Computer simulation of complexation of lysine dendrigraft of second generation with DS dipeptide molecules

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Abstract - Dendrimers and dendrigrafts are frequently used for drug and other molecules delivery to different target cells or organs. In our previous papers we used computer simulation to study the complex formation between dendrimers and dendrigrafts with different short regulatory peptides. The goal of present paper is to study the possibility of complex formation between lysine dendrigraft and molecules of therapeutic DS dipeptide. The system consisting of one lysine dendrigraft of the second generation and 16 therapeutic DS dipeptide molecules in water with explicit counterions was studied by computer simulation. The method of molecular dynamics and full atomic model were used for this goal. It was obtained that DS dipeptide molecules become adsorbed by lysine dendrigraft and form stable complex with it. Structure and conformational properties of this complex were studied. It was demonstrated that formation of complex occurs mainly due to electrostatic interaction between oppositely charged dendrigraft and dipeptide molecules. Such complexes could be used in future for delivery of these or similar peptide molecules to the targeted tissues and organs.

Key-Words: - lysine dendrigrafts, DS peptide, complex, computer simulation

I. Introduction

Therapeutic DS peptide (Asp-Ser) was selected for our study as a model peptide. These peptides are novel synthetic peptides that display both antithrombin and disintegrin activity [1-4]. Today one of the most important directions in pharmaceutics is the search for new biocompatible carriers for targeted delivery of various drugs (including therapeutic peptides) to particular organs. Highly branched polymer macromolecules including dendrimers and dendrigrafts are good candidates for this goal.

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Dendrimers are special class of hyperbranched macromolecules which are regularly branched from single center. Dendrigrafts are highly branched polymers with several branching point in the core. Dendrigrafts could be described from one hand as dendrimers with short linear chain in their core or from another hand as a dendritic brush with short main chain and long side chains. Lysine dendrigrafts consists entirely of biocompatible lysine aminoacid residues. At the same time their terminal groups could be functionalized by other aminoacid residues or by bioactive groups or molecules [5, 6]. Lysine dendrigrafts are polymers that are rich with amines. Due to this reason they could be used as antibacterial [7] or antiviral agents [8]. Also they could make complexes with oppositely charged peptides due to strong electrostatic interaction between their positively charged terminal groups ($NH3+$) and negatively charged aminoacid side groups ($COO-$) of peptides.

During the process of complex formation with regulatory peptides, there are several possible types of interactions: electrostatic interaction between positively charged $NH3+$ side groups of dendrigraft and negatively charged $COO-$ side groups of dipeptide, hydrogen bonds between the internal groups of dendrigraft and amino acid residues and hydrophobic interactions between nonpolar groups. The aim of this work is to study properties of system, consisting of lysine dendrigraft and DS dipeptide molecules in water. The main goal of this paper is to check does dendrigraft forms complex with DS dipeptide molecules and, if yes, to determine the size and other equilibrium characteristics of it.

II. Method of Molecular Dynamics

Molecular dynamics (MD) method is currently the main computer simulation method for study polymer and biopolymer systems. The method consists in numerical solution of the classical Newton equations of motion for all atoms of the all

molecules in the system. In present paper simulation was performed for systems consisting of one lysine dendrigraft of second generation with positively charged NH3+ end groups and 16 DS peptide molecules (with charge -1 in COO- side group of Asp aminoacid residue of each dipeptide molecule). These molecules were placed in water box (cubic cell with periodic boundary conditions) with corresponding number of counterions. The initial conformation of dendrigraft was taken from the end of long simulation of single dendrigraft in water (without peptide molecules). For peptide molecules the initial conformation with dihedral angles $\varphi = -135°$, $\psi = 135°$, $\theta = 180°$ was prepared using AVOGADRO molecular editor. The structures of peptides were first optimized in vacuum using molecular mechanics of AMBER force field. Further energy minimization and simulations of whole system was performed using the GROMACS 4.5.6 software package [9] and AMBER_99SB-ildn force fields [10]. The potential energy of this force field consists of valence bonds and angles deformation energy, internal rotation angles, van der Waals and electrostatic interactions.

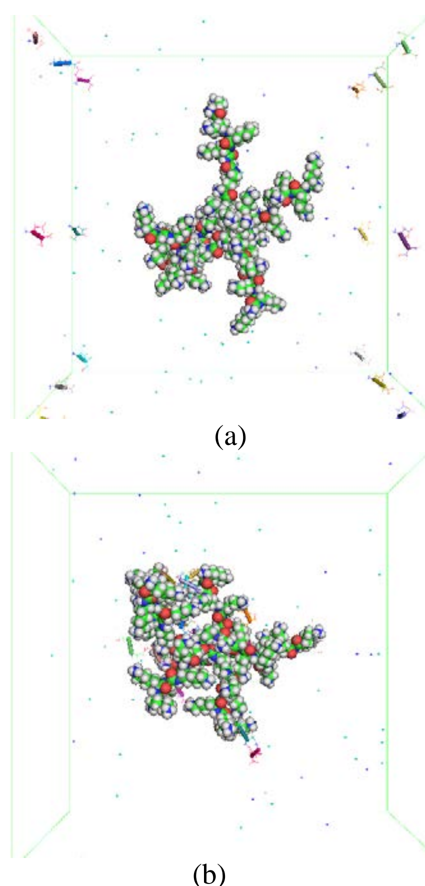
In present simulations we used LINCS algorithm to constraint all valence bonds and increase the discretization time to 0.002 ps. For calculation of non-bonded interaction and, in particular, electrostatic ones we use particle mesh Ewald algorithm (PME) which allows correct calculations of long-range Coulomb potential. We calculated trajectory of all atoms during 100ns time and used first half of it for study of complex formation and second half for calculation of equilibrium average values of different parameters (size, shape and internal structure) of complex

We perform all simulation in NPT ensemble and at normal conditions (temperature 300 K and pressure 1 ATM). The procedure of molecular dynamics simulation for lysine dendrimers and for other linear and branched polymers and polyelectrolytes has been described earlier in [11-75] and further details about simulations could be found there.

III. Complex Formation

Snapshots of a subsystem consisting of dendrigraft of second generation and peptides at the beginning (fig.1a) and at the end of simulation (fig.1b) are shown on fig. 1. It is clearly seen that at the beginning of simulation (fig. 1a) all peptide molecules are far from dendrigraft. At the same time in the end of simulation (fig.1b) all peptide molecules are adsorbed on dendrimer surface.To characterize the size of the subsystems the instant square of radius of gyration $R_g(t)$ was used.

The time dependence of gyration radius $R_g(t)$ of subsystem consisting of dendrigraft and peptide molecules describes the process of equilibration and demonstrate the kinetics of complex formation (if formation of complex occurs) or separation of dendrigraft and peptide molecules (if it not occurs). It can be seen from fig. 2a, that in the beginning of simulation the value of $R_g(t=0)$ equal 3.80 nm for this subsystem. It is rather big because peptides are far from dendrigraft (see fig1a).

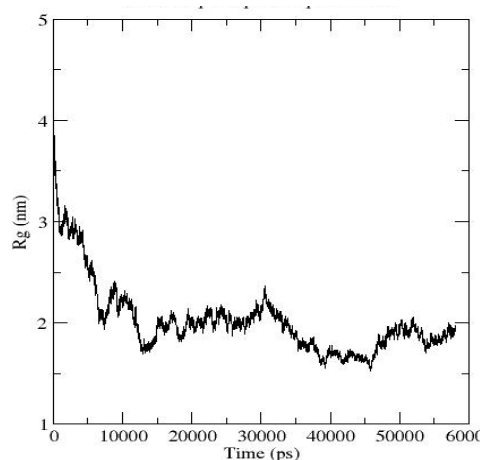


(a)

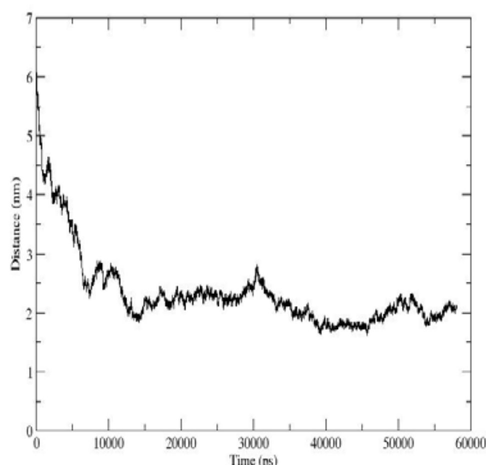
(b)

Fig. 1. (a) Snapshots of initial and b) final conformation of lysine dendrigraft of 2nd generation and DS peptides and

After that radius of gyration of the subsystem become smaller and smaller because peptide molecules attracted by dendrigraft become more and more close to it due to strong intermolecular interactions. The slope of Rg(t) could characterize the rate of complex formation. Finally, the value of Rg(t) goes to plateau value because all peptide molecules become adsorbed on dendrigraft surface. It occurs at time about 15-20 ns. After that, the complex sizes Rg fluctuate, but their average values practically do not change with time.



(a)



(b)

Fig 2. a) Time dependence of a) gyration radius R_g (t) of complex, (b) distance between dendrimer and peptide molecules.

Rg(t) was calculated using g_gyrate function of GROMACS.

The time dependence of distance between dendrigraft and peptide molecules (fig.2b) has similar behaviour. It is rather big at the beginning of simulation than it decreases during about 15 ns. The slope of time dependence of distance could also characterize the rate of complex formation. After first 15ns distance fluctuates but its average value practically does not change with time. Therefore, we can assume that the systems are in equilibrium state after first 15 ns of computer simulation and calculate equilibrium value of $Rg=sqrt(<R_g^2(t)>)$ (where <> mean average on equilibrium (plateau) part of trajectory, i.e. for t>15ns and calculate equilibrium distance between dendrigraft and dipeptide molecules). Function “distance” was calculated using g_bond function of GROMACS package.

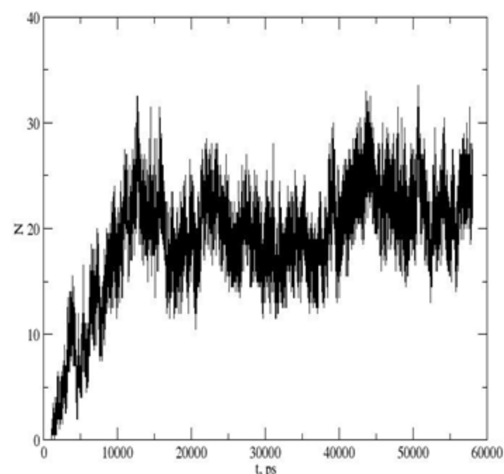


Fig.3 Time dependence of hydrogen bonds number (N) between dendrigraft DG2 and DS dipeptides during the complex formation

Another quantity that can demonstrates kinetic of complex formation and confirm that the complex formation between dendrigraft and peptide molecules really occurs is the time dependence of number of hydrogen bonds N between them (see fig.3). In the beginning of simulation the value of N(t)=0 because dendrigraft and DS peptides are far from each other and thus do not have any contacts. When peptide molecules become closer to dendrigraft the contacts between them appears and the value of N(t) start to increase with time. Thus, the slope of N(t) could characterize the rate of complex formation. After time t=15-20 ns the function N(t) goes to plateau because all peptide molecules already adsorbed on dendigraft. The average value of (N(t) for time t>15ns gives average value of number of hydrogen bonds between dendrigraft and peptide molecules. This function was calculated using g_hbonds function of GROMACS.

IV. Equilibrium Complex

Equilibrium values of $R_g(t)$ for dendrigraft in complex and $R_g(t)$ of whole complex are shown in table 1. It is easy to see that the size of the complex of DG2 with 16 DS dipeptides is in 1,27 larger than the size of the dendrigraft DG2 in the complex (see Table 1). It is quite natural, that complex has larger sizes than dendrigraft since size correlates with the molecular weight of the complex compared to the molecular weight of the individual dendrigraft. The shape of complex can be characterized by main component ratio $(Rg^{11}, Rg^{22}, Rg^{33})$ of tensor of inertia of the system. We used the ratio of longest and shortest components: R_g^{33} / R_g^{11} as estimation of anisotropy of our complex. For dendrigraft DG2 this

value is equal to 1,47, for the complex of DG2 and 16 DS dipeptides it is equal to 1,31. Thus the shapes of dendrigraft and complex slightly deviate from spherical shape and are similar in both subsystems. But these deviations are not big so we can treat both systems as nearly spherical objects in the rest of the paper and study their radial density distribution function.

TABLE 1. R_g^{11}, R_g^{22}, R_g^{33}, R_g of tensor of inertia of dendrigraft of second generation DG2 and of complex of DG2 and 16DS

System	R_g^{11}	R_g^{22},	R_g^{33},	R_g, nm
DG2	1.12	1.41	1.65	1.48
DG2+16DS	1.30	1.57	1.71	1.88

Information about the internal structure of the equilibrium complex could be obtained using radial density distribution function of different subsystem of atoms relatively center of inertia of system. They were calculated using g_rdf function of GROMACS. Fig. 4 demonstrates that atoms of dendrigraft (curve 2, fig.4) are located mainly in the center of the complex (close to radial distance r=0 nm). Peptides atoms (curve 1, fig. 4) could slightly penetrate into dendrimer but two maxima of their density (near r=0.75nm and 1.25nm) and both curve have similar long tails. It means that peptide molecules are always adsorbed by dendrigraft and did not leave its surface.

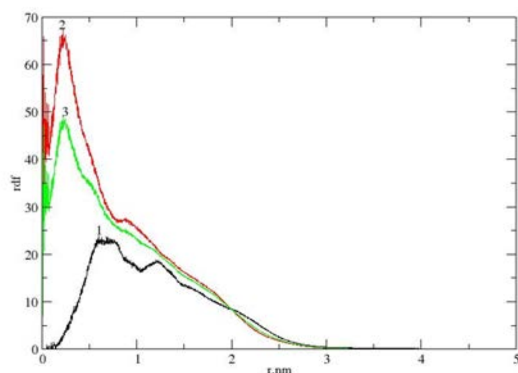


Fig.4 Radial distribution p(r) curves for complex consisting of dendrigraft DG2 and 16 DS dipeptides: for peptide atoms (1); for dendrigraft atoms (2); for all atoms of complex (3)

The other characteristic of interaction between dendrigraft and peptides in complex is the distribution of ion pair numbers between oppositely charged groups of dendrigraft (NH3+) and peptides (COO-). Fig. 5 shows the dependence of ion pair number distribution as function of distance r between them. We also calculated distribution between charged groups of peptides and counterions (see fig.5).

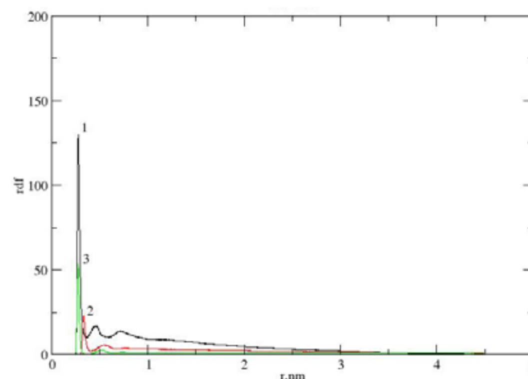


Fig.5 Binary function of ion pair radial distribution (rdf): (1) between NH3+ groups of dendrigraft and COO– groups of peptides, (2) between NH3+ groups of peptides and ions Cl-, (3) between Na+ and Cl- ions.

It is clearly seen from fig.5 that there is a sharp peak (curve 1), corresponding to the direct contact between positively charged groups (NH3+) of dendrigraft and negatively charged groups (COO-) of the aspartic acid in peptide molecules. For pairs of NH3+ groups of dendrigraft with counterions of Cl- the maximum is at similar distances of contacts with counterions but the number of such contacts is significantly (about 5 times) less (curve 2) than number of contacts of peptides with dendrigraft (curve 1). The height of peak of number of contacts between two types of counterions Na+ and Cl- (curve 3) is intermediate between values for two previous types of ion pairs (curve 1 and curve 2). Big peak in curve 1 confirms the stable strong electrostatic interactions between dendrigraft and dipeptide molecules and their great contribution to stabilization of complex. We also calculated energy of electrostatic and van der Waals interactions between dendrigraft and dipeptide molecules using g_energy function of GROMACS package and found that electrostatic interactions are about 3-4 times stronger. Thus the main reason for complex formation between dendrigraft and DS dipeptides are the electrostatic interactions.

To evaluate the translational mobility of our systems, the time dependence of the mean square displacement (MSD) of the center of inertia of the systems was calculated (fig. 6) using g_msd function of GROMACS package. .

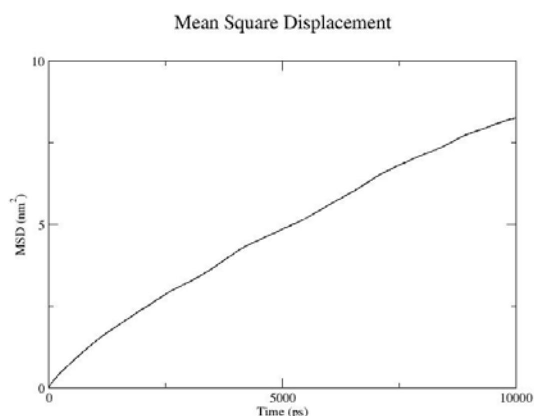


Fig.6 Mean square displacements (MSD) of the centers of inertia for complex of DG2 with 16 DS peptides

Dependence of mean square displacements (MSD) as function on time is close to linear in the interval of time equal to 10 nanoseconds. It means that in this interval the motion of complex is close to diffusion-like motion (see fig. 6). Coefficient of translational diffusion of the complex was determined from the slope of the time dependence of MSD on this interval and is equal $0.14 \pm 0{,}01*10^{-5}$ sm^2/s. This value is close to value of diffusion coefficient of single dendrigraft in water.

V. Conclusion

In this study the process of complex formation in system consisting of lysine dendrigraft of second generation and 16 DS dipeptides was studied. It was shown that stable dendrigraft-peptide complex forms within 15-20 ns. Radial density distribution for atoms of dendrigraft and peptide molecules are rather different: atoms of dendrigraft are mainly in the center of complex while peptide molecules are mainly on its surface and could penetrate into dendrigraft but their two maxima of density are at about 0.75nm and 1.25 from center of mass of complex. There are strong contacts of positively charged NH3+ groups of dendrigraft and COO- groups of aspartic acid of peptide molecules while Cl- counterions form significantly less contacts with dendrigraft NH3+ groups. The diffusion coefficient of complex is also calculated and its value is close to value for single dendrigraft in water (without

peptides).

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