# Degradable Core Cross-Linked Star Polymers via Ring-Opening Polymerization

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Core cross-linked star (CCS) polymers[1] have unique three-dimensional architectures that consist of a cross-linked core surrounded by a number of radiating arms.[2,3] Traditionally, they are synthesized via the "arms first approach" using controlled radical polymerization techniques such as nitroxide-mediated radical polymerization,[4] atom transfer radical polymerization,[5,6] or reverse addition−fragmentation chain transfer polymerization.[7] In this approach, initially synthesized living linear arms are reacted with a cross-linker to join the active arm ends together to form star-shaped polymer with a cross-linked core. A second type of arm can also be added at the cross-linking stage to form CCS polymer with mixed arms. These are referred to as miktoarm stars.

Increasing interest has recently been dedicated to this class of macromolecules due to their unique rheological properties and well-defined structures, which make them very useful in drug delivery,[8] membrane formation,[5] and paint additive[9] applications. CCS polymers also have potential for application as templates for silicate materials with low dielectric constants.[10]

As a result of several potential areas of application, particularly in the electronic materials and drug delivery areas, a need has arisen for CCS polymers that can be degraded under mild conditions. Here we report the first example of the synthesis of a fully degradable CCS polymer. This new type of star polymer was synthesized from lactone-based monomers using a controlled polymerization technique known as ring-opening polymerization (ROP) that has not previously been reported for the synthesis of CCS polymers.

The ROP method allows for the synthesis of CCS polymers with polyester-based structures (both arm and core moieties) and can therefore degrade under controlled conditions[11−13] via hydrolysis of the ester linkages in the polymer. One advantage of a polyester-based CCS polymer is that the degradation products can be absorbed by the body with minimal tissue reaction, making them suitable for a wide variety of medical applications, particularly as tissue scaffolds or potential drug delivery agents.[14]

In this work CCS polymers were synthesized via a two-step one-pot process involving the synthesis of living linear arms followed by a cross-linking step to generate CCS polymers (Scheme 1). In the first step, ring-opening polymerization of a lactone, $\epsilon$-caprolactone (CL), was performed in the presence of a catalyst (stannous 2-ethylhexanoate) and an initiator (1-butanol) in toluene ([CL] = 1 M, 110 °C) to produce living linear polycaprolactone (PCL) arms (number-average molecular weight ($M_n$) = $5.34 \times 10^3$ g/mol, polydispersity (PDI) = 1.07). Several different solvent systems were investigated since bulk polymerization, the most common technique for this type of reaction, was not suitable for the second step of the synthesis due to the inhomogeneous nature of the reaction mixture after addition of the cross-linking monomer as a result of poor mixing. Toluene was the most suitable solvent as it allowed for a polymerization temperature high enough to yield high molecular weights within a reasonable time frame while still being low enough to avoid thermal degradation.

On completion of the first step (CL conversion >99%, 24 h) a bislactone, 4,4′-bioxepanyl-7,7′-dione (BOD) synthesized according to the literature,[15] was added to the reaction solution (BOD/PCL = 10). The BOD acts as a cross-linking component under ROP conditions to give the core structure. Since only one end of the PCL arms is active during the cross-linking step, CCS polymer is formed. In contrast, if both ends of the PCL arms are active toward polymerization, a consequence of the PCL being initiated by a diol or water, a highly cross-linked network would result. This is important since having even a small amount of double-end active PCL present during the cross-linking step (from PCL initiated by water impurities, for example) will result in star−star coupling and potential macrogelation if the impurity concentration is high enough. In the case of coupling via water-initiated chains, the mechanism involves a condensation reaction between a carboxylic acid group in the periphery of one star with a hydroxyl group within the core of another, whereas for diol-initiated chains the coupling mechanism is solely a product of ROP. BOD was used as the cross-linking monomer due to its structural similarity to CL such that the core of the star polymer would chemically resemble PCL only with bridges linking between the pentylene moieties. BOD can also easily be copolymerized with CL to form cross-linked networks using ROP.[15]

The conversion of the BOD monomer during the second stage of the reaction was monitored by gas chromatography mass spectrometry (GC-MS) which showed that after 16 h 86% of the BOD monomer had been consumed. The formation of CCS polymer over time was monitored by gel permeation chromatography equipped with a multiangle laser light scattering detector (GPC-MALLS) (Figure 1a−d) with the final trace at 16 h (Figure 1d) showing that ∼85% of the linear arms at 27 min retention time (Figure 1a) had been converted to yield CCS polymer at 22 min. A small fraction (∼3%) of high molecular weight polymer ($M_n$ = $1.50 \times 10^6$ g/mol) at around 17 min was also observed, which we believe is due to the linking of several stars caused by water impurities during the PCL synthesis, as previously discussed. The final product was fractionated using a GPC fractional collector to yield pure CCS polymer (Figure 1e) with a number-average molecular weight of $3.62 \times 10^5$ g/mol and a polydispersity of 1.13. The average number of arms per star can be deduced from the weight fraction of arms ($Wf_{arms}$) in the CCS polymer and the ratio of the molecular weight of the CCS polymer relative to that of the linear arms. Based on these data, the calculated average number of arms for the CCS polymer is ∼43.

The results described above were based on the optimal reaction conditions as determined from a series of experiments in which several reaction conditions were varied (Table 1). At the optimal reaction conditions the conversion of PCL was high, and a high molecular weight for the CCS polymer was achieved in a relatively short time (Table 1, experiment 1). As shown in Table 1, for a decrease in the relative amount of cross-linker (comparing experiments 1 and 3 or experiments 2 and 4) the

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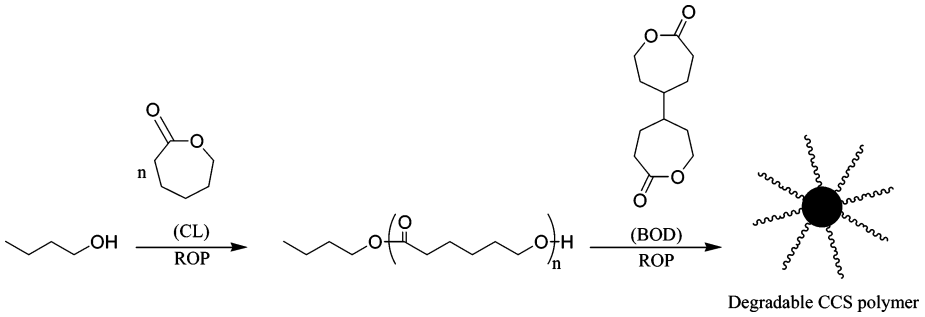
**Scheme 1. Synthesis of Degradable Core Cross-Linked Star (CCS) Polymer via Ring-Opening Polymerization (ROP)**




conversion of PCL is reduced while also leading to increased polymerization times to yield high molecular weight polymer. However, for increased cross-linker ratios the amount of very high molecular weight polymer, believed to be a product arising from the linking of several stars, also increased. The conversion of PCL was also shown to be dependent on the initial monomer concentration and the molecular weight of the PCL arms such that an increase in either variable resulted in decreased arm to CCS polymer conversion.

To quantitatively examine the degradation of these CCS polymers, hydrolysis experiments were conducted in deuterated solvents (THF-$d_8$ and $D_2O$) and analyzed via $^1$H NMR spectroscopy (400 MHz, Unity spectrometer). Since hydrolysis of PCL occurs via the ester bonds in the backbone of the polymer, the major degradation product was 6-hydroxyhexanoic acid. A certain amount of 4,5-bis(2-hydroxyethyl)octanedioic acid, two 6-hydroxyhexanoic acids linked together at the 4 position, also formed part of the degradation products because of the presence of BOD cross-linker in the CCS polymer. However, because of its structural similarity, it was indistinguishable from 6-hydroxyhexanoic acid in the $^1$H NMR spectra. Comparison of the $^1$H NMR spectra before and after hydrolysis (Figure 2) revealed that the triplet at $\delta$ 3.99 ppm corresponding to e-$CH_2$ in the PCL backbone is greatly reduced after hydrolysis and is complemented by the appearance of the triplet at $\delta$ 3.46 ppm corresponding to $\epsilon$-$CH_2$ in the degradation product, 6-hydroxyhexanoic acid. In addition, the peak at $\delta$ 1.58 ppm corresponding to d-$CH_2$ of the polymer initially overlapped with the b-$CH_2$

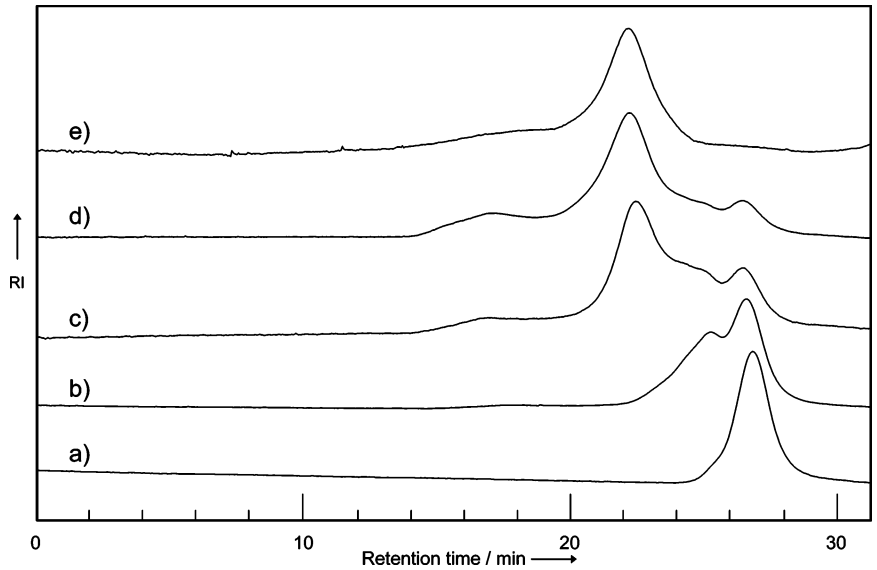



**Figure 1.** Traces of gel permeation chromatography equipped with multiangle laser light scattering (GPC-MALLS) for degradable core cross-linked star (CCS) polymer synthesis ([$\epsilon$-caprolactone] = 1 M, [1-butanol] = $1.92 \times 10^{-2}$, [stannous 2-ethylhexanoate] = $9.60 \times 10^{-3}$ in toluene at 110 °C) after addition of 4,4′-bioxepanyl-7,7′-dione cross-linker: (a) 0 h, (b) 6 h, (c) 12 h, (d) 16 h, and (e) the final fractionated sample. RI = refractive index, relative scale.

**Table 1. Selected Polymerization Data for the Synthesis of Degradable Core Cross-Linked Star (CCS) Polymer**

| expt[a] | [BuOH] (mM) | [CL] (M) | $M_{n,calc}$ [b] PCL | $M_{n,GPC}$ [c] PCL | $t_{PCL}$ (h)[d] | [PCL] (mM) | [BOD] (mM) | [BOD]/ [PCL] | PCL conv (%)[e] | BOD conv (%)[f] | $M_n$ CCS polymer[c] | PDI[g] | $n$[h] | $t_{CCS}$ (h)[i] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 19.2 | 1 | 6000 | 5300 | 25 | 21.4 | 214 | 10 | 85 | 86 | 362 000 | 1.13 | 43 | 16 |
| 2 | 38.5 | 2 | 6000 | 8400 | 24 | 27.3 | 273 | 10 | 80 | 87 | 353 000 | 1.14 | 33 | 18 |
| 3 | 19.2 | 1 | 6000 | 5000 | 24 | 22.8 | 114 | 5 | 60 | –[j] | 54 000 | 1.12 | 9[k] | 48 |
| 4 | 38.5 | 2 | 6000 | 7500 | 24 | 30.3 | 151 | 5 | 46 | –[j] | 182 000 | 1.16 | 24[k] | 48 |
| 5 | 19.2 | 2.5 | 20000 | 12600 | 48 | 22.7 | 227 | 10 | 67 | 90 | 455 000 | 1.22 | 30 | 46 |

[a] All polymerizations were carried out at 110 °C in toluene with initiator (1-butanol (BuOH)), catalyst (stannous 2-ethylhexanoate ($Sn(Oct)_2$) [BuOH]: [$Sn(Oct)_2$] = 2), monomer ($\epsilon$-caprolactone (CL)) and cross-linker (4,4′-bioxepanyl-7,7′-dione (BOD)). [b] Molecular weight ($M_n$) as calculated from $[CL]_0/[BuOH]_0$ for 100% conversion. [c] $M_n$ determined by gel permeation chromatography equipped with multiangle laser light scattering (GPC-MALLS). [d] Polymerization time to achieve >99% CL conversion. [e] Percentage incorporation of linear polycaprolactone (PCL) into CCS polymer. [f] Determined by gas chromatography mass spectroscopy (GC-MS). [g] Polydispersity (PDI) calculated from GPC analysis. [h] Number of arms in CCS polymer = $Wf_{arms} \times M_w(star)/M_w(arms)$. [i] Polymerization time after addition of BOD monomer. [j] Measurements were not taken as concentration was too low to accurately measure. [k] Assuming 87% BOD conversion.

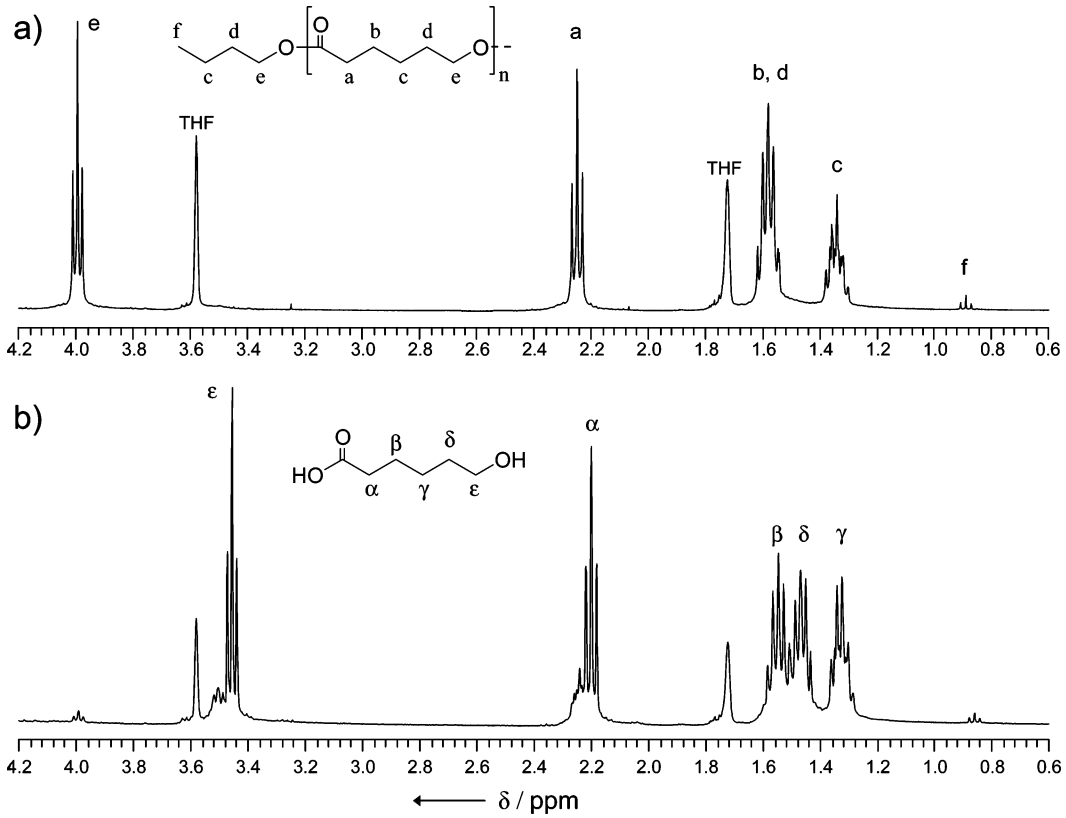



**Figure 2.** $^1$H NMR spectra (400 MHz) of degradable core cross-linked star (CCS) polymer (sample from experiment 1 of Table 1) taken (a) before and (b) after 24 h of hydrolysis (60 °C, deuterated tetrahydrofuran (THF-$d_8$):$D_2O$ (13.3:1), 0.272 M HCl).

peak, but after hydrolysis it was removed and replaced by the $\delta$-$CH_2$ peak of 6-hydroxyhexanoic acid ($\delta$ 1.47 ppm). The disappearance of the d-$CH_2$ and e-$CH_2$ peaks in the polymer and the appearance of the $\delta$-$CH_2$ and $\epsilon$-$CH_2$ peaks in the degradation product show that hydrolysis has occurred, the extent of which can be calculated by comparing the relative peak area of e-$CH_2$ before and after hydrolysis. For the hydrolysis shown in Figure 2 the percentage of hydrolyzed ester bonds was calculated to be ~97%. Since the core segment is indistinguishable from the arms in both the predegradation and postdegradation samples when analyzed by $^1$H NMR spectroscopy, a separate experiment was conducted to confirm that the core had degraded and that the inability to detect it was not due to the reduced segmental mobility of the core.[6e] This was achieved by hydrolyzing CCS polymer with polystyrene arms and BOD core under the same conditions, which resulted in recovery of the polystyrene arms and thus confirmed the degradability of the BOD core.

In summary, ring-opening polymerization can be applied to the synthesis of fully degradable core cross-linked star (CCS) polymers. Similar to nondegradable CCS polymer synthesis via the arms first approach with controlled radical polymerization techniques such as nitroxide-mediated radical polymerization, atom transfer radical polymerization, and reverse addition−fragmentation chain transfer polymerization, this degradable CCS polymer also shows high molecular weight and a narrow polydispersity. The polymerization can be carried out in a two-step one-pot reaction, thus eliminating the need for intermediate isolation and purification of the arms. The degradable CCS polymers synthesized via ROP show a high conversion of arms into CCS polymer and achieve high molecular weight in a reasonable time frame. Perhaps the most exciting property of these CCS polymers is that they are completely degradable, a feature that will increase their usefulness in a range of applications from biomaterials in the medical field to templating materials for use in electronics.

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**Supporting Information Available:** Experimental details for the synthesis of monomers and polymers and the degradation study. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) This class of polymer is also referred to as star microgel or star nanogel in the literature; however, the term "core cross-linked star (CCS) polymer" better represents their molecular architecture.
(2) Worsfold, D. J.; Zilliox, J. G.; Rempp, P. *Can. J. Chem.* **1969**, *47*, 3379−3385.
(3) Tsitsilianis, C.; Graff, S.; Rempp, P. *Eur. Polym. J.* **1991**, *27*, 243−246.
(4) (a) Solomon, D. H.; Abrol, S.; Kambouris, P. A.; Looney, M. G. WO 9831739, 1998, The University of Melbourne, A Process for Preparing Polymeric Microgels. (b) Abrol, S.; Kambouris, P. A.; Looney, M. G.; Solomon, D. H. *Macromol. Rapid Commun.* **1997**, *18*, 755−760. (c) Abrol, S.; Caulfield, M. J.; Qiao, G. G.; Solomon, D. H. *Polymer* **2001**, *42*, 5987−5991. (d) Bosman, A. W.; Vestberg, R.; Heumann, A.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.
(5) Connal, L. A.; Gurr, P. A.; Qiao, G. G.; Solomon, D. H. *J. Mater. Chem.* **2005**, *15*, 1286−1292.
(6) (a) Solomon, D. H.; Qiao, G. G.; Abrol, S. WO 9958588, 1999, The University of Melbourne, Process for Microgel Preparation. (b) Gurr, P. A.; Qiao, G. G.; Solomon, D. H.; Harton, S. E.; Spontak, R. J. *Macromolecules* **2003**, *36*, 5650−5654. (c) Xia, J.; Zhang, X.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 4482. (d) Zhang, X.;

Xia, J.; Matyjaszewski, K. *Macromolecules* **2000**, *33*, 2340−2345. (e) Baek, K. Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2001**, *34*, 215−221. (f) Baek, K. Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2001**, *34*, 7629−7635. (g) Baek, K. Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2002**, *35*, 1493−1498. (h) Baek, K. Y.; Kamigaito, M.; Sawamoto, M. *J. Polym. Sci., Polym. Chem.* **2002**, *40*, 1972−1982. (i) Baek, K. Y.; Kamigaito, M.; Sawamoto, M. *J. Polym. Sci., Polym. Chem.* **2002**, *40*, 633−641.

(7) (a) Lord, H. T.; Quinn, J. F.; Angus, S. D.; Whittaker, M. R.; Stenzel, M. H.; Davis, T. P. *J. Mater. Chem.* **2003**, *13*, 2819−2824. (b) Moad, G.; Mayadunne, R. T. A.; Rizzardo, E.; Skidmore, M.; Thang, S. H. *Macromol. Symp.* **2003**, *192*, 1−12. (c) Zheng, G.; Pan, C. *Polymer* **2005**, *46*, 2802−2810.

(8) Peppas, N.; Nagai, T.; Miyajima, M. *Pharm. Tech. Jpn.* **1994**, *10*, 611−617.

(9) Ho, A. K.; Gurr, P. A.; Mills, M. F.; Qiao, G. G. *Polymer* **2005**, *46*, 6727−6735.

(10) Heise, A.; Nguyen, C.; Malek, R.; Hedrick, J.; Frank, C.; Miller, R. *Macromolecules* **2000**, *33*, 2346−2354.

(11) Pitt, C. G. In *Biodegradable Polymers as Drug Delivery Systems*; Chasin, M., Langer, R., Eds.; Dekker: New York, 1990; p 71.

(12) Vert, M.; Li, S. M.; Spenlehauer, G.; Guerin, P. *J. Mater. Sci.: Mater. Med.* **1992**, *3*, 432−446.

(13) Doi, Y.; Kunioka, M.; Nakamura, Y.; Soga, K. *Macromolecules* **1988**, *21*, 2722−2727.

(14) Gunatillake, P. A.; Adhikari, R. *Eur. Cells Mater.* **2003**, *5*, 1−16.

(15) Nijenhuis, A. J.; Grijpma, D. W.; Pennings, A. J. *Polymer* **1996**, *37*, 2783−2791.

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