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Synthesis and Degradation of Backbone Photodegradable Polyester Dendrimers

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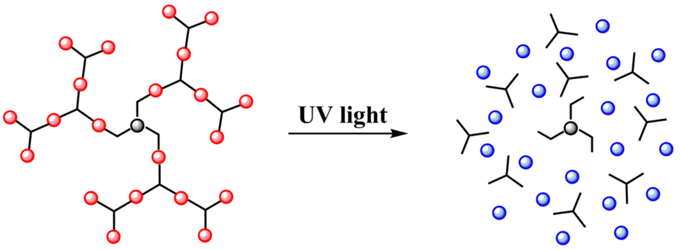
ABSTRACT



Dendrimers with fully photodegradable backbones were synthesized through the incorporation of photodegradable *o*-nitrobenzyl esters into a new dendrimer monomer based on 2,2-bis(hydroxymethyl)propionic acid (bis-MPA). Dendrons were synthesized using a divergent approach, and were subsequently coupled to a core molecule in the final step. Photodegradation was performed and it was demonstrated that the molecules degrade to release bis-MPA. The accessibility of these molecules opens new avenues for the preparation of well-defined, fully photodegradable materials.

Dendrimers are highly branched macromolecules with exact molecular weights or very low polydispersity indices resulting from their stepwise synthesis. Higher generation dendrimers possess large numbers of functional groups on their peripheries and often adopt globular conformations with internal cavities. These properties have led to much research in the application of dendrimers for light-harvesting,[1,2] organic light-emitting diodes,[3,4] catalysis,[5,6] and numerous biomedical areas.[7−9] The development of dendrimers that are responsive to specific stimuli is also of significant interest as this can impart new properties and further expand their scope of applications. For example, the breakdown of a dendrimer in response to a stimulus can provide a means of releasing encapsulated cargo or fragmenting assemblies of dendritic materials.

The first reports on cleavable dendrimers emerged less than two decades ago.[10,11] Since then, a number of examples of dendrimers that cleave in response to stimuli such as pH change,[12−14] light,[15−24] transition metals,[25,26] catalytic antibodies,[27,28] and reducing agents[29,30] have been developed. Among these stimuli, light is of particular interest for the development of smart materials as it can be applied at a specific time and location with control over its intensity and wavelength. Thus far, several photodegradable dendrimer systems have been developed through the incorporation of photodegradable units either at the core of the dendrimer[15,19] or at the junction between the hydrophobic and hydrophilic portions of amphiphilic dendrons.[16,20,22,23] The limitation of these approaches is that following photodegradation, in most cases large residual fragments of the dendrimer remain,

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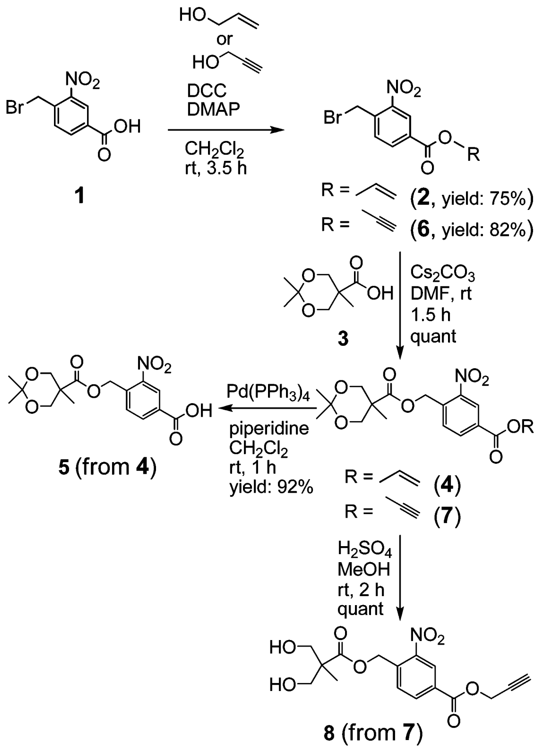
limiting the application of these materials. For example, residual hydrophobic fragments may undergo aggregation in aqueous solutions. Self-immolative dendrons that fragment in response to the cleavage of a photoresponsive focal point moiety have also been developed.[17,18,24] However, due to the inherent design of these materials they have been limited to dendrons rather than dendrimers and are thus far limited to a very select set of backbone monomers that are derivatives of dihydroxybenzylalcohols.

Photodegradable linkages have not previously been incorporated throughout the backbones of dendrimers or dendrons at each monomer unit. This approach would allow for a rapid, simultaneous cleavage of multiple linkages through the dendrimer backbone and is potentially applicable to various dendrimer backbones. However, the incorporation of photodegradable moieties throughout the dendrimer backbone is a significant synthetic challenge due to the requirement for extremely clean and efficient chemistry in dendrimer synthesis. Despite the multitude of reports on dendrimer synthesis over the last few decades, only a limited number of dendrimer backbones have emerged as widely accessible synthetically, and minor modifications to the monomer units can dramatically alter the synthetic process and results. We report here the incorporation of photodegradable *o*-nitrobenzyl ester moieties[31,32] into the widely used 2,2-bis(hydroxymethyl)-propionic acid (bis-MPA) dendrimer backbone and photodegradation studies of the resulting materials.

Scheme 1. Synthesis of Monomer **5** and G1 Dendron **8**



Our synthetic strategy, an adaptation of the polyester dendrimer synthesis developed by Ihre et al.,[33] involved the divergent synthesis of first-, second-, and third-generation (G1−G3) dendrons with alkyne focal points followed by an azide + alkyne "click" conjugation of the dendrons onto a trifunctional azide core to obtain the target G1−G3 dendrimers. Due to the photosensitivity of the target molecules and intermediates, all reaction flasks were protected from light using aluminum foil, but no special measures were required during the isolation and purification steps. 4-Bromomethyl-3-nitrobenzoic acid (**1**) was used as the starting material in the synthesis (Scheme 1). First, it was necessary to mask the carboxylic acid group on **1** using a protecting group that would not require acidic or basic conditions for deprotection as these conditions would cause complications in subsequent steps of the synthesis. Thus, an allyl ester was installed by reaction with allyl alcohol using DCC to provide **2**. Bis-MPA (**3**) was then introduced in the presence of Cs_2CO_3 in DMF to provide **4** in quantitative yield. Finally, the principle monomer for dendrimer growth (**5**) was synthesized by deprotection of the allyl group in **4** using $Pd(PPh_3)_4$ and piperidine.

With the key monomer in hand, the next step was the synthesis of the G1−G3 dendrons. As an alkyne focal point was desired for the eventual dendron coupling to the core, the synthesis of the G1 dendron was carried out in a manner similar to that described above for monomer **5**, but using propargyl alcohol instead of allyl alcohol. This provided first the propargyl ester derivative **6**, followed by the bis-MPA derivative **7** (Scheme 1). Another key difference was that instead of cleaving the focal point propargyl alcohol on **7**, this was left intact and instead the acetonide protecting group was removed using H_2SO_4 in MeOH to provide the G1 dendron **8** in high yield overall.

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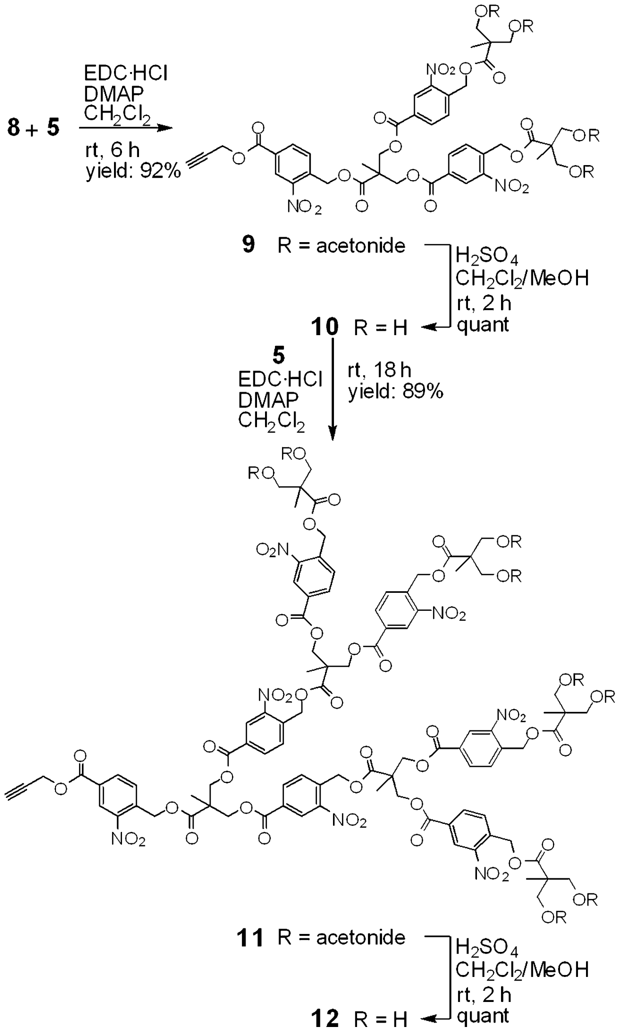
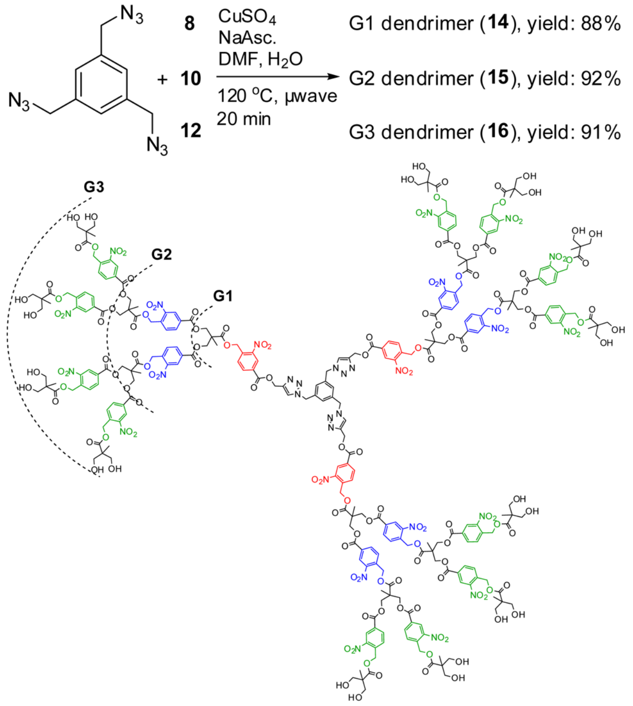
Scheme 2. Synthesis of G2 Dendron **10** and G3 Dendron **12**



Synthesis of the G2 dendron was accomplished by coupling monomer **5** to the deprotected G1 dendron **8** using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl) to provide **9** (Scheme 2). Removal of the acetonide groups under acidic conditions provided **10**. Repetition of this coupling and deprotection sequence provided G3 dendron **12** in high yield.

In order to construct the target photodegradable G1–G3 dendrimers, dendrons **8**, **10**, and **12** were attached to a trifunctional azide core molecule **13**[34] via a copper(I) catalyzed alkyne–azide cycloaddition reaction (Scheme 3). It should be noted that **13** was handled with care as organic polyazides can be potentially explosive (for more details, see the Supporting Information). While heating the reaction vessel in an oil bath at 70 °C overnight resulted in low dendrimer yields, likely due to breakdown of ester linkages under these conditions, the reaction proceeded smoothly

Scheme 3. Synthesis of G1–G3 Dendrimers **14**–**16**



under microwave conditions at 120 °C in 20 min.[35] Follow-up studies showed that the catalyst was still essential under these conditions and that microwave irradiation played a significant role in accelerating the reaction, even at this temperature. The resulting dendrimers were characterized by ^{1}H and ^{13}C NMR spectroscopy, MALDI mass spectrometry, IR spectroscopy, and size exclusion chromatography (SEC). As shown in SEC traces (Figure 1a), the resulting dendrimers exhibited monomodal molecular weight distribution profiles with the expected increases in hydrodynamic volume with each generation, as well as very narrow polydispersity indices (PDIs).

Having the three dendrimers in hand, their photodegradation behaviors were then studied. First, ~20 μg/mL solutions of each dendrimer in THF were irradiated with UV light for 1 h, and the UV–vis absorption spectra of the solutions were recorded in 2 min intervals for the first 10 min followed by 5 min intervals for the remaining 50 min. The results for the G3 dendrimer (**16**) are shown in Figure 1b. A decrease in absorbance was observed for the peak at 225 nm while increases in absorbance were observed at 305 and 350 nm, along with corresponding red shifts in their absorption maxima. The results for photolysis of G1 (**14**) and G2 (**15**) dendrimers are shown in the Supporting Information. These observations are in accordance with the results obtained by other groups for this photolabile group.[15,16,20] The absorption band at 350 nm is attributed to *o*-nitrosobenzaldehyde, which is a product of *o*-nitrobenzyl ester photolysis, and exhibits a weak absorption band at 350–360 nm that is solvent dependent.[16]

^{1}H NMR spectroscopy was also used to study the photodegradation of the dendrimers. A 10 mg/mL solution

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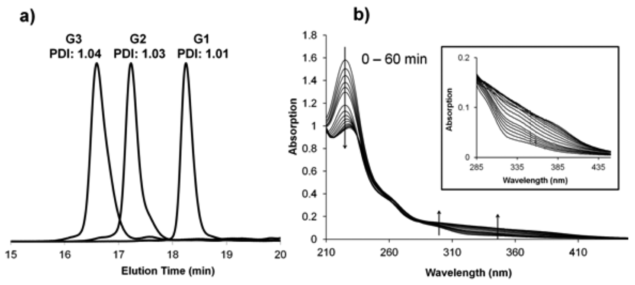

Figure 1. (a) SEC traces of G1 (**14**), G2 (**15**), and G3 (**16**) dendrimers with their corresponding PDIs. (b) UV–vis spectra for G3 dendrimer (**16**) upon irradiation with UV light for 60 min. Inset shows the expanded region between 285 and 450 nm.

of the dendrimer in deuterated DMSO was irradiated with UV light in a quartz NMR tube for 1 h and ^{1}H NMR spectra were collected in 10 min intervals. As shown for the G3 dendrimer (**16**) in Figure 2, the multiplets at 3.57 and 3.46 ppm, corresponding to the methylene groups of bis-MPA in the dendrimer backbone decrease as irradiation time increases. At the same time, a new sharp multiplet at 3.45 ppm appears, corresponding to the same methylene groups in the released product bis-MPA, a starting material for the dendrimer synthesis. The peak intensities of the methyl groups in the dendrimer backbone at 1.46, 1.42, and 1.10 ppm also decrease and a single methyl peak at 1.00 ppm corresponding to the released bis-MPA compound increases in intensity. The appearance of other smaller multiplets in the region of 3.45 ppm and singlets in the region of 1.00 ppm can result from the expected release of other bis-MPA derivatives containing the photocleavable aromatic groups. In addition, a general trend of peak broadening in the aromatic region was observable, which can be attributed to formation of different aromatic species after photodegradation, as nitroso compounds are known to be unstable and undergo side reactions to form other aromatic species such as diazo compounds.[31] However, if the aromatic region is expanded and increased in intensity, it is possible to see that the peaks at 7.27 and 8.31 ppm, corresponding to the core molecule and triazole ring respectively, are still present after 1 h as they do not participate in degradation process. Moreover, SEC traces of the degraded ^{1}H NMR samples showed that only small molecules were present, demonstrating the successful full degradation of the dendrimers (Supporting Information).

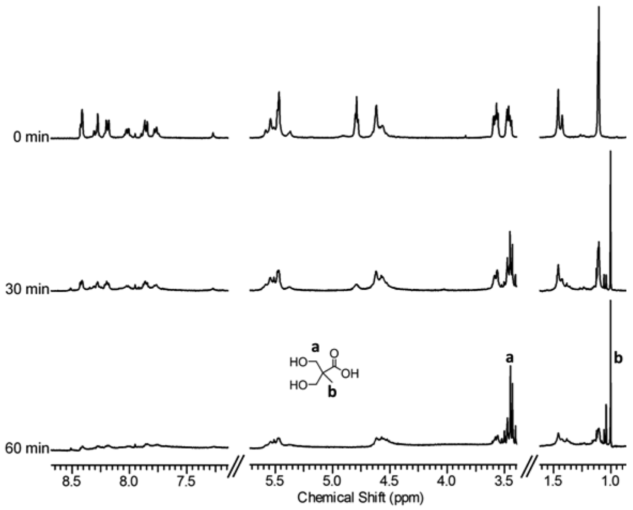

Figure 2. Evolution of ^{1}H NMR spectra during the photolysis of a 10 mg/mL sample of G3 dendrimer (**16**) in DMSO-d_6. The results for photolysis of G1 (**14**) and G2 (**15**) dendrimers as well as extensive peak assignments for the degradation of all three dendrimers are shown in the Supporting Information.

In summary, we have successfully designed and synthesized a new series of dendrons and dendrimers that are able for the first time to undergo complete backbone photodegradation to small molecules. We expect that the incorporation of these dendrons and dendrimers into new materials will impart new photoresponsive properties and functions. In addition, tuning of their optical properties by changing the photochemically responsive group or through the incorporation of other photophysical processes in such a way that they can undergo photodegradation in the visible or nearinfrared region can potentially open up new opportunities to access materials with fully photodegradable hydrophobic blocks suitable for biological or other applications.

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Supporting Information Available. Synthetic procedures and characterization data, additional UV–vis spectra, NMR spectra, and SEC degradation data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.