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Divergent Synthesis of Dendronized Poly(*p*-hydroxystyrene)

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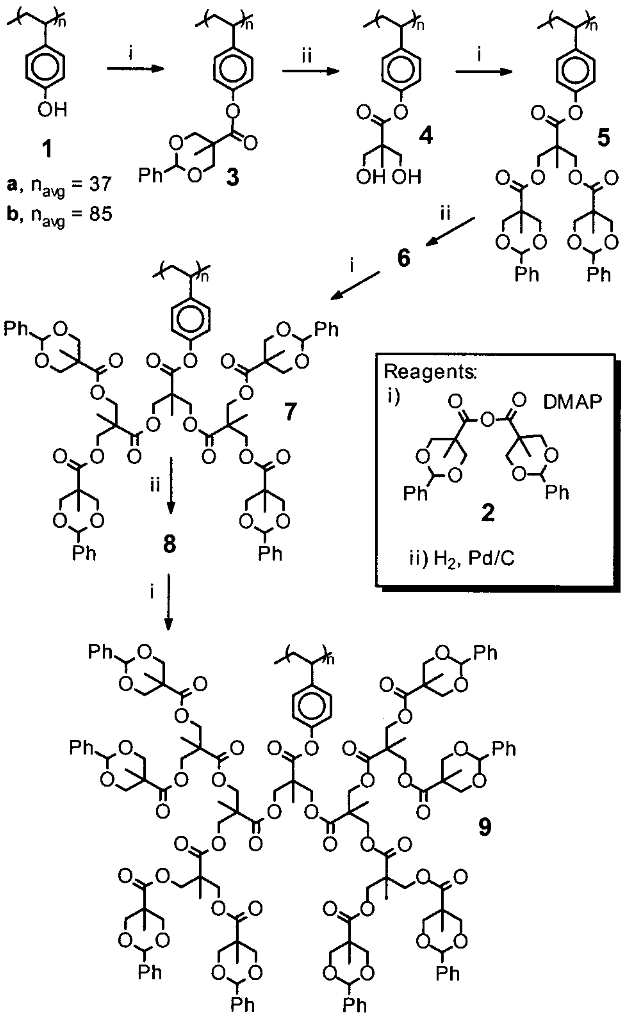
Introduction. As defined by Schlüter, dendronized polymers[1,2] are linear polymers that bear pendant dendrons along the backbone. The synthesis of high generation dendronized polymers with an appreciable degree of polymerization (DP) has proven challenging because of steric considerations. The majority of the attempts to access this architecture have utilized the macromonomer approach[3] attaching the desired dendron to the monomer unit before polymerization. A wide variety of polymerization techniques have been investigated,[2] including radical polymerization, ring-opening metathesis polymerization, Heck or Stille coupling, and Suzuki polycondensation. Although this macromonomer approach ensures that each monomer unit carries a structurally pure dendron, the steric crowding of high generation dendrons can obscure the reactive site, leading to materials with low degrees of polymerization and high polydispersities.[2,4]

An alternative approach entails the attachment of preformed convergent dendrons to a linear polymer after polymerization. This approach enables greater control over the length and dispersity of the linear backbone but suffers from steric complications because, at higher generations, the attachment of dendrons onto the pendant functionalities of the repeat units can hinder neighboring coupling sites, preventing complete dendronization.

The divergent growth approach,[5] though also subject to steric limitations, may prove valuable to prepare dendronized polymers by initiating growth from pendant sites on each repeat unit of a preformed polymer. By carrying out the dendritic coupling reactions on the more accessible periphery, steric complications should be minimized. It is clear however that the method can only be used to full benefit if exceptionally clean chemistry, free of cyclization or other side reactions, is available. Tomalia and co-workers first claimed the divergent growth of dendronized polymers over a decade ago;[6] however, this procedure has not attracted much attention because of the lack of published data and apparent difficulties in characterizing the structure of the product. Although tunneling electron microscopy studies[7] of these materials were published in 1998, the detailed characterization of these materials has yet to be reported, making the structural integrity of divergently prepared materials difficult to evaluate.

Herein, we report the divergent grafting of aliphatic polyester dendrons from a poly(*p*-hydroxystyrene) core. The resulting polymers were characterized by matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF MS), ^{1}H NMR, ^{13}C NMR, and size exclusion chromatography (SEC). These characterization data confirm that the divergent "grafting from" approach can be utilized to afford well-defined dendronized polymers.

Scheme 1. Synthetic Scheme of Divergent Dendronization



Results and Discussion. A recent report from our laboratories[8] has described a highly efficient divergent synthesis of polyester dendrimers based on bis(hydroxymethyl)propanoic acid. This procedure was selected for the dendronization of linear polymers because its technically simple synthesis and purification steps yield exceptionally pure dendritic products. Poly(*p*-hydroxystyrene) (PHS) was selected as the linear backbone as it is commercially available in low polydispersity (<1.10) over a range of molecular weights. In addition, the repeat unit is the polymeric analogue of the trisphenolic core molecule used in previous studies[8] to initiate the polyester dendrimer synthesis. Polymer samples exhibiting two different DPs (approximately 40 and 90) were investigated, with average molecular weights (M_n) of 4450 and 10 200.

The synthesis involves the repetition of coupling and deprotection steps (Scheme 1). The pendant hydroxyl groups of PHS were coupled via a DMAP-catalyzed esterification with the anhydride monomer **2**. The

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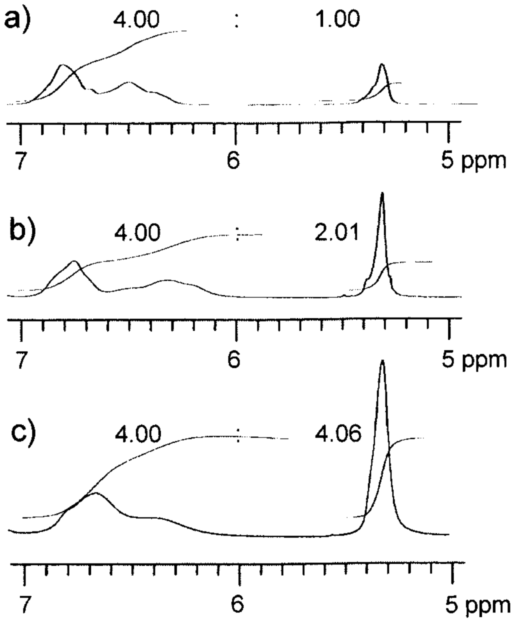

Figure 1. Key region of the ^1H NMR spectra of the linear PHS bearing first (a), second (b), and third (c) generation dendrons.

product, **3**, can be isolated in nearly quantitative yields from the catalyst and excess monomer by simple precipitation into methanol followed by filtration. The benzylidene groups of **3** can be quantitatively removed by a palladium-catalyzed hydrogenation, and the polyhydroxylated product, **4**, purified by a simple filtration.

These coupling steps could be repeated using pyridine solvent through the third generation for the shorter backbone (4450 M_n), and the second generation for longer backbone, affording dendronized polymers with molecular weights of approximately 50 000 Da. Continuation of the reaction sequence was complicated by the formation of an oligomeric species of the dendronized polymer, presumably resulting from either covalent linking or aggregation between individual polymer molecules. Solvent polarity appeared to have a profound effect on this side reaction: less polar solvents such as CH_2Cl_2 give a higher percentage of oligomers, while more polar solvents like DMF appear to suppress the side reaction, enabling an additional generation of growth. The use of a 50/50 DMF/pyridine solvent mixture afforded the fourth generation polymer for the shorter backbone and the third for the longer backbone; however, the polydispersity of these materials increased slightly when compared to the lower generation materials.

The esterified polymers, **3**, **5**, **7**, and **9** could be adequately characterized by ^1H NMR to verify their structural purity. Despite the broadened peaks due to the polymeric nature of the product, key resonances were sufficiently resolved to enable integration. Comparative integration in the ^1H NMR was carried out between the aromatic protons of the styrene units (6.2–7.1 ppm) and the protons of the acetal protecting groups (5.3–5.7 ppm). Although the precision of ^1H NMR integration of polymers is limited, all possible precautions have been taken to minimize the margin of error.[9] The observed ratios correspond closely to the theoretical values, suggesting nearly quantitative coupling reactions (Figure 1).

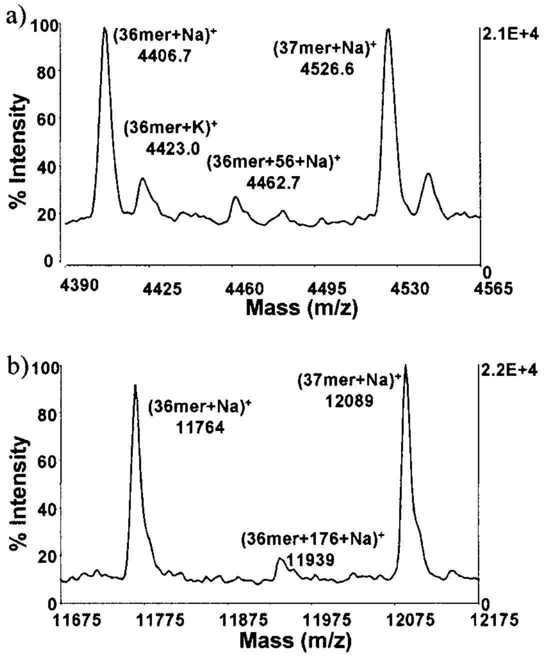

Figure 2. MALDI-TOF mass spectra of (a) an arbitrary region of the 4450 MW starting material **1a** and (b) the corresponding region in the esterified product, **3a**.

Table 1. SEC and MS Data for the Dendritic Grafted Polymers with Poly(hydroxystyrene) Core

		MALDI TOF-MS		SEC	
compound	theor M_n[a]	M_n	PDI	M_n	PDI
	4450 M_n Core				
PHS-5K-OH	4450	4 450	1.07	3 300	1.07
PHS-5K-[G1]-Ph	11 900	11 300	1.09	7 300	1.08
PHS-5K-[G1]-OH$_2$	8700	8 600	1.03		
PHS-5K-[G2]-Ph$_2$	23 500	23 500	1.06	10 200	1.08
PHS-5K-[G2]-OH$_4$	17 100	17 100	1.05		
PHS-5K-[G3]-Ph$_4$	46 800	46 700	1.06	14 400	1.07
PHS-5K-[G3]-OH$_8$	34 900	34 100	1.05		
PHS-5K-[G4]-Ph$_8$	93 400	86 000	1.08	16 100	1.17
	10 200 M_n Core				
PHS-10K–OH	10 200	10 200	1.02		
PHS-10K-[G1]-Ph	27 500	27 300	1.03	14 900	1.06
PHS-10K-[G1]-OH$_2$	20 100	19 300	1.09		
PHS-10K-[G2]-Ph$_2$	54 700	54 700	1.03	21 600	1.09
PHS-10K-[G2]-OH$_4$	39 800	40 300	1.05		
PHS-10K-[G3]-Ph$_4$	109 100	109 600	1.02	27 300	1.14

[a] Based on MALDI-TOF MS data for the corresponding starting material.

The MALDI-TOF MS data also confirmed the efficiency of the coupling reactions. The spectra of the polymeric starting material **1a**, included a series of $[M + Na]^+$ and $[M + K]^+$ peaks, as well as a residual impurity (M + 56) from the synthesis of the polymeric backbone[10] (Figure 2a). After esterification, the mass spectrum of the product, **3**, showed an analogous pattern, but no ions were observed that corresponded to incomplete esterification (M + 120) (Figure 2b). The mass spectra of higher M_n dendronized polymers were not sufficiently resolved to verify the absence of flaws; however, the M_n calculated for the broad peak observed corresponds closely to that of the expected product (Table 1). Only at the fourth generation does the MS data suggest that the coupling reactions may not proceed to completion.

Size exclusion chromatography revealed that the esterified polymer maintained the polydispersity of the initial linear PHS core through the third generation. At the fourth generation, the polydispersity begins to broaden, from less than 1.10 to nearly 1.20. The hydrodynamic volume of the dendronized polymers, like those of dendrimers, does not follow the same trend (vs M_n) as linear polymers. As a result, the M_n calculated by SEC is underestimated more than 2-fold for the second generation, 3-fold for the third, and 4-fold for the fourth.

Conclusion. As a result of the efficiency of the key dendron growth steps involving anhydride coupling followed by catalytic deprotection, the process of divergent dendritic growth from a polymeric backbone affords well-defined dendronized linear polymers. The dendronized polymers exhibit narrow polydispersities and relatively high DPs and appear to have an overall structural precision that rivals that of dendronized materials produced by the well-established “macromonomer” and “grafting to” approaches.[2] The approach shines in its flexibility since a variety of polymer backbones can be used in the dendronization reaction. As with all divergent syntheses, the pendant dendrons may include minor flaws that cannot be removed from the intended “pure” product. However, this is minimized by the highly efficient chemistry used in dendronization, providing a technically simple, accelerated route to relatively well-defined, high MW (>100 000) dendritic materials, well-suited for a variety of applications. In particular, the water solubility and narrow polydispersity of the larger polyhydroxylated compounds makes them interesting candidates for biomedical applications, and studies are presently underway to determine their hemolytic compatibility and cytotoxicity.

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Supporting Information Available: Synthetic details and full characterization of compounds **3b**−**7b** as well as the MALDI-TOF mass spectra of compounds **3b**, **5b**, and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: Oxford, UK, 1987. To optimize the accuracy of the integration, the T_1 of the corresponding protons were measured and the relaxation delay for integration experiments was set to 5 times the largest T_1 value. In addition, enough scans were taken to increase the signal-to-noise ratio above 1000:1. Finally, to prevent biased integration of the broad polymer resonances, the integration boundaries were systematically defined as the area under the curve and above 5% of the maximum peak amplitude. The accuracy of this procedure was tested in a control experiment using toluene with chromium(III) 2,4-pentanedionate added to artificially broaden the resonances. The margin of error is estimated by the authors to be less than 2% for lower generations and up to 5% for highest generation.

(10) Though details of the preparation of this commercial polymer are unavailable, an impurity at M + 56 is likely due to the presence of *tert*-butyl groups used as part of a protecting group in the preparation of **1**: Fréchet, J. M. J.; Eichler, E.; Willson, C. G.; Ito, H. *Polymer* **1983**, *24*, 995−1000.

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