DOI: 10.1021/ma902844m

Macromolecules
ARTICLE

Poly(isoglycerol methacrylate)-*b*-poly(D or L-lactide) Copolymers: A Novel Hydrophilic Methacrylate as Building Block for Supramolecular Aggregates

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Received December 27, 2009; Revised Manuscript Received March 6, 2010

ABSTRACT: On the basis of a new acetal-protected glycerol monomethacrylate monomer (*cis*-1,3-benzylidene glycerol methacrylate/BGMA) a series of potentially biocompatible and partially biodegradable homo- and block copolymers were synthesized. ATRP polymerization of BGMA yielded well-defined polyacrylates with pendant benzylidene acetal groups and high glass transition temperatures (115−130 °C). This hydrophobic poly(*cis*-1,3-benzylidene glycerol methacrylate) could be readily transformed into the hydrophilic and water-soluble poly(1,3-dihydroxypropyl methacrylate), referred to as poly(isoglycerol methacrylate) (PIGMA). It exclusively contains primary hydroxyl groups and therefore differs significantly from the commonly known poly(glycerol methacrylate) (PGMA). Block copolymer systems based on poly(lactide) and BGMA were realized via two orthogonal living polymerization techniques starting from a bifunctional initiator, employing first atom transfer radical polymerization (ATRP) of BGMA and in the second step organo-base catalyzed polymerization of L- or D-lactide. This route provides well-defined block copolymers of low polydispersity (PDI 1.12−1.17) and molecular weights in the range of 7000 to 30 000 g/mol (NMR). Rapid and highly selective acetal hydrolysis of the PBGMA block resulted in the release of the hydrophilic and water-soluble poly(1,3-dihydroxypropyl methacrylate) (poly(isoglycerol methacrylate), PIGMA). Acidic hydrolysis of the acetal protecting groups of poly(BGMA)-*b*-poly(lactide) copolymers proceeded smoothly to amphiphilic structures, notably without affecting the potentially labile polyester block. The novel PIGMA-*b*-PLLA copolymers are capable of supramolecular self-assembly to spherical aggregate structures in aqueous environment. The polymers generally exhibited low aggregation constants (CAC: 8−20 mg/L). Because of the unique feature of stereocomplex formation of poly(lactide), the corresponding aggregate morphology could be adjusted by mixing two nearly identical PIGMA-*b*-PLA copolymers with enantiomeric poly(lactide blocks) in a 1:1 ratio. In this case the uniformly shaped micelles (20 nm) changed to large vesicles with diameters ranging from 600 to 1400 nm. These features render this new type of amphiphilic block copolymers promising for drug delivery applications.

Introduction

Biodegradable polyesters are among the best established, but also most promising materials in current Polymer Science for the design of "smart" biomedical devices, such as drug delivery and controlled release systems in the form of nanoparticles,[1] micelles and polymersomes.[2] Amphiphilic block copolymers are currently subject of intense research with respect to their potential application as encapsulation devices of therapeutic agents exhibiting triggered release.[3] Linear aliphatic polyesters represent excellent building blocks for the formation of hydrophobic domains because of their established *in vivo* degradability and nontoxicity. Poly(lactide) (PLA) has been successfully combined with poly(ethylene glycol) (PEG) and other hydrophilic blocks.[4] Among biocompatible and biodegradable polyesters, poly(lactide) exhibits the unusual feature of stereocomplex-formation of enantiomeric, homochiral chains. This is not only accompanied by a strong increase of the melting temperature by approximately 50 °C, but can also be exploited for the kinetic and thermodynamic stabilization of block copolymer aggregates in aqueous environment.[5] Hedrick and co-workers have shown in elegant recent work that stereocomplex-driven association between PEG-*b*-PDLA and PNIPAM-*b*-PLLA leads to the formation of mixed micelles.[6] Generally, copolymers of PEG and PLA have been in the focus of interest in the aggregate-promoted application as drug delivery vehicles.[7] This is at least partially attributed to their facile synthesis, which relies on commercially available monomethyl ether PEGs. Nevertheless, PEG-based systems show some disadvantages, such as the lack of further functionality and toxicity of the gaseous monomer ethylene oxide. In less academic circles, the ill-founded fear of product contamination by trace amounts of ethylene oxide in PEG-based products is currently developing a market pull for suitable alternatives.

In this context, we have directed our focus on poly(methacrylate)-based polymers, which possess a functional moiety that can easily be adjusted by simple esterification reaction of the respective alcohol with methacrylic acid. In general, poly(methacrylate)s provide access to non degradable, but readily tunable systems in terms of e.g., hydrophilicity,[10] pH- and temperature-induced phase behavior[11] as well as loading with therapeutic agents[12] by simple variation of the substituent, as demonstrated in Scheme 1. Via ATRP single and multiheaded initiators can be conveniently obtained and introduced in polymers with low synthetic effort.[13−15] Block copolymers are accessible by an acrylate- or lactone-first[16−22] strategy or even by simultaneous

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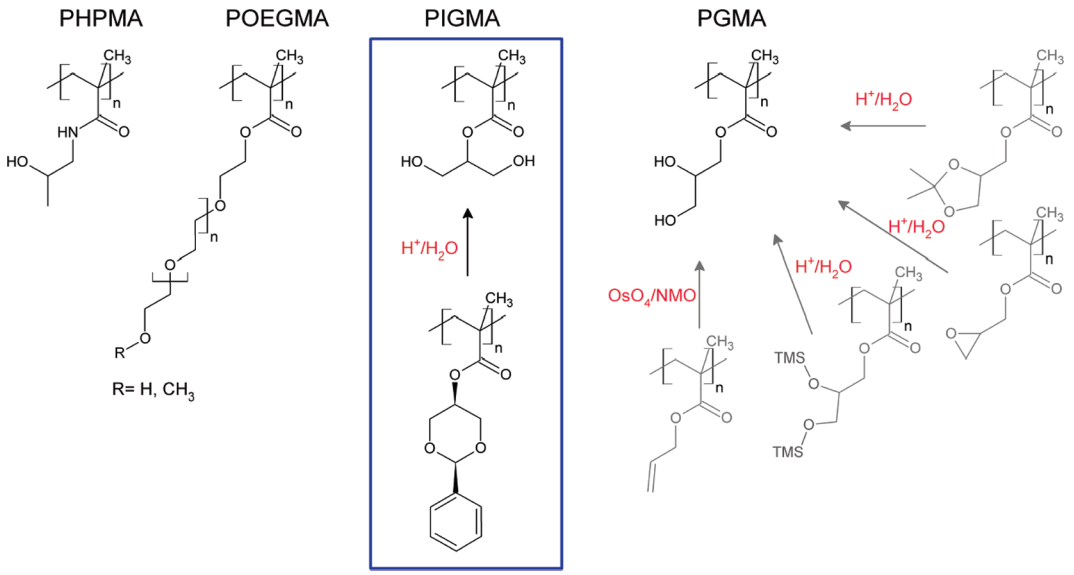
 Published on Web 03/19/2010

Scheme 1. The New Poly(isoglycerol methacrylate) (PIGMA) Can Be Classed in a Family of Hydrophilic Methacrylates/Methacrylamides Representing Suitable Building Blocks for Biomedical Application[a]



[a] Abbreviations: PHPMA (poly(2-hydroxypropyl methacrylamide)),[8] POEGMA (poly(oligoethylene glycol methacrylate)),[9] and PGMA (poly(glycerol methacrylate)).[22,32,33,35]

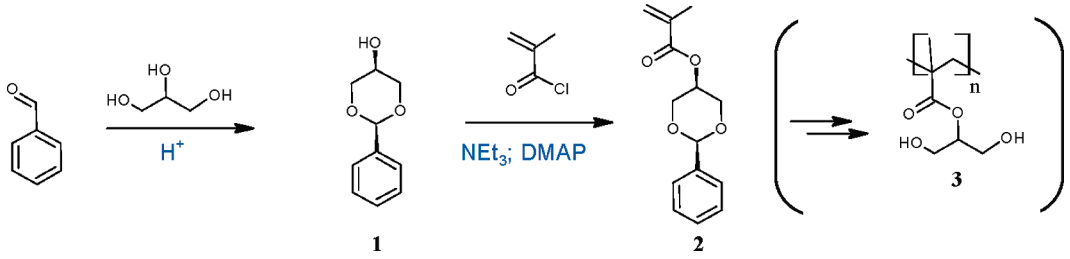
growth of the two blocks under optimized conditions.[23] Very recently, Trimaille et al. have succeeded in combining NMP of *n*-butyl acrylate and the ROP of ε-caprolactone in a one step procedure, starting from a bifunctional, SG1nitroxide functionalized initiator, yielding well-defined block copolymers.[24] In a previous work, we have introduced a straightforward one-pot procedure to poly(lactide)-*b*-poly(HEMA) copolymers.[25] This system represents one of only few examples describing the combination of a hydrophobic, aliphatic polyester with a hydrophilic poly(acrylate), carrying pendant hydroxyl groups.[26−28] Although these block copolymers could be prepared without additional protective groups from plain HEMA, they were not capable of aggregation into stable polymeric aggregates in aqueous solution due to the insufficient water solubility of the poly(HEMA) block.[29] Structurally similar methacrylate monomers are well-known and provide similar (2-hydroxypropyl methacrylate) and superior (glycerol methacrylate, 2-hydroxypropyl methacrylamide) hydrophilicity in their respective polymeric forms.[30,31] An obvious approach to enhance the hydrophilicity of HEMA relies on the increase of the number of hydroxyl groups per repeating unit. To date, this has been realized by poly(2,3-dihydroxypropyl methacrylate), which is commonly known under the name poly(glycerol methacrylate) (PGMA). The synthesis of PGMA is often based on its ketal-protected form: solketyl methacrylate (2,3-isopropylidene glycerol methacrylate), which was first realized in 1990.[32] The PGMA block can either be deprotected in an additional pre- or in a post polymerization step by acid-catalyzed hydrolysis.[33] Nevertheless, alternative pathways have been subject of past and current research. Borsali and co-workers recently employed silylated glycerol monomethacrylate (2,3-bistrimethylsilyloxypropyl methacrylate) to yield amphiphilic block copolymers with poly(ε-caprolactone) block after deprotection.[26] Ruckenstein et al. used the postpolymerization osmylation-reaction for the oxidative introduction of PGMA's bis(hydroxyl) group in poly(styrene)-*b*-poly(allyl methacrylate)s, which was obtained by successive carbanionic polymerization.[34] Davis and co-workers recently obtained poly(glyceryl methacrylate)-*block*-poly(pentafluorostyrene) by hydrolysis of the less polar poly(glycidyl methacrylate) precursor after RAFT polymerization.[35] The increased hydrophilicity and functionality of PGMA[36] and its suitability for drug delivery systems,[37−39] hydrogels for soft contact lenses[40] or antifouling coatings[41] lead to an increasing commercial interest in this kind of polymer.

Considering glycerol methacrylate (GMA), the synthetic methods published to date only offer access to the 2,3-dihydroxypropyl isomer, which provides a primary and a secondary hydroxyl functionality. Depending on the purity of the employed solketal, the methacrylate synthesized in this manner may contain impurities of up to 8% of the 2,3-isopropylidene glycerol isomer of GMA. This results in random incorporation of 1,3-dihydroxyisopropyl methacrylate in the polymer backbone in the respective ratio after polymerization and deprotection.[29] However, poly(1,3-dihydroxyisopropyl methacrylate).[56] has not been obtained in its pure form yet. In this work, we describe the synthesis and ATRP-polymerization of a new methacrylate monomer (**2**), granting access to the 1,3- dihydroxy form of poly(glycerol monomethacrylate) (**3**) (Scheme 2). Furthermore, we present a series of well-defined block copolymers of poly(isoglycerol methacrylate) and poly(lactide) segments and describe their aggregation behavior in aqueous solution with respect to the stereochemistry of the PLA blocks employed.

Experimental Part

Instrumentation. NMR investigation: All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 25 °C, using a Bruker AMX 400 (400.1/100.67 MHz) spectrometer. The spectra were measured in $CDCl_3$ and THF-d_8, and the chemical shifts are assigned by internal calibration on the solvents residual peaks. (^{1}H proton NMR signal, 1.73 ppm for THF-d_8 and 7.26 ppm for $CDCl_3$; ^{13}C carbon NMR signal, 25.37 ppm for THF-d_8 and 77.00 ppm for $CDCl_3$). Size exclusion chromatography (SEC) was performed with an instrument consisting of a Waters 717 plus autosampler, a TSP Spectra Series P 100 pump, and a set of three PSS-SDV 5A columns with 100, 1000, and 10 000 Å porosity. THF was used as an eluent at 30 °C and at a flow rate of 1 mL/min. UV absorptions were detected by a SpectraSYSTEM UV2000. The specific refractive index increment (d*n*/d*c*) was measured at 30 °C, using an Optilab DSP interferometric refractometer (also RI detector) and determined with the Wyatt ASTRA IV software (Version 4.90.08). Calibration was carried out using poly(styrene) standards provided by Polymer Standards Service and performing a third

Scheme 2. Synthesis of Benzylidene Glycerol Methacrylate (BGMA, 2) in Two Steps



order polynomial fit. MALDI−ToF MS measurements of poly(lactide) macroinitiators 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 matrix. Potassium triflate (Aldrich, 98%) was added for ion formation. Good results were obtained for samples prepared from THF 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 auto sampler in the temperature range of 0 to 200 °C at a heating rate of 20 K/min. The melting points of indium (T_m = 156.6 °C) and Millipore water (T_m = 0 °C) were used for calibration. In order to visualize the X-ray diffraction information obtained for BGMA we used the basic version of Mercury Crystal Structure Visualization and Exploration software (version 2.2) available free of charge at http://www.ccdc.cam.ac.uk/mercury.

Materials. All solvents were of analytical grade and purchased from Acros Organics. Methylene chloride was refluxed over phosphorus pentoxide and distilled immediately prior to use. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was obtained from Acros Organics (98%) and distilled from CaH_2 prior to use. Glycerol (25 kg; 99.5%) of plant origin was kindly donated by Caldic (Germany). Deuterated chloroform-d_1 and THF-d_8 were purchased from Deutero GmbH, dried and stored over molecular sieves. Dilactide was purchased from Purac (Gorinchem, NL), recrystallized 3 times from dry toluene and stored under vacuum prior to use. 2-Hydroxyethyl 2-bromo-2-methylpropanoate (HBMP) was synthesized as described previously.[25] 5-Hydroxy-2-phenyl-1,3-dioxane was prepared with a standard rotary evaporator and isolated from cold diethyl ether on a multi 100 g scale according to a procedure adapted from Aasbø et al.[42]

Dialysis of the micellar solution was performed with Cellu SepH1 membranes (Membrane Filtration Products, Inc.) with a molecular weight cutoff of 1000 g/mol.

Monomer Preparation: 2-Phenyl-1,3-dioxan-5yl Methacrylate (BGMA). A 32 g (0.18 mol) sample of 5-hydroxy-2-phenyl-1,3-dioxane, 21 g (0.21 mol, 28.5 mL) of triethylamine, and 50 mg of *N,N*-(dimethylamino)pyridine were dissolved in 400 mL of dry dichloromethane in a 1 L flask equipped with a 250 mL dropping funnel and an argon balloon. Subsequently a solution of 20 g (0.19 mol) of methacryloyl chloride in 150 mL of dry dichloromethane was added dropwise under constant cooling (0−5 °C) over a period of 2 h. The solution was slowly allowed to warm to room temperature and stirred for an additional 72 h. The solution was extracted twice with water and twice with saturated potassium carbonate solution (50 mL each). The organic phase was dried over a 1/10 mixture of anhydrous potassium carbonate and magnesium sulfate. After evaporation of the solvents, the crude product was taken up in 20 mL of THF and poured into 200 mL of a 1:1 mixture of diethyl ether and hexanes. The product crystallized in colorless needles upon standing at −25 °C for 48 h (34.8 g/78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.01 (s, 3H, CCH_3); 4.18−4.35 (m, CHCH_2O); 4.77 (s, 1H, −OCHH(CH_2O)$_2$); 5.58 (s, 1H; −OCHHO); 5.65 (s, 1H, C=CH_2 (*E*)), 6.30 (s, 1H, C=CH_2 (*Z*)); 7.36−7.53 (m, 5H−, aromat.). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 18.23 (CCH_3); 66.10 (−OCH(CH$_2$O)$_2$−); 69.00 (−OCH(CH_2O)$_2$-); 101.30 (CH_2O$_{cycl}$); 126.05 (CH_{aromat} 2 + 6); 126.54 (CCH_2); 128.31 (CH_{aromat} 3 + 5); 129.12 (CH_{aromat} 4); 137.93 (C_{aromat} 1); 167.16 (CCOOCH).

General Procedures for the Synthesis of the First Block: ATRP of BGMA. This was exemplarified for PBGMA-MI (**4**) with a monomer/alkyl halide/copper/ligand ratio of [100]:[1]:[1]:[1]) A 2:1 mixture of benzene and methanol was predegassed by three freeze−pump−thaw cycles. Monomer and initiator were charged into an argon-flushed Schlenk-tube, dissolved in a benzene/methanol mixture and degassed in three freeze pump thaw cycles. The ligand, hexamethyl triethylenetetramine (HMTETA) (2-fold excess) was charged in a separate Schlenk tube, dissolved in 10 mL of benzene/methanol 2:1 and degassed as described above. Then 5 mL of the ligand solution were injected into a pre-evacuated Schlenk-tube, containing the desired amount of CuCl. The tube was flushed with argon and sonicated for 10 min, upon which a nearly colorless solution of the copper complex formed. Polymerization was initiated upon injecting the copper/HMTETA complex to the monomer/initiator solution, preheated to the reaction temperature of 80 °C. Polymerization was quenched after 5 h by removal of the reaction vial from the oil bath followed by exposure to air. A sample was harvested for conversion analysis. Since the block copolymer partially precipitated from the reaction mixture upon cooling, benzene was added and the solution was left to stand to evaporate excess methanol. The less polar environment facilitated catalyst removal via filtration over a short column filled with neutral aluminum oxide (10 mL/g polymer). Further work-up including complete removal of residual monomer was achieved by precipitation in excess methanol (150 mL/g polymer). After filtration, the block copolymer was obtained as a white powder in a yield reflecting the respective conversion.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.94−1.46 (m, C(CH_3)-(COOCH(CH$_2$O−)$_2$); 1.80−2.34 (m,−CH_2C(CH$_3$)(COOCH-(CH$_2$O−)$_2$); 3.56−4.33 (COOCH(CH_2OH)$_2$); 4.20−4.57 (COOCH(CH$_2$O−)$_2$); 5.27−5.49 (COOCH(CH$_2$O−)$_2$CHC$_6$H$_5$); 7.16−7.54 (COOCH(CH$_2$O−)$_2$CHC$_6$$H_5$).

Polymerization of Lactide. The ω-hydroxyl-PBGMA macroinitiator and lactide of the respective D- or L-configuration were charged into a Schlenk-tube at predetermined molar ratios (Table 2). The tube was sealed with a rubber septum and repeatedly flushed with argon after evacuation. Freshly distilled dichloromethane (4 mL/g lactide) was added via a syringe. Polymerization was initiated after 2 min by injecting a 10% (weight) solution of DBU corresponding to 1 mol % of the monomer. Polymerization was quenched after 20 min by injecting 1 mL of methanol. A small sample was removed for conversion analysis prior to precipitation in an excess of methanol. The polymer was collected by filtration.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.94−1.46 (m, C(CH_3)-(COOCH(CH$_2$O−)$_2$); 1.57 (d, ^3J = 7.0 Hz CHCH_3, poly(lactide)), 1.80−2.34 (m,−CH_2C(CH$_3$)(COOCH(CH$_2$O−)$_2$); 3.56−4.33

(COOCH(CH_2OH)$_2$); 4.20−4.57 (COOCH(CH_2O−)$_2$); 5,15 (q, ^3J = 7.0 Hz CH(CH_3), poy(lactide)); 5.27−5.49 (COOCH-(CH_2O−)$_2$CHC$_6$H$_5$); 7.16−7.54 (COOCH(CH_2O−)$_2$CHC$_6H_5$).

Acetal Cleavage: Kinetics via ^{1}H NMR. First, 20 mg of the block copolymer were dissolved in 0.82 mL of deuterated THF and charged into a standard NMR tube. The probe head was preheated to 37 °C prior to injection of 0.15 mL of a 1 N HCl/DCl solution. Spectra were measured in intervals of 15 min with four scans each (approximately 30 s/experiment), the first scan 1 min after the injection. ^{1}H NMR (first spectrum obtained)-(82% THF-d_8, 18% 1 N HCl/DCl; 400 MHz) δ ppm: 0.90−1.22 (m, C(CH_3)(COOCH(CH$_2$OH)$_2$); 1.46 (d, ^3J = 7.0 Hz OCH(CH_3), poly(lactide)); 1.85−2.20 (m,−CH_2C(CH$_3$)(COO-CH(CH$_2$OH)$_2$); 3.69−3.81 (COOCH(CH_2OH)$_2$); 4.65−4.77 (−COOCH(CH$_2$OH)$_2$); 5.15 (q, ^3J = 7.0 Hz CH(CH$_3$); poy-(lactide)); 5.48 (d, ^3J = 6.0 Hz HOCH(CH$_3$), poly(lactide) *term. unit*).

Micelle Preparation. 10−15 mg of the block copolymer were dissolved in 2.7 mL of THF and 0.5 mL of 1 N hydrochloric acid were added. The vial was sealed with a rubber septum and the content stirred at 37 °C for 8 h. Subsequently 10 mL of water were added dropwise under vigorous stirring over a period of 4 h. Samples were dialyzed against 3 × 1 L of water for a total of 48 h. The first dialysis solution was buffered with 0.1 mg of sodium acetate. The aggregate morphologies were studied using a transmission electron microscope (TEM). The TEM samples were prepared by drop casting the above-mentioned aggregate solution (c = 1−1.5 mg/mL) on a plasma treated carbon coated copper grid. The samples were allowed to dry at room temperature under a slight nitrogen flux for at least 16 h prior to examination.

Fluorescence Measurements. The extremely hydrophobic pyrene is preferentially solubilized in the hydrophobic interior of the aggregate. This can be readily observed in the fluorescence excitation spectra of the probe at an emission wavelength of 372 nm.[43] In the concentration range of aqueous micellar solutions, a shift of the excitation band in the 335 nm region toward higher wavelength is observed for the employed block copolymers. The ratio of the fluorescence intensities at 339 and 335 nm was used to validate the shift of the broad excitation band. The critical aggregation concentrations (CAC) were determined from the crossover point in the low concentration range. Pyrene-containing samples were prepared by continuous dilution of the aggregate solution with a saturated pyrene stock solution. The mixtures were allowed to equilibrate for 48 to 64 h prior to investigation by fluorescence spectroscopy.

Results and Discussion

Monomer Synthesis. The synthetic strategy for benzylidene glycerol methacrylate (BGMA) is shown in Scheme 1. The monomer was readily obtained on a multigram scale via a two-step route, starting from the acetal formed by glycerol and benzaldehyde with subsequent esterification of the secondary hydroxyl group with methacryloyl chloride.

In comparison to ketones, as employed in solketyl methacrylate synthesis, benzaldehyde and its derivates show a strong preference for the formation of six-membered cyclic acetals due to the energetically favored equatorial position in the chair conformation of the ring. This acetal protecting group provides excellent stability in neutral and basic environment and is conveniently cleaved under slightly acidic conditions. The isolation of 2-phenyl-5-hydroxyphenyl-1,3-dioxane (**1**) relies on a crystallization step, which exclusively yields the *cis*-isomer of the compound in very high purity (Figure 1). The coupling reaction with methacryloyl chloride was conducted in dichloromethane in the presence of stoichiometric amounts of triethylamine (TEA) and catalytic amounts of dimethylaminopyridine (DMAP). The novel

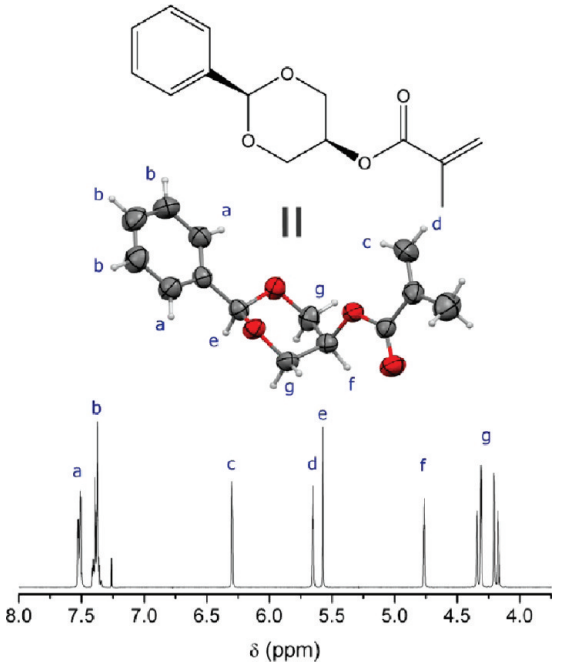


Figure 1. ^{1}H NMR analysis and crystal structure derived from the X-ray diffraction pattern of BGMA.

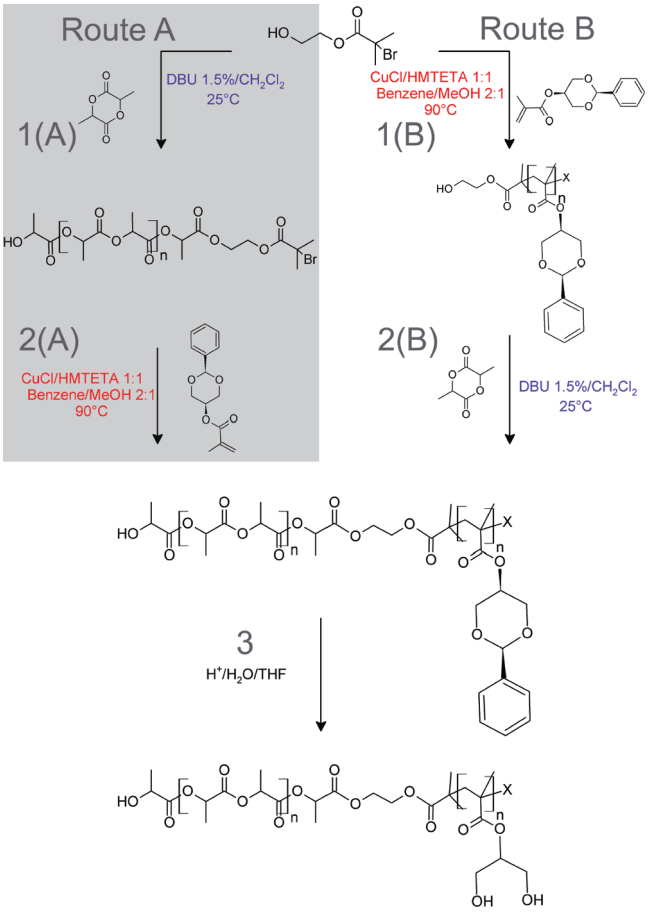
monomer (**2**) could be readily obtained in 78% yield by crystallization from THF/diethyl ether/hexanes (1:10:10), and the white crystals exhibited a melting point of 65.7 °C. This methacrylate significantly differs from 2-phenyl-(1,3-dioxane-4-yl)methyl methacrylate, which was previously described and obtained by an elaborate synthesis from solketyl methacrylate via 2,3-dihydroxypropyl methacrylate and subsequent reprotection as benzylidene acetal.[44]

Considering the bifunctional initiator used for the synthesis of the targeted block copolymers and the quantitative protection of the hydroxyl groups of the monomer, two different synthetic routes appeared to be viable: (A) synthesis of a poly(lactide) macroinitiator and subsequent chain extension with poly(lactide), or (B) preparation in reverse manner, that is, ATRP of BGMA with subsequent chain extension by ROP of lactide (cf. Scheme 3). Both pathways have been tested. To ensure fast initiation, ATRP was conducted with the mixed halide exchange technique,[45] starting from highly reactive isobutyryl-bromide, using copper(I) chloride in combination with stoichiometric amounts of HMTETA. A suitable solvent system providing good polymerization control for the ATRP of BGMA, while offering sufficient solubility for BGMA and lactide based homopolymers, was found with a 1:2 mixture of methanol and benzene. The low polarity of the PBGMA based polymers also ensures convenient removal of the Cu complex after polymerization. Column filtration over neutral aluminum oxide with a low polarity solvent (e.g., benzene) permitted excellent retention of the colored Cu species. Furthermore, PBGMA and poly(L-lactide) as well as their block copolymers of arbitrary composition ratios can be readily purified by (a single) precipitation in their common nonsolvent methanol. A change in block copolymer composition was not observed in this step. Residual monomer and catalyst (DBU−benzoate salt as well as Cu complex) were removed by this procedure. Generally speaking, the benzylidene acetal of BGMA not only contributes to an increase in the monomer and polymer solubility in commonly employed, apolar organic media, but also gives access to

other controlled polymerization methods (e.g., living anionic polymerization), which show far less tolerance toward the presence of functional groups than ATRP. Obviously, block copolymer synthesis involving two or more orthogonal polymerization methods, employing monomers of different functionality and/or polarity necessitates masking of their functional groups.

ATRP of BMGA. ATRP was the obvious method of choice for the preparation of a narrow polydispersity block of the novel monomer. The semilogarithmic plot of the kinetic polymerization data derived from ^{1}H NMR shows a nearly linear correlation throughout the major part of the polymerization, with a small decrease toward high conversion. Hence, the reaction can be considered living with a close to constant radical concentration during the polymerization. The slight flattening of the plot can be explained by traces of oxygen, which might have been introduced during sample harvesting, although all syringes were carefully purged with argon prior to the process. The kinetically evaluated sample reached a conversion of only 66%. The characterization data are shown in Table 1.

Scheme 3. Two Alternative Synthetic Pathways to Poly(isoglycerol (mono)methacrylate)-*b*-poly(lactide) Block Copolymers: (A) Lactide First; (B) BGMA First[a]



[a] While route B resulted in well-defined block copolymers, route A showed inefficient block formation and was not further pursued.

The evolution of molar mass correlated linearly with conversion (Figure 2). The monodisperse SEC-traces observed revealed narrow molecular weight distributions (PDI 1.18−1.30), characteristic for well-controlled CRP/ATRP processes. The decrease in PDI was very pronounced during the earlier stages of the polymerization and became significant after 60 min. We assume that this point is indicative of complete consumption of the initiator, followed by exclusive propagation with constant chain growth. This goes along with the appearance of a nonzero extrapolation of the linear fit and can be explained by the use of the mixed halide exchange technique and hence a significantly faster initiation than propagation reaction, which results in slightly faster monomer consumption at the onset of the polymerization. First DSC studies showed a rather high T_g of the PBGMA homopolymer (115−130 °C depending on M_n), which is due to the high rotational barrier introduced by the bulky benzylidene acetal substituents at the methacrylate polymer chain. We will report in detail on the interesting thermal properties of PBGMA-based polymers in a subsequent publication.

Chain Extension with Poly(lactide). Since the poly(isoglycerol methacrylate) hydroxyl groups are fully protected, the lactide chain growth commences from the single hydroxyl moiety of the bifunctional macroinitiator. Ring-opening polymerization was conducted under organo-base catalysis with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which has proven to work excellent for lactide ring-opening[46] on a laboratory or semibatch scale. It provides superb end group-fidelity, good polymerization control and fast kinetics, even at room temperature. The polymerization time for the samples prepared was kept between 15 and 45 min, depending on the monomer/initiator ratio and resulted in conversion ranging from 85 to 99% (1.5 mol % catalyst loading).

While route B (cf. Scheme 3) resulted in well-defined block copolymers (Table 2), the pathway A led to the formation of less defined structures, presumably composed of a mixture of homo and block copolymers. This was indicated by a change in composition (depletion of the lactide block, sometimes even complete disappearance) after precipitation in a non-solvent for both blocks and broader molecular weight distributions. This is astonishing, since the polylactide macroinitiators were completely functionalized (single distribution

Table 1. Molecular Characterization Data for the Preparation of PBGMA Macroinitiators[a]

	Polymer	Initiator	Monomer	M/I	M_N theo. (100% conv.)	M_N (NMR)	Time (min)	Conv. (NMR)	M_N (SEC)	PDI	Composition (NMR)
1. ATRP of BGMA	PBGMA-MI 1	2-HBMP	BIGMA	25	6400	5480	300	0.85	3830	1.23	$PBGMA_{21}$
	PBGMA-MI 2	2-HBMP	BIGMA	40	9900	9520	300	0.96	5700	1.26	$PBGMA_{38}$
	PBGMA-MI 3	2-HBMP	BIGMA	55	13600	11700	300	0.86	6300	1.30	$PBGMA_{47}$
	PBGMA-MI 4	2-HBMP	BIGMA	100	24800	20200	300	0.80	11700	1.20	$PBGMA_{80}$
	PBGMA-MI 5	2-HBMP	BIGMA	110	27500	22400	300	0.81	11900	1.18	$PBGMA_{89}$
	PBGMA-MI 6	2-HBMP	BIGMA	200	49700	35800	300	0.72	18700	1.15	$PBGMA_{144}$
	PBGMA-MI 7	2-HBMP	BIGMA	400	99300	65900	360	0.66	24400	1.24	$PBGMA_{266}$

[a] SEC in THF, evaluation with polystyrene standards.

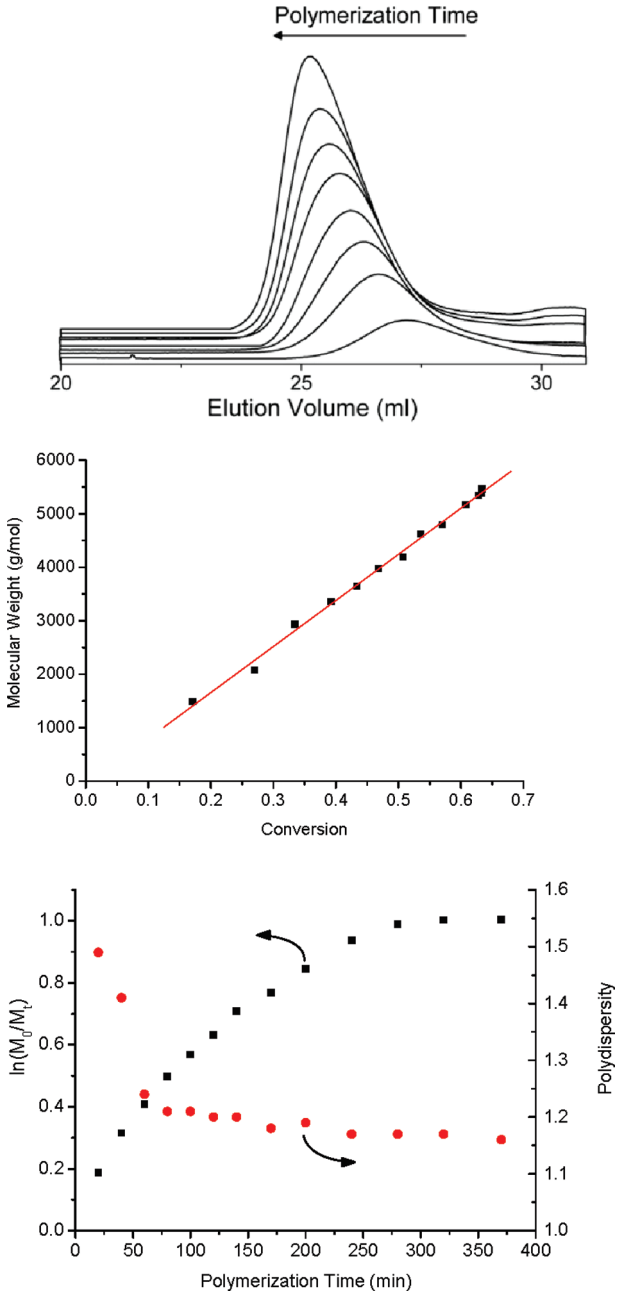


Figure 2. Kinetics of the polymerization of BGMA: SEC traces (top, plotted for 20−170 min reaction time) show a clean shift toward lower elution volumes in the course of the polymerization; middle, linear correlation of molecular weights (SEC_{THF} data), derived from PS standards with conversion; bottom, $\ln(M_0/M_t)$ vs polymerization time.

in MALDI−ToF spectra) and chain extension of these macroinitiators via ATRP has already been conducted successfully with HEMA (in DMSO with CuCl/bipyridyl), as recently described by the authors.[25] However, route B results in the formation of well-defined block copolymers and is slightly more practical, since diversification of the macroinitiator is possible, using the synthetically more convenient ROP of L-lactide (polymerization at room temperature, polymerization time <15 min, no oxygen free environment necessary). In this case, all samples were monomodal and their block ratios remained unchanged during the purification process (filtration, precipitation), as was verified by ^{1}H NMR and SEC (Figure 3).

For the chain extension with poly(lactide) the respective degrees of polymerization were targeted by adjusting the monomer/initiator molar ratio, affording hydroxyl-functional PBGMA homopolymer precursors of varying chain lengths. Because of pronounced underestimation of molecular weight by SEC (PS standards) absolute molecular weights were estimated from the monomer/initiator ratio, considering the specific conversion of the sample calculated from NMR in the case of the PBGMA-macroinitiator. This underestimation is explained by the bulkiness of the substituents along the polymethacrylate backbone. In general, the use of the bifunctional initiator made post polymerization reactions redundant and the completely functionalized macroinitiators allowed quantitative chain extension with lactide.

Cleavage of the Acetal Protecting Group. The formation of the hydrophilic PIGMA from its protected precursor PBGMA was investigated via ^{1}H NMR. We observed that the rate of the acetal hydrolysis depends significantly on the reaction temperature. Screening of suitable time/temperature deprotection conditions was conducted by exposing the initial test sample to 3 different temperatures (A) 19 °C for 23 h (24%), (B) 4 °C for 12 h (6%) and (C) 27 °C, 12 h (100%). The first reaction mixture was composed of 90% THF and 9% D_2O and 1% 10 n HCl (0.1 mol/L). Upon completion of the acetal cleavage during the last deprotection sequence, the polymer precipitated from the reaction mixture and was redissolved by increasing the water/HCl content of the mixture to 18%. These results indicate that acetal cleavage at slightly increased (30−40 °C) temperatures should result in shorter reaction times, which are still tolerable for the polyester backbone of the second block.[47] This was confirmed and monitored via NMR analysis in THF-d_8/1 N DCl in the respective ratio (Figure 4).

As expected, the pronounced amphiphilic nature of the block copolymers did not permit SEC measurements in THF after deprotection. Nevertheless, DMF offers sufficient solubility for homo- and block copolymers of the employed components before as well as after acetal hydrolysis. In Figure 5 monomodal SEC traces with DMF as an eluent reveal narrow monomodal molecular weight distributions and illustrate the successful 3-step process to the amphiphilic block copolymers, free of detrimental side reactions. Remarkably, the block copolymers exhibit a significantly decreased elution volume after deprotection (Table 3). This is in good agreement with the observed underestimation in molecular weight for polymers consisting of PBGMA by evaluation with calibration standards like PEG, PS, and PMMA, which were at hand. PBGMA homopolymers were cleavable under the same conditions and could be redissolved in water (D_2O) after solvent evaporation.

The shelf life of the block copolymers under the acidic conditions of the deprotection reaction was found to be remarkable. Even for times representing a multitude of those required for complete acetal cleavage, no degradation of polylactide or isomerization of the poly(isoglycerol methacrylate) could be observed. This is supported both by ^{1}H NMR and by the constant ratio of lactide and cleaved benzaldehyde-related signals (Figure 6). Furthermore, SEC traces measured 24 and 96 h after deprotection strongly resemble each other.

Aggregate Formation of the PIGMA−PLLA Block Copolymers. Using the so-called indirect dissolution method with subsequent dialysis, well-defined micelles were formed upon self-organization of PIGMA-*b*-PLA. The acetal protecting groups of the double hydrophobic PBGMA-*b*-PLA copolymers were cleaved prior to the aggregation studies without isolation from solution, as described in the previous section. First of all the critical aggregation concentration (CAC) has

Table 2. Molecular Charachterization Data for the Chain Extension of the PBGMA Macroinitiators with Lactide[a]

	Polymer	Initiator	M#	M/I	M_N theo. (100%conv.)	M_N NMR	Time (min)	Conv. (NMR)	M_N (SEC*)	Composition (NMR)
2. ROP of Lactide	PBGMA-PLA 1	$PBGMA_{89}$ (MI 5)	L-LA	35	27400	26100	20	0.74	15200	$PBGMA_{89}$-$PLLA_{27}$
	PBGMA-PLA 2	$PBGMA_{89}$ (MI 5)	D-LA	35	38300	29500	20	0.45	13600	$PBGMA_{89}$-$PDLA_{16}$
	PBGMA-PLA 3	$PBGMA_{47}$ (MI 3)	L-LA	30	16000	15400	45	0.86	9770	$PBGMA_{47}$-$PLLA_{26}$
	PBGMA-PLA 4	$PBGMA_{47}$ (MI 3)	D-LA	30	16000	15700	45	0.92	9970	$PBGMA_{47}$-$PDLA_{28}$
	PBGMA-PLA 5	$PBGMA_{21}$ (MI 1)	L-LA	15	7600	7550	20	0.96	6100	$PBGMA_{21}$-$PLLA_{14}$
	PBGMA-PLA 6	$PBGMA_{21}$ (MI 1)	D-LA	15	7600	7550	20	0.96	6270	$PBGMA_{21}$-$PDLA_{14}$
	PBGMA-PLA 7	$PBGMA_{80}$ (MI 4)	D-LA	46	28600	27900	30	0.88	16900	$PBGMA_{80}$-$PDLA_{40}$

[a] The asterisk indicates SEC in THF; evaluation with polystyrene standards. The # indicates M = monomer (L-/D-LA = L-/D-lactide).

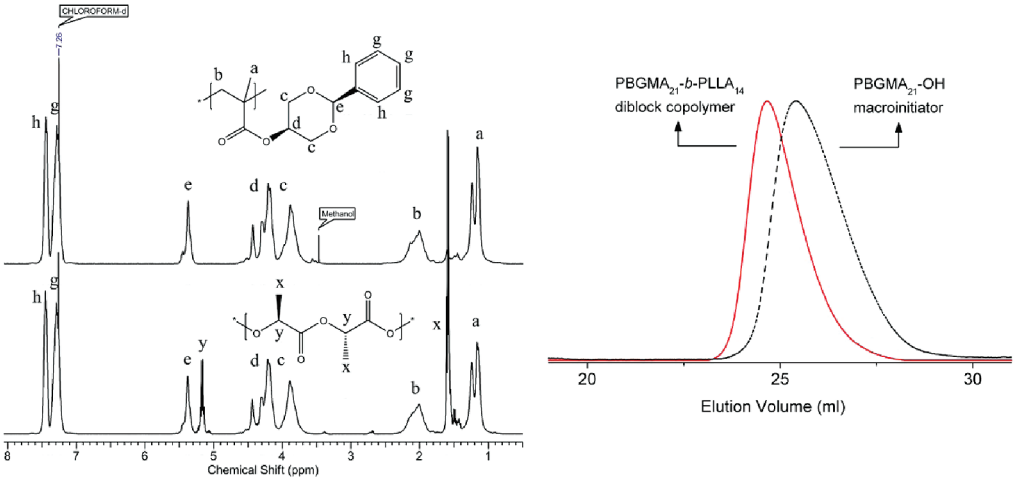


Figure 3. Chain extension of the PBGMA−macroinitiator with poly(lactide) depicted in the form pre/post NMR (left) and SEC (right) measurements. Although the sample chosen is composed of few lactide repeating units (i.e., DP = 14), it shows clean chain extension. This fact is attributed to the high initiating potential of the primary hydroxyl group of the PBGMA prepolymer.

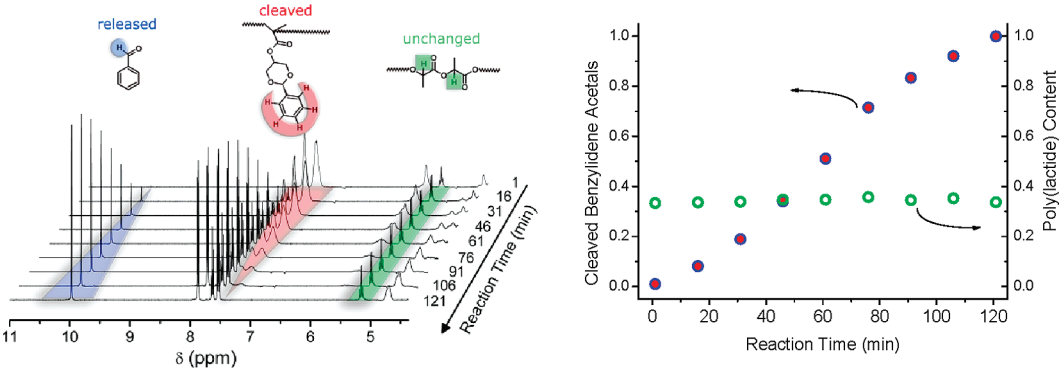


Figure 4. Deprotection of the benzylidene−acetal groups of the diblock copolymer, monitored by ^{1}H NMR in THF-d_8. While the poly(lactide) backbone remains unaffected, the benzylidene protecting groups of the polymer are fully cleaved within only 2 h at 37 °C.

been examined. Fluorescence measurements with pyrene as fluorescent probe are an excellent method to obtain information concerning aggregate formation. The ratio of the fluorescence intensities at 339 and 335 nm was used to evaluate the shift of the excitation spectra. The ratio remained constant below a certain concentration but changed substantially above a critical concentration, reflecting the partitioning of pyrene between the aqueous solution and aggregated phases. It has to be emphasized that the micellar aggregates formed by enantiomerically pure PLA block copolymers already possess high thermodynamic stability in aqueous solution and may perform as favorable drug carriers themselves.[48] Nevertheless, the special stereochemistry of poly(lactide) provides access to non covalent stabilization via stereocomplexation of two isotactic and enantiomeric poly(lactide) chains. This was achieved by dissolving equal amounts of two block copolymers of similar composition with enantiomeric poly(lactide) blocks prior to hydrolysis of the acetal goups.

From the set of synthesized polymers we focused on those with an approximate block ratio of 2:1. (i.e., $PIGMA_{47}$-*b*-$PLLA_{26}$ and $PIGMA_{47}$-*b*-$PDLA_{28}$). Since it is known that crystallization occurs in enantiomeric (1:1) blends at PLA chain lengths shorter than their isotactic counterparts, we aimed at keeping the PLA block length below the critical limit of 30 repeating units. At this chain length (and even below), stabilization by crystalline stereocomplexes in amphiphilic block copolymers based on poly(lactide) is possible.[49] They generally crystallize in a triclinic unit cell, in which the chains exhibit a characteristic 3_1 helical conformation. Figure 7 shows the apparent CAC values obtained for the different amphiphilic block copolymers. The CAC lies in the same order of magnitude—being approximately twice as high for the $PIGMA_{47}$-*b*-$PLLA_{26}$ block copolymer compared to the PEG_{123}-*b*-$PLLA_{29}$ sample (from ref 5). This indicates an increase in hydrophilicity and hence stabilization potential of PIGMA compared to PEG in aqueous solution. Therefore, an increase of the PIGMA chain length at nearly constant PLLA chain lengths resulted in an increase of the CAC by a factor of approximately 2 ($PIGMA_{47}$-*b*-$PLLA_{26}$ to $PIGMA_{89}$-*b*-$PLLA_{27}$). Generally speaking, the low CAC permits application of the block copolymers in highly dilute systems, such as the blood plasma.

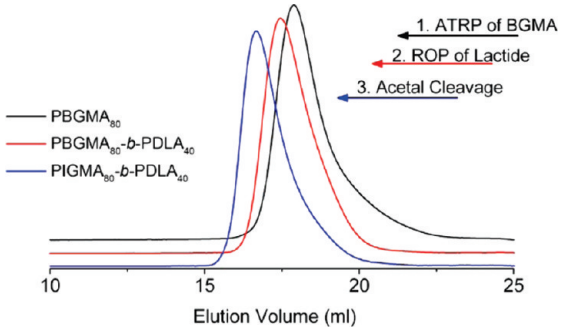


Figure 5. SEC traces (DMF): (1) $PBGMA_{80}$ (right); (2) $PBGMA_{80}$-*b*-$PDLA_{40}$; (3) $PIGMA_{80}$-*b*-$PDLA_{40}$.

The influence of the assumed stereocomplexation (mixture of $PIGMA_{47}$-*b*-$PLLA_{26}$ and $PIGMA_{47}$-*b*-$PDLA_{28}$) on the CAC was small, confirming results obtained by Leroux et al.[5] for PEG−PLA block copolymers. Intriguingly, the diastereomeric mixing of two block copolymers of very similar composition has a strong influence on the aggregates' morphology. As pointed out, the chosen block lengths had a positive hydrophilic to hydrophobic ratio between 3.5 and 2 (e.g., $PIGMA_{47}$-*b*-$PLLA_{26}$), which clearly explains the formation of spherical micelles with an approximate diameter of 20−30 nm (Figure 8, top).

Although block copolymers with a crystallizable hydrophobic block show a tendency toward the formation of nonspherical wormlike micelles—a fact that can be attributed to the lamellar packing of the crystallizable chains—X-ray diffraction studies of PEG−PLLA-based polymeric micelles performed by Leroux et al.[5] showed that the stereoregular poly(lactide) does not crystallize, if the block length remains below 30 repeating units. In the case of mixtures of similar PIGMA-*b*-PLA block ratios with enantiomeric poly(lactide) blocks an entirely different morphology was found. Surprisingly, TEM images of the aggregates prepared from mixed solutions (1/1 mixture) of the diasteromeric block

Table 3. Comparison of SEC Data for the PBGMA−PLA Based Block Copolymers before and after Deprotection[a]

before deprotection				*after deprotection*			
Composition (NMR)	**M_N theo.**	**M_N (SEC)**	**PDI**	**M_N (theo)**	**M_N (SEC)**	**PDI**	**Composition**
$PBGMA_{21}$	5480	3800	1.15	3330	5800	1.22	$PIGMA_{21}$
$PBGMA_{89}$	22400	11500	1.18	14300	18300	1.25	$PIGMA_{89}$
$PBGMA_{89}$-*b*-$PLLA_{27}$	26100	8400	1.17	18100	13900	1.27	$PIGMA_{89}$-*b*-$PLLA_{27}$
$PBGMA_{47}$-*b*-$PLLA_{26}$	15400	8200	1.17	11300	11900	1.26	$PIGMA_{47}$-*b*-$PLLA_{26}$
$PBGMA_{47}$-*b*-$PDLA_{28}$	15700	8500	1.16	11600	11800	1.27	$PIGMA_{47}$-*b*-$PDLA_{28}$
$PBGMA_{47}$-*b*-$PLLA_{26}$ + $PBGMA_{47}$-$PDLA_{28}$	s.a.[b]	s.a.[b]	s.a.[b]	11400	12500	1.31	$PIGMA_{47}$-*b*-$PLLA_{26}$ + $PIGMA_{47}$-b-$PDLA_{28}$
$PBGMA_{21}$-*b*-$PLLA_{14}$	7550	5300	1.12	5400	7450	1.24	$PIGMA_{21}$-*b*-$PLLA_{14}$
$PBGMA_{80}$-*b*-$PDLA_{40}$	27900	13700	1.17	18900	20700	1.18	$PIGMA_{80}$-*b*-$PDLA_{40}$

[a] The apparent increase in molecular weight after hydrolysis is noticeable, despite a nominal weight loss of 40% for the transformation of PBGMA to PIGMA (SEC in DMF; evaluation was achieved with poly(ethylene glycol) standards). [b] See above.

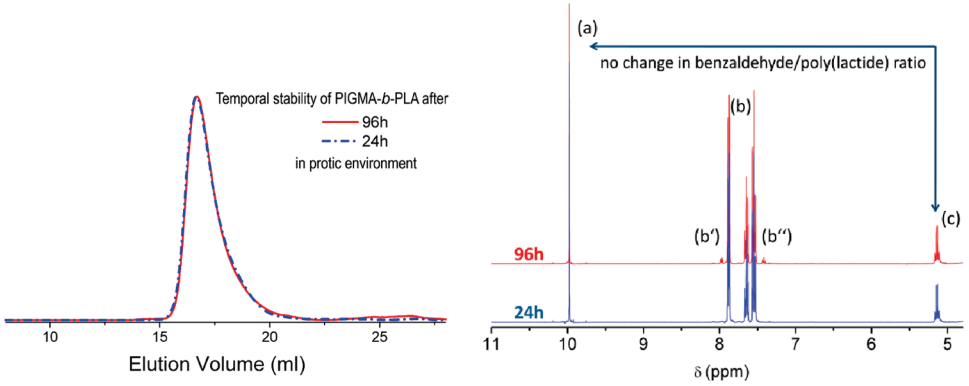


Figure 6. Stability of the amphiphilic PIGMA-*b*-PLA copolymer in acidic environment beyond the time frame required for deprotection of the acetal as indicated by consistent elugrams (left) and unchanged signal ratios in ^{1}H NMR.

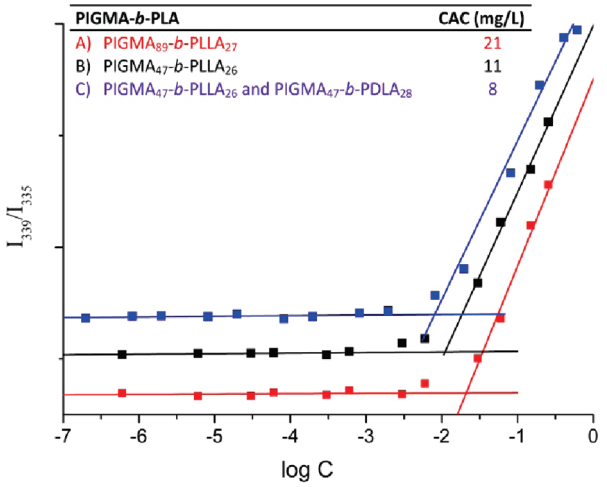


Figure 7. CAC measurements using pyrene fluorescence excitation spectra at an emission wavelength of 372 nm: (A) (red) $PIGMA_{89}$-*b*-$PLLA_{27}$; (B) (black) $PIGMA_{47(7500)}$-$PLLA_{26(3800)}$; (C) (blue) $PIGMA_{47(7500)}$-$PLLA_{26(3800)}$ and $PIGMA_{47(7500)}$-$PDLA_{28(4000)}$ (1:1).

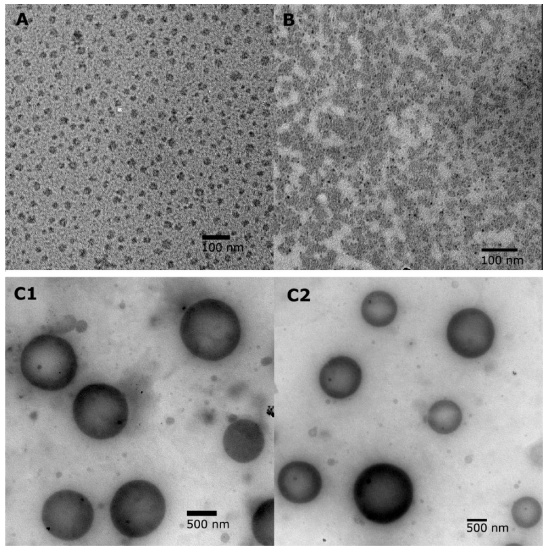


Figure 8. TEM image of (A) $PIGMA_{47}$-*b*-$PLLA_{26}$ and (B) $PIGMA_{47}$-*b*-$PDLA_{28}$[57] micellar aggregates with an average diameter of 20 to 30 nm. Sample preparation was carried out under identical conditions with a 1:1 mixture of $PIGMA_{47}$-*b*-$PLLA_{26}$ and $PIGMA_{47}$-*b*-$PLLA_{28}$ afforded large polymersomes (C1 and C2) with a diameter between 600 and 1400 nm (bottom).

copolymers showed the formation of vesicular aggregates, i.e., "polymersomes" with average diameters between 600 and 1400 nm (Figure 8, bottom). For the hydrophilic to hydrophobic volume ratio chosen, spherical micelles or cylindrical aggregates would have been expected from a conventional point of view—especially since it is known that crystalline domains in the hydrophobic block of an aggregate can promote the formation of cylinders with a small length/width aspect ratio.[50] Since our block copolymers show a significantly increased hydrophilic to hydrophobic ratio, polymersome formation[7] is unlikely and indeed not observed for aggregate solutions with a single homochiral PLA component (Figure 8, top). Since all other parameters remained unchanged during aggregate preparation, stereocomplexation can be considered to be a very likely cause for the change in the aggregate morphology. Here, the question arises, how bilayer formation, as a prerequisite for polymersome formation, is triggered. Since the thermodynamic parameters are not known for this new block copolymer system, we can only argue with the sum of poly(lactide)s' known characteristics[51] to put forward a conclusive explanation. Because of its stereoregular methyl substituent in alpha-position, poly(D/L-lactide) represents a rather stiff hydrophobic part of the block copolymer with a low conformational degree of freedom, resulting in a rather high T_g, i.e., 30−40 K above room temperature. This stiffness is generally known to promote the formation of planar bilayer structures. Although this behavior is obviously not sufficiently pronounced for non crystalline poly(L-lactide), as expected for the employed average number of repeating units (26 and 28), the formation of stereocomplex-induced crystallization appears to be important for the mixed block copolymers. Antonietti and Förster concluded that "*planar assemblies are spontaneously formed in a much broader range in phase space, if there is a tendency of the tecton* (in this case a block copolymer) *to exhibit at least nematic order*".[52] The additional 3-dimensional positional order of the 3_1 helical conformation in the β-form, in which the stereocomplexed poly(lactide) "tecton" is packed in a parallel fashion[53] is based on noncovalent secondary valences and most likely promotes the formation of planar assemblies and hence represents the reason for the formation of polymersome-type structures. We believe that the preparation technique employed via the indirect dissolution[54] from THF with water is an important factor to obtain the defined aggregates we observed. THF is a good solvent for stereoregular PLA of moderate molecular weight and a poor solvent for crystalline, stereocomplexed PLA. This ensured sufficient chain mobility upon aggregate formation, while not endangering the formation of stable crystalline domains, which are not formed unless a controlled amount of water as poor solvent for the inner PLA-block is added.

This is further supported by SEC examination (DMF, from THF/HCl solution) of the freshly prepared 1:1 mixture of $PIGMA_{47}$-*b*-$PLLA_{26}$ and $PIGMA_{47}$-*b*-$PDLA_{28}$ prior to selective dissolution. Intriguingly, the SEC trace of this mixture was monomodal and showed no aggregate formation. Evaluation with PS-standards provided a sample of similar molecular weight and polydispersity resembling those obtained for their homopolymers (Table 3). A more detailed report on the intriguing topic of stereocomplex-induced changes in block copolymer aggregate morphology in solution will be the subject of a forthcoming publication.

An additional interesting feature of the prepared aggregates is the high number of primary hydroxyl groups at their periphery. This provides interesting potential for the block copolymer in targeted drug delivery, since the abundance of hydroxyl groups at the corona allows attachment of (multiple) distinct piloting/targeting functions to the micelle corona by straightforward chemistry. Stereocomplex-induced crystallization knowingly contributes to an enhanced kinetic and thermodynamic stability of aggregates. In their potential application as sustained release devices, stereocomplexation could thus increase plasma circulation time of PIGMA-*b*-PLA copolymers, facilitating their accumulation at the target site.

Conclusion

This work presents the first synthesis of poly(*cis*-benzylidene isoglycerol methacrylate) (PBGMA), a polymer which exhibits interesting materials properties and can easily be transformed into poly(isoglycerol methacrylate (PIGMA), which exclusively contains primary hydroxyl groups along the backbone. This was realized by selective acetal protecting chemistry in form of the new

glycerol based methacrylate monomer BGMA (benzylidene glycerol methacrylate). The monomer is suitable for the preparation of polyester-based block copolymers with a bifunctional initiator via (i) ATRP and (ii) ring-opening polymerization of lactide. Selective acetal cleavage of the benzylidene groups yielding the amphiphilic poly(isoglycerol methacrylate)-*b*-(poly-(L-lactide)), which was capable of self-assembly in micellar solution. Structural similarity is obvious for the recently investigated poly(glyceryl glycerol), which is accessible from oxyanionic polymerization, employing either osmylation chemistry or release from its acetonide protecting group.[55]

Illustrating the aggregation potential of the block copolymers, we have been able to demonstrate that PIGMA is a potential alternative for PEG as hydrophilic component in biocompatible block copolymers with promising attributes for drug delivery systems. In combination with poly(lactide), micelles with low CAC could be obtained. Their morphology could be adjusted from micellar to polymersome type aggregates by changing the physiochemical cross-linking with enantiomeric poly(lactide) blocks via stereocomplexation. With this work, we aim at further exploration of the field of amphiphilic polyester/polyacrylate-based block copolymers suitable for biomedical purposes.

Acknowledgment. Special thanks go to Annika Hörberger and Saskia Mulhjadi for valuable support in the lab. F.K.W. acknowledges the IMPRS of the Max Planck Society for continuous support. A.M.H. is grateful to the graduate class of excellence "POLYMAT" in the context of MAINZ for valuable financial support.

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(56) For reasons of simplicity and clarity, the new poly(1,3-dihydroxyisopropyl methacrylate) will be referred to as poly(isoglycerol (mono)methacrylate) (PIGMA), which exhibits two primary hydroxyl-groups in contrast to the commonly employed isomer poly(glycerol methacrylate) (PGMA).

(57) In the case of sample preparation of the $PIGMA_{47}$-*b*-$PDLA_{28}$, the copper grids were not hydrophilized by argon/oxygen plasma treatment because of an equipment failure. This fact impaired the spreading of the sample on the grid and thus caused higher local aggregate concentrations.