One-Pot Chemoenzymatic Cascade Polymerization under Kinetic Resolution Conditions

Bart A. C. van As,[†] Paul Thomassen,[‡] Bhanu Kalra,[§] Richard A. Gross,[§] E. W. Meijer,[†] Anja R. A. Palmans,[†] and Andreas Heise*,[‡]

DSM Research, P.O. Box 18, 6160 MD Geleen, The Netherlands, Polytechnic University, Department of Chemistry and Chemical Engineering, Six Metrotech Center, Brooklyn, New York 11201, Technische Universiteit Eindhoven, Department of Chemistry and Chemical Engineering, P.O. Box 513, 5600 MB Eindhoven, The Netherlands

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ABSTRACT: A novel concept for the metal-free synthesis of block copolymers combining enzymatic ring-opening polymerization and nitroxide-mediated living free-radical polymerization from a bifunctional initiator is presented. Block copolymers comprising a poly(styrene) and poly(caprolactone) block were obtained in two consecutive polymerization steps (macroinitiation) and in a one-pot cascade approach without intermediate transformation or work up step. By optimization of the reaction conditions a high selectivity of both transformations could be realized in the cascade polymerization, resulting in high block copolymer yields. The same concept was successfully applied to enzymatic resolution polymerization of racemic 4-methyl-ϵ-caprolactone combined with the living free-radical polymerization of styrene yielding block copolymers with high enantiomeric excess in the 4-methyl-ϵ-caprolactone block.

Introduction

Driven by the demand for sustainable processes and new materials, new integrated synthetic strategies and catalysts have to be developed in the future. Cascade conversions, i.e., combined (catalytic) reactions without intermediate recovery steps, are a powerful and elegant concept to meet those demands. Typically, biocatalytic processes in living cells go through a multistep cascade approach to convert a starting material into the final product without the separation of intermediates. However, biotechnology cannot replace all multistep chemical routes. Therefore, the challenge is to combine the power of chemical and enzymatic catalysis to realize the next generation of materials.[1]

Examples of cascade reactions in chemistry are primarily found in organic chemistry, where they are among the most valuable tools leading to a significant increase in molecular complexity and at the same time minimizing the amount of chemicals used in the synthetic procedures.[2−5] Also in polymer chemistry, combination of different synthetic techniques has been successfully applied. In particular, controlled polymerization techniques have been used for the synthesis of block copolymers from dual initiators without an intermediate transformation step.[6−9] Among them are a few examples of real cascade polymerizations, i.e., block copolymer synthesis without intermediate transformation and recovery steps.[10−13]

In-vitro enzyme catalysis has received increased attention in polymer synthesis recently. Lipases, for instance, have shown great promise due to their stability in organic media and ability to promote transesterification and condensation reactions on a broad range of substrates.[14,15] In this regard, Lipase B from *Candida antarctica* (CALB) immobilized on an acrylic macroporous resin (Novozym 435) has shown exceptional activity for a range of polymer-forming reactions including ring-opening polymerization (ROP) of cyclic monomers (e.g., lactones, carbonates) as well as polycondensation reactions.[16,17] However, implementation of an integrated one-pot chemoenzymatic strategy in polymer synthesis similar to the approaches in organic chemistry has not yet been achieved.

In a new approach we have begun to explore the possibilities of integration of enzymatic and chemical polymerization preferably in a one-pot reaction. The motivation is to incorporate the best attributes of both enzymatic and chemical methods to obtain new material designs that were thus not available using one of these methods. We recently reported the combination of atom-transfer radical polymerization (ATRP) with enzymatic ROP yielding block copolymers of styrene (St) and ϵ-caprolactone (CL) in two consecutive polymerization steps from a dual-headed initiator.[9] Unlike with metal-mediated ROP, a one-pot one-step reaction proved difficult due to the simultaneous initiation of both reaction types and in some cases the inhibiting effect of the ATRP metal catalyst on the enzymatic activity.[10,18] When the radical polymerization of styrene occurred too fast, the steric constraints imposed by the polystyrene chain transformed the otherwise effective hydroxy end group into a sterically hindered ineffective nucleophile for formation of the polyester block by lipase catalysis. The result was a severe mixture of block copolymers and corresponding homopolymers.

This paper reports how limitations of the above dual-initiator system were solved by shifting from ATRP to metal-free nitroxide-mediated living free-radical polymerization (LFRP).[19] The nitroxide-mediated system is thermally activated at 90−120 °C, while lipase-catalyzed lactone ring-opening polymerizations can be performed from 25 °C. Because nitroxide-mediated free-radical polymerization has a distinctive temperature window, it can be kinetically separated from the lipase-

* To whom correspondence should be addressed. Phone: ++31-46-4761119. Fax: ++31-46-4763949.
[†] Technische Universiteit Eindhoven.
[‡] DSM Research.
[§] Polytechnic University.

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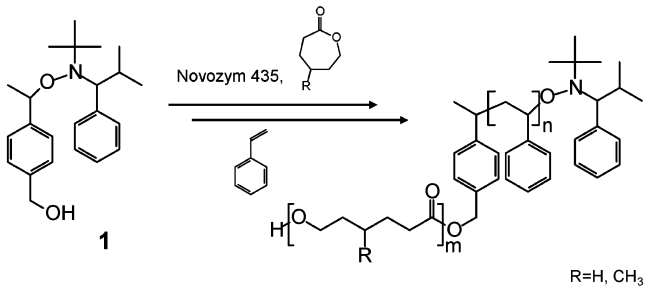
Scheme 1. One-Pot Enzymatic Ring-Opening and Living Free-Radical Cascade Polymerization



catalyzed polymerization. The result is a "push button" system for a one-pot chemoenzymatic cascade polymerization: an enzymatic ROP is followed by the living free-radical polymerization (Scheme 1).

Experimental Section

Materials. All monomers were distilled from CaH_2 under reduced pressure before use. 4-Methyl-ϵ-caprolactone (4MeCL) was synthesized by Baeyer−Villiger oxidation of 4-methylcyclohexanone following a reported procedure.[20] Bifunctional initiator **1** was synthesized according to a literature procedure.[21] Novozym 435 was purchased from Novozymes A/S. All other chemicals were purchased from Aldrich and used as received unless otherwise noted.

Analytical Methods. ^1H and ^{13}C NMR spectra were measured using a Varian Mercury Vx 400 or 300 spectrometer (400 or 300 MHz) in $CDCl_3$ with the delay time (d_1) set at 10 s. Conversion of CL (C_{CL}) and **1** (C_I) were determined from ^1H NMR spectra; for CL by comparison of the integrated peak areas of the $CH_2C{=}O$ proton signal in the monomer at 2.65 ppm ($I_{\delta=2.65}$) and in the polymer at 2.30 ppm ($I_{\delta=2.30}$), i.e., $C_{CL} = (I_{\delta=2.30})/[(I_{\delta=2.30}) + (I_{\delta=2.65})]$. Similarly, conversion of **1** was calculated as $C_I = (I_{\delta=5.10})/[(I_{\delta=5.10}) + (I_{\delta=4.65})]$ comparing the integrated peak areas of the $Ph{-}CH_2{-}O{-}$ protons on the reacted (5.10 ppm) and the unreacted initiator (4.65 ppm).

Chiral gas chromatography (GC) was performed on a Shimadzu 6C-17A GC equipped with an FID employing a Chrompack Chirasil-DEX CB (DF = 0.25) column. Injection and detection temperatures were set at 300 and 325 °C, respectively. Separations were done under isocratic conditions with the column temperature set at 125 °C, which afforded in all cases baseline separation of the enantiomers of 4-MeCL. An internal standard method taking 1,3,5-tri-*tert*-butylbenzene or 2-undecanone as the internal standard was used to determine the lactone conversions and enantiomeric excess (ee_m) of the unreacted monomer. The ee_m was calculated as follows: $ee_m = (R - S)/(R + S)$ where R and S represent the surfaces of the GC peaks of the R- and S-enantiomer, respectively. All samples were injected using a Shimadzu AOC-20i autosampler. The enantiomeric excess of obtained chiral block copolymers (ee_p) was calculated from total lactone conversion and enantiomeric excess of the unreacted monomer.[22]

Gel permeation chromatography (GPC) was carried out on a Waters 712 WISP HPLC system with a Waters 410 differential refractometer detector and a PL gel guard precolumn (5 mm, 50 × 7.5 mm) followed by two PL gel mixed-C columns (10 mm, 300 × 7.5 mm, Polymer Laboratories) using THF as the eluent.

Optical rotations were recorded on a Jasco DIP-370 polarimeter at a wavelength of 589 nm (Na_D line). DSC spectra were measured with a Perkin-Elmer Pyris 1 DSC with heating and cooling rates of 40 K/min.

General Procedure for a Two-Pot Block Copolymer Synthesis. Novozym 435 (213.0 mg) and a magnetic stirring bar were added to a Schlenk tube. The tube was put overnight in a vacuum oven (10 mmHg) at 50 °C in the presence of P_2O_5. The oven was backfilled with nitrogen, and **1** (54.0 mg; 0.15 mmol), CL (2.50 mL; 22.5 mmol), and dry molecular sieves (4 Å) were added to the tube. This mixture was stirred at 60 °C for 3 h. $CHCl_3$ was added to the viscous reaction mixture, and the immobilized enzyme was filtered off. The PCL macroinitiator was obtained by precipitation in cold methanol (yield, 0.90 g; conversion CL, 68%). The PCL (600 mg) was then dissolved in styrene (2.00 mL; 17.3 mmol). After five consecutive freeze−pump−thaw cycles to remove the oxygen from the reaction solution, it was heated for 68 h at 95 °C, allowing the system to reach high styrene conversion as was evident by the increased viscosity of the system. The polymer was recovered by dissolving the mixture in $CHCl_3$, filtration, and precipitation in cold methanol (yield, 1.16 g; conversion St, 92%). All analytical data are in agreement with literature data reported on P(CL-*b*-St).

General Procedure for a One-Pot Block Copolymer Synthesis. Novozym 435 (224.0 mg) and a magnetic stirring bar were added to a Schlenk tube. The tube was put overnight in a vacuum oven (10 mmHg) at 50 °C in the presence of P_2O_5. The oven was backfilled with nitrogen, and CL (1.90 mL; 17.1 mmol), St (3.63 mL; 31.4 mmol), **1** (75.9 mg; 0.21 mmol), and molecular sieves (4 Å) were added to the tube. After five consecutive freeze−pump−thaw cycles to remove the oxygen from the reaction solution, it was stirred at 60 °C for 3 h and subsequently heated to 95 °C for 114 h, allowing the system to reach high St conversion as was evident by the increased viscosity of the system. The polymer was recovered by dissolving the mixture in $CHCl_3$, filtration, and precipitation in cold methanol (yield, 2.66 g; conversion CL, 99%; conversion St, 72%). All analytical data are in agreement with literature data reported on P(CL-*b*-St).

General Procedure for a One-Pot Chiral Block Copolymer Synthesis. *Method A.* Novozym 435 (190 mg) and a magnetic stirring bar were added to a Schlenk tube. The tube was put overnight in a vacuum oven (10 mmHg) at 50 °C in the presence of P_2O_5. The oven was backfilled with nitrogen, and 4-methyl-ϵ-caprolactone (3.00 g; 23.4 mmol), St (2.00 g; 19.2 mmol), initiator **1** (90 mg; 0.25 mmol), and molecular sieves (4 Å) were added to the tube. This mixture was stirred at 45 °C for 28 h. During reaction samples were withdrawn from the reaction mixture using a syringe, and the enzyme was removed from the sample by filtration over cotton wool. The samples were analyzed by ^1H NMR for 4-methyl-ϵ-caprolactone conversion and by chiral GC for enantiomeric excess (ee_m) of the unreacted monomer. At 43% 4-methyl-ϵ-caprolactone conversion, the enzymatic reaction was stopped by the addition of 0.2 mL of a solution of 6.17 mM paraoxon in toluene according to a literature procedure.[23] Then the mixture was subjected to five consecutive freeze−pump−thaw cycles to remove the oxygen from the reaction solution. Subsequently, the flask was heated to 100 °C for 90 h. The polymer was recovered by dissolving the mixture in $CHCl_3$, filtration, and precipitation in cold methanol (yield, 1.88 g; conversion 4MeCL, 43%; conversion St, 89%).

^1H NMR ($CDCl_3$): δ 6.8−7.4 (m, Ar-*H*), 6.3−6.8 (m, Ar-*H*), 5.1 (d, benzyl-CH_2OCO), 4.15 (t, CH_2CH_2OCO), 3.68 (t, CH_2CH_2-OH), 2.2−2.45 (m, $OCOCH_2CH_2$), 1.2−2.2 (m, $OCOCH_2CH_2CH$-$CH_3CH_2CH_2O$ + Ar−$CHCH_2$), 0.8−1.1 (d, CH_3). T_g ((*S*)-4MeCL) block: −51 °C. T_g (St) block: 106 °C. $[\alpha]^{25}_D = -2.6°$ (c = 0.1 g/mL in $CHCl_3$).

Method B. The procedure was conducted in an analogous fashion to Method A, except that the reaction mixture and the paraoxon solution were subjected to five consecutive freeze−pump−thaw cycles prior to the start of the reaction. During the course of the reaction the system was kept under an argon atmosphere. After addition of inhibitor solution, the system was immediately heated to 100 °C without further operations.

Results and Discussion

The bifunctional initiator **1** contains a nitroxide group for controlled free-radical polymerization of St and a hydroxy group for initiation of lipase-catalyzed ROP of CL.[24] Block copolymers can therefore be obtained from **1** without intermediate workup or modification steps. The initiation of styrene from this initiator and respective macroinitiators proceeds in a well-defined fashion, yielding polymers with controlled molecular weight and polydispersity.[19] However, since **1** comprises a relatively

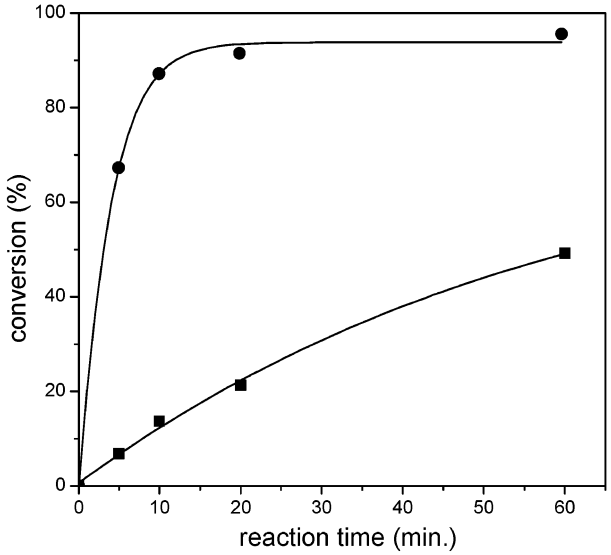


Figure 1. Comparison of ϵ-caprolactone (■) and initiator (●) conversion employing **1** and Novozym 435 at 60 °C in bulk: monomer/initiator = 75. Conversion determined by ^{1}H NMR of samples withdrawn from the reaction mixture.

bulky structure, the feasibility of **1** in a lipase-catalyzed CL polymerization had to be investigated first at a reaction temperature of 60 °C. Inspection of Figure 1 shows a rapid conversion of **1**—exceeding 90% at a CL conversion of less than 20%—and an almost linear increase of the monomer conversion as a function of time. The kinetics of this reaction was found to be first order with respect to monomer consumption. Although these results suggest a quasi-living character of the polymerization, the control of the polymer structure (polydispersity, end-group structure, molecular weight) strongly depends on the frequency of side reactions caused by the water activity when (i) water is the acyl acceptor that initiates the chain growth and (ii) water reacts with intrachain esters causing chain degradation. Both of these reactions can broaden the molecular weight distribution and will alter the composition of groups at the PCL chain ends. It is of paramount importance to control the latter since it determines the degree of incorporation of **1** and thus the block copolymer yield.

An example of the molecular weight and polydispersity of a polymer formed in an enzymatic ROP employing **1** at 60 °C after 3 h is given in Table 1, entry A1. Monomer conversions under these conditions are typically between 65% and 80% with precipitated yields of 40−60%. With carefully dried reagents and polymerization under anhydrous conditions, there were no carboxylic acid chain ends detectable in the ^{1}H NMR spectra as determined following a literature procedure.[25] Therefore, it can be concluded that the mole percentage of polymers without the nitroxide end group is below 5%. Furthermore, ^{1}H NMR analysis of the products in entries A1 and A2 showed a complete shift of the benzylic proton signal of **1** from 4.65 to 5.1 ppm (**h** in Figure 2). This is consistent with **1** linked by an ester to the PCL chain. The precipitated macroinitiator PCL was subsequently used for nitroxide-mediated St polymerization. Upon polymerization an increase in the molecular weight relative to PCL was observed by size exclusion chromatography (Table 1, entry A1.2). Since any unreacted **1** was efficiently removed from PCL during the precipitation step, the initiation of chains must have exclusively occurred from the macroinitiator

Table 1. Characteristics of Polymers Obtained in Enzymatic/Living Free-Radical Cascade Polymerization of CL and St[a]

entry	initiator	molar ratio I:CL:St	polymer	M_w (kDa)[b]	PD[b]
A1	1	1:150:0	PCL	24	1.7
A1.2	PCL	1:0:340	P(CL-*b*-St)	35	1.4
A1.3[c]			PSt	22	1.2
B1	1	1:80:147	P(CL-*b*-St)	21	1.4
B2	1	1:90:125	P(CL-*b*-St)	19	1.7
B2.1[c]			PSt	3	1.2
C1[d]	1	1:92:76	P((*S*)-4-MeCL-*b*-St)	13	1.4
C1.1[c]			PSt	5	1.2
C2[e]	1	1:92:76	P((*S*)-4-MeCL-*b*-St)	12	1.4
C2.1[c]			PSt	5	1.1

[a] Entries A refer to two-pot reactions, entries B to one-pot reactions, entries C to one-pot kinetic resolution polymerization. [b] Data from SEC; poly(styrene) calibration (typically overestimation of M_w of PCL by about factor 2). [c] After decomposition of PCL block. [d] Method A, see Experimental Section. [e] Method B, see Experimental Section.

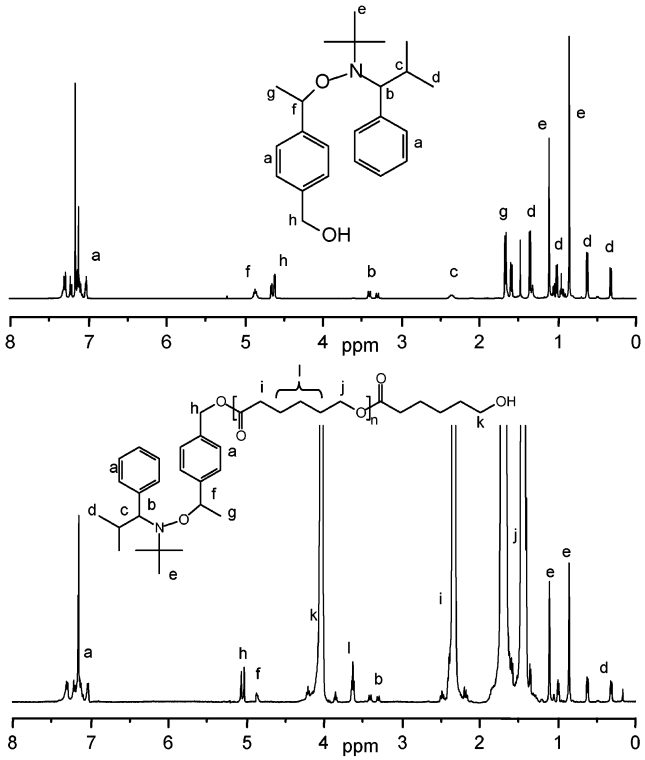


Figure 2. ^{1}H NMR spectra of **1** and PCL initiated by **1**.

chains. To directly analyze the poly(styrene) block of the P(CL-*b*-St) block copolymers (A1.2), the PCL block was degraded according to a literature procedure.[10] Comparison of the SEC trace of the remaining PSt block (entry A1.3) with that of P(CL-*b*-St) reveals a shift to lower molecular weight. Moreover, the low polydispersity (PD) of the PSt is in a typical range for LFRP. This provides further evidence of the block structure and the feasibility of the macroinitiation approach.

Chemoenzymatic Cascade Polymerization. On the basis of the encouraging results in the two-step synthesis, i.e., high degree of initiator incorporation in the enzymatic ROP and efficient macroinitiation in the LFRP, respectively, both polymerizations were run in a one-pot cascade reaction without an intermediate precipitation step. In this case, the presence of unreacted initiator will result in unwanted PSt homopolymer formation. Furthermore, initiation of CL polymerization by water may result in PCL homopolymer. The latter can be reduced by careful drying of the starting materi-

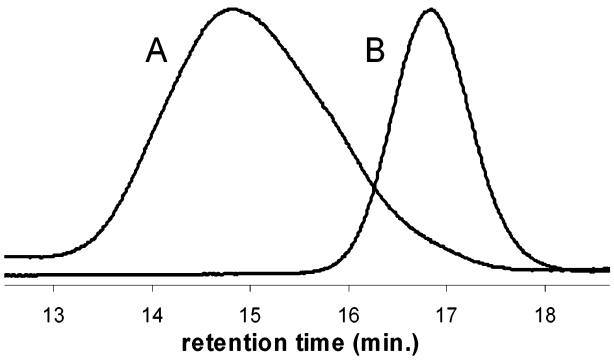


Figure 3. SEC trace of block copolymer obtained in the one-pot reaction before (A) and after (B) degradation of the PCL block (Table 1, entries B2 and B2.1).

als as mentioned earlier. Oxygen was removed from the polymerization mixture containing only CL, St, Novozym 435, and **1** by applying five consecutive freeze−pump−thaw cycles prior to the polymerization. The reaction flask was then heated to 60 °C to initiate enzymatic ROP of CL. Nitroxide polymerization from **1** does not occur at this temperature, as confirmed by a control reaction. After 3 h the temperature was raised to 95 °C for 114 h to activate and perform nitroxide-mediated LFRP of St to form the PSt block.[26] The resulting products were isolated by precipitation (B1, yield 50%, B2, 39%). A quantitative conversion of CL was reached in both examples, while the St conversion was 72% for B1. The SEC traces of these products were all symmetrical with no evidence of radical coupling reactions. The values of M_w and polydispersities from analysis of these traces are listed in Table 1. Their ^{1}H NMR spectra showed signals corresponding to both PSt and PCL. Figure 3 shows the SEC trace of block copolymer B2 (Table 1) that was designed to have a shorter PSt block by stopping the reaction after 20 h at low St conversion. This block copolymer was of particular interest since if PSt was formed and remained in the isolated product it would be easily separated and detected by SEC. Comparison of the SEC trace before and after degrading of the PCL block shows a significant shift of the peak to lower molecular weight (Figure 3). Furthermore, a peak corresponding to trace B was not observed in trace A. These results provide strong evidence that the proposed block copolymer structure was obtained in the one-pot cascade reaction.

The successful preparation of block copolymers by the one-pot method demonstrates the compatibility of biocatalytic lactone polymerization with nitroxide-mediated LFRP. The kinetic characteristics of either polymerization imply that a temperature-induced kinetic separation, i.e., activation in distinct temperature windows, favors the block polymer formation by circumventing the sterically unfavorable enzymatic macroinitiation from polystyrene. To the best of our knowledge, this provides the first example of a metal-free chemoenzymatic one-pot cascade polymerization.

Chemoenzymatic Cascade Resolution Polymerization. The concept of one-pot chemoenzymatic cascade polymerization provides a new route to functional polymers provided the unique features of enzyme catalysis, such as its enantioselectivity, are retained during the process. We therefore extended our approach to a chemoenzymatic one-pot kinetic resolution polymerization of racemic 4-methyl-ϵ-caprolactone (4MeCL). It has been reported in the literature that CALB polymerizes (*S*)-4MeCL at a higher rate than the *R*-enantiomer, resulting in polymers with high enantiomeric excess (ee).[13,22] Typically, in a kinetic resolution of enantiomers, the reactivity of the less favored enantiomer is not zero, i.e., the (*R*)-4MeCL will be consumed once the conversion of (*S*)-4MeCL approaches 100% at 50% total monomer conversion. Therefore, the net ee_p value of the polymer depends strongly on the conversion at which the polymerization is stopped. Enantioenriched polymers are easily achieved in homopolymerizations of racemic 4MeCL by precipitation at the respective monomer conversion. In the case of the one-pot chemoenzymatic synthesis of block copolymers comprising an enantioenriched poly((*S*)-4MeCL) block, the remaining (*R*)-4MeCL cannot be removed from the reaction mixture, although at a lower rate it would continuously be

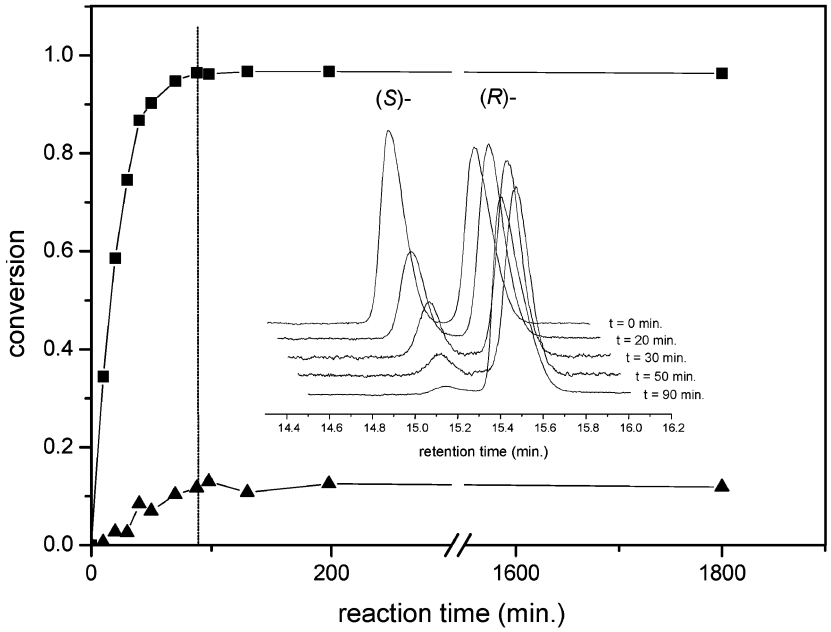


Figure 4. Conversion of *(R)*- (▲) and *(S)*-4-methyl-ϵ-caprolactone (■) from a racemic mixture employing **1** and Novozym 435 in a one-pot cascade kinetic resolution polymerization. The dotted line indicates the addition of paraoxon (enzyme inhibitor). Values are obtained from chiral GC (inset).

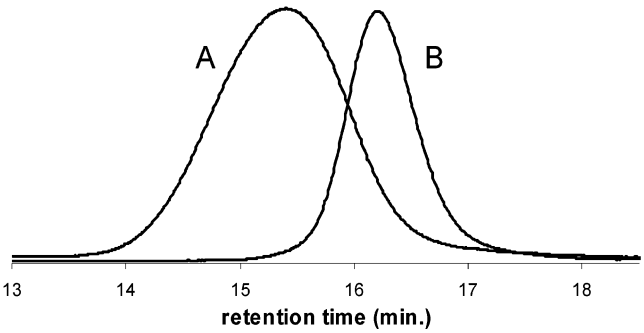


Figure 5. SEC trace of block copolymer obtained in the one-pot cascade kinetic resolution polymerization before (A) and after (B) degradation of the PCL block (Table 1, entries C1 and C1.1).

polymerized by the enzyme during the LFRP of St. To realize high ee values in a one-pot chemoenzymatic reaction, the enzymatic polymerization of 4MeCL has to be quenched at about 50% total monomer conversion before the temperature is increased to initiate the LFRP. This can be accomplished by adding paraoxon, a known irreversible inhibitor for CALB.[23] The efficiency of this procedure was successfully tested in a control reaction, i.e., the enzymatic resolution polymerization of racemic 4MeCL. Inspection of Figure 4 shows the expected fast conversion of (*S*)-4MeCL reaching ca. 95% within 90 min. A slowly increasing conversion of the *R*-enantiomer is observed at this point (10%). Upon addition of a solution of paraoxon in toluene, no further activity of the enzyme was detected.

The chemoenzymatic one-pot synthesis of enantioenriched block copolymers was conducted according to the synthetic protocol developed for the synthesis of P(CL-*b*-St). The reaction mixture containing 4MeCL, St, Novozym 435, and **1** was heated to 45 °C, and consumption of *(R)*- and *(S)*-4MeCL was monitored by chiral GC and ^{1}H NMR on samples withdrawn from the reaction mixture. When the conversion of (*S*)-4MeCL approached 100%, paraoxon was added to the reaction. Subsequently, the reaction mixture was heated to 100 °C for 90 h. A polymer with a molecular weight of 15 kDa and a polydispersity of 1.4 was recovered from this reaction (Table 1, entry C1). Figure 5 shows the corresponding GPC traces of the recovered polymer and the product obtained after degradation of the polyester block. Comparable to Figure 3, both traces are well separated, providing strong evidence that the proposed block copolymer structure was obtained from the one-pot reaction. It has to be noted that similar results were obtained independent of whether the freeze−pump−thaw cycles were conducted prior to the reaction (C1) or immediately before the temperature was increased for the LFRP (C2).

From the ee of the unreacted monomer ($ee_m = 64\%$), an ee_p of the P(4MeCL) block of 86% was calculated for block copolymer C1. The specific rotation $[\alpha]^{25}_D$ of the block copolymer is −2.6°. This is in good agreement with the optical rotation of −7.2° reported by Bisht for P((*S*)-4MeCL) with an ee_p of 90% considering that the block length ratio of chiral to nonchiral block in our block copolymer is ca. 2:1.[22]

Conclusions

In this paper we describe a novel chemoenzymatic approach toward polymeric materials by integration of metal-free enzymatic ROP with nitroxide-mediated LFRP from a bifunctional initiator. Block copolymers were obtained in a cascade approach without an intermediate transformation or workup step. The results imply that the temperature-induced kinetic separation favors the block copolymer formation by circumventing the sterically unfavorable polystyrene macroinitiation. The unique characteristics of enzyme catalysis such as a high stereoselectivity are retained in the process as shown in the synthesis of chiral block copolymers by this cascade approach.

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(26) Although it is known that nitroxide polymerization is most effective at 120 °C, a lower temperature of 95 °C was applied here to maintain enzyme activity for possible completion of the eROP. A higher reaction temperature would, however, significantly shorten the reaction time for the nitroxide-mediated polymerization. For reasons of comparability, a reaction temperature of 95 °C was also applied in the chemoenzymatic cascade resolution polymerization.

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