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RESEARCH ARTICLE

Coarse-Grained Modelling of Urea-Adamantyl Functionalized Poly(Propylene Imine) Dendrimers

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To investigate the behaviour of poly(propylene imine) dendrimers—and urea-adamantyl functionalized ones—in solution using molecular dynamics simulations, we developed a coarse-grained model to tackle the relatively large system sizes and time scales needed. Harmonic bond and angle potentials were derived from atomistic simulations using an iterative Boltzmann inversion scheme, modified to incorporate Gaussian fits of the bond and angle distributions. With the coarse-grained model and accompanying force field simulations of generations 1 to 7 of both dendrimer types in water were performed. They compare favourably with atomistic simulations and experimental results on the basis of size, shape, monomer density, spacer back-folding and atomic form factor measurements. These results show that the structural dynamics of these dendrimers originate from flexible chains constrained by configurational and spatial requirements. Large dendrimers are more rigid and spherical, while small ones are flexible, alternatively rod-like and globular.

Keywords: molecular dynamics simulations; dendrimers; coarse-graining; Boltzmann inversion

1 Introduction

Dendrimers are a class of hyperbranched polymeric macromolecules.[1, 2] Short branches emanate from a multifunctional core, each an anchoring point for a next set of short branches. They are synthesized in an iterative reaction sequence. Each iteration adds another generational shell of branches, multiplying the number of reactive ends. Compared to other polymers, it is a very controlled synthesis leading to well-defined monodisperse structures. Finally the ends can be coupled to functional groups to provide specific features to the dendrimer. The large number of possible cores, branches and end groups [3–5] allows for nanoengineering of properties like size, shape, topology, flexibility and surface chemistry.

Dendrimers have been investigated using computer models for a long time. The first attempts were made by using the principles of statistical models of macromolecules [6, 7] to generate dendrimers with a self-avoiding walk algorithm.[8] To elucidate the dendrimer structure of an archetypal dendritic molecule, various bead-spring models have been researched using lattice Monte Carlo algorithms [9–11] and off-lattice ones,[12–16] mostly with implicit solvent. Other models where the solvent was treated implicitly were made with molecular dynamics [17–19] (MD) and Brownian dynamics.[20–23] One improvement in detail has been including solvent particles.[24–28] Another was using atomistic MD to model specific dendrimers, but still in implicit solvent or actual vacuum. Most notable are poly(propylene imine) (PPI) in vacuum [29, 30]

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Figure 1. Three representations of the fifth generation urea-adamantyl decorated 1,4-diaminobutane poly(propylene imine) dendrimer. (a) Skeletal formula. (b) Fully atomistic model showing the initial connectivity (top) and the form at the end of the simulation (bottom). (c) Coarse-grained model in initial (top) and ultimate form (bottom).

and melt [31, 32] and poly(amido amine) (PAMAM) in vacuum [33–35] and melt,[36] but also various phenyl-[37–40] and carbosilane-based [41, 42] dendrimers have been modelled. As both the solvent and the dendrimer composition influence the behaviour, explicit solvent atomistic simulations have also been performed for, e.g., PPI,[43–46] PAMAM [46–49] and carbosilane [50] dendrimers. The early simulations scarcely lasted more than 1 nanosecond, but the recent examples typically reach time scales of up to tens of nanoseconds. Since experiments are performed with multiple dendrimers in solution and for much longer time scales, these atomistic simulations are only able to reproduce a limited portion of experimental results. For phenomena where dendrimer–dendrimer interactions play a role, while also maintaining chemical specificity, coarse-grained simulations may provide new insight.

For some dendrimers such coarse-grained models have been published. The difference with earlier bead-spring models is that they are fitted on data obtained from atomistic simulations. The first reported coarse-grained model is a study of PAMAM engaging with a lipid bilayer.[51] The dendrimer uses repurposed lipid parameters. The same is true for a recent study of two PAMAM dendrimers interacting.[52] Another model is of stiff polyphenylene dendrimers in the melt phase,[53] where each bead represents 6 phenyl groups. These dendrimers have been made using a Boltzmann-inversion scheme for nonbonded interactions, and a fit of multiple Gaussians for the bonded interactions. Recently two new coarse-grained models have been published. One is a Monte Carlo model for various dendrimers [54] where the atomistic input is based on Langevin dynamics. The second is another PAMAM model in vacuum.[55] Despite the suggested use for larger simulations of multiple dendrimers, these recent models are only shown to reproduce structural properties of single dendrimers.

In this paper we investigate the behaviour in water of poly(propylene imine) dendrimers in regular PPI form (G_5 : DAB–dendr– $(\text{NH}_2)_{64}$) and functionalized with urea-adamantyl groups (PPIUA, G_5 : DAB–dendr–(urea–adamantyl) $_{64}$) (Figure 1(a)). PPIUAs are a useful template for acetic acid-urea guests in host-guest chemistry.[56, 57] PPIs are often used in experiments, and therefore ideally suited to base the coarse-grained model on.

We use molecular dynamics (MD) simulations to recreate and thereby elucidate the behaviour of PPI dendrimers in water. Although the dynamics are fast on a chemical scale, it is impractical to reproduce this a fair amount of times using conventional fully atomistic MD. The size and time scales required are too large to follow dynamic interactions between dendrimer and solvent molecules a reasonable amount of time. It is possible to simulate aggregation in explicit solvent with a coarse-graining (CG) scheme. Herein roughly four heavy atoms are lumped together to form a single particle. This significantly reduces the computational cost as fewer particle and interparticle interactions need to be calculated. Also, as high frequency motions are removed, and the interaction potentials are smoother, larger simulation time steps can be made. Moreover, because the coarse-grained system experiences less friction, the apparent dynamics are faster.[58]

Simulations were performed using our in-house developed MD platform PumMa,[59] which was previously used for coarse-grained simulations on diverse systems as lipid vesicles,[60–66] proteins,[67, 68] and microchannels.[69–71] The coarse-grained model defined in this paper is an extension to the lipid model,[60] meaning the same water parameters are used.

In Section 2 we describe the derivation of a coarse-grained model for PPI and PPIUA dendrimers, using a scheme that iteratively adapts to input distributions obtained from a single atomistic PPIUA dendrimer in water simulation. Subsequently, in Section 3, the CG model is tested against experimental data and atomistic simulations of these dendrimers over a wide range of generations, both to validate the model and to provide an accurate molecular picture behind the experimental data.

2 Model

Coarse-graining to acquire a correct model consists of two phases: deciding on which atoms to group into coarse-grained sites, and determining effective interaction potentials.

2.1 Coarse-Grained Sites

In general, each site should represent a functional group, so chemical specificity can be incorporated as its typical behaviour is known. Also the choice to represent it by a single spherical particle should not be detrimental to the structure generated, i.e., a long chain should not be coarse-grained into a single particle.

The fifth generation dendrimer, subject of the base simulation, consists of a large branched structure of poly(propylene imine) where each end is functionalized with urea and adamantyl moieties (Figure 1(a)). From a structural point of view, the recurring element of the PPI base is a tertiary amine connected to three other tertiary amines by hydrocarbon branches of 3 carbon atoms. Only the core differs, 1,4-diaminobutane being one carbon atom longer. Considering the branches originate at the nitrogens it is appropriate to take them as centres for a CG site. This leaves two options: either place another site at the centre of the intermediate branch or forgo placing additional sites. Not counting hydrogens, the first option results in particles that either represent a branch (2 carbons) or an extended nitrogen (1 nitrogen plus 1.5 carbons). The second option results in particles that represent 1 nitrogen plus 4.5 carbons. While the first option better conveys the idea of focal points and branches, it also limits the degree of coarse-graining, i.e., the reduction of degrees of freedom is not much larger than provided by a united atoms model, and the possible gain in computational reach not that great. Furthermore, we wanted to use the same water particles that were previously used in our lipid model,[60] where the water particles represent 4 water molecules. This dictated that each coarse-grained particle should represent roughly 4 heavy atoms. Thus the option with large coarse-grained particles (named N) was chosen, which provides a large reduction while maintaining the branched structure (Figure 2). This choice in turn reduced the options for the urea and adamantyl moieties. The urea moiety ($\text{CN}_2\text{H}_2\text{O}$) contains 4 heavy atoms, so it forms a fine coarse-grained site by itself. Yet when the atomistic model is considered, it follows that the urea moiety is linked to the tertiary amine via 3 carbon atoms. So another one and a half carbons had to be placed with the urea particle (U) just to account for all the atoms. The adamantyl group finally consists of 10 heavy atoms, so for that amount at least 2 coarse-grained sites are appropriate. However, since it is a dense bulky group, it is better represented by a single spherical particle (A). The chosen coarse-graining is depicted in Figure 2 which results in the dendrimer of Figure 1(c). The coarse-grained sites' approximate chemical names, molecular formulas, corresponding masses, and van der Waals radii are given in Table 1.

Figure 2. Molecular structure of a part of the (a) PPI and (b) PPIUA dendrimers with coarse-grained sites indicated (left), and the equivalent coarse-grained structure (right).

Table 1. Coarse-grained sites

Particle	Chemical name	Formula	Mass (u)	Van der Waals radius (Å)
N	trimethylamine	$C_3NH_6 + \frac{3}{2} CH_2$	77.15	2.66
U	urea	$CN_2H_2O + \frac{3}{2} CH_2$	79.08	2.71
A	adamantyl	$C_{10}H_{15}$	135.23	3.33
W	water	$4 H_2O$	72.05	2.59

2.2 Interaction Potentials

After having defined the coarse-grained particle sites, an appropriate force field governing their interactions was devised. There are several options for developing an effective force field. The input data may be predominantly structural or thermodynamic, the chemical detail may range from highly specific to phenomenological, and the resulting potentials may be of analytical form or tabulated.[58] To obtain a fairly general, transferable, force field, i.e., one that does not need to be reparameterized at every new state of interest, while still incorporating as much structural and chemical detail as possible, a combination of techniques was used. The bonded interactions were derived via Boltzmann inversion of a set of fully atomistic simulations. The overall chain structure of a polymer may depend on the solvent in which it is suspended. That is, the same polymer that is expanded in one (good solvent) may be collapsed in another (bad solvent). At the coarse-grained level this is reflected in the angles. For a general model to be applicable to simulations of different dendrimer sizes and concentrations, the influence of the medium must be conducted via nonbonded interactions, instead of being ingrained into the angle potentials. Therefore neutral intrinsic angle distributions were obtained from a separate atomistic simulation performed in vacuum with the Lennard-Jones and electrostatic interactions switched off. The solvent effect will stem from nonbonded interactions. The bond distributions are obtained from regular atomistic simulations, as in the CG model no van der Waals interactions are calculated between atoms directly bound to each other. The potentials resulting from Boltzmann inversion were not used as is, but fitted with harmonic analytical ones, because the coarse-grained model uses harmonic bond and angle potentials, which lead to practically Gaussian distribution functions. For the nonbonded interactions the Lennard-Jones potential is used, initial parameters were defined phenomenologically, while some were refined to reproduce experimental data.

2.2.1 Atomistic Input

For the bonded interactions fully atomistic simulations of a *G5* PPIUA dendrimer *in vacuo* were used as input (Figure 1(b), top). Since there is a strict relation between the atoms in the atomistic model and the coarse-grained particles, the centre of mass of the constituting heavy atoms was taken as the centre of each CG particle. Thus these CG sites were followed during the atomistic simulation run, continuously collecting the distribution of distances r_{ij} between bonded CG sites i and j and angles θ_{ijk} between sites i , j and k . This was achieved with a version of our PumMa code that performed atomistic simulations with CHARMM27 [72] parameters. Simulations using only the structural parameters (bonds, angles, dihedrals, and improper dihe-

Figure 3. Distributions of coarse-grained site-site bond lengths from regular atomistic simulations and simulations without nonbonded interactions present. Distributions are normalized so the area under the curves equals 1. Each distribution (solid line) is fitted with a Gaussian distribution (dashed line).

Figure 4. Distributions of coarse-grained site-site-site angles for regular and structural only atomistic simulations. Distributions are equalized (divided by $\sin(\text{angle})$) and normalized, having the area under the curves equal 1. Each distribution (solid line) is fitted with a Gaussian distribution (dashed line).

drals) and none of the nonbonded interactions (van der Waals and electrostatics) were performed. This highlights the effect of steric hindrance, electrostatic attraction and repulsion and hydrogen bonding on the innate dendrimer structure. The bond and angle distributions for the 2 ns simulations are shown in Figures 3 and 4. For example, the pincer angle U-N-U normally displays a large sharp peak at 54° . This is entirely the result of steric hindrance. In contrast, the amine-urea-adamantyl (N-U-A) ends are predominately straight independent of the nonbonded interactions. For details of input variables, initial states of the atomistic simulation and partial atomic charges see the Supporting information.

Separating the derivation of the angles from the bonds in this manner is allowed because they are fairly independent. In principle an angle does not change when its constituent bonds are stretched or compressed. Here for example, while the N-U bonds differ little in both simulations, the U-N-U angle is either 60 degrees or unrestricted. Meanwhile the N-N bonds differ most, while the N-N-N angles remain similar.

2.2.2 Structure Parameter Derivation

Using the Boltzmann inversion scheme, effective model potentials can be derived from structural information in the form of pair correlation functions.[58, 73, 74] The pair distributions can be acquired from experimental data to optimize atomistic potentials, or, as is the case here, from atomistic simulations to optimize coarse-grained potentials. As the model is based on structural information, it will reproduce accurate structural details. The method is based on the notion that a one-to-one correspondence exists between the potentials and the radial distributions that follow. Boltzmann inversion has been used to obtain potentials for liquids,[75, 76] homopolymers,[74, 77, 78] and copolymers.[79] It can be done for any pair correlation function, i.e., for obtaining nonbonded, bond, angle, dihedral, etc. potentials. For the atomistic bond distributions, $P(r_{ij})$, the Boltzmann inversion calculation is as follows:

$$V_{\text{bond}}^0(r_{ij}) = -k_B T \ln(P(r_{ij})) \quad (1)$$

with k_B the Boltzmann constant and T the temperature. Because the bond distribution is influenced by the rest of the system, the result is in fact a free energy function. As the influence is minor, the function serves well as an initial guess for the potential energy function. It can be improved in an iterative process: A simulation using $V_{\text{bond}}^n(r_{ij})$ is run and afterwards the output distribution $P^n(r_{ij})$ is compared to the target distribution $P_T(r_{ij})$. Distribution differences are reduced iteratively by decreasing (increasing) the potential at those distances where the output distribution underestimates (overestimates) the target distribution:[76]

$$V_{\text{bond}}^{n+1}(r_{ij}) = V_{\text{bond}}^n(r_{ij}) - k_B T \ln \left(\frac{P_T(r_{ij})}{P^n(r_{ij})} \right) \quad (2)$$

After optimization, this potential is as irregular as the target distribution. Therefore, such potentials are usually applied in tabulated form, i.e., for every interparticle distance sampled, the potential value is stored in a table. During the CG simulation the required potentials are then interpolated from the pre-calculated ones.

When the distribution has a bumpy shape, it implies that the bonds between sites are flexible. For instance, the N–N bond consists of a 3 carbon chain. Depending on its conformation, its end-to-end distance changes, which leads to a narrow bistable distribution (Figure 3(a)). Using tabulated potentials it is easy to put this bistability in the N–N bond. However, in the coarse-graining process the origin of the bistability is lost. In the CG model there is no need for the N–N bond to be bistable as it is just a bond, the different conformations of the bond have no meaning. Therefore we opt to use harmonic analytical potentials for the bonded interactions. They are of the form:

$$V_{\text{bond}}(r_{ij}) = k(r_{ij} - r)^2 \quad (3)$$

To determine the reference bond length r and force constant k the Boltzmann inversion scheme needs to be modified. It is known that harmonic bond potentials give rise to Gaussian distributed bonds (Equation 4). Therefore a Gaussian distribution fitted to the atomistic distribution shows the best possible outcome a harmonic potential can achieve.

$$P_{\text{Gauss}}(r_{ij}) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(r_{ij}-\mu)^2}{2\sigma^2}} \quad (4)$$

Assuming the bond distribution is indeed Gaussian, the harmonic potential can be attained by Boltzmann inversion:

$$V_{\text{bond}}(r_{ij}) = -k_B T \ln \left(\frac{1}{\sigma\sqrt{2\pi}} \right) + k_B T \frac{(r_{ij} - \mu)^2}{2\sigma^2} \quad (5)$$

As the first part on the right hand side is a constant, it can be removed. From the second part the analytical constants for Equation 3 can be derived:

$$k = \frac{k_B T}{2\sigma^2} \quad \text{and} \quad r = \mu \quad (6)$$

Thus, by fitting a Gaussian distribution to the atomistic data (the dashed lines in Figures 3 and 4), target parameters for a coarse-grained harmonic potential can be derived that should produce distributions that match this Gaussian fit. Again, the match is not exact so the parameters are adjusted iteratively to minimize the error. At the start ($n = 0$), the bond potential is

Table 2. Harmonic bond parameters

Type	Length (Å)	Strength (kJ nm ⁻² mol ⁻¹)
N-N	4.897	1243.5
N-U	5.013	408.5
U-A	4.601	4855.6

as follows:

$$V_{\text{bond}}^0(r_{ij}) = k^0 (r_{ij} - r^0)^2 \quad \text{with} \quad (7)$$

$$k^0 = \frac{k_B T}{2 (\sigma_{\text{in}}^0)^2} = \frac{k_B T}{2 (\sigma_T)^2} \quad \text{and} \quad (8)$$

$$r^0 = \mu_{\text{in}}^0 = \mu_T \quad (9)$$

where σ_T and μ_T are the target values from the atomistic Gaussian fit. The output distribution is also fitted, giving the first output mean μ_{out}^0 , thus the relative error is $|\mu_{\text{out}}^0 - \mu_T|/\mu_T$. The input bond length for the next iteration $r^{n+1} = \mu_{\text{in}}^{n+1}$ is derived in the following manner, adjusting k with σ works in the same way:

$$\mu_{\text{in}}^{n+1} = \begin{cases} \mu_{\text{in}}^n (1 + \beta) & \text{if } \frac{\mu_{\text{out}}^n}{\mu_T} < 1 - \frac{\beta}{\alpha}; \\ \mu_{\text{in}}^n \left(1 - \alpha \frac{(\mu_{\text{out}}^n - \mu_T)}{\mu_T}\right) & \text{if } 1 - \frac{\beta}{\alpha} \leq \frac{\mu_{\text{out}}^n}{\mu_T} \leq 1 + \frac{\beta}{\alpha}; \\ \mu_{\text{in}}^n (1 - \beta) & \text{if } \frac{\mu_{\text{out}}^n}{\mu_T} > 1 + \frac{\beta}{\alpha}. \end{cases} \quad (10)$$

where α is the adaptation strength and β is the maximum adaptation. The input is thus the previous input with a slight increase or decrease depending on the relative error that input generated. Parameter α gives the amount of adaptation with respect to the error; at 0 there is no adaptation, at 1 the error is subtracted entirely. Parameter β restricts the amount of adaptation to within limits. During the parameter adjustment phase, α is set to 0.5 to have a steady approach to the target value where overshoots are purely due to interference from the rest of the system, and β is set to 0.25 to further limit the step size taken each iteration.

For the harmonic angle potentials the procedure is similar. The only difference is the normalization of the distribution by dividing by $\sin(\theta_{ijk})$, the random angle distribution, to give each angle the same weight.

$$V_{\text{angle}}(\theta_{ijk}) = -k_B T \ln \left(\frac{P(\theta_{ijk})}{\sin(\theta_{ijk})} \right) \quad (11)$$

Because the system is dense, the distributions depend on all potentials so they have to be optimized in batches. First all bond potentials were iterated concurrently, as they do not depend on the others. Then all angle potentials were optimized. To avoid an unnecessary increase of complexity of the model, no dihedrals were incorporated. As they represent interactions over 4 coarse-grained beads (roughly 16 heavy atoms), they should only be added when more limited potentials fail to produce the required structure. Parameter adjustment was stopped after the total error of adjustable parameters reached a steady minimum, small fluctuations may still occur as the simulations inherently will not behave exactly the same. For details of the input variables and initial states for the coarse-grained simulations and for a demonstration of the iterative tuning of the N-N bond parameters see the Supporting information. By matching the parameters derived by Gaussian fitting the atomistic distributions, the parameter error and the distribution error were indeed simultaneously minimized. The obtained parameters are listed in Tables 2 and 3.

Table 3. Harmonic angle parameters

Type	Angle ($^{\circ}$)	Strength ($\text{kJ rad}^{-2} \text{mol}^{-1}$)
N–N–N	97.00	0.656
N–N–U	82.74	0.880
U–N–U	75.06	1.126
N–U–A	138.60	19.665

2.2.3 Nonbonded Interactions

To derive nonbonded interaction potentials, the Boltzmann inversion scheme may be used again, now with the radial distribution function as input. However, usually this is only applied on systems where just one or two particle types are present; e.g., a homopolymer in implicit solvent [74, 77] or a diblock copolymer in vacuum.[79] Moreover, although it has been done recently,[68, 80] coarse-graining the solvent using Boltzmann inversion is difficult when a single CG bead comprises multiple solvent molecules as the solvent molecules need to be dynamically clustered into beads every time step.

Instead, in our coarse-grained model, the nonbonded interactions between two particle types, being Pauli repulsion, van der Waals attraction, and Coulombic interactions, are all described by a single Lennard-Jones potential. The potentials are parameterized more phenomenologically based on known physical-chemical properties of the chemical compounds best resembling each particle and the overall behaviour of the PPIUA dendrimer in water. This is analogous to our water–lipid model [59, 60] from which we reuse the W (water) particles. The masses of the particle types can be calculated straightforwardly (Table 1) as the sum of the masses of the atoms they represent. Although the physical properties are not known for the exact compounds the particle types represent, they can be found for similar chemical compounds: A being adamantane; N being in between dimethylethylamine and diethylmethylamine; and U being a combination of methylurea, ethylurea and dimethylurea. For each particle type this provides a theoretical density at a certain temperature, a melting point and optionally a boiling point. The van der Waals radii and characteristic Lennard-Jones energies (ϵ) of the particle types are optimized through a series of MD simulations of 2600 particles each. An initial van der Waals radius is calculated from the target density and known mass assuming sphere packing. An initial ϵ follows from the target melting temperature. Locating the actual melting point starts with 0.5 million time steps of equilibration at a temperature 100 K below the expected melting point, followed by heating the system 350 K over 3 million iterations and subsequently cooling it back down, while checking the density for phase transitions. Due to the fast temperature changes ($\sim 5 \text{ K ns}^{-1}$) a hysteresis effect occurs such that the observed crystallization and melting points differ. The true melting point is then taken as the average of both phase transition temperatures, and any difference between this and the target melting point leads to an augmentation of the ϵ . If the change is small ($< 5\%$) the simulated annealing process is stopped. The same strategy is applied for the known boiling points. This may lead to a different ϵ . The final ϵ is obtained via a linear interpolation between both points to room temperature and rounded to a single decimal. Finally another simulation of 1 million time steps is performed to measure the density and augment the van der Waals radius. The so obtained values for the van der Waals radii are reported in Table 1 and those for ϵ on the diagonal of Table 4. Only for the A particle an exception was made as adamantane has an extraordinarily high melting point (540 K) while it also sublimates at room temperature. Because these unusual properties are incompatible with the above strategy the ϵ of butane from the lipid model was used instead. As in the earlier vesicle simulations [60] the water–water interaction is $1.88 \epsilon^*$ which also incorporates both melting and boiling points.

Also the interactions between different particle types are based on the physical-chemical properties of the chemical compounds and the overall behaviour of the PPIUA dendrimer in water. That is, in water the dendrimers aggregate because of the hydrophobic adamantyl ends, but the urea moieties and in a lesser extent the tertiary amines, are water-soluble. Therefore three

Table 4. Interparticle Lennard-Jones well depth in water (ϵ_{ij} (ϵ^*); $1.0 \epsilon^* = 1.967 \text{ kJ mol}^{-1}$)

	A	N	U	W
A	1.0	1.0	1.0	1.0
N		1.0	1.4	1.4
U			2.2	1.88
W				1.88

well depths are used. For the interactions of the hydrophobic adamantyl ends with all other particle types the same value is used as for the hydrophobic interactions like butane–water ($1.0 \epsilon^* = 1.967 \text{ kJ mol}^{-1}$) in the lipid model. For the water-soluble urea moieties the well depth for interaction with water is set to the same value as for water–water ($1.88 \epsilon^*$). For the interaction of the slightly less water soluble tertiary amines with water, as well as for the U–N interaction, an intermediate value ($1.4 \epsilon^*$) is taken. The chosen values are also shown as the off diagonal values in Table 4. Finally, the collision diameters between unlike particle types are obtained using the Lorentz rule ($\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j)$).

3 Results and Discussion

3.1 Simulations

To validate the coarse-grained force field derived in the previous section, its results are compared to atomistic simulations of the same dendrimers and results of PPI dendrimer experiments described in literature. Additionally, predictions are made when the model provides more detail than the experiments. Although the CG dendrimer model was derived with the fifth generation urea-adamantyl dendrimer as a reference, the generalized analytical potentials should make the model applicable to similar molecules. This means correct results should be produced for both PPIUA and PPI dendrimers over a range of generations.

The limiting generation is the final generation at which the volume occupied by a dense space-filling dendrimer is smaller than the volume occupied by a dendrimer with all branches stretched outward.[81] For our PPI dendrimers this limit is at $G10$, so $G7$ should in principle still be attainable and is an appropriate final generation to study. The first part of the tests cover the internal dendrimer structure, followed by interactions between multiple dendrimers in solution.

For the experimental validation, small-angle neutron scattering (SANS) measurements of PPI dendrimers by Scherrenberg et al. [29] in dilute solution are used for structural information. The PPI dendrimers studied range from generation 1 (4 end groups) to 5 (64 end groups).

All simulations described here are performed in an NPT ensemble, with constant pressure (1 bar) and constant temperature (298 K). The coarse-grained simulations were performed on single dendrimers of generations 1 through 7 in water. Dendrimers were generated in an extended configuration, minimized, solvated and again minimized (Figure 1(c)). A simulation was performed for each of the generations. Each simulation encompasses 625 ns, of which the first 6 ns are considered equilibration time, and the final 619 ns production run. Every 0.06 ns a configuration was saved for analysis.

The atomistic simulations were performed on PPI and PPIUA dendrimers of generations 1 through 6, generated with the same software, and solvated with TIP3 water (Figure 1(b)). In water, PPI dendrimers are charged through protonation of the nitrogens. The protonation order of PPI dendrimers of generations 1, 2 and 3 at different pH were investigated using natural abundance ^{15}N -NMR spectroscopy and an Ising model.[82] Their findings indicate that, at each protonation level, most of the charge resides at the primary amines of the outer layer. When more charge is present, subsequent layers of tertiary amines become charged, preferably alternating to keep the charges separate. For the simulations the appropriate extent of protonation was

determined performing a series of simulations with varying degrees of protonation, using the *G5* PPI dendrimer as calibration point. A protonation level of 37.5% was found to match the known radius of gyration best. For simulation results of the search for the appropriate protonation level see the Supporting information. All other PPI dendrimers were generated with the same degree of protonation, of these roughly 90 % reside at the outer layer, the others were proportionally distributed on the nitrogens of alternative layers. As the PPIUA dendrimers lack primary amines, they are much less prone to protonation, therefore, as an approximation, only the protonation level of the tertiary amines of the corresponding PPIs was adopted. Generations 1, 2, and 3 were simulated for 30 ns, the others for 20 ns, of which the final 20 ns or 10 ns were used for analysis, respectively.

The structure of a single dendrimer can be characterized by various measures, of which some can be found through experiment, while others can be directly calculated from simulation. In this paper, we measure the similarity between the simulations and, whenever possible, experiment: the radius of gyration, asphericity, radial monomer density, and the atomic form factor.

3.2 Radius of Gyration

The radius of gyration is a measure of the mass distribution of a molecule around its centre of mass. It is used as a measure of size for near-spherical colloids. It is calculated as:

$$\langle R_g^2 \rangle = \frac{1}{\sum_{i=1}^N m_i} \left\langle \sum_{i=1}^N m_i |\mathbf{r}_i - \mathbf{c}|^2 \right\rangle \quad (12)$$

$$\mathbf{c} = \frac{\sum_{i=1}^N m_i \mathbf{r}_i}{\sum_{i=1}^N m_i} \quad (13)$$

where $\langle \rangle$ denotes the ensemble average, N the number of atoms, m_i the mass of the i th atom, $\mathbf{r}_i$ its position and $\mathbf{c}$ the centre of mass of the molecule. This R_g is a prime measure to evaluate the merits of the coarse-grained model as it can be determined with scattering experiments.[83]

The lower set of curves shown in Figure 5(a) are for the PPI dendrimers. The experimental values [29] match the coarse-grained and atomistic values quite well. Their observation that the relationship $R_g \propto G$ is linear, seems correct for small generations (*G1* to *G4*), but fails once larger generations are also considered. Then the growth appears to be increased. The upper set of curves is for the PPIUA dendrimers. Not only are these dendrimers larger, also the atomistic simulations do not follow the coarse-grained lines as neatly.

To better explain the increase in dendrimer size with larger generations (i.e., number of monomers), usually the relation $R_g \propto N^\nu$ is determined. The best fits for $R_g \propto N^\nu$ are shown in the Supporting information and by the dashed lines in Figure 5(b). The PPI and PPIUA dendrimers follow the same general scaling law. These results, (ν ranging from 0.29 to 0.34) compare favourably with other simulations. For instance, a relationship of $R_g \propto N^{0.29}$ is found with a united atoms simulation of PPI dendrimers (*G2* to *G5*) in melt.[32] Another molecular dynamics simulation of generic dendrimers (*G1* to *G8*) in implicit solvent of various quality follows $R_g \propto N^{0.30}$ for all cases.[17] Reported values for PAMAM dendrimers are $\nu = 0.34$ in water [84] and $\nu = 0.33$ in water under low, medium, and high pH conditions.[47] Results of coarse-grained PAMAM dendrimers in vacuum (*G1* to *G11*) [55] are reported as $R_g \propto N^{0.32}$.

However, the scaling law merely gives the impression to follow $R_g \propto N^{1/3}$ under all solvent conditions. It is only valid for bad solvents, where the polymer collapses and becomes a space-filling object with constant density. Under other conditions different relationships can be derived.[85, 86] The radius of gyration is expected to be proportional to the end-to-end distance (R) of a single linear strand emanating from the central core. According to Flory-theory [87, 88]

Figure 5. Radius of gyration versus (a) generation number and (b) number of monomers as determined for the coarse-grained, fully atomistic and experimental dendrimers. (a) Lines are present to guide the eye. (b) Best fits for the relation between R_g and N : $R_g \propto N^{1/5}(G + [1+]0.5)^{2/5}$. The dashed lines are the best linear fits. Should $R_g \propto N^\nu$ hold, the data points would follow these. Experimental data are adapted with permission from [29], Copyright 1998 American Chemical Society.

the mean-field energy of the strand is

$$\frac{F(R)}{k_B T} \cong \frac{R^2}{R_0^2} + N_S \left(v \frac{N}{R^3} + w \frac{N^2}{R^6} \right) \quad (14)$$

with R_0 the ideal chain length, N_S the number of monomers in the strand, N the total number of monomers in the dendrimer, v the excluded volume parameter, and w the three-body interaction parameter. In the minimum, the derivative should be 0.

$$\frac{F'(R)}{k_B T} \cong 2 R_0^{-2} R - 3 v N_S N R^{-4} - 6 w N_S N^2 R^{-7} = 0 \quad (15)$$

Substituting $\frac{R}{R_0}$ with expansion factor α gives

$$\alpha^5 \cong \frac{3}{2} v N_S N R_0^{-3} + 3 w N_S N^2 \alpha^{-3} R_0^{-6} \quad (16)$$

In a good solvent, the expansion is fairly large, so the α^{-3} term may be removed (and $R_0 \propto \sqrt{N_S}$). Then the end-to-end distance follows

$$R \cong \left(\frac{3}{2} v \right)^{\frac{1}{5}} N_S^{\frac{2}{5}} N^{\frac{1}{5}} \quad (17)$$

with $v > 0$. In a bad solvent, the expansion factor is small so α^5 vanishes and indeed

$$R \cong \left(-2 \frac{w}{v} \right)^{\frac{1}{3}} N^{\frac{1}{3}} \quad (18)$$

with $v < 0$. At the theta point (ideal solvent) the polymer acts like an ideal chain, i.e., without excluded volume effects ($v = 0$) and yields

$$R \cong (3 w)^{\frac{1}{8}} N_S^{\frac{1}{4}} N^{\frac{1}{4}} \quad (19)$$

Figure 6. The asphericity versus generation of the coarse-grained and fully atomistic dendrimers.

For our dendrimers, the number of monomers in a strand $N_S = (G + 0.5)p$ for PPI and $(G + 1.5)p$ for PPIUA dendrimers with the number of monomers per spacer $p = 1$.

For PPI the good solvent fits $R_g \propto N^{\frac{1}{5}}(G + [1+]0.5)^{\frac{2}{5}}$ presented in Figure 5(b) are an improvement over the linear fits, the $G1$ values are no longer outliers. The ideal solvent fits $R_g \propto N^{\frac{1}{4}}(G + [1+]0.5)^{\frac{1}{4}}$ are almost as good. It is therefore difficult to discern the quality of the solvent from this particular graph, comparing dendrimers of different structures would help.[89] For PPIUA the linear fits remain best. Water is not a good solvent for the hydrophobic adamantyl parts.

3.3 Asphericity

The radius of gyration represents the shape of a polymer by a single measure, thus relating it to a sphere. More descriptive measures are available, like the aspect ratios of a polymer as defined by the ratios between the principal axes, i.e., the eigenvalues of the shape tensor ($g_1 \geq g_2 \geq g_3$). These results are available as Supporting information. From these the asphericity [90, 91]¹

$$A = \frac{T^2 - 3M}{T^2} \quad (20)$$

can be calculated with

$$T = g_1 + g_2 + g_3 \quad (21)$$

$$M = g_1 g_2 + g_2 g_3 + g_3 g_1 \quad (22)$$

This asphericity can take values from 0 for a configuration where the atoms are arranged symmetrically around an origin to 1 for a linear configuration. At 0.25 a planar configuration may exist (e.g., $g_1 = g_2 = 1.0$, $g_3 = 0.0$), but a cylindrical object is also possible (e.g., $g_1 = 1.0$, $g_2 = g_3 = 0.25$).

The average asphericity for the generations in solution simulations are shown in Figure 6. The larger dendrimers are more spherical whether that size increase is due to more generations or the addition of urea and adamantyl groups. The atomistic values are in the range of the coarse-grained values, but are more arbitrary than the latter's smooth trend. This is likely due to the calculation wherein small fluctuations of atoms in the molecule lead to significant changes in

¹For a discussion of asphericity calculations see the Supporting information.

Figure 7. Radial monomer densities. (a) Overall density of CG PPIUA dendrimers with shell width $0.5 \text{ \AA}$ and (b) compared to the fully atomistic dendrimers. (c) The radial monomer density of the CG PPI dendrimer ends (solid lines) compared to the dendrimer size represented by the radius of gyration (dashed lines).

the principal axes. In turn the asphericity is quite variable. With longer simulation times the atomistic values are expected to converge with the CG data.

In a related series of 0.4 ns united atoms simulations of PPI generations 2 to 5 in melt, a decline in asphericity of similar magnitude has been observed.[32] Coarse-grained polyphenylene dendrimers have also shown a decline in asphericity, but not nearly as much, as those rigid dendrimers with hardly any back-folding retain their shape with increased generation.[53]

3.4 Radial Monomer Density

The radial monomer density (g_m) is the preferred way to represent the distribution of monomers with respect to the centre of mass. The density is defined as the number of monomers (N) found within the shell of width Δr starting at $r - \frac{\Delta r}{2}$ divided by the volume of this shell:

$$g_m(r) = \frac{N(r)}{\frac{4}{3}\pi \left(r + \frac{\Delta r}{2}\right)^3 - \frac{4}{3}\pi \left(r - \frac{\Delta r}{2}\right)^3} \quad (23)$$

In Figure 7(a) the overall densities are depicted for the coarse-grained PPIUA dendrimers. For low generations ($G1, G2$), the density decreases monotonically from the centre. At higher generations ($G3$ to $G5$), a plateau appears after the initial peak. The initial peak is due to the apparent abundance of monomers near the centre of mass, which does not necessarily contain the dendritic origin. At even higher generations ($G6, G7$) the plateau exhibits oscillations. The radial distribution graph then attains the distinct shape known from simple liquids, i.e., first a high peak a small distance from the origin, followed by several peaks of solvent shells, and finally a plateau when the structure is lost. The radial monomer distribution decays to zero; this shape depends on the roughness of the dendrimer surface. That several peaks are present for $G6$ and $G7$, indicates the dendrimer's coarse-grained sites are relatively fixed with respect to each other. This is in agreement with the observed difficulty to synthesize such large dendrimers correctly in pure form.

In Figure 7(b) the radial monomer densities of a select group of atomistic simulations are depicted with their coarse-grained counterparts. To get comparable results, the positions of the virtual coarse-grained sites were calculated from the atomistic simulations. As there were not enough samples or atoms to get a consistent view of the first few shells, these are omitted. With these adjustments, the observed behaviour, i.e., the monotonic decrease, the plateaus, and the decays, are quite similar.

Looking solely at the distribution of the extremities of the dendrimers, Figure 7(c) shows that for small dendrimers ($G1$ to $G3$) the end groups can be found at the periphery, as hinted at by the radius of gyration (for solid spheres $R_g = \sqrt{3/5}R$). For larger dendrimers ($G5$ to $G7$) there is not enough room at the periphery for all the end groups, therefore their branches must bend

Figure 8. Comparisons between (a) the radial monomer densities of $G5$ PPI and its extension $G5$ PPIUA, and (b) $G5$ PPI and $G4$ PPIUA which has a closer number of monomers. Each generational layer of monomers is labelled with a lower case ‘g’ to distinguish it from full generations.

and distribute them over the available space thus widening the distribution peak. This contrasts with the prediction of Zacharopoulos et al. [32], that states that for higher dendrimers ($G > 5$) the distribution becomes bimodal with a depletion of end groups in the region around R_g . The broad distribution does however coincide with the results of others for large generations.[17, 29]

The fifth generation of coarse-grained PPI contains 126 monomers, while the PPIUA variant contains 190. The fourth generation PPIUA with 94 monomers is in fact a better match in terms of numbers. Recalling the similar origins of $G5$ PPI and PPIUA, DAB–dendr– $(\text{NH}_2)_{64}$ and DAB–dendr–(urea–adamantyl) $_{64}$, wherein the secondary amines effectively become ureas, their connectivity is evidently the same up until the final layer of adamantanes. The question which of the $G4$ or $G5$ PPIUAs has the better monomer distribution match with $G5$ PPI, is answered in Figure 8. It shows that $G5$ PPIUA is indeed an extension of $G5$ PPI. Apart from the 2 monomer $g0$ -layer, only the $g5$ -layer distribution is appreciably different having become urea. The added adamantyl ends are spread evenly across the dendrimer, just as the end groups in Figure 7(c). Conversely, with $G4$ PPIUA, where next to the transformations into urea and adamantyl half the monomers of the $g5$ -layer are removed, the distributions are quite different.

3.5 Spacer Expansion

The distribution of the monomers depends on the shape of the branches in the dendrimer, whether they are extended or crinkled. This behaviour can be calculated with the spacer expansion. The relative expansion (S) of a spacer spanning from branch point m to the next ($m + 1$) is calculated as the projection of its vector ($\mathbf{I}_{m+1}$) on the vector of its parent spacer ($\mathbf{I}_m$) normalized by its theoretical all-trans spacer length (l_{m+1}):[32]

$$S = \frac{\mathbf{I}_m \cdot \mathbf{I}_{m+1}}{|\mathbf{I}_m| l_{m+1}} \quad (24)$$

as shown in the inset of Figure 9(a).

In that figure the average expansions of the spacers originating at each generation of branch points are shown. The coarse-grained PPI dendrimers show that no matter the size of the dendrimer, the final layer is the least expanded, meaning that its final branches are splayed. For small generations ($G1$ to $G4$), the spacers are relatively expanded at the origin and this expansion uniformly drops. For higher generations ($G5$ to $G7$) the expansion around the core is a bit less than in the subsequent shells to accommodate for the greater crowding there. There are two differences in going from PPI to PPIUA via the addition of the urea-adamantyl group. First

Figure 9. Relative expansion of the spacers originating at each branch generation of (a) PPI and (b) PPIUA dendrimers. The coarse-grained simulations have solid lines connecting circular points, the atomistic ones have dashed lines and square points. The legends for the PPI graphs also describe the corresponding PPIUA dendrimer graphs. PPI dendrimers of generation 7 have a final marker at branch point generation 6, etc. PPIUA dendrimers have an extra branch.

the change of the final N–N monomers to N–U which show a similar weak expansion. Secondly the extra U–A spacer which shows extensive expansion. The latter is explained by the preferred N–U–A angle, and the fact that each U particle is the origin of only one spacer. Despite the more flexible four-bond spacers, the atomistic simulations do follow the same trends, albeit more erratic. The least similar is *G5* PPIUA which shows a relatively flat expansion profile across the whole propylene imine part.

Compared with our CG PPI dendrimer, a bead-spring model with a similar topology (except for a trifunctional core), has shown a similar parabolic expansion profile.[13] Some united atoms PPI dendrimer melt simulations have shown a markedly different expansion profile, however;[32] their small dendrimers (*G2*, *G3*) expand more from the core outward, while the larger dendrimers (*G4*, *G5*) have a uniform expansion profile.

At the onset of theoretical dendrimer research, all branches were envisioned to extend towards the surface,[92] leading to a vacant core region and crowding at the surface. This model was thus termed the ‘dense shell’ model. A competing view, the ‘dense core’ model maintains the branches’ end groups through bending and back-folding occupy any region possible, thereby having a dense core and not-so dense shell.[8] Although there is some evidence supporting the dense shell theory,[32] the dense core model is currently favoured. E.g., in *G4* PPI dendrimers decorated with ureaphenyl groups, the ends were found with SANS to be distributed throughout the dendrimer.[93] As seen in Section 3.2, solvent conditions alter dendrimer conformations. In good solvent the branches are more extended and thus appear to follow the dense shell model on average, while in bad solvent the collapsed dendrimers better resemble the dense core model.[12] In this view, the dense shell is still not nearly as dense as the dense core. The results shown in Figures 7(a), 7(b) and 9 agree well with the prevalent dense core view.

3.6 Solvent-Excluded Surface Volume

The space a dendrimer occupies in solution is not merely the sum of the atom volumes. It encompasses the space in between these atoms whether empty or occupied by trapped solvent molecules. The surface of a dendrimer can thus be defined as the smallest outer surface that is inaccessible to the bulk of the solvent. That solvent-excluded surface (SES) is computed for every saved state of the simulations with MSMS [94] using a probe size of 1.5 Å. From the polygon surface the volume is calculated and averages for all generations are depicted in Figure 10.

The PPIUA simulations match each other quite well, indicating the coarse-grained model is correct in overall size and average dynamic structure. The values for the PPI dendrimers are

Figure 10. The volume of the space bounded by the solvent excluded surface of the dendrimers. To give a size indication, the hydrodynamic volumes (VH) in D₂O as reported by Scherrenberg et al. are also shown; they are adapted with permission from [29], Copyright 1998 American Chemical Society.

not so good however. The experimental values are expected to be larger as the solvent-excluded surface constitutes a tight lower bound, while in the hydrodynamic radius calculations the drag of the dendrimer plus accompanying solvent is accounted for. Still, the SES volume of the coarse-grained PPI simulation is a factor off (about 1.7). This is explained by the fact that while branches of the atomistic model are capped by NH₂, the coarse-grained model uses a whole N particle (Figure 2(a)). The radius of gyration (Figure 5(a)) is not much affected by this, as the bigger point mass is in the correct position, but the SES is affected for having traced the surface of those particles.

3.7 Atomic Form Factor

The final test of the dendrimer shape is done by comparison with SANS experiments. In SANS experiments of dilute dendrimer solutions scattering due to different dendrimers is extremely weak and may be ignored. The resulting atomic form factor thus describes the correlation of scatterers in the dendrimer:

$$\begin{aligned}
 F(q) &= \frac{1}{N} \left\langle \sum_{j=1}^N \sum_{k=1}^N e^{-i\mathbf{q} \cdot (\mathbf{r}_j - \mathbf{r}_k)} \right\rangle \\
 &= \frac{1}{N} \left\langle \sum_{j=1}^N \sum_{k=1}^N \frac{\sin(q |\mathbf{r}_j - \mathbf{r}_k|)}{q |\mathbf{r}_j - \mathbf{r}_k|} \right\rangle
 \end{aligned} \tag{25}$$

with q denoting the magnitude of the scattering wave vector $\mathbf{q}$ in Å⁻¹ and $\mathbf{r}_j$ the position vector of particle j ; Note that $F(\mathbf{q}) = F(q)$ because of angular isotropy.[95] Using the correlation between monomers (or CG particles) from the simulations in Equation 25 leads to simulated atomic form factors which can be directly compared with the experimental ones, e.g., in a Kratky plot (Figure 11(a)).

At small angles the scatter intensity comes from large distance scatterers, i.e., the left side of the Kratky plot represents the overall dendrimer shape, while at large angles the small internal distances are represented. The latter is increasingly hard to do well experimentally, and for the coarse-grained simulation the size of the particles puts a limit on the smallest possible distances. This effect is also visible in Figure 11(b), where the difference between atomistic and coarse-grained simulations becomes more pronounced at larger scattering angles.

The simulated atomic form factors in Figure 11(a) follow the experimental one quite nicely.

Figure 11. Kratky plots. (a) The $G5$ PPI dendrimer from experiment and simulations. Simulation values are scaled to match the height of the peak. (b) The coarse-grained (solid lines) and atomistic (dashed lines) PPIUA dendrimers of different generations. For convenience, the dependence of the length scale has been removed by plotting $(q R_g)^2 F(q)/N$ versus $q R_g$. Experimental data are reprinted with permission from [29], Copyright 1998 American Chemical Society.

The atomistic one does a bit better than the coarse-grained one. The clear peak means the dendrimer is a fairly dense globular structure,[96, 97] which is just as expected. Should the curve form a plateau instead, it would imply a chain-like conformation. Such a plateau is present in Figure 11(b) where the coarse-grained first generation dendrimer can indeed be viewed as chain-like, as it consists of few particles. On the opposite end, the seventh generation dendrimer begins to show the characteristic periodicity of a solid sphere.[83, 98]

4 Conclusions

We investigated the behaviour of poly(propylene imine) (PPI) and poly(propylene imine)-urea-adamantyl (PPIUA) dendrimers from generation 1 to 7 in water with coarse-grained simulations.

The coarse-grained model was built to reproduce the bonds and angles of virtual coarse-grained sites accumulated during atomistic simulations of $G5$ PPIUA. With Boltzmann inversion of Gaussian fits harmonic potentials were obtained. By decoupling the atomistic input into a complete simulation for bond distribution and a structural simulation for angle distribution, correct bond potentials and natural innate angle potentials were derived. Thereby leaving the effect of solvent on the dendrimer to separate nonbonded interactions. Thus creating a general model capable to simulate different dendrimer sizes and concentrations.

Although parameterized on $G5$ atomistic PPIUA, the coarse-grained model compares well with the atomistic variants, and with the available experimental results [29] with respect to various structural measurements over a wide range of generations. We have determined the radius of gyration, asphericity, solvent-excluded surface volume, radial monomer densities, spacer expansions and atomic form factors, providing a complete molecular picture. Representative structures for three generations of PPIUA dendrimers are shown in Figure 12.

The amine-amine chains of the base PPI dendrimers are flexible. Therefore the dendrimers are flexible provided the chains have sufficient room to move. The small dendrimers ($\leq G3$) are so capricious they sometimes are rod-like and sometimes globular. Their core does not necessarily reside in the centre of the molecule, something that is inevitable for the ones that approach the limiting generation ($\geq G6$). The latter even exhibit liquid-like crowding around the centre. The middle generations ($G4, 5$) are fairly flexible, fairly spherical and without an exposed core. For all generations, the dendrimer's extremities are distributed over the complete volume through abundant back-folding—thus pointing to dendrimers of sufficient size having a dense core. Finally, with respect to the distribution of its branches, PPIUA is indeed fully an

Figure 12. Representative structures for three PPIUA dendrimer generations at their average radius of gyration and asphericity: (a) $G3$ ($R_g = 11.05\text{\AA}$, asphericity = 0.079), (b) $G5$ ($R_g = 16.46\text{\AA}$, asphericity = 0.030) and (c) $G7$ ($R_g = 24.78\text{\AA}$, asphericity = 0.009). The poly(propylene imine) part is coloured light blue at the core to dark blue at the ends, highlighting the propensity for back-folding.

enhanced PPI molecule of that generation.

Having demonstrated the effectiveness of this coarse-grained model, the next step will be to simulate the behaviour of the PPI dendrimers in concentrated solutions.

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