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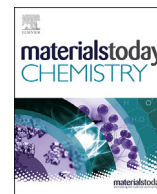
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Poly(amidoamine) dendrimers: covalent and supramolecular synthesis



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ABSTRACT

Dendrimers, a class of synthetic macromolecules which are notable for their well-defined ramified structures and unique multivalent cooperativity, hold great promise for developing various functional materials. Among all the reported dendrimers, poly(amidoamine) (PAMAM) dendrimers are the most extensively studied by virtue of their readily availability via robust synthesis as well as their dendritic structure and peptide/protein mimic features. Since the seminal report by Tomalia et al., various strategies have been made available for PAMAM dendrimers, including divergent and/or convergent synthesis alongside click chemistry. Nevertheless, preparation of high-generation and defect-free PAMAM dendrimers on a large scale remains challenging. To overcome the limitations, an alternative strategy based on self-assembling approach has emerged for dendrimer synthesis, where small dendritic components form large non-covalent supramolecular structures that mimic high-generation covalent dendrimers. This approach is easy to implement in practice and requires much less synthetic effort. Here, we present a brief overview of the different approaches established for PAMAM dendrimer synthesis. We start with a general introduction to dendrimers and the common strategies for dendrimer synthesis, and then we illustrate the specific approaches for PAMAM dendrimer synthesis and highlight the related advantages and limitations using representative examples. Although various strategies have been established for PAMAM dendrimer synthesis, innovative concepts and approaches are still in high demand for reliably preparing defect-free and high-generation dendrimers in large quantity.

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1. Introduction

Dendrimers are a special family of synthetic polymers which have a unique dendritic architecture characterized by regular emanation of cascade-branched repeating units from a focal point and a large number of end groups on the surface (Fig. 1) [1–4]. The term ‘dendrimer’ was coined by chemists to describe molecules with tree-like dendritic feature, and originated from the Greek words ‘dendron’ and ‘mer’, which refer to ‘tree’ and ‘part’, respectively [5,6]. By definition, dendrimers possess a well-defined ramified structure consisting of three distinct parts: (1) a central core, where a dendrimer growth begins; (2) repetitive branching units, which allow for dendrimer growth in geometrically organized

radial layers (named as generations); and (3) the numerous terminal functionalities exposed on the surface (Fig. 1) [5]. These structural features make dendrimers distinctly different from traditional linear, branched, and hyper-branched polymers and endow dendrimers with unique functional properties and multivalent cooperativity confined within a small 3-dimensional space. Dendrimers are therefore extremely appealing materials for a wide variety of applications such as sensors, devices, catalysis, diagnostics, drugs, and delivery systems in areas varying from environmental protection, energy production to human health.

Among all the dendrimers established, poly(amidoamine) (PAMAM) dendrimers (Fig. 2) are the most extensively studied ones. With a large number of amide and tertiary amine functionalities in the interior and primary amine terminals on the surface, the very first PAMAM dendrimers developed by Tomalia et al. were originally envisioned to mimic proteins [5]. The peptide-mimicking amide backbones along with numerous interior and terminal

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which endows them with well-controlled structures and narrow polydispersity. Dendrimer synthesis can be achieved using divergent or convergent approaches or a combination of both (Fig. 3) [1,3,4,17]. The divergent strategy involves construction of the dendrimer from a multifunctional core which is extended outward by a series of repetitive reactions (Fig. 3A). In contrast, in the convergent strategy, dendrimers are built from small molecules that start at the dendrimer surface and eventually end up attached to a central core through a series of inward-oriented reactions (Fig. 3B) [18].

Using the divergent approach, dendrimers can be synthesized up to generation 10 or even more. However, structural defects are a critical concern for the synthesis of high-generation dendrimers because they inevitably arise from incomplete reactions or side-reactions that occur because of the increasing number of reactions and steric hindrance as the dendrimer grows [17]. In addition, dendrimers with structural defects are often extremely difficult to separate from intact dendrimers because of their similar chemical compositions and physical properties. In contrast, using the convergent approach, we can have much better control over dendrimer synthesis, hence reducing or even suppressing structural defects. Also, impurities generated during convergent synthesis can be easily separated as these impurities are usually very different from the synthesized dendrimers in size, structure, and physical properties. However, the reactivity to reach the interior core is often considerably reduced because of the increasing steric congestion as the dendrimer generation increases. Therefore, only low-generation dendrimers can be successfully prepared using the convergent method.

A combined divergent/convergent approach, also called the double-stage convergent approach (Fig. 3C), has been further developed and applied for dendrimer synthesis to combine the advantages of divergent and convergent synthesis [18,19]. This approach involves the synthesis of building blocks using a

divergent approach followed by the convergent dendrimer assembly. In addition, the number of reaction steps required for dendrimer synthesis and purification can be reduced, making the preparation of higher generation dendrimers more efficient compared with either divergent or convergent synthesis [17]. Another advantage of this approach is the ability to modify the building blocks during dendrimer synthesis, thus endowing the dendrimers with structural diversity.

High yield and completion of each individual reaction at each synthetic step is crucial to maintain the purity and consistency of a dendrimer. 'Click chemistry', by virtue of its high yield, high efficiency, high atom economy, short reaction time, and mild reaction conditions [20], has emerged as a popular approach for preparing various dendrimers [21–24]. Successful implementation of click chemistry has been achieved in dendrimer synthesis using the divergent, convergent, or combined divergent/convergent approach. In addition, great strides have been made in using click chemistry to deliver simplified and accelerated dendrimer synthesis yet with diverse structural complexity.

Historically, the first dendritic structures, also called 'cascade molecules', were fabricated using divergent synthesis by Vögtle et al. in 1978 (Fig. 4A) [25]. Although these molecules were small, they marked the beginning of the concept of dendritic molecules. In 1985, Tomalia et al. reported the divergent synthesis of PAMAM dendrimers, the first complete dendrimer family synthesized from generation 1 to 7 (Fig. 4B), with molecular weights reaching over 50000 Da [5]. This seminal work spurred unprecedented interest among the scientific community in all aspects of dendrimer science including chemical synthesis, structural characterization, functional evaluation, and various applications. Later, Fréchet et al. performed the first convergent synthesis of a family of poly(arylether) dendrimers [26,27]. Soon after, they further established a combined divergent/convergent approach for dendrimer

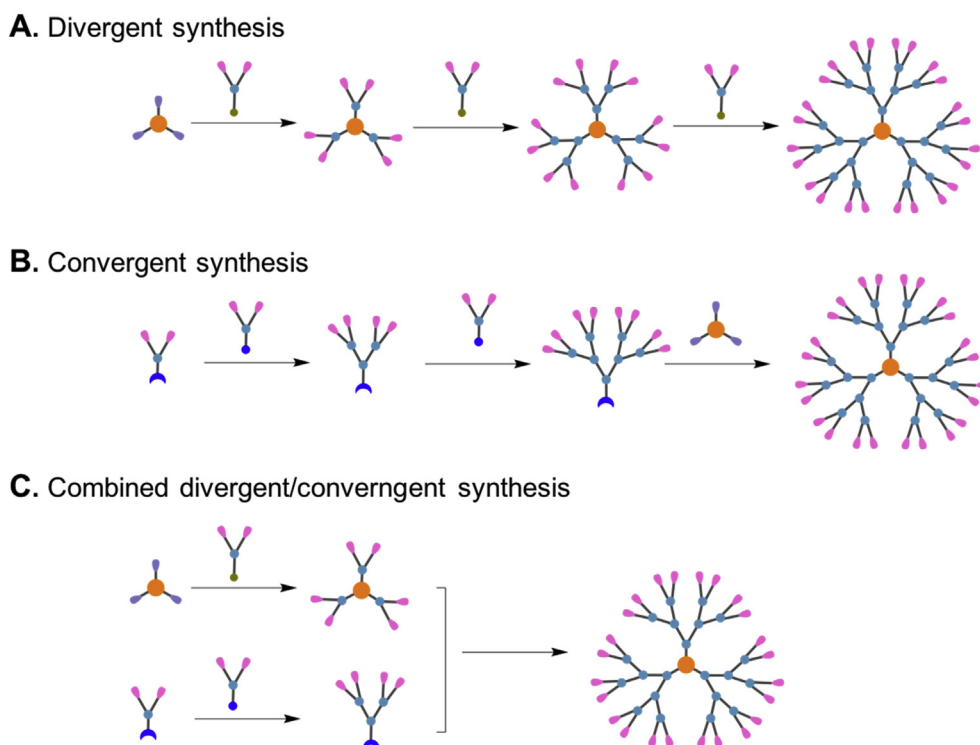


Fig. 3. Cartoon presentation of the different approaches for covalent dendrimer synthesis: (A) the divergent approach, (B) the convergent approach, and (C) the combined divergent and convergent approach.

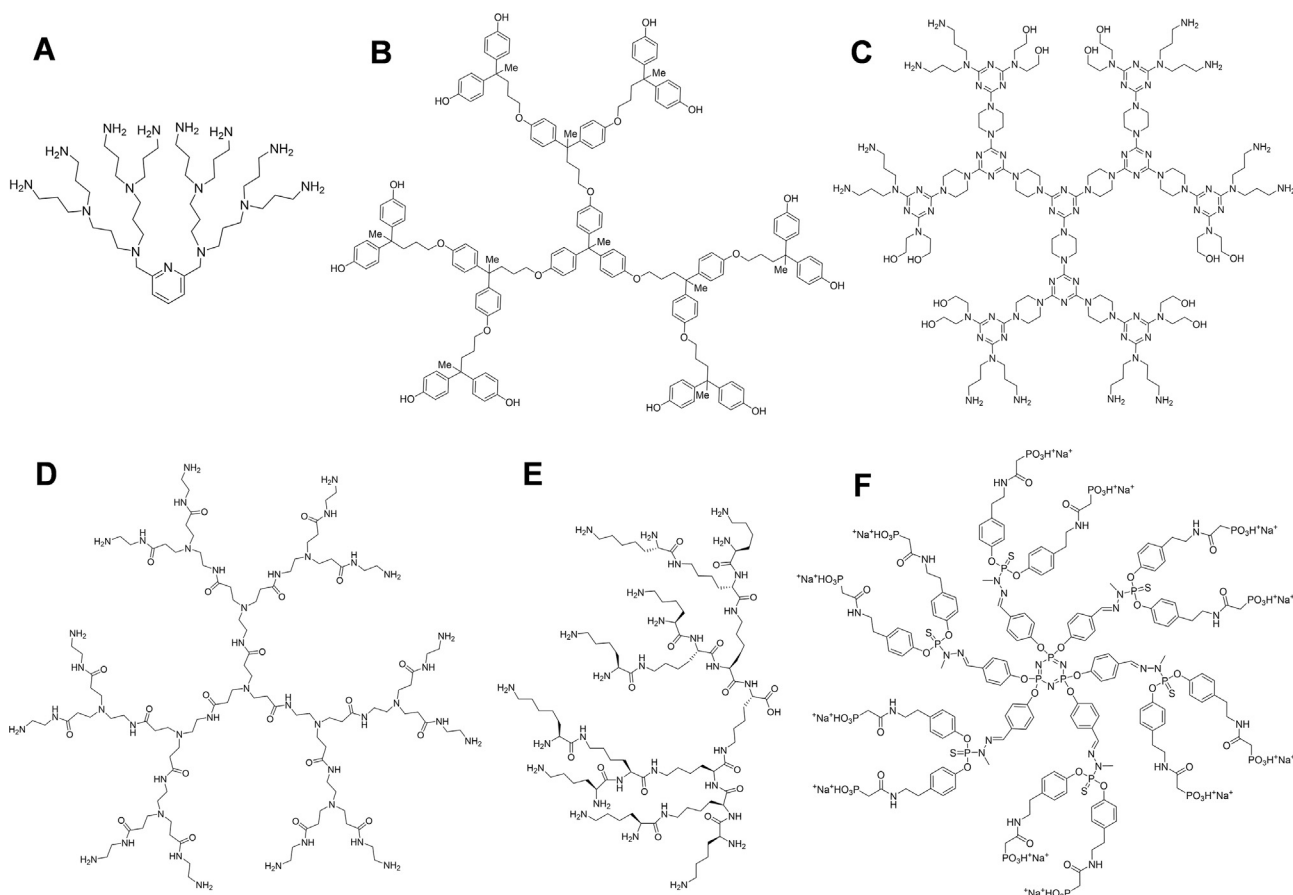


Fig. 4. Examples of different dendrimers: (A) 'cascade molecule' [25], (B) poly(arylether) dendrimer [19], (C) triazine dendrimer [37], (E) polylysine dendrimer [36], (D) NH_3 -core PAMAM dendrimer [5], and (F) phosphorus dendrimer [38]. PAMAM, poly(amidoamine).

synthesis [19]. This double-stage convergent approach combined the advantages of both divergent and convergent methods to deliver accelerated dendrimer synthesis with structural diversity. In 2004, the first example of dendrimer synthesis using click chemistry was reported [24]. Since then, click chemistry has made an important contribution to dendrimer synthesis thanks to its high yield, simplicity, and rapidity, as well as its capacity for structural diversity. Today, a wide variety of dendrimers have been created and reported. These include peptide dendrimers, polyester dendrimers, polyamine dendrimers, polyether dendrimers,

carbohydrate dendrimers, triazine dendrimers, carbosilane dendrimers, and phosphorus dendrimers (Fig. 4) [28–36]. Collectively, the reported dendrimers possess remarkable structural and chemical diversity.

In contrast to the methods listed above for covalent dendrimer synthesis, an alternative concept has recently emerged to advance dendrimer synthesis through the self-assembly of small dendritic components into large non-covalent supramolecular dendrimers (Fig. 5) [39–43]. In the self-assembling process, supramolecular structures can be created in a reversible yet modular and

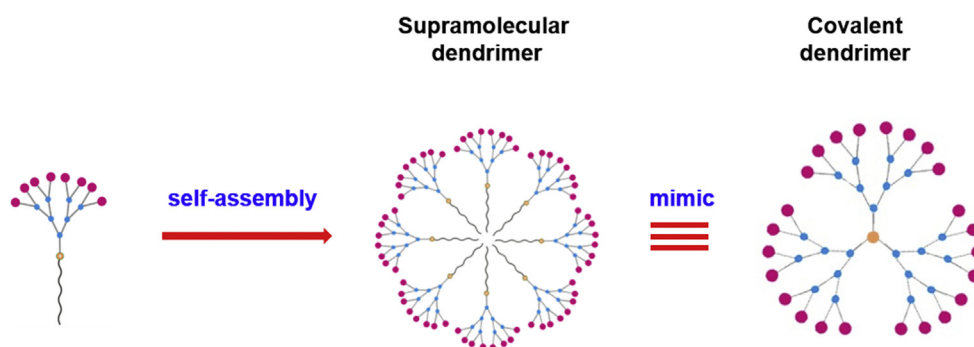


Fig. 5. Cartoon presentation of the self-assembly approach for the synthesis of a non-covalent supramolecular dendrimer to mimic the covalent high-generation dendrimer [43]. Reproduced with permission of Wiley-VCH from Ref. [43].

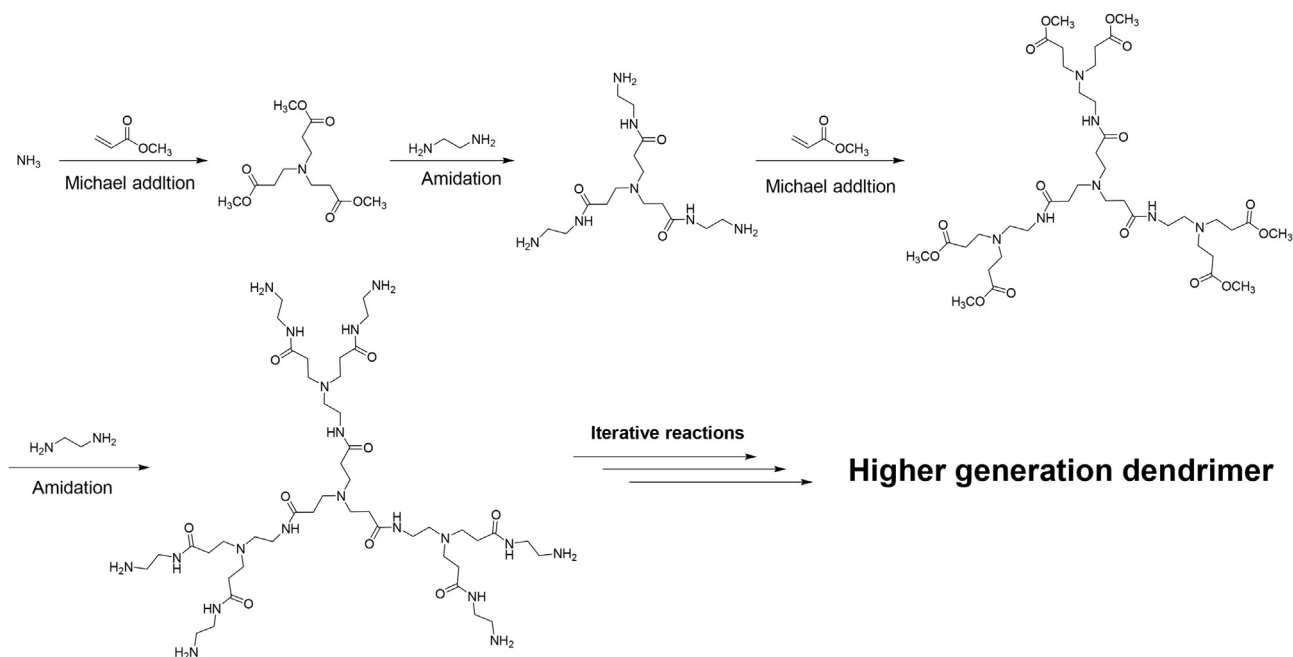


Fig. 6. Divergent synthesis of ammonia core PAMAM dendrimers via the iterative two-reaction sequences consisting of Michael addition and subsequent amidation [5,6]. PAMAM, poly(amidoamine).

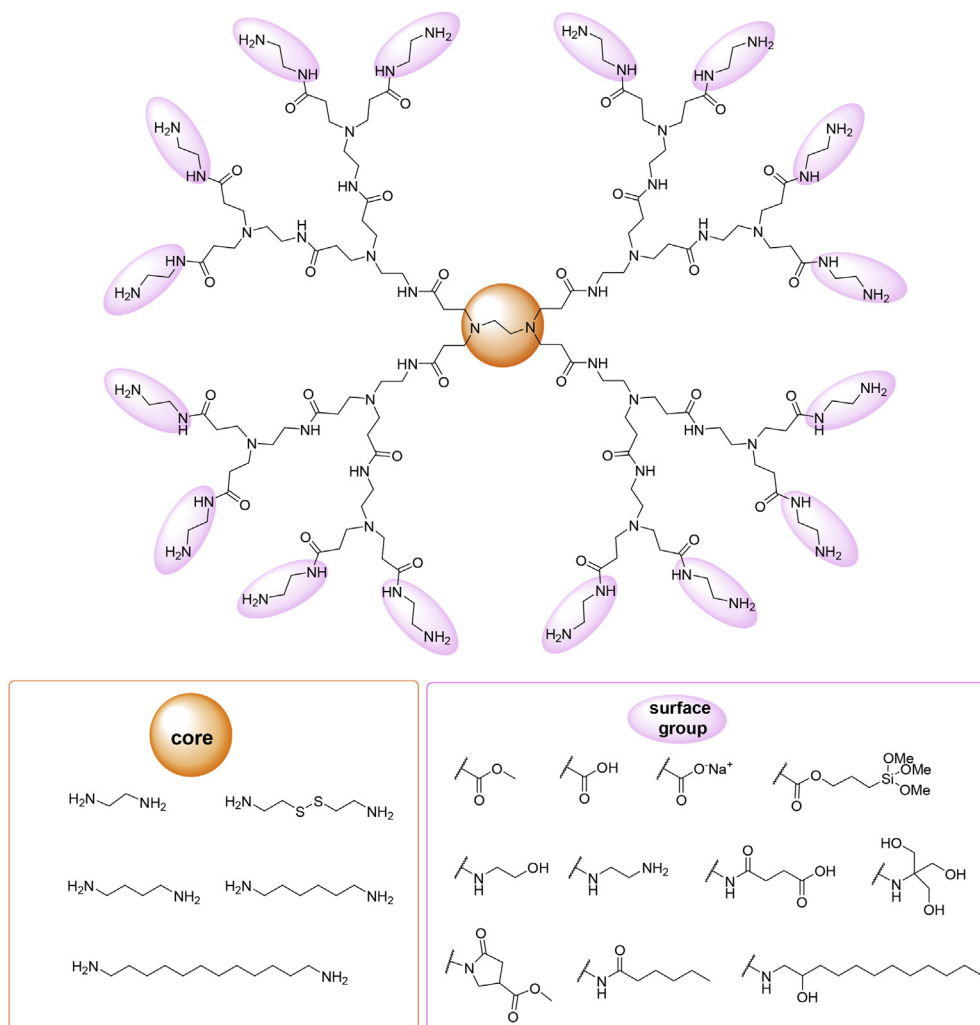
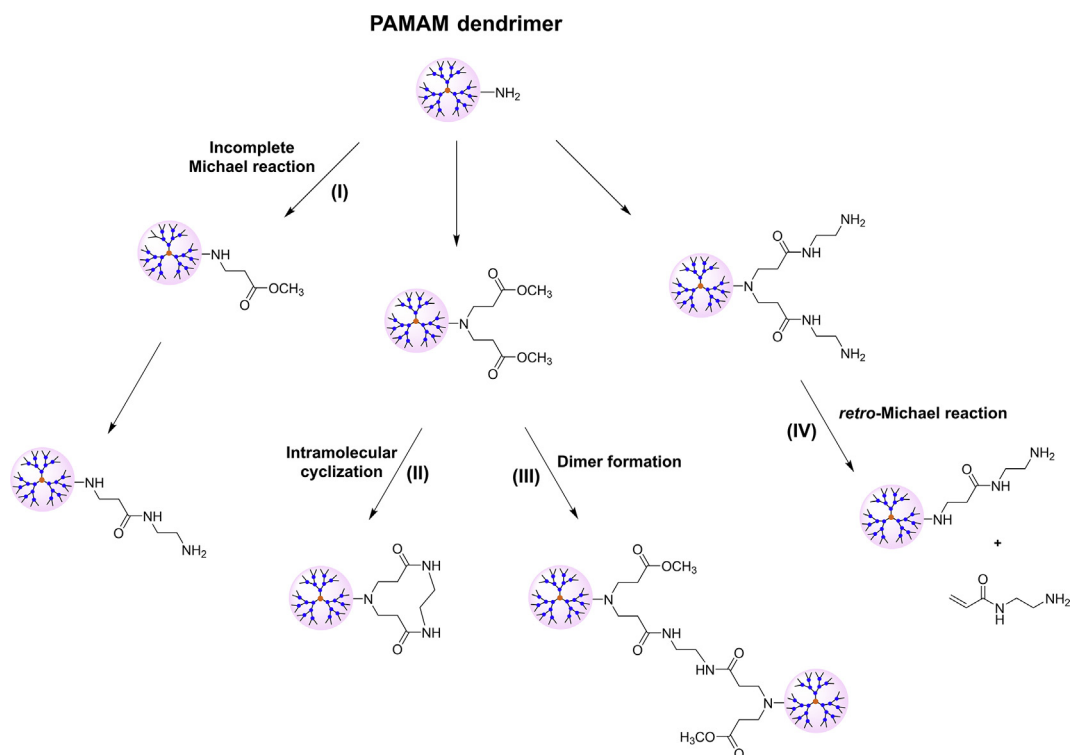


Fig. 7. Commercially available PAMAM dendrimers with different cores and terminal functions [51–54]. PAMAM, poly(amidoamine).



controlable way via multiple non-covalent interactions among small building units. Of particular interest is that the self-assembled structures can have completely new properties which are distinct from those of the component molecules [44]. Therefore, self-assembly is a promising approach in modern molecular science for the creation of new materials [45–47]. Self-assembling supra-molecular dendrimer construction has offered ever simplified and cost-effective synthesis of dendrimers with completely new properties [39–43,48,49]. The concept of self-assembly of supramolecular dendrimers is new, and the synthesis is easy to perform in

practice. It is therefore extremely appealing and offers a fresh input into dendrimer synthesis and the related applications.

3. PAMAM dendrimer synthesis

As we have mentioned in the introduction, PAMAM dendrimers are the most extensively investigated dendrimers for a wide range of applications including molecular devices, sensors, catalysts, drugs, diagnostics, drug-delivery vehicles, etc. PAMAM dendrimers are widely used because they are readily synthesized [50]. Below,

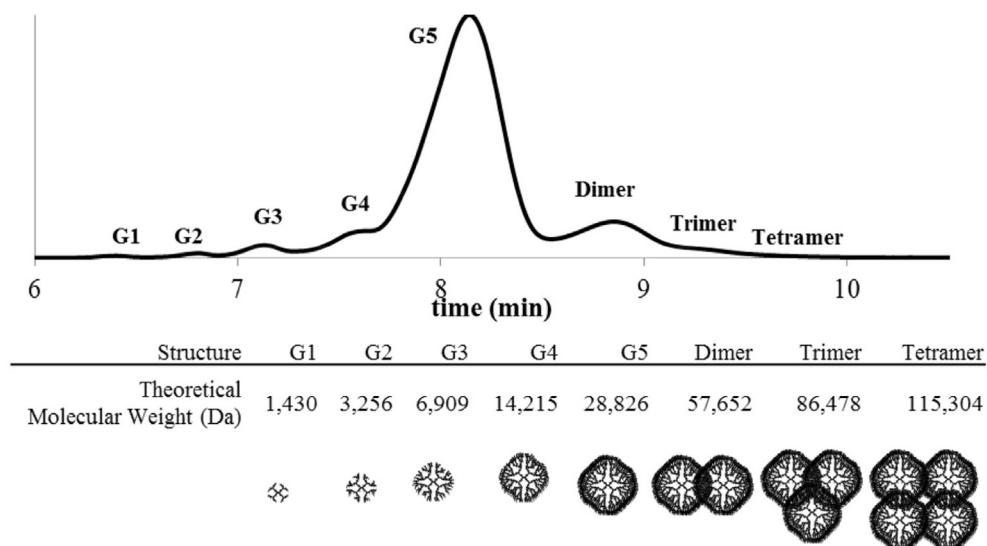


Fig. 9. HPLC chromatogram of as-received PAMAM dendrimer of generation 5 from a commercial source [56]. PAMAM, poly(amidoamine). HPLC, high-performance liquid chromatography. Reproduced with permission of Elsevier from Ref. [56].

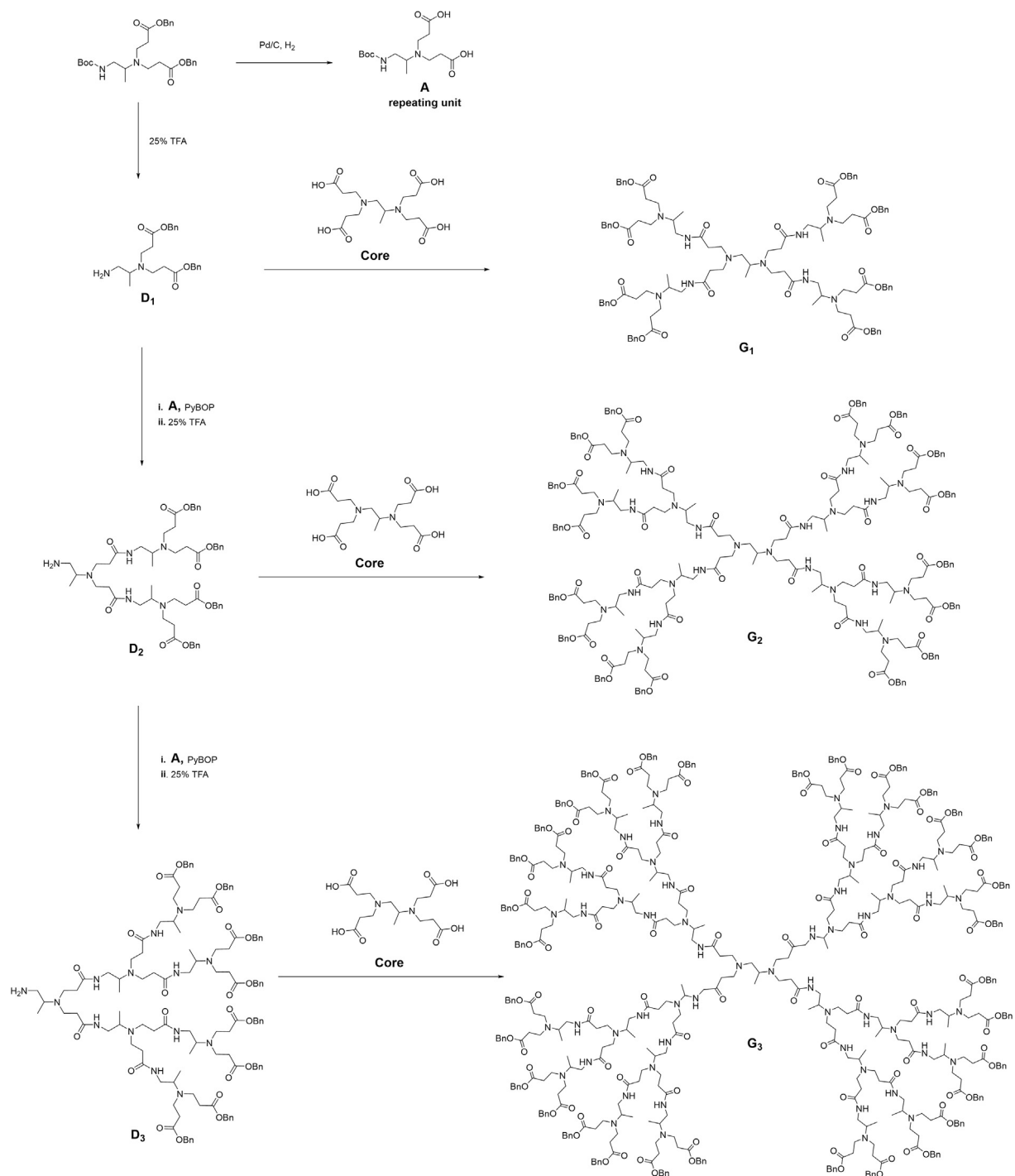


Fig. 10. Convergent synthesis of PAMAM dendrimers using peptide synthesis chemistry [61]. PAMAM, poly(amidoamine).

we will illustrate the different approaches explored and established for PAMAM dendrimer synthesis. These approaches encompass not only covalent dendrimer synthesis using divergent and convergent synthesis alongside click chemistry but also supramolecular dendrimer construction via self-assembly. It is worth noting that PAMAM dendrimers can be also prepared using solid-phase synthesis in addition to the conventional solution-phase synthesis. We will present PAMAM dendrimer synthesis using representative examples of covalent synthesis, supramolecular synthesis, and synthesis on a solid support. For each method, we will comment on

the advantages and restrictions related to dendrimer synthesis in general and PAMAM dendrimers in particular.

3.1. Covalent synthesis

3.1.1. Solution synthesis

3.1.1.1. Divergent synthesis. In 1985, Tomalia et al. reported the first PAMAM dendrimer synthesis using a divergent approach, involving an iterative two-reaction sequence consisting of Michael addition and amidation (Fig. 6) [5,6]. Their synthesis started with an amine-

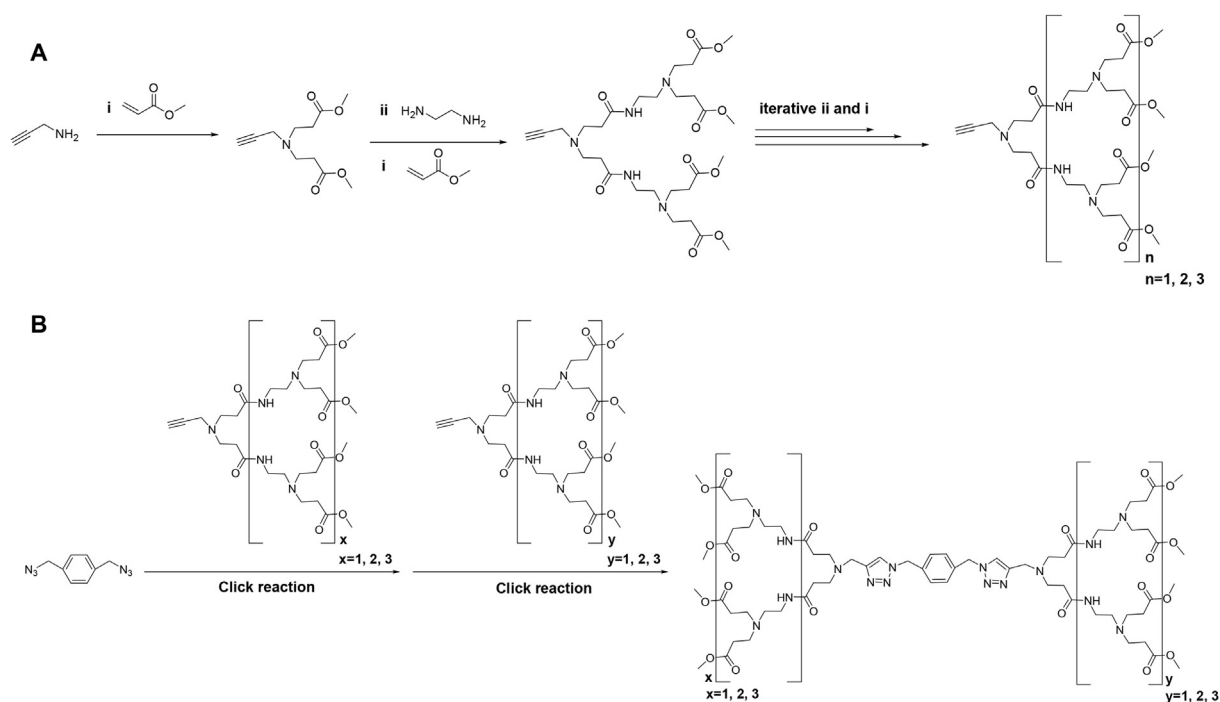


Fig. 11. Convergent synthesis of PAMAM dendrimers involving click chemistry [62]. (A) Divergent synthesis of PAMAM dendrons bearing the alkyne functionality; (B) convergent synthesis of symmetrical and asymmetrical PAMAM dendrimers using click chemistry. PAMAM, poly(amidoamine).

bearing core such as NH_3 or ethylenediamine (EDA), which underwent Michael addition with methyl acrylate to generate ester-terminated dendrimers, also referred to as the half-generation of PAMAM dendrimers. Subsequent amidation of the ester-terminated dendrimers using ethylenediamine yielded the amine-terminated PAMAM dendrimers. The overall synthesis of PAMAM dendrimers was performed under very mild conditions, using a large excess of methyl acrylate in the Michael addition and ethylenediamine in the amidation reaction, which allowed the corresponding dendrimers to be obtained with high yields. The remaining excess methyl acrylate and ethylenediamine were removed conveniently *in vacuo* because both of them are relatively volatile. Further purification procedures such as precipitation and dialysis were also applied to purify the ester-terminated and amine-terminated PAMAM dendrimers, respectively. By repeating these synthesis/purification procedure cycles, higher generations of both the ester-terminated and amine-terminated PAMAM dendrimers were obtained, with generations up to 7 [5].

It is worth noting that the ester-terminated PAMAM dendrimers can be further subjected to hydrolysis to deliver the corresponding carboxylic acid-terminated dendrimers. Alternatively, by replacing ethylenediamine with ethanolamine in the amidation step, hydroxyl-terminated PAMAM dendrimers can be synthesized. Fig. 7 illustrates the commercially available PAMAM dendrimers with different cores and terminal groups [51–54]. The functional terminals, such as amine, hydroxyl, and carboxylic acid groups, can be further modified or conjugated easily to yield various PAMAM dendrimer conjugates with desired properties and functions for diverse applications.

Despite highly efficient synthesis of PAMAM dendrimers using Tomalia's method, multiple structural defects can result from various side-reactions such as incomplete Michael addition, *retro*-Michael reaction, intramolecular cyclization, and/or dimerization during amidation (Fig. 8) [5,6,55]. Incomplete Michael reaction yields dendrimers with missing branching arms, whereas the close

proximity of the terminal groups and the dendrimer molecules gives rise to intramolecular cyclization and intermolecular dimerization during the amidation step. Also, *retro*-Michael reaction is a common problem at elevated temperatures ($>60^\circ\text{C}$), although it can be reduced considerably by using a reaction temperature below 60°C . As a consequence of the *retro*-Michael reaction, a branching chain is cleaved, and a defective dendrimer with one missing branch is formed. The resulting defective dendrimer is able to undergo further Michael addition with ethylenediamine to generate additional defective dendrimers.

In the case of PAMAM dendrimers, defects occur inevitably beyond generation 4 because of structural crowding. Very often, the defective dendrimers are difficult to separate from the intact dendrimers because of their similar chemical compositions and physicochemical properties. Fig. 9 shows the HPLC chromatogram at 210 nm of as-received G5 dendrimer from a commercial source [56]. It highlights the presence of trailing generation impurities as well as oligomerization defects.

Many applications require high-purity dendrimers, in particular biomedical applications [50]. It should be mentioned that dendrimer defects have been implicated in the failure of a significant preclinical trial focused on the development of dendrimer-based targeted delivery of an anticancer drug [57,58]. Therefore, special attention should be paid to the dendrimer synthesis and the related purification process. It is advisable to verify the purity of the commercially available PAMAM dendrimers [59] and further purify them via dialysis or preparative high-performance liquid chromatography when the dendrimer purity is a concern [56,60]. Consequently, the synthesis of high-generation and defect-free PAMAM dendrimers on a large scale is by no means trivial and constitutes a highly demanding technical challenge.

3.1.1.2. Convergent synthesis. Besides divergent synthesis of PAMAM dendrimers, Christensen et al. applied the convergent approach to construct PAMAM dendrimers (Fig. 10) [61]. They

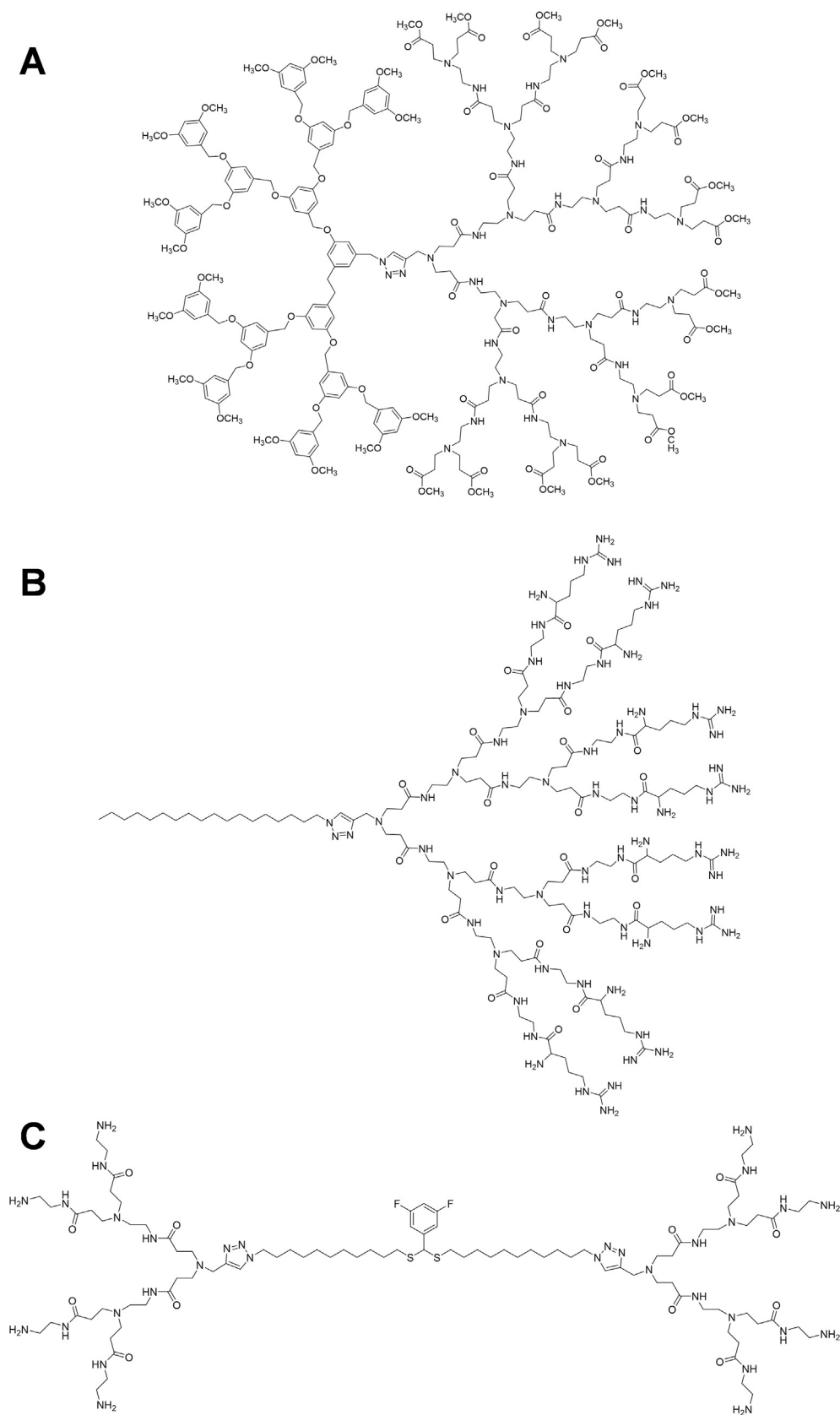


Fig. 12. Examples of (A) a Janus dendrimer [78], (B) an amphiphilic dendrimer [69] and (C) a bola-amphiphilic dendrimer [67] synthesized using the convergent approach in combination with click chemistry.

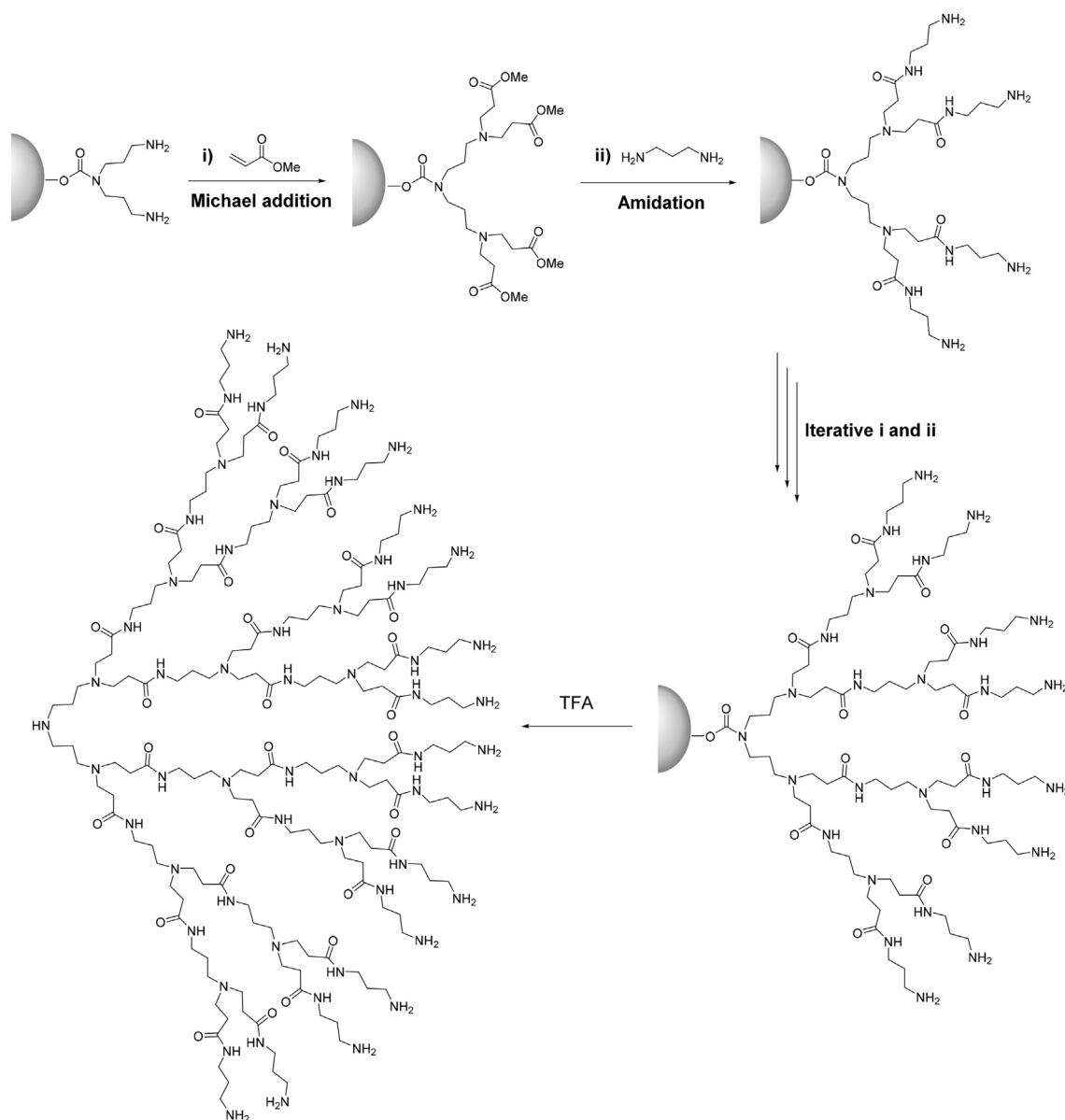


Fig. 13. Solid-phase synthesis of PAMAM dendrimers via iterative Michael addition and amidation [70]. PAMAM, poly(amidoamine).

first prepared PAMAM dendrons from generation 1 to 3 using the divergent approach via iterative amide bond formation and amine-deprotection. This reaction sequence was completely different from Tomalia's synthesis yet widely used in peptide synthesis. The obtained amine-bearing dendrons were then coupled with the dendrimer core harboring four carboxylic acid terminals to deliver the corresponding PAMAM dendrimers. Because of the steric hindrance generated in the convergent synthesis with high-generation dendrons, only dendrimers up to generation 4 could be prepared using this method. This is far lower than the dendrimers prepared using the classical divergent method developed by Tomalia.

Lee et al. further established convergent synthesis by taking advantage of click chemistry to assemble PAMAM dendrimers (Fig. 11) [62,78,79]. PAMAM dendrons bearing the alkyne functionality were prepared first in high yield using the classic divergent method developed by Tomalia (Fig. 10A). Subsequent conjugation with azide-bearing cores via click chemistry offered

either symmetrical or asymmetrical PAMAM dendrimers by assembly of either the same or the different dendrons, respectively (Fig. 10B). Also, only dendrimers up to generation 4 could be prepared because of the steric congestion created in high-generation dendrons. It is worth noting that click chemistry in combination with convergent synthesis has been then widely applied to prepare various Janus dendrimers, amphiphilic dendrimers, and bola-amphiphilic dendrimers [63–68]. Fig. 12 illustrates some representative examples of such PAMAM dendrimers.

3.1.2. Solid-phase synthesis

Apart from solution synthesis, solid-phase synthesis has been also applied to construct PAMAM dendrimers (Fig. 13) [70]. Bradley et al. explored solid-phase synthesis of PAMAM dendrimers by making use of the same chemistry developed by Tomalia for solution synthesis, namely, the iterative reaction sequence consisting of Michael addition and amidation. In this way, they obtained PAMAM dendrimers up to generation 4 on a solid support [70]. Bradley et al.

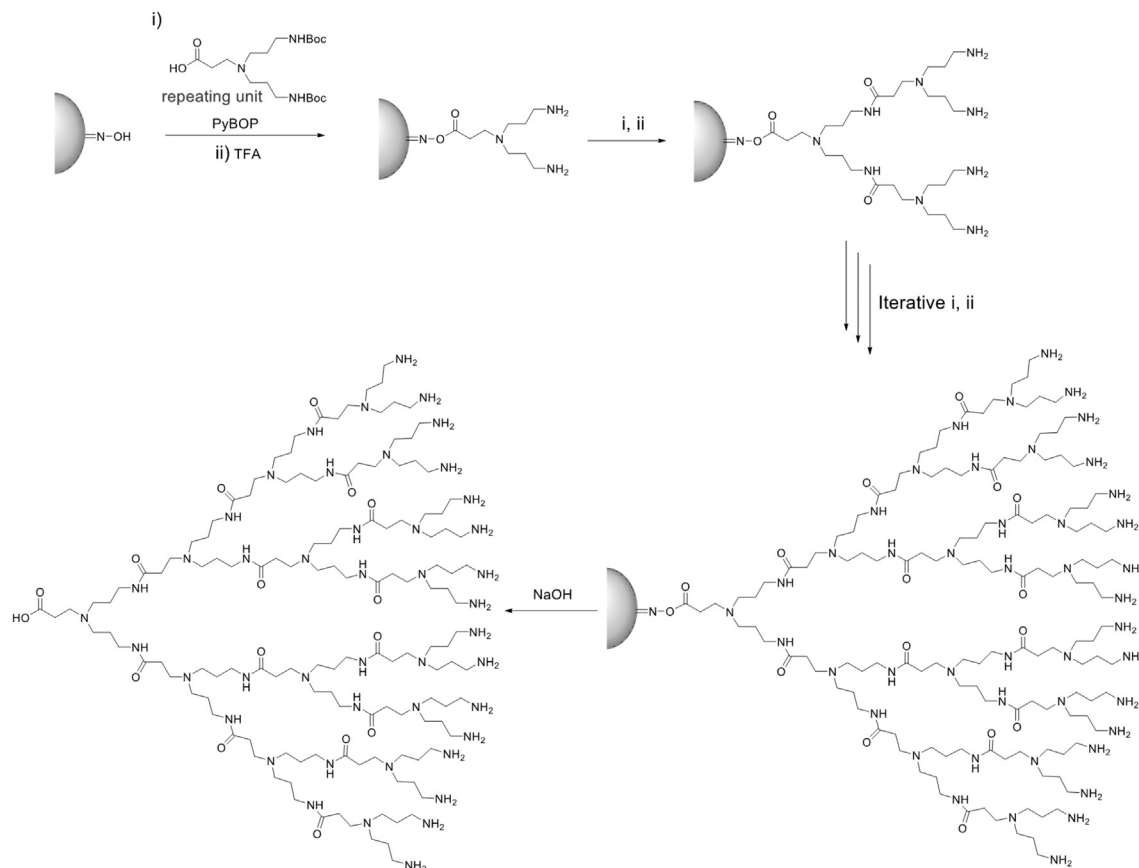


Fig. 14. Solid-phase synthesis of PAMAM dendrimers using peptide synthesis chemistry [73]. PAMAM, poly(amidoamine); TFA, trifluoroacetic acid; PyBOP, (Benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate.

proposed that the dendrimer-functionalized solid supports could be used as super high-loading reagents for solid-phase synthesis [71,72]. By virtue of their multivalency, dendrimer-modified solid supports provide more reactive sites and allow more reactions to occur simultaneously when compared with the conventional solid-phase support [71].

Huang et al. established an ingenious and concise solid-phase synthesis method for PAMAM dendrimers by harnessing peptide synthesis chemistry (Fig. 14) [73]. Using a branching unit which harbors both carboxylic acid and amine terminals, PAMAM dendrimers were synthesized via iterative amide bond formations under the classical peptide synthesis conditions for solid-phase synthesis (Fig. 14). In contrast to the conventional PAMAM synthesis using the two-step iterative protocol consisting of Michael addition and amidation, the peptide synthetic approach significantly shortened the reaction steps, simplified the product purification, and at the same time, prevented the structural defects originating from Michael addition and amidation. This highly efficient protocol was carried out both manually and automatically using a solid-phase peptide synthesizer, enabling synthesis of dendrimers up to generation 7 [74]. Despite all these beneficial advantages, solid-phase dendrimer synthesis has not yet been widely used in practice. This is mainly because the production of dendrimers in the desired large quantities is still a challenging task for solid-phase synthesis.

It is worth mentioning that the PAMAM dendrimers prepared using the peptide synthesis strategy by Huang et al. have the amide bond linkage in the opposite direction [73] compared with the conventional PAMAM dendrimers synthesized using Tomalia's

procedure (Fig. 15). Therefore, these dendrimers are also referred to as inverse PAMAM dendrimers. Also of note is that these inverse PAMAM dendrimers have one more methylene unit in the diamine connecting unit than the conventional PAMAM dendrimers obtained using Tomalia's method [73]. This longer diamine unit is able to prevent the self-cyclization side-reaction during dendrimer growth, and it also ensures that the inverse PAMAM dendrimers are similar in size to the PAMAM dendrimers prepared using Tomalia's approach.

3.2. Supramolecular synthesis

Self-assembly of small dendritic components into large non-covalent supramolecular dendrimer systems is a practical and cost-effective approach to create large dendrimers. This is because the cumulative effects of multiple non-covalent interactions allow the assembly of small dendritic building blocks into large supramolecular dendrimers in a reversible and controllable way, which can be harnessed to establish specially designed functional materials. For example, we have recently established supramolecular dendrimers using various self-assembling small amphiphilic dendrimers which bear long hydrophobic alkyl chains and small hydrophilic PAMAM dendrons (Fig. 16) [43,49,64,65,67,69,75,76]. The synthesis of the small amphiphilic dendrimers was achieved via click chemistry by convergent coupling of the hydrophobic core with hydrophilic PAMAM dendrons obtained by the divergent approach using Tomalia's method [49,64–66,69]. The obtained amphiphilic dendrimers were able to form stable, spherical,

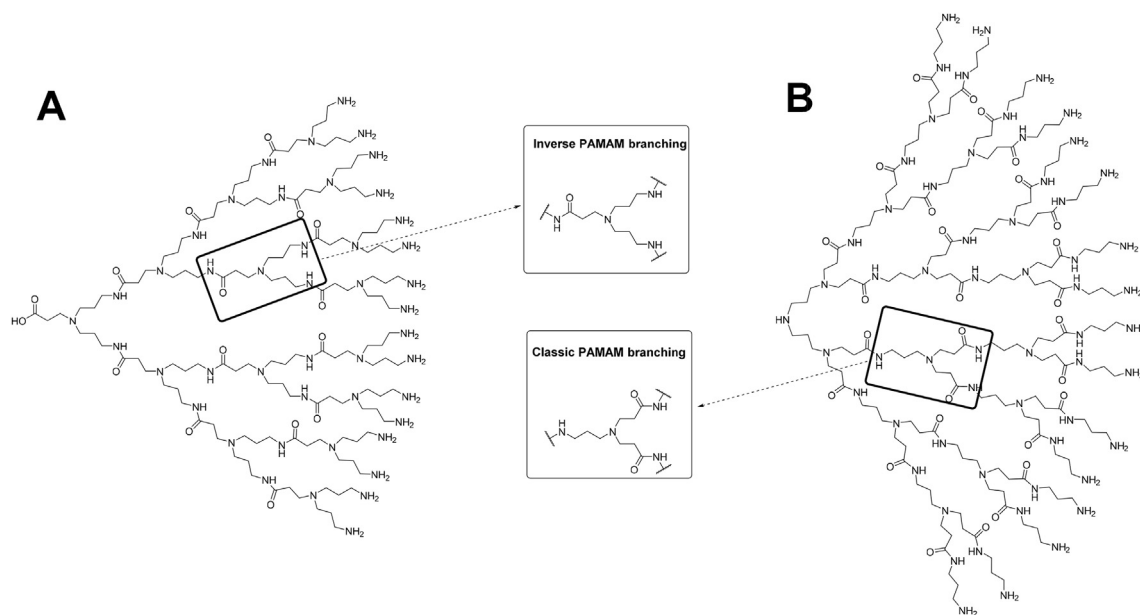


Fig. 15. (A) A PAMAM dendrimer synthesized in the solid phase using the peptide synthesis strategy has the amide bond linkage in the opposite direction compared to (B) a PAMAM dendrimer prepared using the conventional two-reaction procedure [73]. PAMAM, poly(amidoamine).

nanoscale supramolecular dendrimers. These non-covalently constructed dendrimers can be readily controlled and modulated in size and shape by varying the length of the hydrophobic chain and/or the generation of the hydrophilic PAMAM dendron [43,49,75].

Importantly, the supramolecular dendrimers can mimic the covalently constructed high-generation dendrimers for drug delivery and bioimaging. For example, the large void space in the hydrophobic interior was harnessed to encapsulate the anticancer drug doxorubicin with high loading capacity (Fig. 17). This effectively enhanced the potency of the drug and reduced the drug resistance by promoting cellular uptake and decreasing drug efflux [75]. The amphiphilic dendrimers could also be chemically conjugated with multiple copies of a bioactive molecule [66] or an imaging functionality [49] at the PAMAM terminals to construct

self-assembling supramolecular dendrimers for drug delivery and bioimaging, respectively. It is worth noting that the self-assembled supramolecular dendrimer shown in Fig. 16B, which was developed for positron emission tomography imaging, accumulated in tumors via passive tumor targeting mediated by the ‘enhanced permeability and retention (EPR)’ effect [49]. This supramolecular dendrimer, which benefited from both dendrimeric multivalence and EPR-mediated passive tumor targeting, demonstrated superior sensitivity and specificity for tumor imaging when compared with the clinical golden reference, [^{18}F] FDG (2-fluorodeoxyglucose).

It should also be mentioned that the large number of terminal amine groups on the surface of supramolecular PAMAM dendrimers are positively charged at physiological pH, and hence can interact with negatively charged nucleic acids to form stable and

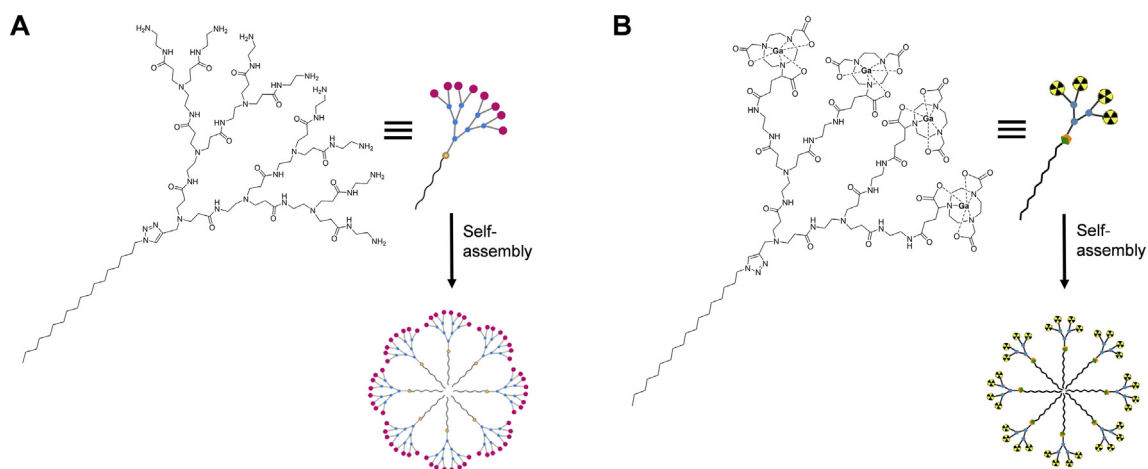


Fig. 16. Supramolecular dendrimers constructed via self-assembly of small amphiphilic dendrimers bearing (A) a hydrophobic C18 alkyl chain and a hydrophilic PAMAM dendron with 8 amine-terminals for nucleic acid delivery [43] Reproduced with permission of Wiley -VCH from Ref. [43] and (B) a hydrophobic C18 alkyl chain and a hydrophilic PAMAM dendron with 4 terminals carrying the radioactive Ga/NOTA-entities for PET imaging of tumors [49]. Reproduced with permission of PNAS from Ref. [49]. PET, positron emission tomography. PAMAM, poly(amidoamine).

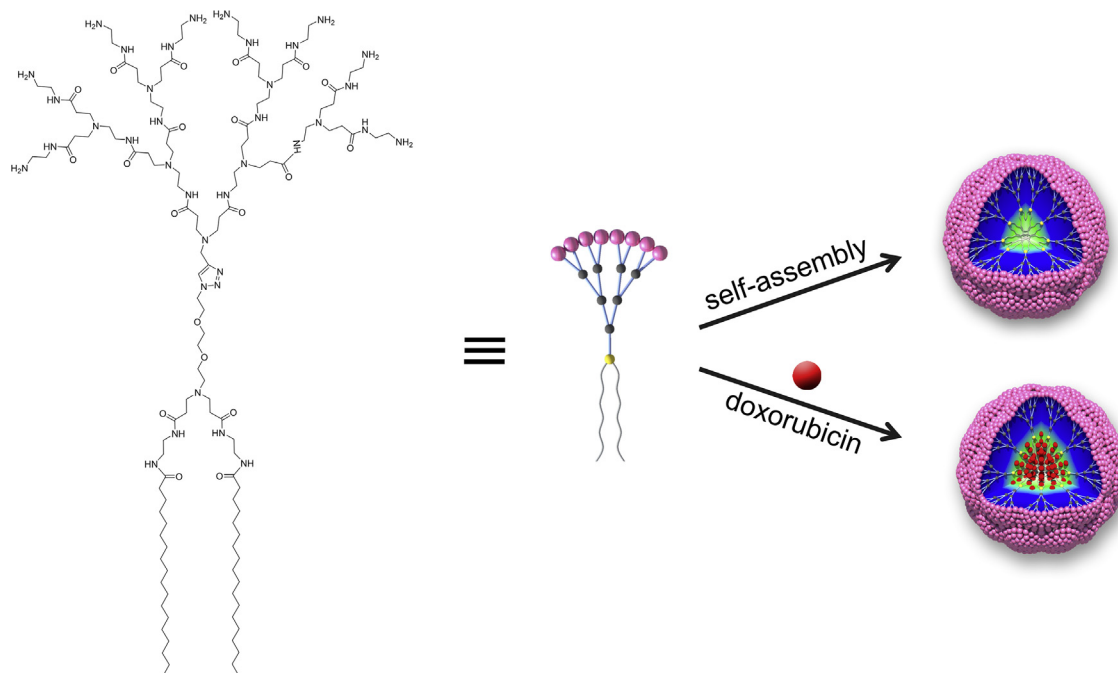


Fig. 17. Self-assembled supramolecular PAMAM dendrimers for drug delivery by physical encapsulation of drug molecules within the interior [75]. PAMAM, poly(amidoamine). Reproduced with permission of PNAS from Ref. [77].

compact nanoscale dendriplexes for nucleic acid delivery (Fig. 18) [43,65]. Some of these supramolecular PAMAM dendrimers even outperformed the currently existing vectors for functional delivery of small interfering RNA, and one of the dendrimers has been scheduled for preclinical and clinical studies [77]. Further decoration on the surface of the formed dendriplexes with a targeting peptide resulted in targeted and specific delivery, leading to much better delivery efficiency [76]. Collectively, these studies

demonstrate that construction of non-covalent supramolecular dendrimers using the self-assembly approach provides a new perspective for creating functional dendrimers with novel and promising properties. We foresee that this self-assembly approach may transform dendrimer synthesis in general and give a fresh boost to the various applications of PAMAM dendrimers as well as other dendrimers.

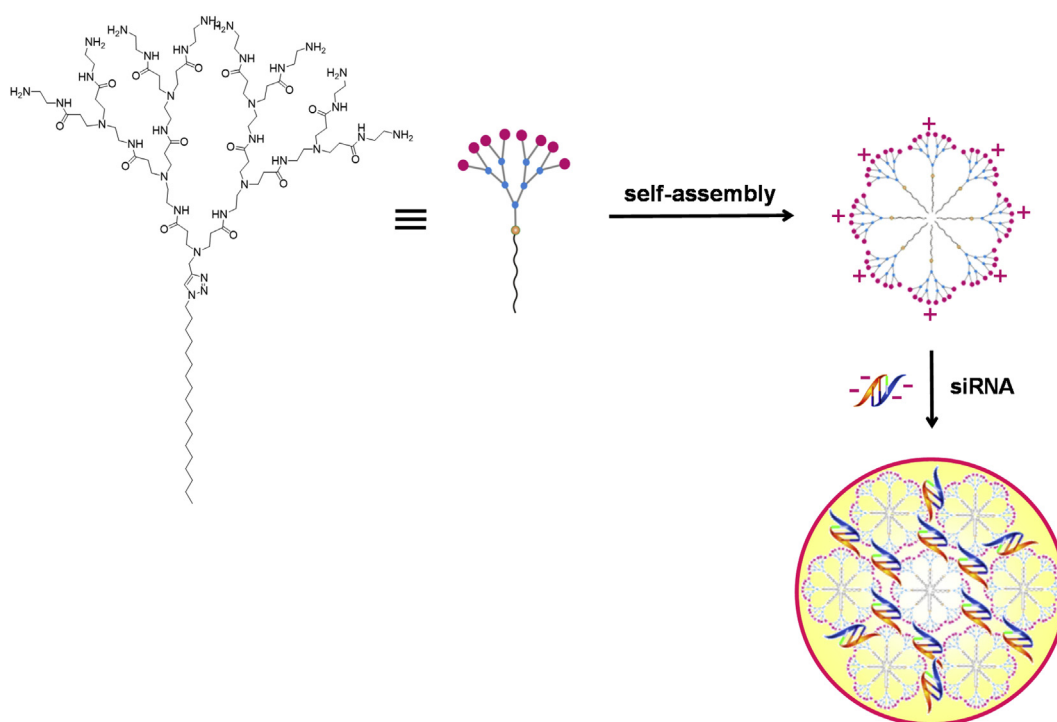


Fig. 18. Exploiting the positively charged amine terminals of self-assembled supramolecular PAMAM dendrimers to compact negatively charged nucleic acid molecules for nucleic acid delivery [43,65,76]. siRNA, small interfering RNA; PAMAM, poly(amidoamine). Reproduced with permission of Wiley-VCH from Ref. [65].

4. Concluding remarks

In this short review, we have presented various approaches for synthesizing PAMAM dendrimers, the most extensively studied dendrimer class. The applications of PAMAM dendrimers in various fields are largely because of their ready availability and peptide/protein mimic features in addition to their well-defined dendritic structures and intrinsically generated multivalent cooperativity. PAMAM dendrimers can be readily prepared using the iterative reaction sequence developed by Tomalia and are easily conjugated with various functionalities. Importantly, some PAMAM dendrimers are commercially available at an affordable price. Therefore, the study of PAMAM dendrimers has flourished, and they have been widely implemented in various applications ranging from molecular devices, sensors, and catalysts to drugs and drug-delivery systems.

Despite the procedures established by Tomalia et al. and the availability of alternative approaches using divergent and/or convergent synthesis in combination with click chemistry, the synthesis of high-generation and defect-free PAMAM dendrimers on a large scale remains a great challenge. The major obstacles include tedious synthesis accompanied by inevitable structural defects and laborious purification. To overcome these limitations, solid-phase synthesis of PAMAM dendrimers has been developed, using either the same chemistry developed by Tomalia or the chemistry stemming from peptide synthesis. However, the practical utility and applications of solid-phase dendrimer synthesis have not yet been fully exploited and approved, in contrast to solid-phase peptide synthesis, which is well established for achieving reliable synthesis of any peptide. We expect continuous interest and engagement in this direction, which will improve solid-phase chemistry for the convenient and efficient synthesis of high-generation and defect-free dendrimers with widely applicable chemistry and structural diversity.

Self-assembly of small and easily synthesized dendritic components into large supramolecular dendrimers has recently emerged as a completely new concept for dendrimer construction. Supramolecular dendrimers can be easily adapted and modulated to generate the desired properties and functions yet with relatively little synthetic effort. This approach has been successfully applied to create non-covalent dendrimers which can mimic covalently constructed high-generation PAMAM dendrimers for nucleic acid and drug delivery. Some of them have proved to be greatly superior to the current lipid and polymer delivery systems. Compared with other polymers and dendrimers, PAMAM dendrimers have many outstanding characteristics that make them highly suitable for biological applications, including their peptide-mimicking amide backbones and their numerous interior and terminal amine functionalities. The advantageous features of supramolecular PAMAM dendrimers, together with their easy synthesis and implementation, hold great promise for various applications in many different fields. Advances in cost-effective synthesis of defect-free and high-generation dendrimers on a large scale are still of paramount importance and will be a key driving force for the practical implementation of dendrimers in serving and benefiting our society. Scientists with dedication and strong determination are actively working in this direction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mtchem.2019.04.004>.

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