

## Synthesis of Cored Dendrimers

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The unique structure of dendrimers gives rise to properties that have, in turn, led to applications ranging from bulk polymer additives to biomedical agents.<sup>1</sup> Three structural components are common to all dendrimers: a core unit, peripheral groups, and the multiple branching units that span the two. The core unit is indispensable because it covalently links the dendritic “wedges” (dendrons). At the same time, the ability to “core” a dendrimer could greatly facilitate the development of new dendritic catalysts, delivery vehicles, and recognition systems. Maintaining the structural integrity of a cored dendrimer would, however, require an alternative connection between the dendritic wedges. Herein we report the first example of a dendrimer whose peripheral groups are extensively cross-linked and whose core is subsequently removed.<sup>2</sup>

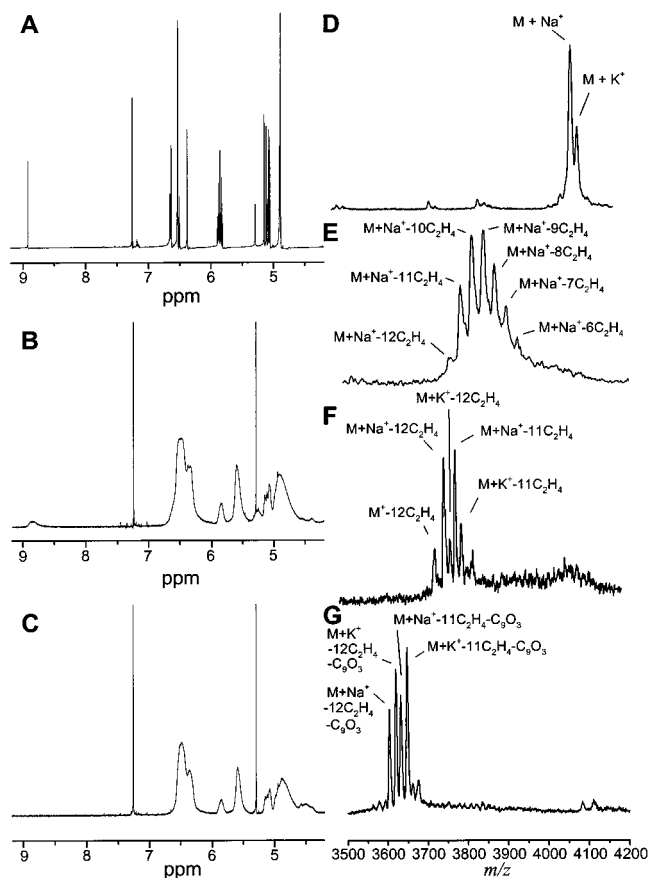
Dendrimers **1a** and **1b** were designed with homoallyl ether groups on their periphery, which could be intramolecularly linked through a ring-closing metathesis (RCM) reaction.<sup>3</sup> Model studies showed that homoallyl groups attached to the same benzene ring cannot undergo metathesis, increasing the probability of inter-wedge reactions. The required dendrons were synthesized from homoallyl alcohol and methyl 3,5-dihydroxybenzoate with, iteratively, the Mitsunobu etherification followed by lithium aluminum hydride reduction.<sup>4</sup> Dendrimers **1a** and **1b** were produced, respectively, by a Mitsunobu esterification of trimesic acid with the appropriate third-generation alcohol, and by Mitsunobu esterification of a third-generation dendritic carboxylic acid and 1,3,5-tris(hydroxymethyl)benzene.<sup>5</sup> The dendrimers, which are similar to those reported by Hawker and Fréchet,<sup>6</sup> contain three cleavable ester bonds at their core, but robust ether linkages throughout the remaining structure.

The RCM reaction of dendrimer **1a** with 4 mol % of Grubbs' ruthenium alkylidene catalyst **2**<sup>3c</sup> per dendrimer was found to give exclusively the intramolecular product **3a**<sup>7</sup> when carried out in benzene under a nitrogen atmosphere at high dilution (10<sup>-5</sup> M). The intramolecularity was established by size-exclusion chromatography (SEC) and matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF-MS). At concentrations higher than 10<sup>-5</sup> M, dimer and trimer were observed by both SEC and MALDI-TOF-MS. The polystyrene equivalent molecular weight of **3a** determined by SEC is lower than the

**Table 1.** Comparison of Selected Theoretical and Experimental Molecular Weights Determined by SEC or MALDI-TOF-MS<sup>a</sup>

compd	molecular weight			peak assignment
	SEC <sup>b</sup>	calcd <sup>c</sup>	MALDI	
<b>1a</b>	3440	4095.9	4095.0	M + Na <sup>+</sup>
<b>3a</b> <sup>d</sup>	2074	3759.3	3760.2	M + Na <sup>+</sup> - 12C <sub>2</sub> H <sub>4</sub>
		3787.3	3788.8	M + Na <sup>+</sup> - 11C <sub>2</sub> H <sub>4</sub>
<b>4a</b> <sup>d</sup>	2285	3603.2	3603.1	M + Na <sup>+</sup> - 12C <sub>2</sub> H <sub>4</sub> - C <sub>9</sub> O <sub>3</sub>
		3631.2	3631.3	M + Na <sup>+</sup> - 11C <sub>2</sub> H <sub>4</sub> - C <sub>9</sub> O <sub>3</sub>

<sup>a</sup> M + K<sup>+</sup> peaks are also present, but are not shown. <sup>b</sup> THF eluent with polystyrene calibration. Triplicate runs, error <15%. <sup>c</sup> Calculated with peak assignment indicated. <sup>d</sup> Compound prepared with higher catalyst loading.



**Figure 1.** <sup>1</sup>H NMR of (A) **1a**, (B) **3a**, and (C) **4a**. In spectra B and C the compound was prepared by using the low catalyst loading. MALDI-MS of (D) **1a**, (E, F) **3a** (see text), and (G) **4a**. An older MALDI-MS machine was used in part E, where potassium peaks appear as shoulders.

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(2) An attempted synthesis of a polysilane shell entrapping a dendrimer was reported very recently: Niu, Y.; Chai, M.; Rinaldi, P. L.; Tessier, C. A.; Youngs, W. J. *Polym. Prepr.* **1998**, *39*, 629–630.

(3) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452 and references therein. (b) Coates, G. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 229–230. (c) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.

(4) Höger, S. *Synthesis* **1997**, 20–22. (b) L'Abbé, G.; Forier, B.; Dehaen, W. *Chem. Commun.* **1996**, 2143–2144.

(5) Dendrimers **1a** and **1b** gave a passing elemental analysis and were shown to be pure by NMR, SEC, and MALDI-TOF-MS.

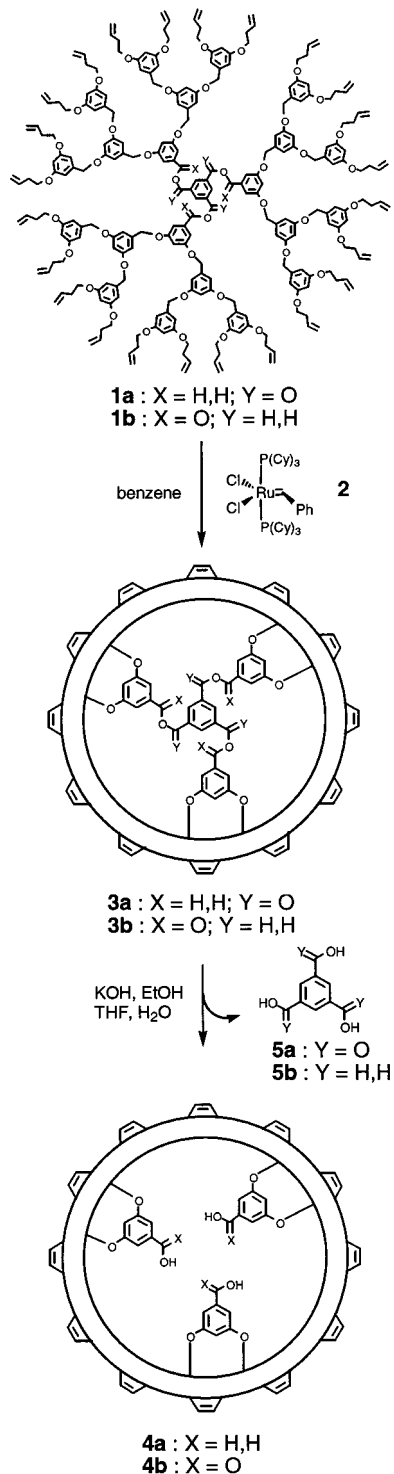
(6) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.

(7) The structure of **3** and **4** is unknown. The schematic illustrations are not meant to suggest any particular shape.

theoretical value, suggesting that the cross-linking leads to a more compact structure (Table 1). The <sup>1</sup>H NMR spectrum of **3a** is significantly broadened in comparison to **1a** (Figure 1A,B) either due to restricted internal motion or the fact that many isomers can be produced. Indeed, without considering topological isomers or that some structures might be kinetically or thermodynamically inaccessible, nearly 1.7 million isomers are possible for the RCM product with six cross-links. Despite the broad peaks, the <sup>1</sup>H NMR spectrum shows clear evidence of a high degree of metathesis. The methine peak due to the terminal alkene at  $\delta$  5.86 ppm is diminished, and a new peak at ca. 5.60 ppm is consistent with the presence of disubstituted alkenes.

More definitive evidence for the cross-linking came from mass spectral analysis. Product **3a** gave MALDI-TOF mass spectra

Scheme 1



indicating the loss of between 6 and 12 ethylene molecules (Figure 1E) in the metathesis reaction. Assuming the peak intensities

correspond to the relative amounts, the major product contains 9 of 12 possible cross-links, but a broad range of cross-linked products was seen. Importantly, it was found that by carrying out the metathesis reaction with 4 mol % catalyst *per alkene*, **1a** afforded **3a**, which was almost fully cross-linked (Figure 1F). Product **3a**, obtained from RCM reactions with both high and low catalyst loadings, was purified by silica gel chromatography to remove the ruthenium catalyst, with isolated yields of 80–95%.

With the peripheral groups cross-linked, **3a** was “cored” by reaction with potassium hydroxide in a tetrahydrofuran–ethanol–water mixture. The cored dendrimer **4a** was isolated in 70–75% yield, indicating that in most cases **3a** underwent at least two inter-wedge metathesis reactions.<sup>8</sup> The core unit **5a** was separated from **4a**, but at best only 47% of **5a** was isolated. Nonetheless, the mass spectra indicated the coring to be quantitative (vide infra). Because of the small amount of **5a** produced, it is likely some losses occurred in the workup. The <sup>1</sup>H NMR and MALDI-TOF-MS are fully consistent with loss of the core. Thus, the <sup>1</sup>H NMR spectra of **4a** shows the loss of the core signal at  $\delta$  8.87 (Figure 1C) and the MALDI-TOF-MS (Figure 1G) shows peaks that are ca. 156 amu lower in mass than for **3a** due to the loss of the core (C<sub>9</sub>O<sub>3</sub>). The silica gel retention of **4a** was noticeably higher for **4a** than for **3a**, suggesting that the alcohol groups are at least partially exposed. The SEC indicates only a small change in size following the coring (Table 1).

The conversion of **1b**  $\rightarrow$  **3b**  $\rightarrow$  **4b** occurred in an analogous fashion in 46% yield. Beyond demonstrating the generality of the overall synthetic protocol, the synthesis of **4b** shows that the functionality left on the interior can be controlled. Many variants on this process can be envisioned. The location of the linking functional groups might be changed to the dendrimer interior, allowing both higher concentrations for the cross-linking and more variability in the surface functionality. The cross-linking could also be replaced by an intramolecular polymerization reaction. A noncovalent version might also be possible where the core would serve as a supramolecular template.<sup>9</sup> There is an obvious conceptual analogy between the processes described herein and polymer imprinting.<sup>10</sup> The possibility of using this as a “molding” process to form soluble endo-receptors for small molecules is under active investigation, as are the many other alternatives described above.

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**Supporting Information Available:** Synthetic schemes, experimental procedures, and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(8) Two inter-wedge cross-links are the minimum needed to covalently link the three dendrons. The mass spectrum does not otherwise distinguish inter- from intra-wedge metatheses.

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(10) Wülfel, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1812–1832.