Selectively Degradable Core Cross-Linked Star Polymers

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ABSTRACT: A range of selectively degradable core cross-linked star (CCS) polymers were synthesized via a combination of atom transfer radical polymerization (ATRP) and ring-opening polymerization (ROP) using the "arm first" method. The multifunctional initiator 2-hydroxyethyl 2′-methyl-2′-bromopropionate was used to synthesize degradable poly(ϵ-caprolactone) (PCL) and nondegradable polystyrene (PSt) and poly(methyl methacrylate) (PMMA) macroinitiators which were subsequently cross-linked to generate CCS polymers. By using nondegradable (divinylbenzene (DVB), ethylene glycol dimethacrylate (EGDMA)) and degradable (4,4′-bioxepanyl-7,7′-dione (BOD), 2,2-bis(ϵ-caprolactone-4-yl)propane (BCP)) monomers to cross-link the different macroinitiators, a range of CCS polymers were synthesized where either the arm or the core domain can be selectively degraded. PCL/DVB and PCL/EGDMA arm-degradable CCS polymers were synthesized under various conditions to determine the optimal reaction conditions with hydrolysis yielding DVB and EGDMA cores, for which the hydrodynamic diameter was determined. Hydrolysis of PCL/PMMA/EGDMA miktoarm CCS polymer resulted in CCS polymer with a reduced number of arms, whereas PSt/BOD core-degradable CCS polymer yielded the original linear PSt arms upon hydrolysis. PCL/BOD and PCL/BCP fully degradable CCS polymers were also synthesized and shown to be completely degradable upon hydrolysis of the ester linkages to generate small-chain acid units.

Introduction

Core cross-linked star (CCS) polymers[1] have a unique three-dimensional architecture that consists of a cross-linked core surrounded by a number of radiating linear arms.[2,3] Synthesis of this class of polymer is usually carried out in a two-step process known as the "arm first" approach where living linear arms capable of further chain extension are initially synthesized. These terminally reactive linear polymer chains are subsequently used to initiate the polymerization of a cross-linkable monomer such that the active arm ends are coupled together to form star-shaped polymer with a cross-linked core. Controlled radical polymerization techniques such as nitroxide-mediated radical polymerization (NMP),[4] atom transfer radical polymerization (ATRP),[5,6] and reverse addition−fragmentation chain transfer (RAFT)[7] polymerization are typically employed to synthesize CCS polymers, resulting in a high degree of structural control and narrow molecular weight distribution.

CCS polymers represent an interesting class of macromolecule due to the fact that they are of very high molecular weight but have a solubility and viscosity similar to linear or branched polymers of relatively low molecular weight.[8] The combination of unique rheological properties and the ability to employ controlled polymerization techniques to obtain well-defined structures has recently led to increasing interest toward this class of macromolecule. A wide range of potential applications for CCS polymers have arisen such as in drug delivery,[9] membrane formation,[5] and paint additive applications.[10] CCS polymers also have potential for application as templates for silicate materials with low dielectric constants.[11]

The structural architecture of CCS polymers is such that it can be divided into two separate domains, that of the arm and the core. This allows for the selective incorporation of a degradable functionality into either of these domains, thereby generating degradable CCS polymer where either the arms or the core can be selectively targeted for degradation. We recently published a short communication on the synthesis of fully degradable CCS polymer[12] (both arm and core moieties) using a two-step one-pot process entirely based on ring-opening polymerization (ROP) of lactone-based monomers. Here we report the synthesis of a range of CCS polymers with degradable functionality such that different domains can be selectively degraded to produce either arm-degradable, partially arm-degradable, core-degradable, or fully degradable CCS polymer.

The selectively degradable CCS polymers reported here represent an important development in the quest to better understand the absolute morphology of this unique class of macromolecule, particularly in relation to the relative size and nature of the core. They also increase the scope of potential applications for CCS polymers, including use as a template for nanoporous materials or as drug carriers where the core domain could be selectively degraded to release encapsulated drug in a controlled fashion.

Experimental Section

Materials. 2-Bromoisobutyryl bromide (98%), anisole (anhydrous, 99.7%), copper(I) bromide (CuBr, 98%), 2,2′-bipyridine (bpy, 99%), ethylene glycol (>99%), stannous 2-ethylhexanoate (Sn(Oct)$_2$, 95%), and urea hydrogen peroxide adduct (98%) were purchased from Aldrich and used as received. Formic acid (99%, Ajax Finechem), 4,4′-bicyclohexanone (Lomb Scientific), and 2,2-bis(4-oxocyclohexyl)propane (Lomb Scientific) were also used as received. Tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl and sodium metal under argon and stored over 4 Å molecular sieves. Butanol (Merck) and ϵ-caprolactone (CL, 99+%) (Aldrich) were dried over CaH_2 for 24 h and distilled under high vacuum prior to use. Methyl methacrylate (MMA, 99%), styrene (St, 99%), ethylene glycol dimethacrylate (EGDMA, 98%), divinylbenzene (DVB, 80% mixture of isomers), and *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA, 99%) were all purchased from Aldrich and washed three times with 5% w/w aqueous NaOH, once with water, then distilled from calcium hydride, and stored at −5 °C. *p*-Toluenesulfonyl chloride (TsCl,

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99+%) (Aldrich) was dissolved in minimum chloroform, diluted with petroleum ether (bp 40−60 °C), clarified with charcoal, filtered, concentrated, and collected by filtration.

Instrumentation. Size exclusion chromatography was performed on a Shimadzu system with a Wyatt DAWN DSP multiangle laser light scattering detector (690 nm, 30 mW) and a Wyatt OPTILAB EOS interferometric refractometer (690 nm). THF was used as the eluent with three Phenomenex phenogel columns (500, 10^4, and 10^6 Å porosity; 5 μm bead size) operated at 1 mL/min with the column temperature set at 30 °C. Astra software (Wyatt Technology Corp.) was used to process the data using known d*n*/d*c* values to determine the molecular weight or an assumption of 100% mass recovery of the polymer where the d*n*/d*c* value was unknown. ^{1}H NMR spectra were collected in deuterated chloroform (unless otherwise stated) using a Varian Unity Plus 400 MHz spectrometer. Monomer conversion was determined by gas chromatography using a Shimadzu GC 17-A gas chromatograph equipped with a DB-5 capillary column (30 m, 5% phenylsiloxane) and coupled to a GCMS-QP5000 mass spectrometer. Dynamic light scattering measurements were performed using a Malvern HPPS particle sizer with a 3.0 mW He−Ne laser operated at 633 nm. Analysis was performed at an angle of 173° and a constant temperature of 25 °C.

Synthesis of 2-Hydroxyethyl 2′-Methyl-2′-bromopropionate. 2-Bromoisobutyryl bromide (5.45 g, 23.7 mmol) was added into a molar excess (25 times) of ethylene glycol (33 mL, 593 mmol) and stirred for 16 h at 0 °C. The mixture was then dissolved in water and extracted with dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution followed by water and dried with $MgSO_4$. The solvent was distilled off under reduced pressure to yield a colorless liquid (3.90 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.95 (s, 6H, $-C(CH_3)_2$), 2.17 (s, 1H, $-OH$), 3.87 (t, 2H, $-CH_2OH$), 4.31 (t, 2H, $-COOCH_2-$).

Synthesis of 4,4′-Bioxepanyl-7,7′-dione (BOD). A solution of urea hydrogen peroxide ($CO(NH_2)_2{\cdot}H_2O_2$) (10.0 g, 106 mmol) in 50 mL of formic acid (99%) was stirred at 23 °C for 90 min. 4,4′-Bicyclohexanone (5.0 g, 25.7 mmol) was then slowly added over 5−10 min and stirred for a further 4 h. 200 mL of water was added to the mixture followed by extraction with chloroform. The organic fractions were collected, washed with a saturated aqueous sodium bicarbonate solution, and dried with Na_2SO_4. The organic fraction was concentrated, and the solvent was removed under reduced pressure to yield a white powder (3.50 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.34 (R, R) 4.17 (S, R) (t, 2H, $-CH_2$-OOC−), 2.73 (R, R) 2.60 (S, R) (t, 2H, $-CH_2COO-$), 1.93−1.83 (m, 2H, $-CH_2CH_2OOC-$), 1.70−1.60 (m, 2H, $-CH_2CH_2COO-$), 1.49 (q, 1H, $-CHCH_2-$).

Synthesis of 2,2-Bis(ϵ-caprolactone-4-yl)propane (BCP). A solution of urea hydrogen peroxide ($CO(NH_2)_2{\cdot}H_2O_2$) (8.16 g, 86.7 mmol) in 50 mL of formic acid (99%) was stirred at 23 °C for 90 min. 2,2-Bis(4-oxocyclohexyl)propane (5.0 g, 21.2 mmol) was then slowly added over 5−10 min and stirred for a further 5 h. 200 mL of water was added to the mixture followed by extraction with chloroform. The organic fractions were collected, washed with a saturated aqueous sodium bicarbonate solution, and dried with Na_2SO_4. The organic fraction was concentrated, and the solvent was removed under reduced pressure to yield a white powder (4.72 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.35 (R, R) 4.15 (S, R) (t, 2H, $-CH_2OOC-$), 2.73 (R, R) 2.57 (S, R) (t, 2H, $-CH_2$-COO−), 2.01−1.90 (m, 2H, $-CH_2CH_2OOC-$), 1.66−1.52 (m, 2H, $-CH_2CH_2COO-$), 1.40 (q, 1H, $-CHCH_2-$), 0.80 (t, 3H, $-CCH_3$).

Synthesis of PCL-Br Macroinitiator. In a typical reaction a round-bottom flask was charged with a mixture of CL (10 g, 87.6 mmol), $Sn(Oct)_2$ (2.366 g, 5.84 mmol), and 2-hydroxyethyl 2′-methyl-2′-bromopropionate (2.465 g, 11.7 mmol). A condenser and $CaCl_2$ drying tube were attached to the flask which was heated at 130 °C. After 24 h the reaction solution was diluted with THF and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16 h in a desiccator to yield PCL-Br macroinitiator (yield: 8.73 g; M_n = 2700 g/mol, M_w/M_n = 1.12).

Synthesis of PMMA-Cl Macroinitiator. A mixture of MMA (1.95 mL, 18.2 mmol), CuBr (0.093 g, 0.650 mmol), bpy (0.305 g, 1.95 mmol), TsCl (0.124 g, 0.650 mmol), and anisole (2.60 mL) was added to a Schlenk flask and degassed by three freeze−pump−thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100 °C. After 48 h (87% MMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16 h in a desiccator to yield PMMA-Cl macroinitiator (yield: 1.51 g; M_n = 7500 g/mol, M_w/M_n = 1.08).

Synthesis of PSt-OH Macroinitiator. A mixture of St (3.26 mL, 28.4 mmol), CuBr (0.068 g, 0.474 mmol), bpy (0.222 g, 1.42 mmol), and 2-hydroxyethyl 2′-methyl-2′-bromopropionate (0.10 g, 0.474 mmol) was added to a Schlenk flask and degassed by three freeze−pump−thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 80 °C for 16 h. The reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into cold methanol with the precipitate being collected by filtration and dried for 16 h in a desiccator to afford PSt-OH macroinitiator (yield: 1.90 g; M_n = 10 700 g/mol, M_w/M_n = 1.09).

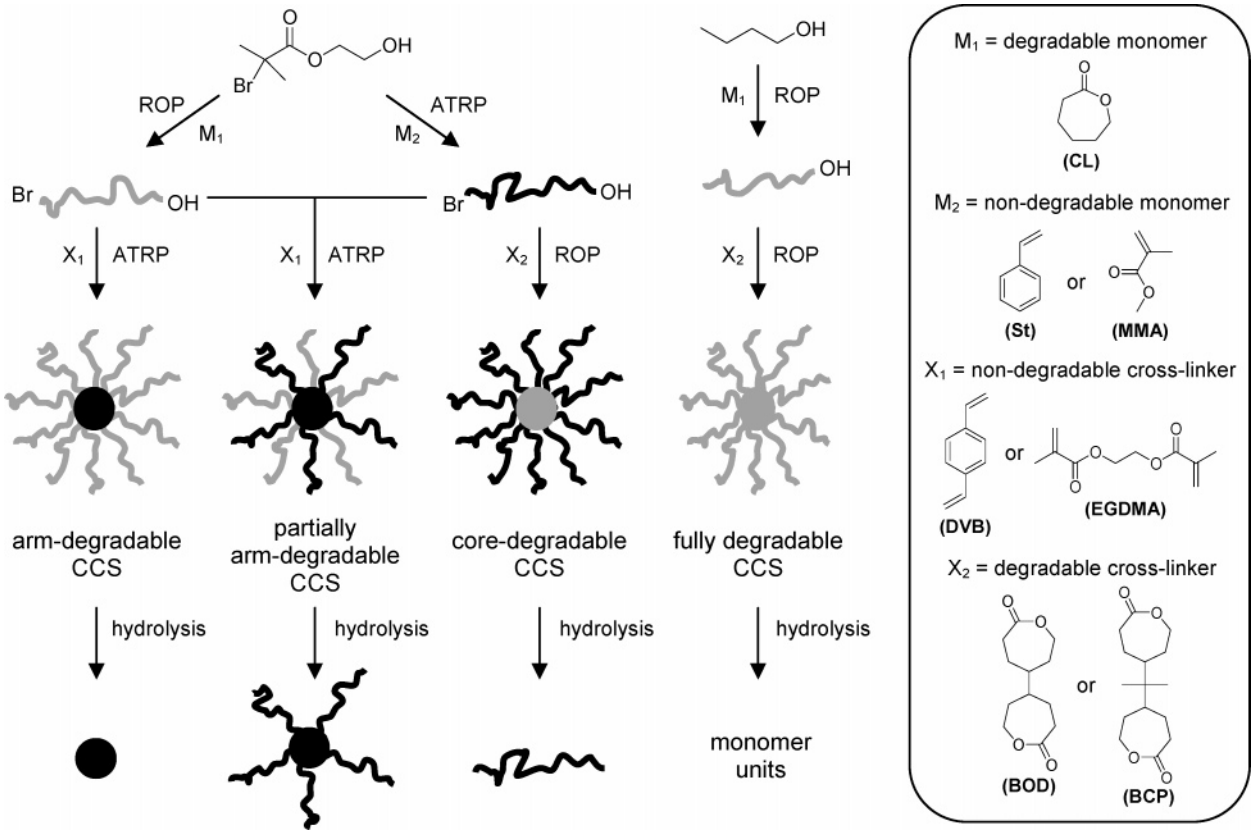
Synthesis of Arm-Degradable CCS Polymer. In a typical reaction PCL-Br macroinitiator (0.3 g, 0.132 mmol; M_n = 2300 g/mol) was reacted with a mixture of CuBr (0.025 g, 0.172 mmol), PMDETA (36.0 μL, 0.172 mmol), EGDMA (0.622 mL, 3.30 mmol), and anisole (26 mL) in a Schlenk flask and degassed by three freeze−pump−thaw cycles. The flask was then backfilled with argon and immersed in an oil bath at 100 °C. After 65 h (93% EGDMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum.

Synthesis of Partially Arm-Degradable CCS Polymer. A mixture of PCL-Br macroinitiator (0.250 g, 0.110 mmol; M_n = 2300 g/mol) and PMMA-Cl macroinitiator (0.825 g, 0.110 mmol; M_n = 7500 g/mol) was reacted with CuBr (0.025 g, 0.172 mmol), PMDETA (36.0 μL, 0.172 mmol), EGDMA (0.374 mL, 1.98 mmol), and anisole (17 mL) in a Schlenk flask. The flask was degassed by three freeze−pump−thaw cycles and backfilled with argon before being immersed in an oil bath at 100 °C. After 68 h (80% EGDMA conversion) the reaction was stopped via exposure to air and diluted with THF before being passed through a column of basic alumina to remove the copper complex. The solution was then concentrated and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum.

Synthesis of Core-Degradable CCS Polymer. PSt-OH macroinitiator (1.52 g, 0.142 mmol; M_n = 10 700 g/mol) was reacted with a mixture of $Sn(Oct)_2$ (23.0 μL, 0.071 mmol), BOD (0.321 g, 1.42 mmol), and toluene (7.1 mL) in a dry round-bottom flask at 110 °C with a condenser and $CaCl_2$ drying tube attached. After 48 h (87% BOD conversion) the reaction solution was filtered and precipitated into methanol with the precipitate being collected by filtration and dried under vacuum.

Synthesis of Fully Degradable CCS Polymer. CL (2.0 g, 17.5 mmol) was added to a mixture of toluene (17.5 mL), butanol (30.8 μL, 0.337 mmol), and $Sn(Oct)_2$ (54.5 μL, 0.169 mmol). A condenser and $CaCl_2$ drying tube were attached to the flask, which was then heated at 110 °C with stirring. After 24 h (CL conversion >99%; M_n = 5300 g/mol) a solution of BOD (0.762 g, 3.37 mmol) in 3 mL of chloroform was injected into the reaction mixture ([BOD]/[PCL] = 10) and left to react for a further 16 h (86% BOD conversion). The reaction mixture was then cooled, and the solvent was removed under reduced pressure with the crude polymer being dissolved in THF and precipitated into methanol. The precipitate was collected by filtration and dried under vacuum. Similar reaction

Scheme 1. Generalized Schematic of Selectively Degradable Core Cross-Linked Star (CCS) Polymer Formation and Subsequent Hydrolysis To Remove the Labile Component



conditions were employed for synthesis of BCP/PCL-based CCS polymer with BCP replacing BOD such that [BCP]/[PCL] = 10.

Hydrolysis. In a typical hydrolysis reaction 40 mg of degradable polymer was dissolved in 4 mL of THF, to which was added 0.3 mL of H_2O and 0.1 mL of 12 M HCl. Hydrolysis was carried out at 60 °C for 24 h. For reactions where degradation was monitored using ^1H NMR, THF and H_2O were replaced with deuterated solvents (CD_3COCD_3 and D_2O, respectively).

Results and Discussion

The incorporation of a degradable functionality into CCS polymers can be achieved by combining controlled radical polymerization techniques, such as ATRP, of nondegradable monomers with ring-opening polymerization (ROP) of lactone-based monomers. The ROP method allows for the synthesis of CCS polymers with polyester-based structures (arm and/or core moieties) which can therefore be degraded under controlled conditions[13−15] via hydrolysis of the ester linkages in the polymer. Since ROP is a controlled polymerization technique, its use to synthesize selectively degradable CCS polymers results in well-defined structures with narrow polydispersities comparable to traditional nondegradable CCS polymers synthesized by ATRP, NMP, or RAFT polymerization.

By combining the use of degradable and nondegradable monomers, it is possible to synthesize a range of CCS polymers with degradable functionality such that different domains of the CCS polymer can be selectively degraded to produce arm-degradable CCS, partially arm-degradable CCS, core-degradable CCS, and fully degradable CCS polymer (Scheme 1). This is achieved by making use of an activated bromine containing alcohol which can act as a duel initiator suitable for initiating ATRP of nondegradable monomers (methyl methacrylate, styrene) from the activated bromine end group or ROP of degradable monomers (ϵ-caprolactone) from the hydroxyl end group. This allows for the synthesis of degradable and nondegradable living linear arms which can be cross-linked through one active end group, either by ATRP of nondegradable cross-linker (divinylbenzene, ethylene glycol dimethacrylate) or ROP of degradable cross-linker (4,4′-bioxepanyl-7,7′-dione, 2,2-bis(ϵ-caprolactone-4-yl)propane). By using different combinations of degradable and nondegradable arms and cross-linkers, it is possible to synthesize a range of selectively degradable CCS polymers which can be structurally modified by hydrolysis of the degradable component, resulting in polymers that can be tailored to suit specific applications.

Synthesis of Arm-Degradable CCS Polymer. The asymmetric difunctional initiator, 2-hydroxyethyl 2′-methyl-2′-bromopropionate, was selected as the initiator for the synthesis of arm-degradable CCS polymer since it has previously been shown to be an efficient initiator for both the ATRP of vinyl monomers and the ROP of lactone-based monomers.[16] Using this initiator, linear bromoisobutyryl polycaprolactone (PCL-Br) (M_n = 2700 g/mol, M_w/M_n = 1.12) was synthesized via ROP of ϵ-caprolactone (CL) with stannous 2-ethylhexanoate ($Sn(Oct)_2$) as catalyst at 130 °C.

ATRP chain extension of the PCL-Br macroinitiator with methyl methacrylate (MMA) monomer was performed to test for livingness. As shown by the gel permeation chromatography (GPC) traces in Figure 1, a monomodal peak of PCL-*b*-PMMA block copolymer with low molecular weight distribution was obtained (M_n = 6900 g/mol, M_w/M_n = 1.09). This confirms the high initiation efficiency of PCL-Br macroinitiator since there is no residual "dead polymer" observed in the GPC trace, suggesting that all the PCL-Br chains initiated ATRP chain extension. The high initiation efficiency, narrow polydispersity, and living nature of the PCL-Br chains make it an ideal

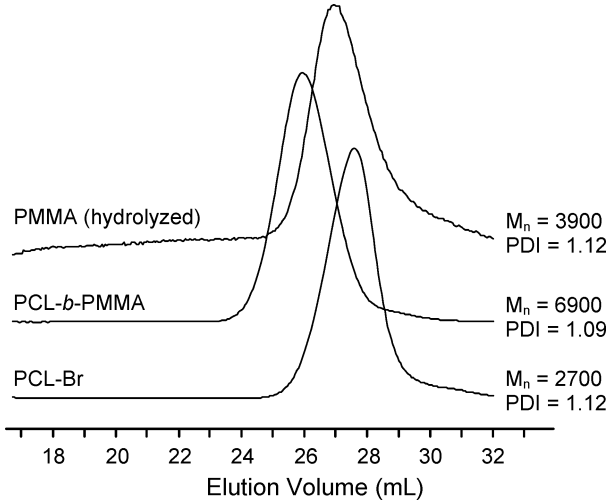


Figure 1. Gel permeation chromatography traces of atom transfer radical polymerization (ATRP) chain extension of polycaprolactone macroinitiator (PCL-Br) by methyl methacrylate (MMA) ([PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3 = [MMA]/40 at 100 °C in 38.0 mL of anisole) followed by hydrolysis of the PCL-*b*-PMMA block copolymer.

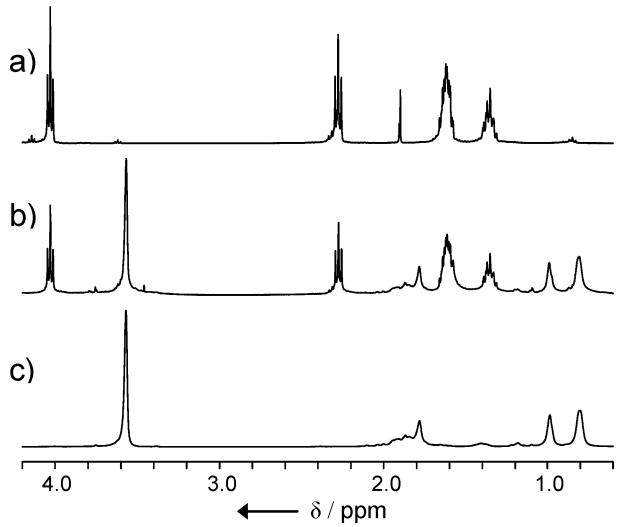


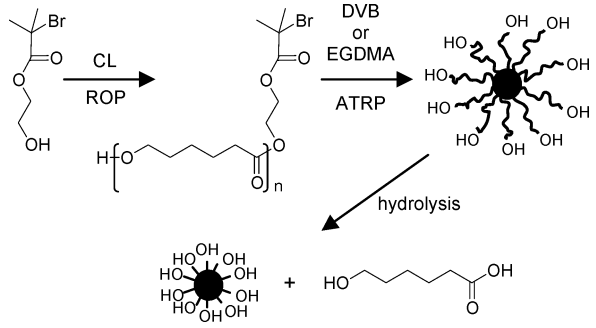
Figure 2. ^{1}H NMR (400 MHz) of (a) polycaprolactone macroinitiator (PCL-Br), (b) polycaprolactone-*b*-poly(methyl methacrylate) block copolymer (PCL-*b*-PMMA), and (c) PMMA from the hydrolysis of PCL-*b*-PMMA block copolymer ($CDCl_3$).

macroinitiator for the synthesis of CCS polymer via the "arm first" approach.

The degradability of the PCL segment was tested by hydrolyzing the PCL-*b*-PMMA block copolymer under acidic conditions (12 M HCl/H_2O/THF = 1/3/40 volumetric ratio). The hydrolysis reaction was stopped after 24 h by the addition of methanol to precipitate any unhydrolyzed polymer. ^{1}H NMR analysis of the unhydrolyzed polymer (Figure 2) showed it to be pure PMMA, as expected, with no residual peaks due to the aliphatic protons of the PCL chain. The molecular weight of the unhydrolyzed PMMA as determined by GPC (Figure 1) was 3900 g/mol, which corresponds to the theoretical molecular weight of the PMMA segment of the PCL-*b*-PMMA block copolymer (4200 g/mol). The combined ^{1}H NMR and GPC results of the PCL-*b*-PMMA block copolymer hydrolysis confirm that the PCL segment of a polymer can be completely degraded under the acidic conditions described without affecting nondegradable polymer segments such as PMMA.

The PCL-Br macroinitiator was used to synthesize arm-degradable CCS polymer by cross-linking the ATRP active

Scheme 2. Synthesis of Arm-Degradable CCS Polymer and Subsequent Hydrolysis



chain ends with divinylbenzene (DVB) or ethylene glycol dimethacrylate (EGDMA) (Scheme 2). Both DVB and EGDMA were chosen to act as the cross-linking agent since both have been widely used in the "arm first" approach to synthesizing nondegradable CCS polymers.[4−7] The choice of cross-linker is also important as the core of the CCS polymer needs to be stable under the hydrolysis conditions used to degrade the PCL arms. This was shown to be true for both DVB- and EGDMA-based CCS polymers which were capable of producing stable core domains upon hydrolysis as described in later results.

Because of the fact that CCS polymers have a more compact structure than corresponding linear polymers of the same molecular weight, GPC measurements using a mass-sensitive detector (e.g., RI detector) calibrated based on linear polymer standards will give an apparent molecular weight smaller than the true molecular weight. A more advanced and accurate technique to measure the molecular weight of CCS polymers uses light scattering techniques. For this reason a multiangle laser light scattering (MALLS) detector was used in conjunction with GPC to determine the absolute molecular weight of the CCS polymers reported in this work.

A series of arm-degradable CCS polymers were synthesized under various reaction conditions using PCL-Br macroinitiator (M_n = 2700 g/mol, M_w/M_n = 1.12) with DVB or EGDMA cross-linker (Table 1, experiments 1−6, and Table 2, experiments 8−12, respectively). The effects of the molar ratio of cross-linker to linear PCL-Br and the reaction concentration were found to have a significant impact on the extent of CCS formation. When DVB was used as the cross-linker, the highest conversion of arms into CCS polymer occurred at a cross-linker to macroinitiator molar ratio of 15:1 and a macroinitiator concentration of 40 mM (Table 1, experiment 4). Varying the amount of cross-linker and the reaction concentration resulted in decreased arm conversion or gelation of the reaction solution (Figure 3a). For the arm-degradable CCS polymer formed using EGDMA the optimal reaction conditions were found to occur at a cross-linker to macroinitiator molar ratio of 25:1 with an arm concentration of 5 mM (Table 2, experiment 10) with deviation from these conditions also resulting in decreased arm conversion or gelation (Figure 3b).

The optimal reaction condition for the DVB-based arm-degradable CCS polymer was found to occur at a much higher concentration (40 mM) compared to that of the EGDMA-based arm-degradable CCS polymer (5 mM). Conversion of arms into CCS polymer was also much less when DVB was used as the cross-linking agent as opposed to EGDMA (42% compared to 78%). This suggests that DVB is a less reactive cross-linker than EGDMA under these reaction conditions. The choice of catalyst system, solvent, reaction temperature, and the molecular weight of the macroinitiator also play an important role in the extent of CCS conversion. By using smaller molecular weight

Table 1. Synthesis of Arm-Degradable Core Cross-Linked Star (CCS) Polymer Using Polycaprolactone Macroinitiator (PCL-Br) and Divinylbenzene (DVB) Cross-Linker

expt no.[a]	M_n PCL-Br (g/mol)[b]	PDI PCL-Br[b]	[PCL-Br] (mM)	[DVB]/[PCL-Br]	PCL conv (%)[c]	M_n (g/mol)[b]	PDI[b]	f[d]
1	2700	1.12	7.5	15	0	2 700	1.12	
2	2700	1.12	20	15	19	190 600	1.25	15.0
3	2700	1.12	30	15	29	212 500	1.56	22.6
4	2700	1.12	40	15	42	234 400	1.45	32.1
5	2700	1.12	70	15	gel			
6	2700	1.12	40	20	gel			
7	2300	1.05	40	15	57	85 200	1.16	15.1

[a] All polymerizations were carried out at 100 °C in anisole [PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3. [b] Number-average molecular weight (M_n) and polydispersity (PDI) measured by gel permeation chromatography equipped with multiangle laser light scattering (GPC-MALLS). [c] Percentage of incorporated linear PCL precursor into CCS polymer. [d] Number of arms in CCS polymer, determined from eq 1.

Table 2. Synthesis of Arm-Degradable Core Cross-Linked Star (CCS) Polymer Using Polycaprolactone Macroinitiator (PCL-Br) and Ethylene Glycol Dimethacrylate (EGDMA) Cross-Linker

expt no.[a]	M_n PCL-Br (g/mol)[b]	PDI PCL-Br[b]	[PCL-Br] (mM)	[EGDMA]/[PCL-Br]	PCL conv (%)[c]	M_n (g/mol)[b]	PDI[b]	f[d]
8	2700	1.12	5	15	59	287 800	1.48	38.0
9	2700	1.12	5	20	71	264 200	1.45	35.7
10	2700	1.12	5	25	78	382 900	1.36	42.9
11	2700	1.12	10	25	gel			
12	2700	1.12	15	25	gel			
13	2300	1.05	5	25	85	367 100	1.19	55.1

[a] All polymerizations were carried out at 100 °C in anisole [PCL-Br] = [CuBr]/1.3 = [PMDETA]/1.3. [b] Number-average molecular weight (M_n) and polydispersity (PDI) measured by gel permeation chromatography equipped with multiangle laser light scattering (GPC-MALLS). [c] Percentage of incorporated linear PCL precursor into CCS polymer. [d] Number of arms in CCS polymer, determined from eq 1.

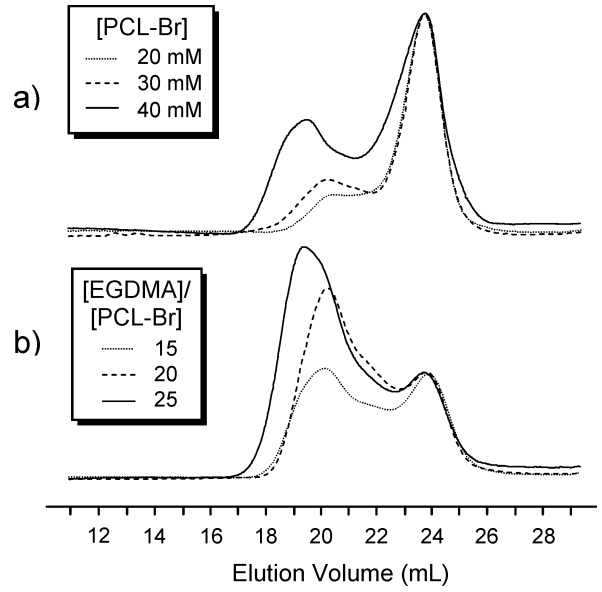


Figure 3. Gel permeation chromatography traces of polycaprolactone (PCL) arm-degradable core cross-linked star (CCS) polymer formation for (a) divinylbenzene (DVB) cross-linker with variable reaction concentration (Table 1, experiments 2−4) and (b) ethylene glycol dimethacrylate (EGDMA) cross-linker with variable cross-linker amount (Table 2, experiments 8−10).

PCL-Br macroinitiator (M_n = 2300 g/mol, M_w/M_n = 1.05) to form CCS polymer at the previously determined optimal conditions (Table 1, experiment 7, and Table 2, experiment 13), it was found that the arm conversion could be increased from 42% to 57% for the DVB-based CCS polymer and from 78% to 85% for the EGDMA-based CCS polymer. These results are in accordance with findings from our earlier work[5,17] and that of Matyjaszewski et al.,[18] who showed that employing shorter arm lengths led to higher CCS polymer yields.

The number of linear polymeric arms incorporated into the CCS polymer (f) was calculated using the following equation:

$$f = \frac{WF_{\text{arms}} M_{\text{w,CCS}}}{M_{\text{w,arms}}} \quad (1)$$

where the CCS molecular weight ($M_{w,CCS}$) and the molecular weight of the linear arms ($M_{w,arms}$) were determined by GPC-MALLS. The weight fraction of arms (WF_{arms}) can be determined according to eq 2 where the conversion of cross-linker (χ_C) was determined by gas chromatography (GC) analysis and the conversion of arms (χ_A) determined by GPC analysis.

$$WF_{\text{arms}} = \frac{m(\text{arms})\chi_A}{m(\text{cross-linker})\chi_C + m(\text{arms})\chi_A} \quad (2)$$

The DVB and EGDMA arm-degradable CCS polymers with the highest conversion (Table 1, experiment 7, and Table 2, experiment 13) were hydrolyzed under acidic conditions to degrade the polycaprolactone arms and liberate the cross-linked core. GPC traces were obtained for the hydrolyzed products (Figure 4a,b) which revealed the number-average molecular weight (M_n) of the DVB cores to be 30 600 g/mol (M_w/M_n = 1.84) while the EGDMA cores had a M_n of 232 300 g/mol (M_w/M_n = 1.47) (Table 3, samples 1 and 2). The theoretical molecular weight of the cores can be calculated by multiplying the molecular weight of the CCS polymer and the weight fraction of cross-linker (1 − WF_{arms}). For the CCS polymers analyzed here the DVB and EGDMA cores were determined to have theoretical molecular weights of 43 700 and 215 700 g/mol, respectively, closely matching the experimentally determined values of 30 600 and 232 300 g/mol. Experimental observations indicate that the shoulder peak in the hydrolyzed product of Figure 4a (28 mL elution volume) corresponds to the hydrolyzed product of macroinitiator which has undergone chain extension but has not been incorporated into CCS polymer. Similar results are also observed for the hydrolyzed product in Figure 4b (29 mL elution volume) with the peak being significantly reduced due to the smaller amount of unconverted macroinitiator before hydrolysis.

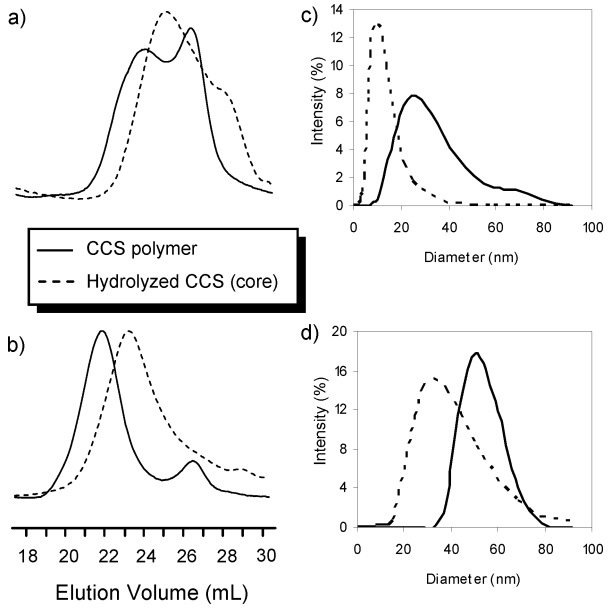


Figure 4. Gel permeation chromatography traces of arm-degradable core cross-linked star (CCS) polymer synthesized with (a) divinylbenzene (DVB) (Table 3 sample 1) and (b) ethylene glycol dimethacrylate (EGDMA) cross-linker (Table 3 sample 2) before and after hydrolysis and corresponding dynamic light scattering measurements [(c) = DVB, (d) = EGDMA].

Dynamic light scattering measurements of the hydrolysis reaction solution were recorded before and after hydrolysis (Figure 4c,d) in order to compare the diameter of the CCS polymer to that of the liberated core. The average diameter based on scattering intensity for the DVB and EGDMA CCS polymers was found to be 27 and 52 nm, respectively, which corresponds with previous findings for other nondegradable CCS polymers.[6b] After hydrolysis the diameter of the remaining polymer was found to have been reduced to yield DVB and EGDMA cores with average diameters of 11 and 37 nm, respectively. The reduction in size for both the DVB and EGDMA CCS polymers was found to be very similar (16 and 15 nm, respectively), owing to the same PCL-Br macroinitiator (M_n = 2300 g/mol) being used in both instances. However, the magnitude of this size reduction is not solely due to the length of the removed arm since shrinkage of the exposed core will also occur. This shrinkage occurs due to the highly cross-linked core particles becoming less soluble upon removal of the arms.

Synthesis of Partially Arm-Degradable CCS Polymer. The synthesis of partially arm-degradable CCS polymer involves the introduction of a second type of arm to create miktoarm CCS polymer with a mixture of degradable and nondegradable arms. Traditionally, miktoarm CCS is generated by the "in−out" method[8,19−21] where the "arm first" approach is used to create CCS polymer from polyA macroinitiator and a divinyl cross-linker. A second monomer (B) is then used to grow arms out from the initiating sites in the core to generate miktoarm CCS polymer with polyA and polyB arms. One drawback of the "in−out" method is the unknown efficiency of the chain extension reaction with the second monomer since not all of the initiation sites in the core will be accessible due to the high cross-linking density in the core and the steric hindrance created by the arms. Alternatively, miktoarm CCS can be synthesized using the "arm first" approach by simply cross-linking two different polymeric macroinitiators (polyA and polyB) simultaneously. However, this requires the two macroinitiators to have similar reactivity so that the resultant miktoarm CCS contains both polyA and polyB arms.

The method of cross-linking two macroinitiators simultaneously, as opposed to the "in−out" method, was employed for this work using PCL-Br (M_n = 2300 g/mol, M_w/M_n = 1.05) as the degradable arm component and tosyl chloride initiated poly(methyl methacrylate) (PMMA-Cl) (M_n = 7500 g/mol, M_w/M_n = 1.08) as the nondegradable arm component. EGDMA was used to cross-link the PCL-Br and PMMA-Cl macroinitiators under ATRP conditions to synthesize miktoarm CCS polymer (Scheme 3) with a number-average molecular weight of 559 600 g/mol and a polydispersity (M_w/M_n) of 1.24 (Figure 5). The extent of CCS formation was limited (28% conversion of arms into CCS polymer) and as such was fractionated to remove any unconverted arms and yield pure miktoarm CCS polymer.

Since the molecular weights of the PCL and PMMA arms were different, it is expected that their reactivity will also be different, resulting in miktoarm CCS polymer with a higher ratio of one type of arm compared to the other. ^{1}H NMR was used to determine the relative amount of PCL and PMMA arms incorporated into the miktoarm CCS polymer (Figure 6) by comparing the peak area of *a* (CH_2COO from PCL unit) to *h* (OCH_3 from PMMA unit). The molar ratio of PCL to PMMA was determined to be 2.6:1, showing that the smaller PCL arms were more readily incorporated into the miktoarm CCS polymer. From this data it was possible to calculate the average number of arms (*f*) incorporated into the CCS polymer as being 53.1 (14.8 PMMA and 38.3 PCL arms).

The miktoarm CCS polymer reported here can be classified as partially arm-degradable CCS polymer since one type of arm, the PCL component, can be selectively degraded to produce CCS polymer with a reduced number of arms. By hydrolyzing the partially arm-degradable CCS polymer, we can create CCS polymer which would potentially have very different physical properties to that of standard CCS polymer since the number of arms would be much less compared to CCS polymer of a similar arm molecular weight.

GPC traces show a reduction in molecular weight after hydrolysis of the miktoarm CCS polymer (Figure 5) such that the resultant CCS polymer had a M_n of 460 800 g/mol and a polydispersity of 1.36 (Table 3, sample 3). ^{1}H NMR analysis of the hydrolyzed polymer confirmed that all of the PCL arms had been removed to yield pure PMMA arm CCS polymer. Since the number and molecular weight of the degradable PCL arms in the miktoarm CCS polymer are known, the theoretical molecular weight of the CCS polymer after hydrolysis can be calculated. For the miktoarm CCS polymer reported here the theoretical M_n after hydrolysis was calculated to be 472 500 g/mol, which is in accordance with that measured by GPC-MALLS (460 800 g/mol).

Synthesis of Core-Degradable CCS Polymer. To synthesize core-degradable CCS polymer, a hydrolyzable monomer must be employed as the cross-linking agent. For this work the bislactone 4,4′-bioxepanyl-7,7′-dione (BOD), synthesized according to literature,[22] was chosen as the degradable cross-linker due to its structural similarity to ϵ-caprolactone, with BOD consisting of two caprolactone rings bridged at the 4-position (Scheme 1). By cross-linking linear arms with BOD under ROP conditions, the resultant CCS polymer will possess a polyester-based core which can be degraded via hydrolysis of the incorporated ester linkages.

Since the cross-linking step is performed under ROP conditions, the macroinitiator arms need to be hydroxyl end-functionalized so they can initiate the polymerization of the BOD cross-linker. For this reason the duel ATRP/ROP initiator, 2-hydroxyethyl 2′-methyl-2′-bromopropionate, was used to

Table 3. Selectively Degradable Core Cross-Linked Star (CCS) Polymers

					CCS			hydrolyzed CCS		
sample[a]	arm[b]	X[c]	arm conv (%)[d]	X conv (%)[e]	M_n (g/mol)[f]	PDI[f]	f[g]	M_n (g/mol)[f]	PDI[f]	$M_{n,theory}$ (g/mol)
1	PCL	DVB	57	70	85 200	1.16	15.1	30 600	1.84	43 700
2	PCL	EGDMA	85	93	367 100	1.19	55.1	232 300	1.47	215 700
3	PMMA PCL	EGDMA	28	80	559 600	1.24	53.1	460 800	1.36	472 500
4	PSt	BOD	55	87	214 800	1.18	13.6	10 700	1.09	10 700
5	PCL	BOD	85	86	362 000	1.13	43.0			
6	PCL	BCP	41	83	335 800	1.27	34.4			

[a] Reaction conditions for CCS polymers as defined in text (sample 1 = Table 1 experiment 7, sample 2 = Table 2, experiment 13). [b] Type of arm used to synthesize CCS polymer; definitions: PCL = poly(ϵ-caprolactone), PMMA = poly(methyl methacrylate), PSt = polystyrene. [c] Type of cross-linker (X) used to synthesize CCS polymer; definitions: DVB = divinylbenzene, EGDMA = ethylene glycol dimethacrylate, BOD = 4,4′-bioxepanyl-7,7′-dione, BCP = 2,2-bis(ϵ-caprolactone-4-yl)propane. [d] Percentage of incorporated linear arm precursor into CCS polymer. [e] Determined by gas chromatography. [f] Number-average molecular weight (M_n) and polydispersity (PDI) measured by gel permeation chromatography equipped with multiangle laser light scattering (GPC-MALLS). [g] Number of arms in CCS polymer, determined from eq 1.

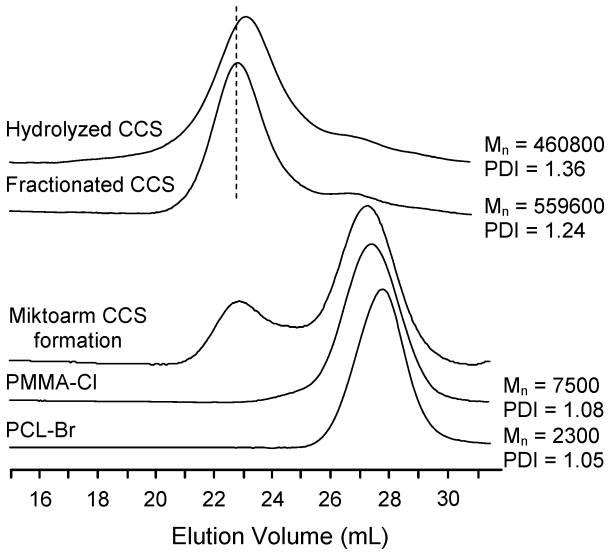


Figure 5. Gel permeation chromatography traces of polycaprolactone (PCL) poly(methyl methacrylate) (PMMA) miktoarm core cross-linked star (CCS) polymer and subsequent hydrolysis (Table 3, sample 3).

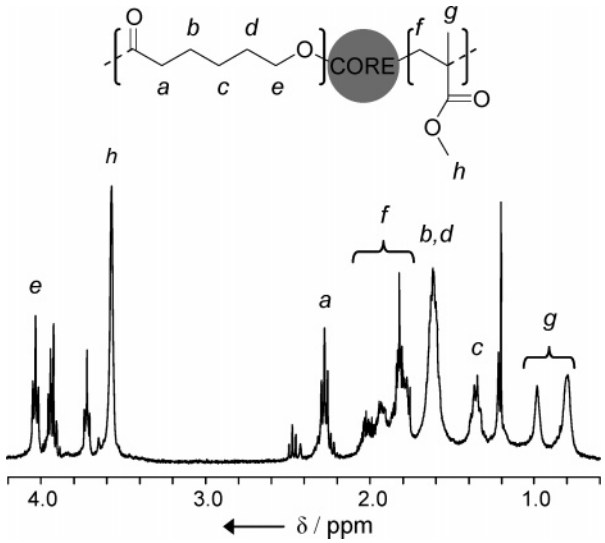
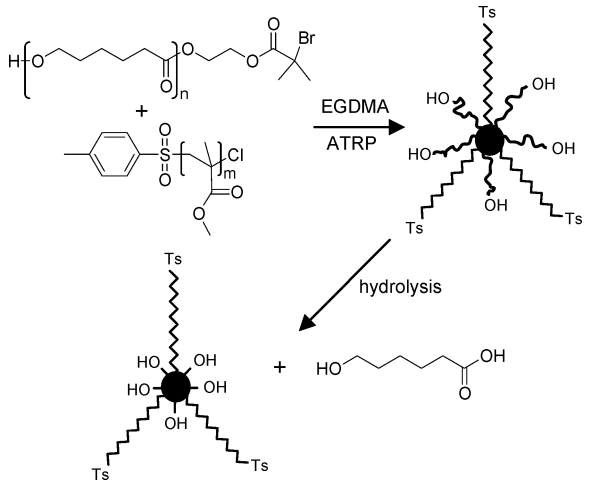


Figure 6. ^{1}H NMR (400 MHz) of polycaprolactone poly(methyl methacrylate) miktoarm core cross-linked star (CCS) polymer ($CDCl_3$) (Table 3, sample 3).

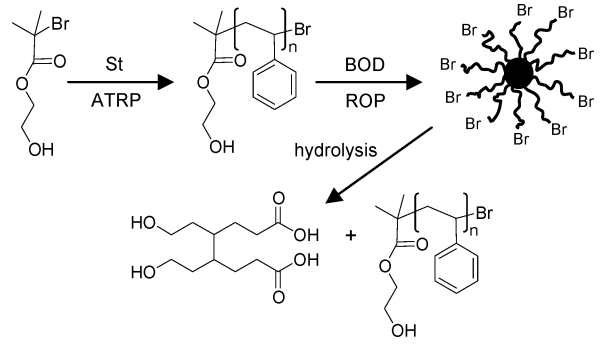
Scheme 3. Synthesis of Partially Arm-Degradable CCS Polymer and Subsequent Hydrolysis



synthesize hydroxyl end-functionalized polystyrene macroinitiator (PSt-OH) via ATRP (M_n = 10 700 g/mol, M_w/M_n = 1.09).

BOD cross-linker was polymerized with the PSt-OH macroinitiator in toluene at 110 °C ([BOD]/[PSt-OH] = 10, [PSt-OH] = 0.02 M) using $Sn(Oct)_2$ catalyst (Scheme 4). The conversion of BOD monomer was monitored by gas chromatography mass spectrometry which showed that after 48 h 87% of the BOD monomer had been consumed. GPC analysis (Figure

Scheme 4. Synthesis of Core-Degradable CCS Polymer and Subsequent Hydrolysis



7) revealed that ~55% of the linear PSt-OH had been converted into CCS polymer, which was subsequently fractionated to remove any unconverted arms to yield pure CCS polymer with a M_n of 214 800 g/mol (M_w/M_n = 1.18) and an average of 13.6 arms (calculated from eq 1).

Hydrolysis of this type of CCS polymer resulted in degradation of the core domain and liberation of the nondegradable PSt arms (Table 3, sample 4), effectively converting high molecular weight CCS polymer into low molecular weight linear polymer. GPC analysis (Figure 7) confirmed this with the CCS polymer being completely degraded to yield the original linear PSt arms (M_n = 10 700 g/mol, M_w/M_n = 1.09).

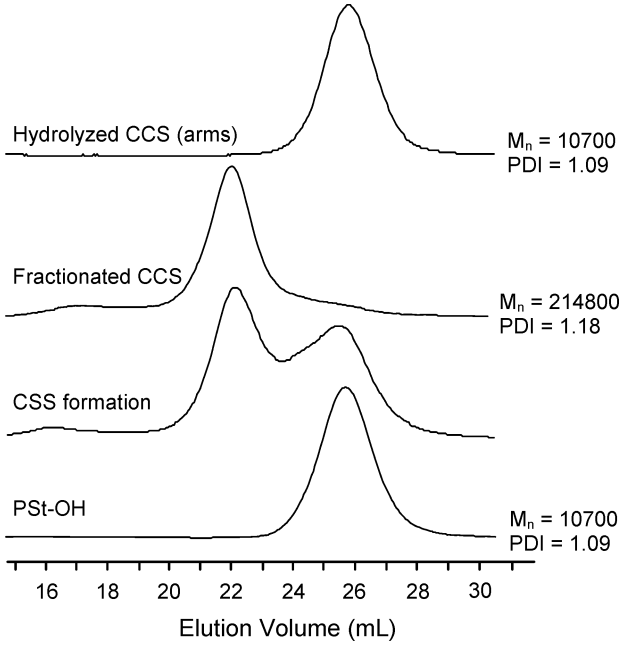
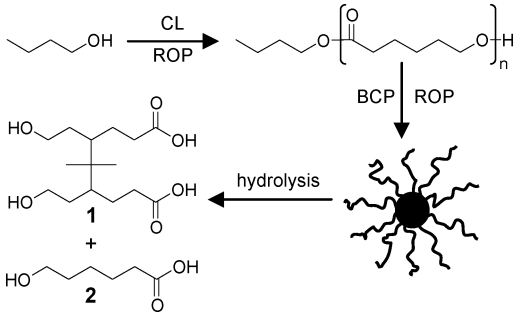


Figure 7. Gel permeation chromatography traces of polystyrene (PSt) core-degradable core cross-linked star (CCS) polymer and subsequent hydrolysis (Table 3, sample 4).

Scheme 5. Synthesis of Fully Degradable CCS Polymer and Subsequent Hydrolysis



Synthesis of Fully Degradable CCS Polymer. We recently reported a procedure for the synthesis of fully degradable CCS polymer based on ROP of lactone-based monomers.[12] A similar procedure was also reported at the same time by Biela et al.[23] The ROP method is different to the previous methods described for synthesizing arm-degradable or core-degradable CCS polymer since only one form of controlled polymerization is required rather than a combination of ROP and ATRP. This allows for the synthesis of CCS polymer via a two-step one-pot process whereby living linear PCL arms are synthesized under ROP conditions. On completion of this reaction a bislactone is added to the reaction mixture to cross-link the arms and form a completely polyester-based CCS polymer (Scheme 5).

As shown earlier,[12] a range of reaction conditions for the synthesis of fully degradable BOD/PCL-based CCS polymer have been investigated, and it was found that optimal CCS formation occurred when 1-butanol ([BuOH] = 19.2 mM) was used to initiate the ring-opening polymerization of ϵ-caprolactone ([CL] = 1 M) in toluene at 110 °C using stannous 2-ethylhexanoate ([$Sn(Oct)_2$]/[BuOH] = 0.5) as catalyst. Once this reaction reached completion (CL conversion >99%, 24 h, M_n = 5300 g/mol, M_w/M_n = 1.07), the BOD cross-linker was added ([BOD]/[PCL] = 10) and allowed to react for a further 16 h until 86% of the BOD monomer had been consumed, and a high conversion of arms into CCS polymer (85%) was achieved. The CCS polymer generated was calculated to have

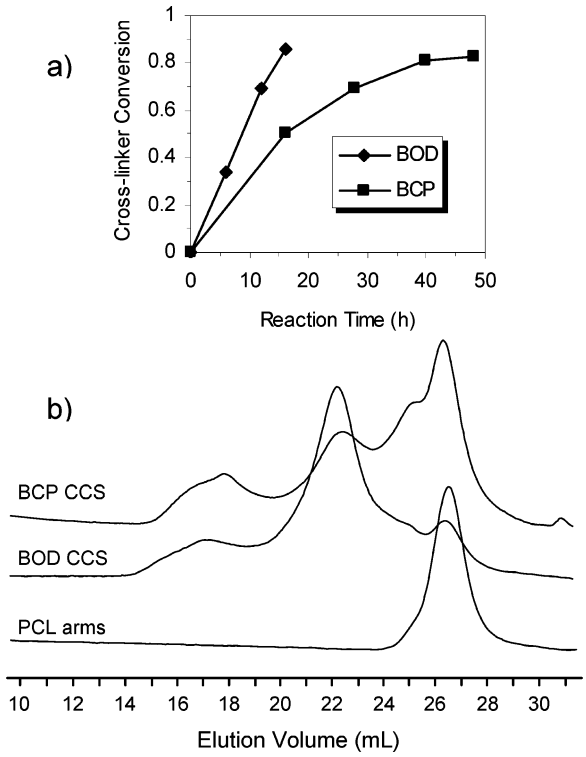


Figure 8. (a) Cross-linker conversion (BOD = 4,4′-bioxepanyl-7,7′-dione, BCP = 2,2-bis(ϵ-caprolactone-4-yl)propane) during the synthesis of fully degradable core cross-linked star (CCS) polymer and (b) gel permeation chromatography traces of fully degradable CCS polymers and precursor polycaprolactone (PCL) arms (Table 3, samples 5 and 6).

a number-average molecular weight of 362 000 g/mol (M_w/M_n = 1.13) with an average of 43.0 arms.

Here, we also report the use of an alternative degradable bislactone cross-linker, 2,2-bis(ϵ-caprolactone-4-yl)propane (BCP). The structure of BCP is very similar to that of BOD, except that the bridging unit between the ϵ-caprolactone rings in BCP consists of a methylated quaternary carbon (Scheme 1). The BCP cross-linker was polymerized under the optimal reaction conditions previously described to synthesize BOD cross-linked CCS polymer with BOD being directly substituted with BCP. 48 h after addition of the BCP cross-linker 83% of the BCP monomer had been consumed, but the conversion of arms into CCS was only 41%. The resultant CCS polymer generated was calculated to have a number-average molecular weight of 335 800 g/mol (M_w/M_n = 1.27) with an average of 34.4 arms.

A comparison of the two fully degradable CCS polymers (Figure 8) synthesized under the same reaction conditions shows that similar molecular weight CCS polymer (elution volume = 22 mL) is generated in both instances, M_n = 362 000 g/mol for the BOD-based CCS compared to 335 800 g/mol for the BCP-based CCS (Table 3, samples 5 and 6). However, the reaction time to reach similar cross-linker conversion (83−86%) took 3 times longer for the BCP reaction (Figure 8a) with the resultant conversion of arms into CCS polymer also being significantly reduced, less than half that achieved for the BOD-based reaction. These results suggest that the BCP cross-linker is less reactive toward the formation of CCS polymer than BOD cross-linker, possibly due to the bulky methyl groups creating steric hindrance, which makes it harder to generate the dense core region during the cross-linking step.

GPC traces of the two fully degradable CCS polymers (Figure 8b) reveal that in addition to the synthesis of CCS polymer (elution volume = 22 mL) the generation of very high molecular

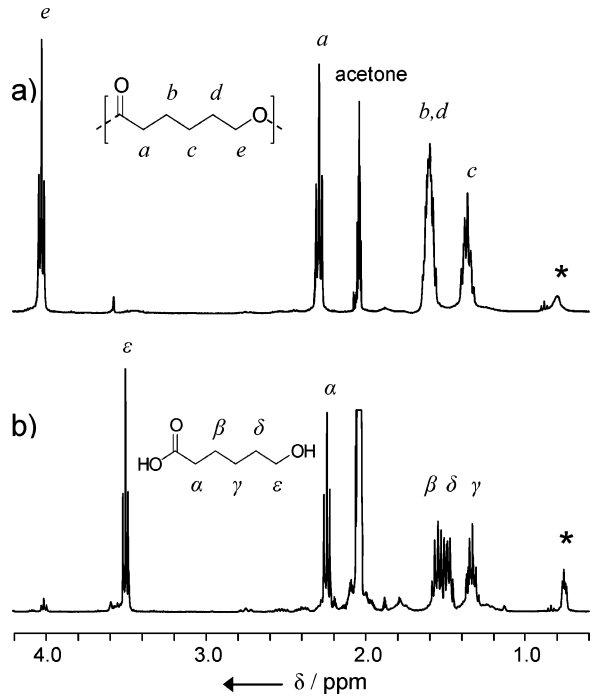


Figure 9. ^{1}H NMR (400 MHz) of 2,2-bis(ϵ-caprolactone-4-yl)propane (BCP) core cross-linked star (CCS) polymer (Table 3, sample 6) taken (a) before and (b) after 24 h of hydrolysis (60 °C, CD_3COCD_3:D_2O (13.3:1), 0.272 M HCl), $*$ = bridging methyl groups from BCP cross-linker.

weight polymer (1−2 million) has also occurred (elution volume ∼ 17 mL). This high molecular weight polymer is believed to be a product of star−star coupling and is more prevalent in the BCP cross-linked reaction due to the longer reaction time required for CCS formation, resulting in an increased probability of star−star coupling occurring.

Our previous work[12] has shown that PCL/BOD-based CCS polymer can be completely degraded by hydrolyzing the ester bonds in the polymer to generate small chain acids. This degradation reaction was quantitatively monitored by conducting the hydrolysis experiment in deuterated solvents (THF-d_8 and D_2O) and analyzing the reaction solution over time with ^{1}H NMR spectroscopy. Similar experiments were conducted for the hydrolysis of BCP/PCL-based CCS polymer with comparison of the ^{1}H NMR spectra before and after hydrolysis (Figure 9), revealing that the triplet at δ 4.02 ppm corresponding to ϵ-CH_2 in the polyester backbone is greatly reduced after hydrolysis and is complemented by the appearance of the triplet at δ 3.50 ppm corresponding to ϵ-CH_2 of the hydrolyzed ester. The extent of hydrolysis can be calculated by comparing the relative peak area of ϵ-CH_2 before and after hydrolysis, which revealed that for the BCP/PCL-based CCS polymer ∼97% of the ester linkages had been hydrolyzed back to their monomeric constituents.

When BOD is used to synthesize fully degradable CCS polymer, ^{1}H NMR spectroscopy of the star cannot be used to detect the BOD core structure due to the reduced segmental mobility of the core which results in broadening of the characteristic peaks of the core such that they disappear into the baseline. However, when BCP is used as the cross-linker, the two methyl groups in the bridging unit between the lactone rings are flexible enough and of a high enough intensity that they can be detected by ^{1}H NMR spectroscopy (Figure 9a: $*$ δ 0.80 ppm), even though significant broadening is still observed. For the ^{1}H NMR spectra of the hydrolyzed product the peak due to the bridging methyl groups becomes stronger and sharper (Figure 9b: $*$ δ 0.76 ppm) as it is no longer bound within the rigid core structure but instead exists as a small-chain hydrolysis product resembling two 6-hydroxyhexanoic acid units bridged at the 4-position by a methylated quaternary carbon (**1** in Scheme 5). The other characteristic peaks of **1** are obscured by the peaks associated with the hydrolysis product of the linear arms, 6-hydroxyhexanoic acid (**2** in Scheme 5), due to their structural similarity and the smaller amount of **1** relative to **2**.

Conclusions

A range of selectively degradable CCS polymers were successfully synthesized by combining ATRP of nondegradable monomers with ROP of degradable lactone-based monomers. Utilizing this method, degradable PCL arm CCS polymers were synthesized with both EGDMA and DVB cores. Various reaction parameters, especially the macroinitiator concentration and the molar ratio of cross-linker to macroinitiator, were studied to determine the optimal reaction conditions with EGDMA being found to yield higher conversion of arms into CCS polymer compared to DVB. Hydrolysis experiments showed that the PCL arms could be selectively degraded to yield EGDMA and DVB cores, for which the size was directly determined.

Miktoarm CCS polymer was synthesized in a similar fashion with a mixture of degradable PCL and nondegradable PMMA arms. The higher molecular weight PMMA macroinitiator showed lower reactivity than the PCL with less PMMA arms being incorporated into the CCS polymer. Acidic hydrolysis conditions were used to selectively degrade the PCL arms and yield CCS polymer with a reduced number of arms. Degradable functionality was also incorporated into the core domain using a degradable bislactone, BOD, to cross-link nondegradable linear PSt-OH macroinitiator under ROP conditions. Hydrolysis of this CCS polymer resulted in degradation of the core and full recovery of the original linear PSt arms.

Degradable bislactone monomer was also shown to be able to cross-link degradable PCL arms via a two-step one-pot reaction to produce fully degradable CCS polymer. The effectiveness of two bislactone cross-linkers, BOD and BCP, was examined with a higher conversion of arms into CCS polymer being achieved when BOD was used compared to BCP, possibly due to the added steric bulk of the BCP monomer making formation of the dense core region unfavorable. Both bislactone-based CCS polymers were shown to be fully degradable being hydrolyzed back to monomeric constituents.

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