Solvent-Dependent Swelling of Poly(amido amine) Starburst Dendrimers

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Dendrimer molecules are regularly branched macromolecules comprised of short multifunctional monomers.[1,2] Stepwise synthesis around an initiator core leads to a treelike fractal structure of the polymer.[3] Such structures have been designed from various dendritic precursor components.[4−6] For PAMAM dendrimers, either ammonia or ethylenediamine is used as the core, which results in three or four dendrons growing from the center of the molecule. The following building blocks (so-called generations, *g*) consist of methyl methacrylate and ethylenediamine.

There is a growing interest in dedrimeric molecules from a scientific and technical point of view. Dendrimers can be viewed as model compounds for self-assembling biological systems like vesicles or micellar systems. A potential technical application of these polymers includes nanosize reaction vessels and chemical sensors. Some researchers take dendrimer molecules as subunits to synthesize even more complex supramolecular assemblies.[7] It is known that with increasing generation number a considerable part of the inner surface and volume of the dendrimer molecules is accessible to the solvent.[8] Therefore, it is expected that the dendrimers have a swelling capability (e.g. dependent on the solvent quality), which could be used in separation media and drug delivery systems.[9]

There have appeared a number of theoretical studies to describe the detailed molecular structure of dendritic polymers. In a first mean-field model by de Gennes and Hervet[10] it was assumed that successive generations of monomers lie in concentric shells about the core, leading to an onion-like structure. Following coarse-grained kinetic models,[11] Monte Carlo,[12,13] and molecular dynamics simulations[8,14] on an atomic level have questioned this finding. In general, these investigations indicate that for early generations a high monomer density region appears, where the monomer units exist in a rather stretched conformation, extending from the central core. Higher generations ($g > 5$) exhibit a significant flexibility, and chain backfolding was observed. The monomers of the higher generations can be found in all regions of the dendrimer molecule, including the core region. Very recent predictions from a self-consistent mean-field model are in line with these findings.[15]

Murat and Grest[14] have performed a molecular dynamics study to investigate the effect of solvent quality on the molecular dimensions of dendrimers. The density profile reveals a high-density core domain, followed by a plateau region where the dendron density depends on the solvent quality, being higher under poor solvent conditions. The dendrimer size was found to scale with the number of monomers N as $R_g \propto N^{\nu}$ with $\nu = 0.33$. Their results confirm that monomer segments of later generations do fold back and can occupy the central region of the molecules. Based on a kinetic growth model, Lesanec and Muthukumar[11] have obtained a slightly different scaling exponent with $\nu = 0.22 \pm 0.02$.

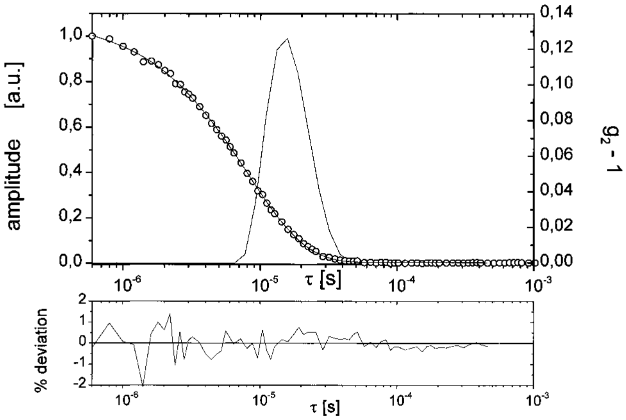

Figure 1. Typical intensity autocorrelation function for PAMAM dendrimers (generation 6; 6.98 g/L in methanol) together with a fit to a single-exponential decay and the distribution of relaxation rates from an inverse Laplace transformation of the correlation function by CONTIN. The residuals correspond to the single-exponential fit. Similar dynamic light scattering data have been obtained for the higher generation dendrimers in all solvents. The low molecular weight dendrimers were not investigated because of their low scattering intensity.

We have investigated the hydrodynamic properties of PAMAM dendrimers in different solvents by holographic relaxation spectroscopy (HRS). Our main emphasis was to characterize the influence of solvent quality on the molecular dimensions in solution. In addition, we have tested theoretical scaling relationships predicted for these molecules.

Experimental Section. The PAMAM dendrimers with an ethylenediamine core were obtained from Polyscience Europe GmbH ($g = 6$) and Aldrich Chemical Co. ($g = 2, 3, 4, 8, 10$), and the labeling compound 4-(dimethylamino)-4′-isothiocyanatoazobenzene (DABITC) was purchased from Fluka Chemie GmbH. The unlabeled dendrimer molecules have been characterized by dynamic light scattering. As shown in Figure 1, the intensity autocorrelation function is well represented by a single-exponential decay. The molecular weight distribution was estimated from the variance σ of a cumulant and CONTIN analysis,[16,17] respectively. Both methods gave $M_w/M_n \leq 1.04$ (according to $M_w/M_n = 1 + \sigma$).

The dye molecules were chemically attached to the dendrimers in the following way: 100 μL of the 10% methanolic solution of the dendrimer was added to 900 μL of a freshly prepared mixture of 0.3 mg/mL DABITC in methanol. The solution was stirred at room temperature for 24 h. After the solvent was evaporated under vacuum, the labeled dendrimer was dissolved in 1.0 mL of the corresponding solvent. The aqueous solution contained 0.1 M NaCl in a Tris buffer at pH 8.0. The labeled dendrimer was purified by gel chromatography using Sephadex 25G. The amount of dye molecules per dendrimer was estimated from UV spectra, assuming the same absorption coefficient for free and attached DABITC dye molecules. The values presented in Table 1 are in good agreement with theoretical label densities as expected from the molar ratio during synthesis. In general, 2−6% of the amino end groups of the PAMAM dendrimer molecules were modified. For the HRS measurements, the samples were diluted to a final concentration of 1.0 mg/mL and filtered through a 0.2

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Table 1

	ethylenediamine core					NH_3 core	
generation	MW[a] (g/mol)	% of labeled end groups	$R_h(H_2O)$ (nm)	R_h(MeOH) (nm)	R_h(BuOH) (nm)	MW[a] (g/mol)	lit R_h (nm)
2	3244	6.3[b]	1.46	1.53	1.48	2411	1.11*c*
3	6896	3.1[b]	1.99	1.99	1.85	5147	1.55[c]
4	14202	2.1	2.66	2.48	2.30	10619	2.00[c]
5						21563	2.65,[c] 2.80[d]
6	58035	2.9	4.78	3.82	2.85	43451	3.35[c]
7						87227	3.80,[c] 4.10[d]
8	233366	2.0	7.14	5.79	4.49	174779	4.50[c]
10	934691	2.4	9.11	7.23		700091	6.50[d]

[a] Calculated for the ideal structure of the dendrimers. [b] Assuming one label molecule per dendrimer (the average ratio of dye to dendrimer molecules was below one). [c] From intrinsic viscosity measurements (ref 20). [d] From dynamic light scattering data (ref 21).

μm filter (Anotop 10, Whatman Inc.) into dust-free scattering cells. Table 1 gives an overview of the dendrimers studied together with the label concentration.

The HRS apparatus is described in detail elsewhere.[18] The writing beam of an Ar ion laser (Spectra-Physics, Model 2020) was split into two beams of equal intensity, which were focused into the sample cell to create the holographic grating. The intensity of the reading beam from a He–Ne laser, diffracted from the concentration grating of the photoexcited dye, was detected by a photomultiplier tube and analyzed by a computer-controlled MCS card (Oxford Instruments Inc.). The intensity of the writing beam was in the range of 1–3 mW with a typical pulse width of about 0.5 ms. Using the phase shift with addition method,[19] about 100 spectra were accumulated. The decay profile was fitted to an exponential function

$$I(t) = A\mathrm{e}^{-2t/\tau} + B \tag{1}$$

with

$$\frac{1}{\tau} = \frac{1}{\tau_{\mathrm{life}}} + q^2 D$$

where q ($=4\pi n/\lambda \sin(\theta/2)$) is the wave vector, τ is the characteristic decay time, A is proportional to the amplitude of the optical grating, B is the background intensity, τ_{life} is the lifetime of the photoexcited state, and D the translational diffusion coefficient.

Results and Discussion. We have investigated the translational diffusion of PAMAM dendrimers of generation 2–10 in water, methanol, and butanol, solvents that are known to be of decreasing quality for the monomers. A typical HRS spectrum is presented in Figure 2. As judged from the random distribution of the residuals, it can be described by a single-exponential decay with a characteristic decay time τ, which is related to the translational diffusion coefficient according to eq 1. For all systems studied, the diffusion coefficient was obtained from q-dependent measurements (data not shown). According to the Stokes–Einstein equation

$$D = \frac{kT}{6\pi\eta_0 R_h} \tag{2}$$

we have calculated an apparent hydrodynamic radius from the translational diffusion coefficient D, where η_0 is the solvent viscosity. The experimental data for the dendrimers in different solvents are presented in Figure 3a. For the low-generation dendrimers ($g \leq 4$), we observed that the translational diffusion coefficient, and hence the size of the molecules, is not significantly different in the various solvents. It is reasonable to assume that for the low-generation dendrimers the configuration of the molecules is determined by the entropic part of the free energy while the excluded-volume interaction between monomers gives a minor contribution. For the higher dendrimer generations however we found a strong influence of the solvent quality on the hydrodynamic dimensions of the particles. The size of the dendrimer molecules increases significantly with increasing polarity of the solvent (water > methanol > butanol). Our experimental results are consistent with computer simulations on dendritic molecules, which predict that high molecular weight PAMAM dendrimers exhibit an increasing solvent-accessible surface and interior volume. The polar character of the poly(amido amine) chains favors the interaction with polar solvent molecules, leading to an uptake of solvent, and hence to a swelling of the dendrimer molecules.

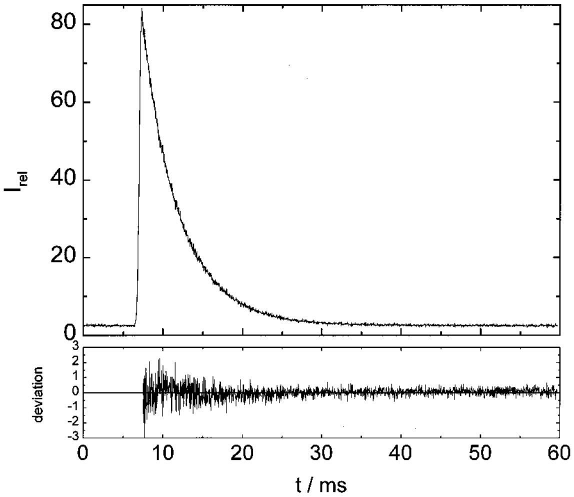

Figure 2. Typical HRS spectrum together with a single-exponential fit according to eq 1. Experimental conditions: dendrimer generation 6 (0.5 mg/mL in water); $T = 25$ °C; $\theta = 4.24^0$.

Murat and Grest[14] have presented a molecular dynamics simulation of dendrimers, considering the difference in solvent quality. They observed an increase of the average mean squared radius of gyration, going from athermal to good solvent conditions. According to their results, R_g should roughly increase as $R_g \propto N^{1/3}$, with N being the number of monomers per dendrimer molecule. Lescanec and Muthukumar have simulated the growth of starburst dendrimers by a kinetic model. They found that the radius of gyration scales with $R_g \propto N^{0.22}$. Figure 3b shows our experimental data for the hydrodynamic radius as a function of the molecular weight. In the following, we assume that a fixed

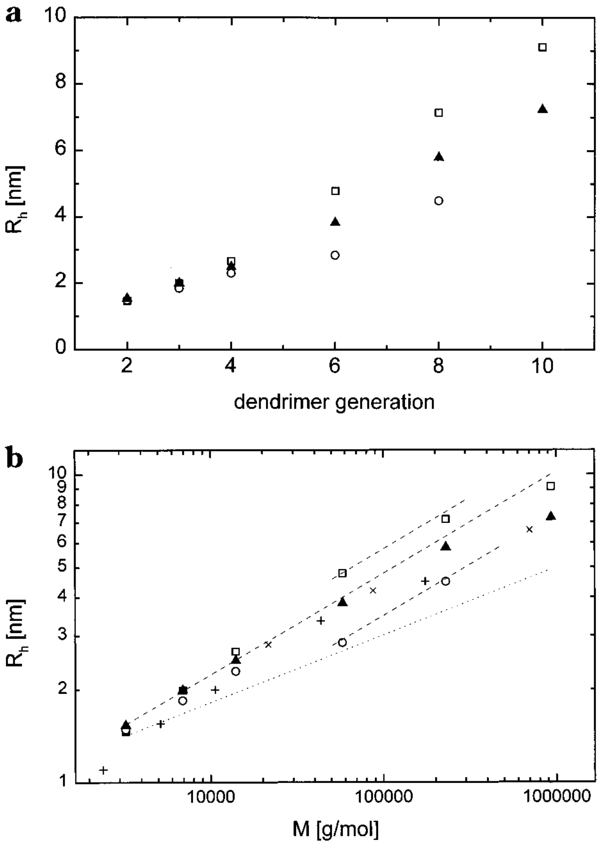

Figure 3. (a) Hydrodynamic radius of PAMAM dendrimers of different generations in water (□), methanol (▲), and butanol (○). (b) The same quantity as a function of the molecular weight in a double-logarithmic plot; water (□), methanol (▲), and butanol (○). We have also included experimental data for PAMAM dendrimers with an ammonium core from intrinsic viscosity (×) and dynamic light scattering (+) data. (- - -) lines with a slope of $\nu = 0.33$ according to the scaling predictions of Murat and Grest;[14] (···) similar line with a slope of $\nu = 0.22$ as obtained by Lescanec and Muthukumar.[11]

relationship between the hydrodynamic radius and the radius of gyration exists. For methanol as a marginal solvent, the predicted scaling behavior by Murat and Grest is accomplished for all dendrimer generations, except for $g = 10$. The data for the other solvents are at least not in disagreement with the theoretical predictions, although the low number of data points prohibits us from drawing a final conclusion. Similar to the situation in methanol, we observed that the hydrodynamic radius for the dendrimer of generation 10 in water is again significantly smaller than expected from the scaling law. At this point, we do not have a well-reasoned explanation for this effect. However, with generation 10 the dense-packed stage for this dendrimer family is reached, and one cannot exclude severe defects during the synthesis of these molecules.

In Figure 3b, we have also included experimental data for PAMAM dendrimers with three dendrons (ammonia core) from viscosity measurements[20] and dynamic light scattering.[21] It is worth noticing that the hydrodynamic radii for the PAMAM dendrimers with an ammonia core do not follow the scaling predictions although the molecular structures for the theoretical studies were derived from three dendron molecules. For a final assessment of the theoretical model predictions it is therefore necessary to investigate whether the different molecular design of the dendrimers studied here would lead to the same scaling exponent. The dotted line in Figure 3b represents the scaling behavior given by Lescanec and Muthukumar[8] with $R_g \propto N^{0.22}$. Obviously, the experimental data are in better agreement with the MD simulations results, which predict a stronger increase in the hydrodynamic radius with dendrimer molecular weight.

In conclusion, our experimental data reveal that low-generation PAMAM dendrimers exhibit similar hydrodynamic dimensions in various solvents. A significant swelling in good solvent conditions is observed for larger dendrimer molecules ($g > 4$), which is consistent with recent model calculations. This finding might have implications for technical applications of these polymers, e.g. as separation or transport media. A change in the solvent quality could be used to control the trapping and release of molecules from the interior of the dendritic particles.

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References and Notes

(1) Tomalia, D. A. *Aldrichim. Acta* **1993**, *26*, 91.
(2) Issberger, J.; Moors, R.; Voegtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2413.
(3) Tomalia, D. A.; Maylor, A. M.; Goddard, W. A., III. *Angew. Chem.* **1990**, *102*, 119; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138.
(4) Gitsov, I.; Frechet, J. M. J. *Macromolecules* **1993**, *26*, 6536.
(5) Newkome, G. R.; Moorefield, C. C. In *Advances in Dendritic Macromolecules*; Newkome, G. R., Ed.; JAI Press: Greenwich, 1993.
(6) Lorentz, K.; Holder, D.; Stühn, B.; Mülhaupt, R.; Frey, H. *Adv. Mater.* **1996**, *8*, 414.
(7) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095.
(8) Naylor, A. M.; Goddard, W. A., III; Kiefer, G. E.; Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339.
(9) Jansen, J. F. G. A.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.
(10) de Gennes, P. G.; Hervet, H. *J. Phys. Lett.* **1983**, *44*, L351–L360.
(11) Lescanec, R. L.; Muthukumar, M. *Macromolecules* **1990**, *23*, 2280.
(12) Mansfield, M. L.; Klushin, L. I. *Macromolecules* **1993**, *26*, 4262.
(13) Mansfield, M. L. *Polymer* **1994**, *35*, 1827.
(14) Murat, M.; Grest, G. S. *Macromolecules* **1996**, *29*, 1278.
(15) Boris, D.; Rubinstein, M. *Macromolecules* **1996**, *29*, 7251.
(16) Provencher, S. W. *Comput. Phys. Commun.* **1982**, *27*, 213.
(17) Provencher, S. W. *Comput. Phys. Commun.* **1982**, *27*, 229.
(18) Kottmann, J. *Holographische Relaxationsspektroskopie*, 1st ed.; Cuvillier: Göttingen, 1996.
(19) Miles, D. G.; Lamb, P. D.; Rhee, K. W.; Johnson, C. S., Jr. *J. Phys. Chem.* **1983**, *87*, 4815.
(20) Mansfield, M. L.; Klushin, L. I. *J. Phys. Chem.* **1992**, *96*, 3994.
(21) Guo, Y.; Langley, K. H.; Karasz, F. E. *Macromolecules* **1992**, *25*, 4902.

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