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# Photolabile Dendrimers Using *o*-Nitrobenzyl Ether Linkages

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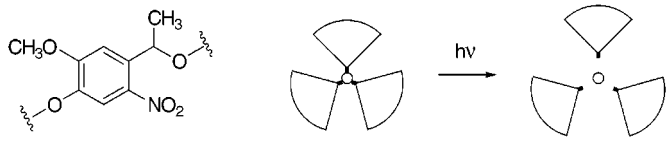
## ABSTRACT




**Benzyl aryl ether dendrimers containing photosensitive, veratryl-based *o*-nitrobenzyl AB linkages (bold bonds) were prepared to the third generation and shown to undergo site-specific degradation when irradiated with ultraviolet light.**

Dendritic macromolecules with a variety of functions have been prepared by precise synthetic placement of groups within the structural interior or periphery.[1] With several discrete structural regions within dendritic architecture, simple incorporation of photolabile linkages into dendrimers could provide a wide range of materials with many potential functions including light-assisted drug delivery, polymer-supported organic synthesis, or other applications where selective degradation of material is necessary.[2]

In this paper we present the installation of photolabile linkages proximal to the core unit of benzyl aryl ether dendrimers. Our approach employs the photolabile *o*-nitrobenzyl ether moiety, well known as a versatile protecting group in organic synthesis,[3] as a readily cleavable linker for solid-phase synthesis,[4] as a masking group for "caged" biological molecules and prodrugs,[5] and as cleavable units in host−guest[6] and materials chemistry.[7,8]

Racemic secondary alcohol **1**[9] was used to prepare a series of photolabile dendrimers containing α-substituted-*o*-nitrobenzyl[10] linkages. Alkylation of **1** with first-, second-, and third-generation benzyl aryl ether dendrons in the presence of $K_2CO_3$ in acetone yielded photolabile dendrons **2a**−**c**. Dendrimers **3a**−**c** were obtained directly from **2a**−**c** and 1,3,5-benzenetricarbonyl chloride as mixtures of two diastereomers (homo- and heterochiral) in racemic form (i.e., *RRR*, *SSS*, *RRS*, *RSS*) in moderate yields (Scheme 1).[11] The

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(10) For leading references on α-substituted-*o*-nitrobenzyl linkages, see: Holmes, C. P.; Jones, D. G. *J. Org. Chem.* **1995**, *60*, 2318−2319. Holmes, C. P. *J. Org. Chem.* **1997**, *62*, 2370−2380.

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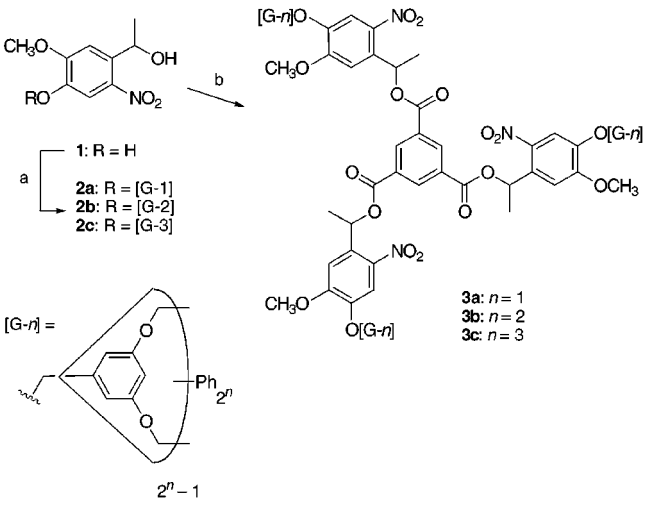
**Scheme 1**[a]




[a] (a) [G-*n*]Br, $K_2CO_3$, 18-crown-6, acetone, reflux, 86, 83, and 42%, respectively; (b) benzene-1,3,5-tricarbonyl chloride, DMAP, $CH_2Cl_2$, 48, 43, and 50%, respectively.

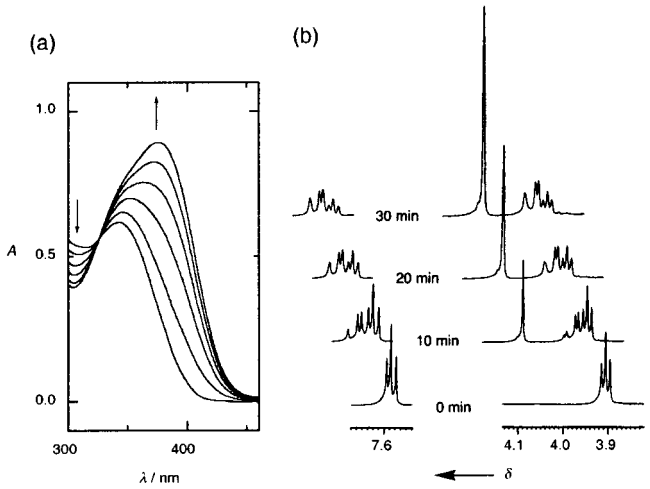
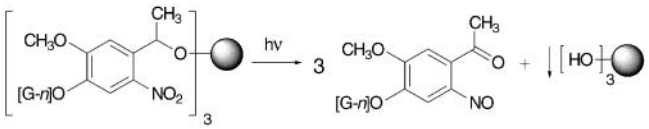



**Figure 1.** Photolysis experiments[13] on (a) dendrimer **3c** ($CHCl_3$, 40 $\mu$M) irradiated for 0, 2, 5, 8, 11, and 17 min monitored by absorption spectroscopy (detail) and (b) dendrimer **3a** ($CDCl_3$, 5 mM) monitored by $^1$H NMR.

presence and approximate ratio of the stereoisomers was confirmed by the appearance of certain key resonances in the $^1$H NMR spectrum. For example, the resonances for the methoxy group of the photolabile linker in **3a** appeared as a set of three singlets in a 1:2:1 ratio at 3.91 ppm (Figure 1b, 0 min).[12] Similar patterns were observed for both aromatic protons of the photolabile linker at 7.59 and 7.10 ppm. No attempt was made to separate the diastereomeric mixtures. Their presence is actually extremely beneficial in the analysis of the photodegradation process (vide infra).

Photolabile dendrimers **3a**−**c** were thermally stable (acetone, 55 °C, overnight; solid state, rt, 6 months), yet photodegradation occurred upon irradiation with 350 nm light.[13] Photolysis proceeded cleanly, and all evidence was in accord with photocleavage according to Scheme 2.

**Scheme 2**




Apparent isosbestic points were evident in the absorption spectra (approximately 255, 288, and 237 nm), and discrete photoproducts were observed by $^1$H NMR (Figure 1a). For example, in the $^1$H NMR, the mixture of methyl doublets at 1.77 ppm decreased steadily in intensity in a first-order fashion with excellent linearity and were eventually replaced by a singlet at 2.94 ppm (not shown) corresponding to the methyl ketone residue on the *o*-nitrosoacetophenone photoproduct (Scheme 2).[14] Likewise, the peaks at ca. 8.9 ppm corresponding to the trimesate core decreased in intensity and eventually disappeared from the spectrum, consistent with the precipitation of trimesic acid that is observed in both the UV and NMR experiments.

The benefit of **3a**−**c** being diastereomeric mixtures was that close inspection of the $^1$H NMR spectrum during the course of photolysis (Figure 1b) revealed the intermediate stages of the dendrimer degradation sequence (Figure 2). For example, the three methoxy singlets at 3.91 ppm correspond-

(11) Satisfactory characterization data were obtained for all new compounds reported (see Supporting Information).

(12) This 1:2:1 ratio of peaks is consistent with a statistical mixture of 1:3 homochiral/heterochiral diastereomers. The ratio of the same peaks in **3b** was closer to 2:4:3, consistent with a 1:2 ratio of diastereomers. The stereoisomer ratio for **3c** was again 1:3. Despite the apparent implication for stereoselectivity in the formation of **3b**, we must note that these peaks are barely resolved, so the ratios are at best approximate (see Figure 1b). Any conclusions regarding inherent stereoselectivity in the coupling reactions leading to **3a**−**c** are unfortunately precluded until such time that these ratios can be more accurately determined. For an example of stereoselectivity in the preparation of chiral dendrimers see: Murer, P. K.; Lapierre, J.-M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 1648−1681.

(13) Photolyses were performed under argon at room temperature on $CHCl_3$ (**3a**−**c**) solutions with dendrimer concentrations that resulted in an optical density of 0.5−1.0 at the ca. 345 nm band. The prepared samples were irradiated for successive intervals using a Spectroline 36-380 miniature UV quartz pencil lamp (365 nm). Photolyses monitored by $^1$H NMR were performed on 5 mM solutions in $CDCl_3$ with irradiation from a high-pressure Hg lamp. Control experiments confirmed that the photolyses were unaffected by the nature of the solvent ($CH_2Cl_2$, $CHCl_3$, THF).

(14) The identity of the *o*-nitrosoacetophenone photoproduct was verified by comparison to the $^1$H NMR spectrum, provided by Dr. C. P. Holmes of Affymax Research Institute, Palo Alto, CA, of an authentic sample of 4,5-dimethoxy-2-nitrosoacetophenone. In the presence of oxygen a peak appears at 2.48 ppm which is presumably *o*-nitroacetophenone formed upon oxidation of initially formed *o*-nitrosoacetophenone.

(15) Photocleavage was also be observed by GPC ($CH_2Cl_2$, 500 Å, 1000 Å, 10 000 Å Jordi DVB columns), but the resolution is insufficient to fully separate the individual fragments.

(16) The occurrence of two intermediates in the stepwise degradation between **A** and **D** (Figure 2), and the appearance of isosbestic points implies that this system may be considered "pseudo-two-component" or a depolymerization process (i.e., $P_n \rightarrow n$M) where polymer subunits and monomer units are distinct chromophores. See: Cohen, M. D.; Fischer, E. *J. Chem. Soc.* **1962**, 3044−3052.

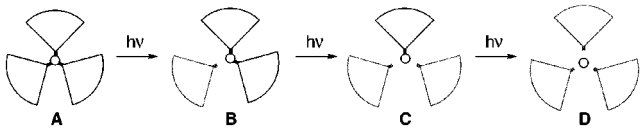



**Figure 2.** Schematic representation of the sequential photodegradation of a three-arm dendrimer (**A**) into a two-arm dendrimer (**B**), a one-arm dendrimer (**C**), and full degradation (**D**).

ing to the mixture of homo- and heterochiral three-arm dendrimers (**A**) yield to two methoxy singlets of equal intensity at 3.93 ppm (Figure 1b, 10 min) assignable to the new diastereomeric mixture (*RR*, *RS*, *SS*) of singly degraded two-arm dendrimers (**B**). In turn, a broad singlet appears at 3.95 ppm (Figure 1b, 20 min) and is assignable to the doubly degraded one-arm dendrimer (**C**). The appearance and continual growth of the singlet at 4.05 ppm throughout the process is assignable to the methoxy singlet on free, degraded dendron. The lone presence of this resonance after extended irradiation time indicates full dendrimer degradation (**D**). A similar evolution is also observed clearly in the aromatic resonance at 7.59 ppm (Figure 1b, left), as well as other peaks throughout the spectrum.[15,16]

In conclusion, we have provided the first examples of photolabile dendrimers and demonstrated their photocleavage into discrete dendrimer fragments. Further development and application of these materials is a current effort in our laboratory.

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**Supporting Information Available:** Synthetic details and characterization data for all new compounds reported and details and full spectral data of photoyses of **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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