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Polymerization of Enantiopure Monomers Using Syndiospecific Catalysts: A New Approach To Sequence Control in Polymer Synthesis

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The properties of many naturally occurring macromolecules, such as polypeptides, DNA, and polysaccharides, are vitally dependent on their sequence. In contrast, most synthetic polymers, especially commercial ones, are either simple homopolymers or random copolymers. A long-standing frontier in polymer chemistry is the control of the monomer sequences along a macromolecular backbone, which can give rise to a much wider array of polymeric materials from a limited set of commodity monomeric feedstocks.[1] Although impressive advances in living polymerization[2] techniques have made possible block copolymers with precise control over polymer architecture,[3] there are in comparison significantly fewer viable routes to the most simple sequentially controlled materials, alternating copolymers.[4,5] Although alternating copolymers can be easily constructed from difunctional A−A and B−B comonomers or A−B type monomers, step-growth processes allow little opportunity to tailor molecular architecture or control molecular weight. Although chain-growth processes generally allow better control of these features, they are limited in their ability to control the sequence of individual monomers.[6] In general, there is no central paradigm for the synthesis of alternating polymers using ionic, radical, and catalyst mediated processes, although several approaches have been successful. The most common approach is the alternating copolymerization of pairs of monomers having high rates for cross-propagation. Examples of monomer sets include electron-rich and -poor monomers via radical initiation;[7] using metal-based catalysts, epoxides and CO_2,[8] epoxides and anhydrides,[9] epoxides and CO,[10] aziridines and CO,[11] and alkenes and CO[12] have been alternatingly copolymerized. Another approach is choosing two monomers where only one homopolymerizes; if the other is used in large excess, polymers rich in alternation are formed.[13] Other unique approaches include ethylene-*alt*-propylene copolymerization using C_1-symmetric metallocenes,[14] ring-opening insertion metathesis polymerization,[15] solid- or liquid-phase iterative synthesis,[16] and selective ring-opening polymerization (ROP) of cyclic monomers containing two or more monomer units.[17]

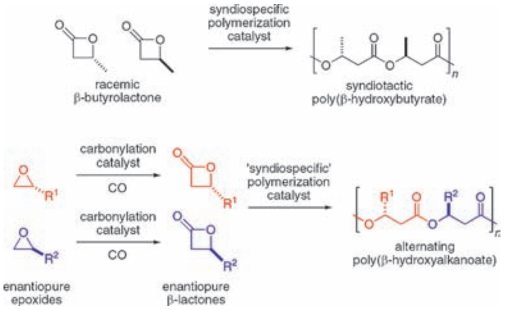

Figure 1. Synthesis of syndiotactic poly(β-hydroxybutyrate) and an alternating poly(β-hydroxyalkanoate).

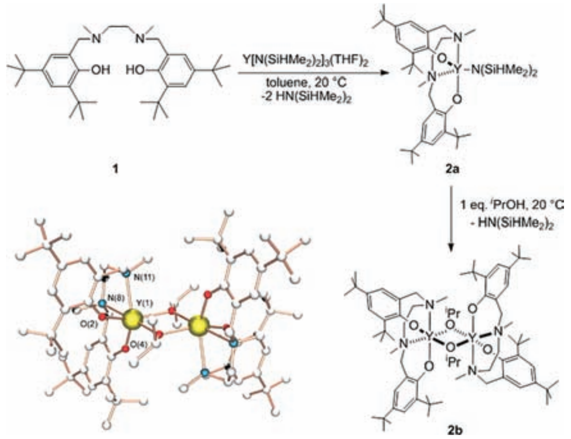

Figure 2. Synthesis of complexes **2a** and **2b** and molecular structure of **2b**.

Of course the simplest type of alternating copolymer is a syndiotactic polymer, where the stereogenic centers of adjacent units are of opposite stereochemistry. Syndiotactic polymers can be catalytically synthesized from prochiral monomers (propylene, styrene, methyl methacrylate, and 1,3-butadiene)[18] or from racemic, chiral monomers (propylene oxide,[19] lactide,[20] and β-butyrolactone[21]). In the case of racemic monomers, the most common mode of syndiospecific stereocontrol is a chain-end control mechanism, where the stereogenic center of the last inserted monomer biases the catalyst to enchain a monomer of the opposite stereochemistry. When the level of stereochemical control is high, a syndiotactic polymer results. It occurred to us that, in the case of a syndiospecific chain end control mechanism, if instead of using a racemic mixture of one monomer, a mixture of enantiomerically pure *but different* monomers was used, an alternating polymer would result. Unlike other cases of alternating polymerizations where monomer pairs must be discovered empirically, in this case a wide range of polymers could be prepared if a broad set of enantiomerically pure monomers could be synthesized. Taking into account recent developments in our prior research, (1) the syndiospecific polymerization of β-lactones[21] and (2) the synthesis of enantiomerically pure β-lactones by epoxide carbonylation,[22] we set out to capitalize on these advances jointly to make alternated polyesters (Figure 1). Herein we describe the initial results of our studies.

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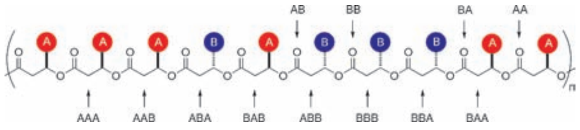
Table 1. Alternating Polymerization of Enantiopure β-Lactones[a]

entry	complex	[M]/[Y]	R^1	R^2	time (min)	yield[b] (%)	M_n[c] (g · mol^{-1})	PDI[c]	% of alternation[d]	T_m[e] (°C)
1	**2b**	400	CH_3	–	5	98	37100	1.10	–	178
2	**2b**	400	C_2H_5	–	10	98	47200	1.10	–	108
3	**2a**	200	CH_3	C_2H_5	5	98	16800	1.49	91	83
4	**2a**	400	C_2H_5	C_2H_5	20	95	34200	1.39	94	79
5	**2b**	400	C_2H_5	C_2H_5	20	98	38600	1.15	93	78
6[f]	**2b**	30	$CH_2C_4F_9$	$CH_2C_4F_9$	90	94	9500	1.15	ND	210
7	**2a**	400	CH_3	C_4H_9	120	98	49400	1.41	93	47
8	**2b**	200	CH_3	C_2H_5	10	98	15500	1.15	90	87
9	**2b**	400	CH_3	C_2H_5	30	95	37100	1.13	91	88
10	**2b**	500	CH_3	$CH_2OC_2H_5$	120	95	57400	1.23	94	80
11[f]	**2b**	50	CH_3	$CH_2C_4F_9$	90	97	11300	1.19	91	161

[a] All reactions performed at 20 °C in benzene-d_6 at [lactone] = 2.45 M. [b] As determined by the integration of ^{1}H NMR methine resonances of lactones and PHA. [c] M_n and M_w/M_n of polymer determined by SEC-RI in THF at RT using polystyrene standards. [d] The percentage of alternation is the probability of alternating linkages between two monomer units of opposite configurations and is determined from the carbonyl region of the $^{13}C\{^1H\}$ NMR spectrum. [e] Determined by differential scanning calorimetry, run from −60 to 210 at 10 °C/min. [f] Polymerization performed in THF-d_8

Our attention was drawn to the tetradentate phenoxyamine (*salan*)[23] ligand **1** (Figure 2), which has recently given interesting performances in zirconium-catalyzed olefin polymerization and aluminum-catalyzed ROP of lactide.[24] Reaction of $Y[N(SiHMe_2)_2]_3(THF)_2$ with the *salan* ligand **1** produces the yttrium complex $[(\mathbf{1})YN(SiHMe_2)_2]$ (**2a**) in quantitative yield. Although this complex initiates the polymerization of different β-lactones (*vide infra*), we decided to transform the sterically bulky amido group of this complex into an isopropoxide group that would be a more suitable mimic of the putative propagating secondary alkoxide species (Figure 2). Reaction of complex **2a** with 2-propanol produces the bimetallic complex $[(\mathbf{1})YO^iPr]_2$ (**2b**) in 90% isolated yield following crystallization (Figure 2). The molecular structures of **2a** and **2b**, determined by X-ray diffraction, confirm a monomeric species for **2a** in the solid state and a dimeric species for **2b** (see Supporting Information). The alternating copolymerization of a series of two different enantiopure β-lactones of the opposite absolute configuration using complexes **2a** and **2b** was then investigated. The results are summarized in Table 1. Both (*salan*)-Y(III) complexes **2a** and **2b** proved to be active under mild conditions, allowing full conversion of 30−500 equiv of 50:50 mixtures of lactones in 5−120 min (reaction times not optimized) at 20 °C in either benzene-d_6 or THF-d_8 solutions. The resulting copolymers formed had narrow polydispersities (PDI = M_w/M_n) and number average molecular weights and monomer compositions in close agreement with the predicted values. In accordance with previous observations,[25] the polymerization reactions initiated by the isopropoxide derivative **2b** resulted in narrower polydispersities (PDI = 1.10−1.23).

Scheme 1. Possible Comonomer Sequences in PHAs from Enantiopure β-Lactones



Microstructural analysis of the different polyhydroxyalkanoates (PHAs) formed from 50:50 mixtures revealed that complexes **2a** and **2b** exert a significant influence at room temperature on the alternating nature of the polymer formed. Under all polymerization conditions, new highly alternating PHAs were formed (up to 94% alternation) as determined by ^{1}H and ^{13}C NMR spectroscopy. First, during all copolymerization reactions involving enantiomeric β-lactones with different substitution, we found that both monomers are consumed at the same rate (without any induction period). As a control, we also determined that the copolymerization rate of both monomers is different from the homopolymerization rate of each monomer. For instance, over a period of 2 h, 24 *in situ* ^{1}H NMR spectra were recorded every 5 min at 20 °C during the reaction of **2b** with 200 equiv of (*R*)-BBL and 200 equiv of (*S*)-4-butyl-2-propiolactone (see Supporting Information). These *in situ* ^{1}H NMR spectra were in full agreement with the formation of a highly alternating PHA. ^{13}C NMR spectroscopy allowed us to clarify the alternating tendency of the pseudoenantiomeric comonomer units in these copolymers using previously reported assignments.[21c,d,26,27] Possible sequences available in PHA copolymers derived from enantiomeric β-lactones are depicted in Scheme 1. The ^{13}C NMR spectra of both crude and precipitated polymers reveal a fine structure in two diagnostic peaks of PHAs. Based on previous assignments,[27] these peaks correspond to the carbonyl and methylene carbons of PHAs. The overall pattern of signals remains persistent despite the changing content of lactones incorporated in those alternating copolymers and is consistent with the presence of triad (methylene) and dyad (carbonyl) sequences alternatively distributed throughout the polymer chain. In control experiments, catalyst $[Zn(BDI)O^iPr]_2$ (BDI = *N*,*N*′-bis(2,6-diisopropylphenyl)-2,4-pentanediiminato) which is known to produce atactic PHB,[28] was systematically used for comparison of the different ^{13}C NMR spectra obtained. Moreover, we also synthesized the corresponding isotactic PHAs. The ^{13}C NMR spectra were analyzed using the expanded signals from the methylene and carbonyl regions. Notably new methylene and carbonyl signals that differ from both parent (isotactic) homopolymers were found. For instance, the polymer resulting from the ROP of 250 equiv of (*R*)-BBL and 250 equiv of 4-ethoxymethyl-2-propiolactone of opposite relative stereochemistry (Table 1, entry 10) features two sets of peaks which correspond to triad sensitivity in the methylene region (Figure 3). One set at ∼41 ppm corresponds to A-centered methylenes, and the other at 36 ppm can be attributed to B-centered triads. We correlated the most intense resonance at δ 40.85 ppm to the (BAB) triad, and we attributed the resonances at δ 40.77, 41.08, and 41.13 ppm, respectively, to the BAA, the AAA, and the AAB triads.[29] For the

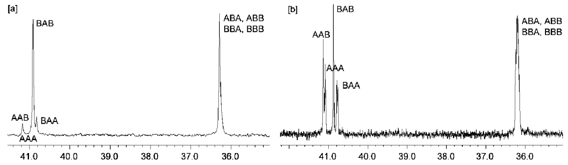


Figure 3. Main-chain methylene regions of the $^{13}C\{^1H\}$ NMR spectra (125 MHz, $CDCl_3$, 20 °C) of PHAs prepared with (a) complex **2b** (Table 1, entry 10) and (b) $[Zn(BDI)O^iPr]_2$.

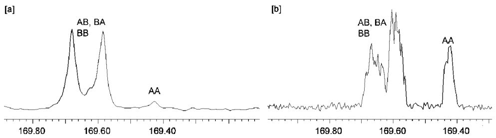


Figure 4. Carbonyl regions of the $^{13}C\{^1H\}$ NMR spectra (125 MHz, $CDCl_3$, 20 °C) of PHAs prepared with (a) complex **2b** (Table 1, entry 10) and (b) $[Zn(BDI)O^iPr]_2$.

corresponding random copolymer prepared with $[Zn(BDI)O^iPr]$ (Figure 3b), the $^{13}C\{^1H\}$ NMR spectra show an increase in the intensity of the resonances attributable to AAA (δ 41.08 ppm), BAA, and AAB sequences. The carbonyl regions of the $^{13}C\{^1H\}$ NMR spectra proved to be more complicated (Figure 4), but as shown earlier for PHB,[21c] the signals at 169.45 ppm can be attributed to AA dyads and as a consequence the two other peaks (δ 169.71 and δ 169.61 ppm) correspond to the three remaining dyads.

DSC measurements of PHA samples showed the strong influence of the nature of the side chain on the melting temperature. Indeed, the melting temperature decreased for most of the poly(3-hydroxybutyrate-*alt*-3-hydroxyalkanoate) copolymers, which is consistent with previous reports for PHAs.[30] For example, the melting temperature of isotactic PHB (Table 1, entry 1) is 178 °C, while that of isotactic PHV is 108 °C (Table 1, entry 2). As expected, the melting point for highly syndiotactic PHV (Table 1, entry 4) is 79 °C, 30 °C lower than that of the isotactic version. Except for fluorinated copolymers (Table 1, entries 6, 11), T_m values decreased as the length of the side chain was increased (Table 1, entries 2−5, 7−10), and the DSC traces display single broad transition endotherms at temperatures ranging from 47 to 88 °C. Their overall lower crystallinity should confer on PHA enhanced mechanical properties, such as toughness and softness, that make them more interesting thermoplastics than pure isotactic or highly syndiotactic PHB.[21c] Also, the rate of PHA biodegradation is increased with a decrease in the crystallinity.

In conclusion, we have developed a new strategy for the synthesis of biodegradable polyesters. By using highly efficient bis(phenolate) group 3 metal complexes as initiators, we were able to synthesize highly alternating copolymers by ring-opening polymerization of a mixture of enantiomerically pure but different monomers. Given the growing need for inexpensive biodegradable plastics for use in various applications, the future for metal-catalyzed ring-opening polymerization is certainly promising. Therefore, the development of synthetic methods for the polymerization of a wide range of monomers with control over the stereochemistry, molecular weight, and comonomer incorporation is of particular importance. The cobalt-catalyzed carbonylation of epoxides to make optically active β-lactones followed by the ring-opening polymerization of these monomers using yttrium initiators represents an efficient route to alternating copolymers. This efficient catalytic system makes copolymers that would be very difficult to make through any other method. This strategy of copolymerization suggests a number of new avenues for biodegradable polymers.

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Supporting Information Available: Complete experimental procedures, characterization data, and crystallographic details. This information is available free of charge via the Internet at http://pubs.acs.org.

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