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Synthesis of [3]-Rotaxane Dendrimers by Host-mediated Click Chemistry

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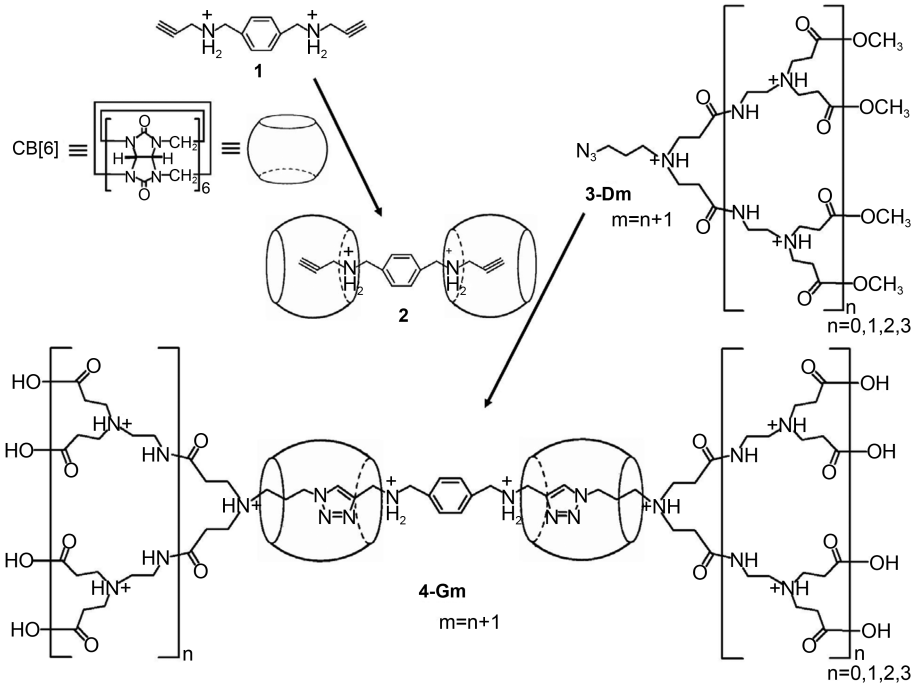
The 1,3-dipolar cycloaddition between azides and alkynes first reported by Huisgen *et al.*[1] has attracted much attention due to the synthetic importance of five-membered [1,2,3]-triazole heterocycles.[2] Since the traditional method working only at elevated temperatures produces a mixture of 1,4- and 1,5-disubstituted triazoles as a product, many research efforts have been devoted to overcoming the regioselectivity problem.[3] Among them, a Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition is currently regarded as the most efficient method that was developed by Sharpless and Tornøe,[4] and now is known as *click chemistry*. This reaction has many advantages: very high yields, mild and simple reaction conditions, oxygen and water tolerance, and easy isolation of product. In addition, it is highly chemoselective, affording 1,4-regiospecific 1,2,3-triazole even in the presence of various functional groups.[5] This reaction has been also applied successfully to the synthesis of dendrimers.[6,7]

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.[8] Concurrently with this, another fascinating development in chemistry has been the efficient synthesis of rotaxane dendrimers containing rotaxane-like mechanical bonds in dendritic components, which have also attracted considerable attention not only due to their aesthetic appeal but also their potential applications.[9] We have developed novel fusion and stitching methods for the synthesis of various dendrimers by the click chemistry between alkyne and azide.[7] Here, we add a new method, a host-mediated 1,3-dipolar cycloaddition reaction between alkyne and azide for the synthesis of rotaxane dendrimers. The used host is cucurbitu[6]ril (CB[6]) that can accelerate azide-alkyne cycloadditions by stabilizing an activated complex in its cavity.[10] In more detail, we report the synthesis of [3]-rotaxane dendrimers (**4-Gm**) using cucurbit[6]uril as a



Scheme 1. Synthetic strategy of [3]rotaxane dendrimers: **1**, *N*,*N*′-dipropargyl-*p*-xylylenediammoniume; **2**, [3]-pseudorotaxane; **3-Dm**, azide-functionalized PAMAM dendrons; **4-Gm**, [3]rotaxane dendrimers.

host by the stitching of [3]-pseudorotaxane (**2**) with azido-dendrons (**3-Dm**) (Scheme 1).

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 and 500 MHz NMR spectrometers. ESI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daejeon.

Preparation of *N,N′*-Dipropargyl-*p*-xylylenediammonium dichloride 1. A solution of phthalic dicarboxaldehyde (0.5 g, 3.73 mmol) in dichloromethane was treated with propargylamine (0.56 mL, 2.2 equiv) and the mixture was stirred for 6 hrs at rt. The resulting solution was evaporated and redissolved in MeOH. The redissolved solution was treated with sodium borohydride (0.6 g, 4.0 equiv) under ice bath and followed by stirring for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then conc. HCl was dropped into the solution under ice bath to give the product as hydrochloric salts (0.99 g, 93%). ^{1}H NMR (300 MHz, D_2O) δ 3.10 (s, 2H), 3.98 (d, J = 1.96 Hz, 4H), 4.44 (s, 4H), 7.63 (s, 4H); ^{13}C NMR (125 MHz, D_2O) δ 36.2, 49.8, 73.4, 78.9, 131.2, 132.2; ESI-MS: *m/z* calcd for $C_{14}H_{17}N_2$: 213.14 $[M\text{-}Cl\text{-}HCl]^+$; found: 213.1.

Synthesis of [3]-Pseudorotaxane 2. CB[6] (349 mg, 2.0 equiv) was slowly added to the solution of *N,N′*-dipropargyl-*p*-xylylenediammonium dichloride **1** (50 mg, 0.17 mmol) in distilled water (20 mL) and heated at 100 ºC for 5 min. Slow cooling of the solution to room temperature produced colorless crystals of [3]pseudorotaxane **2** (380 mg, 95%). ^{1}H NMR (300 MHz, D_2O) δ 2.06 (s, 2H), 3.59 (s, 4H), 4.34 (d, J = 15.5 Hz, 24H), 4.42 (s, 4H), 5.61 (s, 24H), 5.76 (d, J = 15.6 Hz, 24H), 7.93 (s, 4H); ESI-MS: *m/z* calcd for $C_{86}H_{90}N_{50}O_{24}$: 1103.37 $[M\text{-}2Cl]^{2+}$; found: 1103.7.

General Procedure for Synthesis of [3]Rotaxane dendrimer 4-Gm. A solution of [3]-pseudorotaxane **2** (84 mg, 37 μmol) and the azide-functionalized PAMAM dendrons **3-Dm**·xHCl (2 equiv) in distilled water (2 mL) was stirred for specified time at specified temperature. Then EtOH and THF were added to precipitate the product. The precipitates were collected by centrifugation. The solids were dried in vacuum to afford the [3]rotaxane dendrimer **4-Gm**.

4-G1: A white solid; 96% yield; ^{1}H NMR (300 MHz, D_2O) δ 2.38 (br, 4H), 3.25-3.31 (m, 8H), 3.39 (t, J = 6.7 Hz, 4H), 3.58 (t, J = 7.4 Hz, 4H), 3.74-3.78 (m, 4H), 4.01-4.05 (m, 4H), 4.24 (d, J = 14.1 Hz, 24H), 4.46 (s, 4H), 4.60 (s, 4H), 5.49 (s, 24H), 5.68 (d, J = 15.5 Hz, 12H), 5.77 (d, J = 15.5 Hz, 12H), 6.48 (s, 2H), 7.96 (s, 4H); ESI-MS: *m/z* calcd for $C_{104}H_{124}N_{58}O_{32}$: 1347.49 $[M\text{-}2Cl\text{-}2HCl]^{2+}$, 898.66 $[M\text{-}3Cl\text{-}HCl]^{3+}$, 674.25 $[M\text{-}4Cl]^{4+}$; found: 1347.9, 899.2, 674.8.

4-G2: A white solid; 96% yield; ^{1}H NMR (300 MHz, D_2O) δ 2.33 (br, 4H), 2.97 (t, J = 6.2 Hz, 16H), 3.22-3.28 (m, 8H), 3.36-3.44 (m, 8H), 3.57-3.59 (m, 32H), 3.70-3.75 (m, 4H), 3.97-3.99 (m, 4H), 4.21 (d, J = 15.4 Hz, 24H), 4.42 (s, 4H), 4.56 (s, 4H), 5.47 (s, 24H), 5.64 (d, J = 15.3 Hz, 12H), 5.73 (d, J = 15.6 Hz, 12H), 6.44 (s, 2H), 7.92 (s, 4H); ESI-MS: *m/z* calcd for $C_{136}H_{182}Cl_3N_{66}O_{44}$: 1183.89 $[M\text{-}3Cl\text{-}2HCl]^{3+}$, 888.17 $[M\text{-}4Cl\text{-}HCl]^{4+}$; found: 1184.6, 888.8.

4-G3: A white solid; 96% yield; ^{1}H NMR (300 MHz, D_2O): δ 2.36 (br, 4H), 2.97 (m, 48H), 3.27 (m, 8H), 3.37 (m, 8H), 3.45 (m, 8H), 3.56-3.69 (m, 88H), 3.77 (m, 4H), 4.01 (m, 4H), 4.23 (d, J = 15.4 Hz, 24H), 4.44 (s, 4H), 4.58 (s, 4H), 5.48 (s, 24H), 5.55-5.78 (m, 24H), 6.46 (s, 2H), 7.94 (s, 4H); ESI-MS: *m/z* calcd for $C_{200}H_{294}Cl_3N_{82}O_{68}$: 1680.45 $[M\text{-}3Cl\text{-}10HCl]^{3+}$, 1260.59 $[M\text{-}4Cl\text{-}9HCl]^{4+}$; found: 1681.1, 1261.1.

Results and Discussion

A convergent approach introduced by Fréchet and coworkers revolutionized the synthetic approaches to monodisperse dendrimers.[11,12] Since the synthetic approach installs the core in the final reaction step, it can allow various functional groups to be incorporated in dendrimers. Moreover, the approach enables the preparation of ordered and symmetrical dendrimeric structures, which is very attractive in terms of dendrimer syntheses. These characteristics of the convergent synthesis are ideal for the synthesis of rotaxane dendrimers whose rotaxane unit is located at the core region.[9] Therefore, we have proposed a synthetic strategy as show in Scheme 1; [3]-rotaxane dendrimers with [3]-rotaxane at core, linked by the triazole units are assembled by the convergent method using the [3]-pseudorotaxane with cucurbit[6]uril as a host and the azide-functionalized PAMAM dendrons.

First, the *N,N′*-diproparyl-*p*-xylylenediammonium dichloride (**1**) was synthesized *via* a reductive amination reaction between phthalic dicarboxaldehyde and propargylamine. It contains two terminal alkyne groups so that dendrimer can grow *via* click reactions with the dendrons. Then, [3]-pseudorotaxne (**2**) was prepared by threading of *N,N′*-diproparyl-*p*-xylylenediammonium in CB[6]. Separately, the azide-functionalized PAMAM dendrons were synthesized by a divergent approach using azidopropylamine as an azide-focal points,[7g] and treated with conc. HCl in THF to give the azide-functionalized PAMAM dendrons **3-Dm** (m = 1-4: generations of dendrons) as hydrochloric salts.

CB[6] is one of the CB[n] (n = 4-10) homologues that have different cavity sizes respectively. Therefore, each CB homologue can recognize the guest molecules exhibiting proper sizes.[13] It is reported that two CB[6] molecules are required to capture one *N,N′*-diallyl-*p*-xylylenediammonium ion because the aromatic moiety in the guest is too big to be encapsulated in the cavity of CB[6].[14] A similar guest-binding mode can applied to **2**; each propargylic unit is held by CB[6] through the hydrogen bonds between the -NH_2- and carbonyl oxygen atoms in the portal of CB[6], and the proparyl groups are present completely inside the CB[6] cavities (Scheme 1). Figure 1 shows the ^{1}H NMR spectra of **1** and **2**. When **1** forms a complex with CB[6], the phenylene protons showed down-field shifts while the propargylic

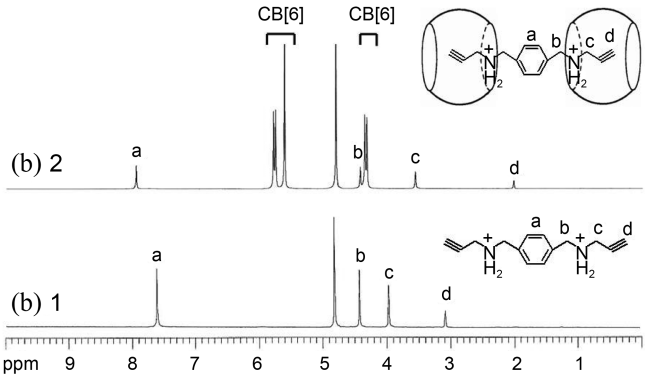


Figure 1. ^{1}H-NMR spectra for (a) ligand **1** and (b) [3]pseudorotaxne **2**.

protons showed up-field shifts. This observation clearly supports that the phenylene moiety is located outside CB[6] whereas the propargylic groups are located inside CB[6]. The parent ion peak at 1103.7 [M^{2+}/2] in the ESI-MS spectrum also suggests the formation of [3]-pseudorotaxane between **1** and CB[6]. Thus, these analyses confirm that the ligand **1** forms a dumbbell-shaped [3]-pseudorotaxane, **2** with two CB[6] molecules.

When **2** (1 equiv.) was reacted with 2 equivalents of the azide-functionalized PAMAM dendrons **3-D1** or **3-D2** in water (0.05 M) at ambient temperature, precipitates were obtained respectively by slow addition of EtOH to the reaction mixtures. The measured ^{1}H-NMR spectra indicated that the products suffered from a partial hydrolysis of the methyl ester groups. Therefore, the coupling reaction between **2** and **3-D1** was conducted again in 5% HCl solution (0.05 M) for 14 h at ambient temperature to produce the rotaxane dendrimer **4-G1** as precipitate in yield of 96% after adding EtOH and THF. The ^{1}H NMR spectrum of the product indicated that the triazole moiety is located inside CB[6]; the triazole proton in **4-G1** was observed at 6.48 ppm, and shifted up-field compared with those of free triazoles (ca. 7.50 ppm). Indeed, the ion peaks in the ESI-MS spectrum supported the successful formation of the [3]-rotaxane dendrimer.

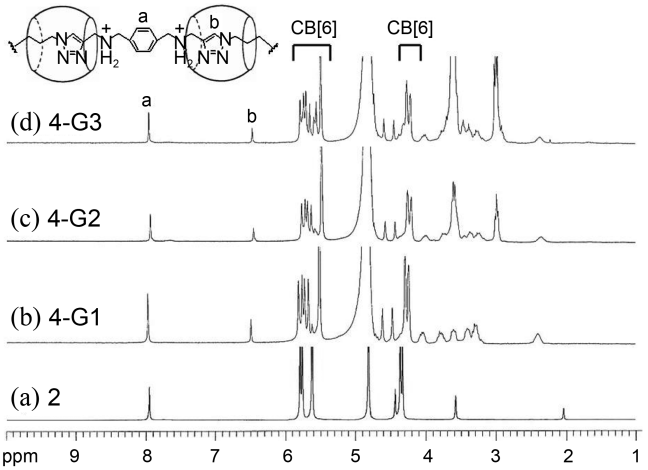


Figure 2. ^{1}H-NMR spectra for (a) [3]pseudorotaxne **2**, (b) **4-G1**, (c) **4-G2**, and (d) **4-G3**.

Given the first generation dendrimer, we applied repeatedly the host-mediated 1,3-dipolar cycloaddition reaction to get higher-generation dendrimers. The reaction of **2** and 2 equiv. of the azide-functionalized PAMAM dendrons **3-D2** in 5% HCl solution (0.05 M) for 48 h at ambient temperature gave the desired product **4-G2** in yield of 96%. In contrast, a same reaction with the third-generation dendrons **3-D3** was not finished over 1 week. Therefore, the reaction temperature was increased to 60 °C. The reaction was completed within 24 h, and the product **4-G3** was obtained in a high yield, 96%.

In the case of **3-D4**, the dendrimer **4-G4** could not be obtained in a satisfactory yield. As the generation increases, the repulsion between host and dendron will affect the reaction more significantly. Therefore, the azide group in **3-D4** may have decreased accessibility to **2** compared to that in **3-D3**. The ^{1}H NMR signals of the phenylene, triazole, methylene protons adjacent to the carbon of triazole, and core benzylic protons in dendrimers **4-Gm** were observed at 7.96, 6.48, 4.60, and 4.46 ppm for **4-G1**, 7.92, 6.44, 4.56, and 4.42 ppm for **4-G2**, 7.92, 6.46, 4.58, and 4.44 ppm for **4-G3**, respectively (Figure 2). The proton signals for the terminal alkyne of **1** were not shown at 2.06 ppm in the spectra of **4-Gm**. Indeed, the ESI mass spectrometry confirmed the formation of those rotaxane dendrimers.

In summary, we have demonstrated the formation of [3]rotaxane dendrimers having [3]rotaxane unit at core *via* host-mediated click chemistry which is based on the cucurbit[6]uril mediated 1,3-dipolar cycloaddition reaction between alkyne and azide. The [3]-pseudorotaxne, which is derived by *N,N′*-diproparyl-*p*-xylylenediammonium dichloride with 2 equiv of cucurbit[6]uril, reacted with the azide-functionalized PAMAM dendrons to provided efficiently the rotaxane dendrimers. Because of the high yields and lack of byproducts provided by the host-mediated 1,3-dipolar cycloaddition reaction between alkyne and azide for stitching together dendrons and [3]-pseudorotaxane as core unit, the various rotaxane materials could be constructed easily and shown the characteristic behaviors.

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