

Organic Nanoparticles Whose Size and Rigidity Are Finely Tuned by Cross-Linking the End Groups of Dendrimers

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The chemical or physical cross-linking of polymers is a well-studied process of incalculable practical importance. Recent interest has focused on cross-linking fewer polymer molecules within self-assembled structures or organized materials.¹ In contrast, the intramolecular cross-linking of preformed polymers has attracted much less attention, although as early as 1955 Kuhn noted that such a process would produce a contraction, altering the properties of the macromolecule.² Very recently intramolecular cross-linking was used to make small (<20 nm) organic nanoparticles.³ We reported the cross-linking of dendrimer end groups and subsequent core removal.⁴ The degree of rigidity imposed on these dendrimers in the cross-linking process creates a molecular memory of the core, and thus, a type of synthetic antibody can be made by covalent imprinting.⁵ Herein we show that the extent of dendrimer cross-linking can be controlled and leads in a regular and predictable way to more compact and rigid macromolecular nanoparticles.

The dendrimers used in this study (1–5, Figure 1) feature cores holding two (1, 2), three (3), four (4), and eight dendrons (5), molecular weights ranging from ca. 2700 to 11 000 and from 16 to 64 homoallyl ether end groups for cross-linking. The preparation of 1–5 involved esterifying the previously described homoallyl ether terminated, Fréchet-type⁶ dendron carboxylic acid with the appropriate alcohol core.^{5,7} The purity of 1–4 was demonstrated by analytical SEC, MALDI-TOF-MS, and ¹H NMR. Although 5 was previously purified to homogeneity,⁵ the material used in this study contained ca. 5% structural defects, including hexa- and heptadendrons (incomplete esterification).

The dendrimers underwent ring-closing metathesis (RCM) mediated cross-linking using 5 mol % (per alkene) of Grubbs type 1 catalyst 6 in benzene at high dilution (ca. 10⁻⁵ M).^{4,5,8} Although the high dilution conditions limit the amount of material that can be prepared, this limitation was previously overcome by locating the alkene groups on the interior branching units of the dendrimer⁹ and by Hawker using a staged addition of cross-linking agents to polymers.¹⁰ Upon full cross-linking, 1–5 lose between 8 and 32 ethylene units, which represents in each case less than 10% of the overall mass (Table 1). The molecular weights (MW_{PS}) determined by SEC shown in Table 1 reveal a more pronounced drop, particularly at longer RCM reaction times, reflecting the more compact size of the cross-linked dendrimers.

To quantify the extent of size contraction with cross-linking, the RCM reaction of 1–5 was monitored by quenching aliquots with ethyl vinyl ether and analyzing the samples by MALDI-TOF-MS or ¹H NMR.⁷ In the former method, peaks corresponding to dendrimers with different numbers of cross-links were readily discernible, and the weighted mean average of their peak heights gave the average percentage cross-linking. Alternatively, in the ¹H NMR spectrum at all stages of the RCM reaction the alkene methine proton of uncross-linked and cross-linked alkene groups appears

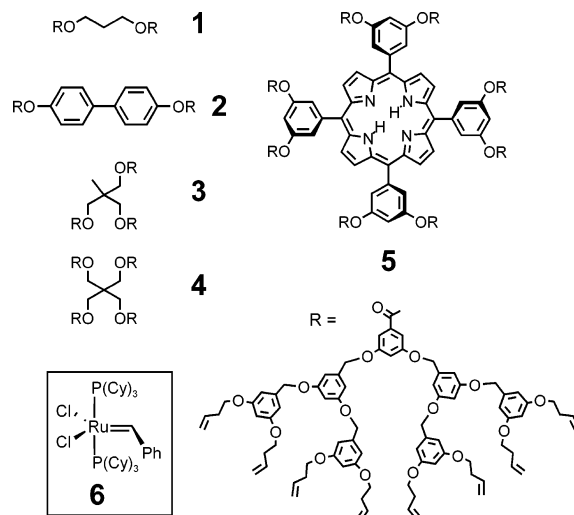


Figure 1. Dendrimers 1–5 and Grubbs catalyst 6 used for cross-linking.

Table 1. Calculated and SEC Molecular Weights at Various Times during the RCM-Mediated Cross-Linking Reaction^a

cmpd	MW calcd	CL-MW reduction ^b	SEC MW (polystyrene standard)			
			0 min	20 min	3 hr	24 hr
1	2679	8%	3380	2970	1930	1520
2	2789	8%	4100	3860	2770	2240
3	4025	8%	4480	3990	2920	2280
4	5342	8%	5260	4650	3350	2820
5	11 155	8%	7550	6630	5620	4660

^a See text and Supporting Information for details. ^b Calculated % reduction in mass if all possible cross-links (CL) are formed.

at ca. 5.85 and 5.65 ppm, respectively. Thus, the ratio of these peak areas also gives the percentage of cross-linking. Both methods (¹H NMR and MALDI) agree within a few percent.⁷

Plots of radius of gyration (R_g) against the percentage cross-linking are shown in Figure 2 for dendrimers 1–5. Strikingly, the plots are linear (all $R^2 > 0.98$), indicating that each cross-link produces a similar size reduction irrespective of when it forms. The reduction in R_g ranged from 21% for 5 to 31% for 1. Assuming a spherical structure and an R_g that approximates the molecular radius, the volumes ($V = 4/3\pi r^3$) of 1–5 are reduced to between ca. 33% (1) and 39% (5) of their original value when ca. 95% cross-linked. This size contraction with a <10% reduction in mass (Table 1) implies a significant increase in density.

Dendrimer 5 and its RCM products at various stages of cross-linking were spin-coated onto mica and examined by noncontact AFM.^{7,11} As seen in Figure 3, dendrimer 5 with ca. 74% of its alkenes cross-linked showed a significantly higher height in air than 5 itself (5.4 vs 3.0 nm). The most consistent results were obtained

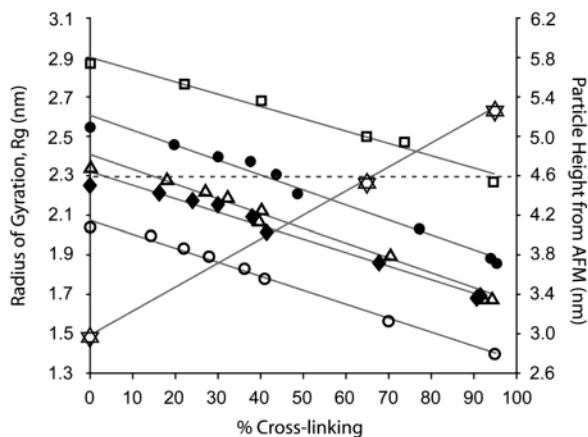


Figure 2. Plot of R_g , determined from the sample's intrinsic viscosity, against extent of cross-linking for dendrimers **1** (○), **2** (◆), **3** (△), **4** (●), and **5** (□). Best fit lines shown in solid gray. Dendrimer height of **5** (✱) from AFM plotted against extent of cross-linking. See text and Supporting Information for details.

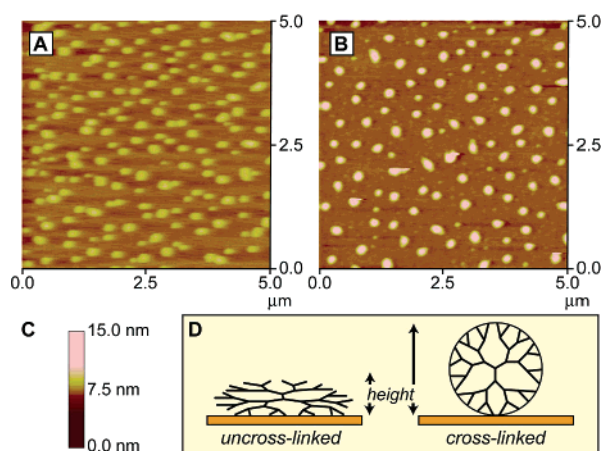


Figure 3. AFM images in air of dendrimers spin-coated onto a mica substrate. See Supporting Information for details including other AFM images, some of which show clustering and specific interactions between tip and fully cross-linked dendrimers. (A) Uncross-linked dendrimer **5**. (B) Dendrimer **5** 74% cross-linked. (C) Height legend. (D) Model showing flattening of uncross-linked dendrimer on surface.

by performing the AFM in ethanol containing tetrabutylammonium perchlorate (TBAP). Thus, **5** with 0, 65, and ca. 95% cross-linking showed heights of 3.0, 4.5, and 5.3 nm, respectively. The former two values are slightly smaller than those measured in air. The AFM height for the 95% cross-linked **5** is consistent with its R_g value and within 30% of the diameter measured by molecular modeling. However, in air this one sample showed a height (18.6 nm) that was much larger than expected and suggestive of some specific interaction between this dendrimer and the AFM tip (e.g., an electrostatic repulsion screened by TBAP). The precise origin of this effect is not known at this time.

As seen in Figure 2, the linear decrease in R_g with degree of cross-linking for **5** occurs with a marked increase in the AFM particle height. Although AFM can directly probe the nanome-

chanical properties of dendrimers,^{11c,12} a comparison of dendrimer height in the images with the R_g values can also provide information about their physical properties. Thus, a model that explains the seemingly contradictory data involves the RCM-mediated cross-linking producing a more compact, but also more rigid particle. As seen in Figure 3D, the flexible **5** (uncross-linked) can flatten on the mica surface, whereas the heavily cross-linked dendrimer stands rigidly.^{11b}

Finally, the reversibility of the olefin metathesis reaction adds another tool for controlling the extent of cross-linking and, thus, the size and rigidity of these nanoparticles. For example, **5** that is 95% cross-linked can be treated with **6** in benzene, under an ethylene atmosphere and reversed to **5**, which is between 40 and 60% cross-linked depending on the exact conditions used.

If the model presented in Figure 3D is correct, then both the size and rigidity of these nanoparticles can be finely and independently tuned with the extent of cross-linking. For example, the horizontal dashed line in Figure 2 intersects four of the five R_g vs % cross-linking plots. Thus, at constant size the extent of cross-linking and resultant rigidity can be adjusted. Current efforts are directed at testing this idea, determining more precisely the nature of the cross-linking process and applying this chemistry to new dendrimer architectures.

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Supporting Information Available: Synthetic and characterization details for **1–5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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