Properties of Amphiphilic Janus Dendrimers

Subjects: Materials Science, Biomaterials

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Amphiphilic Janus dendrimers are arrangements containing both hydrophilic and hydrophobic units, capable of forming ordered aggregates by intermolecular noncovalent interactions between the dendrimer units. Compared to conventional dendrimers, these molecular self-assemblies possess particular and effective attributes i.e., the presence of different terminal groups, essential to design new elaborated materials.

dendrimers amphiphilic Janus dendrimers dendrimersome glycodendrimers

1. Introduction

The dendritic (or tree-like) configuration is one of the most widespread patterns observed in nature, both in the non-living world (e.g., lightning, snowflakes, river networks, mountains) and biological systems (e.g., tree branching/roots, flowers, lungs and vasculatory system, neuronal system, bacterial colonies, stony corals) [1][2][3]. These natural tree-like patterns have been a real source of inspiration for chemists who tried to reproduce the well-defined branched structure from nano to macromolecular levels.

Although the concept of highly branched structures in macromolecular systems was initially proposed by Flory in the early 1940s [4][5][6], the first example of branched macromolecules obtained by “cascade syntheses” was reported in 1978 by Vögtle’s group [7]. The first article using the term “dendrimer” was published in 1985 by the Tomalia group [8] describing in detail the synthesis of polyamidoamine dendrimers (PAMAM) by “time sequenced propagation techniques”. Independently, in the same year, Newkome et al. [9] reported the synthesis of “monocascade spheres (arborols)”.

The term “dendrimer” originates from the Greek words ‘*Dendron*’, meaning “tree”, and ‘*meros*’, meaning “part”. Dendrimers are three-dimensional macromolecular entities with radial symmetry having a globular, tree-like structure and a large number of functional groups [10].

Typically, they are composed of three main structural parts: a central core, repeating units, and surface terminal groups [11][12]. The repeating branching units of dendrimers are organized around a focal point, and on the outside, they present an increasing number of exposed terminal groups that can be functionalized, thereby changing their physicochemical or biological properties [13][14].

Due to their unique structures and characteristics, dendrimers are suitable for a wide variety of applications in various fields such as: biomedicine [15][16][17][18], drug delivery [19][20][21][22][23], tissue engineering [24][25], catalysis

[26][27][28][29], sensing [30][31][32][33], imaging [34][35][36], hybrid materials [37][38], and solar cells [39][40][41][42].

These compounds have sparked a large number of publications and many expectations, especially in the medical field, but their application in clinical studies has been very weak so far [43]. However, a very recent example refers to a dendrimer (hydroxyl-polyamidoamine dendrimer–*N*-acetylcysteine conjugate) therapy against severe COVID-19 that has entered into Phase II clinical trial and proved the attenuation of inflammatory and neurological injury markers [44]. In spite of their advantageous characteristics and the great potential as drug delivery carriers, dendrimers present also certain limitations such as: difficulties associated with purification [45], toxicity in biological systems, especially of cationic dendrimers [16][46][47][48], difficulties in obtaining consistent drug loading efficiencies and controlled drug release [49], and non-degradability in the physiological environment, causing side effects induced by their accumulation in cells and tissues [50].

To counteract the limitations of symmetrical conventional dendrimers, several strategies have been proposed and developed by different scientists. For example, in recent years, many researchers have focused on the development of biocompatible and biodegradable dendrimers [51][52][53]. The use of biodegradable dendrimers allows the excretion or elimination of non-toxic small dendritic fragments through metabolic pathways [50][54]. A common way to improve the biocompatibility and bioactivity of conventional dendrimers and to reduce their toxicity is chemical modification of their surface, the peripheral charge modifications having a key influence for enhancing their biocompatibility and precisely customizing their properties [55][56][57][58][59].

Furthermore, dendrimers can also be designed to incorporate regions of chemically and structurally distinct groups [49]. These dendrimers are known as “Janus dendrimers” (JDs), named after the ancient Roman god “Janus”, usually depicted as having two faces. In recent years, this new class of dendrimers also known as diblock dendrimers, ‘‘surface-block’’ dendrimers, block co-dendrimers, diblock co-dendrimers, asymmetrical or bow-tie dendrimers [60], aroused the interest of researchers due to their asymmetric structures and their potential to overcome some of the limitations of conventional dendrimers.

In 1989, Casagrande et al. [61] reported the first “Janus beads”, glass spherical particles with diameters in the range of 50–90 µm with one hemisphere hydrophilic, and the other side hydrophobic. They studied the properties of these unique amphiphilic solids at oil/water interfaces and noted their special behavior and the promising advantages for further development and applications. This study triggered the interest of the Nobel Laureate, Pierre-Gilles de Gennes. In 1991, in his Nobel Prize lecture entitled “Soft matter”, he presented “Janus grains”, particles having two sides, one polar and one non-polar [62]. Since then, these asymmetric structures have fascinated the scientific community and research in the field has expanded far beyond the initial two-faced amphiphilic structure towards more complex structures, including Janus dendrimers.

The general structure of Janus dendrimers consists of two dendrimeric halves with different terminal functions joined through the core [60]. They are synthesized by coupling two different dendrons in terms of size and functionality to obtain a single amphiphilic or heterofunctional molecule with distinctive properties [63]. A schematic representation of an amphiphilic Janus dendrimer is illustrated in **Figure 1**. The synthesis of unsymmetrically

surface-functionalized dendritic molecules (**Figure 2**) was initiated by Fréchet and co-workers in the early 1990s [64][65], then in the following years, the research in this field has expanded. In recent years, a crucial contribution in the development and investigation of Janus dendrimers was made by the research group of the American of Romanian origins chemist Virgil Percec. They developed new synthetic routes leading to several distinct libraries of uncharged or positively charged amphiphilic Janus dendrimers, and studied their supramolecular assembly in water into giant dendrimersomes with excellent mechanical properties [66]. In addition, they reported the first attempt to predict the dimensions and some properties of monodisperse dendrimersomes and demonstrated that the molecular structure of amphiphilic Janus dendrimers determines the morphology of the supramolecular assemblies [67]. They synthesized the first examples of amphiphilic Janus glycodendrimers (sugar-containing dendrimers) that can self-assemble in aqueous solutions, leading to monodisperse vesicles named glycodendrimersomes (GDSs) and studied their interactions with lectins [68][69][70][71]. Additionally, the designing of a one-component multifunctional sequence-defined ionizable amphiphilic Janus dendrimer (IAJD) delivery system for mRNA [72][73] could have a profound impact on the future of genetic nanomedicine.

Figure 1. Schematic representation of an amphiphilic Janus dendrimer.

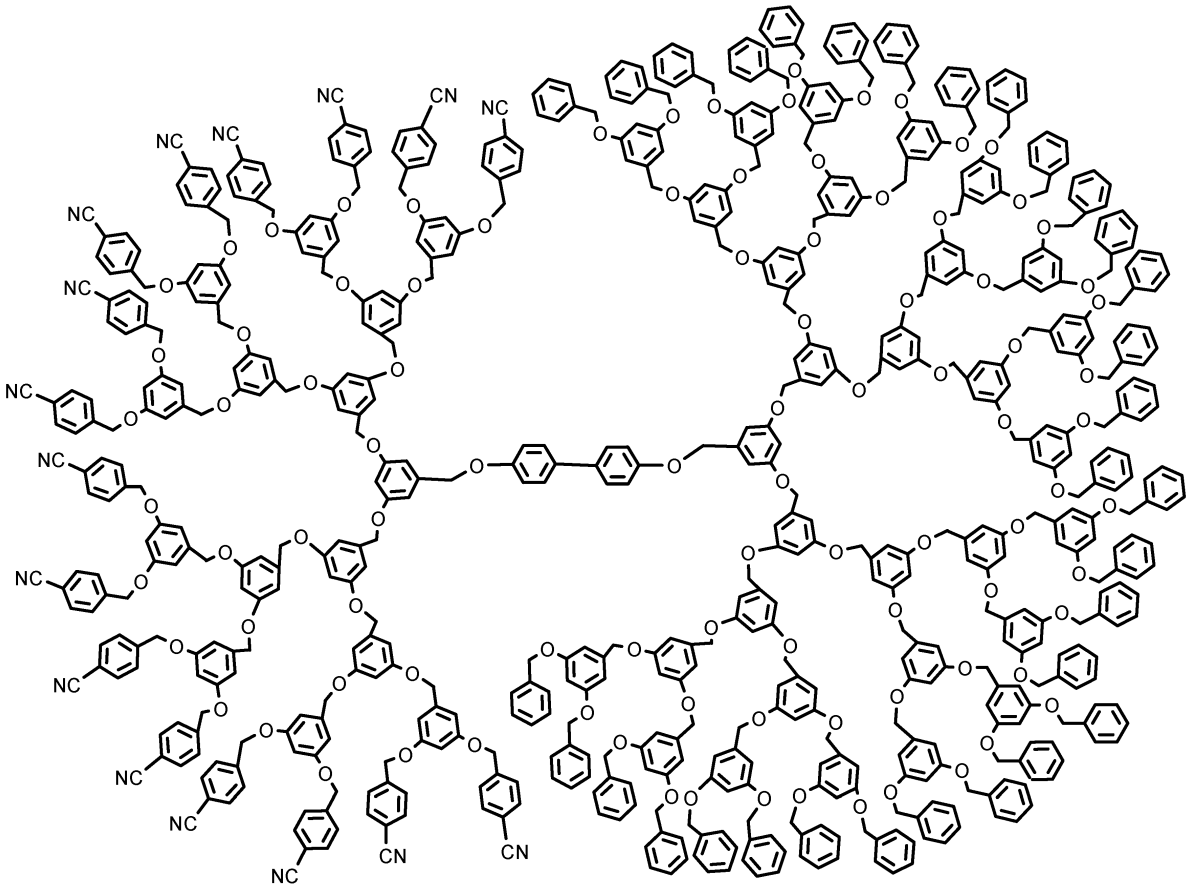

Figure 2. A dipolar dendritic molecule designed by Fréchet group [65]

The broken symmetry structure of Janus dendrimers and their self-assembly ability to form various complex molecular architectures give them the flexibility and versatility to be applied in different fields such as biomedicine (especially as nanocarriers) [63], molecular imaging, especially MRI (magnetic resonance imaging) [74][75][76][77], optoelectronics [78][79][80][81][82], catalysis [83], ionic liquids [84][85], and thermal actuators [86].

2. Classification of Amphiphilic Janus Dendrimers

Among JDs, two significant categories are distinguished, JDs: amphiphilic Janus dendrimers and amphiphilic Janus glycodendrimers.

Amphiphilic Janus dendrimers can be divided into three groups, twin−twin, with two lipophilic dendrons coupled to two hydrophilic dendrons, twin−single, with two lipophilic dendrons coupled to one hydrophilic dendron, and single−single, with one lipophilic dendron coupled to one hydrophilic dendron. Depending on the presence of specific moieties in their molecule or based on their special architectures, amphiphilic Janus dendrimers can be divided into fluorinated JDs, Janus metallodendrimers, hyperbranched JDs, and so on [87].

Amphiphilic Janus glycodendrimers (JGDs), containing sugars like D-galactose, D-mannose, and D-lactose in their structure, can be classified into twin−twin, with two lipophilic dendrons linked to two glycosylated hydrophilic

dendrons, single−single, containing one lipophilic dendron linked to a glycosylated hydrophilic dendron, and twin−mixed, with twin hydrophobic dendrons linked to one hydrophilic and one glycosylated hydrophilic dendron. If the sugar sequence and density are well-defined, JGDs are called sequence-defined JGDs [87].

Percec and co-workers reported extensive libraries of twin–twin [66][68], single–single [88] and sequence-defined [70][89][90][91] amphiphilic Janus dendrimers and glycodendrimers.

3. Characteristics of Amphiphilic Janus Dendrimers and Dendrimersomes (DSs)

According to their definition, amphiphilic JDs benefit from the characteristics of dendritic macromolecules, like defined structure and opportunity of expanded functionalization, and from the features derived from their amphiphilic character, such as the possibility of self-assembling in different media [92]. Considering the unique structure of amphiphilic JDs, which results from the controllable size, assembly, density, generation and number of terminal groups of their dendrons [92], and the enhanced solubility, along with the presence of internal cavities, the possibility of using JDs in various applications can be clearly predicted [93].

Amphiphilic JDs are molecules comprising both of polar and non-polar dendrons, which is the main reason for their self-assembly in water forming complex molecular architectures. These form stable structures with uniform size and various chemical functionalities [93].

The injection, thin-film hydration, and oil-in-water methods were used for the self-assembly of JDs to form uniform dendrimersomes (DSs) and other varied complex architectures including tubular vesicles, cubosomes, and micellar structures such as rods, disks, and helical ribbons [66][68][86][87].

Generally, DSs showed predictable thickness and diameter and outstanding stability in time and many environments, even in the presence of competitive guest or host molecules [87]. There were reported DSs stable in the first 50 days after preparation at 25 °C in ultrapure water, and sometimes with a constant size for up to 244 days at room temperature, or DSs stable upon annealing from 22 to 80 °C, with almost a constant size, but also DSs which displayed an evident increase in size when heated to at least 50 °C [66]. Some DSs also demonstrated the ability to retain most of their cargo under physiological temperature and pH 7.4 for over 100 h [66]. DSs self-assembled from the hyperbranched JDs were stable in size and morphology after 6 months at room temperature, or when heated from 20 to 70 °C [94]. Good stability after photopolymerization and in buffer solutions was reported in the case of some DSs, even when more JD was added [95]. To enhance the stability of DSs, the co-assembly stabilization method using an anionic lipid that can reduce electrostatic forces was also reported. Such stabilized DSs unveiled payload retention and stability comparable to that of conventional liposomes [74]. Obviously, there are also examples of DSs with poor retention and deficient stability in human serum at physiological temperature [74].

Along with stability, many DSs proved to have also minimal toxicity both in vitro and in vivo [87]. Some DSs exhibited levels of toxicity similar to polymersomes, in some cases with no significant reduction in cell viability [66];

their breakdown products, i.e., phenolic acids, are known to lack toxicity [87]. On the other hand, great biocompatibility was obtained for DSs containing siRNA [96][97], the evaluation of inflammatory cytokines revealing no substantial inflammatory response [96].

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