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ARTICLE

Poly(lactide)-*block*-Poly(HEMA) Block Copolymers: An Orthogonal One-Pot Combination of ROP and ATRP, Using a Bifunctional Initiator

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ABSTRACT: We describe an orthogonal polymerization strategy for the preparation of amphiphilic poly(lactide)-*block*-poly(2-hydroxyethyl methacrylate) (PLA-*b*-PHEMA) copolymers with a partially biodegradable and a potentially biocompatible polymer backbone segment. The strategy is based on an orthogonal polymerization from a double-headed initiator, which has been realized in a rapid one-pot or in a two-pot route. The "lactide first" strategy permits exclusive chain growth from the hydroxyl group of the initiator, 2-hydroxyethyl 2-bromo-2-methylpropanoate. 2-Hydroxyethyl methacrylate (HEMA) was polymerized in a second step by controlled radical polymerization (ATRP) without the use of hydroxyl protecting groups. Because of the heterogeneous character of the two blocks, ATRP had to be conducted in dimethyl sulfoxide at 80 °C, both granting sufficient solubility for the stereoregular, semicrystalline poly(lactide) block and permitting fast chain growth of the poly(HEMA) block. The PLLA/PDLA macroinitiators were synthesized using $Sn(Oct)_2$ as a catalyst in solution (PDI = 1.07−1.17; M_n = 2000−9000 g/mol). NMR spectroscopy and MALDI-ToF MS confirmed complete terminal functionalization with the bifunctional initiator 2-hydroxyethyl 2-bromo-2-methylpropanoate. Fast growth (< 10 min, 45−60% conversion) of the poly(HEMA) block was achieved with a CuCl/bipyridine or $CuCl/CuCl_2$/bipyridene system. SEC measurements indicated complete attachment of the second block resulting in narrow polydispersity of M_w/M_n = 1.2−1.3 (M_n = 5000−9000 g/mol). Developing the concept further, removal of residual lactide monomer and $Sn(Oct)_2$ catalyst has been proven to be redundant by a variation in the synthetic procedure. In consistence with new AGET (activators generated by electron transfer) ATRP methods, grafting of free lactide monomer onto the HEMA backbone could be avoided by oxidative deactivation of $Sn(Oct)_2$ by small amounts of copper(II), obtaining the PLA-*b*-PHEMA block copolymers in one single step. DSC measurements demonstrate phase segregation of the blocks after cooling from the melt as well as work-up from solution.

Introduction

Acrylate- and lactone-based materials find application in the fabrication of polymer systems for a variety of biomedical application. While the former group offers access to nondegradable, but readily tunable systems in terms of e.g. hydrophilicity,[1,2] pH- and temperature-induced phase behavior,[3] and loading with therapeutic agents[4] by simple variation of the acrylate substituent, the latter often offers access to a hydrophobic polyester backbone, which is in vivo degradable to nontoxic components. This feature renders copolymers consisting of these blocks highly interesting for a variety of biomedical applications, ranging from controlled release systems in drug delivery[5] to the fabrication of degradable surgical implants. Further advantages of the combination of these blocks include the selective introduction of large amounts of functional groups via the polyacrylate block, the generation of amphiphilic block copolymers,[6] and partially biodegradable structures.[7]

Nevertheless, only a few examples for the synthesis of polyester-*block*-polyacrylate copolymers via ROP of a lactone and controlled radical polymerization of an acrylate have been described in the literature so far.[8−11] From the vast number of potential comonomer combinations, lactide and 2-hydroxyethyl methacrylate (HEMA) based polymers have not been combined to block copolymer systems to date, although each of these polymers represents successfully employed and important materials with respect to biomedical applications. While poly(HEMA) exhibits excellent blood compatibility[12] and is furthermore widely used in the fabrication of intra ocular and soft contact lenses, poly(lactic acid) is fully biocompatible and biodegradable.[13]

However, combinations of poly(HEMA) and polyester systems in general are not completely unknown and have been realized in a few works in different approaches. Copolymerization via α,ω-heterobifunctional acrylate macromonomers[14] with HEMA was exploited for the formation of degradable hydrogels. Ratner et al. synthesized these materials for tissue engineering applications from oligo(caprolactone) macromonomers, relying on ATRP copolymerization with 2-hydroxyethyl methacrylate.[15] Furthermore, poly(HEMA) homo- and block copolymers have proven to be suitable for grafting poly(caprolactone) and poly(lactide) onto the primary hydroxyl groups.[16−20]

Examples for the use of poly(lactide)s as macroinitiators are rare. To date, the combination of ROP and ATRP has been applied successfully in the synthesis of star−block copolymers.[21−23] Recently, we reported on the synthesis of biocompatible multiarm star−block copolymers based on a hyperbranched polyglycerol macroinitiator with 56−90 poly(HEMA) arms.[24] Storey et al. were the first to use (α,ω)-chloride-functionalized PLA as macroinitiators in an ATRP-based acrylate polymerization leading to triblock copolymers.[25] A first step toward the synthesis of linear poly(acrylate)/poly(ester) block copolymers with intended application in drug delivery was presented by Wulff et al. and Guillaume et al. in the form of poly(methyl methacrylate)−poly(vinyl sugars)[26] and poly(methyl methacrylate)−poyl(caprolactone)[9]

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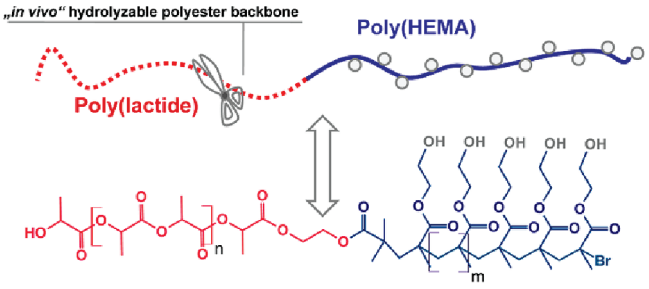


Figure 1. Poly(lactide)-*block*-poly(HEMA) copolymer structure, illustrating its potential use as a drug carrier.

block copolymers. Unlike the synthetic strategy presented in this paper, the polyester macroinitiators used in these works were obtained by postpolymerization modification of the polyester end groups, resulting in a procedure comprising at least three synthetic steps. An elegant route to ATRP/ROP based A_2B_2 PCl/acrylate miktoarm polymers involving a double-headed, tetrafunctional initiator was presented by Hadjichristidis et al.[27] We modified the concept using a heterofunctional initiator[10] to combine dilactide and HEMA in a block copolymer without the use of hydroxyl protecting groups (Figure 1).

In this work we present the first example of a one-pot synthesis of a poly(lactide)−poly(HEMA) block copolymer by a synthetic two-step ROP/ATRP strategy, involving a double-headed initiator. We demonstrate that the synthesis can be carried out in one pot without intermediate work-up.

Experimental Part

Instrumentation. NMR investigation: All ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded at 25 °C, using a Bruker AC 300 (300 MHz) or a Bruker AMX 400 (400 MHz) spectrometer. The spectra were measured in $CDCl_3$ and DMSO-d_6, and the chemical shifts are referred to the internal calibration on the solvents' residual peaks. (^{1}H NMR signal: 2.50 ppm for DMSO-d_6 and 7.26 ppm for $CDCl_3$; ^{13}C carbon NMR signal: 39.52 ppm for DMSO-d_6 and 77.36 ppm for $CDCl_3$). For SEC measurements in DMF (containing 1 g/L of lithium bromide as an additive), an Agilent 1100 series system was used as an integrated instrument, including three HEMA-based-columns ($10^5/10^3/10^2$ Å porosity) from MZ-Analysentechnik GmbH, a UV (275 nm), and a RI detector. Calibration was achieved with poly(styrene) standards provided by Polymer Standards Service (PSS). MALDI-ToF MS measurements were performed on a Shimadzu Axima CFR MALDI-ToF MS mass spectrometer, equipped with a nitrogen laser delivering 3 ns laser pulses at 337 nm. Dithranol, 1,8-dihydroxy-9(10*H*)-anthracetone (Aldrich, 97%), was used as a a matrix. Potassium triflate (Aldrich, 98%) was added for ion formation. The best results were obtained for samples prepared from chloroform solution by mixing matrix (10 mg/mL), polymer (10 mg/mL), and salt (0.1 N solution) in a ratio of 5:1:1. A volume of 0.9 μL sample solution was deposited on the MALDI target and allowed to dry at room temperature for 2 h prior to the measurement. Differential scanning calorimetry (DSC) measurements were carried out on a Perkin-Elmer 7 Series thermal analysis system with autosampler in the temperature range of 0−200 °C at a heating rate of 10 K/min. The melting points of indium (T_m = 156.6 °C) and Millipore water (T_m = 0 °C) were used for calibration.

Materials. All solvents were of analytical grade. In order to remove the stabilizer, THF used for dialysis was freshly distilled prior to use. HEMA was purified according to literature procedures prior to polymerization.[24] Stanneous 2-ethylhexanoate ($Sn(Oct)_2$) (99%) was purchased from Acros and used as received. Deuterated chloroform-d_1 and DMSO-d_6 were purchased from Deutero GmbH and dried and stored over molecular sieves. DMSO and DMSO-d_6 were degassed by three freeze−pump−thaw cycles without previous drying of the solvent. Dilactide was purchased from Purac/Gorinchem (Netherlands) and recrystallized three times from dry toluene and stored under vacuum prior to use. Dialysis of block copolymers was performed with Cellu SepH1 membranes with a molecular weight cutoff of 1000 g/mol.

Initiator Synthesis. *2-Hydroxyethyl 2-Bromo-2-methylpropanoate (HBMP).* 93.06 g (1.50 mol) of dry glycol and 6.48 g (0.064 mol) of dry triethylamine were placed in a 500 mL round-bottom flask, kept under a nitrogen atmosphere. Within 2 h, 14.6 g (0.063 mol) of 2-bromoisobutyryl bromide was added at 0−5 °C. After an additional hour the reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was warmed to 50 °C for 15 min. 200 mL of water was added and extracted with 3×80 mL of chloroform. The organic phase was subsequently washed with 50 mL of 1 N hydrochloric acid, saturated sodium carbonate solution, and brine. After drying over magnesium sulfate, the solvent was evaporated, and the product was purified by distillation in vacuum (83 °C/0.1 mbar). 7.79 g (58%) of a colorless oil was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ^{1}H/ppm: 1.85 (s, 1H, −O*H*); 1.97 (s, 6H, −CH_3); 3.89 (t, ^3J = 4.5 Hz, 2H, −CH_2OH); 4.33 (t, ^3J = 4.5 Hz, −OCHH_2−).

General Procedures for the Synthesis of the First Block: Poly(L-lactide)/Poly(D-lactide) Macroinitiators (Route A): Two-Step Approach. 2-Hydroxyethyl 2-bromo-2-methylpropanoate and lactide were charged to a Schlenk tube at predetermined molar ratio (see Table 1), sealed with a rubber septum, and repeatedly flashed with argon after evacuation. Freshly distilled toluene (2 mL/g dilactide) was added via a syringe, and the tube was immersed in an oil bath heated to 120 °C. Polymerization was initiated after 2 min by injecting a 5% solution of the catalyst $Sn(Oct)_2$ in toluene corresponding to 0.1% of the monomer. Polymerization was quenched after 18 h by cooling to room temperature. An aliquot of the sample for conversion analysis was harvested prior to precipitation in excess methanol. The polymer was collected by centrifugation or filtration and taken up in CH_2Cl_2 for a second precipitation in diethyl ether. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ^{1}H/ppm: 1.57 (d, ^3J = 7.0 Hz CHCH_3, poly(lactide) chain); 1.91 (s, BrC(CH_3)$_2$; 4.34 (q, ^3J = 7.0 Hz HOC*H*(CH$_3$)); 4.31−4.46 (m, −OCHH_2CH_2O−); 5.15 (q, ^3J = 7.0 Hz C*H*(CH$_3$), poy(lactide) chain).

General Procedures for the Synthesis of the Second Block: ATRP of HEMA in DMSO (Route A): Two-Step Approach. In a typical polymerization, the poly(lactide) macroinitiator (MI) (0.5 g), bipyridine [L], and HEMA [M] were placed in a Schlenk tube in the ratio of MI[1]:L[2]:M[50] and subsequently dissolved in 4 mL of DMSO. Argon was bubbled through the mixture for 20 min, followed by degassing in three freeze−pump−thaw cycles. The mixture was immersed in an oil bath and heated to 80 °C. The polymerization was initiated by adding an equivalent of CuCl(I) under argon counterflow. The reaction vessel was subsequently sealed with a rubber septum. Polymerization was quenched rapidly by cooling by immersing the tube in an ice bath (upon which the polymer remained soluble). The mixture was diluted with THF and flashed over a short column with neutral aluminum oxide to remove the copper catalyst. Residual HEMA monomer was removed by precipitation in methanol. To remove traces of low molecular weight compounds for DSC analysis, the block copolymer was dialyzed in $CHCl_3$/MeOH (1:1) or THF for 2 days with a molecular weight cutoff of 1000 g/mol. After drying in vacuum, a white solid was obtained. ^{1}H NMR (DMSO-d_6, 400 MHz) δ ^{1}H/ppm: 0.70−1.10 (m, C(CH_3)(COOCH$_2$CH$_2$OH)); 1.28 (d, ^3J = 7.0 Hz HOCH(CH_3), poly(lactide) *term. unit*); 1.46 (d, ^3J = 7.0 Hz OCH(CH_3), poly(lactide) chain), 1.70−2.05 (m, −CH_2C(CH$_3$)(COOCH$_2$CH$_2$OH)); 3.58 (s, −COOCH$_2$CH_2OH); 3.89 (s, −COOCH_2CH$_2$OH); 4.20 (p, ^3J = 7.0 Hz HOC*H*(CH$_3$); poly(lactide) *term. unit*); 4.82 (s, −COOCH$_2$CH$_2$O*H*); 5.20 (q, ^3J = 7.0 Hz C*H*(CH$_3$); poy(lactide) chain); 5.48 (d, ^3J = 6.0 Hz *H*OCH-(CH$_3$), poly(lactide) *term. unit*).

Table 1. Molecular Weights and Composition Data for PLA-Based Macroinitiators and the Resulting PLLA-*b*-PHEMA Block Copolymer

polymer	initiator (I)	monomer (M)	M/I	M_n theor (100% conv)	M_n (NMR)	polym time	conv (NMR)	M_n (SEC)	PDI	composition (NMR)
PLLA-MI 1	2-HBMP	L-lactide	20	3100	2980	18 h	0.91	3500	1.17	$PLLA_{19}$
PLLA-MI 2	2-HBMP	L-lactide	20	3100	2620	18 h	0.85	3200	1.09	$PLLA_{17}$
PLLA-MI 3	2-HBMP	L-lactide	50	7420	6910	18 h	0.93	8600	1.17	$PLLA_{46}$
PDLA-MI 4	2-HBMP	D-lactide	30	4540	4500	18 h	0.99	6500	1.15	$PDLA_{30}$
PLLA-MI 5	2-HBMP	L-lactide	40	5980	5320	18 h	0.89	5800	1.08	$PLLA_{37}$
PLLA-MI 6	2-HBMP	L-lactide	20	3090	2780	18 h	0.90	3400	1.07	$PLLA_{27}$
PHEMA[b]	2-HBMP	HEMA	50	6930	2750	80 min	0.40	5900	1.25	$PHEMA_{20}$
PLLA-*co*-PHEMA 1	PLLA-MI 1	HEMA	50	9490	6510	320 min	0.54	10800	1.30	$PLLA_{19}$-*b*-$PHEMA_{26}$
PLLA-*co*-PHEMA 2[a]	PLLA-MI 2	HEMA	50	9130	6150	47 h	0.53	10200	1.27	$PLLA_{18}$-*b*-$PHEMA_{29}$
PLLA-*co*-PHEMA 3[b]	PLLA-MI 2	HEMA	50	9130	5100	80 min	0.38	8400	1.21	$PLLA_{18}$-*b*-$PHEMA_{21}$
PLLA-*co*-PHEMA 4	PLLA-MI 2	HEMA	50	9130	5140	160 min	0.38	8400	1.28	$PLLA_{18}$-*b*-$PHEMA_{21}$
PLLA-*co*-PHEMA 5	PLLA-MI 3	HEMA	100	19900		7 h		13200	1.32	$PLLA_{46}$-*b*-$PHEMA_{XX}$
PLLA-*co*-PHEMA 6	PLLA-MI 2	HEMA	50	9130		7 h		9700	1.28	$PLLA_{18}$-*b*-$PHEMA_{XX}$
PDLA-*co*-PHEMA 7	PDLA-MI 4	HEMA	70	13600	8750	320 min	0.46	13100	1.27	$PDLA_{30}$-*b*-$PHEMA_{33}$
PLLA-*co*-PHEMA 8[a]	PDLA-MI 5	HEMA	140	23500	14900	80 min	0.51	22000	1.24	$PLLA_{37}$-*b*-$PHEMA_{74}$
PLLA-*co*-PHEMA 9[a]	PDLA-MI 6	HEMA	70	11900	6550	80 min	0.41	9100	1.18	$PLLA_{18}$-*b*-$PHEMA_{29}$

[a] Synthesized without prior work-up of the macroinitiator in a one-pot reaction. [b] Polymerization in DMSO-d_6 with conversion analysis.

Modification of the Synthetic Route to a One-Pot Procedure (Route B): General Procedure for the ROP of Lactide with Subsequent ATRP of HEMA in DMSO. The polymerization of lactide (0.5 g) was conducted in a rubber sealed Schlenk tube, as described above. After 18 h the polymerization was quenched, and toluene, which was used as the polymerization medium, was removed by freeze-drying. Subsequently, bipyridine [L] and HEMA [M] were added in a ratio of MI[1]:L[2]:M[50] and subsequently dissolved in 4 mL of DMSO-d_6. After degassing the mixture by three freeze−pump−thaw cycles, a mixture of Cu(I)Cl[1]:Cu(II)Cl_2[0.05] was added to the preheated reaction mixture (80 °C) under an argon stream. Polymerization and work-up of the samples were carried out as described above.

Results and Discussion

Poly(HEMA) and poly(lactide) represent two highly established polymer materials in the field of biocompatible polymers for medical and healthcare applications. Despite many interesting implications of such a topology, these polymers have not yet been combined to block copolymers to the best of our knowledge. ATRP of acrylates and ROP of cyclic esters are fully orthogonal polymerization methods, which motivated us to combine both techniques. 2-Hydroxyethyl-2-bromo-2-methylpropanoate (HBMP), which was introduced by Matyjaszewski et al.,[8] was chosen as an asymmetric bifunctional initiator for the block copolymer synthesis. The primary nature of the hydroxyl group and the tertiary α-carboxy halogenide ensures fast initiation for both ROP and ATRP, respectively, rendering the compound suitable as a double-headed initiator. The advantage of this approach lies in the redundance of protective groups for the poly(HEMA) backbone, when starting with a polylactide-first strategy that gives access to an α-hydroxy, ω-bromoester-telechelic macroinitiator for ATRP. Limited solublity of the polylactide-based macroinitiator in polar solvents and solvent mixtures like water/methanol, methanol,[28] and 1-propanol/MEK[29] necessitated substitution of these conventional solvents known to be suitable for the ATRP of HEMA. DMSO is rarely used in this context but represents a good solvent for the ATRP of HEMA. It guarantees both sufficient solubility of the stereoregular poly(L-lactide) (PLLA)/poly(D-lactide) (PDLA) macroinitiator and good reactivity for the polymerization of HEMA. The use of a protective group (e.g., the trimethylsilyl group (TMS)[30]), which would permit performing the polymerization in a less polar solvent, would require further synthetic steps that were avoided in this manner. Both synthetic approaches developed in the current paper are shown in Scheme 1. The two-pot approach involving purification of the PLLA block will be discussed first (route A) in the ensuing paragraph, since it permitted detailed characterization of the telechelic PLLA block precursor with respect to full terminal functionalization. Subsequently, it will be demonstrated that the polymerization can also be carried out in one reaction vessel, omitting the intermediate purification step (route B, Scheme 1).

A. Two-Pot Approach: Route A. MALDI-ToF spectrometry is a crucial method to support quantitative functionalization of all polymer chains formed and thus to monitor the first step of the block copolymer synthesis. A typical MALDI-ToF spectrum, obtained after formation of the PLLA block, is presented in Figure 2. The spectrum indicates complete attachment of the bromoisobutyryl group to the PLA backbone. This is also confirmed by comparison of NMR signal intensities from the α- with the ω-telechelic end group of the PLA formed. The extent of transesterification was minimized by thermal quenching of the reaction mixture before reaching the polymer/monomer equilibrium. Consequently, narrow PDIs (1.09−1.17, Table 1) and only a minor subdistribution of PLLA species with a noneven number of lactic acid repeat units is observed in the MALDI-ToF spectrum. As can be shown by ^{1}H NMR spectroscopy and is also indicated by the MALDI-ToF data, molecular weights of the linear poly(L-lactide) macroinitiators are overestimated by SEC in DMF (calibrated with polystyrene standards). A correction factor of 0.81 for molecular weights determined by SEC appears to be appropriate for the analyzed mass range (2000−8000 g/mol), assuming that the MALDI-ToF values are representative of the actual molecular weights and molecular weight distribution. This is not unreasonable in our case, since the PLA samples possess narrow molecular weight distribution and the MALDI-ToF spectrum (Figure 2) is symmetrical.

In the usual procedure (Scheme 1: route A), prior to polymerization of the second block, poly(lactide)s were precipitated in (1) methanol and (2) diethyl ether to remove residual (lactide) monomer and catalyst.

To promote fast initiation and quantitative attachment of HEMA to the poly(lactide) macroinitiator, we used the mixed halide exchange technique, changing from bromine to chlorine.[31] ATRP conducted with CuCl(I) instead of CuBr(I) in DMSO was sufficiently fast to guarantee short polymerization times, as could be shown by a time-dependent conversion

analysis in DMSO-d_6 (Figure 3). In fact, we were not able to monitor the onset and early stage of the polymerization. The first value obtained after 5 min already revealed a conversion of 32−34%, which is fairly high compared to a total conversion of ~39% obtained after 90 min. Although we assume that the polymerization kinetics is of a living nature in the early phase of the reaction, the polymerization rate significantly decreases in the examined period, as the $\ln([M_0]/[M_t])$ vs conversion plot in Figure 3 indicates. Apart from bi- or monomolecular termination reactions, oxidation due to air unintentionally introduced during sample harvesting cannot be totally precluded. It is important to note that the polymer nature of the PLA-macroinitiator had no effect on the ATRP reaction rate, which is a consequence of its excellent solubility in DMSO at 80 °C, i.e., at the polymerization conditions employed for the synthesis of the poly(HEMA) block. Thus, we were able to use the well-established combination of Cu(I)Cl and 2,2′-bipyridine as ATRP-mediating transition metal complex. Although no copper(II) salt was added as regulating deactivator at the beginning of the polymerization, polydispersities could be kept low ($M_w/M_n = 1.21-1.30$; cf. Table 1), and no significant amount of prematurely terminated macroinitiator was detected.

SEC data confirm complete attachment of the second block to the PLA macroinitiators (PLA-MI) with a symmetrical, monomodal molar mass distribution of the block copolymers. Figure 5 shows a clean shift of the distribution mode toward lower elution volumes. Only the first samples taken (after 5 and 10 min polymerization time) show a small shoulder toward higher elution volumes (lower molecular weights). Since we employed the mixed halide exchange technique to prevent slow initiation, we assume that this phenomenon is attributed to slow propagation immediately after initiation. This could be explained by an enhancement in the reactivity of the chain ends with increasing amount of HEMA units attached, since the reaction medium DMSO presumably represents a better solvent for PHEMA (homopolymer is readily soluble in DMSO at room temperature) than for poly(lactide), which is only poorly soluble in DMSO

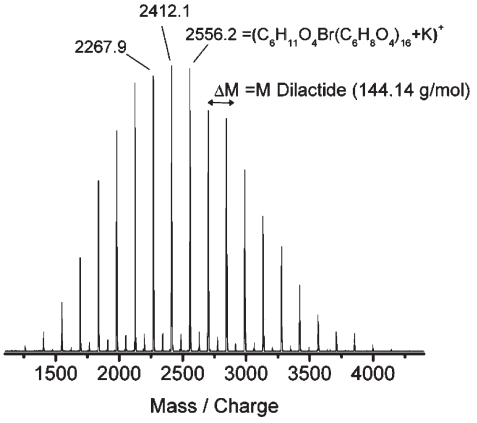


Figure 2. MALDI-ToF spectrum of PLLA-MI 2, supporting quantitative attachment of the bifunctional initiator to the PLA block.

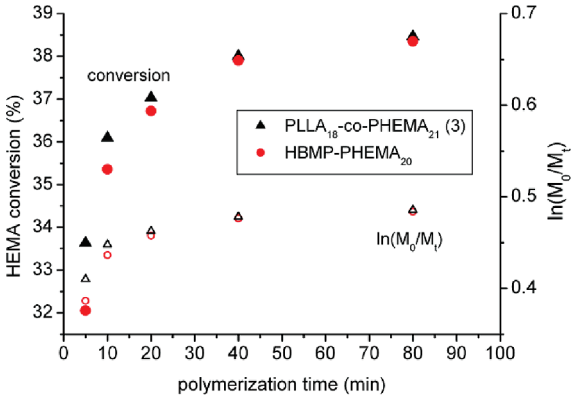
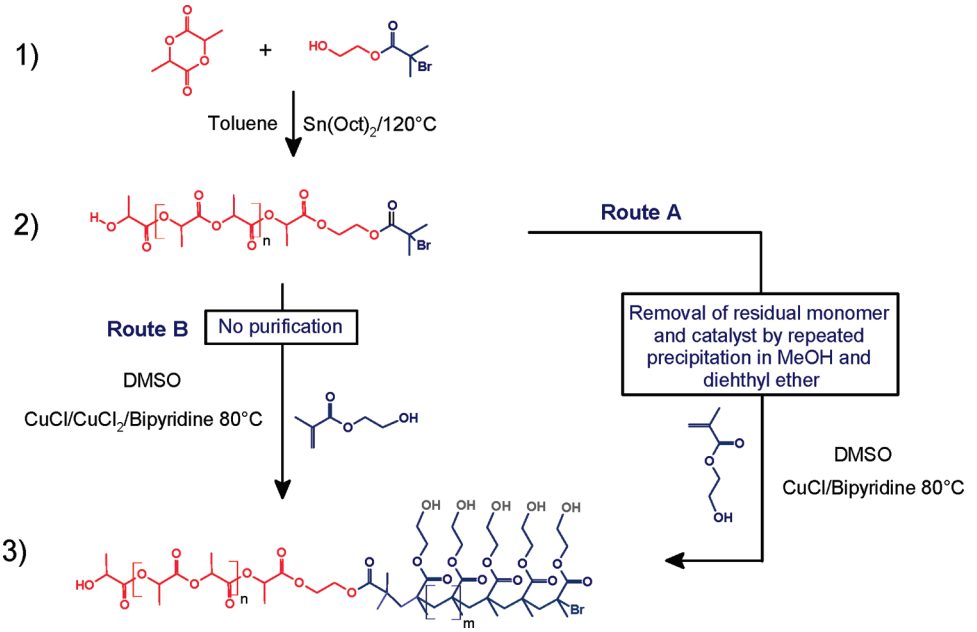


Figure 3. Development of HEMA conversion and $\ln([M_0]/[M_t])$ in the course of the ATRP reaction, using 2-hydroxyethyl-2-bromo-2-methylpropionate (HBMP) (circles) and a PLLA−HBMP−macroinitiator (triangles).

Scheme 1. Synthesis of Poly(lactide)-*block*-Poly(HEMA) Copolymers by Ring-Opening Polymerization of Lactide Initiated from the Hydroxyl Moiety of the Initiator and Subsequent ATRP of HEMA, Initiated by the Isobutyryl Bromide Part of the α-Haloester[a]



[a] Two routes, with (route A) and without prior workup of the macroinitiator (route B), have been employed successfully in the synthesis of block copolymers. Molecular characterization data of the polymers obtained are summarized in Table 1.

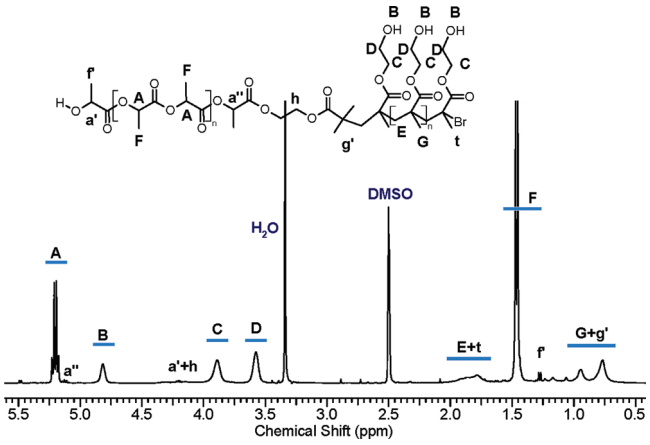


Figure 4. ^{1}H NMR spectrum (400 MHz) of $PDLA_{30}$-*b*-$PHEMA_{33}$ in DMSO-d_6 (after purification by dialysis).

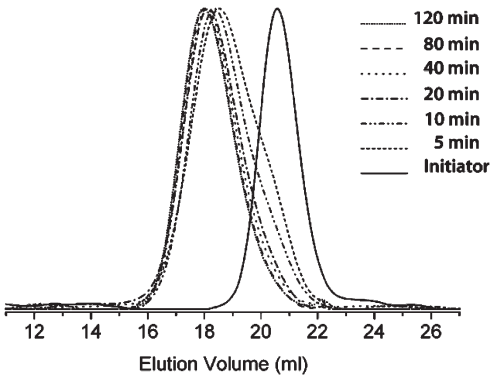


Figure 5. Kinetic study of the chain growth of PLLA-MI 2 to $PLLA_{18}$-*b*-$PHEMA_{XX}$(5).

(at room temperature and in the molecular mass range presented). Hence, this effect is strongest in the early phase of the reaction, when poly(lactide)s with only few HEMA units attached are still present. Nevertheless, it can be concluded that no undesired homopolymer is present.

Molar mass evaluation by SEC (DMF, calibration with polystyrene standards) shows an overestimation of molecular weights of the PLA−PHEMA block copolymers compared to the more reliable results obtained from ^{1}H NMR spectra, which lead to well-distinguishable signals from both block copolymers. The ^{1}H NMR structure/signal assignment is shown in Figure 4. The terminal groups of the poly (lactide) are clearly distinguishable from the backbone signals in this well-resolved spectrum (the respective chemical shifts are given in the Experimental Part). Furthermore, no residual HEMA and dilactide monomer could be observed after work-up.

B. One-Pot Approach: Route B. Since the introduction of the initiator for both blocks in the first step avoids a postpolymerization functionalization with an ATRP initiator, it is an intriguing issue whether one can further simplify the synthesis to a two-step, yet *one-pot*, procedure, in which a prior purification of the poly(lactide) macroinitiator is redundant. As has been pointed out before, the $Sn(Oct_2)$-promoted ring-opening polymerization is known to be accompanied by side reactions like inter- and intramolecular transesterification, since $Sn(Oct_2)$ acts as a transesterification catalyst when approaching the polymer/monomer equilibrium. Therefore, quenching of the polymerization prior or close to completion of the monomer consumption is crucial

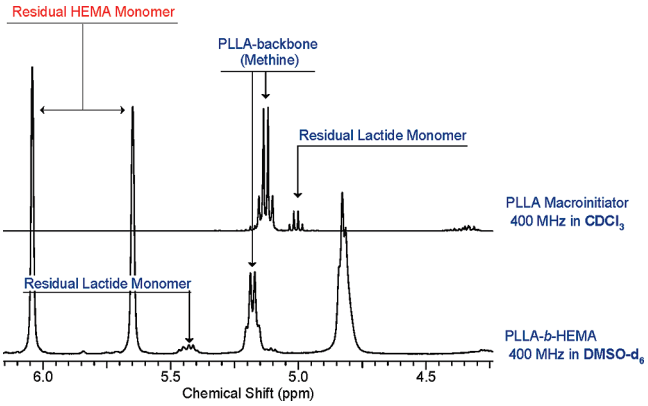


Figure 6. ^{1}H NMR spectra PLLA-MI 6 of and the corresponding block copolymer $PLLA_{18}$-*b*-$PHEMA_{29}$ prepared thereof.

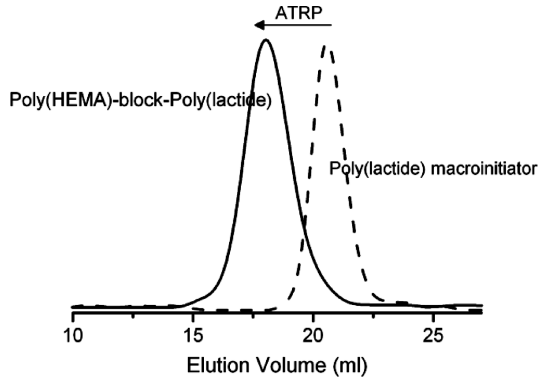


Figure 7. SEC elugram of PLLA-MI 2 which is converted into $PLLA_{18}$-*b*-$PHEMA_{29}$ in a one-pot reaction.

to obtain well-defined PLA. In order to circumvent the intermediate purification step, it was essential that residual lactide monomer and $Sn(Oct)_2$ catalyst would not be reactive during the ATRP of HEMA. This represents a particular challenge in this case, since it has been shown in numerous works that the hydroxyethyl group of HEMA enabled facile and even simultaneous grafting and polymerization of lactones onto the poly(acrylate) backbone.[16−20] In other words, for the synthesis of block copolymers, further reaction of residual lactide monomer during the ATRP of HEMA by active $Sn(Oct)_2$ species has to be prevented.

$Sn(Oct)_2$ itself has been discovered to act as an active reducing agent in the special AGET ATRP[10,32,33] polymerization, which permits the use of very small amounts of copper. In classic AGET ATRP, Cu(II), which is generated by oxidation throughout the reaction, is reduced by Sn(II) and thereby regenerates the active Cu(I) species. In our approach, we employed the AGET principle in a reverse manner to oxidatively deactivate the Sn(II) species by addition of Cu(II) in slight excess (2−3 times) to the employed amount of $Sn(Oct)_2$ (cf. Scheme 1: route B). Detailed NMR studies show that in this case the amount of residual lactide monomer does not decrease throughout the ATRP of HEMA. Figure 6 shows the lactide/PLLA methyl group related groups of protons, which both appear as a quartet and are well distinguishable in the NMR solvent employed (δ^1H/ppm of dilactide OCOC*H*(CH_3) (1. $CDCl_3$ = 5.03; 2. DMSO-d_6 = 5.44). Furthermore, no signals characteristic for the grafting of lactide onto the PHEMA backbone were observed.

SEC evidenced (Figure 7) that chain extension of the PHEMA block from the PLLA macroinitiator proceeded

Table 2. Thermal Properties of the $PDLA_{30}$-*b*-$PHEMA_{33}$ Block Copolymer

polymer sample	program	run	T_m (°C)	ΔH_m (J/g)	ΔH_m (J/g PDLA)	X_m[d]
$PDLA_{30}$-MI	A[b]	1	156.1	59.0	59.0	0.63
		2	152.4	67.9	67.9	0.72
		3	152.6[a]	65.6	65.6	0.70
$PDLA_{30}$-*b*-$PHEMA_{33}$	A[b]	1	137.4	28.5	51.9	0.61
		2	133.7	20.1	36.6	0.43
		3	134.1	21.1	38.4	0.45
$PDLA_{30}$-*b*-$PHEMA_{33}$	B[c]	1	135.0	31.3	57.0	0.67
		2	134.3	18.3	33.3	0.39
		3	135.2	16.9	30.8	0.36

[a] Double melting peak/center of two melting peaks. [b] (1) Program A: heating from 0 to 200 °C at 20 °C/min; (2) cooling from 200 to 120 °C at 10 °C/min; (3) holding at 120 for 15 min; (4) cooling from 120 to 0 °C. [c] (1) Program B: heating from 0 to 200 °C at 10 °C/min; (2) cooling from 200 to 0 °C at 10 °C/min. [d] Degree of crystallization.

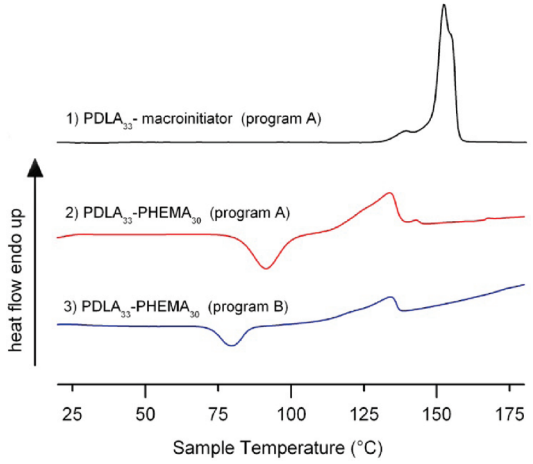


Figure 8. Heating traces (second heat run) of PDLA macroinitiator (1) and the $PDLA_{30}$−$PHEMA_{33}$ block copolymers (2) and (3).

smoothly in the one-pot case, without the presence of unreacted PLLA macroinitiator via route B. Both conversions and polydispersities were low (1.18−1.27) and comparable to those obtained via route A after removal of residual monomer/catalyst by precipitation (Table 1).

In general, all polymers regardless of the discussed synthetic pathway were obtained as white powders, which indicates complete removal of the copper salts used in the ATRP by filtration and/or dialysis.

Thermal Characterization of the PLLA-*co*-PHEMA Block Copolymers. Differential scanning calorimetry (DSC) was conducted with a selected block copolymer sample with nearly equal block ratios of stereoregular PDLA and PHEMA, i.e., $PDLA_{30}$-*b*-$PHEMA_{33}$. The behavior of this material with two strongly incompatible blocks was of particular interest in this study in order to obtain information on phase segregation. Furthermore, the corresponding PLA macroinitiators have also been examined. In the case of the block copolymer, solvent and monomer free samples were obtained by careful drying after dialysis in THF, while the PDLA macroinitiator was examined after purification by repeated precipitation in both methanol and diethyl ether and subsequent drying in vacuum. The theoretical enthalpy of fusion (ΔH_f) for a pure PDLA crystal (100% degree of crystallization) was calculated to be 93.7 J/g by extrapolation by Fischer et al.[34] The crystalline PDLA macroinitiator exhibits a distinct melting peak at 156 °C (Figure 8) and an initial enthalpy of fusion of 59 J/g, which could be increased to 67 J/g by keeping the sample at 120 °C for extended periods. This represents a high degree of crystallization. These results are in good agreement with the high mobility of the relatively short polymer chains (M_n = 4500 g/mol), resulting in a high crystallization rate that is typical for low molecular weight PDLA and PLLA.[35]

The block copolymer was examined employing two different temperature programs. Program A (Table 2) involved a tempering step at 120 °C to promote crystallization, while program B was conducted by direct heating and cooling at 10 °C/min for comparison (Figure 8). The heating trace of the macroinititor does not exhibit a recrystallization peak in the heating run, suggesting completion of the crystallization during the previous cooling scan. This is not the case for the block copolymer which shows recrystallization exotherms during the heating process at (A) 91.4 °C and (B) 79.5 °C with matching crystallization/melting enthalpies. The initial (first heating run) degrees of crystallization (X_m) (61%) of the PDLA block copolymer correspond to the macroinitiator homopolymer. Interestingly, glass transitions were not observed for the examined homo and block copolymers under the measuring conditions employed. The sample $PDLA_{30}$−MI showed a significant endothermic thermal relaxation peak during the first heating run at 56.1 °C, but no change in heat capacity could be observed in the second or third heating run. As expected, the PDLA−PHEMA block copolymer melts over a broader range (113−138 °C) and at a lower temperature compared to the macroinititor, which exhibits a rather sharp melting peak at around 134 °C. In case of the block copolymers, a glass transition of the PHEMA block might be obscured by the early onset of the endothermic melting peak of the poly(lactide) block. Since PHEMA is a noncrystalline polymer, the crystallization enthalpy can be fully attributed to the PDLA block, which represents 50.2 wt % of the total block copolymer in this case. The degree of crystallization of the block copolymer samples from the second and third heating run still leads to rather high melting enthalpies corresponding to a degree of crystallization of the polylactide block of 36−45%. In view of the peculiar structure of the present block copolymer, consisting of a cleavable polyester backbone on the one hand and a polyacrylate backbone with a large number of primary hydroxyl groups on the other, transesterification during prolonged thermal treatment (up to 200 °C) is a non-negligible issue. For instance, the sample $PDLA_{30}$-*b*-$PHEMA_{33}$ revealed a significant broadening in the molecular weight distribution (M_n: 8750; PDI: 1.27 → M_n: 7300; PDI: 2.65 (monomodal)) after three heating/cooling cycles. Nevertheless, these results confirm that the novel PLA-*b*-PHEMA block copolymers are present in a phase-segregated state at room temperature.

Conclusions

We have developed a rapid two-step, one-pot strategy to new poly(lactide)-*block*-poly(HEMA) block copolymers, combining

two highly established biocompatible materials. The amphiphilic, well-defined AB diblock structures are obtained by the use of a heterobifunctional initiator, employing two controlled, fundamentally different polymerization techniques: (i) ROP of dilactide and (ii) ATRP of HEMA, resulting in low polydispersities (1.18−1.3). To the best of our knowledge, such block copolymers have not been prepared to date.

Chain extension of the poly(lactide) macroinitiator with poly(HEMA) without prior work-up and removal of residual $Sn(Oct)_2$ catalyst and unreacted lactide monomer was possible by oxidative deactivation of the Sn catalyst with small amounts of Cu(II) salts in analogy to the AGET principle. In a more general sense, this work demonstrates that the use of polylactide-based macroinitiators for the ATRP of a monomer of a very different polarity is possible without additional protection/deprotection steps. Therefore, this method represents a new, general approach for the synthesis of hydrophobic polyester/hydrophilic polyacrylate copolymers in a convenient two-step sequence.

As expected from the different chemical nature of the blocks, phase segregation is observed, leading to crystalline domains of the apolar PLA in the hydrophilic poly(HEMA) matrix. The novel amphiphilic block copolymer structures can be used for the transport and release of therapeutic agents, covalently bound to the functional polymer backbone in a poly(lactide) matrix. This might result in a release behavior superior to plain incorporation by physical mixing of the biodegradable polymer matrix and the therapeutic agent.

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References and Notes

(1) Amado, E.; Augsten, Ch.; Mäder, K.; Blume, A.; Kressler, J. *Macromolecules* **2006**, *39*, 9486–9496.
(2) Save, M.; Weaver, J. V. M.; Armes, S. P.; McKenna, P. *Macromolecules* **2002**, *35*, 1152–1159.
(3) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *Macromolecules* **1993**, *26*, 2496–2500.
(4) Barz, M.; Tarantola, M.; Fischer, K.; Schmidt, M.; Luxenhofer, R.; Janshoff, A.; Theato, P.; Zentel, R. *Biomacromolecules* **2008**, *9*, 3114–3118.
(5) Jeong, B.; Bae, Y. H.; Lee, D. S.; Kim, S. W. *Nature (London)* **1997**, *388*, 860–862.
(6) Weaver, J. V. M.; Bannister, I.; Robinson, K. L.; Bories-Azeau, X.; Smallridge, M.; McKenna, P.; Armes, S. P. *Macromolecules* **2004**, *37*, 2395–2403.
(7) Noga, D. E.; Petrie, T. A.; Kumar, A.; Weck, M.; García, A. J.; Collard, D. M. *Biomacromolecules* **2008**, *9*, 2056–2062.
(8) Jakubowski, W.; Lutz, J. F.; Slomkowski, S.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1498–1510.
(9) Schappacher, M.; Fur, N.; Guillaume, S. M. *Macromolecules* **2007**, *40*, 8887–8896.
(10) Jakubowski, W.; Matyjaszewski, K. *Macromol. Symp.* **2006**, *240*, 213–223.
(11) Messman, J. M.; Scheuer, A. D.; Storey, R. F. *Polymer* **2005**, *46*, 3628–3638.
(12) Prasitsilp, M.; Siriwittayakorn, T.; Molloy, R.; Suebsanit, N.; Siriwittayakorn, P.; Veeranondha, S. *J. Mater. Sci.: Mater. Med.* **2003**, *14*, 595–600.
(13) Vert, M.; Li, S. M.; Spenlehauer, G.; Guerin, P. *J. Mater. Sci.: Mater. Med.* **1992**, *3*, 432–446.
(14) Barakat, I.; Dubois, P.; Jérôme, R.; Teyssié, P.; Goethals, E. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 2099–2110.
(15) Atzet, S.; Curtin, S.; Trinth, P.; Bryant, S.; Ratner, B. *Biomacromolecules* **2008**, *9*, 3370–3377.
(16) Ydens, I.; Degee, P.; Dubois, P.; Libiszowski, J.; Duda, A.; Penczek, S. *Macromol. Chem. Phys.* **2003**, *204*, 171–179.
(17) Lee, H.; Matyjaszewski, K.; Yu-Su, S.; Sheiko, S. S. *Macromolecules* **2008**, *41*, 6073–6080.
(18) Zhao, C.; Wu, D.; Huang, N.; Zhao, H. *J. Polym. Sci., Part A: Polym. Phys.* **2008**, *46*, 589–598.
(19) Wu, D.; Yang, Y.; Cheng, X.; Liu, L.; Tian, J.; Zhao, H. *Macromolecules* **2006**, *39*, 7513–7519.
(20) Hellaye, M. L.; Lefay, C.; Davis, T. P.; Stenzel, M. H.; Barner-Kowollik, C. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 3058–3067.
(21) Hedrick, J. L.; Trollsas, M.; Hawker, C. J.; Atthoff, B.; Claesson, H.; Heise, A.; Miller, A. D.; Mecerreyes, D.; Jérome, R.; Dubois, P. *Macromolecules* **1998**, *31*, 8691–8705.
(22) Johnson, R. M.; Fraser, C. L. *Macromolecules* **2004**, *37*, 2718–2727.
(23) Zhao, Y.; Shuai, X.; Chen, Ch.; Xi, F. *Macromolecules* **2004**, *37*, 8854–8862.
(24) Chen, Y.; Shen, Z.; Barriau, E.; Kautz, H.; Frey, H. *Biomacromolecules* **2006**, *7*, 919–926.
(25) Messman, J. M.; Scheuer, A. D.; Storey, R. F. *Polymer* **2005**, *46*, 3628–3638.
(26) Chen, Y. M.; Wulff, G. *Macromol. Rapid Commun.* **2002**, *23*, 59–63.
(27) Priftis, D.; Pitsikalis, M.; Hadjichristidis, N. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 5164–5181.
(28) Robinson, K. L.; Khan, M. A.; de Paz Báñez, M. V.; Wang, X. S.; Armes, S. P. *Macromolecules* **2001**, *34*, 3155–3158.
(29) Beers, K. L.; Boo, S.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 5772–5776.
(30) Beers, K. L.; Gaynor, S. G.; Matyjaszewski, K.; Sheiko, S. S.; Möller, M. *Macromolecules* **1998**, *31*, 9413–9415.
(31) Matyjaszewski, K.; Shipp, D. A.; Wang, J. L.; Grimaud, T.; Patten, T. E. *Macromolecules* **1998**, *31*, 6836–6840.
(32) Jakubowski, W.; Min, K.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 39–45.
(33) Min, K.; Gao, H.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2005**, *127*, 3825−3830.
(34) Fischer, E. W.; Sterzel, H. J.; Wegner, G. *Kolloid Z. Z. Polym.* **1972**, *251*, 980–990.
(35) Pan, P.; Kai, W.; Zhu, B.; Dong, T.; Inoue, Y. *Macromolecules* **2007**, *40*, 6898–6905.