Dendrimer Disassembly by Benzyl Ether Depolymerization

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Degradable polymeric systems are the basis of several established and emerging technologies such as controlled-release systems for drug delivery[1,2] and photoresist methodology for microlithography[3-5] among other applications.[6] However, as the demands on these and other technologies have increased, higher levels of control over the structure, properties, and performance of degradable materials are necessary. Extremely few reports have addressed strategies for the controlled degradation of dendritic structures[7-12] or the implications of the development of such systems. Certainly, degradable subunits could easily be engineered into the dendritic architecture, and a limited number of reports have demonstrated selective fragmentation of dendrimers at the periphery, core, and interior residues of the architecture.[7-12] However, we envision a more efficient process whereby an initial stimulus causes a change in a dendritic structure that triggers a subsequent cascading destruction of the material into a number of smaller fragments, i.e., a chemically amplified[13] dendrimer degradation. Herein we introduce a new, controlled method of dendrimer degradation that takes advantage of the ubiquitous benzyl aryl ether dendritic subunit as a cleavable backbone. This degradation method, or "dendrimer disassembly" process, fragments a dendrimer through a cascade of cleavage reactions initiated by a single triggering event.

It was recently reported that 4-*O*-substituted benzyl ethers used as protecting groups could be removed in nearly quantitative yield either thermally or by mild oxidation after removal of the *O*-substituent (eq 1, R = Ac, SEM).[14,15] We also recently discovered

(eq 1)
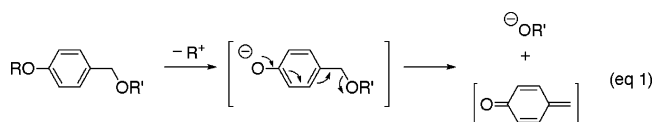
that the *p*-allyloxybenzyl ether group could be similarly removed under standard conditions[16] for allyl deprotection (eq 1, R = allyl).[17] The *p*-benzyl ether phenoxide generated by removal of the *O*-substituent R in eq 1 is the key intermediate in these deprotections. This phenoxide, a vinylogous hemiacetal anion, cleaves to yield an alkoxide (⁻OR' in eq 1), which is the conjugate base of the protected alcohol HOR', as well as *p*-quinone methide, which is presumably trapped by a weak nucleophile under the reaction conditions, consistent with the electrophilic nature of quinone methides.[18] We reasoned that if the alkoxide ⁻OR' was also a *p*-benzyl ether phenoxide, then a subsequent cleavage would occur. Multiple cleavages would constitute a depolymerization, and this became our strategy for disassembling benzyl ether-based dendritic structures.

To test this dendrimer disassembly strategy, we prepared zeroth-through second-generation dendrons **1**–**3** (Chart 1). Compounds **1**–**3** consist of a single 4-allyloxy residue at the periphery and a continuous chain of *p*-benzyl ether linkages extending to the focal point. Since *p*-benzyl ether linkages are necessary to maintain the cleavage pathway through each generational shell, 3,4-branched subunits were used in the required parts of the dendrons rather than

Chart 1
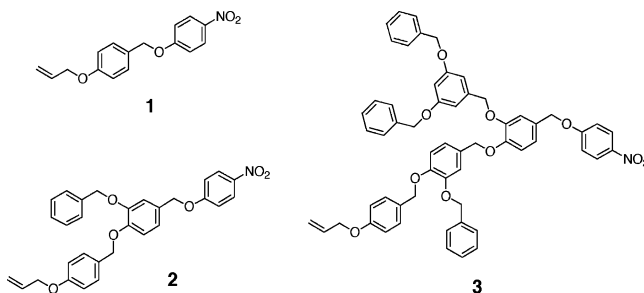
the standard 3,5-branched subunits. Where 3,4-branched subunits were not necessary for maintaining the cleavage pathway, 3,5-branched units were used. When deprotection of the allyl group occurs as the initial event, subsequent cleavages should result in a cascade disassembly of the dendron toward the central core. A *p*-nitrophenoxy moiety was intentionally installed at the focal point of each dendron so that complete cleavage would be indicated by the UV absorbance of liberated *p*-nitrophenoxide ion (~400 nm).

To investigate the disassembly process, compounds **1**–**3** were subjected to several variations on standard allyl deprotection conditions.[16] Optimum conditions for rapid disassembly proved to be in DMF solution with a mixture of Pd(PPh₃)₄ and NaBH₄.[19] The absorption spectrum of the reaction mixture was monitored at intervals. Smooth disassembly was observed, after an initial incubation period,[20] by a simultaneous rapid decrease in the initial absorption at 312 nm with a concomitant increase in the absorption of *p*-nitrophenoxide ion (~432 nm). This spectral evolution takes place within 15 min under the conditions used (Figure 1a). The final absorbance values observed at 432 nm indicated complete disassembly (i.e., disassembly proceeding to the focal point) of **1**–**3** in 85–100% yield based on the measured absorptivity of *p*-nitrophenoxide under the reaction conditions (Figure 1b).

The fragments liberated during the disassembly of compounds **1**–**3** were characterized by a combination of GC–MS and LC–MS. Molecular weights were consistent with the trapping of quinone methide intermediates by excess hydride in solution. For example, fragments identified in the disassembly of **3** were 4-methylphenol, 2-benzyloxy-4-methylphenol, 2-(3,5-dibenzyloxy)benzyloxy-4-methylphenol, and *p*-nitrophenol. Triphenylphosphine and triphenylphosphine oxide were also observed from catalyst decomposition.

The disassembly process was also investigated in tetrahydrofuran (THF) solvent, in which the reaction proceeded more slowly than in DMF. The spectral evolution during the disassembly reactions of **1**–**3** in tetrahydrofuran also indicated decreasing starting material absorption at ca. 305 nm and increasing *p*-nitrophenoxide absorption at ca. 405 nm over the course of the disassembly (Figure 1c and Supporting Information). However, a new absorption band emerged during the disassembly of **2** and **3** in THF. Specifically, the absorption band at ca. 305 nm decreased within 50 min for **2** and **3**, while during the same time period a band at 340 nm increased
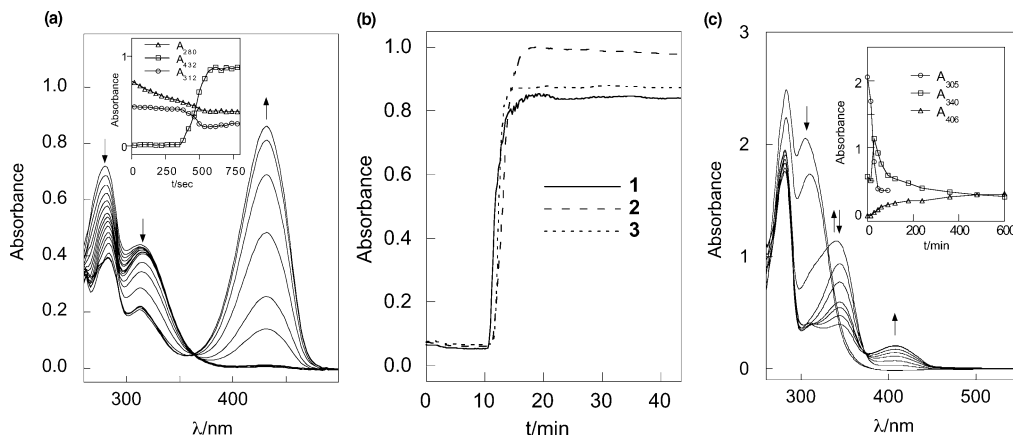
Figure 1. (a) UV spectra recorded during the disassembly reaction of **3** in DMF (40 s intervals). Inset: UV absorbance of the main absorption bands as a function of time. (b) UV absorbance at 432 nm as a function of time in the disassembly of **1−3** in DMF. (c) UV spectra recorded during the disassembly reaction of **3** in THF (time intervals are 0, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, and 600 min). Inset: UV absorbance of the main absorption bands as a function of time.

in absorbance. The *p*-nitrophenoxide absorption then increased over a longer time period at the expense of the 340 nm band. This can be seen readily in a plot of absorbance at these three wavelengths versus time in the disassembly of second generation dendron **3** (Figure 1c, inset). We assign this 340 nm band to phenoxide intermediates on the basis of independent generation and observation of these species under similar spectral conditions.

The results in both DMF and THF solutions support our proposed disassembly process of eq 1 as taking place in two stages. The first stage is the removal of the allyl group and generation of the initial, and subsequently generated, phenoxide intermediates. The second stage is progression of the disassembly to the dendron focal point and appearance of the *p*-nitrophenoxide absorption. In DMF, the rate-limiting step in the process appears to be the removal of the allyl triggering group, as disappearance of the starting material band coincides with appearance of the *p*-nitrophenoxide absorption. However, in THF, the rate of disassembly is slower than the rate of removal of the allyl trigger, and phenoxide intermediates are observed during the course of the disassembly.

In summary, we have demonstrated the disassembly of dendritic structures by a benzyl ether depolymerization reaction. In accord with previous work,[14] we anticipate that the initiating site may be constructed with any manner of protecting group and not just the allyl group investigated here. Hence, the initial stimulus for disassembly may be varied.

Supporting Information Available: Details of the syntheses, characterization data, and complete UV spectra of the disassembly of dendrons **1−3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) General procedure for the disassembly of compounds **1−3** in DMF: A quartz cuvette is 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 3 mM solution of substrate in DMF, followed by 20 µL of a solution of Pd(PPh₃)₄ in DMSO (1.0 mg/1.0 mL). Monitoring of the reaction begins exactly 75 s following the final addition.
(20) During the incubation period for all runs in DMF, a decrease in the Pd(PPh₃)₄ catalyst absorbance band at ca. 287 nm is observed (see Supporting Information). Hence, although we find the reproducibility of this incubation period to be only moderate under these particular conditions, it is clearly related to catalyst activation. Further studies are underway.

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