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Cyclodextrin-Centered Polyesters: Controlled Ring-Opening Polymerization of Cyclic Esters from β-Cyclodextrin-Diol

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Supporting Information

INTRODUCTION

Cyclodextrins (CDs) are currently being widely used in pharmaceuticals, cosmetics and food industries.[1] In particular, CD host−guest inclusion complexes may be applied as drug-carrier systems via oral, parenteral, or other administration routes, providing solubility to lipophilic drugs thereby enhancing their bioavailability and/or reducing adverse effects. CD-polymers find further applications as gels or DNA transfection vectors.[2] Aliphatic polyesters, including polycarbonates and polyhydroxyalkanoates form biocompatible, bio- and hydrolytically degradable (co)polymers that exhibit good thermo-mechanical properties. These (co)polymers are highly valuable as various biomaterials including controlled/sustained release drug-delivery systems and tissue engineering devices.[3] The conjugation of CDs to polyesters thus appears highly promising in the biomedical/pharmaceutical sciences.

Among the different types of CD-polymers reported, one can distinguish between those including linear polymers either end-capped by CD unit(s),[4] or incorporating CDs into their backbone,[5] with pending CDs,[6] forming inclusion complexes with CD,[7] centered on CD,[8] or leading to self-assembled supramolecular architectures.[9] Most of the reported work on CD-polyesters is dealing with polylactides, polylactones (ε-caprolactone, δ-valerolactone) and poly(ethylene glycol), the former two types of polymers being commonly prepared upon ring-opening polymerization (ROP) of the corresponding monomer using CD as initiator in water or in bulk,[4a−c,7] possibly in the presence of tin octanoate ($Sn(Oct)_2$).[8a−e] In such a procedure, the monomer is included and activated within the CD; the assumed mechanism is similar to that of an enzymatic-mediated ROP in that the monomer is not covalently bound to the active CD site, and the polymers are eventually released from the active site.[4a−c] In the presence of $Sn(Oct)_2$ as ROP catalyst, the seven primary hydroxyl groups located at the smaller side of the CD or the fourteen secondary hydroxyl groups at the periphery of the largest side of the CD cone, can act as a multifunctional initiator.[8a−c] Thus, one, seven, or fourteen polymer arms per CD have been claimed in these CD-centered polymers. The resulting polymer chains are end-capped by a CD. The molar mass generally remained below 7 800 g·mol^{-1} for 1-arm CDs and up to 36 300 g·mol^{-1} for a 14-arms CD, with molar mass distribution values in the 1.1−2.5 range.[4−8]

In the general approach to design conjugated polyesters aimed at biomedical/pharmaceutical applications and to develop polymers within environmentally friendly considerations, we preferentially select monomers such as lactides (LA), β-butyrolactone (BL), and trimethylene carbonate (TMC) and coreagents (diol or triol co-initiators such as 1,3-propanediol and glycerol) that are derived from biomass. We also favor "green" polymerization procedures such as the bulk (i.e., solvent-free), controlled "immortal" ring-opening polymerization (iROP) promoted by a biofriendly metal or an organic catalyst.[10,11]

Herein we report the iROP of LA, BL, and TMC, under mild operating conditions, with the binary system composed of the amido zinc catalyst $[(BDI^{iPr})Zn(N(SiMe_3)_2)]$ (BDI^{iPr} = 2-((2,6-diisopropylphenyl)amido)-4-((2,6-diisopropylphenyl)-imino)-2-pentene) initially developed by Coates,[12] and β-CD-$(OBn)_{19}(OH)_2$ acting as a diol co-initiator and chain transfer agent. The controlled growth of two macromolecular chains per β-CD allowed the synthesis of well-defined β-CD-centered polymers. The limitation of the hydroxyl groups on CD available as polymerization site to two was anticipated to enable better control and understanding of the polymerization, while the benzyloxy moieties impart lipophilicity (and hence solubility) to this reagent. The resulting β-CD$(OBn)_{19}$(O-polyester/polycarbonate)$_2$ were thoroughly characterized by NMR, FT-IR, SEC, DSC, and MALDI−ToF MS techniques. This work provides an in-depth complementary approach to the recent communication by Zinck and co-workers who briefly reported the ROP of LA in the presence of β-CD$(OBn)_{19}(OH)_2$ (among other carbohydrates) and 4-*N*,*N*-dimethylaminopyridine (DMAP) as catalyst.[13] Also, mass spectrometry insights of polyester-β-CD conjugates is provided in light of the work reported by Kowalczuk and co-workers on the ROP of BL from β-cyclodextrintriol (β-CD$(OH)_3$).[14]

EXPERIMENTAL SECTION

Materials. All manipulations involving air-sensitive compounds (i.e., polymerizations mediated by the Zn catalyst) were performed under inert atmosphere (argon, <3 ppm of O_2) using standard Schlenk, vacuum line and glovebox techniques. Solvents were thoroughly dried and deoxygenated by standard methods and distilled before use. $CDCl_3$ was dried over a mixture of 3 and 4 Å molecular sieves. Native β-cyclodextrin (β-CD, Aldrich) was dried *in vacuo* for 24 h at 40 °C before use. Perbenzylated β-cyclodextrin (β-CD$(OBn)_{21}$;[15] ^{1}H NMR, Figure S1 in the Supporting Information) and β-cyclodextrin-diol (β-CD-$(OBn)_{19}(OH)_2$,[16] hereafter abbreviated as β-CD$(OH)_2$; ^{1}H NMR, Figure S2; ^{13}C NMR, Figure S3; MALDI−ToF MS, Figure S4 in the Supporting Information) were prepared as previously described. Yet, the purification of β-CD$(OH)_2$ from other *n*-ol side-products was optimized by column chromatography on neutral alumina using a 1:3 (*v*/*v*) mixture of EtOAc/heptane. *rac*-Lactide (*rac*-LA) was received from Acros, and L-lactide (L-LA) was kindly provided by Total

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Table 1. iROP of LA, TMC and BL Initiated by the Catalytic System $[(BDI^{iPr})Zn(N(SiMe_3)_2)]/(\beta\text{-}CD(OH)_2)$ at 60 °C

entry	monomer	$[monomer]_0/[(BDI)Zn]_0/[(\beta\text{-}CD(OH)_2)]_0$	solvent	reaction time[a] (min)	convn[b] (%)	$\bar{M}_{n_{theo}}$[c] × 10^3 (g mol^{-1})	$\bar{M}_{n_{NMR}}$[d] × 10^3 (g mol^{-1})	$\bar{M}_{n_{SEC}}$[e] × 10^3 (g mol^{-1})	$\bar{M}_w/\bar{M}_n$[f]
1	*rac*-LA	40:2:1	toluene	10	100	8.6	11.5	5.4	1.45
2	*rac*-LA	100:2:1	toluene	10	87	15.4	nd	5.2	1.49
3	*rac*-LA	250:2:1	toluene	15	98	38.1	44.4	20.6	1.36
4	*rac*-LA	400:2:10	toluene	10	96	8.6	nd	9.7	1.28
5	*rac*-LA	500:2:1	toluene	20	98	73.5	83.4	37.4	1.41
6	*rac*-LA	1 000:2:1	toluene	15	98	147.0	57.4	61.6	1.42
7	*rac*-LA	1 000:2:4	toluene	10	98	38.1	41.3	28.3	1.36
8	*rac*-LA	1 000:2:4	DMF	10	0	-	-	-	-
9	*rac*-LA	1 000:2:10	toluene	10	84	17.2	nd	18.5	1.27
10	L-LA	1 000:1:5	toluene	30	65	21.6	28.7	25.8	1.31
11	L-LA	1 000:2:4	toluene	10	94	36.7	38.4	29.8	1.35
12	L-LA	5 000:1:5	toluene	30	59	88.9	nd	72.0	1.34
13[g]	*rac*-BL	1 000:2:4	toluene	20	0	-	-	-	-
14	*rac*-BL	250:2:4	-	12 × 60	46	5.3	nd	8.3	1.08
15	*rac*-BL	500:2:4	-	18 × 60	67	10.0	14.0	12.2	1.08
16	*rac*-BL	1 000:2:4	-	2 × 60	0	-	-	-	-
17	*rac*-BL	1 000:2:4	-	19 × 60	71	15.2	17.8	14.1	1.14
18	*rac*-BL	1 000:2:4	-	26 × 60	98	21.1	nd	22.0	1.11
19	TMC	200:1:5	toluene	10	100	6.9	nd	8.4	1.67
20	TMC	500:2:4	toluene	10	100	15.6	nd	26.1	1.96
21[g]	TMC	500:2/4	toluene	15	40	5.1	19.7	10.1	1.30
22[g]	TMC	1 000:2:4	toluene	10	100	28.4	66.0	34.0	1.80
23	TMC	3 000:2:4	toluene	15	100	79.4	87.1	49.6	2.13
24[g]	TMC	3 000:2:4	toluene	30	35	26.8	nd	33.0	1.79
25	TMC	5 000:2:4	toluene	15	100	130.0	145.2	56.9	2.13

[a]Reaction times were not necessarily optimized; results are representative of at least duplicated experiments. [b]Monomer conversion determined by ^{1}H NMR. [c]Calculated from $[monomer]_0/[\beta\text{-}CD(OH)_2]_0$ × monomer conversion × $M_{monomer}$ + $M_{\beta\text{-}CD(OH)2}$, with M_{LA} = 114 g mol^{-1}, M_{TMC} = 102 g mol^{-1}, M_{BL} = 86 g mol^{-1}, and $M_{\beta\text{-}CD(OH)2}$ = 2847 g mol^{-1}. [d]Determined from the relative intensity ratios of the β-CD−OCHH$_2$C$_6$H$_5$ and main chain polyesters groups ^{1}H NMR signals +2800 g mol^{-1} for $M_{\beta\text{-}CD(OBn)19}$; refer to Experimental Section. [e]Determined by SEC vs. polystyrene standards and corrected by a factor of 0.58 for PLA[17] and 0.73 for PTMC.[18] [f]Molar mass distribution determined from SEC traces. [g]Experiment run at 23 °C.

Petrochemicals. Purification of either *rac*-LA or L-LA required a three-step procedure involving first a recrystallization from a hot, concentrated *i*PrOH solution (80 °C), followed by two subsequent recrystallizations in hot toluene (100 °C). After purification, *rac*-LA was stored at a temperature of −30 °C in the glovebox. Trimethylene carbonate (TMC, 1,3-dioxane-2-one, kindly provided by Labso Chimie Fine, Blanquefort, France) was first dissolved in THF and stirred over CaH_2 for 2 days, before being filtered and dried; TMC was then recrystallized from cold THF. Racemic β-butyrolactone (*rac*-BL, TCI Europe) was dried three times over CaH_2 and then distilled before use. Benzyl alcohol (Acros) was distilled over Mg turnings under argon atmosphere and kept over activated 4 Å molecular sieves. $[(BDI^{iPr})Zn(N(SiMe_3)_2)]$ was synthesized following the literature procedure.[12]

Instrumentation and Measurements. ^{1}H (500 or 400 MHz) and ^{13}C (125 or 100 MHz) NMR spectra were recorded in $CDCl_3$ on Bruker Avance AM 500 and AM-400 spectrometers at 23 °C. Chemical shifts (δ) are reported in ppm and were referenced internally relative to tetramethylsilane (δ 0 ppm) using the residual ^{1}H and ^{13}C solvent resonance.

Average molar mass ($\bar{M}_{n_{SEC}}$) and molar mass distribution ($\bar{M}_w/\bar{M}_n$) values were determined by SEC in THF at 30 °C (flow rate =1.0 mL·min^{-1}) on a Polymer Laboratories PL50 apparatus equipped with a refractive index detector and two ResiPore 300 × 7.5 mm columns. The polymer samples were dissolved in THF (2 mg.mL^{-1}). Reported experimental SEC molar mass values ($\bar{M}_{n_{SEC}}$) for PLA and PTMC samples were corrected by a factor of 0.58[17] and 0.73,[18] respectively, as previously established. The SEC traces of the polymers all exhibited a unimodal and symmetrical peak.

Monomer conversions were calculated from ^{1}H NMR spectra of the crude reaction mixtures in $CDCl_3$, from the integration (Int.) ratio $Int._{polymer}/[Int._{polymer}+Int._{monomer}]$, using the methyl hydrogen resonances for PLA at δ 1.49 ppm and for LA at δ 1.16 ppm, the methine hydrogen resonances for PHB at δ 5.25 ppm and for *rac*-BL at δ 4.66 ppm, and the methine hydrogen resonances for PTMC at δ 4.47 ppm and for TMC at δ 4.25 ppm.

Molar masses of β-CD(OBn)$_{19}$(O-polyester/polycarbonate)$_2$ samples, hereafter abbreviated as β-CD(O-polyester)$_2$, were determined by ^{1}H NMR spectroscopy in THF-d_8, taking into account the relative intensities of signals for the benzyloxy and the main chain ester units. For β-CD(OPLA)$_2$: $\bar{M}_{n_{NMR}}$ = [Int(CH_{LA})/2]/[Int(CH_2C$_6$H$_5$]/(5 × 19)] × 114 (=M_{LA}) + 2 800 (=$M_{\beta\text{-}CD(OBn)19}$) g mol^{-1} using the methine hydrogens of PLA at δ 5.15 and 5.21 ppm. For β-CD(OPHB)$_2$ and β-CD(OPTMC)$_2$ samples, the methine hydrogens of PHB at δ 5.25 ppm and the methylene hydrogens of PTMC at δ 4.47 ppm were used, correspondingly.

MALDI−ToF mass spectra were recorded with an AutoFlex LT high-resolution spectrometer (Bruker) equipped with a pulsed N_2 laser source (337 nm, 4 ns pulse width) and time-delayed extracted ion source. Spectra were recorded in the positive-ion mode using the reflectron mode and an accelerating voltage of 20 kV. The polymer sample was dissolved in THF (HPLC grade, 10 mg.mL^{-1}) and a saturated solution of α-cyano-4-hydroxycinnamic acid (10 mg.mL^{-1}) in acetonitrile (HPLC grade) was prepared. Then this latter solution was mixed in a 3:2 volume ratio with a 0.1% TFA solution in water. Both solutions were deposited sequentially on the sample target and then air-dried. Bruker Care Peptide Calibration and Protein Calibration 1 Standards were used for external calibration.

FTIR spectra of the polymers were acquired on a Shimadzu IRAffinity-1 equipped with an ATR.

Differential scanning calorimetry (DSC) analyses were performed on a Setaram DSC 131 apparatus calibrated with indium at a rate of

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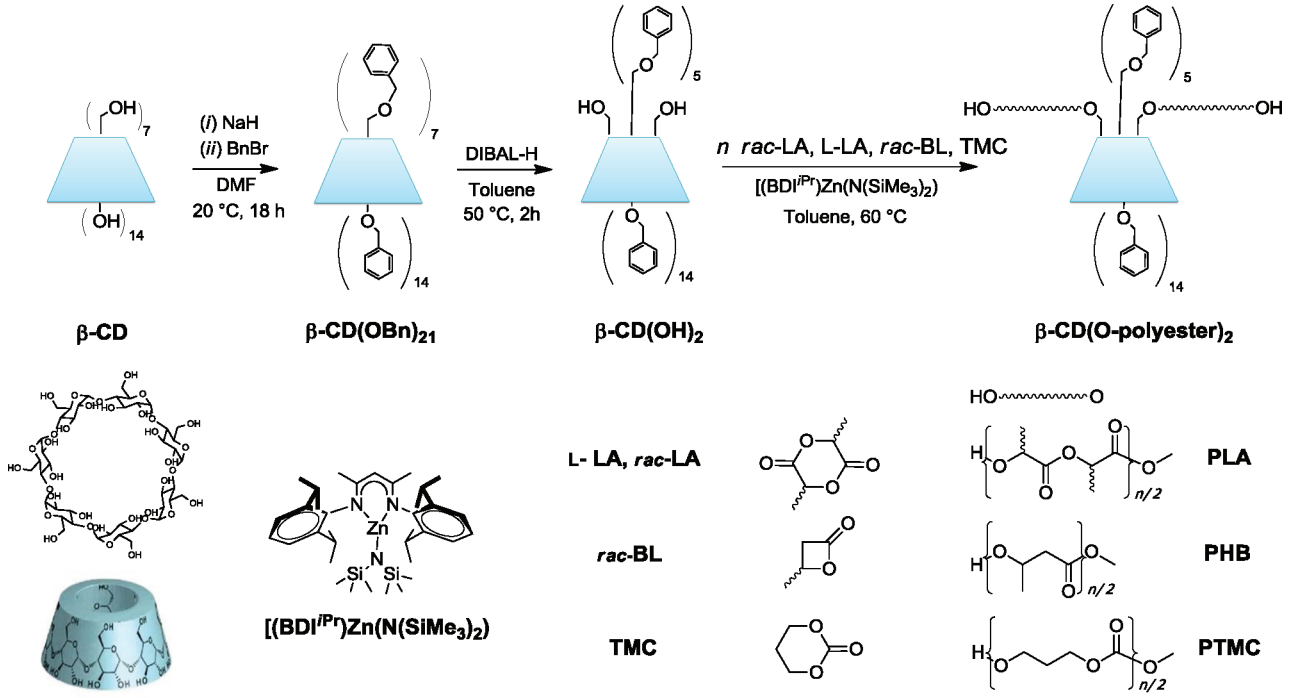
Scheme 1. Synthesis of β-CD(O-polyester/polycarbonate)$_2$ upon (i)ROP of LA, BL, or TMC from the Catalytic System [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$



10 °C·min^{-1}, under continuous flow of helium (25 mL·min^{-1}), using aluminum capsules. The thermograms were recorded according to the following cycles: 50 to 220 °C at 10 °C·min^{-1}; 220 to 50 °C at 50 °C·min^{-1}; 50 °C for 17 min.

Typical Polymerization Procedure. In a typical experiment (Table 1, entry 7), [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)] (2.3 mg, 3.5 μmol) and β-CD(OH)$_2$ (2 equiv vs Zn, 20 mg, 7.0 μmol) were charged in a Schlenk flask in the glovebox. Toluene (880 μL) was then added and the solution stirred for 2 min. *rac*-LA (254 mg, 1760 μmol) was then added to the solution, and the flask was immerged in an oil bath preset at the desired temperature. The reaction mixture was stirred over the appropriate time (10 min; note that reaction times have not been systematically optimized). The reaction was quenched by addition of an excess of H_2O (ca. 2 mL of a 10% H_2O solution in THF). The resulting mixture was then concentrated under vacuum and the conversion determined by ^{1}H NMR analysis of the residue. Finally, the crude polymer was dissolved in CH_2Cl_2 and purified upon precipitation in pentane (ca. 15 mL), filtered and dried under vacuum. The recovered polymer was then analyzed by NMR, IR, SEC, DSC, and MALDI–ToF MS.

RESULTS AND DISCUSSION

β-Cyclodextrindiol (β-CD(OH)$_2$) bearing two primary hydroxyl groups on the narrow side of the CD cone (Figures S2 and S3, Supporting Information) was first synthesized in a two-step procedure starting from native β-CD via the perbenzylated analogue (β-CD(OBn)$_{21}$) (Scheme 1), as previously described.[15,16] The protecting benzyl groups provided lipophilicity to the CD, thus allowing to perform the polymerization in organic solvents.[19] The iROP of LAs, BL or TMC from the catalytic system composed of [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)] associated with β-CD(OH)$_2$ in a ratio of at least 2:1 (each zinc center undergoes a protonolysis reaction with one of the two OH groups of β-CD(OH)$_2$; the loading in β-CD(OH)$_2$ chain transfer agent could also be increased) was carried out under mild operating conditions (toluene,[19] 60 °C, Scheme 1).[20] The most significant results are reported in Table 1.

The iROP of both *rac*-LA and L-LA could be achieved within 10–20 min with almost quantitative monomer conversion and similar reactivity, thereby highlighting a quite good activity (120 < TOF[21] (h^{-1}) < 5 900) of the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$ catalytic system (Table 1, entries 1–12). Increasing the initial loading of *rac*-LA from 40 to 1 000 equiv allowed the synthesis of PLAs of high molar mass (up to 72 000 and 83 400 g·mol^{-1} as determined by SEC and NMR, respectively). A fairly good control over the polymerization was achieved as evaluated from the global agreement of the molar mass values determined by SEC ($\bar{M}_{n_{SEC}}$) and NMR ($\bar{M}_{n_{NMR}}$) and the expected ones ($\bar{M}_{n_{theo}}$), as well as regarding the molar mass distribution values which remained below 1.5. However, although the SEC traces were not that broad and remained always unimodal, these results are indicative of the occurrence of some side-reactions (which are commonly encountered in ROP of cyclic esters, e.g., transesterification). Increasing the initial loading of β-CD(OH)$_2$ from 1 to 10 proportionally decreased the molar mass of PLA (compare entries 6, 7 and 9).[10a] These results demonstrated an overall efficiency of the chain transfer between growing PLA chains and dormant (macro)alcohols. Attempts to ring-open polymerize *rac*-LA in DMF, a more polar solvent that better solubilizes the native β-CD, did not allow the formation of any polymer (entry 8). This behavior results most likely from the competition between DMF and *rac*-LA for coordination to the zinc center in favor of the solvent, as often observed in such ROP reactions promoted by oxophilic metallic initiators.

^{1}H NMR and ^{13}C{^{1}H} NMR analyses of the precipitated polymers demonstrated the formation of β-CD(OPLA)$_2$ consistent with the role of β-CD(OH)$_2$ as co-initiator and chain transfer agent (Figures 1, 2; Figure S6, Supporting Information). A typical 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of a β-CD(OPLA)$_2$ sample ($\bar{M}_{n_{theo}}$ = 8 600 g·mol^{-1}; $\bar{M}_{n_{SEC}}$ = 5 400 g·mol^{-1}, $\bar{M}n_{NMR}$ = ca. 11 500 g·mol^{-1}; Table 1, entry 1) is depicted in Figure 1. The β-CD moiety was clearly evidenced by the typical set of low intensity broad resonances at δ 3.45, 3.96, 4.35, 4.41, and 4.69 ppm and of the benzyloxy groups at δ 7.13 ppm. The PLA signals

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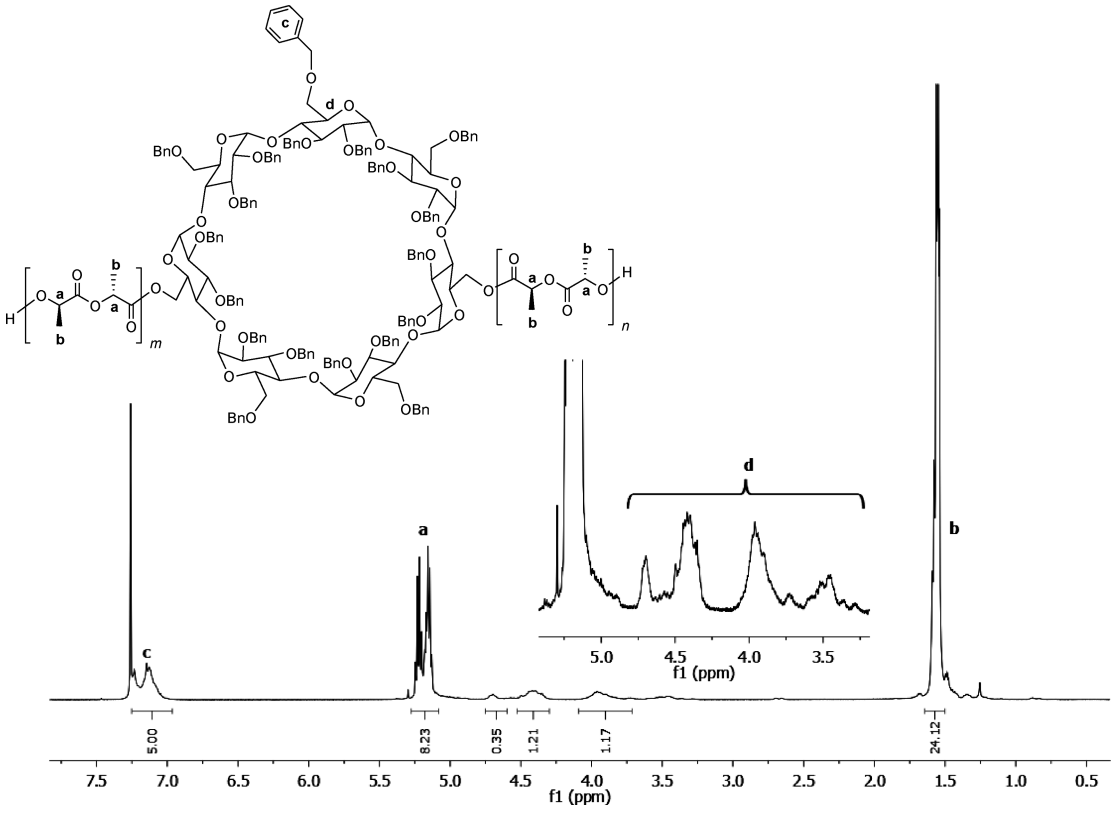

Figure 1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 23 °C) of a β-CD(OBn)$_{19}$(OPLA)$_2$ sample prepared upon iROP of *rac*-LA from the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$ system (Table 1, entry 1).

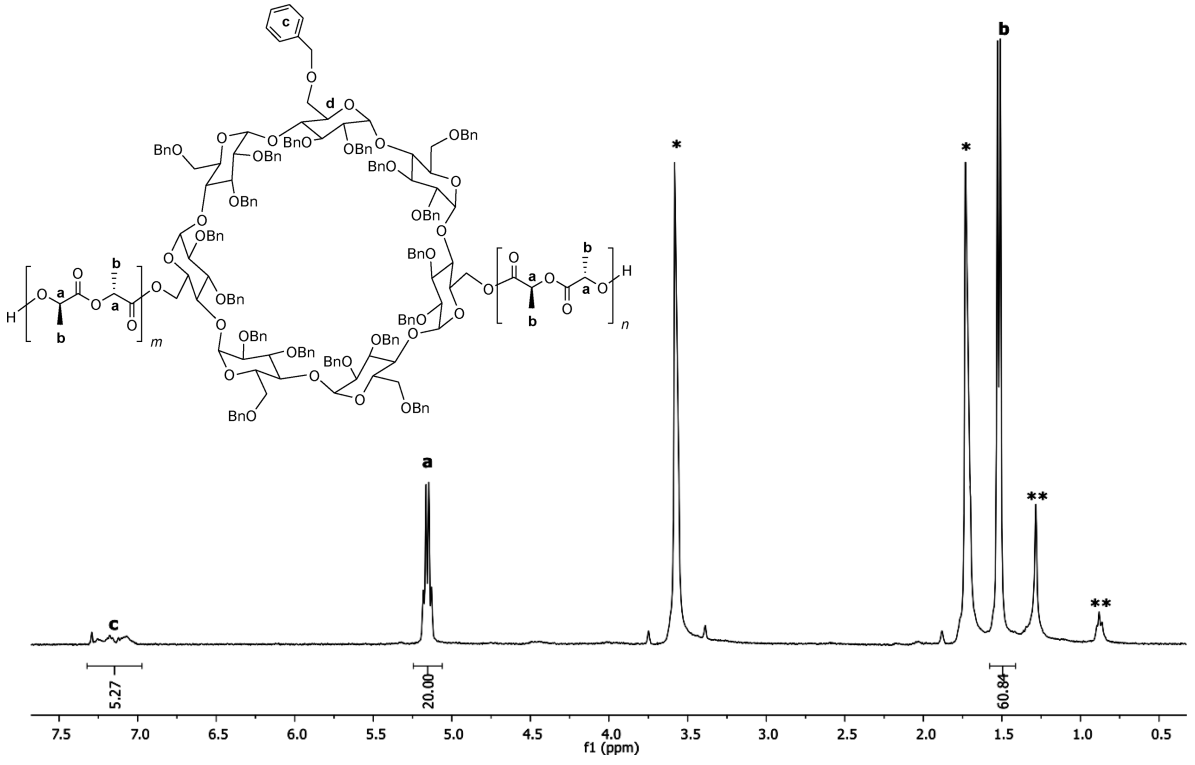

Figure 2. ^{1}H NMR spectrum (400 MHz, THF-d_8, 23 °C) of a β-CD(OBn)$_{19}$(OPLLA)$_2$ sample prepared upon ROP of L-LA from the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$ system (Table 1, entry 10). Markers * and ** stand for residual signals from THF-d_8 and pentane, respectively (the intensity of these residual signals stem from the poor solubility of these isotactic polymers, even in THF).

were clearly observed in the ^{1}H NMR spectrum in $CDCl_3$ at δ 5.15 and 5.21 (OC(O)C*H*Me) and 1.55 (OC(O)CH*Me*) ppm. The two former strong signals for the PLA methine hydrogens are indicative of a heterotactic-enriched microstructure, which was

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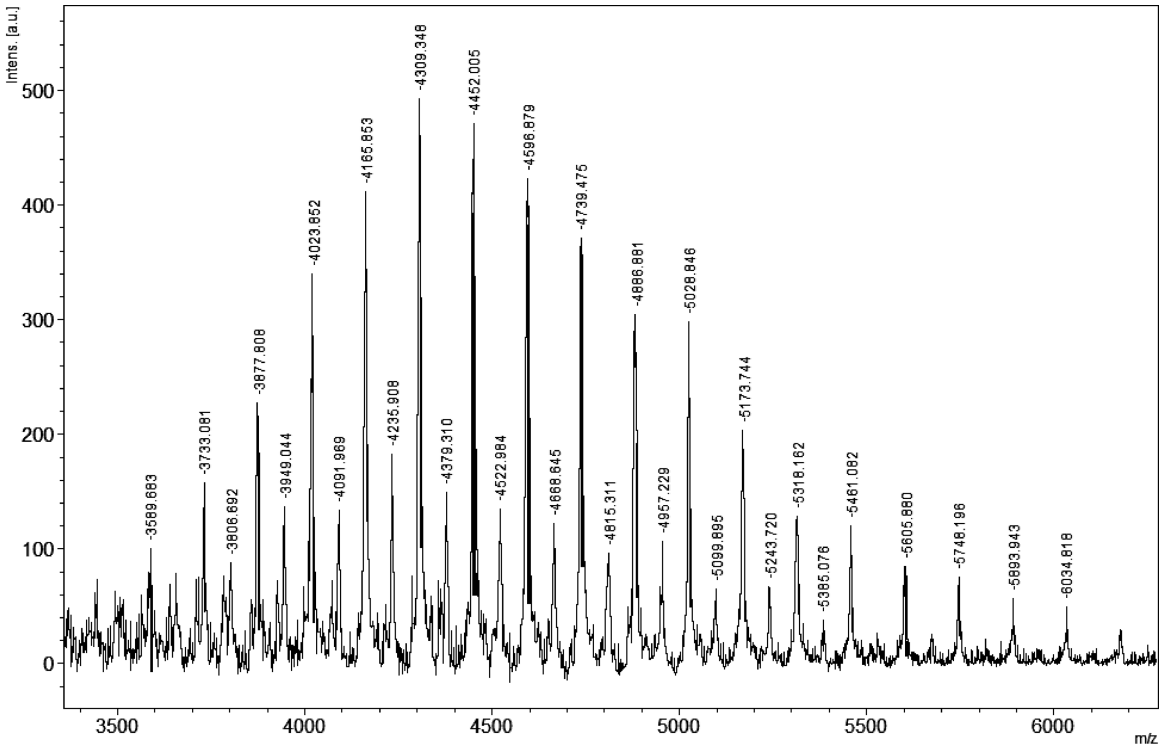

Figure 3. MALDI−ToF mass spectrum of a low molar mass β-CD(OBn)$_{19}${H[(OCHMeC(O)OCHMeC(O)]$_5$}$_2$Na$^+$ sample prepared upon iROP of *rac*-LA from the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$ system (Table 1, entry 1).

unambiguously confirmed by homodecoupling ^{1}H NMR experiments (P_r = 0.81; see Figure S5 in the Supporting Information). The formation of heterotactic-enriched PLA segments in those β-CD(OPLA)$_2$ synthesized from *rac*-LA (entries 1−9) is clearly ascribed to the use of the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)] catalyst;[12] apparently, the presence of β-CD(OH)$_2$ did not affect significantly the stereoselectivity of the growing polymer chain [as observed also for the iROP of *rac*-BL; vide infra]. On the other hand, polymers prepared from L-LA resulted in perfectly isotactic β-CD(OPLLA)$_2$ (P_m > 0.99), as indicated by a sharp quartet at δ 5.17 ppm (Figure 2),[22] revealing no epimerization under the conditions used.

These ^{1}H NMR spectra allowed to determine the molar masses of β-CD(OPLA)$_2$ samples, taking into account the relative intensities of signals for benzyloxy and main chain lactic units. This was best done in THF-d_8 in which the above signals do not overlap with residual solvent resonances (Figure 2), in contrast to other usual solvents (i.e., C_6D_6, CD_2Cl_2 or $CDCl_3$, Figure 1). As mentioned above, the $\bar{M}_{n_{NMR}}$ values thus determined ($\bar{M}_{n_{NMR}}$ = [Int(CH_{LA})/2]/[Int(C$H_2C_6H_5$)/(5 × 19)] × 114 (M_{LA}) + 2 800 (=$M_{\beta\text{-CD(OBn)19}}$) g mol^{-1}) were generally in quite good agreement with the theoretical ones calculated from the conversion and the [LA]$_0$/[β-CD(OH)$_2$]$_0$ ratio. On the other hand, the molar masses determined by SEC ($\bar{M}_{n_{SEC}}$) were in several cases significantly lower than $\bar{M}_{n_{NMR}}$ and $\bar{M}_{n_{theo}}$ values. This suggests that the factor used for correcting the $\bar{M}n_{SEC}$ values (established for regular PLA samples made from L-LA)[17] of these β-CD(OPLLA)$_2$ materials might not be appropriate and/or that inclusion phenomena (i.e., of the PLA chains in the β-CDs cavities)[4,7] may affect the hydrodynamic volumes of such materials. Similar observations were made for β-CD(OPTMC)$_2$ materials (*vide infra*).

The ROP of the four-membered ring lactone, *racemic* β-butyrolactone (*rac*-BL), a monomer more reluctant to undergo polymerization,[23] was first attempted under similar operating conditions in solution within a similar reaction time, yet without success (Table 1, entry 13). The ROP was then carried out in bulk conditions to improve the kinetics (Table 1, entries 14−18), but still required prolonged reaction times (18−26 h, TOF_{BL} up to 37 h^{-1}) to form the β-CD(OPHB)$_2$. The operating conditions used in the present work for the iROP of *rac*-BL were, however, milder than those previously reported in the presence of native β-CD alone, which proceeded in bulk at 100 °C.[4b,c] In fact, the activity was greatly improved upon using the zinc catalyst in combination to β-CD(OH)$_2$: up to 113 turnovers could be reached within 26 h (Table 1, entry 18), whereas less than 15 turnovers were obtained in 96 h without the zinc catalyst.[4b,c] The activity and productivity were thus significantly improved without any detrimental effect on the PHBs molecular features. The atactic PHB chains thus produced featured also larger molar mass ($\bar{M}_{n_{NMR}} \approx \bar{M}_{n_{SEC}}$ up to 22 000 g·mol^{-1}) and narrower molar mass distribution values ($\bar{M}_w/\bar{M}_n$ = 1.08−1.14) in comparison to the ones previously reported ($\bar{M}_n$ < 5 700 g·mol^{-1}, $\bar{M}_w/\bar{M}_n$ = 2.3−2.5).[4b,c] The iROP of *rac*-BL thus afforded β-CD(OPHB)$_2$ in a quite well controlled process. The ^{1}H NMR spectra of these β-CD(OPHB)$_2$ displayed the signals of the β-CD moiety along with the typical resonances corresponding to the methine, methylene or methyl groups of the polyester main chain (Figures S7−S9, Supporting Information). The ^{13}C{^{1}H} NMR spectrum of β-CD(OPHB)$_2$ (Figure S9, Supporting Information) confirmed these features and revealed atactic PHB segments [as observed with the same Zn catalyst used as initiator].[12b]

The same strategy was successfully applied to the synthesis of β-CD(O-polycarbonate)$_2$ samples from the iROP of TMC (Table 1, entries 19−25). Under these conditions, the PTMC molar mass increased monotonously with the [TMC]$_0$/

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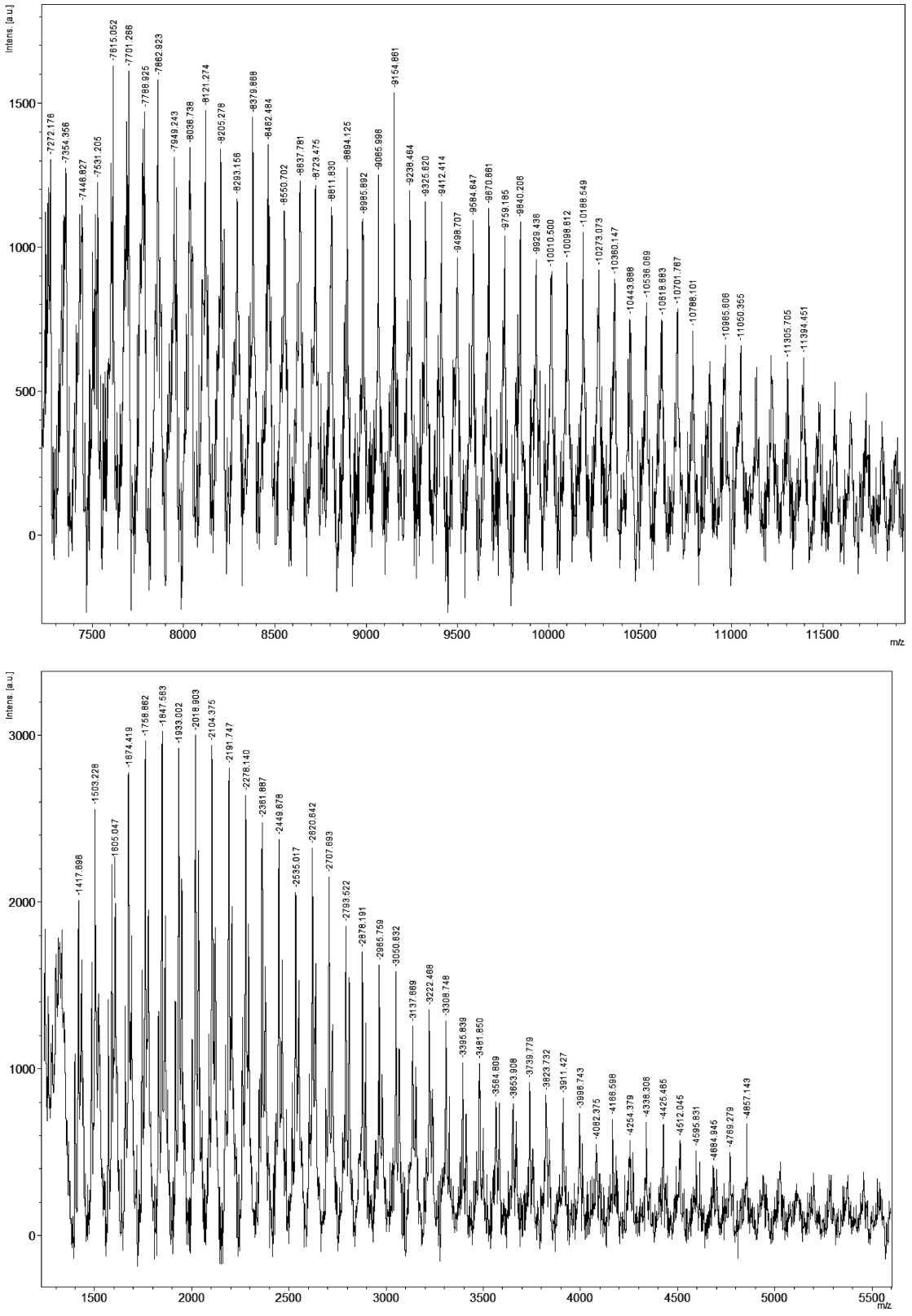

Figure 4. High (top) and low (bottom) molar mass region of the MALDI-ToF mass spectrum of a PHB sample prepared upon iROP of *rac*-BL from the $[(BDI^{iPr})Zn(N(SiMe_3)_2)]/\beta$-$CD(OH)_2$ system (Table 1, entry 14). The high molar mass species correspond to β-$CD(OBn)_{19}\{H-[(OCHMeCH_2C(O)]_n\}_2Na^+$ and the low molar mass species correspond to $\{H[(OCHMeCH_2C(O)]_nOH\}Na^+$.

$[\beta$-$CD(OH)_2]_0$ ratio. Up to 5 000 TMC units were converted quite rapidly (within 30 min), affording well-defined β-CD-$(OPTMC)_2$ (Figure S10, Supporting Information) with $\bar{M}_{n_{NMR}}$ up to 145 000 g·mol^{-1}. When the polymerizations were carried out at 23 °C (entries 21, 22, 24), the $\bar{M}_{n_{NMR}}$ values were much larger than the theoretical ones. This observation suggests moderate initiation efficiency (30−45%) at this temperature. On the other hand, the $\bar{M}_{n_{NMR}}$ and $\bar{M}_{n_{theo}}$ values matched quite well for

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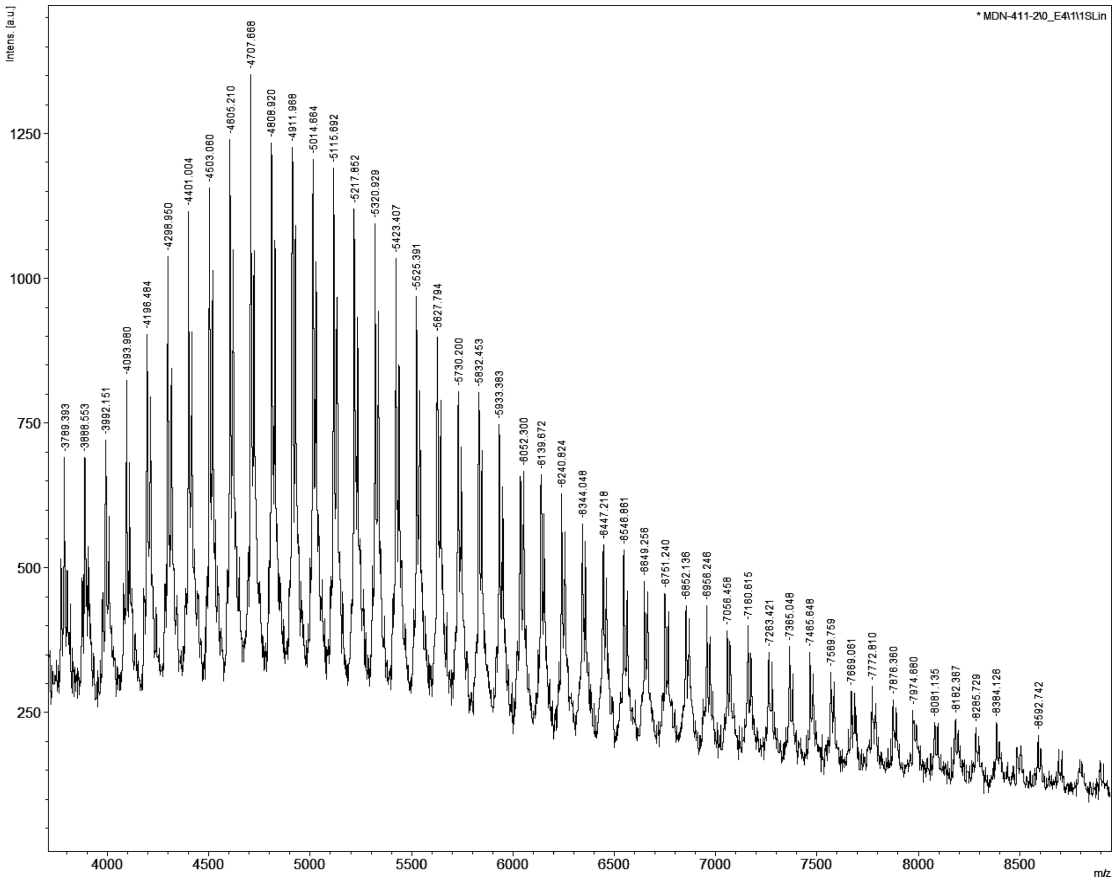

Figure 5. MALDI−ToF mass spectrum of a low molar mass β-CD(OBn)$_{19}${H-[(O(CH$_2$)$_3$OC(O)]$_9$}$_2$ sample cationized by Na$^+$/K$^+$ prepared upon iROP of TMC from the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/β-CD(OH)$_2$ system (Table 1, entry 19).

β-CD(OPTMC)$_2$ prepared at 60 °C (entries 23, 25). As observed for β-CD(OPLA)$_2$, the $\bar{M}_{n_{SEC}}$ values of the β-CD(OPTMC)$_2$ were always significantly lower than the $\bar{M}_{n_{NMR}}$ values.

Evidence for the formation of α,ω-hydroxy β-cyclodextrin-(polyester)$_2$ materials was further confirmed through MALDI−ToF MS investigations. The MALDI−ToF mass spectrum of an heterotactic β-CD(OPLA)$_2$ sample is depicted in Figure 3. It features one major distribution of peaks unambiguously assignable to β-CD(OBn)$_{19}$(OPLA-H)$_2$ macromolecules cationized by Na$^+$ ions with a repeat unit of 144 g·mol^{-1} (i.e., the molar mass of LA). The most intense signal detected at m/z = 4 309 g·mol^{-1} corresponds to the species β-CD(OCH$_2$Ph)$_{19}$-{H[(OCHMeC(O)OCHMeC(O)]$_5$}$_2$Na$^+$ (calculated isotopic mass for $^{12}C_{235}{}^{1}H_{264}{}^{3}Na_1{}^{16}O_{75}$: 4 309 g·mol^{-1}). The other minor population observed at m/z + 72 corresponds to the analogous series depleted from one lactic fragment of the LA diester ($O_2C_3H_4$), consistent with the occurrence of minor transesterification side-reactions, as hinted by the molar mass distribution value of 1.4 determined by SEC (*vide supra*).

Similarly, the MALDI−ToF mass spectrum of a low molar mass PHB sample (Table 1, entry 14) precipitated in cold pentane (see Figure S8, Supporting Information for ^{1}H NMR spectrum)[24] displayed one major distribution of peaks unambiguously assignable to β-CD(OBn)$_{19}$(OPHB-H)$_2$ macromolecules cationized by Na$^+$ ions, with a repeat unit of 86 g·mol^{-1} (i.e., the molar mass of BL) (Figure 4). For instance, one of the most intense signals detected at m/z = 8 380 g·mol^{-1} corresponds to the species β-CD(OCH$_2$Ph)$_{19}${H[(OCHMeCH$_2$C(O)]$_{32}$}$_2$Na$^+$ (calculated isotopic mass for $^{12}C_{431}{}^{1}H_{568}{}^{23}Na_1{}^{16}O_{163}$: 8 380 g·mol^{-1}). The other population observed at lower molar mass (centered at m/z = ca. 2 000 g·mol^{-1}) apparently corresponds to β-CD-free homopolymers, i.e. {H[(OCHMeCH$_2$C-(O)]$_n$OH}Na$^+$ (n, obsvd and calcd m/z: 21, 1 848, 1 847; 22, 5 000, 1 933). This observation was unexpected since the SEC analyses of these β-CD-PHBs displayed a single monomodal trace at relatively high molar masses (Figure S10, Supporting Information), with no lower molar mass signal assignable to β-CD-free PHB homopolymers or free β-CD(OH)$_2$. It is possible that this second set of macromolecules is produced by hydrolysis of the former population β-CD(OBn)$_{19}$(OPHB-H)$_2$ under ionization conditions,[25] rather than during the polymerization process. In comparison, such β-CD-free PHB homopolymers were recovered in much larger amounts in the sparteine-catalyzed ROP of BL carried out at 50 °C in the presence of β-CD(OH)$_3$).[14]

Finally, the MALDI−ToF MS analysis of a low molar mass β-CD(OPTMC)$_2$ sample prepared (Table 1, entry 19) depicted in Figure 5, displayed one major distribution of peaks unambiguously assignable to β-CD(OBn)$_{19}$(OPTMC-H)$_2$ macromolecules cationized by Na$^+$ ions, with a repeat unit of 102 g·mol^{-1} (i.e., the molar mass of TMC). The most intense signal detected at m/z = 4 707 g·mol^{-1} corresponds to the species β-CD(OCH$_2$Ph)$_{19}${H[(O(CH$_2$)$_3$OC(O)]$_9$}$_2$Na$^+$ (calculated isotopic mass for $^{12}C_{247}{}^{1}H_{292}{}^{23}Na_1{}^{16}O_{89}$: 4 705 g·mol^{-1}). The other minor population observed at m/z + 16 corresponds to the analogous β-CD(OCH$_2$Ph)$_{19}${H[(OCHMeC(O)-OCHMeC(O)]$_9$}$_2$K$^+$ series.

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FTIR analysis of a β-CD(OPLA)$_2$ sample prepared upon iROP of *rac*-LA (Table 1, entry 4; Figure S12, Supporting Information) confirmed the presence of both the β-CD and PLA segments. In particular, the typical stretching modes of the β-CD symmetric and antisymmetric O−H at 3 028 cm^{-1} were no longer observed in the spectrum of the conjugated polyester, as compared to the spectrum of β-CD(OH)$_2$ (Figure S13, Supporting Information), and the characteristic carbonyl stretching absorption of the carbonyl polyester segment was recorded at 1 747 cm^{-1}.

The thermal behavior of a β-CD(OPLLA)$_2$ sample prepared upon iROP of L-LA (Table 1, entry 11) was compared to that of β-CD(OH)$_2$ and of a PLLA sample (Figures S16, S14, S15, respectively; see Supporting Information). The new material featured the typical glass transition (T_g = 52 °C) and melting (T_m = 173 °C) temperatures of isotactic PLLA segments. Interestingly, a crystallization peak (T_c = 99 °C) was observed during the heating phase of the second and third cycles, indicating a lower crystallization rate of this material as compared to native PLLA. This may be correlated with the somewhat lower crystalline character of the conjugated β-CD-polyester (ΔH_m = 54 J·g^{-1}; ΔH_c = −25 J·g^{-1}) as compared to native PLLA (ΔH_m = 73 J·g^{-1}; ΔH_c = −53 J·g^{-1}).

All these analyses supported the covalent linking of β-CD to the PLA, PHB, or PTMC segments. This demonstrated in turn that β-CD(OH)$_2$ indeed acted as an effective co-initiator and chain transfer agent in the iROP of LAs, BL, and TMC. In the present case, the polymerization is assumed to proceed through a typical coordination−insertion mechanism, involving incorporation of monomer units into covalently bonded [Zn]−(O-polymer), eventually resulting in β-CD end-capped polymer chains.[10a]

CONCLUSION

The controlled immortal ring-opening polymerization of *rac*-LA, L-LA, *rac*-BL, and TMC was achieved successfully by using the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)]/[β-CD(OH)$_2$] catalytic system, under mild conditions. This survey of different monomers including lactides, lactone and carbonate, showed that the order of reactivity of the various monomers (TMC > *rac*-LA ≈ L-LA > *rac*-BL) reflects the one commonly observed in (i)ROP of these cyclic esters for a given catalytic system, including [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)].[10] Well-defined β-CD(OBn)$_{19}$(O-polyester/polycarbonate)$_2$ of molar mass ranging from 11 500 up to 145 200 g·mol^{-1} were prepared and thoroughly characterized by ^{1}H and ^{13}C NMR and FT-IR spectroscopies, MALDI−ToF mass spectrometry, SEC and DSC analyses. These investigations at the molecular and thermal level supported the linking of β-CD to the PLA, PHB, or PTMC segments. Such an approach is prone to the general elaboration of polyester/polycarbonate−cyclodextrin conjugates for further valuable applications in the vectorization of drugs.

ASSOCIATED CONTENT

Supporting Information

Additional NMR, IR, and MALDI−ToF spectra, and SEC profile, and DSC traces of monomer and polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The main advantages of successful iROPs using active species such as metal-alkoxide derivatives are that (1) both solution and solvent-free (bulk) procedures are efficient, (2) the initial catalyst loading can be lowered down to a few (10) ppm, thereby minimizing residual metallic traces in the isolated polymer, (3) the number of growing polymer chains per metal center can be largely increased upon raising the alcohol content (as much as 1 000 equiv successfully

added), thereby making the process truly "catalytic" with respect to both the monomer and the polymer chains, (4) the molar mass of the polymer can be tuned according to the initial [monomer]/[chain transfer agent] ratio, and (5) the process still allows one to prepare high molar mass polymers upon increasing the initial monomer amount (evaluated up to 100 000 monomer units), without altering neither the control of the ROP, nor the activity or productivity of the catalytic system, nor the macromolecular features (molar mass measured in agreement with the predicted ones, relatively narrow molar mass distribution values, chain-end fidelity relative to the nature of the alcohol introduced, control of the microstructure) of the polymers thus prepared.[10]

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(19) Note that the iROP of LA was run in solution (rather than in bulk) to enable solubilization of the monomer. For comparison purposes, the ROP of TMC was similarly run in solution, whereas the ROP of BL, initially carried out in solution, was next studied in bulk so as to improve the kinetics of the reaction.

(20) Note that, as demonstrated in our previous work (see refs 10 and 22b), the presence of an alcohol (either monoalcohol, diol, or triol) acting as a co-initiator and chain transfer agent is required for the (i)ROP of LA, BL and TMC catalyzed by the [(BDI^{iPr})Zn(N(SiMe$_3$)$_2$)] to be controlled. Indeed, in absence of any added alcohol, the zinc amido complex cannot provide polyesters with expected molar mass values and with narrow molar mass distribution values.

(21) Turnover frequency values expressed in $mol_{Monomer}{\cdot}mol_{Catalyst}^{-1}{\cdot}h^{-1}$; these values are derived from high conversion values and reaction times that were not necessarily optimized, and are therefore lower estimates.

(22) ^{1}H NMR analysis of the β-CD(OPLLA)$_2$ sample was also recorded in THF-d_8 (Figure 2), in which solvent the β-CD benzyl groups do not overlap with other resonance (in contrast to CDCl$_3$), thus allowing to determine accurately the molar mass.

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(24) Note that the precipitation filtrate was not analyzed since high BL conversion (refer to Table 1) and high yields (gravimetrically determined at ≈ 85%) were always reached.

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