1618 *Macromolecules* **2008,** *41,* 1618−1626

Sequential and Single-Step, One-Pot Strategies for the Transformation of Hydrolytically Degradable Polyesters into Multifunctional Systems

Brooke A. Van Horn,[†] Rhiannon K. Iha, and Karen L. Wooley*

Departments of Chemistry and Radiology, Center for Materials Innovation, Washington University, One Brookings Drive, Saint Louis, Missouri 63130

Received December 4, 2007; Revised Manuscript Received December 20, 2007

ABSTRACT: Because of the significant interest in synthetic polymer systems with increasing degrees of complexity, we have focused attention upon the development of chemistries for the conversion of polyester backbones into functional materials. Facile conjugation strategies involving the reactions of both aminooxy and sulfonyl hydrazide nucleophiles with poly(ϵ-caprolactone-*co*-2-oxepane-1,5-dione) (P(CL-*co*-OPD)) are studied as general methodologies employing a sequential vs a single-step approach. Agreement between product and feed stoichiometries was achieved with both of the model hydroxylamines, *O*-dodecylhydroxylamine or *O*-benzylhydroxylamine. However, when sequential reactions were performed with either hydroxylamine together with dansyl hydrazide, considerable deviations in the product composition, relative to the reaction feed stoichiometries, were noted. For a sequential series of reactions, the successful use of aminooxy and sulfonyl hydrazide molecules required ketoxime ether formation prior to sulfonyl hydrazone formation to ensure the maximum retention of the ligand linkages throughout the process. Multigraft polymers, produced by the single-step method using exclusively aminooxy compounds with an excess of backbone ketone units, were efficient and had observed incorporation ratios in agreement with reaction stoichiometry. The incorporation of dansyl hydrazone linkages in this one-pot, single-step method suffered from low coupling efficiency, as was observed also in the sequential reactions.

Introduction

As a consequence of important advances in polymer synthesis and processing, and growing needs in specialized applications, general methods for the preparation of complex, yet well-defined, tailor-made materials are increasingly desired and are the target of many avenues of current research.[1−11] Within the scope of tailored materials are multifunctional polymers, whose specific function relies upon the presentation of recognizable pendant units, which perform in a manner not achievable through the simple macroscopic combination of the singly functional counterparts. Such polyvalent polymeric products are of interest for many applications, including sensors,[12−14] micro- and nanoarrays,[15−17] drug delivery,[18−21] tissue engineering,[22−25] and therapeutic imaging.[26−32] Recently, significant advances in the integration of organic chemistries with polymerization methods[33,34] have resulted in creative, effective strategies for the preparation of heterogeneously functional polymeric systems. For example, direct copolymerization of specialized functional monomers by controlled living radical polymerizations have given biohydrid and bioconjugate multifunctional materials.[35] The aqueous self-assembly of amphiphilic diblock copolymers with variable chain ends has allowed for the preparation of both core and surface heterogeneously functionalized nanoparticle systems.[36−39] These methodologies have advanced synthetic polymers in the fabrication of multifunctional materials and allowed for preliminary investigations into the types of characterization techniques needed to understand such complex systems. The synthetic effort required for the preparation of a new functional monomer or initiator for each unique purpose, however, could introduce limitations and reduce the broad applicability of these materials.

Alternatively, the exploration of selective and efficient chemistries for the postpolymerization or postassembly functionalization, including "click"-type chemistries,[40−44] has led to new approaches toward multifunctionality from common polymer precursors and assembled materials.[37,45,46] A few examples of the extension of robust, efficient, and orthogonal (REO)[47] chemistries to polymer backbones that are degradable[48−55] further enhance the synthetic capabilities and are working toward transfer of the ease of incorporating multifunctionalities into materials scaffolds that can be made to undergo triggered disintegration.

Given their general biocompatibility and (bio)degradability aliphatic polyesters, including poly(ϵ-caprolactone) (PCL), poly(glycolic acid), and poly(lactic acid), continue to receive significant attention. Even so, common natural and synthetic aliphatic polyesters are limited as degradable and modular systems due to their inherent lack of reactive chemical handles for the incorporation of functionalities, such as specific drugs, ligands, chromophores, and epitopes. Strategies have emerged that employ a variety of routes and chemistries for the functionalization of synthetic polyesters via copolymerization with specialty monomers,[56−58] postpolymerization modification,[59,60] or a combination of these two strategies.[54,61−63] The combination of a simple polyester platform with a versatile chemistry for coupling of numerous pendant units in a single step could allow for the construction of highly desirable, degradable, multifunctional materials.

Oxime, hydrazone, and (thio)semicarbazone linkages have been employed broadly in the production of functional materials through condensation of pendant aldehyde or ketone units with nitrogen-containing nucleophiles. Chemoselective chemistries are now being applied to the construction of amphiphilic[64−67] and cross-linked[68] PCL materials from a common ketone-bearing poly(ϵ-caprolactone-*co*-2-oxepane-1,5-dione) (P(CL-*co*-OPD)), **1**.[69] Specifically, Prime et al. recently reported the postpoly-

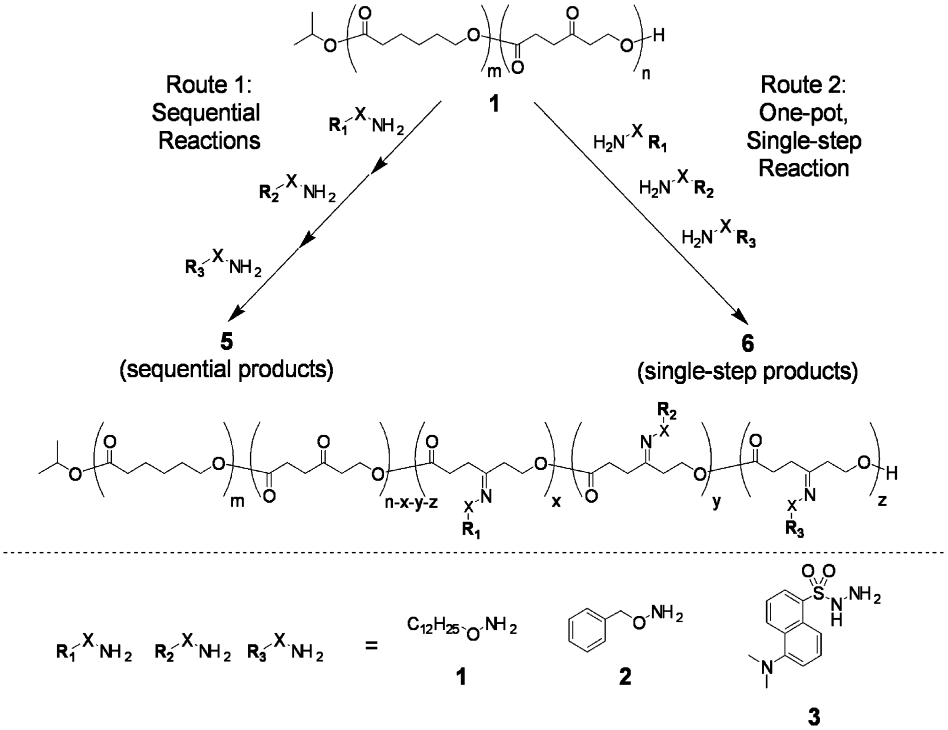
---

* Corresponding author: e-mail klwooley@wustl.edu; Tel (314) 935-7136; Fax (314) 935-9844.

[†] Current address: Princeton University, Department of Chemical Engineering, A413 Engineering Quadrangle, Princeton, NJ 08544.

10.1021/ma7026963 CCC: $40.75

Scheme 1



merization coupling of hydrazine-containing molecules, including poly(L-lysine)[67] and the cell adhesion peptide, GRGDS,[66] using hydrazone linkages onto P(CL-*co*-OPD). Mayes, Griffith, and co-workers illustrated the synthesis of poly(ethylene oxide) (PEO)-grafted PCL copolymers from the solution-state reaction of synthetic α-methoxy-ω-aminooxy-PEO with P(CL-*co*-OPD) for the preparation of cell adhesion substrates.[64,65] However, the formation of the oxime required long reaction times (days), high stoichiometry (up to 25 equiv of aminooxy PEO to ketone), and heat to maximize the coupling.

We were encouraged by the demonstrated versatility of the ketone units within the P(CL-*co*-OPD) copolymers and were interested in exploiting their chemistries further. Consequently, our group has recently explored the utility of acid-catalyzed oxime formation reactions using mono- and bis-functional aminooxy small molecules to produce graft and cross-linked PCL products, respectively.[68] The resultant simple graft copolymers served as a model system, confirming that acid catalysis accelerates the reaction rate (<6 h) without causing unwanted degradation of the polyester backbone. Additionally, excellent agreement was found between the equivalents of feed hydroxylamine per polymer and the number of oxime groups formed per chain.

With our strong interest in the construction of multifunctional and chromophore-labeled PCL systems, we present herein our recent investigations utilizing ketoxime ether and sulfonyl hydrazone linkages for the postpolymerization derivatization of P(CL-*co*-OPD) with various nitrogen-containing nucleophiles using acid catalysis. Results from sequential vs single-step functionalization of P(CL-*co*-OPD) with multiple aminooxy-terminated small molecules and the commercially available fluorescent probe, dansyl hydrazide, are described. Our findings demonstrate how sequential postpolymerization reactions can be utilized for the multiple functionalization and fluorescent labeling of degradable PCL materials and also highlight complications with a multistage process vs the advantages of a single-step strategy.

Results and Discussion

In an effort to extend from recent work showing the promise of polyester platforms capable of bearing multiple functional ligands,[48,63,64,67,68] we explored sequential (Scheme 1, route 1) and single-step (Scheme 1, route 2) reactions of ketone-containing P(CL-*co*-OPD) polymers, **1**. In each case, reactions were performed with combinations of aminooxy small molecules, *O*-dodecylhydroxylamine, **2**, and *O*-benzylhydroxylamine, **3**, and a sulfonylhydrazide-terminated fluorophore, dansyl hydrazide, **4**, to afford PCL materials with a mixture of pendant agents. We have examined if sequential postpolymerization reactions are complicated by oxime or hydrazone exchange, evaluated at both low (<1 equiv of nucleophile to available ketone) and moderate (>1 equiv of nucleophile to available ketone) equivalences. Moreover, we have investigated if the analogous one-pot, single-step reactions yield isolated polymer products with agreement between the stoichiometries of the reactants and the grafts produced.

Sequential Functionalization. Sequential functionalization reactions were explored as a general strategy that could be developed to produce a library of materials from a parent polymeric substrate. This approach allowed for the full characterization of the intermediate polymers, followed by further reactions to attach additional ligands. ^{1}H NMR spectroscopy and gel permeation chromatography (GPC) aided the evaluation of the extent of oxime or hydrazone formation and confirmed that degradation of the polyester chains did not occur when subjected to the multiple acid-catalyzed reaction steps, under the 6 h reaction times employed. Interestingly, these studies revealed that differing levels of oxime- and hydrazone-exchange reactions took place during multiple-step functionalizations. The extent of exchange and its dependence upon both the type of nucleophile used in the sequential reactions and the stability of the previously formed linkage (oxime or sulfonyl hydrazone) were examined. The final materials produced via sequential modification were characterized by ^{13}C NMR and infrared (IR) spectroscopies, thermogravimetric analysis (TGA), and dif-

Scheme 2

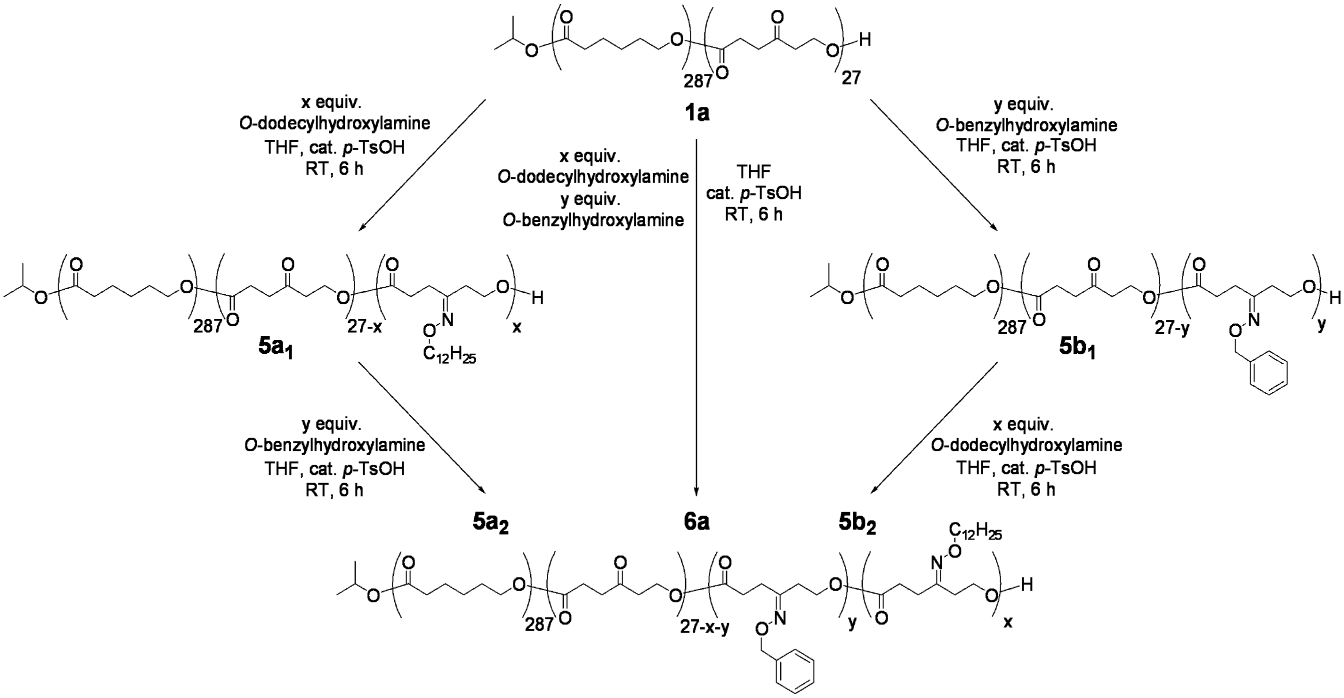


Table 1. Sequential Functionalization Reactions Conducted with Limited Aminooxy or Hydrazide Agent: Calculated Amounts of Functionalization for Various Polymer Samples with Their Molecular Weight Values and Distributions

		no. of repeat units observed in polymer[a]							
polymers		CL	OPD	dodecyl	benzyl	dansyl	M_n[a]	M_n[b]	PDI[b]
1a		287	27				36 200	33 200	1.4
5a	**1**	287	17	10(10)[c]			38 300	41 500	1.4
	2	287	8	10(10)[c]	9(10)[c]		39 000	45 600	1.4
5b	**1**	287	18		9(10)[c]		37 300	31 100	1.5
	2	287	7	11(11)[c]	9(10)[c]		39 200	33 100	1.5
5c	**1**	287	18	9(9.5)[c]			38 000	41 000	1.4
	2	287	15	9(9.5)[c]		3(10)[c]	38 600	45 200	1.4
5d	**1**	287	25			4(10)[c]	36 700	33 100	1.5
	2	287	15	10(10.6)[c]		2(10)[c]	38 500	32 100	1.5
5e	**1**	287	17		10(10)[c]		37 400	32 900	1.5
	2	287	10		10(10)[c]	7(9.5)[c]	39 000	36 100	1.4
5f	**1**	287	22			6(10)[c]	37 400	31 100	1.5
	2	287	12		10(11)[c]	5(10)[c]	39 500	33 700	1.4

[a] Da, calculated from integral values obtained from ^{1}H NMR spectroscopy. [b] Da, measured by GPC analysis. [c] Equivalents of small molecule per polymer chain used in the reaction noted in parentheses.

Table 2. Sequential Functionalization Reactions Conducted with Excess Aminooxy Agent in the Second Step of the Sequence: Calculated Amounts of Functionalization for Various Polymer Samples with Their Molecular Weight Values and Distributions

		no. of repeat units observed in polymer[a]							
polymers		CL	OPD	dodecyl	benzyl	dansyl	M_n[a]	M_n[b]	PDI[b]
1b		148	22				19 800	27 300	1.4
5g	**1**	148	0	22			24 100	33 600	1.4
	2	148	0	20	2		23 400	34 500	1.4
5h	**1**	148	0		22		22 400	29 100	1.4
	2	148	0	2	20		22 300	28 700	1.5
5i	**1**	148	10.5	0		11.5	22 700	25 500	1.5
	2	148	1	0	18	3	22 700	25 700	1.5

[a] Da, calculated from integral values obtained from ^{1}H NMR spectroscopy. [b] Da, measured by GPC analysis.

ferential scanning calorimetry (DSC) to determine the chemical and physical properties of the polymers after each of the derivatization steps.

O-Dodecylhydroxylamine and *O*-benzylhydroxylamine were chosen as the model ligands in this study to facilitate the quantification of their incorporation in the polymer products due to their significant structural and resultant spectroscopic differences. As illustrated in Scheme 2, the order of addition of the two aminooxy compounds for the sequential reaction sequence was varied, and the two ligands could alternatively be attached in a single-step, one-pot reaction (vide infra) to afford similar bifunctionally substituted polymers (Tables 1 and 3). The ^{1}H NMR spectrum of a polymer that was fully converted to its *O*-benzyl ketoxime ether analogue contained signature resonances at 7.35−7.3 and 5.05 ppm, corresponding to the new aromatic and isomeric benzylic protons (blue g in Figure 1) of the grafted polymer (Figure 1b). In contrast, Figure 1c illustrates that *O*-dodecyl ketoxime ether graft copolymer products exhibit

Table 3. One-Pot, Single-Step Functionalization Reactions Conducted with Limited Aminooxy or Hydrazide Agent: Calculated Amounts of Functionalization for Various Polymer Samples with Their Molecular Weight Values and Distributions

		no. of repeat units observed in polymer[a]							
polymers		CL	OPD	dodecyl	benzyl	dansyl	M_n[a]	M_n[b]	PDI[b]
1a		287	27				36 200	33 200	1.4
6a	**1**	287	2	10(10.4)[c]	15(17.4)[c]		40 000	45 600	1.4
6b	**2**	287	13	8(10)[c]		6(10.5)[c]	39 400	33 100	1.5
6c	**1**	287	13		10(11.2)[c]	4(10.2)[c]	38 700	45 200	1.4

[a] Da, calculated from integral values obtained from ^{1}H NMR spectroscopy. [b] Da, measured by GPC analysis. [c] Equivalents of small molecule per polymer chain used in the reaction noted in parentheses.

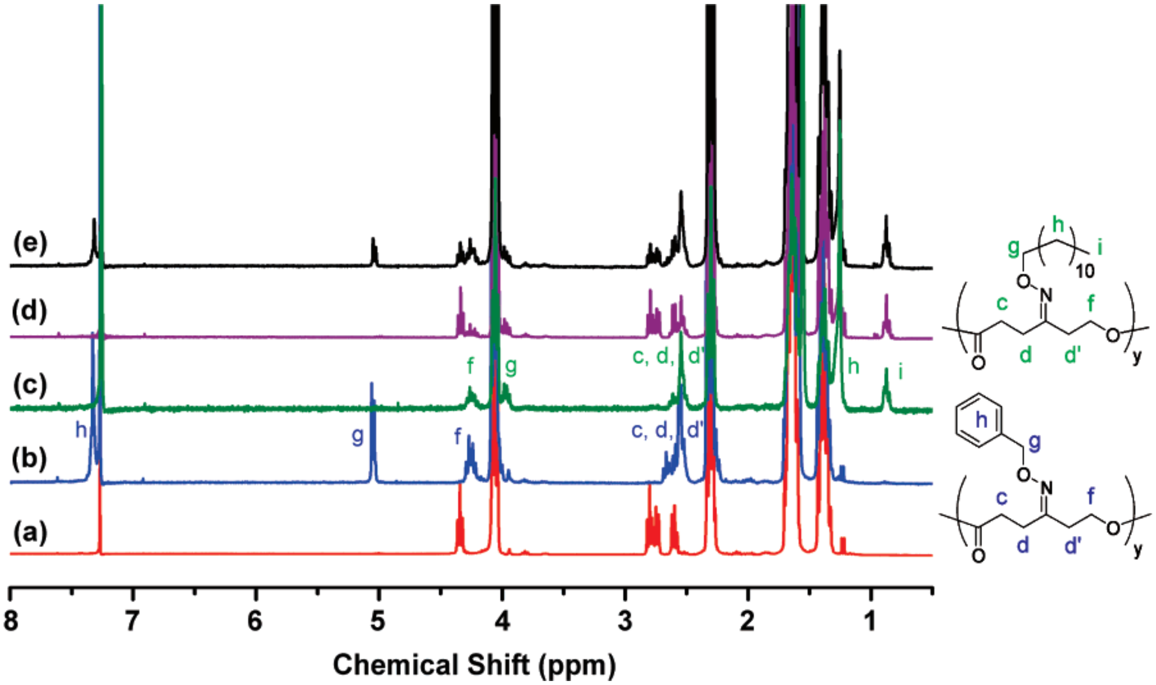


Figure 1. An overlay of proton NMR spectra (300 MHz, $CDCl_3$) for **(a)** the parent polymer, P(CL_{287}-*co*-OPD_{22}), **1a**, **(b)** a fully grafted *O*-benzyl ketoxime ether polymer, P(CL_{287}-*co*-(OPD-*g*-benzyl)$_{22}$), **(c)** a fully grafted *O*-dodecyl ketoxime ether polymer, P(CL_{287}-*co*-(OPD-*g*-dodecyl)$_{22}$), **(d)** *O*-dodecyl ketoxime ether partial graft, P(CL_{287}-*co*-OPD_{12}-*co*-(OPD-*g*-dodecyl)$_{10}$), **5a$_1$**, and **(e)** the final sequential reaction product, P(CL_{287}-*co*-OPD_3-*co*-(OPD-*g*-dodecyl)$_{10}$-*co*-(OPD-*g*-benzyl)$_9$), **5a$_2$**.

new proton resonances for the dodecyl =NO−CH_2− methylene unit (green g in Figure 1) and the methyl chain end at 3.9 and 0.9 ppm, respectively. A decrease in the OPD unit −CH_2−OC(O)− signal at 4.35 ppm correlated with the growth of different resonances for the four −CH_2−OC(O)− (f in Figure 1) ketoxime ether isomers detected between 4.15 and 4.30 ppm. Using these signals, a series of calculations were performed to determine the relative amounts of OPD, OPD-*g*-*O*-dodecyl ketoxime ether, and OPD-*g*-*O*-benzyl ketoxime ether that were present in the products of the two sets of sequential reactions (Table 1). The results of these sequential oxime-forming reactions indicated that the extent of oxime exchange was negligible when polymer backbone ketone units were present in excess of the aminooxy agents, as suggested by ^{1}H NMR spectroscopy. Retention of the first oxime linkage was observed following the reaction to generate the second linkage. For example, reaction of the P(CL_{287}-*co*-OPD_{22}), **1a**, with 10 equiv of *O*-dodecylhydroxylamine afforded a ketoxime ether polymer product, **5a$_1$** (Figure 1d). Subsequent incubation of the partially functionalized polymer with 10 equiv of *O*-benzylhydroxylamine yielded a polymer product, **5a$_2$**, that contained nine *O*-benzyl ketoxime ether linkages per polymer chain, in addition to the 10 original *O*-dodecyl ketoxime ether moieties produced in the first reaction step. Furthermore, the oxime ratios of the products were in agreement with the feed stoichiometries (noted in parentheses in Table 1) regardless of the order of addition (**5a** or **5b**) or differences in chemical nature (aliphatic vs benzylic) of the two model hydroxylamines. Although these materials were produced through two acidic reaction steps, no significant degradation of the polyester backbone was observed by GPC (Figure 2), and each sample had a similar polystyrene-equivalent

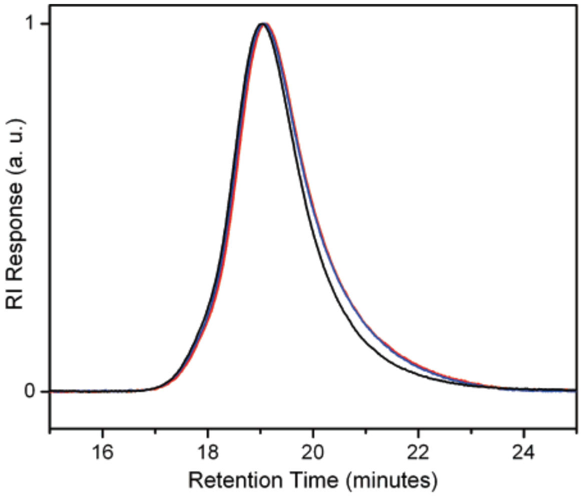
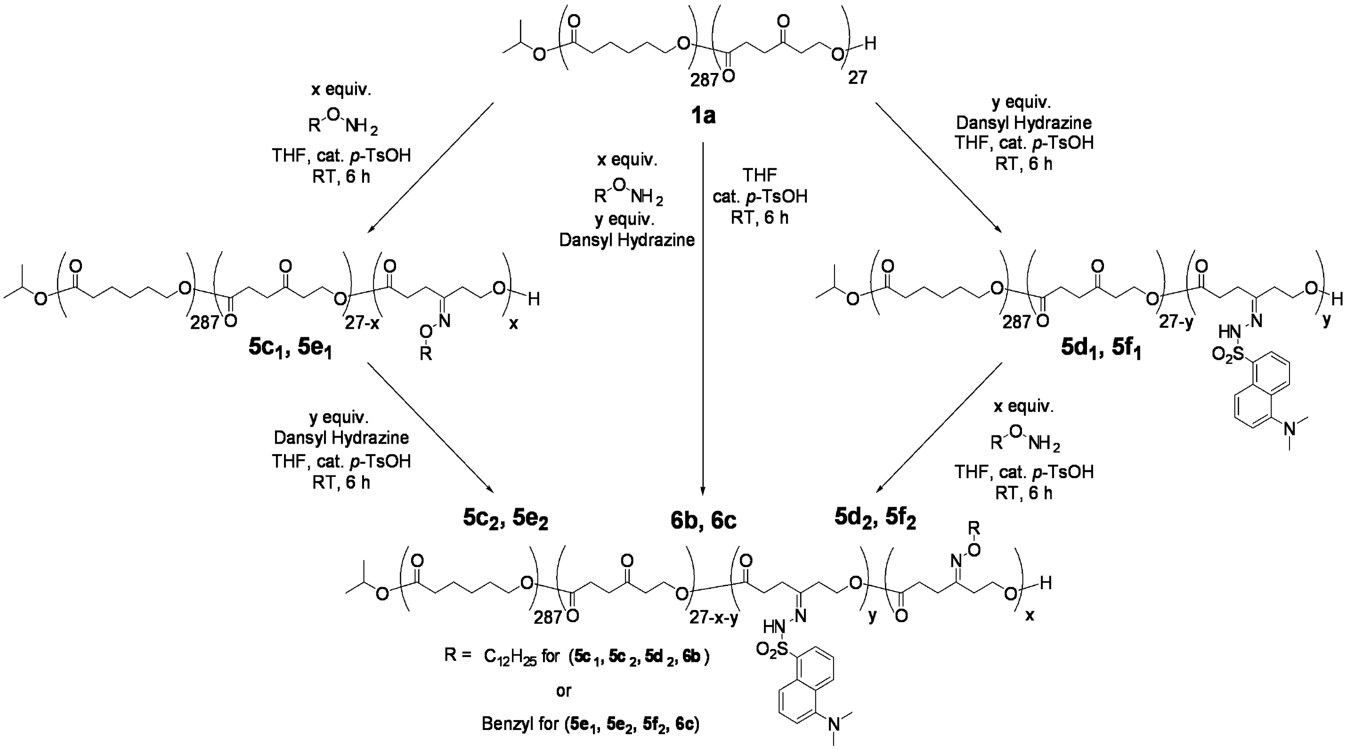


Figure 2. An overlay of GPC RI traces for the parent polymer, P(CL_{287}-*co*-OPD_{22}), **1a** (red), with the isolated graft copolymer intermediate, **5a$_1$** (blue), and the final sequential reaction product, **5a$_2$** (black).

Scheme 3



molecular weight after each graft introduction step. These findings suggest that agreement between the theoretical maximum and observed ketoxime ether linkages is achieved for multistep sequences when grafting-onto functionalization reactions are conducted with an excess of ketone in the reaction mixture.

When sequential reactions were performed with one of the two model hydroxylamines and dansyl hydrazide (Scheme 3), considerable deviations in the product composition relative to the reaction feed stoichiometries were noted by ^{1}H NMR spectroscopy, although no increase in polymer product polydispersity was detected by GPC. Between 30 and 60% formation of sulfonyl hydrazone, relative to the feed ratio, was detected with indicative resonances appearing at 8.6−7.1, 4.0, and 2.9 ppm for the aromatic, $-CH_2-OC(O)$ of the hydrazone-OPD, and dansyl $-N(CH_3)_2$ protons, respectively, in the various product ^{1}H NMR spectra (Figure 3). Performing the reaction in the presence of sodium sulfate as a drying agent did not promote the reaction further. Analysis of functionalized copolymer products, **5c**−**5f** of Table 1, revealed that significantly fewer dansyl units were grafted onto the polymer backbone than were predicted from the reaction stoichiometry. The observed reduced ratio of incorporation is most likely due to reduced nucleophilicity of the sulfonyl hydrazide primary nitrogen in comparison to that of the hydroxylamines and differences in the relative stabilities of the sulfonyl hydrazone and ketoxime ether linkages under the acid catalysis conditions.[70−74] Additionally, it was possible for reequilibration to occur during the second step of the sequential reactions, and a reduction in the number of dansyl hydrazone moieties per chain was noted by ^{1}H NMR spectroscopy when either *O*-benzylhydroxylamine or *O*-dodecylhydroxylamine was added in the second step of the sequence (**5d** and **5f** in Table 1). If the order of addition in the hydroxylamine/dansyl hydrazide reactions generated the ketoxime ether first, no substitution or loss of oxime was apparent in the ^{1}H NMR spectra after the sulfonyl hydrazone formation reaction. Interestingly, the sulfonyl hydrazone linkages were noted to reequilibrate during sequential steps in the presence of hydroxylamines, regardless of the availability of any additional electrophilic ketone groups of the polymer backbone. Therefore, the successful use of mixed nucleophilic reactions of aminooxy and sulfonyl hydrazide molecules for sequential functionalization of P(CL-*co*-OPD) required ketoxime ether formation prior to sulfonyl hydrazone formation to ensure the maximum retention of the ligand linkages throughout the process.

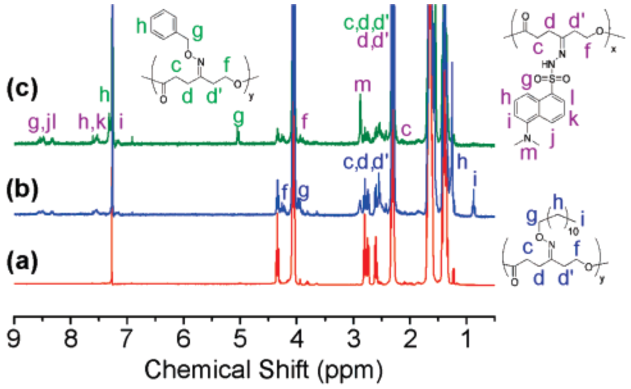


Figure 3. Stack plot of ^{1}H NMR spectra (300 MHz, $CDCl_3$) for (a) P(CL_{287}-*co*-OPD_{22}), **1a**, and the final graft functionalized products (b) **5c**$_2$ and (c) **5e**$_2$, illustrating the appearance of new proton resonances arising from the (b) *O*-dodecyl or (c) *O*-benzyl ketoxime ether linkages of the first reaction and the dansyl hydrazone moieties of the second step.

In contrast to the sequential functionalization method for which the ratio of ketone to nucleophile was kept >1 (vide supra), the following discussion highlights the results from reactions performed on polymer samples containing few or no residual ketones. The use of an excess of ligating small molecule allows for rapid conjugation when a limited number of "grafting-onto" functionalities is present on the polymer backbone, and this technique has proven to be useful in many polymer and biomacromolecular (i.e., peptide, polysaccharide) conjugation

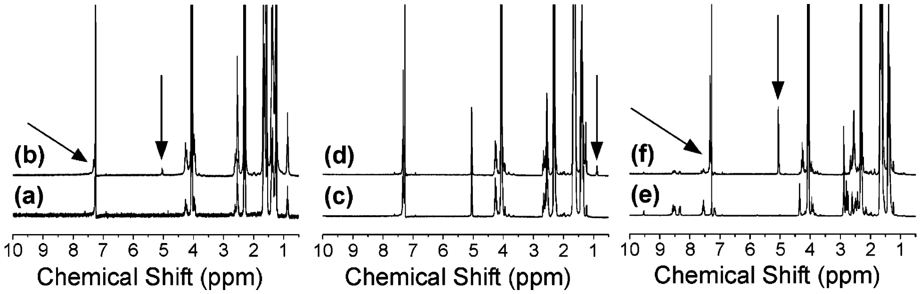


Figure 4. Proton NMR spectra (300 MHz, $CDCl_3$) comparing a series of initial graft products, **(**a**)** **5**g**$_1$**, **(**c**)** **5h$_1$**, **(**e**)** and **5i$_1$,** and the products of the three sequential reactions conducted with a molar excess of the second nucleophile (relative to the remaining ketone units available per polymer) **(**b**)** **5**g$_2$, **(**d**)** **5h**$_2$, **(**f**)** **5i**$_2$. [The arrows indicate resonances that have resulted in new grafts from the second nucleophile.]

strategies.[75−78] We chose to investigate these reaction conditions to determine whether an excess of aminooxy groups to ketone would complicate the functionalization of this PCL platform in sequential reactions by oxime- or sulfonyl hydrazone exchange. Fully grafted ketoxime ether polymer samples were prepared from *O*-dodecylhydroxylamine and *O*-benzylhydroxylamine, and these products, **5**g$_1$ and **5h$_1$** of Table 2, respectively, were subject to reaction with the opposite hydroxylamine to ascertain the extent of exchange under acid-catalyzed reaction conditions. Specifically, the reaction of **5**g$_1$, containing only *O*-dodecyl ketoxime ether functionalities, and therefore, no remaining ketones, with 15 equiv of *O*-benzylhydroxylamine in THF solution with a catalytic amount of *p*-TsOH, was monitored over 24 h. At 1 h of reaction, a small amount of exchange of the *O*-dodecyl ketoxime ether linkages (~1 per chain) was observed by ^{1}H NMR spectroscopy. Signals corresponding to the benzylic methylene protons from formation of *O*-benzyl ketoxime ether linkages, noted at 5.1 ppm, were detected and increased slightly in intensity over 24 h of reaction (Figure 4a,b). The isolated final product contained approximately two new *O*-benzyl grafts per polymer chain and retained 20 of the original *O*-dodecyl ketoxime ether linkages. A similar degree of exchange was observed when a polymer containing 22 equiv of *O*-benzyl ketoxime ether and no residual OPD units was challenged with 15 equiv of *O*-dodecylhydroxylamine (Figure 4c,d). GPC analysis confirmed that the lengthy exposure of the polymers to the acidic conditions did not give degradation byproducts, as noted by negligible difference in the molecular weight and polydispersity of the polymers before and after reaction (Table 2).

To evaluate further the stability and, therefore, the utility of sulfonyl hydrazone linkages in the attachment of dansyl units to the PCL backbone, a similar excess of nucleophile to carbonyl ratio (calculated including both residual ketone and previously formed sulfonyl hydrazone units) was employed in a "challenge" reaction with a dansyl grafted PCL sample. Because of the previously noted poor conjugation of dansyl hydrazide to these ketone-bearing copolymers, a partially functionalized polymer, **5i$_1$** (Table 2), containing approximately half of its 22 ketone units converted to the dansyl hydrazone was allowed to undergo reaction with 20 equiv of *O*-benzylhydroxylamine. Initially, we were interested in whether ketoxime ether formation in the early stages of the reaction would consume any residual ketone units and whether such reaction conditions would result, at longer reaction times, in a significant loss of the previously formed sulfonyl hydrazone linkages through reequilibration and subsequent reaction to establish ketoxime ethers.[73,74] At 1 h of incubation, significant formation of *O*-benzyl ketoxime ether was noted by ^{1}H NMR analysis (Figure 4e,f). Moreover, a marked decrease (~1/2) in the integration of resonances from dansyl hydrazone grafts and a corresponding increase in free dansyl hydrazine in solution were observed. Interestingly, proton resonances indicative of free OPD units were present throughout the 24 h of reaction and in the final product, even though the reaction stoichiometry of 20 equiv of *O*-benzylhydroxylamine to 10.5 equiv of ketone and 11.5 equiv of dansyl hydrazone could theoretically yield 20 *O*-benzyl ketoxime ether and two remaining dansyl hydrazone linkages, if full reequilibration of the hydrazone through the ketone was possible. The isolated PCL graft product was found to contain an average of one OPD unit, 18 *O*-benzyl ketoxime ether grafts, and three dansyl hydrazone grafts per polymer chain. At this point, we cannot confirm the mechanism or mechanisms of reactions, which could include competing equilibria and/or direct displacements, that lead to the reequilibration products. These results point to the complexities that result when working with both a polymer system and reversible functionalization reactions.

One-Pot, Single-Step Functionalization. Alternatively, we have also implemented a one-pot, single-step reaction approach to the preparation of multifunctional PCL materials. This method offers the convenience of a single reaction, for any desired number or stoichiometric ratio of ligands, without intermediate purification and isolation, and may be employed when the characterization of the individually modified polymer products is not required. The same three two-molecule combinations, *O*-dodecylhydroxylamine and *O*-benzylhydroxylamine, *O*-dodecylhydroxylamine and dansyl hydrazide, and *O*-benzylhydroxylamine and dansyl hydrazide, were investigated for the synthesis of functional PCL materials. Table 3 lists the observed (and feed) equivalents of ketoxime ether and/or dansyl hydrazone per polymer chain calculated from ^{1}H NMR analysis performed for the three one-pot reaction products, **6a**, **6b**, and **6c**. These functionalized polymers contained the same $-CH_2-OC(O)$ OPD−ketoxime ether and $-CH_2-OC(O)$ OPD−dansyl hydrazone resonances between 4.30 and 4.15 ppm and at 4.0 ppm, respectively, as observed for the sequential reaction products. A similar level and low efficiency of dansyl hydrazide incorporation were also observed in the single-step reactions, **6b** and **6c**, as was noted in the sequential reactions. The GPC traces exhibited in Figure 5 demonstrate the similarity in the polystyrene equivalent molecular weights for these one-pot reaction products when compared with the sequential reaction products.

To demonstrate the versatility of this one-pot approach, a reaction resulting in a triply functionalized polymer was carried out with *O*-dodecylhydroxylamine, *O*-benzylhydroxylamine, and dansyl hydrazide. The reaction stoichiometry was chosen for full functionalization of the $P(CL_{327}$-*co*-$OPD_{45})$ ketone units with a slight excess of nucleophile to ketone (20 equiv of each hydroxylamine and of the dansyl hydrazide, giving 60 equiv of reactive units per polymer chain bearing 45 equiv of ketone). The final product, **6d**, contained 14 units of *O*-benzyl and 14 units of *O*-dodecyl grafts, 14 remaining OPD ketone-bearing

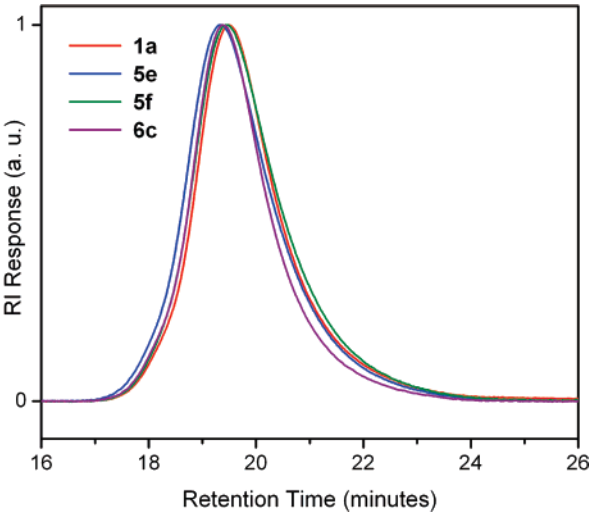


Figure 5. An overlay of GPC RI traces for the parent polymer, P(CL_{287}-*co*-OPD_{22}), **1a**, with the two sequential reaction products, **$5e_2$** and **$5f_2$**, and the one-pot, single-step product, **6c**, that each resulted in polymers with ~287 CL, 12 OPD, 10 OPD-*g*-*O*-benzyl ketoxime ether and 5 OPD-*g*-dansyl hydrazone units per chain (based upon ^{1}H NMR analysis).

units, and only three units of dansyl hydrazone, supporting the preference of the ketoxime ether formation over the sulfonyl hydrazone, while also demonstrating the complex interplay between conjugated and unconjugated ketone moieties.

Conclusions and Outlook

Sequential and single-step, one-pot postpolymerization modifications of ketone-containing P(CL-*co*-OPD) aliphatic polyesters have been conducted in an effort to extend the utility of nitrogen-containing nucleophiles and their "iminyl" formation chemistries as a strategy for the convenient and flexible synthesis of multifunctional PCL materials. Both methods yield materials with good agreement between the reaction stoichiometry and the observed incorporation for model hydroxylamines, but sequential functionalization demonstrated that the order of addition of the hydroxylamine and sulfonyl hydrazide and relative ratio to the ketone units of the polymer backbone were important for minimizing oxime or hydrazone exchange under these acidic conditions. The ketoxime ether linkage was formed preferentially to the sulfonyl hydrazone, and reequilibration and hydrazone exchange were possible when functionalization was conducted in the reverse order. Also, the choice of a sulfonyl hydrazide for conjugation presented an additional challenge in that a reduced coupling of the fluorophore was observed relative to the feed hydrazide:ketone ratio. Nonetheless, this chemistry is being further explored as a convenient means for the covalent attachment of multiple chromophores to a polyester backbone.

Additionally, we have found that the one-pot functionalization strategy allows for the single-step preparation of ligand-bearing PCL materials through formation of ketoxime ethers and sulfonyl hydrazones. Multigraft polymers, produced by the single-step method using exclusively aminooxy compounds with an excess of backbone ketone units, had observed incorporation ratios that were in excellent agreement with the theoretical ratios based upon the reaction stoichiometry. However, when considering the incorporation of dansyl hydrazone linkages, this one-pot, single-step method suffered from the same low coupling efficiency observed in the sequential reactions. Although the tunable attachment of a commercially available fluorescent dye to PCL polymers has been achieved using a sulfonyl hydrazone linkage, we are currently investigating the construction of other dye−polymer conjugates by use of the more efficient ketoxime ether formation with aminooxy-terminated synthetic dyes. Moreover, investigations are underway to exploit the single-step, one-pot approach to construct functional PCL copolymers with PEO and a variety of potential imaging agents.

Experimental Section

Materials. The synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone (TOSUO) has been described elsewhere.[79−81] ϵ-Caprolactone (CL) (Aldrich Chemical Co.) was distilled from CaH_2 and stored under argon. Toluene (Aldrich Chemical Co.) was dried by heating at reflux over sodium and distilled under argon prior to use. Aluminum triisopropoxide $Al(OiPr)_3$ (Aldrich Chemical Co.) was purified by sublimation and dissolved in dry toluene prior to use. Tetrahydrofuran-d_8 (Cambridge Isotopes, Inc.) was purchased as 0.75 or 1.0 mL ampules and used as received. Dansyl hydrazine (termed dansyl hydrazide throughout the paper; Aldrich Chemical Co.) was used as received. *O*-Benzylhydroxylamine was free based with triethylamine from the commercially available hydrochloride salt (*O*-benzylhydroxylamine hydrochloride, Aldrich Chemical Co.) and used as the free base hydroxylamine in all reported reactions. All other reagents (solvents, methyl levulinate, *p*-toluenesulfonic acid (*p*-TsOH), etc.) were purchased from Aldrich and used as received.

Instrumentation. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired in $CDCl_3$ or THF-d_8 unless otherwise noted on a Varian Mercury 300 spectrometer using the residual solvent signal as the internal reference. Infrared spectra were recorded on a Perkin-Elmer Spectrum RX FT-IR system by film deposition onto NaCl salt plates. Differential scanning calorimetry was performed under a nitrogen atmosphere using 40 μL aluminum pans on a Mettler Toledo DSC822 with heating and cooling at 10 °C/min from −100 to 100 °C. T_m and T_g values were obtained from the third heating scan, as the peak values from the thermogram and from the midpoint of the line between the tangents (or as the minimum of a derivative plot of the thermogram when the method of tangents was not possible), respectively. Thermogravimetric analysis data were obtained under a nitrogen atmosphere using 100 μL aluminum open pans in a Mettler Toledo TGA/SDTA851^e thermogravimetric balance with heating rates of 10 °C/min from 25 to 550 °C. Gel permeation chromatography was performed on a Waters Chromatography, Inc., 1515 isocratic HPLC pump equipped with an inline degasser, a model PD2020 dual-angle (15° and 90°) light scattering detector (Precision Detectors, Inc.), a model 2414 differential refractometer (Waters, Inc.), and four Pl_{gel} polystyrene-*co*-divinylbenzene gel columns (Polymer Laboratories, Inc.) connected in series: 5 μm guard (50 × 7.5 mm), 5 μm mixed C (300 × 7.5 mm), 5 μm 10^4 (300 × 7.5 mm), and 5 μm 500 Å (300 × 7.5 mm) using the Breeze (version 3.30, Waters, Inc.) software. The instrument was operated at 35 °C with THF as eluent. Data collection was performed with Precision Acquire 32 Acquisition program (Precision Detectors, Inc.), and analyses were carried out using Discovery32 software (Precision Detectors, Inc.) with a system calibration curve generated from plotting molecular weight as a function of retention time for a series of broad polydispersity poly(styrene) standards.

Synthesis. P(CL-*co*-OPD) Copolymer Synthesis. Random copolymers of CL and 2-oxepane-1,5-dione (OPD) were prepared by ring-opening polymerization of CL and the synthetic monomer TOSUO by initiation with $Al(OiPr)_3$, followed by deprotection using triphenylcarbenium tetrafluoroborate as reported elsewhere.[69,79−84]

Poly(CL_{287}-*co*-OPD_{27}) (1a). GPC: $M_{n,PS} = 33\,200$ Da, $M_{w,PS} = 47\,200$ Da, $PDI_{PS} = 1.4$. M_n(^{1}H NMR) = 36 200 Da.

Poly(CL_{148}-*co*-OPD_{22}) (1b). GPC: $M_{n,PS} = 27\,600$ Da, $M_{w,PS} = 39\,900$ Da, $PDI_{PS} = 1.4$. M_n(^{1}H NMR) = 19 800 Da.

Poly(CL_{327}-*co*-OPD_{49}) (1c). GPC: $M_{n,PS} = 38\,700$ Da, $M_{w,PS} = 50\,400$ Da, $PDI_{PS} = 1.3$. M_n(^{1}H NMR) = 43 600 Da

Sample Procedure for Sequential Functionalization: *O*-Dodecylhydroxylamine Followed by *O*-Benzylhydroxylamine ($5a_2$). P(CL_{287}-*co*-OPD_{27}) (144 mg, 0.0039 mmol of polymer, **1**, 0.11 mmol of ketone) was massed into a 1 dram shell vial.

O-Dodecylhydroxylamine (7.8 mg, 0.039 mmol of $-ONH_2$) was massed into a 1 dram shell vial, dissolved with 2.6 g of THF-d_8, and transferred to the vial containing the polymer. Two drops of a 0.02 M *p*-TsOH in THF solution were added quickly to the vial, and the reaction was allowed to proceed at RT for 6 h with monitoring by ^{1}H NMR spectroscopy. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold hexanes, collected as a white powder by vacuum filtration, and dried under vacuum for 24 h (isolated yield: 116 mg, 77%). The product polymer (84 mg, 0.022 mmol of polymer, 0.038 mmol of ketone) was then mixed with *O*-benzylhydroxylamine (2.7 mg, 0.022 mmol of $-ONH_2$, dissolved in 1.5 g THF-d_8), and two drops of a 0.02 M *p*-TsOH in THF solution were added. The reaction was allowed to proceed at RT for 6 h with monitoring by ^{1}H NMR spectroscopy. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold hexanes, collected as a white powder by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 66 mg, 77%. GPC: $M_{n,\ PS} = 45\,600$ Da, $M_{w,\ PS} = 62\,000$ Da, $PDI_{PS} = 1.4$. M_n(^{1}H NMR) = 39 000 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (singlet, 5 H, aromatic), 5.1−5.0 (two singlets, 2 H, $Ph-C\mathbf{H}_2$), 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, $(CH_3)_2C\mathbf{H}O$), 4.35 (t, $J = 7.2$ Hz, 2 H of OPD units, $C\mathbf{H}_2OCO$), 4.30−4.20 (pair of t, $J = 7.2$ Hz, 2 H of ketoxime ether isomers of OPD-*g*-dodecyl units, $C\mathbf{H}_2OCO$), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, $C\mathbf{H}_2OCO$), 4.00 (m, $J = 7.2$ Hz, 2 H of $=NO-C\mathbf{H}_2-C_{11}H_{23}$), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, $C\mathbf{H}_2OH$), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2C\mathbf{H}_2COO$), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)C\mathbf{H}_2CH_2$), 2.62−2.5 (t, $J = 7.5$ Hz, 2 H of OPD units; m, 6 H of OPD-*g*-dodecyl; m, 6 H of OPD-*g*-benzyl, $C\mathbf{H}_2COOCH_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, $C\mathbf{H}_2COOCH_2$), 1.65 (m, 4 H of CL units, $OCH_2C\mathbf{H}_2$ and $C\mathbf{H}_2CH_2COO$), 1.45 (m, 2 H of CL units, $C\mathbf{H}_2CH_2CH_2COO$), 1.3 (broad singlet, 20 H of dodecyl graft, $=NOCH_2-C_{10}\mathbf{H}_{20}-CH_3$), 1.25 (d, $J = 6.3$ Hz, 6 H of initiated chain end, $(C\mathbf{H}_3)_2CHO$), 0.9 (broad t, 3 H of dodecyl graft, $-C\mathbf{H}_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.9, 173.8, 173.6, 172.9, 156.5, 155.6, 138.3, 128.6, 128.3, 128.2, 128.0, 76.0, 74.1, 64.7, 64.4, 61.2, 60.9, 59.3, 41.7, 37.7, 34.4, 34.0, 32.2, 30.6, 30.4, 29.9, 29.8, 29.6, 29.4, 28.6, 28.0, 26.2, 25.8, 24.8, 23.0, 14.4 ppm. IR (cm^{-1}): 3600−3000, 2946, 2866, 1727 (str, multiple modes), 1640, 1471, 1419, 1397, 1366, 1239, 1296, 1242, 1191, 1108, 1061, 1046, 962, 934, 842, 806, 771, 733, 707. DSC: $T_g = -58.4$ °C, $T_m = 46, 51$ °C. TGA: 25−182 °C, ∼0% total mass loss, 295 °C, 5% total mass loss, 336 °C, 10% total mass loss, 382 °C, 25% total mass loss, 430 °C, 90% total mass loss, 6.3% mass remaining at 550 °C.

Sample Procedure for a One-Pot Functionalization. *O*-Dodecylhydroxylamine and *O*-Benzylhydroxylamine (6a). *O*-Dodecylhydroxylamine (3.8 mg, 0.0189 mmol of $-ONH_2$) and *O*-benzylhydroxylamine (3.8 mg, 0.0309 mmol of $-ONH_2$) were each massed into and dissolved in a 1 dram shell vial with 0.5 mL of THF-d_8 and transferred to the vial containing $P(CL_{287}\text{-}co\text{-}OPD_{22})$ (65.8 mg, 0.0018 mmol of polymer, 0.049 mmol of ketone). Two drops of a 0.02 M *p*-TsOH in THF solution were added quickly to the vial, and the reaction was allowed to proceed at RT for 6 h with monitoring by ^{1}H NMR spectroscopy. The reaction mixture was diluted with an additional 0.25 mL of THF, and the product was precipitated into cold hexanes, collected as a white powder by vacuum filtration, and dried under vacuum for 24 h. Isolated yield: 46.9 mg, 64%. GPC: $M_{n,\ PS} = 33\,500$ Da, $M_{w,\ PS} = 51\,000$ Da, $PDI_{PS} = 1.5$. M_n(^{1}H NMR) = 39 600 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (singlet, 5 H, aromatic), 5.1−5.0 (two singlets, 2 H, $Ph-C\mathbf{H}_2$), 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, $(CH_3)_2C\mathbf{H}O$), 4.35 (t, $J = 7.2$ Hz, 2 H of OPD units, $C\mathbf{H}_2OCO$), 4.30−4.20 (pair of t, $J = 7.2$ Hz, 2 H of ketoxime ether isomers of OPD-*g*-dodecyl units, $C\mathbf{H}_2OCO$), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, $C\mathbf{H}_2OCO$), 4.00 (m, $J = 7.2$ Hz, 2 H of $=NO-C\mathbf{H}_2-C_{11}H_{23}$), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, $C\mathbf{H}_2OH$), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2C\mathbf{H}_2COO$), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)C\mathbf{H}_2CH_2$), 2.62−2.5 (t, $J = 7.5$ Hz, 2 H of OPD units; m, 6 H of OPD-*g*-dodecyl; m, 6 H of OPD-*g*-benzyl, $C\mathbf{H}_2COOCH_2$), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, $C\mathbf{H}_2COOCH_2$), 1.65 (m, 4 H of CL units, $OCH_2C\mathbf{H}_2$ and $C\mathbf{H}_2CH_2COO$), 1.45 (m, 2 H of CL units, $C\mathbf{H}_2CH_2CH_2COO$), 1.3 (broad singlet, 20 H of dodecyl graft, $=NOCH_2-C_{10}\mathbf{H}_{20}-CH_3$), 1.25 (d, $J = 6.3$ Hz, 6 H of initiated chain end, $(C\mathbf{H}_3)_2CHO$), 0.9 ppm (broad t, 3 H of dodecyl graft, $-C\mathbf{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 173.4, 173.0, 172.9, 172.8, 156.4, 155.6, 155.5, 154.6, 138.1, 128.4, 128.1, 128.0, 127.8, 78.0, 77.5, 77.0, 75.8, 74.0, 64.6, 62.3, 61.1, 60.8, 60.7, 37.5, 34.2, 33.8, 32.0, 30.4, 30.2, 30.1, 30.0, 29.8, 29.6, 29.4, 29.2, 29.0, 28.9, 28.5, 27.9, 26.1, 25.6, 24.7, 24.4, 22.8, 22.0 ppm. IR (cm^{-1}): 3600−3000, 3027, 2956, 2941, 2896, 2864, 1733 (str, multiple modes), 1641, 1630, 1461, 1438, 1420, 1392, 1365, 1295, 1242, 1191, 1165, 1105, 1065, 1046, 962, 732. DSC: $T_g = -57.0$ °C, $T_m = 39.1, 47.2$ °C. TGA: 25−181 °C, ∼0% total mass loss, 284 °C, 5% total mass loss, 315 °C, 10% total mass loss, 377 °C, 25% total mass loss, 428 °C, 90% total mass loss, 5.0% mass remaining at 550 °C.

***O*-Dodecylhydroxylamine, *O*-Benzylhydroxylamine, and Dansyl Hydrazide (6d).** GPC: $M_{n,\ PS} = 38\,300$ Da, $M_{w,\ PS} = 49\,800$ Da, $PDI_{PS} = 1.3$. M_n(^{1}H NMR) = 38 200 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.6−7.15 (four m, 6 H, aromatic of dansyl), 7.35 (singlet, 5 H, aromatic of benzyl), 5.1−5.0 (two singlets, 2 H, $Ph-C\mathbf{H}_2$), 5.0 (septet, $J = 6.3$ Hz, 1 H of initiated chain end, $(CH_3)_2C\mathbf{H}O$), 4.35 (t, $J = 7.2$ Hz, 2 H of OPD units, $C\mathbf{H}_2OCO$), 4.30−4.20 (pair of t, $J = 7.2$ Hz, 4 H of ketoxime ether isomers of OPD-*g*-benzyl and OPD-*g*-dodecyl units, $C\mathbf{H}_2OCO$), 4.05 (t, $J = 6.6$ Hz, 2 H of CL units, $C\mathbf{H}_2OCO$), 4.00 (m, $J = 7.2$ Hz, 2 H of $=NO-C\mathbf{H}_2-C_{11}H_{23}$ and m, $J = 7.2$ Hz, 2 H of OPD-*g*-dansyl, $C\mathbf{H}_2OCO$),), 3.65 (t, $J = 6.3$ Hz, 2 H of terminated chain end, $C\mathbf{H}_2OH$), 2.90 (broad singlet, 6 H of dansyl units, $-N(C\mathbf{H}_3)_2$), 2.82 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)CH_2C\mathbf{H}_2COO$), 2.75 (t, $J = 7.2$ Hz, 2 H of OPD units, $C(O)C\mathbf{H}_2CH_2$), 2.70−2.4 (t, $J = 7.5$ Hz, 2 H of OPD units; m, 6 H of OPD-*g*-benzyl; m, 4 H of OPD-*g*-dodecyl; m, 4 H of OPD-*g*-dansyl), 2.3 (t, $J = 7.5$ Hz, 2 H of CL units, $C\mathbf{H}_2COOCH_2$), 1.65 (m, 4 H of CL units, $OCH_2C\mathbf{H}_2$ and $C\mathbf{H}_2CH_2COO$), 1.45 (m, 2 H of CL units, $C\mathbf{H}_2CH_2CH_2COO$), 1.25 (d, $J = 6.3$ Hz, 6 H of initiated chain end, $(C\mathbf{H}_3)_2CHO$), 0.9 ppm (broad t, 3 H of dodecyl graft, $-C\mathbf{H}_3$).

Acknowledgment. This material is based upon work supported by the National Science Foundation under Grant DMR-0451490 and Grant ECS-0506309 (a Nanoscale Interdisciplinary Research Team grant) and by the National Heart Lung and Blood Institute of the National Institutes of Health as a Program of Excellence in Nanotechnology (HL080729).

Supporting Information Available: All characterization data (GPC, ^{1}H and ^{13}C NMR, IR, DSC, TGA) for $\mathbf{5b_2}$−$\mathbf{5i_2}$ and **6b,c**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2719−2728.
(2) Bosman, A. W.; Vestberg, R.; Heumann, A.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.
(3) Helms, B.; Meijer, E. W. *Science* **2006**, *313*, 929−930.
(4) Euliss, L. E.; DuPont, J. A.; Gratton, S.; DeSimone, J. *Chem. Soc. Rev.* **2006**, *35*, 1095−1104.
(5) Harth, E.; Croce, T. A. *Aust. J. Chem.* **2006**, *59*, 525−533.
(6) Lord, S. J.; Sheiko, S.; LaRue, I.; Lee, H.-I.; Matyjaszewski, K. *Macromolecules* **2004**, *37*, 4235−4240.
(7) Sun, F. C.; Dobrynin, A. V.; Shirvanyants, D.; Lee, H.-I.; Matyjaszewski, K.; Rubinstein, G. J.; Rubinstein, M.; Sheiko, S. *Phys. Rev. Lett.* **2007**, *99*, 137801.
(8) Zschech, D.; Kim, D. H.; Milenin, A. P.; Scholz, R.; Hillebrand, R.; Hawker, C. J.; Russell, T. P.; Steinhart, M.; Gösele, U. *Nano Lett.* **2007**, *7*, 1516−1520.
(9) Percec, V.; Smidrkal, J.; Peterca, M.; Mitchell, C. M.; Nummelin, S.; Dulcey, A. E.; Sienkowska, M. J.; Heiney, P. A. *Chem.—Eur. J.* **2007**, *13*, 3989−4007.
(10) Hoogboom, J.; Elemans, J. A. A. W.; Rasing, T.; Rowan, A. E.; Nolte, R. J. *Polym. Int.* **2007**, *56*, 1186−1191.

(11) Storrie, H.; Guler, M. O.; Abu-Amara, S. N.; Volberg, T.; Rao, M.; Geiger, B.; Stupp, S. I. *Biomaterials* **2007**, *28*, 4608−4618.

(12) Satyanarayana, S.; McCormick, D. T.; Majumdar, A. *Sens. Actuators, B* **2006**, *115*, 494−502.

(13) Li, G. X.; Sun, S. H.; Wilson, R. J.; White, R. L.; Pourmand, N.; Wang, S. X. *Sens. Actuators, A* **2006**, *126*, 98−106.

(14) Kim, J.-M.; Lee, Y. B.; Yang, D. H.; Lee, J.-S.; Lee, G. S.; Ahn, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17580−17581.

(15) Christman, K. L.; Broyer, R. M.; Tolstyka, Z. P.; Maynard, H. D. *J. Mater. Chem.* **2007**, *17*, 2021−2027.

(16) Raddatz, S.; Mueller-Ibeler, J.; Kluge, J.; Wab, L.; Burdinski, G.; Havens, J. R.; Onofrey, T. J.; Wang, D.; Schweitzer, M. *Nucleic Acids Res.* **2002**, *30*, 4793−4802.

(17) Xu, Q.; Miyamoto, S.; Lam, K. S. *Mol. Divers.* **2004**, *8*, 301−310.

(18) Goldberg, M.; Langer, R.; Jia, X. *J. Biomater. Sci., Polym. Ed.* **2007**, *18*, 241−268.

(19) Sawant, R. M.; Hurley, J. P.; Salmaso, S.; Kale, A.; Tolcheva, E.; Levchenko, T. S.; Torchilin, V. P. *Bioconjugate Chem.* **2006**, *17*, 943−949.

(20) Piotrowicz, A.; Shoichet, M. S. *Biomaterials* **2006**, *27*, 2018−2027.

(21) Schmieder, A. H.; Grabski, L. E.; Moore, N. M.; Dempsey, L. A.; Sakiyama-Elbert, S. E. *Biotechnol. Bioeng.* **2007**, *96*, 967−976.

(22) Thomas, F. *Biopolyesters in Tissue Engineering Applications*; Springer: Berlin/Heidelberg, 2006; p 1−61.

(23) Navarro, M.; Aparicio, C.; Charles-Harris, M.; Ginebra, M. P.; Engel, E.; Planell, J. A. *Development of a Biodegradable Composite Scaffold for Bone Tissue Engineering: Physicochemical, Topographical, Mechanical, Degradation, and Biological Properties*; Springer: Berlin/Heidelberg, 2006; pp 209−231.

(24) Mahoney, M. J.; Anseth, K. S. *Biomaterials* **2006**, *27*, 2265−2274.

(25) Boccaccini, A. R.; Blaker, J. J. *Exp. Rev. Med. Dev.* **2005**, *2*, 303−317.

(26) Kobayashi, H.; Kawamoto, S.; Bernardo, M.; Brechbiel, M. W.; Knopp, M. V.; Choyke, P. L. *J. Controlled Release* **2006**, *111*, 343−351.

(27) Rabin, O.; Perez, J. M.; Grimm, J.; Wojtkiewicz, G.; Weissleder, R. *Nat. Mater.* **2006**, *5*, 118−122.

(28) Frias, J. C.; Ma, Y. Q.; Williams, K. J.; Fayad, Z. A.; Fisher, E. A. *Nano Lett.* **2006**, *6*, 2220−2224.

(29) Nasongkla, N.; Bey, E.; Ren, J.; Ai, H.; Khemtong, C.; Guthi, J. S.; Chin, S.-F.; Sherry, A. D.; Boothman, D. A.; Gao, J. *Nano Lett.* **2006**, *6*, 2427−2430.

(30) Rossin, R.; Pan, D.; Qi, K.; Turner, J. L.; Sun, X.; Wooley, K. L.; Welch, M. J. *J. Nucl. Med.* **2005**, *46*, 1210−1218.

(31) Stayton, P. S.; Hoffman, A. S.; El-Sayed, M.; Kulkarni, S.; Shimoboji, T.; Murthy, N.; Bulmus, V.; Lackey, C. *Proc. IEEE* **2005**, *93*, 726−736.

(32) Michalet, X.; Pinaud, F. F.; Bentolila, L. A.; Tsay, J. M.; Doose, S.; Li, J. J.; Sundaresan, A.; Wu, A. M.; Gambhir, S. S.; Weiss, S. *Science* **2005**, *307*, 538−544.

(33) Coullerez, G.; Seeberger, P. H.; Textor, M. *Macromol. Biosci.* **2006**, *6*, 634−647.

(34) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200−1205.

(35) Nicolas, J.; Mantovani, G.; Haddelton, D. M. *Macromol. Rapid Commun.* **2007**, *28*, 1083−1111.

(36) Giacomelli, C.; Le Men, L.; Borsali, R.; Lai-Kee-Him, J.; Brisson, A.; Armes, S. P.; Lewis, A. L. *Biomacromolecules* **2006**, *7*, 817−828.

(37) O'Reilly, R. K.; Hawker, C. J.; Wooley, K. L. *Chem. Soc. Rev.* **2006**, *35*, 1068−1083.

(38) Joralemon, M. J.; Smith, N. L.; Holowka, D.; Baird, B.; Wooley, K. L. *Bioconjugate Chem.* **2005**, *16*, 1246−1256.

(39) Becker, M. L.; Liu, J.; Wooley, K. L. *Biomacromolecules* **2005**, *6*, 220−228.

(40) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369−1380.

(41) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(42) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018−1025.

(43) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249−1262.

(44) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197−2208.

(45) Kiessling, L. L.; Gestwicki, J. E.; Strong, L. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2348−2368.

(46) Li, R. C.; Broyer, R. M.; Maynard, H. D. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5004−5013.

(47) Takizawa, K.; Nulwala, H.; Thibault, R. J.; Lowenhielm, P.; Wooley, K. L.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.*, submitted for publication.

(48) Li, H.; Riva, R.; Jérôme, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 824−831.

(49) Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J. *Macromolecules* **2007**, *40*, 3589−3598.

(50) Johnson, J. A.; Lewis, D. R.; Diaz, D. D.; Finn, M.; G.; Koberstein, J. T.; Turro, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 6564−6565.

(51) Riva, R.; Schmeits, S.; Jérôme, C.; Jérôme, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 796−803.

(52) Riva, R.; Schmeits, S.; Stoffelbach, F.; Jérôme, C.; Jérôme, R.; Lecomte, P. *Chem. Commun.* **2005**, 5334−5336.

(53) Parrish, B.; Breitenkamp, R. B.; Emrick, T. *J. Am. Chem. Soc.* **2005**, *127*, 7404−7410.

(54) Parrish, B.; Emrick, T. *Bioconjugate Chem.* **2007**, *18*, 263−267.

(55) Jiang, X.; Lok, M. C.; Hennink, W. E. *Bioconjugate Chem.* **2007**, *18*, 2077−2084.

(56) Lou, X.; Detrembleur, C.; Jérôme, R. *Macromol. Rapid Commun.* **2003**, *24*, 161−172.

(57) Gerhardt, W. W.; Noga, D. E.; Hardcastle, K. I.; García, A. J.; Collard, D. M.; Weck, M. *Biomacromolecules* **2006**, *7*, 1735−1742.

(58) Rieger, J.; Passirani, C.; Benoit, J. P.; Van Butsele, K.; Jérôme, R.; Jérôme, C. *Adv. Funct. Mater.* **2006**, *16*, 1506−1514.

(59) Nottelet, B.; Coudane, J.; Vert, M. *Biomaterials* **2006**, *27*, 4948−4954.

(60) Nottelet, B.; El, Ghzaoui, A.; Coudane, J.; Vert, M. *Biomacromolecules* **2007**, *8*, 2594−2601.

(61) Gautier, S.; D'Aloia, V.; Halleux, O.; Mazza, M.; Lecomte, P.; Jérôme, R. *J. Biomater. Sci., Polym. Ed.* **2003**, *14*, 63−85.

(62) Lecomte, P.; Riva, R.; Schmeits, S.; Riegerr, J.; Van Butsele, K.; Jérôme, R.; Jérôme, C. *Macromol. Symp.* **2006**, *240*, 157−165 and references therein.

(63) Parrish, B.; Emrick, T. *Strategies in Aliphatic Polyester Synthesis for Biomaterial and Drug Delivery Application*; American Chemical Society: Washington, DC, 2006; Vol. 939, pp 248−266.

(64) Taniguchi, I.; Mayes, A. M.; Chan, E. W. L.; Griffith, L. G. *Macromolecules* **2005**, *38*, 216−219.

(65) Taniguchi, I.; Kuhlman, W. A.; Mayes, A. M.; Griffith, L. G. *Polym. Int.* **2006**, *55*, 1385−1397.

(66) Prime, E. L.; Hamid, Z. A. A.; Cooper-White, J. J.; Qiao, G. G. *Biomacromolecules* **2007**, *8*, 2416−2421.

(67) Prime, E. L.; Cooper-White, J. J.; Qiao, G. G. *Aust. J. Chem.* **2006**, *59*, (8), 534−538.

(68) Van Horn, B. A.; Wooley, K. L. *Soft Matter* **2007**, *8*, 1032−1040.

(69) Latere Dwan'Isa, J.-P.; Lecomte, P.; Dubois, P.; Jérôme, R. *Macromolecules* **2003**, *36*, 2609−2615.

(70) Jencks, W. P. *J. Org. Chem.* **1959**, *81*, 473−481.

(71) Banks, B. E. C.; Banthorpe, D. V.; Butler, A. R.; Challis, B. C.; Chuchani, G.; Daudel, R.; Gibson, M. S.; Martin, R. B.; Smith, J. W.; Sollenberger, P. Y.; White, E. H.; Wolman, Y.; Woodcock, D. J.; Zabicky, J. *The Chemistry of the Amino Group*; John Wiley and Sons, Ltd.: London, 1968.

(72) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N-N Bonds*; The Benjamin/Cummings Publishing Co.: Reading, MA, 1983.

(73) Maynez, S. R.; Pelavin, L.; Erker, G. *J. Org. Chem.* **1975**, *40*, 3302−3303.

(74) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677−681.

(75) Heredia, K. L.; Tolstyka, Z. P.; Maynard, H. D. *Macromolecules* **2007**, *40*, 4772−4779.

(76) Langenhan, J. M.; Thorson, J. S. *Curr. Org. Synth.* **2005**, *2*, 59−81.

(77) Marcaurelle, L. A.; Bertozzi, C. R. *Glycobiology* **2002**, *12*, 69R-67R.

(78) Zhao, Y.; Kent, S. B. H.; Chait, B. T. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 1629−1633.

(79) Tian, D.; Dubois, P.; Grandfils, C.; Jérôme, R. *Macromolecules* **1997**, *30*, 406−409.

(80) Tian, D.; Dubois, P.; Jérôme, R. *Macromolecules* **1997**, *30*, 2575−2581.

(81) Tian, D.; Dubois, P.; Jérôme, R. *Macromolecules* **1997**, *30*, 1947−1954.

(82) Latere Dwan'Isa, J.-P.; Lecomte, P.; Dubois, P.; Jérôme, R. *Macromol. Chem. Phys.* **2003**, *204*, 1191−1201.

(83) Tian, D.; Halleux, O.; Dubois, P.; Jérôme, R.; Sobryj, R.; Van, der Bossche, G. *Macromolecules* **1998**, *31*, 924−927.

(84) Latere, J.-P.; Lecomte, P.; Dubois, P.; Jérôme, R. *Macromolecules* **2002**, *35*, 7857−7859.

MA7026963