

Interaction of lysine dendrimer and Semax peptides. Molecular dynamics simulation.

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Abstract: - Interaction between lysine dendrimer and therapeutic Semax peptides was investigated using molecular dynamics method. Dendrimers were used for drug and other molecules delivery to different cells. It was shown earlier that dendrimers and in particular lysine dendrimers could penetrate blood brain barrier. In present paper we study three systems containing such dendrimer and 8, 16 or 24 oppositely charged Semax peptides. It was obtained that lysine dendrimer attracts Semax peptides and forms stable complexes with them. The sizes and structures of these complexes were investigated. These complexes can be used in future for delivery of Semax peptides to brain since these peptides have significant neuroprotective effects.

Key-Words: - lysine dendrimer, Semax peptides, computer simulation, molecular dynamics

1 Introduction

The very first dendrimers were synthesized in the early 80s of the last century [1]. By now a great number of papers about dendrimer synthesis and their behaviour in different physical and chemical conditions *in vitro* and *in vivo* were published. Dendrimers are the macromolecules with regular star-like (“star-burst”) branched structure. Dendrimers usually have shape close to spherical one, constant size and a great number of terminal groups available for functionalization. It makes possible the creation of well-characterized complexes with other compounds. Up to now the most widely studied dendrimers are polyamidoamine (PAMAM) dendrimers. But these and some other dendrimers are quite toxic, so we used the dendrimers on the base of lysine monomer (i.e. on the base of natural amino acid residues).

Today the use of dendrimers in industrial and biomedical applications is very wide. They were used as drug and gene delivery systems, as a branched carrier for multiple antigen peptides (MAPs), as antiviral and antibacterial agents. They are also promising anti-amyloid agents for treatment of neurodegenerative diseases (Alzheimer's, Parkinson's and etc.).

It was shown earlier (see for example [2]) that in some cases dendrimer complexes with some drugs are hundred and thousand times more effective than drugs without dendrimers at the same concentration. Dendrimers also protect drugs from degradation and from contact with healthy cells during delivery process and thus increase stability and reduce toxicity of these drugs. In present simulation we use lysine dendrimers of 3rd generation (see Fig.1).

Therapeutic Semax peptide was selected as a model peptide in our study because it belongs to a class of regulatory peptides and has an antioxidant, antihypoxic and neuroprotective properties. Semax peptide is used for acute ischemic stroke prevention, during traumatic brain injury treatment, recovery of a patients after a stroke, in the case of optic nerve disease and glaucoma optic neuropathy. The drug is used in the form of solution for injection and as a spray. This peptide has molecular weight 863 Da and isoelectric point (pI) 5,13. Peptide and its amino acid sequence are shown on Fig.1.

The use of dendrimers as potential peptide carriers has many advantages. In particular dendrimers could increase the time of their circulation in blood, and could be used for targeted delivery of peptides to specific tissues. They also could improve crossing different biological barriers.

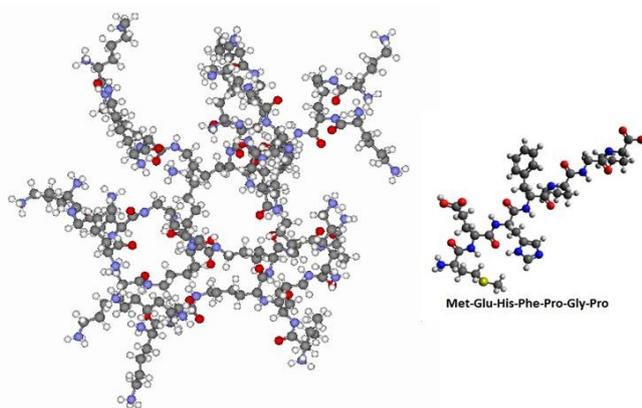


Fig.1. Lysine dendrimer of 3rd generation and one Semax peptide

It is known that electrostatic interaction are very important for the complex formation. In the case of lysine dendrimers and Semax peptides there are electrostatic interaction between multiple positively charged end groups of dendrimer (NH_3^+) and one negatively charged amino acid side group (COO^-) of each peptide. Hydrogen bonds between dendrimer and peptide and hydrophobic interactions between their nonpolar groups are also important.

The goal of this paper is to study the interaction between lysine dendrimer and therapeutic Semax peptides using molecular dynamics method to determine whether the dendrimer could form complex with these peptide molecules and thus could be used for their delivery into cells.

2 Methods and materials

2.1 Molecular dynamics method

Molecular dynamics (MD) method is currently 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. It was used first in the mid-fifties of the last century [3] for two-dimensional modeling of hard disks system (2D-model of a monoatomic gas), and then was used to simulate a variety of liquids, including water [4, 5]. In 1972 this method was first applied to the simulation of a simple model of a linear polymer chain consisting of atoms connected by rigid bonds [6]. In 1974 MD method was applied for simulation of two models of linear macromolecules: consisting of atoms connected by elastic or by rigid bonds [7]. In 1975

the dynamics of short n-alkanes was studied [8]. In subsequent years MD was used for detailed study of many specific molecules using both detailed full-atomic models as well as more general coarse-grained models. The potential energy of these models usually include valence bonds, valence angles and dihedral angle contributions as well as van der Waals and electrostatic energies. The definition of parameters adequately describing the test molecule properties (force-field) is challenging task. It requires analysis of the experimental data for these molecules, quantum chemical calculations as well as iterative procedures and a very large amount of computer time. These calculations can be made only by large groups of specialists. Due to this reason several packages of standard computer programs, in which these parameters are defined for a fairly wide range of molecules become widely used in recent years. Currently the most popular molecular modeling packages are GROMACS, AMBER, CHARMM, and some others. Our simulation was performed by molecular dynamics method using the GROMACS 4.5.6 software package [9] and one of the most modern AMBER_99SB-ildn force fields [10].

2.2 Model and calculation method

Simulation was performed using the molecular dynamics method for systems consisting of one lysine dendrimer of third generation with positively charged NH_3^+ end groups and 8, 16 or 24 Semax peptides (with charge -1 each). This molecules were placed in water box (cubic cell 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). For peptides the initial conformation with internal rotation angles of $\varphi = -135^\circ$, $\psi = 135^\circ$, $\theta = 180^\circ$ was prepared using Avogadro molecular editor. The structures of peptides were first optimized in vacuum using molecular mechanics and AMBER force field. Further energy minimization and simulations of whole system was performed using the GROMACS 4.5.6 software package and AMBER_99SB-ildn force fields. The potential energy of this force field consists of valence bonds and angles deformation energy, internal rotation angles, van der Waals and electrostatic interactions. The procedure of molecular dynamics simulation used both for lysine dendrimers and for polyelectrolytes has been described earlier in [11-23]. In all calculations the normal conditions (temperature 300 K, pressure 1 ATM) were used. Computing resources on

supercomputers “Lomonosov” were provided by supercomputer center of Moscow State University [24].

3 Results and discussion

We made snapshots of a system consisting of dendrimers, peptides, ions and water during simulation with equal time intervals. Some of them are shown on Fig. 2 (water molecules are not shown for clarity). It is clear seen that at the beginning of the process (Fig. 2, a, d, h) all peptide molecules are far from dendrimer. After 20 ns (Fig. 2, b, e, i) some part of peptide molecules are already adsorbed on the surface of dendrimer, and in the end (Fig. 2, c, f, j) all peptide molecules in all three systems are on its surface.

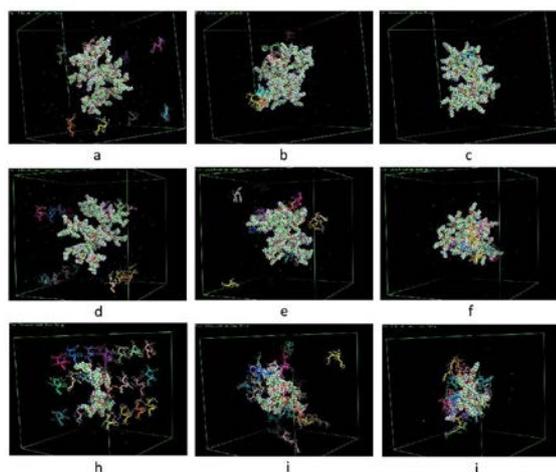


Fig. 2. Stages of the dendrimer and Semax peptides complex formation (initial, intermediate and final): system of dendrimer and 8 peptides: t = 0 (a); t = 20 ns (b); t = 160 ns (c); system of dendrimer and 16 peptides: t = 0 (d); t = 20 ns; (e); t = 160 ns (f); system of dendrimer and 24 peptides: t = 0 (h); t = 20 ns; (i); t = 160 ns (j).

Atoms of dendrimer molecule are shown as beads with diameter equal to their van der Waals radii. Valence bonds inside peptides are shown with thin lines. Backbones of different peptides are shown by thick lines of different colours).

To characterize the size of the systems instant Rg^2 and mean square radius of gyration $\langle Rg^2 \rangle$ were used (where $\langle \rangle$ mean time averaging). $\langle Rg^2 \rangle$ was calculated using (1):

$$\langle R_g^2 \rangle = \frac{1}{M} \times \left\langle \left[\sum_{i=1}^N m_i \times |r_i - R|^2 \right] \right\rangle \quad (1)$$

where R – is the center mass of dendrimer, r_i и m_i

coordinates and masses of i atom correspondingly, N – is the total number of atoms in dendrimer, M is the total mass of dendrimer. $\langle \rangle$ means time averaging of the instantaneous radius of gyration during equilibrium part of MD trajectory. This function was calculated using g_gyrate function of GROMACS.

3.1 Modelling equilibrium process establishment

The time dependence of gyration radius R_g at the beginning of calculation describes the process of equilibrium establishment during complex formation (Fig. 3). It can be seen that dendrimer complex with 8 peptides forms within 30 ns. In case of system with 16 peptides, complex forms for the first time nearly for 30 ns but at 40 ns (see local peak of R_g on curve 2 of fig.3) some peptide molecules were detached (we checked it using snapshots; not shown) from dendrimer and finally it takes almost twice to get stable complex in second system. In case of system with 24 peptides, complex forms also within 40 ns. After that, the complex sizes R_g fluctuate slightly, but their average values practically do not change with time. Therefore, we can assume that the systems are in equilibrium state.

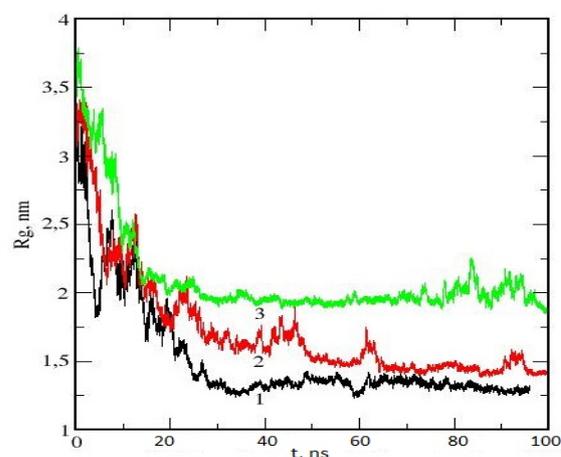


Fig. 3. Time dependence of gyration radius. System of dendrimer G3 and: 8 Semax peptides (1); 16 Semax peptides (2); 24 Semax peptides (3)

Another quantity that can characterize the rate of complex formation is the total number of hydrogen bonds (N) between dendrimers and peptides. The dependence of this value on time is shown on Fig.4 and it demonstrates how the number of specific contacts between them increases during complex formation. This function was calculated using

g_hbonds function of GROMACS.

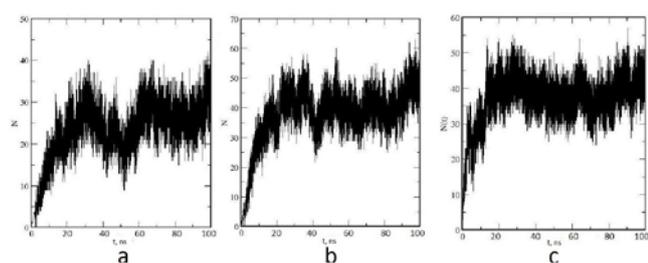


Fig. 4. Time dependence of hydrogen bonds number (N) during the complex formation: G3 and 8 Semax (a), G3 and 16 Semax (b), G3 and 24 Semax (c)

From Fig. 4 it can be concluded that the first system (Fig. 4, a) reaches equilibrium (plateau) after 30 ns. The second and the third systems (Fig. 4, b, c) reach equilibrium later. It correlates with the results of the inertia radii balance obtained in Fig. 3.

3.2 Modelling of the equilibrium state

In equilibrium state the size of the first complex (G3 and 8 Semax peptides) is larger than the size of dendrimer, and the size of the complex G3 and 16 Semax is slightly larger than the size of the first one (see Tab. 1). The size of the complex G3 and 24 Semax is also larger than the size of the previous ones. It is quite natural, since it correlates with the molecular weight of the complexes increase compared to the molecular weight of the individual dendrimer. The shape of both complexes can be characterized by their tensor of inertia main component ratio (R_g^{11} , R_g^{22} , R_g^{33}), that are in Tab. 1. For example, in the simplest case, anisotropy can be characterized by R_g^{33} / R_g^{11} .

Table 1. R_g^{11} , R_g^{22} , R_g^{33} , R_g of tensor of inertia in dendrimer and three complexes

System	R_g^{11} (nm)	R_g^{22} (nm)	R_g^{33} (nm)	R_g (nm)
G3Dendrimer (G3)	0.98	1.224	1.316	1.444
G3& 8Semax	1.044	1.308	1.452	1.581
G3&16Semax	1.236	1.340	1.512	1.663
G3&24 Semax	1.304	1.656	1.780	1.944

The shape of complex could be roughly

characterised by ratio of largest and smallest components of inertia tensor describing our system R_g^{33}/R_g^{11} . Calculated values of these anisotropy for our systems are presented in Tab. 2. The molecular weight dependences of the anisotropy for systems are not monotonous. The largest component of inertia tensor R_g^{33} of complex with 16 peptides is 1.04 times larger than this component in complex with 8 peptides and is 1.18 times smaller than in complex with 24 peptides. At the same time, the smallest component R_g^{11} of the complex with 16 peptides is just 1.18 times larger than that component in complexes with 8 peptides and in 1.05 times smaller than in complex with 24 peptides.

Table 2. The values of anisotropy of shape R_g^{33}/R_g^{11} for dendrimer and for its two complexes with peptides

System	G3
Dendrimer	1.34
Dendrimer +8 Semax	1.39
Dendrimer +16 Semax	1.22
Dendrimer +24 Semax	1.36

The distribution function $p(R_g)$ of gyration radius R_g gives more detailed information about the variation of R_g of dendrimers-peptides complexes and the amplitude of their fluctuations. These functions are shown in Fig. 5. From the curves it is clear that peptides in the second complex with 16 peptides are on larger distance from center of inertia of dendrimer than in complex with 8 peptides. The same result is in case of complex with 24 peptides. Also, the distribution of R_g in complexes with 16 and 24 peptides have "tail" of function which means that fluctuations of complex size in systems is greater and peptides are probably adsorbed on dendrimer not so strong as in the first system with 8 peptides.

Information about the internal structure of the equilibrium complex could be obtained using radial density distribution of different groups of atoms relatively center of inertia of system.

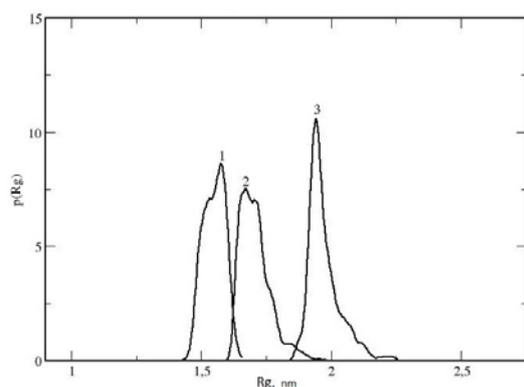


Fig. 5. Distribution function $p(R_g)$ of gyration radius R_g : complex G3 and 8 Semax (1); complex G3 and 16 Semax (2); complex G3 and 24 Semax (3)

$$p(r) = \frac{m_{\text{комп}}(r)}{V_{\text{комп}}(r)} \quad (2)$$

where m_{comp} – mass of all atoms in complexes; $V_{\text{комп}}$ – volume of complexes.

These radial distribution functions (not normalized) are shown on Fig. 6. They were calculated using g_rdf function of GROMACS.

Fig. 6 demonstrates that dendrimer (curve 1, Fig. 6) is located in the center of the complexes and peptides (curve 2, Fig. 6) mainly on the surface of complex in all systems with 8, 16 and 24 peptides. At the same time, some fraction of peptides could slightly penetrate into dendrimer but this penetration decrease with increase of number of peptides in system (see Fig. 6).

The number of hydrogen bonds between peptides and dendrimers per one peptide shows how tightly peptides associate with dendrimers. From Fig. 4 it follows that average hydrogen bonds number in equilibrium state ($t > 30$ ns) for G3 + 8 Semax complex is close to 23, for G3 and 16 Semax ($t > 40$ ns) to approximately 39 and for G3 and 24 Semax ($t > 40$ ns) is about 60. The ratio of number N of H-bonds in first and second systems is 1.7 and in second and third system is 1.5. Because ratio is less than 2 and decrease, it can be concluded, that peptides in second systems (with 16 peptides) are associated with dendrimer by H-bonds not so strong as in first system (with 8 peptides) and in third systems less strong than in second one.

The distribution function of hydrogen bonds number (Fig. 7) shows how the number of hydrogen bonds in the equilibrium state can fluctuate relative to the average value. We obtained that the resulting function for both complexes has a peak of numbers of bonds that are close to the average (23, 39 and 40) and are quite symmetrical. Fluctuations in

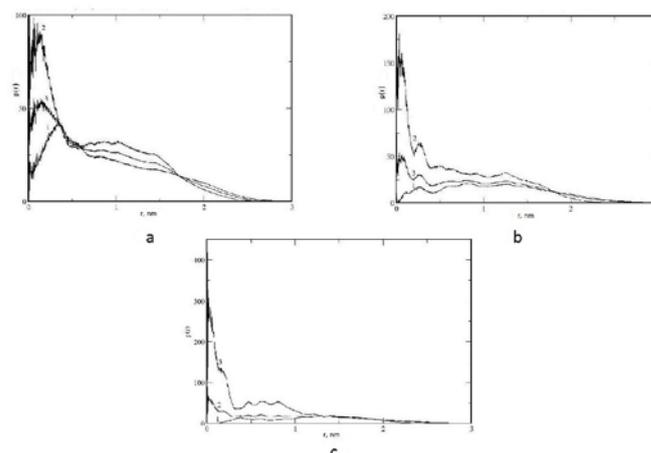


Fig. 6. Radial distribution $p(r)$ curves: dendrimer G3 and 8 Semax (a), dendrimer G3 and 16 Semax (b), dendrimer G3 and 24 Semax (c). Distribution curves: peptide atoms (1); dendrimer atoms (2); all atoms of complex (3)

hydrogen bonds number for the first system are in the range of 15-33, for the second system in the range of 27-49 and for the third system in the range of 27-53. The increase of fluctuations of number of H-bonds with number of peptides in the complex is also support the conclusion that the association of peptide with dendrimer due to H-bonds is the strongest in the first system and the weakest in the third system.

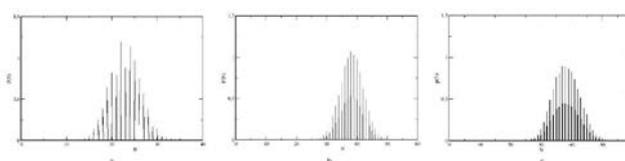


Fig. 7. The distribution function $P(N)$ of hydrogen bonds number N of complexes: complex G3 and 8 Semax (a); complex G3 and 16 Semax (b); complex G3 and 24 Semax (c).

The other characteristic of interaction between dendrimer and peptides in complex is the distribution of ion pair number between their oppositely charged groups. Fig. 8 shows the dependence of ion pairs number on the distance between dendrimer and peptides in all complexes. It is seen that in our complexes there is a sharp peak, corresponding to the direct contact between positively charged groups (NH_3^+) of dendrimer and negatively charged groups (COO^-) of the glutamic acid in peptides. In case of complex of G3 with 8 peptides (curve 1) the peak was approximately 1.8 times larger than the peak of G3 with 16 peptides

(curve 2) and 1.3 times larger than the peak of G3 with 24 peptides (curve 3). It confirms our earlier results about more strong contact of peptides and dendrimer in first system with 8 peptides.

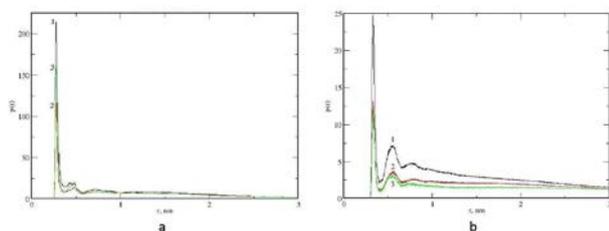


Fig. 8. Function of ion pairs radial distribution: a – NH_3^+ groups of dendrimer and COO^- groups of peptides, b - NH_3^+ groups of dendrimer and Cl^- ions
. 1 - G3+8Semax, 2 - G3+16Semax, 3 – G3+24Semax.

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 were calculated (Fig. 9). MSD was calculated using `g_msd` function of GROMACS.

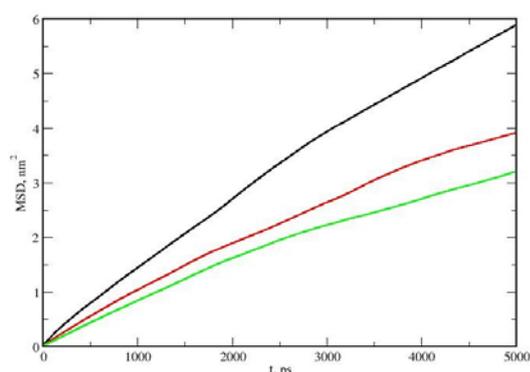


Fig. 9. Mean square displacements of the centers of inertia: complex of G3 and 8 Semax (1); complex of G3 and 16 Semax (2); complex of G3 and 24 Semax (3)

We have found that the dependence of MSD function on time is almost linear in some interval of time t in double logarithm coordinates (not shown) and its slope is close to 1. It means that in this interval the motion of complex is the diffusion-like motion (see Fig.9). Coefficients of translational diffusion of the complexes were determined from the slope of the time dependences of MSD for all three systems (Tab. 3).

It was obtained that translational diffusion coefficient of the first complex with a dendrimer and 16 peptides is approximately 1.54 times larger

than that of the complex with 16 peptides.

Table 3. Diffusion coefficients for dendrimer-peptide complexes

System	$D \times 10^5 \text{ (sm}^2\text{/s)}$
G3 and 8 Semax	0.17 ± 0.02
G3 and 16 Semax	0.12 ± 0.05
G3 and 24 Semax	0.10 ± 0.03

It means that hydrodynamic radii of second complex should be 1.4 times greater than of first complex/. Since the ratio of inertia radii R_g of the second complex (1.66 nm^2) and first complex (1.58 nm^2) is close to 1.05, the additional differences can be explained by the fact that the anisotropy of shape of second complex is larger, or that a larger number of water molecules are attached to the surface of second complex. As the anisotropy of shape of two complexes differ only slightly, we can choose only our second guess. To check it, we calculated number of hydrogen bonds between molecules, that form our complexes, and water. For the first complex the number of such hydrogen bonds was equal to 275, for the second it is equal 415 and for third it is equal 561. The ratio of these values for 1 and first system is near 1.5, which is close to value 1.4 for ratio of hydrodynamic radii. So the greater difference in hydrodynamic radii than for inertia radii for first and second complexes can be explained at least partly by greater number of water molecules associated with second complex. The ratio of hydrodynamic radii for second and third complexes is also greater than ratio of their inertia radii but this ratio (1.2) is less than between 1 and 2 systems. This result is in agreement with smaller ratio of hydrogen bond numbers in third and second complexes in comparison with that for first and second systems.

4 Conclusion

The process of complex formation by lysine dendrimer and therapeutic Semax peptides and the equilibrium structure of complex were investigated by the method of molecular dynamics simulation. Three systems consisting of third generation dendrimer with 8, 16 and 24 Semax molecules in water were studied. It was shown that dendrimer-peptide complexes formation occurs rather quickly (30–40 ns). The equilibrium size (radius of gyration) were rather close to each other. At the same time,

the hydrodynamic radius of the complex with 16 peptides was about 1.4 times larger than with 8 peptides. This difference in hydrodynamic radii can be explained by the difference in the number of water molecules "associated" with complexes. The radial distribution function of atom number in all complexes shows that dendrimer was mainly inside the complex, while the peptides are mainly on its surface. The number of hydrogen bonds and ion pairs per peptide molecule in complexes with 16 and 24 peptides was smaller than in complex with 8 peptides. It means that dendrimer and peptides contacts are less strong in last two complexes.

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