Research progress on synthesis and characteristic about dendrimers

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Abstract. Dendrimers are hyper-branched polymers which have perfectly defined structures. Different from the common polymers, dendrimers are synthesized by a step-by-step iterative style, which starts from a central core and forms branching parts outward. The dendrimers also have different physical and chemical characteristics from common polymers. In this paper, contributions to dendrimer synthesis from different researchers with different scientific background, synthesis of different dendrimers, and applications of them will be reviewed.

1. Introduction

Dendrimers are hyper-branched molecules synthesized in a different method from common polymers, and the branched part of the molecules is composed by multiple ligands or metal-ligand systems emanating radially from central core [1]. Due to the very special synthetic way and method, many dendrimers have very specific physical and chemical properties.

The word dendrimer emerges from two Greek words dendron (dendron=tree) and meros (meros = part) and it graphically describes the structure of this new type of molecule. The earlier name, cascade molecule, is in fact a better name to describe its own nomenclature, but the expression dendrimers has been established at the same time. The very first example of dendrimers was proposed by F. Vögtle et al. in 1978 (called "cascade structure"), then R.G. Denkewalter et al. patented (but not published) the synthesis of poly-lysine dendrimers in 1981 [1]. The order of the synthesis of dendrimers by different scientists is shown in Table 1.

Table. 1 Summary of the contribution of dendrimers synthesized by different scientists

Type of dendrimers	Inventors	Year	Reference
Poly(Propylene Imine) PPI dendrimer	Vogtle et al.	1978	[2]
PolyAmido-Amine PAMAM dendrimer	Tomalia et al.	1983, 1985	[3]
Arbosols	Newkome et al.	1985	[4]
Poly(aryl ether) dendrimer	Frechet and Hawker	1990	[5]
Polylysine dendrimer	Denkewalter et al.	1981	[6]
Polyether dendrimer	Frechet and Grayson	2001	[7]

Since the first dendrimer was synthesized several decades ago, the production, characterization, and literatures about dendrimers have grown dramatically. Nowadays, more than 50,000 patents and

literature citations related to this kind of molecules emerges. Dendrimer molecules currently plays a key role in real applications.

For example, dendrimers are used in drug delivery carriers, fuel cells, light emitting diodes liquid crystals chemical modification and membrane separation [8]. Due to the structure specificity of dendrimers, the interactions between dendrimers and solid or liquid surfaces have been studied and provide much useful information about their possible functions as catalysts, absorbents, etc. Since the dendrimers' structure is very special, which is totally different from traditional polymers, scientists used specific synthetic ways instead of polymerization to synthesize them.

2. General structures and synthesis of dendrimers

As mentioned before, the dendrimers are synthesized in step-by-step iterative way, which is different from those of the traditional linear polymers. Thus, the structure of dendrimers is tree-like, radially. The general structure of a part of dendrimer is shown in figure 1.

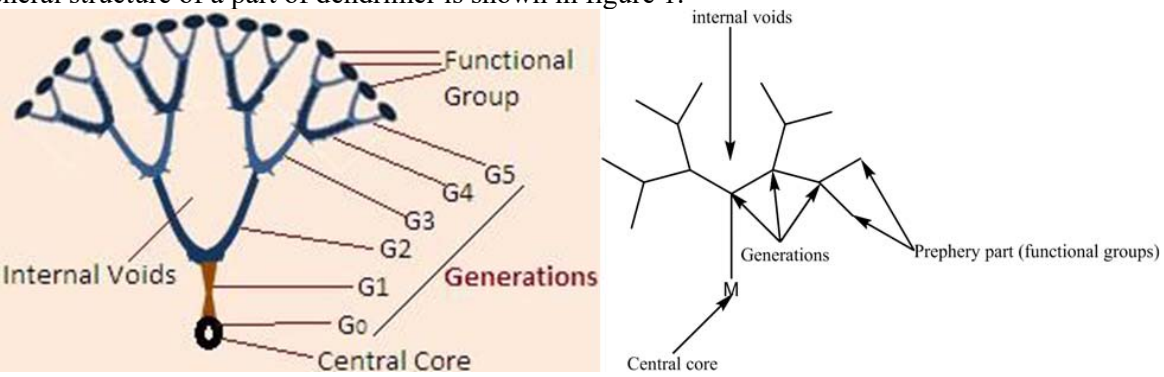

Figure 1. General structure of dendrimers [9]

Dendrimers are generated by changing functionality in each of their constituent parts (core, inner shell and periphery) to index properties such as solubility, thermal stability and addition of compounds for particular applications. Dendrimers are assembled from multifunctional core which is extended outward by Michael addition reactions [10]. In general, there are two established methods of synthesizing dendrimers: convergent method and divergent method. The general scheme of Michael additions in dendrimer synthesis is shown in figure 2.

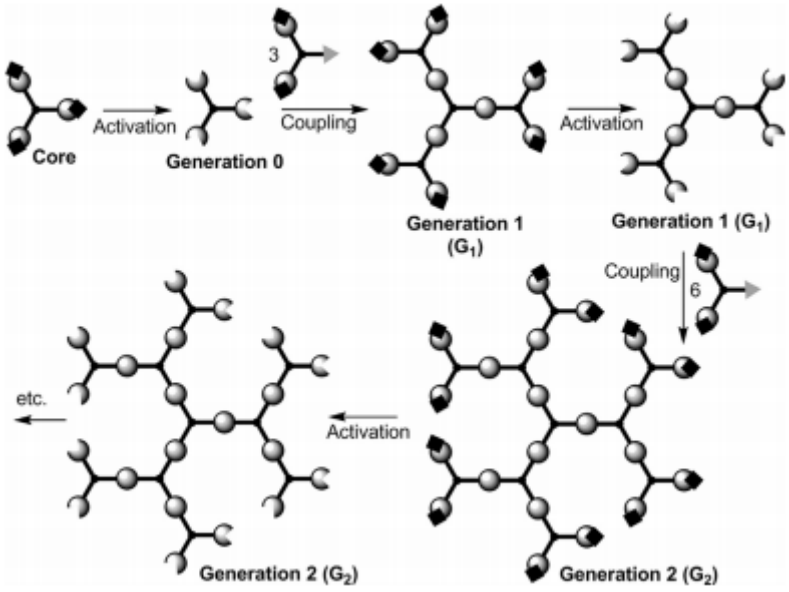

Figure 2. General Scheme of Michael Additions in dendrimer synthesis [8]

2.1 Divergent method

As one of the earliest developed method, the divergent method is the most popular way of synthesizing dendrimers. This method synthesizes dendrimer molecules from the inner core to the periphery. In this method, scientists build up the molecule towards the periphery using two basic operations. First, the monomer is coupled up to form a periphery part, then the functional groups of these monomers are transformed, which makes their chemical properties change, and form a new reactive surface for coupling in next step. After several repetitions of this process, dendrimer molecules are produced. In other words, scientists just need to repeat the same step to increase the dendrimers' sizes and add more and more ligands in each generation, since the surface area for each generation grows bigger and bigger. Without any convoluted step, this divergent rout for dendrimer synthesis is believed to be advantageous and very useful for commercial scale production because of the high yield with low purity. Impurities are encountered in the divergent synthesis of dendrimer as a result of either of the following side reactions missing repeating units, intra molecular/intermolecular cyclization or Retro-Michael addition [10]. As mentioned above, since in every step, more reagent is added compared to the previous step, the amount of impurities encountered into the dendrimer molecules also increases in every step. Hence, this method is not suitable for producing high-purity dendrimers.

2.2 Convergent synthesis:

This process is like a reverse process compared to the divergent synthesis, which starts from the periphery part and inwards toward to the core, thereby creating dendritic segments. By "sticking" multiple segments together, dendrimer molecules could be synthesized. During convergent synthesis of dendrimers, the number of reactive sites found during the proliferation stage is usually minimal and this results to faster reaction rates with better yields. The rate of synthesizing a certain segment is faster when the structure grows inward. In addition, since the convergent synthesis starts from outside part toward the core, it only synthesis one segment at one time. Therefore, it is a very practical way to produce dendrimers with heterogeneous morphologies [1,8] because different segments could be coupled to the same core in this process. The advantage of this method is that it can produce the dendrimers with different core functions, and the dendrimer molecules synthesized by this method have less impurities with more monodispersity and symmetry because better purification is achieved before dendrons are finally attached to the core. However, due to stearic hindrance between dendrons trying to get attached to the core, the size of dendrimers synthesized via this route has limitations.

3. Properties of dendrimers in relative reactions

As mentioned above, the dendrimers are composed by three parts: surfaces, outer shell, and the core. Each of these parts has different characteristics and functions. The surface of the dendrimers, which composed by lots of functional groups, could act as the active part when dendrimers act the absorbents or catalysts. Also, it can shield off the interior parts due to its steric hindrance, and solvent molecule's diffusion rate into the dendrimer interior may also be reduced by the surface of dendrimers. The outer shell has a restricted microenvironment, and for somewhat the dendrimer surface blocked it from the surrounding environment. The very high number of functional groups located on the periphery part of dendrimer molecules could be used for host–guest interactions and catalysis since the functional motifs' similarity is important. The core is blocked from the surroundings by the dendritic wedges increasingly while the dendrimer's generations increasing. The interior of the dendrimer creates a microenvironment which have very different characteristics from surroundings [12]. In other words, the surrounding layer of a certain dendrimer molecule could be protic and hydrophilic, but the core of a certain dendrimer molecule could be aprotic and hydrophobic, and their functions are also different. As a result, the biological property of dendrimer molecules is like a medium-size protein molecule. Indeed, in the early history of dendrimers, it is believed by scientists that these nanoscale polymers would act as synthetic mimics of proteins. However, there are also some restrictions for dendrimers to mimic proteins. Since dendrimer creates a highly multivalent surface, the number of functional groups on the periphery is relative much higher than a protein molecule with similar size [12]. Moreover, the structure of

dendrimers is radial, and tree like, so the molecular density of dendrimer molecules is much smaller than that of the proteins. Since there are lots of extensive intramolecular bonding, such as ion pairing, hydrogen bonds, and disulphide cross-binding, the linear-chain of polypeptide could be folded into three-dimensional structure. Thus the molecular density of protein is very high [13]. Even though the dendrimer molecules have a relative smaller molecular density than the protein, their molecular density is still higher than traditional linear polymers. Overall, considered all the pros and cons of the dendrimers, although it is not an accurate mimics of proteins, many properties of dendrimers are still like proteins and they indeed have biological applications.

3.1 Dendritic effect

The dendritic effect is observed when a functional group has different properties when it is alone or linked to a dendrimer; its property could change while the generation of the dendrimers caries. The dendritic effects could be positive or negative, but this effect is very crucial for dendrimers as a catalyst in a certain reaction, since the dendrimer molecules changes the reactivity of certain functional groups in a certain molecule, thus make the reaction possible.

First of all, the dendritic effect could have effect on the reaction yield. For some reactions, this effect is small, but for the others, the effect is dramatic. When the catalytic Stille Coupling reactions were carried out which catalyst was iminophosphine-palladium complex, researchers observed the absence of dendritic effect [14], and this phenomenon was also observed for the palladium-catalyz++ed asymmetric allylic alkylation reaction when the catalyst was dendrimer molecules contain chiral ferrocenyl phosphine-thioether ligands [15]. For dendrimers-catalyzed catalytic C-C cross-coupling reactions which dendrimers' terminal groups were palladium complexes of diphosphino tyramine derivatives, a small dendritic effect has been observed [16]. The dramatic change of the catalytic properties for N-arylations has been observed with a series of dendrimers ended by pyridine-imine ligands complexing copper (I), and the same number of catalytic sites were used in every cases. When the arylation agent in the reaction is iodobenzene, the monomeric complex has no activity. However, all dendrimers from generations 1 to 3 had a very high activity. On the other hand, when the bromobenzene was used in this reaction, the dendrimers' efficiency increased dramatically when the generation increases while the monomer molecules were still not active. This result shows that there is an existence of dendritic effect (Fig. 11) [17]. In a water-hexane biphasic media, when the ruthenium complexes of PTA [18] was used for catalyzing the isomerization of 1-octen-3-ol into3-octanone under strong stirring, the dendritic effect was observed by scientists. On the dendrimers' surfaces, the positive charges existed, which induces solubility in water [19,20], and the reactants and products are both soluble in the organic phase.

In addition, the dendritic effect also has an impact on metal leaching. In the catalysis of metal derivatives, the metal leaching is a serious problem, because it may pollute the products. Thus the cost of the products would increase because of the purification of the products and the loss of valuable metals. In an experiment of biphenyl synthesis using Suzuki Coupling, the Pd leaching was measured, and its amount was decreased while the recycled catalyst was used. Indeed, the Pd leaching measured by ICP-MS. After the first run, it was 274 ppm (ca. 14% of introduced Pd). After the second run, it was110 ppm (ca. 6%). After the fifth run, it was 35 ppm (ca. 2%) and after the 10th run, it was 9 ppm (ca. 0.5%). These results showed that outside the ligand, there was a non-specific binding of Pd, and most of it was removed in the extraction procedures during first two runs. [21].

3.2 Redox catalysis

Redox-switchable catalysis, a.k.a RSC, is now more and more important. In RSC, the electron donating ability of a ligand was influenced by the oxidation and reduction. Thus, the catalyst's selectivity and activity may also change [22]. Although this phenomenon has been noticed and studied by scientists for a long time, this method has not been applied very often to dendrimers as catalyst before. The method was applied to the dendrimer with ferrocenyl phosphane ligands for complexing Ru(p-cym)Cl2 (cym = cymene) and the monomer was used as a catalyst to the isomerization of allylic alcohol. Overall, the

dendrimer has relatively higher efficiency than the monomer of catalyzing this reaction. During oxidation process, addition of 1 equivalent of [Fe{5-C5H4C(O)Me}Cp][BF_4] per catalytic function causes an obvious reduced rate. In this step, some catalyst precipitated, and cause the loss of activity of reagents. After reduction with [FeCp*2] (Cp* = C_5Me_5), all the catalysts become soluble again, and the catalyst, which is nearly fully conversed, remains the similar properties and reactivity with the one before the reaction, as shown in figure 3 [23]. And figure 4 shows the reaction of copper catalyzed arylations.

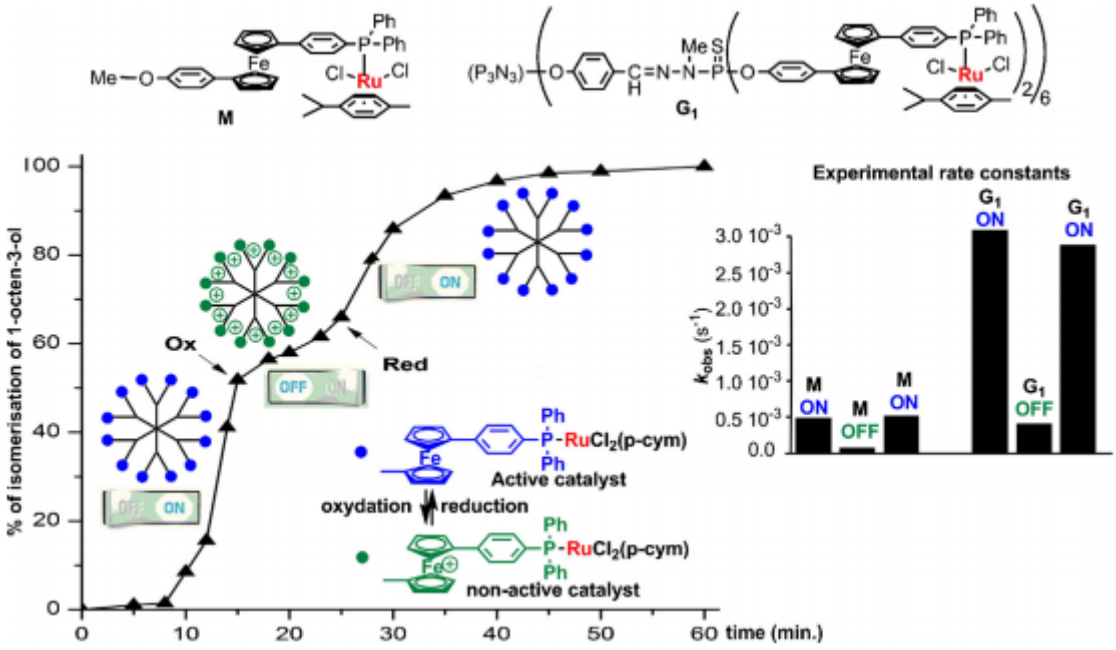

Figure 3. Switch ON/OFF/ON experiments carried out with a monomer and a first generation dendrimer for the isomerization of 1-octen-3-ol into 3-octanone (the graph on the left corresponds to the percentage of isomerization with time induced by the dendrimer in the switch process) [23]

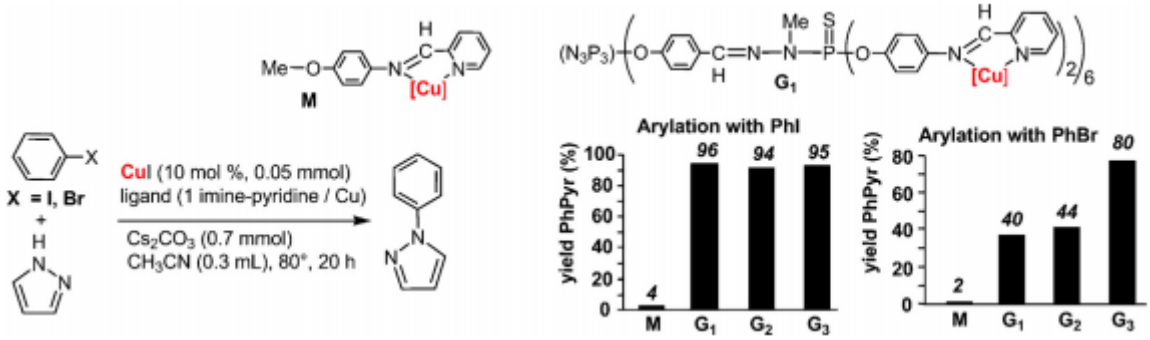

Figure 4. Copper catalysed arylations [23]

4. Applications of dendrimers

4.1 Biological applications of dendrimers

Metallodrugs are traditionally believed as good anti-cancer medicines. However, the applications of dendrimers are not only limited as anti-tumor therapies, but also more broaden uses, such as antimalarial, antibacterial, or neuro-protector agents, anti-arthritis medicine, etc. Dendrimers and their corresponding monomers, which have either N-(pyridin-2-ylmethylene)ethanamine, or N-(di(pyridin-2-yl)methylene)ethanamine, or 2-(2-methylenehydrazinyl)pyridine terminal groups were synthesized from generation 1 to generation 3, which is shown in figure 5. All of these compounds show very great

resistance to the tumor cells and very good anti-proliferate activities. Dendrimers have been applied therapeutically in gene therapy as well [24]. Also, there are also more other uses of dendrimers. For example, Pravinkumar et al., reported that people could use the branches of dendrimers to encapsulate the drug molecules. Thus, this method provides the possibility of dendrimers to interact with poorly soluble drugs, and it improves drug stability, bioavailability and control of drug release [25]. Their size, ease of preparation, functionalization and possibility to attach multiple surface groups renders dendrimers as suitable vehicles for ophthalmic drug delivery [26]. Vandamme et al., reported that the residence time of Pilocarpine in the eyes improved with the use of Poly(Amidoamine) dendrimer with carboxylic or hydroxyl surface groups [27].

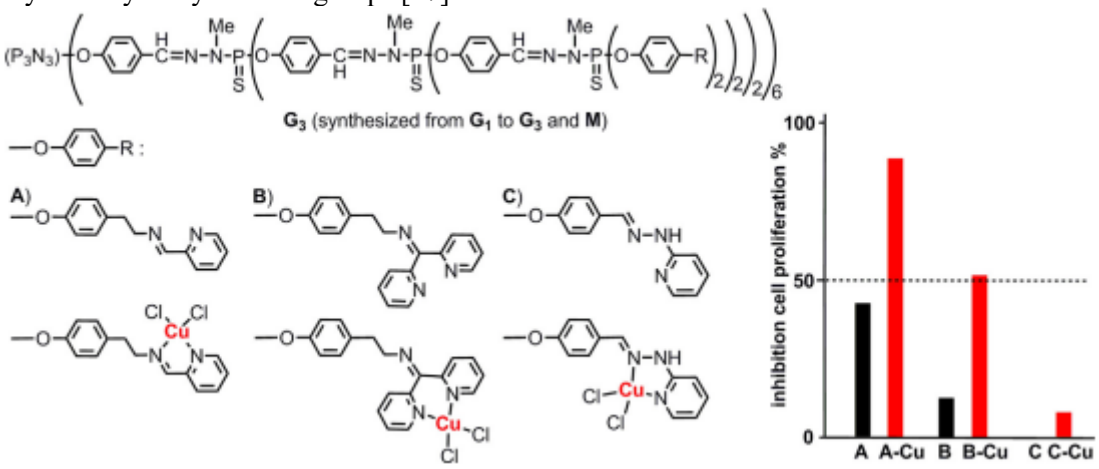

Figure 5. Dendrimers with different diaza ligands as terminal groups and the corresponding copper (II) complexes. (A) N-(pyridin-2-ylmethylene) ethanamine series; (B) N-(di(pyridin-2-yl)methylene)ethanamine series; (C) 2-(2-methylenehydrazinyl)pyridine series. Graph: Anti-proliferative activity of couples of G3 dendrimers (free ligands and complexes) toward HL60 cells after a 72 h exposure, expressed as the percentage of cell growth inhibition at 1 M concentration of dendrimers [24].

4.2 Environment

Since dendrimers have large number of surface functional groups, they can attach to different substances' surface, therefore they would act as useful adsorbents for analytical and electro-analytical procedures in environmental studies. Shahbazi et al., accounted the use of functionalized SBA-15 mesoporous silica gel with Poly (Amidoamine) dendrimer (PAMAM-SBA-15) for the removal of Cu(II), Pb(II) and Cd(II) ions from aqueous solutions [28]. Similarly, Carmo and Piam reported their investigation of Copper adsorption on Chloropropylsilica gel surface functionalization with G-3 Poly (Propyleneimine) hexadecaamine dendrimer (Dab-Am-16) [29].

4.3 Sensors

The unique structures and properties of dendrimers evolved interest in interfacing nanoscale dendrimers in the sensing of chemical and biological species. It is on record that various nanoparticles are used in the development of miniaturized, rapid, ultrasensitive and inexpensive environmental monitoring devices.

5. Conclusions

In the past few decades, the researches and reviews of the synthesis and characteristics of dendrimers are already revealed a lot of useful facts about the dendrimers. As relatively new developed molecules, dendrimers have different structures from traditional polymers and thus have more advantages compared to traditional polymers in certain roles, therefore scientists figured out many applications of dendrimers. Moreover, since scientists have more recognitions about dendrimers themselves, structural and

functional groups can be incorporated into dendrimers in specific positions. Potentially, it gives the chemist so much control over dendritic architecture and functionality, which could improve certain functions of the periphery groups. However, more work should be done in order to make the process of functionalizing dendrimers more cost effective, so future researches about dendrimers are still necessary.

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