Self-Assembly

Complete Self-Assembly of Discrete Supramolecular Dendrimers**

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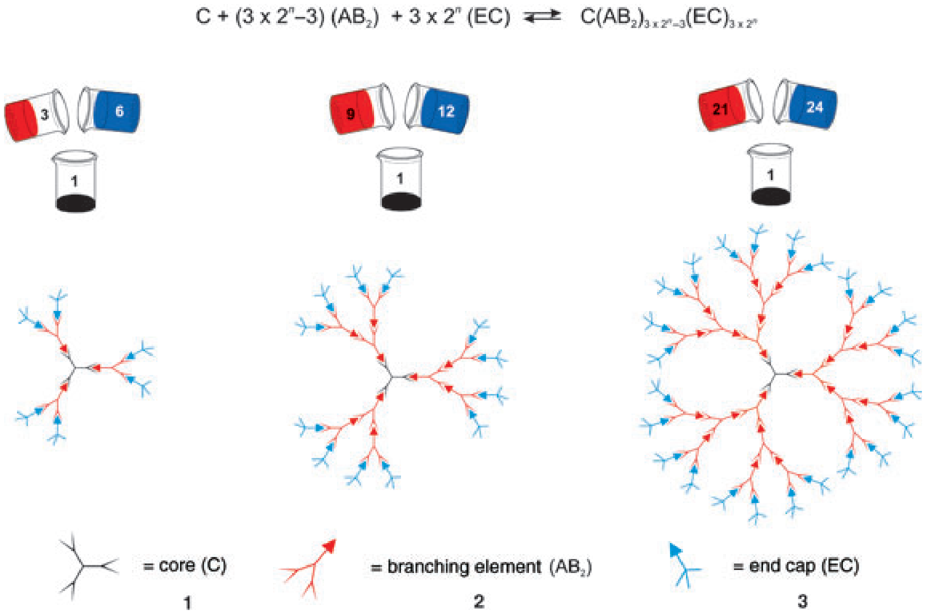


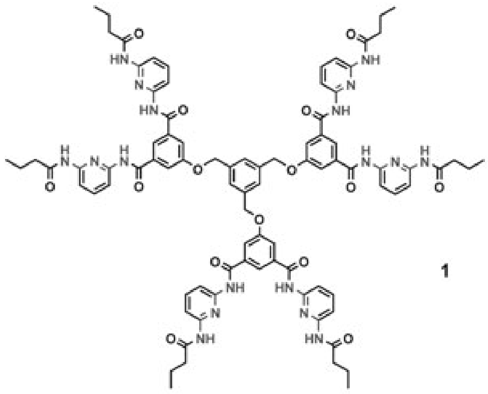
Figure 1. Supramolecular assembly of discrete dendrimers by using the homotritopic core **1**, heterotritopic AB_2 block **2**, and end caps **3**.

The complete self-assembly of dendrimers based on noncovalent interactions presents a great challenge. By analogy with supramolecular polymers,[1–4] the reversible and thermodynamically controlled linkage of the basic building blocks leads to dynamic materials which are able to react to external stimuli and which are able to undergo self-healing processes. However, the hitherto presented concepts for the self-assembly of discrete and purely organic dendrimers employed preassembled dendritic systems in most cases. These entities have been linked to form discrete superstructures, for example, 1) by intermolecular hydrogen bonds with each other[5–7] or with other molecules,[8,9] 2) by electrostatic interactions between oppositely charged units,[10] and 3) as a result of structural and hydrophobic effects in the case of amphiphilic dendrimers.[11]

We here present the first approach for the complete self-assembly of discrete supramolecular dendrimers where the repetition motif is no longer based on dendritic subunits (Figure 1). We employ the homotritopic Hamilton receptor **1**,[2,12] which can form six hydrogen bonds to cyanuric and barbituric acid derivatives. We have developed the heterotritopic AB_2 unit **2** as a branching element, which contains two Hamilton receptors as well as a complimentary cyanuric acid substrate.

The synthesis of **2** started with **4**, which was converted into the the corresponding acid chloride and treated with **5** to give compound **6**. After cleavage of the ester with KOH, treatment with 0.5 equivalents of **8** led to ether formation in a twofold S_N reaction (Scheme 1). Steglich coupling of the cyanuric acid derivative **11** with compound **10** (deprotected by trifluroacetic acid) leads to the AB_2 branching unit **2** in good yields.

A total of $3\times2^n-3$ molecules of **2** (n = generation number) links the core **1** with end caps **3** in the supramolecular dendrimer. When components **1, 2**, and **3** are mixed in a



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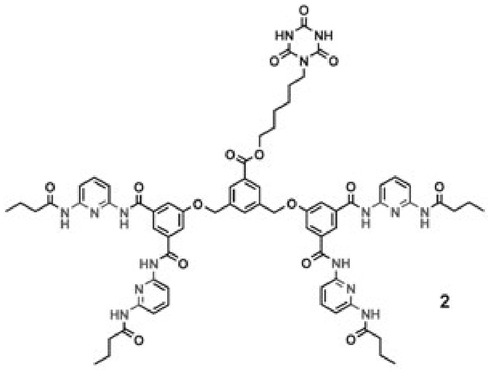

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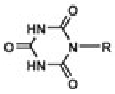

3

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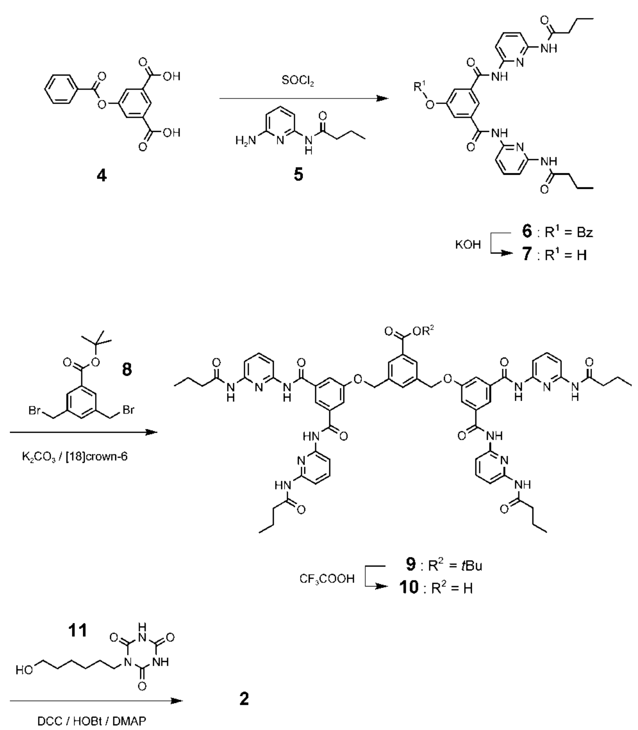
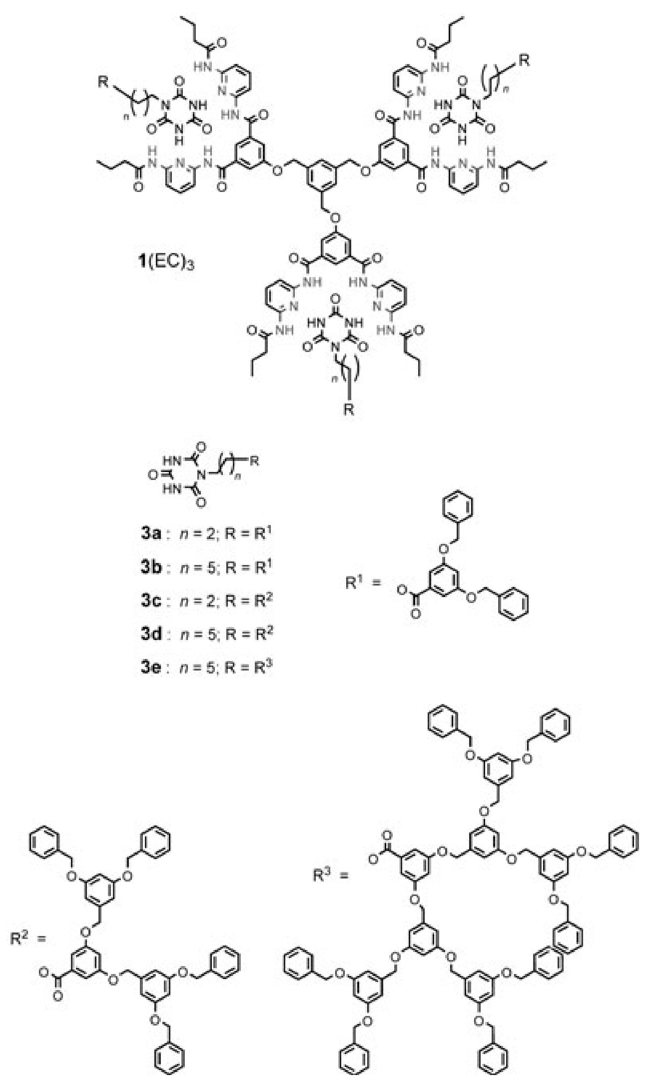


Scheme 1. Synthesis of the branching element **2**. Bz = benzoyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, HOBt = 1-hydroxybenzotriazole.

1:(3 × 2^n−3):(3 × 2^n) ratio, complete self-assembly of a supramolecular dendrimer of generation n can be expected, provided that all possible hydrogen bonds are formed (Figure 1).

For comparison, we first investigated the formation of **1**(EC)$_3$ aggregates, in which the core **1** is complexed directly by three dendritic end caps **3a**–**3e** (Scheme 2).[13,14] To achieve this, end caps **3a**–**3e** were added by titration to core **1**. During this process the characteristic ^{1}H NMR chemical shifts of the NH protons to higher frequency (lower field) were monitored.[2] From the titration curves the association constants of complexes **1**(EC)$_3$ were derived by using a method by Solov'ev et al.[15] and by using the computer program Chem-Equili (Table 1). The values obtained are in good agreement with literature data for comparable systems.[2] The Scatchard plots[16] of these data are indicative of pronounced cooperativity in the formation of **1**(EC)$_3$. Due to the increase in size, the aggregation yielding dendritic complexes **1**(EC)$_3$ results in shorter retention times t_{SEC} relative to those of free **1** and **3a**–**3e** in size exclusion chromatography experiments. Plots of the glass transition temperatures T_g versus $n_e M^{-1}$ (n_e = number of benzyl end groups, M = molecular mass) give a linear relationship for dendrons **3b**, **3d**, and **3e**, as well as for the corresponding supramolecular dendrimers **1**(EC)$_3$ (Table 1, Figure 2). This behavior is in complete agreement with the chain end–free volume theory for dendrimers, which is expressed as $T_g = T_{g\infty} - K'(n_e M^{-1})$. On the other hand, the observed coincidence proves the existence of **1**(EC)$_3$ as discrete dendrimers.

Now we focus on the systems described in Figure 1 and formed by the stoichiometric mixing of core unit **1**, branching



Scheme 2. Aggregates **1**(EC)$_3$ with different end caps EC = **3a**–**e**.

Table 1: Physical properties of core **1** (C), end caps **3a**–**e** (EC), complexes **1**(EC)$_3$, and the AB$_2$ unit **2**.

	T_g [K][a]	n_e[b]	d [nm][c]	log K$_1$ [l mol^{-1}][f]	log K$_2$ [l mol^{-1}][g]	log K$_3$ [l mol^{-1}][h]	t_{SEC} [min][i]
1	418.66	–	0.82[d]	–	–	–	9.74
3a	322.98	2	1.38[e]	–	–	–	10.03
3b	310.20	2	2.14[d]	–	–	–	10.66
3c	324.98	4	1.70[e]	–	–	–	10.46
3d	317.64	4	0.66[d]	–	–	–	8.75
3e	321.72	8	0.67[d]	–	–	–	–
1(**3a**)$_3$	–	6	–	1.66	1.29	26.73	8.05
1(**3c**)$_3$	–	12	2.66[d]	4.21	4.71	7.48	7.22
1(**3b**)$_3$	312.60	6	–	3.82	2.60	8.99	7.96
1(**3d**)$_3$	316.04	12	2.38[d]	4.46	4.46	6.33	8.18
1(**3e**)$_3$	318.34	24	–	3.51	4.51	4.09	–
2	407.07	–	2.46[e]	–	–	–	9.73

[a] T_g = glass transition temperature. [b] n_e = number of terminal benzyl groups. [c] d = particle diameter (according to PFG NMR). [d] In CDCl$_3$. [e] In [D$_6$]DMSO. [f] K_1: C + EC ⇄ C(EC). [g] K_2: C(EC) + EC ⇄ C(EC)$_2$. [h] K_3: C(EC)$_2$ + EC ⇄ C(EC)$_3$. [i] t_{SEC} = retention time in size-exclusion chromatography (SEC) with MN Nucleogel GPC 500-5.

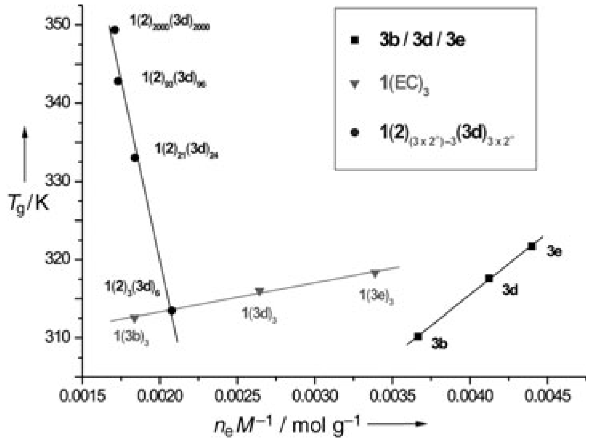


Figure 2. Plot of the glass transition temperature T_g vs. $n_e M^{-1}$, the quotient of the number of terminal benzyl groups and the molar mass, for the isolated end caps **3b**, **3d**, and **3e**, and for the complexes **1**(EC)$_3$, and the supramolecular dendrimer $\mathbf{1}\cdot\mathbf{2}_{(3\times2n-3)}\cdot\mathbf{3d}_{(3\times2n)}$.

element **2**, and end cap **3d** in a ratio of 1:(3 × 2^n−3):(3 × 2^n). DSC measurements of the AB_2 unit **2** afford a high glass transition temperature, indicative of aggregation to polymeric structures. As a result of the addition of core **1** and end cap **3d**, the polymer is disrupted, and a perfectly linear relationship between the glass transition temperature T_g and the $n_e M^{-1}$ ratio (and, thus, the generation number n) results (Figure 2). This demonstrates that discrete supramolecular dendrimers must be present in the solid state.

Due to the complexity of the associated exchange processes, the ^{1}H NMR shift of the NH proton signals during the titration of components **1**, **2**, and end cap **3a**–**3e** may no longer be employed to determine the various association constants. However, when one examines the determined equilibrium constants for the **1**(EC)$_3$ complexes (Table 1) one can assume that exchange processes will take place in solution. Nonetheless, by using pulsed field gradient (PFG) NMR spectroscopy we proved the existence of discrete

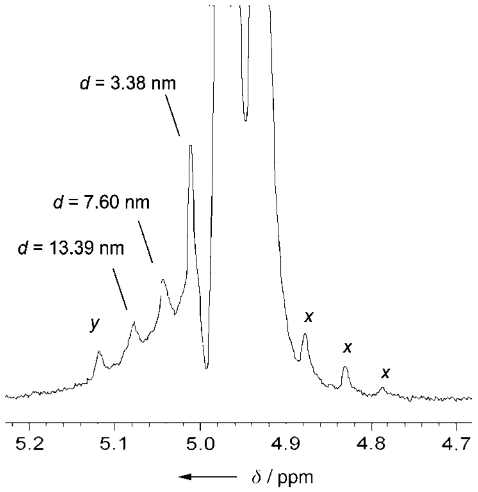


Figure 3. Section of the ^{1}H PFG NMR spectrum of a mixture of **1**, **2**, and **3d** in the G3 stoichiometry. The appearance of several discrete structures 3.4, 7.6, and 13.4 nm in diameter is evident. In addition, larger particles *y* are found, whose size cannot be determined due to unfavorable signal-to-noise ratio. This also holds for aggregates *x*.

dendrimers in chloroform. This method can be used to determine the diffusion constants of the dendrimers and thus, in turn, the dendrimer sizes. We employed the intensity decrease of the benzyl proton signals of core unit **1** as a probe. Components **1**, **2**, and **3d** were dissolved in $CDCl_3$, in stoichiometric amounts corresponding to dendrimers of the first, third, and fifth generation. For the G1 system $\mathbf{1}\cdot\mathbf{2}_3\cdot\mathbf{3d}_6$, aggregates of uniform size and with a diameter of 2.0 nm were found.[17] This particle size was confirmed by dynamic light-scattering experiments (3.12 nm). For complete self assembly of the dendrimers of lower generation, the required stoichiometric ratio of branching unit **2** and end caps **3a**–**3e** differs more than for higher generations (where a 1:1 limit is approached). Thus, it can be assumed that comprehensive discrimination will become increasingly difficult. This expectation has been verified. Figure 3 shows the ^{1}H NMR spectrum

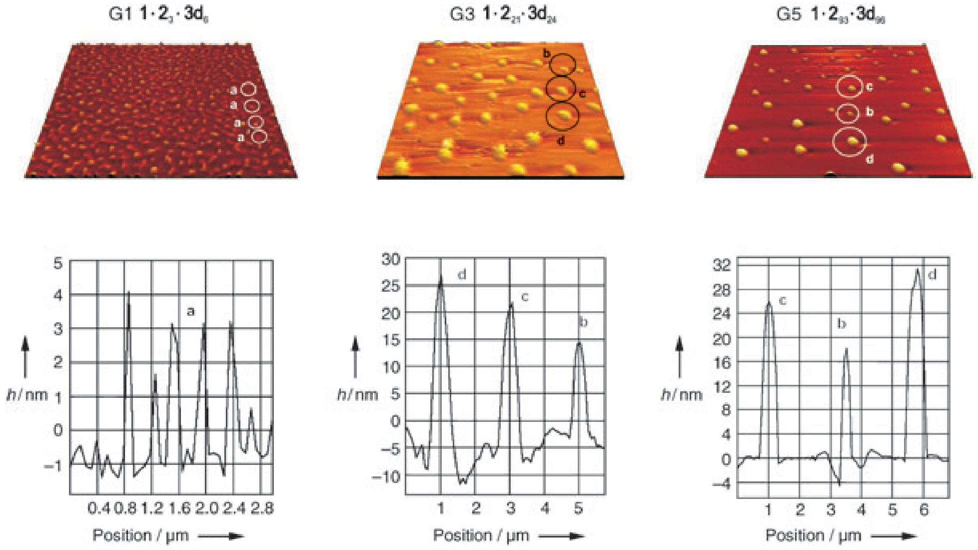


Figure 4. AFM images of supramolecular dendrimers with G1, G3, and G5 stoichiometry adsorbed on a Si wafer. Note the uniform structures with 4 nm (height profile)in the micrograph for G1. In addition, note the perfect globular shape of the higher generation aggregates.

of a mixture of components **1**, **2**, and **3d** in a stoichiometry corresponding to the G3 dendrimer. Besides the G3 dendrimer $\mathbf{1}\cdot\mathbf{2}_{21}\cdot\mathbf{3d}_{24}$ itself (3.4 nm), higher dendrimers are observed in low concentration (Figure 3). Similar observations are made for stoichiometries that correspond to even larger values of *n*. Nonetheless, all NMR experiments confirm unequivocally that discrete dendrimers are formed. Branching unit **2** exhibits very broad ^{1}H NMR signals in chloroform. However, these signals become sharp exactly at the point where core **1** and end cap **3** are added in amounts that correspond to a ratio of $1{:}(3\times2^n-3){:}(3\times2^n)$ (**1**:**2**:**3**), which is the stoichiometry of a dendritic assembly. This indicates the spontaneous formation of supramolecular dendrimers, in complete agreement with DSC results.

The existence of defined dendrimers is further corroborated by AFM investigations. After adsorption of the G1 dendrimer $\mathbf{1}\cdot\mathbf{2}_{3}\cdot\mathbf{3d}_{6}$ on a Si surface, uniform and widespread distribution of completely homogeneous objects is observed with a diameter of 4 nm (Figure 4, left), which is in agreement with the expected size of $\mathbf{1}\cdot\mathbf{2}_{3}\cdot\mathbf{3d}_{6}$. Repeated sample preparations gave completely analogous pictures. In no case were objects of different sizes observed. Similar preparations of solutions of higher generations such as $\mathbf{1}\cdot\mathbf{2}_{21}\cdot\mathbf{3d}_{24}$ (G3) and $\mathbf{1}\cdot\mathbf{2}_{93}\cdot\mathbf{3d}_{96}$ (G5) showed in a reproducible way that in addition to small discrete objects with diameters of 4, 7, and 12 nm larger objects are formed. The vast majority of these structures have diameters of 24, 28, and 32 nm (height profiles). These objects are too large to be attributed to isolated dendrimers. Presumably, these objects are clusters of higher generation dendrimers formed during an incomplete drying process in the course of the sample preparation. The discontinuity in the size distribution of aggregates is also a striking feature for the higher generation dendrimers. To summarize, the investigations presented here prove for the first time the programmed self-assembly of discrete supramolecular dendrimers from nondendritic units.

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