

On the Nature of Dendrimer Cross-Linking by Ring-Closing Metathesis

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Despite the extraordinary commercial importance of cross-linked polymers, it is often difficult to determine the number, location, and precise structure of individual cross-links within a single macromolecule.¹ The monodispersity of dendrimers² makes it possible to address structural questions unanswerable with other polymers. In an effort to develop molecularly imprinted dendrimers (MIDs),³ nanoparticles,⁴ and nanotubes,⁵ we showed⁶ that Fréchet-type dendrimers⁷ with homoallyl ether end-groups could be extensively cross-linked^{8,9} (intramolecularly) using the ring-closing metathesis (RCM) reaction.¹⁰ Only a trace of fragmentation was observed following removal of their cores indicating that at least a few cross-links formed between dendrons. Herein we report model studies using dendrimer **1** and its constituent subunits that reveal considerably more detail about the cross-linking process.

In dendrimer **1** a homoallyl ether group (highlighted in red) potentially can undergo the RCM reaction with four different kinds of alkenes, labeled as type **a–d** (Figure 1). Whereas proximity favors the nearest neighbor (type **a**), a purely statistical RCM reaction would lead to a preference for one of the eight alkene groups in the other dendron (i.e., type **d** > **c** > **b** > **a**). The outcome will also depend on steric effects and on whether the reaction is under kinetic or thermodynamic control.

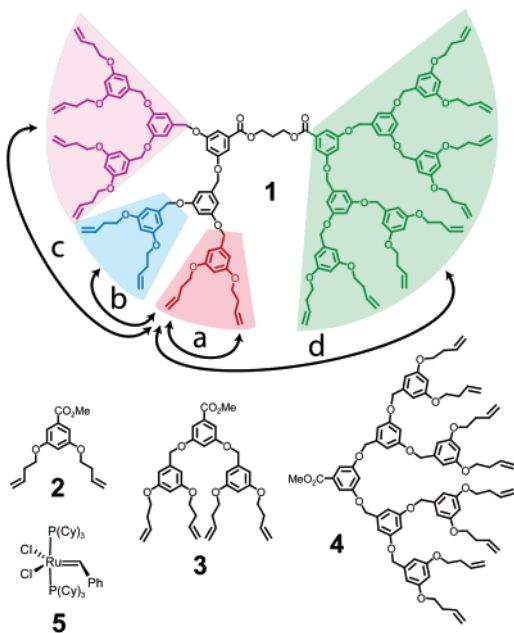


Figure 1. Cross-linking connectivity within **1**; compounds **2–5**.

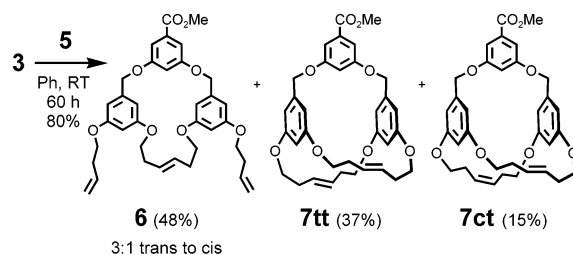
To investigate the general preference for formation of type **a–d** cross-links in **1**, the RCM reaction of **2–4** with **5** was examined.

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Thus, using a standard protocol,^{3,6} dendron **2** was treated with Grubbs catalyst **5** in benzene at room temperature and at a concentration of 10 μ M. After a week during which additional portions of **5** were added, no RCM was observed. At higher concentrations oligomerization of **2** occurs.¹¹ This result suggests that type **a** cross-links are highly disfavored, presumably for steric reasons.

Applying the standard RCM reaction conditions to **3** led to a total consumption of starting material after 60 h. Both singly (**6**) and doubly (**7tt** and **7ct**) cross-linked products were isolated (Scheme 1), the structure of the latter elucidated by a combination

Scheme 1



of ¹H NMR and X-ray analysis (Figure 2). The presence of **6** under conditions where larger dendrimers underwent full RCM reaction suggested some difficulty in forming two type **b** cross-links in **7**.

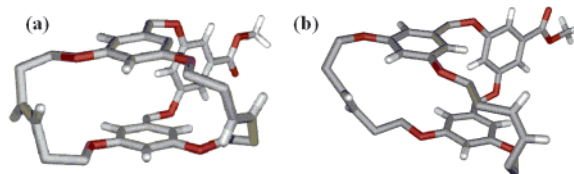
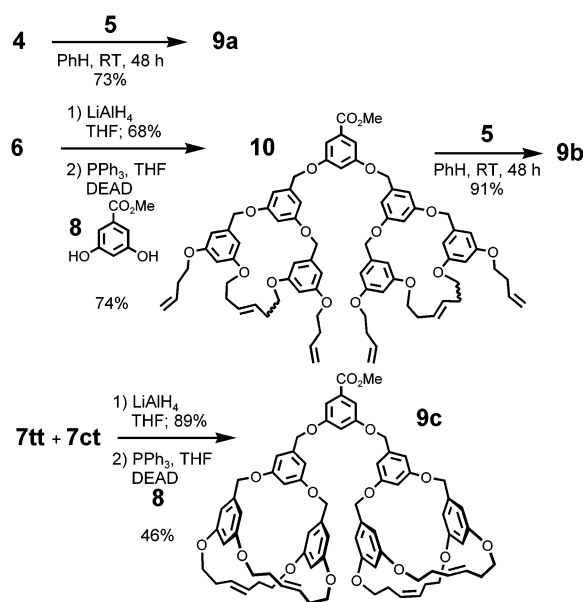


Figure 2. X-ray structure of (a) **7tt** and (b) **7ct**. Most protons removed for clarity. See Supporting Information for details.

The products formed in Scheme 1 are likely kinetic products because when **7ct** was treated with **5** under the standard RCM conditions it did not equilibrate to **7tt**. The same experiment was performed starting with a 9:1 ratio of **7ct** to **3** to ensure that the active catalyst can form during the reaction. Again, the ¹H NMR of the crude product showed negligible equilibration to **7tt** or **6**.

The peripheral aromatic rings in **7tt** and **7ct** (Figure 2) are proximal and shield one another, their protons appearing in a group of peaks centered at $\delta = 6.1$ ppm in the ¹H NMR spectrum. To see whether such upfield shifts are diagnostic of similar type **b** cross-links in larger dendrons, and whether they form, the fully cross-linked product from **4** was synthesized in three different ways (Scheme 2). First, **4** was treated with **5** to produce **9a**. Second, **6** and a 1:1 mixture of **7tt** and **7ct** were separately reduced with LiAlH₄, followed by Mitsunobu etherification with **8** to produce the desired **10** and **9c**, respectively. Finally, **10** was subjected to RCM to form **9b**.

Scheme 2



In comparing the integrals of the two key aromatic regions in the ¹H NMR spectra of **9a–9c** (δ 5.9–6.2 vs 6.25–6.6, Figure 3) it is clear that the RCM reaction of **4** produces fully cross-linked product **9a** containing only ca. 1% of **9c**. If the RCM reaction of **10** occurred with random linking of the four terminal alkene groups, then **9b** would contain 33% of isomer **9c**, yet only ca. 8% is observed. This indicates that even with the two type **b** cross-links in **10** additional type **b** links are disfavored. Given that ca. 1% of **9c** is formed in the RCM reaction of **4**, it can further be said that **10** is not a significant intermediate and, indeed, the early cross-links favored are type **c**.

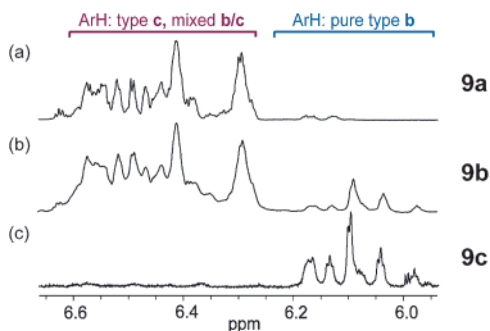


Figure 3. ¹H NMR spectra showing aromatic region for RCM product of (a) **4** (**9a**) and (b) **10** (**9b**), and (c) type **b** cross-linked **9c**.

Finally, the relative preference of type **d** cross-links were examined in **1**. This study took advantage of several findings: (1) both ¹H NMR and MALDI can quantify the degree of cross-linking in **1**, both methods agreeing within a few percent,^{4,12} (2) at very short reaction times (low % cross-links), hydrolysis and size exclusion chromatography (SEC) gives the relative amount of di- to mono-dendron (fragmentation), and (3) these data combined with MALDI analysis pre- and posthydrolysis can give the relative amount of intra- and interdendron cross-linking (i.e., types **b**, **c** vs type **d** cross-links).¹² Thus, a 10 μ M solution of **1** in benzene was reacted with **5** and aliquots of the mixture were removed at short

Table 1. Representative Data for Types **b**, **c** vs **d** Cross-Links (CLs)^a

time (min)	% alkene RCM in 1 ^b	% of 1 with 1 (>1) CL ^c	di- to mono-dendron ratio ^d	% type d CL in 1 with 1 CL
1	4	21 (4)	18:82	66
5	8	33 (17)	42:58	76
10	11	35 (23)	50:50	75
20	15	34 (36)	58:42	
180	31	20 (74)	84:16	

^a For details of methods used see Supporting Information. ^b RCM of all 16 alkenes. ^c By MALDI. ^d After hydrolysis determined by SEC. intervals and analyzed.¹² As seen in Table 1, an average of ca. 72% of the first cross-links formed in **1** are type **d**. Given the purely statistical outcome would be ca. 66% type **d**, this result suggests a slight preference for the formation of type **d** cross-links (vs type **c**).

For many of the applications envisioned for cross-linked dendrimers, inter-dendron cross-links are preferable because they should lead to greater rigidity. Dendron **4** and dendrimers prepared from it were not specifically designed to favor any particular cross-link,^{3–6} yet the results reported herein indicate that they do. The relative preference observed, type **d** \geq type **c** > type **b** \gg type **a**, shows that geometrical preferences may be used to control the location of cross-linking within a macromolecular architecture. Our current efforts are directed toward chemical control of cross-link placement.

Acknowledgment. Funding of this work by the National Institutes of Health (GM61067) is gratefully acknowledged.

Supporting Information Available: Details on the synthesis and characterization of **6**, **7**, **9**, **10**, including MALDI and SEC data and X-ray crystallographic files (CIF) for **7ct** and **7tt**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA045885J