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Synthesis of azide-functionalized PAMAM dendrons at the focal point and their application for synthesis of PAMAM-like dendrimers

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Abstract—For the first time, the divergent synthesis of azide-functionalized PAMAM dendrons using azidopropyl amine as an azide focal point and convergent synthesis of symmetric PAMAM-like dendrimers containing 1,2,3-triazole rings as connectors via click chemistry with a dialkyne core is described.

Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.[1] The two most widely studied dendrimer families are the Fréchet-type polyether and the Tomalia-type PAMAM dendrimers. PAMAM dendrimers are synthesized by the divergent approach. This methodology involves building the dendrimers from the core by an iterative synthetic procedure.[2] The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.[3] The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. The most attractive feature of the convergent synthesis is the ability to prepare well-defined symmetrical dendrimers due to its relatively low number of coupling reactions at the final step. Although many methods for the convergent synthesis of various dendrimers were developed, a relatively few methods for PAMAM dendrimer have been reported in the literature.[4] Future applications of dendrimers rely on efficient and practical synthetic procedures. Due to our interest in developing new functional dendrimers, we herein present the first synthesis of azide-functionalized poly(amidoamine) (PAMAM) dendrons **1-Dm** and their application to the convergent synthesis of poly(amidoamine) (PAMAM) dendrimers.

PAMAM dendrons **1-Dm** ($m = 1$–3: generation of dendron) are synthesized by the divergent approach using azidopropyl amine as an azide focal point shown in Scheme 1. Although we have screened several Lewis acid catalyzed Michael addition reactions to find the efficient condition in conjugate addition of free amine, we utilized a standard PAMAM synthesis eventually furnishing us with the ester-terminated dendrons. This methodology involves typical stepwise and iterative two-step reaction sequences, consisting of amidation of methyl ester groups with a large excess of ethylenediamine (EDA) and Michael addition of primary amines with methyl acrylate (MA) to produce methyl ester terminal groups. The reaction of azidopropyl amine and 3.5 equiv of MA in methanol gave dendron **1-D1** in 86% yield. For dendron **1-D2**, dendron **1-D1** reacted with 20 equiv of EDA in methanol and then removal of methanol and excess EDA under vacuum produced the amine-terminated dendron, which was reacted with 7 equiv of MA in methanol to afford dendron **1-D2** in 91% yield. Dendron **1-D3** was obtained from **1-D2** by the consecutive amidation and Michael addition reactions in yield of 64%. All dendrons **1-Dm** were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and their FAB mass spectra.

Building dendrimers via the convergent approach allows the synthesis of symmetric dendrimers and for specific

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Keywords: Alkyne; Azide; Cycloaddition; Dendrimer; PAMAM dendron.

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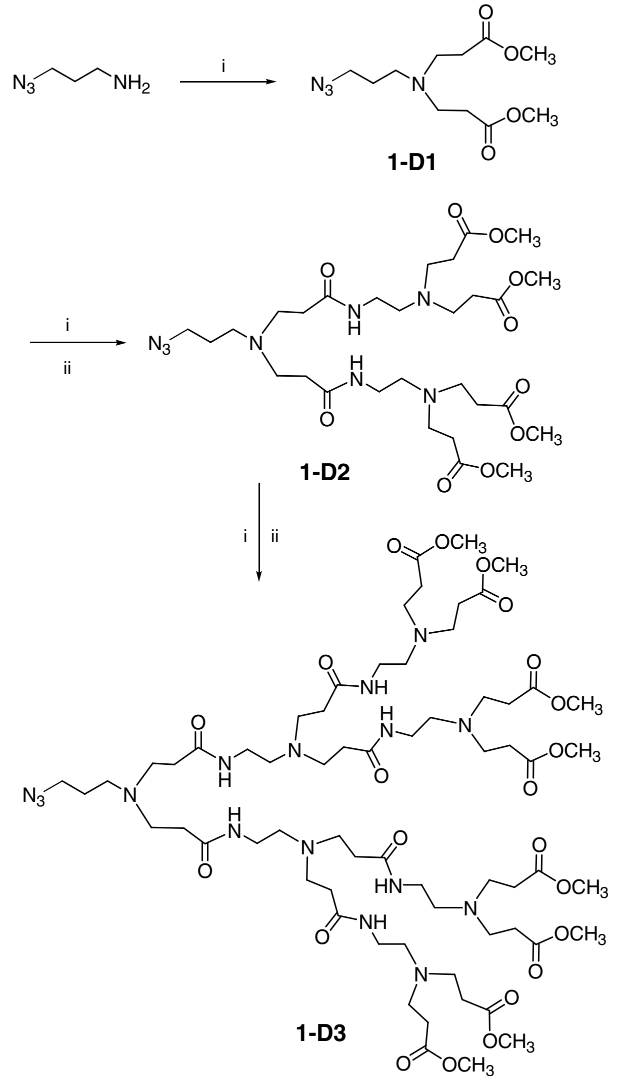


Scheme 1. Reagents and conditions: (i) methyl acrylate, MeOH, rt; (ii) ethylenediamine, MeOH, rt.

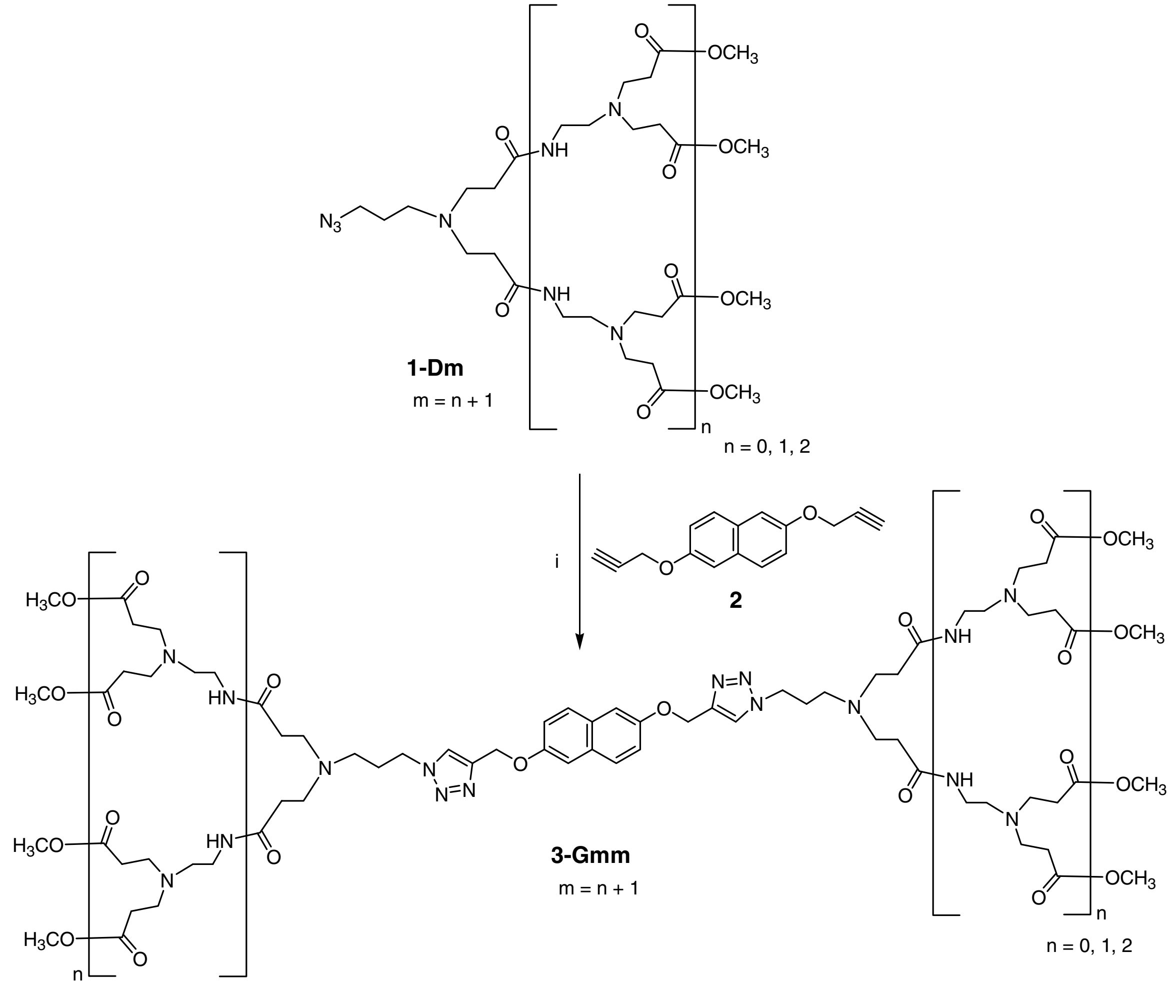
incorporation of function into the dendrimer interior. But, an example in the convergent synthesis of PAMAM dendrimers by the amide coupling between carboxylic acid and amine is reported.[4] To efficiently connect the azido focal point PAMAM dendrons with core unit, we intended to use the click condition using Cu(I) species (Scheme 2). The Cu(I)-catalyzed Huisgen [2+3] dipolar cycloaddition reaction between azides and alkynes is characterized by reliable 1,4-regiospecific 1,2,3-triazole formations, water tolerance, and toleration of a wide range of functionalities,[5] and now appears to offer a simple and reliable dendrimer synthesis method.[6] 2,6-Bis-prop-2-ynyloxynaphthalene **2**, available for dendrimer growth via click reactions with the dendron, was synthesized readily from 2,6-dihydroxynaphthalene and propargyl bromide.[7]

To test the effectiveness of the dipolar cycloaddition reactions of the bis(alkyne) core **2** and azide-dendrons **1-Dm**, we have screened several conditions using various Cu(I) sources in different solvents. We have found that the reaction conducted from the condition of 10 mol % $CuSO_4{\cdot}5H_2O$ with 20 mol % sodium ascorbate in a 4:1 solvent ratio of THF to H_2O for 2.5 h at room temperature afforded the desired product **3-G11** in yield of 99%. The generation and disappearance of the mono-triazole derivative were monitored by TLC runs of the reaction mixture. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers with 5 mol % $CuSO_4{\cdot}5H_2O$ with 10 mol % sodium ascorbate with respect to alkyne in a 4:1 solvent ratio of THF to H_2O. Reactions of the core **2** with 2.1 equiv of **1-D2** and **1-D3** afforded the PAMAM dendrimers **3-G22** and **3-G33** in yields of 95% and 91%, respectively, after 4 and 6.5 h. For completion of the reaction between the dendritic azide and the core, the higher generation dendron takes longer time than the lower generation dendron which can be differentiated by the steric hindrance (bulkiness) of dendron. This result showed that the formation of triazole can be regarded as a new connector to construct the symmetric PAMAM-like dendrimers from dendrons. The triazole residues existing in dendrimers can stabilize Cu(I) species even under aqueous aerobic conditions which may play a crucial role in biological applications. Their copper-binding ability may be used as the ligand properties in homogeneous catalysis.

All symmetric PAMAM dendrimers were confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and FAB mass spectra.[7] From their ^1H NMR spectra ($CDCl_3$), the peaks of the methylene protons adjacent to the nitrogen of triazole and the triazole proton in dendrimers **3-Gmm** were found at 4.36 and 7.77 ppm for **3-G11**, 4.39 and 7.85 ppm for **3-G22**, and 4.41 and 7.93 ppm for **3-G33**, respectively. As the dendrimer generation increased, the peaks of the methylene protons adjacent to the nitrogen of triazole and the triazole proton shifted gradually to downfield, which may be influenced by the dendritic effect. IR data also confirmed that neither alkyne ($\sim 3277\ cm^{-1}$) nor azide ($2098\ cm^{-1}$) residues remain in the final dendrimer (Fig. 1). Their FAB mass spectra were exhibited in very good correlation with the calculated molecular masses (Fig. 2).

A general procedure is described as follows for the preparation of dendrimers **3-Gmm**: A mixture of azido-dendrons **1-Dm** (0.21 mmol) and 2,6-bis-prop-2-ynyloxynaphthalene **2** (0.10 mmol) in THF–H_2O (4:1, 1 mL) in the presence of 10 mol % $CuSO_4{\cdot}5H_2O$ with 20 mol % sodium ascorbate was stirred at room temperature for ~7 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 (EtOAc/methanol system) to afford the desired product.

We have demonstrated for the first time that the azide-functionalized PAMAM dendrons are synthesized by the divergent approach using azidopropyl amine as an azide focal point and that click reactions between bis(alkyne) core and the azide-functionalized PAMAM dendrons lead to the formation of symmetric



Scheme 2. Reagents and conditions: (i) $CuSO_4 \cdot 5H_2O$/sodium ascorbate, THF/H_2O (4:1), rt.

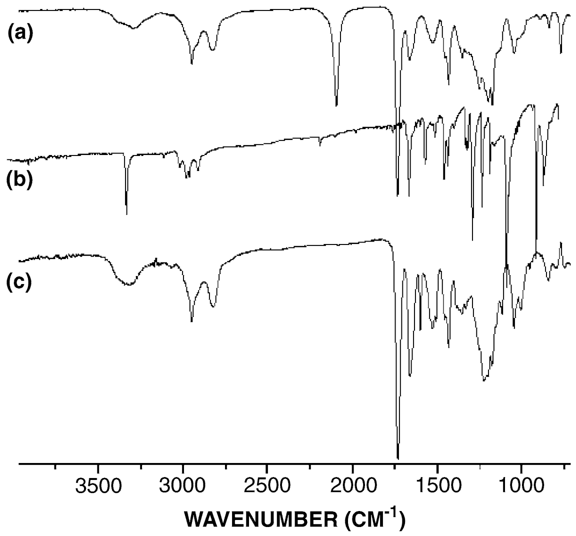


Figure 1. IR spectra for (a) **1-D2**, (b) **2**, and (c) **3-G22**.

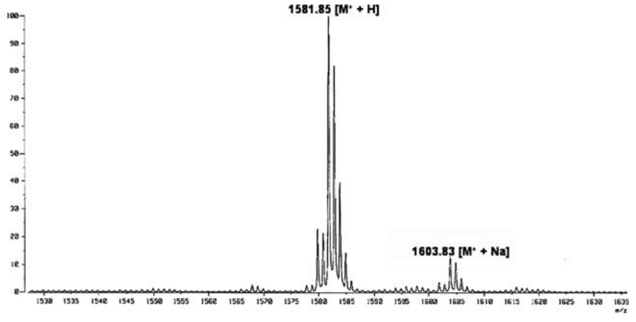


Figure 2. FAB mass spectrum of dendrimer **3-G22**.

PAMAM-like dendrimers in high yields. The application using multi-arm cores is in progress. This method can be applied for the fast synthesis of PAMAM-like dendrimers with different lengths (spacers) at core and may then provide an insight into designing various functional dendrimers. We are currently working towards synthesis of various functional dendrimers using this strategy for various applications.

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7. Spectral data for 2,6-bis-prop-2-ynyloxynaphthalene **2**: 87% yield; IR 3277, 2964, 2924, 2853, 2131, 1604, 1508, 1399, 1229, 1168, 1022 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 2.55$ (t, $J = 2.1$ Hz, 2H), 4.80 (d, $J = 2.1$ Hz, 4H), 7.19–7.22 (m, 4H), 7.69 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 154.72$, 130.35, 128.92, 119.59, 108.29, 79.01, 75.99, 56.37; MS (FAB): $m/z = 236$ [M^{+}], 197; HRMS (FAB) calcd for $C_{16}H_{12}O_2$: 236.0837, found: 237.0916 [M^{+}+H].

   Spectral data for dendrimer (**3-Dmm**). Compound **3-G11**: 99% yield; IR 3142, 2954, 2845, 1735, 1604, 1436, 1226, 1167, 1113 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 2.08$ (m, 4H), 2.41 (m, 12H), 2.73 (m, 8H), 3.63 (s, 12H), 4.36 (t, $J = 6.7$ Hz, 4H), 5.27 (s, 4H), 7.14 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 1.7$ Hz, 2H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.77 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 172.65$, 154.83, 143.84, 129.76, 128.32, 123.28, 119.14, 107.51, 62.06, 51.59, 50.35, 49.01, 47.82, 32.85; MS (FAB): $m/z = 782$ [M^{+}+2H]; HRMS (FAB) calcd for $C_{38}H_{52}N_8O_{10}$: 780.3806, found: 781.3885 [M^{+}+H]. Compound **3-G22**: 93% yield; IR 3318, 2952, 2827, 1736, 1666, 1604, 1531, 1436, 1225, 1198, 1175 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 2.03$ (m, 4H), 2.33 (m, 8H), 2.39 (t, $J = 6.6$ Hz, 16H), 2.44 (m, 4H), 2.50 (t, $J = 5.8$ Hz, 8H), 2.71 (t, $J = 6.6$ Hz, 16H), 2.74 (m, 8H), 3.23–3.27 (m, 8H), 3.64 (s, 24H), 4.39 (t, $J = 6.8$ Hz, 4H), 5.26 (s, 4H), 6.89 (br s, 4H), 7.15 (dd, $J = 8.8$, 2.2 Hz, 2H), 7.22 (d, $J = 2.2$ Hz, 2H), 7.64 (d, $J = 8.8$ Hz, 2H), 7.85 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 172.87$, 172.14, 154.77, 143.71, 129.63, 128.20, 123.18, 119.02, 107.22, 61.85, 52.71, 51.48, 49.70, 49.44, 49.01, 47.81, 36.96, 33.77, 32.50; MS (FAB): $m/z = 1582$ [M^{+}+2H]; HRMS (FAB) calcd for $C_{74}H_{116}N_{16}O_{22}$: 1580.8450, found: 1581.8528 [M^{+}+H]. Compound **3-G33**: 91% yield; IR 3308, 2954, 2828, 1735, 1659, 1647, 1604, 1544, 1437, 1227, 1196, 1178 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): $\delta = 2.05$ (m, 4H), 2.35 (m, 24H), 2.41 (t, $J = 6.4$ Hz, 32H), 2.53–2.54 (m, 20H), 2.57 (m, 8H), 2.74 (t, $J = 6.5$ Hz, 40H), 2.78 (m, 16H), 3.27 (m, 24H), 3.66 (s, 48H), 4.41 (t, $J = 6.5$ Hz, 4H), 5.26 (s, 4H), 7.00 (br s, 8H), 7.16 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 2.2$ Hz, 2H), 7.55 (br s, 4H), 7.66 (d, $J = 8.8$ Hz, 2H), 7.93 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 173.45$, 172.83, 172.72, 155.46, 144.27, 130.28, 128.82, 123.87, 119.63, 107.86, 62.46, 53.34, 52.97, 52.05, 50.21, 49.66, 48.56, 37.98, 37.60, 34.22, 33.11.