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Effects of Polymer Architecture and Nanoenvironment in Acylation Reactions Employing Dendritic (Dialkylamino)pyridine Catalysts

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ABSTRACT: The role of architecture and nanoenvironment in the catalytic properties of dendritic polymers containing 4-(dialkylamino)pyridines was investigated in the context of acylation reactions employing sterically demanding tertiary alcohols as substrates. Fréchet-type benzyl ether and aliphatic ester dendrimers were prepared in a convergent manner from a common trivalent core containing three DMAP groups while a linear polymer was dendronized with aliphatic esters using a divergent growth scheme. Catalysis experiments clearly indicate that nanoenvironment plays the dominant role in determining the activity of the polymer catalysts, with the polyester platform being superior to the benzyl ether. Polymer architecture played little or no role in affecting catalysis. With respect to molecular transport and catalysis, this represents the first comparative study of the effect of architecture and nanoenvironment using structurally similar dendritic materials.

Introduction

During the past few decades, interest in organocatalysis has grown in part due to its important role in the economically and ecologically sound production of fine chemicals and pharmaceuticals.[1−3] Research in this field is typically divided into the main areas of homogeneous and heterogeneous catalysis.[4] While the former offers the unique advantage of well-defined catalytic sites that can systematically be optimized, the latter is of great industrial importance due to the inherent retention of the catalysts, which facilitates product separation.[5,6] In recent years, functional polymers carrying catalytically active sites have emerged that combine the advantages of both homogeneous and heterogeneous catalysis. In particular, polymeric macromolecules with branched architectures, such as dendrimers, have proven effective as nanoscale reactors to affect specific chemical transformations within a controlled environment.[7−11]

Dendrimers have received considerable attention with regard to catalysis due to (a) the possibility of catalyst recovery using membrane or nanofiltration techniques, (b) the control of catalyst activity through its nanoenvironment, (c) the alteration of catalyst solubility by peripheral modification, and (d) the potential for positive cooperative interactions between the catalytically active subunits. Depending on the location of the catalytic site(s), dendritic catalysts with either multiple peripheral active sites[11−18] or a catalytically active core[19−22] have been described. The first approach offers the advantage of relatively high catalyst loading; however, the dendritic backbone merely serves as a support, and no benefit is derived from its unique structural and functional features. In contrast, the second approach enables encapsulation[23] of the active site, thereby offering protection from deactivation. Moreover, the placement of catalytic moieties at the core or the interior of a globular dendritic structure allows for the fine-tuning of overall molecular properties and catalytic activity by modification of the periphery and the interior environment, respectively. Such properties, resulting from dendritic encapsulation, are frequently found in natural enzymatic systems where they are employed to high efficacy.

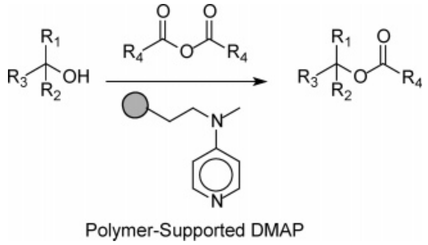

Figure 1. Acylation of alcohols by polymer-supported 4-(dialkylamino)pyridines.

To this end, we report our investigation of dendritic polymer architectures employing a radial gradient of polarity around a catalytic core for the design of new macromolecular catalysts. Given the fundamental nature of this study, we chose to focus on acylation reactions, specifically the esterification of sterically hindered tertiary alcohols by an anhydride using 4-(dialkylamino)pyridines[24,25] as the catalysts (Figure 1). Our group has previously synthesized heterogeneous, polymer-supported 4-(dialkylamino)pyridine beads[26,27] whose activity compared favorably to the widely used 4-(dimethylamino)pyridine (DMAP). However, it was found that highly loaded beads were susceptible to product inhibition as well as self-inhibitory, nonproductive effects between neighboring catalytic residues. The rate of reaction was also highly dependent on the catalysts' local microenvironment, making this an attractive system to study with better-defined macromolecules.

Three such macromolecular catalysts have been prepared from different dendritic platforms and interior functionality in order to assess the effects of polymer architecture and local nanoenvironment on the catalytic

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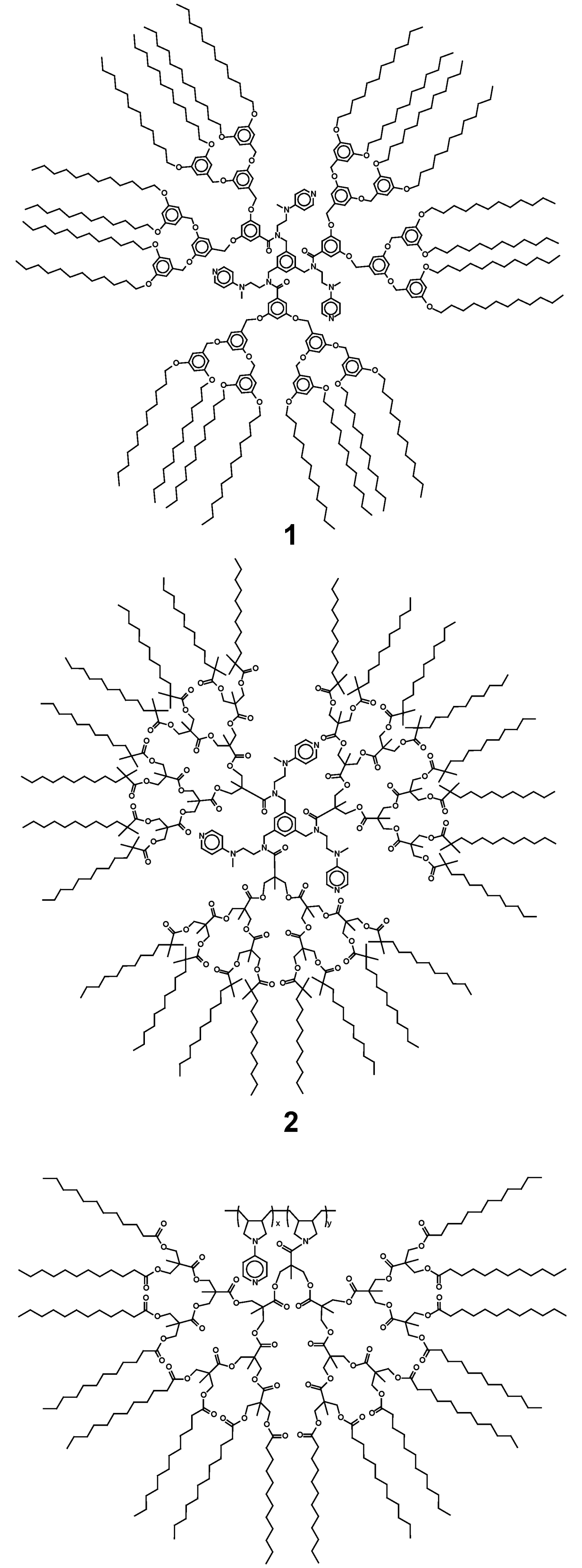


1

2

3

Figure 2. Dendritic 4-(dialkylamino)pyridine catalysts used in this study.

properties of the material. Specifically, we describe herein the synthesis of two dendrimers, each containing three 4-(dialkylamino)pyridine (DAP) moieties within their interiors. Dendrimers **1** and **2** have a common nonpolar corona and triamino core to which is appended either poly(benzyl ether) or poly(aliphatic ester) dendrons, respectively (Figure 2). We also tested a dendronized linear polymer **3** containing 4-(pyrrolidino)pyridine (PPY) units along its backbone surrounded by poly(aliphatic ester) dendrons (Figure 2).[28] In comparing the catalytic activity between dendrimers **1** and **2**, we probe the specific role of the polymeric nanoenvironment. In contrast, a comparison of dendrimer **2** and the dendronized linear polymer **3** probes the role of polymer architecture. We hypothesize that in utilizing amphiphilic, branched polymer architectures for DAP-catalyzed acylations there would be substantial opportunity to prevent product inhibition using a free energy-driven catalytic pump[7,22−23] that favors the migration of the less polar acetylated substrate back into the nonpolar medium. In addition, the precise placement of DAP and PPY moieties within the dendritic interiors was expected to mitigate neighboring-residue deactivation, seen previously in highly loaded beads, due to their site isolation within a more shape-persistent nanoenvironment.

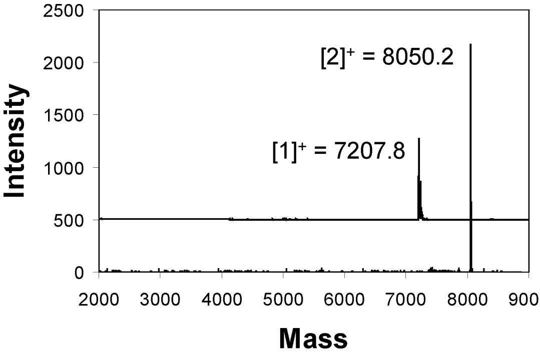


Figure 3. MALDI−TOF spectra for dendrimers **1** (top) and **2** (bottom).

Experimental Section

Preparation of Dendritic Catalysts. Dendrimers **1** and **2** were synthesized in a convergent manner[29] from dendrons containing a carboxylic acid at their focal point and a triamino core containing three 4-(dialkylamino)pyridine residues. The benzyl ether and aliphatic ester third-generation dendrons were prepared in high yield using standard methodologies.[30−32] The 4-(dialkylamino)pyridine-containing core **4** was synthesized by reductive amination of 1,3,5-triformylbenzene with 4-[(2′-aminoethyl)methylamino]pyridine, which was prepared in two steps from 4-[(2′-hydroxyethyl)methylamino]pyridine using a Gabriel synthesis approach (Scheme 1). The third-generation dendrimers were obtained in moderate yields via an amidation between the DMAP core and either of the alkyl-terminated dendrons (Scheme 2). The catalyst loading in **1** and **2** (416 and 372 μmol/g, respectively) was confirmed by UV spectroscopy using DMAP for the calibration curve in hexane. The integrity of these materials was established by NMR, elemental analysis, GPC, and MALDI−TOF mass spectroscopy (Figure 3) (see Supporting Information).

The dendronized linear polymer **3** was synthesized as previously described, using a divergent growth approach from a linear cyclocopolymer prepared from diallylamine and 4-(diallylamino)pyridine.[28,33−34] The pyrrolidine groups of the cyclocopolymer were reacted with an isopropylidene-protected bis(hydroxymethyl)propionic acid anhydride.[22,32] Subsequent deprotection of the 1,3-diols under acidic conditions activates the end groups for further dendrimer growth. The fourth-generation material was end-capped with myristoyl groups to produce the final catalyst. The catalyst loading in **3** (17.1 μmol/g) was calculated by UV spectroscopy using PPY for the calibration curve in hexane. The ratio of catalyst repeat units to dendron repeat units was measured to be 1:11.

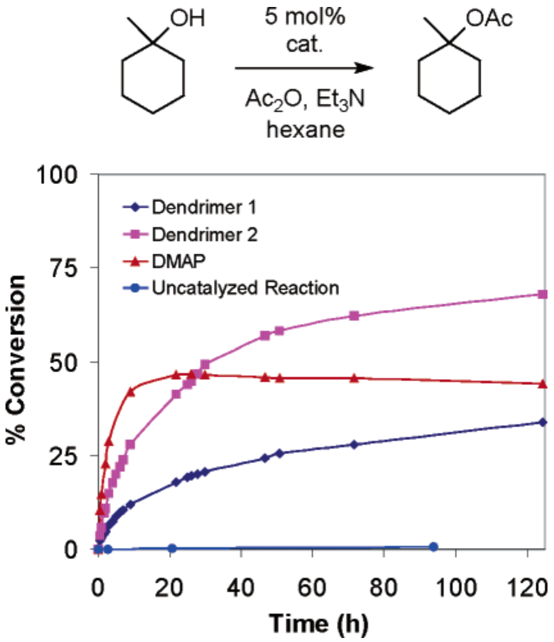
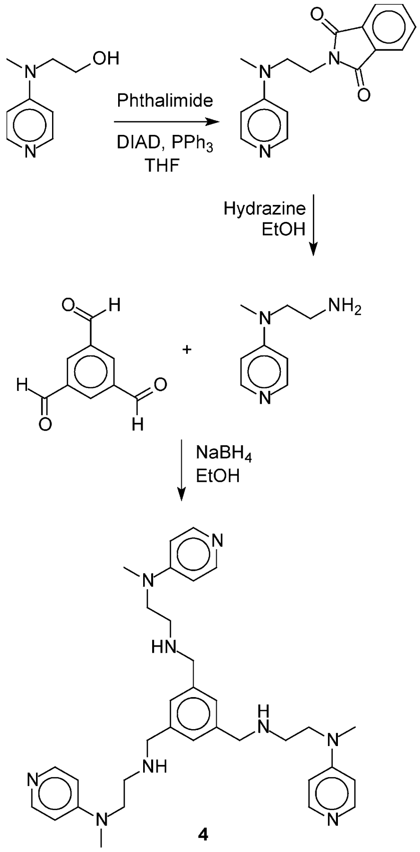
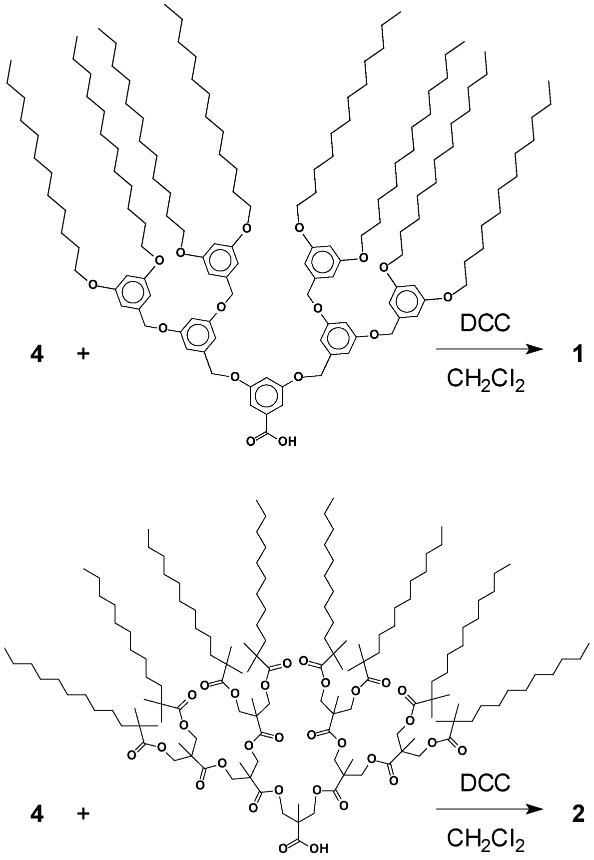


Figure 4. Acylation of 1-methylcyclohexanol (0.50 M in hexanes) at 22 °C using 5 mol % 4-(dialkylamino)pyridine catalysts and 1.5 equiv of acetic anhydride and triethylamine.

Scheme 1. Synthesis of 4-(Dialkylaminopyridine)-Containing Triamino Core (4) for Dendrimers



Scheme 2. Convergent Synthesis of Dendrimers 1 and 2 from Trivalent Core 4



Catalysis Experiments. Catalysis experiments were carried out in sealed vials in a temperature-controlled oil bath. Conversion was measured using gas chromatography (GC) using tetralin as an internal standard. In the first set of experiments, 1-methylcyclohexanol (0.50 M in hexane) was reacted at 22 °C with 1.5 equiv of both acetic anhydride and triethylamine. Catalyzed reactions employed 5 mol % of DMAP, or the corresponding mol % of dendrimer **1** or dendrimer **2**, taking into account the fact that three 4-(dialkylamino)pyridines reside in each dendrimer molecule. The reaction progress, monitored over a 120 h period, is shown in Figure 4. In the second set of experiments, linalool (0.15 M in cyclohexane) was reacted at 60 °C with a 3-fold excess of both pivalic anhydride and triethylamine. As described above, the catalyzed reactions employed the equivalent of 2.5 mol % of DMAP, dendrimer **1**, dendrimer **2**, or dendronized linear polymer **3**, accounting for the multiplicity of 4-(dialkylamino)pyridines in each. Figure 5 gives the conversion with time over the course of these experiments.

Catalyst recycling experiments were carried out with dendrimers **1** and **2** using the acylation of 2-butanol as a measure of their activity with repeated use. Each run was carried out with 5 mol % dendrimer catalyst at 22 °C with a 3-fold excess of acetic anhydride and triethylamine relative to 2-butanol (1.0 M in hexane). Conversion was measured by GC after 24 h. At the end of each run, the reaction mixture was diluted with hexane, washed with water, dried, and concentrated. The crude mixture was then heated at 80 °C in vacuo for 24 h to remove volatiles. The recovered dendrimers were examined for volatile impurities using GC relative to tetralin as an internal standard. In each case, there were less than 3% impurities consisting primarily of acetic acid and 2-butanol in the recovered polymer. This procedure was repeated four times to establish a trend. These data are given in Table 1. Catalyst recyclability had been previously identified for **3** as involving a simple precipitation.[28]

Results and Discussion

Earlier investigations into the transport properties of dendritic materials with a radial gradient of polarity had previously led to the development of the first dendronized cyclocopolymer containing catalytic groups along the linear backbone. In this report, we have expanded our study to include dendronized variants

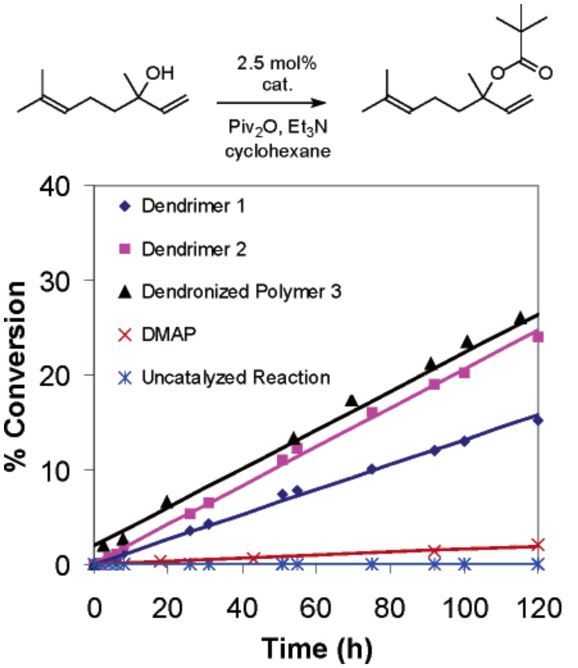
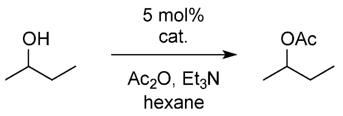


Figure 5. Formation of linalyl pivalate from linalool (0.15 M in cyclohexane) at 60 °C using 2.5 mol % 4-(dialkylamino)-pyridine catalysts and 3 equiv of pivalic anhydride and triethylamine.

Table 1. Catalyst Recycling Experiments for Dendrimers 1 and 2 Using the Acylation of 2-Butanol as a Diagnostic



	yield (%) of *sec*-butyl acetate	
run	dendrimer **1**	dendrimer **2**
1	85	90
2	82	92
3	83	88
4	81	89

that further probe the effects of nanoenvironment and architecture on transport in the context of an organic reaction catalyzed by 4-(dialkylamino)pyridines at the interior of the macromolecules. Since 4-(dialkylamino)-pyridines are extremely efficient at catalyzing reactions requiring nucleophilic amines, our efforts were focused toward substrates that may be outside the normal scope afforded by these reagents. The slow and difficult acylations of 1-methylcyclohexanol or linalool with acetic anhydride or pivalic anhydride, respectively, fit this criterion. Since the substrates exhibit a polar character due to the presence of a hydroxyl group, they should accumulate in the polar interior of the amphiphillic polymers when nonpolar solvents are used as reaction media. This advantageous substrate preconcentration shall hence be referred to as the “concentrator effect”.

This “concentrator effect” was first examined with dendrimer catalysts **1** and **2** by following the conversion with time for the acylation of 1-methylcyclohexanol. At 5 mol % catalyst loading, the rate of formation of 1-methylcyclohexyl acetate was initially fastest with the small molecule DMAP catalyst; however, conversion appeared to level off at 45%. In contrast, each of the reactions catalyzed by dendrimers **1** and **2** exhibited monotonic increases in conversion with time, reaching 70% with the polyester dendrimer, albeit at lower initial rates than observed with DMAP. Significant differences in initial rates were observed for dendrimers **1** and **2**, with the more compact polyester dendrimer outperforming the dendrimer based on the polybenzyl ether platform. We speculate that the polyester dendrimer is better able to concentrate the substrates; however, it is not clear whether this difference in initial rates derives from other factors, including transition state stabilization or other dielectric effects. In any event, nanoenvironment appears to be a dominant factor in catalysis with DMAP-like moieties in polymers, an aspect that manifests itself particularly with such well-defined catalytic species as dendrimers.

The influence of polymer architecture on acylation catalysis was discerned through the initial rates of formation of linalyl pivalate from linalool and pivalic anhydride. Given the highly hindered structure of the reactants, an elevated temperature was required for this reaction. Despite the difficult nature of the reaction, all of the dendronized polymers were competent, even outperforming DMAP. In the case of **3**, 27% conversion was reached after 120 h compared to 2% conversion for DMAP alone during the same period. As with the previous data, initial rates of reaction were highly dependent on catalyst nanoenvironment, with the polyester system being superior. The data also permit a comparison between the different dendritic polymer architectures **2** and **3**. Relative to the initial rate of the DMAP-catalyzed reaction, the dendrimer rate was 12.9 times faster while the dendronized linear polymer was 13.6 times faster. The difference, however, is not significantly different at the 95% confidence level and is most likely attributed to the difference in reactivity between the DMAP-like and PPY-like groups in the respective polymers.

Given the poor reactivity of DMAP under these conditions, it is possible to invoke the “concentrator effect” as a viable argument for the improved performance of the polymer-based systems. In other words, under these conditions DMAP does not appear to compete favorably with the ability of the dendrimers or dendronized polymer to concentrate a sterically demanding substrate such as linalool in closer proximity to the pivalylpyridinium species within the interior space of the polymers. Additionally, given the catalyst-to-dendron ratio for dendronized polymer **3** and dendrimer **2**—1:11 and 1:1, respectively—there should be considerably more void volume to fill with reactants in the case of **3**. If that is the case, the catalyzed reaction using **3** should be more efficient respecting the higher effective molarity of substrates and catalyst within the dendritic interior. Given the absence of a significant difference between the initial rates for **2** and **3**, however, it is likely that the rate-limiting step in these reactions is more affected by the hindered nature of the substrates rather than their higher effective concentration afforded by the dendritic polymers.

With respect to catalyst recyclability, dendronized linear polymer **3** had been shown to retain activity after simple precipitation from the crude reaction mixture into methanol. The dendrimers could not be treated in the same manner since they were isolated as oils. Instead, it was possible reisolate the polymers after a simple water wash to remove triethylammonium salts followed by evaporation of volatiles in vacuo. The recovered material was >97% pure in most cases, and activity was not observed to diminish with repeated use. Yields for simple acylations, such as 2-butanol, were consistent with the literature values for DMAP or PPY and a slight difference in reactivity was observed for dendrimers **1** and **2**, again emphasizing the effect of catalyst nanoenvironment on the kinetics.

Conclusion

Using amphiphilic 4-(dialkylamino)pyridine containing dendrimers **1** and **2** and dendronized polymer **3**, we have examined the role of catalyst nanoenvironment and polymer architecture in the context of sterically demanding acylation reactions employing tertiary alcohols and various anhydride electrophiles. The data clearly indicate a preference for the more compact polyester-based polymers **2** and **3**. These polymers were found to promote the desired transformations with greater efficacy than polymers based on a benzyl ether platform and in some instances with greater efficacy than the small-molecule catalyst DMAP. The rationale for this behavior has been attributed to a “concentrator effect” whereby reactions employing the polymer catalysts benefit from the gradient polarity of the core−shell macromolecules that accumulates substrates within the interior of the polymers, in closer proximity to the catalytic moieties than would be possible in solution with free catalyst. Moreover, since the product of the acylation reaction is more nonpolar than its alcohol precursor, product inhibition is thought to be mitigated by the preferential migration of the product from the polymer interior space back into the surrounding nonpolar medium. It should be pointed out that other dielectric effects may be operating here, and these effects will have to be probed in future work before a more definitive answer can be reached. The effect of different architectures on the catalytic ability of these polymers in acylation reactions was less pronounced. The polyester dendrimer **2** and dendronized polymer **3** had similar reactivity profiles, while reflecting somewhat the difference in reactivity between the DMAP-like and PPY-like groups that reside in each, respectively.

As this work represents the first step in understanding the effects of subtle manipulations of nanoenvironment and geometry on the function of complex macromolecules such as dendrimers and dendronized polymers, we can expect more research in this area in the future.

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Supporting Information Available: Detailed experimental procedures and characterization for dendrimers **1** and **2**. This information is available free of charge via the Internet at http://pubs.acs.org.

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