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Multi-Scale Simulation of the Conformation and Dynamics of Dendrimeric Macromolecules

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Summary: In this work, we propose simple physical models and simulation methodologies for the simulation of solution properties of dendrimer molecules. We employ a multi-scale approach, in which the basic entities in the bead-and-connector models are first parameterized by comparison of the outcome from fully atomic molecular dynamics simulation with that of Monte Carlo calculations of the simple model. Employing experimental data of the radius of gyration for this parameterization, the calculated values of other properties, like the intrinsic viscosity and hydrodynamic radius are in good agreement with experimental data. The dynamics of our simple physical model can be studied by Brownian dynamics with hydrodynamic interaction. Thus one can make predictions for other dynamic properties of the dendrimer molecules, like NMR relaxation and rheology.

Keywords: bead-and-spring model; Brownian Dynamics simulation; computer modeling; dendrimers; Monte Carlo simulation

Introduction

Dendrimers are regularly hyperbranched structures which, in a few years have evolved from a mere academic curiosity to become extremely useful molecules.[1] The prediction of their conformation and dynamics in solution is then of practical interest.[2] Atomistic molecular dynamics can be employed for conformational studies in a short time scale. However, this approach can not reach the long time scales in which the dynamics of these entities take place.

We propose the possibility of simulating properties of dendrimers in a multi-scale approach, combining atomistic molecular dynamics with Monte Carlo simulation of coarser-grained models, which retain the main features of the molecular topology, and are parameterized from the finer-grain MD simulation.[3] For such a purpose we present here simple models, procedures, and illustrative results.

Models

The mechanical model of the dendrimer consists of beads connected by springs with a stretching potential which has been devised in this work:

$$V = -0.5\,H\,l_{max}[l_{max}\ln(1-(l/l_{max})2) - l_e\ln((l_{max}+l)/(l_{max}-l))] \quad (1)$$

This potential equation has three parametes: l_e determines the equilibrium, most probable elongation, H determines the hardness of the connector, and l_{max} is its maximum length. The angles between neighbor branches can be represented by a potential quadratic in the bending angle, and the excluded volume effect is represented by simple hard-spheres or Lennard-Jones potentials.

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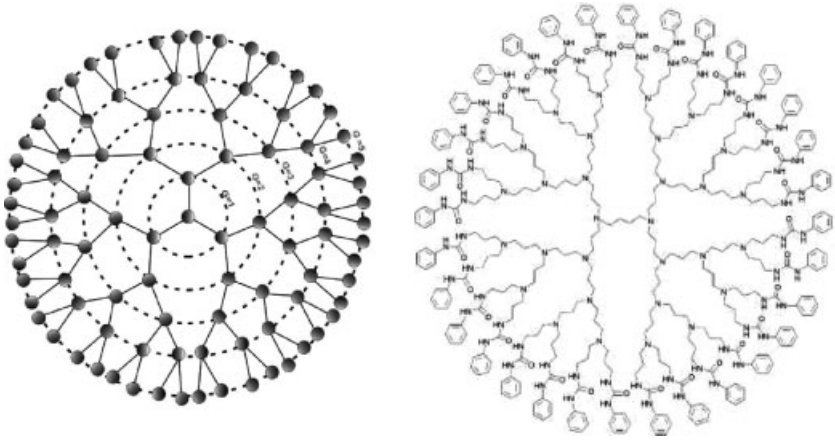

Figure 1.
Chemical composition of a functionalized PAMAM (polyamidoamine) dendrimer. Scheme (irreal, 2D) of a G = 5 dendrimer (five generations), with "Y" core.

Simulation Methods

As indicated above, the first step in our multi-scale approach is a simulation of an atomic model, using either molecular dynamics (MD) or Langevin dynamics (LD) simulation, that provides information about the conformational statistics of the dendrimer units (branches), used to parameterize the springs and bending angles. A variety of existing MD packages can be employed. We used Accelrys (San Diego, CA, USA) or HyperChem (Gainesville, FL, USA). Then, the conformational statistics of the dendrimer can be simulated, by a standard Monte Carlo (MC) procedure. For bead-and-connectors models like that used for our dendrimers, the public-domain MONTEHYDRO program,[4] which is a module of the BROWFLEX package,[5] is particularly helpful. Hydrodynamic coefficients (intrinsic viscosity, diffusion coefficient, etc.) can be calculated using the "Monte-Carlo rigid-body" approach (MCRB),[6] from the same MC trajectories, but the full, rigorous simulation of dynamic behavior (internal dynamics, rheology, etc.) has to be done by means of Brownian dynamics (BD) simulation with hydrodynamic interactions. The BD of the bead-and-connector models has been simulated with the predictor-corrector algorithm[7] using the SIMULFLEX module of BROWFLEX.

Results

As examples of the utility of our multi-scale methodology for dendrimer molecules, we present here preliminary results for monodendrons of polybenzylether (mono-PBzE), with a "V" (bifunctional) core and the repeating unit displayed in Figure 2.

MD simulations were carried out to parameterize the connector spring, with the following results: $H = 20.2 \times 10^{-12}$ erg/nm^2, $l_e = 0.65$ nm and $l_{max} = 0.72$ nm. In a first calculation, angular (bending interactions) were neglected, and the bead size and excluded volume parameters were adjusted

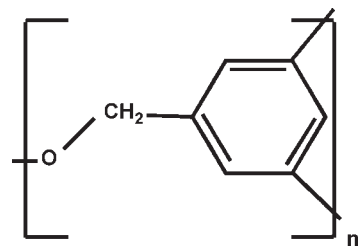

Figure 2.
PBzE repeating unit.

Table 1.
Calculated and experimental values of the radius of gyration, R_g, intrinsic viscosity, [η], and hydrodynamic (Stokes) radius, R_h, of mono-PBzE dendrimers of succesive generations, G.

G	R_g (nm)		[η] (cm^3/g)		R_h (nm)
	Calculated	Experiment	Calculated	Experiment	Calculated
1	0.461	*****	*****	*****	0.429
2	0.688	*****	3.70	3.7	0.630
3	1.030	0.99	5.07	4.5	0.974
4	1.175	1.16	5.10	5.2	1.261
5	1.418	1.39	5.33	5.3	1.649
6	1.507	*****	4.50	5.0	1.864

as to reproduce the experimental data of the radius of gyration, R_g.[8] The Lennard-Jones parameters so found were $\sigma_{LJ} = 0.36$ nm and $\varepsilon_{LJ} = 4.04 \times 10^{-15}$ erg (all at T = 293 K). With this information, a MC-RB simulation (MONTEHYDRO) of the dendrimer molecule yields for the hydrodynamic properties the results reported in Table 1.

The intrinsic viscosity results also show a good agreement with the available experimental data.[9] These favourable comparisons warrant the adequacy of the model and parameters, which are then used for dynamics, BD-HI simulation. Immediate outcome of these simulations are again, calculated values for the hydrodynamic coefficients, which turn out to be rather similar to those of the less rigorous but computationally effective RB-MC treatment.

But the most relevant possibilities offered by BD simulation is the study of internal dynamics of the appreciably flexible structure of dendrimers. The internal motion can be characterized by the Brownian reorientation of some characteristic vectors. For instance, the time function

$$\langle P_2(t)\rangle = \langle (3[\mathbf{u}(t_0)\cdot\mathbf{u}(t_0+t)]2-1)/2\rangle_{t_0} \quad (2)$$

where $\mathbf{u}(t_0)\cdot\mathbf{u}(t_0+t)$ is the cosine of the angle subtended by two succesive orientations of vector **v** (with unitary **u**) separated by time t . This function is related to NMR relaxation times that may be characterized experimentally. Computed values of the $\langle P_2(t)\rangle$ function for the core-to-end vector, and for the connector (spring direction) vector of more or less internal branches, are depicted in Figure 3.

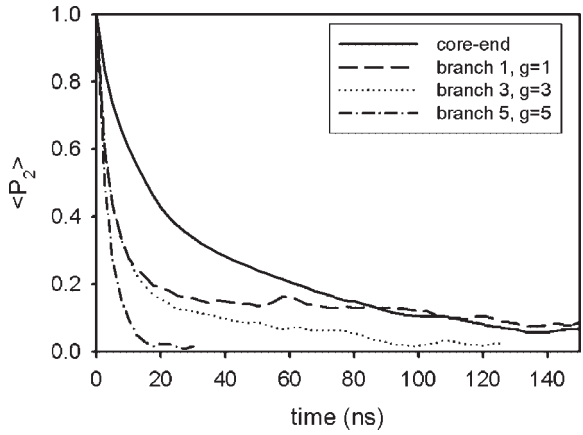

Figure 3.
$\langle P_2(t)\rangle$ decay for a mono-PbzE dendrimer of G = 5, for the core-end vector, and other vectors along the direction of various, more or less external branches.

It is clear that the relevant time scale for dendrimer dynamics is in the range 10-100 ns. Dynamic trajectories must be much longer than these typical relaxation times, with durations of the order of microseconds, which is only accessible in BD simulations.

Conclusion

Multi-scale methodologies allow for parameterization of coarse-grain macromolecular models, as it is the bead-and-spring model proposed in this work in order to simulate the dynamics of a dendritic molecule. First, atomic level simulations of relevant pieces of the macromolecule are performed via Molecular Dynamics to get adequate values for the coarse-grain model parameters. Then simulations using the coarse-grain model, able to capture the large time-scale dynamics of the macromolecule, are carried out by using the Monte Carlo or the Brownian Dynamics technique. The Monte Carlo technique gives acceptable results for conformational and hydrodynamic properties of the dendrimer at equilibrium. In order to study the dendrimer dynamics, as reflected for instance by the time evolution of the orientational correlation function of some characteristic vector of the molecule, we must use Brownian Dynamics.

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