Molecular dynamics simulation of complexes of lysine dendrimer and dendrigraft with AENG tetrapeptide

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Abstract: - Computer simulation of complexes of lysine dendrimer and dendrigraft with therapeutic AENG tetrapeptide was carried out using molecular dynamics simulation method. Dendrimers were tested earlier for drug and gene delivery to different cells.. In this study two systems consisting of one lysine dendrimer or dendrigraft of the second generation and 16 tetrapeptides were studied.. It was obtained that in both cases the peptide molecules become adsorbed by branched lysine molecules and forms stable nanocomplex with them. The size and internal structure of the nanocomplexes were compared. Similar complexes and conjugates could be used in future for delivery of different therapeutic peptides to the target organs.

Key-Words - lysine dendrimers and dendrigrafts, tetrapeptides, complex, molecular dynamics simulation

I. Introduction

In this paper we compare complexes of lysine dendrimer and dendrigraft of second generations with therapeutic tetrapeptide Epithalon. Lysine dendrimers and dendrigrafts are highly branched regular structures consisting of only one type of repeating units - lysine aminoacid residues. Dendrimers are regularly branched molecules with many terminal groups available for functionalization [1-6]. They have internal voids and were tested in many medical applications as possible drug, gene and other molecules delivery systems [7-9] as well as antibacterial, antivirus and antiamyloid agents [10-13].

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Lysine dendrimers are important class of dendrimers consisting of lysine amino acid residues as branching repeating units [5,6,10,13]. Lysine and more general peptide dendrimers were widely used for different biomedical application [10,13-16]. Lysine dendrimer usually branched from single core while recently introduced new lysine dendrigrafts has linear core consisting of 8 lysine residues. Dendrigrafts were widely used in recent year in biomedical applications [17-22].

Epithalon is a regulatory tetrapeptide with the amino acid sequence of alanine-glutamate-asparagine-glycine (AENG), synthesized to mimic the peptide drug “epithalamin” extracted from the pineal gland of animals [23]. Currently, there are four ways of introducing of this drug into the body – oral, nasal, intramuscular and subcutaneous. The main problem of these formulations of drug is a fast degradation of the peptide in a body and its low permeability through the blood-brain barrier. At the same time the increase of the drug concentration to keep its therapeutic concentration leads to strong immune response take place [24].

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. Branched polymer macromolecules including dendrimers are good candidates for using as such carriers. Dendrimers are special class of hyperbranched macromolecules which are regularly branched from single center. They have a large number of terminal groups and constant size. It makes possible to create a well-characterized complexes and conjugates of dendrimers with different compounds.

During the process of complex formation with regulatory peptides, there are several possible types of interactions: electrostatic interaction between the end groups of dendrimer and charged amino acid groups of the peptide; hydrogen bonds between the internal groups of dendrimer and amino acid residues; hydrophobic interactions between

nonpolar groups; and chemical bonding of peptides with dendrimers using peptide bonds.

The aim of this work is to study properties of two systems: first consisting of lysine dendrimer of second generation and 16 free Epithalon tetrapeptides and second consisting of lysine dendrigraft of second generation with the same number of the same tetrapeptide. We would like to check first do dendrimer and dendrigraft forms a complex with Epitalon peptides and, if yes, to compare the size and other equilibrium characteristics of these complexes.

II. Method of Molecular Dynamics

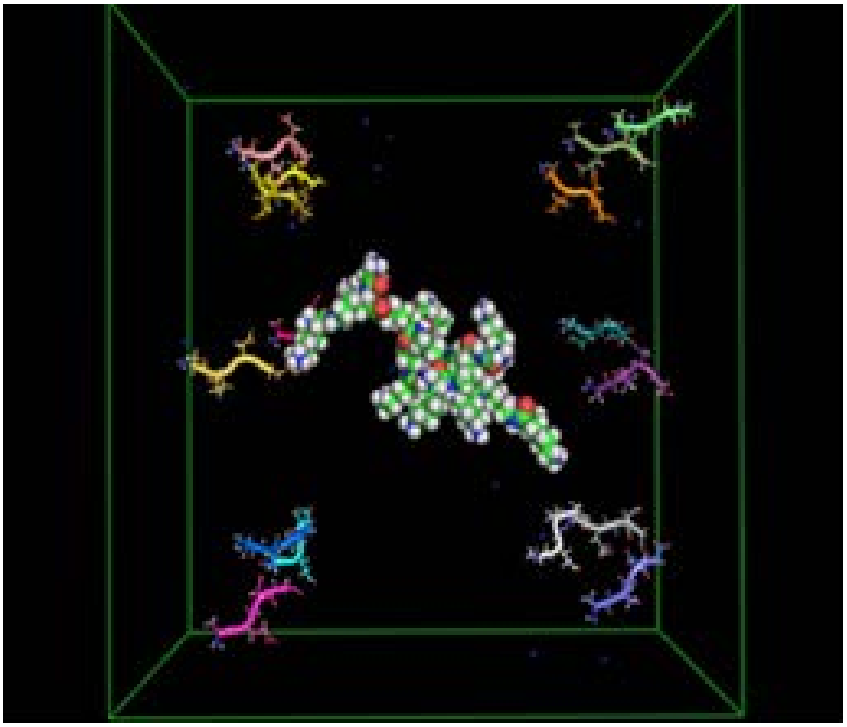
The method of molecular dynamics (MD) is the main method for simulation of polymer and biopolymer systems. The method consists in numerical solution of the classical Newton equations of motion for all atoms of the all molecules in the system. In present paper simulation was performed for systems consisting of one lysine dendrimer or dendrigrafts of second generation with positively charged NH3+ end groups and 16 free Epithalon peptides with charge of each peptide equal -2 (see Fig. 1a and Fig.1b, correspondingly). These molecules were placed in water box (the size of cubic cell is 9nm in each direction with periodic boundary conditions) with chlorine counterions. The initial conformation of dendrimer was taken from the end of long simulation of dendrimer in water (without peptides). Peptides were places near the edges of periodic box. For peptides the initial conformation with dihedral angles phi = –135º, psi = 135º and theta = 180º was prepared using Avogadro chemical 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 [25] and AMBER_99SB-ildn force fields [26]. 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 “tails” of Coulombic potential. We calculated trajectory of all atoms during 100ns time and used first half of it for study of cimplex formation and second half of for calculation of equilibrium average values of different parameters (size, shape and internal strcucture) of complex

We perform all simulation in NPT ensemble and in all calculations in present paper the normal conditions (temperature 300 K and pressure 1 ATM) were used. The procedure of molecular dynamics simulation for lysine dendrimers and for other linear and branched polymers and polyelectrolytes has been described earlier in [27-54] and further details about simualtions could be found there.

III. Complex Formation

To characterize the size of the systems the instant square of radius of gyration Rg(t) was used. The time dependence of gyration radius Rg(t) at the beginning of calculation describes the process of equilibration of subsystem consisting of dendrimer (or dendrigraft) and peptides. It can be seen from Fig. 2a, that for first system the initial value of Rg(t=0)=3.70 nm is rather big because peptides are far from dendrimer at the beginning of simulation (see Fig1a).After that peptides become more and more close to dendrimer due to intermolecular and especially electrostatic interactions and radius of gyration of this subsystem become smaller and smaller. Finally all peptides become adsorbed on dendrimer and dendrimer-peptide complex with 16 Epithalon peptides forms within 7-10 ns. After that, the complex sizes Rg fluctuate, but their average values practically do not change with time. Therefore, we can assume that after this time the systems are in equilibrium state. and calculate equilibrium value of <Rg> (where <> mean average in equilibrium part of trajectory, i.e. for t>30ns.



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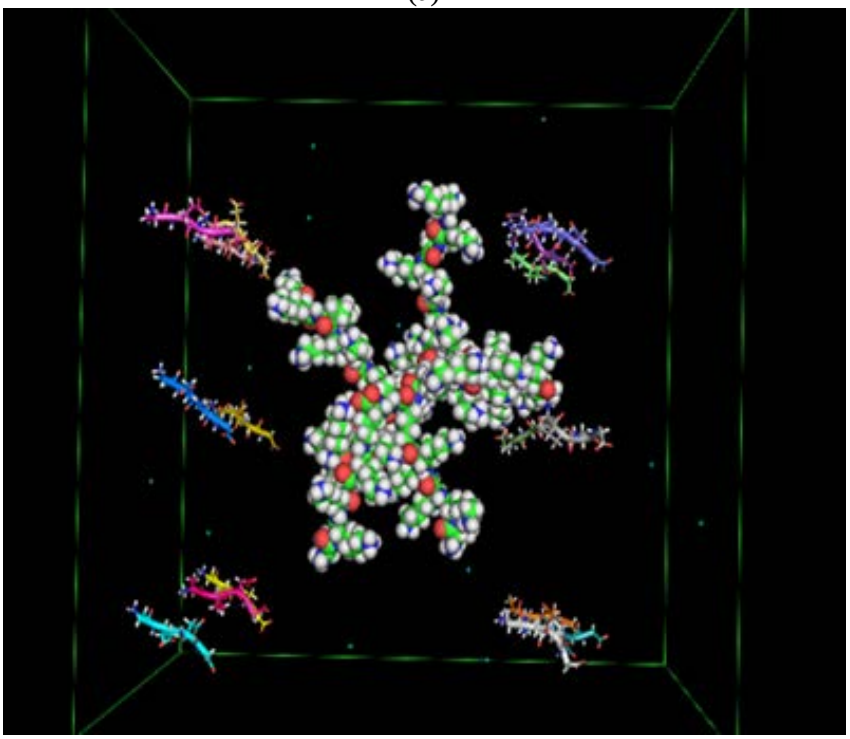
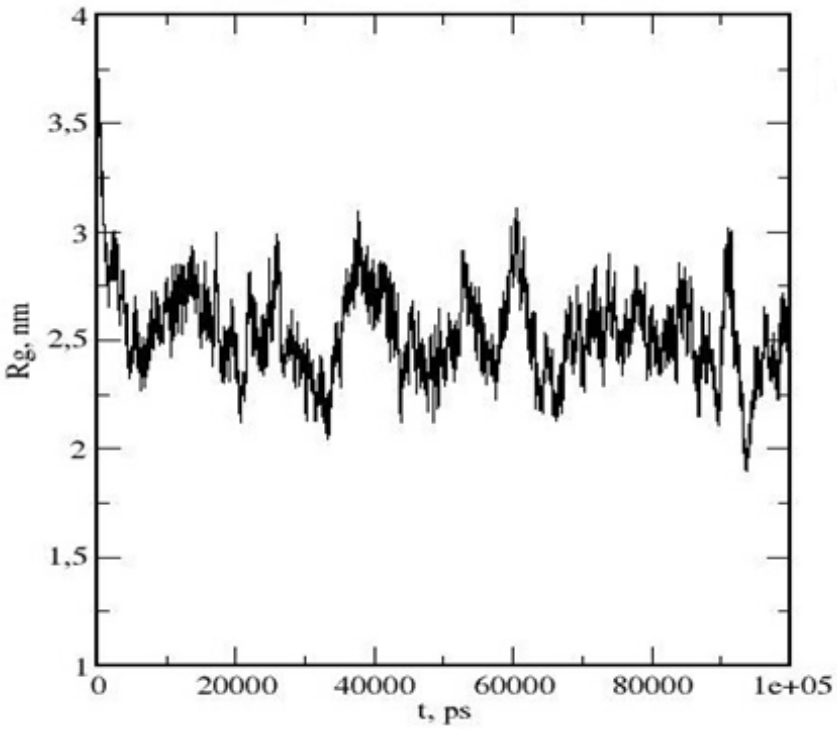


(b)

Fig. 1. Initial conformation of (a) lysine dendrimer of 2nd generation and free peptides and (b) the lysine dendrigraft of 2nd generation and the same free peptides



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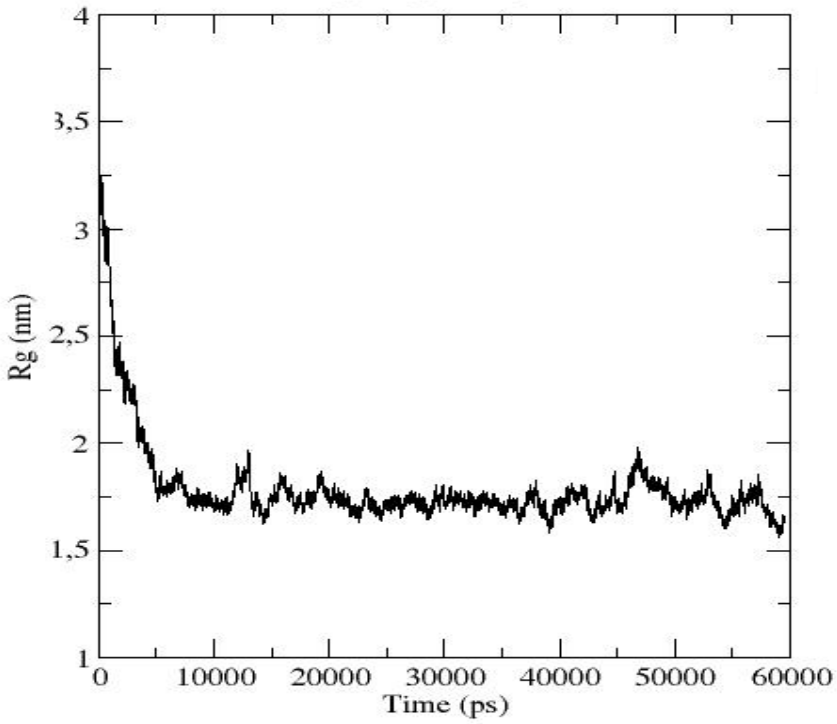
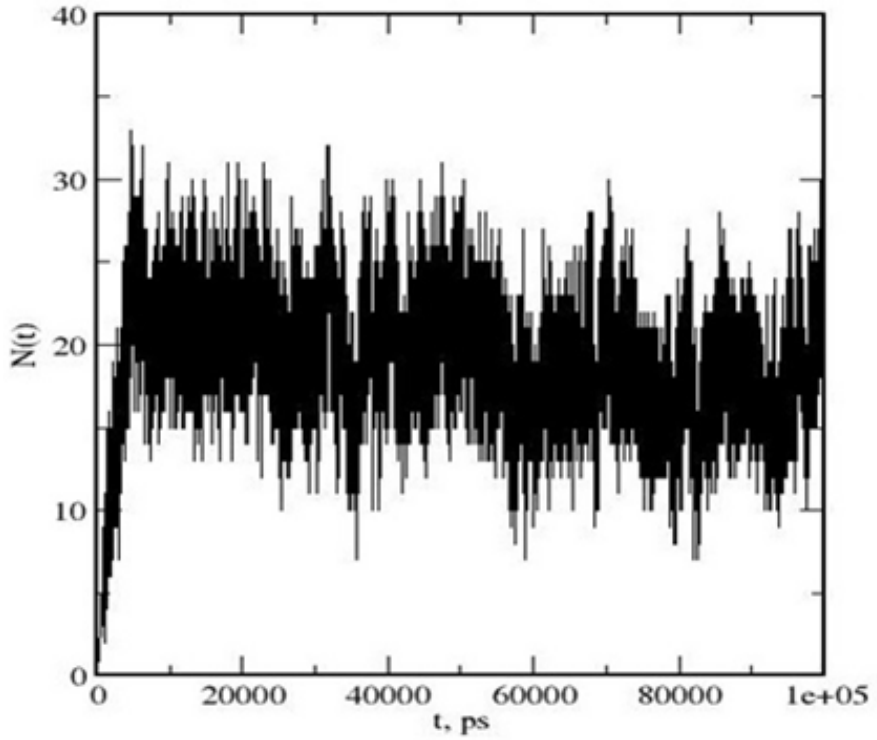


(b)

Fig 2. Time dependence of gyration radius Rg of complexes: (a) – complex of 2nd generation dendrimer with 16 peptides; (b) - complexe of 2nd generation dendrimer with peptides chemically linked to dendrimer ends



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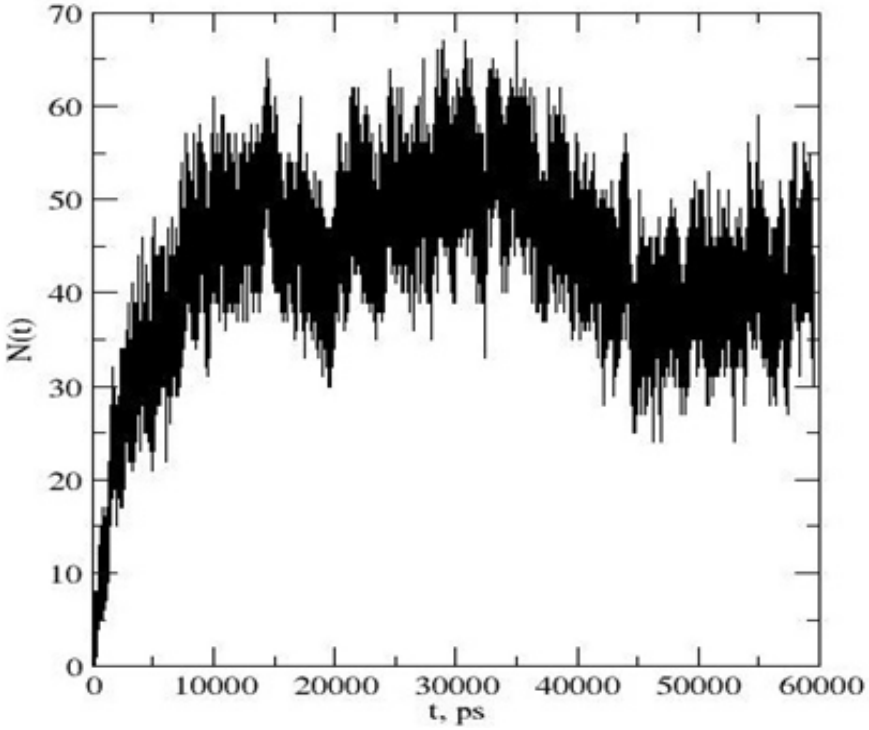


(b)

Fig.3 Time dependence of hydrogen bonds number (N) between dendrimer or dendrigraft with peptides during the complex formation: (a) dendrimer with peptides; (b) dendrigraft with peptides.

For second system consisting of the dendrigraft with 16 Epithalon peptides (see Fig.2b) the initial value of Rg(t=0)=3.25. This value again is rather large because peptides are far from dendrigraft in the beginning of simulation. This value also decrease with time t for first 7-10 ns and reaches the equilibrium state after that as for previous systems.

Another quantity that can demonstrate formation of complex is the instant number of hydrogen bonds N(t) between dendrimer and peptides. In the beginning of simulation in the first system Fig.3a

N(t=0)=0 because dendrimer are far from free peptides and thus do not have any contacts with them. When peptides become closer to dendrimer the contacts between them occur and number N(t) increase with time. Thus slope of N(t) during this time characterize the rate of complex formation. The dependence of N(t) between dendrimer and peptides is shown for first system in Fig.3a. This value was calculated using g_hbonds function of GROMACS. It is clear seen from this plot that the first system reaches equilibrium (plateau) after about 7-10 ns.

In second system (Fig. 3b) the instant number of hydrogen bonds N(t) between dendrigraft and peptides in the beginning of simulation is also equal zero because the peptides are initially far from dendrigraft. When peptides become closer to it the contacts between them occurs and number N(t) increase with time. The dependence of N(t) between dendrigraft and peptides is shown in Fig.3b. This value was also calculated using g_hbonds function of GROMACS. It is clear seen from this plot that the second system reaches equilibrium (plateau) also after about 7-10 ns.

The number of hydrogen bonds between peptides and dendrimer or dendrigraft shows how tightly peptides associate with them. From Fig. 3 it follows that average hydrogen bonds number in equilibrium state (t > 10 ns) for the first complex is close to 20. For the second complex, it is close to 43.

IV. Equilibrium Complex

After our system reach equilibrium state we can calculate equilibrium value of Rg=sqrt(<Rg2(t)> for t>teq (where <> mean average over equilibrium part of trajectory t>teq (in present paper we choose teq=30ns for both systems).

In equilibrium state the size of the first system i.e. of the complex of G2 with 16 peptides is in 1.41 larger than the size of the complex of dendrigraft with the same peptides (see Table 1). It is so because the dendrimer has essentially smaller charge (+16) in comparison with dendrigraft (charge +48). Due to this reason dendrimer could not tightly bind peptides. Visual analysis of snapshots shows that in the first system the peptides are usually attached to dendrimer by one end only and their second end is in average rather far from dendrimer center. Contrary to this in the second system all peptides are connected with dendrigraft in two or more points. Thus in second systems all parts of peptides are in average on dendrigraft surface.

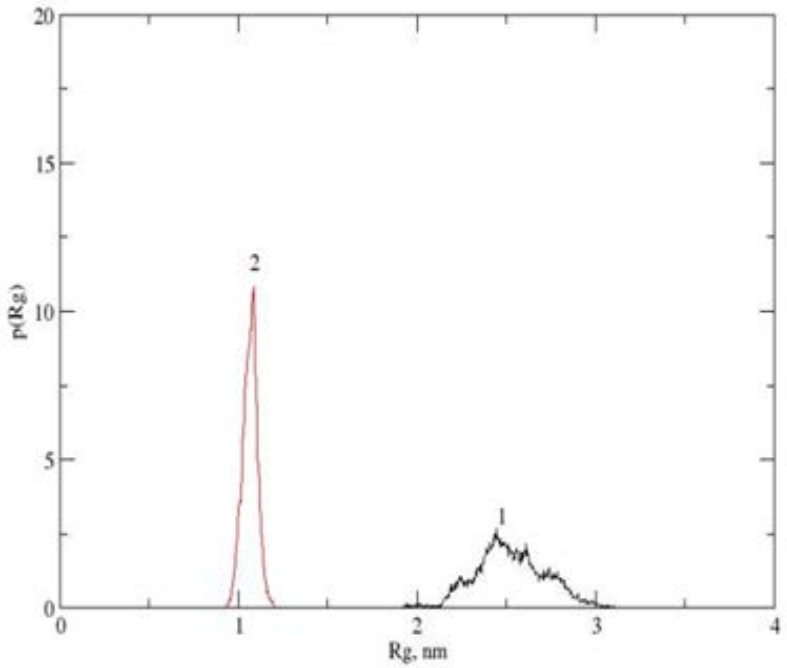
TABLE 1. Rg11, Rg22, Rg33 components of tensor of inertia and radius of gyration Rg of two complexes

System	Rg^{11}	Rg^{22},	Rg^{33},	Rg, nm
1	1.76	2.08	2.26	2.44
2	1.20	1.45	1.56	1.73

The shape of both complexes can be characterized by main component ratio (Rg^{11}, Rg^{22}, Rg^{33}) of tensors of inertia of these systems, that are collected in Tab. 1. For example, in the simplest case, anisotropy can be characterized by ratio of longest and shortest axes of equivalent ellipsoid: Rg^{33} / Rg^{11}. For the first complex this value is equal to 1,28, for the complex of dendrigraft with 16 peptides it is equal to 1,11. Thus in both cases the anisotropy is close to 1 and both complexes have shape close to spherical.

The distribution function p(Rg) of gyration radius Rg gives more detailed information about the variation of Rg of dendrimers-peptides and dendrigraft-peptide complexes and, in particular, the amplitude of their fluctuations in these systems. These functions are shown in Fig. 4. From comparison of Fig.4a and Fig4.b it is clear that p(Rg) for dendrimer (curve 2) is shifted to smaller values of Rg in comparison with p(Rg) for dendrigraft which is quite natural due to higher molecular weight of dendrigraft. At the same time p(Rg) for complex as a whole (curve1) for first system are shifted to greater Rg in comparison with p(Rg) for complex with dendrrigraft (curve1). This result is in accordance with results of Tab.1 and confirm that the first complex is less compact than second one due to weaker electrostatic interactions.
dendrimer in this complex;b – (1) for dendrigraft-peptide complex; (2) for dendrigraft in this complex.

We also calculated distribution of average values N of hydrogen bonds in equilibrium state and compared them for both systems (see Fig. 5a and Fig.5b). We found that distributions of numbers of hydrogen bonds for first system are quite



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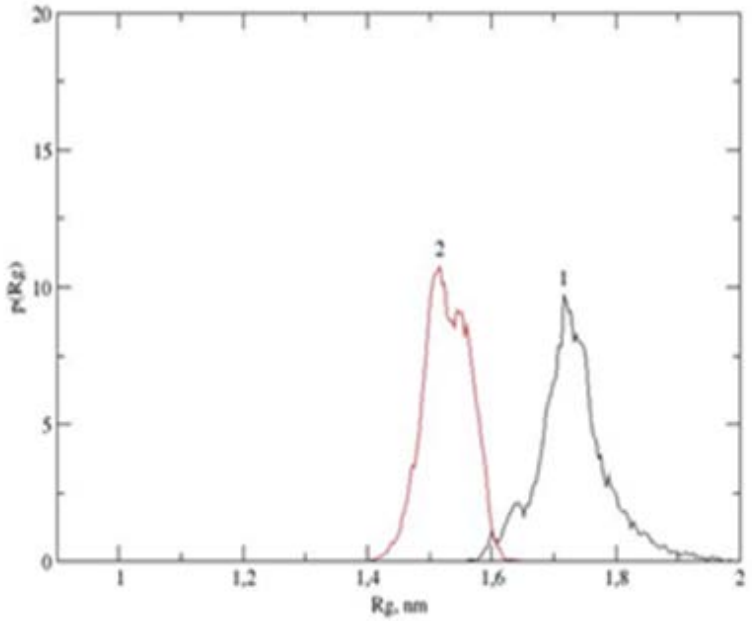
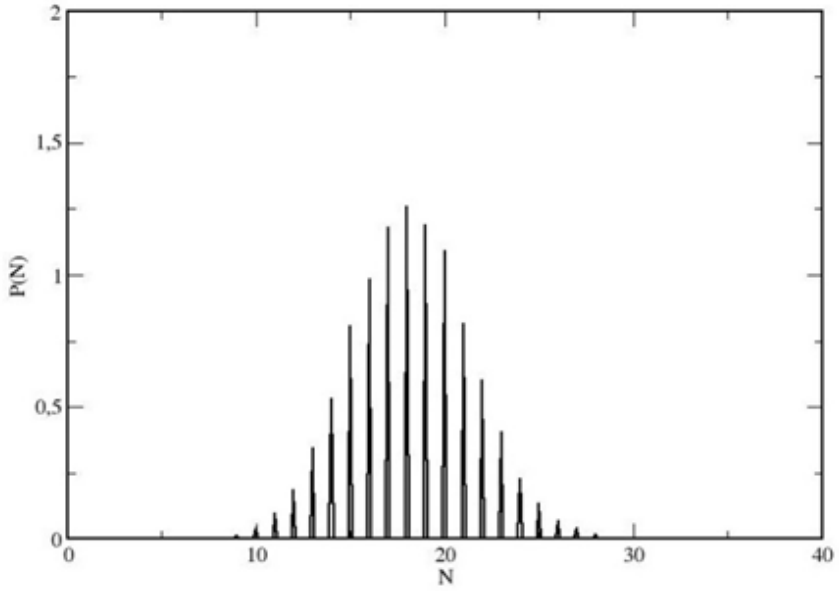


Fig.4 Distribution function p(Rg) of gyration radius Rg: a – (1) of dendrimer-peptide complex; (2) for



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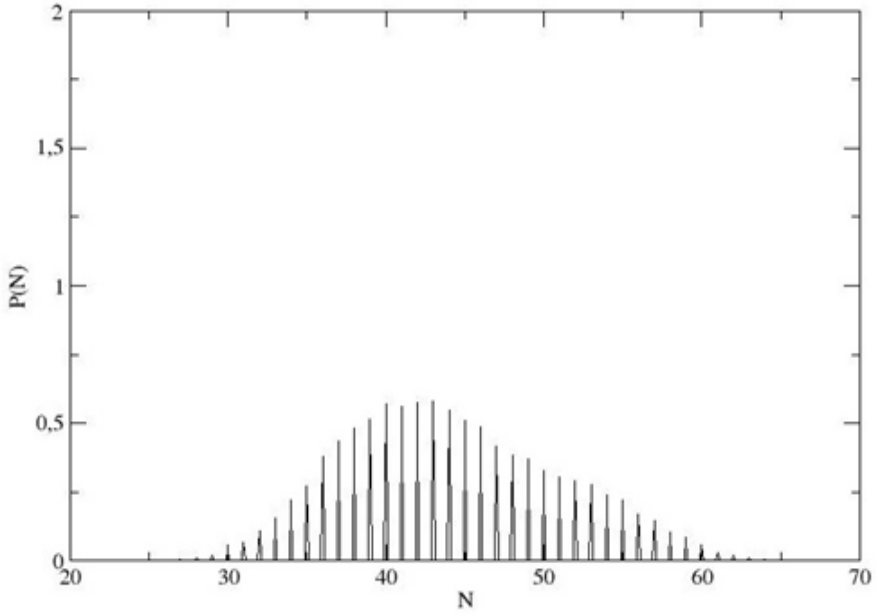
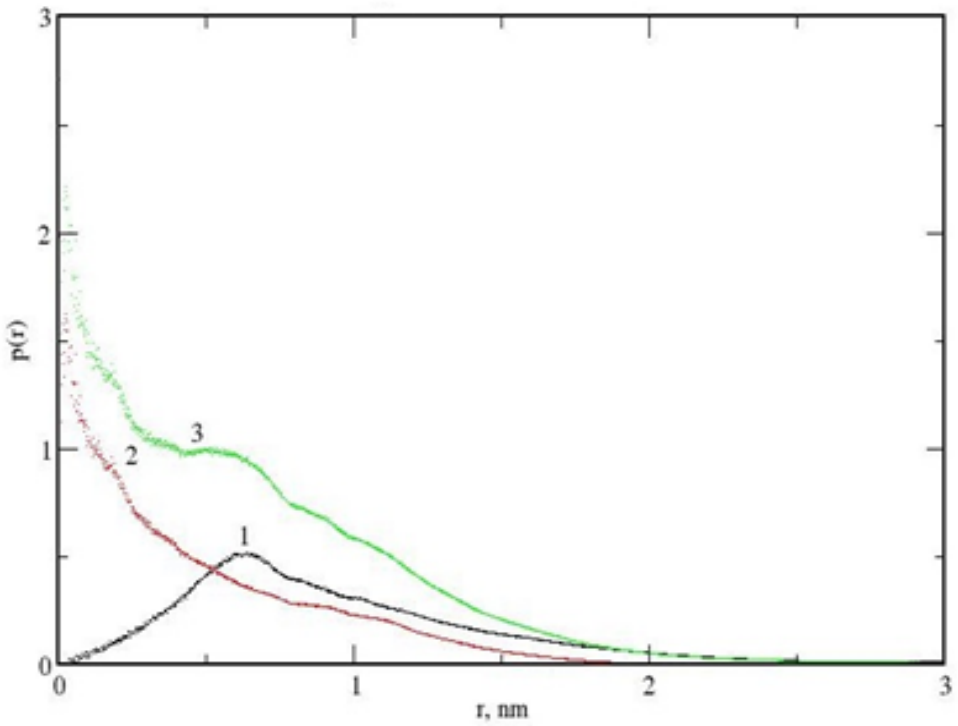


(b)

Fig.5. The distribution function P(N) of hydrogen bonds number N of dendrimer with peptides (a); dendrigraft with peptides (b)



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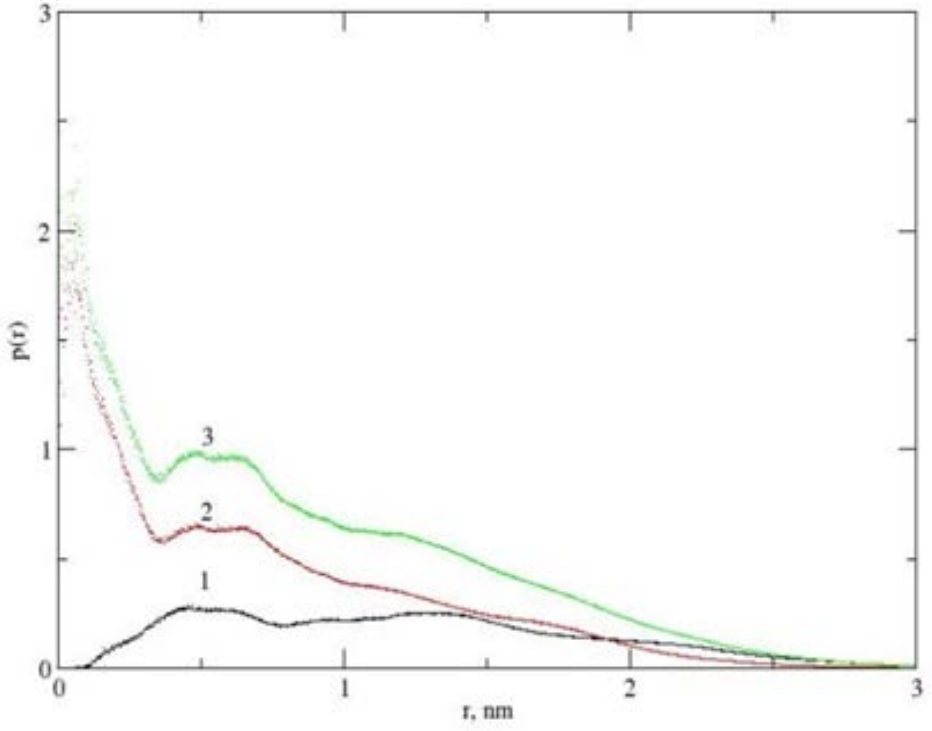
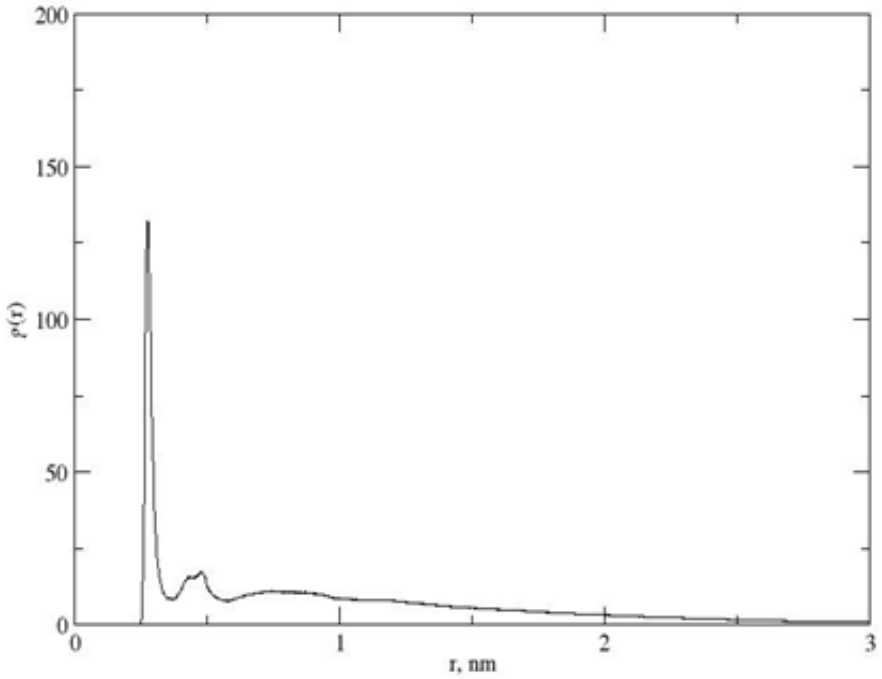


(b)

Fig.6 Radial distribution p(r) curves: (a) complex consisting of: dendrimer and 16 Epithalon peptides and (b) dendrigraft and 16 Epithalon peptides. Peptide atoms (1); dendrimer or dendrigraft atoms (2); all atoms of complex (3).



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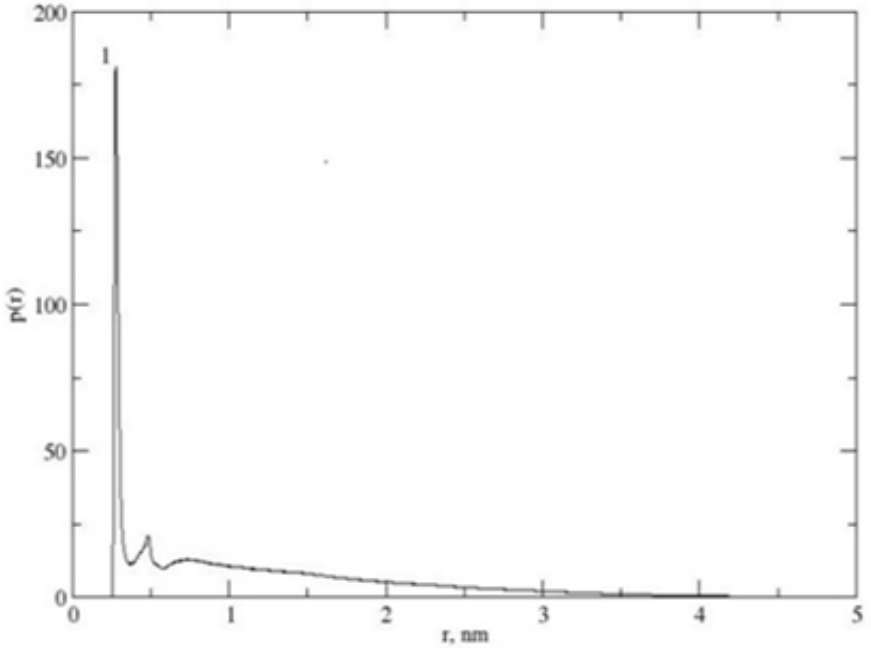
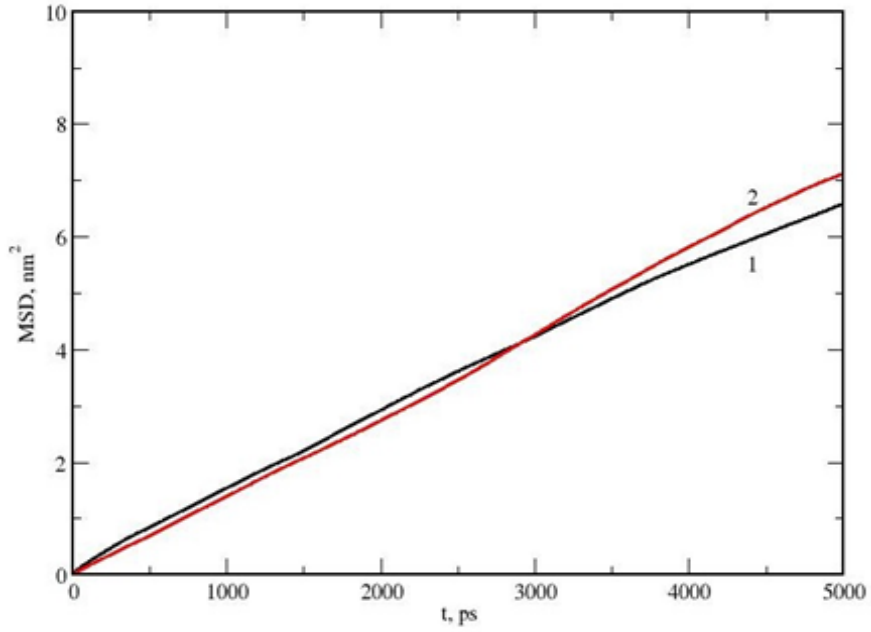


(b)

Fig.7. Binary function of ion pairs distribution: a - between NH3+ groups of dendrimer and COO– groups of peptides: b – between NH3+ groups of dendrigraft and COO– groups of peptides.



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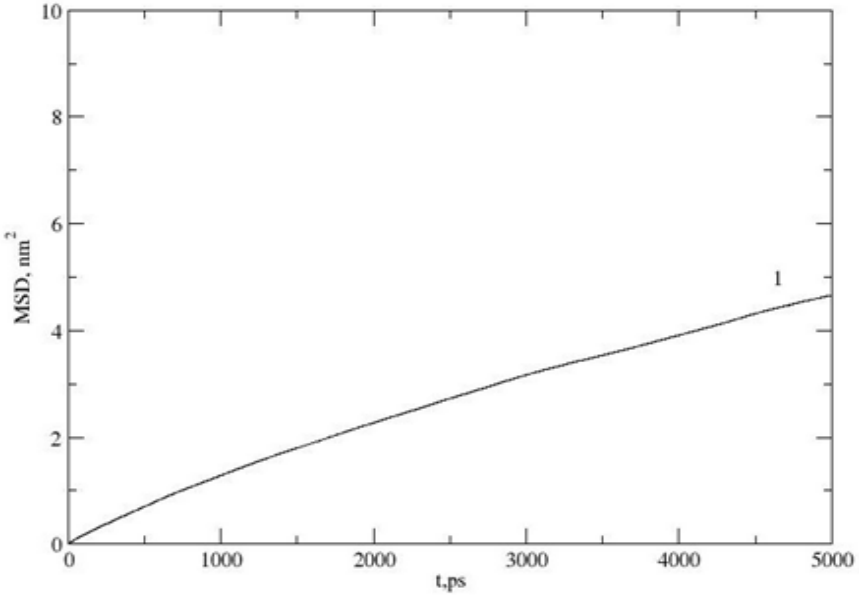

(b)

Fig.8 Mean square displacements (MSD) of the centers of inertia: (a) for complex of dendrimer with 16 Epithalon peptides; (b) for complex of dendrigraft with 16 Epithalon peptides

symmetrical but for second system it has longer tail at high N. In agreement with results of Fig.3 the positions of peaks of P(N) are close to the 18 and 43, correspondingly. Fluctuations in hydrogen bonds number for the first system are in the range of 9-29, while for the second system they are in the range of 30–60.

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 (see Fig. 6). They were calculated using g_rdf function of GROMACS. It is easy to see that atoms of dendrimer (curve 2, Fig.6a) are located mainly in the center of the complex (i/e/ at small distances r from center of the complex). Peptides atoms in the complex with dendrimer (curve 1, Fig. 6a) could be both on the surface of complex and penetrate to its center to some extent. In the case of dendrigraft-peptide complex the atoms of dendrigraft are also mainly in the center of the system (curve 2, Fig. 6b) but in this case there is small local minimum of density of dendrimer atoms at r=0.4nm.

Peptide density in this system has two broad maxima at r close to 0.5 and r near 1.4nm and shallow minimum between them (see curve 1, Fig. 6b) and peptide does not penetrate so close to the center of complex as in the first system.

The other characteristic of interaction between dendrimer and dendrimer-peptides and dendrigraft-peptide complexes is the distribution of ion pair numbers between oppositely charged groups of dendrimer or dendrigraft (NH3+) and peptides COO-, correspondingly. Fig. 7a shows the dependence of ion pairs number distribution as function of distance r between them.

It is clearly seen from Fig.7a and 7b that there are sharp peaks, corresponding to the direct contact between positively charged groups (NH3+) of dendrimer or dendrigraft with negatively charged groups (COO-) of the glutamic acid and asparagine in peptides. The pictures for both systems are very similar but the number of contacts is greater in second system due to greater number of positive charges in the dendrigraft in comparison with the number of positive charges in dendrimer.

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. 8) using g_msd function of GROMACS.

The dependence of mean square displacements (MSD) as function on time in both cases is close to linear in the interval of time equal to several nanoseconds. It means that in this interval the motion of complex is close to diffusion-like motion (see Fig. 8). Coefficients of translational diffusion of the complexes 0.21*10-5 cm2/s and 0.14*10-5 cm2/s were determined from the slope of the time dependences of MSD. The value of diffusion

coefficient in first system is about 1.5 greater than diffusion coefficient of first complex.

V. Conclusion

In this study the processes of complex formation in two systems consisting of lysine dendrimer and 16 Epithalon peptide molecules as well as of lysine dendrigraft and the same16 Epithalon peptide molecules were studied. The equilibrium structures of complexes were also compared. It was shown that dendrimer-peptide complex forms rather quickly (for 10 ns). The equilibrium size of the complexes are rather different due to different charge of dendrimer (+16) and dendrigraft (+48). Radial distribution of density in these systems are rather close to each other. In the first system the peptides could penetrate closer to dendrimer center. In both cases, the strong contacts of positively charged groups of NH3+ groups of dendrimers and carboxyl groups of glutamic acid and asparagine of peptides exist. The diffusion coefficients of dendrimer-peptide complex is greater than the corresponding coefficient of dendrigraft-peptide complex.

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