Covalent Linkage of Melamine and Cyanurate Improves the Thermodynamic Stability of Hydrogen-Bonded Double Rosettes in Polar Solvents

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This paper describes studies on the synthesis, self-assembly behavior, and thermodynamic stabilities of eight different calix[4]arene di(melamine-cyanurate) or di(melamine-barbiturate) conjugates. The successful synthetic strategy comprises the preparation of amino-*n*-alkyl-functionalized calix[4]arene dimelamines coupled with a carboxyl-functionalized cyanurate or barbiturate by an amide bond-forming reaction. ^{1}H NMR experiments show that three of the eight conjugates form well-defined double rosette assemblies. DMSO titration experiments illustrate that the covalent linkage between the cyanurate and dimelamine moieties produces a significant increase in the thermodynamic stabilities of these conjugates. The relative stability of the assemblies seems to be primarily governed by the structure of the component connecting the melamine and cyanurate units. The highest stability (χ_{DMSO} = 70%) was observed for the di(melamine-cyanurate) assembly in which the components are connected through an *n*-heptylamidomethyl linker. Increasing the linker size from *n*-heptylamidomethyl to *n*-decylamidomethyl slightly reduced the thermodynamic stability ($\Delta\chi_{DMSO} \approx 10\%$) of the corresponding double rosette assembly. The thermodynamic stability of the double rosette structure decreases drastically, however, on introduction of substituents at the position α to the methylcarbonyl group. With benzyl substituents (based on D-phenylalanine), neither the *n*-heptyl- nor the *n*-decylamidomethyl-linked compounds any longer form the double rosette structure in solution. For the conjugates with a methyl substituent at this position (based on L-alanine), only the heptyl-linked compound still forms the double rosette structure, the χ_{DMSO} value being reduced in this case by 15%. Neither of the di(melamine-barbiturate) conjugates form double rosette structures at all.

Introduction

During the last decade, the self-assembly of small molecular entities into larger, well-defined structures[1−4] has been intensively studied for the design of artificial receptors[5−8] and novel materials.[9−11] Apart from metal-coordinated assemblies,[12,13] the majority of self-assembled structures are held together by relatively weak interactions,[14] such as hydrogen bonding,[15−18] van der Waals interactions,[19,20] and electrostatic interactions.[21] One major drawback of supramolecular architectures based on hydrogen bonding is their inherently low stability in polar solvents.[22,23] However, examples of supramolecular structures stable in more polar solvents such as DMSO and water have been reported,[24−29] but most of them involve a combination of hydrogen bonding with electrostatic interactions.[30−33]

We are currently exploring different strategies to increase the thermodynamic stabilities of calix[4]arene double rosette assemblies $\mathbf{1}_3$·(DEB)$_6$ or $\mathbf{1}_3$·(CYA)$_6$ (see Figure 1) in polar solvents.[34] These strategies have in common that they stabilize the hydrogen-bonded assemblies by increasing the I_{Tm} value (I_{Tm} = HB/N − 1): the number of hydrogen bonds (HB) per components (N).[24] Previous studies in our group have shown that these assemblies are stable in apolar solvents such as chloroform, benzene, and toluene,[4,35] but tend to dissociate in the presence of small amounts of polar solvent such as DMSO.[36] The first strategy, which is described elsewhere,[37] is based on the covalent linkage of multiple melamines, resulting in the synthesis of tetra- (I_{Tm} = 5.1) and hexamelamines (I_{Tm} = 5.4). The resulting tetra- and hexarosette assemblies, possessing 72 and 108 hydrogen bonds, respectively, express much higher stabilities than the corresponding double rosettes in the presence of polar solvents, in particular MeOH. In this paper we describe a slightly different approach, based on reducing the total number of particles (N) in the assembly while keeping the number of hydrogen bonds (HB) constant. Our approach has produced a new type of hydrogen-bonded assemblies, achieved practically through covalent connection of the cyanuric or barbituric acid residues to the melamine units by means of a flexible linker (Figure 1). We have used linkers of variable size and rigidity and studied their influ-

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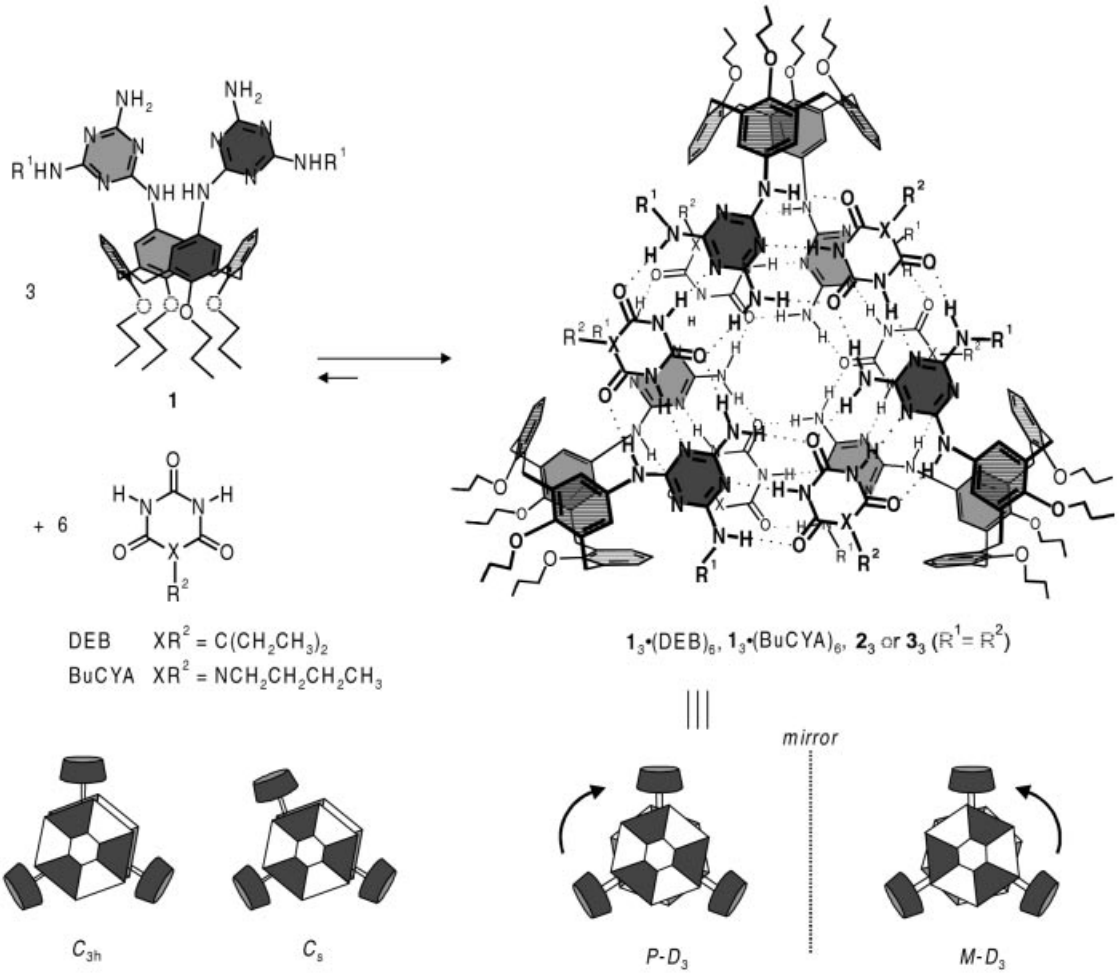


Figure 1. Molecular structure and schematic representations of the nine-component double rosette assemblies $\mathbf{1}_3$·(DEB)$_6$ and $\mathbf{1}_3$·(BuCYA)$_6$ and the three-component assemblies $\mathbf{2}_3$ and $\mathbf{3}_3$, together with all possible isomeric conformations

ence on the thermodynamic stabilities of the corresponding assemblies by DMSO titrations monitored by ^{1}H NMR and CD spectroscopy.

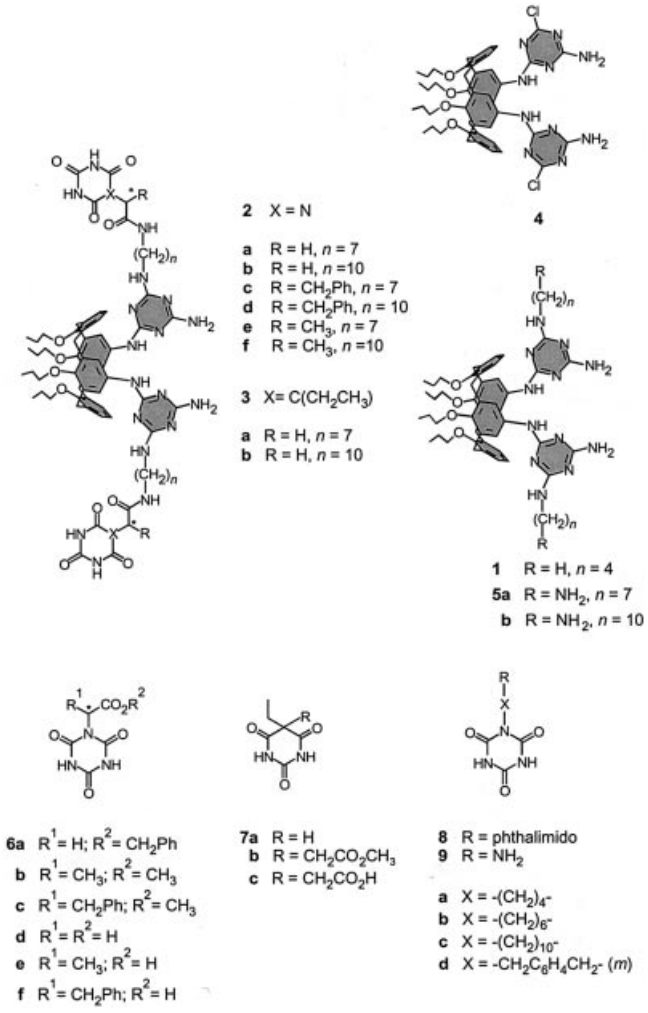
Results and Discussion

Synthesis of Di(melamine-cyanurate) and Di(melamine-barbiturate) Conjugates 2 and 3

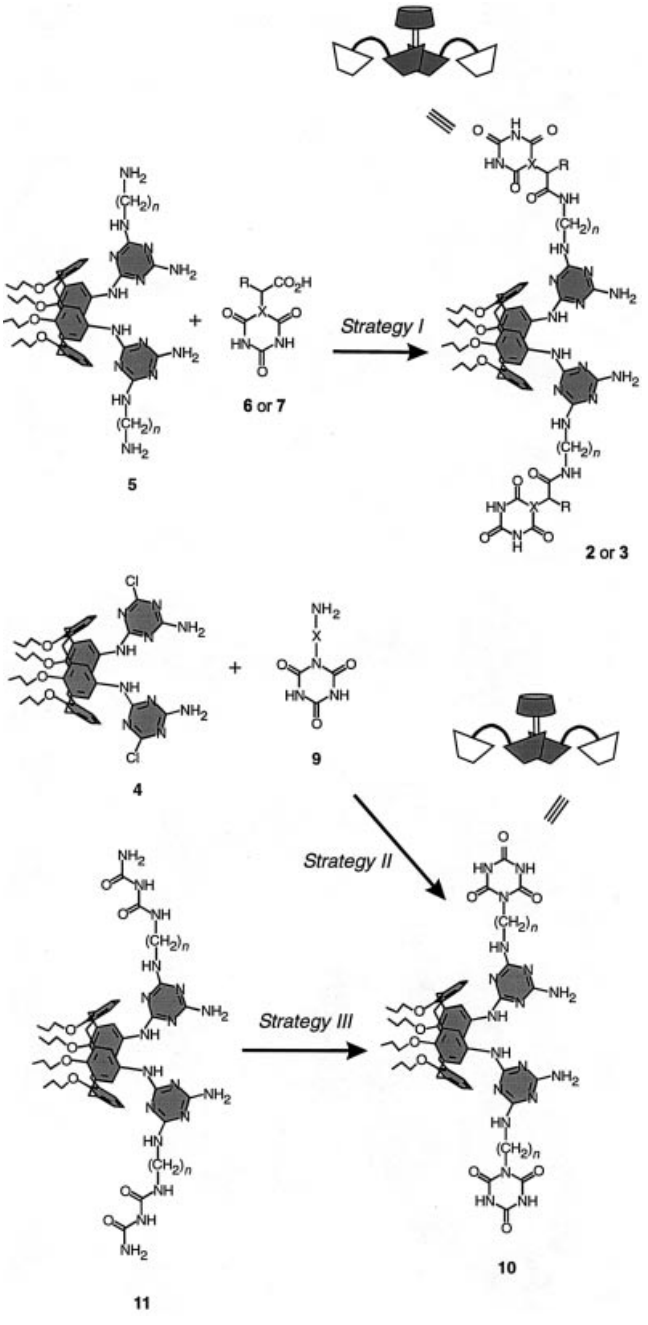
Three different synthetic strategies for the covalent connection of cyanuric or barbituric acids to calix[4]arene dimelamines were investigated (Scheme 1). The most general and successful strategy (I) is an amide coupling reaction between the diamino dimelamines **5** and the carboxyl-functionalized cyanurates **6d**−**f** or the barbiturate **7c** (Scheme 1). The diamino dimelamines **5a** and **5b** were obtained in good yields (85−90%) from bis(chlorotriazine) **4**[35] by treatment with excess 1,7-diaminoheptane or 1,10-diaminodecane in THF. Cyanurate **6d** was synthesized by treatment of cyanuric acid with benzyl 2-bromoacetate and DBU in DMF to give the benzyl ester **6a** in 33% yield.[38] Saponification of **6a** with NaOH gave the corresponding acid **6d** in 100% yield. Cyanurates **6e** and **6f** were prepared from L-alanine methyl ester and D-phenylalanine methyl ester. The first step involves the conversion of the amino function into a cyanurate unit by treatment with *N*-chlorocarbonyl isocyanate in THF according to the procedure reported by Kunitake (42 and 62% yields, respectively).[39] Subsequent hydrolysis of the resulting methyl esters **6b** and **6c** with NaOH gave the corresponding carboxylic acid derivatives **6e** and **6f** in 100% yields. Barbiturate **7c** was prepared from 5-ethylbarbituric acid (**7a**)[40,41] by treatment with methyl bromoacetate and triethanolamine in H_2O (45% yield).[42] The resulting ester **7b** was saponified by treatment with NaOH to give **7c** in 100% yield.

Finally, the amide coupling reactions between **5** and **6d**−**f** or **7c** were performed with the aid of *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and triethylamine in DMF/THF to give the di(melamine-cyanurates) **2** and di(melamine-barbiturates) **3**, all of which were fully characterized, in excellent yields (87−100%).

Two other strategies for the coupling of cyanurates to calix[4]arene dimelamines were also investigated (Scheme 1). Strategy II involves treatment of bis(chlorotriazine) **4** with amino-functionalized cyanurates **9a**−**d**.[35] The cyan-



urates were prepared in two steps starting from cyanuric acid. Treatment of cyanuric acid with the corresponding bromophthalimides in the presence of DBU in DMF gave the phthalimido-substituted cyanurates **8a**−**d** in 15−31% yields.[39] Removal of the phthalimide groups by treatment with CH_3NH_2 in EtOH (33%) gave the amino-functionalized cyanurates **9a**−**d** in 85−100% yields. The coupling reactions between **4** and **9a**−**d** proved to be very difficult because compounds **9a**−**d** are not very soluble even in DMSO or DMPU at elevated temperatures. Only in the case of the aminohexyl-substituted cyanurate **9b** was the desired product **10** obtained, in 22% yield. The very low solubilities and reactivities of these derivatives are most probably due to the formation of zwitterions ($pK_{a,cyanurate}$ = 6.2 and $pK_{a,amine}$ = 10.0),[43] in combination with the intrinsically low solubilities of cyanurate derivatives. To overcome this solubility problem, a different strategy (III) was investigated, starting from amino-functionalized dimelamine **5b**. Introduction of the cyanurate function was attempted by the procedure developed by Whitesides.[18,44] The first step involves treatment of **5b** with nitrobiuret to give biuret derivative **11** (n = 10) in 92% yield. Attempted ring closure of this compound by treatment with diethyl carbonate, either with NaH_2PO_4 or with NaOEt as a base, did not result in the formation of the desired compound **10** (n = 10). We attribute this failure to secondary reactions taking



Scheme 1. Different synthetic strategies (I−III) for the preparation of di(melamine-cyanurate) and di(melamine-barbiturate) conjugates

place at the amino functionalities present in the two melamine units in **5b**.

Noncovalent Synthesis of Stabilized Double Rosette Assemblies 2_3 and 3_3

We first investigated the assembly behavior of di(melamine-cyanurate) conjugates **2a** and **2b**, in which the melamine and cyanurate units are linked either through an *n*-heptylamidomethyl (n = 7) or through a *n*-decylamidomethyl (n = 10) spacer, by ^{1}H NMR spectroscopy. The conjugates are scarcely soluble in neat $CDCl_3$, which prevented

^{1}H NMR measurements in this solvent, but the formation of double rosette assemblies **2a**$_3$ and **2b**$_3$ was clearly observed in $CDCl_3$/[D_6]DMSO (9:1, v/v). Two sharp signals were observed at δ = 13.97 and 14.85 ppm for **2a**$_3$ and at δ = 14.08 and 14.62 ppm for **2b**$_3$ (Figure 2a,b), which is highly characteristic of double rosette formation.[35] The presence of only two peaks in the δ = 13−16 ppm region clearly indicates that the chiral D_3 isomer (see Figure 1) is formed exclusively. Previous work in our group has shown that the D_3 isomer is the only one formed with barbiturates and alkyl-substituted cyanurates.[45] If all three isomers (D_3, C_{3h}, C_s, see Figure 1) had been formed, at least 10 separate signals should have been observed in this region.

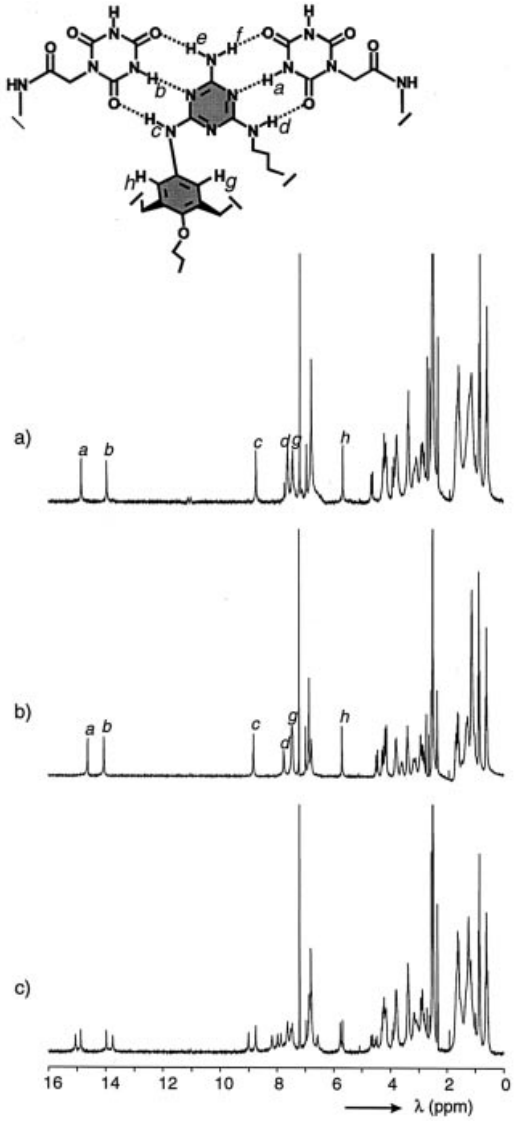


Figure 2. ^{1}H NMR spectra of double rosette assemblies: a) **2a**$_3$ (at thermodynamic equilibrium), b) **2b**$_3$, c) **2a**$_3$ at t = 0 s; all spectra were recorded in $CDCl_3$/[D_6]DMSO (9:1, v/v)

To evaluate the effect of covalently linking the melamine and cyanurate units we compared the thermodynamic stabilities of the three-component assemblies **2a**$_3$ and **2b**$_3$ with that of the 9-component assembly **1**$_3$·(BuCYA)$_6$. We therefore measured the ratio of free and assembled conjugate **2** as a function of the percentage of DMSO in the sample by $CHCl_3$/DMSO titration experiments. From the titration curves, we can extrapolate the so-called χ_{DMSO} values (the mol fraction of [D_6]DMSO in $CDCl_3$ at which 50% of the assembly has decomposed into the free components[24]) for each assembly and use them to compare the thermodynamic stabilities. The percentage of assembly formation was determined by comparison of the integrals for various characteristic ^{1}H NMR signals (for details see Exp. Sect.). The results are depicted in Figures 3 and 4 and summarized in Table 1.

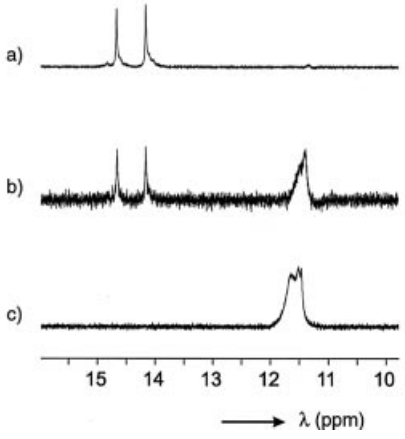


Figure 3. DMSO titration for assembly **2b**$_3$ in $CDCl_3$: a) 50%, b) 60%, and c) 70% [D_6]DMSO in $CDCl_3$; the disassembly of **2b**$_3$ is characterized by the disappearance of the NH proton signals at δ = 14.08 and 14.62 ppm and the appearance of the broad signal around δ = 11.5 ppm

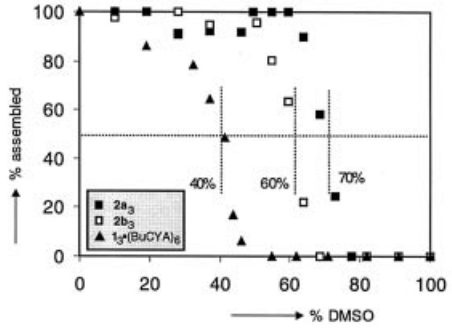


Figure 4. Graphical representation of the results of ^{1}H NMR DMSO titration experiments for double rosette assemblies **2a**$_3$, **2b**$_3$, and **1**$_3$·(BuCYA)$_6$

Table 1. χ_{DMSO} values for three- and nine-component hydrogen-bonded assemblies

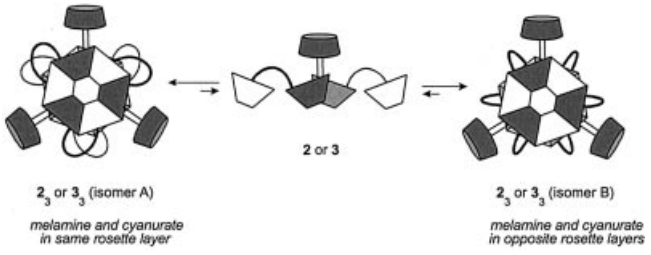
χ_{DMSO} values (%)	**1**$_3$·(CYA)$_6$	**2a**$_3$	**2b**$_3$	**2e**$_3$
NMR	40	70	60	55
CD	–	–	–	57

As would be expected, the three-component di(melamine-cyanurate) assemblies **2a**$_3$ (χ_{DMSO} = 70%) and **2b**$_3$ (χ_{DMSO} = 60%) exhibit thermodynamic stabilities signifi-

cantly higher than that of the nine-component assembly $\mathbf{1}_3$·(BuCYA)$_6$ (χ_{DMSO} = 40%). The observed increase in stability is reasonable (30 and 20% for $\mathbf{2a}_3$ and $\mathbf{2b}_3$) but does not follow the predicted fourfold increase in the I_{Tm} value [18 for $\mathbf{2a}_3$ and $\mathbf{2b}_3$ versus 4.5 for $\mathbf{1}_3$·(BuCYA)$_6$], which emphasizes the fact that the I_{Tm} value is a qualitative rather than a quantitative predictor. Nevertheless, some conformation penalties should also be expected, because the chains linking the rosette components cannot diverge outward to adopt the preferred all-*anti* arrangement. Furthermore, there is a clearcut influence of spacer flexibility. On an increase in the spacer length from heptyl to decyl the assembly stability decreases by about 10%. This suggests that shortening of the spacer should make the assembly even more stable. However, molecular models suggest that assembly formation with very short spacers is sterically impossible. The ^{1}H NMR spectrum of conjugate **10** (*n*-hexyl spacer, n = 6), for example, did not show any kind of evidence of formation of the proposed double rosette structure either in $CDCl_3$ or $CDCl_3$/[D_8]THF mixtures, most probably due to the very short spacer.

In order to confirm the improved stabilities of aggregates $\mathbf{2a}_3$ and $\mathbf{2b}_3$ with respect to that of assembly $\mathbf{1}_3$·(BuCYA)$_6$ we studied whether BuCYA has the ability to compete in assembly formation. BuCYA was added both before (direct method) and after (indirect method) the formation of assemblies $\mathbf{2a}_3$ and $\mathbf{2b}_3$ in order to rule out any favorable kinetic factors in this experiment. It was found that addition of 2 equiv. of BuCYA to either assembly in $CDCl_3$/[D_6]DMSO (9:1) did not result in the formation of mixed rosette assemblies. This experiment clearly shows that intramolecular complexation of the cyanurates that are linked to the melamines is energetically by far the more favorable.

During our studies we found that the ^{1}H NMR spectra of assemblies $\mathbf{2a}_3$ and $\mathbf{2b}_3$ are strongly dependent on the mode of preparation of the NMR samples (see Figure 2a and c for comparison). When the conjugate **2a** or **2b** is dissolved in $CDCl_3$/[D_6]DMSO (9:1, v/v) and subsequently heated for 5−10 min, the spectrum shows only one set of signals (i.e., only two peaks in the δ = 13−16 ppm region). However, when the ^{1}H NMR spectrum is run *without prior heating* of the sample, two additional signals are observed at δ = 13.77 and 15.05 ppm for $\mathbf{2a}_3$ and at δ = 13.85 and 14.85 ppm for $\mathbf{2b}_3$ (see Figure 2c). The presence of these additional signals corresponds to the initial formation of two different isomeric assemblies (isomers A and B, see Scheme 2), the result of the fact that the cyanurate fragments connected to the melamines can participate either in the same or in the opposite rosette layer. The isomers are formed in almost equal amounts, which shows that they are formed equally rapidly under these conditions. However, evolution of the isomer mixture over time at room temperature (or by heating the sample at 55 °C for a short time) results in complete conversion into one single isomer (Figure 2a and b). This clearly shows that the assemblies are kinetically not inert and that they still form in a reversible manner through breaking and reforming of multiple hydrogen bonds. The isomerization process is significantly faster



Scheme 2. Formation of two different isomers (A and B) for the self-assembly of the 3-component double-rosette assemblies $\mathbf{2}_3$ and $\mathbf{3}_3$

for assembly $\mathbf{2b}_3$ (ca. 15 h at room temperature) than for assembly $\mathbf{2a}_3$ (ca. 4 d at room temperature), which reflects the lower rate of dissociation and the higher thermodynamic stability of $\mathbf{2b}_3$. Assemblies $\mathbf{2a}_3$ and $\mathbf{2b}_3$ are perfectly stable over time in $CHCl_3$/DMSO (9:1) (100% assembly after heating the samples at 55 °C for 5 d).

The two isomers are most probably energetically different, but it is hard to predict a priori which one should be the more stable. Molecular simulations for assembly $\mathbf{2a}_3$ show that both topologies (isomers A and B, see Figure 5) can be adopted by the spacer without destroying the rosette motif. However, the calculated energy difference for the minimized structure in the gas phase is significant (15 kcal/mol), with isomer B being the more stable structure. This may suggest that isomer B represents the thermodynamic product, but it should be borne in mind that these studies were performed in vacuo. The presence of solvent molecules, particularly in the first solvation shell, can drastically alter the energetics of the system. It was also experimentally shown by different experiments that isomer B was the more stable isomer in solution.

The 1D ^{1}H NMR spectra (Figure 3a,b) each clearly show one set of peaks, indicating one isomer. Since the two isomers have exactly the same symmetry (D_3), the ^{1}H NMR spectrum would display the same number of signals in the 1D ^{1}H NMR spectrum for either isomer A or B. The identity of the isomer cannot therefore be determined by simple 1D NMR spectroscopy, and so 2D NMR spectroscopy was applied. With the aid of some measured distances for isomers A and B in the minimized structures (see Figure 5), we were able to use some key NOE cross-peaks in the 2D 1H-1H NOESY spectrum to rule out the existence of isomer A: (i) a strong NOE connectivity between H_g and NCH_2CH_2 for $\mathbf{2a}_3$ is consistent with the corresponding significantly shorter distance in isomer B (2.5 Å) than in isomer A (3.8 Å), and (ii) the absence of NOE cross-peaks between H_g and $NCH_2C(=O)$ and between the chain CH_2 protons (δ = 1.3−1.7 ppm) and the aromatic protons at δ = 7.0 ppm also corresponds much better with the measured distances in isomer B (> 5 Å and > 4.5 Å) than with those in isomer A (2.5−3.5 Å and 3−4 Å). Finally, the observation that the thermodynamic stabilities of assemblies $\mathbf{2}_3$ are very sensitive to the presence of R substituents at the α-carbon atom of the cyanurate moiety (vide infra) is fully in accordance with the formation of isomer B, as these sub-

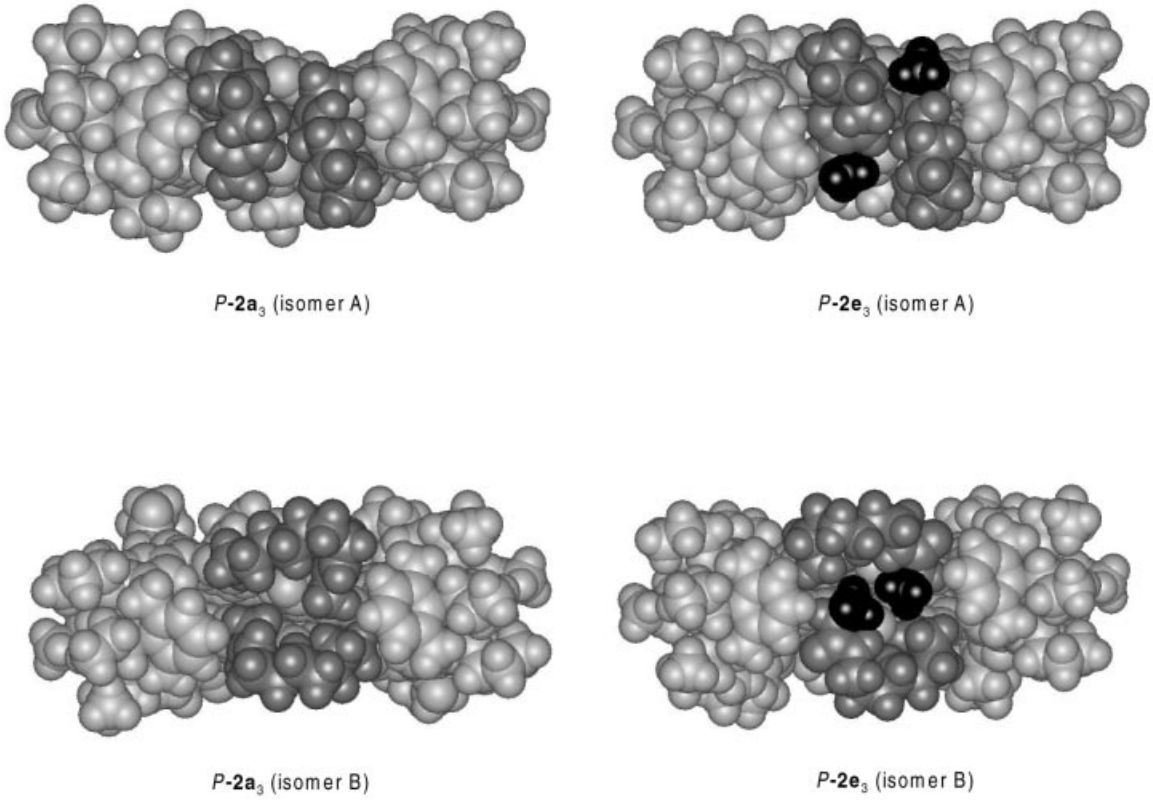


Figure 5. Gas-phase-minimized structures of both isomers (A and B) of assemblies $\mathbf{2a}_3$, and $\mathbf{2e}_3$; these structures clearly illustrate the very different environments that the methyl (**2e**) substituents experience in the two isomers

stituents are located in a sterically congested part of the assembly in this isomer. The gas-phase-minimized structure for assembly $\mathbf{2e}_3$ clearly shows that these substituents are located on the outside of the assembly in the case of isomer A (see Figure 5), unlikely to cause any steric clutter, while in the case of isomer B they are located in a more shielded region of the assembly and are likely to cause severe steric hindrance.

We next studied the self-assembly behavior of the D-phenylalanine derivatives **2c** ($n = 7$) and **2d** ($n = 10$) and the L-alanine derivatives **2e** ($n = 7$) and **2f** ($n = 10$). Each of these conjugates has an R substituent at the α-carbon atom of the cyanurate moiety, differing in size from R = methyl (**2e** and **2f**) to R = benzyl (**2c** and **2d**). To our surprise it was found that only the ^{1}H NMR spectrum of the conjugate **2e** in $CDCl_3$/[D_6]DMSO (9:1) clearly indicated formation of a well-defined assembly $\mathbf{2e}_3$, characterized by two peaks at $\delta = 13.88$ and 14.63 ppm (Figure 6a). No formation of two different isomers (A and B) was observed for assembly $\mathbf{2e}_3$, most probably the result of chiral induction by the alanine groups (vide infra). In sharp contrast to this, the ^{1}H NMR spectrum of **2f** in $CDCl_3$/[D_6]DMSO (9:1, v/v) exhibited broad signals in the $\delta = 13-16$ ppm region even after the sample had been heated at 55 °C for 24 h, which is most probably due to the formation of oligomeric assemblies. The broad ^{1}H NMR spectra observed for conjugates **2c** and **2d** did not show any kind of signal in the $\delta = 13-16$ ppm region. It is not clear whether this indicates that no hydrogen bonding takes place, or whether there is extensive exchange between different protons.

The thermodynamic stability of chiral assembly $\mathbf{2e}_3$ was determined by DMSO titration experiments monitored both by ^{1}H NMR and by CD spectroscopy (Figures 6 and 7). The latter technique makes use of the fact that chiral double rosette assemblies are strongly active in circular dichroism ($\Delta\varepsilon_{max} \approx 100$ cm^2·mmol^{-1}), while the individual components are CD-inactive.[46] The observed CD signal is therefore a direct measure of assembly formation and can be used to study the thermodynamic stabilities of these assemblies. The CD spectrum of assembly $\mathbf{2e}_3$ shows a positive curve, which is fully in accordance with earlier observations that (*S*)-cyanurates induce (*M*) helicity in the assembly. The titration curves obtained by ^{1}H NMR and CD spectroscopy are very similar in shape, and both techniques give almost identical χ_{DMSO} values (55 vs. 57%, see Figure 7b). Comparison of these values with that found for assembly $\mathbf{2a}_3$ ($\chi_{DMSO} = 70\%$) made us conclude that the introduction of a methyl group at the α-position of the cyanurate reduces the stability by 13−15%.

Finally, we investigated the assembly behavior of the di(melamine-barbiturate) conjugates **3a** and **3b**, possessing either an *n*-heptylamidomethyl ($n = 7$) or an *n*-decylamidomethyl ($n = 10$) linker unit. The very low solubility of these compounds in pure $CDCl_3$ prevented a detailed NMR study in this solvent. The ^{1}H NMR spectrum of **3a** in $CDCl_3$/[D_6]DMSO (9:1) is broad and shows no proton sig-

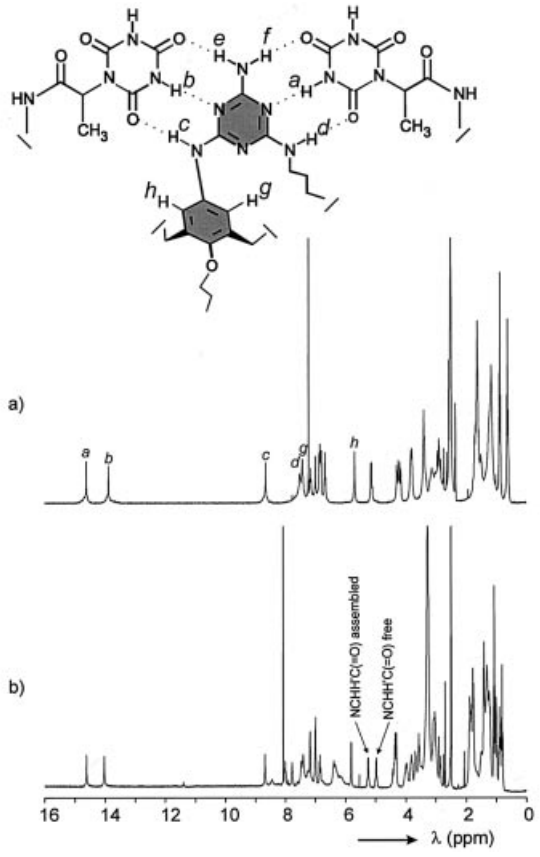


Figure 6. ^{1}H NMR spectra for double rosette assemblies **2e**$_3$ in: a) $CDCl_3$/[D_6]DMSO (9:1), b) $CDCl_3$/[D_6]DMSO (45:55); the latter shows the coexistence of assembly **2e**$_3$ and of free **2e**, shown by two separate peaks for the α-CH_2 of the cyanurate

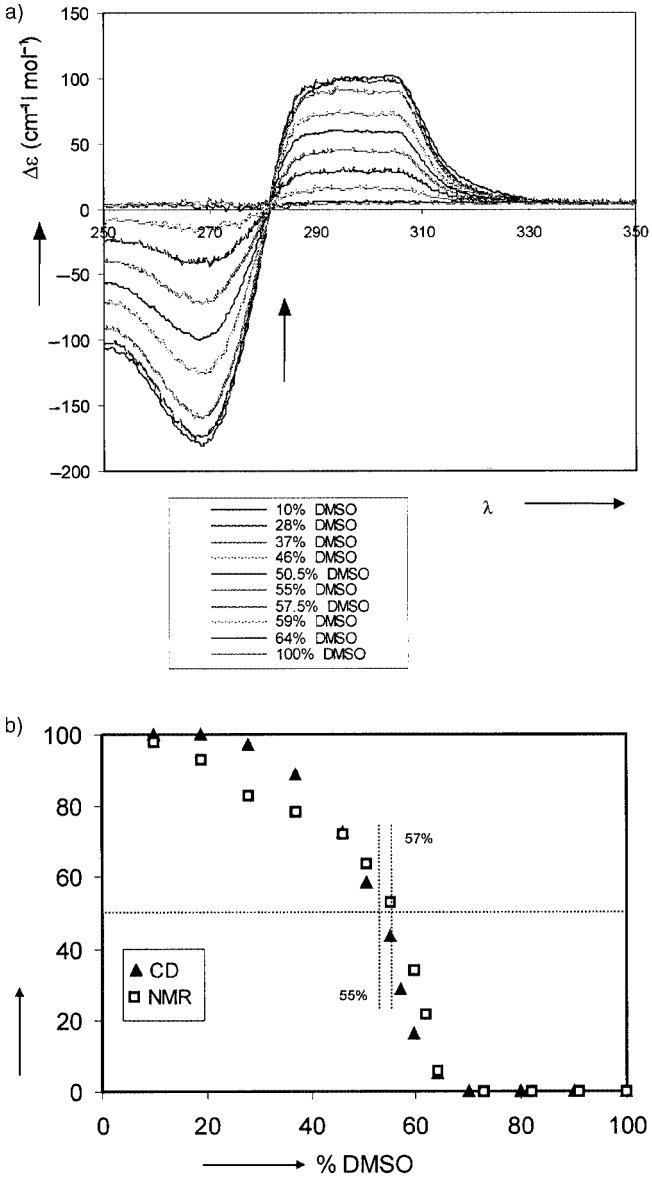


Figure 7. a) CD titration curve for assembly **2e**$_3$; b) thermodynamic stability measurement for assembly **2e**$_3$ as obtained by ^{1}H NMR and CD titration experiments; both methods give similar χ_{DMSO} values

nals in the region between δ = 13 and 16 ppm. Compound **3b**, however, showed broad signals corresponding to complete [$CDCl_3$/[D_6]DMSO (9:1)] or partial ([D_8]THF) assembly both in a mixture of $CDCl_3$/[D_6]DMSO (9:1) and in [D_8]THF. The broadness of the spectra most probably indicates that oligomeric structures are also being formed in this case, in accordance with the increased steric crowding in the linker unit.

Conclusions

The results described in this paper show that the thermodynamic stabilities of double rosette hydrogen-bonded assemblies can be significantly increased by covalently linking the dimelamine and cyanurate units. The relative stabilities of the assemblies seem to be strongly influenced by the length and structure of the linker unit. The shortest spacer (heptyl) gives the highest thermodynamic stability (χ_{DMSO} = 70%), whereas an increase to a decyl spacer slightly reduces the stability of the corresponding assembly (χ_{DMSO} = 60%). Introduction of substituents at the α-position of the cyanurate unit strongly affects the thermodynamic stability of the corresponding double rosette assemblies, however. With methyl substituents (based on L-alanine) the heptyl-linked conjugate is still formed, but the stability is significantly lower than that of the unsubstituted analogue (χ_{DMSO} = 55−57%). In contrast to this, the decyl-linked conjugate does not form well-defined assemblies at all, but oligomeric structures are formed instead. In the case of benzyl substituents (based on D-phenylalanine) neither the heptyl- nor the decyl-linked conjugate double rosette assemblies can be detected any longer in solution. Similarly, the dimelamine-barbiturate conjugates **3a** and **3b** also show no sign of assembly formation, again most probably as the result of steric interactions.

Experimental Section

General: THF was freshly distilled from Na/benzophenone and DMF was dried with molecular sieves. All chemicals were of reagent grade and were used without further purification. NMR spectra were recorded with a Varian Unity 300 (^{1}H NMR 300 MHz) spectrometer at room temperature. Residual solvent protons were used as internal standard, and chemical shifts are given relative to tetramethylsilane (TMS). The 2D 1H-1H NOESY spectra were recorded at 400 MHz with a Bruker AMX 400 instrument in $CDCl_3$ solutions with TMS as internal reference with a mixing time of 150 ms, 1024 data points in t_2, and 512 increments in t_1. FAB-MS data were recorded with a Finningan MAT 90 spectrometer with *m*-nitrobenzyl alcohol (NBA), *m*-nitrobenzyl alcohol/*o*-nitrophenyloctyl ether (NBA/NPOE), or glycerol (Gly) as matrix. Elemental analyses were performed with a Carlo Erba EA1160. The presence of solvents in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Column chromatography was performed on silica gel (SiO_2, E. Merck, 0.040−0.063 mm, 230−240 mesh). Melting points were determined with a Reichert melting point apparatus and are uncorrected. 1,7-Diaminoheptane, 1,10-diaminodecane, methyl 2-bromoacetate, triethanolamine, cyanuric acid, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzyl 2-bromoacetate, *N*-chlorocarbonyl isocyanate, L-alanine methyl ester hydrochloride, D-phenylalanine methyl ester hydrochloride, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), triethylamine, *N*-(4-bromobutyl)phthalimide, *N*-(6-bromohexyl)phthalimide, *N*-(10-bromodecyl)phthalimide, methylamine solution (33% in ethanol), diisopropylethylamine (DIPEA), and *N*,*N*′-dimethylpropyleneurea (DMPU) were commercially available and were used without further purification. Bis(chlorotriazine) **4**,[47] 5-ethylbarbituratic acid (**7a**),[16,25,45] 1-(bromomethyl)-3-(phthalimidomethyl)benzene, and nitrobiuret[36,48] were prepared according to literature procedures.

5,17-Bis({4-amino-6-[(7-aminoheptyl)amino]-1,3,5-triazine-2-yl}-amino)-25,26,27,28-tetrapropoxycalix[4]arene (5a): Bis(chlorotriazine) **4** (1.0 g, 1.1 mmol) and 1,7-diaminoheptane (3.0 g, 22.7 mmol) were dissolved in dry THF (10 mL) under Ar and the mixture was heated at 95 °C overnight. After the mixture had cooled, H_2O (70 mL) was added and the resulting precipitate was filtered off. The solid was recrystallized from THF (10 mL) and H_2O (80 mL). Compound **5a** was obtained as a yellowish solid (1.0 g, 85%); m.p. 125−132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10−6.60 (br. m, 6 H, Ar*H*), 6.60−5.90 (br. m, 4 H, Ar*H*), 5.10 (br. m, 4 H, NH_2 melamine), 4.36 and 3.03 (ABq, 8 H, *J* = 13.2 Hz, ArCH_2Ar), 3.92 (br. s, 4 H, OCH_2), 3.60 (br. s, 4 H, OCH_2), 3.20 (br. s, 4 H, CH_2NH), 2.63 (br. s, 4 H, CH_2NH$_2$), 1.83 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.60−1.10 (m, 20 H, other CH_2 chain), 1.00 (t, *J* = 7.4 Hz, 6 H, OCH$_2$CH$_2$CH_3), 0.82 (t, *J* = 7.2 Hz, 6 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): *m*/*z* = 1067.8 ([M + H$^+$], calcd. 1067.7). $C_{60}H_{86}N_{14}O_4$·3.13H_2O: calcd. C 64.13, H 8.27, N 17.45; found C 64.13, H 7.65, N 17.10.

5,17-Bis({4-amino-6-[(10-aminodecyl)amino]-1,3,5-triazin-2-yl}-amino)-25,26,27,28-tetrapropoxycalix[4]arene (5b): Bis(chlorotriazine) **4** (1.0 g, 1.1 mmol) and 1,10-diaminodecane (11.0 g, 64 mmol) were dissolved in dry THF (15 mL) under Ar and the mixture was heated at 90 °C overnight. H_2O (70 mL) was added to the warm (not boiling) reaction mixture. After the mixture had cooled, a precipitate had formed. This was filtered off and redissolved in refluxing THF (15 mL). H_2O (70 mL) was added to the clear solution, and the precipitate was filtered off. After drying, di(melamine) **5b** was obtained as a white solid (977 mg, 77%); m.p. 125−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10−6.70 (br. m, 6 H, Ar*H*), 6.60−5.90 (br. m, 4 H, Ar*H*), 4.84 (br. s, 4 H, NH_2 melamine), 4.36 and 3.04 (ABq, 8 H, *J* = 13.4 Hz, ArCH_2Ar), 3.90 (t, *J* = 7.7 Hz, 4 H, OCH_2), 3.62 (t, *J* = 6.6 Hz, 4 H, OCH_2), 3.23 (q, *J* = 6.5 Hz, 4 H, CH_2NH), 2.60 (t, *J* = 6.8 Hz, 4 H, CH_2NH$_2$), 1.85 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.48 (m, 4 H, CH_2CH$_2$NH), 1.35 (m, 4 H, CH_2CH$_2$NH$_2$), 1.21 (m, 24 H, other CH_2 chain), 0.99 (t, *J* = 7.5 Hz, 6 H, OCH$_2$CH$_2$CH_3), 0.84 (t, *J* = 7.2 Hz, 6 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): *m*/*z* = 1151.8 ([M + H$^+$], calcd. 1151.8). $C_{66}H_{98}N_{14}O_4$·1.5H_2O: calcd. C 67.26, H 8.64, N 16.64; found C 67.32, H 8.25, N 16.29.

Benzyl (2,4,6-Trioxo-1,3,5-triazin-1-yl)acetate (6a): DBU (1.15 mL, 7.8 mmol) and benzyl 2-bromoacetate (1.2 mL, 7.8 mmol) were added to a solution of cyanuric acid (5.0 g, 38.7 mmol) in dry DMF (80 mL). The mixture was stirred under Ar at room temperature for 1 h and heated overnight at 70 °C. After the reaction mixture had cooled, DMF was removed under vacuum to give a precipitate that was filtered and washed with THF. The filtrate was concentrated and poured into cold water. The obtained precipitate was filtered and dried. After purification of the combined solid fractions by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 96:4), cyanuric acid derivative **6a** was obtained as a white solid (708 mg, 33%); m.p. 237−240 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.69 (s, 2 H, N*H*), 7.34 (m, 5 H, Ar*H*), 5.15 (s, 2 H, PheCH_2O), 4.46 (s, 2 H, CH_2N) ppm. MS (FAB): *m*/*z* = 276.1 ([M − H$^+$], calcd. 276.1). $C_{12}H_{11}N_3O_5$: calcd. C 51.99, H 4.00, N 15.16; found C 51.77, H 4.09, N 15.15.

(2,4,6-Trioxo-1,3,5-triazin-1-yl)acetic Acid (6d): Benzyl ester **6a** (661 mg, 2.4 mmol) was added to a solution of NaOH (477 mg, 11.9 mmol) in H_2O (15 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was then acidified (36% HCl, pH = 1) and the water was removed under vacuum. The remaining white residue was extracted several times with THF, and the solution recovered after filtration was concentrated, giving carboxylic derivative **6d** as a white solid (414 mg, 92%); m.p. 249−251 °C. ^{1}H NMR (300 MHz, [D$_8$]THF): δ 11.60 (br, 1 H, CO$_2$*H*), 10.72 (br. s, 2 H, N*H*), 4.55 (s, 2 H, CH_2N) ppm. MS (FAB): *m*/*z* = 186.0 ([M − H$^+$], calcd. 186.0). $C_5H_5N_3O_5$·0.8H_2O: calcd. C 29.80, H 3.30, N 20.85; found C 29.73, H 3.38, N 19.28.

***N*-(2,4,6-Trioxo-1,3,5-triazin-1-yl)-L-alanine Methyl Ester (6b):** This compound was prepared by a literature procedure.[38] Crude **6b** was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) (321 mg, 42%); m.p. 185−187 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.61 (br, 2 H, N*H*), 5.18 (q, *J* = 6.9 Hz, 1 H, C*H*CH$_3$), 3.61 (s, 3 H, CO$_2$CH_3), 1.40 (d, *J* = 6.9 Hz, 3 H, CHCH_3) ppm. MS (FAB): *m*/*z* = 216.0 ([M + H$^+$], calcd. 216.1). $C_7H_9N_3O_5$: calcd. C 39.08, H 4.22, N 19.53; found C 39.10, H 4.24, N 19.64.

***N*-(2,4,6-Trioxo-1,3,5-triazin-1-yl)-L-alanine (6e):** Methyl ester **6b** (150 mg, 0.7 mmol) was added to a solution of NaOH (111 mg, 2.8 mmol) in H_2O (4 mL), and the mixture was stirred at room temperature overnight. The solution was then acidified (36% HCl, pH = 1) and the water was removed under vacuum. The white residue was extracted several times with THF, and the solution recovered after filtration was concentrated to give carboxylic derivative **6e** as a white solid (138 mg, 98%); m.p. 203−205 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.76 (br, 1 H, CO$_2$*H*), 11.58 (br, 2 H, N*H*), 5.07 (m, 1 H, C*H*CH$_3$), 1.40 (d, *J* = 6.9 Hz, 3 H, CHCH_3) ppm. MS (FAB): *m*/*z* = 200.0 ([M − H$^+$], calcd. 200.0). $C_6H_7N_3O_5$·0.03THF: calcd. C 36.16, H 3.59, N 20.67; found C 36.08, H 3.58, N 20.58.

***N*-(2,4,6-Trioxo-1,3,5-triazin-1-yl)-D-phenylalanine Methyl Ester (6c):** This compound was prepared by a literature procedure.[38] Crude **6c** was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 90:9.5:0.5) (450 mg, 62%); m.p. 188−191 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.64 (br, 2 H, N*H*), 7.30−7.10 (m, 5 H, Ar*H*), 5.45 (q, *J* = 5.6 Hz, 1 H, C*H*CH_2Phe), 3.66 (s, 3 H, CO_2CH_3), 3.44−3.12 (m, 2 H, CHCH_2Phe) ppm. MS (FAB): *m*/*z* = 292.2 ([M + H$^+$], calcd. 292.1). $C_{13}H_{13}N_3O_5$: calcd. C 53.61, H 4.50, N 14.43; found C 53.45, H 4.45, N 14.39.

***N*-(2,4,6-Trioxo-1,3,5-triazin-1-yl)-D-phenylalanine (6f):** Methyl ester **6c** (100 mg, 0.3 mmol) was added to a solution of NaOH (55 mg, 1.4 mmol) in H_2O (3 mL), and the mixture was stirred at room temperature overnight. The solution was then acidified (36% HCl, pH = 1) and the water was removed under vacuum. The white residue was extracted several times with THF, and the solution recovered after filtration was concentrated to give carboxylic derivative **6f** as a white solid (93 mg, 98%); m.p. 285−287 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 13.05 (br, 1 H, CO_2H), 11.58 (br, 2 H, N*H*), 7.30−7.10 (m, 5 H, Ar*H*), 5.30 (q, *J* = 5.6 Hz, 1 H, C*H*CH_2Phe), 3.44−3.12 (m, 2 H, CHCH_2Phe) ppm. MS (FAB): *m*/*z* = 276.1 ([M − H$^+$], calcd. 276.1). $C_{12}H_{11}N_3O_5$·0.20H_2O: calcd. C 51.32, H 4.09, N 14.96; found C 51.33, H 4.13, N 15.07.

Methyl (5-Ethyl-2,4,6-trioxo-hexahydropyrimidin-5-yl)acetate (7b): 5-Ethylbarbituric acid **7a** (1.0 g, 6.4 mmol) was suspended in H_2O (50 mL), and triethanolamine (0.85 mL, 6.4 mmol) was added. Methyl 2-bromoacetate (0.6 mL, 7.0 mmol, 1.1 equiv.) was then added dropwise over 10 min, giving a clear solution. After the solution had been stirred at room temperature for 4 d, a white precipitate had formed, and this was isolated by filtration. After drying under vacuum, ester **7b** was obtained as a white solid (0.66 g, 45%); m.p. 195−198 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.49 (s, 2 H, N*H*), 3.57 (s, 3 H, CO_2CH_3), 3.00 (s, 2 H, $CH_2CO_2CH_3$), 1.61 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 0.81 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3) ppm. MS (FAB): *m*/*z* = 229.1 ([M + H$^+$], calcd. 229.1). $C_9H_{12}N_2O_5$: calcd. C 47.37, H 5.30, N 12.28; found C 47.38, H 5.20, N 12.02.

(5-Ethyl-2,4,6-trioxo-hexahydropyrimidin-5-yl)acetic Acid (7c): Methyl ester **7b** (400 mg, 1.8 mmol) was added to a solution of NaOH (210 mg, 5.3 mmol) in H_2O (6 mL), and the mixture was stirred at room temperature overnight. The solution was then acidified (36% HCl, pH = 1), giving the carboxylic acid derivative **7c** as a white precipitate that was separated by filtration. Subsequently, the filtrate was concentrated and the white residue was extracted several times with dry THF. After filtration and removal of THF, a second crop of white solid was obtained. Both solid fractions were combined to give pure **7c** (365 mg, 97%); m.p. 274−276 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 12.70 (br, 1 H, CO_2H), 11.40 (s, 2 H, N*H*), 2.90 (s, 2 H, CH_2CO_2H), 1.74 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 0.80 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3) ppm. MS (FAB): *m*/*z* = 213.0 ([M − H$^+$], calcd. 213.1).

General Procedure for the Preparation of Di(melamine-cyanurate) 2a−f and Di(melamine-barbiturate) 3a−b: The appropriate cyanurate **6** or barbiturate **7** (2.1 equiv.), triethylamine (4.0 equiv.), and HBTU (2.1 equiv.) were added to a solution of dimelamine **5a−b** in dry THF/DMF (2:1). The solution was stirred under Ar at room temperature for 4 h and then poured into cold H_2O (100 mL). The obtained precipitate was filtered off and dried to give the desired product as a white solid.

Di(melamine−C_7−GlyCyan) (2a): This compound was prepared from dimelamine **5a** and cyanurate **6d**. Yield: 128 mg (94%). M.p. > 300 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.56 (br, 2 H, N*H* cyan), 8.70−8.30 (br. m, 2 H, N*H* calix), 7.99 (br, 2 H, N*H*-CO), 7.48 (br. m, 4 H, Ar*H*), 6.90−6.40 (br. m, 2 H, N*H* calix), 6.22 (br. m, 10 H, N*H* calix + Ar*H*), 4.32 (d, *J* = 11.4 Hz, 4 H, ArCH_2Ar), 4.17 (s, 4 H, CH_2CO), 3.89 (t, *J* = 7.8 Hz, 4 H, OCH_2), 3.60 (br. t, 4 H, OCH_2), 3.10−2.90 (m, 8 H, CH_2NHCO + ArCH_2Ar), 2.00−1.74 (m, 8 H, $OCH_2CH_2CH_3$), 1.60−1.10 (br. m, 20 H, other CH_2 chain), 1.06 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 0.87 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$) ppm. MS (FAB): *m*/*z* = 1406.2 ([M + H$^+$], calcd. 1405.7). $C_{70}H_{92}N_{20}O_{12}$·3.3H_2O: calcd. C 57.39, H 6.78, N 19.12; found C 57.06, H 6.28, N 18.77.

Di(melamine-C_{10}-GlyCyan) (2b): This compound was prepared from dimelamine **5b** and cyanurate **6d**. Yield: 127 mg (98%). M.p. 278−280 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.59 (br, 2 H, N*H* cyan), 8.80−8.30 (br. m, 2 H, N*H* calix), 8.01 (t, *J* = 5.1 Hz, 2 H, N*H*-CO), 7.48 (br. m, 4 H, Ar*H*), 6.90−6.40 (br. m, 2 H, N*H* calix), 6.21 (br. m, 6 H, Ar*H*), 6.11 (br, 4 H, NH_2), 4.32 (d, *J* = 12.3 Hz, 4 H, ArCH_2Ar), 4.17 (s, 4 H, CH_2CO), 3.89 (t, *J* = 7.7 Hz, 4 H, OCH_2), 3.59 (br. t, 4 H, OCH_2), 3.26 (br. m, 4 H, CH_2NH mela), 3.10−2.90 (m, 8 H, CH_2NHCO + ArCH_2Ar), 2.00−1.74 (m, 8 H, $OCH_2CH_2CH_3$), 1.60−1.08 (br. m, 32 H, other CH_2 chain), 1.06 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 0.87 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$) ppm. MS (FAB): *m*/*z* = 1490.9 ([M + H$^+$], calcd. 1491.8). $C_{76}H_{106}N_{20}O_{12}$·1.9$H_2O$: calcd. C 59.82, H 7.25, N 18.36; found C 59.72, H 6.81, N 17.85.

Di(melamine-C_7-D-PheCyan) (2c): This compound was prepared from dimelamine **5a** and cyanurate **6f**. Yield: 97 mg (83%). M.p. 214−220 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.42 (br. s, 2 H, N*H* cyan), 8.80−8.30 (br. m, 2 H, N*H* calix), 7.91 (br. s, 2 H, N*H*-CO), 7.49 (br. m, 4 H, Ar*H* calix), 7.15 (m, 10 H, Ar*H* benzyl), 6.90−6.50 (br. m, 2 H, N*H* calix), 6.21 (br. m, 6 H, Ar*H*), 6.10 (br, 4 H, NH_2), 5.16 (q, *J* = 5.1 Hz, 2 H, C*H*benzyl), 4.32 (d, *J* = 12.6 Hz, 4 H, ArCH_2Ar), 3.89 (t, *J* = 7.8 Hz, 4 H, OCH_2), 3.59 (br. t, 4 H, OCH_2), 3.45−2.95 (m, 16 H, CH_2NH mela + CH_2benzyl + CH_2NHCO + ArCH_2Ar), 2.06−1.72 (m, 8 H, $OCH_2CH_2CH_3$), 1.60−1.08 (m, 20 H, other CH_2 chain), 1.06 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 0.87 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$) ppm. MS (FAB): *m*/*z* = 1586.6 ([M + H$^+$], calcd. 1585.8). $C_{84}H_{104}N_{20}O_{12}$·3.5$H_2O$: calcd. C 61.19, H 6.79, N 16.99; found. C 60.99, H 6.43, N 16.33.

Di(melamine-C_{10}-D-PheCyan) (2d): This compound was prepared from dimelamine **5b** and cyanurate **6f**. Yield: 79 mg (90%). M.p. 210−214 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.42 (br, 2 H, N*H* cyan), 8.80−8.30 (br. m, 2 H, N*H* calix), 7.91 (t, *J* = 5.4 Hz, 2 H, N*H*-CO), 7.49 (br. m, 4 H, Ar*H* calix), 7.15 (m, 10 H, Ar*H* benzyl), 6.90−6.50 (br. m, 2 H, N*H* calix), 6.21 (br. m, 6 H, Ar*H*), 6.10 (br, 4 H, NH_2), 5.16 (q, *J* = 5.1 Hz, 2 H, C*H*benzyl), 4.32 (d, *J* = 12.6 Hz, 4 H, ArCH_2Ar), 3.89 (t, *J* = 7.8 Hz, 4 H, OCH_2), 3.59 (br. t, 4 H, OCH_2), 3.45−2.95 (m, 16 H, CH_2NH mela + CH_2 benzyl + CH_2NHCO + ArCH_2Ar), 2.06−1.72 (m, 8 H, $OCH_2CH_2CH_3$), 1.60−1.08 (m, 32 H, other CH_2 chain), 1.06 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 0.87 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$) ppm. MS (FAB): *m*/*z* = 1670.6 ([M + H$^+$], calcd. 1669.9). $C_{90}H_{116}N_{20}O_{12}$·4.0$H_2O$: calcd. C 62.05, H 7.17, N 16.08; found C 62.08, H 6.73, N 15.86.

Di(melamine-C_7-L-AlaCyan) (2e): This compound was prepared from dimelamine **5a** and cyanurate **6e**. Yield: 120 mg (89%). M.p. 251−253 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 11.50 (br, 2 H, N*H* cyan), 8.80−8.30 (br. m, 2 H, N*H* calix), 7.81 (br, 2 H, N*H*-CO), 7.48 (br. m, 4 H, Ar*H*), 6.90−6.50 (br. m, 2 H, N*H* calix), 6.23 (br. m, 6 H, Ar*H*), 6.13 (br, 4 H, NH_2), 4.91 (m, 2 H, C*H*CO), 4.32 (d, *J* = 12.3 Hz, 4 H, ArCH_2Ar), 3.89 (t, *J* = 7.7 Hz, 4 H,

OCH_2), 3.61 (br. t, 4 H, OCH_2), 3.10−2.90 (m, 8 H, CH_2NHCO + ArCH_2Ar), 2.10−1.74 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.60−1.08 (br. m, 26 H, other CH_2 chain + CHCH_3), 1.06 (t, J = 7.5 Hz, 3 H, OCH$_2$CH$_2$CH_3), 0.88 (t, J = 7.5 Hz, 3 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): m/z = 1433.8 ([M + H$^+$], calcd. 1433.8). $C_{72}H_{96}N_{20}O_{12}$·3H_2O: calcd. C 58.13, H 6.91, N 18.83; found C 58.28, H 6.66, N 18.35.

Di(melamine-C_{10}-L-AlaCyan) (2f): This compound was prepared from dimelamine **5b** and cyanurate **6e**. Yield: 125 mg (95%). M.p. 233−236 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.51 (br, 2 H, NH cyan), 8.80−8.30 (br. m, 2 H, NH calix), 7.81 (br, 2 H, NH-CO), 7.47 (br. m, 4 H, ArH), 6.90−6.50 (br. m, 2 H, NH calix), 6.21 (br. m, 6 H, ArH), 6.12 (br, 4 H, NH_2), 4.92 (q, J = 6.9 Hz, 2 H, CHCO), 4.32 (d, J = 12.3 Hz, 4 H, ArCH_2Ar), 3.89 (t, J = 7.7 Hz, 4 H, OCH_2), 3.59 (br. t, 4 H, OCH_2), 3.10−2.90 (m, 8 H, CH_2NHCO + ArCH_2Ar), 2.10−1.72 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.68−0.98 (m, 44 H, other CH_2 chain + CHCH_3 + OCH$_2$CH$_2$CH_3), 0.87 (t, J = 7.5 Hz, 3 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): m/z = 1518.1 ([M + H$^+$], calcd. 1517.9). $C_{78}H_{108}N_{20}O_{12}$·2.7$H_2O$: calcd. C 59.81, H 7.30, N 17.88; found C 59.75, H 7.03, N 17.33.

Di(melamine−C_7−GlyBarb) (3a): This compound was prepared from dimelamine **5a** and barbiturate **7c**. Yield: 127 mg (92%). M.p. 197−200 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.27 (br, 2 H, NH barb), 8.80−8.40 (br. m, 2 H, NH calix), 7.89 (br, 2 H, NH-CO), 7.47 (br. m, 4 H, ArH), 7.00−6.60 (br. m, 2 H, NH calix), 6.23 (br. m, 10 H, NH calix + ArH), 4.32 and 3.04 (ABq, 8 H, J = 12.9 Hz, ArCH_2Ar), 3.89 (t, J = 7.8 Hz, 4 H, OCH_2), 3.60 (br. t, 4 H, OCH_2), 2.90 (br. m, 4 H, CH_2NHCO), 2.81 (s, 4 H, CH_2CO), 2.00−1.76 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.69 (q, J = 7.4 Hz, 2 H, CH_2CH$_3$ barb), 1.60−1.10 (br. m, 20 H, other CH_2 chain), 1.06 (t, J = 7.6 Hz, 3 H, OCH$_2$CH$_2$CH_3), 0.87 (t, J = 7.5 Hz, 3 H, OCH$_2$CH$_2$CH_3), 0.78 (t, J = 7.4 Hz, 3 H, CH$_2$CH_3 barb) ppm. MS (FAB): m/z = 1459.4 ([M + H$^+$], calcd. 1459.8). $C_{76}H_{102}N_{18}O_{12}$·4.5$H_2O$: calcd. C 59.24, H 7.26, N 16.36; found C 58.85, H 6.66, N 16.35.

Di(melamine-C_{10}-GlyBarb) (3b): This compound was prepared from dimelamine **5b** and barbiturate **7c**. Yield: 178 mg (85%). M.p. 185−190 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.26 (br, 2 H, NH barb), 8.80−8.40 (br. m, 2 H, NH calix), 7.91 (t, J = 5.1 Hz, 2 H, NH-CO), 7.31 (br. m, 4 H, ArH), 7.05−6.60 (br. m, 2 H, NH calix), 6.37 (br, 4 H, NH_2 calix), 6.22 (br. m, 6 H, ArH), 4.32 and 3.03 (ABq, 8 H, J = 12.6 Hz, ArCH_2Ar), 3.89 (t, J = 7.8 Hz, 4 H, OCH_2), 3.60 (br. t, 4 H, OCH_2), 2.89 (br. m, 4 H, CH_2NHCO), 2.82 (s, 4 H, CH_2CO), 2.00−1.76 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.69 (q, J = 7.5 Hz, 2 H, CH_2CH$_3$ barb), 1.60−1.08 (br. m, 32 H, other CH_2 chain), 1.06 (t, J = 7.4 Hz, 3 H, OCH$_2$CH$_2$CH_3), 0.87 (t, J = 7.5 Hz, 3 H, OCH$_2$CH$_2$CH_3), 0.78 (t, J = 7.5 Hz, 3 H, CH$_2$CH$_3$ barb) ppm. MS (FAB): m/z = 1544.3 ([M + H$^+$], calcd. 1543.9). $C_{82}H_{114}N_{18}O_{12}$·5.9$H_2O$: calcd. C 59.68, H 7.68, N 15.28; found C 59.59, H 7.05, N 15.63.

General Procedure for the Synthesis of Phthalimide-Protected Cyanurates 8a−d: A solution of cyanuric acid (1.0 equiv.), *N*-(bromoalkyl)phthalimide (1.0 equiv.), and DBU (1.0 equiv.) in dry DMF (40 mL) was heated at 70 °C under Ar for 7 h. After cooling, the yellow solution was poured into cold H_2O (300 mL), and the resulting white precipitate was filtered off and dried under vacuum. The obtained white solid was purified by flash column chromatography.

1-(4-Phthalimidobutyl)-1,3,5-triazine-2,4,6-trione (8a): Flash column chromatography: SiO_2, CH_2Cl_2/MeOH, 9:1. Yield: 400 mg (16%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.32 (br. s, 2 H, NH), 7.83 (m, 4 H, ArH), 3.63 (t, J = 6.6 Hz, 2 H, CH_2Ncyan), 3.56 (t, J = 6.5 Hz, 2 H, CH_2NPht), 1.53 (br. s, 4 H, NCH$_2$CH_2CH_2CH$_2$N) ppm. MS (FAB): m/z = 329.0 ([M − H$^+$], calcd. 329.1).

1-(6-Phthalimidohexyl)-1,3,5-triazine-2,4,6-trione (8b): Flash column chromatography: SiO_2, CH_2Cl_2/MeOH, 99:1. Yield: 175 mg (15%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.35 (s, 2 H, NH), 7.83 (m, 4 H, ArH), 3.59 (t, J = 6.9 Hz, 2 H, CH_2Ncyan), 3.54 (t, J = 6.9 Hz, 2 H, CH_2NPht), 1.56−1.47 (m, 4 H, CH_2CH$_2$N), 1.26 (br. s, 4 H, CH_2CH$_2$CH$_2$N) ppm. MS (FAB): m/z = 359.0 ([M + H$^+$], calcd. 359.1).

1-(10-Phthalimidodecyl)-1,3,5-triazine-2,4,6-trione (8c): Flash column chromatography: SiO_2, CH_2Cl_2/MeOH, 95:5. Yield: 991 mg (31%). M.p. 211−213 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.36 (s, 2 H, NH), 7.83 (m, 4 H, ArH), 3.58 (t, J = 7.2 Hz, 2 H, CH_2Ncyan), 3.54 (t, J = 7.2 Hz, 2 H, CH_2NPht), 1.56−1.46 (m, 4 H, CH_2CH$_2$N), 1.21 (br. s, 12 H, other CH_2) ppm. MS (FAB): m/z = 415.1 ([M + H$^+$], calcd. 415.2). $C_{21}H_{26}N_4O_5$·0.21H_2O: calcd. C 60.31, H 6.37, N 13.40; found C 60.27, H 6.18, N 13.03.

1-(Phthalimidomethyl)-3-{[(2,4,6-trioxo-1,3,5-triazin-1-yl)amino]-methyl}benzene (8d): Flash column chromatography: SiO_2, CH_2Cl_2/MeOH, 95:5. Yield: 0.50 g (17%). M.p. > 300 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.52 (s, 2 H, NH), 7.87 (m, 4 H, ArH Pht), 7.21 (m, 4 H, ArH *m*-xylene) 4.78 (s, 2 H, CH_2Ncyan), 4.74 (s, 2 H, CH_2NPht) ppm. MS (FAB): m/z = 379.0 ([M + H$^+$], calcd. 379.1). $C_{19}H_{14}N_4O_5$: calcd. C 60.32, H 3.73, N 14.81; found C 60.66, H 3.78, N 14.36.

General Procedure for the Synthesis of Amino-Substituted Cyanurates 9a−d: A solution of methylamine (33% in EtOH, 40 equiv.) was added to a solution of phthalimide **8a−d** (1.0 equiv.) in EtOH (10 mL), and the mixture was heated at 70 °C under Ar for 150 min. After the mixture had cooled, the resulting white precipitate was filtered off, washed with EtOH (3 ×), and dried under vacuum. Cyanuric acids **9a−d** were obtained as white solids.

1-(4-Aminobutyl)-1,3,5-triazine-2,4,6-trione (9a): Yield: 105 mg (91%). ^{1}H NMR (300 MHz, D_2O): δ = 3.66 (br. s, 2 H, CH_2Ncyan), 2.88 (br. s, 2 H, CH_2NH$_2$), 1.54 (br. s, 4 H, NCH$_2$CH_2CH_2CH$_2$N) ppm. MS (EI): m/z = 200.0 ([M$^+$], calcd. 200.1).

1-(6-Aminohexyl)-1,3,5-triazine-2,4,6-trione (9b): Yield: 175 mg (88%). ^{1}H NMR (300 MHz, D_2O): δ = 3.62 (t, J = 6.9 Hz, 2 H, CH_2Ncyan), 2.83 (t, J = 6.9 Hz, 2 H, CH_2NH$_2$), 1.49 (m, 4 H, CH_2CH$_2$N), 1.24 (m, 4 H, CH_2CH$_2$CH$_2$N) ppm. MS (FAB): m/z = 229.2 ([M + H$^+$], calcd. 229.1).

1-(10-Aminodecyl)-1,3,5-triazine-2,4,6-trione (9c): Yield: 132 mg (96%). M.p. 255−257 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO + 1 drop HCl): δ = 11.37 (s, 2 H, NH), 8.01 (br. s, 3 H, NH_3^+), 3.58 (t, J = 7.2 Hz, 2 H, CH_2Ncyan), 2.70 (t, J = 6.0 Hz, 2 H, CH_2NH$_2$), 1.51 (m, 4 H, CH_2CH$_2$N), 1.21 (br. s, 12 H, other CH_2) ppm. MS (FAB): m/z = 285.1 ([M + H$^+$], calcd. 285.2). $C_{13}H_{24}N_4O_3$·0.53H_2O: calcd. C 53.13, H 8.59, N 19.06; found C 53.13, H 8.06, N 18.45.

1-(Aminomethyl)-3-{[(2,4,6-trioxo-1,3,5-triazin-1-yl)amino]-methyl}benzene (9d): Yield: 111 mg (85%). M.p. 278−281 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO + 1 drop HCl): δ = 11.53 (s, 2 H, NH), 8.48 (br. s, 3 H, NH_3^+), 7.32 (m, 4 H, ArH *m*-xylene) 4.80 (s, 2 H, CH_2Ncyan), 3.93 (s, 2 H, CH_2NH$_2$) ppm. MS (FAB): m/z = 249.1 ([M + H$^+$], calcd. 249.1).

5,17-Bis{[4-amino-6-({6-[(2,4,6-trioxo-1,3,5-triazin-1-yl)amino]-hexyl}amino)-1,3,5-triazin-2-yl]amino}-25,26,27,28-tetrapropoxycalix[4]arene (10): Bis(chlorotriazine) **4** (105.5 mg, 0.12 mmol), **9b** (58 mg, 0.25 mmol), and DIPEA (0.13 mL, 0.76 mmol) were dissolved in a 1:1 mixture of *N*,*N*-dimethylacetamide (DMA) and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) (5 mL). The mixture was heated at 90 °C under Ar for 3 d. After the mixture had cooled, H_2O was added and the formed precipitate was filtered. Impurities were removed by repeated washing with hot THF to give **10** as an off-white solid (32 mg, 21%); m.p. 282−285 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.31 (br. s, 2 H, N*H* cyan), 8.55−8.35 (2br. s, 2 H, N*H* calix), 7.43 (m, 4 H, Ar*H*), 6.68−6.55 (2br. s, 2 H, N*H* calix), 6.17 (s, 6 H, Ar*H*), 6.04 (br. s, 4 H, NH_2 calix), 4.25 and 3.00 (ABq, 8 H, *J* = 12.9 Hz, ArCH_2Ar), 3.82 (t, *J* = 7.8 Hz, 4 H, OCH_2), 3.54 (m, 8 H, OCH_2 + CH_2Ncyan), 1.85−1.75 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.44 (m, 8 H, CH$_2$CH_2CH$_2$N), 1.20 (m, 8 H, CH_2CH$_2$CH$_2$N), 1.00 (t, *J* = 7.4 Hz, 6 H, OCH$_2$CH$_2$CH_3), 0.81 (t, *J* = 7.4 Hz, 6 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): *m*/*z* = 1264.1 ([M + H$^+$], calcd. 1263.7).

5,17-Bis[(4-amino-6-{[10-(aminobiuret)decyl]amino}-1,3,5-triazin-2-yl)amino]-25,26,27,28-tetrapropoxycalix[4]arene (11): Compound **5b** (400 mg, 0.35 mmol), nitrobiuret (103 mg, 0.70 mmol), and Na_2HPO_4 (99 mg, 0.70 mmol) were dissolved in a mixture of DMF/H_2O (1:4) and the mixture was heated at 90 °C under Ar for 1 h. A second portion of nitrobiuret (103 mg, 0.70 mmol, 2 equiv.) and Na_2HPO_4 (99 mg, 0.70 mmol, 2 equiv.) were then added and the mixture was heated for another 1 h at 90 °C. Finally, a third portion of nitrobiuret (103 mg, 0.70 mmol, 2 equiv.) and Na_2HPO_4 (99 mg, 0.70 mmol, 2 equiv.) were added, and heating at 90 °C was continued for 1 h. After cooling, the solution was poured into H_2O (100 mL) and the resulting precipitate was filtered off. After drying under vacuum, the biuret derivative **11** was obtained as a white solid (393 mg, 85%); m.p. 136−146 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.70−8.30 (br. m, 4 H, N*H* calix + N*H* biuret), 7.50 (br. s, 4 H, Ar*H*), 7.44 (br. s, 2 H, N*H* biuret), 6.90−6.50 (br. m, 6 H, N*H* calix + NH_2 biuret), 6.20 (br. s, 6 H, Ar*H*), 6.06 (br. s, 2 H, NH_2 calix), 4.31 (d, *J* = 12.3 Hz, 4 H, ArCH_2Ar), 3.88 (t, *J* = 8.0 Hz, 4 H, OCH_2), 3.58 (br. t, 4 H, OCH_2), 3.23 (br, 4 H, CH_2NHcalix), 3.04 (br. m, 8 H, ArCH_2Ar + CH_2NHbiuret), 2.00−1.70 (m, 8 H, OCH$_2$CH_2CH$_3$), 1.60−0.96 (m, 38 H, CH_2CH$_2$NH + other CH_2 + OCH$_2$CH$_2$CH_3), 0.86 (t, *J* = 7.5 Hz, 6 H, OCH$_2$CH$_2$CH_3) ppm. MS (FAB): *m*/*z* = 1321.8 ([M − H$^+$], calcd. 1321.8). $C_{70}H_{102}N_{18}O_8 \cdot 3.3H_2O$: calcd. C 60.79, H 7.91, N 18.23; found C 60.78, H 7.46, N 17.83.

Preparation of Hydrogen-Bonded Assemblies 2−3: Typically, the di(melamine-cyanurate) **2** or di(melamine-barbiturate) conjugates **3** (or a 1:2 mixture of calix[4]arene dimelamine and BuCYA) were first dissolved in hot DMSO and subsequently, after cooling, diluted with $CHCl_3$. ^{1}H NMR titration studies were typically performed with 1.6 mM solutions of assemblies **2** and **3** and a 6.5 mM solution of assembly **1**$_3$·(BuCYA)$_6$. CD titration studies were performed with a 1.0 mM solution of the chiral assembly **2e**$_3$.

^{1}H NMR Titration Experiments: DMSO titrations were carried out by gradually increasing the percentage of DMSO (10−100%) in the solvent mixture, while monitoring the ratio of free and assembled **1−3** species by integration of characteristic proton signals. For **1**$_3$·(BuCYA)$_6$: H$_g$ (assembled), ArCH_2Ar (free + assembled); for **2a**$_3$ and **2b**$_3$: H$_g$ (assembled), ArCH_2Ar (free + assembled) and α-CH_2 of cyanurate (assembled); for **2e**$_3$: H$_g$ (assembled), α-CH_2 of cyanurate (free + assembled).

Molecular Simulation Studies: Initial structures were generated by manual modification of the X-ray crystal structure of **1**$_3$·(DEB)$_6$ by use of Quanta97.[49] Molecular simulations were run with CHARMm, version 24.0.[9,10,50] Parameters were taken from Quanta97, and point charges were assigned with the charge template option in Quanta/CHARMm.

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