

An Alternative Synthetic Approach toward Dendritic Macromolecules: Novel Benzene-Core Dendrimers via Alkyne Cyclotrimerization

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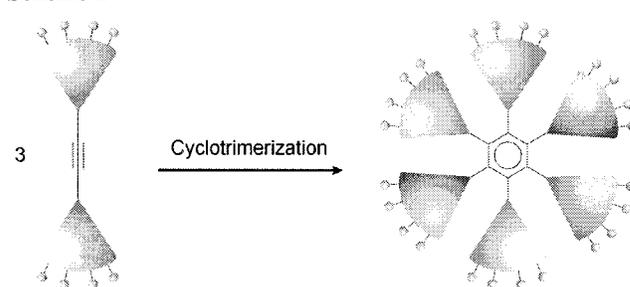
Received December 7, 1998

We report an alternative method for the convergent¹ synthesis of dendrimers in which the dendrimer core is generated from a dendritic precursor by an alkyne cyclotrimerization reaction.² In this method, convergent dendrons^{1,3} attached to an acetylenic moiety are cyclized in a [2 + 2 + 2] cycloaddition process. The cycloaddition can be mediated by various transition-metal complexes and exhibits a high degree of chemoselectivity toward triple bonds, rendering the reaction tolerant of many functional groups.² If carried out with a difunctionalized dendritic alkyne, this reaction affords a benzene moiety surrounded by six dendrons as depicted in Scheme 1. A related approach was used by Duchêne and Vögtle⁴ for the synthesis of a dodecafunctionalized host–molecule.

An acetylenic system consisting of benzylic ethers of 2-butyne-1,4-diol was chosen for commercial availability as well as its synthetic compatibility. In particular, this linkage prevents the occurrence of a Claisen rearrangement.⁵ The substituted alkynes **1a–d** were obtained by the Williamson ether coupling of 2-butyne-1,4-diol with the appropriate polybenzyl ether-type¹ dendritic bromide (Scheme 2). The trimerization reaction of **1a–d** was carried out in refluxing toluene using dicobalt octacarbonyl⁶ as the catalyst to afford the novel structures **2a–d**. To our knowledge, this represents the first time that such large and precisely defined macromolecules (MW \approx 10 000 for the third generation) have been successfully prepared by a cyclotrimerization reaction.

As expected, the time required to complete the trimerization reaction increased with generation (Table 1), while the yield decreased as a result of steric crowding around the nascent core. Because of the nature of the transformation, the reaction is extremely clean, and no partially reacted products can be formed. Therefore, aside from recovered starting materials, compounds **2a–d** were the only products isolated after reaction. As a result, their purification by column chromatography was greatly facilitated. The catalyst, dicobalt octacarbonyl, applied in amounts of

Scheme 1



Scheme 2

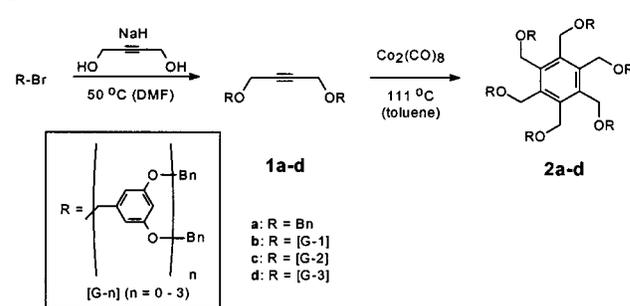


Table 1. Synthesis of Dendritic Alkynes **1a–d** and Benzene-Cored Dendrimers **2a–d**

compound	R	yield of 1 ^a	yield of 2 ^a	time _{1–2} ^b
a	Bn	62%	83%	0.5 h
b	[G-1]	62%	80%	2 h
c	[G-2]	50%	50%	20 h
d	[G-3]	41%	36%	48 h

^a Yields given are after chromatographic separation. Cyclotrimerization conditions: substrate **1a–d** (0.5 M in toluene) with 5 mol % catalyst Co₂(CO)₈ at 111 °C.

5 mol % or less, is fairly robust and easy to handle since it operates in a variety of different solvents.⁷

Benzene-core dendrimers **2a–d** have been fully characterized by a variety of spectroscopic techniques. Both the MALDI-TOF mass spectra and the size-exclusion chromatography traces (Figure 1) of the dendrimers confirm their monodispersity and high purity.

To probe their solution dynamics, NMR relaxation time (*T*₁) measurements were performed. Herein, a correlation of the relaxation behavior of the spectroscopic probe, i.e., the proton, with its local environment can be used to gain information about the relative density distribution within the macromolecule.⁸ Because of the high spectral resolution allowing clear observation of the different layers (Scheme 3) of the structure, this approach was used to gain information about the entire dendrimer framework.

As shown in Figure 2, the *T*₁ values for the terminal benzylic protons (e) are almost constant while a slight decrease in *T*₁ is observed for the exterior phenyl protons (f). This suggests that there is no change in steric congestion at the periphery of the dendrimer as the generation increases. The relaxation times for the successive layers within the dendrimer decrease from the core to the periphery, suggesting a radial increase in density of the macromolecule. This finding fits the simplified model of de

(7) A cobalt-catalyzed cyclotrimerization has recently been performed in aqueous solution: Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130.

(8) (a) Tomoyose, Y.; Jiang, D.-L.; Jin, R.-H.; Aida, T.; Yamashita, T.; Horie, K. *Macromolecules* **1996**, *29*, 5236. (b) Jiang, D.-L.; Aida, T. *Nature* **1997**, *388*, 454. (c) Jiang, D.-L.; Aida, T. *J. Am. Chem. Soc.* **1998**, *120*, 10895.

(1) (a) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638. (b) Fréchet, J. M. J.; Jiang, Y.; Hawker, C. J.; Philippides, A. E. *Proc. IUPAC Int. Symp., Macromol.* **1989**, 19.

(2) For recent reviews on transition-metal-mediated [2 + 2 + 2]cycloadditions, see: (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. A., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 741–770. (d) Melikyan, G. G.; Nicholas, K. M. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 99–138. (e) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1129–1162.

(3) (a) Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010. (b) Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346. (c) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252. (d) Kwock, E. W.; Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1991**, *3*, 775. (e) Leon, J. W.; Kawa, M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 8847. (f) Jayaraman, M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12996–12997. (g) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules: Concepts, Synthesis, Perspectives*; VCH: Weinheim, 1996; Chapter 5 and references therein.

(4) Duchêne, K. H.; Vögtle, F. *Synthesis* **1986**, 659.

(5) Olsman, H.; Graveland, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 301.

(6) (a) Kaufman, R. J.; Sidhu, R. S. *J. Org. Chem.* **1982**, *47*, 4941. (b) Hübel, W.; Hoogzand, C. *Chem. Ber.* **1960**, *93*, 103.

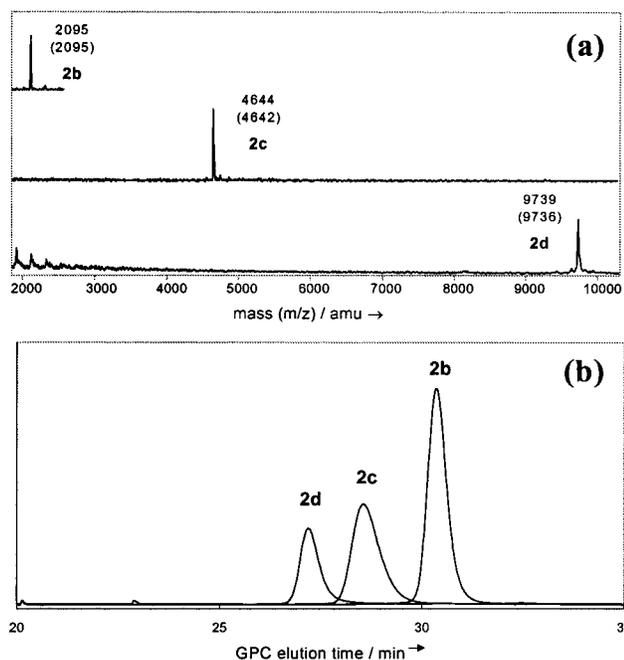


Figure 1. (a) MALDI-TOF mass spectra of compounds **2b–d** (as Na^+ adducts); (b) GPC traces of compounds **2b–d**.

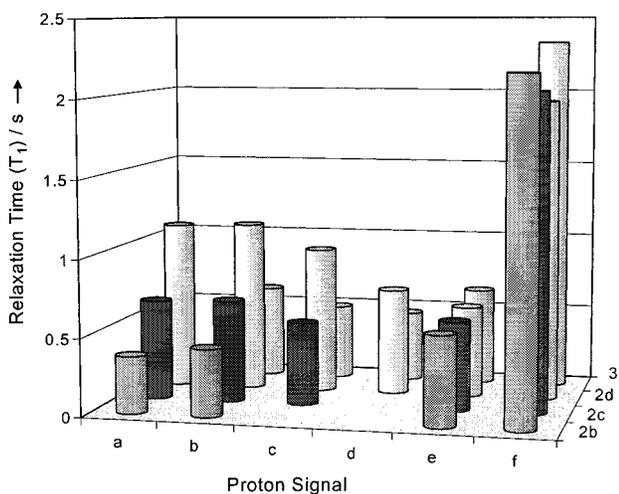
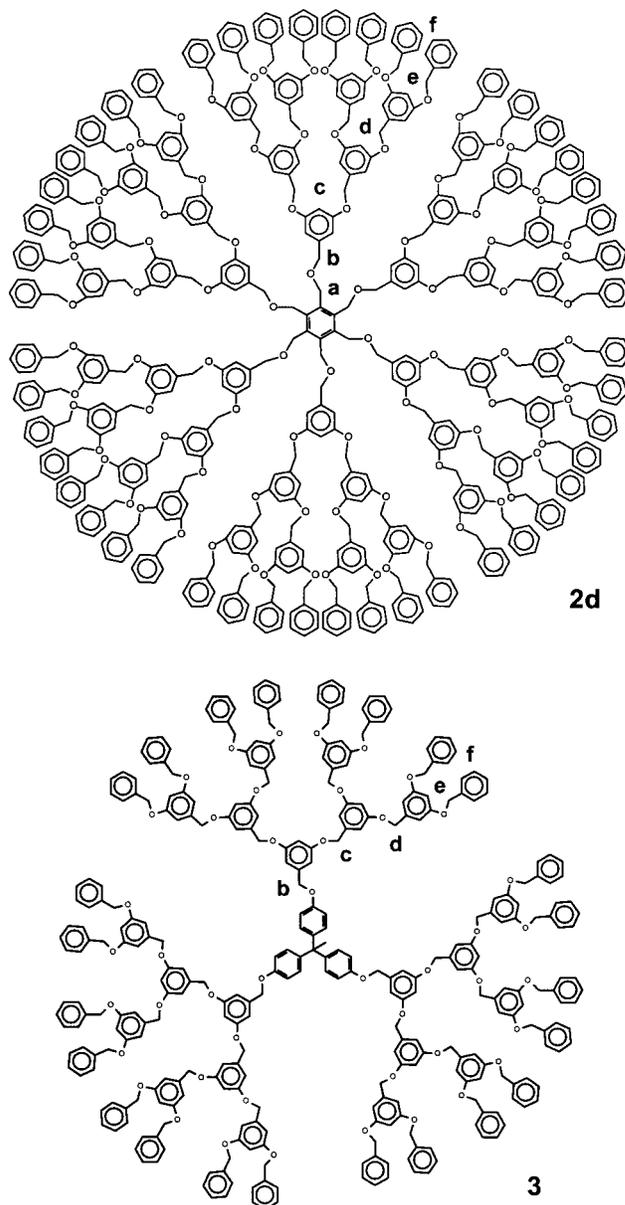


Figure 2. ^1H NMR spin-lattice relaxation times (T_1) of compounds **2b–d** and **3** as external reference in CDCl_3 at 298 K (proton assignments refer to Scheme 3).

Genes and Hervet.⁹ A comparison with the model tridendron molecule **3**¹ (Scheme 3, Figure 2) reveals a similar trend in T_1 values. Our findings are also in agreement with those of Aida and co-workers,⁸ who reported that the protons at the periphery of higher generation dendrimers exhibit shorter relaxation times, suggesting that their local environment is more congested than that of the core. Surprisingly, the T_1 values of the benzylic protons nearest the core almost double with each successive generation. This unprecedented observation suggests enhanced flexibility at the core as the molecule becomes larger. Perhaps the molecules adopt more extended conformations to accommodate the rapidly increasing steric requirements of the larger dendrons. A comparison with reference compound **3** suggests that the presence of an additional methylene unit (a) in **2c** is responsible for this additional mobility.

(9) de Gennes, P.-G.; Hervet, H. *J. Phys. Lett.* **1983**, *44*, L 351.

Scheme 3



The cyclotrimerization of bisdendritic alkynes has been demonstrated to be of synthetic use in the construction of novel benzene-cored dendrimers. Dendrimer assembly via “in-situ” generation of the core molecule makes this a versatile approach for the construction of precise macromolecular structures. This approach benefits from the ease of purification of the trimerized product and may prove valuable in the highly convergent synthesis of hybrid dendrimers from asymmetric, i.e., differently substituted, alkyne precursors.

Acknowledgment. Financial support from the AFOSR-MURI program and the National Science Foundation (NSF-DMR 9816166) is acknowledged with thanks.

Supporting Information Available: Experimental details and chemical characterization data of the synthesis of **1a–d** and **2a–d** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.