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Investigation of complex of lysine dendrimer of 2nd generation with molecules of therapeutic KED peptide by computer simulation

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Abstract. Lysine dendrimers could be used in many biomedical applications. For example these dendrimers could be used for delivery of short regulatory peptides consisting of several aminoacid residues. We investigated earlier interactions between lysine dendrigraft of 2nd generation and molecules of KED peptide. In present paper we study interaction of lysine dendrimer and molecules of KED peptide. The system containing one dendrimer of 2nd generation and 8 molecules of KED in water with explicit account of counterions was studied by computer simulation. The method of molecular dynamics was used for this goal. We obtained that formation of complex consisting of the dendrimer and all peptide molecules occurs during initial time (t < 40 ns) of simulation. The size, anisotropy of shape and radial density profile of stable complex (after t > 40ns) were studied also. We have shown that formation of complex occurs due to electrostatic interaction between oppositely charged dendrimer. At the same time other interactions, for example hydrogen bonds, also give their contribution to this process. Stable dendrimer-peptide complex has size close to 1,5nm and small shape anisotropy. Density of dendrimer atoms is highest in the centre of complex while density of peptides atoms has maximum at radial distance r=1nm. It total we have shown that lysine dendrimers is suitable carrier for molecules of KED peptide.

1. Introduction

Dendrimers are hyperbranched molecules with regular spherically symmetric branching from central core [1]. Different types of dendrimers were used earlier for multiple biomedical applications [2]. Lysine dendrimer consist of many lysine aminoacid residues. Its terminal residues have positively charged amine groups [3] and strongly interact with oppositely charged molecules including DNA, RNA and some peptides. Molecules of KED peptide (Lys-Glu-Asp) have one positively (Lys) and 2 negatively (Glu and Asp) charged aminoacid residues [4-5]. This regulatory peptide molecules have antioxidant and geroprotective properties.

The main task of this paper is to perform molecular dynamics simulation of interaction of lysine dendrimer with KED molecules and check does complex formation between them occurs.

2. Method and Materials

2.1 Molecular dynamics method

We apply molecular dynamics (MD) simulation approach for study the dendrimer-peptide system. These method use mechanical bead-spring of bead-rod models of polymers and biopolymers and was described in many paper. Most recent realizations of MD method include the use of standard packages with contemporary force fields. Our MD simulation was performed using the GROMACS software and one of the most reliable AMBER_99SB-ildn force fields [6,7].

2.2 Model and details of calculations

Model system consists of one lysine dendrimer of 2nd generation, 8 KED peptide molecules , water molecules and Cl- and Na+ counterions in a cubic cell with periodic boundary conditions. The charge of dendrimer termilal groups was equal +16 and charge of each peptide was equal -1. The initial



conformation for peptide with peptide dihedral angles of fi, psi and theta corresponding to beta- sheet was prepared by Avogadro molecular editor. Peptide molecules were placed near each vertex of the periodic cubic cell. The system was minimized first in vacuum using general AMBER force field and later in water using GROMACS and AMBER_99SB-ildn force fields. The details of simulation approach used in this paper for lysine dendrimer and peptides were described earlier in several papers: on MD and BD simulation of non-charged polymer chains [8-21, linear polyelectrolytes [22-27] as well as of dendrimers and other highly branched polymers like hyperbranched polymers [28-53] or polymer brushes [54-57]. In several papers we used for simulation of similar branched polymers the numerical calculations on the base of method of self consistent field (SCF) and scaling approach [58-61]. We used NPT ensemble with pressure 1 ATM and temperature 300 K. For calculation of electrostatic interactions we used PME algorithm.

3. Results and discussion

3.1 Snapshots

Snapshots of a system consisting of dendrimer of second generation, peptides, ions and water during simulation are shown on Fig. 1 (water molecules are not shown for clarity). Atoms of dendrigmer are shown as grey beads with diameter equal to their van der Waals radii. Backbones of KED-peptide molecules are shown by thick black line. It is easy to see that in the initial conformation (see Fig,1a, at simulation time t=0) all peptides are far from dendrimers and from each other. At the same time in final conformation (see Fig,1b, after full simulation time t=100ns) all peptides are on surface of dendrimer. Thus visual evaluation of this pictures and of more frequent snapshots made every 10 ps of simulation (not shown) demonstrate that at the end of simulation (as well as at all other simulation times t>40ps) peptide molecules are attached to dendrimer surface and form stable complex with dendrimer.



Fig. 1. Stages of the complex formation (initial and final) between dendrimer and 8 molecules of KED peptide at time: t = 0 (a); t = 100 ns (b).

3.2 Complex formation

To characterize the size of the subsystem consisting of dendrimer and peptide molecules we use the radius of gyration $R_g(t)$. We calculate it by g_gyrate function of GROMACS package. It is easy to see in Fig.2a that R_g value decreases during first 40ns of (see Fig. 2) and after that slightly fluctuate but its average value almost does not change with time. It means that process of formation of complex between dendrimer and peptide occurs during first 40ns of simulation. At times greater 40ns (in interval of time between 40 and 100 ns of simulation) the stable complex already exist.



Fig. 2. Time dependence Rg(t) for dendrimer DG2+8 molecules of KED peptides (a) and for dendrimer DG2 only (b).

The distance between dendrimer and peptide molecules (fig.2b) also decrease during about 40 ns and than goes to plateau value. This behavior is in agreement with behavior of snapshots and Rg values and confirms that complex formation occurs during first 40ns and after this time the stable complex is already formed.

We could monitor the complex formation also by number of hydrogen bonds (N) between dendrimer and peptide molecules. We calculated it using g_hbonds function of GROMACS package. The time dependence of this value is shown in Fig. 3a. It is easy to see that N increases during first 40ns and after that goes to plateau value. The behavior of this function confirms results obtained in Fig1 and Fig 2 that complex formation occur during 40ns.



Fig. 3.a) Number of hydrogen bonds N between G2 dendrimer and 8 molecules of KED peptide vs time (b), b) radial density profile p(r) for: all atoms (1), dendrimer atoms (2), peptide atoms in complex (3).

3.3 Equilibrium characteristics of complex

We calculated equilibrium characteristics of stable complex using interval of simulation times between 40 and 100ns. The values of mean square sizes (R_g), main components of inertia tensor (R_g^{11} , R_g^{22} and R_g^{33}) and axial ratio R_g^{33}/R_g^{11} of complex and dendrimer are shown in table 1.

Table 1.Size R_g , main components of inertia tensor Rg^{11} , Rg^{22} and Rg^{33} and axial ratio Rg^{33}/Rg^{11}

System	<i>R</i> ¹¹ _g , (nm)	R_{g}^{22} , (nm)	<i>R_g</i> ³³ , (nm)	<i>Rg</i> , (nm)	R_g^{33}/R_g^{11}
G2+8KED	0,85	1,35	1.43,	1,52	1,68
G2	0,59	0,89	0,95	1,00	1,61

Comparison of sizes of the complex G2+8KED and dendrimer G2 (see Table) shows that: 1) size of complex is about 1.5 time larger than size of dendrimer. The shape of the complex was evaluated using ratio of longest and shortest Rg³³ / Rg¹¹. This ratio is equal 1.68 for dendrimer and 1.61 for complex. Thus the anisotropy of shape of dendrimer and complex is close to each other and shapes not far from spherical ones.

We also calculated radial density profile, i.e. distribution of atoms of dendrimer, peptides and all atoms relatively center of inertia of dendrimer using g_rdf function of GROMACS (see Fig. 3b). It is easy to see that distribution of dendrimer atoms have maximum in the center (close to distance r=0), atoms of peptides near r=1nm which is close to distance from center to dendrimer surface. Distribution of all atoms of complex is between distribution for dendrimer atoms and for peptide atoms. Thus these functions confirm that peptides could not penetrate deeply to center of complex and stay mainly on its surface.

4. Conclusion

In this paper we used MD simulation to study interaction of lysine dendrimer G2 with molecules of peptide KED in water and formation of dendrimer-peptide complex. We also have studied its equilibrium size and shape as well as radial density profile inside it. We have shown that both dendrimer and complex have similar shape close to spherical but radial density distribution for dendrimer and peptide molecules are rather different and peptide molecules could not penetrate to core of dendrimer.

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