Brownian dynamics simulation of charged dendrimers

Lyulin, S.V.; Lyulin, A.; Darinski, A. A.

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INTRODUCTION

Dendrimers are monodisperse macromolecules with a highly branched regular architecture [1–3]. Their unique properties, which are due to their regularity, make them the object of intense theoretical and experimental investigations. Active research concerning the behavior of dendrimers in solutions has recently developed due to their use in microbiology and medicine.

The diversity of synthetic dendrimers makes it possible to use them as molecular “containers” for the transport of various compounds [4] (e.g., for the delivery of medicines, genes, DNA, etc.).

There are many theoretical works and numerical simulations concerning conformational and statistical properties of dendrimers in dilute solutions. They show that, in contrast to theoretical predictions made by De Gennes and Hervet [5], dendrimers exist as fairly compact structures even in a good solvent; their density decreases from the core to the periphery. Such a structure is due to the presence of excluded-volume interactions. Terminal groups of dendrimers are not localized on the surface but distributed over the entire volume. The majority of analytical and numerical investigations concern the properties of neutral dendrimers. However, most water-soluble dendrimers contain functional groups, which may be ionized by changing the pH value of the solution. As an example, one can mention Astramol [6, 7] and poly(amidoamine) [8] dendrimers.

Welch and Muthukumar [9] performed a Monte Carlo simulation of the statistical properties of charged dendrimers in dilute solutions. They showed that dendrimers may change their size and density profile as the concentration of salt in the solution increases, since electrostatic interactions become stronger. Terminal groups shift to the periphery. The Monte Carlo method was also used to study complexes consisting of charged dendrimers and oppositely charged polymer chains [10]. However, this method [9, 10] is not suitable for studying the dynamic properties of dendrimers.

The most precise computer simulation technique for dendrimers in solution is the method of molecular dynamics (MD) [11]. In this case, the solvent must be explicitly considered, and therefore a much longer machine time is required for obtaining representative results. The potential of the MD method is limited to studies of movements at relatively small space and time scales.

The method of Brownian dynamics is a compromise that makes it possible to study dynamic processes at large scales. This method has already been successfully used by one of the authors for numerical simulation of dilute dendrimer solutions under the action of a shear flow [12–15]. In those studies, for example, the characteristic viscosity at zero flow displays a nonmonotonic

Brownian Dynamics Simulation of Charged Dendrimers: Statistical Properties

S. V. Lyulin*, A. V. Lyulin**, and A. A. Darinskiï*

* Institute of Macromolecular Compounds, Russian Academy of Sciences, Bol’shoy pr. 31, St. Petersburg, 199004 Russia
** Dutch Polymer Institute and Department of Applied Physics, Technische Universiteit Eindhoven, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

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Abstract—Computer simulation by the method of Brownian dynamics is used to study the statistical properties of neutral and charged dendrimers up to the sixth generation (382 groups) in dilute solutions. Excluded-volume interactions are described by the Lennard–Jones repulsive potential corresponding to an athermal solvent. Electrostatic interactions are considered in the Debye–Hückel approximation. The resultant radial functions of monomer density distribution have a maximum in the core and decline toward the periphery. The average radius of gyration changes with increasing Debye radius \( r_D \) to a minor extent. The swelling of a neutral dendrimer is adequately described by the Flory mean-field theory. The fractal dimension found for neutral dendrimers is \( d_f = 2.77 \); for charged dendrimers, it amounts to \( d_f = 2.63 \) at \( r_D = 0.8 \) and \( d_f = 2.42 \) at \( r_D = 100 \). Terminal groups are distributed all over the dendrimer volume. The maximum in the distribution of terminal groups shifts toward the periphery as \( r_D \) increases.

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2 E-mail: serge@ime.macro.ru
behavior with increasing MM, a fact agreeing with known experimental data.

In this paper, we use the method of Brownian dynamics for studying the equilibrium statistical properties of neutral and charged dendrimers of various generations with allowance for electrostatic and excluded-volume interactions. The results will be further used to analyze the dynamic properties of dilute solutions of neutral and charged dendrimers.

**DENDRIMER MODEL AND SIMULATION TECHNIQUE**

We consider the bead–rod model of a dendrimer. It contains “rods” of length \( l \) and “beads” with the friction coefficient \( \zeta \) (Fig. 1). Dendrimers with trifunctional groups were studied. The generations of a dendrimer may be determined as

\[
N = 3s(2^g + 1) + 1,
\]

where \( s \) is the length of the spacer between the branching points. The case considered in this paper is \( s = 1 \).

Dendrimers up to the sixth generation inclusive \((N = 382)\) were studied. Most results were obtained for dendrimers up to \( g = 5 \).

Excluded-volume and electrostatic interactions are taken into account in the system. Hydrodynamic interactions should also be taken into account in the description of the dendrimer dynamics. However, this is not necessary for analyzing the equilibrium statistical properties. Therefore, this study considers the free-draining model of a dendrimer. The solvent is represented as a viscous medium acting on the dendrimer beads via frictional and random forces. The finite-difference scheme used in the study is based on the Ermak–McCammon equation [12–16]

\[
\mathbf{r}_i = \mathbf{r}_i^0 + \frac{\Delta t}{k_B T} \sum_j D_{ij}^0 \mathbf{r}_j^0 + \Phi_i^0(\Delta t). \tag{2}
\]

Here \( \mathbf{r}_i^0 \) is the radius vector of the \( i \)th particle \((i = 0\) corresponds to the core\), \( k_B \) is the Boltzmann constant, \( T \) is the absolute temperature, \( D_{ij}^0 \) is the diffusion tensor, and \( \Delta t \) is the integration step.

\( \mathbf{F}_j^0 \) in Eq. (2) is the total force acting on the \( j \)th bead:

\[
\mathbf{F}_j^0 = -\sum_{k=1}^N \mu_k \left( \frac{\partial \sigma_j}{\partial \mathbf{r}_j} \right)_r - \partial U_{LJ} / \partial \mathbf{r}_j^0 - \partial U_C / \partial \mathbf{r}_j^0, \tag{3}
\]

where \( U_{LJ} \) corresponds to excluded-volume interactions between particles, \( U_C \) is the potential of electrostatic interactions, \( \sigma_j \) is the equation of rigid constraint for the \( k \)th bond, and \( \mu_k \) is the corresponding Lagrange multiplier.

The random force \( \Phi_0^0 \) in Eq. (2) satisfies the conditions

\[
\langle \Phi_0^0 \rangle = 0, \tag{4}
\]

\[
\langle \Phi_i^0(\Delta t) \Phi_j^0(\Delta t) \rangle = 2\Delta t D_{ij}^0. \tag{5}
\]

In the absence of hydrodynamic interactions, the diffusion tensor \( D_{ij}^0 \) is diagonal, \( D_{ii}^0 = k_B T / \zeta \). To preserve a fixed value of the bond length \( l \), the SHAKE algorithm [17] with a tolerance of \( 2 \times 10^{-6} \) is used. The method used here is described in more detail in earlier papers [12–15].

Excluded-volume interactions in Eq. (3) are described by the Lennard-Jones repulsive potential \( U_{LJ} \) with a cutoff radius of \( r_{\text{cutoff}} = 2.5 \sigma \). Excluded-volume interactions take place between beads that are not chemically bound to each other. The selected repulsive interaction potential \( U_{LJ}(r_{ij}) \) between beads \( i \) and \( j \) corresponds to an athermal solvent:

\[
U_{LJ}(r_{ij}) = \sum_{ij} 4\epsilon \left( \frac{\sigma}{r_{ij}} \right)^{12}, \tag{6}
\]

where \( r_{ij} \) is the distance between beads \( i \) and \( j \). We selected the previously used parameters of the Lennard-Jones potential: \( \sigma = 0.8l \) and \( \epsilon = 0.3k_B T \) [12–15].
In the simulated dendrimers, only terminal groups were charged. Electrostatic interactions were described by the Debye–Hückel potential

\[
\frac{U_C}{k_B T} = \lambda_B [q]^2 \sum_{i,j = 1}^{N_T} \exp\left(-\frac{r_{ij}}{r_D}\right), \tag{7}
\]

where \(N_T\) is the total number of terminal groups in the dendrimer; \(r_{ij}\) is the distance between the \(i\)th and \(j\)th terminal groups of charge \(q_i\); \(\lambda_B\) is the Bjerrum length, which characterizes the intensity of Coulomb interactions in a medium of permittivity \(\varepsilon\):

\[
\lambda_B = \frac{e^2}{4\pi\varepsilon k_B T}, \tag{8}
\]

and \(r_D\) in Eq. (7) is the Debye radius, which characterizes the ionic strength of the solution and depends on the concentration and charge of ions in it:

\[
1/r_D^2 = 4\pi\lambda_B \sum_i c_i z_i^2 \tag{9}
\]

\((c_i\) and \(z_i\) are the concentration and charge of the \(i\)th ion, respectively).

The \(\lambda_B\) value in water at room temperature amounts to \(\sim 7\, \text{Å}\), which is close to the segment length for typical flexible polymers. Therefore, without loss of generality, we may assume \(\lambda_B = l\).

Two cases were considered: \(q = 0\) (neutral dendrimer) and \(q = 1\). In this work, we use the same values of the Debye radius as Welch and Muthukumar [10]:

\[
r_D = \frac{r_D}{l} \lambda_B = 0.8, 1.54, 8.96, \text{ and } 100 \text{ for different concentrations of salt in water (from 0.28 mol/l to a salt-free solution).}
\]

Just as usual, we use dimensionless quantities expressed in the following units: length \(l\), energy \(k_B T\), friction coefficient \(\zeta\), time \(\zeta^2/k_B T\), and charge \(e\). The dimensionless integration step is \(\Delta t = 10^{-4}\). This \(\Delta t\) value was chosen to ensure that the maximal bead displacement in a single step would not exceed 10% of the bond length.

To generate the initial configuration of the dendrimer, we used the procedure proposed by Murat and Grest [11]. The \(g = 0\) generation is created by attaching \(b = 3\) chains consisting of \(s = 1\) monomer to the core in three arbitrarily chosen directions. Each bead is linked to the adjacent one by a rigid bond of length \(l\). The next generation is produced by attaching \(b - 1\) bonds to each terminal group of the previous generation. The new monomer is regarded as attached if the distance from it to any monomer attached earlier is \(r \geq r_{\text{min}} = 0.08\sigma\). If a new monomer cannot be added after 500 attempts, the construction procedure is repeated again with other values of random numbers.

After the initial configuration of the dendrimer had been generated, this dendrimer was brought into equilibrium in \(5 \times 10^5\) to \(10^6\) steps. The duration of the equilibration procedure depended on the dendrimer size and salt concentration in the solution. The attainment of equilibrium was controlled using instantaneous values of the squared radius of gyration. After the equilibration, 9 to 11 simulation series with \(10^6\) integration steps each were performed. The calculated characteristics were averaged over all the series.

**SIMULATION RESULTS**

**Mean-Square Radius of Gyration**

As the characteristic size of a dendrimer, one can use the mean-square radius of gyration \(R_g^2\), which is defined as follows:

\[
R_g^2 = \frac{1}{N+1} \sum_{n=0}^{N} \langle (r_n - r_C)^2 \rangle, \tag{10}
\]

where \(r_C\) is the radius vector of the mass center of the dendrimer. \(R_g^2\) may be experimentally measured, for example, using small-angle neutron scattering (SANS) [18].

The resultant \(R_g^2\) values as functions of the number of generations \(g\) are shown in Fig. 2a in the logarithmic scale.

The calculated radii of gyration may be compared with those predicted by Boris and Rubinstein [19] within the Flory mean-field theory. In their paper, those authors supposed that the radius of gyration of a dendrimer is proportional to the average size of the linear chain between the core and a terminal group. Then the free energy of a dendrimer is represented as

\[
\frac{F}{k_B T} \approx \frac{3}{2} \left(\frac{R_g^2}{R_{g0}^2}\right) - 3 \ln \left(\frac{R_g}{R_{g0}}\right) + g s \phi \tag{11}
\]

\[
= \frac{3}{2} \alpha^2 - 3 \ln \alpha + g s \phi_0 \alpha^{-3}.
\]

Here \(R_g\) is the radius of gyration of the dendrimer, \(R_{g0}\) is the radius of gyration of the ideal (without excluded-volume interactions) dendrimer, and \(\alpha = R_g/R_{g0}\) is the swelling ratio for this dendrimer. The first term of the equation corresponds to elastic Gaussian extension, the second one is due to entropic losses because of volume limitations, and the third one corresponds to the energy of pairwise excluded-volume interactions.
The average density \( \phi \) of segments in a dendrimer is described as

\[
\phi = \frac{N\nu}{R_g^3} = \frac{N\nu}{R_{g0}^3} \alpha^{-3} \equiv \phi_0 \alpha^{-3},
\]

where \( N \) is the total number of monomers in the dendrimer, \( \nu \) is the parameter of excluded-volume interactions of one monomer, and \( \phi_0 \) is the average density of the ideal dendrimer. The minimum of the free energy determines the equilibrium value of the swelling parameter \( \alpha \).

For \( R_{g0} \), Boris and Rubinstein [19] used the expression for the size of a Gaussian coil:

\[
R_{g0} = (g + 1)^{1/2}.
\]

To determine the values of the \( \alpha \) parameter for dendrimers considered in this paper, we compared the \( R_g \) values obtained by the method of Brownian dynamics with the corresponding \( R_{g0} \) values for an ideal dendrimer without excluded-volume interactions. Instead of Eq. (13), we used the expression for \( R_{g0} \) derived by la Ferla and coauthors [20] with the use of the Wiener topological index [21]:

\[
R_{g0}^2 = \frac{3(12 \times 2^{g+1} + 4(3g + 1 - 2)2^{2g+1} - 1)}{(3(2^{g+2} - 1) + 1)^2}.
\]

Figure 3 shows the \( \alpha \) value plotted vs. number of generations in the simulation using this method. The excluded-volume interaction parameter in the Flory theory was selected to be equal to \( \nu = 0.41 \) in order to achieve the best agreement with the results of the Brownian dynamics simulation (solid line).

On the other hand, the second virial coefficient \( \nu \) of the interaction of point-sized particles adheres to the equation [22]

\[
\nu = \frac{1}{2} \int (1 - e^{-U_{LJ}(r)/k_B T}) d^3 r.
\]

For the Lennard-Jones potential used in this work [see Eq. (6)], the value obtained for the coefficient is \( \nu = 0.46 \), in good agreement with the above results. Thus, the swelling of a neutral dendrimer is adequately described within the framework of the Flory mean-field theory.

For charged dendrimers, the increase in the Debye radius (decrease in the salt concentration in solution) leads to slightly larger \( R_g^2 \) values in comparison with neutral dendrimers (Fig. 2a). Figure 2b shows the root-mean-square radius of gyration \( R_g = \sqrt{R_g^2} \) as a function of the molecular mass. Using this plot, one can calculate the fractal dimension \( d_f \) of the dendrimer according
to the middle portions of the curves (10 ≤ N ≤ 100), assuming their linearity:

\[ R_g \sim N^{1/d_f} \]  \hspace{1cm} (16)

For neutral dendrimers of generations \( g = 0–4 \), we obtain \( d_f = 2.77 \).

The fractal dimensions of neutral dendrimers have earlier been discussed by various authors. Using the scaling approach, Zimm and Stockmayer [23] found the fractal dimension of dendrimers to be equal to \( d_f = 4 \). The value provided by De Gennes and Hervet [5] is \( d_f = 5 \). Lescanec and Muthukumar [24] used the kinetic growth model and arrived at \( d_f = 4.55 \). Murat and Grest [11] performed a molecular dynamics simulation with allowance for excluded-volume interactions in solvents of various qualities, and their data yield \( d_f = 3 \) for all the considered cases. Mansfield [25], using the Monte Carlo technique within the lattice model of a dendrimer, obtained fractal dimensions lying in the 2.45–2.76 range. The latter results show a good agreement with ours.

Charged dendrimers displayed a slight decrease in the fractal dimensions (\( d_f = 2.63 \) at \( r_D = 0.8 \) and \( d_f = 2.42 \) at \( r_D = 100 \)) compared to the neutral dendrimer. This implies that the amount of “vacant” space inside the charged dendrimer increases with increasing scale of electrostatic interactions. This corresponds to an increase in \( r_D \); i.e., the dendrimer becomes more “penetrable.”

This conclusion is confirmed by analyzing the instantaneous configurations of dendrimers (Fig. 4). A charged dendrimer has a looser structure than a neutral one.

**Radial Density Distribution Function**

The distribution of monomers in a dendrimer may be characterized by the radial density distribution function \( \rho(r) \). To calculate it, we partitioned the space into concentric spheres with the center at the mass center of the dendrimer. The average density \( \rho(r) \) of monomers in a spherical layer at distance \( r \) from the center is defined as

\[ \rho(r) = \frac{\langle n(r) \rangle}{V(r)}, \]  \hspace{1cm} (17)

where \( \langle n(r) \rangle \) is the average number of beads in a layer of volume \( V(r) \).

De Gennes and Hervet assumed [5] that the radial density distribution function has a minimum in the core of the dendrimer and then monotonically increases toward the periphery. However, subsequent numerical simulations showed [9–13, 24–26] that the radial density distribution function has a maximum at the center and decreases with the distance from the center. The results of our simulation for dendrimers up to the sixth generation inclusive agree with these concepts (Fig. 5).

Local maxima and minima of the distribution function are observed at short distances from the center (Fig. 5). This is explained by the presence of rigid fixed-length bonds. Beads located far away from the center are more uniformly distributed within the dendrimer. After a plateau regime (its length increases with the dendrimer generation number), the distribution function monotonically tends to zero. This behavior shows a good agreement with the MD data [11] and with the results of a Monte Carlo simulation on a lattice [26].

The radial density distribution functions \( \rho(r) \) for charged dendrimers of generations \( g = 4 \) and \( g = 5 \) are shown in Fig. 6 for various values of the Debye radius \( r_D \). The pattern of the distribution function in this case does not markedly change in comparison with the neutral dendrimers. However, the maxima and minima
become more pronounced, in accordance with a higher internal stress in the system.

**Distribution of Terminal Groups**

The location of terminal groups in a dendrimer is important for many applications, because often it is the terminal groups that determine the possibility of one or another application of dendrimers. Earlier numerical and theoretical investigations predict that terminal groups are distributed all over the volume of a neutral dendrimer. Our results agree with these data. The distribution $\rho_{t}(r)$ of terminal groups in the simulated dendrimers is shown in Fig. 7 for neutral and charged dendrimers. Apparently, terminal groups are distributed over the entire dendrimer volume with a feebly marked maximum. However, as the Debye radius increases, terminal groups shift to the periphery because of the effect of electrostatic repulsion.

The maximum in the distribution of terminal groups shifts away from the center and becomes more pronounced as the Debye radius increases.

Welch and Muthukumar also observed a similar behavior in their Monte Carlo simulations [9, 10] both for dendrimers where all branching points are charged and for dendrimers with charged terminal groups. Above a certain $r_D$ value, a further increase in the Debye radius does not affect $\rho_{t}(r)$. This is explained by the fact that the intensity of electrostatic interactions between terminal groups ceases to change when the Debye radius starts to exceed the dendrimer size.

The position $R_t$ of the maximum in the radial function of terminal group distribution for $r_D = 8.96$ is shown in Fig. 8 vs. number of generations in the den-
The mean-square radius of gyration $R_g$ is shown for comparison. Apparently, $R_t > R_g$, especially for large $g$ values.

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