JOC Notes

Facile Approach for Diblock Codendrimers by Fusion between Fréchet Dendrons and PAMAM Dendrons

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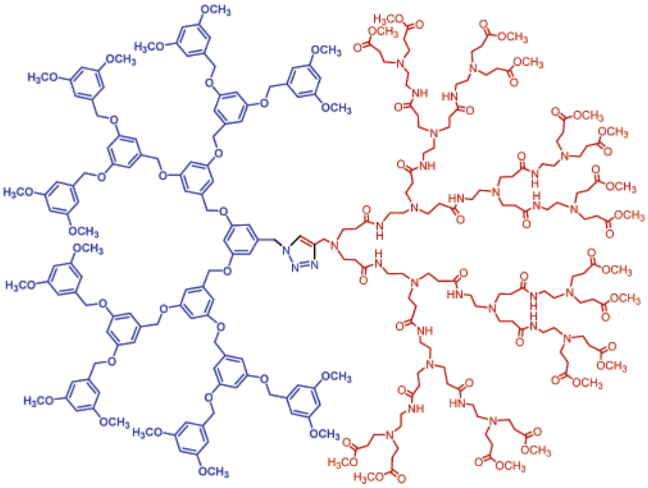

For the first time, a simple and facile approach for the synthesis of diblock codendrimers by fusion between the azide focal point functionalized Fréchet-type polyether and the propargyl focal point functionalized Tomalia-type PAMAM dendrons has been described based on click chemistry, i.e., the copper-catalyzed cycloaddition reaction between alkyne and azide.

Dendrons and dendrimers are the most intensively investigated subset of dendrimers. Dendrimers, prepared by repetition of a given set of reactions using either divergent or convergent methods, are highly branched and regular macromolecules with well-defined structures and used widely as functional objects in nanotechnology and nanoscience.[1] Amphiphilic dendrimers consisting of both hydrophobic and hydrophilic regions within one molecule are an important class of material because of their self-assembly properties. This type of dendrimers has been utilized for various applications from model membranes to drug delivery. The dendritic polymer amphiphiles possessing a hydrophilic dendritic component and a hydrophobic linear polymer (or vice versa) and unimolecular dendritic amphiphiles are well-known,[2] but relatively only few diblock codendrimers have been reported so far. Most of the diblock codendrimers are the surface-modified block dendrimers.[3] The diblock codendrimers composed of two different dendrons can promise superior performance. A general strategy for the synthesis of componently differentiated diblock codendrimers has not been reported.[4] To address this, we herein present a facile approach for the convergent synthesis of block dendrimers by fusion between the Fréchet-type polyether and the Tomalia-type PAMAM dendrons, which are the most widely studied dendrimers. The Fréchet-type polyether[5] dendrons are soluble in organic solvents without any further modification, whereas the Tomalia-type PAMAM[6] dendrons are soluble in both aqueous and organic solvents.

How can different dendrons be stitched together without any problems such as defect(s) or isolation and purification difficulties? The clue was provided by click chemistry, which is the copper-catalyzed 1,3-dipolar cycloaddition reaction between alkyne and azide.[7] This is characterized by reliable 1,4-regiospecific 1,2,3-triazole formations, water tolerance, and toleration of a wide range of functionalities. This reaction has been used in the synthesis of dendrimers and dendritic materials,[8] but the use of this reaction for the synthesis of componently differentiated diblock codendrimers has not been reported. Therefore, in this research, we provided the general methodology to elaborate a synthesis of diblock codendrimers.

A convergent synthetic strategy was used for the synthesis of diblock codendrimers **3-G*mn*** using the Fréchet-type azido-

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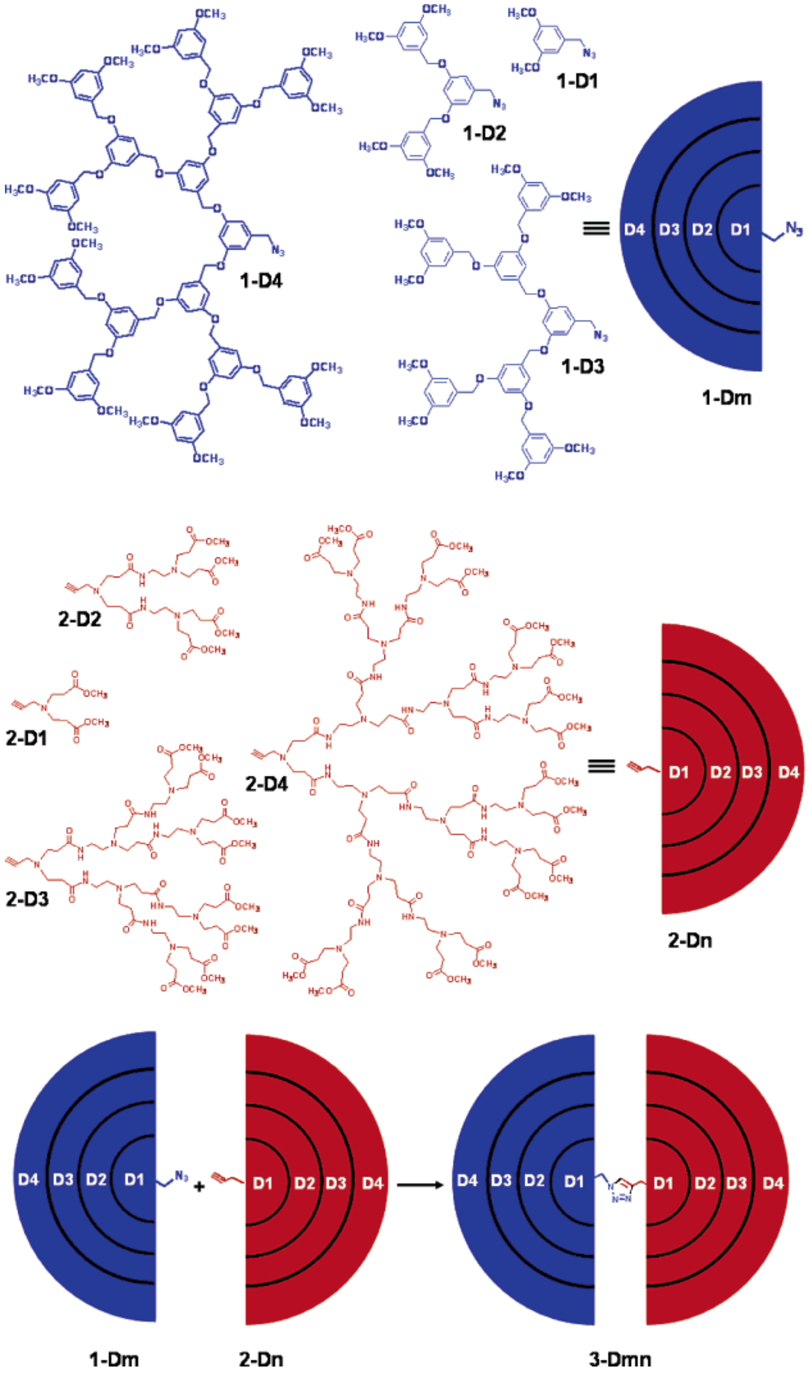

FIGURE 1. Structures of the Fréchet-type azido-dendrons **1-D*m*** and the alkyne-functionalized PAMAM dendrons **2-D*n*** and synthetic strategies of diblock codendrimers via the Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions. Conditions: 5 mol % of $CuSO_4 \cdot 5H_2O$/10 mol % of sodium ascorbate, THF/H_2O (4:1), rt.

dendrons **1-D*m*** and the propargyl-functionalized PAMAM dendrons **2-D*n*** (Figure 1). The Fréchet-type azido-dendrons **1-D*m*** ($m = 1-4$: generation of dendron) were prepared according to the reported procedure.[8f] The propargyl-functionalized PAMAM dendrons **2-D*n*** ($n = 1-4$: generation of dendron) are synthesized by the divergent approach using propargylamine as a propargyl focal point.[9] This approach involves typical stepwise and iterative two-step reaction sequences consisting of amidation of methyl ester groups with a large excess of ethylenediamine and Michael addition of primary amines with methyl acrylate to produce methyl ester terminal groups.

To demonstrate the effectiveness of the dipolar cycloaddition reactions of the azido-dendrons **1-D*m*** and alkyne-dendrons **2-D*n*** in the synthesis of diblock codendrimers, we have experimented with several conditions using various Cu(I) sources in different solvents. Representatively, the reaction of azido-dendrons **1-D1** and alkyne-dendron **2-D1** in the presence of 0.1 equiv of CuI in THF at room temperature for 16 h afforded the desired product **3-G11** with 95% yield. The reaction conducted from the conditions of 5 mol % of $CuSO_4{\cdot}5H_2O$ with 10 mol % of sodium ascorbate in a 4:1 solvent ratio of THF/H_2O for 1.5 h at room temperature afforded the desired product **3-G11** in a yield of 99%. It was found that the desired product was obtained from only the catalytic amount of CuI without amine additive in THF at room temperature and the reaction with Cu(I) species generated in situ from $CuSO_4{\cdot}5H_2O$ was completed within a short time. The accelerated rate of reactions may potentially be explained by anchimeric assistance due to the amine moiety presented in PAMAM dendrons **2-D*n***.

With the success in the synthesis of first generation dendrimer **3-G11**, we extended the same strategy to obtain higher generation dendrimers. The reactions of **1-D2** with **2-D2** and of **1-D3** with **2-D3** afforded the block dendrimers **3-G22** and **3-G33** in yields of 99% and 94%, respectively, after 2 and 3 h. The reaction of **1-D4** with **2-D4** provided the block dendrimer **3-G44** in 89% yield after 4 h. For completion of the reaction between the dendrons, the higher generation dendron takes a longer time than the lower generation dendron due to the steric hindrance (bulkiness) of the dendron. This result showed that the formation of triazole can be regarded as a new connector to construct the diblock codendrimers from two componently different dendrons.

All diblock codendrimers were purified by column chromatography and confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB or MALDI mass spectra. From their ^1H NMR spectra ($CDCl_3$), the peaks of the benzylic protons adjacent to the nitrogen of triazole and the triazole proton in dendrimers **3-G*mn*** were found at 5.42 and 7.39 ppm for **3-G11**, 5.39 and 7.49 ppm for **3-G22**, 5.43 and 7.59 ppm for **3-G33**, and 5.42 and 7.64 ppm for **3-G44**, respectively. As the dendrimer generation increased, the peaks of the triazole proton shifted gradually to downfield, which may be influenced by the PAMAM dendritic effect. However, the peaks of the benzylic protons adjacent to the nitrogen of triazole did not show characteristic difference according to the dendrimer generations. Analysis of the dendrimers by mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete coupling (Figure 2). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI = 1.01−1.08). IR data also confirmed that neither alkyne (~ 3277 cm^{-1}) nor azide (2098 cm^{-1}) residues remain in the final dendrimer (Figure 3).

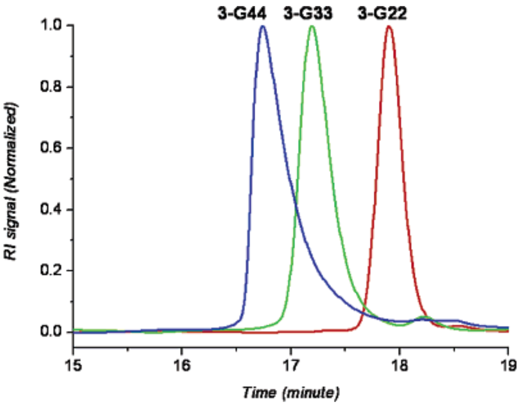

FIGURE 2. GPC diagrams of dendrimers **3-G*mn*** obtained from THF eluent.

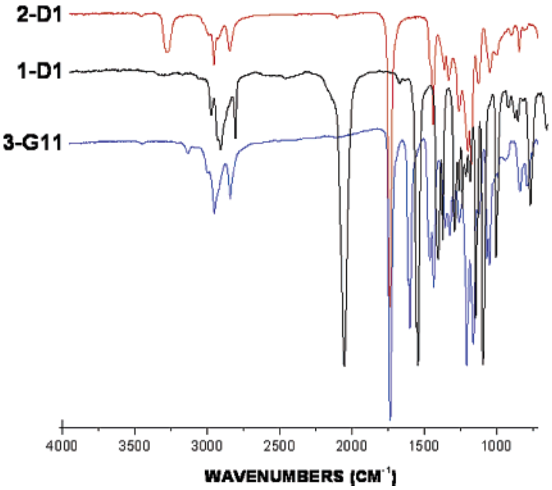

FIGURE 3. IR spectra for **1-D1**, **2-D1**, and **3-G11**.

To probe the viability of our approach, we further extended our work toward the construction of unsymmetrical diblock codendrimers, which are differentiated by the means of the generation of dendrons. We have investigated two synthetic strategies. The first one is based on the reactions of the third-generation Fréchet-type azido-dendron **1-D3** with the alkyne-dendrons. The second strategy involves the reactions using the fourth-generation Fréchet-type azido-dendron **1-D4** with the alkyne-dendrons. The reactions of third-generation azido-focal dendron **1-D3** with **2-D1**, **2-D2**, and **2-D4** in the presence of 5 mol % of $CuSO_4{\cdot}5H_2O$ with 10 mol % of sodium ascorbate in a 4:1 solvent ratio of THF/H_2O afforded the unsymmetrical diblock codendrimers **3-G31**, **3-G32**, and **3-G34** in yields of 99%, 97%, and 94%, respectively, after 2, 3, and 4 h. The reactions of fourth-generation azido-focal dendron **1-D4** with **1-D1**, **1-D2**, and **1-D3** provided the unsymmetrical codendrimers **3-G41**, **3-G42**, and **3-G43** in yields of 99%, 99%, and 95%, respectively, after 1 h 50 min, 2.5 h, and 3.5 h. This result showed that the formation of triazole is found to be an efficient method for the synthesis of unsymmetric diblock codendrimers using the different generations of dendrons. These unsymmetric diblock codendrimers were also confirmed by ^1H and ^{13}C NMR spectroscopy, MALDI mass spectra, and gel-permeation chromatography (GPC).

In summary, we have demonstrated for the first time a general and facile meothod for the synthesis of componently differen-

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ciated diblock codendrimers by fusion between the Fréchet-type polyether and the Tomalia-type PAMAM dendrons based on the copper-catalyzed cycloaddition reaction between alkyne and azide. Furthermore, the coupling between the different generation dendrons afforded the size- and component-differenciated diblock codendrimers. This method may provide insight into design of various block dendrimers such as amphiphilic dendrimers. We are currently studying about the aggregation behavior of the codendrimer.

Experimental Section

General Procedure for the Preparation of Diblock Codendrimers 3-G*mn* from Azido-Fréchet Dendrons 1-D*m* and Propargyl-PAMAM Dendrons 2-D*n*. A mixture of azido-Fréchet dendrons **1-D*m*** (0.11 mmol) and propargyl-dendrons **2-D*n*** (0.10 mmol) in THF−H_2O (4:1, 1 mL) in the presence of 5 mol % of $CuSO_4 \cdot 5H_2O$ with 10 mol % of sodium ascorbate was stirred at room temperature for ∼4 h. The reaction mixture was poured into brine (20 mL), and the resulting solution was extracted with EtOAc (20 mL × 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product **3-G*mn***.

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Supporting Information Available: General methods, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for compounds **3-G*mn***. This material is available free of charge via the Internet at http://pubs.acs.org.

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