Polymerization Catalysis

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Exploitation of a Chain-End-Control Mechanism for the Synthesis of Alternating Copolymers

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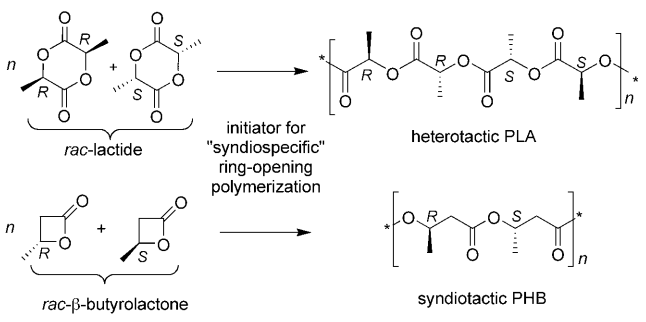
Linear aliphatic polyesters, such as poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), and poly(hydroxyalkanoate)s (PHAs), have emerged over the past two decades as a class of materials with huge potential.[1] These polyesters are at the forefront of research on biodegradable and biocompatible polymers, as they and their degradation products following (biotic or abiotic) hydrolysis are both nontoxic. Such resorbability and bioassimilability characteristics have led to the use of some of these materials, especially PLLA, PGA, and related poly(lactic-co-glycolic acid) copolymers, in a range of pharmaceutical and medical applications.[1,2] PLLA is also produced as a commodity thermoplastic for the packaging industries through the ring-opening polymerization (ROP) of L-lactide (L-LA, the cyclic dimer of lactic acid), a 100% bioresourced monomer produced by the fermentation of starch obtained from various sources, for example, sugar beets or corn. In the context of the recurring economical and societal issues associated with the depletion of fossil feedstocks and severe accumulation in the environment of traditional polyolefinic plastics (e.g. polyethylene, polypropylene, polystyrene), the use of such renewable resources and the degradability of these polyesters are other major driving forces for the current boom of some of these materials, in particular PLLA.[1c] On the other hand, although PLLA represents for these reasons the very paradigm of the polymer of the future, and despite its good balance of properties (physical, mechanical, rheological, and chemical), which meet the requirements of a broad range of applications, it is clear that this material alone[3] will never substitute the vast array of traditional polyolefins with their wide variety of properties. Needless to say, it is of paramount importance that brand-new materials are developed with original and controlled macromolecular architectures to enable manipulation of the aforementioned properties at will.

The ROP of lactones and related monomers, in which the relief of ring strain is the driving force for polymerization, is arguably the most efficient method to prepare aliphatic polyester materials.[4] This chain-growth process proceeds with significantly better control in terms of molecular weight and molecular-weight distribution (M_w/M_n) than step-growth processes, that is, the polycondensation of diacid/diol comonomers or hydroxyacid monomers. Over the last decade, the field of ROP of lactone-type monomers has experienced major breakthroughs, notably as a result of the advent of highly efficient metal-based catalysts that enable fine tailoring of the polymer topology.[4] Particularly outstanding are the high levels of stereoselectivity observed in the ROP of monomers containing stereogenic centers. Thus, the ROP of racemic lactide (*rac*-LA is composed of equal amounts of L-LA and D-LA), for example, with an achiral [(salen)Al(OR)] catalyst,[4b,5] can afford a stereoblock isotactic polymer, [PLLA-*b*-PDLA]$_n$, with high stereoregularity ($P_m = 0.91$; P_m is the probability of *meso* linkage). On the other hand, so-called heterotactic PLA, in which the enantiomers L-LA and D-LA are enchained alternately along the macromolecules, has been obtained with high stereoregularity ($P_r = 0.90$–0.96; P_r is the probability of racemic linkage) and overall control of the polymerization parameters for the ROP of *rac*-LA, for example, with amido or alkoxide initiators/catalysts based on β-diiminate–Zn,[6] tris(pyrazolyl)borate–Ca,[7] and aminoalkoxybis(phenolate)–Y platforms (Scheme 1).[8] The yttrium initiators/catalysts proved particularly useful for the syndiospecific ROP of racemic β-butyrolactone (*rac*-BBL): they afforded poly(3-hydroxybutyrate) (PHB)—the most common PHA—for the first time with high molecular weight, narrow polydispersity ($M_w/M_n = 1.05$–1.15), and very high levels of syndiotacticity (P_r up to 0.95; Scheme 1).[9] The syndiospecific stereocontrol exerted in these polymerizations that lead to highly heterotactic PLA and syndiotactic PHB is based on a



Scheme 1. Syndiospecific ring-opening polymerization of racemic lactones.

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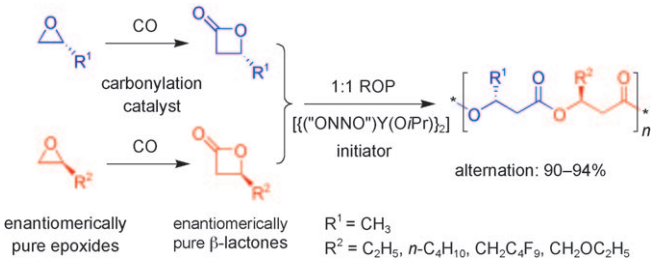
so-called "chain-end-control mechanism" (CEM), in which the stereogenic center of the last-inserted monomer in the growing polymer chain biases the catalyst to enchain a monomer of opposite configuration.

On the basis of this principle, Thomas, Coates, and co-workers recently devised a smart approach toward new sequentially controlled PHAs.[10] Their original strategy relies on the use of a syndiospecific single-site catalyst for the ROP of a mixture of enantiomerically pure but different monomers (Scheme 2), instead of a racemic mixture of a given monomer as described above (Scheme 1). For this purpose, they



Scheme 2. Synthesis of alternating poly(β-hydroxyalkanoate)s.

selected a series of enantiomerically pure, differently 4-substituted β-propiolactones, which can be synthesized efficiently through a cobalt-catalyzed carbonylation of the corresponding optically active epoxides (Scheme 2).[11] The alternating copolymerization of two such enantiomerically pure β-lactones of opposite absolute configuration was carried out in the presence of an yttrium complex structurally related to those first implemented for the syndiospecific ROP of *rac*-BBL[8] with a salan-type diaminobis(phenolate) ligand. Besides the high activity observed and the good level of control over molecular weight and polydispersity, especially with the yttrium–isopropoxide initiator ($M_w/M_n = 1.1$–1.2), these polymerizations proceeded with a high degree of alternation. Microstructural analysis by ^{13}C NMR spectroscopy of the PHAs obtained with the yttrium syndiospecific initiator (and, for comparison, of random copolymers obtained with a nonstereoselective β-diiminate–Zinc initiator[12]) were consistent with a degree of alternation between the two monomer units of 90–94%; that is, the level of sequential control was similar to that observed for the syndiospecific ROP of *rac*-β-valerolactone ($R^1 = R^2 = Et$) with this catalyst under the same conditions. Consistent with these results, kinetic measurements showed that both monomers were consumed at the same rate during the copolymerization; this rate was different from the homopolymerization rate of each enantiomerically pure monomer. As an indication of the markedly different properties anticipated for these new poly(3-hydroxybutyrate-*alt*-3-hydroxyalkanoate) copolymers, differential scanning calorimetry measurements revealed melting temperatures spanning a wide range ($T_m = 47$–$210\,°C$).

These results are of fundamental importance, as they establish a new viable approach to sequence control in ring-opening polymerization through exploitation of the well-established CEM in a different manner. This study also provided access to a set of thus far unknown highly alternating copolymers, the properties of which remain to be explored. Notably, these materials are based on formally different but inherently similar monomers (namely, 4-substituted β-propiolactones), in marked contrast with other main classes of alternating copolymers that rely on strongly electronically differentiated monomer combinations (e.g. CO, CO_2 versus epoxides, aziridines, alkenes).

Although the current findings by Thomas, Coates, and co-workers are highly interesting, they constitute only the first step in a series of potential investigations. One key question that needs to be addressed is the generality and scope of this synthetic strategy. With a focus on β-lactones, it will be important to investigate the kinetic requirements of the copolymerization: that is, how different the reactivity of the two different, configurationally opposite monomers can be if a high level of alternation is to be maintained. A further challenge will be the production of highly alternating copolymers from sets of inherently different enantiomerically pure monomers, for example, lactides and β-lactones.

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