pH measurements were made with a Corning 440 pH meter equipped with an Aldrich micro-combination electrode calibrated with standard buffer solutions of pH 4, 7, and 10.

Electrospray mass spectrometry (ESI-MS) was performed on a LCQ spectrometer (Finnigan Corporation). The sample was infused at $3\,\mu L\,min^{-1}$, and the ions were produced in an atmospheric-pressure ionization (API)/ESI ion source. The source temperature was 453–473 K, and the flow rate of the drying gas was $0.9\,L\,min^{-1}$. A potential of 3.5 kV was applied to the probe tip, and a cone voltage of 5–10 V over 200–2000 Da was used. The quadrupole was scanned at $100\,amu\,s^{-1}$. The mass accuracy of all measurements was within 0.5 m/z units. Data acquisition and processing were performed with the Microsoft Windows NT operating system. The mass spectrum was simulated on a PC with IsoPro 3.0.

Molecular modeling was performed by using INSIGHT II (95.0, Biosym-MSI software) with the ESFF force field under the optimized pulldown in the builder module.

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Supramolecular Modification of the Periphery of Dendrimers Resulting in Rigidity and Functionality**

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The number, size, and function of peripheral groups of dendritic macromolecules determine many of the typical dendrimer properties, such as dense-shell packing, overall shape, and multivalency.[1] Properties related to solubility or physical state—semi-crystalline, glass, liquid crystalline, or liquid—are also strongly dependent on the nature of the dendritic end group.[2] Finally, specific interactions of guest molecules with the dendritic hosts rely on both the core and the shell of the dendrimer.[3–11] Most of the end-group modifications are based on covalent bonding, while the use of supramolecular interactions to obtain new dendritic peripheries is limited. Chechik and Crooks showed that ionic bonding between an amine-terminated poly(aminoamine) (PAMAM) and a fatty acid resulted in similar host–guest properties as those of the corresponding covalent amide analogues, while Tomalia and co-workers recently used ionic interactions to assemble dendrimers into higher aggregates.[12] We anticipated that the combination of a dense packing of the shell with the possibility of tuning the functionality of the periphery is of great importance in making dendrimers that can be used as shape-persistent building blocks in nanotechnology. Herein we disclose a general methodology to modify the periphery of poly(propyleneimine) dendrimers using such a supramolecular approach. The covalently attached adamantylurea end groups of the dendrimer are used as a scaffold to reversibly bind glycinylurea building blocks through strong and directional multiple interactions (Scheme 1).

The design of the modification is given in Scheme 1 and the scaffold is based upon DAB-dendr-(NHCONH-Ad)$_n$ (**1**, with $n = 4$, 8, 16, 32, and 64 for **1a–e**, respectively). These dendrimers were selected after studying DAB-dendr-(NHCO-Ad)$_n$ (**2a–e**), DAB-dendr-(NHCONH-$C_{12}H_{25}$)$_n$, and DAB-dendr-(NHCO-$C_{12}H_{25}$)$_n$ as well. All dendrimers were synthesized in quantitative yield from DAB-dendr-$(NH_2)_n$ and the corresponding isocyanate or acid chloride and were fully characterized.[13a] The concept of the supramolec-

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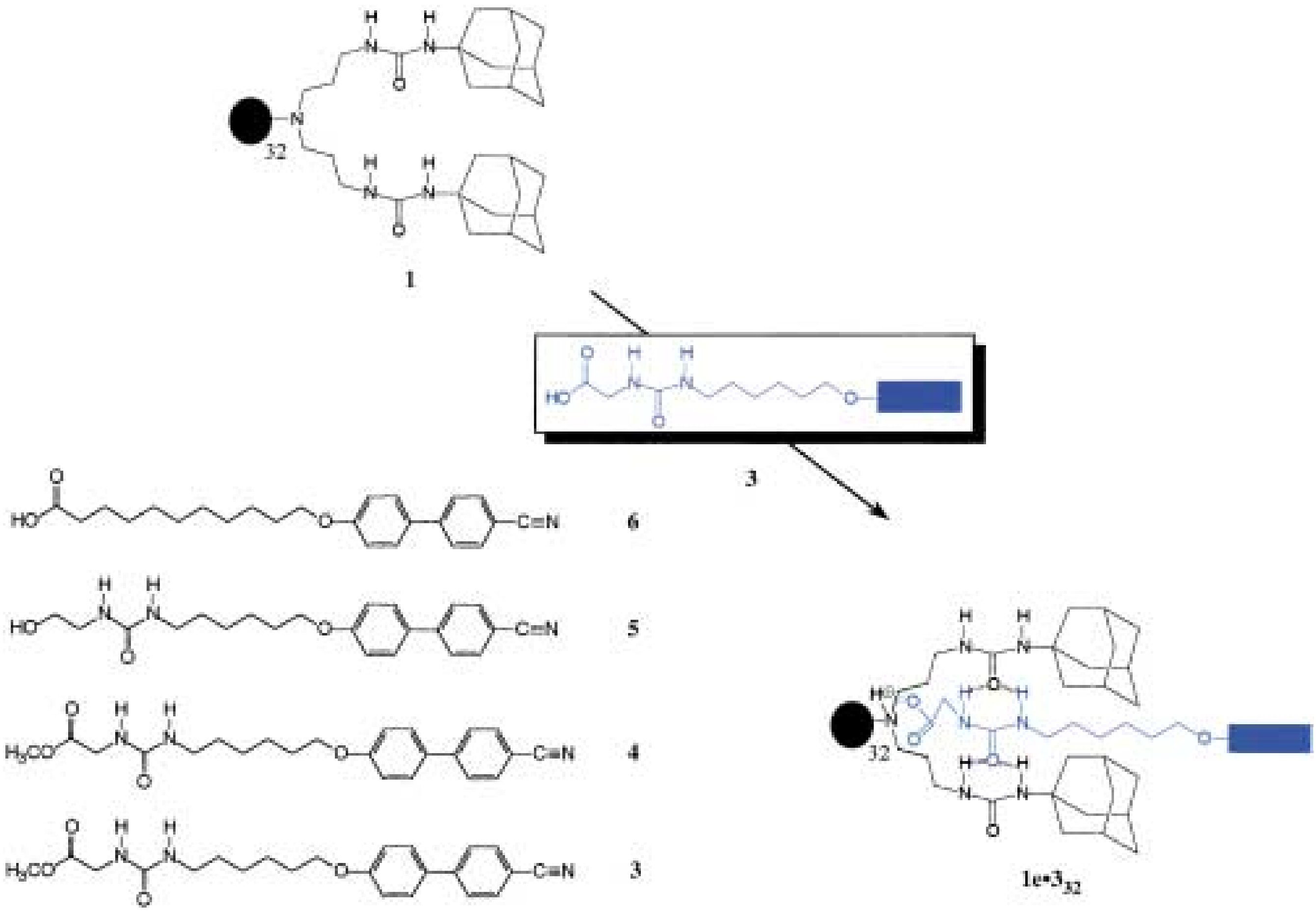

Scheme 1.

ular modification is illustrated with the glycinylurea derivative **3**, while **4**–**6** are used to emphasize the need for multiple interactions.[13b]

Compound **3** is barely soluble in chloroform (0.1 mg mL^{-1} for a saturated solution at room temperature),[14] however, upon adding an excess of **3** to a 10 mg mL^{-1} solution of **1e** in chloroform, most of **3** dissolves and it is evident after column chromatography on Biobeads that 32 molecules of **3** are assembled around one dendrimer molecule **1e**. ^{1}H NMR and IR spectroscopy were used to elucidate the structure of the complex (Figure 1).[15]

A comparison of the ^{1}H NMR spectrum of **1e** (Figure 1a) with that of **1e·3₃₂** (Figure 1c) shows there is a downfield shift from $\delta = 6.19$ and 5.44 (with an integral ratio of 1:1) to $\delta = 6.35$ and 5.70 (with an integral ratio of 2:1) for the two signals corresponding to the urea hydrogen atoms, while the methylene groups adjacent to the tertiary amines of the outermost shell are shifted from $\delta = 2.37$ to 2.83 as a result of the protonation of the adjacent tertiary amine. These shifts are in full agreement with the mechanism suggested in Scheme 1. The presence of adhered **3** in the mixture is discernable in the ^{1}H NMR spectrum before column chromatography on Biobeads (Figure 1b), but this is removed easily. Repeated chromatography does not decrease the number of molecules that are selectively assembled, which is illustrative of a high association constant (see below). The increased number of hydrogen-bonding interactions arising from the presence of the urea unit within the complex is also evident from IR spectroscopy, while there is no evidence in the spectra of nonbonded hydrogen atoms in **1e**, **1e·3₃₂**, and **4** (Figure 2).

Similar experiments were performed with the other generations of **1** and in all cases a 1:1 ratio of scaffold and clicking molecule **3** was observed. Dendrimer **2** with a bis(propylamide) pincer was also able to assemble with **3**, again using a 1:1 ratio of scaffold and **3**. Although the dodecyl-modified dendrimers with either the amide or urea linkage are able to assemble with compound **3** as well, the strong intramolecular hydrogen-bonding character of the native dendrimers limits their use. It is a prerequisite, however, to have both the carboxylic acid and the urea functionality present in the molecule to be attached; all three other molecules (**4**–**6**) as well as **1e** are obtained as pure compounds after chromatography on Biobeads when **4**–**6** and **1e** are mixed in a similar way as **3** and **1e**.

Unfortunately, the low solubility of **3** in chloroform hampers a detailed determination of the association constant at different ratios and generations of **1**.[15] However, an estimate of $K_{ass} = 10^5\,\mathrm{M}^{-1}$ in chloroform was made by using bis(propylurea)methylamine as a model compound for complexing with **3**.[16] Competition experiments were performed to analyze the cooperativity and the difference in the strength of the binding between **1e** and **2e**. The ^{1}H NMR spectra of a series of competition experiments using 1–32 moles of **3** for every mole of **1e** and **2e** showed that when **3**:**1e** is less than

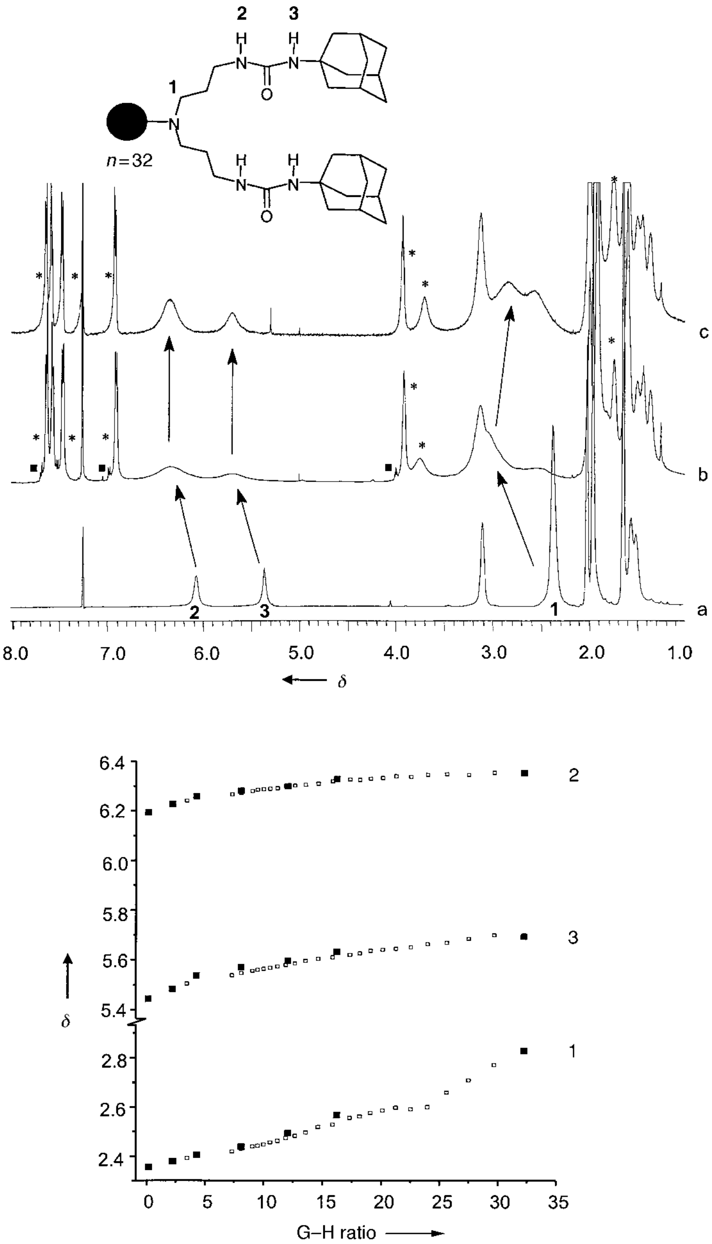

Figure 1. Top: ^{1}H NMR spectra (obtained at 500 MHz) of 1 mM solutions of a) **1e**, b) **1e**+$\mathbf{3}_n$ before column chromatography on Biobeads, and c) **1e** · $\mathbf{3}_{32}$ after column chromatography on Biobeads at 25 ± 0.5 °C in $CDCl_3$. Bottom: The shift of the methylene protons adjacent to the tertiary amines of the outermost shell (1) and of the urea hydrogen atoms (2 and 3) with an increasing number of molecules attached to **1e**.

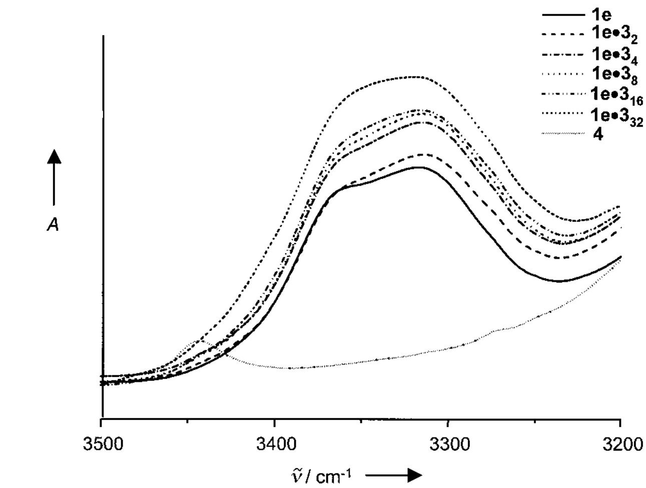

Figure 2. Partial IR spectra (showing N-H stretch vibrations) obtained from 1.5 mM solutions of **1e**, **1e** · $\mathbf{3}_{2-32}$, and **4** in CH_2Cl_2 at 25 °C.

16:1 all of **3** is bound to **1e**. When the guest:host ratio is 32:1, 24 molecules of **3** are bound to each molecule of **1e** and 8 to **2e**. These experiments show both the better fit of **3** with **1**, as well as the nonlinear association behavior.

NMR relaxation and NOE experiments in $CDCl_3$ solutions were performed to investigate the idea that the shell of the dendrimer should become denser as a consequence of the attachment of **3** and to investigate the location of the molecules attached. Some overlapping of the signals occurred in the ^{1}H NMR spectrum of the complex **1e** · $\mathbf{3}_{32}$ in $CDCl_3$, so the solution structures were further investigated for the complex **2e** · $\mathbf{3}_{32}$. The ^{1}H-^{1}H NOESY spectra (Figure 3) of the complex **2e** · $\mathbf{3}_{32}$ in $CDCl_3$ recorded at 25 °C showed clear NOE interactions as indicated.

We found that the T_1 relaxation times for **3** in compounds **1e** · $\mathbf{3}_n$ (***n*** = 2, 4, 8, 12, 16, and 32) decrease upon increasing the number ***n*** of molecules attached (Figure 4). A decrease in the T_1 relaxation time is indicative of a decrease in the molecular motion of **3**. Moreover, an increase in relaxation times is observed for the atoms in the dendritic shell. Such a behavior in T_1 is indicative of a decrease in molecular motion, that is, an

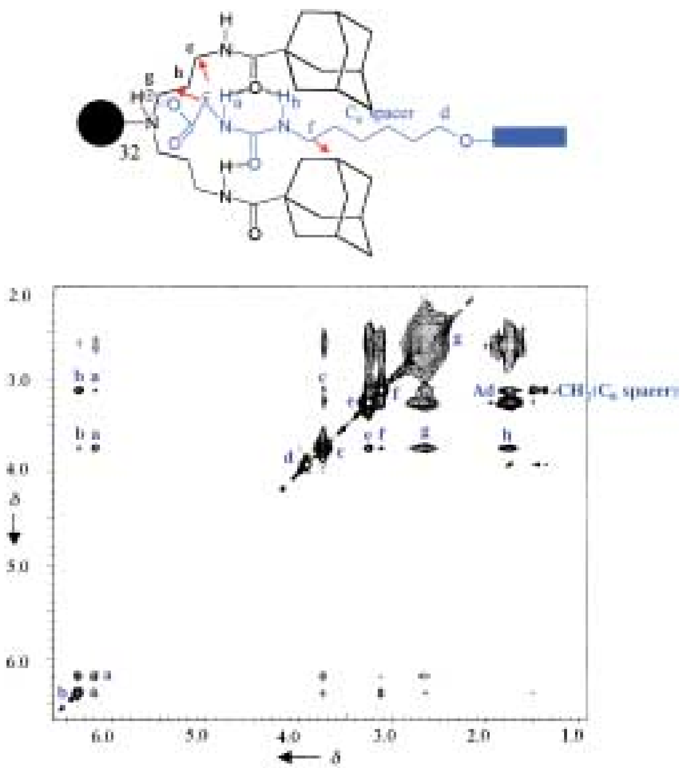

Figure 3. ^{1}H-^{1}H NOESY spectra (obtained at 500 MHz) of the complex **2e** · $\mathbf{3}_{32}$ in $CDCl_3$ recorded at 25 ± 0.5 °C.

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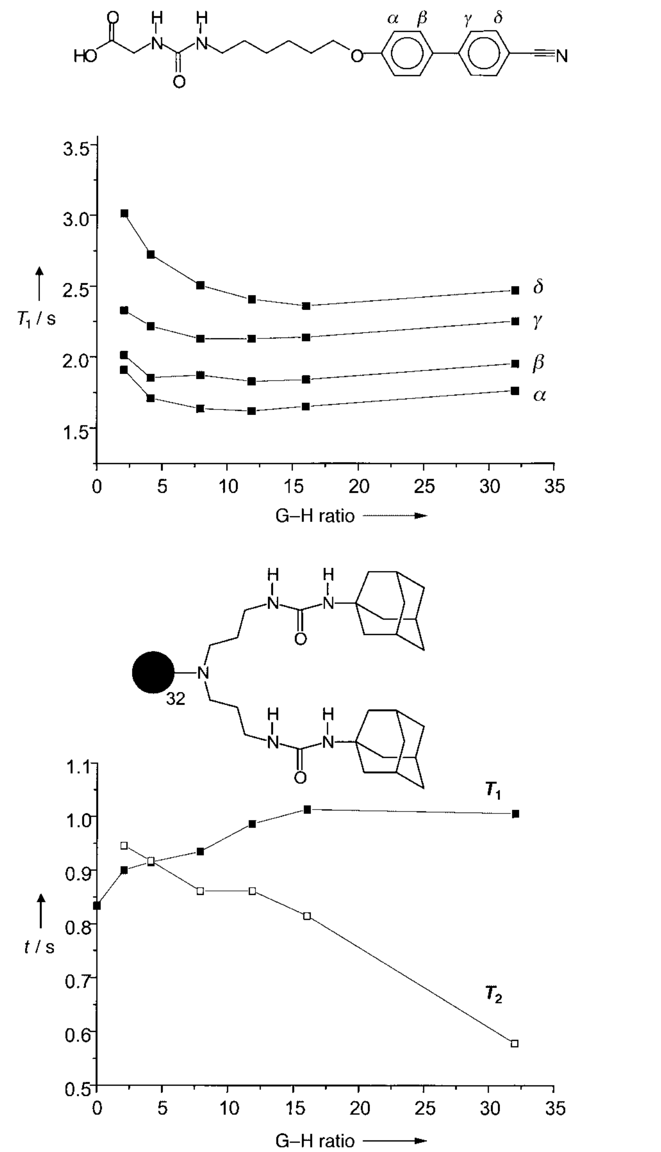

Figure 4. T_1 and T_2 ^{1}H NMR relaxation data versus guest–host ratio for atoms α, β, γ, δ (top), and the CH_2 group (bottom) in the bispropylurea moiety of the dendrimer in complex **1e·3$_{32}$**.

almost solid-phase behavior is obtained, similar to that obtained with the dendritic box.[17]

Furthermore, we have investigated the changes in the packing of the dendritic shell as a function of generation in compounds **1a–e·3$_n$** (**a**: $n=2$, **b**: $n=4$, **c**: $n=8$, **d**: $n=16$, and **e**: $n=32$). The T_1 relaxation times for the atoms close to the glycinylurea unit in **3** increase for higher dendrimer generations, that is, the mobility of these atoms decreases. However, the T_1 values for the atoms in the cyanobiphenyl unit remains constant, which means that the mobility of these atoms remain unperturbed. Moreover, we found that the T_1 relaxation data for the atoms in the dendritic shell increases with dendrimer generation. These results are indicative of an almost solid-phase behavior for higher generation dendrimers, and as a result dense-shell packing in solution is proposed.

This dense-shell packing of the supramolecular assemblies is, furthermore, illustrated by the physical properties of **1a–e·3$_n$**. We have shown before that, when the cyanobiphenyl unit is covalently attached to the poly(propyleneimine) dendrimers by a spacer, the resulting dendrimers are liquid crystalline as a result of the flexibility of the dendrimer itself.[18] However, the new concept yields materials that are glasses for all generations of **1a–e·3$_n$** and that start to flow at their glass transition temperatures of 45–50 °C, as determined by polarizing microscopy and differential scanning calorimetry (DSC).

In conclusion, we have presented results on a new general methodology to self-assemble end groups in a reversible way at the periphery of poly(propyleneimine) dendrimers using multiple secondary interactions. The globular shape of the dendrimer is used to confine the ionic and hydrogen-bonded interactions in the curved two-dimensional plane of the periphery. The architectures obtained show increased rigidity at the periphery of the core, while local conformational flexibility remains at the end of the molecule that is selectively bound. We foresee a great potential for this methodology, for example, in catalysis, drug delivery, and dynamic libraries, and work along these lines is in progress.

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[13] a) DAB-dendr-$(NH_2)_n$ denotes a dendrimer with a diaminobutane (DAB) core and n primary end groups. For the synthesis and characterization of the dendrimers, see the Supporting Information and A. P. H. J. Schenning, C. Elissen-Roman, J. W. Weener, M. P. P. L. Baars, S. J. van der Gaast, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, *120*, 8199–8208; b) for the synthesis of the glycinylurea derivative **3** and **4**–**6**, see the Supporting Information.
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[15] We propose to use the notation **1e·3$_{32}$**, meaning that 32 molecules of **3** are attached (·) to dendrimer **1e**.
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