

Geometric Disassembly of Dendrimers: Dendritic Amplification

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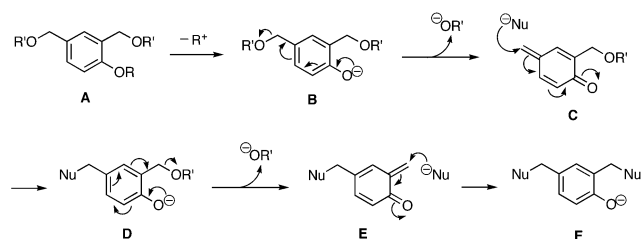
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Since their development over two decades ago, dendrimers have been used in an overwhelming variety of chemical and biological systems.¹ However, advantage has not yet been taken of the nature of dendrimers as covalent assemblages of potentially active monomeric species, nor has the impact that these species could have on the properties of a system been considered. In a recent report, we demonstrated *linear dendrimer disassembly*² whereby fragmentation of a dendrimer occurs through a cascade of cleavage reactions initiated by a single triggering event. In this contribution we demonstrate the degradation of dendrimers whereby each cleavage event leads to two subsequent fragmentations per subunit, or *geometric dendrimer disassembly*.³ In addition, we introduce the concept of “dendritic amplification,” where an initial stimulus triggers the efficient disassembly of a dendrimer that results in the amplification of a certain property or quality of a system due to the large increase in molecular species (dendrimer fragments) contained therein.

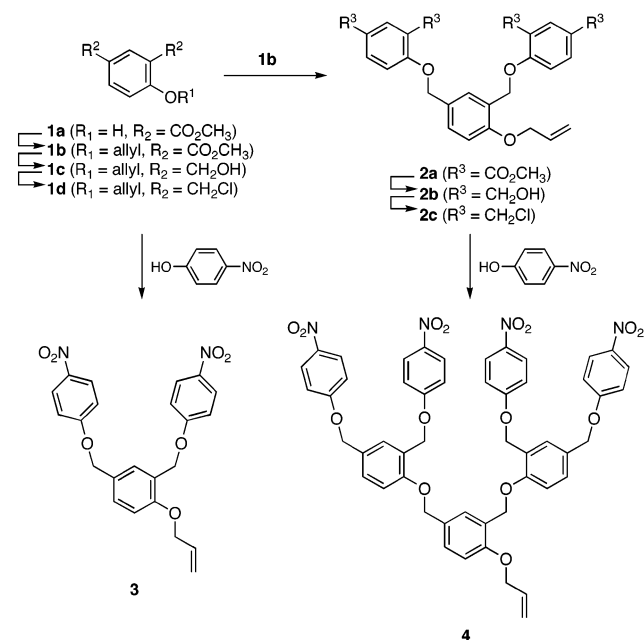
Dendrimers with 2,4-bis(hydroxymethyl)phenol repeat units should be capable of geometric disassembly since the corresponding anionic phenoxide species are labile vinylogous hemiacetals as shown in Scheme 1. Removal of the trigger group R from 2,4-bis(hydroxymethyl)phenol-based dendrimer subunit **A** results in the formation of an *o,p*-bis(benzyl ether)phenoxide (**B**). This phenoxide, a bis(vinylogous hemiacetal) anion, should cleave to liberate alkoxide (OR' in Scheme 1) and *p*-quinone methide **C**, which will be trapped by an appropriate nucleophile under the reaction conditions, consistent with the electrophilic nature of quinone methides.⁴ The resulting phenoxide **D** should cleave to liberate a second equivalent of alkoxide OR' and *o*-quinone methide **E**, in turn trapped by nucleophile to yield the fully cleaved phenoxide **F**. We reasoned that if alkoxide OR' was analogous in structure to phenoxide **B**, then subsequent cleavages could occur, resulting in a geometric fragmentation through a dendrimer.

Scheme 1. Proposed Disassembly Pathway of 2,4-Bis(hydroxymethyl)phenol-based Dendrons

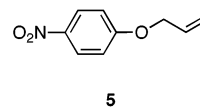


To test this geometric dendrimer disassembly strategy, we prepared first- and second-generation dendrons **3** and **4** (Scheme 2). Compounds **3** and **4** consist of a single allyloxy residue at the focal point and 2,4-branched benzyl ether dendrimer subunits. When deprotection of the allyl group occurs as the initial triggering event, subsequent cleavages should result in a disassembly according to Scheme 1 toward the dendron periphery. *p*-Nitrophenoxy moieties were intentionally installed at the periphery of each dendron so

Scheme 2. Divergent Synthesis of 2,4-Bis(hydroxymethyl)phenol-based Disassembling Dendrons with Allyl Triggers



that complete cleavage would be indicated by the UV absorbance of liberated *p*-nitrophenoxide ion. As a control, we prepared 4-allyloxynitrobenzene (**5**) with the allyl trigger group directly attached to the nitrophenoxy reporter group.



To investigate the geometric disassembly process, compounds **3–5** were subjected to typical allyl deprotection conditions.⁵ The absorption spectrum of the reaction mixture was monitored at intervals. Rapid disassembly was indicated, after an initial incubation period,² by a simultaneous rapid decrease in the initial absorption at 310 nm with a sharp increase in the absorption of *p*-nitrophenoxide ion (~ 431 nm). Once begun, *p*-nitrophenoxide generation from **3** and **5** was complete after approximately 1 min, while the time course for molecule **4** indicated a slightly slower process after the initial rapid increase. The entire spectral evolution takes place within 15 min under these conditions (Figure 1). The final absorbance values observed at 431 nm indicated disassembly of dendrons **3** and **4** in yields of ca. 95% based on the measured absorptivity of *p*-nitrophenoxide under the reaction conditions. Under these conditions, the rate-limiting step in the disassembly process appears to be the removal of the allyl trigger group, as disappearance of the starting material band coincides with the

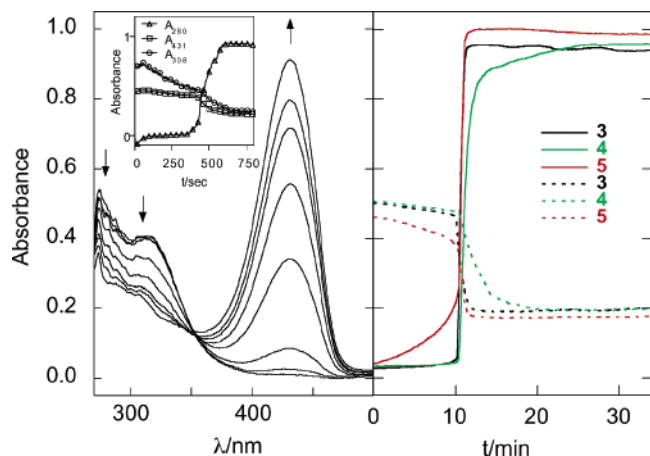


Figure 1. (Left) UV spectra recorded during the disassembly of **4** (37 s intervals). (Inset) UV absorbance of the main absorption bands as a function of time. (Right) UV absorbance at 431 nm (—) and 310 nm (---) as a function of time during the disassembly of **3–5**. Concentrations of **3–5** were normalized such that quantitative disassembly would result in the same final concentrations of released *p*-nitrophenoxide.⁵

appearance of the *p*-nitrophenoxide absorption. While optimum for rapid disassembly, these conditions are inappropriate for kinetic analysis of the disassembly process as a function of generation.

The fragments liberated during the disassembly of **3** and **4** were characterized by a combination of NMR and GC–MS. In the ¹H NMR spectra⁶ the allyl resonances broaden and decrease with an immediate growth of two singlets at ~2.1 ppm, indicative of the formation of 2,4-dimethylphenoxide. In addition, the resonances of the *p*-nitrophenoxy moieties decrease, and new resonances (AA'BB' pattern, 7.7 and 6.0 ppm), consistent with *p*-nitrophenoxide ion, arise. Molecular weights from GC–MS were consistent with the formation of 2,4-dimethylphenol and *p*-nitrophenol as the major products of disassembly. Trace amounts of triphenylphosphine and triphenylphosphine oxide were also detected from catalyst decomposition. These results support our proposed disassembly pathway (Scheme 1), with the trapping of quinone methide species **C** and **E** by excess hydride in solution to yield 2,4-dimethylphenol.

The successful implementation of geometric dendrimer disassembly has herein demonstrated an enhanced capability for controlled dendrimer degradation technology. For a single cleavage event at the focal point of a dendron the total number of periphery and branching subunits released in a geometric disassembly is,

$$\text{released subunits} = \underbrace{N_b^G}_{\text{\# periphery subunits}} + \underbrace{\left(\frac{N_b^G - 1}{N_b - 1}\right)}_{\text{\# branching subunits}}$$

where N_b is the branching multiplicity and G is the generation.⁷ Hence, an exponential number of fragments are generated by a single triggering event, and since dendrimers possess an overall globular form in solution and in the condensed state,^{8,9} these fragments are released into a relatively small volume, resulting in a high local concentration. The combination of these two aspects

of dendrimer fragmentation—geometric disassembly and the release of a high local concentration of subunits—constitutes a concept we term “dendritic amplification,” whereby dendrimer disassembly is used to amplify a certain property or quality of a system by increasing the number of molecular species contained therein. The level of amplification depends on dendrimer generation as well as the number of released subunits that participate in the amplification (i.e., are “active” species). The nature of the amplification depends on the nature of the released subunits. In the system described herein, we released *p*-nitrophenoxide periphery units as “active” species, amplifying the absorbance at 431 nm, although other possibilities for dendritic amplification are dependent on the nature of the properties of the released dendrimer fragments (e.g., drugs, fluorescent dyes, catalysts, etc.).

In summary, we have demonstrated a method for the *geometric disassembly* of dendritic structures into their individual subunit components after a single initial triggering event.¹⁰ Disassembly occurs rapidly and completely under the reported conditions. Synthesis of higher-generation dendrons and the development of further dendritic amplification systems is currently underway.

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Supporting Information Available: Details of the syntheses, characterization data, and complete UV spectra of the disassembly of compounds **3–4** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*; VCH: New York, 2001. (b) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; John Wiley: New York, 2002.
- (2) Li, S.; Szalai, M. L.; Kevitch, R. M.; McGrath, D. V. *J. Am. Chem. Soc.* **2003**, *125*, 10516–10517.
- (3) Szalai, M. L.; McGrath, D. V. *Polym. Mater. Sci. Eng.* **2003**, *89*, 406–407.
- (4) (a) Wan, P.; Barker, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465–475. (b) Veldhuyzen, W. F.; Shalloo, A. J.; Jones, R. A.; Rokita, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 11126–11132 and references therein.
- (5) General procedure for the disassembly of compounds **3–5**: A quartz cuvette was charged with 2.00 mL of a solution of NaBH₄ in DMF (1.0 mg/1.0 mL). To this is added 20 μL of a solution of substrate in DMF (**3**: 1.5 mM.; **4**: 0.75 mM.; **5**: 3.0 mM) followed by 20 μL of a solution of Pd(PPh₃)₄ in DMSO (4.0 mg/1.0 mL). Monitoring of the reaction on an Ocean Optics CCD Array spectrometer began exactly 75 s following the final addition.
- (6) ¹H NMR conditions: 15 mM **3** or 7.5 mM **4**; 6 mM Pd(PPh₃)₄; 190 mM NaBH₄ in DMSO-*d*₆.
- (7) For the geometric cleavage of a dendrimer, rather than a dendron, the total number of subunits released is multiplied by N_c , the multiplicity of the core subunit.
- (8) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138–175.
- (9) Hawker, C. J.; Malmström, E. E.; Frank, C. W.; Kampf, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 9903–9904.
- (10) During the editorial review of this manuscript, two independent literature reports appeared introducing the concept of geometric dendrimer disassembly, although both used different chemical structures and trigger groups than reported herein: (a) de Groot, F. H. M.; Albrecht, C.; Koekoek, R.; Beusker, P. H.; Scheeren, H. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 4490–4494. (b) Amir, R. J.; Pessah, N.; Shamis, M.; Shabat, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 4494–4499.

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