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RESEARCH ARTICLE

Tacticity Control of Cyclic Poly(3-Thiobutyrate) Prepared by Ring-Opening Polymerization of Racemic β -Thiobutyrolactone

Hui Li, Jérôme Ollivier, Sophie M. Guillaume,* Jean-François Carpentier*

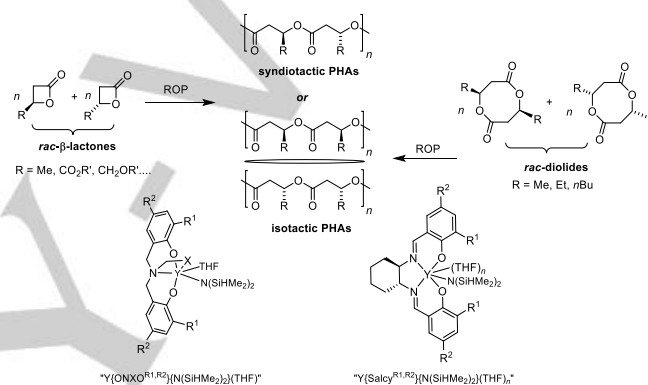
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Abstract: We report here on the ring-opening polymerization (ROP) of racemic β -thiobutyrolactone (*rac*-TBL), as the first chemical synthesis of poly(3-thiobutyrolactone) (P3TB), the thioester analogue of the ubiquitous poly(3-hydroxybutyrate) (P3HB). The ROP reactions proceed very fast (TOF > 12,000 h⁻¹ at r.t.) in the presence of various metal-based catalysts. Remarkably, catalyst systems based on non-chiral yttrium complexes stabilized by tetradentate amino alkoxy- or diamino-bis(phenolate) ligands {ONXO^{R1,R2}}²⁻ (X = O, N) provide access to cyclic P3TB with either high isoselectivity (*P_m* up to 0.90) or high syndiotactic bias (*P_r* up to 0.70). The stereoselectivity can be controlled by manipulation of the substituents on the ligand platform and adequate choice of the reaction solvent and temperature as well. The cyclic polymer topology is evidenced by MALDI-ToF MS, NMR and TGA. Highly isotactic cyclic P3TB is a semi-crystalline material as revealed by DSC.

Introduction

Poly(hydroxyalkanoate)s (PHAs) are a valuable class of polyesters, representing a possible alternative to more and more controversial petrochemical-based plastics.^[1] They feature different side-chain substituents along the backbone, of which both the chemical nature along with the overall architecture, especially the stereoregularity of the polymer chain, dictate / modulate the physical, thermo-mechanical, and biological properties of the resulting polymer materials. PHAs find a variety of packaging, agricultural, biomedical, and pharmaceutical applications, in particular thanks to their biocompatibility and degradability. Among the large variety of PHAs, poly(3-hydroxybutyrate) (P3HB) stands out. When prepared by fermentation of naturally occurring biomass-derived sugars (e.g., sucrose, glucose) with microorganisms, it is a purely (*R*)-isotactic, highly crystalline thermoplastic polyester that resembles to some extent to isotactic polypropylene.^[1a,e] Alternatively, P3HB can be prepared chemically by the ring-opening polymerization (ROP) of racemic β -butyrolactone or diolide, where the relief of ring-strain is the driving force for polymerization (Scheme 1). Key advantages of ROP include fine control of molar mass, dispersity, end-groups and, when relevant, of stereoselectivity.^[2] Yet, rather few catalysts/initiators enable the ROP of these β -lactones and diolides, and even less address stereoselectivity.^[2e]



Scheme 1. Chemical preparation of simple and functional poly(3-hydroxyalkanoate)s (PHAs) as syndiotactic or isotactic (as 1:1 mixture of enantiomeric chains) polyesters by ROP of racemic β -lactones or diolides with yttrium-based catalysts.^[4,9]

Our group reported that yttrium catalysts stabilized by nonchiral tetradentate amino alkoxy- or diamino-bis(phenolate) ligands {ONXO^{R1,R2}}²⁻ (X = O, N)^[3] provide access to highly syndiotactic P3HB with a probability for *racemic* enchainment (*P_r*) up to 0.96, provided that bulky aryl-containing R¹ substituents are installed at the *ortho* positions of the phenolate platform.^[4] Such stereoselective yttrium-based ROP catalysis has been extended to racemic functional or higher β -lactones,^[5,6] in particular to β -malolactonates (4-alkoxycarbonyl- β -propiolactones, MLA^R; R = allyl, benzyl),^[7] which are of high interest because of the readily tunable/transformable pendant carboxylate moieties. Surprisingly enough, for this latter class of β -lactones, only yttrium catalysts with an uncrowded *ortho*-substituted {ONXO^{R1,R2}}²⁻ ligand, e.g. R¹ = Me or Cl, allowed for highly syndiotactic polymerizations (*P_r* > 0.95). Catalysts with sterically crowded R¹ alkyl/aryl *ortho*-substituents on the {ONXO^{R1,R2}}²⁻ ancillary afforded only modest syndioselectivity. Such stereoselective ROP by yttrium complexes was extended to *rac*-4-alkoxymethylene- β -propiolactones (*rac*-BPL^{OR}s).^[8] Interestingly, the simple modification of the *ortho* R¹ substituents on the {ONXO^{R1,R2}}²⁻ platform of the yttrium catalyst induced a complete switch from syndioselective to isoselective polymerization of this specific class of *rac*-BPL^{OR}s: an yttrium complex bearing an *o,p*-dihalogeno (F, Cl, Br)-substituted ligand generated highly isotactic polyesters (probability for *meso* enchainment, *P_m* = 1 – *P_r* up to 0.95), while complexes with bulky *tert*-butyl and cumyl-

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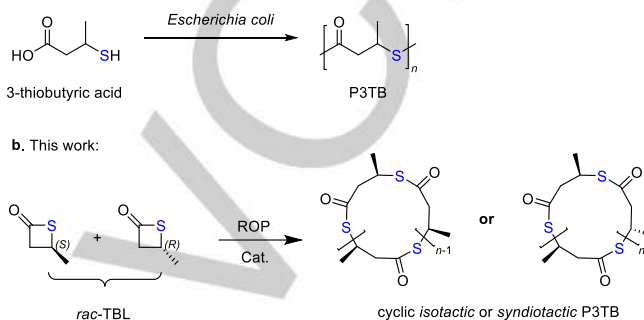
substituted R¹ ligands gave syndio-enriched PBPL^{OR}s ($P_r = 0.90$). DFT computations performed for the first elementary steps of the ROP of *rac*-BPL^{OR} suggested that the origin of the isoselectivity could be traced back to attractive C–H···X non-covalent interactions between hydrogen from the alkoxyethylene group in the last ring-opened monomer unit in the growing chain and the *ortho*-halogeno substituents of the ligand platform.^[5,8]

Chen's group recently developed the highly effective synthesis of P3HB by the stereoselective ROP of the bio-sourced racemic eight-membered diolide (*rac*-8DL^{Me}), the cyclic dimer of 3-hydroxybutyric acid. By using racemic yttrium catalysts supported by C₂-symmetric cyclohexyldiamino-based salen-type ligands, perfectly isotactic P3HB was recovered (Scheme 1).^[9] The methodology was successfully extended to the preparation of higher isotactic homoPHAs as well as crystalline isotactic PHA copolymers made of *rac*-8DL^{Me} and *rac*-8DL^R (R = Et, *n*Bu), that exhibit polyolefin-like thermal and mechanical properties.^[10]

It is also well-known that the introduction of sulfur atoms into the polymer backbone can impart polymers with special properties, significantly differentiated from those of regular hydrocarbon-based polymer analogues.^[11] Hence, polythioesters (PTEs), that is polyester counterparts with thioester linkages within the backbone, are of great interest due to their biocompatibility and degradability properties for biomedical applications, their high refractive index for optical applications, and their sorbent properties for wastewater treatment.^[12] PTEs remain, however, less explored than their corresponding polyesters. Poly(3-thiobutyrate) (P3TB)^(a) is the first bio-homopolymer with thioester linkages in the backbone that was isolated from a recombinant strain of *E. coli* cultured with thioalkanoic acids (Scheme 2).^[13] This fermentation approach generates P3TB with a high molar mass ($M_n = \text{ca. } 175 \text{ kg mol}^{-1}$) and moderately broad dispersity ($\mathcal{D}_M = 1.9$); yet, the composition, microstructure (presumed to be highly isotactic,^b *vide infra*) and thermo-mechanical performance of biosynthetic P3TB are difficult to adjust. On the other hand, there are a limited number of reports on the ROP conversion of thiolactones, and even less of β -thiolactones, to high molar mass PTEs. Notable examples of suitable monomers for chemical synthesis of PTEs via ROP include amino-functional β -thiolactones, thiocarboxyanhydrides, dithiolactones, δ - and ϵ -thiolactones (See Scheme S1 in the ESI).^[14,15,16] Early examples traced back to 1960s report the ROP of δ -thiovalerolactone and ϵ -thiocaprolactone with simple inorganic bases,^[14] and of (*S*)- α -*p*-toluenesulfonamido- β -propiolactone, initiated in the presence of water or benzyl thioalcohol, or even thermally without any initiator, to produce the corresponding optically active P3TEs.^[15] In 2016, Suzuki *et al.* reported the ROP of a cysteine-derived β -thiolactone mediated by *N*-Boc-*L*-cysteine methyl ester.^[16c] In these latter two examples, the produced P3TEs have relatively low molar mass and broad dispersity, which is at least in part attributable to the extensive transthioesterification side-reactions occurring during the polymerization. Noteworthy, thioester bonds are more reactive than their oxoester analogs and some PTEs can readily revert back to cyclic thioester monomers.^[16g] To alleviate transthioesterification and tune more favorably the

thermodynamics closer to equilibrium, Lu *et al.* recently modified the β -thiolactone structure by introducing a geminal dimethyl group on the four-membered ring (*N*^R-PenTL); interestingly, its ROP organocatalyzed by DBU returned poly(*N*^R-PenTL) with high molar mass but also improved the propensity of degradation back to the original monomer.^[16g] Hence, almost all of the examples of the ROP of thiolactones reported so far used organocatalysts (Scheme S1),^c and returned atactic PTEs, unless starting from enantiomerically pure monomers.

a. Biosynthesis: Steinbuechel *et al. Nat. Mater.* **2002**, *1*, 236-240 [13].



Scheme 2. a) Fermentation approach towards P3TB;^[13] b) ROP of racemic 3-thiobutyrolactone (*rac*-TBL) mediated by discrete catalysts (Scheme 3) towards stereoregular cyclic poly(3-thiobutyrolactone) (P3TB) reported in this study.

We herein report on the chemical synthesis of P3TB via ROP of *rac*-thiobutyrolactone (*rac*-TBL) promoted by metal-based catalysts (Scheme 2). The reactions are shown to proceed with very high rates under mild conditions and return PTEs with unprecedented microstructure and topology. The stereoselective ROP of *rac*-TBL is best achieved by discrete yttrium complexes, where the substituents installed on the phenolate rings induce the switch from iso-enriched to syndio-biased P3TBs. To our knowledge, this is the first highly stereoselective ROP of a *racemic* chiral β -thiolactone reported, and a rare case where fine tuning of a single family of discrete ROP catalysts allows accessing *both* isotactic and syndiotactic polymers from a single monomer.^[5,8,17] The resulting P3TBs were characterized by MALDI-ToF MS analysis, revealing, also quite unexpectedly, the formation of purely cyclic polymers.

Results and Discussion

The results of the preliminary screening of the ROP of *rac*-TBL (see ESI for the preparation of the monomer) with a variety of well-established metal-based catalysts / initiators (Scheme 3)^[2] are summarized in Table 1. As anticipated, a simple highly nucleophilic initiator such as NaOMe enables the ROP of *rac*-TBL at room temperature, but returns ill-defined P3TB (*vide infra*). Surprisingly, the zinc β -diketiminato complex (BDI)ZnO^{Pr} (**2a**), which is quite active for the polymerization of β -lactones and lactide, and the alternating copolymerization of carbon dioxide and epoxides,^[18] turned out inactive towards *rac*-TBL at room

^a This material is sometimes also referred to as poly(3-mercapto-butyrate) (P3MB) but, for the sake of consistency, the thio nomenclature is used throughout this manuscript.

^b The stereoregularity of P3TB prepared by fermentation is not explicitly documented in the literature; see reference [13]. Yet, it can be presumed to be

highly isotactic, as compared to other PHAs prepared by microorganisms, such as P3HB; see reference [1].

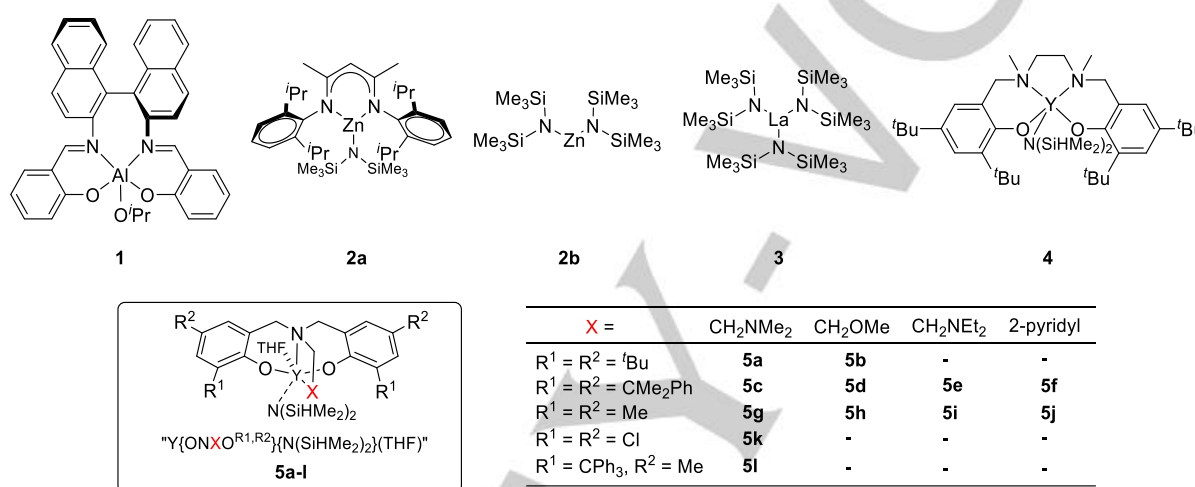
^c Chen *et al.* mentioned briefly the ROP of the bridged bicyclic thiolactone monomer BTL (see Scheme S1) mediated by the La[N(SiMe₃)₂]₃BnOH system, which provided a modest conversion and no stereocontrol; see reference [14d].

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temperature. Similarly, no activity was observed under the same conditions with $\text{Zn}[\text{N}(\text{SiMe}_3)_2]_2$ (**2b**) (alone or with 2 equiv. of BnOH as co-initiator), an established initiator for the isoselective ROP of cyclic *O*-carboxyanhydrides.^[19] The chiral aluminum complex (*R*)-(SalBinam)AlO^{*i*}Pr (**1**), another effective catalyst for the stereoselective ROP of *rac*(*meso*)-lactide via enantiomorphosite control,^[20] allowed full conversion of 25 equiv. of *rac*-TBL at room temperature. Yet, the recovered P3TB featured a M_n value as determined by SEC much higher than the theoretical one, suggesting a poor initiating efficiency and/or undesirable side-reactions. The lanthanum trisamide **3**, alone or in combination with an external co-initiator, proved also a quite active system at room temperature. However, inspection of the microstructure of the polymers formed from NaOMe, **1** or **3** by ^{13}C NMR (*vide infra*),

revealed the formation of atactic P3TBs (see the ESI, Figures S33, S54–S55).

As yttrium catalysts have shown excellent performances in a variety of (stereoselective) ROPs of cyclic esters,^[3–10] we next explored two different families of such achiral complexes. The amido yttrium-salan complex **4**, which produces – thanks to chain-end stereocontrol – highly alternating poly(3-hydroxyalkanoate) copolymers via ROP of equimolar mixtures of opposite enantiomers of different chiral β -lactones,^[21] features very high activity toward *rac*-TBL in toluene at ambient temperature: with or without a co-initiator (such as ^{*i*}PrOH), full conversion of 25–100 equiv. of the monomer proceeded within less than 1 min.^d However, the resulting polymers were again atactic, as assessed by ^{13}C NMR spectroscopy (see the ESI, Figures S33, S57).



Scheme 3. Chemical structure of the catalysts/initiators used for the ROP of *rac*-TBL in this study.

Table 1. Selected results for the preliminary screening of the ROP of *rac*-TBL.^a

Entry	Cat.	Init. ^b	[TBL] ₀ /[Cat.] /[Init.]	Solvent	Reaction time ^c (min)	TBL Conv. ^d (%)	$M_{n,theo}$ ^e (kg mol ⁻¹)	$M_{n,SEC}$ ^f (kg mol ⁻¹)	\bar{D}_M ^f	P_m ^g
1	-	NaOMe	23:0:1	C ₆ D ₆	60	>99	2.4	3.9	1.61	0.51
2	1	-	25:1:0	Toluene	72	>99	2.6	14.5	1.46	0.48
3	2a	^{<i>i</i>} PrOH	50:1:1	Toluene	120	0	-	-	-	-
4	2b	-	50:1:0	Toluene	180	0	-	-	-	-
5	2b	BnOH	50:1:2	Toluene	180	0	-	-	-	-
6	3	-	25:1:0	C ₆ D ₆	1	>99	2.6	5.2	1.53	0.50
7	3	BnSH	100:1:3	Toluene	6	>99	3.4	1.7	1.17	0.48
8	4	-	25:1:0	Toluene	1	>99	2.6	6.0	2.15	0.54
9	4	^{<i>i</i>} PrOH	100:1:1	Toluene	1	>99	10.3	46.5	1.45	0.52
10	5a	-	25:1:0	Toluene	5	>99	2.6	4.9	1.47	0.37
11	5a	-	50:1:0	Toluene	1	>99	5.1	3.7	1.48	0.32
12	5a	^{<i>i</i>} PrOH	50:1:1	Toluene	1	>99	5.1	3.8	1.42	0.34
13	5a	^{<i>i</i>} PrSH	50:1:1	Toluene	1	>99	5.1	3.9	1.66	0.32
14	5a	BnSH	50:1:1	Toluene	1	>99	5.1	3.5	1.65	0.32
15	5a	BnSH	100:1:1	Toluene	5	>99	10.3	6.1	1.59	0.31

^a Polymerization performed at ambient temperature (15–20 °C), [TBL]₀ = 0.5 M. ^b (co)Initiator. ^c Reaction times were not optimized. ^d Conversion of *rac*-TBL as determined by ¹H NMR analysis of the crude polymerization mixture. ^e Molar mass calculated according to $M_{n,theo} = [\text{TBL}]_0 / [\text{Cat.}]_0 \times \text{Conv.}_{TBL} \times M_{TBL}$. ^f Number-average molar mass ($M_{n,SEC}$) and dispersity (\bar{D}_M) determined by SEC analysis in THF at 30 °C vs. polystyrene standards (uncorrected values). ^g P_m is the probability of *meso* enchainment between TBL units as determined by $^{13}\text{C}\{^1\text{H}\}$ NMR analysis of the isolated P3TBs.

^d At this stage of our studies, because of the very fast reactions at room temperature with La and Y systems, detailed kinetics were not established.

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More promising results were obtained with the discrete yttrium amido complex **5a** supported by a diamino-bis(phenolate) ligand bearing sterically bulky *t*Bu substituents, that is a prototypical example among the family developed by our group since the early 2000s.^[3] The ROP of *rac*-TBL in toluene promoted by **5a**, with or without a protic co-initiator, proceeded also very rapidly at ambient temperature. Although no detailed kinetics could be determined under these conditions,^d the turnover frequencies (TOF) exceed 3,000 h⁻¹; these values are at least comparable, possibly higher than those obtained in the ROP of the parent β -lactone *rac*-BL under the same conditions.^[3,4] ¹³C NMR spectroscopy revealed that all P3TBs formed under these conditions are syndiotactic-enriched ($P_m = 0.31$ – 0.37), providing further opportunities in terms of stereocontrol improvement upon ligand tuning and optimization of the reaction conditions (*vide infra*). On the other hand, the experimental molar mass values determined by SEC, $M_{n,SEC}$, did not vary proportionally with the values calculated from the monomer-to-initiator ratio; also the dispersity values were somewhat high (\bar{D}_M , $M_w/M_n = 1.42$ – 1.66), and definitively higher than those typically observed ($\bar{D}_M = 1.05$ – 1.3) for P3HB obtained from ROP of *rac*-BL under similar conditions^[4] (*vide infra*).

The ¹H and ¹³C{¹H} NMR spectra of the P3TBs isolated from catalysts **1–5a** (Table 1) clearly displayed the characteristic signals corresponding to TBL repeat units (see the ESI, Figures S9–S10 and S17–S18). However, whether **5a** was used alone^e or in the presence of a co-initiator such as ¹PrOH, ¹PrSH, or BnSH, no chain-end groups were detected in the NMR spectra of the polymers. Similar observations were made in the NMR spectra of

P3TBs prepared with the aluminum complex **1**, the trisamido lanthanum precursor **3**/BnOH (1:3) system and the yttrium-salan complex **4**. Only for the P3TB prepared from NaOMe (entry 1) was the methoxycarbonyl end-group unambiguously observed by ¹H and ¹³C NMR spectroscopy (see the ESI, Figures S17–S18). For this latter polymer, the molar mass estimated by NMR ($M_{n,NMR} = \text{ca. } 3900 \text{ g mol}^{-1}$) was higher than the theoretical one ($M_{n,theo} = \text{ca. } 2400 \text{ g mol}^{-1}$), indicating a poor initiation efficiency and/or unselective formation of linear and cyclic macromolecules under these conditions.

To get a better insight, the topology of the isolated polymers was further investigated by matrix-assisted laser desorption / ionization time-of-flight mass spectrometry (MALDI-ToF MS). In line with the abovementioned NMR data, analysis of P3TB samples prepared from NaOMe evidenced the formation of mixtures of linear MeO-[C₄H₆OS]_n-H and cyclic [C₄H₆OS]_n macromolecules; these experiments were hardly reproducible as little changes in the reactions conditions returned variable amounts of linear and cyclic structures, as assessed by MS (see the ESI; Figures S19–S21). Conversely, P3TBs resulting from the ROP of *rac*-TBL promoted by discrete complexes **1**, **4** or **5a** revealed a single population of cyclic macromolecules,^f i.e. without chain-end groups. For the latter complex, regardless of the use of a co-initiator (¹PrOH, ¹PrSH, or BnSH, 1 equiv. vs. Y) or not, and no matter the ROP solvent (toluene or THF), the observed *m/z* values match the data calculated for [C₄H₆OS]_n macromolecules (Figure 1 and Figures S11–S16). Another indirect support of the formation of cyclic (vs. linear) polymers arises from thermal studies (*vide infra*).

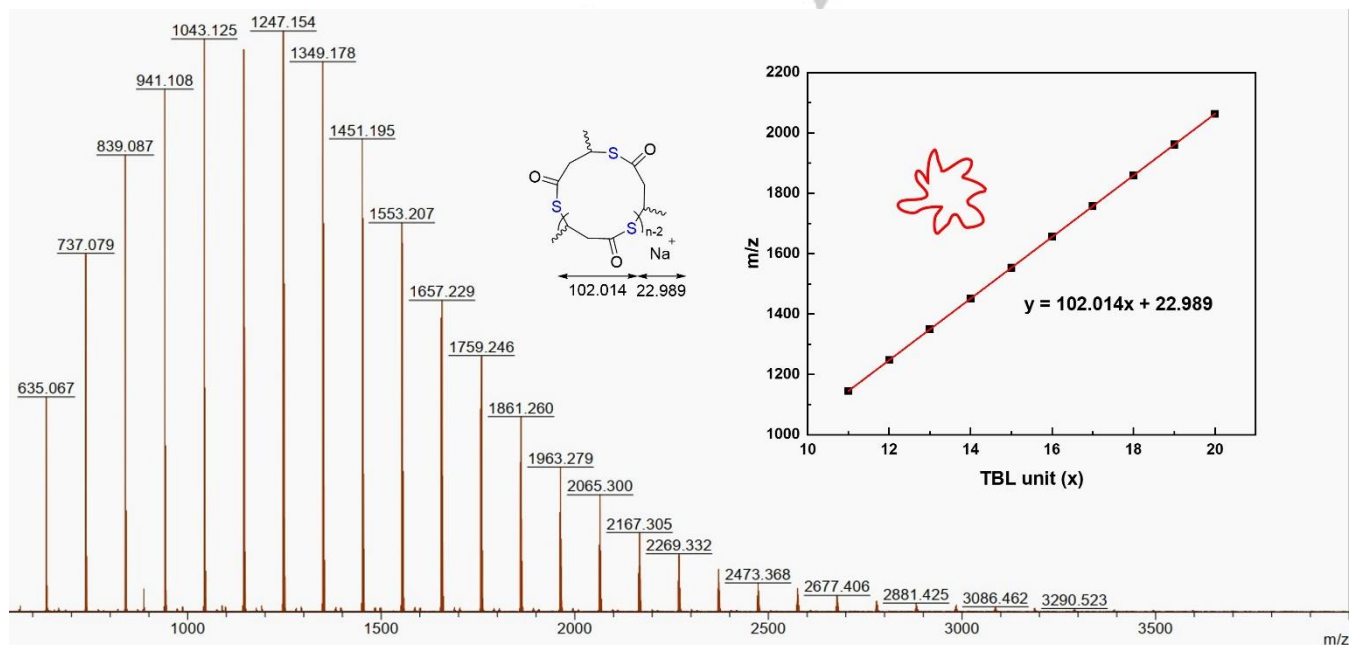
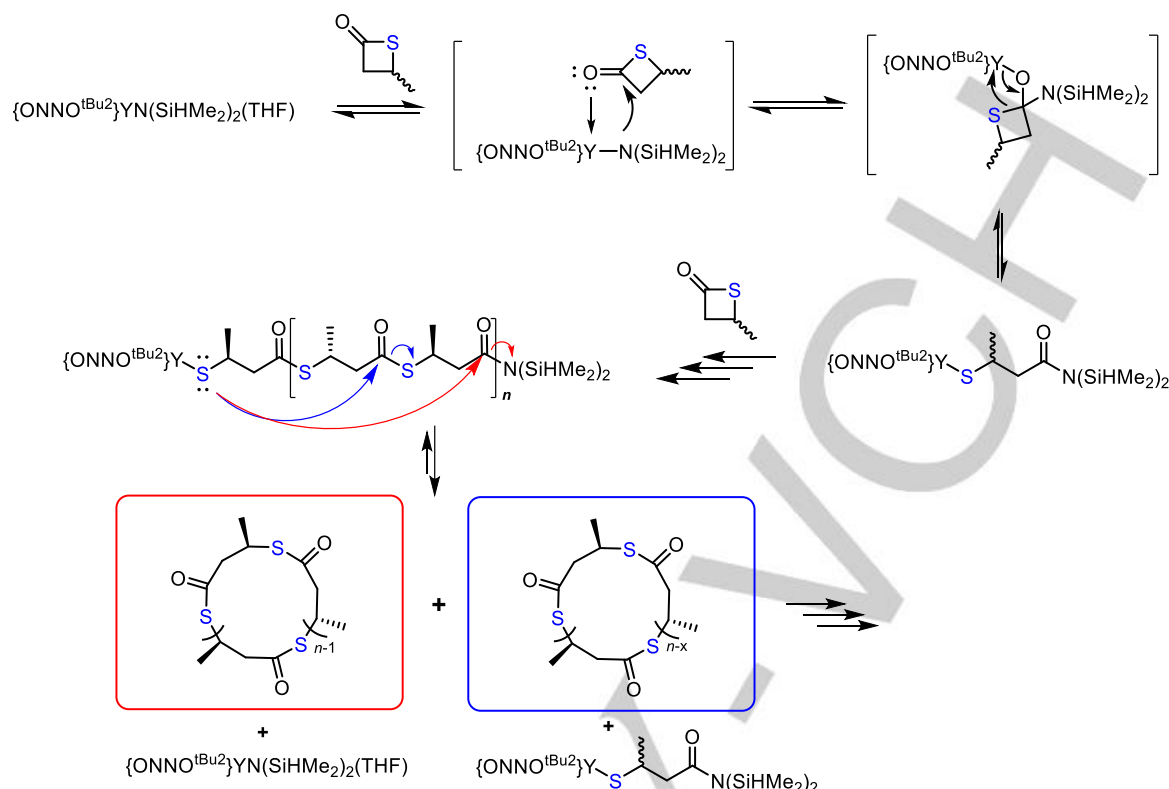


Figure 1. MALDI-ToF mass spectrum of a cyclic P3TB produced by Y{ONNO^tBu₂}N(SiHMe₂)₂(THF) (**5a**) in toluene in the absence of co-initiator (Table 1, entry 10), with a plot of experimental *m/z* values vs. theoretical number of TBL repeat units.

^e Note that the -C(=O)N(SiHMe₂)₂ terminal group is usually not observed in polymers (PLA, P3HB...) prepared from ROP with a M-N(SiHMe₂)₂ initiator, as this functional group is sensitive to hydrolytic workup and readily converts into -C(=O)NH₂ (See: H. Ma, J. Okuda, *Macromolecules* **2005**, *38*, 2665-2673).

^f No MALDI-ToF mass spectra could be obtained for P3TB prepared with the lanthanum trisamide **3**; the corresponding ESI mass spectra were complicated, showing several populations of macromolecules, but no cyclic population was observed.

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Scheme 4. Proposed mechanism for the ROP of *rac*-TBL promoted by **5a** with initiation, propagation, back-biting and ring-expansion steps.

Cyclic polymers are a unique class of macromolecules with specific properties, e.g., higher density, higher glass transition temperature and melting point, lower intrinsic viscosity, increased crystallization rate, and higher refractive index than their linear counterparts.^[22] Cyclic P3HB has been prepared by ROP of BL with lipase,^[23] organic spirocyclic initiators,^[24] or amido-oxazolinane zinc complexes;^[25] note that in the latter case, in the presence of a mono- or bifunctional co-initiator (e.g., EtOH, 1,4-cyclohexanediol), the same zinc catalysts promote the formation of linear P3HBs. Other studies have noted that the co-initiator in metal-catalyzed ROP may have a significant effect on the topology of the resulting polymer.⁹ Hence, Chen *et al.* reported the ROP of γ -butyrolactone using $\text{La}[\text{N}(\text{SiMe}_3)_2]_3$; in the absence of a co-initiator, controlled cyclic topology was then achieved, but upon addition of 1, 2 or 3 equiv. of *BnOH* or *^tPrOH* vs. *La*, the resulting polymer structure shifted from a predominantly cyclic one to a mixture of cyclic and linear structures, to a mostly linear structure, respectively.^[26] The authors proposed that the formation of the cyclic polyester results from back-biting, and that this pathway is favored within chains initiated by $-\text{N}(\text{SiMe}_3)_2$, a better leaving group.

We assume that, similarly to this state of the art,^[24,25] back-biting process occurs during the ROP of *rac*-TBL promoted by the present metal-catalysts. However, in our ROPs, the co-initiator / initiating group does not play such a decisive role in determining the topology of the resultant polymers. Indeed, catalyst systems herein generated *in situ* – upon addition of 1 equiv. of *^tPrOH*, *^tPrSH* or *BnSH* onto **4** or **5a** (see the Experimental section) – revealed as the real yttrium-alkoxy or -thioalkoxy initiating species,

respectively, towards the formation of cyclic P3TB (Table 1, entries 8–15; ESI, Figures S11–S16). In fact, the intrinsically labile thioester bonds make transthioesterification a facile process (*vide supra*),^[14e,h,27] much easier than transesterification,^[2] and make back-biting possible at any electrophilic site within the P3TB chain. A simple representation of the typical coordination-insertion putative mechanism at play in the ROP of cyclic (thio)esters for initiation and propagation steps, as well as dynamic processes that lead to the formation of cyclic P3TB and ring-expansion, are depicted in Scheme 4. Obviously, to account for the formation of high molar mass P3TB, this model implies a propagation rate significantly faster than the cyclization rate.^[22b] Note that an increase in the monomer-to-catalyst ratio leads to the formation of cyclic P3TBs with a corresponding increase of their molecular weights (as illustrated with 150 up to 400 equiv. vs. **5c**/*^tPrOH*; see entries 21–23, Table 2, below).

Another indication of easy transthioesterification is provided by the narrowing of dispersity values of P3TBs upon running the ROP of *rac*-TBL at low temperatures (typically $D_M = M_w/M_n = 1.3$ – 1.7 at r.t. vs. 1.15 – 1.35 at $T \leq -70$ °C; see below, Table 2). Similar observations have been made in the polymerization of lactones with highly reactive metal-alkoxide catalyst systems.^[2,18b]

The tacticity in the various isolated P3TBs can be appreciated by ^{13}C NMR spectroscopy, especially from the carbonyl and methyl regions; at 100–125 MHz, the methine and methylene regions do not display resolved resonances (Figure 2). The carbonyl region of regular P3TBs $^{13}\text{C}\{^1\text{H}\}$ NMR spectra (δ ca. 195.8 ppm) essentially features two broad, yet well-resolved

⁹ The ROP of *O*-carboxyanhydride with $\text{La}[\text{N}(\text{SiMe}_3)_2]_3$ as catalyst in the absence of co-initiator gave a cyclic polymer, while the use of $\text{Zn}[\text{N}(\text{SiMe}_3)_2]_2$

in the presence of *BnOH* favored the formation of a linear polymer; see: reference [19].

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resonances,^{h,[28]} the most downfield of which was assigned to a *meso* (*m*, isotactic) dyad and the most upfield one to the *racemo* (*r*, syndiotactic) dyad. These assignments were based on those made for the carbonyl region of P3HB.^[4a,29] The methyl region of regular ¹³C{¹H} NMR spectra (δ ca. 20.3–20.5 ppm) is better resolved and shows four resonances corresponding to triads; they actually form two (essentially non-overlapping) groups of two (partly overlapping) resonances, which are assigned, from high-to-low field, to the four triads *mm*, *rm*, *mr* and *rr*, respectively. A similar triads distribution was also observed in the methine region (δ ca. 68.4–68.8 ppm) of the parent PMLA^Rs.^[7a] Careful deconvolution of these four resonances allows extracting P_m (and $P_r = 1 - P_m$) values in good agreement with those determined from the carbonyl resonances, hence validating their assignment (see the ESI). Definitive confirmation of these assignments was gained from the ¹³C NMR spectrum of a pure isotactic P3TB (Figure 2, top), independently prepared from the ROP of enantiopure (*S*)-TBL (see the ESI).

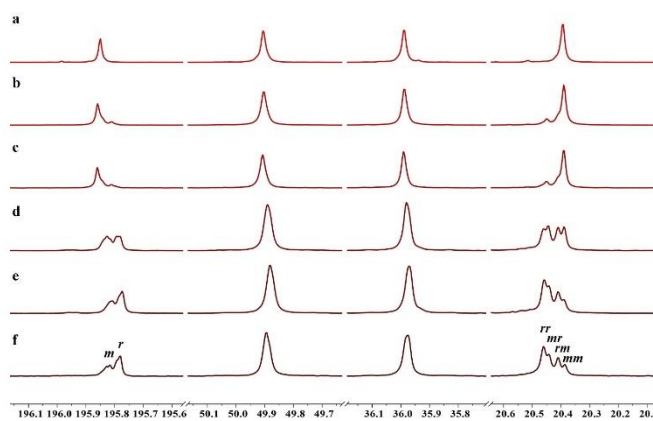


Figure 2. Carbonyl, methine, methylene and methyl regions of the ¹³C{¹H} NMR spectra (125 MHz, CDCl₃, 25 °C) of: a) a highly isotactic cyclic P3TB ($P_m > 0.95$, $M_n = 3.2$ kg mol⁻¹, $D_M = 1.52$) prepared from the ROP of enantiopure (*S*)-TBL (with the **5a**/PrOH (1:1) system); and isotactic-, syndiotactic-enriched cyclic P3TBs prepared from the ROP of *rac*-TBL mediated by: b) complex **5k** ([TBL]₀/[**5**]/[init.] = 50:1:0, -80 °C, THF, $P_m = 0.90$, Table 2, entry 48); c) complex **5g** (50:1:0, -80 °C, THF, $P_m = 0.89$, Table 2, entry 34); d) system **5d**/PrOH (100:1:1, 18 °C, toluene, $P_m = 0.52$, Table 2, entry 26); e) system **5a**/PrOH (50:1:1, 18 °C, toluene, $P_m = 0.34$, Table 1, entry 12); f) system **5c**/PrOH (100:1:1, -50 °C, toluene, $P_m = 0.30$, Table 2, entry 24).

Following the preliminary study of the ROP of *rac*-TBL promoted by catalyst **5a** (Table 1), the impact of the catalyst structure on the tacticity of P3TBs was further investigated with a set of ligands **a–I** well established for the stereoselective ROP of lactide and functional β -lactones (Scheme 3). Representative results are summarized in Table 2 and complementary data are provided in Tables S1 and S2. The different yttrium catalyst systems based on **5a–I** are quite active for the ROP of *rac*-TBL (TOF in the range 2,400–12,000 h⁻¹ at r.t.),^d thus allowing near quantitative conversion of 25–400 equiv. of *rac*-TBL within 6 min at ambient temperature. As mentioned above, the use of a co-initiator such as ⁱPrOH, ⁱPrSH or BnSH basically does not affect

the stereoselectivity of the polymerizations; only the nature of the ligand's substituents, of course of the reaction temperature, and, in some of cases, of the solvent, drive the tacticity of the produced P3TB.

As expected from previous works on the ROP of *rac*-BL and related functional β -lactones,^[4,5,7,8] catalyst systems based on complexes **5a** and **5c** with bulky R¹ substituents (^tBu or cumyl groups) installed on the *ortho*-positions of the phenolate rings generated syndiotactic-biased P3TBs ($P_m \approx 0.32$ –0.38) from the ROP of *rac*-TBL performed at ambient temperature in toluene. Decreasing the temperature down to -70 °C did not improve the syndioselectivity. Surprisingly enough, installation of a very bulky R¹ trityl substituent such as in **5l** reversed the trend, as the resulting P3TB produced in toluene at ambient temperature featured an isotactic bias ($P_m = 0.58$, entry 49); the isoselectivity of this latter system improved significantly upon lowering the temperature down to -80 °C ($P_m = 0.83$, entry 50). On the other hand, significant differences were observed depending on the nature of the X donor group in the “capping” moiety of the {ONXO^{R1,R2}}₂- ligand (X = CH₂OMe, CH₂NMe₂, CH₂NEt₂, 2-pyridyl). This pendant group X in the side arm of the ligand may affect the catalyst's electronics and/or sterics, and thus the catalytic activity and stereoselectivity in ROP reactions.^[3,6,30] In the ROP of *rac*-TBL, changing the side arm donor from β -NMe₂ in **5a** or **5c** to β -OMe as in **5b** or **5d**, respectively, reduced drastically the catalyst syndioselectivity and returned atactic P3TBs ($P_m = 0.38$, 0.32 vs. 0.48, 0.52, entries 17, 20 vs. 19 and 26, respectively). The β -NEt₂ system **5e** performed similarly to the β -NMe₂ system **5b**, in contrast to the pyridyl one (**5f**) which also produced atactic P3TB under these same conditions (entries 27, 19, 28).

Also unexpected and unprecedented to our knowledge, yttrium complexes bearing non-bulky substituents, namely the *o,p*-dimethyl-substituted systems **5g–5j** gave *isotactic*-enriched P3TBs. At ambient temperature in toluene or THF, these catalysts are highly active for the ROP of *rac*-TBL, however with only a mild preference for isoselectivity ($P_m = 0.54$ –0.58). Upon lowering the polymerization temperature down to -70 or -80 °C, isotacticity raised in toluene ($P_m = 0.73$, entry 30), and improved even more significantly in THF (P_m up to 0.89; entry 34). Also, the X capping moiety affected the performance in this series of *o,p*-dimethyl-substituted catalysts and the best isotacticity was again observed with the NMe₂-capped complex **5g**. The *o,p*-dichloro-substituted analogue **5k** had the same behavior as its dimethyl-substituted analogue **5g** (P_m up to 0.90 in THF at -80 °C; entry 48); this suggests that, in the ROP of *rac*-TBL, methyl and chloro substituents apparently behave similarly to a non-bulky group (and without electronic contribution for Cl^[8]); this is reminiscent of the ROP of *rac*- β -malolactonates,^[7] which yet offered syndiotactic PMLA^Rs in contrast to the present isotactic P3TBs. The high activity of the *o,p*-dichloro-substituted system **5k**, even at low temperature (TOF > 3,000 h⁻¹ at r.t. and 88 h⁻¹ at -50 °C), is also noteworthy, as it contrasts strikingly with the ROP of *rac*-BL where only alkyl/aryl-substituted complexes are highly active, while {ONOO^{Cl2}}₂Y catalysts proved poorly active (TOF = 12 h⁻¹ at r.t.).^[4c] This further testifies of the high intrinsic reactivity of TBL and its singular behavior as compared to parent β -lactones.

^h In some of the regular ¹³C{¹H} NMR spectra, four resonances can be identified in the carbonyl region; yet, they cannot be deconvoluted confidently. On the other hand, ¹³C projections of 2D band-selective HMBC and HSQC experiments allows a better resolution of this carbonyl region, hence featuring the corresponding four triads *mm*, *rm*, *mr* and *rr*. Deconvolution and analysis

of these four resonances returned P_m/P_r values fully consistent with those determined from the two *m* and *r* dyads of regular ¹³C{¹H} NMR spectra and also from the triads in the methyl region. See the ESI, Figures S37–S40 and Tables S4–S5; see reference [28].

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Table 2. Stereoselective ROP of *rac*-TBL mediated by yttrium complexes **5a-k**.

Entry	Cat.	[TBL] ₀ /[Cat.] /[Init] ^a	Reaction temp. (°C)	Solvent	[TBL] ₀ (mol/L)	Reaction time (min) ^b	TBL Conv.(%) ^c	<i>M_{n,theo}</i> (kg/mol) ^d	<i>M_{n,SEC}</i> (kg/mol) ^d	<i>D_M</i> ^e	<i>P_m</i> ^f
16	5a	50:1:1	18	Toluene	0.5	1	>99	5.1	3.8	1.42	0.34
17	5a	100:1:1	18	Toluene	0.65	6	>99	10.2	18.7	1.43	0.38
18	5a	100:1:1	-70	Toluene	0.5	16	>99	10.2	46.5	1.14	0.42
19	5b	100:1:1	18	Toluene	1.0	1	>99	10.2	7.6	1.39	0.48
20	5c	100:1:0	18	Toluene	1.0	1	>99	10.2	42.7	1.68	0.32
21	5c	150:1:1	18	Toluene	1.0	2	>99	15.4	25.0	1.58	0.35
22	5c	200:1:1	18	Toluene	1.0	1	>99	20.4	30.2	1.59	0.35
23	5c	400:1:1	18	Toluene	1.0	2	>99	40.8	59.2	1.68	0.34
24	5c	100:1:1	-50	Toluene	0.5	15	98	10.0	31.9	1.50	0.30
25	5c	100:1:1	-70	Toluene	0.5	30	50	5.1	21.9	1.37	0.32
26	5d	100:1:1	18	Toluene	0.65	5	>99	10.2	7.2	1.42	0.52
27	5e	50:1:1	18	Toluene	0.5	1	>99	5.1	21.4	1.31	0.41
28	5f	50:1:1	18	Toluene	0.5	2	>99	5.1	13.3	1.67	0.52
29	5g	75:1:1	18	Toluene	0.5	2	>99	7.6	6.8	1.42	0.58
30	5g	100:1:1	-70	Toluene	0.5	2	69	7.2	24.3	1.22	0.73
31	5g	50:1:0	18	THF	0.5	1	>99	5.1	4.9	1.80	0.53
32	5g	50:1:0	-50	THF	0.5	40	>99	5.1	43.4	1.62	0.63
33	5g	100:1:0	-70	THF	0.5	11	50	5.1	23.0	1.28	0.87
34	5g	50:1:0	-80	THF	0.5	45	83	4.2	21.4	1.22	0.89
35	5h	100:1:1	18	Toluene	1.0	5	>99	10.2	2.5	1.24	0.54
36	5h	100:1:1	18	Toluene	1.0	5	>99	10.2	32.5	1.59	0.57
37	5h	50:1:1	18	THF	0.5	1	>99	5.1	3.2	1.28	0.55
38	5h	50:1:1	-20	THF	0.5	60	>99	5.1	4.2	1.48	0.65
39	5h	50:1:1	-50	THF	0.5	450	26	1.3	n.d.	n.d.	0.73
40	5i	100:1:1	18	Toluene	1.0	1	41	4.1	1.9	1.21	0.54
41	5i	50:1:0	18	THF	0.5	1	>99	5.1	4.8	1.61	0.58
42	5i	50:1:0	-80	THF	0.5	95	>99	5.1	5.9	1.79	0.69
43	5j	50:1:0	18	THF	0.5	1	>99	5.1	4.5	1.42	0.58
44	5j	50:1:0	-50	THF	0.5	60	>99	5.1	5.9	1.65	0.75
45	5k	50:1:0	18	Toluene	0.5	1	>99	5.1	4.2	1.48	0.55
46	5k	50:1:0	18	THF	0.5	1	>99	5.1	4.8	1.53	0.57
47	5k	50:1:0	-50	THF	0.5	34	>99	5.1	5.2	1.37	0.72
48	5k	50:1:0	-80	THF	0.5	45	76	3.9	25.0	1.28	0.90
49	5l	50:1:1	18	Toluene	1.0	1	88	9.0	18.2	1.83	0.58
50	5l	50:1:1	-80	Toluene	0.5	30	90	4.6	5.1	1.21	0.83
51	5l	50:1:0	-80	THF	0.5	40	29	1.5	6.3	1.33	0.63

^a Init. = co-initiator = ^tPrOH. ^b The reaction times were not necessarily optimized. ^c Conversion of *rac*-TBL as determined by ¹H NMR analysis of the crude polymerization mixture (refer to the ESI). ^d Molar mass calculated according to $M_{n,theo} = [TBL]_0/[Cat.]_0 \times Conv_{TBL} \times M_{TBL}$. ^e Number-average molar mass (*M_{n,SEC}*) and dispersity (*D_M*) as determined by SEC analysis in THF at 30 °C vs. polystyrene standards (uncorrected values). ^f *P_m* is the probability of *meso* enchainment between TBL units as determined by ¹³C{¹H} NMR analysis of the isolated P3TBs.

The aforementioned positive influence of THF on the isoselective ROP of *rac*-TBL mediated by **5g** and **5k** prompted us to explore in a more systematic manner the influence of the solvent. A variety of solvents (*n*-hexane, 1,4-dioxane, toluene, 2-MeTHF, THF, dichloromethane, acetonitrile) was investigated using both the isoselective catalyst **5k** (Table S1) and the syndioselective catalyst **5c** (Table S2). Yet, at ambient temperature, no significant difference and further possible improvements were noted. Only THF seemed to have a differentiated behavior, making non-stereoselective the catalyst **5c** that is otherwise syndioselective in other solvents. We speculate this may be due to THF coordination (in contrast to the more sterically crowded 2-MeTHF) onto the active site of the propagating species.

Analysis of the triad stereosequence distribution in both syndio- and iso-enriched P3TBs evidenced that it agrees well with Bernoullian statistics for a chain-end stereocontrol.^[31] In fact, the Bernoulli model triad test, $B = [(mm) \times (rr)]/[(rm) \times (mr)]$, returned values very close to 1, usually in the range 0.8–1.35 (see the ESI; Tables S4–S6), which falls within an acceptable range due to errors in deconvoluting the four respective triad peaks.^[31] This indicates that, in agreement with the achiral nature of these yttrium catalysts, the stereocontrol in this *rac*-TBL ROP process is a consequence of either (1) interactions between the last two TBL units in the P3TB chain (penultimate control) or (2) interactions between the last TBL unit in the chain and the incoming monomer (ultimate control).

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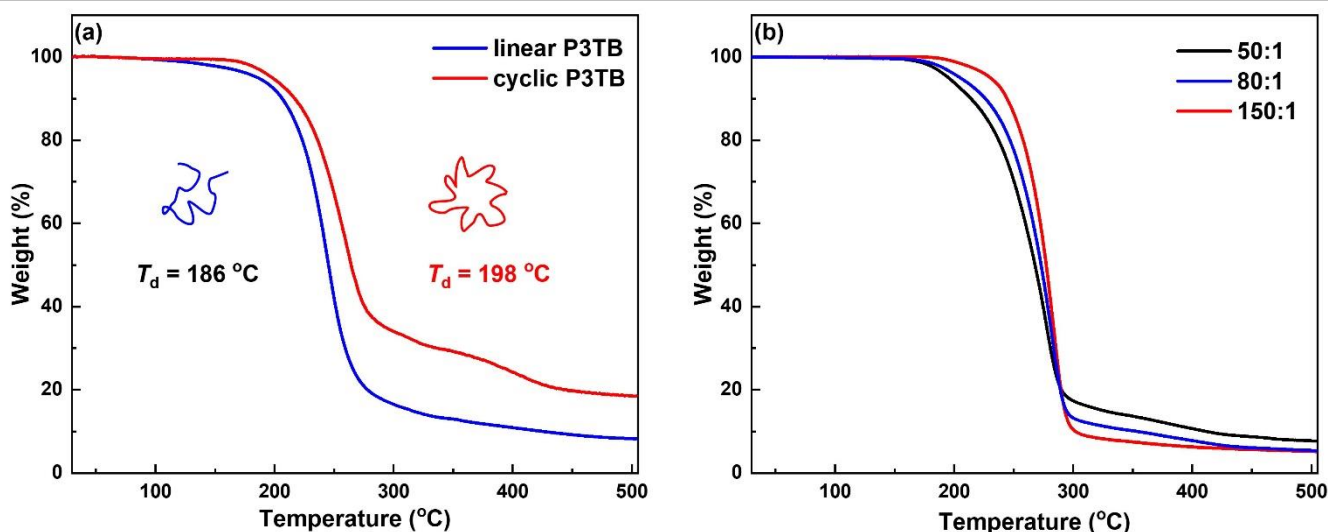


Figure 3. (a, left) TGA thermograms of P3TBs with different topologies: an essentially linear P3TB produced from NaOMe (blue line, $M_{n,SEC} = 3.9 \text{ kg mol}^{-1}$, $P_m = 0.50$, Table 1, entry 1) and a cyclic P3TB produced from complex **5a** (red line, $M_{n,SEC} = 4.9 \text{ kg mol}^{-1}$, $P_m = 0.37$, Table 1, entry 10). (b, right) TGA thermograms of cyclic P3TBs produced from complex **5a** or **5c** in toluene at room temperature as a function of the monomer-to-initiator ratio: $T_d = 195 \text{ °C}$ ([TBL]₀/[**5a**] = 50:1, $M_{n,SEC} = 3.8 \text{ kg mol}^{-1}$, $P_m = 0.34$; Table 1, entry 12), 205 °C ([TBL]₀/[**5a**] = 80:1, $M_{n,SEC} = 7.8 \text{ kg mol}^{-1}$, $\bar{D} = 1.65$, $P_m = 0.34$), 230 °C ([TBL]₀/[**5c**]/[PrOH] = 150:1:1, $M_{n,SEC} = 25.0 \text{ kg mol}^{-1}$, $P_m = 0.35$; Table 2, entry 21). Heating rate = 10 °C min^{-1} in both cases.

Preliminary studies were conducted to determine the thermal behavior of P3TBs by thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC). Typical TGA curves of P3TB samples are shown in Figures 3 and S70–S73. A cyclic atactic P3TB produced by complex **5a** features a degradation temperature (T_d , defined as the temperature for 5% weight loss) of ca. 198 °C , that is 12 °C higher than the corresponding value for a linear (as assessed by MS; see Figure S19) atactic P3TB produced with NaOMe system with a comparable molar mass (Figure S17). Also, the degradation extent at higher temperature is significantly more pronounced on the linear than on the cyclic polymer (e.g., at 300 °C , 83.5% vs. 66% weight loss, respectively). This higher thermal stability of cyclic P3TB can be accounted for by the extra energy needed to cleave cyclic polymers as compared to linear ones, as reported recently for other polyesters.^[22a,c,26] A noticeable enhancement of the degradation temperature of cyclic P3TBs from $T_d = 195$ to 230 °C was observed when the monomer-to-initiator ratio increased from 50:1 to 150:1, thus presumably with a P3TB of higher molar mass (Figure 3). On the other hand, the stereochemistry of cyclic P3TBs with similar molar mass, with P_m varying in the range 0.35–0.90, had a little influence on the thermal stability (Figure S73). This is in line with the weak tacticity effect noted on the thermal stability of syndio- and isotactic (linear) polystyrenes,^[32] but contrasts with previous studies on hetero-, syndio- and isotactic (linear) PLAs where T_d (5%) values spanned over a rather broad range (258 – 323 °C).^[33]

The DSC curve of a cyclic isotactic P3TB sample ($M_n = 25.0 \text{ kg mol}^{-1}$, $P_m = 0.90$) features a glass-transition temperature (T_g) of 4 °C (Figure 4); in addition, a single exothermic transition with a crystallization temperature (T_c) of 95 °C and a single endothermic transition with a melting-transition temperature (T_m) of 101 °C are observed. The latter T_m value is very close to that determined for pure isotactic P3TB ($T_m = 102 \text{ °C}$) prepared by ROP of enantiopure (S)-TBL and also to that reported for P3TB

prepared with *E. coli* ($T_m = 100 \text{ °C}$),^[13] indirectly corroborating that the latter material is indeed also highly (purely) isotactic. The semi-crystalline isotactic P3TB produced by ROP of *rac*-TBL has a notably lower T_m than isotactic P3HB (T_m ca. 170 °C)^[9a], highlighting that the introduction of the sulfur atom into the backbone of P3HB greatly impacts chain folding and packing into the crystal lattice.^[26,34] P3TBs with lower isotacticity ($P_m < 0.73$), as well as atactic and syndiotactic (P_r up to 0.70) ones, do not feature semi-crystallinity, as revealed by DSC. On the other hand, the stereoregularity of cyclic P3TB has a negligible influence on their T_g values (see the ESI, Figure S74–S77).

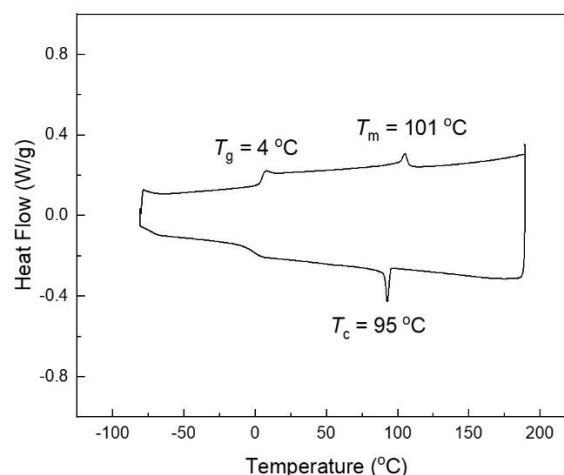


Figure 4. DSC curve of a highly isotactic cyclic P3TB produced from complex **5k** in toluene at room temperature ($P_m = 0.90$, Table 2, entry 48) (2nd heating cycle; heating rate = 10 °C min^{-1} , cooling rate = 10 °C min^{-1}).

Conclusion

In summary, we have reported herein an efficient chemical synthesis of P3TB via ring-opening polymerization; the reactions proceed fast and with complete conversion of the TBL monomer

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into the corresponding polythioester. With the most effective yttrium-based catalysts, cyclic polymers are formed, most likely as a result of easy transthioesterification. Interestingly, using a *single family of achiral catalysts*, upon simple tuning of the substituents on the bis(phenolato) platform, the stereoselectivity of the ROP of *rac*-TBL can be switched from highly isoselective to syndioselective. To our knowledge, this is quite a rare feature in ROP catalysis and observed previously only for *rac*-lactide with aluminum complexes supported by tetradentate aminophenoxide ligands^[17] and for *rac*-BPL^{CH₂OR} (R = Me, allyl, benzyl) monomers with the same yttrium complexes as those used in this study.^[5,8] However, the mechanisms at work for the stereocontrol are obviously not the same within the two classes of monomers: for TBL, a simple “uncrowded” dimethyl-substituted catalyst affords highly isotactic P3TB, while for BPL^{CH₂OR} only a catalyst with a dichloro-substituted ligand platform enabled reaching isotactic polymers, thanks to attractive Cl[⋯]H non-covalent interactions in the alkoxymethylene group in the last ring-opened monomer unit of the growing polymer chain.^[5,8] Also noteworthy and quite distinctive from previous works is the possibility to access isotactic P3TB with the bulky trityl-*ortho*-substituted catalyst, which evidences how subtle the stereocontrol is. At this stage of our studies, we cannot elaborate more confidently on the origin of this stereocontrol; neither can we state on the exact nature of isotactic P3TB: it may be a racemic mixture of two isotactic homopolymers, a stereoblock copolymer, or a tapered blocked copolymer. Kinetic studies as well as preparation of model compounds are underway to decipher mechanistic considerations. We anticipate that this stereoselective ROP of the simplest, prototypical four-membered racemic-β-thiolactone may open up opportunities for the development of new valuable polymer materials.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: β-thiolactone • ring-opening polymerization • yttrium • polythioester • stereoselective catalysis • cyclic polymer

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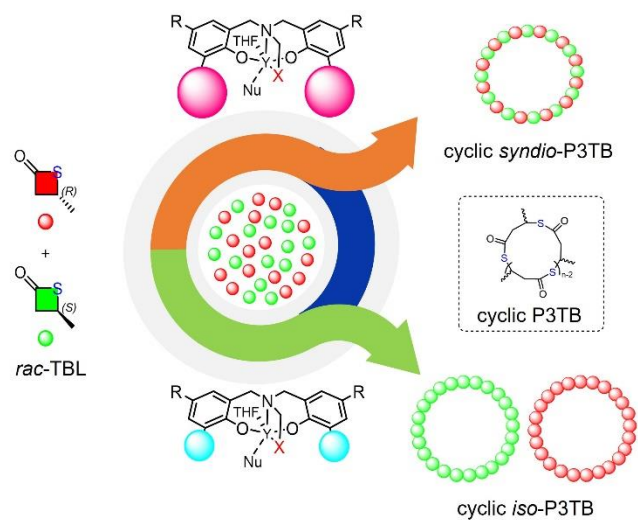
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Isotactic or syndiotactic cyclic poly(3-thiobutyrolactone) (P3TB) was obtained from ring-opening polymerization of racemic β -thiobutyrolactone (*rac*-TBL) promoted by achiral yttrium catalysts. The tacticity of cyclic polythioesters can be readily switched upon tuning the bulkiness of the substituents on the catalyst ligand.

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