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REVIEW PAPER

PAMAM dendrimer-based macromolecules and their potential applications: recent advances in theoretical studies

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Abstract

The dendrimer has a high degree of geometric symmetry, a precise and controllable molecular size, a large number of surface-active functional groups, a rich cavity inside the molecule, and a controlled molecular chain growth. The unique structural properties of the above-mentioned macromolecules have made it a research hot spot in many fields. Molecular simulation technology, as a new scientific research method, plays an important role in the basic theory and applied research of dendrimers. This paper reviews the basic progress of molecular simulation technology in the field of dendrimers in recent years, including the application of dendrimers in medicine, DNA, pharmaceutical carriers, proteins, amino acids, and so on.

Keywords Macromolecule · Dendrimer · PAMAM · Molecular dynamics simulation

Introduction

The important member in the macromolecular system is dendrimers. Dendrimer is firstly reported in 1978 by Vögtel et al. by applying Michael addition and reduction approaches [1]. They succeeded to synthesize a branched tripropylamine-based macromolecule by utilizing a primary amine and acrylonitrile to give a dinitrile, which called it a cascade molecule. Following this achievement, Tomalia et al. synthesized branched polyamide-amine (PAMAM) for the first time in 1985 [2]. Accordingly,

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the word of dendrimer as a specific member of macromolecule has become popular in scientific researches since the 1990s. In this regard, Tomalia and Fréchet wrote an interesting review article about the historical perspective concerning the discovery of dendrimers [3]. The features of a dendrimer are an exact molecular structure, a precise molecular weight, and monodispersity with repeated and regular branch [4]. Contrary to linear polymers, dendrimers illustrate a unique class of synthetic polymers, highly rigid and strongly branched molecules which can be synthesized from a branch point or central segment [5].

In general, a dendrimer consists of three distinct segments: a core, scaffold, and surface structure. The core is placed in the center of the molecule and attached with a given number of branches which are called dendrons. Each dendron is composed of the scaffold (number of branching points) and surface groups. The number of branches characterizes the generation and the scale of a dendrimer, i.e., the number of branch points, the functionality, and the length of the spacer. It should be noted that the physical and chemical properties of the dendrimer are determined by the nature of functional groups, which extend to the surroundings [6].

Some of the important structural features of dendrimers are: abundant surface functional groups, various types of functionalized, precise molecular arrangements, precise nanoscale structure, highly geometric symmetry, and homologous series of cavity size. Therefore, they have many performance characteristics such as: solubility, hydrodynamic performance, unique viscosity behavior, and versatility [7]. Various potential applications of dendrimers, including biological [8], biomedical [9], detection therapeutic, diagnostic, and detection [10] for cancer treatment [11], pharmaceutical, nanocarriers, and drug delivery [12], tissue engineering [13], brain delivery and cancer therapy [14], sensing [15], catalysis [16], molecular electronics [17], photonics [18], nanomedicine [19], magnetic resonance imaging [20], gene delivery [21], optoelectronic applications [22], dendrimer liquid membranes for gas separation [23], and so on [24, 25], have been proposed because of their unique nanostructures and excellent physical properties.

Synthesis of dendrimers

There are two major routes to synthesize dendrimers consisting divergent and convergent. The divergent methodology was first introduced independently by Newkome et al. [26] and Tomalia et al. [2]. Divergent method is summarized in four steps as below: Firstly, a reaction starts with a core, and this core must have some features such as have reactive groups and a small functional molecule. Secondly, this core reacts with some blocks with some characterizations such as having a well-designed building and having some functional groups which are able to transform into a new reactive point to form the first-generation dendrimer (G1). This procedure is well known as dendritic growth. Thirdly, the G1 dendrimer will expose the reactive points on its surface, and G2 could be made after the second-stage dendritic growth. Finally, by repeating activation and growth process, higher-generation dendrimers could be achieved [27].

On the other hand, the synthesis dendrimers from divergent method suffer from some important issues such as time-consuming and steric-shielding effects. It should be noted that both of these limitations have a strong effect for synthesis of a big dendrimer. Besides the mentioned problems, if the final functional groups react with the interior of the dendrimer, it is unable to react with the building blocks. This procedure is known as dense-core theory and is common in the flexible dendrimers. After each generation growth, surface space for each active point is reduced, leading to a defect in the structure and unreacted active when making higher-generation dendrimers. This procedure is called a dense-shell concept and is common in the rigid dendrimers [28]. It should be noted that according to the flexibility of the backbones of dendrimers, they are divided into flexible and rigid dendrimers.

On the other hand, the convergence methodology was reported by Hawker and Fréchet in 1990 while they synthesized the poly (aryl ether) dendrimers [29]. This applies a reverse growth process as compared with the divergent one. Convergence approach starts from the building block and reacts with a focal-activated building block to form a dendron inward toward to the core to give birth to the dendrimer [30].

Dendrimers are designed into a given category base on the diverse functional groups, types of functionalized, and architecture of dendrimers. The important categories of dendrimers are: (1) carbon- or oxygen-based dendrimers such as polyether, polyester, and glycodendrimers [31], (2) chiral dendrimers including chirality base on the core and chirality base on the branching unit [32], (3) metallodendrimer such as poly (propylene imine) pyridyl imine palladium [33] and poly (bis (imino) pyridyl) iron(II) [34], (4) peptide dendrimers which consists of a peptidyl branching core or covalently attached surface functional points such as multiple antigen peptide (MAP) [35], (5) phosphorus dendrimers [36], (6) porphyrin dendrimers [37], (7) silicon dendrimers including silane, carbosilane, siloxane, and carbosiloxane [38], (8) triazine dendrimers [39], (9) hybrid dendrimers [40], (10) PAMAM dendrimers [41], (11) polyamidoamine organosilicon (PAMANOS) dendrimers [42], (12) poly propylene imine (PPI) dendrimers [43], and (13) polylysine (PLL) dendrimers [44].

Characterization of dendrimers

A wide range of analytical techniques has been proposed for characterization of dendrimers according to the various applications of dendrimers. Much scientific research is focused on developing and improving on techniques for characterization of dendrimers. These techniques define the feature, property, and structure of dendrimers, such as optical activity, structural properties, thermodynamic properties, chemical composition, molecular mass, surface structure, size, shape, morphology, and homogeneity of dendrimers. Table 1 illustrates the summary of the technique for characterization of dendrimers.

Table 1 Characterization of dendrimers

Method	Purpose	References
UV–Vis spectroscopy	Degree of protonation	[45]
Capillary zone electrophoresis	Dendrimer charge and hydrodynamic radius	[46]
Circular dichroism	Optical activity	[47]
Electron paramagnetic resonance	Surface structure	[48]
Differential scanning calorimetry	Thermodynamic properties	[49]
X-ray diffraction	Structural properties	[50]
X-ray photoelectron spectroscopy	Chemical composition	[51]
Small angle neutron scattering	Molecular characterization	[52]
Laser light scattering	Internal structure	[53]
Electrospray ionization mass spectrometry	Molecular mass	[54]
Atom bombardment mass spectrometry	Molecular mass	[55]
Matrix-assisted laser desorption ionization mass spectrometry	Molecular mass	[56]
Size exclusion chromatography	Molecular weight	[57]
Gel permeation chromatography	Molecular weight	[58]
Dielectric spectroscopy	Dielectric, mechanical and molecular dynamic	[59]
Nuclear magnetic resonance	Structural characterization	[60]
Infrared spectroscopy	Surface engineering	[61]
Fourier transform infrared spectroscopy	Surface engineering	[62]
Atomic force microscopy	Visualization and characterization	[63]
Transition electron microscopy	Size and shape	[64]
Analytical techniques	Morphology and homogeneity	[65]
Electrospray ionization	Structural defects	[66]

PAMAM dendrimer

The first dendritic structure synthesized concerning to the divergent route which received widespread attention was Tomalia's polyamide-amine (PAMAM) dendrimer.

Today, PAMAM dendrimer is commercially available and has been studied extensively. PAMAM dendrimer is the first commercial and synthetic dendrimer member based on ethylene diamine core and amide repeating branched structures [67, 68]. Ethylene diamine (EDA)-based poly amide dendrimers have been extensively investigated in biomedical applications and composite base materials since synthesis [69]. The molecular structure of PAMAM is shown in Fig. 1.

Molecular dynamics (MD) simulation

Simultaneously with the technology development, the applications and functions of molecular simulation techniques are becoming more and more demanding. In the

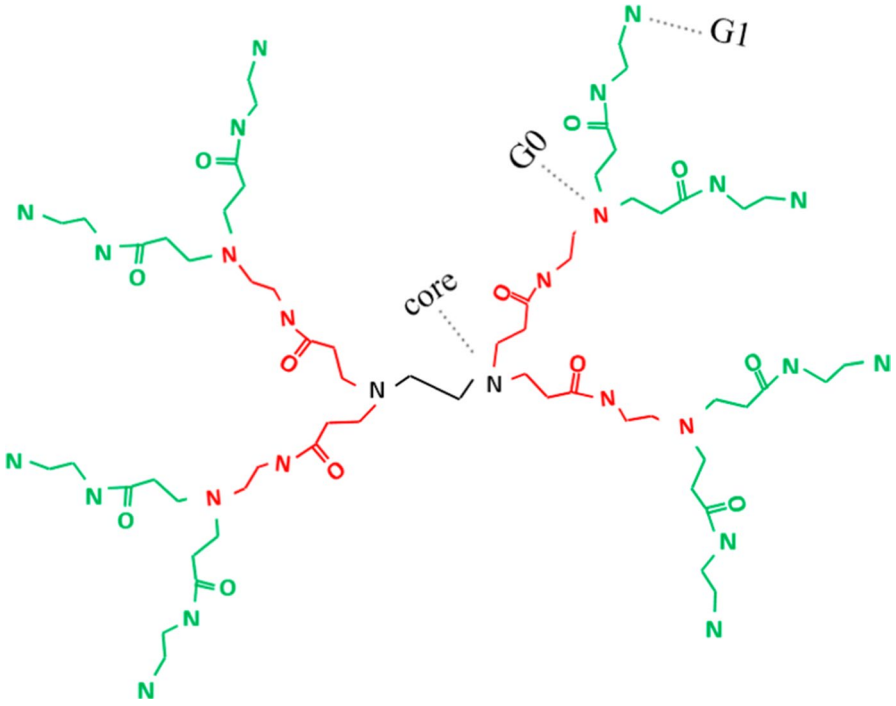

Fig. 1 PAMAM dendrimer. The core, G0, and G1 are shown, reprinted with permission from Ref. [116] copyright 2019 American Chemical Society

environmental protection, chemical and chemical industry and energy conservation are constant themes, and the improvement and promotion of new functional products will be one of the major development trends in the future. The development of computers has introduced the calculation methods and theoretical techniques of chemical, physical, and materials science, which has promoted the progression of new products. With the rapid development of molecular simulation technology, the world's major companies in order to meet the research needs of different fields have developed a variety of molecular simulation calculation software, such as TINKER, Gromacs, Materials Studio, and LAMMPS. MD simulation method is a widely used computer simulation method [70–74]. In a nutshell, molecular simulation is a systematic computer simulation of real experimental molecules. Since the computer can clearly display the microstructure of the molecule and calculate the performance of the target product, some experiments, in which it is difficult or impossible to get the data, can be done using molecular simulation. Based on the experiment, a set of calculation algorithms and calculation models through some basic principles are established, on the basis of which a reasonable molecular structure and molecular behavior are calculated. Molecular simulation methods mainly have four theoretical methods, including quantum mechanical method, molecular mechanics method, molecular dynamics method, and Monte Carlo method, in which quantum mechanics can describe the change of electronic structure, and molecular mechanics can

describe the changes in the ground state atomic structure. These two methods, strictly speaking, describe the molecular structure of absolute zero. MD can be used to describe the physical structure of the average structure and molecular structure at various temperatures. With MD simulations, the particles are moved based on Newton's equations of motion and the forces the particles exert on each other. In this case, the particles follow realistic trajectories which are important for the study of dynamic properties and systems that are out of equilibrium. The simulations can be done in an NVE, NVT, or NPT ensemble. Here the letters indicate which quantities are kept constant during the simulation. N is the number of particles, V the volume, E the energy, T the temperature, and P the pressure. The time steps the system take cannot be too big; otherwise, the trajectory of the particles is no longer realistic. For the NVE ensemble, the steps need to be even shorter to ensure that energy is conserved. The fact that particles follow a realistic trajectory can also be a disadvantage. When the system gets stuck in a local minimum, it may take a long time before it crosses the barrier. If we are only interested in the equilibrium properties of the system and not in the dynamics/time evolution, it is better to use a Monte Carlo method. The Monte Carlo method of the molecule can describe the average structure of various temperatures by the introduction of the Boltzmann factor. In terms of obtaining a statistical average structure of a certain state, the Monte Carlo method of the molecule is often more effective than the molecular dynamics method. MD methods have irreplaceable advantages when studying dynamic processes on short timescales.

Application of PAMAM evaluated using MD simulation

The first MD investigations of dendrimer base macromolecules were achieved by Goddard and coworkers [75]. They applied many ligand molecules to encapsulate inside the dendrimer and succeeded to coat fifth-generation poly propylene imine dendrimers with Bengal Rose. Ivanov and Jacobson applied molecular modeling (MM) to purify the molecular model proposed by the PAMAM protein agonist (CGS21680) bound to the A_{2A} adenosine receptor dimerization in the guest molecule inside the dendrimer [76]. Efficient encapsulation was noticed in the interior of the backfolded molecule in comparison with their extended isomeric counterparts [77].

Application of PAMAM in medicine

MD simulation can obtain the structure of the complex and the driving effect behind it, but it is difficult to study the whole process of drug encapsulation and release. MD studies the PAMAM-based dendrimers and drug interactions mainly used in the full atomic MD. On this premise, Alderete et al. applied MD to investigate the complexation of mefenamic acid (MA) with low-generation (PAMAM-G2 and PAMAM-G3) PAMAM dendrimers [78]. They found that by increasing the dendrimer generation, the internal drug encapsulation is enhanced. They suggested that

the PAMAM with the positively charged surface is the most relevant factor for drug association. Their MD results are in good agreement with experimental findings.

pH environment has a large effect on the efficacy of the drug in the human body, and therefore, MD is able to analyze the effects of drugs with different pH values, which can significantly improve the drug development rate. On this premise, Caballero and coworkers investigated the interaction between the nicotinic acid (NA) as a drug and PAMAM-G3 dendrimer at different pH by applying MD simulations [79]. They found that at pH = 3 the internal amine groups are protonated and the PAMAM cavities become less hydrophobic; therefore, the PAMAM–drug interactions become similar to solvent–drug interactions. They showed that VdW interactions between the methylene groups of the PAMAM-G3 dendrimer and drug stabilized the drug inside the PAMAM-G3 dendrimer at pH = 6 (Fig. 2).

Figure 2 illustrates the conformation of drug and the relation of them with a surface amine of PAMAM-G3 dendrimer (Fig. 2a–c). RDFs of dendrimer–drug and water–drug are shown in Fig. 2d and e, respectively. Drug is more exposed to the water in conformation A rather than conformation B, and drug is closer to methylene groups of PAMAM-G3 dendrimer in conformation C. Their simulation results showed that PAMAM-G3 dendrimer is more favorable for drug entrapment when pH = 6, and their complexes are very stable. Giri et al. investigated the impact of core chemistry, terminal group, and generation of dendrimer in binding of human serum albumin (HSA) to PAMAM dendrimers by measuring the HSA binding constants (Kb) of PAMAM dendrimers [80]. Their MD simulation results illustrated that Kb of HAS to PAMAM depends on their chemical composition and size of their

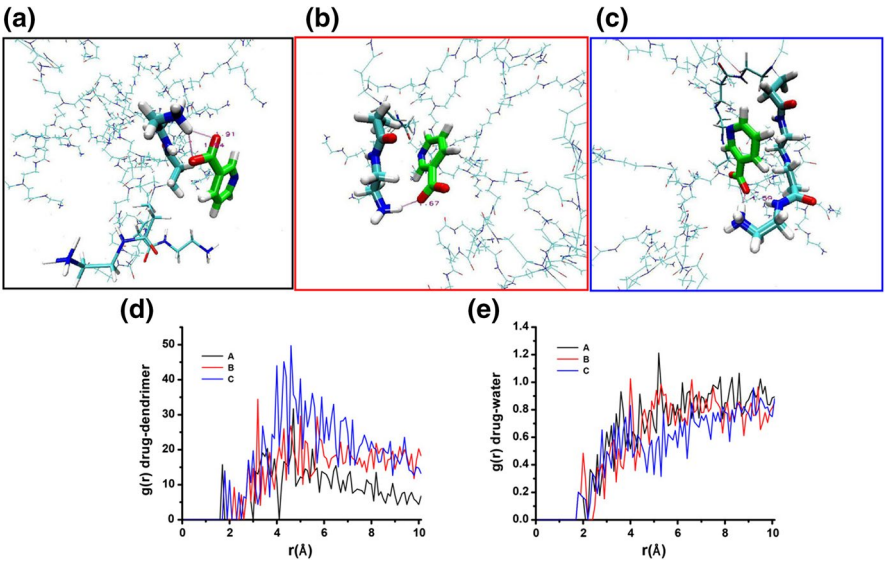

Fig. 2 Simulation snapshots of drug inside PAMAM-G3 at pH = 6, **a** conformation A, **b** conformation B, **c** conformation C, **d** radial distribution function (RDF) of the dendrimer around drug for conformations A, B, and C, **e** RDF of the water molecules around drug for conformations A, B, and C, reprinted from Ref. [79] Copyright (2019), with permission from Elsevier

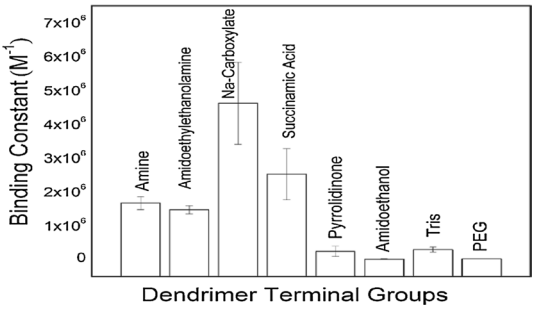

Fig. 3 Effects of the dendrimer terminal group on the HAS Kb of PAMAM-G4 dendrimer, reprinted with permission from Ref. [80] copyright 2019 American Chemical Society

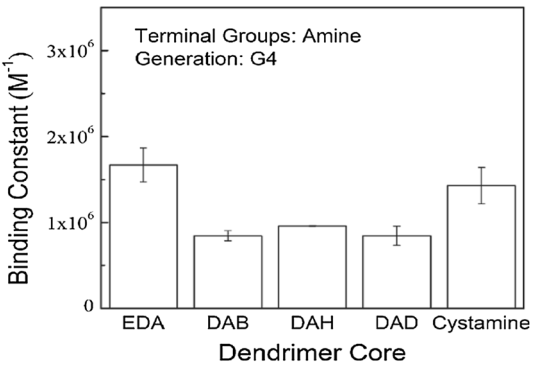

Fig. 4 Effects of dendrimer core chemistry on the HAS Kb of PAMAM-G4 dendrimer, reprinted with permission from Ref. [80] copyright 2019 American Chemical Society

terminal groups. Figure 3 shows the impact of the dendrimer terminal group on the HAS Kb of PAMAM-G4 dendrimer.

Figure 3 illustrates that the lowest Kb values are observed for the PAMAM-G4 dendrimer with neutral terminal groups due to weak hydrogen bonding interactions between the protein amino acid residues and terminal groups of PAMAM-G4 dendrimer. Figure 4 highlights the impact of dendrimer core chemistry on the HAS Kb of PAMAM-G4 dendrimer. From Fig. 3, it can be deduced that the HAS Kb of PAMAM-G4 dendrimer is not significantly related to core chemistry. Their results of the Kb value reveal some critical effects and interactions between the HSA protein and PAMAM dendrimer. Their MD results are in good agreement with their experimental findings. By using MD simulations, Maiti et al. tested the release pattern of two soluble drugs including L-alanine and (Ala) salicylic acid (Sal) and two insoluble drugs including primidone (Prim) and phenylbutazone (Pbz) [81]. These four ligands were placed inside the ethylenediamine (EDA) core of PAMAM-G5 dendrimer. Their potential of mean force (PMF) results showed that insoluble drugs (Prim and Pbz) have higher energy barriers than soluble drugs (Ala and Sal) (see Fig. 5). However, their biological activity depends on the surface charge properties of dendrimers. These data help to optimize and design the dendrimer-based drug delivery system.

Tanis and Karatasos used atomistic MD simulation and applied AMBER force field to investigate the complexation of ibuprofen and PAMAM-G3 dendrimer in aqueous solution under various pH conditions [82]. They indicated that the

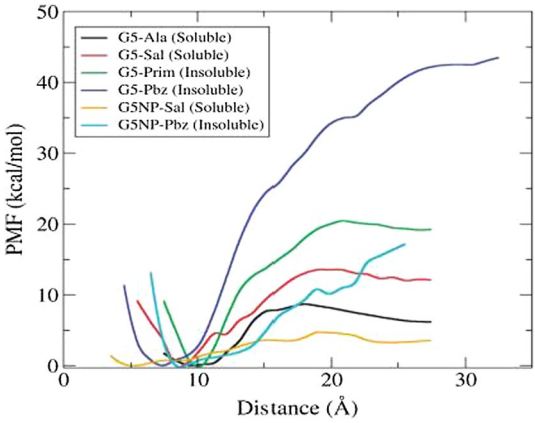

Fig. 5 PMF variation as a function of the drug–dendrimer, reprinted with permission from Ref. [81] copyright 2019 American Chemical Society

PAMAM-G3 dendrimer–ibuprofen complex is unstable at low pH due to the lack of hydrogen bonding. No stable drug/dendrimer complex was detected at low pH, and the electrostatic interaction between ibuprofen and PAMAM-G3 dendrimer allows them to form stable complexes as shown in Fig. 6.

Also, Liu et al. used the Dreiding force field to find that surface grafting of PEG which promoted the PAMAM dendrimer to accommodate more drug molecules [83]. They found that at high pH, the PMF energy barrier of PAMAM dendrimers with anticancer drug molecules including CE6, SN38, DOX, and MTX is much lower than that of physiological pH, so the high pH environment is suitable for drug embedding because the drug–dendrimer complex is formed.

Application of PAMAM in DNA

By individualized analysis of tumor DNA, chemotherapy patients may prolong survival by a factor of six. Doctors have determined that the precise treatment of cancer is increasingly dependent on the genetic test results and guidance of tumors.

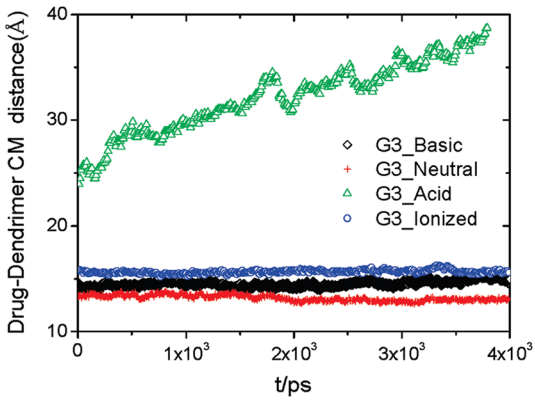

Fig. 6 Average distance between the drug and the PAMAM-G3 dendrimer centers of mass, reprinted with permission from Ref. [82] copyright 2019 American Chemical Society

PAMAM different algebras have different entanglement effects on single-stranded DNA. On this premise, Maiti and Bagchi studied sequence-dependent complexation between single-strand DNA (ssDNA) and various generation EDA-cored PAMAM dendrimers by using MD simulations and calculating free energy [84]. They revealed that the G2 and G3 did not have enough surface charge to neutralize ssDNA because part of the ssDNA far from PAMAM spread out in solution as shown in Fig. 7.

In another close study, the complexation between various generations of PAMAM dendrimers (G3–G5) and double-stranded DNA (dsDNA) have been studied by Nandy and Maiti [85]. They illustrated that dsDNA can be completely entangled on PAMAM-G5 dendrimers. Therefore, it is generally believed that the charge between the positively charged dendrimer and the negatively charged genetic material plays a key role in the structure of the complex. From the snapshots in Fig. 8, it is revealed that the dendrimer continues to search for a suitable binding position on DNA at the beginning and the dendrimer slides along the DNA backbone for both G3 and G4. They found that binding energies of the complexation follow the trend G5 > G4 > G3.

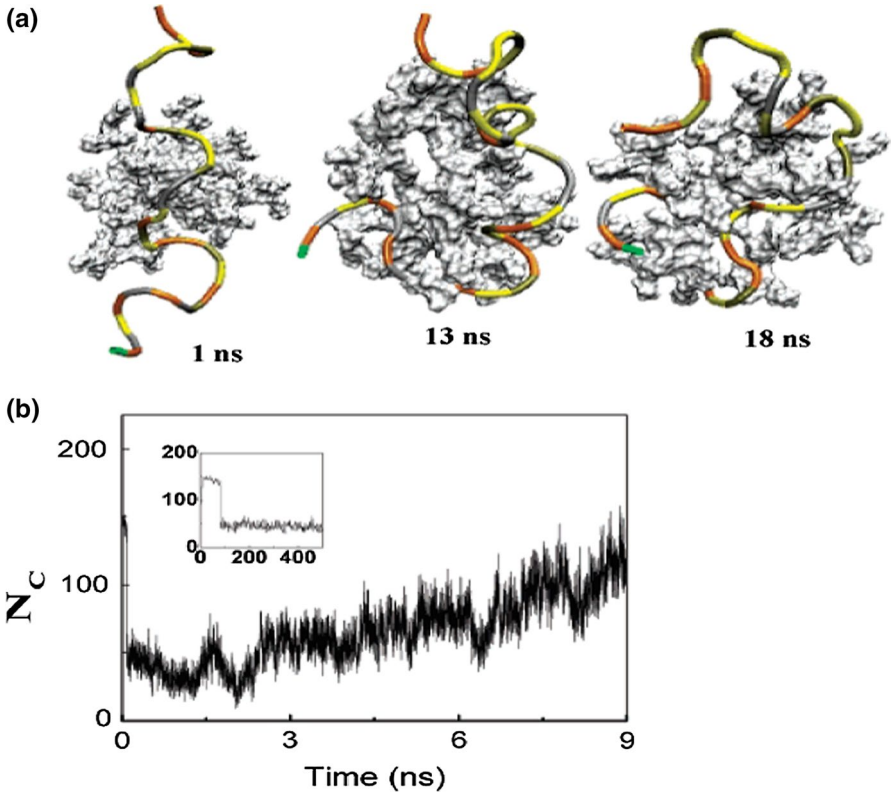

Fig. 7 **a** Structure of ssDNA–dendrimer complex during various stages of the wrapping process at the interval of few ns. **b** Variation of the number of contact points between DNA and dendrimer, reprinted with permission from Ref. [84] copyright 2019 American Chemical Society

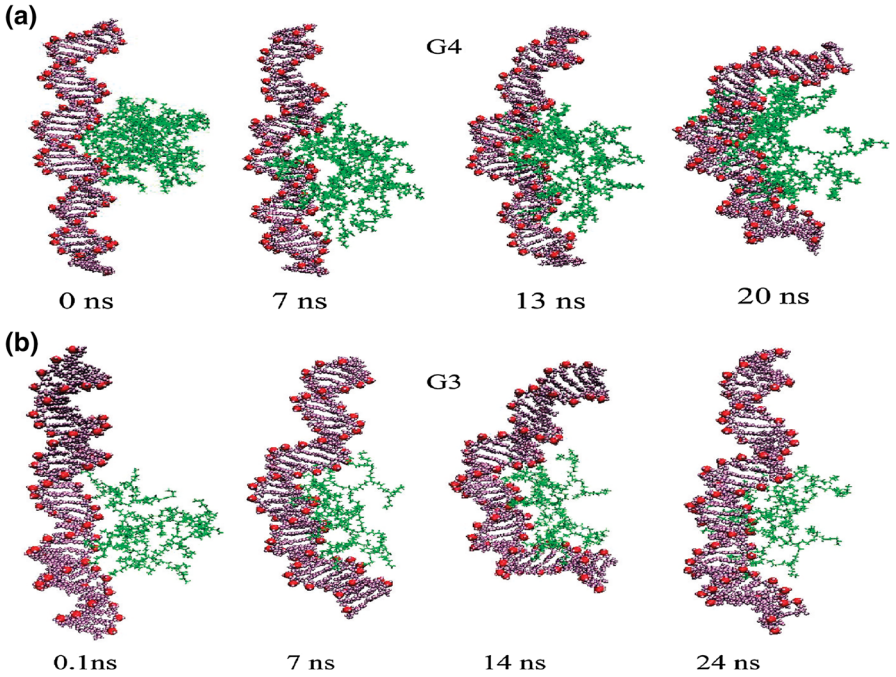

Fig. 8 **a** Structure of the DNA-PAMAM-G4 dendrimer complex during various stages of complex formation. **b** the same for the DNA-PAMAM-G3 dendrimer complex, reprinted with permission from Ref. [85] copyright 2019 American Chemical Society

The stability of dsDNA entanglement on PAMAM is also one of the important indicators. In this regard, Yu and Larson used Monte Carlo simulation system to investigate the effects of PAMAM algebra, surface amidation, and solution salt concentration on the stability of PAMAM dendrimer and dsDNA complexes [86]. They showed that high salt concentration is not conducive to dsDNA and increased PAMAM dendrimer algebra in complex compress dsDNA more tightly. Also, Márquez-Miranda et al. applied MD simulations to study the effects of different surface chemical groups of PAMAM dendrimers on nucleic acid molecules [87, 88]. They demonstrated that the PAMAM can form a stable complex with ssDNA, when the PAMAM terminal group is an amine group and the PAMAM cannot form a stable complex with ssDNA when the terminal group is a hydroxyl group because ssDNA has only a small amount of contact with PAMAM, and they cannot pass through the cell membrane.

Not only the size and surface chemistry of dendrimers focus of attention, but also flexibility and stiffness of PAMAM dendrimers are another critical factor in the formation of dendrimers. On this premise, Pavan and coworkers used MD to investigate the effect of the stiffness of dendrimers on the structure of dendrimer–gene complexes [89]. The MD simulation results showed that the stiffness of PAMAM dendrimers plays a crucial role in the binding state. It is mainly regulated by combining the competition between enthalpy and entropy.

The curves of RDF in Fig. 9 demonstrate the atomic density with respect to time, and the high peaks correspond to areas of low atomic mobility and high density of atoms. They found that flexible molecules tend to form a spherical composite structure, while rigid molecules are rearranged such that their terminal groups make more contact with the oligonucleotide. Ainalem and Nylander wrote an interesting review article and discussed about the PAMAM algebra, ionic strength, and other factors which affect the morphology of PAMAM and DNA complexes [90].

PAMAM for pharmaceutical carriers and biomedical applications

The development of novel PAMAM drugs and gene delivery with the greatest therapeutic potential and minimal side effects is a huge challenge for nanomedicine. As a delivery vector, the PAMAM must exceed many of the obstacles encountered before the biological agent is delivered to the target within the cell. As an important supplement to experimental methods, computer simulation has a good advantage for studying intermolecular interactions [91–93]. As transporters, when PAMAM-based dendrimers approach cells, they first interact with the cell membrane. Therefore, understanding the interaction between dendrimers and biofilms is important for designing efficient dendrimer-based carriers. Maiti et al. simulated the structure of the first to 11th-generation PAMAM dendrimers [94]. They found very little strain in these structures up to G6; however, for G10 there is considerable strain throughout the entire structure, which increases dramatically for G11. They suggested that the steric interactions of the surface groups prevent growth of full generations beyond G10. For example, in the case of PAMAM dendrimers with ethylenediamine as the initial nucleus, G1 to G3 cannot form a dense spatial internal structure, and each branch sparsely forms an ellipsoid [95]. Until G4 and G5, this macromolecule has a relatively complete spherical outline and internal space. Ma et al. recently studied the role of PAMAM and negatively charged asymmetric membranes, revealing the physical mechanism of dendrimers as carriers in gene transfection to cause gene–carrier complexes to escape from endocytosis [96, 97] and proposed utilization of pH-responsive and possible pathways for gene-targeted transport

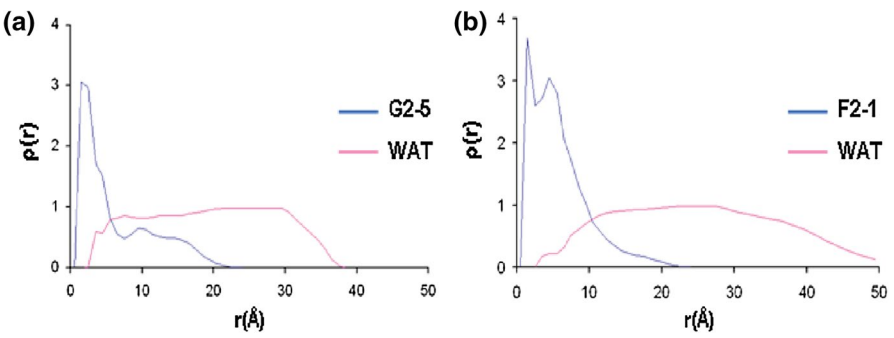

Fig. 9 RDF of G2-5 (**a**) and F2-1 (**b**), reprinted with permission from Ref. [89] copyright 2019 American Chemical Society

based on complex charge reversal [98]. Whether the stiffness of the dendrimer as a carrier can reach the index is key to successful delivery, so it must be considered whether the stiffness is optimal. Lyulin et al. used the coarse-grained MD simulation method to simulate the interaction between dendrimers and linear polyelectrolyte [99]. They observed the formation of compact dendrimer polyelectrolyte complexes, while strong electrostatic interactions induced dendrimer size reduction. Moreover, Lyulin et al. studied the structure and dynamics of dendritic macromolecules in dilute solutes by explicitly excluding volume and hydrodynamic interaction Brownian dynamics simulation, and compared the results with the mean field theory [100, 101]. In addition, the influence of the stiffness of polyelectrolyte on the dendrimer polyelectrolyte complex was also studied by coarse-grained MD simulation method [102]. It was found that with the increase in polyelectrolyte stiffness, the polyelectrolyte structure composited with PAMAM changed interestingly from curling. If the U or V shape becomes bar shape, there may be an optimal stiffness for the transport and release of biologically active guest molecules.

The PAMAM dendrimers need to penetrate into the drug body to act on the target cell, so there is a certain requirement for the target product embedding degree. Wang et al. used dissipative particle dynamics to find that increasing the PAMAM dendrimer algebra would enhance its permeability to bilayer membranes [103]. Yan et al. systematically studied the interactions between charged dendrimers and phospholipid bilayers and their complex structures by using dissipative particle dynamics [104]. They found that the effect of increasing the hydrophilic component and phospholipid head on the surface of the phospholipid bilayer led to the spreading of the dendrimer on the surface of the phospholipid bilayer, while the effect of increasing the hydrophobic component on the inside of the dendrimer on the phospholipid tail group led to the deeper embedding of the dendrimer into the phospholipid bilayer. Figure 10 shows the snapshots of the complexes comprised the charged G5 dendrimer with the lipid bilayer membrane.

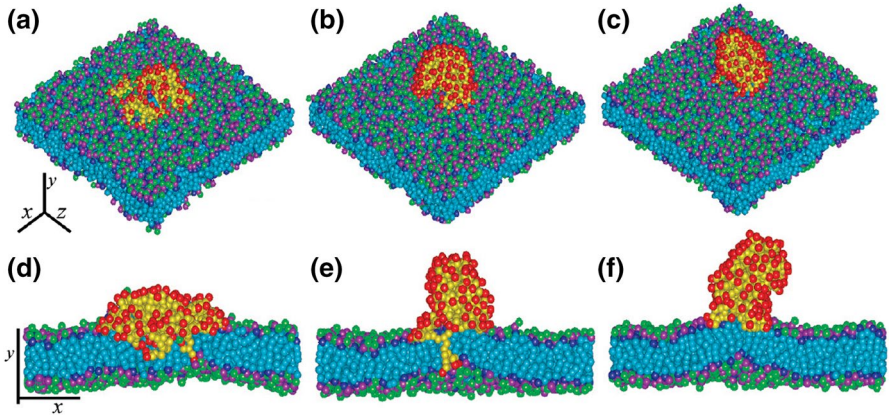

Fig. 10 Complexes between the charged G5 dendrimer and the lipid bilayer membrane. Panels **d–f** are the cross-sectional views of panels **a–c** respectively, reprinted with permission from Ref. [104] copyright 2019 American Chemical Society

In addition to considering the environmental pH as a drug, it is also necessary to consider the pH value of the carrier as a carrier. On this premise, Terao and Nakayama studied the structure of charged dendrimers at different pH values, as well as multiple generations (G5, G6, and G7) by random MD simulations [105]. Gurtovenko et al. used MD to simulate the calculated amount of charged dendrimers under explicit counterions and solvent molecules under neutral pH conditions [106]. They found that the addition of explicit counterions to the simulation has a large effect on the structure and kinetics of the charged dendrimer. Guo et al. used dissipative particle dynamic methods to study the structure–performance relationship of a series of pH-responsive polymer transport systems [107, 108]. Luo and Jiang combined MD and dissipative particle dynamics methods to study the loading and release of pH-responsive amphiphilic copolymer poly(-amino ester)-polyethylene glycol (PAE-PEG) anticancer drug camptothecin [109]. In addition, the terminal primary amino group of the PAMAM molecule is distributed throughout the molecule and can be close to the core inside the molecule, rather than being located entirely on the surface of the molecule. This indicates that the terminal group of the dendrimer has sufficient flexibility to be folded back into the interior of the molecule. It is consistent with the coarse-grained MD simulation performed by Zhong et al. using the Martini force field [91] and the all-atom MD results by Mait et al. using the Dreiding force field [110].

Application of dendrimers in proteins and amino acids

A large number of terminal functional groups and tight and precisely controlled molecular structure are the unique properties of dendrimers, which make them a good use in the field of proteins and amino acids. Su ling Chen et al. used coarse-grained molecular dynamics to simulate the interaction of G4 PAMAM dendrimers with KALP peptides in different pH solutions [111]. They found that KALP peptide had little effect on the size, shape, and density distribution of dendrimers in two pH environments, and there was a certain space inside the dendrimer to accommodate KALP polypeptide molecules. The calculation of free energy shows that the two molecules are not easy to form a stable composite structure in acidic and neutral environments. Also, Schneider et al. demonstrated the MD simulation of G0 dendritic macromolecules with alpha-chymotrypsinogen A (aCgn) and surface-modified guanidine (Gdm) and studied the effects of salt ions such as Cl^{-}, SO_4^{2-}, and H_2PO^{4-} [112]. They proposed a priority coefficient of action, the thermodynamics of free energy in the migration of proteins from water to additives, and insight into how dendrimer salts affect protein–protein interactions. It can also be used to measure the tendency of protein surface additives. The multi-surface group binds the dendrimer to the protein more strongly than the single functional group. Poly-L-lysine (PLL) dendrimers are amino acid macromolecules that act as drug delivery agents. Their branched structure allows them to be functionalized by different groups to encapsulate drugs into their structures. Rahimi et al. designed a process particle size model of PLL dendrimers and determined its parameters for simulating three generations of PLL dendrimers [113]. The results show that as the amount of production

increases, dendrimers change. It is more spherical. At pH = 7, the PLL dendrimer has more holes, allowing more water molecules to be encapsulated inside. The formation of the spherical structure of the PLL dendrimer was confirmed by calculating the moment of inertia and the aspect ratio. Robert et al. [114] studied the structural changes of PLL dendrimers from the first-generation (G1) to the fifth-generation (G6) by means of all-atomic MD simulation and pointed out that the complexes of G1 and G6 dendrimers were spherical and regular, with highly recessed surfaces and dense nuclear structures. Neelov et al. [115] studied the properties of different PLL dendrimers using atomic MD simulations and reported that their properties are not dependent on temperature, but their internal group mobility is dependent on their formation. Kavyani et al. [116] used the GC-MD method to show that the length and nature of the PAMAM dendrimer core have an effect on the size and encapsulation capacity of dendrimers. Figure 11 highlights that at pH 7 the dendrimer terminals are closer to the core than at pH 5 and also proves that the PAMAM with the DAH core has the lowest RDF values, so the DAH core can create more cavities in the dendrimer structure.

In another work, Lee and Larson used GC-MD simulation to study the effects of PLL and PAMAM dendrimers on the DMPC bilayer membrane [117]. They obtained the bonding interaction parameters of coarse crystal PAMAM dendrimers with histidine and arginine terminal groups at pH 5 and 7 [118]. They pointed out that as the amount of histidine in the terminal group of the dendrimer increases, the size of the formed complex becomes larger.

Dendrimers in other applications

MD simulation provides a general simulation method. There are efficient methods for simulating various natural processes at the molecular level [119–123]. Dendrimers have great application prospects in new nanocomposites. Therefore, understanding the interaction between dendrimers and surfaces is of great significance.

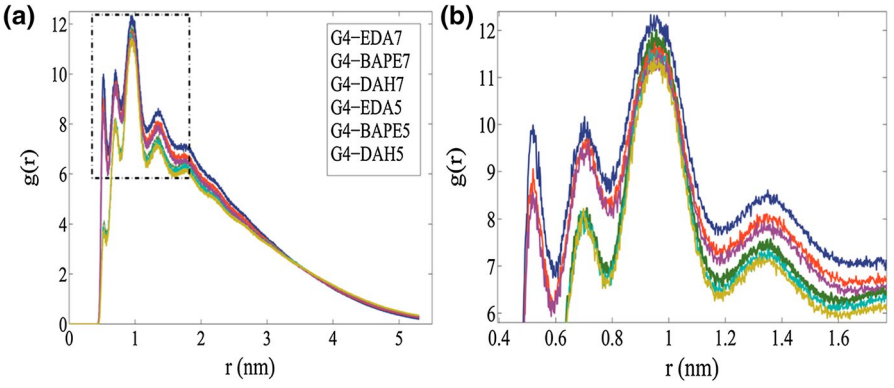

Fig. 11 RDF of G4s dendrimer terminal beads at both pHs 5 and 7 with various cores. The dotted rectangular in (**a**) is extended in (**b**), reprinted with permission from Ref. [116] copyright 2019 American Chemical Society

Wolski and Wolski used the all-atom MD simulation method to study the behavior of PAMAM dendrimers adsorbed on the polarization model of gold surface [124]. The study found that with increase in pH value, the structure of dendrimers became more compact. Also, other applications of PAMAM dendrimers are fingerprint detection [125], biomedical applications [126], methanol oxidation [127], optical sensing [128], and so on [129].

Conclusions and perspectives

In recent years, due to the rapid development of fluid mechanics, quantum mechanics, quantum science, and other disciplines, providing solid theoretical techniques for experimental design, computational molecular simulation has received more and more attention, which will become the mainstream development trend in the future. Molecular modeling can help researchers get a lot of information that is difficult or impossible to obtain during the experiment. As the application of molecular simulation technology continues to expand, the simulation of dendrimers will be deeper. At present, the molecular simulation of dendrimers around the world is mainly focused on medicine, but dendrimers have a wide range of applications in the fields of surfactants, photographic materials, nanomaterials, and catalysis. Research on these areas has focused on theory rather than on practical applications in a specific area. Therefore, the future development trend of molecular simulation technology will be toward the practical application of broadening the dendrimer field.

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