AMPHIPHILIC BLOCK COPOLYMERS OF POLY(L–LACTIDE) AND POLY(2–DIMETHYLAMINOETHYL METHACRYLATE): EXPLORING SYNTHETIC PATHWAYS

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Introduction

Interest in polymers based on poly(L–lactic acid) (PLLA) has been on–going for more than three decades, as reflected in numerous publications on the synthesis and characterization of homopolymers and random and block copolymers of PLLA. This interest is related not only to the fact that PLLA is derived from renewable resources, but also to its physical and chemical properties that make it a versatile material for engineering and biomedical applications. Biodegradability and biocompatibility, along with suitable mechanical properties, make it ideal for sutures and tissue engineering [1,2]. Hydrophobicity and pH–dependent degradability allow drug encapsulation for safe and efficient drug delivery formulations [3]. On the other hand, poly(2–dimethylaminoethyl methacrylate) (PDMAEMA) is known for its bacteriostatic activity [4] and DNA–binding capabilities [5]. It can also bind other functional molecules with, for example, hydrogen–bonding or proton transfer moieties, or, after quaternization, to oppositely charged molecules, and thus allow the facile introduction of additional functions. Thus, a combination of these two polymers in one block copolymer system is expected to lead to novel pH– and stimuli–responsive materials with unique properties. Here we explore two different approaches towards PLLA–b–PDMAEMA synthesis, one using a double initiator and the other sequential initiation. Particular complications are addressed, and successfully controlled polymerization of high molecular weight block copolymers is described.

Experimental

Materials. All reagents were purchased from Aldrich; all solvents were supplied by EMD. L–lactide (LLA) was recrystallized twice from ethyl acetate distilled over P_4O_{10}. CuBr was refluxed in glacial acetic acid prior to use.

Instrumentation. ^{1}H–NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using deuterated chloroform (Aldrich) solutions containing 0.03% of tetramethylsilane (TMS) as an internal standard.

Sequential size–exclusion chromatography (SEC) and light scattering (LS) data were collected by means of a Waters 510 HPLC pump, PLgel columns (Polymer Laboratories) with 5 µm pore sizes (50x7.5, 300x7.5 and 600x7.5 mm), a Wyatt EOS RI detector and a Wyatt QUELS LS instrument (Wyatt Technology). Tetrahydrofuran (THF) with 2–3 % v/v of triethylamine (TEA) was used as the mobile phase at a flow rate of 1 mL/min. The performance of the SEC–LS system was verified using polystyrene standards. Differential scanning calorimetry (DSC) was done using a TA Instruments Q1000 DSC.

Synthesis. The 2′–hydroxyethyl 2–bromo–2–methylpropionate double–initiator was synthesized as described elsewhere [6]. Atom–transfer radical polymerization (ATRP) of DMAEMA monomer, initiated by either the double–initiator or by PLLA macroinitiators, was conducted following a procedure similar to that described elsewhere [7]. Ring–opening polymerization (ROP) of LLA monomer, initiated either by PDMAEMA macroinitiators or by the double–initiator, was carried out via a procedure similar to that described for ε–caprolactone [6].

Results and Discussion

Double initiation via ω–hydroxy PDMAEMA. The greater solubility of PDMAEMA in toluene compared to PLLA is one consideration for choosing PDMAEMA as macroinitiator. The synthesis of ω–hydroxy PDMAEMA, shown as the first step in **Figure 1**, was conducted with a minimal amount of solvent (toluene). A polymer with a molecular weight of 31,000 (n = 200) was targeted. Polymerization, monitored by NMR, was arrested at ca. 95% monomer conversion by diluting the reaction mixture with THF. The molecular weight characteristics of the macroinitiator obtained are shown in **Table 1**.

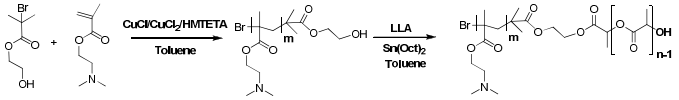

Figure 1. Synthesis of PDMAEMA–b–PLA polymers using a double initiator via ω–hydroxy PDMAEMA.

Table 1. Molecular weight characteristics of PDMAEMA and PDMAEMA–b–PLA polymerized by a double initiator via ω–hydroxy PDMAEMA.

Sample	M_n, NMR	M_n, SEC–LS	M_n, theor.	PDI
$PDMAEMA_{31k}$	—	40,700	31,400	1.20
$PDMAEMA_{31k}$–PLA_{31k}	76,500	43,600	69,500	1.18
Free PLA_{12k}	—	11,900	—	1.20

Despite the reported possibility of interaction of the PDMAEMA amino groups with tin octoate catalyst in ROP leading to its deactivation [6], L–lactide polymerized successfully (**Figure 1**, step 2). Polymerization was arrested at ca. 90% conversion by cooling the reaction mixture. The NMR spectra of the copolymer obtained showed a block ratio close to that theoretically expected, but, in addition, revealed that LLA racemized during polymerization (**Figure 2**), as shown by broad multiplets at 5.15 and 1.58 ppm instead of a quadruplet and a doublet, respectively. Thus, ROP can proceed, but stereocontrol is lacking during polymerization. This was verified by ROP of LLA in the presence of PDMAEMA homopolymer, which also leads to racemized PLA, attributed to complexation of the PDMAEMA amino groups to tin octoate.

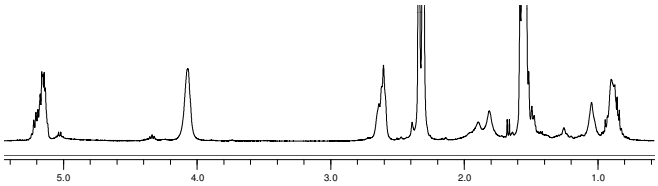

Figure 2. NMR spectra of $PDMAEMA_{31k}$–b–PLA_{31k} polymerized by a double initiator via ω–hydroxy PDMAEMA.

The molecular weight determined by LS for the PDMAEMA macroinitiator is somewhat larger than theoretically expected, whereas that for the block copolymer is much lower than theoretical as well as that determined by NMR (**Table 1**). It was also found that PDMAEMA homopolymer itself can polymerize LLA (giving racemic PLA). This implies that the amino groups of PDMAEMA, whether or not complexed with tin octoate, create alternative initiating sites for LLA polymerization, probably via a nucleophilic polymerization mechanism [8]. This leads to the formation of free PLA, thus rationalizing the discrepancy between the SEC–LS and NMR data. Direct evidence of the presence of free PLA was obtained by quaternizing the PDMAEMA block (using CH_3I in dichloromethane), leading to precipitation of the block copolymer. NMR and GPC analysis of the filtrate revealed the presence of PLA homopolymer (70% of the total PLA) with M_n = 12,000.

Double initiation via α–bromo PLLA. Next, the polymerization sequence was reversed to avoid DMAEMA and tin octoate interactions (**Figure 3**). The molecular weight of PLLA was kept low (5,000 and 10,000), to prevent precipitation of α–bromo PLLA on addition of DMAEMA monomer. Polymerization was arrested at ca. 80% conversion by cooling. NMR spectra of the PLLAs contained a well–defined quadruplet at 5.16 and a doublet at 1.58 ppm, indicating isotactic PLLA. The molecular weights of the PLLA macroinitiators were lower than expected, but with a narrow polydispersity of 1.1. ATRP of DMAEMA was carried out with more solvent than in the previous case, to ensure that the polymer remains soluble during polymerization, and the reaction was arrested after ca. 85% conversion.

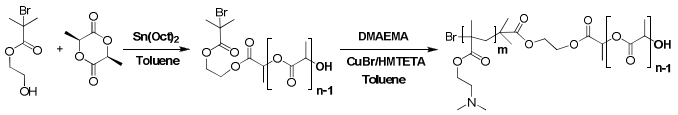

Figure 3. Synthesis of PLLA–b–PDMAEMA polymers using a double initiator via α–bromo PLLA.

The NMR spectra of the reaction mixture before polymer purification showed a much higher PLLA content than after purification (**Figure 4**, signals circled in red). This indicates the presence of PLLA homopolymer, which is also visible in the SEC traces as a shoulder on the long elution time side. NMR of the PLLA homopolymer, isolated after quaternization of the block copolymer, showed the absence of BrC(CH_3)$_2$ signals at 1.98 ppm. This indicates that the PLLA homopolymer is formed via an undesired side reaction (**Figure 5**), probably initiated by tin octoate [9], and it does not contain an initiating site for ATRP.

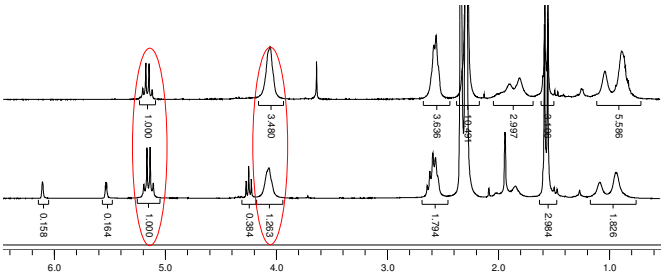

Figure 4. NMR spectra of PLLA–b–PDMAEMA, polymerized by a double initiator via α–bromo PLLA, before (lower curve) and after (upper curve) isolation.

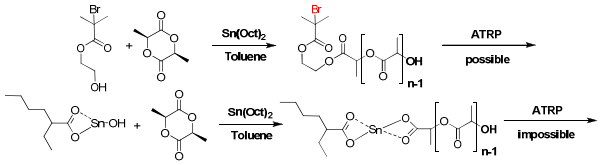

Figure 5. Parallel polymerization, leading to ATRP–inert PLLA, in the synthesis of PLLA–b–PDMAEMA using a double initiator via α–bromo PLLA.

Thus, whichever monomer, DMAEMA or LLA, is polymerized first using the double initiator approach, P(L)LA homopolymer is produced, making the achievement of block copolymers with the desired composition difficult. Therefore, sequential polymerization involving macroinitiator terminal group modification appears to be the only option for the controlled polymerization of PLLA–b–PDMAEMA polymers [10].

Sequential initiation via ω–bromo PLLA. 4–Isopropyl benzyl alcohol was chosen as the initiator for ROP of LLA by tin octoate, to facilitate NMR molecular weight determination taking advantage of a 6–proton reference signal. The resulting hydroxy–terminated PLLAs were modified with 2–bromoisobutyryl bromide (BIB), followed by ATRP of DMAEMA in the presence of CuBr/HMTETA catalyst (**Figure 6**). Molecular weight characterization of several members of the series prepared are given in **Table 2**. High molecular weight block copolymers, up to 20,000 for PLLA and 35,000 for PDMAEMA, were achieved. No traces of free PLLA were found in the filtrates following PDMAEMA quaternization.

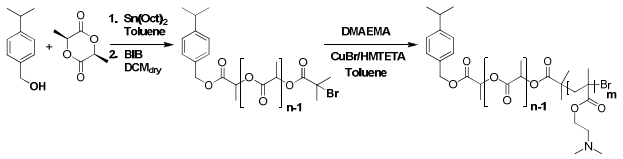

Figure 6. Synthesis of PLLA–b–PDMAEMA polymers by sequential polymerization and macroinitiator terminal group modification.

Table 2. Molecular weight characterization of PLLA and PDMAEMA–b–PLLA polymers synthesized by sequential initiation via ω–bromo PLLA.

Sample	M_n (NMR), PLLA	M_n (NMR), PDMAEMA	M_n/PDI (SEC–LS), PLLA–b–PDMAEMA
$PLLA_{13.8k}$–b–$PDMAEMA_{13.0k}$	13800	13000	26000 / 1.16
$PLLA_{13.8k}$–b–$PDMAEMA_{24.7k}$	13800	24700	38300 / 1.20
$PLLA_{18.9k}$–b–$PDMAEMA_{16.3k}$	18900	16300	37300 / 1.11
$PLLA_{18.9k}$–b–$PDMAEMA_{34.5k}$	18900	34500	54200 / 1.19

DSC analysis of the polymers listed in **Table 2** show two Tg's, at ca. 21 and 55 °C, and a melting peak near 165 °C. Lower molecular weight block copolymers (not shown in **Table 2**), when completely amorphous, show a single, intermediate Tg, indicative of miscible blocks, and two Tg's when crystallized, with a lower and broader melting peak. The detailed synthesis and characterization of these copolymers will be reported elsewhere [11].

Conclusions

Utilization of a double initiator is unsuitable for obtaining well–controlled PLLA–PDMAEMA block copolymers. Whichever block is initially synthesized, P(L)LA homopolymer is also produced by this method. In addition, racemization occurs when PDMAEMA is the macroinitiator, due to reaction between the amino groups and the catalytic system. An effective method to reveal and quantify PLLA homopolymer impurity in PLLA–b–PDMAEMA is via quaternization of the amine–containing block. Well controlled synthesis of high molecular weight PLLA–PDMAEMA was achieved by sequential polymerization involving macroinitiator terminal group modification.

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