

Rapid Synthesis of Polyamide Dendrimers from Unprotected AB₂ Building Blocks

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Dendrimers are well-defined, highly branched, three-dimensional molecules with a large number of reactive end groups. Thus, they are receiving interest as new polymeric materials for applications in areas such as molecular light harvesting,¹ catalysts,² liquid crystals,³ molecular encapsulation,⁴ and drug-delivery systems.⁵

The synthesis of dendrimers via a divergent⁶ or convergent⁷ route involves reiterative growth strategies that require a tedious multistep procedure with a repetitive protection–deprotection and purification processes in each generation. Several methods to shorten these syntheses have been reported⁸ and include double stage, double exponential growth, hypermonomer, and orthogonal coupling strategies. However, these approaches still require multiple steps to obtain high-generation dendrimers.

Rannard et al. recently reported a one-pot multiple-addition convergent synthesis of polycarbonate dendrimers, in which the second-generation dendrimer was obtained by sequential activation of an alcohol unit with 1,1-carbonyl diimidazole and an AB₂ triol.^{9a} In a similar manner, they reported a rapid synthesis of polyamide dendrimers from two kinds of building blocks, dialkylenetriamines and succinic anhydride; however, this method has not been applied to the AB₂ monomer.^{9b}

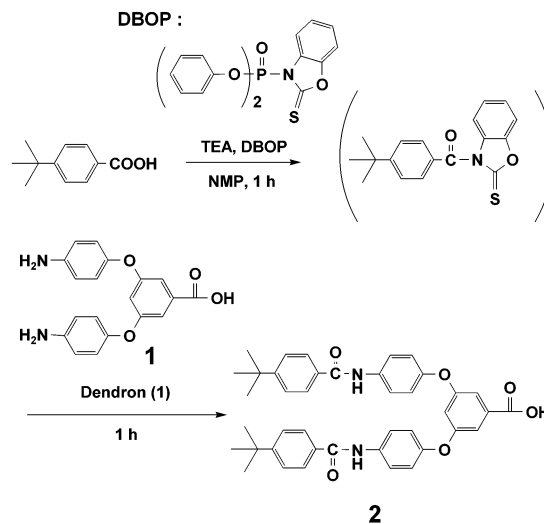
Although various synthetic methods have been developed to prepare dendrimers containing amide functions, they have problems such as poor yield and tedious multisynthetic steps.¹⁰ A simple and convenient synthetic method for polyamide dendrimers has not yet been reported.

We have developed a one-pot synthesis of dendritic polyamides by a divergent method.¹¹ This procedure involves activation of end carboxyl groups with a condensing agent, diphenyl (2,3-dihydro-2-thioxo-3-benzoxazolyl)phosphonate (DBOP),¹² followed by condensation of the active amide with the aminodicarboxylic acid 5-[3-(4-aminophenyl)propionylamino]isophthalic acid hydrochloride as an AB₂ monomer. The resulting dendritic polymers had a high degree of branching (91%) and a narrow molecular weight distribution (<1.1).^{11c} These findings prompted us to develop a rapid synthesis of polyamide dendrimers from unprotected dendrons without repetitive protection–deprotection procedures.

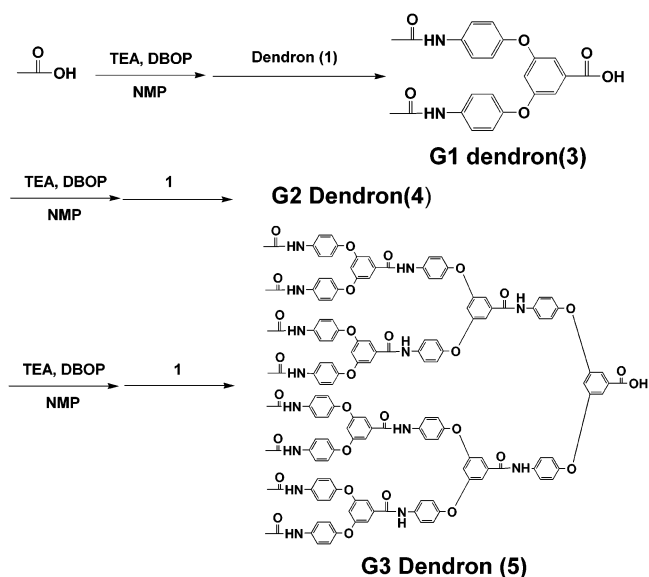
Here, we present a successful rapid synthesis of a perfectly branched third-generation polyamide dendrimer (6) from unprotected 3,5-bis(4-aminophenoxy)benzoic acid (1) as an AB₂ building block by a convergent method using DBOP.

An AB₂ building block should contain one carboxyl and two amino groups to achieve a convergent polyamide dendrimer synthesis using DBOP. Thus we selected 1 as a dendron.¹³ Coupling reactions for the synthesis of dendrons were conducted by a two-step method consisting of (1) activation of a carboxylic acid by DBOP, i.e., generation of an active amide and (2) condensation of this active amide with 1. The molar ratio of DBOP to carboxyl group was very important for the quantitative formation of the active amide and prevention of side reactions such as self-condensation

Scheme 1



Scheme 2



of 1. The reaction of *tert*-butylbenzoic acid with 1 was performed to determine the optimum molar ratio of DBOP to a carboxylic acid in the presence of triethylamine (TEA) in 1-methyl-2-pyrrolidinone (NMP) at room temperature (Scheme 1). The reaction of 1.01 equiv of DBOP with 1 yielded compound 2 in quantitative yield.

The synthetic route of the third-generation dendron is shown in Scheme 2. Dendron 1 reacted with acetic acid as the terminal unit in the presence of DBOP and TEA to yield G1 dendron 3. Both

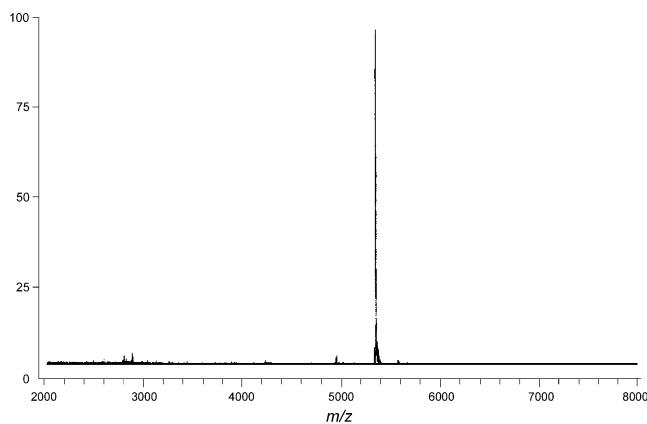
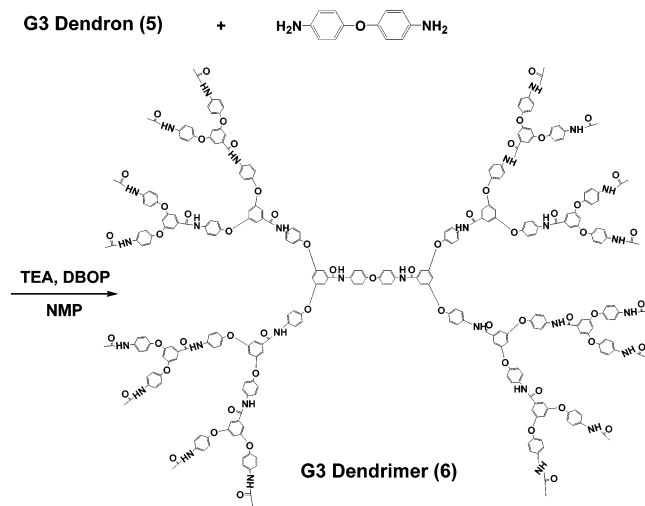


Figure 1. MALDI TOF MS spectrum of G3 dendrimer (6).

Scheme 3



activation and condensation reactions were conducted in NMP for 1 h. The reaction mixture was diluted with methanol and poured into water, producing **3** in 90% yield. The structure of **3** was confirmed by IR and NMR spectroscopy. The IR spectrum of **3** showed strong carbonyl peaks at 1697 and 1658 cm⁻¹ due to carboxyl and amide groups, respectively. All signals in the ¹H NMR spectrum of **3** were clearly assigned to each proton of **3**.

G2 (**4**) and G3 (**5**) dendrons also were prepared by the same coupling method. The activation time of the carboxylic acid and the time for condensation were 1.5 and 2 h, respectively. Each dendron was purified simply by reprecipitation to remove the earlier generation of the dendron. Both dendrons were isolated in 90% yield and characterized by IR, NMR, and MALDI-TOF MS spectroscopy. The MALDI-TOF MS spectra of **4** and **5** showed the expected peaks at 1142.1 and 2606.2 ([M + Na]⁺), respectively. These findings clearly indicated the formation of the desired dendrons.

A dumbbell-shaped dendrimer, **6**, was synthesized from **5** and 4,4'-oxydianiline (Scheme 3). The reaction of **5** and 4,4'-oxydianiline was performed in one step in the presence of DBOP (1.2 equiv for the carboxyl group) and TEA for 2 h and the solution poured into aqueous 3% sodium carbonate. The precipitate was collected, washed with methanol, and then dissolved in *N,N*-

dimethylformamide and the resulting solution was reprecipitated with a mixture of THF and methanol. Dendrimer **6** was obtained in 99% yield. IR, NMR, and MALDI-TOF MS measurements were used to characterize **6**. Figure 1 shows the MALDI-TOF MS spectrum of G3 polyamide dendrimer (**6**) (5354.3, [M + Na]⁺).

Our novel method for the synthesis of dendrimers involves several advantages over the conventional ones. First, protection and de-protection steps are not required for the synthesis of each generation dendron. Second, this new route is rapid and able to produce dendrons each generation that are easily purified by simple solvent extraction and reprecipitation.

In summary, a rapid synthesis of aromatic polyamide dendrimers has been demonstrated by a convergent method, which consists of direct condensation of carboxylic acid and unprotected AB₂ building block using DBOP in NMP. Reactions of each generation proceeded smoothly and chemoselectively to produce product in high yields. The MALDI-TOF MS spectra supported the formation of dendrons and dendrimer. This methodology allows the large-scale and rapid synthesis of dendrimers.

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Supporting Information Available: Synthesis and characterization of G1 (**3**), G2 (**4**), and G3 (**5**) dendrons and G3 (**6**) dendrimer. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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