Location of Terminal Groups of Dendrimers in the Solid State by Rotational-Echo Double-Resonance NMR

Hsien-Ming Kao,† Andrei D. Stefanescu,‡ Karen L. Wooley, and Jacob Schaefer*

Department of Chemistry, Washington University, St. Louis, Missouri 63130

Received April 6, 2000

Dendrimers are globular macromolecules constructed around a central core.[1,2] During synthesis, the addition of each successive repeat unit introduces a branch point so that the final structure conceivably could have a great many functional end groups on its surface. One of the most prominent and ongoing debates in the effort to relate the structure of dendrimers to their physical and chemical properties focuses on the location of the chain ends relative to the central core.[3−5] Recently, small-angle neutron scattering of seventh-generation poly(amido amine) dendrimers in solution has indicated that the terminal groups are concentrated near the periphery of the molecule.[6] The question arises whether the same sort of geometry is generally present for dendrimers in the solid state as well as in solution.

In this communication, we report the results of ^{13}C-{^{19}F} rotational-echo double-resonance[7] (REDOR) NMR experiments performed on fifth-generation poly(benzyl ether) dendrimers synthesized by convergent methods.[8] Fluorine was used to label the *ring*-C-1 of the first generation and ^{13}C to label the methylene carbons of either the third or fifth generations. In this terminology, the generational layer is the monomeric repeat-unit layer counted outward from the focal point (first generation); the first methylene carbons are considered part of the first generation, so that the dendrimer terminates with the fifth-generation methylene carbons coupled to the chain-end phenyl rings. The ^{13}C label was incorporated in the third generation by alkylation of 3,5-dihydroxybenzyl-($^{13}CH_2$) alcohol. The labeled alcohol was prepared from benzoic-*carboxy*-^{13}C acid (Isotec, Inc.) by sulfonation of the 3- and 5-positions of the aromatic ring by reaction with sulfuric acid and sulfur trioxide for 5 h at 250−270 °C, followed by conversion to the resorcinol by treatment with a sodium and potassium hydroxide melt at 300 °C for 2 h. The ^{19}F label was incorporated in the first generation by coupling of two dendritic benzyl ethers containing a benzylic bromide focal-point functionality to the two phenolic sites of 1-fluoro-3,5-dihydroxybenzene under standard alkylation conditions using potassium carbonate and 18-crown-6 in acetone or tetrahydrofuran. 1-Fluoro-3,5-dihydroxybenzene was prepared from 1-fluoro-3,5-dimethoxybenzene by demethylation with boron tribromide in chloroform.[9] Purification at each stage of the synthesis was accomplished by silica gel flash column chromatography and confirmed by size-exclusion chromatography, which, for the convergent-growth synthetic approach used here, is sensitive to the presence of even a few percent of lower generation number.

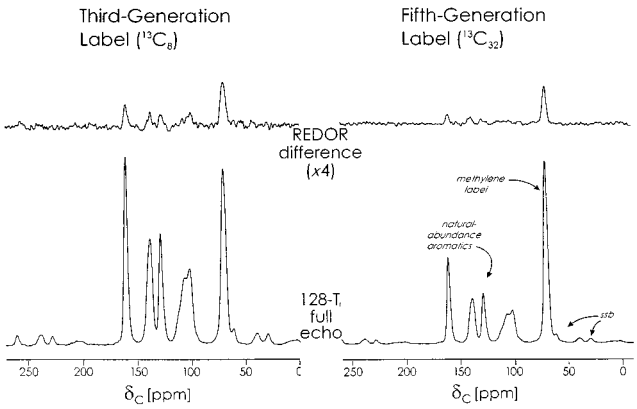

Figure 1. The 50.3 MHz ^{13}C\{^{19}F\} REDOR NMR spectra of two fifth-generation poly(benzyl ether) dendrimers with ^{13}C-labeled methylene carbons in the third (left) or fifth (right) generations. Both dendrimers were labeled by ^{19}F in the *ring*-C-1 position of the first generation and have been diluted 10-fold by homogeneous mixing with a fifth-generation dendrimer having neither ^{13}C nor ^{19}F labels. REDOR differences ($\Delta S = S_0 - S$, where S and S_0 are the echo intensities with and without dephasing, respectively) are shown at the top of the figure, and full echoes (S_0) at the bottom, after 128 rotor cycles of dipolar evolution. Magic-angle spinning was at 5 kHz. Representative spinning sidebands are marked "ssb". The intensities of the sidebands are consistent with the absence of large-amplitude motions in the solid state.

Typical REDOR spectra are shown in Figure 1. Line assignments for the spectra, preparation of samples for NMR analysis, and details of the REDOR pulse sequence, spectrometer, and transmission-line probe used to collect the spectra have been presented earlier.[10] The present measurements differ from the earlier ones in that, first, the ^{19}F label is closer to the center of the dendrimer and, second, the third-generation label is now in a fifth rather than in a third-generation dendrimer. The average distances from the center of the dendrimer (the fluorine lablel) to the nominal midpoint and periphery of the dendrimer are therefore directly dependent on the dephasing of the methylene-carbon signals by rotor-synchronized ^{19}F π pulses.[7]

The intensity of the oxygenated methylene-carbon peak at 60 ppm relative to the intensities of the natural-abundance aromatic-carbon peaks clustered around 140 ppm depends on whether the third- or fifth-generation positions are labeled. If the third generation is labeled, there are eight methylene-carbon ^{13}C's per dendrimer molecule contributing to the δ_C 60 peak (Figure 1, left), whereas if the fifth generation is labeled, there are 32 (Figure 1, right). Local dynamics, as measured by the homogeneous ^{13}C spin echo lifetimes, are essentially the same for both types of labels (Figure 2). REDOR dephasing, S/S_0, where S and S_0 are the echo intensities with and without dephasing, respectively, for the two labels (in samples diluted 10-fold by mixing with fifth-generation dendrimers having neither ^{19}F nor ^{13}C labels) is also closely similar (Figure 3, circles). This dephasing corresponds to an average distance from the fluorine to the methylene carbon of about 13 Å (third generation) or 14 Å (fifth generation). The hydrodynamic radius of the fifth-generation dendrimer is 13 Å.[11]

† Present address: Department of Chemistry, National Central University, Chung-Li, Taiwan 32054.

‡ Present address: MEMC Electronics, St. Louis, MO 63043.

* Corresponding author. Phone 314-935-6844; Fax 314-935-4481; E-mail schaefer@wuchem.wustl.edu.

10.1021/ma0006124 CCC: $19.00
Published on Web 07/26/2000

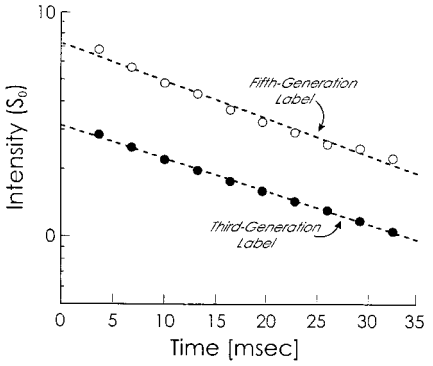

Figure 2. Rotor-synchronized Hahn-echo signal intensities (S_0) for the methylene-carbon peaks of the two dendrimers of Figure 1. The homogeneous ^{13}C T_2 is 26 ms for the fifth-generation label and 29 ms for the third-generation label.

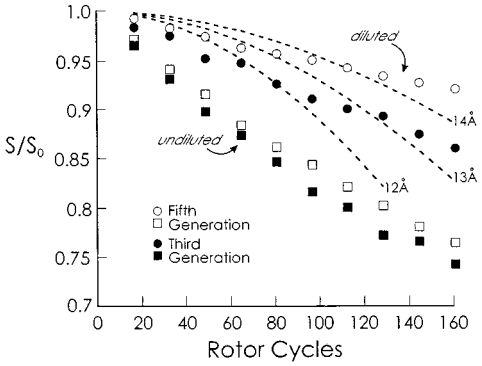

Figure 3. $^{13}C\{^{19}F\}$ REDOR dephasing (S/S_0) for two fifth-generation poly(benzyl ether) dendrimers with ^{13}C-labeled methylene carbons in the third (solid symbols) or fifth (open symbols) generations, with (circles) or without (squares) 10-fold dilution by homogeneous mixing with an unlabeled fifth-generation dendrimer. The dephasing for the diluted dendrimers was corrected by subtracting from both S (dephased echo) and S_0 (full echo) estimated contributions from the natural-abundance ^{13}C background for all five generations, assuming equal echo lifetimes (Figure 2), and the applicability of measured dephasing for generations 1−5 (see ref 10). Magic-angle spinning was at 5 kHz. The dotted lines show the calculated dephasing for an isolated $^{13}C-^{19}F$ pair as a function of the internuclear distance. These calculations provide a convenient set of rulers and are not attempts to fit the experimental data, which clearly indicate that distributions of C−F dipolar couplings (distances) are responsible for the dephasing.

Preliminary molecular modeling based on energy minimization, restrained by a 14 Å distance to the periphery, for a single *isolated* dendrimer suggests an average distance to the third-generation methylene carbon of about 9−10 Å. This is an arrangement similar to that shown schematically in Figure 4. The 12−13 Å distance to labels in the third generation observed experimentally, however, indicates a significant relative extension of the lower generation conformations or an inward folding of the higher generation conformations, some combination of which makes a large fraction of the internal third-generation methylene carbons about as close to the surface of the dendrimer as the fifth-generation chain ends. Furthermore, the similarity in the dependence of S/S_0 on dilution for third- and fifth-generation labels (Figure 3) also indicates a comparable concentration of the two kinds of labels near the dendrimer surface.[10] This means that a first-generation ^{19}F label of one dendrimer molecule is about equally distant to either the third- or fifth-generation ^{13}C labels of its neighbors. This surprising qualitative conclusion

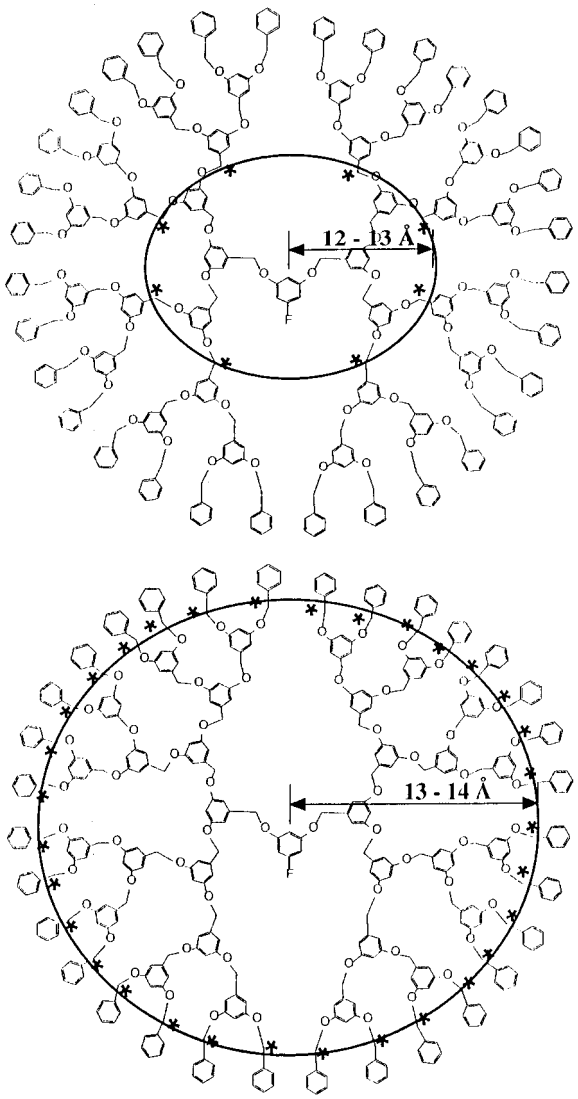

Figure 4. Schematic representation of a fifth-generation poly(benzyl ether) dendrimer showing the nominal positions of methylene-carbon ^{13}C labels in generations three (top) and five (bottom). These positions are in disagreement with the REDOR dephasing of Figure 3 (circles), which indicates only about a 1 Å difference in the average distance of the two types of methylene-carbon labels to the central fluorine.

is independent of the choice of a model to describe the intermolecular chain packing and the details of the considerable interpenetration of nearest-neighbor dendrimers. Molecular modeling to account for the ($1/r^3$ weighted) REDOR results is in progress.

Acknowledgment. This work was supported by U.S. Army Research Office Grant DAAH04-96-1-0158 (K.L.W.) and NSF Grant DMR-9729734 (J.S.).

References and Notes

(1) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138.
(2) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665.
(3) de Gennes, P. G.; Hervat, H. J. *J. Phys., Lett.* **1983**, *44*, L-351.
(4) Mansfield, M. L.; Klushin, L. I. *Macromolecules* **1993**, *26*, 4262.
(5) Lescanec, R. L.; Muthukumar, M. *Macromolecules* **1990**, *23*, 2280.

(6) Topp, A.; Bauer, B. J.; Klimash, J. W.; Spindler, R.; Tomalia, D. A.; Amis, E. J. *Macromolecules* **1999**, *32*, 7226.
(7) Gullion, T.; Schaefer, J. *Adv. Magn. Reson.* **1989**, *13*, 57.
(8) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.
(9) Durrani, A. A.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1980**, *8*, 1658.
(10) Wooley, K. L.; Klug, C. A.; Tasaki, K.; Schaefer, J. *J. Am. Chem. Soc.* **1997**, *117*, 53.
(11) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401.

MA0006124