Organic Nanoparticles

DOI: 10.1002/anie.200702580

Cross-Linked Glycerol Dendrimers and Hyperbranched Polymers as Ionophoric, Organic Nanoparticles Soluble in Water and Organic Solvents**

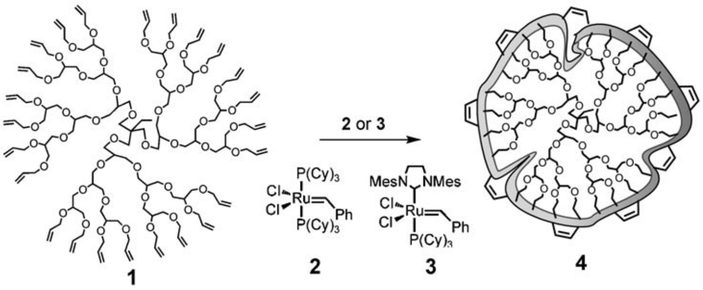
Steven C. Zimmerman, Jordan R. Quinn, Ewelina Burakowska, and Rainer Haag**

The usefulness of dendrimers and hyperbranched polymers in specific applications depends on the ability to tune their properties in a predictable fashion.[1] We recently showed that allyl and homoallyl ether end groups of dendrimers can be covalently linked using the ring-closing metathesis (RCM) reaction.[2–4] In addition to creating molecularly imprinted dendrimers[5] and organic nanotubes,[6] cross-linking of the end-groups was shown to produce a significant decrease in the size of the dendrimer.[7] At the same time, these organic nanoparticles became more rigid. The extent of cross-linking could be controlled, thus allowing the dendrimer size and rigidity to be finely and independently modulated. However, attempts to functionalize the cross-linked dendrimers, particularly with an eye toward water-soluble analogues, were unsuccessful.

Herein we report the ring-closing metathesis of polyallyl glycerol (Haag-type) dendrimers[8] and the analogous hyperbranched polymers.[9] The synthesis of these non-absorbing, organic nanoparticles is straightforward and readily scalable. Furthermore, the cross-linked dendrimers and hyperbranched polymers act as weak ionophores in organic solvents and can be readily dihydroxylated to make fully water-soluble nanoparticles.

Generation 3.5 (G-3.5) polyallylated glycerol dendrimer **1** was prepared in seven steps (45% overall yield) from tris(hydroxymethyl)propane using an iterative process of Williamson etherification and catalytic dihydroxylation.[8] Dendrimer **1** contains a mixture of many diastereomers, but its purity could be estimated by ^{1}H NMR spectroscopy, MALDI-MS, and analytical size-exclusion chromatography (SEC) to be higher than 97%.

Initial cross-linking studies were performed using the Grubbs catalyst **2** in benzene at room temperature (Scheme 1). The reaction typically required at least 24 h for near-complete conversion. The progress was monitored by MALDI-MS with aliquots periodically removed and quenched with ethyl vinyl ether. Initially, the MALDI mass spectrum showed dendrimers with a broad mass range corresponding to partial RCM reactions. However, the distribution of peaks narrowed until after about one day the mass spectrum indicated three main products with 10, 11, and 12 cross-links (Figure 1).



Scheme 1. RCM-mediated cross-linking of dendrimer **1**. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

Previous work had avoided use of catalyst **3**, because its residual activity was found to cause some interdendrimer metathesis during workup. After considerable exploration, conditions were found that allowed use of **3** at higher concentrations than were possible previously.[10] With portionwise addition of **3** to a 0.05 mM solution of dendrimer **1** in refluxing methylene chloride, gram quantities of dendrimer were available at much shorter reaction times (1.5–2.5 h). Catalyst **3** was added in two portions of 2.5 mol% per alkene unit. The cross-linking slows considerably after about 30 min, leaving **4** with mostly 12 cross-links (see the Supporting Information).

In the RCM reaction of Fréchet dendrimers, it was shown that nearest-neighbor cross-links are less favorable than longer distant ones.[11] Three observations suggest a similar RCM process in **1** as opposed to a series of eight-membered rings.[12] First, significant broadening is seen in the ^{1}H NMR spectrum, consistent with a large mixture of isomers arising from macrocycle formation. Secondly, SEC data indicated a

---

[*] Prof. S. C. Zimmerman, J. R. Quinn
Department of Chemistry
University of Illinois
600 S. Mathews Avenue, Urbana, IL 61801 (USA)
Fax: (+1) 217-244-9919
E-mail: sczimmer@uiuc.edu
E. Burakowska, Prof. Dr. R. Haag
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
Fax: (+49) 30-838-53357
E-mail: haag@chemie.fu-berlin.de

[**] Funding of this work by the National Institutes of Health (S.C.Z.) is gratefully acknowledged (GM61067). R.H. is grateful to a NanoFutur award from the German Ministry of Science.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

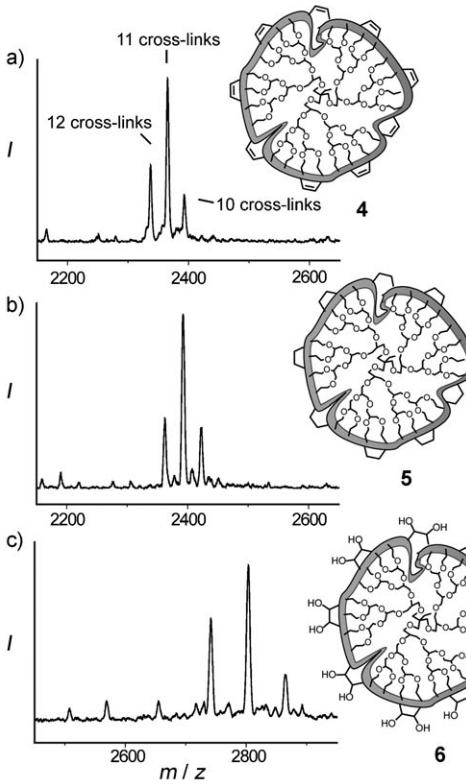


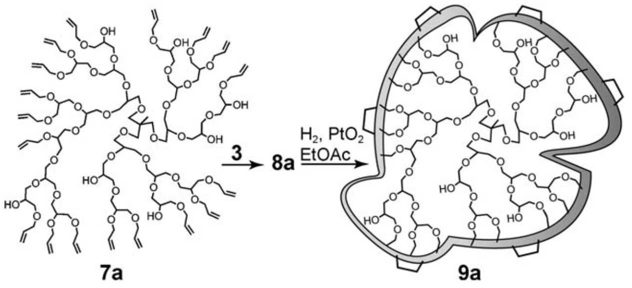
Figure 1. MALDI mass spectra for a) cross-linked G-3.5 glycerol dendrimer **4**, b) hydrogenated **5**, and c) dihydroxylated **6**. Cross-linking was performed using catalyst **2** in benzene at 20 °C.

change in mass of 900 Da, whereas the theoretical change is 336 Da for loss of 12 ethylene groups. The large reduction in mass by SEC relative to the theoretical change indicates a significant reduction of dendrimer size and has been observed in reported cross-linked dendrimers.[7] Finally, the last one or two pairs of alkene groups proved difficult to close. This observation was made in nearly all previous cross-linking reactions of Fréchet dendrimers and was attributed to distal terminal alkene groups requiring reorganization of the cross-linked structure to bring them into proximity for the final RCM reactions.

The cross-linked dendrimer **4** was found to undergo two post-RCM modifications. First, hydrogenation of **4** over the Adams catalyst was found to produce **5** smoothly, with 96 % mass recovery. Quantitative conversion was seen in the MALDI mass spectrum, in which the peak for **4** with 12 cross-links shifted by 24 mass units, corresponding to the addition of 12 H_2, and the two other main peaks shifted by the expected mass (Figure 1). This observation suggests that the alkene groups in **4** are located at its surface or that **4** is sufficiently flexible to allow the catalyst to access each alkene group. The polyalkene dendrimers tend to polymerize in the presence of air or traces of ruthenium, so hydrogenation makes the cross-linked dendrimer considerably more stable.

It was also found that **4** could be dihydroxylated using osmium tetroxide to afford **6**, which was fully soluble in water. Although **6** was not purified other than by removing the volatiles in the reaction mixture, the MALDI mass spectrum showed that the alkene derivatization was again essentially quantitative (Figure 1). The ability to synthesize water-soluble cross-linked dendrimers should open new avenues with regard to the applications described above.

It has been shown that hyperbranched polymers with an internal structure analogous to **1** can be synthesized from glycidol on a multikilogram scale.[8,9,13] The corresponding polyallyl ethers (**7a**,**b**; Scheme 2) were prepared by allylation



Scheme 2. RCM-mediated cross-linking and hydrogenation of hyperbranched **7a**. The structure is representative; the actual structure has $M_n = 5000\ \mathrm{g\,mol^{-1}}$.

of hyperbranched polyglycerol (**7a** $M_n = 5000\ \mathrm{g\,mol^{-1}}$; **7b** $M_n = 10\,000\ \mathrm{g\,mol^{-1}}$) using the simple phase-transfer protocol employed in the synthesis of **1**. Polymers **7a**,**b** were cross-linked using **3** to give **8a**,**b** (structures not shown). The degree of cross-linking was estimated by NMR spectroscopy, and the reaction was further monitored by SEC (see the Supporting Information).

Different conditions were examined to optimize the extent of cross-linking (Table 1). The results show that with catalyst loadings of 0.8 mol % per alkene unit, the degree of cross-linking did not surpass 50 % even after prolonged reaction times or with elevated temperature. High RCM conversion required 4 mol % of **3** for **7a** and 8 mol % for **7b**; the latter required a longer reaction time. The rate of the RCM reaction was not constant over time, with a large number of cross-links formed quite rapidly (in less than 1 h) but afterwards a much slower conversion rate.

Table 1: Conditions for optimizing the RCM reaction of hyperbranched **7**.

Run	Starting compound	*t* [h]	**3** [mol %][a]	*T* [°C]	Conversion [%][b]
1	**7a**	7	0.8	RT	45
2	**7a**	14	0.8	RT	50
3	**7a**	14	0.8	40	49
4	**7a**	1	4	RT	87
5	**7a**	14	4	RT	96
6	**7b**	14	4	RT	45
7	**7b**	28	8	RT	96

[a] All amounts of catalyst given as mol% relative to alkene units. [b] Determined by ^{1}H NMR spectroscopy.

The high oxygen content of glycerol dendrimers suggests their use as synthetic ionophores. Just as crown ethers bind metal ions more strongly than their acyclic analogues, cross-linked dendrimers and hyperbranched polymers may be more ionophoric than their precursors. At the same time, guest accessibility of cross-linked dendrimers might be decreased. Metal picrates are commonly used to measure the extraction ability of crown ethers because of the intensely absorbing picrate counterion. Bathochromic shifts are commonly observed in the optical absorbance spectra of picrates when tight ion pairs are converted into loose ion pairs.[14]

To probe the ability of cross-linked dendrimers to extract cations from water to an organic phase, extraction studies in chloroform/water and benzene/water systems were performed. Aqueous picrate solutions were mixed with solutions of **1**, **4**, or **5** in chloroform or benzene, and the absorbance of each organic layer was measured after the phases completely separated (see the Supporting Information). Red shifts of 17–18 nm for cesium picrate in the presence of dendrimer **4** indicate that the cross-linked dendrimer forms crown-separated ion pairs. Remarkably, **1**, **4**, and **5** display similar absorbance intensities, thus indicating that non-cross-linked dendrimers are as effective as cross-linked dendrimers at extracting cesium ions. An apparent $\log K_{ex} = 2.1$ was determined for dendrimer **5** and cesium picrate in the benzene/water system. This extraction constant is approximately that of [15]crown-5 but is significantly less than [18]crown-6 for this system (Figure 2a).[15] Cross-linked and non-cross-linked glycerol dendrimers were also effective in extracting potassium, europium, ammonium, and guanidinium picrates into chloroform, but little selectivity has been observed.

The ionophoric potential of hyperbranched polyglycerols was also examined. Not only do **8** and **9** represent less expensive alternatives to **4** and **5** that can be easily synthesized on a multikilogram scale by polymerization of glycidol (see above), but the achievable molecular weights are significantly higher. Thus, the molecular weights of **8a** and **8b** are over two- and fourfold higher, respectively, than that of **4**.

To check the ability of hyperbranched dendrimers to extract metal ions from aqueous media and to compare them to the dendrimers, similar extraction experiments were performed. A few differences were observed. First, unlike **1**, hyperbranched polymer **7a** exhibited a very low ability to complex metal ions (Figure 2b). Another difference was that cross-linked **8a** did not show the bathochromic shift of **4**, thus indicating that its metal complexes remain tight ion pairs. Both differences can be attributed to a looser overall structure arising from the defects but could also originate in the higher molecular weight. Similar to the dendrimer extraction experiments, **8** and **9** were found to extract multiple metal picrates with minimal selectivity.

The reduced polyether **9a** was found to extract less metal than **8a**, which, in turn, was found to be somewhat more effective than **5** ($\log K_{ex} = 2.6$ vs. $\log K_{ex} = 2.1$ for cesium picrate extraction in the benzene/water system, see above and the Supporting Information). Table 2 shows that the larger molecular weight hyperbranched polymers (**8b**, **9b**) extracted significantly more potassium, cesium, or ammonium picrate than did **8a** or **9a**.

Table 2: Ion extraction with hyperbranched polymers **7** and **8a**,**b** and **9a**,**b**.[a]

Hyperbranched polymer	Mole cation per mole polymer K^+	Cs^+	NH_4^+
8a	0.58	0.47	0.48
8b	5.32	4.8	4.96
9a	0.27	0.23	0.3
9b	2.08	1.68	2.2

[a] Extraction from water to chloroform of 10 mM metal or ammonium picrate. See the Supporting Information for full details.

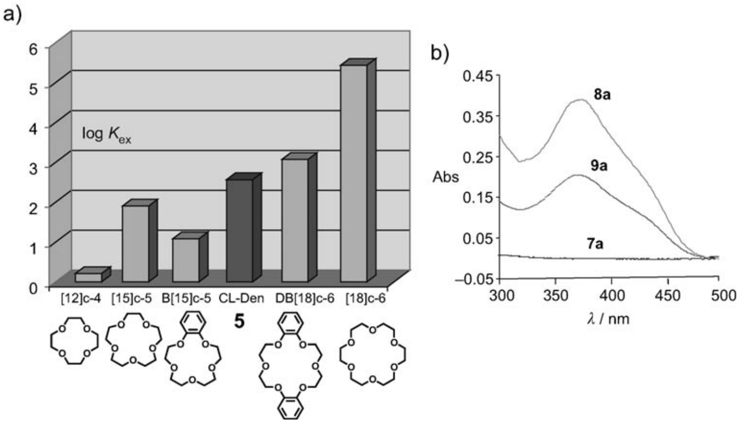


Figure 2. a) Values of $\log K_{ex}$ for cesium picrate extraction into benzene using **5** and various commercially obtained crown ethers. b) UV/Vis spectra of cesium salts extracted by compound **7a**, **8a**, and **9a** in chloroform (normalized absorbances).[15] Duplicate runs agreed within 10%.

In conclusion, glycerol dendrimers and the analogous hyperbranched systems were polyallylated and treated with catalyst **3** to give nearly complete cross-linking. These cross-linked, organic nanoparticles were readily prepared in much larger quantities than previously available.[2,5,7] This class of dendritic polymers was also found to undergo post-RCM functionalization. Thus, the cross-linked dendrimers could be fully hydrogenated or dihydroxylated to produce fully water-soluble cross-linked dendrimers and hyperbranched polymers. Cross-linked glycerol dendrimers as well as the analogous hyperbranched polymers displayed crown-type binding of picrate ions in organic phases. The ion affinity and selectivity of these compounds are comparable to some crown ethers and point to a number of potential applications in complexation and catalysis. The use of this chemistry in other applications involving imprinting, encapsulation, and chemoprotection is being investigated.

Received: June 13, 2007

Keywords: dendrimers · metathesis · nanostructures · polymers

---

[1] a) J. M. J. Fréchet, D. A. Tomalia, *Dendrimers and Other Dendritic Polymers*, Wiley, New York, **2002**; b) G. R. Newkome, C. N. Moorefield, F. Vögtle,

Dendrimer and Dendrons: Concepts, Syntheses, Applications; VCH, Weinheim, **2001**.

[2] a) M. S. Wendland, S. C. Zimmerman, *J. Am. Chem. Soc.* **1999**, *121*, 1389–1390; b) S. L. Elmer, S. C. Zimmerman, *J. Org. Chem.* **2004**, *69*, 7363–7366.

[3] Selected examples of dendrimers cross-linked through end-groups: a) W. Guo, J. J. Li, Y. A. Wang, X. J. Peng, *J. Am. Chem. Soc.* **2003**, *125*, 3901–3909; b) J. J. Becker, M. R. Gagné, *Organometallics* **2003**, *22*, 4984–4998; c) M. A. Carnahan, C. Middleton, J. Kim, T. Kim, M. W. Grinstaff, *J. Am. Chem. Soc.* **2002**, *124*, 5291–5293; d) J. Wang, X. Jia, H, Zhong, H. Wu, Y. Li, X. Xu, M. Li, Y. Wei, *J. Polym. Sci. Part A* **2000**, *38*, 4147–4153.

[4] Review of olefin metathesis on nanostructures: X. Liu, A. Basu, *J. Organomet. Chem.* **2006**, *691*, 5148–5154.

[5] a) S. C. Zimmerman, M. S. Wendland, N. A. Rakow, I. Zharov, K. S. Suslick, *Nature* **2002**, *418*, 399–403; b) E. Mertz, S. C. Zimmerman, *J. Am. Chem. Soc.* **2003**, *125*, 3424–3425; c) J. B. Beil, S. C. Zimmerman, *Chem. Commun.* **2004**, 488–489.

[6] Y. Kim, M. F. Mayer, S. C. Zimmerman, *Angew. Chem.* **2003**, *115*, 1153–1158; *Angew. Chem. Int. Ed.* **2003**, *42*, 1121–1126.

[7] N. G. Lemcoff, T. A. Spurlin, A. A. Gewirth, S. C. Zimmerman, J. B. Beil, S. L. Elmer, H. G. Vandeveer, *J. Am. Chem. Soc.* **2004**, *126*, 11420–11421.

[8] R. Haag, A. Sunder, J.-F. Stumbé, *J. Am. Chem. Soc.* **2000**, *122*, 2954–2955.

[9] A. Sunder, R. Hanselmann, H. Frey, R. Mülhaupt, *Macromolecules* **1999**, *32*, 4240–4246; A. Sunder, R. Mülhaupt, R. Haag, H. Frey, *Macromolecules* **2000**, *33*, 253–254.

[10] L. G. Schultz, Y. Zhao, S. C. Zimmerman, *Angew. Chem.* **2001**, *113*, 2016–2020; *Angew. Chem. Int. Ed.* **2001**, *40*, 1962–1966.

[11] J. B. Beil, N. G. Lemcoff, S. C. Zimmerman, *J. Am. Chem. Soc.* **2004**, *126*, 13576–13577.

[12] S. J. Miller, S.-H. Kim, Z.-R. Chen, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.

[13] A. Sunder, H. Türk, R. Haag, H. Frey, *Macromolecules* **2000**, *33*, 7682–7692.

[14] K. H. Wong, M. Bourgoin, J. Smid, *J. Chem. Soc. Chem. Commun.* **1974**, 715–716; M. Bourgoin, K. H. Wong, J. Y. Hui, J. Smid, *J. Am. Chem. Soc.* **1975**, *97*, 3462–3467.

[15] Y. Takeda, *Top. Curr. Chem.* **1984**, *121*, 6.