Top Curr Chem (2005) 245: 239–252
DOI 10.1007/b98170

Equilibrium Structure of Dendrimers – Results and Open Questions

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Abstract We review the problem of the structure of dendrimers in solution. Special emphasis is placed on recent theoretical work and computer simulations of the equilibrium structure of dissolved dendrimers. These investigations have led to the irrefutable conclusion that flexible dendrimers exhibit a dense-core structure in which the terminal groups are partially folded back. Hence, flexible dendrimers do not have a well-defined surface or interior. These conclusions are in total accord with recent experimental studies employing small-angle neutron scattering.

Keywords Dendrimers · Small-angle neutron scattering · Small-angle X-ray scattering · Monte-Carlo simulation · Molecular Dynamics · Effective interaction

1
Introduction

Dendrimers and dendritic polymers present one of the most active fields in modern research of supramolecular chemistry. Since the first pioneering studies by Vögtle et al. [1] and by Tomalia et al. [2] in the late 1970s and early 1980s there has been an exponential growth of the number of papers devoted to dendrimers and related systems [3, 4]. In particular, the regular tree-like molecular dendrimers have been a major challenge for modern synthesis. Hence, a tremendous amount of activity has been devoted to purely synthetic aspects in this field in the last 20 years. Surveys of work done on the synthesis of dendrimers may be found in recent reviews [3, 4].

Much less attention has been paid to the physical chemistry and physics of dendrimers. The physical properties of dendritic molecules dissolved in suitable solvents, however, are decisive for most of the applications now envisioned for dendrimers. Indeed, the further development of the field will now depend mainly on the number of applications that may materialize in the course of research over the next few years.

A question that is central to this point is the equilibrium structure of dendrimers in solution. Figure 1 illustrates the main point by showing the chemical structure of a flexible fourth-generation dendrimer with well-defined endgroups. This picture suggests that the density of segments grows from the center to the periphery of the molecule. This "dense-shell" picture of dendrimers has dominated the field for nearly two decades. It obtained strong support owing to a much-cited paper of Hervet and de Gennes from 1983 [5], which gave the first theoretical treatment of this dense-shell model of dendrimers. Recently, Zook and Pickett [6] have re-examined this approach. These authors have delineated the weak points of the approach used by Hervet and de Gennes [5] and demonstrated that the most probably conformation of a dendrimer has its maximum in the center of the molecule. This is in general accord with a great number of theoretical studies that have appeared since 1990, when Lescanec and Muthukumar [7] demonstrated for the first time the validity of the "dense-core" picture of dendrimers. Owing to the flexible dendritic scaffold (see Fig. 1), the overall structure is an average of a large number of possible conformers. In particular, in many conformers the endgroups will fold back into the interior of the molecule. Hence, theory demonstrated unambiguously that flexible dendrimers would have no well-defined structure in solution that could be characterized by a "surface" and internal holes. A survey of the large number of theoretical studies has been given recently [8]. It is fair to say that the theory of dendritic structure is now well-developed and has come to irrefutable conclusions.

Scattering methods such as small-angle neutron scattering (SANS) and small-angle X-ray scattering (SAXS) are the only experimental tools available to analyze the spatial structure of dissolved dendrimers in detail [9]. The analysis of dendrimers by SANS and SAXS is less straightforward than is anticipated in many recent studies, however. As discussed at length recently [8, 10], the information furnished by the scattering intensity measured for dilute solutions of dendrimers is rather limited and subject to a number of experimental uncertainties. Under no circumstances does small-angle scattering give the sort of complete information obtained from, e.g., the analysis of a crystal structure by wide-angle scattering. As demonstrated recently, studies of small-angle scattering must be supplemented by computer simulations in order to avoid faulty conclusions [11].

Despite these problems, studies using small-angle scattering have provided strong support for the dense-core picture of dendrimers. In particular, a recent investigation by SANS demonstrated directly that endgroups fold back into the interior of the molecule as has long been predicted by theory. For a sur-

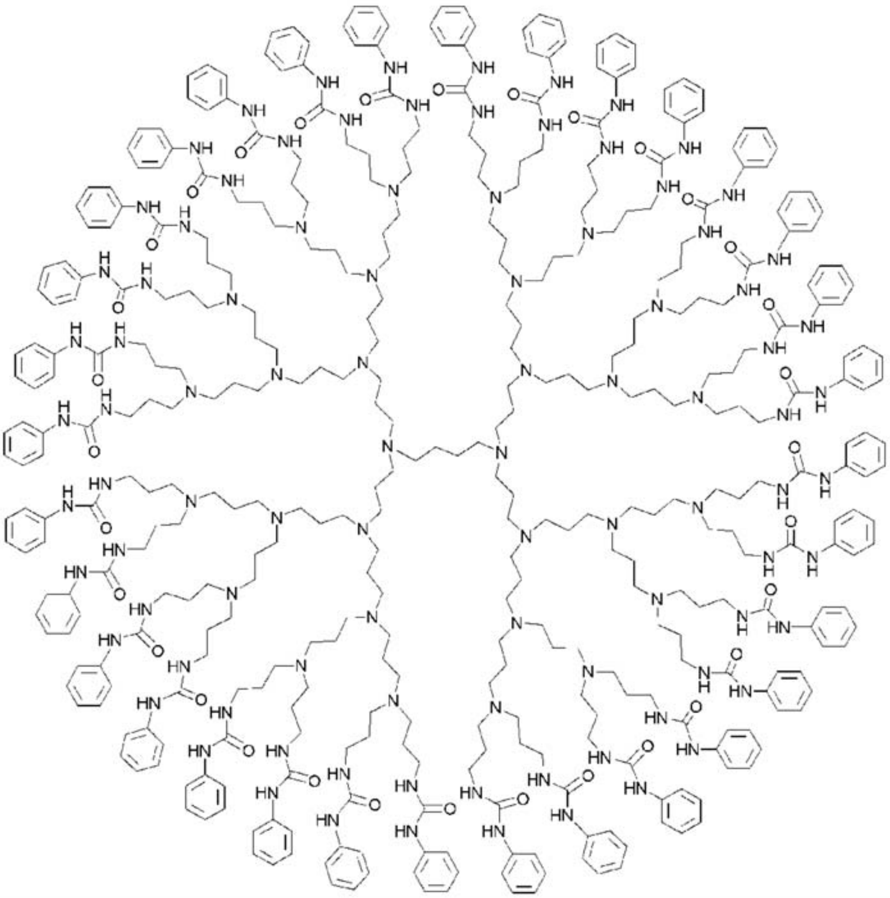

Fig. 1 The chemical structure of the urea-functionalized poly(propyleneamine) fourth-generation dendrimer G4-H

vey of recent studies employing small-angle scattering the reader is referred to [8].

In this review we wish to give a brief overview of the problem of the equilibrium structure of dissolved dendrimers. The main emphasis is placed on the combination of scattering methods and simulations. Rather than presenting a complete survey of all studies done in this field (see [8]), we shall give the main results of this analysis and delineate the most important conclusions reached so far in the realm of dilute solutions.

A further question to be discussed in this context is the interaction of dendrimers at higher concentrations. Recent work by Likos and coworkers clearly demonstrated that dendrimers exhibit an effective interaction potential that may be described by a Gaussian function [12, 13]. Hence, dendrimers provide an experimental system of particles interacting through a bounded potential.

In this way, dendrimers have become a new model system in colloid physics. This new and exciting development has passed almost unnoticed by the community of chemists working on the synthesis of dendrimers.

The review is organized as follows: section 2 outlines the main results by recent studies of dissolved dendrimers employing SANS and SAXS. It also surveys the problems for this type of analysis and the need for simulations to circumvent these problems. Section 3 in turn reviews recent theoretical developments and how these results may be used to interpret the SANS and SAXS data. Here, we shall mainly discuss recent results that are in direct relation to quantitative experimental findings. A final section will be devoted to open questions and directions for further research.

2
Scattering methods

The analysis of the equilibrium of dissolved dendrimers proceeds by the determination of the small-angle intensity $I(q)$ as a function of the magnitude of the scattering vector q [$q=(4\pi/\lambda)\sin(\theta/2)$; λ is the wavelength of radiation and θ the scattering angle] [9, 10]. Hence, $I(q)$ is determined by SAXS or SANS at a given number density N. In general, the intensity thus obtained may be rendered as the product of the intensity $I_0(q)$ related to the isolated molecule and the structure factor $S(q)$:

$$I(q) = NI_0(q)\, S(q) \tag{1}$$

Both $I_0(q)$ as well as $S(q)$ can be obtained from theory and simulations and thus directly compared to the experimental result [8]. In particular, the region of small angle, i.e., of small q leads to the radius of gyration R_g [9] that may be taken as a measure of the overall size of the dissolved dendrimer. With full generality this quantity follows from $I_0(q)$ by Guinier's law [9]

$$I_0\,(q) \cong N \cdot V_p^2 \cdot (\bar{\rho} - \rho_m)^2 \cdot \exp\left(-\frac{R_g^2}{3} \cdot q^2\right) \tag{2}$$

where V_p is the volume occupied by the dendrimer in the particular solvent and $\bar{\rho} - \rho_m$ is the contrast of the dissolved dendrimer (cf. [10]). The latter quantity follows from the difference of the average scattering length density $\bar{\rho}$ of the dendrimer and the scattering length density ρ_m of the solvent. In principle, Eq. 2 gives directly the overall size of the dissolved molecule in terms of V_p and R_g. V_p in turn leads to the molecular weight M through $M = V_p/\bar{v}_2$ where $\bar{v}_2$ is the partial specific volume. Moreover, the structural details of the dissolved molecule follow from $I_0(q)$ by comparison with model calculations or inversion into the real space through appropriate techniques. As mentioned in the Introduction, however, this comparison is more difficult than in the well-known case of linear polymers [8, 10]:

1. Dendrimers are small structures with diameters of a few nanometers only. Their radius of gyration R_g is hence of same the order of magnitude. Reliable structural information can only be obtained from $I(q)$ if $q{\cdot}R_g$ is considerably larger than unity [9, 10]. The measured scattering data must therefore extend far beyond the Guinier region. Because of the small V_p of typical dendrimers, $I_0(q{=}0)$ is much lower than the scattering intensities measured from, e.g., high polymers in solution. Moreover, $I_0(q)$ rapidly decays with higher $q{\cdot}R_g$. This is followed by poor statistical treatment of the data in the q-range where most of the information is to be gained. As a remedy to this problem, data are often taken at higher concentrations. This in turn requires a careful extrapolation to vanishing concentration [13, 14].
2. As a consequence of this, the experimental determination of the scattering intensity at high $q{\cdot}R_g$ requires special care. Here the influence of instrumental problems and of possible *incoherent* contributions must be taken into account and carefully subtracted prior to further interpretation of the data. SANS data have a strong incoherent part of the measured scattering intensity and its removal must be done by special procedures [14].
3. Small-angle scattering intensities $I_0(q)$ of fluctuating objects often exhibit only a few structural features such as, e.g., side maxima. For small dendrimers, $I_0(q)$ of dissolved dendrimers is a monotonically decaying function of q. Hence, the information embodied in such a curve is rather small and can under no circumstances be compared to the results of a crystallographic analysis. The inversion of $I_0(q)$ into the real space therefore requires special care. It can be done only in conjunction with simulations, as discussed in section 3.
4. Dendritic molecules are often envisioned as an assembly of units that have the same scattering power. Hence, it is assumed that inversion of $I_0(q)$ would give the structural information sought. In general, this is not the case and an analysis along these lines may lead to erroneous results [10].

Problems 1 and 2 are related to experimental difficulties and may be solved by appropriate treatment of the data. Problem 3 can be solved by resort to computer simulation and theory. This will be discussed further below. Problem 4 is the main difficulty with small-angle scattering and requires special attention. Contrast variation provides a means to solve this problem [9, 10, 15]. The intensity $I_0(q)$ is determined at different contrasts $\bar{\rho} - \rho_m$ and subsequently split into three partial intensities [10]:

$$I_0(q) = [\bar{\rho} - \rho_m]^2 \, I_S(q) + 2 \cdot [\bar{\rho} - \rho_m] \, I_{SI}(q) + I_I(q) \tag{3}$$

The first term (“shape term”) $I_S(q)$ is related to the scattering intensity extrapolated to infinite contrast. Here the difference between the scattering power vanishes and $I_S(q)$ gives the intensity of an assembly of scattering units that have equal magnitude. It is the Fourier-transform of the shape function $T(r)$ that describes the statistical average over all possible conformations of the dendrimers. $I_S(q)$ and $T(r)$ can therefore be compared directly to the result of simulations to be discussed further below [8]. The term $I_\mathrm{I}(q)$, on the other hand, is solely related to internal differences in the scattering length density. If a dendrimer is set up of groups containing deuterons in place of hydrogen atoms, there is a strong difference in scattering power in the case of SANS. This will lead to a finite scattering intensity even at the match point, i.e., in a solvent where the contrast $\bar{\rho} - \rho_\mathrm{m}$ is zero. On the other hand, $I_\mathrm{I}(q)$ furnishes further useful information about the internal structure and may be use to localize the terminal groups ([15]; see below). The term $I_\mathrm{SI}(q)$ presents the cross term between the former contributions. These three terms furnish all the information that can be obtained by a scattering experiment. Obviously, the three independent functions $I_\mathrm{S}(q)$, $I_\mathrm{SI}(q)$ and $I_\mathrm{I}(q)$ furnish a lot more information than just a single intensity $I_0(q)$ taken at a given contrast.

All terms, as well as the dependence of R_g on contrast, have been discussed at length recently [9, 10]. Here we only demonstrate the power of contrast variation for the structural analysis of a fourth-generation dendrimer [15]. Its chemical structure is given in Fig. 1. Two types of molecules have been studied: in one case the terminal groups were bearing hydrogen atoms, whilst in the other the terminal groups were fully deuterated [15]. As mentioned before, the SANS intensity originating from these two types of endgroups will be markedly different. As a consequence of this, $I_\mathrm{I}(q)$ will be different from zero and contrast variation should give all terms enumerated in Eq. 3.

As shown recently, a SANS analysis of both dendrimers can indeed furnish this information [15, 16]. The full information to be obtained from a scattering experiment, namely the three partial intensities $I_\mathrm{S}(q)$, $I_\mathrm{SI}(q)$ and $I_\mathrm{I}(q)$ can be obtained and compared to data obtained from simulations. Contrast variation can be done by measurements of solutions in a mixture of protonated and deuterated dimethylacetamide. These mixtures differ widely with regard to ρ_m. Thus, the contrast $\bar{\rho} - \rho_m$ can be varied widely and the partial intensities can be securely obtained by a fit of Eq. 3 to the experimental data. Details of this procedure are given in [15, 16].

Figure 2 shows the shape term $I_\mathrm{S}(q)$ obtained from the deuterated and the protonated dendrimer. As anticipated from the previous discussion, $I_\mathrm{S}(q)$ must be independent of the partial deuteration of the molecule. As demonstrated in Fig. 2, this is indeed found from the experimental data. This term contains all structural information on the spatial arrangement of the dendritic units, irrespective of their contrast. The solid line represents a Gaussian function, which upon inversion leads the shape function $T(r)$, also a Gaussian function [11]. The problems of this inversion will be discussed in the subsequent section. Here, it suffices to state that $T(r)$ has its maximum at $r=0$, i.e., at the center of the molecule. This result hence demonstrates that flexible dendrimers have a dense-core structure. It is supported by many other investigations employing scattering methods [8].

If $T(r)$ has its maximum right at the center, some of the terminal groups must fold back. As shown in [15, 16], the localization of the endgroups can be done through an analysis of the terms $I_\mathrm{SI}(q)$ and $I_\mathrm{I}(q)$. Figure 3 gives these terms

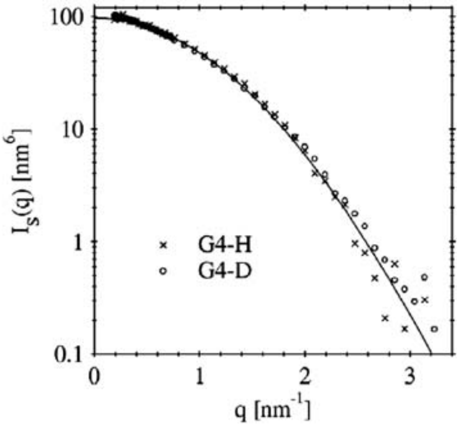

Fig. 2 The partial intensity $I_S(q)$ (cf. Eq. 3) determined by contrast variation for dendrimer G4-H (*crosses*; see also [16]) and for G4-D (*circles*). The *solid line* shows the fit of the data by a Gaussian function defined in Eq. 6. Taken from [15]

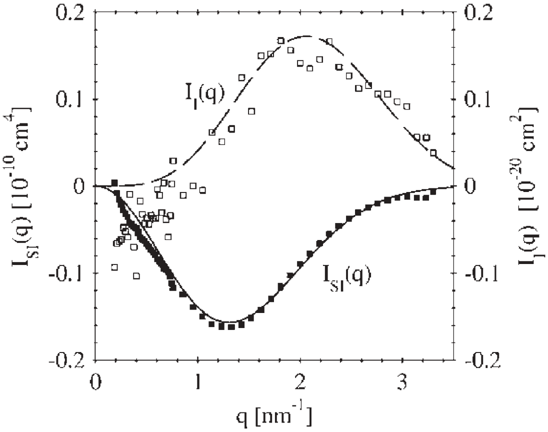

Fig. 3 The partial scattering functions $I_{SI}(q)$ (*black squares*) and $I_I(q)$ (*white squares*) as function of q (see Eq. 3) [15]

as function of q. Evidently, these partial intensities are more difficult to obtain, and there is some uncertainty of both functions in the vicinity of q=0. Theory states clearly, however, that $I_{SI}(q)$ and $I_I(q)$ must vanish in this limit. This renders a fit of the distribution of endgroups a do-able task. The solid line in Fig. 3 shows that both distributions can be fitted by a single endgroup distribution that will be discussed in further detail below (see also references [8, 15, 16]). Figure 4 displays the distribution of endgroups in terms of the function $\rho_p(r)$ taken from this analysis [15]. This function is proportional to the true distribution of endgroups (see the discussion in [15]) and demonstrates that the end-

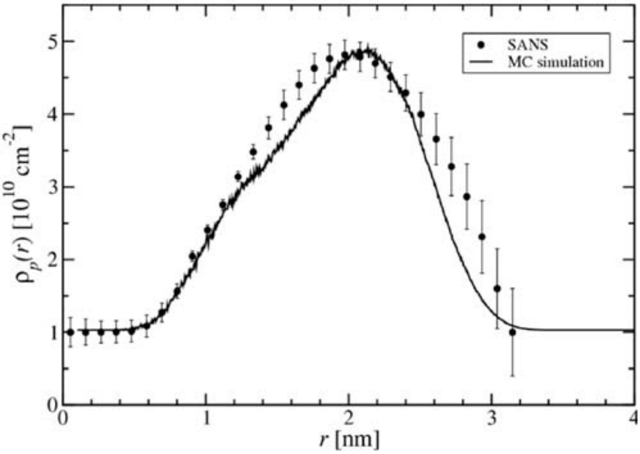

Fig. 4 Distribution $\rho_{\mathrm{p}}(r)$ of endgroups in a fourth-generation dendrimer (see Fig. 1). The *points* refer to the experimental result [15] whereas the *solid line* was obtained from the theoretical model [19]

groups are dispersed throughout the dendritic molecule. Clearly they are not localized at the "surface" of the dendrimer, as anticipated by the dense-shell model.

Having discussed the scattering intensity $I_0(q)$ related to a single molecule, it remains to determine the structure factor $S(q)$ defined in Eq. 1. By virtue of its definition, $S(q)$ describes all alterations of the measured scattering intensity $I(q)$ by the interaction of the dissolved dendrimers that result from finite concentrations. Often this term is omitted by assuming that $S(q)=1$ for dilute solutions. Hence, concentrations of the order of 1wt% are defined as being small and the subsequent analysis is based on $S(q)=1$. The assumption that some arbitrary concentration is "small", however, is not correct (see the discussion in [14]). The effect of finite concentrations makes itself felt at small q and leads to radii of gyration that may be considerably lower. Working at low concentrations, on the other hand, leads to poor statistical resultsat high q.

As a matter of fact, no assumption of this sort is necessary but measurements should be done at several finite concentrations. Extrapolation to vanishing concentration according to well-established procedures provides no difficulty at all, thus leading to both $I_0(q)$ and $S(q)$ [14]. No excuses for incomplete experimental data should be accepted anymore in the course of a meaningful analysis of dissolved dendrimers or other structures. Hence, measurements at finite concentrations must become an integral part of the experimental protocol.

The interpretation of $S(q)$ can be done again with resort to theory and simulations [12, 13]. This will be the subject of the next section. There it will be demonstrated that low-generation dendrimers present a new kind of soft particle.

All previous discussion has been related solely to the case of *flexible* dendrimers, i.e., to dendritic structures that can assume a vast number of different shapes. If, on the other hand, the dendritic scaffold is set up of stiff units, no backfolding should occur and a dense-shell dendrimer must indeed result. This has been shown recently by a SANS study of a fully aromatic dendrimer synthesized by Müllen and coworkers [17]. Applying the method devised in [15, 16] to a fully aromatic fourth-generation dendrimer, it could be demonstrated that there is a crowding of endgroups in the periphery. Stiff units are hence suitable building blocks for true dense-shell dendrimers whereas flexible units inevitably lead to backfolding and a dense-core structure.

3

Theory of Dendrimers

When dealing with macromolecules that feature the complicated architecture of dendrimers, it is customary and useful to resort to simplified models that capture the salient characteristics of their architecture, while ignoring the specific details of the molecular bonding and interactions. This approach greatly simplifies the analysis by theory and simulation, and at the same time helps to shed light onto the basic physics that governs the conformations of single dendrimers as well as their mutual interactions in a concentrated solution. To this end, various so-called "coarse-grained" models have been introduced in the last few years; for an extensive review, see [8]. In what follows, we give only a brief overview of very recent work on this subject.

The conformations of isolated dendrimers have been examined by computer simulations employing a simplified model in which monomers are modelled as Lennard-Jones beads that are connected by inelastic springs [11]. This simple model turns out to reproduce the experimental results for the form factor of fourth-generation dendrimers. At the same time, other quantities of interest can also be resolved in a simulation, such as the distribution of monomers around the center of mass of the molecule (density profiles) as well as the distribution of endgroups. Figure 4 shows a characteristic example of the comparison of experimental results regarding the terminal group distribution with the prediction from simulations. The excellent agreement between the two demonstrates both the fact that endgroups are back-folded and the validity of the simplified simulation model.

An additional question that has been addressed in [11] is that of the importance of intramolecular fluctuations of the monomers. This is a central problem that has already been mentioned in the preceding section. It is related to the analysis of dissolved dendrimers by scattering methods: can the spatial structure be described by an average profile or do intramolecular fluctuations contribute significantly to the measured intensity? The experimental data provide no solution to this problem.

Here, simulations [11] have turned out to be an indispensable tool for a meaningful analysis of dendrimers by directly comparing the exact expression for the pair correlation function between the monomers

$$G(\vec{r}) = \frac{1}{N}\left\langle \sum_{i=1}^{N} \sum_{i=1}^{N} \delta(\vec{r} - \vec{r}_i - \vec{r}_j) \right\rangle; \tag{4}$$

where r denotes the magnitude of the separation vector $\vec{r}$ between any two monomers with coordinates $\vec{r}_i$ and $\vec{r}_j$; to the mean-field approximation for the same quantity

$$G(\vec{r}) = \frac{1}{N}\rho(\vec{r})^{*}\rho(\vec{r}); \tag{5}$$

where $\rho(r)$ is the density distribution around the center of mass and the asterisk denotes a convolution. In Eq. 4 above, the symbol <…> denotes an expectation value over all conformations of the dendrimer and N is the number of monomers. Equation 5 is the result that holds for rigid, colloidal particles without internal fluctuations. The excellent agreement between the exact result, Eq. 4, as was measured in the simulation, and the approximate expression, Eq. 5, demonstrates that the internal fluctuations of fourth-generation dendrimers are weak and correlated only at length scales of the order of a few Ångströms [11]. Thereby, the experimental procedure of employing an inverse Fourier transform of the form factor in order to obtain the shape function $T(r)$ that is subsequently identified with the density profile $\rho(r)$ has been explicitly confirmed [8].

The experimental findings point to a Gaussian-like density profile around the center of mass of a dendrimer. A Flory-type theory has been employed by Likos et al. [12, 13] that utilizes this information to derive a Gaussian effective interaction between the centers of the dendrimers. The generic form of this effective interaction, denoted $w(r)$, reads as:

$$w(r) = N^2 kT v \left(\frac{3}{4\pi R_g^2}\right)^{3/2} \exp\left(-\frac{3r^2}{4R_g^2}\right) \tag{6}$$

where v is the excluded volume parameter, R_g the gyration radius (see preceding section), k denotes Boltzmann's constant and T is the absolute temperature. Subsequently, standard tools from the theory of structure of classical fluids have been employed in order to calculate theoretically the static structure factors from concentrated dendrimer solutions and compare them with experimental results from SANS. Figure 5 shows a representative example of the agreement between theory and experiment, demonstrating that flexible dendrimers provide a physical realization of bounded, Gaussian interactions [13]. We emphasize that such types of interaction potentials are unknown in the realm of atomic or molecular physics, where the strong electrostatic or exclu-

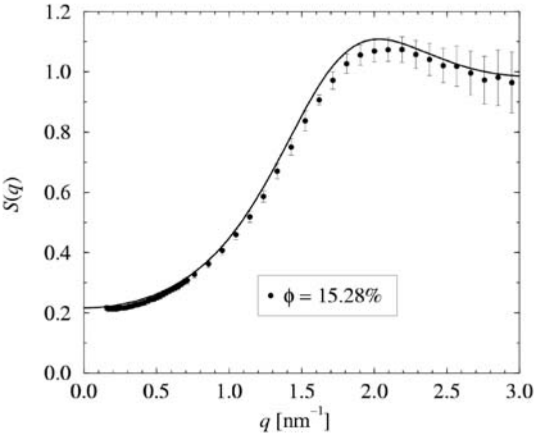

Fig. 5 Structure factor $S(q)$ (see Eq. 1) of a fourth-generation dendrimer [13]. The *points* mark the experimental data taken at a volume fraction of 15.28%. The *solid line* shows the result from the theory based on Eq. 6. See also [13] and [8]

sion-principle repulsions between the electrons bring about a concomitant interaction that strongly diverges at close approaches. Here, the soft character of the dendritic "colloids" reflects itself in a similarly soft interaction potential. The signature of the softness in the scattering profiles is a lack of pronounced correlation peaks in the structure factor.

An even simpler simulation model has been introduced by Götze and Likos [18]. Here, the monomers have been modelled as hard spheres connected by threads, with the ratio b between the maximal thread extension and the hard sphere diameter serving as a parameter that allows for tuning the flexibility of the dendrimer. Due to its simplicity and its purely entropic (excluded-volume) nature, the model is very well suited for fast Monte Carlo simulations. Thereby, dendrimers of generation numbers from 4 to 9 have been simulated and it has been demonstrated that with increasing generation number the dendrimers naturally bridge between polymeric entities and hard spheres. Indeed, with increasing generation numbers the form factors of the dendrimers, as measured in simulations, evolve towards shapes that characterize hard colloids, developing pronounced oscillations at high values of the wavevector. The latter denote an increasingly sharp boundary of the molecule and they follow Porod's law [9, 10].

A common feature of dendrimers of all generations, however, is the strong back-folding of the terminal groups in the molecule's interior. As a matter of fact, this tendency *grows* with increasing generation number, since the number of terminal monomers grows exponentially and the space available to the boundary of the molecule is not sufficient to accommodate them. Furthermore, a striking insensitivity of the density profiles was found, irrespective of the model used to describe the dendrimers: both the model of [18] and the aforementioned model of [11] yield form factors that are in excellent agreement with SANS.

Very recently, the hard-sphere–thread model has also been employed to measure in a simulation the effective interaction between dendrimers of various flexibilities and generations [19]. This simulation study nicely confirms the results of the Flory theory of [12] and [13]. The resulting effective interactions turn out to have a Gaussian form. The strength of the Gaussian interaction, compared to the thermal energy kT, can be tuned by the value of the flexibility ratio b and the terminal generation number. The smaller b is, the stiffer the interaction for a given terminal generation. On the other hand, increasing the generation for a given b brings about the same effect of making the interaction stronger. Thereby, a change of the interaction strength by as much as one order of magnitude can be achieved, pointing to the fact that dendrimers are excellent physical systems for realizing bounded and tuneable effective interactions.

4

Open Questions and Directions of Further Research

Most simulational models applied to date employ a coarse-grained description of the monomer interactions and their bonding, with a few notable exceptions in which atomistic, force-field models have been employed [20–22]. With the development of faster and more efficient computers, detailed atomistic simulations are feasible and certainly desirable as a future research perspective. The important question to be addressed in this respect is whether specific monomer–monomer or monomer–solvent interactions can bring about deviations from the dense-core model that is unanimously predicted by all coarse-grained simulation models. There are several conceivable factors that have to be taken into special consideration in this respect, namely the following.

1. The rigidity of the bonds connecting the monomers. In most studies to date, the bonds have been modelled as fully flexible, i.e., torsional constraints in their conformations have been ignored (see, however, [21] for an important exception). Though there is no doubt that flexibility causes backfolding of the endgroups, stiff bonds may lead to conformational changes in the dendrimers, as demonstrated recently experimentally for a system of stiff dendrimers ([17]; see preceding section). It would thus be of great importance to model and tune this rigidity in a simulation, in order to be able to make meaningful predictions that could be used as a guide for intelligent design of new materials. In this way simulations would become a direct guideline for the synthesis of dendrimers.
2. Specific interactions between the terminal monomers and the solvent. In most cases, solvent molecules have not been simulated explicitly. The possibility, however, that there exist specific chemical interactions between ter-

minal groups and solvent, leading, e.g., to the formation of hydrogen bonds, may again lead to a localization of the endgroups at the periphery of the molecule. Some preliminary investigations in which attractive, directional interactions between the endgroups have been introduced in a phenomenological way [23] show that there is no spectacular change of the conformation of the dendrimer under these conditions. Nevertheless, this question is worthy of further investigation.
3. Associated with the above is also the possibility of replacing the endgroups with ones that have a different size, or even shape, than those in the interior of the dendrimer. If there is a strong thermodynamic tendency that the species of the interior component and the species of the endgroups demix (e.g., spheres and rods under appropriate conditions), this may be reflected by a separation between the endgroups and the rest of the molecule, i.e., into a localization of the former at the periphery.

Another very important topic that is unsettled, and which deserves close consideration in the future, is that of *charged* dendrimers. In their pioneering work, Welch and Muthukumar [24] predicted a dramatic change of the dendrimer's size upon charging the endgroups, as well as a nontrivial dependence of the radius of gyration of the macromolecule on the salt concentration in the solution. Recent simulations of Lee et al. [25] are rather inconclusive as to the veracity of this phenomenon, which has been also called into question in the experimental work of Nisato et al. [26]. From the theoretical point of view, the great challenge lies therein, that the typical size of the dendrimers is rather small compared, say, with typical colloidal particles. The same holds, naturally, for the typical separations between the charged monomers in the dendrimer's interior, so that it becomes questionable whether a linear screening theory with a spatially uniform dielectric constant for the solvent is applicable in this case. In other words, it seems that here one has to take the solvent's granular nature explicitly into account and resort to more sophisticated simulations in which the solvent molecules are considered explicitly. This is similar to the case of dissolved proteins, for which it has been amply demonstrated that taking into account the water molecules brings about nontrivial effects that cannot be taken into account in any theory in which the solvent is modelled as a dielectric continuum [27].

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