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Chain Dynamics in Poly(amido amine) Dendrimers. A Study of ^{2}H NMR Relaxation Parameters

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ABSTRACT: ^{2}H NMR relaxation measurements were used in an extensive study of chain mobility in poly(amido amine) (PAMAM) dendrimers as a function of molecular weight and position along the chain. For ^{2}H labels in the terminal generation, the spin–lattice relaxation times (T_1) were found to decrease as the number of chain termini increased from 3 ($T_1 = 30 \pm 3$ ms, at 46.0 MHz) to 384 ($T_1 = 7.6 \pm 0.7$ ms, at 46.0 MHz) and were smaller than the T_1 observed when the polymers were labeled in the interior. The values of T_1 determined at lower field strength (4.7 T) were lower than those at higher field strength (7.05 T). By using the spin–spin relaxation time (T_2) as a second variable, consistent correlation times (τ) were obtained at the two field strengths upon application of Schaefer's log χ^2 distribution function. No dependence of τ on position along the chain was observed when the label was located in the interior repeating units of PAMAM dendrimers of constant molecular weight. No evidence of radial gradients was found. The data are interpreted in terms of alternative theoretical treatments of dendritic macromolecules.

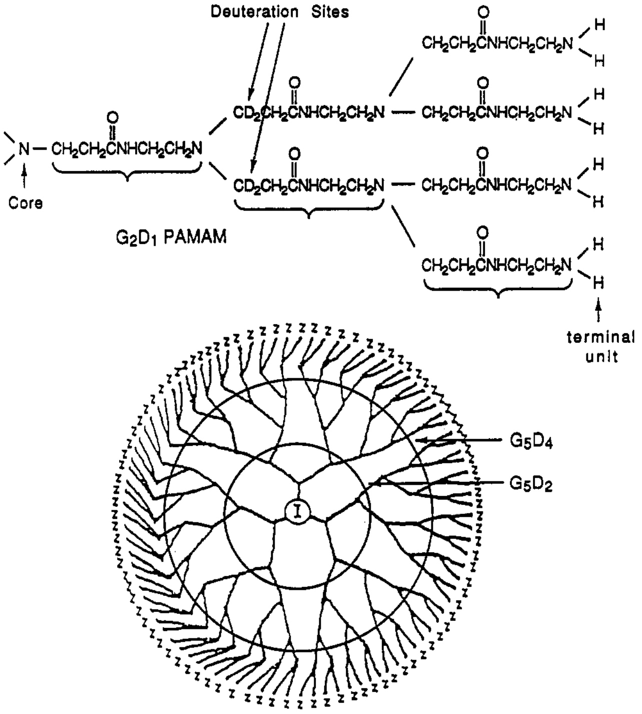
Introduction

In the preceding paper in this issue, we described a series of ^{13}C NMR relaxation measurements on poly(amido amine) (PAMAM) dendrimers.[1] The salient conclusions from that work were two: first, that there is no anomalous suppression of chain-end mobility that would suggest the onset of dense packing of functional groups at the molecular "surface", and second, that the average correlation time (τ) increases markedly with molecular size at interior chain positions. The latter observation we ascribe to increasing segment density in the molecular interior, a prediction of the simulation of dendritic growth reported by Lescanec and Muthukumar.[2] Nevertheless, detailed interpretation of these results, particularly with respect to relaxation at interior sites, is rendered difficult by the fact that resonances from all interior carbons are overlapped. It is therefore impossible to distinguish the relaxation behavior of sites buried deeply in the "core" of the dendritic molecule from that of interior sites near the "surface". In particular, we were unable to explore the possibility that interesting radial gradients in mobility exist in dendritic macromolecules.

We describe in the present paper a series of ^{2}H NMR relaxation measurements on specifically labeled PAMAM dendrimers. As shown in Scheme I, the standard PAMAM synthesis[1,3] was modified by the use of methyl-β,β-d_2 acrylate in one—and only one—growth cycle.[4] This provides for deuterium labeling at a single radial position[5] and allows mapping of relaxation properties as a function of molecular location. In addition, the mechanism of relaxation is well understood for deuterium, and relaxation rates are insensitive to interatomic distances.[6] Interpretation of relaxation data in terms of the dynamic properties of the chain is thus relatively straightforward.

Scheme I illustrates the nomenclature used to describe the selectively deuterated PAMAM dendrimers. Molecular size is specified as G_n, where n is the total number of growth cycles, or generations, and the site of deuteration is specified by D_m, where ^{2}H has been introduced in the mth growth cycle. A 5-generation PAMAM labeled in the fourth generation is thus designated G_5D_4, as shown in Scheme I.

Scheme I
Synthesis of ^{2}H-Labeled Dendritic Macromolecules



Measurements have been carried out on a series of amine-terminated PAMAM of sizes ranging from generation 0 to generation 7. In all, 30 selectively labeled polymers were examined, as summarized in Table I. Within this set, one can examine relaxation behavior (i) as a function of radial position[7] for dendritic molecules of a fixed size (by proceeding horizontally in Table I) or (ii) as a function of molecular size, at radial positions fixed

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Table I
Selectively Deuterated PAMAM Samples

molecular size (generations)	labeled generation 0	1	2	3	4	5	6	7
0	G_0D_0							
1	G_1D_0	G_1D_1						
2	G_2D_0	G_2D_1	G_2D_2					
3	G_3D_0	G_3D_1	G_3D_2	G_3D_3				
4	G_4D_0	G_4D_1	G_4D_2	G_4D_3	G_4D_4			
5	*a*	G_5D_1	G_5D_2	G_5D_3	G_5D_4	G_5D_5		
6	*a*	*a*	G_6D_2	G_6D_3	G_6D_4	G_6D_5	G_6D_6	
7	*a*	*a*	*a*	G_7D_3	G_7D_4	G_7D_5	G_7D_6	G_7D_7

[a] The concentration of ^{2}H due to the 0.015% natural abundance is comparable to that present due to the selective labeling in these samples. Hence, no determination of changes in mobility with radial position was possible.

with respect to either the "core" (by proceeding vertically) or the "surface" (by proceeding diagonally). The results of these experiments are described below.

Experimental Section

Materials. Sources and purification of materials were described previously, as were the methods used to prepare and characterize the dendritic PAMAM samples.[1]

Preparations. Methyl-β,β-d_2 Acrylate (d_2-MA). The synthesis of the d_2-MA used in this work was carried out in a manner similar to that reported by Nugent and McKinney.[8] To a 300-mL three-neck flask were added 104 g (0.032 mol) of methyl (triphenylphosphoranylidene)acetate, 50 mg of hydroquinone, and 10 g (0.031 mol) of paraformaldehyde-d_2. The reaction vessel was flushed with N_2, and the escaping gas was passed through a dry ice trap. Dibutyl phthalate (100 mL) was cannulated into the reaction vessel. The mixture was heated to 80 °C for 2 h before raising the temperature to 110 °C for 30 min. The reaction was allowed to cool to room temperature. The reaction vessel was connected to a vacuum pump, and the remaining d_2-MA was collected in the dry ice trap. Gas chromatography–mass spectrometry indicated the isotopic purity of the acrylate to be >99%. ^{13}C NMR (75 MHz, $CDCl_3$): 51, 128, 131 (quintet), and 167 ppm.

Measurements. ^{2}H NMR spectra were obtained on Varian XL-300 and Bruker AC-200 spectrometers operating at 46.0 and 30.7 MHz, respectively. All of the spin–lattice relaxation time (T_1) measurements were performed using the standard inversion–recovery method with a pulse sequence 180°–variable delay–90°–acquistion–fixed delay. The temperature inside the probe was maintained at 25 ± 0.2 °C by passing a steady flow of air over the sample. The concentration of polymer in H_2O was approximately 3% in all cases. Choices of delay times and actual T_1 calculations were performed using standard commands (DOT1 and T1(all)) contained within the standard Varian VXR version 4.1 software package.

Results and Discussion

^{2}H spin–lattice relaxation times (T_1) and spin–spin relaxation times (T_2) were measured for each of the polymers listed in Table I. A typical experiment from which the relaxation parameters were calculated as shown in Figure 1. T_1 was determined from the peak heights observed at the delay times indicated, and T_2 was calculated from the signal width at half-height (W) according to[6]

$$T_2 = 1/2\pi W \tag{1}$$

Figures 2 and 3 illustrate the dependence of the relaxation times on molecular size and radial position. Inspection of these figures shows that (i) T_1 and T_2 for nuclei located in the terminal generation decrease with increasing molecular weight, (ii) relaxation times observed for PAMAM dendrimers labeled in the terminal generation are larger than those observed when the deuterium is further from the ends of the chain, and (iii) for interior labeling sites, relaxation rates are independent of the location of the label.

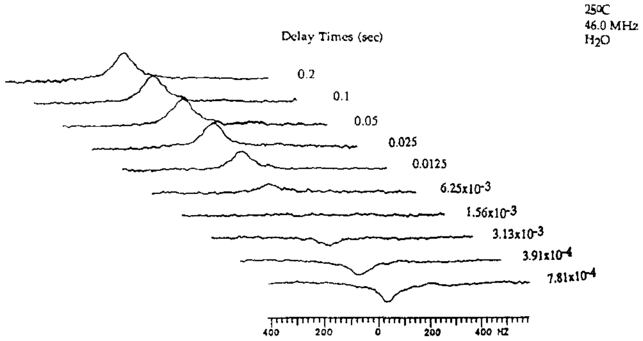

Figure 1. An inversion–recovery experiment from which the ^{2}H T_1 was calculated for a G_2D_0 PAMAM (46 MHz, H_2O, 25 °C).

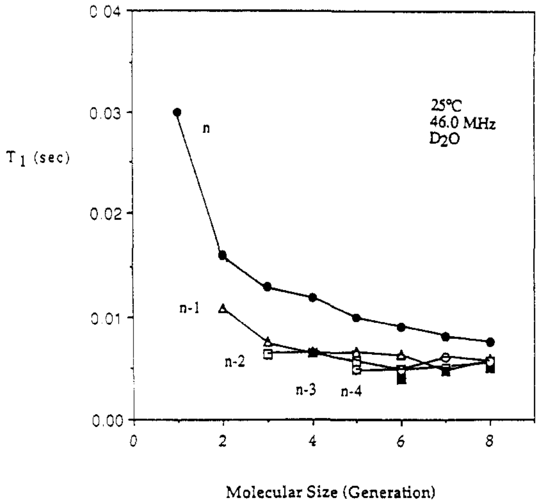

Figure 2. Dependence of T_1 on molecular size for dendritic PAMAM polymers (46 MHz, D_2O, 25 °C): (●) $m = n$; (△) $m = n - 1$; (□) $m = n - 2$; (■) $m = n - 3$; (○) $m = n - 4$.

The relaxation times were converted to correlation times (τ) by employing Schaefer's log χ^2 distribution. By assuming isotropic motion and a distribution of τ to describe the segmental motion of long chains, Schaefer[9] showed that

$$1/T_1 = {}^3/_{20}h^{-2}(e^2qQ/h)^2[J(\omega_0) + 4J(2\omega_0)] \tag{2}$$

and

$$1/T_2 = {}^3/_{40}(e^2qQ/h)^2[3J(0) + 5J(\omega_0) + 2J(2\omega_0)] \tag{3}$$

where

$$J(\omega) = \int \frac{F(s)\{b^2 - 1\}\,ds}{(b-1)(1 + \omega^2\tau^2[(b^s - 1)/(b-1)]^2)} \tag{4}$$

where

$$s = \log_b\,[1 + (b-1)\tau_0/\tau] \tag{5}$$

and

$$F(s) = P\Gamma(P)^{-1}(P^s)^{P-1}\exp(-Ps) \tag{6}$$

Here, $\Gamma(P)$ represents the gamma function, b, P, and τ are chosen to fit the data, τ_0 is defined to be a correlation time proportional to τ, ω_0 is the ^{2}H resonance frequency, h is Planck's constant, and e^2qQ/h is the quadrupolar coupling constant. It is generally agreed that b and P, which control the width of the distribution of τ, are not totally independent and the model is essentially a pseudo-two-parameter model.[10,11]

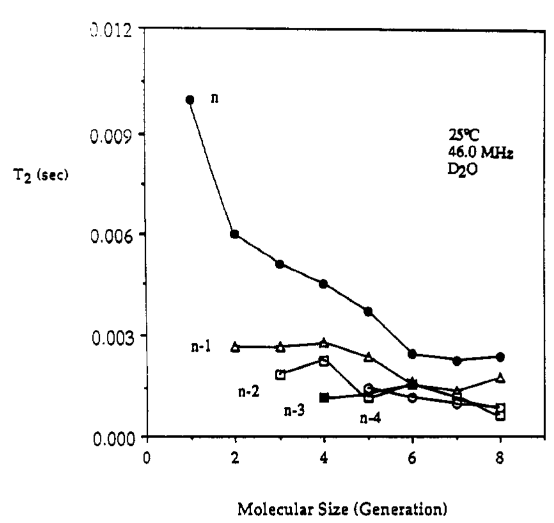

Figure 3. Dependence of T_2 on molecular size for dendritic PAMAM polymers (46 MHz, D_2O, 25 °C). Symbols as in Figure 2.

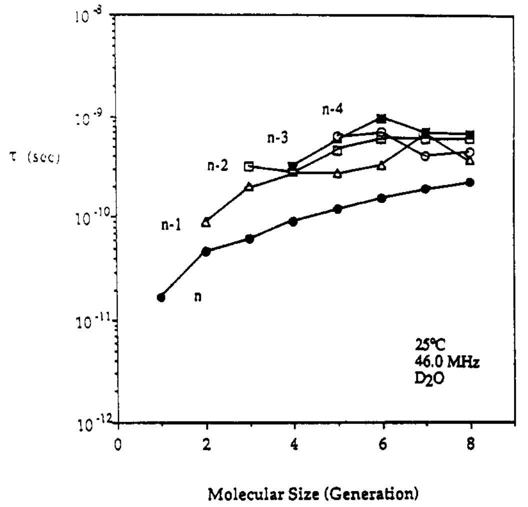

Figure 4. Dependence of τ on molecular size for dendritic PAMAM polymers (46 MHz, D_2O, 25 °C). Symbols as in Figure 2.

The quadrupolar coupling constant necessary for the implementation of Schaefer's equation was determined by substituting the values of T_{1,CH_2} and $T_{1,{}^2H}$ determined for a generation 0 PAMAM dendrimer ($T_{1,{}^2H}$ was determined for a G_0D_0 polymer) into eq 7

$$\frac{1/T_{1,CH_2}}{1/T_{1,{}^2H}} = \frac{20h^4\gamma_H^2\gamma_C^2r^{-6}N}{3\pi^4(e^2qQ)^2} \qquad (7)$$

where γ_H and γ_C are the gyromagnetic ratios of ^1H and ^{13}C, respectively, r is the C–H internuclear distance, and N is the number of ^1H directly bonded to the ^{13}C nucleus of interest. A value of 170 kHz was obtained. Correlation times were calculated by assuming $b = 1000$ in eq 4 and fitting P and τ to the T_1 and T_2 values obtained at 46.0 MHz, making certain that the calculated values of P and τ yielded values of T_1 and T_2 at 30.7 MHz that fell within the error of the experimentally determined values. In every case, the values of τ calculated from the ^2H relaxation data are in good agreement with those calculated from the ^{13}C relaxation data.[1] This supports the applicability of Schaefer's model to the PAMAM system and indicates that the quadrupolar coupling constant employed is correct and that the calculated τ is independent of the frequency of the measurement.

The calculated values of τ are plotted in Figure 4 as a function of the molecular size of the PAMAM and the generation labeled. As in the preceding figures, the data are linked according to the radial position of the label with respect to the molecular "surface"; i.e., data from terminal labels are linked, as are results from labels in the penultimate ($n - 1$) generation, the $n - 2$ generation, and so on. In general, the results indicate a slowing of molecular motion with increasing molecular size. Chain motion is most rapid near the terminus and slower in the molecular interior. The apparent discrepancy between the correlation times reported here for the terminal generation and those calculated from the ^{13}C relaxation data of the preceding paper[1] can be reconciled on the basis of the difference in the location of the observed nucleus; the site of deuteration in the terminal generation is in fact five bonds removed from the chain end, and direct comparison with the correlation time of the terminal carbon is unwarranted. For the interior sites, the agreement with the ^{13}C results is striking, as noted above.

The most important conclusion to be drawn from Figure 4 is that ^2H relaxation measurements provide no evidence for significant radial gradients in segmental mobility within the interior of the dendritic macromolecule. Examination of the results for the 7-generation polymers, for example, shows no systematic variation in τ with radial position. Segmental motion is slower in the interior than at the molecular "surface", but all interior chain positions appear to be characterized by similar correlation times.

Concluding Remarks. The measurements reported herein are fully consistent with the results of the ^{13}C relaxation measurements reported in the preceding paper. In each case, the results suggest (i) segmental motion is most rapid at the chain terminus and slower at interior sites and (ii) the average correlation time used to describe segmental motion increases with molecular size but shows no anomaly suggestive of steric suppression of chain dynamics.

In the preceding paper, these results were interpreted on the basis of the simulation of dendritic growth reported by Lescanec and Muthukumar,[2] which predicts a monotonic decrease of segment density with radial distance[12] from the topological center of the dendritic molecule. We proposed that the relatively large, molecular size dependent segment density in the interior might account for the observed increase in τ with molecular weight. This argument must now be reconciled with the observation that segmental motions at radial positions differing by three generations are characterized by virtually identical correlation times. We believe this also to be consistent with the results of the Lescanec–Muthukumar treatment in that the simulation indicates significant radial "smearing" of successive generations. If segment density is in fact an important determinant of τ, as we propose, then spatial intermixing of neighboring chain units would serve to flatten any radial gradient in segmental mobility.

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References and Notes

(1) Meltzer, A. D.; Tirrell, D. A.; Jones, A. A.; Inglefield, P. T.; Hedstrand, D. M.; Tomalia, D. A. *Macromolecules*, preceding paper in this issue.
(2) Lescanec, R.; Muthukumar, M. *Macromolecules* **1990**, *23*, 2280.
(3) (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138 and references therein.

(4) Methyl acrylate was chosen for deuteration because the PAMAM synthesis uses large excesses of ethylenediamine in each amidation step.[1] Deuteration of the necessary quantities of ethylenediamine would be prohibitively expensive.

(5) The 0.015% natural abundance of ^{2}H makes an insignificant (<2%) contribution to the total number of ^{2}H nuclei in the sample. (Meltzer, A. D. Ph.D. Thesis, University of Massachusetts, 1990).

(6) Abragam, A. *The Principles of Nuclear Magnetism*; Oxford University Press: London, 1961.

(7) We use the term "radial position" only in a topological sense. We do not mean to imply that the relevant internuclear distances are either fixed or known.

(8) Nugent, W. A.; McKinney, F. J. *J. Mol. Cryst.* **1985**, *29*, 65.

(9) Schaefer, J. *Macromolecules* **1973**, *6*, 882.

(10) Heatley, F. *Prog. NMR Spectrosc.* **1979**, *13*, 47.

(11) Levy, G. C. *Topics in Carbon-13 NMR Spectroscopy*; John Wiley and Sons, Inc.: New York, 1974; Vol. 1.

(12) Lescanec and Muthukumar[2] use the term "radial distance" in a geometrical, rather than a topological, sense.