Macromolecules 2008, 41, 7892−7897

Iron-Centered Star Polymers with Pentablock Bipyridine-Centered PEG-PCL-PLA Macroligands

Gina L. Fiore and Cassandra L. Fraser*

Department of Chemistry, University of Virginia, McCormick Road, P.O. Box 400319, Charlottesville, Virginia 22904

Received June 16, 2008; Revised Manuscript Received August 6, 2008

ABSTRACT: Elaborate biocompatible block copolymer architectures are achievable via controlled ring opening polymerization (ROP). Selective incorporation of donor groups results in macroligands that can coordinate metals to form site-isolated metallopolymers. A hydroxyl-functionalized bipyridine, bpy(CH$_2$OH)$_2$, was employed as an initiator for the ROP of ethylene oxide, producing bpyPEG$_2$. Subsequent reaction with ε-caprolactone followed by lactide (D,L- and L-) results in well-defined bpy-centered triblock PCL-PEG-bpy-PEG-PCL and pentablock PLA-PCL-PEG-bpy-PEG-PCL-PLA and PLLA-PCL-PEG-bpy-PEG-PCL-PLLA macroligands, respectively, with low polydispersity indices (PLA = D,L-polylactide, PCL = poly(ε-caprolactone), PEG = poly(ethylene glycol), PLLA = L-polylactide). These systems were combined with FeCl$_2$ to produce iron-centered star blocks [Fe{bpy(PEG-PCL)$_2$}$_3$]Cl$_2$, [Fe{bpy(PEG-PCL-PLA)$_2$}$_3$]Cl$_2$, and [Fe{bpy(PEG-PCL-PLLA)$_2$}$_3$]Cl$_2$ with six diblock and triblock arms. Materials were characterized by gel permeation chromatography (GPC), ^{1}H NMR, and UV−vis spectroscopy, verifying that synthetic targets were achieved. Thermal gravimetric analysis shows decomposition temperatures corresponding to PEG, PCL, and PLA blocks, and melting temperatures are typical for these materials.

Introduction

Sophisticated macromolecular architectures can be generated by living polymerization methods. Compositional segments may be introduced at reactive chain ends in a stepwise fashion to generate a wide range of block copolymer structures capable of self-assembly into higher order solution[1−4] and film morphologies.[4−7] Functional elements, such as metal complexes, can be incorporated into specific sites to introduce responsive features into materials.[8−13] For example, luminescent metalloblock copolymer assemblies are known for europium heteroarm star films[14] and ruthenium terpyridine systems as films[15] and micelles.[16−18] In some cases, demetalation of ruthenium metallo-supramolecular micelles is possible via introduction of a competitive ligand, resulting in the dissociation of terpyridine macroligands from the metal center.[19] Patterned block copolymer films have also served as templates for mineralization and iron oxide nanoparticle formation upon macroligand dissociation.[20] Ligand-functionalized block copolymers have also been used for the arrangement and stabilization of inorganic nanoparticles.[21−25]

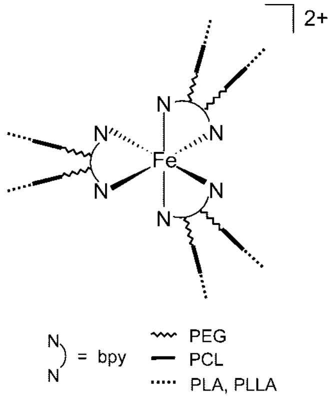


Figure 1. Schematic representation of iron(II) tris(bipyridine)-centered star block copolymer with PEG-PCL-PLA triblock copolymer arms.

Here, we employ hydroxyl-functionalized bipyridine initiators for the sequential living/controlled ring opening polymerization (ROP) of ethylene oxide, ε-caprolactone, and D,L- or L-lactide and show that the resulting PLA-PCL-PEG-bpy-PEG-PCL-PLA and PLLA-PCL-PEG-bpy-PEG-PCL-PLLA pentablock macroligands are competent for iron(II) binding, producing iron-centered six arm, star block copolymers with PEG-PCL-PLA triblock arms (PLA = D,L-polylactide, PLLA = L-polylactide) (Figure 1). Hydrophilic poly(ethylene glycol) (PEG) and hydrophobic polyesters, such as poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL), are biocompatible polymers that find wide application in medicine. Amphiphilic block copolymers based on PEG-PCL and PEG-PLA can form solution,[4,26−28] film,[4,29] and hydrogel assemblies.[30,31] For example, PEG-PLA and PEG-PCL polymerosomes form vesicles and wormlike micelles that have been used for drug delivery both *in vitro*[26,32] and *in vivo*.[33,34] Furthermore, degradation rates of PCL are modulated by the introduction of faster degrading PLA[35−37] or hydrophilic PEG,[26−28] the latter of which facilitates diffusion of water into the polymer matrix and thus hydrolysis of the polyester chain. The introduction of metal complexes into polymers imparts color and chemically responsive cross-links. For example, polymeric iron tris(bipyridine) (tris(bpy)) complexes are sensitive to acid, base, or oxidants such as peroxides or dioxygen.[38−40] Associated bleaching of the red-violet iron tris(bpy) chromophores serves as a sensitive indicator of star polymer fragmentation and thus biomaterials degradation. Metals and polymers can mutually affect each other in these hybrid materials. Metals may influence rates of polymer degradation, while the surrounding polymer environment, both chemical composition and assembly morphology, can affect metal reactivity. The synthesis of state-of-the-art iron tris(bpy)-centered star block copolymers and their molecular weight, spectroscopic, and thermal analyses are described below.

Experimental Section

Materials. The difunctional initiator 4,4′-bis(hydroxymethyl)-2,2′-bipyridine (bpy(CH$_2$OH)$_2$) was prepared as previously reported.[41] ε-Caprolactone was dried over CaH$_2$ and distilled under reduced pressure prior to use. 3,6-Dimethyl-1,4-dioxane-2,5-dione

---

* To whom correspondence should be addressed. E-mail: fraser@virginia.edu.

10.1021/ma801353b CCC: $40.75

(D,L-lactide, Aldrich) and (3*S*)-*cis*-3,6-dimethyl-1,4-dioxane-2,5-dione (L-lactide) were recrystallized from ethyl acetate (2×) and stored in a drybox under a nitrogen atmosphere. Ethylene oxide (EO) (CAUTION, Aldrich) was dried over dibutyl magnesium (Aldrich), distilled under reduced pressure (2×), and stored in an air-free buret. Potassium naphthalenide was prepared by reaction of potassium and naphthalene in tetrahydrofuran (THF) and titrated (3×) with a standardized HCl solution.[42] Iron(II) chloride (Strem) was titrated with 2,2′-bipyridine (Aldrich) in 3:1 CH_2Cl_2/MeOH prior to use to verify the iron concentration. Tetrahydrofuran and methylene chloride (Fisher) were purified by passage through alumina columns.[43] Methanol (Fisher) was purged with argon prior to use in titrations, chelation reactions, and UV−vis spectroscopy. Chloroform-*d* ($CDCl_3$) was passed through a short plug of dry, activated (Brockman I) basic alumina prior to use in ^1H NMR analysis of polymeric iron complexes. Tin(II) 2-ethylhexanoate ($Sn(oct)_2$, Spectrum) and all other reagents were used as received.

Methods. ^1H NMR (300 MHz) spectra were recorded on a Varian UnityInova spectrometer in $CDCl_3$ unless otherwise indicated. Resonances were referenced to the signal for residual protiochloroform at 7.260 ppm. ^1H NMR coupling constants are given in hertz. UV−vis spectra were recorded on a Hewlett-Packard 8452A diode-array spectrophotometer in CH_2Cl_2/CH_3OH (3:1). Molecular weights were determined by gel permeation chromatography (GPC) (THF, 25 °C, 1.0 mL/min) using multiangle laser light scattering (MALLS) ($\lambda = 633$ nm, 25 °C) and refractive index (RI) ($\lambda = 633$ nm, 40 °C) detection. A Polymer Laboratories 5 μm mixed-C guard column and two GPC columns along with Wyatt Technology Corp. (Optilab DSP interferometric refractometer, DAWN DSP laser photometer) and Agilent Technologies instrumentation (series 1100 HPLC) and Wyatt Technology software (ASTRA) were used in GPC analysis. The incremental refractive indices (d*n*/dc values) for polymer samples were determined by a single injection method that assumed 100% mass recovery from the columns. Thermal gravimetric analysis (TGA) was conducted using a TA Instruments TGA 2050 thermogravimetric analyzer from 30 to 500 °C with a heating/cooling rate of 10 °C/min under N_2. Differential scanning calorimetry (DSC) measurements were performed using a TA Instruments DSC 2920 modulated differential scanning calorimeter. Analyses were carried out in modulated mode under a nitrogen atmosphere (amplitude = ±1 °C; period = 60 s; heating rate = 5 °C/min; range −10 to 200 °C or −10 to 170 °C). Reported values of thermal events are from the second heating cycle and the reversing heat flow curve unless indicated otherwise (T_d = onset point of decomposition; T_m reported as the peak maximum).

BpyPEG₂, 1. The polymerization was performed in a 250 mL glass reactor equipped with three internal Ace-Threds threaded glass connectors and a glass covered stir bar. Using Teflon ferrules, nylon bushings, and FETFE O-rings, the reactor was fitted with a glass plug, a Teflon valve, and a glass Y-connector. The Y-connector was equipped with a Teflon valve, purge valve, compound gauge, and port capped with a Teflon-coated septum. The valve on the Y-connector was connected to a vacuum/nitrogen manifold. The apparatus was evacuated to ~10^{-3} Torr, flame-dried, and backfilled with N_2 (3×). An air-free pretared buret containing EO was then attached to the Teflon valve on the reaction flask with flexible metal tubing equipped with Swagelok unions and Teflon ferrules. The buret was kept cold in an ice H_2O bath. The apparatus and metal tubing were evacuated and backfilled with N_2 (4×). A solution of bpy$(CH_2OH)_2$ (0.451 g, 0.209 mmol) in THF (40 mL) was added to the reaction flask through the Teflon coated septum using a N_2 flushed syringe. Additional THF (54 mL) was added to establish an initiator concentration of 18−20 mM. Potassium naphthalenide (10.4 mL of a 0.20 M solution, 2.08 mmol) was then added dropwise. The reaction apparatus was isolated from the manifold under a N_2 atmosphere and then cooled to −78 °C. The EO (5.20 g, 118 mmol) was added to the reaction mixture. The Teflon valves to the buret and reaction flask were then sealed, and the metal tubing and EO buret were removed. The reaction mixture was removed from the ice bath and warmed to room temperature, immersed in an oil bath at room temperature, and then slowly warmed to 40 °C, upon which the pressure increased significantly. The reaction pressure (i.e., EO monomer consumption) was monitored via the attached compound gauge (below ~10 psi deemed safe; above ~10 psi, the pressure is released via the preset purge valve). When the pressure dropped to ~2 psi, the reaction flask was cooled to room temperature. An acidic methanol solution (1 mL of a stock solution of 1.5 mL of concentrated HCl in 25 mL of methanol) was added to the dark green solution through the glass plug port. The resulting golden yellow-brown mixture was stirred at room temperature for 2 h, passed through a neutral alumina plug, concentrated *in vacuo*, and precipitated from a minimal amount of CH_2Cl_2 into cold diethyl ether (~250 mL, −78 °C). The resulting white solid was collected by filtration, washed with cold diethyl ether, and dried *in vacuo*: 3.12 g (55%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, $J = 4.9$ Hz, H-6, H-6′), 8.32 (s, H-3, H-3′), 7.37 (dd, $J = 5.0$ Hz, $J = 1.4$ Hz, H-5, H-5′), 4.67 (s, bpyCH_2), 3.64 (m, PEG CH_2CH_2), 2.57 (t, $J = 6.2$ Hz, RCH₂O*H*). M_w (MALLS) = 3800, PDI = 1.05, d*n*/dc = 0.066 mL/g.

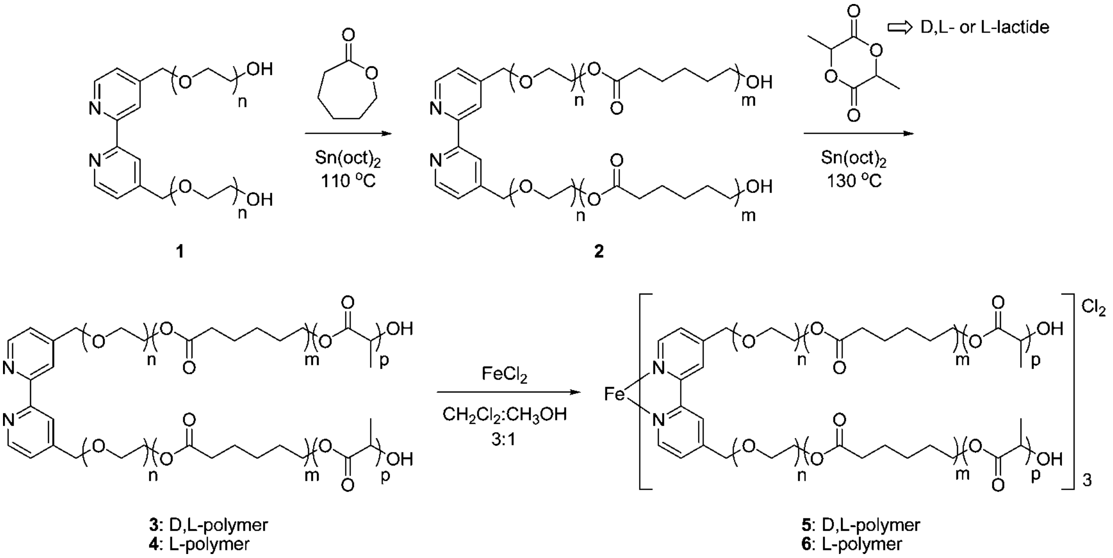
Bpy(PEG-PCL)₂, 2. A representative procedure is provided. A dry Kontes flask was charged with bpyPEG₂ (0.250 g, 0.066 mmol, 3800 Da) and *ε*-caprolactone (0.940 g, 8.23 mmol) under a nitrogen atmosphere. The flask was sealed and placed in an oil bath at 110 °C to create a homogeneous melt. Under a flow of nitrogen, a 29.6 mM solution of $Sn(oct)_2$ in hexanes (89 μL, 2.6 μmol) was added to the reaction mixture. The reaction vessel was resealed and heated at 110 °C until an extremely viscous mixture resulted (~5.5 h). The reaction mixture was cooled to room temperature, dissolved in a minimal amount of CH_2Cl_2, and precipitated by dropwise addition to cold stirring hexanes (−78 °C). The supernatant was decanted, and the solid residue was washed with cold hexanes and dried *in vacuo* to afford bpy(PEG-PCL)₂ as a white solid: 1.15 g (97%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, $J = 4.6$ Hz, H-6, H-6′), 8.36 (s, H-3, H-3′), 7.37 (m, H-5, H-5′), 4.67 (s, bpyCH_2), 4.06 (t, $J = 6.7$ Hz, RCO₂CH_2), 3.64 (m, PEG CH_2CH_2), 2.30 (t, $J = 7.5$ Hz, CH_2CO₂R), 1.70−1.56 (m, CH_2), 1.43−1.32 (m, CH_2). M_w (MALLS) = 19 800, PDI = 1.11, d*n*/dc = 0.072 mL/g.

Bpy(PEG-PCL-PLA)₂, 3. A dry Kontes flask was charged with bpy(PEG-PCL)₂ (0.251 g, 0.015 mmol, 17 800 Da) and D,L-lactide (0.207 g, 1.44 mmol). The flask was evacuated, backfilled with nitrogen, sealed, and immersed in an oil bath at 130 °C to create a homogeneous melt. Under a flow of nitrogen, a 46.4 mM solution of $Sn(oct)_2$ in hexanes (12 μL, 0.6 μmol) was added to the reaction mixture. The reaction vessel was resealed and heated at 130 °C until an extremely viscous mixture resulted (~3.5 h). The reaction mixture was cooled to room temperature, dissolved in a minimal amount of CH_2Cl_2, and precipitated by dropwise addition to cold stirring hexanes (−78 °C). The supernatant was decanted, and the solid residue was reprecipitated (2×) from CH_2Cl_2/hexanes (−78 °C), washed with cold hexanes, and dried *in vacuo* to afford bpy(PEG-PCL-PLA)₂ as a white solid: 0.288 g (63% uncorrected for monomer conversion). ^1H NMR (300 MHz, $CDCl_3$): δ 5.25−5.11 (m, C*H*), 4.06 (t, $J = 6.7$ Hz, RCO₂CH_2), 3.64 (m, PEG CH_2CH_2), 2.30 (t, $J = 7.5$ Hz, CH_2CO₂R), 1.70−1.49 (m, CH_2, CH_3), 1.43−1.32 (m, CH_2). M_w (MALLS) = 19 300, PDI = 1.11, d*n*/dc = 0.053 mL/g.

Bpy(PEG-PCL-PLLA)₂, 4. The PLLA pentablock macroligand was synthesized as described for **3** with the following reagent loadings: bpy(PEG-PCL)₂ (0.261 g, 0.014 mmol, 19 000 Da), L-lactide (0.204 g, 1.42 mmol), and a solution of $Sn(oct)_2$ in hexanes (12 μL, 46.4 mM, 0.6 μmol). Bpy(PEG-PCL-PLLA)₂ was obtained as a white solid: 0.277 g (59% uncorrected for monomer conversion). ^1H NMR (300 MHz, $CDCl_3$): δ 5.16 (q, $J = 7.0$ Hz, C*H*), 4.06 (t, $J = 6.7$ Hz, RCO₂CH_2), 3.64 (m, PEG CH_2CH_2), 2.31 (t, $J = 7.5$ Hz, CH_2CO₂R), 1.70−1.52 (m, CH_2, CH_3), 1.43−1.32 (m, CH_2). M_w (MALLS) = 21 300, PDI = 1.12, d*n*/dc = 0.056 mL/g.

[Fe{bpy(PEG-PCL-PLA)₂}₃]Cl₂, 5. A methanol stock solution of iron(II) chloride hydrate ($FeCl_2 \cdot 4H_2O$) was prepared and spectrophotometrically titrated with 2,2′-bipyridine prior to use. A portion of the $FeCl_2 \cdot 4H_2O$ methanol stock solution (309 μL, 5.09 mM, 0.002 mmol) was diluted in CH_2Cl_2 (2.5 mL) and MeOH (1.2 mL), followed by dropwise addition of a solution of bpy(PEG-

Scheme 1



PCL-PLA)$_2$ (0.124 g, 0.005 mmol, M_n = 25 600) in CH_2Cl_2 (2 mL). The resulting red-violet mixture (CH_2Cl_2/MeOH, 3:1) was stirred at room temperature under Ar for ~15−20 min and concentrated *in vacuo*. The crude product was precipitated from CH_2Cl_2/cold Et_2O (−78 °C) and dried *in vacuo* to provide the iron-centered polymeric complex as a pink solid: 0.089 g (71%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.25−5.11 (m, C*H*), 4.05 (t, J = 6.7 Hz, RCO_2CH_2), 3.64 (m, PEG CH_2CH_2), 2.30 (t, J = 7.5 Hz, CH_2CO_2R), 1.70−1.52 (m, CH_2, CH_3), 1.42−1.32 (m, CH_2). UV−vis (CH_2Cl_2/MeOH, 3:1) λ_{max} (ε) = 531 nm (10 500 M^{-1} cm^{-1}).

[Fe{bpy(PEG-PCL-PLLA)$_2$}$_3$]Cl$_2$, 6. The iron triblock complex **6** was synthesized as described for **5** with the following reagent loadings: $FeCl_2 \cdot 4H_2O$ (319 μL, 5.09 mM, 0.002 mmol), MeOH (1.1 mL), CH_2Cl_2 (4.5 mL), and bpy(PEG-PCL-PLLA)$_2$ (0.129 g, 0.005 mmol, M_n = 25 900). A pink solid was obtained: 0.106 g (82%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (q, J = 7.0 Hz, C*H*), 4.05 (t, J = 6.7 Hz, RCO_2CH_2), 3.64 (m, PEG CH_2CH_2), 2.30 (t, J = 7.5 Hz, CH_2CO_2R), 1.70−1.56 (m, CH_2, CH_3), 1.42−1.32 (m, CH_2). UV−vis (CH_2Cl_2/MeOH, 3:1) λ_{max} (ε) = 531 nm (8000 M^{-1} cm^{-1}).

Results and Discussion

Pentablock Macroligands. The synthesis of pentablock bpy(PEG-PCL-PLA)$_2$ macroligands was achieved in three controlled ring opening polymerization steps with each block serving as an initiator for the next. Specifically, bpy(CH_2OH)$_2$ was used as a difunctional initiator for the anionic ring opening polymerization of ethylene oxide to produce a bpyPEG$_2$ macroligand (**1**) (M_n = 3800, PDI = 1.05). The polymerization was quenched with acidic methanol to afford PEG chains with hydroxyl termini. This method offers an advantage over common coupling methods that produce materials with a terminal methoxy or other functional groups.[44−46] Here, the polymer product can be precipitated from solution and readily separated from unreacted starting materials, and the terminal hydroxyl group can be further modified.

The resulting bpy-centered polymer HO-PEG-bpy-PEG-OH serves as a difunctional macroinitiator for the polymerization of PCL blocks. Specifically, bpyPEG$_2$, ε-caprolactone, and Sn(oct)$_2$ catalyst were combined and stirred at 110 °C for ~5.5 h until an extremely viscous reaction mixture was obtained. The triblock macroligands were purified by precipitation from CH_2Cl_2 into cold stirring hexanes. This procedure afforded well-defined bpy(PEG-PCL)$_2$ macroligands (**2**) (M_n = 17 800, PDI =1.11; M_n = 19 000, PDI = 1.18) with terminal OH groups. As with PEG, the hydroxyl end groups in PCL can also serve as initiator sites for subsequent polymerization. Using controlled ring opening polymerization (ROP) of ε-caprolactone followed by lactide, PCL-PLA block copolymers are readily produced.[35−37,47−50] This order of addition minimizes tranesterification by taking advantage of the stronger nucleophilicity of ring opened ε-caprolactone (1° ROH) versus lactide (more sterically hindered 2° ROH).[51] Even sophisticated CBABC pentablock materials with three compositional segments are possible with this approach. Previously, PLA-PCL-PEG-PCL-PLA materials have been produced from PEG macroinitiators using anionic[52] or zinc catalyzed[48] ROP of D,L-lactide in one-pot or stepwise procedures. In this study, we extend this concept to bpy(PEG-PCL)$_2$ macroinitiators and both D,L- and L-lactide with Sn(oct)$_2$ as the catalyst yielding PLA-PCL-PEG-bpy-PEG-PCL-PLA products (**3**, D,L-polymer; **4**, L-polymer) (Table 1 and Scheme 1). Here, a bipyridine ligand serves as the junction between two PEG-PCL-PLA triblocks. Compared to work by Deng et al.[52] and Huang et al.,[48] PDIs are lower for bpy-centered polymers (1.2 vs >1.4) and reaction times are shorter (3.5 h versus 8 days) with tin catalysts compared to zinc.

The resulting pentablock macroligands were characterized by GPC and ^1H NMR spectroscopy. GPC overlays of the bpyPEG$_2$ starting material as well as the bpy(PEG-PCL)$_2$ triblock and bpy(PEG-PCL-PLA)$_2$ pentablock copolymers are shown in Figures 2 and 3. A shift to smaller elution volume (i.e., higher M_n) for the pentablock compared to macroligand precursors and the absence of low molecular weight shoulders suggest that the hydroxyl chain ends on the bpyPEG$_2$ and bpy(PEG-PCL)$_2$ macroinitiators are active in the polymerization of D,L-lactide (Figure 2). The expected shift to higher molecular weight is also observed for reactions with L-lactide, indicative of active bpy(PEG-PCL)$_2$ chain ends, and the PDI remained low; however, a slight low molecular weight shoulder is evident in the GPC trace for the L-lactide pentablock **4** (Figure 3). In this case, challenges associated with complete dissolution of the macroinitiator in bulk monomer are a likely cause.

The ^1H NMR spectra of bpy(PEG-PCL-PLA)$_2$ and bpy(PEG-PCL-PLLA)$_2$ are shown in Figure 4. Characteristic signals for PEG, PCL, and PLA were observed (PEG: 3.64, m, $-CH_2$-CH_2-; PCL: 4.06, t, $-RCO_2CH_2-$, 2.30, t, $-RCH_2CO_2-$, and 1.60 and 1.38, m, $-CH_2-$; PLA: 5.25−5.11, m, $-CH-$, 1.52, m, $-CH_3$; PLLA: 5.16, q, $-CH-$, 1.52, m, $-CH_3$). The spectra for PLA- and PLLA-containing macroligands are nearly identical except that the −CH− signal at 5.25−5.11 ppm is a multiplet

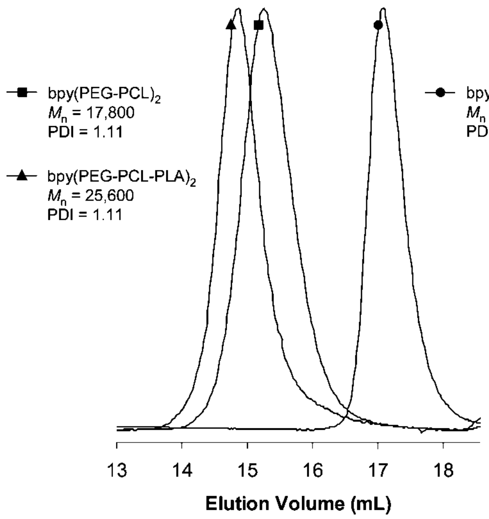


Figure 2. GPC overlay of bpy(PEG-PCL-PLA)$_2$ (▲) pentablock macroligand with bpy(PEG-PCL)$_2$ (■) and bpyPEG$_2$ (●) precursors.

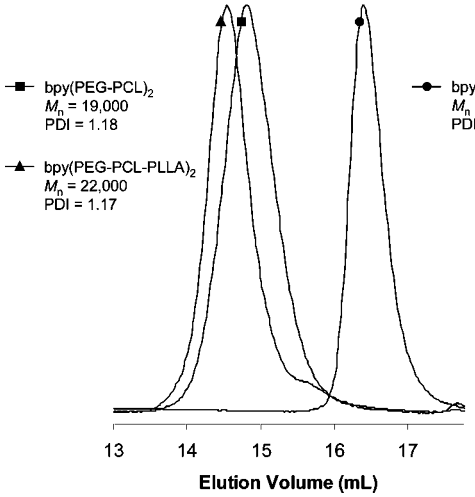


Figure 3. GPC overlay of bpy(PEG-PCL-PLLA)$_2$ (▲) with bpy(PEG-PCL)$_2$ (■) and bpyPEG$_2$ (●) precursors in THF.

for the D,L-polymer whereas the L-polymer resonance at 5.16 ppm is a quartet. The weight fraction of PEG and molecular weights of the tri- and pentablock macroligands were calculated based on the relative integrations of the PCL $-CH_2CO_2R-$ triplet at 2.30 ppm and the PLA or PLLA $-CH-$ at ~5.2 ppm versus the PEG $-CH_2CH_2-$ peak at 3.64 ppm (Table 1). Given that the macroligand molecular weights are high, bpy resonances were not evident in the ^{1}H NMR spectra.

Iron(II) Star Block Copolymers. Given the metal binding potential of bipyridine, pentablock macroligands can serve as precursors to metal-centered block copolymers too. In this study, bpy(PEG-PCL-PLA)$_2$ and bpy(PEG-PCL-PLLA)$_2$ were combined with the iron(II) salt $FeCl_2 \cdot 4H_2O$ in a CH_2Cl_2/MeOH cosolvent system under nitrogen[53] to produce iron tris(bpy)-centered stars with six triblock arms that feature a PEG core, PCL central block, and PLA corona (Figure 1 and Scheme 1). The resulting materials were evaluated by ^{1}H NMR and UV−vis spectroscopy. The ^{1}H NMR spectra of the iron(II) triblock star polymers were nearly identical to those for the respective macroligand precursors. The molar absorptivities of [Fe{bpy(PEG-PCL-PLA)$_2$}$_3$]Cl$_2$ (**5**) and [Fe{bpy(PEG-PCL-PLLA)$_2$}$_3$]Cl$_2$ (**6**) were determined to be 10 500 and 8000 M^{-1} cm^{-1}, respectively, in good agreement with the nonpolymeric parent compound, [Fe(bpy)$_3$]Cl$_2$ ($\varepsilon = 9420$ M^{-1} cm^{-1}).

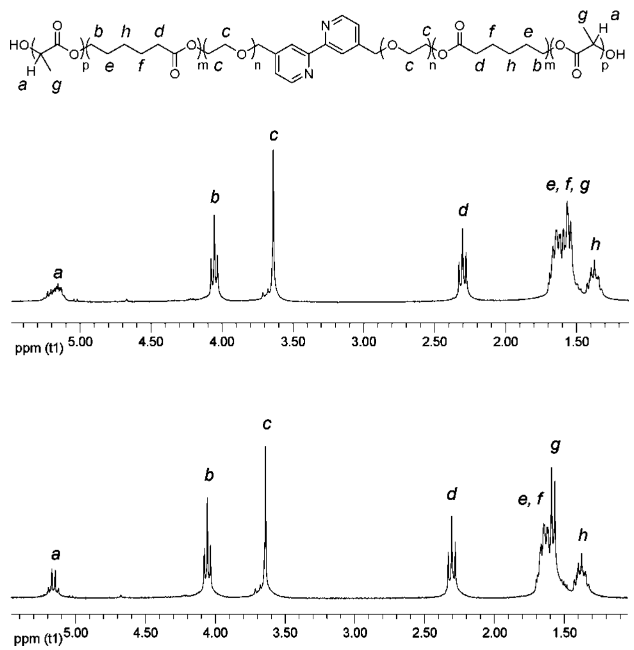


Figure 4. ^{1}H NMR spectra of bpy(PEG-PCL-PLA)$_2$ (top) and bpy(PEG-PCL-PLLA)$_2$ (bottom) in CDCl$_3$.

Table 1. Molecular Weight Data for Bpy-Centered Macroligands

polymer	M_n (NMR)	M_n	M_w	PDI	w_{PEG}[a]
bpyPEG$_2$	3200[b]	3800[d]	4000[d]	1.05	1
bpy(PEG-PCL)$_2$	16 400[b]	17 800[e]	19 800[e]	1.11	0.19
	19 200[b]	19 000[f]	22 400[f]	1.18	0.17
bpy(PEG-PCL-PLA)$_2$	29 300[c]	25 600[g]	28 500[g]	1.11	0.11
bpy(PEG-PCL-PLLA)$_2$	29 400[c]	22 000[h]	25 800[h]	1.17	0.11

[a] Weight percent of PEG in polymer chain as determined by ^{1}H NMR analysis. [b] Determined from integration of PEG $-CH_2CH_2-$ (3.64 ppm) and PCL $-CH_2CO_2R-$ (2.30 ppm) resonances versus the bpyCH_2 (4.67 ppm) peak. [c] Determined from the relative integration of PEG $-CH_2CH_2-$ (3.64 ppm), PCL $-CH_2CO_2R-$ (2.30 ppm), and PLA $-CH-$ (5.25−5.11 ppm) or PLLA $-CH-$ (5.16 ppm) peaks. [d] d*n*/dc = 0.066 mL/g. [e] d*n*/dc = 0.072 mL/g. [f] Molecular weight data estimated using the d*n*/dc value for PEG (0.066 mL/g). [g] d*n*/dc = 0.053 mL/g. [h] d*n*/dc = 0.056 mL/g.

Thermal Analysis. Thermal properties of pentablock macroligands and associated polymeric iron complexes were explored by thermal gravimetric analysis (TGA) and modulated differential scanning calorimetry (DSC). The decomposition traces of the polymers **3**−**6** are provided in Figure 5, and the melting (T_m) and decomposition temperatures (T_d) are reported in Table 2. The thermal decomposition was clearly observed for each block in both macroligands and iron stars. For example, compare the onset temperatures for decomposition for bpy(PEG-PCL-PLA)$_2$ (PLA: 251 °C; PCL: 309 °C; PEG: 376 °C) with those for [Fe{bpy(PEG-PCL-PLA)$_2$}$_3$]Cl$_2$ (PLA: 202 °C; PCL: 314 °C; PEG: 360 °C). As is typical for PCL materials, T_d values drop for block copolymers (~310 °C) versus homopolymers (PCL: ~350 °C).[48] Thermal properties of PEG and PLA[54] blocks are in accord with literature values.[55] As can be seen in Table 2, decomposition temperatures for PLA and PLLA materials vary only slightly. The most dramatic changes appear upon metal complexation, which results in a decrease of the T_d onset values for PLA and PLLA. Decomposition temperatures for PEG and PCL also drop upon metal complexation, with the exception of bpy(PEG-PCL-PLA)$_2$ ($T_{d,PCL} = 309$ °C) compared to [Fe{bpy(PEG-PCL-PLA)$_2$}$_3$]Cl$_2$ ($T_{d,PCL} = 314$ °C). Melting temperatures, T_m, are nearly identical for all block copolymers with and without iron. Though the presence of metals is known to increase the stability of polymers, here where the metal/polymer loading is very low, thermal properties are only slightly affected.[56−58]

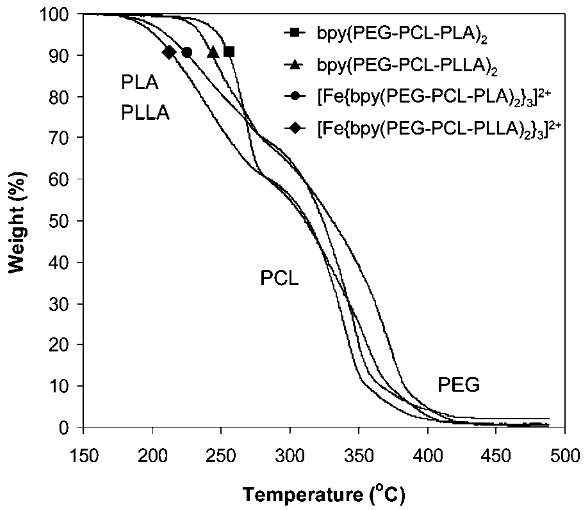


Figure 5. TGA traces of pentablock macroligands, **3** (■) and **4** (▲), and iron(II) triblock star polymers, **5** (●) and **6** (◆).

Table 2. Thermal Analysis of Pentablock Macroligands and Triblock Iron(II) Complexes

polymer	T_m (°C)	$T_{d,PEG}$ (°C)[a]	$T_{d,PCL}$ (°C)[a]	$T_{d,PLA}$ (°C)[a]
bpyPEG$_2$	37	363		
bpy(PEG-PCL)$_2$	51	370	298	
bpy(PEG-PCL-PLA)$_2$	50	376	309	251
bpy(PEG-PCL-PLLA)$_2$	49	391	330	229
[Fe{bpy(PEG-PCL-PLA)$_2$}$_3$]Cl$_2$	50	360	314	202
[Fe{bpy(PEG-PCL-PLLA)$_2$}$_3$]Cl$_2$	48	371	314	206

[a] Determined from the onset temperature for decomposition for the indicated block.

Conclusion

Well-defined block copolymer materials with site-isolated ligand and metal functionalities are achieved via living polymerization. Using this strategy, tri- and pentablock bipyridine-centered macroligands were generated by sequential ring opening polymerization of ethylene oxide, ε-caprolactone, and lactide. Coordination of the resulting macroligands to metal ions leads to star block copolymer complexes. Here, iron(II)-centered stars with PEG-PCL-PLA triblock arms were targeted, and GPC and ^{1}H NMR and UV−vis spectral analyses confirm that well-defined materials were obtained. Fine tuning of physical properties, including biomaterials degradation, can be achieved with multiblock polymers. The presence of a metal at the center of the polymer architecture allows for two-stage degradation, along the polymer backbone and at the metal center, via macroligand dissociation. These metalloblock copolymers have the potential to form elaborate assembly structures incorporating either bipyridine chelating sites or iron complexes capable of stimuli responsive metal release, serving as a model for next generation biomaterials and delivery systems. Investigation of the assembly properties of these block copolymer materials serves as the subject of future reports.

Acknowledgment. We thank the National Science Foundation (BES 0402212, CHE 0350121, and CHE 0718879) for support of this research and Prof. Marc A. Hillmyer, Dr. Huiming Mao, and Mr. William Shoup for advice and assistance with the ethylene oxide polymerization apparatus and procedure.

References and Notes

(1) Won, Y.-Y.; Bates, F. S. In *Surfactant Science Series*; Zana, R., Kaler, E. W., Eds.; CRC Press LLC: Boca Raton, FL, 2007; Vol. *140*, pp 417−451.
(2) Dalhaimer, P.; Bates, F. S.; Aranda-Espinoza, H.; Discher, D. C. R. *Physique* **2003**, *4*, 251–258.
(3) Li, Z.; Hillmyer, M. A.; Lodge, T. P. *Langmuir* **2006**, *22*, 9409–9417.
(4) Förster, S.; Plantenberg, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 688–714.
(5) Olson, D. A.; Chen, L.; Hillmyer, M. A. *Chem. Mater.* **2008**, *20*, 869–890.
(6) Hillmyer, M. A. *Adv. Polym. Sci.* **2005**, *190*, 137–181.
(7) Park, C.; Yoon, J.; Thomas, E. L. *Polymer* **2003**, *44*, 6725–6760.
(8) Manners, I. *Synthetic Metal-containing Polymers*; Wiley VCH: Weinhem, 2004; p 288.
(9) Manners, I. *Science* **2001**, *294*, 1664–1666.
(10) Fraser, C. L.; Smith, A. P. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 4704–4716.
(11) Schubert, U. S.; Heller, M. *Chem.−Eur. J.* **2001**, *7*, 5252–5259.
(12) Schubert, U. S.; Eschbaumer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2892–2926.
(13) Andres, P. R.; Schubert, U. S. *Adv. Mater.* **2004**, *16*, 1043–1068.
(14) Bender, J. L.; Corbin, P. S.; Fraser, C. L.; Metcalf, D. H.; Richardson, F. S.; Thomas, E. L.; Urbas, A. M. *J. Am. Chem. Soc.* **2002**, *124*, 8526–8527.
(15) Fustin, C.-A.; Guillet, P.; Schubert, U. S.; Gohy, J. F. *Adv. Mater.* **2007**, *19*, 1665–1673.
(16) Gohy, J. F.; Lohmeijer, B. G. G.; Varshney, S. K.; Schubert, U. S. *Macromolecules* **2002**, *35*, 7427–7435.
(17) Gohy, J.-F.; Hofmeier, H.; Alexeev, A.; Schubert, U. S. *Macromol. Chem. Phys.* **2003**, *204*, 1524–1530.
(18) Meier, M. A. R.; Wouters, D.; Ott, C.; Guillet, P.; Fustin, C. A.; Gohy, J. F.; Schubert, U. S. *Macromolecules* **2006**, *39*, 1569–1576.
(19) Gohy, J.-F.; Lohmeijer, B. G. G.; Schubert, U. S. *Macromol. Rapid Commun.* **2002**, *23*, 555–560.
(20) Park, C.; McAlvin, J. E.; Fraser, C. L.; Thomas, E. L. *Chem. Mater.* **2002**, *14*, 1225–1230.
(21) Grubbs, R. B. *Polym. Rev.* **2007**, *47*, 197–215.
(22) Shenhar, R.; Norsten, T. B.; Rotello, V. M. *Adv. Mater.* **2005**, *17*, 657–669.
(23) Ciebien, J. F.; Clay, R. T.; Sohn, B. H.; Cohen, R. E. *New J. Chem.* **1998**, *22*, 685–691.
(24) Cohen, R. E. *Curr. Opin. Solid State Mater. Sci.* **1999**, *4*, 587–590.
(25) Bennett, R. D.; Xiong, G. Y.; Ren, Z. F.; Cohen, R. E. *Chem. Mater.* **2004**, *16*, 5589–5595.
(26) Ahmed, F.; Discher, D. E. *J. Controlled Release* **2004**, *96*, 37–53.
(27) Geng, Y.; Discher, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 12780–12781.
(28) Geng, Y.; Discher, D. E. *Polymer* **2006**, *47*, 2519–2525.
(29) He, C.; Sun, J.; Deng, C.; Zhao, T.; Deng, M.; Chen, X.; Jing, X. *Biomacromolecules* **2004**, *5*, 2042–2047.
(30) Agrawal, S. K.; Sanabria-DeLong, N.; Tew, G. N.; Bhatia, S. R. *Macromolecules* **2008**, *41*, 1774–1784.
(31) Bae, S. J.; Suh, J. M.; Sohn, Y. S.; Bae, Y. H.; Kim, S. W.; Jeong, B. *Macromolecules* **2005**, *38*, 5260–5265.
(32) Discher, D. E.; Ahmed, F. *Annu. Rev. Biomed. Eng.* **2006**, *8*, 323–341.
(33) Discher, D. E.; Ortiz, V.; Srinivas, G.; Klein, M. L.; Kim, Y.; Christian, D.; Cai, S.; Photos, P.; Ahmed, F. *Prog. Polym. Sci.* **2007**, *32*, 838–857.
(34) Ahmed, F.; Pakunlu, R. I.; Srinivas, G.; Brannan, A.; Bates, F.; Klein, M. L.; Minko, T.; Discher, D. E. *Mol. Pharmaceutics* **2006**, *3*, 340–350.
(35) Qian, H.; Bei, J.; Wang, S. *Polym. Degrad. Stab.* **2000**, *68*, 423–429.
(36) Ye, W. P.; Du, F. S.; Jin, W. H.; Yang, J. Y.; Xu, Y. *React. Funct. Polym.* **1997**, *32*, 161–168.
(37) Huang, M.-H.; Li, S.; Vert, M. *Polymer* **2004**, *45*, 8675–8681.
(38) Pfister, A.; Fraser, C. L. *Biomacromolecules* **2006**, *7*, 459–468.
(39) McAlvin, J. E.; Scott, S. B.; Fraser, C. L. *Macromolecules* **2000**, *33*, 6953–6964.
(40) McAlvin, J. E.; Fraser, C. L. *Macromolecules* **1999**, *32*, 1341–1347.
(41) Smith, A. P.; Corbin, P. S.; Fraser, C. L. *Tetrahedron Lett.* **2000**, *41*, 2787–2789.
(42) Yasugi, K.; Nakamura, T.; Nagasaki, Y.; Kato, M.; Kataoka, K. *Macromolecules* **1999**, *32*, 8024–8032.
(43) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
(44) Zalipsky, S. *Bioconjugate Chem.* **1995**, *6*, 150–165.
(45) Roberts, M. J.; Bentley, M. D.; Harris, J. M. *Adv. Drug Delivery Rev.* **2002**, *54*, 459–476.
(46) Hermanson, G. T. *Bioconjugate Techniques*; Academic Press: San Diego, 1996; p 785.
(47) Corbin, P. S.; Webb, M. P.; McAlvin, J. E.; Fraser, C. L. *Biomacromolecules* **2001**, *2*, 223–232.
(48) Huang, M.-H.; Li, S.; Coudane, J.; Vert, M. *Macromol. Chem. Phys.* **2003**, *204*, 1994–2001.
(49) Cui, Y.; Tang, X.; Huang, X.; Chen, Y. *Biomacromolecules* **2003**, *4*, 1491–1494.

(50) Kim, J. K.; Park, D.-J.; Lee, M.-S.; Ihn, K. J. *Polymer* **2001**, *42*, 7429–7441.

(51) In't Veld, P. J. A.; Velner, E. M.; Van De Witte, P.; Hamhuis, J.; Dijkstra, P. J.; Feijen, J. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 219–226.

(52) Deng, X.; Zhu, Z.; Xiong, C.; Zhang, L. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 703–708.

(53) Johnson, R. M.; Fraser, C. L. *Macromolecules* **2004**, *37*, 2718–2727.

(54) Jamshidi, K.; Hyon, S. H.; Ikada, Y. *Polymer* **1988**, *29*, 2229–2234.

(55) Sanabria-DeLong, N.; Aamer, K. A.; Agrawal, S. K.; Bhatia, S. R.; Tew, G. N. In *Degradable Polymers and Materials*; Khemani, K., Scholz, C., Eds.; American Chemical Society: Washington, DC, 2006; Vol. *939*.

(56) Cyr, P. W.; Tzolov, M.; Hines, M. A.; Manners, I.; Sargent, E. H.; Scholes, G. D. *J. Mater. Chem.* **2003**, *13*, 2213–2219.

(57) Qin, Y.; Cui, C.; Jakle, F. *Macromolecules* **2008**, *41*, 2972–2974.

(58) Hofmeier, H.; Wouters, M.; Wouters, D.; Schubert, U. S. In *Metal-Containing and Metallosupramolecular Polymers and Materials*; Schubert, U. S., Newkome, G. R., Manners, I., Eds.; American Chemical Society: Washington, DC, 2006; Vol. *928*, pp 113−125.

MA801353B