Computer Simulation of Complexation of GluAsp Peptide Molecules and Lysine-Based Dendrimer with ArgHis Spacers

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Abstract: - Lysine-based dendrimers of the second generation containing alanine, glycine, lysine, arginine, and leucine spacers (2Ala, 2Gly, 2Lys, 2Arg, and 2Leu), as well as double histidine (2His) spacers inserted between their branching points, have been studied earlier. This study examined the complexes formed by bioactive GluAsp peptide and dendrimer that contain an arginine-histidine (ArgHis) spacer. The main difference from previous studies is that amino acid residues (Arg and His) in the dendrimer spacers are not the same. We conducted molecular simulations to study the interactions of 16 GluAsp molecules and a single dendrimer with neutral histidines (His) and with fully charged histidines (Hisp) in an aqueous solution containing explicit counterions. We have shown that the complex of the dendrimer with protonated Hisp residues in spacers contains a larger number of GluAsp molecules, which penetrate deeper into the center of this dendrimer than in the same dendrimer with neutral His.

Key-Words: – Stimuli-responsive molecules, histidine-containing lysine dendrimers, oligopeptides, complexes, computer simulation, molecular dynamics.

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1 Introduction

Dendrimers are macromolecules, [1], grown from a single core, [2], and consisting of AB_2, AB_3, or AB_4 fork-like repeating units. These distinctive structural features have enabled dendrimers to be applied broadly in both industrial, [3], and many other, [4], contexts. In particular, dendrimers can serve as nanocontainers for drug delivery, including targeted approaches, [5], [6]. The potential of dendrimers for gene delivery, [7], [8], [9], and for drug and gene delivery, [10], has been demonstrated also. Early peptide dendrimers were composed solely of lysine monomers, [11], [12]. Experimental investigations of lysine dendrimers included measurements of their size as a function of generation number, with data reported for generations (G) equal 1–10 (G1–10) in dimethylformamide, [12], and for G1–5, [13], G1–3, [14], and G1–6, [15], in aqueous solutions. General description of synthesis, modification, properties and applications of lysine dendrimers are described, [16], [17], [18], [19]. More complex peptide dendrimers, containing terminal peptide tails, were introduced in 1988 as multiple antigen peptides (MAPs), [20]. Later, dendrimers bearing 24-residue peptides at their ends were synthesized, [21]. Variants in which an additional amino acid was incorporated as a spacer between branching points were also reported, including G1–5, [13], [14], and G2, [22]. Beyond these, dendrimers functionalized at the periphery with single amino acid residues have been investigated: for example, arginine-functionalized peptide dendrimers of generations 5 and 6, [23]. PAMAM dendrimers of generations 4 terminated with lysine or arginine, [24], and polyethyleneimine

dendrimers carrying leucine, lysine, or arginine, [25]. PAMAM dendrimers of generation 4 (G4) bearing terminal histidine or arginine were analyzed in [26]. Polyglycerol amine dendrimers with terminal histidine or arginine were studied also, [27].

Lysine dendrimers with lysine, arginine, or histidine terminal groups were described in [28]. A review of peptide dendrimers with various amino acid residues in terminal groups was done in [29]. Dendrimers with various amino acids in internal spacers were described for generations G5 in [13], G2 in [22].

Subsequently, peptide dendrimers containing internal spacers made of amino acid residues were obtained and characterized. Examples include dendrimers bearing internal double glycine, double lysine, [30], double histidine spacers, [31]. The same types of dendrimers with glycine/lysine, and histidine spacers containing protonated or non-protonated imidazole, were investigated using the molecular dynamics simulations and by NMR methods. Similar dendrimers containing stimuli-responsive spacers of two different amino acid residues with high charge, for example, arginine-histidine (RH) could be prepared also. The first residue is positively charged at all biological pH values, whereas the second is neutral at normal pH and becomes protonated under acidic conditions. In the present paper, we studied the complex formation between this dendrimer and bioactive dipeptide molecules composed of glutamic and aspartic acid (ED), using MD simulations at two different pH values.

2 Model and Method

Full-atomic model of lysine-arginine-histidine (LysArgHis, KRH) peptide dendrimer, interacting with 16 glutamic-aspartic acid (GluAsp, ED) dipeptide molecules was studied in cubic water box with periodic boundary condition. Molecular dynamics (MD) simulation method was used. GROMACS2023 program with Amber99sb-ildn potentials and the TIP3P water model was employed, [32].

Subsequent equilibration of the system was performed after filling the simulation cell with water and counterions in several stages. In the first stage, the energy of the entire system, including water and counterions, was minimized. In the next stage, a short molecular dynamics simulation was performed with a small simulation step, starting from 0.0001 ps. Then, the simulation step was gradually increased and brought to the standard simulation step of 0.002 ps. At this preliminary stage, additional constraints were imposed on the mobility of heavy atoms to prevent the destruction of the native structure of the peptides due to possible overlaps of atoms of neighboring molecules at the initial stage of the simulation and also to prevent the emergence of long-lived metastable cis-states of internal rotation angles in the peptide chains under the action of large forces arising for the same reasons.

The NVT ensemble was applied for short initial equilibration of systems, and the NPT ensemble was used for main simulations during 500 ns. Simulations were carried out at two different pH levels: at neutral pH, when all histidines of the KRH dendrimer were uncharged (H), and at lower pH, when all histidines of the KRHp dendrimer were protonated (Hp). For the analysis of MD trajectories, we applied functions, algorithms, and programs previously developed for studying the properties of linear, [33], [34], and branched [35], [36], [37], [38], [39], [40], [41], systems.

3 Results and Discussion

To investigate complex formation, we first analyzed the time dependences of instantaneous characteristics of the complexes: the distance (d) between DE molecules and dendrimer, the size (Rg) of complex, the number of hydrogen bonds (n_{HB}) between DE molecules and dendrimer, as well as the number of DE molecules (n) in the complex.

At the start of the MD calculations, the distance between each ED dipeptide and dendrimer is large (it is close 4 nm) since the dendrimer initially was in the center of cell, while all ED peptide molecules were positioned near its edges. Evolution of distance d between the dendrimer and DE molecules was calculated (Figure 1). It was obtained that distance d quickly drops for the initial 20-60 ns of the MD calculations and become almost constant after that. This behavior reflects the formation of a stable complex in which d fluctuates but its average value remains essentially constant after the initial drop.

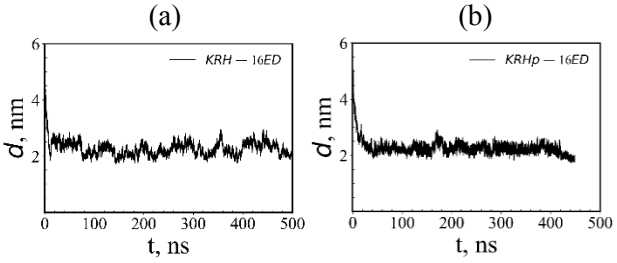

Fig. 1: Evolution o пf the dendrimer-peptide distances d(t) for: (a) KRH with all His residues (H) in the dendrimer spacers are neutral, (b) KRHP with all Hisp in the dendrimer spacers are protonated (Hp)

Source: created by the authors

To verify complexation of DE molecules with dendrimers, we examined also the radius of gyration (*Rg*) of the subsystem consisting the dipeptide molecules with dendrimer KRH (with uncharged histidines) (Figure 2a) or KRHp (with protonated histidines) (Figure 2b). The larger initial size of the second system arises from the bigger volume of the KRHp dendrimer, caused by coulombic repulsion among protonated histidines within its branches.

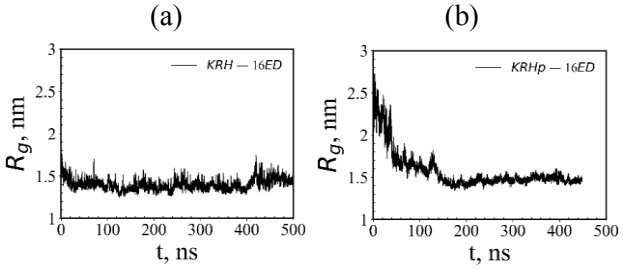

Fig. 2: Evolution of *Rg* of complex of the ED molecules with dendrimer for: (a) KRH with all His residues (H) in the dendrimer spacers are neutral, (b) KRHp with all Hisp in the dendrimer spacers are protonated (Hp).
Source: created by the authors

Another measure of dendrimer-dipeptide complexation formation is the number of hydrogen bonds formed between them (Figure 3). Before any peptide–dendrimer contact, this value is zero. It rises during the first 30-50 ns of the MD run. As the simulation proceeds to longer times, the number of hydrogen bonds stabilizes, giving an average of about 60 for the dendrimer with neutral histidines (Figure 3a) and about 75 for the dendrimer with charged histidines (Figure 3b). These values suggest that protonation of histidines promotes the association of a greater number of GluAsp molecules with the dendrimer.

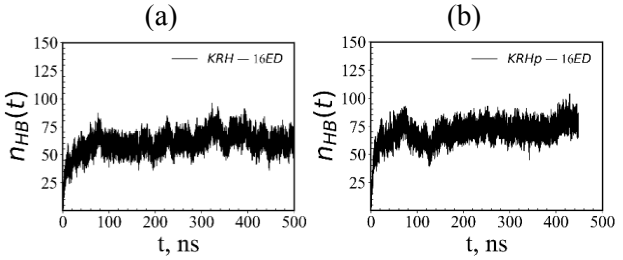

Fig. 3: Evolution of the number of hydrogen bonds n_{HB}(t) between ED dipeptides and the dendrimer for: (a) KRH with all His residues (H) in the dendrimer spacers are neutral, (b) KRHp with all Hisp in the dendrimer spacers are protonated (Hp).
Source: created by the authors

Evolution of the number of dipeptides *n(t)* in the dendrimer-peptide complex is shown in Figure 4. At the beginning of the trajectory, no peptides are included in the complex. During the first ~20 ns their number increases rapidly, after which the values fluctuate around nearly constant levels. Averaging through equilibrated part of the trajectory gives average (through last 250ns) values of $n \approx 13$–14 DE molecules for the KRH dendrimer with neutral histidines (Figure 4a) and $n \approx 15$–16 for KRHp dendrimer with protonated histidines (Figure 4b).

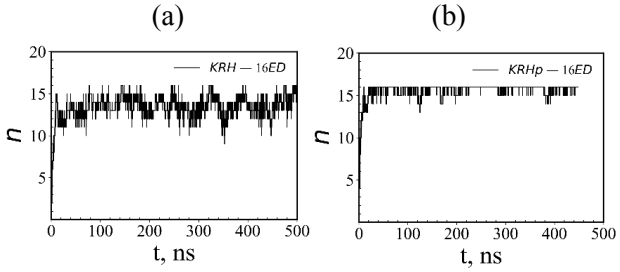

Fig. 4: Evolution of the number of ED molecules *n* in the complex vs time t for: (a) KRH when all His residues (H) in the dendrimer spacers are neutral, (b) KRHp when all Hisp in the dendrimer spacers are protonated (Hp).
Source: created by the authors

The results presented in Figure 1, Figure 2, Figure 3, and Figure 4 on complex formation are illustrated by snapshots of systems consisting of a dendrimer with uncharged side inserts (Figure 5a, b) or charged side inserts (Figure 5c, d), each interacting with 16 ED peptides at both the beginning and at the end of the trajectory. The images show that the dendrimer with neutral histidines accommodates only about 14 of the 16 dipeptides, whereas the dendrimer with protonated histidines incorporates all 16.

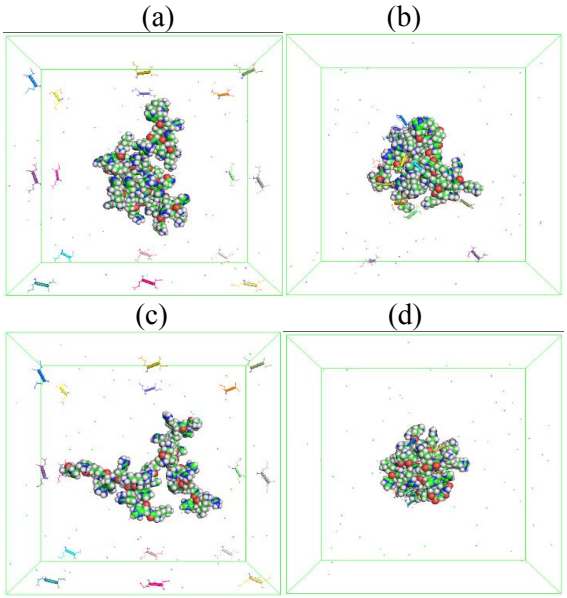

Fig. 5: Positions of 16 ED molecules and dendrimer: KRH (a, b) or dendrimer KRHp (c, d). Positions a)

and c) are at the initial time moment (t = 0). Positions b) and d) are at the end of calculations (at time moment t=500 ns). Atoms of dendrimers are shown by spheres, and ED molecules by sticks.
Source: created by the authors

After all the characteristics of both complexes stabilize (within the first 250 ns), their equilibrium values can be obtained by averaging through the last 250 ns of the 500 ns trajectory.

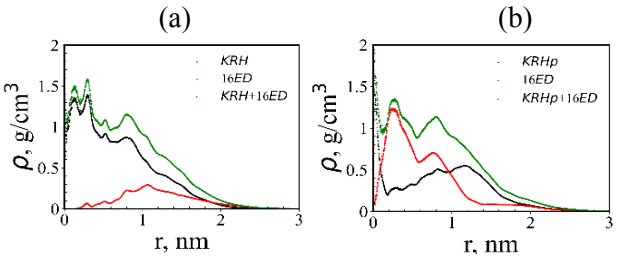

Fig. 6: Equilibrium radial distribution function ρ (radial density profile r) of atoms of KRH/KRHp dendrimer (black), atoms of ED peptide (red) and all atoms of complex (green) relative to the dendrimer center (r=0) for: (a) KRH with all His residues (H) in the dendrimer spacers are neutral, (b) KRHp with all Hisp in the dendrimer spacers are protonated (Hp).
Source: created by the authors

The key equilibrium characteristic describing the distribution of atoms of dendrimer, ED molecules, and the complex with respect to the dendrimer center is the radial distribution of density ρ. In the case of the complex of KRH dendrimer with neutral His (Figure 6a, black curve), the density ρ of dendrimer atoms peaks at the very center (near r ≈ 0). It reflects the presence of a compact dendrimer core and a linear decrease of ρ the dendrimer with r. Consequently, DE molecules cannot penetrate into the central region, and density ρ (red curve) of their atoms has broad peak at r ≈ 1.1 nm. The total ρ of the complex (green curve) corresponds to the sum of the contributions of the dendrimer and DE dipeptide atoms. For the KRHp dendrimer containing protonated histidines (Hp) (Figure 6b, black curve), the density ρ in the core region is markedly reduced and extends to a higher and broader range of radial distances r. It occurs due to additional coulombic repulsion among the protonated Hisp (Hp) residues. At the same time, the negatively charged Glu and Asp residues of the ED dipeptide molecules are attracted to these additional positive charges of Hisp, which promotes penetration of ED molecules into dendrimer and closer association with it. As a result, ρ the ED dipeptide atoms (red curve) exhibit a pronounced peak near the core (at r ≈ 0.1-0.3nm). The atoms of the KRHp dendrimer (black curves) in the complex are partially expelled from the center by the atoms of the ED molecules. It leads to a decrease in the density ρ of dendrimer atoms between r=0 and r=1.0 nm, minimum of ρ of dendrimer atoms at r ≈ 0.2 and a shift in the position of the maximum of ρ (r) to approximately r ≈ 1.2 nm.

Table 1. Mean values of the characteristics of the complexes: the distance between each ED molecules and dendrimer <*d*>, the hydrogen bonds number between them <n_{HB}>, the number of ED molecules in the complexes <*n*>, and the size <*Rg*> of the complex

System	<*d*>	<n_{HB}>	<*n*>	<*Rg*>
KRH+16ED	2.28	64	13.6	1.41
KRHp+16ED	2.18	74	15.9	1.48

Source: created by the authors

In Table 1 we summarize the average structural characteristics of the studied systems: the mean distance between ED oligopeptide molecules and dendrimer, the number of hydrogen bonds between them, the overall size of the complexes, and the number of ED molecules in it. These average values are consistent with the trends observed in Figure 1, Figure 2, Figure 3 and Figure 4. The average value of distance between dendrimer and peptides is smaller for complex with more charged KRHp dendrimer due to stronger electrostatic interactions with oppositely charged oligopeptide molecules. The average values of <n_{HB}>, <*n*> and <*Rg*> are higher for the complex with KRHp dendrimer for the same reason.

4 Conclusion

In this work, MD calculations were applied to understand the difference in interactions of ED dipeptide molecules with a second-generation lysine dendrimer at two different pH. that incorporates heterogeneous, stimuli-responsive arginine-histidine (RH) spacers. The simulations showed that protonated histidines promote the formation of complexes containing a larger number of ED molecules, which penetrate deeper into KRHp dendrimer in comparison with KRH dendrimer.
Looking ahead, we plan to extend this work by synthesizing, experimentally characterizing their interactionswith amyloid peptides, and with other bioactive molecules.

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Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

Sofia Mikhtaniuk, Alexey Vakulyuk and Alina Zaitseva prepared initial conformations, carried out the energy minimization/MD simulation, calculated characteristics of molecules and complexes and prepared graphics and tables. Emil Fatullaev organized and verified data of long-term computer simulation. Sofia Mikhtaniuk, Igor Neelov and Oleg Shavykin formulated the goal and plan of MD simulations, discussed and finalized the scientific results.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.