chloroform, whereas compound **15b**, obtained in 83% yield, is reasonably soluble in chloroform (~ 4.5 mg/ml), due to the long alkyl chains. To improve the solubility (and the hydrogen-bond-donating capacity) of diaminotriazine **15a**, this compound was acylated using hexanoyl chloride in pyridine with 4-(dimethylamino)pyridine as a catalyst to give the very soluble **16** in 50% yield²⁶.

Hydrogen bonding interactions

Before the interaction between different calix[4]arenes was studied, the behavior of neat bisuracil **4** was studied. The $^1\text{H-NMR}$ spectra of solutions of **4** in CDCl_3 showed that the shift of one of the NH groups of this compound was strongly concentration-dependent, while the other showed virtually no change (Figure 1). This suggested the presence of self-association phenomena. By means of a dilution experiment in CDCl_3 , a self-association constant of $(3.4 \pm 0.2) \cdot 10^3 \text{ M}^{-1}$ was determined, assuming dimerization²⁷. This value is exceptionally high, especially when compared to the self-association of simple uracils ($K_a = 6.1 \text{ M}^{-1}$)¹⁶. In terms of ΔG^0 values the self-association is more than four times as strong as that of simple uracils (-4.8 vs. -1.1 kcal/mol). This may be caused by a combination of a large positive entropic contribution and an increase in hydrogen-bonding capacity of the uracil by alkylation at the 6-position.

There are several possible origins for a positive contribution of the self-association entropy. One of these is the preorganization of the two uracils being covalently connected via the calix[4]arene. This contribution in itself is not expected to be very large, since these moieties can still rotate around the carbon and oxygen atom of the linker. This rotation may, however, be decreased by the formation of one or two *intramolecular* hydrogen bonds. The possible existence of these intramolecular hydrogen bonds was confirmed by studying CPK molecular models of **4**, and is further suggested by the permanent downfield shift of one of the two NH signals. Such intramolecular hydrogen bonds cannot be completely linear but may cause the two uracil moieties to be substantially preorganized. In Figure 2, the structure of a dimer involving both intermolecular and intramolecular hydrogen bonds is depicted. In this structure, the intermolecular hydrogen bonds

are not completely linear, which affects their strength negatively. However, the secondary interactions are less unfavorable, since one of the carbonyls and one of the NHs is turned away from the hydrogen bonding site, and this may partly offset the negative effect of the nonlinearity of the intermolecular hydrogen bonds.

A slightly different situation, in which intramolecular hydrogen bonding contributes to intermolecular association, was described by Wuest et al. (Figure 2, II). The authors suggested, that the intermolecular interaction between the bispyridones is strengthened as the result of partial deprotonation due to intramolecular hydrogen bonding²⁸. Kuroda et al. determined that the cyclic intramolecularly hydrogen-bonded structure of a flexible bisuracil associates more strongly with adenine than the open form, even though the former process is enthalpically less favorable²⁹. The groups of Hamilton³⁰, Rebek^{14b}, and Rose³¹ also studied the association behavior of bisthymines. These authors report an increased association constant for the interaction with bis(diamidopyridine) receptors but in all three cases the change in free energy is less than twice the value which was determined for interactions of simple thymines with single diamidopyridines (Hamilton: -4.6 vs. -2.7 kcal/mol; Rebek: -5.0 vs. -4.1 kcal/mol)³². None of the authors mentions the occurrence of self-association of the bisthymines. The latter could be an explanation for the observation that the values for the association constants are lower than expected. It should be mentioned that, in the above cases, the thymines are fixed in a parallel fashion, above one another, whereas in **4** the two uracils are almost co-planar.

The first interaction between two different complementary calix[4]arenes that was investigated was the one between bisuracil **4** and bisdiaminopyridine **10**. Upon addition of one equivalent of **10** to a solution of **4** in CDCl_3 the NH signals of both disappear completely. This indicates that hydrogen-bonded interaction between these two molecules leads to chemical exchange of the NH protons at the NMR timescale. This process makes assessment of the strength and character of the interaction impossible. A $^1\text{H-NMR}$ dilution experiment with bis(diaminopyrimidine)calix[4]arene **10** showed that this molecule does not self-associate, since no shift of the NH protons was observed.

When bisuracil **4** was mixed with bis(diamidotriazine) **16**, to our surprise, no interaction was observed in the $^1\text{H-NMR}$ spectrum. The NH resonances of **4** are at exactly the same chemical shift as in free **4** at the equivalent concentration and the signal for the amido NHs of **16** is still broadened. These observations prompted a closer investigation of the behavior of **16**. In the $^1\text{H-NMR}$ spectrum of **16** in CD_2Cl_2 (and CDCl_3) the resonances of the protons of the substituted aromatic rings are observed at 7.09 ppm, while in solvents like THF- d_8 and DMSO- d_6 these resonances are observed at much lower field, i.e. 8.16 ppm. This indicates that, in apolar solvents, **16** is present in a pinched-cone conformation³³ with the two para-substituted aromatic rings coming towards one another (Figure 3). Such a situation implies that the two

Figure 3. Pinched-cone conformation of **16** [$R_1 = \text{C}_3\text{H}_7$, $R_2 = \text{C}(\text{O})\text{C}_3\text{H}_7$].

Figure 4. ^1H -NMR spectra of **16** at decreased temperatures (CD_2Cl_2).

diamidotriazine moieties are also more or less parallel, a position in which hydrogen bonding of the two diamidotriazine moieties of **16** with the two uracil moieties of **4** is highly likely. The broadened resonance of the NH protons in apolar solvents may be the result of chemical exchange at the NMR timescale, but it is also possible that some hydrogen-bonding phenomenon was present in neat **16**. When a sample of **16** in CD_2Cl_2 was cooled to -65°C , the broad signal of the NHs split into two separate signals (Figure 4). A dilution experiment at this decreased temperature showed that these resonances were not concentration-dependent. From this, it was concluded that the observed broadening of

the amido NHs at room temperature is the result of intramolecular hydrogen bonding. A possible structure involving such intramolecular hydrogen bonding, is schematically depicted in Figure 5. The amido groups are twisted out of the plane of the triazine ring and form hydrogen bonds with the amido groups of the neighboring triazine ring. Of the four amido NHs, only two are involved in a hydrogen-bond interaction while the other two are free. This explains the presence of two amido NH resonances at low temperature. At room temperature, the equilibrium between the different structures is faster, which leads to broadening of the NH signal. Based on these results it was concluded that the pinched cone of **16** is the result of intramolecular hydrogen bonding between the amido groups of the triazines. The intramolecular hydrogen bonding in **16** inhibits the amido NHs from taking part in an intermolecular association with **4**. This explains why no interaction between bisuracil **4** and bis(diamidotriazine) **16** is observed in the ^1H -NMR spectrum³⁴.

The intramolecular hydrogen bonding as described above for **16** is not possible for bis(diaminotriazine) **15b**. However, the ^1H -NMR spectrum of this compound in CDCl_3 is completely broadened³⁵. The fact that it becomes sharp on addition of $\text{THF}-d_8$ suggests that hydrogen-bonded self-association plays a significant role here as well. The addition of one equivalent of bisuracil **4** did not cause any sharpening of the spectrum of **15b**, nor did the addition of a large excess of 5-ethyl-5-phenylbarbituric acid (**17**). There was, however, one remarkable observation: mixing one equivalent of **15b** with one equivalent of barbituric acid **17** caused the chloroform solution to become very viscous³⁶. The gel formed was stable for about two weeks at room temperature. Similar gel formation has been observed previously for a system which comprises the same hydrogen-bonding interactions^{37,38}. In that case, the formation of the gel was explained by assuming that the two components form hydrogen-bonded ribbons. Such ribbons, but then in the solid state, have been described by Lehn et al.³⁹ In the IR spectrum of the gel, a signal appears at 3343

Figure 5. Intramolecular hydrogen bonding in **16** (top view).

Figure 6. Schematic representation of a hydrogen-bonded strand of **15b** and **17**.

Figure 7. Transmission electron micrograph of the 1:1 mixture of **15b** and **17**; magnification: 25740 $\times$.

cm^{-1} , which was assigned to a hydrogen-bonded NH-stretch vibration. For the free bis(diaminotriazine)calix[4]arene **15b** in chloroform, NH-stretch resonances were observed at 3468, 3421, 3317, 3206, and 3142 cm^{-1} , while for the barbituric acid in chloroform a strong NH stretch frequency is observed at 3381 cm^{-1} , along with weaker resonances at 3215, 3100, 3066, and 2955 cm^{-1} . Additionally, the IR spectrum of the mixture of **15b** and **17** shows sharp resonances at 1739, 1719 and 1701 cm^{-1} , while for the neat barbituric acid only two resonances, at 1738 and 1716 cm^{-1} , are present. The formation of hydrogen-bonded strands as depicted in Figure 6 was further supported by transmission electron microscopy of a 1:1 mixture of bis(diaminotriazine) **15b** and barbituric acid **17** (Figure 7). The picture shows a network of fibers with a diameter of up to ca. 100 nm. This suggests that these fibers consist of a large number of hydrogen-bonded strands, since the diameter of the latter is estimated to be ca. 20–30 Å, based on CPK molecular models.

The observation that the gelation strongly decreases upon addition of another equivalent of the barbituric acid also suggests that the proposed hydrogen-bonded strands are formed in the 1:1 mixture of **15b** and **17**. In THF- d_8 , the resonances of the protons of the triazine-substituted aromatic rings are observed at relatively low field (8.16 ppm), while the resonance of the other aromatic protons are observed at much higher field (6.06 ppm). In the dicyano derivative **14b** (the precursor of **15b**), the latter are observed at 6.74 ppm. This indicates that the molecule is present in the pinched-cone conformation, but in this case the two diaminotriazine units assume a divergent position.

It is unclear what causes the pinching of **15b**. Sterically, there appears to be no reason for this behavior. The divergent orientation of the diaminotriazine moieties is very unfavorable for the formation of a hydrogen-bonded 1:1 adduct with **4**⁴⁰. It is possible that the two molecules form hydrogen-bonded strands, but, unlike the mixture of **15b** with **17**, no gelation was observed for mixtures of **15b** and **4**.

Upper-rim-substituted bisuracil **8** was synthesized as a more preorganized alternative of bisuracil **4**. This molecule exploits the intramolecular hydrogen bond that is formed between the amide groups connecting the uracil moieties with the calix[4]arene skeleton. Again, the spectrum of this compound is broad in CDCl_3 , but sharp in THF- d_8 , suggesting self-association. From $^1\text{H-NMR}$ spectra recorded in mixtures of CDCl_3 and THF- d_8 it was determined that, in apolar environments, **8** indeed assumes a pinched-cone conformation with the two substituted rings coming towards one another, and that the degree of pinching decreases when the environment becomes increasingly polar. In an attempt to get an idea of the strength of the self-association of **8**, a dilution experiment was

performed in a mixture of THF and CDCl_3 , but also in this medium the $^1\text{H-NMR}$ spectra are severely broadened, making determination of an association constant impossible. Like **4**, **8** does not show any interaction with **15b**, which is most probably due to a combination of self-association of **8** and an unfavorable geometry of **15b**.

Conclusions

It has been shown that, by preorganization of two uracil moieties on a calix[4]arene, a molecule is obtained which has a strong tendency to form hydrogen-bonded dimers. Further, it has been demonstrated that the residual flexibility of the calix[4]arene skeleton plays a large role in the way the calix[4]arenes functionalized with hydrogen-bonding groups interact with themselves and with other molecules. The absence of any interaction of the bisuracil **4** with bis(diaminotriazine) **16** was explained by the observation that the latter assumes a pinched-cone conformation which is stabilized by intramolecular hydrogen bonding. The association between **4** and **16** is further hampered by the self-association of **4**. The divergent structure of bis(diaminotriazine) **15b** did not allow for the formation of well-defined 1:1 adducts with the bisuracil compounds **4** and **8**. However, interaction with the complementary barbituric acid **17** led to gelation of a 1:1 mixture of these components in chloroform. This gelation is most probably the result of the formation of hydrogen-bonded strands.

Experimental

Melting points were determined with a Reichert melting point apparatus and are uncorrected. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded in CDCl_3 (unless otherwise stated) using residual solvent protons as internal reference on a Bruker AC 250 spectrometer. Mass spectra were recorded with a Finnigan MAT 90 spectrometer using *m*-nitrobenzyl alcohol as a matrix. THF was freshly distilled from sodium benzophenone ketyl, hexanes (referring to petroleum ether with b.p. 60–80°C), CH_2Cl_2 and EtOAc from K_2CO_3 . DMF and CH_3CN were dried over molecular sieves (4 Å and 3 Å, respectively) for at least three days. Pyridine was stored over KOH for at least one week before use. NaH was a 55–65% dispersion in mineral oil. Hexanoyl chloride was distilled prior to use. 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) from Merck. All reactions were carried out in an argon atmosphere, unless otherwise stated. The presence of solvent in the analytical samples was confirmed by $^1\text{H-NMR}$ spectroscopy. Calix[4]arene **1**⁴¹ and tetrahexylcalix[4]arene **2**²¹ were synthesized according to literature procedures.

Synthesis

6,6'-[(Calix[4]arene-25,27-diyl)bis(oxymethylene)]bis[pyrimidine-2,4(1H,3H)-dione] (**3**). To a suspension of calix[4]arene **1** (7.97 g, 18.8 mmol), K_2CO_3 (2.86 g, 20.7 mmol), and KI (0.15 g, 0.90 mmol) in CH_3CN (350 ml) was added 6-(chloromethyl)uracil (7.50 g, 46.7 mmol). The mixture was refluxed for three days, after which it was cooled to room temperature and concentrated under reduced pressure. The residue was stirred in $\text{H}_2\text{O}/\text{MeOH}$ (100 ml/100 ml) for 3 h, filtered, and stirred in refluxing methanol for 18 h. The crude product was then filtered off and recrystallized from hot DMF to give a white powder. Trituration with MeOH (to remove traces of DMF) afforded the product in 90% yield; m.p. 290°C (dec). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 11.04 (s, 2 H, NH), 10.87 (br s, 2 H, NH), 7.84 (br s, 2 H, OH), 7.20 (d, 4 H, J 7.5 Hz, ArH), 7.06 (d, 4 H, J 7.6 Hz, ArH), 6.90–6.80 (m, 2 H, ArH), 6.70–6.60 (m, 2 H, ArH), 6.20 (s, 2 H, pyH), 4.84 (s, 4 H, OCH_2), 4.16 and 3.50 (ABq, 8 H, J 13.1 Hz, ArCH_2Ar). $^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$): δ 164.1 (s, C=O), 152.3 (s), 151.3 (s), 151.0 (s), 150.4 (s), 133.4 and 127.4 (s, ArCCH_2), 129.2 and 128.8 (d, ArH), 125.9 and 119.5 (d, ArH), 98.6 (d, $\text{C}(\text{O})\text{CH}$), 72.2 (t, OCH_2), 30.5 (t, ArCH_2Ar). FAB-MS: m/z 672.9 ($[\text{M}+\text{H}]^+$ calcd. 673.2). IR (KBr) 1722 cm^{-1} (C=O), 1693 cm^{-1} (C=O). Anal. calcd. for $\text{C}_{38}\text{H}_{32}\text{N}_4\text{O}_8 \cdot 1.7\text{H}_2\text{O}$: C 64.89, H 4.59, N 7.97; found: C 64.83, H 4.49, N 7.76%.

6,6'-[(5,11,17,23-Tetrahexylcalix[4]arene-25,27-diyl)bis(oxy-methyl-ene)]bis[pyrimidine-2,4-(1H,3H)-dione] (4). To a solution of 2 (0.60 g, 7.89 mmol), K_2CO_3 (0.24 g, 1.74 mmol), and KI (0.06 g, 4 mmol) was added 6-(chloromethyl)uracil (0.32 g, 1.97 mmol). After refluxing for four days the reaction mixture was concentrated under reduced pressure and the residue was taken up in CH_2Cl_2/H_2O (100 ml/25 ml). After separation, the organic layer was washed with 1N HCl (3×75 ml), H_2O (50 ml), and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was recrystallized from diethyl ether to give 4 in 74% yield; m.p. 167–168°C. 1H -NMR: δ 10.83 (s, 2 H, NH), 10.74 (s, 2 H, NH), 8.21 (s, 2 H, OH), 6.85, 6.81 (s, 4 H, ArH), 5.77 (s, 2 H, pyH), 4.96 (s, 4 H, OCH_2), 4.11 and 3.43 (ABq, 8 H, J 13.3 Hz, $ArCH_2Ar$), 2.44 (t, 4 H, J 7.5 Hz, $ArCH_2CH_2$), 2.33 (t, 4 H, J 7.6 Hz, $ArCH_2CH_2$), 1.60–1.40 (m, 8 H, $ArCH_2CH_2$), 1.35–1.15 (m, 24 H, CH_2), 0.95–0.75 (m, 12 H, CH_3). ^{13}C -NMR: δ 165.2 [s, NC(O)N], 152.2 [s, NC(O)C], 150.2 (s, $NCCH_2$), 149.7 (s, ArCO), 148.4 (s, ArCOH), 141.0 (s, $ArCCH_2CH_2$), 134.7 ($ArCCH_2CH_2$), 132.7 (s, $ArCCH_2$), 129.5, 128.8 (d, ArCH), 126.9 (s, $ArCCH_2$), 98.5 [d, C(O)CH], 72.4 (t, OCH_2), 35.5, 35.1 (t, $ArCCH_2CH_2$), 31.8, 31.7, and 31.2 (t, $ArCH_2Ar$, $ArCCH_2CH_2$), 29.1, 29.0, 22.7, 22.6 (t, CH_2), 14.2, 14.1 (q, CH_3). FAB-MS: m/z 1010.2 ($[M+H]^+$ calcd. 1009.6). IR (KBr) 1717 cm^{-1} (C=O), 1682 cm^{-1} (C=O). Anal. calcd. for $C_{62}H_{80}N_4O_8 \cdot 1.8H_2O$: C 71.48, H 8.09, N 5.38; found: C 71.19, H 7.69, N 5.31%.

25,26,27,28-Tetrakis(dodecyloxy)calix[4]arene (5). Calix[4]arene 1 (5.00 g, 11.8 mmol) was added to a suspension of NaH (3.55 g, 118 mmol, 60% in oil, washed with hexanes) in dry DMF (150 ml). After hydrogen formation had stopped (30 min), *n*-dodecyl bromide (40 ml, 0.24 mol) was added dropwise. The reaction was stirred at room temperature for 1 h followed by stirring overnight at 75°C. After cooling to room temperature, the reaction was quenched carefully with MeOH (10 ml) and subsequently concentrated using an oil pump. The residue was taken up in $CH_2Cl_2/1N-HCl$ (300 ml/100 ml) and after separation of the layers, the organic layer was washed with 1N HCl (6×150 ml) and brine (100 ml). After drying over $MgSO_4$, the solution was concentrated in vacuo and the residue was triturated with EtOH to give pure 5 as a white solid in 80% yield; m.p. 56–58°C. 1H -NMR: δ 6.65–6.50 (m, 12 H, ArH), 4.44 and 3.14 (ABq, 8 H, J 13.3 Hz, $ArCH_2Ar$), 3.87 (t, 8 H, J 7.4 Hz, OCH_2), 2.00–1.80 (m, 8 H, OCH_2CH_2), 1.50–1.15 (m, 72 H, CH_2), 0.88 (t, 12 H, J 6.6 Hz, CH_3). ^{13}C -NMR: δ 156.6 (s, ArCO), 135.2 (s, $ArCCH_2$), 128.1 (d, ArCH), 121.9 (d, ArCH), 75.2 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 31.0, 30.4, 30.1, 30.0, 29.9, 29.9, 29.8, 29.5, 26.4, 22.8 (t, CH_2), 14.2 (q, CH_3). FAB-MS: m/z 1097.1 (M^+ , calcd. 1096.9). Anal. calcd. for $C_{76}H_{120}O_4$: C 83.15, H 11.02; found: C 83.11, H 11.32%.

5,17-Dinitro-25,26,27,28-tetrakis(dodecyloxy)calix[4]arene (6). To a solution of calix[4]arene 5 (1.00 g, 0.912 mmol) in CH_2Cl_2 (55 ml) and glacial acetic acid (8.6 ml), 65% aqueous nitric acid (4.3 ml, 67 mmol) was added dropwise. After stirring the mixture for 7 h, H_2O (25 ml) was added, the aqueous and organic layer were separated, and the organic layer was washed with H_2O till neutral pH. The organic layer was dried over $MgSO_4$, and the solution was concentrated under reduced pressure. The residue was precipitated from hot EtOH after which it was recrystallized from 1-propanol giving pure white 6 in 32% yield; m.p. 107–109°C. 1H -NMR: δ 7.41 [s, 4 H, o- $Ar(NO_2)H$], 6.72 (s, 6 H, ArH), 4.45 and 3.23 (ABq, 8 H, J 13.7 Hz, $ArCH_2Ar$), 4.00–3.85 (m, 8 H, OCH_2), 2.00–1.85 (m, 8 H, OCH_2CH_2), 1.50–1.20 (s, 72 H, CH_2), 0.87 (t, 12 H, J 6.6 Hz, CH_3). ^{13}C -NMR: δ 161.9, 156.3 (s, ArCO), 142.5 (s, $ArCNO_2$), 136.3, 134.2 (s, $ArCCH_2$), 128.9, 123.4 (d, ArCH), 123.1 (d, ArCH), 75.8, 75.4 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 31.1, 30.4, 30.2, 29.9, 29.8, 29.8, 29.4, 26.2, 22.7 (t, CH_2), 14.1 (q, CH_3). FAB-MS: m/z 1187.8 ($[M+H]^+$, calcd. for $C_{76}H_{119}N_2O_8$: 1187.9). Anal. calcd. for $C_{76}H_{118}N_2O_8$: C 76.85, H 10.01, N 2.36; found: C 76.56, H 10.06, N 2.30%.

5,17-Diamino-25,26,27,28-tetrakis(dodecyloxy)calix[4]arene (7). A mixture of 6 (2.80 g, 2.36 mmol) and $SnCl_2 \cdot 2H_2O$ (5.32 g, 23.6 mmol) in EtOH (100 ml) was refluxed for 18 h. After allowing to cool to ambient temperature the solution was poured into ice/water and aqueous KOH (1.0 M) was added till basic pH. The resulting solution was extracted with CH_2Cl_2 (3×100 ml) and the organic layer was washed with brine (3×50 ml) and dried over Na_2SO_4 . After filtration, the solution was concentrated in vacuo to give pure 7 in a yield of 98%. 1H -NMR: δ 6.70 (d, 4 H, J 6.8 Hz, ArH), 6.65–6.55 (m, 2 H, ArH), 5.82 (s, 4 H, ArH), 4.37 and 2.95 (ABq, 8 H, J 13.3 Hz, $ArCH_2Ar$), 3.86 (t, 4 H, J 7.5 Hz, OCH_2), 3.70 (t, 4 H, J 7.1 Hz, OCH_2), 2.98 (s, 4 H, NH_2), 2.00–1.75 (m, 8 H, OCH_2CH_2), 1.50–1.15 (m, 72 H, CH_2), 0.88 (t, 12 H, J 6.5 Hz, CH_3). ^{13}C -NMR: δ 157.1, 150.0 (s, ArCO), 140.0 (s, $ArCNH_2$), 135.6, 135.4 (s, $ArCCH_2$), 128.3, 121.8, 116.0 (d, ArCH), 75.2, 75.1 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 31.1, 30.4, 30.3, 30.1, 29.9, 29.9, 29.8, 29.5, 26.5, 26.3, 22.7 (t, CH_2), 14.1 (q, CH_3). FAB-MS: m/z 1127.7 ($[M+H]^+$, calcd. for $C_{76}H_{123}N_2O_4$: 1127.9).

N,N' -[25,26,27,28-Tetrakis(dodecyloxy)calix[4]arene-5,17-diyl]bis-[1,2,3,6-tetrahydro-2,6-dioxypyrimidine-4-carboxamide] (8). To a solution of orotic acid monohydrate (1.54 g, 0.886 mmol) in dry DMF (200 ml), a solution of N,N' -carbonyldiimidazole (2.88 g, 17.7 mmol) in dry DMF (5 ml) was added. The mixture was heated to 80°C and after 30 min a solution of 7 (1.00 g, 0.886 mmol) in dry DMF (5 ml) was added via a septum. After 18 h, the reaction was cooled to room temperature and concentrated to dryness using an oil pump. The residue was taken up in $CH_2Cl_2/1N-HCl$ (300 ml/100 ml) and after separation of the layers the organic layer was washed with 1N HCl (3×150 ml) and brine (2×100 ml), dried over Na_2SO_4 , and concentrated in vacuo. After flash column chromatography ($CH_2Cl_2/MeOH$, 95/5) and precipitation from hot EtOAc, the product was obtained as a yellow solid in 16% yield; m.p. > 330°C. 1H -NMR (THF- d_6): δ 10.32 (br s, 2 H, NH), 10.14 (br s, 2 H, NH), 9.40 (s, 2 H, NH), 7.28 (s, 4 H, ArH), 6.65–6.45 (m, 6 H, ArH), 6.14 (s, 2 H, pyH), 4.55 and 3.20 (ABq, 8 H, J 13.1 Hz, $ArCH_2Ar$), 4.03 (t, 4 H, J 7.6 Hz, OCH_2), 3.95 (t, 4 H, J 7.1 Hz, OCH_2), 2.15–1.95 (m, 8 H, OCH_2CH_2), 1.65–1.2 (m, 72 H, CH_2), 0.97 (t, 12 H, J 6.5 Hz, CH_3). FAB-MS: m/z 1401.6 ($[M-H]^-$ calcd. 1401.9). Anal. calcd. for $C_{86}H_{126}N_6O_{10} \cdot 3H_2O$: C 70.85, H 9.13, N 5.76; found: C 70.61, H 8.79, N 5.62%.

25,27-Bis[(2,4-dichloropyrimidine-6-methyl)oxy]calix[4]arene (9). A mixture of 3 (3.64 g, 5.41 mmol) and $POCl_3$ (15 ml, 161 mmol) was refluxed for 2 h, producing a red solution. The excess $POCl_3$ was distilled off under reduced pressure using an oil pump. The brown residue was diluted with CH_2Cl_2 (200 ml) and poured into ice/water (200 ml). After separation of the layers, the organic layer was washed with H_2O (2×100 ml), $NaHCO_3$ (satd. aq. solution, 3×100 ml) and brine (75 ml). After drying over $MgSO_4$, the solvent was removed under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) gave a yellowish crystalline product in 59% yield; m.p. 222–224°C. 1H -NMR: δ 8.68 (s, 2 H, OH), 7.57 (s, 2 H, 5-pyH), 7.13 (d, 4 H, J 7.49 Hz, ArH), 6.96 (d, 4 H, J 7.08, ArH), 6.90–6.80 (m, 2 H, ArH), 6.80–6.70 (m, 2 H, ArH), 5.17 (s, 4 H, OCH_2), 4.20 and 3.50 (ABq, 8 H, J 13.3 Hz, $ArCH_2Ar$). ^{13}C -NMR: δ 170.6 (s, 6-pyCCH₂), 164.0 (s, 2-pyCCl), 160.5 (s, 4-pyCCl), 152.7, 151.0 (s, ArCO), 132.6, 127.5 (s, $ArCCH_2$), 129.6, 128.9, 126.5, 120.0 (d, ArCH), 117.3 (d, pyCH), 76.5 (t, OCH_2), 31.4 (t, $ArCH_2Ar$). FAB-MS: m/z 747.9 ($[M+H]^+$ calcd. 747.1). Anal. calcd. for $C_{38}H_{28}Cl_4N_4O_4$: C 61.14, H 3.78, N 7.51, Cl 19.00; found: C 61.19, H 3.72, N 7.41, Cl 18.83%.

25,27-Bis[(2,4-bis(butylamino)pyrimidine-6-methyl)oxy]calix[4]arene (10). To a solution of calix[4]arene 9 (0.30 g, 0.40 mmol) in dioxane (15 ml) was added *n*-butylamine (1.0 ml, 10 mmol). After refluxing the mixture for three days, extra *n*-butylamine (1.0 ml, 10 mmol) was added and the mixture was refluxed for another three days. The solution was then cooled to room temperature and the solvent removed under reduced pressure. The residue was taken up in CH_2Cl_2 (150 ml), and the resulting solution washed with 1N HCl (3×100 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated to dryness in vacuo. Trituration with MeOH followed by recrystallization from $CH_2Cl_2/MeOH$ gave 10 as colorless flakes in 44% yield; m.p. 143–145°C. 1H -NMR: δ 8.03 (br s, 2 H, OH), 7.07 (d, 4 H, J 7.5 Hz, ArH), 6.91 (d, 4 H, J 7.5 Hz, ArH), 6.86 (s, 2 H, 5-pyH), 6.80–6.75 (m, 2 H, ArH), 6.70–6.60 (m, 2 H, ArH), 4.83 (s, 4 H, OCH_2), 4.80–4.55 (m, 4 H, ArH), 4.34 (part of ABq, 4 H, J 13.1 Hz, $ArCH_2Ar$), 3.50–3.30 (m, 8 H, $ArCH_2Ar$ and $NHCH_2$), 3.15 (br, 4 H, $NHCH_2$), 1.65–1.15 (m, 16 H, $CH_2CH_2CH_3$), 1.05–0.70 (m, 12 H, CH_3). ^{13}C -NMR: δ 164.1, 162.3 (s, pyC), 153.3, 151.9 (s, ArCO), 133.1, 127.9 (s, $ArCCH_2$), 129.2, 128.6, 125.7, 119.2 (d, ArCH), 77.7 (t, OCH_2), 41.1 (t, $NHCH_2$), 32.1, 31.6, 31.3, 20.2, 20.2 (t, CH_2), 13.9, 13.8 (q, CH_3). FAB-MS: m/z 893.5 ($[M+H]^+$ calcd. 893.5). Anal. calcd. for $C_{54}H_{68}N_8O_4$: C 72.62, H 7.67, N 12.55; found: C 72.21, H 7.74, N 12.62%.

25,27-Dipropoxy-calix[4]arene (11a). To a suspension of 1 (8.00 g, 18.8 mmol) and K_2CO_3 (2.87 g, 20.7 mmol) in CH_3CN (135 ml) was added *n*-propyl iodide (4.0 ml, 41 mmol). The mixture was refluxed for 18 h, cooled to room temperature, and concentrated under reduced pressure. The residue was taken up in $CH_2Cl_2/1N-HCl$ (200 ml/100 ml), and after separation of the layers the organic layer was washed with 1N HCl (3×100 ml), H_2O (100 ml), and brine (100 ml), dried over $MgSO_4$ and concentrated in vacuo. Trituration with MeOH gave the pure product as a white powder in 96% yield; m.p. 250–252°C. 1H -NMR: δ 8.32 (s, 2 H, OH), 7.05 (d, 4 H, J 7.4 Hz, ArH), 6.92 (d, 4 H, J 7.5 Hz, ArH), 6.80–6.70, 6.70–6.60 (m, 2 H, ArH), 4.32 and 3.38 (ABq, 8 H, J 12.9 Hz, $ArCH_2Ar$), 3.98 (t, 4 H, J 6.2 Hz, OCH_3), 2.15–1.95 (m, 4 H, CH_2CH_3), 1.32 (t, 4 H, J 7.4 Hz, CH_3). ^{13}C -NMR: δ 153.4, 151.9 (s, ArCO), 133.5, 128.2 (s, $ArCCH_2$), 129.0, 128.5, 125.3, 119.0 (d, ArCH), 78.4 (t, OCH_2), 31.5 (t, $ArCH_2Ar$), 23.6 (t, CH_2CH_3), 11.0 (q, CH_3).

FAB-MS: m/z 508.2 (M^+ calcd. 508.3). Anal. calcd. for $C_{34}H_{36}O_4$: C 80.28, H 7.13; found: C 80.08, H 7.05%.

25,27-Bis(dodecyloxy)calix[4]arene (11b). To a suspension of **1** (5.40 g, 11.8 mmol) and K_2CO_3 (1.79 g, 13.0 mmol) in CH_3CN (200 ml) was added *n*-dodecyl bromide (4.4 ml, 26 mmol). The mixture was refluxed for four days, cooled to room temperature, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 / 1N-HCl (200 ml/100 ml), and after separation of the layers the organic layer was washed with 1N HCl (3 × 100 ml), H_2O (100 ml), and brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (CH_2Cl_2 / hexanes, 30/70) gave the pure product in 51% yield as a white powder; m.p. 112–114°C. 1H -NMR: δ 8.25 (s, 2 H, OH), 7.05 (d, 4 H, J 7.5 Hz, ArH), 6.91 (d, 4 H, J 7.5 Hz, ArH), 6.80–6.70, 6.70–6.60 (m, 2 H, ArH), 4.31 and 3.37 (ABq, 8 H, J 12.9 Hz, $ArCH_2Ar$), 3.99 (t, 4 H, J 6.7 Hz, OCH_2), 2.15–1.95 (m, 4 H, OCH_2CH_2), 1.90–1.60 (m, 4 H, $OCH_2CH_2CH_2$), 1.55–1.20 (m, 32 H, CH_2), 0.88 (t, 6 H, J 6.6 Hz, CH_3). ^{13}C -NMR: δ 153.5, 152.1 (s, ArCO), 133.5, 128.3 (s, $ArCCH_2$), 129.0, 128.5 (d, ArH), 125.4, 119.0 (d, ArH), 76.9 (t, OCH_2), 32.1, 31.6, 30.2, 29.9, 29.9, 29.7, 29.6, 26.2, 22.9 (t, CH_2), 14.3 (q, CH_3). FAB-MS: m/z 759.9 ($[M-H]^+$ calcd. 759.5). Anal. calcd. for $C_{52}H_{72}O_4$: C 82.06, H 9.53; found: C 81.88, H 9.48%.

5,17-Dibromo-25,27-dipropoxycalix[4]arene (12a). To a solution of **11a** (2.00 g, 3.93 mmol) in dry CH_2Cl_2 (100 ml) was added dropwise a solution of Br_2 (1.39 g, 8.7 mmol) in dry CH_2Cl_2 (100 ml) over $1\frac{1}{2}$ h. The reaction was stirred for an additional 15 min, and subsequently the white precipitate was filtered off and rinsed with a small amount of CH_2Cl_2 to give the product in 69% yield. The filtrate was quenched with $NaHSO_3$ (5% aq.), the layers were separated, and the organic layer was washed with $NaHSO_3$ (5% aq., 2 × 75 ml), H_2O (75 ml), and brine (75 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was triturated with CH_2Cl_2 , to yield another 14% of the product; m.p. > 330°C. 1H -NMR: δ 8.35 (s, 2 H, OH), 7.16 (s, 6 H, ArH), 6.93 (d, 4 H, J 7.4 Hz, ArH), 6.85–6.75 (m, 2 H, ArH), 4.25 and 3.32 (ABq, 8 H, J 13.0 Hz, $ArCH_2Ar$), 3.94 (t, 4 H, J 6.7 Hz, OCH_2), 2.10–1.95 (m, 4 H, OCH_2CH_2), 1.28 (t, 6 H, J 7.4 Hz, CH_3). FAB-MS: m/z 666.8 ($[M+H]^+$ calcd. 667.0). Anal. calcd. for $C_{34}H_{34}Br_2O_4$: C 61.28, H 5.14, Br 23.98; found: C 61.27, H 5.06, Br 24.22%.

5,17-Dibromo-25,27-bis(dodecyloxy)calix[4]arene (12b). To a solution of **11b** (3.74 g, 4.91 mmol) in dry CH_2Cl_2 (150 ml) was added dropwise a solution of Br_2 (1.73 g, 10.8 mmol) in dry CH_2Cl_2 (100 ml) over $1\frac{1}{2}$ h. The reaction was stirred for an additional 15 min before being quenched with $NaHSO_3$ (5% aq.). The layers were separated and the organic layer was washed with $NaHSO_3$ (5% aq., 2 × 100 ml), H_2O (100 ml), and brine (75 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give the product in quantitative yield; m.p. 155–157°C. 1H -NMR: δ 8.31 (s, 2 H, OH), 7.17 (s, 6 H, ArH), 6.93 (d, 4 H, J 7.4 Hz, ArH), 6.85–6.75 (m, 2 H, ArH), 4.25 and 3.32 (ABq, 8 H, J 13.0 Hz, $ArCH_2Ar$), 3.97 (t, 4 H, J 6.7 Hz, OCH_2), 2.10–1.95 (m, 4 H, OCH_2CH_2), 1.75–1.55 (m, 4 H, $OCH_2CH_2CH_2$), 1.55–1.15 (m, 32 H, CH_2), 0.89 (t, 6 H, J 6.6 Hz, CH_3). ^{13}C -NMR: δ 152.5, 152.0 (s, ArCO), 132.7, 130.1 (s, $ArCCH_2$), 130.7, 129.2, 125.4 (d, ArCH), 110.4 (s, $ArCBr$), 76.9 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 31.2, 30.0, 29.8, 29.7, 29.7, 29.5, 29.4, 25.9, 22.7 (t, CH_2), 14.2 (q, CH_3). FAB-MS: m/z 918.5 (M^+ calcd. 918.4). Anal. calcd. for $C_{52}H_{70}Br_2O_4 \cdot 0.4H_2O$: C 67.44, H 7.71, Br 17.26; found: C 67.12, H 7.32, Br 17.76%.

5,17-Dibromo-25,26,27,28-tetrapropoxycalix[4]arene (13a). Calix[4]arene **12a** was added to a suspension of NaH (0.75 g, 1.13 mmol, 60% in oil, washed with hexanes) in dry DMF (40 ml). After stirring at room temperature for 30 min, *n*-propyl iodide (1.0 ml, 10 mmol) was added. The reaction was stirred for 18 h at 60°C, after which it was cooled to room temperature and concentrated to dryness using an oil pump. The residue was taken up in CH_2Cl_2 / 1N-HCl (100 ml/50 ml) and after separation of the layers the organic layer was washed with 1N HCl (4 × 50 ml) and brine (50 ml). The solution was dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization from CH_2Cl_2 / MeOH yielded the pure product as a white solid in 90% yield; m.p. > 330°C. 1H -NMR: δ 6.77 (s, 4 H, ArH), 6.64 (s, 6 H, ArH), 4.40 and 3.11 (ABq, 8 H, J 13.4 Hz, $ArCH_2Ar$), 3.90–3.75 (m, 8 H, OCH_2), 2.00–1.80 (m, 8 H, OCH_2CH_2), 1.05–0.90 (m, 12 H, CH_3). ^{13}C -NMR: δ 156.4, 155.7 (s, ArCO), 137.2, 134.4 (s, $ArCCH_2$), 130.8, 128.4, 122.5 (d, ArCH), 114.7 (s, $ArCBr$), 76.9, 76.8 (t, OCH_2), 30.9 (t, $ArCH_2Ar$), 23.2 (t, CH_2CH_3), 10.3, 10.3 (q, CH_3).

5,17-Dibromo-25,26,27,28-tetrakis(dodecyloxy)calix[4]arene (13b). Calix[4]arene **12b** was added to a suspension of NaH (1.15 g, 47.9 mmol, 60% in oil, washed with hexanes) in dry DMF (200 ml). After stirring at room temperature for 30 min, *n*-dodecyl bromide (6.0 ml, 35.1 mmol) was added dropwise with a syringe via a septum. The reaction was stirred

for 18 h at 60°C after which it was cooled to room temperature and concentrated to dryness using an oil pump. The residue was taken up in CH_2Cl_2 / 1N-HCl (300 ml/100 ml) and after separation of the layers the organic layer was washed with 1N HCl (4 × 150 ml) and brine (100 ml). The solution was dried over $MgSO_4$ and concentrated *in vacuo*. Trituration with MeOH yielded the pure product as a white solid in 91% yield; m.p. 50–52°C. 1H -NMR: δ 6.76 (s, 4 H, ArH), 6.62 (s, 6 H, ArH), 4.38 and 3.09 (ABq, 8 H, J 13.4 Hz, $ArCH_2Ar$), 3.90–3.80 (m, 8 H, OCH_2), 1.95–1.80 (m, 8 H, OCH_2CH_2), 1.45–1.15 (m, 72 H, CH_2), 0.88 (t, 12 H, J 6.5 Hz, CH_3). ^{13}C -NMR: δ 156.4, 155.8 (s, ArCO), 137.3, 134.4 (s, $ArCCH_2$), 130.8, 128.4 (d, ArCH), 122.5 (d, ArCH), 114.8 (s, $ArCBr$), 75.4, 75.3 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 30.91, 30.32, 30.0, 29.9, 29.8, 29.5, 26.4, 22.8 (t, CH_2), 14.2 (q, CH_3). FAB-MS: m/z 1255.2 ($[M+H]^+$ calcd. 1255.7). Anal. calcd. for $C_{76}H_{118}Br_2O_4$: C 72.70, H 9.47; found: C 73.02, H 9.75%.

5,17-Dicyano-25,26,27,28-tetrapropoxycalix[4]arene (14a). A solution of **13a** (0.70 g, 0.93 mmol) and CuCN (0.33 g, 3.7 mmol) in *N*-methylpyrrolidone (20 ml) was refluxed for 18 h. The reaction was cooled to 100°C, a solution of $FeCl_3$ (hexahydrate, 1.0 g, 3.7 mmol) in 3N HCl (20 ml) was added and the mixture was stirred at 100°C for 1 h. After cooling the mixture to room temperature and stirring it for 2 h the precipitate was filtered off and rinsed thoroughly with H_2O . The residue was dissolved in CH_2Cl_2 (100 ml) and the obtained solution was washed with H_2O (3 × 50 ml) and brine (50 ml). After drying over $MgSO_4$ the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 / hexanes, 90/10) to give **14a** as a white crystalline powder in 85% yield; m.p. 304–306°C. 1H -NMR: δ 6.82 (s, 4 H, ArH), 6.76 (s, 4 H, ArH), 4.43 and 3.17 (ABq, 8 H, J 13.6 Hz, $ArCH_2Ar$), 3.90–3.75 (m, 8 H, OCH_2), 2.00–1.80 (m, 8 H, CH_2CH_3), 1.03, 0.93 (t, 6 H, J 6.5 Hz, CH_3). ^{13}C -NMR: δ 160.0, 156.5 (s, ArCO), 136.2, 134.6 (s, $ArCCH_2$), 132.0, 128.8, 122.9 (d, ArCH), 119.0 (s, $C\equiv N$), 105.7 (s, CCN), 77.2, 76.8 (t, OCH_2), 30.7 (t, $ArCH_2Ar$), 23.3, 23.1 (t, CH_2), 10.4, 10.1 (q, CH_3). FAB-MS: m/z 643.1 ($[M+H]^+$ calcd. 643.3). IR (KBr): 2224 cm^{-1} ($C\equiv N$). Anal. calcd. for $C_{42}H_{46}N_2O_4$: C 78.47, H 7.21, N 4.36; found: C 78.55, H 7.40, N 4.31%.

5,17-Dicyano-25,26,27,28-tetrakis(dodecyloxy)calix[4]arene (14b). A solution of **13b** (3.00 g, 2.39 mmol) and CuCN (0.90 g, 10.5 mmol) in *N*-methylpyrrolidone (90 ml) was refluxed during 18 h. After the reaction was cooled to 100°C, a solution of $FeCl_3$ (hexahydrate, 2.84 g, 10.5 mmol) in 3N HCl (90 ml) was added and the mixture was stirred at 100°C for 1 h. After cooling the mixture to room temperature and stirring it for 2 h, the precipitate was filtered off and rinsed thoroughly with H_2O . The residue was dissolved in CH_2Cl_2 (200 ml) and the obtained solution was washed with H_2O (3 × 150 ml) and brine (100 ml). After drying over $MgSO_4$ the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 / hexanes, 80/20) to give **14b** as a white crystalline powder in 75% yield; m.p. 124–125°C. 1H -NMR: δ 6.82 (s, 4 H, ArH), 6.74 (s, 4 H, ArH), 4.42 and 3.16 (ABq, 8 H, J 13.6 Hz, $ArCH_2Ar$), 3.95–3.80 (m, 8 H, OCH_2), 1.95–1.75 (m, 8 H, OCH_2CH_2), 1.50–1.15 (m, 72 H, CH_2), 0.88 (t, 12 H, J 6.5 Hz, CH_3). ^{13}C -NMR: δ 160.0, 156.5 (s, ArCO), 136.2, 134.6 (s, $ArCCH_2$), 132.0, 128.8 (d, ArCH), 122.9 (d, ArCH), 119.0 (s, CN), 105.7 (s, CCN), 75.7, 75.3 (t, OCH_2), 32.0 (t, $ArCH_2Ar$), 30.7, 30.3, 30.2, 30.0, 29.9, 29.8, 29.7, 29.4, 26.3, 26.2, 22.7 (t, CH_2), 14.1 (q, CH_3). FAB-MS: m/z 1148.6 ($[M+H]^+$ calcd. 1148.9). IR (KBr): 2225 cm^{-1} ($C\equiv N$). Anal. calcd. for $C_{78}H_{118}N_2O_4$: C 81.62, H 10.36, N 2.44; found: C 81.52, H 10.49, N 2.47%.

5,17-Bis(4,6-diamino-1,3,5-triazine-2-yl)tetrapropoxycalix[4]arene (15a). To a solution of KOH (0.70 g, 12.5 mmol) and dicyanodiamide (6.50 g, 77.3 mmol) in 2-(2-methoxyethoxy)ethanol (30 ml) was added **14a** (0.50 g, 0.78 mmol). The reaction was stirred for 8 days at 120°C, and after cooling to room temperature the precipitate was filtered off, and rinsed with H_2O . The residue was stirred in H_2O at 80°C for three hours, whereupon the suspension was filtered while still hot. The residue was rinsed thoroughly with hot H_2O , dried over P_2O_5 and recrystallized from THF to give **15a** as a white solid in 68% yield; m.p. > 335°C. 1H -NMR (THF- d_6): δ 8.08 (s, 4 H, ArH), 6.73 (br s, 8 H, NH_2), 6.25–6.15 (m, 2 H, ArH), 6.09 (d, 4 H, J 7.5 Hz, ArH), 4.42 and 3.24 (ABq, 8 H, J 13.2 Hz, $ArCH_2Ar$), 4.08 (t, 4 H, J 8.0 Hz, OCH_2), 3.66 (t, 4 H, J 6.4 Hz, OCH_2), 2.08–1.80 (m, 8 H, CH_2CH_3), 1.11 (t, 6 H, J 7.4 Hz, CH_3), 0.91 (t, 6 H, J 7.5 Hz, CH_3). ^{13}C -NMR (THF- d_6): δ 170.3 (s, CN_2), 167.4 (s, CCN), 160.2, 154.7 (s, ArCO), 135.9 (s, ArCCN), 132.5, 130.7 (s, $ArCCH_2$), 128.5, 127.1 (d, ArCH), 121.8 (d, ArCH), 76.7, 76.1 (t, OCH_2), 30.4 (t, $ArCH_2Ar$), 23.1, 22.7 (t, CH_2CH_3), 10.7, 9.7 (q, CH_3). FAB-MS: m/z 811.5 ($[M+H]^+$ calcd. 811.4). Anal. calcd. for $C_{46}H_{54}N_{10}O_4 \cdot 0.5H_2O$: C 67.38, H 6.64, N 17.08; found: C 67.19, H 6.74, N 17.28%. Karl–Fischer titration calcd. for 0.5 H_2O : 1.10; found: 1.10%.

5,17-Bis(4,6-diamino-1,3,5-triazine-2-yl)tetrakis(dodecyloxy)calix[4]-arene (**15b**). To a solution of KOH (1.00 g, 17.8 mmol) and dicyanodiamide (4.00 g, 48 mmol) in 2-(2-methoxyethoxy)ethanol (100 ml) was added **14b** (1.10 g, 0.96 mmol). The reaction was stirred for two days at 120°C and, after cooling to room temperature, the precipitate was filtered off and rinsed with H₂O. The residue was stirred in H₂O at 80°C for three hours, whereupon the suspension was filtered while still hot. The residue was rinsed thoroughly with hot H₂O and dried over P₂O₅ yielding the pure product as a white solid in 83%; m.p. 290°C (dec.). ¹H-NMR (THF-*d*₆): δ 8.20 (s, 4 H, ArH), 6.11 (s, 4 H, ArH), 5.98 (br s, 8 H, NH₂), 4.51 and 3.20 (ABq, 8 H, J 13.1 Hz, ArCH₂Ar), 4.23 (t, 4 H, J 8.4 Hz, OCH₂), 3.72 (t, 4 H, J 7.1 Hz, ArCH₂Ar), 2.15–1.85 (m, 8 H, OCH₂CH₂), 1.70–1.20 (m, 72 H, CH₂), 0.95–0.85 (m, 12 H, CH₃). ¹³C-NMR (THF-*d*₆): δ 173.5 (s, CNH₂), 170.6 (s, CNC), 162.9, 157.4 (s, CO), 138.6 (s, CCNC), 135.0, 133.6 (s, CCH₂), 131.4, 129.8 (d, ArCH), 124.3 (d, ArCH), 77.6, 77.4 (t, OCH₂), 15.9 (q, CH₃). FAB-MS: *m/z* 1316.5 ([M+H]⁺ calcd. 1316.0). Anal. calcd. for C₈₂H₁₂₆N₁₀O₄: C 74.84, H 9.65, N 10.64; found: C 74.73, H 9.82, N 10.63%.

N,N',N'',N'''-[(25,26,27,28-Tetrapropoxycalix[4]arene-5,17-diyl)di-1,3,5-triazine-6,2,4-triyl]tetrakis[hexanamide] (**16**). To a solution of **15a** (0.20 g, 0.25 mmol) and 4-(dimethylamino)pyridine (0.05 g, 0.4 mmol) in dry pyridine (20 ml) was added hexanoyl chloride (0.8 ml, 5 mmol) with a syringe via a septum, and the solution was stirred at 70°C for three days. After cooling the reaction mixture to room temperature it was poured into CH₂Cl₂ (100 ml). The resulting solution was washed with 1N HCl (5 × 100 ml), and brine (50 ml), dried over MgSO₄, and concentrated to dryness under reduced pressure. The product was recrystallized twice from CH₂Cl₂/MeOH to give **16** in 50% yield; m.p. 293–295°C. ¹H-NMR (CD₂Cl₂): δ 9.95 (br s, 4 H, NH), 7.12 (d, 4 H, J 7.1 Hz, ArH), 7.09 (s, 4 H, ArH), 7.00–6.90 (m, 2 H, ArH), 4.44 and 3.16 (ABq, 8 H, J 13.6 Hz, ArCH₂Ar), 4.00 (t, 4 H, J 8.8 Hz, OCH₂), 3.64 (t, 4 H, J 6.7 Hz, OCH₂), 3.10–2.40 [m, 8 H, C(O)CH₂], 1.95–1.75 (m, 8 H, OCH₂CH₂), 1.66 [br s, 8 H, C(O)CH₂CH₂], 1.45–1.30 (m, 24 H, CH₂), 1.04 (t, 6 H, J 7.4 Hz, OCH₂CH₂CH₃), 0.90 (t, 12 H, J 6.9 Hz, CH₃), 0.82 (t, 6 H, J 7.5 Hz, OCH₂CH₂CH₃). FAB-MS: *m/z* 1203.7 ([M+H]⁺ calcd. 1203.7). IR (KBr): 3256 cm⁻¹ (N-H), 1692 cm⁻¹ (C=O). Anal. calcd. for C₇₀H₉₄N₁₀O₈·0.5H₂O: C 69.34, H 7.90, N 11.55; found: C 69.44, H 7.88, N 11.78%.

Transmission electron microscopy

To a vial containing 5 μmol of **15b** was added 1.00 ml of a 5 mM solution of **17** in CDCl₃ and the mixture was slightly warmed until all the **15b** had dissolved. A drop of the viscous solution was applied to a carbon-coated copper grid and the solvent was allowed to evaporate. Subsequently the grid was shadowed with platinum and the sample was studied by transmission electron microscopy.

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