Computer Simulation of Polyamidoamine Dendrimers and Their Complexes with Cisplatin Molecules in Water Environment

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ABSTRACT: Molecular dynamics simulations with explicit water were carried out for guest-host systems on the base of PAMAM-4.5 dendrimers and cisplatin $PtCl_2(NH_3)_2$ molecules. Single dendrimer molecule and cisplatin molecules chemically attached to dendrimer terminal groups or adsorbed on the macromolecular surface were considered. AMBER force field, TIP3P water molecules and periodical boundary conditions were used for calculations. It is no protonated amines of PAMAM that correspond to pH $\geq$ 10. Computer experiments were conducted at temperatures 293, 310, and 350 K and pressure 1 bar. The structure and dynamics of guest-host systems was analysing. In all considered cases the dendrimers form a compact globule, which shape is far from spherical. Moreover the dendrimer cores dispose on the molecule surface in all considered cases. The chemically attached cisplatin penetrate into dendrimer deeper then non-attached one and decrease a large-scale intramolecular mobility.

1. INTRODUCTION

The compound cis-$PtCl_2(NH_3)_2$ (cisplatin), has become one of the most widely used drugs for the treatment of cancer [1,2]. Its mechanism of interaction with cells has been studied on a molecular level and it is well established, that death of the cell is induced by complexes of the platinum compound to two adjacent guanine bases [2]. But its remarkable anticancer properties can be accompanied by marked toxic effects as well as the development of resistance to the drug. Recently a polyamidoamine (PAMAM) dendrimer generation 4.5 was conjugated to cisplatin giving a dendrimer-platinate (dendrimer-Pt) which was highly water soluble and released platinum slowly in vitro [3,4]. In these works was shown that the dendrimer-Pt improved cisplatin efficiency and was less toxic (3- to 15-fold).

PAMAM dendrimers are the polymers with unidispersed and well-defined molecular structures. These molecules can be synthesized in large quantities and have a large number of potential biomedical applications [5,6]. Highly branched, functionalized polymers have potential to act as a gene delivery and as efficient drug carrier systems [5,7-9]. There are a lot of publications devoted to the study of structure and mobility both single dendrimers, and dendrimer-guest systems. However till now our knowledge of molecular structure of this systems are rather fragmentary.

The essential contribution to our understanding of the dendrimer molecules structure was achieved by molecular dynamic (MD) simulation [10-13]. Recently, more exhaustive atomistic MD simulations of dendrimers were carried out [14-25] including simulation PAMAM molecules [17,19,21,24] and research a solution behavior of dendrimers in explicit solvent [20,22,24]. Unlike simple coarse-grain dendrimer models the simulation of detailed molecular systems is rather complicated, as requires a substantiation for the large number of used parameters, very expensive, the received results, as a rule, and do not suppose wide generalization. However now it is the only way to receive the detailed information on spatial structure and mobility of separate molecules in solvent.

In this study, we used atomistic MD simulations with explicit water to study the guest-host systems on the base of PAMAM-4.5 and cisplatin molecules chemically attached to dendrimer terminal groups or adsorbed on the macromolecular surface were considered.

International Journal of Innovative Research in Computer and Communication Engineering

(An ISO 3297: 2007 Certified Organization)

Vol. 2, Issue 4, April 2014

II. THE MODEL AND SIMULATION DETAILS

Calculations were performed for three systems: a) water solutions of PAMAM-4.5, b) water solutions of PAMAM-4.5 with cisplatine, and c) water solutions of dendrimer-Pt molecule. PAMAM have tetrafunctional core $-NCH_2CH_2N-$ with three radiating branches of $-CH_2CH_2CONHCH_2CH_2N-$ and 64 terminal groups $-CH_2CH_2COOH$ (Fig.1a). The dendrimer–Pt made up by joining 7 cisplatines
$-PtCl(NH_3)_2$ to random choosen termal groups (Fig.1b). The molecular weights of cisplatine, PAMAM-4.5 and dendrimer-Pt are correspondingly 299 a.u., 11380 a.u. and 13164 a.u.. The calculation cell contained one dendrimer molecule, explicit water molecules, and 8 cisplatin molecules in system b (Tabl.1).
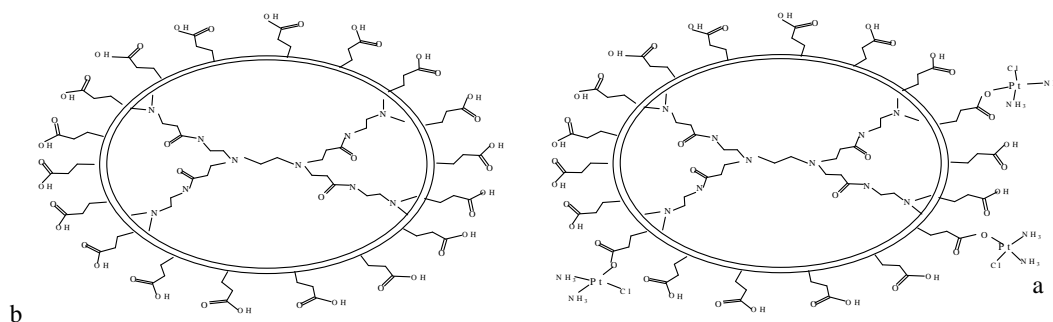

Fig. **1**. Schematic drawing of PAMAM-4.5 (a) and dendrimer-Pt molecule (b).

Tabl. 1. Some details of considered systems.
[a] for $-PtCl(NH_3)_2$.

The AMBER force field [26] was used for calculation. The potential energy comprising potential terms of bond U_b, angle U_a, torsion U_t, van der Waals U_{vdw} and electrostatic U_e interactions was used:

$$U_b = \sum K_l (l - l_0)^2,$$

$$U_a = \sum K_\Theta (\Theta - \Theta_0)^2,$$

$$U_t = \sum K_\varphi [1 + \delta \cos(n_0 \varphi)],$$

$$U_{vdw} = \sum \sum U_{LJ}(r_{ij}) W(r_{ij}),$$

where

$$U_{LJ} = 4\varepsilon_{ij} [(\sigma_{ij} / r_{ij})^{12} - (\sigma_{ij} / r_{ij})^6]$$

and $W(r_{ij})$ is the switching function in interval $0.9 \leq r_{ij} \leq 1.05$ nm,

$$U_e = \sum \sum [q_i q_j / (\varepsilon r_{ij})] W_e(r_{ij}),$$

where W_e is the screening function ($R_e = 1.05$ nm),

$$W_e(r_{ij}) = \begin{cases} (1 - r_{ij}/R_e)^2, & r_{ij} \le R_e \\ 0, & r_{ij} > R_e \end{cases}$$

In this equations the following notations are used: l is the bond length, Θ is the bond angle, φ is the torsion angle, l_0, Θ_0 are equilibrium values for the bond lengths and angles; K_l, K_Θ, K_φ are force constants for the bonds, angles, dihedrals angles, respectively; n_0 is the dihedral multiplicity; r_{ij} is the distance between nonbonded atoms i and j; ε_{ij}, σ_{ij} are Lennard-Jones parameters for the atom pairs, q_i, q_j are the partial charges on atoms i, j, ε is the dielectric constant, R_e is the screening radius. It is no protonated amines of PAMAM that correspond to pH $\ge$ 10.

The H_2O geometry parameters, the partial charges [27], and the force constants [28] for TIP3P water molecules are fixed. The parameters of force field and partial charges of cisplatin were taken same, as in [29]. Periodical boundary conditions were applied and the cells size was large enough ($\sim4.8^3$ nm) to exclude any intaraction between dendrimers. Molecular dynamics techniques [30] were used for the equilibration and regular simulation. Collisional thermostat [31] and Berendsen barostat [32] were used for temperature and pressure support. The integration time step $\Delta t=0.5$ fs was used and the times of regular runs were 1 ns.

Initial structure of a complex polymer system (coordinates and velocities of all atoms) plays the key role for successful modeling of its behavior. The preparation of representative structure of the system is usually complex and expensive procedure. Some technology was elaborated to construct dendrimers under consideration. At the first stage the special procedure was used to assemble the dendrimer structure, which was like a dandelion flower (Fig.2). A combination of constructor and collisional dy-
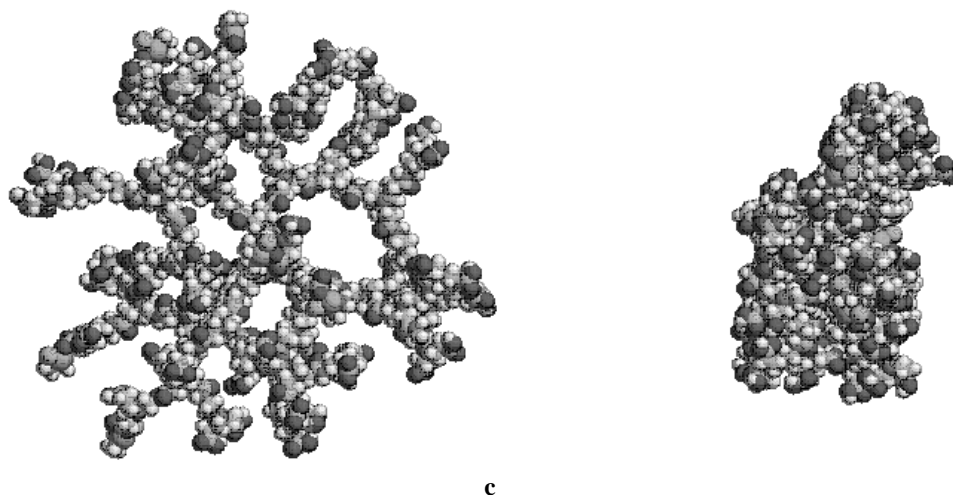

a
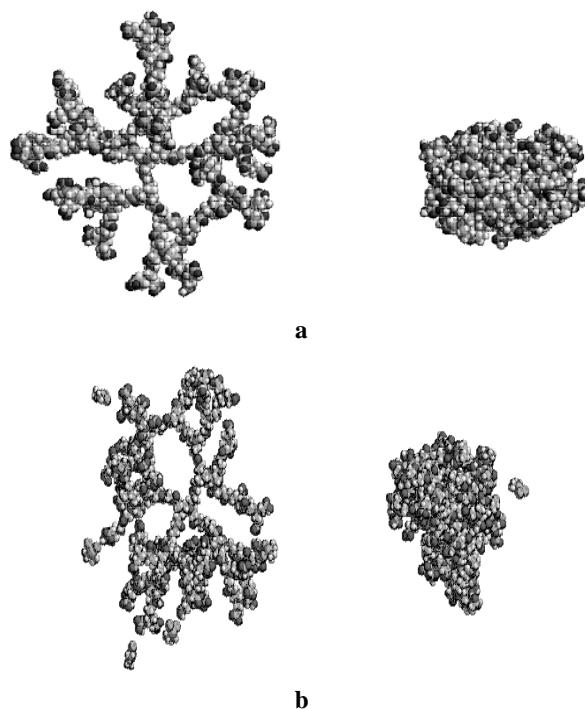
b

c

Figure **2**. Simulated snapshot of initial dandelion structure at the first stage (left) and configurations of dendrimers after 1 nsec runs (right). (a) PAMAM-4.5, (b) PAMAM-4.5 and cisplatin, (c) dendrimer-Pt. Water molecules are not shown to not complicate a picture.

namics computer programs were used to build up each next generation of isolated dendrimer molecule during this procedure. At the second stage collissional molecular
dynamics technique was applied to equilibrate initial configuration of the dendrimer molecule. Than the macromolecule was immersed in water and equilibration of the total system was accomplished. The structure received was initial one for productive run of the system.

III. RESULTS AND DISCUSSIONS

One of the characteristics of the dendrimer size is the radius of gyration R_G. Its values averaged over the whole trajectory are given in Table 2. From this table we notice that this value of PAMAM in water correlate well with the evidence of another authors [14,18,20]. The radiuses of gyration of dendrimers with adsorbed and with chemically attached cisplatin are bigger and at the same. That curiously enough so in the former case the cisplatin molecules were not taken into account along calcculations.

In all considered cases the dendrimers forms rather compact globule, which shape is far from spherical (Fig. 2). This is apparent also from Table 2 where the values of the main radiuses of inertia $R_\alpha = \sqrt{J_\alpha / M}$ (J_α are the principal moments of gyration tensor, α=1,2,3, $J_1 > J_2 > J_3$) and relative values J_2/J_1 and J_3/J_1 are shown. The difference of this ratios from 1 characterise the deviation of dendrimer shape from the sphericity. In our case we see a strong asymmetrical molecules that consistent with the another simulation data for PAMAM [14,18,20], and the deviation from the sphericity increase in the presence of cisplatin. The dendrimer size and shape are independent of temperature at considered interval of temperatures.

The internal structure of the dendrimer and the distribution of the solvent inside of it can be seen from radial density distribution functions for dendrimer and solvent atoms relative to the centre of mass (CM) of the macromolecule (Fig. 3a). By calculation of the density distribution, all atoms were treated as uniform spheres with corresponding van-der-Waals diameters. It is seen that water molecules are not incorporated into the dendrimer. Only one water molecule dispose near the dendrimer CM in the system with adsorbed cisplatin. The density profiles are not essentially changed with the temperature.

It was rather unexpectedly to discover that the dendrimer core during the run was far from CM the center of mass of the macromolecules and for PAMAM-4.5 in water even is farther, than for another cases (Fig. 3b). Moreover as can be seen in Fig.4 the dendrimer cores dispose on the molecule surface. So asymmetrical structure is likely to be

characteristic for small generation of PAMAM in water at high pH, that distinguishes its from carbosilane and polya-mindoamine dendrimers [18,24,33].
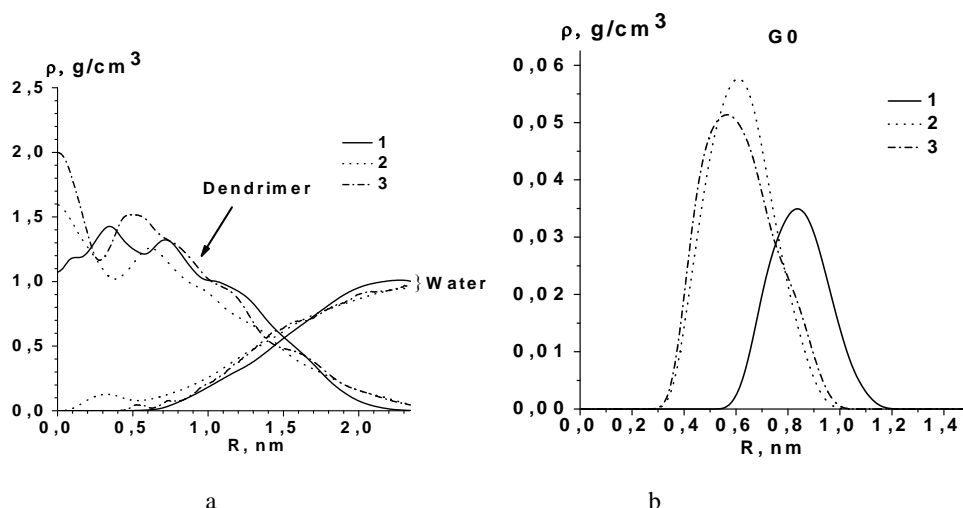

a

b

Fig. **3.** Radial density distribution relative to the centre of mass of dendrimer at T=293 K. (a) Dendrimer and water atoms; (b) the contribution of dendrimer core atoms. 1 – PAMAM-4.5 in water solvent; 2 – PAMAM-4.5 in water solvent with cisplatin; 3 – dendrimer-Pt in water solvent.
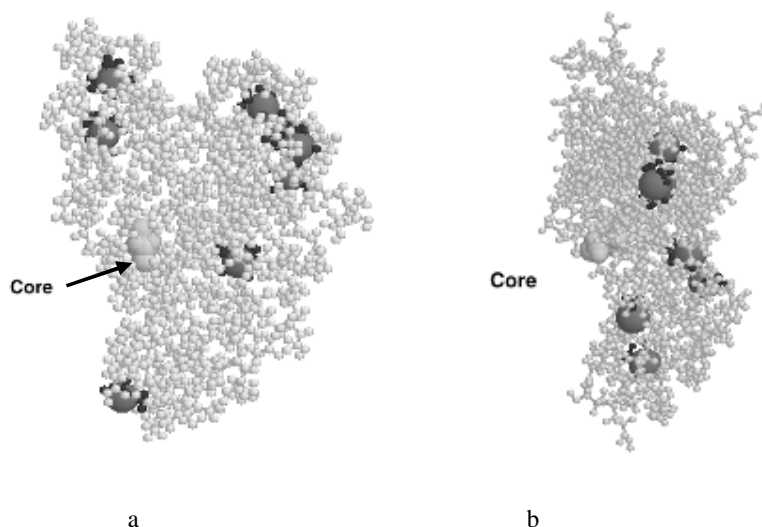

a

b

Fig. **4**. Snapshots of PAMAM with adsorbed (a) and chemically attached (b) cisplatin at 293 K. Here the dendrimers are shown as a ball-stick model while the core and cisplatin as a spacefilling union of spheres model where each atom is drawn as a sphere of its Van der Waals radius.

The allocation of the adsorbed and chemically attached cisplatin in dendrimer is considerably differing: in the latter case it penetrates deeper in macromolecule (Fig. 5). Chemically non-connected cisplatin can desorbs as may be seen on snapshots (see, for example, in Fig.2b) and as evidenced a high probability to find out the cisplatin on distances more than 2.3 nm from CM (Fig.5).
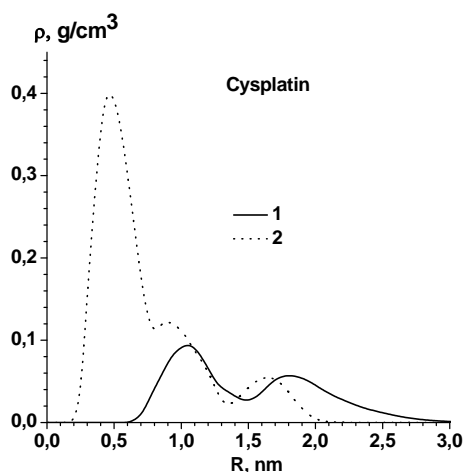
Fig. **5**. Radial density distribution of cisplatin relative to the centre of mass of dendrimer at T=293 K. 1 – adsorbed cisplatin; 2 – chemically attached cisplatin.

Intramolecular dynamics of dendrimers was assessed as a mobility of branch centers and hydroxyl hydrogen atoms of the end groups. For that we calculated the time dependences of the distances L(t) between concerned atoms and CM. As would be expected the atom mobility depend on temperature, but even at temperature 293 K L(t) of some ends groups vary more than 0.8 nm during 1 ns for all cases. However the mobility of chemically connected and adsorbed cisplatin is essentially different (Fig.6). In the first case the mean value of maximum variation of L(t) is 0.3 nm while one for chemically non-connected cisplatin is 0.9 nm. At that a chemically connection of the heavy groups to the dendrimer ends cause some decrease of intramolecular mobility dendrimer-Pt.
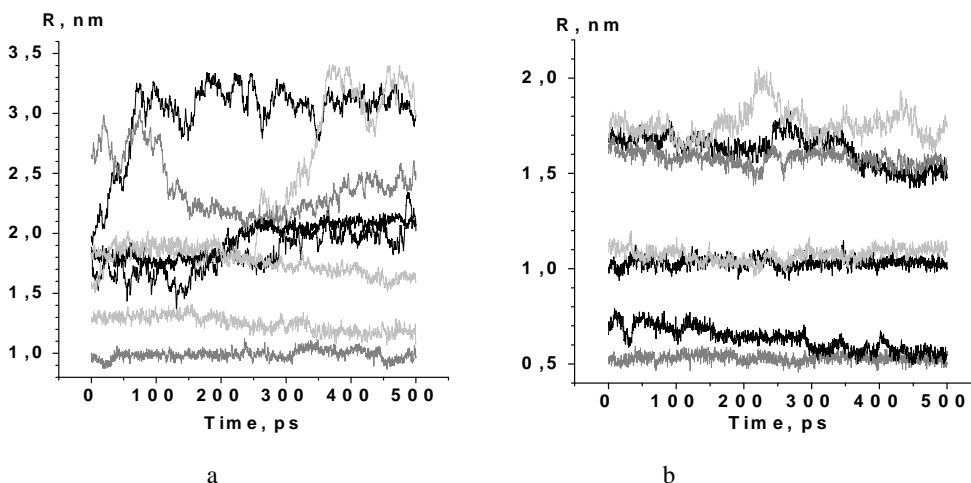

a   b

Fig. **6**. Time dependence of the distances L(t) between adsorbed (a) and chemically attached (b) cisplatins at 293 K.

ACKNOWLEDGMENT

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