Cooligomers from morpholine-2,5-dione and *para*-dioxanone and catalyst complex SnOct_2 /2-hydroxyethyl sulfide

Xiao Liang¹ · Marc Behl¹ · Karola Luetzow¹ · Andreas Lendlein^{1,2} Received: 20 April 2021 / Accepted: 7 June 2021 / Published online: 22 July 2021
© Helmholtz-Zentrum Hereon 2021

Abstract

Complexes from catalysts and initiator can be used to insert a specific number of additional chemical functional groups in (co)polymers prepared by ring-opening polymerization (ROP) of lactones. We report on the synthesis of cooligomers from *sec*-butyl-morpholine-2,5-dione (SBMD) and *para*-dioxanone (PDX) by ROP with varied feed ratios in the bulk using the catalyst complex SnOct_2 /2-hydroxyethyl sulfide. M_n of the cooligomers (determined by GPC) decreased with decreasing SBMD feed ratio from 4200 ± 420 to $800 \pm 80 \text{ g mol}^{-1}$. When the feed ratio was reduced from 80 to 50 mol% the molar ratio of SBMD of the cooligomers (determined by $^1\text{H-NMR}$) remained nearly unchanged between 81 and 86 mol% and was attributed to a higher reactivity of SBMD. This assumption was confirmed by fractionation of GPC, in which an increase of SBMD with increasing molecular weight was observed. The catalyst/initiator system provides a high potential to create orthogonal building blocks by cleavage of the sulfide bond.

Introduction

ROP is well-established in research and industrial production for the synthesis of biodegradable (co)polymers. Tin (II) 2-ethylhexanoate (SnOct_2) is a commonly used catalyst for ROP because of its high efficiency. Although soluble tin compounds are in general cytotoxic, the usage of low amounts of this catalyst complies with FDA regulations. However, serious drawbacks of SnOct_2 as catalyst are the significant amount of cyclic byproducts and transesterification formed during polymerization as well as the variety of endgroups [1].

We recently reported on the catalyst complex SnOct_2 /2-hydroxyethyl sulfide (SnOct_2 /HES) enabling ter-oligodepsipeptides (ter-ODP) with a high content of reactive terminal groups and a significantly lower amount of macrocycles as byproducts when compared with SnOct_2 [2]. Another advantage of this catalyst is the possibility to cleave the disulfide group of the synthesized polymers with a reducing agent [2] such as dithiothreitol and thereby generating a

bifunctional oligomer carrying a sulfide group on one side and a hydroxyl group on the other as demonstrated earlier [2]. We investigated this catalyst complex for the ROP of a morpholine-2,5-dione (MD) [3–7], PDX and their cooligomers. A series of homo- and cooligomers was synthesized by ROP of SBMD (1) and PDX (2) in one-pot reactions, in which the ratio of SBMD to PDX was varied. The structure of the oligomers was characterized by $^1\text{H-NMR}$. The number average molecular weight (M_n) was calculated from gel permeation chromatography (GPC), $^1\text{H-NMR}$ spectroscopy, and MALDI-TOF-MS.

Materials and methods

Chemicals

2-Hydroxyethyl disulfide (99.8%), dibutyl tin(II) oxide (DBTO, 98%) and 4 Å molecular sieves were obtained from Sigma-Aldrich (Steinheim, Germany). SBMD was synthesized according to the method described in reference [6]. *p*-dioxanone (PDX, purity > 99%) was purchased from Daiwa Kasei Ind. (Japan). 2-Hydroxyethyl disulfide was dried over 4 Å molecular sieves, DBTO was dried in high vacuum. Dimethyl sulfoxide- d_6 ($\text{DMSO-}d_6$, 99.9%) was purchased from Merck (Darmstadt, Germany).

✉ Andreas Lendlein
lendlein@uni-potsdam.de

¹ Institute of Active Polymers, Helmholtz-Zentrum Hereon, 14513 Teltow, Germany

² Institute of Chemistry, University of Potsdam, 14476 Potsdam, Germany

Methods

Instrumental methods

Instrumental methods have been described in Supplementary Information.

Synthesis methods

The synthesis of $\text{SnOct}_2/\text{HES}$ has been described in reference [2]. In brief, equimolar amounts of 2-hydroxyethyl disulfide and dibutyl tin(II) oxide were refluxed in toluene over molecular sieves at 120 °C for 24 h under inert conditions yielding 72% of $\text{SnOct}_2/\text{HES}$.

Homo- and cooligomers were polymerized via ROP of the PDX, SBMD and mixtures thereof using the tin(IV) alkoxide (**3**) as catalyst-initiator complex. The M_n aimed at was 1500 g mol^{-1} . SBMD and PDX were recrystallized and dried over molecular sieve (4 Å) for two days before use. The homo- and cooligomers were synthesized in 25 mL pre-dried Schlenk tubes under nitrogen atmosphere at 135 °C (3 h) under intensive stirring. In detail for Oligo_B50P50, under a counter nitrogen flow 1.5 mmol (0.15 g) PDX and 1.5 mmol (0.25 g) SBMD were placed in a flame dried Schlenk flask equipped with a magnetic stirring bar. 0.2 mmol (0.08 g) of the tin alkoxide catalyst were added. Then the Schlenk flask was placed in the oil bath of 135 °C for 3 h, in which the oligomers precipitated from the monomer feed. The crude products were dissolved in 5 mL chloroform (for the second precipitation in 5 mL dimethylene chloride), precipitated

twice in 30 mL of cold diethyl ether, and dried under vacuum at room temperature until constant weights were achieved. The yields after precipitation were in the range of 50 to 80%.

Results and discussion

Cooligomers with varied feed rate were synthesized by ROP. The monomer to catalyst complex ($\text{SnOct}_2/\text{HES}$) ratio was calculated to obtain a targeted M_n of 1500 g mol^{-1} . The samples were named oligo_BaPβ to indicate the initial molar ratio of the two repeating units, where Ba presents the molar fraction of SBMD and Pβ the molar fraction of PDX (Scheme 1). The molar feed ratio of SBMD was reduced stepwise from 100 to 80 to 65 to 50 and 0%. The received oligomers were purified by two-fold precipitation yielding 50 to 80% oligomer. For selected cooligomers the residual SBMD content could be determined before precipitation by $^1\text{H-NMR}$ and ranged around 16% whereas the PDX signals were overlaid and prevented determination.

The obtained oligomers were analyzed by $^1\text{H-NMR}$ spectroscopy in DMSO (Fig. 1). In case of the SBMD unit, the multiplett at 1.0–0.7 ppm has been assigned to the methyl groups of the SBMD repeating unit. The methine and methylene groups of the SBMD alkyl chain appear at 2.0–1.12 ppm. The methine proton between the carbonyl and the amide group of the SBMD appears at 4.36 ppm and is followed by the multiplett at 4.73–4.48 ppm. The proton of the amide group appears at 8.3 ppm. The two signals for the two methylene groups of the initiator were assigned to the signal at 3.0 ppm (protons vicinal to the disulfide group)

Scheme 1 Synthesis route for cooligomers by ROP carrying one disulfide group per molecule

Table 1 Composition and M_n characterization of homo- and copolymers

Sample ID	M_n (GPC) ^a (g mol ⁻¹)	$\bar{D}$ ¹	M_n (NMR) ^b (g mol ⁻¹)	M_n (MALDI) ^c (g mol ⁻¹)	SBMD molar ratio (NMR) ^b (%)	Residual SBMD content (NMR) ^d (%)
Oligo_B100P0	5300	1.1	3400	2334	100	16
Oligo_B80P20	3300	1.3	3200	1877	86	15
Oligo_B80P20-F1	7200	1.1	2500	nd	88	
Oligo_B80P20-F2	4700	1.1	3300	nd	91	
Oligo_B80P20-F3	3400	1.1	3100	nd	90	
Oligo_B80P20-F4	2300	1.1	2100	nd	88	
Oligo_B80P20-F5	900	1.4	2000	nd	74	
Oligo_B65P35	3200	1.4	2600	1079	81	17
Oligo_B50P50	800	3.1	2300	nd	85	nd
Oligo_B0P100	2700	1.3	2500	1533	0	nd

nd Not determined

^a M_n of precipitated product determined by GPC (universal calibration), fractionated samples (F1-F5) by standard calibration; M_n is the number average molecular weight, $\bar{D}$ the polydispersity. SD $\pm 10\%$

^bDetermined by ¹H-NMR. SD $\pm 10\%$

^c M_n of most dominant series

^dResidual SBMD content determined before precipitation by ¹H-NMR

determined by ¹H-NMR were for Oligo_B α P β with $\beta > 50$ lower than the values obtained from GPC and showed a similar decrease of M_n when the SBMD feed ratio decreased. The low achievable PDX molar ratio suggests a more facile polymerization of SBMD compared to PDX. This finding is in line with the observation that synthesis of co-oligomers with a lower SBMD feed rate than 50 mol% did not result in the amounts and molecular weights as expected and maybe be explained by a lower reactivity of PDX in presence of SBMD or the catalyst complex.

In order to investigate a dependency of the SBMD molar ratio of the fractions, Oligo_B80P20 was fractionated by preparative GPC into five fractions. GPC and ¹H-NMR investigations showed the expected decrease of M_n in the order of fraction collection from 7200 ± 720 to 900 ± 90 g mol⁻¹ (GPC), which agrees with the M_n determined by NMR evaluation from 3300 ± 720 to 1900 ± 190 g mol⁻¹ considering that for the fractions only standard calibrated GPC was applicable. An exception was M_n (NMR) of Oligo_B80P20-F1 presumably because of the low concentration of oligomer present in this fraction. The SBMD molar ratio decreased from 91 to 74 mol% as determined by ¹H-NMR.

Conclusion

Cooligomers of SBMD and PDX were synthesized by ROP in the presence of the catalyst complex SnOct₂/HES, which allows thiol functionalization of oligomers after polymerization by reduction of the disulfide bond as demonstrated for ter-oligomers from morpholindiones

[2]. Molecular weights as determined by universal calibrated multidetector GPC were for PDX = 50 mol% lower than those determined from ¹H-NMR, whereas for SBMD content > 50 mol% higher values were determined by GPC. Molar ratios of the SBMD-PDX differed from the molar ratios of the feed compositions, which may be explained by a lower reactivity of PDX in the presence of SBMD or the catalyst complex. However, the oligomers provided a high degree of hydroxyl end groups as concluded from ¹H-NMR spectra. In case of SBMD homo and cooligomers also the presence of carboxylic end groups could be confirmed. MALDI measurements revealed OH end groups for the SBMD homooligomer and Oligo_B80P20. The M_n determined by MALDI are lower than M_n (NMR), which may be explained by fragmentation of the oligomers containing PDX. Future MALDI-TOF-MS investigations are expected to provide more insights for the end group analysis as well in the elucidation of the copolymerization and possible fragmentation behavior.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1557/s43580-021-00082-5>.

Acknowledgments The authors acknowledge gratefully the support of Mr. Olaf Lettau for technical support and GPC measurements and Ms. Susanne Schwanz for MALDI measurements. This work was financially supported by the Helmholtz Association through program-oriented funding and the Helmholtz Graduate School for Macromolecular Bioscience (MacroBio, VH-GS-503).

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. H.R. Kricheldorf, S.M. Weidner, High molecular weight poly(l-lactide) via ring-opening polymerization with bismuth subsalicylate—the role of cocatalysts. *J. Appl. Polym. Sci.* **138**, 50394 (2020).
2. X. Liang, M. Behl, A. Lendlein, Dihydroxy terminated teroligomers from morpholine-2,5-diones. *Eur. Polym. J.* **143**, 110189 (2021).
3. P.J.A. i'nt Veld, P.J. Dijkstra, J.H. van Lochem, J. Feijen, Synthesis of alternating polydepsipeptides by ring-opening polymerization of morpholine-2,5-dione derivatives. *Die Makromolekulare Chemie* **191**, 1813 (1990)
4. Y. Feng, J. Lu, M. Behl, A. Lendlein, Progress in depsipeptide-based biomaterials. *Macromol. Biosci.* **10**, 1008 (2010)
5. L. Elomaa, Y. Kang, J.V. Seppälä, Y. Yang, Biodegradable photocrosslinkable poly(depsipeptide-co- ϵ -caprolactone) for tissue engineering: synthesis, characterization, and In vitro evaluation. *J. Polym. Sci. Part A* **52**, 3307 (2014)
6. X. Peng, M. Behl, P. Zhang, M. Mazurek-Budzynska, Y. Feng, A. Lendlein, Synthesis of well-defined dihydroxy telechelics by (co)polymerization of morpholine-2,5-diones catalyzed by Sn(IV) alkoxide. *Macromol. Biosci.* **18**, 1800257 (2018)
7. T.F. Burton, J. Pinaud, O. Giani, Rapid and controlled organocatalyzed ring-opening polymerization of 3S-(Isobutyl)morpholine-2,5-dione and copolymerization with lactide. *Macromolecules* **53**, 6598 (2020)
1. H.R. Kricheldorf, S.M. Weidner, High molecular weight poly(l-lactide) via ring-opening polymerization with bismuth