

Scheme 1.

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better fit of 3 with 1, as well as the nonlinear association behavior.

NMR relaxation and NOE experiments in  $\text{CDCl}_3$  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  $^1\text{H}$  NMR spectrum of the complex  $1\text{e}\cdot 3_{32}$  in  $\text{CDCl}_3$ , so the solution structures were further investigated for the complex  $2\text{e}\cdot 3_{32}$ . The  $^1\text{H}$ - $^1\text{H}$  NOESY spectra (Figure 3) of the complex  $2\text{e}\cdot 3_{32}$  in  $\text{CDCl}_3$  recorded at  $25^\circ\text{C}$  showed clear NOE interactions as indicated.

We found that the  $T_1$  relaxation times for 3 in compounds  $1\text{e}\cdot 3$ , ( $n=2, 4, 8, 12, 16$ , 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 almost solid-phase behavior is obtained, similar to that obtained with the dendritic box.<sup>[17]</sup>

Furthermore, we have investigated the changes in the packing of the dendritic shell as a function of generation in compounds  $1\text{a}\cdot\text{e}\cdot 3_n$  ( $a: n=2, b: n=4, c: n=8, d: n=16$ , and  $e: n=32$ ). The  $T_1$  relaxation times for the atoms close to the glycinyurea 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  $1\text{a}\cdot\text{e}\cdot 3_n$ . 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.<sup>[18]</sup> However, the new concept yields materials that are glasses for all generations of  $1\text{a}\cdot\text{e}\cdot 3_n$ , and that start to flow at their glass transition temperatures of  $45$ – $50^\circ\text{C}$ , 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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- [1] D. A. Tomalia, A. Naylor, W. A. Goddard III, *Angew. Chem.* 1990, 92, 119–156; *Angew. Chem. Int. Ed. Engl.* 1990, 29, 138–173.
- [2] A. W. Boorman, H. M. Jansen, E. W. Meijer, *Chem. Rev.* 1999, 99, 1665–1688, and references therein.
- [3] F. Zeng, S. C. Zimmerman, *Chem. Rev.* 1997, 97, 1681–1712, and references therein.
- [4] M. W. P. L. Baars, E. W. Meijer, *Top. Curr. Chem.* 2000, 210, 131–182.
- [5] a) C. Valerio, J. L. Filhaut, J. Ruiz, J. Guinard, J. C. Blais, D. Astruc, *J. Am. Chem. Soc.* 1997, 119, 2588–2589; b) C. Valerio, E. Alonso, J. Ruiz, J. C. Blais, D. Astruc, *Angew. Chem.* 1999, 111, 1855–1859; *Angew. Chem. Int. Ed.* 1999, 38, 1747–1751.
- [6] M. W. P. L. Baars, F. E. Froehling, E. W. Meijer, *Chem. Commun.* 1997, 1959–1960.
- [7] D. A. Tomalia in *Modular Chemistry, Nato ASI Series, Vol. 499* (Ed.: J. Michl), Kluwer, Dordrecht, 1997, pp. 183–191.
- [8] V. V. Narayanan, G. R. Newkome, *Top. Curr. Chem.* 1998, 197, 19–77.
- [9] S. C. Zimmerman, F. W. Zeng, D. E. C. Reichert, S. V. Kolonichin, *Science* 1996, 271, 1095–1098.
- [10] G. R. Newkome, B. D. Wooley, E. He, R. Guther, G. R. Baker, O. H. Escamilla, J. Merrill, H. Luftmann, *Chem. Commun.* 1996, 2737–2738.
- [11] G. R. Newkome, C. N. Moorefield, F. Vogtle, *Dendritic molecules: Concepts, Syntheses, perspectives*, VCH, Weinheim, 1996, chap. 9.
- [12] a) V. Chechik, M. Zhao, R. M. Crooks, *J. Am. Chem. Soc.* 1999, 121, 4910–4911; b) S. Uppuluri, D. R. Swanson, L. T. Pfläher, J. Li, G. L. Magnauer, D. A. Tomalia, *Adv. Mater.* 2000, 12, 796–800.
- [13] a) DAB-dendr-(NH<sub>2</sub>)<sub>n</sub> denotes a dendrimer with a diamisobutane (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. W. 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 glycinyurea derivative 3 and 4–6 see the Supporting Information.
- [14] The solubility of 3 in chloroform was determined by UV spectroscopy.
- [15] We propose to use the notation  $1\text{e}\cdot 3_{32}$  meaning that 32 molecules of 3 are attached (·) to dendrimer 1a.
- [16] The association constant  $K_a$  was investigated by UV spectroscopy. The concentration of the free guest was determined from its solubility in chloroform.
- [17] J. F. G. A. Jansen, E. M. M. de Brabander-van den Berg, E. W. Meijer, *Science* 1994, 265, 1226–1229.
- [18] M. W. P. L. Baars, S. H. M. Sontjens, H. M. Fisher, H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* 1998, 4, 2456–2466.

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### Supramolecular Modification of the Periphery of Dendrimers: Assessing 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.<sup>[1]</sup> 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.<sup>[2]</sup> Finally, specific interactions of guest molecules with the dendritic hosts rely on both the core and the shell of the dendrimer.<sup>[3–11]</sup> 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(aminocaine) (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.<sup>[12]</sup> 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 glycylurea 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)<sub>n</sub> (1, with  $n = 4, 8, 16, 32$ , and  $64$  for 1a–e, respectively). These dendrimers were selected after studying DAB-dendr-(NHCO-Ad)<sub>n</sub> (2a–e), DAB-dendr-(NHCONH-C<sub>12</sub>H<sub>25</sub>)<sub>n</sub>, and DAB-dendr-(NHCO-C<sub>12</sub>H<sub>25</sub>)<sub>n</sub> as well. All dendrimers were synthesized in quantitative yield from DAB-dendr-(NH<sub>2</sub>)<sub>n</sub> and the corresponding isocyanate or acid chloride and

were fully characterized.<sup>[13a]</sup> The concept of the supramolecular modification is illustrated with the glycylurea derivative 3, while 4–6 are used to emphasize the need for multiple interactions.<sup>[13b]</sup>

Compound 3 is barely soluble in chloroform (0.1 mgmL<sup>−1</sup> for a saturated solution at room temperature),<sup>[14]</sup> however, upon adding an excess of 3 to a 10 mgmL<sup>−1</sup> 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. <sup>1</sup>H NMR and IR spectroscopy were used to elucidate the structure of the complex (Figure 1).<sup>[15]</sup>

A comparison of the <sup>1</sup>H NMR spectrum of 1e (Figure 1a) with that of 1e·3<sub>32</sub> (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 <sup>1</sup>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·3<sub>32</sub>, 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.<sup>[15]</sup> However, an estimate of  $K_{\text{ass}} = 10^5 \text{ M}^{-1}$  in chloroform was made by using bis(propylurea)methylamine as a model compound for complexing with 3.<sup>[16]</sup> Competition experiments were performed to analyze the cooperativity and the difference in the strength of the binding between 1e and 2a. The <sup>1</sup>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 16:1 all of 3 is bound to 1e, while when the guest:host ratio is 32:1, ~~either 24~~ 24 molecules of 3 are bound to each molecule of 1e and 8 ~~to~~ to 2e. These experiments show both the

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

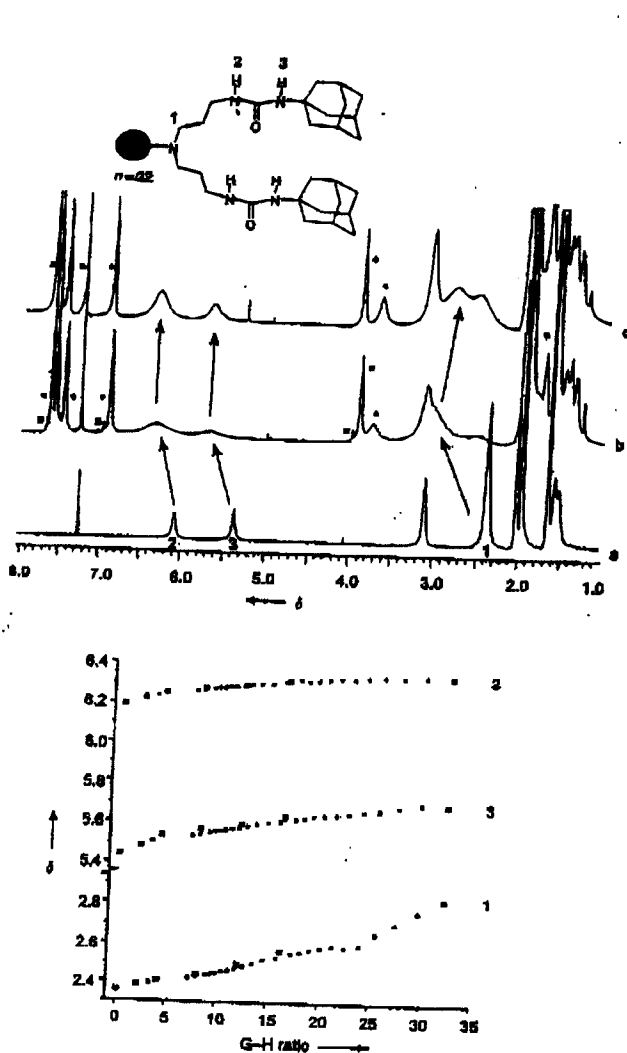


Figure 1. Top: <sup>1</sup>H NMR spectra (obtained at 500 MHz) of 1 mM solutions of a) 1a, b) 1a-3, before column chromatography on Biobeads, and c) 1a-3<sub>n</sub> after column chromatography on Biobeads at 25 ± 0.5 °C in CDCl<sub>3</sub>. Bottom: The shift of the methylene protons adjacent to the tertiary amines of the outermost shell (1) and of the urea hydrogen atoms (2 and 3) with an increasing number of molecules attached to 1a.

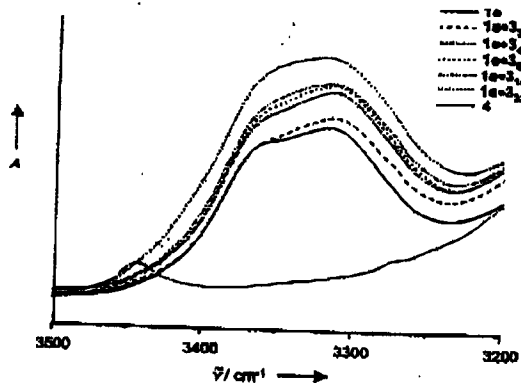


Figure 2. Partial IR spectra (showing N-H stretch vibrations) obtained from 1.5 mM solutions of 1a, 1a-3, 1a-3<sub>n</sub>, and 4 in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C.

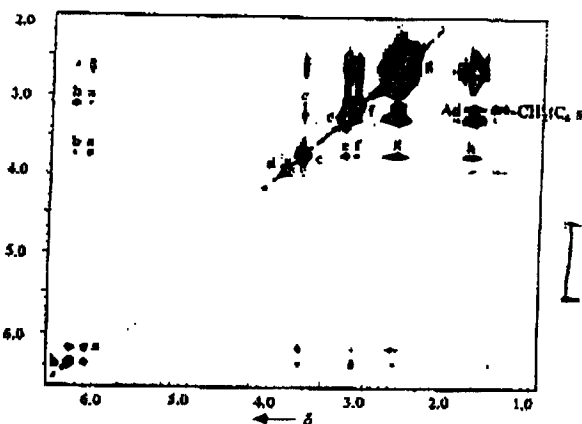
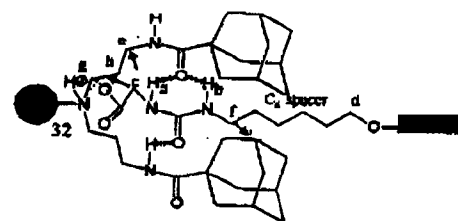


Figure 3. <sup>1</sup>H-<sup>1</sup>H NOESY spectra (obtained at 500 MHz) of the complex 2a-3<sub>n</sub> in CDCl<sub>3</sub>, recorded at 25 ± 0.5 °C.

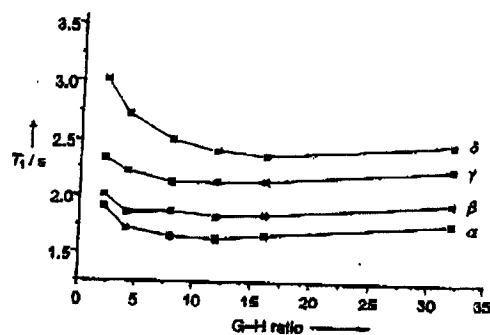
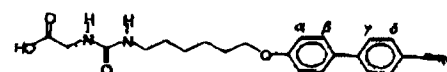


Figure 4. T<sub>1</sub> and T<sub>2</sub> <sup>1</sup>H NMR relaxation data versus guest-host ratio for atoms α, β, γ, δ (left), and the CH<sub>2</sub> group (right) in the bispropylurea moiety of the dendrimer in complex 1a-3<sub>n</sub>.