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-linked8,9 (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.

Thus, using a standard protocol,1,6 dendron 2 was treated with Grubbs catalyst 5 in benzene at room temperature and at a concentration of 10 μM. 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 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.

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 δ = 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.

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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Scheme 1

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.

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In comparing the integrals of the two key aromatic regions in the $^1$H 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.

![Scheme 2](image)

**Figure 3.** $^1$H 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 $^1$H 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 mM solution of 1 in benzene was reacted with 5 and aliquots of the mixture were removed at short 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).

| Table 1. Representative Data for Types b, c vs d Cross-Links (CLs)$^a$ |
|-----------------|----------|----------|----------|
| time (min)      | % alkene | % of 1 CL | di- to mono-dendron |
| % type d CL     | in 1$^b$ | (1 + CL) | ratio$^c$ | 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.

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,4,12 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.

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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 7ett and 7tct. This material is available free of charge via the Internet at http://pubs.acs.org.

References


8. (Although not a classical polymer network, the term cross-link can be applied because four chains (two AB2 units) emanate from the linkage.


12. See Supporting Information for details.

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