SIMULATION AND ANALYSIS OF THE DIFFUSION PROPERTIES OF CHLOROFORM SOLUTION OF CARBOSILANE DENDRIMERS

Lappeenranta-Lahti University of Technology LUT

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ABSTRACT

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Diffusion properties of macromolecules are important for theoretical studies and practical application. The hydrodynamic radius R_h, calculated from simulation data is usually used as a test of the correctness of the simulation, in other words, the radius is used to calibrate the simulation using its experimental values. However, as it was shown in this work, the traditional method of the extraction of the diffusion coefficient and hence the calculation of R_h, for dendrimers, as a rule, faces difficulties that require simulation resources several times more than, for example, a linear analogue. Here we study translation mobility of poly(butyl)carbosilane dendrimers in chloroform solution using molecular dynamics simulations. Different methods to estimate R_h for a dendrimer are discussed comparing to experimental data. Features, such as simulation time, substance characteristics, types of barostats, sizes of the involved elements, that may influence on accuracy of the result are considered and compared to existing papers. Based on problems, which occur during translational mobility studies, we offer an alternative way: to consider rotational diffusion which gives practically the same results for R_h compared to traditional method.

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Khusnutdinova Naira

LIST OF ABBREVIATIONS

MD	Molecular Dynamics
MSD	mean-square displacement
PAMAM	polyamidoamine dendrimer
ACF	autocorrelation function
NVT	Number of particles, Volume, Temperature
NPT	Number of particles, Pressure, Temperature
NMR	nuclear magnetic resonance
SANS	small-angle neutron scattering
SAXS	small-angle X-ray scattering
SAS	small-angle scattering
CSD	carbosilane dendrimer

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1 INTRODUCTION

1.1 Background

Dendrimers are a relatively new class of macromolecules with a perfect tree-like structure [1, 2]. This architecture gives dendrimers a number of features that make them popular in various practical applications [3, 4]. Therefore, systematic studies of equilibrium and dynamic properties are important for the synthesis of new structures and for the creation of new methods of use.

Dendrimers are used in various fields of polymer chemistry, medicine and biology, as drug delivery systems [4–11], nanoscale catalysts [12], fuel cells [13, 14], etc. The study of the structural and dynamic properties of dendrimers is very important for understanding their behavior and interactions with the environment and other structures / components [15–17]. This makes it possible to purposefully obtain new dendrimeric structures with desired properties. Therefore, systematic studies of equilibrium and dynamic properties are important for the synthesis of new structures and for the creation of new methods of use.

Diffusion is one of the most important dynamic characteristics used for the practical use of dendrimers, especially in main areas of applications, such as drug delivery [10] and nanoparticle synthesis [18]. Diffusion properties of dendrimers are experimentally studied by various methods, including nuclear magnetic resonance methods. Diffusion data make it possible to directly estimate the hydrodynamic radius (R_h) of a macromolecule using the well-known Stokes-Einstein formula. We should note that the use of this formula for a dendrimeric macromolecule is justified, since the shape of the dendrimer is close to spherical.

For a theoretical study of the diffusion of dendrimeric macromolecules, as a rule, molecular dynamics (MD) simulation is used. To do this, the mean-square displacement (MSD) of the center of mass of the macromolecule is calculated from the simulation trajectory as a function of time ($MSD(t)$). Next, a segment is selected from this curve, where the dependence is linear, and the diffusion coefficient of macromolecule is calculated using the Einstein formula. It is important to note that in the classical Einstein formula, only linear dependence corresponds to the diffusion regime. However, in the case of curves obtained from simulation data, the areas of diffusion coefficient calculation are not always linear - which may reflect ranges with anomalous diffusion.

1.2 Objectives and delimitations

Despite the simplicity of calculating the diffusion coefficient and hydrodynamic radius from simulation data, there are many "traps" in this approach, associated both with simulation parameters that can give artifacts in the calculation (for example, cell size or insufficient length of the simulation trajectory), and the presence of additional subdiffusion modes.

Thus, the purpose of this work is to study the problem of translational mobility in molecular dynamics simulations. For that the following tasks are set:

- Simulate carbosilane dendrimer of different generations in chloroform solution.
- Obtain MSD versus time for various cell sizes.
- Obtain MSD versus time for various time trajectories.
- Determine the presence of a diffusion mode for various simulation options.
- Determine the diffusion coefficient for each generation.
- Determine the necessary parameters to accurately determine the diffusion coefficients.
- Determine the hydrodynamic radius of three generations of dendrimers.
- Determine the hydrodynamic radius using rotational diffusion.

Let us highlight the last point, since a separate method was proposed and tested for the dendrimer under consideration. This method is interesting because, due to the use of rotational diffusion, it becomes possible to obtain results with less computational resources.

1.3 Structure of the thesis

The process of achievement this goals is given in this work in following order: first of all in Chapter 2 is provided basic information regarding the study. Here Section Overview of the area presents both a chronological overview of the area of study and current papers on the topic under study. Also, Section Objects of study briefly explains both about dendrimers in general, and about the examples in the study in particular. Sections Diffusion and Rotational mobility are devoted to brief explanation of theoretical aspects, later used in calculations. And also this Chapter includes some experimental methods, which are used for dendrimers research. Last three Sections of this Chapter provide us information about methods and theoretical data used. Chapter 3 consists of Sections about package which was used for simulation, as it is designed for simulations

of different macromolecules and last Section contains information about methods and details used in this work. In Chapter 4 there are three sections about results in three main areas of research, such as influence of simulation parameters on the data, calculation of diffusion coefficient and rotational diffusion, which is of a great interest, as it is a new proposed method. Finally, Chapter 5 describing all the work done and listing the extent to which the aims were met, as well as indicating directions for further research leads to in Chapter 6 where the conclusions are given.

2 RELATED WORK

2.1 Overview of the area

Considering the development of dendrimers chronologically, we should start from their first description by Vogtle's group in 1978 [1] originally mentioned as cascade molecules. They synthesized the polymer based on the amino group by stepwise synthesis. In 1985, Newcome and his group pioneered the field as it exists today and described the synthesis of arborolesc [19]. At the same time, an additional breakthrough in the field of dendrimers was achieved by an industry group at Dow Chemical Tomalia and colleagues was prepared polyamidoamine dendrimers (PAMAM) [2], which are the most common type of dendrimers in commercial research [20]. The dendrimers of the last two scientific groups are designed differently - the synthesis begins with a multifunctional nuclear molecule and is finalized to the periphery. Later, based on original work by Vogtle, Mühlhaupt and de Brabander reported the preparation of divergently produced polypropyleneimine dendrimers [21, 22].

In 1990, Fréchet introduced a convergent approach to dendrimers [23]. In convergent procedures, synthesis begins at the periphery and is brought to the core. Aromatic polyester Fréchet dendrimers are readily available and are often studied not only by Fréchet's group, but also by other researchers. Finally, convergently obtained phenylacetylene Moore dendrimers [24] are located at the source of this field. In addition, many other types of interesting and valuable dendritic systems have been developed, and thus various dendritic frameworks with certain nanoscopic dimensions and a discrete number of functional terminal groups have become available [25].

When considering the applications of dendrimers, various possibilities are mentioned, of which we would like to highlight two for a more detailed consideration and understanding of the benefits of the architecture of the studied macromolecules.

Dendrimers are particularly well suited to accommodate metal nanoparticles in the diameter range from less than 1 nm to 10 nm for the following reasons [26]:

- The dendrimers themselves have a fairly uniform composition and structure, and therefore they give well-defined copies of the nanoparticles;
- The nanoparticles are stabilized by being encapsulated in a dendrimer and therefore they do not agglomerate;
- Encapsulated nanoparticles are limited mainly by steric effects, and therefore a

significant part of their surface is not passivated and is available for participation in catalytic reactions;

- Dendrimer branches can be used as selective gates to control the access of small molecules (substrates) to encapsulated (catalytic) nanoparticles;
- Terminal groups at the periphery of dendrimers can be adapted to control the solubility of the hybrid nanocomposite and used as handles to facilitate bonding to surfaces and other polymers.

The second area of great interest in dendrimers is medicine. A high number of functional groups at the ends means that the resulting interaction between the array of ligands and the target cell can turn dendrimer into a highly interacting reagent. Due to these properties, dendrimers are used in various fields of biology and medicine [27]. By attaching a drug to a suitable carrier, it is possible to increase its water solubility, increase its lifespan, target the drug to specific tissues, improve drug transport across various biological barriers, and slow down drug metabolism. Optimizing these properties to increase and maximize drug bio-availability to diseased tissues while minimizing drug exposure to healthy tissue results in increased therapeutic efficacy.

As dendrimer densification with generation growth is used as a means to obtain concentrated drug payloads or spectroscopic labels for therapeutic applications and imaging.

The terminal groups can strongly control the solubility of the dendrimer: hydrophilic terminal groups will make the dendrimer water soluble with a hydrophobic core, hydrophobic peripheral moieties can make the dendrimer oil soluble, which causes undeniable benefits in the application.

At the moment, one of the most important theoretical methods for studying dendrimers is simulation, therefore, relevant works were analyzed to determine the existing simulation algorithms, during which some details were noticed.

For example, in [5, 9, 17, 28, 29], while creating a cell for simulation, the cell size was determined irrespective of the dendrimer size, often by adding a layer with a thickness less than 20% of its linear size. This is dangerous because in the case of simulation taking into account periodic conditions the dendrimer can begin to interact with itself.

In papers [10, 12–14, 30, 31], the simulation time is less than 10 ns, which, under the conditions of simulation of large systems, is not enough to balance the system.

We should note, that for papers with published plots, the MSD versus time dependencies were also examined to find a range with a slope of 1 on a double logarithmic scale. Although it is important condition for diffusion mode, it still is not considered in all studies, for example [32, 33].

2.2 Objects of study

Dendrimers are highly branched synthetic polymers, usually consisting of three main types of structural blocks: the main (core) as the center of the beginning of branching, repeating structures and functional groups as the final structures. The model of second generation with generations allocated is shown below in Fig. 1.

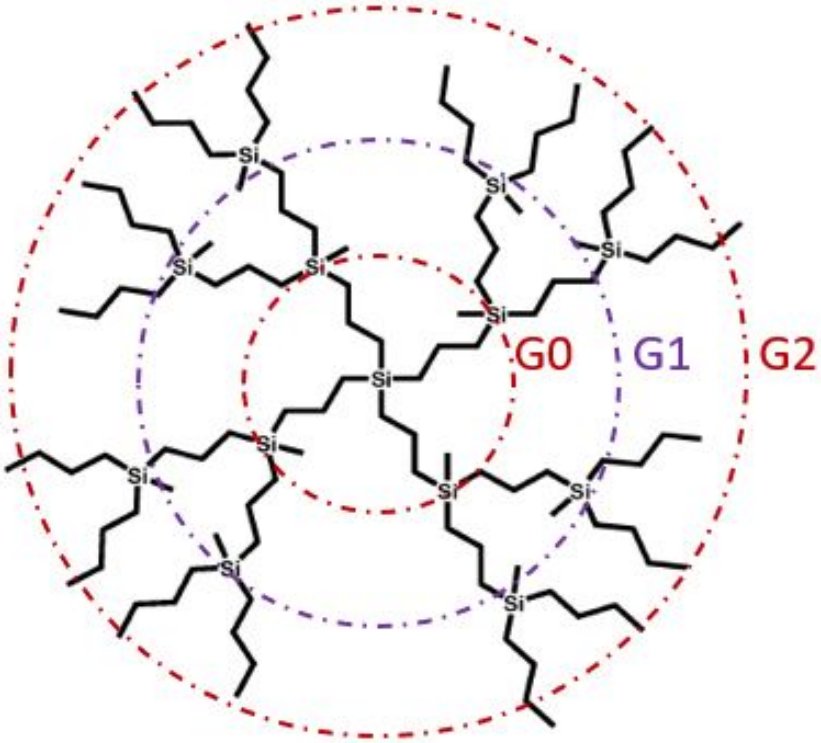

Figure 1. Dendrimer molecule model of G2 generation

In this work, a polybutylcarbosilane dendrimer was investigated, since it, due to the absence of terminal functional groups, that can be involved in complex interactions, is a suitable option for basic research.

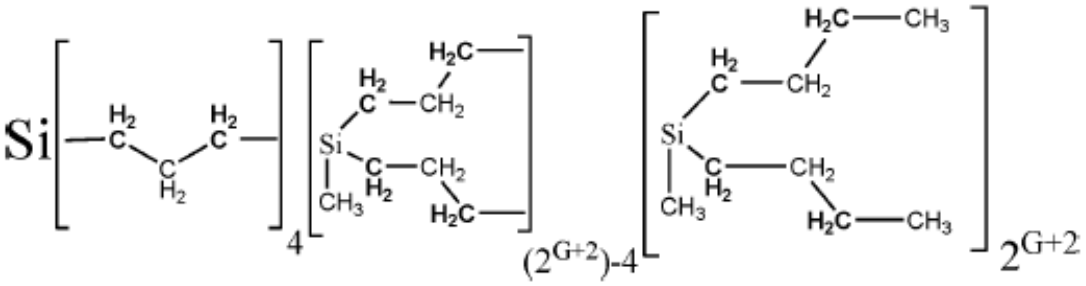

Figure 2. Chemical formula of polybutylcarbosilane dendrimer

In the given chemical formula in Fig. 2, we can see the dependence on the generation number, index G, which reflects branching and the increase in the number of structural blocks with increasing generation.

For dendrimer under investigation was calculated asphericity coefficient [34] which turned out to be 0.045. By this value we can judge the proximity of the macromolecule to the sphere, because this value reflects the proximity of the value to 0.

Polybutylcarbosilane dendrimers from the second to the fourth generation were studied in a chloroform solution at a temperature of 300 K.

2.3 Method of molecular dynamics

In this work, coordinates of the dendrimer atoms were obtained by molecular dynamics simulation. In this method, for each atom, the equations of motion of classical mechanics are solved numerically step by step, for which the forces are determined from the potential energy, which can be written as:

$$\frac{m_i d^2 \vec{r_i}}{dt^2} = \vec{f}_i, \quad \text{with} \quad \vec{f}_i = -\vec{\nabla} U(\vec{r_i}), \tag{1}$$

where $\vec{f}_i$ are the potential forces acting on the i particle, $\vec{r_i}$ is its position, and m_i is its mass. To solve this equation, it is necessary to calculate the forces acting on the atoms at each simulation step.

In the potential energy U, two terms can be distinguished, corresponding to bounded and non-bounded interactions of atoms. One takes into account the external potential field, as

well as the effects of the walls of the simulated container. In our case, periodic boundary conditions were used, in addition, the cell size was determined taking into account the size of the dendrimer in order to avoid interaction with itself. An estimate of the electron density over the entire molecule was carried out in [35].

Taking into account the potential energy, by setting the initial coordinates of all atoms of the system and solving the equations, during the simulation it is possible to obtain the values of the coordinates of atoms after a certain time step. By repeating this procedure a given number of times, as a result of MD, the trajectories of all atoms of the system are obtained. At the same time, additional restrictions are used in MD programs. For example, at each step of the simulation, the mean-square velocity of molecules is calculated and a correction to the velocity is determined, such that the mean-square velocity corresponds to the given temperature of the model, as well as the pressure using the barostats built into the MD program.

Thus, by solving equations (1), it is possible to obtain the coordinates of all the atoms of interest to us by the MD method after a certain time step over the required time. However, in the conditions of simulations of large systems (from 1000 dendrimer atoms and from 24000 solvent atoms), we face limitations in computing power.

2.4 Diffusion

Diffusion is one of the most important dynamic characteristics used to study the practical application of dendrimers.

For a theoretical study of the diffusion of dendrimeric macromolecules, as a rule, molecular dynamics simulation is used. To do this, the mean-square displacement of the center of mass of the macromolecule is calculated from the simulation trajectory as a function of time ($MSD(t)$).

$$MSD(t) =< (\vec{r}(t_0 + t) - (\vec{r}(t_0))^2 >_{t_0}, \tag{2}$$

where square of the step corresponding to the current time (t) relative to the initial one t_0 is calculated.

To obtain diffusion coefficients knowing $MSD(t)$ we use well-known Stokes-Einstein equation:

$$\lim_{t\to\infty} MSD(t) = 6Dt^{\alpha}, \tag{3}$$

where D is diffusion coefficient and α reflects the nature of diffusion. Normal diffusion is $\alpha = 1$ and anomalous diffusion $\alpha \neq 1$, where $\alpha < 1$ is connected to subdiffusion and $\alpha > 1$ to superdiffusion.

We should note here that the use of this formula for a dendrimeric macromolecule is justified, since the shape of the dendrimer is close to spherical - the resulting asphericity coefficient is very small (equal to 0.045), while its value equal to 0 would correspond to a sphere.

Next, a section is selected from this curve, from which it is possible to calculate the diffusion coefficient of a macromolecule. For this it is necessary to determine the diffusion mode, characterized by $\alpha = 1$.

Hence, to establish that the diffusion regime has been reached, the following criterion is used: the slope of the MSD (t) function against time in a double logarithmic scale must be equal to 1, based on formula 3.

The case when $\alpha < 1$ is called the subdiffusion regime, while $\alpha > 1$ is called the superdiffusion regime. But it is also important to note that in the case of curves obtained from simulation data, the value of α is not strictly equal to one, but the error should be small, usually less than 5%.

Diffusion data make it possible to directly estimate the hydrodynamic radius (R_h) of a macromolecule using the generalized Stokes-Einstein formula (3).

It is also important to take into account that the viscosity of the solvent in the simulation and in the experiment may differ. Therefore, for comparison with the experiment, it is more convenient to use the value of hydradynamic radius in the simulation, which can be obtained using the Stokes formula:

$$R_h = \frac{k_B T}{6\pi\eta_{solv} D}, \tag{4}$$

where k_B is Boltzmann constant, T is temperature, η_{solv} is viscosity of a solvent and D is diffusion coefficient.

An alternative method to estimate the hydrodynamic radius of a dendrimer is to use the

radius of gyration of the dendrimer (R_g), which is an equilibrium characteristic and is not as sensitive to simulation parameters and diffusion properties of the macromolecule. This method is based on the well-known relation $R_g/R_h = \sqrt{3/5}$, which was obtained for a spherical particle with a uniform density distribution in the internal volume. This relation, as a rule, holds well for various macromolecules (for example, see [36]), but exists doubt if it gives the correct results in the case of dendrimers. We are aware of at least two experimental works in which this relation is not fulfilled, namely for PAMAM [37] and carbosilane [38] dendrimers.

2.5 Rotational mobility

Considering the fact that dendrimer shape is close to sphere, we may assume, that rotational diffusion would let us estimate hydrodynamical radius correctly. Rotational mobility of macromolecule could be evaluated with autocorrelation function (ACF) $P_1^{rot}(t, g)$.

$$P_1^{rot}(t, g) = \frac{1}{n_g} \sum_{i=1}^{n_g} P_1^i(t, g), \tag{5}$$

where

$$P_1^i(t, g) =< (\vec{b_i}(t + t_0, g) \cdot \vec{b_i}(t_0, g)) >_{t_0}, \tag{6}$$

where $\vec{b_i}(t, g)$ is the unit vector directed from the dendrimer core to the ith branching point of last generation. The brackets $< ... >$ represent similar averaging as in case of eq. 2. Equation 5 represents averaging over all n_g terminal bonding groups.

This means that the behavior of $P_1^{rot}(t, g)$ at these times is determined by the rotation of a dendrimer as a whole. From the slope of $ln(P_1^{rot}(t, g))$ at long times one can estimate the characteristic time τ_{rot} of the dendrimer rotation as a whole.

For the model of an impenetrable sphere of the radius R_h in the viscous medium may be used following equation [39]:

$$\tau_{rot} = \frac{4}{3} \frac{\pi \eta_{solv} R_h^3}{k_B T}. \tag{7}$$

On the one hand, rotational diffusion is dynamical characteristic and may describe translational mobility more correct. On the other hand, unlike translational mobility, which depend linearly on size of dendrimer, characteristic time of rotation depend on R_h^3, which leads to a faster reaching the diffusion regime, and needs less time of system simulation. Rotational diffusion of dendrimer as a whole was estimated by using autocorrelation function $P_1^{rot}(t, g)$.

2.6 Experimental methods

Diffusion of dendrimers can be studied by the following experimental methods: NMR [40], fluorescence depolarization [41], SANS [42] and birefringence [43].

For biophysicists, fluorescence has become a fast and sensitive method for studying the structure, dynamics, and functions of biological macromolecules. In the case of fluorescence depolarization, we can obtain data on dendrimers by adding light absorbers to the periphery. For example, densylated poly(propyleneamine) dendrimers (POPAM) [44] are efficient UV harvesters. Due to the formation of highly fluorescent compounds by the reaction of dansyl chloride with free amino groups in proteins, dansyl substitution is widely used in biological labeling. The fluorescent properties (emission wavelength and quantum yield) of dansyl-labeled compounds make them environmentally sensitive [45].

Small-angle scattering is used to study the structure of various objects, including biological and complex polymers. Small-angle X-ray scattering (SAXS) and small-angle neutron scattering (SANS) are two complementary techniques collectively known as small-angle scattering (SAS). SAS is a technique similar to X-ray and neutron diffraction and wide-angle X-ray scattering. This method provides information on the sizes and shapes of both crystalline and non-crystalline particles. When used to study biological materials that are very often in solution, the scattering pattern is averaged over orientation. At the beginning of the study of dendrimers by the SANS method, there were some difficulties due to the low concentration required, but later these problems were investigated and solved [46].

Optical methods have also found wide application in solving problems of the chemical structure and physical properties of macromolecules. To determine the principal values of the electronic polarizability tensor, data from several methods are used, including birefringence (the electric Kerr effect). Because the polarizability of a polymer molecule in the direction of the main axis and across it is different. Since the main axes of polymer molecules are oriented perpendicular to the radius of the spherulite, such aggregates are capable of birefringence and scatter light rays if their size is commensurate with the

wavelength of visible light [47].

Pulsed field gradient nuclear magnetic resonance is a convenient and non-invasive way to measure translational motion. In this method, the attenuation of the echo from a pulse train containing a pulse of the magnetic field gradient in each period t is used to measure the displacement of the observed spins [48]. There are two main ways to use NMR to study diffusion coefficients: a) analysis of relaxation data; b) NMR with pulsed field gradient.

3 RESEARCH METHODOLOGY

3.1 Simulation in the GROMACS package

Molecular dynamics simulation was carried out in the GROMACS package [49–53], a software package for simulation of the physicochemical processes of macromolecules that have many coupled interactions between atoms, but also provides high speed calculations for unbound interactions. Obtaining the initial data (charges and force constants) on the structures of the dendrimer and solvent molecules is described in [35]. For chloroform they were calculated using the 3Dmol quantum chemical package in the Materials Studio program and additionally calibrated to obtain the experimental temperature dependence of the density of the chloroform solution using Gromos53a6 force field (1). For the simulated systems, the model viscosity was determined: $\eta = 2.69 \cdot 10^{-3} Pa/s$.

However, to create a system in a state of thermal equilibrium, it is necessary not only to minimize the energy to refine the geometry of the system, but also to balance - to achieve the correct distribution of atoms over velocities and avoid a significant deviation of the potential energy of the system from the average value.

To do this, two auxiliary simulations were carried out before, shorter in time - in the NVT ensemble (constant number of particles, constant volume and temperature), and in the NPT ensemble (constant number of particles, pressure and temperature). In addition, a mixing procedure was carried out so that the initial configuration of the system did not affect the results. A necessary condition for good mixing is the displacement of the macromolecule by two gyration radius ($2R_g$) meaning its diameter. Method of calculating R_g according to GROMACs:

$$R_g = \sqrt{\frac{\sum_i \|r_i\|^2 \cdot m_i}{\sum_i m_i}}, \tag{8}$$

where where m_i is mass of ith atom and r_i is its position relative to the center of mass of the molecule.

For this purpose, a solution with a dendrimer was simulated for 100 ns, the time selected here is for the slowest system of forth generation (4), which allowed the mean square displacement (MSD) to significantly exceed the value of $(2R_g)^2$. The resulting final configurations were used to further model the trajectories needed for the analysis.

During the main simulation, the trajectories of all atoms of the dendrimer were collected with a simulation step of 1 femtosecond, while the coordinates were saved at every 100 step (every 0.1 ps). The total simulation time varied for different conditions for each generation. Some simulation parameters are shown in Table 1.

Table 1. Simulation parameters.

Force field Gromos53a6	
Berendsen barostat[43]	1.0 bar
Thermostat V-rescale[44]	300 K
Energy minimization	50 ps
NVT equilibration	10 ps
NPT equilibration	10 ps
Preliminary equilibration	100 ns

3.2 Computer simulation details

The initial configuration was created in the Materials Studio program.

The resulting initial configuration was used to run molecular dynamics simulations in the GROMACs package. Step-by-step algorithm for obtaining diffusion coefficients was:

1. Creating a cell with chloroform;
2. Energy minimization;
3. NVT - equilibration;
4. NPT - equilibration;
5. Preliminary equilibration;
6. Running the simulation;
7. Obtaining time dependency of MSD;
8. Processing of results;
9. Calculation of the diffusion coefficient and other characteristics of the dendrimer.

The parameters of the simulated systems varied depending on the generation of the dendrimer, their differences are shown in table (2).

Table 2. The main parameters of the simulated systems.

	Number of $CHCl_3$ molecules	Cell size, nm^3	R_g, nm	Simulation time, ns
G2	300	3.528^3	0.8	1000
G2	500	4.137^3	0.8	1000
G2	1000	5.170^3	0.8	1000
G2	2000	11.296^3	0.8	2000
G3	4000	8.893^3	1	2000
G4	8000	10.305^3	1.4	3200

4 RESULTS

4.1 Influence of different simulation conditions

The first parameter studied was the simulation time. For the second generation in a chloroform solution, various time trajectories were obtained, from 10 ns to 900 ns. In Fig.3, four trajectories can be observed in a double logarithmic scale, in addition, an area is highlighted in which the slope of the largest trajectories is 1. The deviation of the shortest trajectory is most noticeable and it can be observed that the longest one is the most even.

However, the time interval of diffusion calculation is limited by the required minimum value of the mean-square displacement (at least by the inertial radius of the dendrimer, for the second generation this value is 0.64 nm^2). Thus, the area suitable for determining the diffusion coefficient is the smallest for the shortest trajectory. But also relative to the longest one, is only 5% of the total length.

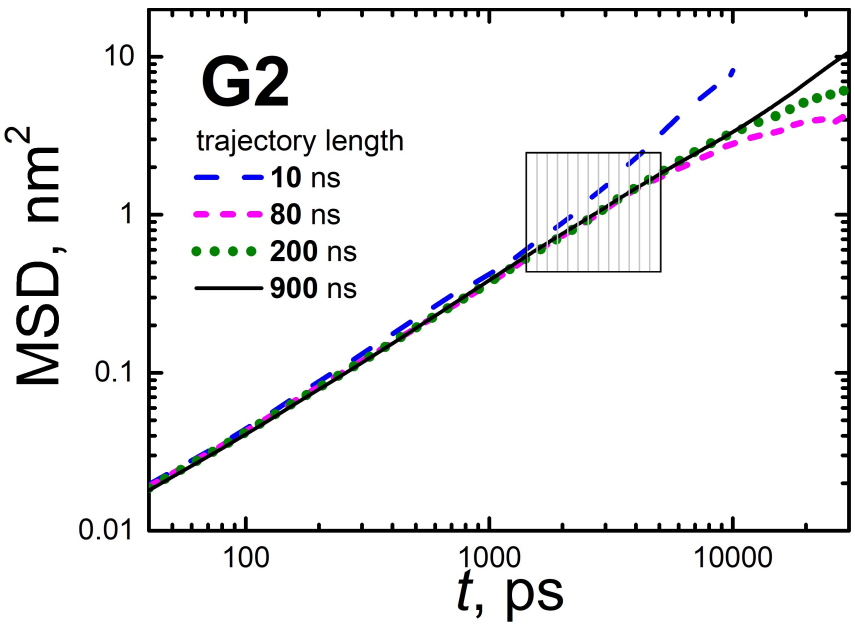

Figure 3. MSD as a function of time averaged over different time trajectories (see legend) for G2 on a logarithmic scale. In the selected region the slope of MSD is 1.

Fig. 4 shows the same trajectories on a linear scale and, in addition, the hydrodynamic radius calculated by formula (4) using the diffusion coefficient are plotted. Thus, it is

shown that for trajectories that differ by a factor of 9 in time, the calculated radius differs by 40%.

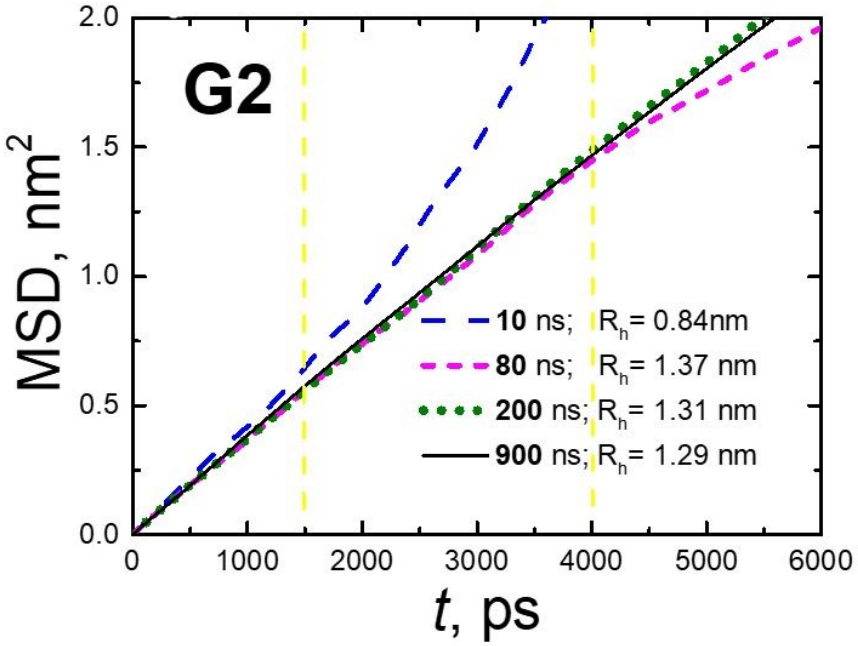

Figure 4. MSD as a function of time averaged over different time paths (see legend) for G2 on a linear scale.

The second parameter under study is the influence of the boundary conditions on the simulation, and accordingly the cell size. For this, cells with 300, 500, 1000, and 2000 chloroform molecules were simulated; for a more convenient comparison, the cell size on the graphs was determined through the radius of gyration (R_g) of the dendrimer.

For the smallest sizes were constructed density profiles in Fig. 5. They describe the change in density with distance from the reference particle. We should note that even for the smallest cell size, there is no deviation from 0 at a distance greater than 1.5 nm.

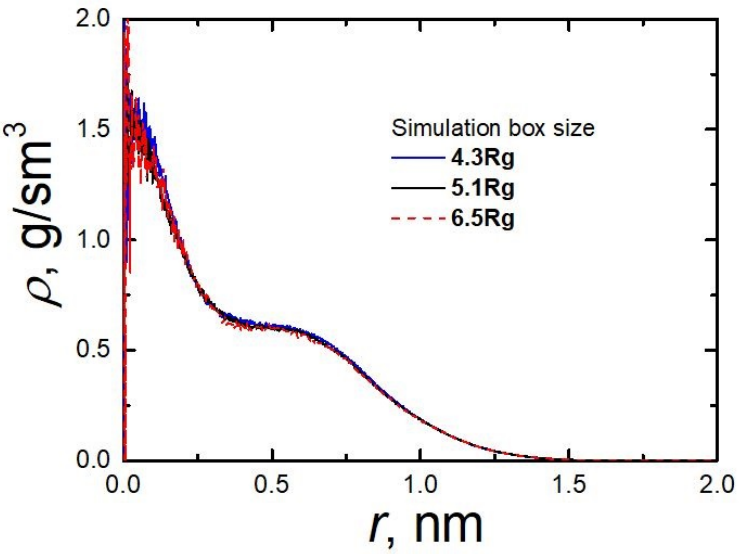

Figure 5. Dendrimer G2 density profiles at various simulation cell sizes.

However, Fig. 6 and 7 show that there are noticeable deviations, both in the double logarithmic scale and linear one. In the first case deviations are observable relative to the region of interest with a slope close to 1, and, more noticeable, they are in the linear scale, which shows a significant difference for the calculated coefficient diffusion.

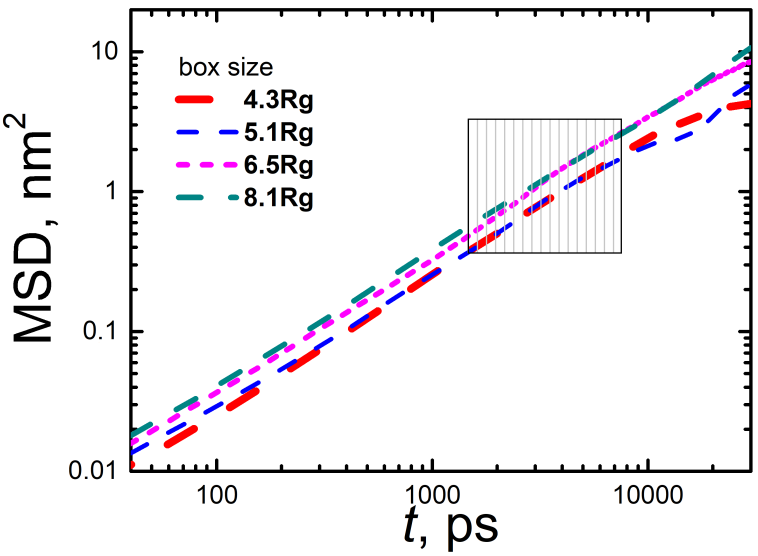

Figure 6. MSD as a function of time averaged over different time trajectories (see legend) for G2 on a logarithmic scale. Rectangle here represents the region, where the diffusion coefficient is calculated.

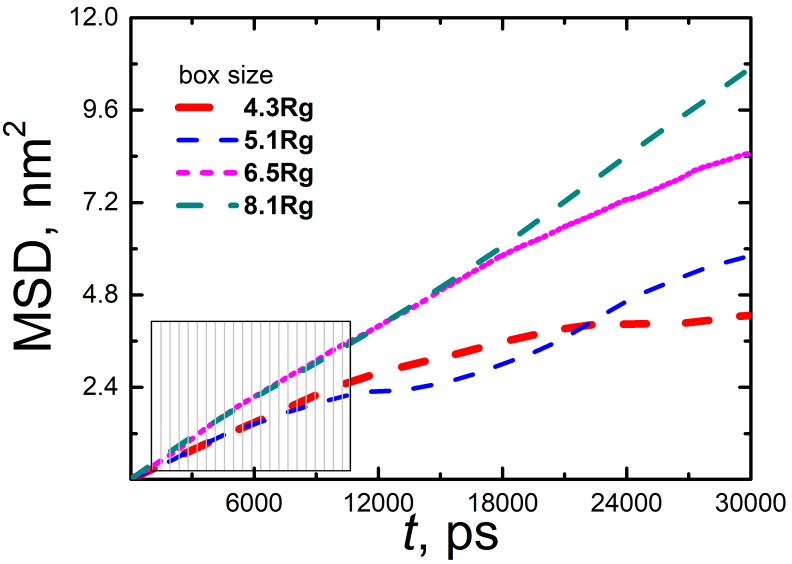

Figure 7. MSD as a function of time averaged over different time paths (see legend) for G2 on a linear scale. Rectangle here represents the region, where the diffusion coefficient is calculated.

We also performed simulations with various barostats - Parrinello-Raman [54], Berendsen [55] and without them. For different barostats, the slope in the logarithmic scale differs by less than 2%. Without a barostat, there are significant deviations in individual simulations.

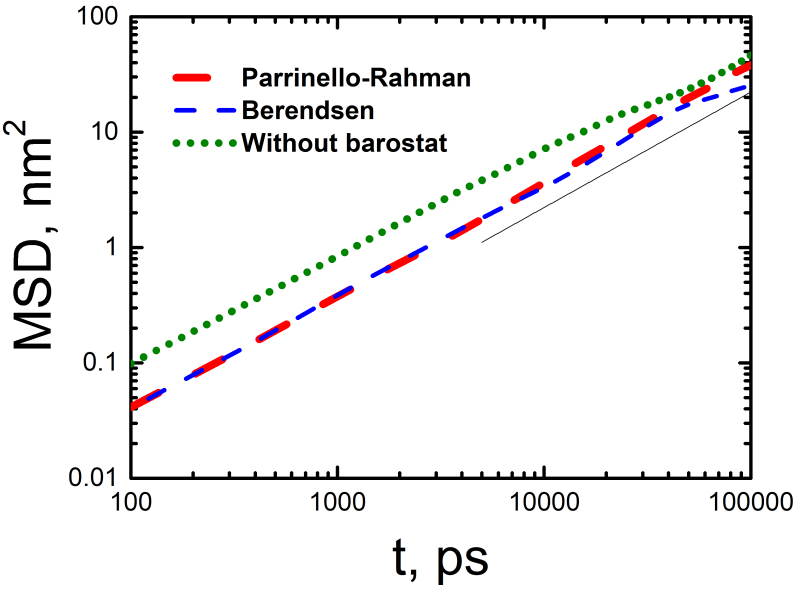

Figure 8. MSD obtained for various barostats as a function of time on a double logarithmic scale.

Fig. 8 shows a comparison of various barostats. It can be seen that the largest deviation is observed in the absence of a barostat, which can be explained by the setting of certain simulation parameters and one can expect an improvement in the curve by averaging several parameters. That is, to get a decent result, it is necessary to conduct more than one simulation for subsequent averaging. Thus, it can be assumed that the type of barostat does not affect the results.

In addition, it was found that the translational mobility of the considered dendrimer in solution can be described by two modes: ballistic and diffusion. The absence of a subdiffusion regime is confirmed by the observation of the slope of the curve in a double logarithmic scale, and this was also confirmed by considering the autocorrelation functions for the velocity of the center of mass of the dendrimer. The absence of a subdiffusion regime in CSD in solution made it possible to develop a technique for studying the diffusion properties of a macromolecule.

4.2 Diffusion coefficient

Taking into account the parameters defined in the previous chapter, three generations of polybutylcarbosilane dendrimer in chloroform solution were simulated.

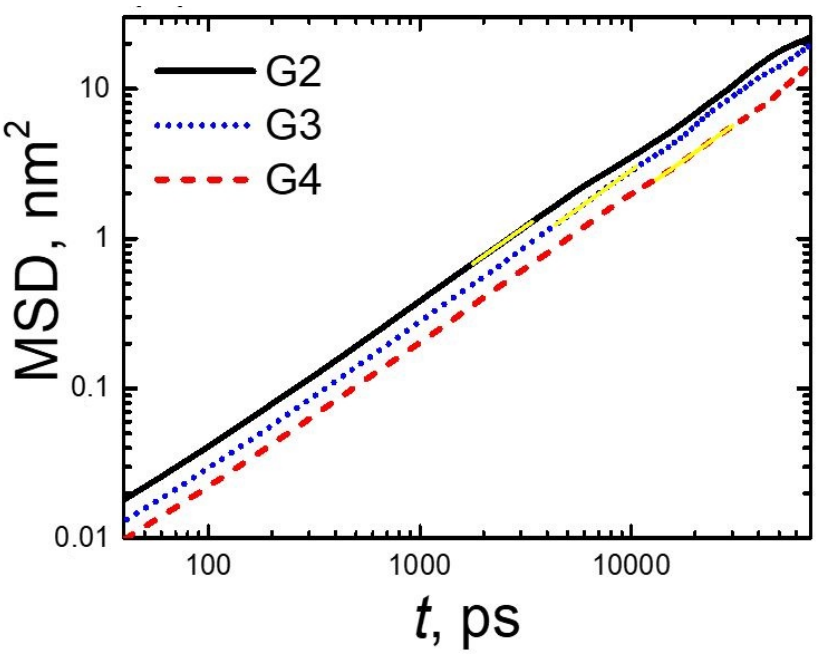

Figure 9. MSD as a function of time for various generations on a double logarithmic scale. Diffusion mode for each generation is marked in yellow.

In Fig. 9, 10, 11 are shown the MSD versus time at different scales. Diffusion regions were determined from Fig. 9 on a double logarithmic scale, based on Eq. (3), in these regions the slope is close to 1: the values are given in Table (3). Also taking into account, that diffusion modes were determined in regions where MSD is greater than R_g^2. Further, in these certain ranges, but on a linear scale, the diffusion coefficients were determined.

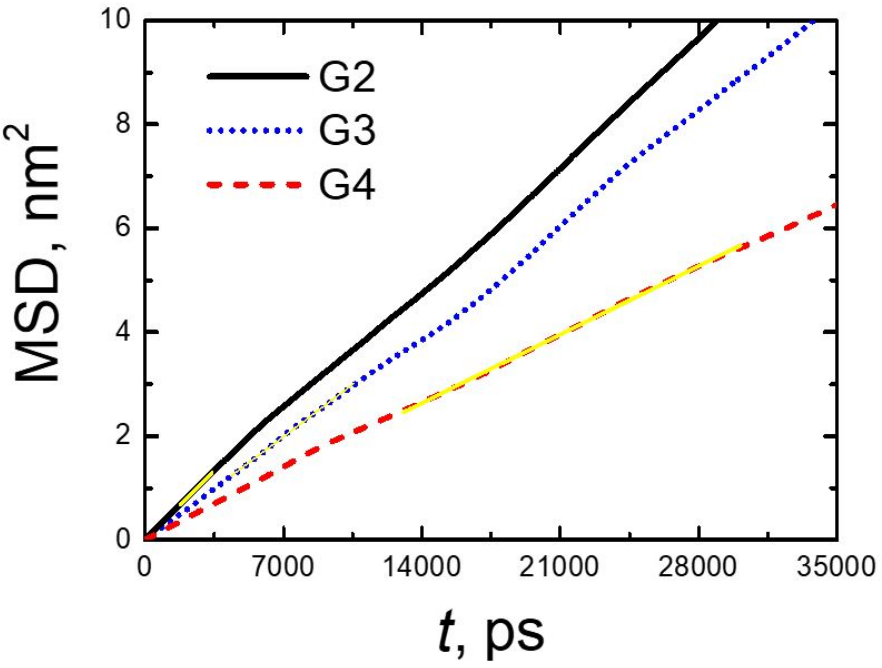

Figure 10. MSD as a function of time for various generations on a linear scale. Diffusion mode for each generation is marked in yellow.

A plot of MSD/t versus time is shown here to show that the ratio of these values is constant over time. At the end of the range, a deviation from a constant value can be seen, which can be explained by an increase in the measurement error.

From the coefficients obtained, according to the formula (4), R_h were calculated. All numbers, related to calculations of this Section are presented in Table 3.

Table 3. Simulation results.

Generation	Maximum MSD, nm^2	R_g^2, nm^2	Slope	$D * 10^{10}, m^2/s$	R_h, nm	R_{hRot}, nm
G2	1.3	0.64	0.996	0.202	1.29	1.20
G3	3.2	1	1.007	0.161	1.61	1.67
G4	5.8	1.96	1.04	0.103	2.51	2.47

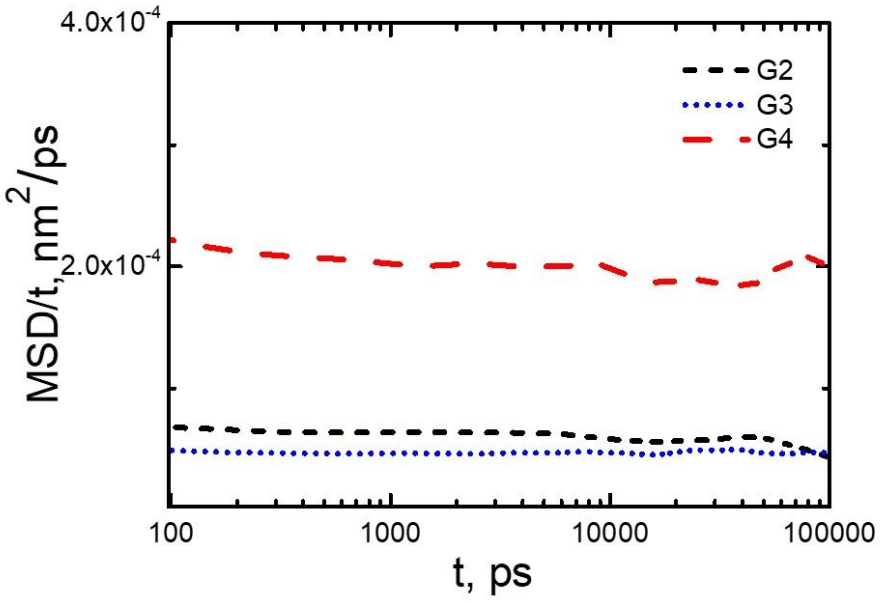

Figure 11. Ratio of MSD to time as a function of time.

4.3 Rotational mobility of the dendrimer

The rotational mobility of the dendrimer macromolecule as a whole was evaluated using the autocorrelation function ($P_1^{rot}(t, g)$). The characteristic rotation times for three generations of the dendrimer were determined from Fig. 12.

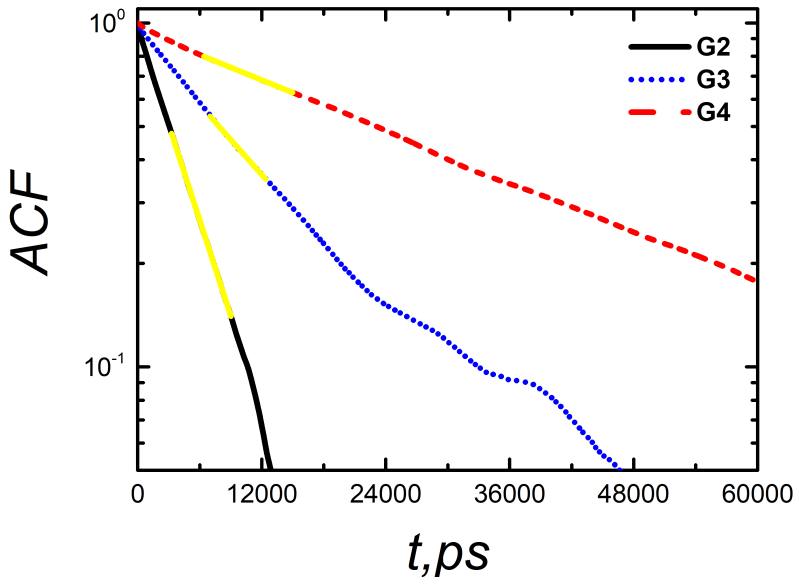

Figure 12. Autocorrelation function $P_1^{rot}(t, g)$ versus time for three different generations

According to eq. 7 were obtained hydradynamical radiuses for each generation. Values are presented in table (3).

So, alternative way of calculation R_h using characteristic time of rotation of dendrimer lets us use shorter trajectory length. It is interesting to note that the calculation of the hydrodynamic radius from the dynamic parameter τ_{rot} gives an adequate result, in contrast to the calculation using $\sqrt{3/5}$ where the equilibrium parameter R_g is used. It is important to note that both approaches are based on a spherically symmetric macromolecule model.

Also were studied influence of size of cell with chloroform on rotational diffusion calculation. For this, four different cells with dendrimer of second generations were used. As one may see from results in Table 4, values of R_h varies not significantly, less then 5%.

Table 4. *Results for various cell sizes and various generations in case of rotational diffusion calculation. R_h is hydrodynamical radius calculated using Eq.7.*

Generation	Cell	Slope	τ_{rot} , ns	R_h, nm
G2	$4.3R_g$	$2.14 \cdot 10^{-4}$	4.7	1.20
G2	$5.1R_g$	$2.05 \cdot 10^{-4}$	4.9	1.21
G2	$6.5R_g$	$2.08 \cdot 10^{-4}$	4.8	1.21
G2	$14R_g$	$1.94 \cdot 10^{-4}$	5.2	1.24
G3	$8.9R_g$	$0.78 \cdot 10^{-4}$	12.8	1.61
G4	$7.4R_g$	$0.24 \cdot 10^{-4}$	41.0	2.51

Non-significant deviation in calculating area is also shown on Fig. 13.

Apparently, the presence of a complex relaxation spectrum of the dendrimer, such as branch relaxation, does not allow one to assess the translation properties of dendrimers using radius of gyration. We believe that for the same reason, to study diffusion using MSD, it is necessary to simulate trajectories much longer than could be expected, for example, for a linear macromolecule of similar molecular weight. Additional simulation is needed to average the pulsation movements that can affect the translational mobility.

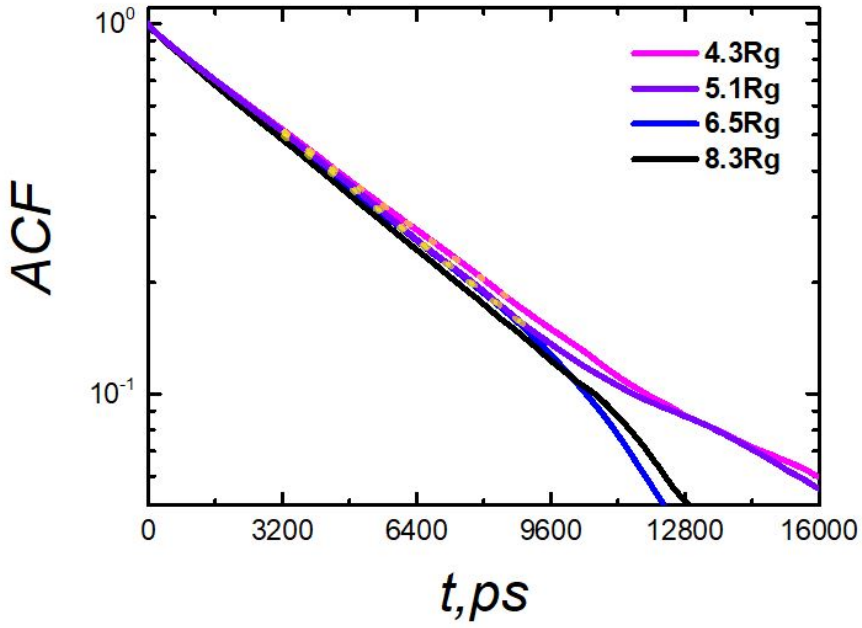

Figure 13. *Autocorrelation function* $P_1^{rot}(t, g)$ *depending on time for G2 in different cell sizes*

5 DISCUSSION

5.1 Current study

During this work, different studies on dendrimer computer simulation were considered and a list of "traps" associated with dendrimers investigations was listed.

a) Not enough trajectory averaging statistics
b) Boundary conditions, i.e. simulated cell size
c) Wide range of anomalous diffusion

a) It is shown that the interval of a regular trajectory narrows significantly with a decrease in the average length of the trajectory. This is because the averaging statistics for the MSD function is not sufficient for long time periods. And also that in the case of small trajectory lengths, the slope of the curve noticeably deviates from 1. It follows that the time is needed, which first of all will allow the dendrimer to shift by at least R_g, and the time for calculating the diffusion coefficient should be only 5% of the total trajectory due to increased error.

b) During simulation, it is necessary to create a cell not only with the condition that there is some shell around the dendrimer, but it is also necessary to take into account the possibility of shifting the dendrimer by $(2R_g)^2$.

c) In the presence of a sub-diffusion mode or under the influence of a ballistic mode, it is possible to determine the wrong diffusion coefficient by mistakenly choosing a range or using the entire curve without checking the slope in a double logarithmic scale.

Knowing this, CSD dendrimer in chloroform solution was simulated using GROMACS package. After, time dependencies of MSD were obtained and diffusion coefficients were calculated in different conditions, to check presence of the influence as noted before. This helped to list the necessary parameters to accurate determination of diffusion coefficients.

Also, hydradynamical radius for each generation was obtained, and in this case was proposed second method of its calculation: method of rotational diffusion.

5.2 Future work

Now, after proposing and comparing different methods to obtain dendrimer characteristics, it is important to investigate and understand the nature of such behavior. Further work includes not only theoretical studies of dendrimers behavior, but also researches including different solvents, dendrimers with more complicated structure (for example, containing different functional groups) and examination of transfer of discovered features to dendrimer in melts.

6 CONCLUSION

In conclusion, we would like to point out, that during this work, we considered the unique structure of dendrimers and analyzed literature about computer simulations of such macromolecules. This helped to find out that researches face a lot of difficulties by using simulations. Here we have identified them.

To understand contribution of their influence on dynamical characteristics, we simulated polybutylcarbosilane dendrimer in chloroform solution in different conditions. In doing so, we have directly monitored main system parameters: different cell sizes, different time, different barostates to compare results. From obtained dependences of mean-square displacement on time we calculated diffusion coefficients and hydradynamical radiuses. The influence of trajectory length, cell size and presence (or absence) of diffusion regime were noted.

New approach of calculating hydradynamical radius - using rotational diffusion was proposed and obtained values of different used methods were compared, showing good agreement between the results. This method showed some advantages over the first approach using translational mobility.

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