

Divergent Synthesis of Hydrophilic Dendrons Based on Tri(ethylene glycol) Spacers

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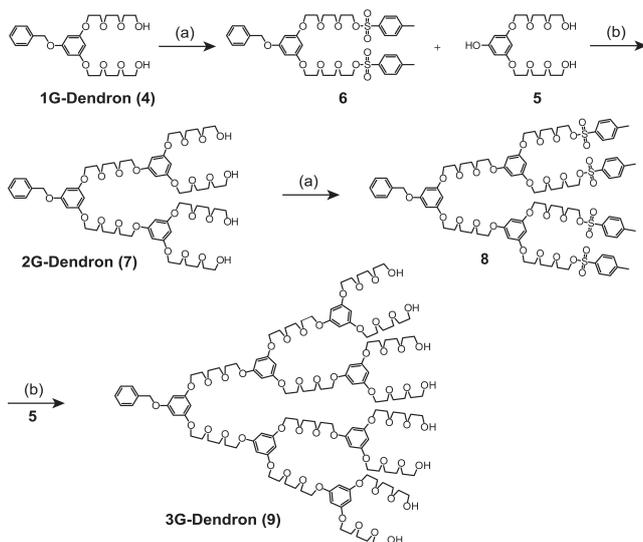
Dendritic molecules have received a great deal of attention because of their peculiar 3-D architecture, capable of confining and releasing certain drugs under certain conditions.¹ As a prerequisite for biological applications, dendritic molecules must gain water solubility. To date researchers have achieved appropriate water solubility by using either charged² or non-ionic^{3,4} moieties. Charged compounds, however, can cause cytotoxicity such as undesired cell lysis. Therefore, researchers have considered using neutral polymeric or oligomeric coils on dendritic compounds as an alternative for *in vivo* applications. Particularly, oligo- or poly(ethylene glycol) (PEG) could be a useful candidate for endowing these compounds with water solubility.⁴

Herein, we report on the synthesis of hydrophilic polyether dendrons from first to third generation. As Scheme 1 shows, the dendrons possess tri(ethylene glycol) (TEG) spacers and phloroglucinol branching junctures. Because of their oxygen-rich compositions and multiple hydroxyl termini, the dendrons are hydrophilic enough to be water-soluble. Indeed, the third generation favors water over ethyl acetate in the extraction. To synthesize dendrons, we adopted a divergent route consisting of i) the tosylation of terminal alcohols and ii) the Williamson etherification as the activation and coupling steps, respectively. In the synthesis, the key molecule is the AB₂-type monomeric unit (**5**) where A and B are phenol and aliphatic alcohol, res-

pectively. In particular, these alcohols are well-known to have different pK_a values. In the presence of potassium carbonate (K₂CO₃), the phenol group is completely deprotonated, but the aliphatic alcohol remains intact. As a result of this selective deprotonation, only the phenol group reacts during the coupling step. On the other hand, the two unreacted aliphatic alcohols can be converted easily into tosylate as a good leaving group in the next step. This monomer design eliminates an involvement of a tedious benzyl protection/deprotection (commonly used in dendrimer synthesis)⁵ sequence during the generation growth.

The synthesis began with the preparation of monobenzylated phloroglucinol. Although the monobenylation seems to be done simply by one-step etherification under potassium carbonate, the compound actually was prepared by a three-step reaction: i) acetylation, ii) benzylation, and iii) hydrolysis (Scheme S1). This is because one-step synthesis from phloroglucinol produced an undesirable C-benzylated product⁶ and gave only a 9% yield.⁷ Thus, to avoid this byproduct, the electron-density of phloroglucinol should be reduced by acetylation.⁸ In the next benzylation step, to obtain the monobenzylated product, 1 molar equiv. of water was added dropwise into a mixture of sodium hydride and benzyl bromide.⁹ In this reaction, the phenoxides formed by the hydrolysis of the acetoxy groups react with benzyl bromide. The remaining acetyl groups were removed under a 5 M KOH solution, resulting in 5-benzyloxy-resorcinol (**3**). The overall yield was approximately 43%, which is much bigger than that (9%) from the one-step synthesis. In the ¹H-NMR spectrum, the two distinct aromatic protons of the phloroglucinol ring were observed at 5.97 ppm and 6.08 ppm, respectively, and any proton resonance for the C-benzylated product was not exhibited. The first generation dendron (**1G-Dendron**) was synthesized by the Williamson etherification of compound **3** with monotosylated TEG with a yield of 87%. The next debenylation, using 10% Pd/C and H₂, led to the monomeric unit (**5**).

The generations up to the third were grown successfully by a divergent method (Scheme 1). As noted previously, this divergent route consists of tosylation and the Williamson etherification. These elemental reactions are well-known to be conventional and free of side reactions. Most tosylation and etherification reactions showed high reaction yields of more than 70%. However, the third generation (**3G-Dendron**) gave only a 27% yield, perhaps because of the steric effect of the multi-branches. The obtained dendrons (**nG-Dendron**) were characterized by ¹H- and ¹³C-NMR, gel permeation chromatography (GPC), elemental analysis, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).



Scheme 1. Divergent synthesis of the hydrophilic dendrons (**nG-Dendron**, n = 1, 2, and 3). Reagents: (a) TsCl, pyridine, and CH₂Cl₂; (b) K₂CO₃, KI, and CH₃CN.

Figure 1(a-c) represents the $^1\text{H-NMR}$ spectra of the dendrons. As the generation increases, the intensities of the TEG protons exceed those of the aromatic protons. Also, the integral ratios of the two *ortho*-protons (assigned as *c*) to the benzyloxy group versus the other phloroglucinol protons (*d*) are approximately 0.5, 3.5, and 9.5 for the first, second, and third generations, respectively, consistent with the theoretical values. As well as

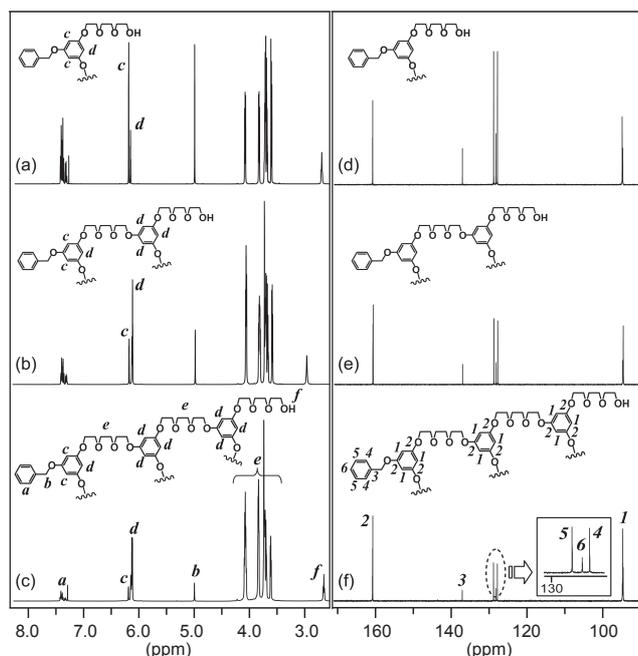


Figure 1. Proton (left) and carbon (right) NMR spectra of (a,d) 1G-Dendron, (b,e) 2G-Dendron, and (c,f) 3G-Dendron.

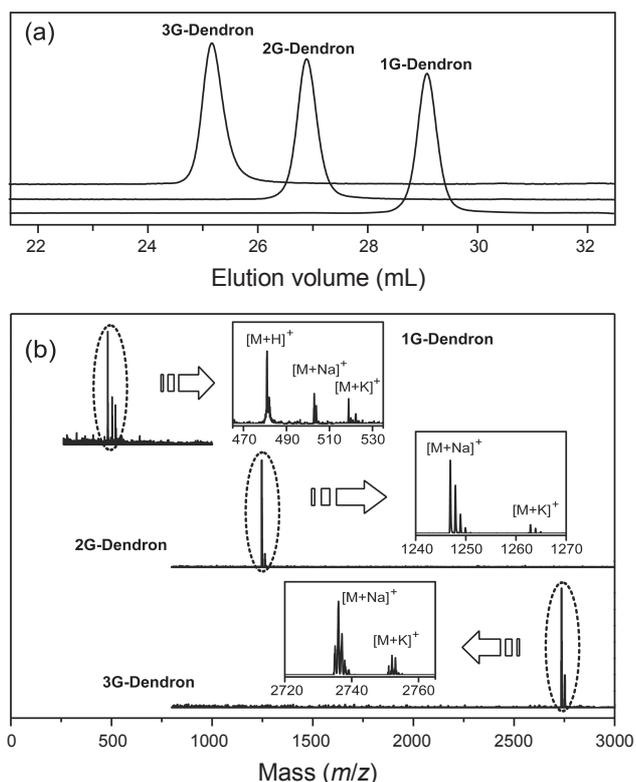


Figure 2. (a) GPC elugrams, and (b) MALDI-TOF MS spectra.

the $^1\text{H-NMR}$ results, six distinct aromatic carbon resonances were observed in all the $^{13}\text{C-NMR}$ spectra, which corroborate the successful synthesis of the designed molecular structures (Figure 1(d-f)).

An analysis of the GPC and MALDI-TOF MS data revealed no structural defect, which can occur from incomplete coupling in divergent methods.¹⁰ In the GPC data, the polydispersity values (M_w/M_n) for the second and third generations were less than 1.03, suggesting high purity (Figure 2(a)). In Figure 2(b), the MALDI-TOF MS spectra provide direct evidence of no structural defect. The mass spectrum of 1G-Dendron shows three signals corresponding to the H, Na, and K adducts of the molecular ions; and 2G-Dendron and 3G-Dendron exhibit Na and K adducts. And the measured molecular masses of 1G-Dendron, 2G-Dendron and 3G-Dendron are 479.9 g/mol, 1223.9 g/mol, and 2713.1 g/mol, respectively, which closely match their theoretical molecular masses.¹¹

In summary, we prepared a series of hydrophilic dendrons based on TEG spacers and phloroglucinol branching junctures. A divergent synthetic route consisting of tosylation and the Williamson etherification as the activation and coupling steps, respectively, was applied. Iterating the two-step reactions enabled the generation to reach the third one. Structural analysis demonstrated that the obtained dendrons showed their designed molecular structure with no structural defects.

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Supporting Information. The supporting Information is available on request from the corresponding author (E-mail: chobk@dankook.ac.kr).

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- The theoretical molecular masses for 1G-Dendron, 2G-Dendron and 3G-Dendron are 480.2 g/mol, 1224.6 g/mol, 2713.3 g/mol, respectively. The measured molecular masses were obtained from the highest peaks in the spectra.