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Dendrimer Disassembly as a New Paradigm for the Application of Dendritic Structures

Dominic V. McGrath*

Department of Chemistry, University of Arizona, Tucson, Arizona 85721-0041

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Abstract: We present an overview of an entirely new concept in nanotechnology, dendrimer disassembly. Dendrimer disassembly is a process that relies on a single triggering event to initiate multiple cleavages throughout a dendritic structure that result in release of individual dendrimer subunits or larger dendrimer fragments. The potential of this process lies in (1) the nature of dendrimers as covalent assemblages of active species, and using the chemistry of disassembly to release these species into a system; and (2) the role of dendritic components of a system in influencing solubility, energy harvesting, or insulating capabilities, etc., and using the chemistry of disassembly to reverse those contributions to a system. This is a powerful construct, in that dendrimers and dendritic structures can be made up of a wide variety of subunits, compatibilized with many different environments, and incorporated into countless systems. We anticipate that dendritic materials with disassembly capabilities will (a) be useful for traditional polymer degradation technologies and (b) have potential applications in nanotechnology, biomedicine, sensors, etc.

Keywords: Dendrimers; dendrimer disassembly; drug delivery

Introduction

Dendrimer synthesis[1−41] is an active area of research with new developments emerging at a rapid pace, including efforts in the synthesis of new materials and the development of new strategies for their preparation (e.g., divergent,[5,6] convergent,[7,8] double exponential,[9] orthogonal[10]). However, dendrimer synthesis is also a mature field,[11,12] in that many of the synthetic, purification, and characterization techniques

* Author to whom correspondence should be addressed. Mailing address: Department of Chemistry, University of Arizona, P.O. Box 210041, 1306 E. University Blvd., Tucson, AZ 85721-0041. Tel: 520-626-4690. Fax: 520-621-8407. E-mail: mcgrath@u.arizona.edu.

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have been perfected to the point that dendrimers and dendritic components are fairly common players in molecular, macromolecular, and nanoscale systems.[13−21] The frontline of current dendrimer research is in applications for which they are uniquely suited, as we must now delve deeper, past the initial synthetic challenges, to see what technologies and fields these distinctive macromolecules are truly capable of impacting.

Both traditional polymer- and non-polymer-based technologies are being impacted by dendritic architectures. Recent developments in the field of dendrimers/dendritic macromolecules have explored potential applications in drug delivery, display technology, catalyst supports, sensor technology, imaging contrast, gene therapy, chemical separations, and viscosity and rheology modification, among others.[17,18,22−30] These uses of dendrimers effectively rely on the unique nature of the dendritic architecture with its high degree of branching, large number of chain ends, and overall globular morphology.

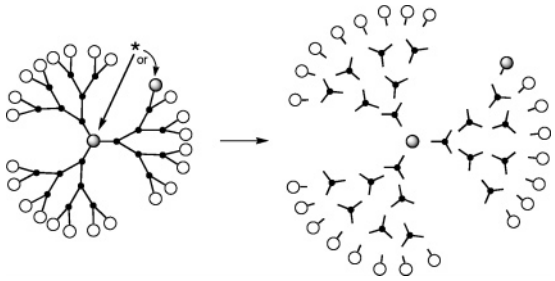

Figure 1. "Dendrimer disassembly": stimulus (*) to a triggering group in a dendritic structure results in a cascade fragmentation into constituent subunits.

However, most applications of dendrimers involve what might be termed "passive" dendrimer use, where the dendritic architecture and its inherently globular morphology are used to effectively passivate, insulate, or simply separate molecular components of a system by covalent or noncovalent encapsulation. Related applications use the dendritic architecture to display or host chemically or physically reactive components, such as catalytic sites, chromophores, or mesogens, often in precise relation to each other. In all of these applications the dendrimer serves as a type of scaffold, albeit critical for function, and in some applications the dendrimer scaffold is responsible for communication of physical events within the system, such as energy transfer or self-organization.[13−19]

In contrast, not common are "active" applications of dendrimers, in which the dendritic structure is the reactive component of the system and chemical events are propagated throughout the dendritic network, directly taking advantage of the inherent generational amplification that dendrimers possess. In this sense we believe that dendrimers have an untapped potential in which the dendrimer structure can be activated for chemical events—cleavage reactions—that propagate through the dendritic architecture, disassembling it into component subunits.

Accordingly, we have recently developed a new controlled dendrimer degradation process known as "dendrimer disassembly" (Figure 1) that takes advantage of a chemical event propagating through the dendritic architecture, rendering the structure an "active" component of a system.[31−33] Dendrimer

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disassembly relies on a single triggering event to initiate multiple cleavages throughout a dendritic structure that results in release of individual dendrimer subunits or larger dendrimer fragments. The potential of this process lies in two new classes of applications for dendrimer chemistry relying on (1) the established roles of dendritic components in nanotechnology for influencing solubility, energy harvesting, or insulating capabilities, etc., and using the chemistry of disassembly to significantly alter those contributions to a system by stripping the dendrimer away tracelessly; and (2) the nature of dendrimers as a reservoir—or compact covalent assemblage—of active species, and using the chemistry of disassembly to release these species into a system ("dendritic amplification").

Hence, the ability to degrade dendrimers in this fashion has the potential to impact previously established uses of dendrimers, as well as introduces a new paradigm for their roles in chemical systems, i.e., as compact reservoirs of releasable active species. We find this a powerful construct, in that dendrimers and dendritic structures can be made up of a wide variety of subunits, made compatible with many different environments, and incorporated into countless systems, including the biological arena. This review details the current state of development of dendrimer disassembly,[31−36] significant related contributions from other laboratories,[37−40] and the potential for significant positive impact of dendrimer disassembly on the emerging use of dendrimers and dendritic polymers in advanced technologies including drug delivery.

Fundamentals of Dendrimer Disassembly

In this section we describe the fundamental concept of dendrimer disassembly and the capabilities it provides that we anticipate exploiting. Unlike previously reported materials with discrete degradable subunits that have to be independently cleaved,[41−45] dendrimers engineered for disassembly require only a single subunit within the structure to be triggered by a physical or chemical stimulus to initiate a spontaneous cascading cleavage (Figure 1). Although this concept is a new means of degrading dendrimers, it is in essence a depolymerization,[46] yet since the actual cascade cleavage process is not technically depropagation of a polymeric structure (i.e., the reverse of propagation where monomer units are released successively from the polymer chain end), we have used the new term "dendrimer disassembly".

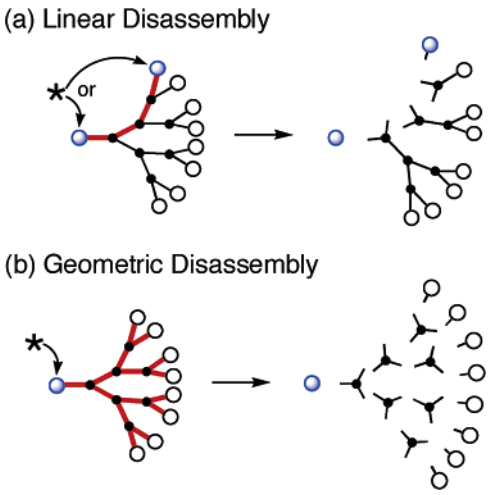

Figure 2. (a) Linear disassembly through a dendritic structure leading to degradation into several large fragments. (b) Geometric disassembly leading to degradation into a large number of small fragments. (Red = cleavage vector; blue = trigger groups.)

We distinguish between two limiting types of dendrimer disassembly based on the nature of the cleavage cascade (Figure 2). *Linear disassembly* (arithmetic cleavage) takes place along a single cleavage vector through the dendrimer, breaking the structure up into several relatively large fragments after triggering at the focal point or periphery (Figure 2a). Although an efficient method to degrade a material, linear disassembly does not propagate in a dendritic

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fashion. *Geometric disassembly*, in contrast, does take advantage of the inherent branching in the dendritic structure (Figure 2b). In a dendritic structure that has a 1:2 branching ratio, each cleavage event leads to two subsequent cleavage events, fragmenting the dendrimer into its individual constituent subunits.

It is in geometric disassembly of a dendrimer structure that an enhanced capability for controlled dendrimer degradation technology arises. For a single cleavage event at the focal point of a dendron, the total number of periphery and branching subunits released is shown in eq 1, where N_b is the branching multiplicity and G is the generation.[47] Hence, an exponential number of fragments are generated by a single triggering event, and since these fragments can have properties that are dramatically different from those of the intact dendrimer, the nature of the system changes as well. This constitutes a concept we term "dendritic amplification", whereby dendrimer disassembly, triggered by a specific stimulus (light, heat, pH, etc.), amplifies a certain property or quality of a system by increasing the number of molecular species contained therein.[32,38] The level of amplification depends on dendrimer generation while the nature of amplification depends on the identity of the released subunits, and could include (i) increase in the concentration of a certain chemical agent, e.g., a polymerization initiator or therapeutic agent;[48] (ii) change in solvent/medium parameters, e.g., polarity or dielectric constant; (iii) change in the interaction of the medium with light, e.g., absorbance, fluorescence emission, or refractive index; or (iv) solubility of the released subunits themselves, e.g., precipitation.

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

Linear polymer systems can degrade quite rapidly upon main chain scission, releasing fragments into their local environment.[46] So why is geometric disassembly of dendrimers better for releasing active species into a system than degradable linear polymers? We see distinct advantages in using dendritic structures in particular for the release of "active" species that extend beyond the increased efficiency of fragment release. First, the intrinsically globular nature of the dendritic structure[49,50] dictates that, if disassembly is rapid, then the release of active species will be in a confined region of space, i.e., high local concentration. Second, a dendrimer has different structural regions, including a distinct exterior which can be engineered for desired macroscopic properties (e.g., solubility, pharmacokinetics, film-forming properties), while the interior can contain the subunits that will be "activated" upon disassembly of the structure.[51−54] Third, within the interior of a dendrimer a subunit is relatively insulated from the external environment,[24,55] so the masking of the activity of a subunit can merely be its incorporation into the interior of a dendritic framework. Similarly, the coisolation of certain chromophores, such as self-quenching emissive units, can also be a form of masking. Disassembly would decrease quenching and enhance emission. Fourth, if trigger groups are on the periphery of the dendrimer, then there are numerous sites per dendrimer to initiate disassembly, making the process more efficient from an initiation standpoint.

Dendrimer Disassembly Mechanism

We present here the chemistry we have used to develop disassembling dendrimer systems.[31−36] Selective transformation of a 4-O-substituted benzyl ether precursor **1** into vinylogous[56] hemiacetal anion **2** (Scheme 1) initiates an electronic cleavage cascade to yield by 1,6-elimination a *p*-quinone methide (***p*-QM**)—nucleophilically trapped under the reaction conditions (i.e., by water, alcohols, thiol, etc.)[57]

(47) For the geometric cleavage of a dendrimer, rather than a dendron, the total number of subunits released is multipled by N_c, the multiplicity of the core subunit.

(48) The unmasking of active species in linear polymers for therapuetic effect has been demonstrated: (a) Synthesis and degradation characteristics of salicylic acid-derived poly(anhydride-esters). Erdmann, L.; Uhrich, K. E. *Biomaterials* **2000**, *21*, 1941−1946. (b) Degradable poly(anhydride ester) implants: effects of localized salicylic acid release on bone. Erdmann, L.; Macedo, B.; Uhrich, K. E. *Biomaterials* **2000**, *21*, 2507−2512.

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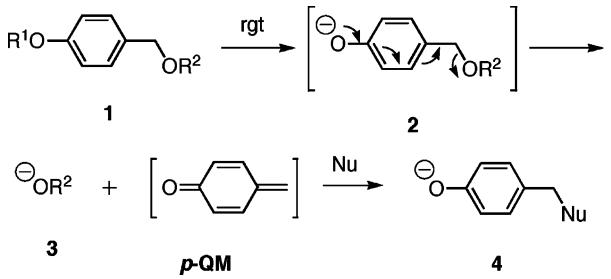
Scheme 1. Linear Para Disassembly Pathway

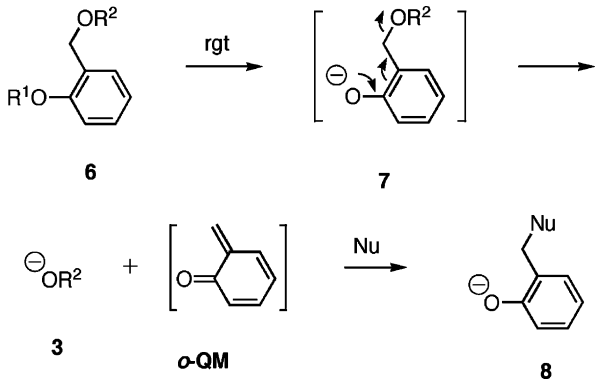


and a liberated alkoxide ($^{-}OR^2$, **3**). This 1,6-elimination mechanism and similar schemes (both 1,6- and 1,4-eliminations) have been reported as the basis for the mechanism of protecting groups, enzyme-activated inhibitors, and prodrugs.[58−61] Note that in principle any phenolic protecting group can serve as R^1 (e.g., R^1 = acetyl,[60] trimethylsilylethoxymethyl (SEM),[60] allyl,[59] enzyme substrates[58]) and be removed using the appropriate conditions. If alkoxide $^{-}OR^2$ were also a vinylogous hemiacetal anion akin to **2**, then a subsequent cleavage should occur. Accordingly, oligomeric sequences of structure **1** in a dendritic framework (e.g., **5**, Chart 1) successfully undergo linear disassembly along this "para cleavage pathway" when the triggering group, R^1, is removed under the appropriate conditions.[31] (Note the similarity to acetal resin depolymerization.[62])

An analogous electronic cascade cleavage occurs when vinylogous hemiacetal anion **7** (Scheme 2) is generated from 2-O-substituted benzyl ether precursor **6**[58] by a 1,4-elimination to yield *o*-quinone methide (***o*-QM**), also trapped by a nucleophile, and alkoxide $^{-}OR^2$ (**3**). Oligomeric sequences of structure **6** in a dendritic framework (e.g., **9**, Chart 1) also successfully undergo linear disassembly along this "ortho cleavage pathway" under the appropriate conditions.[63,64]

The combination of the electronic cascade cleavage chemistries in Scheme 1 and Scheme 2 into a single subunit makes it possible to construct dendritic structures that disassemble in a geometric fashion, where each phenoxide

Scheme 2. Linear Ortho Disassembly Pathway



ion cleaves through a benzyl group to create two new phenoxide ions. Consider structure **10** (Scheme 3), which has both *o*- and *p*-benzyl ether linkages with respect to the initially triggered R^1 group. Removal of the triggering group R^1 initiates two sequential cleavage cascades via QMs **12** and **14**. The end result is the release of two equivalents of alkoxide $^{-}OR^2$ which, if analogous to phenoxide **11**, will both continue along a geometric disassembly pathway. Accordingly, incorporation of a geometric disassembly pathway based on Scheme 3 has been carried out and shown to be successful (e.g., third generation dendron **16**, Chart 1).[32−35]

Two other research groups concurrently published similar systems with geometric dendrimer disassembly capability. These groups have used the terms "cascade-release"[37] and "self-immolative"[38−40] to describe their systems. "Self-immolative" is borrowed from the prodrug literature and specifically refers to a class of benzyl ether or amine units linking a trigger (specifier) moiety to active drug. Activation of the trigger (specifier), typically by enzymatic cleavage, spontaneously releases the drug through a 1,4- or 1,6-elimination cascade, an example of the double prodrug approach.[65−67] Although these systems use different chemical structures and trigger groups (vide infra), the cleavage pathways are all essentially based on generation of a benzyl-based vinylogous hemiacetal anion and the subsequent spontaneous electronic cleavage cascade described above (Chart 2).

We note that despite the relatively straightforward concept, the current structural diversity in disassembling dendrimers is limited. Only three cleavage pathways[31,32,37,38] and six trigger groups (Chart 3) (allyl,[31,32] *o*-nitrobenzyl,[33,38] *p*-aminobenzyl,[37] *t*-Boc,[38] retro-aldol/retro-Michael,[39] and phenylacetamide[40]) have been reported. The specific triggers

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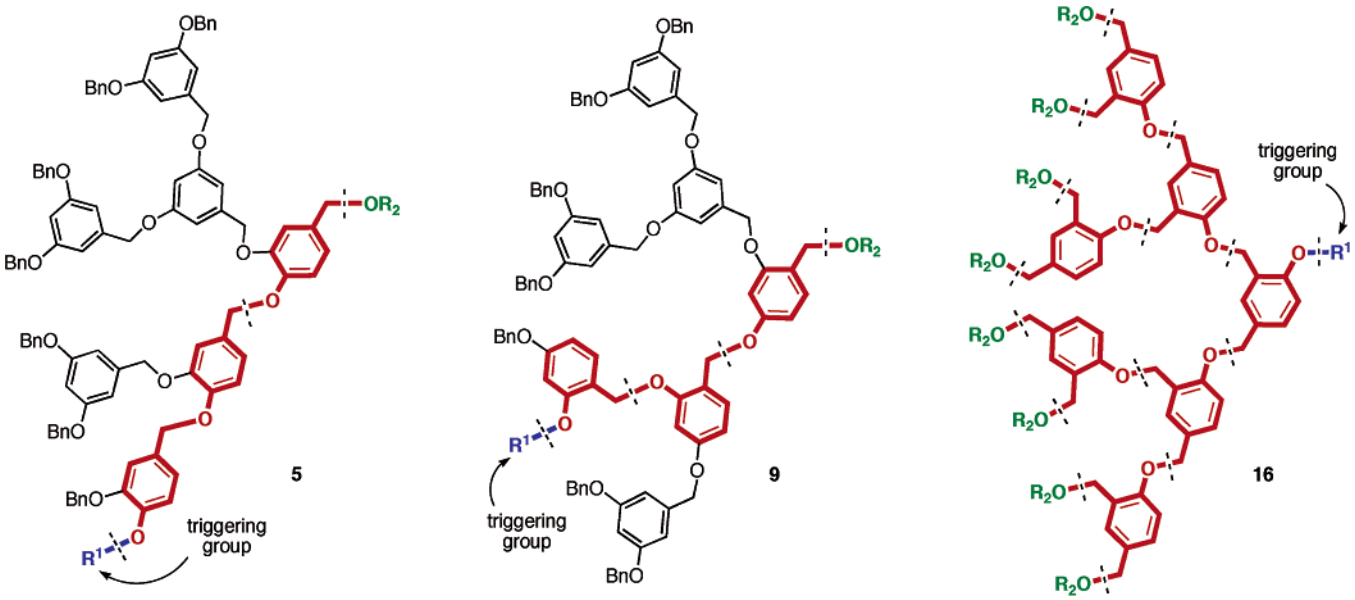
Chart 1. Dendrons Capable of Linear Para, Linear Ortho, and Geometric Disassembly



Scheme 3. Geometric Disassembly Pathway

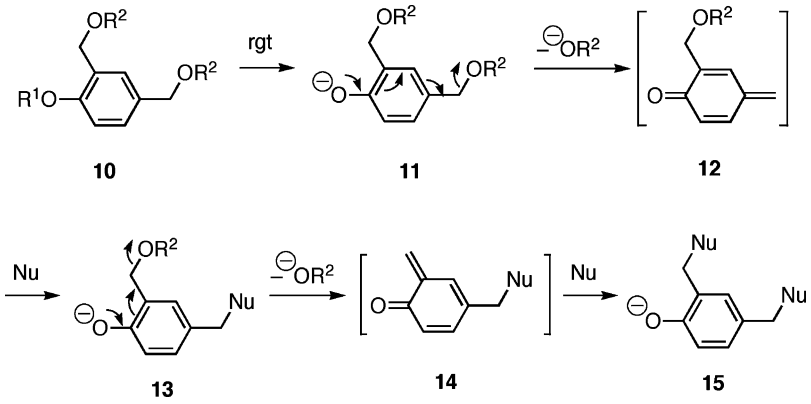
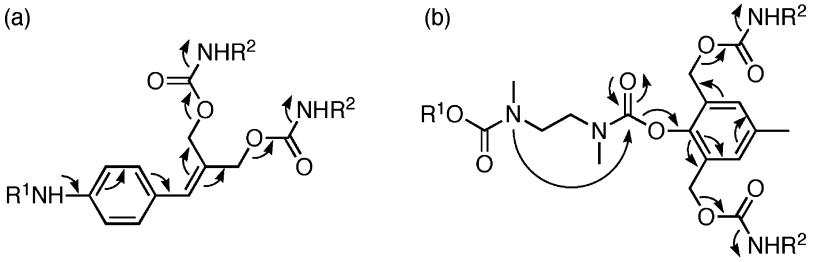


Chart 2. Other Geometric Disassembly Pathways[37,38]



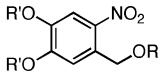
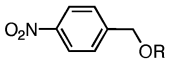
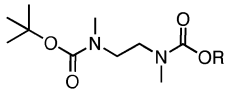
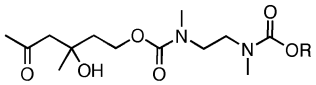
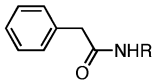
used in our systems, the conditions of disassembly, and the methods of assaying the disassembly process are all described in the next section.

Examples of Dendrimer Disassembly Systems

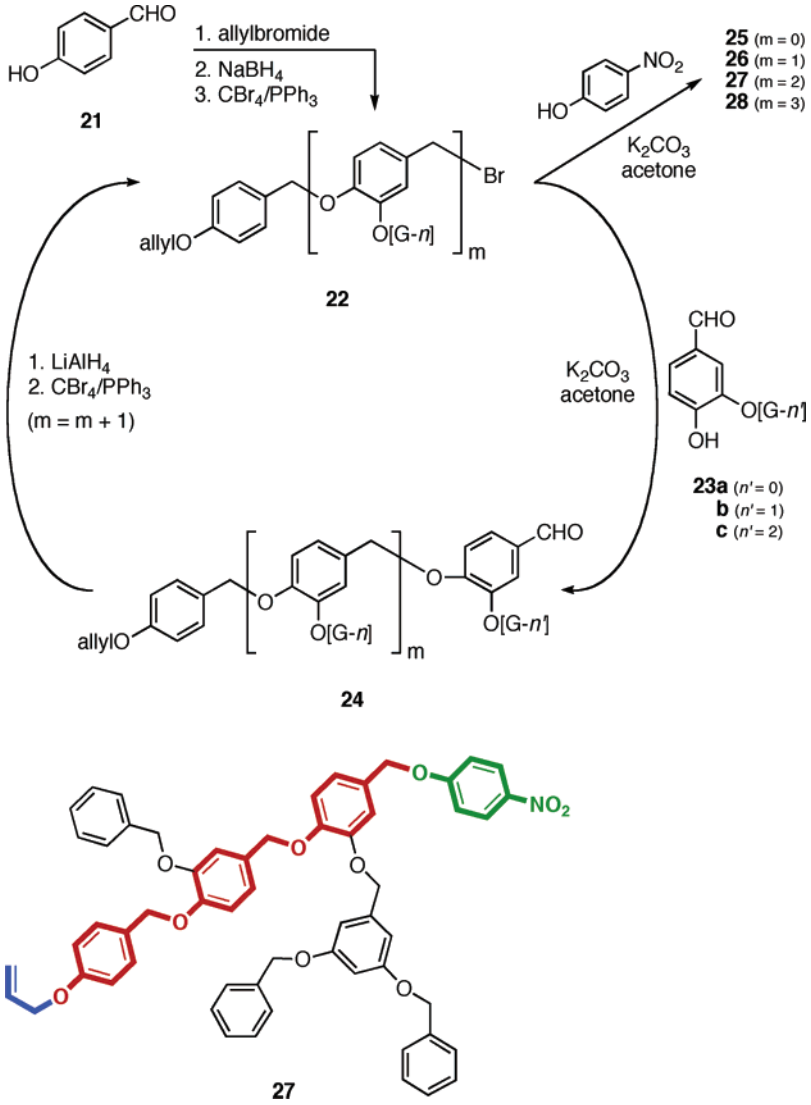
We present here the synthesis and assay of disassembling dendritic systems. We have to date reported examples of both linear and geometric disassembly with allyl and *o*-nitrobenzyl trigger groups.

Linear Disassembly.[31,63] Using an iterative convergent synthesis (Scheme 4), we prepared zeroth through third generation dendrons (e.g., **27**) capable of linear disassembly through a para cleavage vector. The trigger was the allyl group, and a *p*-nitrophenoxy (PNP) reporter group was intentionally installed at the focal point of the dendrons so that complete disassembly could be assayed by the UV absorbance of liberated *p*-nitrophenoxide (PNP) ion (ca. 430 nm in DMF). Experimental conditions for rapid disassembly, $Pd(PPh_3)_4/NaBH_4$ in DMF, were a variation on standard allyl

Chart 3. Reported Disassembly Triggering Groups (Triggering Conditions)

Allyl (Pd^0/BH_4^-):  Szalai, Kevwitch, McGrath *J. Am. Chem. Soc.* **2003**, *125*, 15688; Li, Szalai, Kevwitch, McGrath, *J. Am. Chem. Soc.* **2003**, *125*, 10516.	***o*-Nitrobenzyl (*hν*):**  Amir, Pessah, Shamis, Shabat, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4494; Szalai, McGrath *Tetrahedron* **2004**, *60*, 7261.	***p*-Aminobenzyl (Zn^0/AcOH):**  de Groot, Albrecht, Koekkoek, Beusker, Scheeren, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4490.
***t*BOC (1. TFA; 2. TEA):**  Amir, Pessah, Shamis, Shabat, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4494.	**Retro-aldol/retro-Michael (cat. antibody 38C2):**  Amir, Pessah, Shamis, Shabat, *J. Am. Chem. Soc.* **2004**, *126*, 1726.	**Phenylacetamide (penicillin-G-amidase):**  Amir, Shabat *Chem. Commun.* **2004**, 1614.

Scheme 4. Linear Disassembly Synthesis



deprotection conditions.[68] Smooth disassembly was observed for all compounds in 85−100% yields based on final absorptivity of PNP at 432 nm by UV spectrophotometry (Figure 3). The liberated fragments of the disassembly process were characterized by GC− and LC−MS, and their molecular weights were consistent with trapping of QM intermediates by excess hydride in solution.

Geometric Disassembly.[32−35] We have explored the divergent synthesis of geometrically disassembling dendrons based on the 2,4-bis(hydroxymethyl)phenol subunit from two

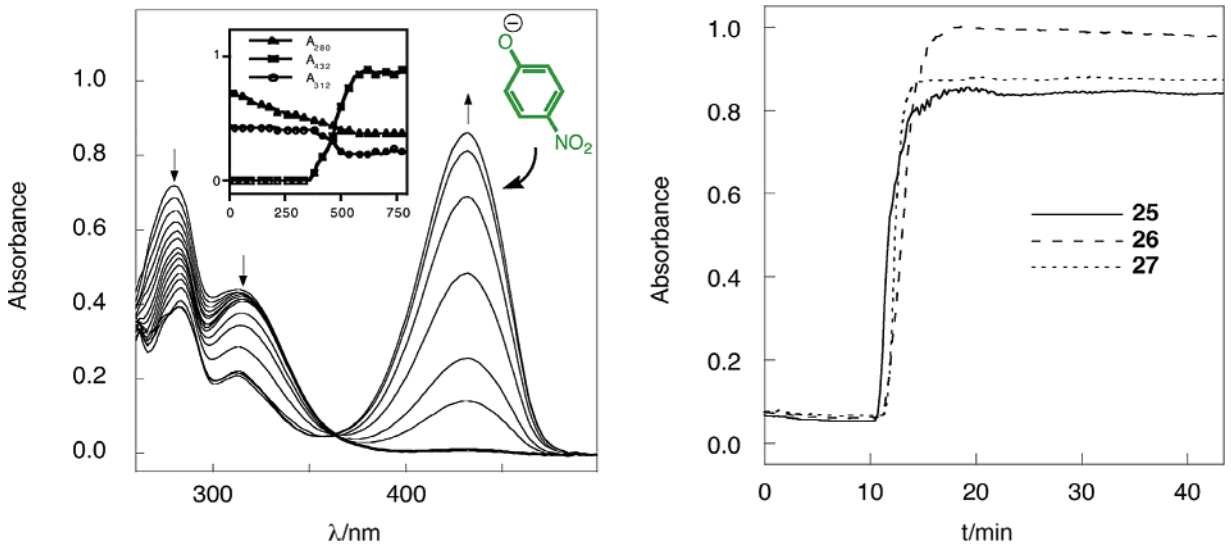
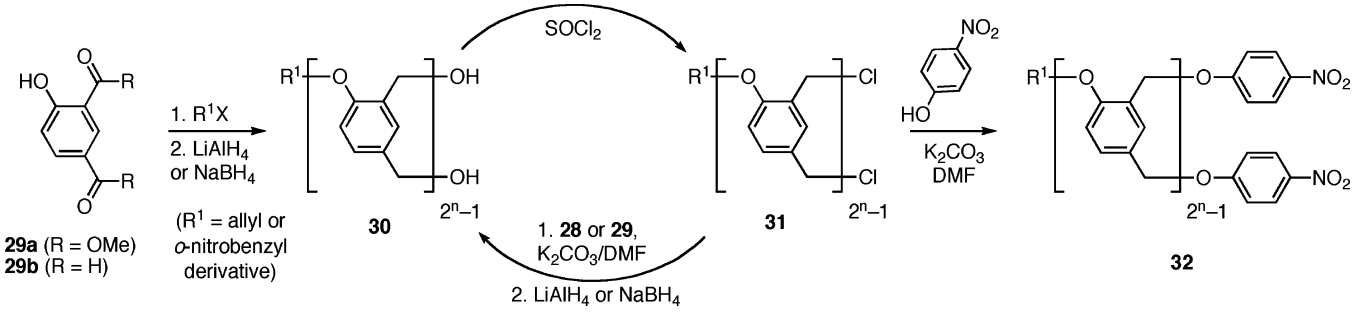
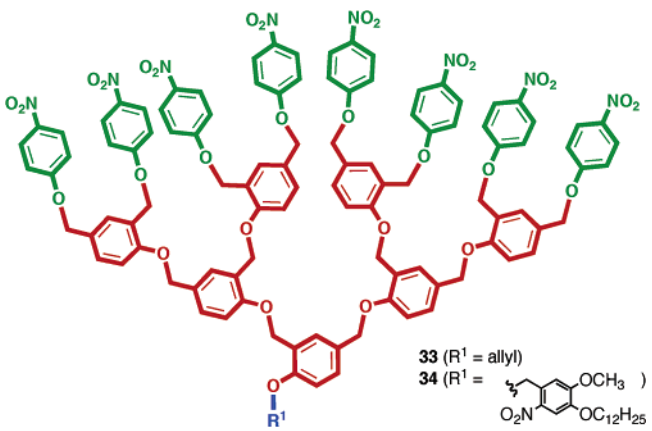


Figure 3. Left: UV spectra during disassembly of **27**. Inset: Absorbance at 280, 312, and 432 nm with time. Right: Absorbance at 432 nm as a function of time during disassembly of **25**−**27**.

Scheme 5. Geometric Disassembly Synthesis with Isophthalate or Isophthalaldehyde



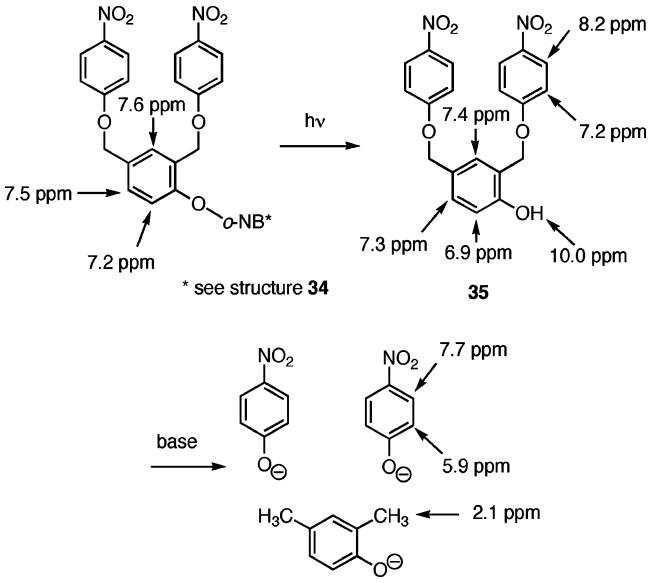
readily available precursors: isophthalate **29a** and isophthalaldehyde **29b** (Scheme 5). While both routes proved viable, $LiAlH_4$ was the necessary reducing agent in the route using **29a**, and this was not compatible with easily reduced trigger groups such as photolabile *o*-nitrobenzyl derivatives. In this case, the route using **29b** where $NaBH_4$ was the reducing agent was required. Geometric disassembly has been successfully effected in dendrons up to the third generation (e.g., **33**, **34**) with either allyl or *o*-nitrobenzyl trigger groups. Disassembly was again monitored by UV absorbance of liberated PNP ion and was found to proceed in ca. 95% yields.



Phototriggered Geometric Disassembly.[33,35] Phototriggered dendrimers capable of geometric disassembly were prepared up to the third generation (e.g., **34**) using the isophthalaldehyde **29b** based synthesis detailed above (Scheme 5). Disassembly in DMF solution with $NaBH_4$ (1 mg/mL) proceeded to 75−80% completion after irradiation at 310 nm for 60 min as monitored by absorbance of PNP ion. A control experiment with a zeroth generation compound that cleaved in 80% yield indicated that the dendrimer disassembly yields were limited by an inefficient photochemical deprotection and not the disassembly chemistry. By monitoring these disassembly reactions by ^1H NMR spectroscopy in DMSO-d_6 we were able to confirm that base is indeed necessary to initiate disassembly subsequent to trigger removal. Stable free phenols (e.g., **35**) were observed upon irradiation in the absence of $NaBH_4$, and disassembly was subsequently initiated by addition of this or other bases (Scheme 6). $NaBH_4$ as the base provided the cleanest results, presumably due to its serving as both a base and an efficient

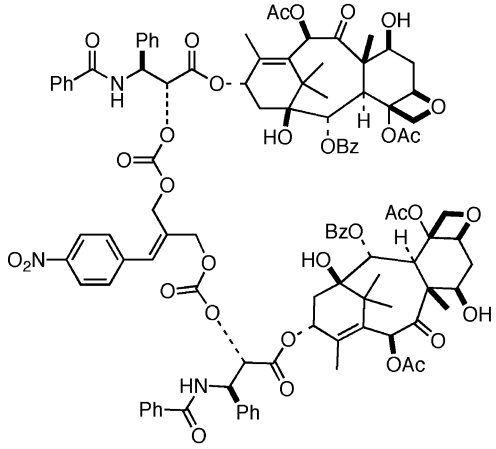
(68) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J.-P. Reductive deprotection of aryl allyl ethers with $Pd(PPh_3)_4/NaBH_4$. *Tetrahedron Lett.* **1994**, *35*, 4349.

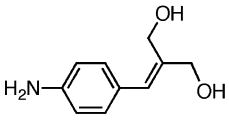
Scheme 6. ^{1}H NMR Data of Phototriggered Disassembly

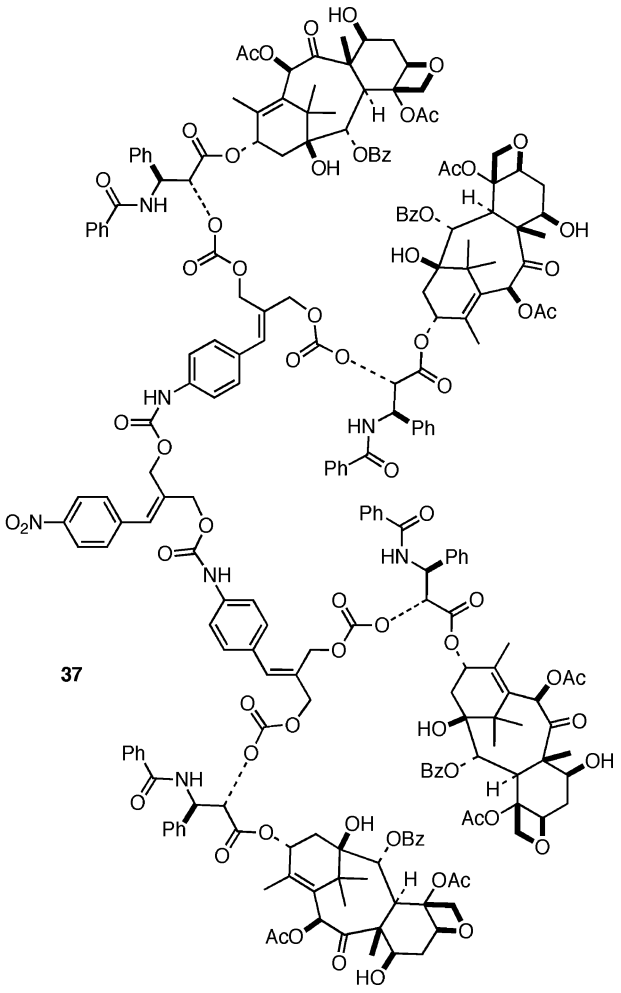


trapping nucleophile for the reactive QMs generated during disassembly. In geometric disassembly, the two cleavage events per subunit occur sequentially, and efficient trapping of QM after the first cleavage is necessary for the second cleavage to occur.

Chart 4. Paclitaxel-Releasing Disassembling Dendrimers[37]





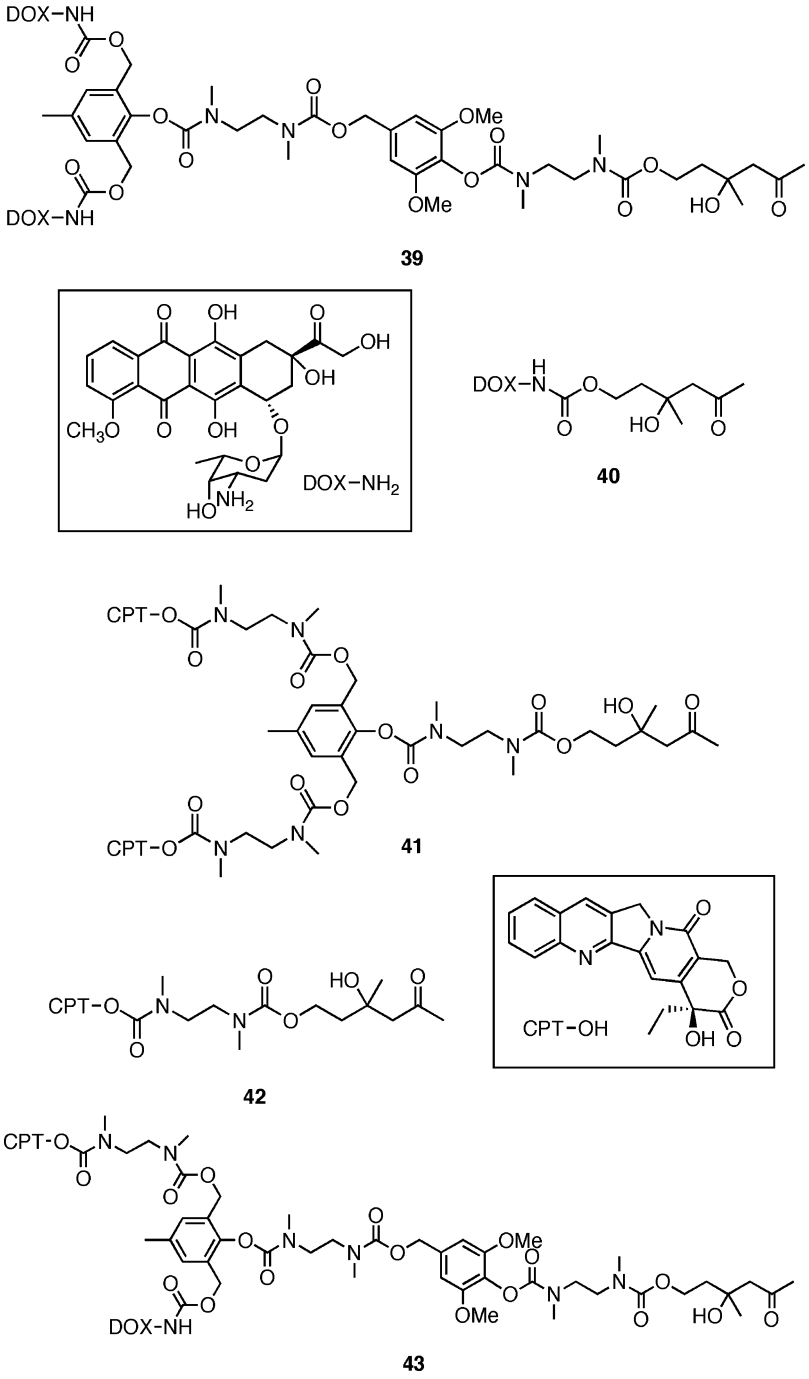


Drug Delivery with Disassembling Dendrimers

The potential of disassembling dendritic systems in drug delivery has been demonstrated separately by the groups of de Groot[37] and Shabat.[38−40] Using a 1,8-elimination geometrically disassembling subunit (Chart 2a), de Groot synthesized first and second generation geometrically disassembling dendrimers **36** and **37**, respectively (Chart 4).[37] The peripheral subunits were the chemotherapeutic drug paclitaxel, and triggering of disassembly occurred by reduction of the nitro group to the amine under mild conditions (Zn/AcOH). Two and four equivalents of paclitaxel were released from **36** and **37**, respectively, as evidenced by NMR, mass spectrometry, and chromatography. Furthermore, byproduct aminodiol **38**, formed by trapping of a quinoidal intermediate with water, was found to display no cytotoxicity in seven human tumor cell lines.

Following an initial communication of dendrimers constructed from a bis(1,4-elimination) geometrically disassembling subunit (Chart 2b),[38] Shabat and co-workers reported dendritic homo- and heterodimeric prodrugs based on this subunit that released 2 equiv of chemotherapeutic drugs doxorubicin (DOX), camptothecin (CPT), or both.[39] The trigger group was a retro-aldol/retro-Michael substrate

Chart 5. Doxorubicin (DOX) and Camptothecin (CPT) Containing Disassembling Dendritic Prodrugs



for catalytic antibody 38C2 that was attached to the focal point of the dendron through an appropriate linker. Bioactivation of the dendritic prodrugs was evaluated by growth inhibition assays on the Molt-3 luekemia cell line. A mild to significant increase in toxicity (2−4 times) was observed for homodimeric dendritic prodrugs **39** and **41** in comparison to analogous monomeric prodrugs **40** and **42** when activated by catalytic antibody 38C2 (Chart 5). Most remarkable, however, was the effect observed upon activation of heterodimeric prodrug **43**. The toxicity of prodrug **43** was 50-fold higher than a combination of two monomeric prodrugs (**40** and **42**), suggesting that different drugs can be released from the same dendritic platform to achieve synergistic effects. The authors speculate that precise drug combinations could be tailored to specific types of cancer and their ratios determined by their incorporation into a dendritic prodrug platform. In a further contribution, the same authors report dendrons with multiple enzymatic triggers sensitive to penicillin-G-amidase, effectively increasing the sensitivity of these potential prodrugs to the triggering agent.[40]

Conclusion

Although it is a new and still-developing concept in dendrimer chemistry, we have confidence that disassembling

dendrimers and dendritic structures will find use in many applications in materials and other areas of chemistry, including drug delivery. We are currently focusing our efforts on the design and implementation of improved synthetic strategies for preparing disassembling dendrimers, and the application of disassembling dendritic structures in materials and biological chemistry. These efforts are critical to the successful implementation of applied research in disassembling dendrimers in our group and will facilitate research efforts in other laboratories desiring to use this technology.

Acknowledgment. This work was generously supported by grants from the National Science Foundation (CHE-0213537) and the Petroleum Research Fund (38421 AC-7).

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