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Metal-Free Catalyzed Ring-Opening Polymerization of β-Lactones: Synthesis of Amphiphilic Triblock Copolymers Based on Poly(dimethylmalic acid)

Olivier Coulembier,[†] Laetitia Mespouille,[†] James L. Hedrick,[‡] Robert M. Waymouth,[§] and Philippe Dubois*,[†]

Laboratory of Polymeric and Composite Materials (LPCM), University of Mons-Hainaut, Place du Parc 20, B-7000 Mons, Belgium, IBM Almaden Research Center, 650 Harry Road, San Jose, California 95120, and Department of Chemistry, Stanford University, Stanford, California 94305

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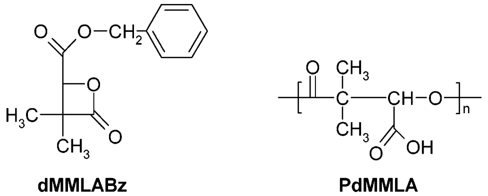
ABSTRACT: A polylactide-*block*-(dimethyl β-malic acid-*co*-β-butyrolactone)-*block*-polylactide (PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA) triblock copolymer has been synthesized according to a totally original three-step strategy. In a first step, the ring-opening polymerization (ROP) of dimethyl benzyl β-malolactonate (dMMLABz) and β-butyrolactone (BL) has been carried out in a toluene/*t*-BuOH solvent mixture at 80 °C by using ethylene glycol as initiator and the commercially available 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene carbene **1** as catalyst. The ROP mechanism selectively involves O-acyl cleavage of both dMMLABz and BL cyclic comonomers with a preferential incorporation of dMMLABz units in the growing polyester chains as attested by ^{1}H NMR spectroscopy. In a second step, the so-produced α,ω-dihydroxy P(dMMLABz-*co*-BL) copolyester have been further considered as difunctional macroinitiatior in L,L-lactide (LA) monomer ROP at 90 °C. In the third and last step, the benzylic ester functions pending along the recovered PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA triblock copolymer have been reduced/deprotected by catalytic hydrogenation leading to the expected PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA symmetric triblock copolyester. The amphiphilic character of this novel type of A−B−A triblock copolymers has been evidenced by some preliminary dynamic light scattering experiments in aqueous solution. While "flower" type micelles are formed at low temperature (e.g., 4 °C), microgelation occurs at higher temperature (at ca. 25 °C). By a further increase in the temperature and consistent with a temperature-dependent reversible gel−sol transition, the microgel dissolves at ca. 40 °C to the benefit of primary micelles. These observations have allowed for drawing a preliminary sol−gel phase diagram in water characterized by lower and upper concentration-dependent critical gelation temperatures.

Introduction

The delivery of drugs into a human body can be achieved through oral, transdermal, topical, and parenteral administrations. A great deal of work has been carried out during the past 2 decades to develop degradable drug-delivery systems (DDS) adapted to these administration routes.[1,2] Two types of DDS can be distinguished, i.e., implantable and injectable systems. Implantable devices in the form of cylinders, pellets, slabs, disks, and films provide advantages such as prolonged release of drugs, reproducibility of drug-release profiles, ease of fabrication, and so forth.[1−4] However, the implantation of such systems requires surgery with the risk of infection. Injectable systems have been largely investigated in recent years because they circumvent the need for a surgical incision. Among the various injectable DDS, micro- or nanoparticles are the most widely studied ones since they can be readily introduced into the living body by subcutaneous, intramuscular, or intravenous injections.[5−8] However, microparticles can be taken up by lung capillary embolization or by macrophages of the reticuloendothelial system, finally ending up in Kupffer cells in the liver.[9]

Injectable hydrogels are promising substrates for applications in DDS owing to their excellent biocompatibility related to the presence of large amounts of water swelling the polymer network linked either chemically through covalent bonds or physically through hydrogen bonds, crystallized domains, or hydrophobic interactions.[10] For these purposes, the synthesis of functionalized macromolecules with strict adjustment of their structures and properties is required, yielding complex architectures, in particular built up biodegradable/hydrolyzable (co)-polymers. In that context, aliphatic polyesters such as polylactide (PLA), polyglycolide (PGA), and poly(ϵ-caprolactone) (PCL), have been widely investigated. Much more than their biodegradable character, the huge interest for these polyesters is explained by not only their bioresorbability but also their biocompatibility.[9−12] Accordingly these polyesters have found many applications as temporary therapeutic systems such as sutures, osteosynthetic devices, sustained drug-delivery systems, and scaffolds in tissue engineering.

Scheme 1. Molecular Structures of dMMLABz and PdMMLA



Poly([*R*,*S*]-3,3-dimethylmalic acid) (PdMMLA) appears to be an attractive water-soluble aliphatic polyester with carboxylic acid groups pendant all along the chain (Scheme 1).[13] PdMMLA proved to be biocompatible and degrades in vivo into (*R*,*S*)-3,3-dimethylmalic acid, a nontoxic molecule.[14]

[†] Laboratory of Polymeric and Composite Materials (LPCM), University of Mons-Hainaut.

[‡] IBM Almaden Research Center.

[§] Department of Chemistry, Stanford University.

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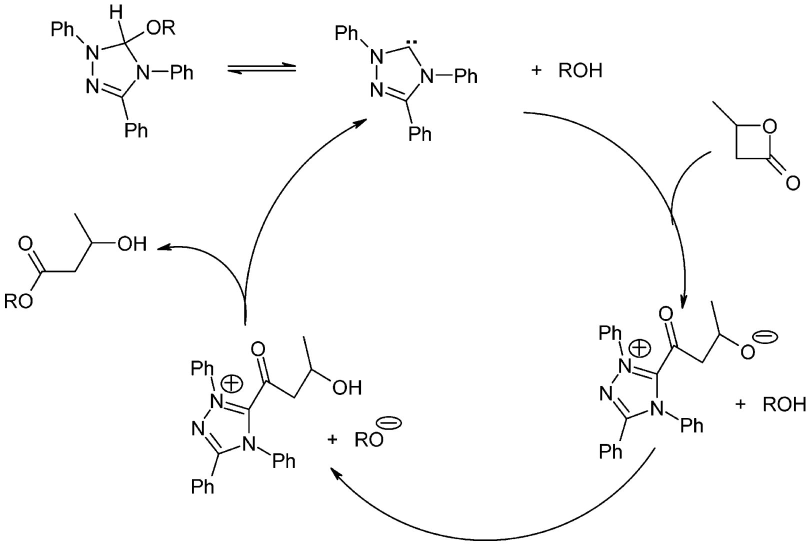
Scheme 2. Proposed Mechanism for the Polymerization of *β*-Butyrolactone with Triazole Carbenes[18f]



The most common synthetic routes to aliphatic polyesters involve metal-containing compounds to catalyze the ring-opening polymerization (ROP) of the respective cyclic ester monomers.[15] While these routes provide facile and direct access to aliphatic polyesters, removal of the metal contaminants trapped within the polyester chains must be considered in biomedical applications as resorbable biomaterials. Interestingly enough, the use of simple organic molecules as catalysts or promoters in asymmetric synthesis represents an attractive organocatalytic alternative to traditional organometallic reagents.[16] Among these metal-free catalysts, *N*-heterocyclic carbenes (NHCs) are known for their high activity and stereospecificity in a number of useful organic transformations.[17] In particular, it has been recently reported that some NHCs can display remarkable activity in metal-free ROP of cyclic esters such as lactide (LA) and *β*-butyrolactone (BL).[18] For instance, the commercially available 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene, the so-called triazole carbene **1**, catalyzes the "living" polymerization of BL using hydroxyl functionalized (macro)molecules as initiators under very mild conditions, yielding PBL chains of predictable molecular weight and very narrow molecular weight distribution.[18] Mechanistic studies have suggested that the NHC-catalyzed ROP proceeds via a monomer-activated mechanism in which the monomer is opened by the carbene to form an "acyl imidazole" intermediate, followed by the monomer addition into this lactone-carbene complex and the formation of a new alcohol (see Scheme 2). All of this occurs in a manner similar to the monomer-activated mechanism taking place in ROP of cyclic esters promoted by enzymes.[19]

This work aims at focusing on the synthesis of well-defined amphiphilic triblock copolymers with a central hydrophilic sequence containing [*R*,*S*]-3,3-dimethylmalic acid units (dMMLA) and lateral hydrophobic polylactide (PLA) blocks. The key-step of this synthesis relies upon the ROP of 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone, actually a protected dimethyl benzyl *β*-malolactonate (dMMLABz; see Scheme 1), using ethylene glycol as initiator and triazole carbene **1** as catalyst. The resulting α,*ω*-dihydroxypoly(malolactonate) chains can further initiate the ROP of LA added in a second step. In the third and last step, the protective benzyl ester functions are removed by catalytic hydrogenation providing the expected amphiphilic triblock copolymer.

Experimental Part

Materials. [*R*,*S*]-4-Benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (dMMLABz) was synthesized and purified starting from racemic diethyl oxalpropionate as published elsewhere.[13] It was stored at −18 °C just before use. *β*-Butyrolactone (Acros, 99+%), ethylene glycol (Chem-Lab, 99+%) and *tert*-BuOH (Acros, 98%) were dried over calcium hydride at room temperature for 48 h and then distilled under reduced pressure. (L,L)-Lactide (LA) (Purac) was recrystallized three times in dried toluene (20 wt %/vol) at 70 °C and then dried under vacuum overnight. Toluene and THF were dried using a Lab-Chem apparatus and stored over 3 Å molecular sieves. 1,3,4-Triphenyl-4,5-dihydro-*1H*-1,2-triazol-5-ylidene (Acros) and carbon disulfide (CS_2) (Aldrich) were used without further purification.

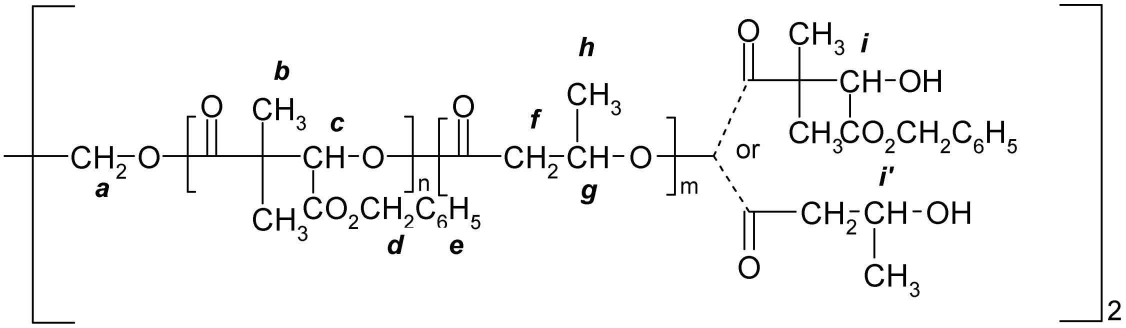
Synthesis of Poly(benzyl dimethyl *β*-malolactonate-*co*-butyrolactone) Copolyesters. In a glovebox, a vial equipped with a stirbar was charged with 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (0.06 g, 2.48×10^{-4} mol, 10 mol %), *β*-butyrolactone (0.21 g, 2.42×10^{-3} mol, 90 mol %), ethylene glycol (1.6 mg, 2.6×10^{-5} mol), *tert*-butyl alcohol (0.2 g), 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene (153 mg, 5.1×10^{-5} mol), and 0.2 mL of anhydrous toluene. The sealed vial was stirred at 80 °C in an oil bath. After 48 h, the reaction was quenched with a few drops of carbon disulfide (CS_2). The polymer was recovered by precipitation into 10 volumes of cold hexane (15 mL) and dried under reduced pressure at room temperature until constant weight. Yield = 90%. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1−1.2 (m, 5H), 1.2−1.25 (s, 3H), 2.3−2.6 (dd, 2H), 4.15 (m, 1H), 4.25 (t, 2H), 5.1 (d, 2H), 5.2 (m, 1H), 5.25 (s, 1H), 7.25 (s, 5H). $M_n = 4650$. $M_w/M_n = 1.11$ (determined by SEC, in reference to polystyrene standards).

Synthesis of Polylactide-*block*-poly(benzyl dimethyl *β*-malolactonate-*co*-butyrolactone)-*block*-polylactide Triblock Copolyesters. In a glovebox, a vial equipped with a stirbar was charged with 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (0.27 g, 1.16×10^{-3} mol, 80 mol %), *β*-butyrolactone (0.02 g, 2.19×10^{-4} mol, 20 mol %), ethylene glycol (0.9 mg, 1.5×10^{-5} mol), *tert*-butyl alcohol (0.06 g), 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene (86 mg, 2.9×10^{-5} mol), and 0.1 mL of anhydrous toluene. The sealed vial was stirred at 80 °C in an oil bath. After 48 h, the medium was diluted by 0.7 mL of anhydrous toluene and 0.1 g of (L,L)-lactide (6.9×10^{-4} mol) was added. The sealed vial was stirred at 90 °C in an oil bath. After 380 h, the reaction was quenched with a few drops of carbon disulfide (CS_2). The polymer was recovered by precipitation into 10 volumes of cold hexane (20 mL) and dried under reduced pressure at 40 °C until constant weight. Yield = 60%. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 0.9 (t, 3H), 1.2−1.4 (m, 3H), 1.4−1.6 (m, 3H), 2.4−2.8 (dd, 2H), 4.2 (m, 1H), 5.2 (m, 4H), 5.3 (s, 1H), 7.25 (s, 5H). $M_n = 2000$, $M_w/M_n = 1.38$ (determined by SEC, in reference to polystyrene standards).

Table 1. Molecular Characteristics of Poly(dimethyl benzyl β-malolactonate-*co*-butyrolactone) (P(dMMLABz-*co*-BL)) Copolymers as Obtained by Copolymerization of 4-Benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (dMMLABz) and β-Butyrolactone (BL) Initiated by Ethylene Glycol Added to the Triazole Carbene 1 in Toluene/*t*-BuOH (8/2: v/v) at 80 °C for 48 h ([dMMLABz+BL]$_0$ = 4 mol·L^{-1} and [*t*-BuOH]$_0$/[1] = 50)

entry	F_{dMMLABz}[a]	f_{dMMLABz}[b]	convn[c] (%)	M_{ntheor}[d] (g·mol^{-1})	M_{nNMR}[e] (g·mol^{-1})	M_w/M_n[f]
1	0.10	0.09	99	10 200	8500	1.11
2	0.20	0.22	99	10 700	11 200	1.09
3	0.40	0.38	95	9800	7300	1.17
4	0.60	0.58	97	10 300	9500	1.27

[a] F_{dMMLABz} = molar fraction of dMMLABz in the feed. [b] f_{dMMLABz} = dMMLABz molar fraction in the recovered copolymer as determined by ^{1}H NMR from the relative intensity of the benzylic protons of dMMLABz and the methylene protons of BL (see text). [c] Monomer conversion as determined by gravimetry. [d] Theoretical molecular weight (see text). [e] Experimental molar mass as determined by ^{1}H NMR (see text). [f] Molecular weight distribution as determined by SEC with reference to polystyrene standards.



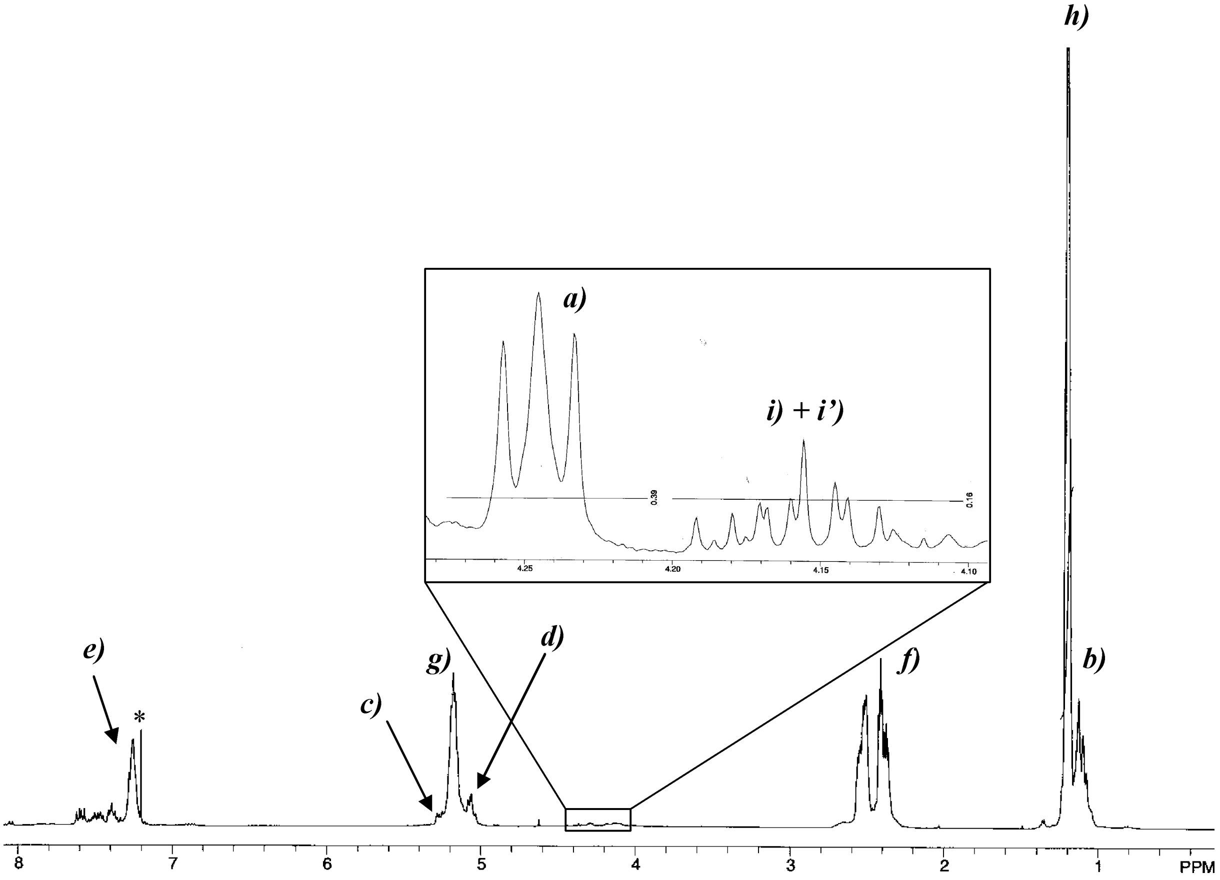


Figure 1. ^{1}H NMR spectrum of a P(dMMLABz-*co*-BL) copolymer as obtained by copolymerization of dMMLABz and BL by using ethylene glycol and the triazole carbene **1** as initiator and catalyst, respectively, in toluene/*t*-BuOH solvent mixture at 80 °C for 48 h ($F_{\mathrm{dMMLABz}} = 0.1$; entry 1 in Table 1) (∗: $CHCl_3$ in $CDCl_3$).

Removal of Benzyl Ester Protective Groups. In a round-bottom flask, 0.1 g of the copolymer (1.4×10^{-5} mol, $M_n = 7100$) was dissolved into 20 mL of acetone at room temperature and then added with 0.1 g of Pd/C 10 wt %. A continuous flow of hydrogen was bubbled into the solution for 7 h. After filtration through Celite, a clear copolymer solution was obtained. The solvent was evaporated under reduced pressure (10 mmHg) before recovering the polymer by extensive drying at 40 °C under reduced pressure (0.085 g). Yield = 96%. ^{1}H NMR (300 MHz,CD_3COCD_3, δ ppm) 0.9 (t, 3H), 1.2−1.4 (m, 3H), 1.4−1.6 (m, 3H), 2.4−2.8 (dd, 2H), 4.2 (m, 1H), 5.2 (m, 2H), 5.3 (s, 1H). Molecular weight and composition: see Results and Discussion.

Characterization. ^{1}H NMR spectra were recorded in various deuterated solvents (acetone-d_6, THF-d_8, or toluene-d_6) at a concentration of 30 mg/0.6 mL (^{1}H NMR) or 100 mg/0.6 mL (^{13}C NMR) using either a Bruker AMX300 (300 MHz) or a Bruker Avance 2000 (400 MHz). Size exclusion chromatography (SEC) was performed in THF at 35 °C using a Waters chromatography instrument connected to a Waters 410 differential refractor and four 5 μm Waters columns (300 × 7.7 mm) connected in series in order of increasing pore size (100, 1000, 10^5, 10^6 Å). Molar masses and their distribution were calculated with reference to polystyrene standards. Dynamic light scattering measurements were carried out using a BI-160 apparatus (Brookhaven Instruments Corporation) with a He−Ne laser source operating at 17 mW and delivering a vertically polarized light ($\lambda = 633$ nm). The particle sizes and size distribution were calculated using CONTIN algorithms.

"Tube Inversion" Experiment. Copolymer solutions were prepared by mixing given amounts copolymer and water into small glass tubes (internal diameter 5 mm). The tubes were then stored for 12 h at low temperature (~5 °C). In so-called "tube inversion" experiments, each solution was heated (or cooled) to a selected temperature (ca. 5 °C·min^{-1} in a water bath) before inverting the tube up side down in order to observe the solution or gel state of the medium and to determine the presence of any sol−gel transition.

Results and Discussion

In a first approach, the polymerization of 4-benzyloxycarbonyl-3,3-dimethyl-2-oxetanone (dMMLABz) (1 mol·L^{-1}) has been initiated by ethylene glycol added with 2 equiv of 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene triazole carbene **1**, ($[\mathbf{1}]_0/[\mathrm{OH}]_0 = 1$) in dry THF at 50 °C for an initial $[\mathrm{dMMLABz}]_0/[\mathrm{OH}]_0$ molar ratio of 40. Under such conditions, the triazole carbene **1** only displayed a low activity limiting the monomer conversion to 15% even after 7 days at 50 °C. Substituting THF for toluene and increasing the temperature up to 80 °C did not show any improvement of the monomer conversion.

Some of us have recently reported on the controlled ROP of BL as catalyzed by the triazole carbene **1** in toluene at 80 °C.[18f] It has been shown that the catalytic activity of **1** could be largely increased by the simple addition of *tert*-BuOH to the reaction medium. Under such conditions, PBL chains characterized by a very narrow molecular weight distribution ($M_w/M_n \sim 1.1$) could be produced by a controlled way allowing the number-average molecular weight to be predetermined by the initial $[\mathrm{BL}]_0/[\mathrm{initiator}]_0$ molar ratio. The role of *tert*-BuOH has been previously investigated and recently reported.[18f] Briefly, the triazole carbene **1** is actually characterized by a quite important inherent basicity leading to undesired elimination reactions directly from the BL monomer and generating crotonate derivatives in the reaction medium. It has been further evidenced that bulky tertiary alcohol, e.g., *tert*-BuOH cannot initiate the polymerization of cyclic esters such as BL. *tert*-BuOH is therefore used as cosolvent and is assumed to favor adduct formation between the free carbene **1** and ethylene glycol added as initiator. As a result, the concentration of free carbene **1** is significantly decreased, limiting the extent of elimination side-reactions and so increasing the control over the polymerization.

Accordingly, the copolymerization of dMMLABz and BL was initiated by ethylene glycol with 2 equiv of triazole carbene **1** at 80 °C in toluene/*tert*-BuOH (4/1: vol/vol) solvent mixture ($[t\text{-BuOH}]_0/[\mathbf{1}]_0 = 50$). After 48 h reaction time, a few drops of CS_2 were added to the copolymerization medium before recovering the copolyester chains by precipitation from cold heptane. Table 1 shows the effect of the comonomer feed ratio on the copolymer molecular characteristics as determined by ^{1}H NMR. As an illustration, Figure 1 shows the ^{1}H NMR spectrum of a typical P(dMMLABz-*co*-BL) copolymer as obtained by ROP starting from an initial molar fraction in dMMLABz (F_{dMMLABz}) of 0.1 (entry 1 in Table 1). The polymerization mechanism clearly involves a selective O-acyl cleavage of both dMMLABz and BL comonomers as evidenced by the appearance of both a triplet signal at 4.25 ppm assigned to the methyleneoxycarbonyl protons (Ha) issued from the ethylene glycol initiator residue and a multiplet between 4.1 and 4.2 ppm attributed to the α-hydroxy methine protons (Hi and Hi′). It is worth noting that the low intensity signals observed between 7.3 and 7.6 ppm can be assigned to the presence of triazolylidene carbene residues. Accordingly, the copolymer composition has been calculated from the proton intensities of dMMLABz and BL repeating units (respectively, Hd and Hf) while the experimental number-average molar mass of the copolymers (M_{nNMR}) estimated by comparison with the relative intensity of the methyleneoxycarbonyl protons (Ha).

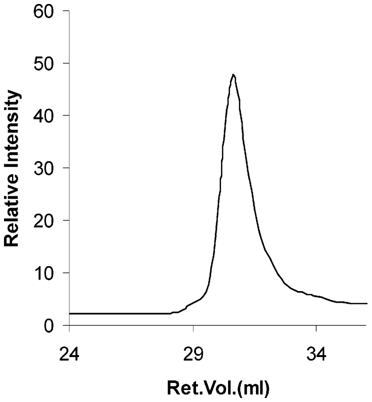


Figure 2. SEC chromatogram of a P(dMMLABz-*co*-BL) copolymer (entry 1, Table 1).

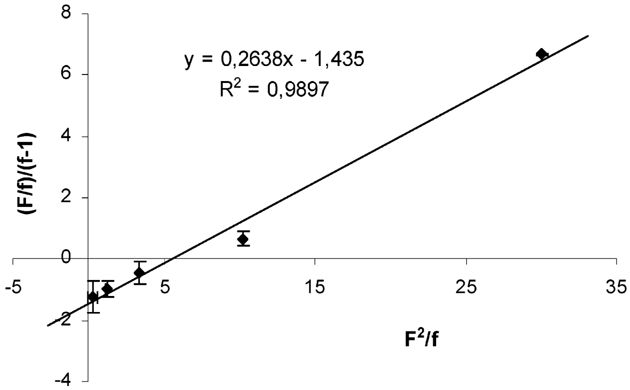


Figure 3. Determination of reactivity ratios of dMMLABz and BL using the Fineman−Ross method.

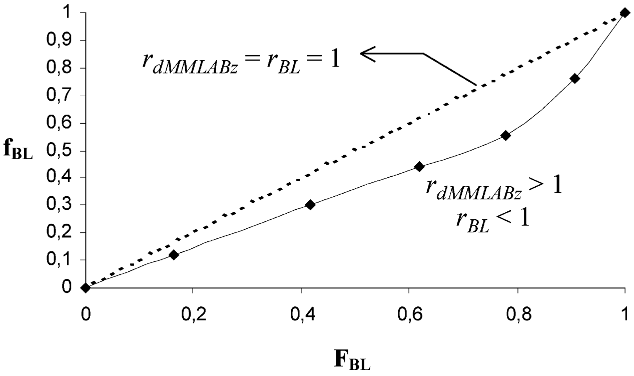
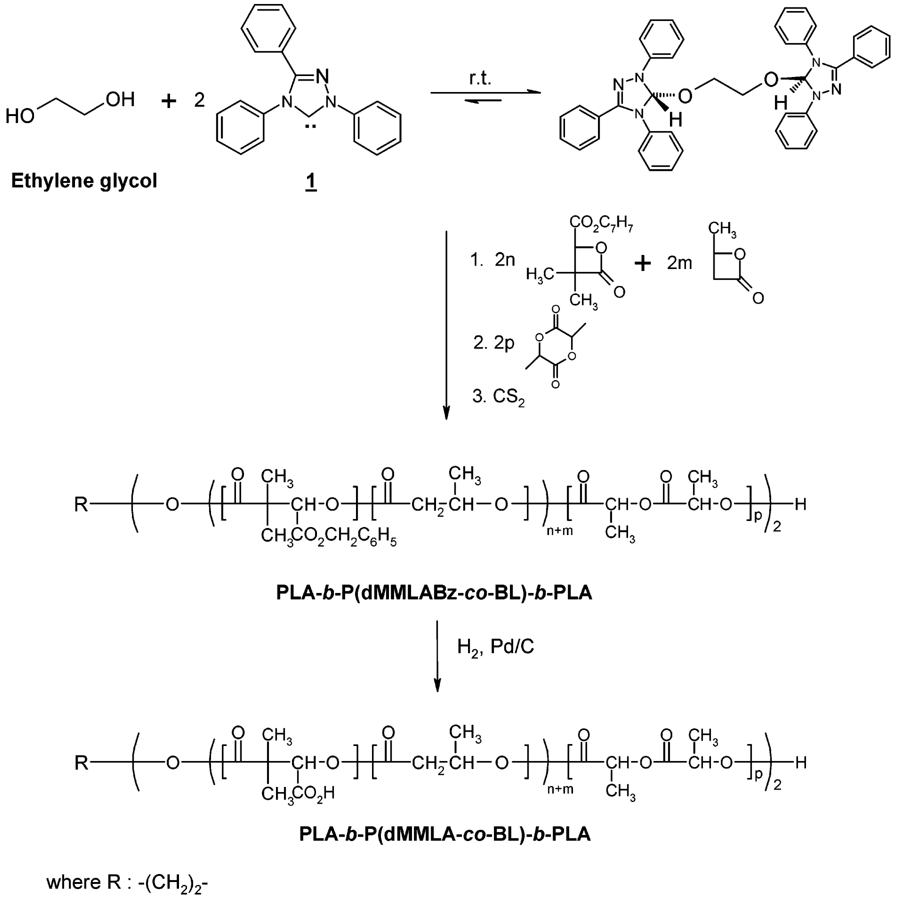


Figure 4. Instantaneous comonomer composition of P(dMMLABz-*co*-BL) copolymer as a function of the initial feed at low conversion.

Scheme 3. Three-Step Strategy Route for the Synthesis of Amphiphilic PLA-*b*-P(dMMLA-*co*-Bl)-*b*-PLA Triblock Copolymers (where R = −CH$_2$−CH$_2$−)



Within the ^{1}H NMR spectroscopy precision, a rather good agreement was observed between M_{nNMR} and M_{ntheor} taking into account the comonomer conversion: $M_{\mathrm{ntheor}} = 2 \times [\mathrm{dMMLABz} + \mathrm{BL}]_0/[\mathrm{OH}]_0 \times \mathrm{conv.}(\%) \times (f_{\mathrm{dMMLABz}} \times M_{\mathrm{WdMMLABz}} + (1 - f_{\mathrm{dMMLABz}}) \times M_{\mathrm{WBL}})$. Interestingly enough, the polydispersity indexes of the as-recovered copolyester chains were narrow ($1.09 \leq M_w/M_n \leq 1.27$) as attested to by size exclusion chromatography (see Figure 2, corresponding to entry 1 in Table 1).

To highlight the comonomer distribution along the copolyester chains, their reactivity ratios (r_{BL} and r_{dMMLABz}) have been estimated by the Fineman−Ross method applied at low comonomer conversions (10−15%).[20] For that purpose, the copolymerization of dMMLABz and BL has been initiated by ethylene glycol added with 2 equiv of **1** in toluene-d_8/*t*-BuOH (4/1: vol/vol) at 80 °C. Monomer conversions and copolymer compositions have been monitored by ^{1}H NMR performing the copolymerization directly in NMR tubes. According to Fineman−Ross equation at low comonomer conversion, the comonomer reactivity ratios are given by $r_1 = k_{11}/k_{12}$ and $r_2 = k_{22}/k_{21}$ while M_1/M_2, m_1/m_2, and $\mathrm{d}M_1/\mathrm{d}M_2$ denote the comonomer ratios in the feed, in the copolymer and the ratio of consumed monomers as determined by ^{1}H NMR, respectively (1 and 2 refer to BL and dMMLABz monomers, respectively).

$$\frac{\mathrm{d}M_1}{\mathrm{d}M_2} = \frac{M_1}{M_2}\frac{r_1M_1 + M_2}{r_2M_2 + M_1} \sim \frac{m_1}{m_2} \text{ (low comonomer conversions)}$$

If $f = (m_1/m_2)$ and $F = (M_1/M_2)$, the equation can be rewritten as

$$f = F\frac{r_1F + 1}{r_2 + F}$$

By rearranging terms one obtains

$$\frac{F}{f}(f - 1) = r_1\frac{F_2}{f} - r_2$$

Figure 3 shows the plot of (F/f) $(f - 1)$ vs (F/f) allowing the calculation of $r_{\mathrm{BL}} = 0.26$ (±0.16) and $r_{\mathrm{dMMLABz}} = 1.44$ (±0.35) from the slope and *Y*-axis intercept, respectively. It turns out that the dMMLABz units are preferentially incorporated in the growing chains as shown by the evolution of the instantaneous comonomer composition with the initial BL molar fraction (F_{BL}) recorded at low conversion (Figure 4). On the basis of these data, it can thus be assumed that the α,*ω*-dihydroxy P(dMMLABz-*co*-BL) copolyesters formed at high conversion (>95%) are mainly terminated by opened BL units (rather than dMMLABz ones). Such an assumption seems to be confirmed by the ^{1}H NMR spectra, which show multiplets centered on 4.15 ppm attributed to the α-hydroxymethyne protons (Hi′) of the (BL) end groups (rather than a simple singlet, which would have been assigned to Hi from dMMLABz units) (see Figure 1).

In the following step (Scheme 3), the lactide polymerization has been promoted using α,*ω*-dihydroxy P(dMMLABz-*co*-BL) as a difunctional macroinitiator, actually prepared according to the aforementioned conditions and starting from an initial molar

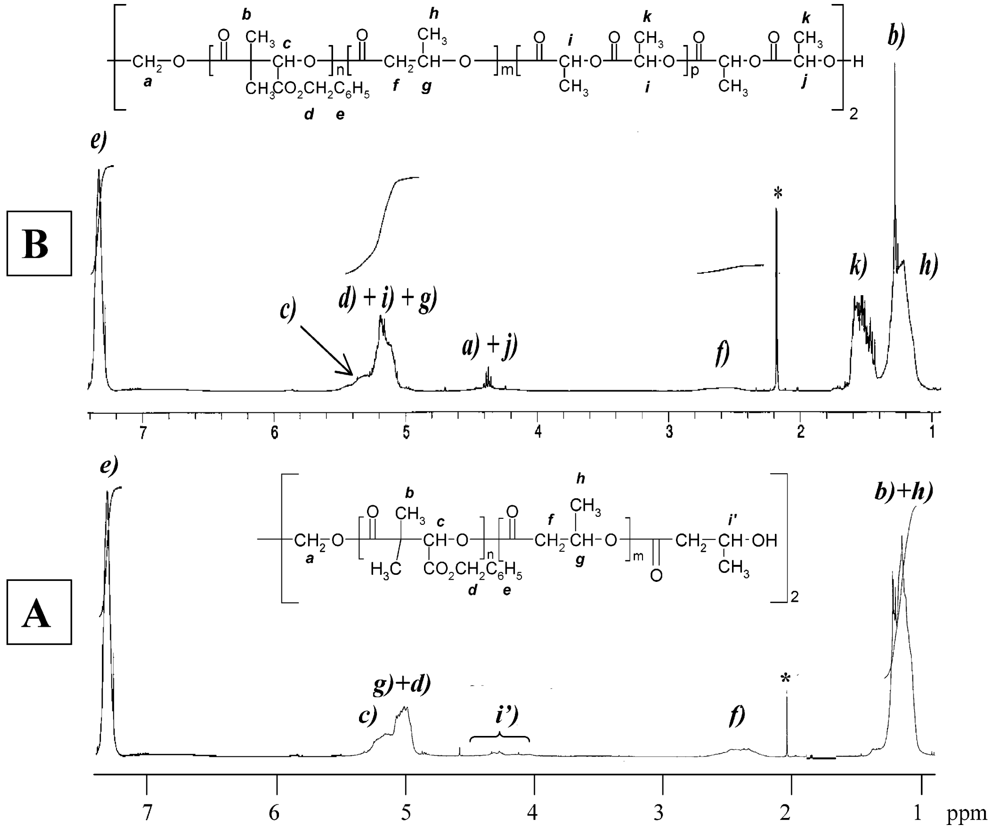


Figure 5. ^{1}H NMR spectrum of a PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA (spectrum B) as obtained in a one-step process using ethylene glycol and **1** as initiator and catalyst, respectively. Spectrum A shows the P(dMMLABz-*co*-BL) copolymer before addition of LA (∗: $(CH_3)_2CO$ in $(CD_3)_2CO$).

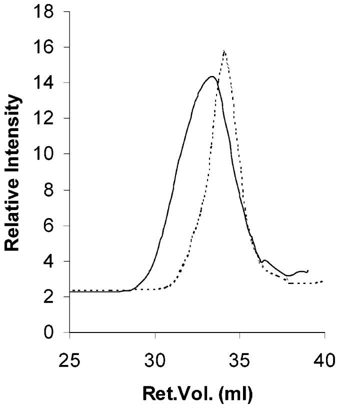


Figure 6. SEC traces of PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA triblock copolymer (full line) and P(dMMLABz-*co*-BL) macroinitiator (dashed line).

fraction in dMMLABz of 0.8 and an initial molar ratio $[\text{dMMLABz} + \text{BL}]_0/[\text{OH}]_0$ of 25 ($M_{\text{ntheor.}} = 5000$ g·mol^{-1} at 100% conversion). After 48 h at 80 °C, an aliquot was pickedout and characterized by ^{1}H NMR spectroscopy (Figure 5A). Complete comonomer conversion was attained, and as expected, a molar fraction in dMMLABz of 0.84 was determined. Furthermore, analysis by SEC revealed a monomodal and narrow molecular weight distribution with a polydispersity index of 1.24 (Figure 6). Then LA has been added into the reaction medium ($[\text{LA}]_0 = 1$ mol·L^{-1}; $[\text{LA}]_0/[\text{OH}]_0 = 35$) and the temperature increased to 90 °C. Actually and as previously reported, N-heterocyclic carbenes are known to undergo C−H insertion reactions with compounds containing acidic protons.[21] For instance, treatment of the triazole carbene **1** with a slight excess of MeOH at room temperature readily generates the methoxytriazoline adduct.[22] This alcohol adduct is stable at low temperature but reversibly dissociates at 90 °C into free carbene **1** and methanol.[18e,f] Cooling down this mixture to room-temperature regenerates the methoxytriazoline, thus revealing a thermodynamic equilibrium between the free carbene **1** and its methanol-based adduct.[18e,f]

Accordingly, the temperature of the reaction medium has been increased to 90 °C in order to promote the controlled polymerization of LA from the alcohol end groups generated by the reversible dissociation of the adduct formed between the α,*ω*-dihydroxy P(dMMLABz-*co*-BL) and carbene **1**. After 380 h of reaction time, the temperature of the polymerization medium has been decreased to room temperature and the catalytic activity of the carbene **1** has been quenched by adding a few drops of CS_2[18c] leading to an inactive carbene-CS_2 adduct and the expected α,*ω*-dihydroxy PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA copolymer. This last is then precipitated out from a large excess of hexane (Yield = 60%).

Figure 5B shows the ^{1}H NMR spectrum of the polylactide-*block*-poly(dimethyl benzyl *β*-malolactonate-*co*-butyrolactone)-*block*-polylactide (PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA) triblock copolymer. In addition to new signals assigned to the PLA segments (protons Hi and Hk), a multiplet combining both the α-hydroxy methine end groups (Hj) and oxycarbonyl methine (Ha) protons issued from the initiator residue is clearly observed. On the basis of the relative intensity of the comonomer repeating unit protons (LA, Hk; BL, Hf; dMMLABz, Hc) and both the α-hydroxy methine and methyleneoxycarbonyl (Hj + Ha) protons, the contribution of each comonomer in the molar mass of the triblock copolymer has been calculated: $M_{\text{nPdMMLABz}} = 4000$; $M_{\text{nPBL}} = 280$; $M_{\text{nPLA}} = 2800$. A polydispersity index of 1.38 has been determined by SEC while the apparent molar mass is shifted to lower retention volume with regard to the macroinitiator trace ($M_{\text{ncopo}} = 2000$ g·mol^{-1}) (Figure 6).

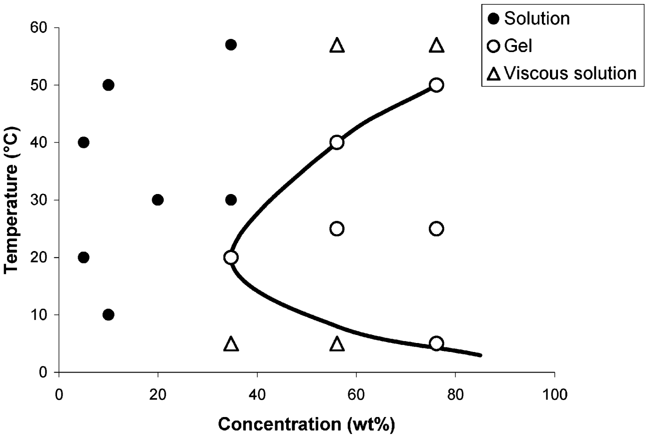


Figure 7. Phase diagram of PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA (1500-(3000-*co*-300)-1500) triblock copolymer in H_2O.

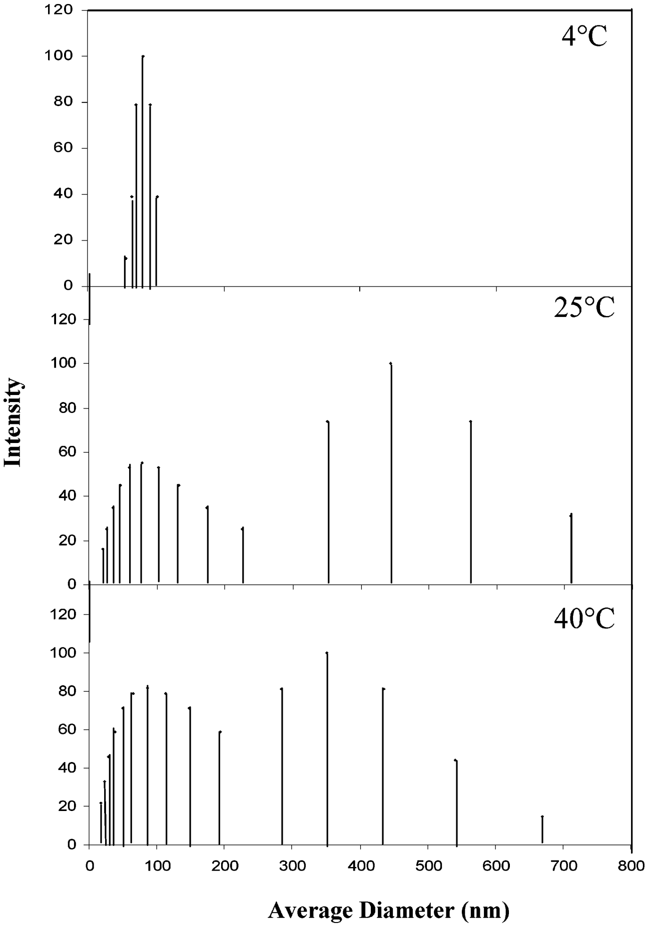


Figure 8. The size and size distribution of PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA (1500-(3000-*co*-300)-1500) triblock copolymer micellar aggregates (concentration: 0.3 g·mL^{-1}) in water at various temperatures.

In a third and ultimate step, the targeted amphiphilic polylactide-*block*-poly(dimethyl malic acid-*co*-butyrolactone)-*block*-polylactide (PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA) triblock copolymer has been generated by hydrogenation/deprotection of the benzylic ester functions.[23] The ^{1}H NMR spectroscopy of the recovered copolymer attests for the quantitative deprotection reaction (not shown here) and following the procedure previously described for the protected triblock copolymer, the molecular mass of each sequence could be determined as $M_{nPdMMLA} = 3000$, $M_{nPBL} = 300$, and $M_{nPLA} = 3000$.

Since a potential application for such amphiphilic PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA triblock copolymers could be their use as hydrogels, their ability to form physically cross-linked network in water has been studied in function of the copolymer concentration as well as temperature. Figure 7 shows the phase diagram of the investigated PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA triblock copolymer ($M_{ncopo} = 6300$ g·mol^{-1}, $f_{PdMMLA} = 0.48$) in water as recorded by the so-called "tube inversion" technique (see Experimental Section). A critical gel concentration (CGC) has been observed following a lower transition temperature curve from sol-to-gel and an upper transition temperature curve from gel-to-sol. These two parts are usually defined as lower and upper concentration-dependent critical gelation temperatures (CGTs).[24]

The lower CGT smoothly decreases by about 15 °C as the copolymer concentration varies from 35% to 76% while the upper CGT increases by 30 °C in the same concentration range. This indicates that the lower phase transition is less dependent on the solution concentration than the upper phase transition. Such a behavior was also reported by Kim et al. for PEO-based di- and triblock copolymers, which displayed a thermoreversible sol−gel transition where the transition temperature was a function of both the concentration and the composition of the block copolymer.[24]

Micelle formation and micellar behavior in water, known to be dependent on the polymeric molecular structure and related hydrophobic−hydrophilic balance, play also an important role in the gelation of "A−B−A" type triblock copolymers.[25] The average size and size distribution of the triblock copolymer micellar aggregates in water (copolymer concentration: 0.3 g·mL^{-1} ~ 30 wt %) was recorded by dynamic light scattering (DLS) at various temperatures (Figure 8). At 4 °C, a monomodal population with an apparent mean diameter of 81 nm is observed and more likely corresponds to the formation of "flower" type micelles (see hereafter). Increasing the temperature from 4 to 25 °C contributes to a broadening of micelle size distribution and the formation of micellar aggregates with an apparent mean diameter close to 450 nm. Such a behavior is typical for so-called "bridging" micelles, which initiate the microgelation process.[26] At 40 °C, the relative content of larger micellar aggregates tends to decrease to the benefit of primary micelles, consistently with the reversibility of the gelation process.

Clearly, at temperature lower than the lower CGT (i.e., at 4 °C), the PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA triblock copolymer associates into micelles formed on a PLA core surrounded by loops of P(dMMLA-*co*-BL) blocks. By increasing the temperature, micellar aggregates start to be observed as well as microgelation. At ca. 25 °C, a stable gel is finally obtained. Increasing further the temperature (i.e., at 40 °C) allows for dissociating the aggregates and reversing the microgelation. A low viscous solution is then reached at temperature higher than CGT.

In conclusion, new polylactide-*block*-poly(dimethyl β-malic acid-*co*-β-butyrolactone)-*block*-polylactide (PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA) triblock copolymers can be synthesized according to a three-step strategy, which relies upon the controlled ROP of (di)lactones initiated by ethylene glycol in the presence of commercially available metal-free 1,3,4-triphenyl-4,5-dihydro-*1H*-1,2,4-triazol-5-ylidene carbene **1**. As a result of its limited reactivity in homopolymerization, dMMLABz has been copolymerized with BL using ethylene glycol as the initiator added with 2 equiv of **1** in toluene/*t*-BuOH solvent mixture at 80 °C. It comes out from ^{1}H NMR spectra that the dMMLABz comonomer is preferentially incorporated in the growing copolyester chains. The comonomer reactivity ratios have been determined as $r_{dMMLABz} = 1.44 \pm 0.35$ and $r_{BL} = 0.26 \pm 0.16$.

The copolymerization proceeds by a selective O-acyl cleavage of both dMMLABz and BL monomers. The resulting α,ω-dihydroxy P(dMMLABz-*co*-BL) macroinitiator has been used, after complete comonomer conversion, as difunctional macroinitiator in LA polymerization carried out at 90 °C. Finally, the PLA-*b*-P(dMMLABz-*co*-BL)-*b*-PLA triblock copolymer has been deprotected by catalytic hydrogenation of the pendant benzylic ester functions leading to the expected PLA-*b*-P(dMMLA-*co*-BL)-*b*-PLA symmetric triblock copolyester. Preliminary DLS experiments have evidenced the amphiphilic character of this triblock copolymer. At low temperature (e.g., 4 °C), “flower” type micelles are formed in water while microgelation occurs at higher temperature (ca. 25 °C). By further increasing the temperature (to ca. 40 °C) and consistently with a temperature reversible gel−sol transition, dissolution of the microgel is observed to the benefit of primary micelles. These observations have allowed for drawing a preliminary sol−gel phase diagram characterized by lower and upper concentration-dependent critical gelation temperatures.

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