Epoxy functionalised poly(ε-caprolactone): synthesis and application†

Jiaxiang Zhou, Wenxin Wang, Silvia Villarroya, Kristofer J. Thurecht and Steven M. Howdle*

Received (in Cambridge, UK) 18th June 2008, Accepted 4th August 2008
First published as an Advance Article on the web 1st October 2008
DOI: 10.1039/b810297j

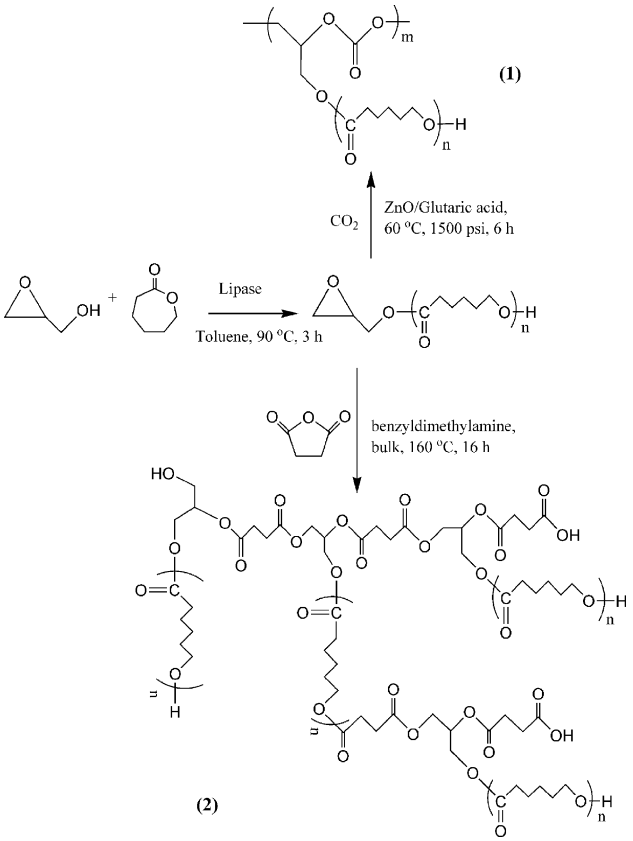
Glycidol is used as an initiator for ring-opening polymerisation of ε-caprolactone (ε-CL) to synthesise epoxy-functionalised poly(ε-caprolactone) (PCL) in a reaction catalysed by lipase, and the epoxy-functionalised PCL was further copolymerised with carbon dioxide or anhydride to produce novel graft or hyperbranched copolymers.

The synthesis of polymers with tailored reactive functionalities plays an important role in the development of various materials for industrial and biomedical applications. As a versatile functional group, the epoxy group not only facilitates the covalent attachment of drugs, proteins and genes,[1–5] but also enables copolymerisation with monomers such as carbon dioxide[6–9] and anhydride[10,11] to produce a wide variety of copolymers.

Epoxy-functionalised polyesters can be synthesised by polycondensation of monomers incorporating an epoxy group[12] or by post-oxidation of a double bond in the polyester.[13,14] However, these two approaches require specially designed monomers or initiators, which decreases the versatility of such methodologies. Glycidol and ε-caprolactone (ε-CL) are commercially available in bulk quantities. It would therefore be highly advantageous if glycidol could be used simply as the initiator for the ring-opening polymerisation (ROP) of ε-CL, and hence epoxy-functionalised PCL obtained. However, this is not an easy task, since the epoxy ring must be kept intact while the lactone ring-opening and polymerisation occurs.

ROP reactions of lactones are usually initiated by either an organometallic complex[15,16] or an enzyme.[17–19] However, very different characteristics are found with these two systems. ROP by chemical initiators strongly depends on the strain in the lactone ring, *i.e.*, the smaller the ring, the faster it can be polymerised.[20] On the other hand, the rate of polymerisation increases with increasing lactone ring size when using the lipase of *Pseudomonas fluorescens* (Lipase PF)[20,21] or Novozym 435, an immobilised *Candida antarctica* Lipase B (CALB).[22] Interestingly, this rule also applies to glycidol. In the investigation of the copolymerisation of glycidol with ε-caprolactone, we discovered that $Sn(Oct)_2$ catalyses the ring-opening of glycidol while CALB does not (see S2.1, ESI†). Therefore, this opens up the possibility that epoxy-functionalised PCL might be synthesised by glycidol initiated ROP of ε-CL using CALB as catalyst (Scheme 1). This epoxy-functionalised PCL could then further copolymerise with CO_2 or succinic anhydride to produce either graft copolymers ((**1**), Scheme 1) or hyperbranched copolymers ((**2**), Scheme 1).

The glycidol-initiated ring-opening polymerisation of ε-caprolactone was carried out in toluene using Novozym-435 as the catalyst (Table 1). Glycidol acts solely as an initiator in this polymerisation, hence the more glycidol that is present, the lower the molecular weight of the PCL product. However, the M_n analysed by SEC is much larger than would be predicted by stoichiometry. This may be attributed to two possibilities. Firstly, the M_n of PCL is usually overestimated by SEC using polystyrene standards. Secondly, hydrophobic substrates are generally favourable for lipase-catalysed reactions. Thus the hydroxyl group at the chain end of PCL is more active towards the addition of the enzyme-activated monomer because of the higher hydrophobicity of PCL than glycidol, leaving some glycidol



Scheme 1 Enzymatic synthesis of epoxy-functionalised PCL and the further copolymerisation with CO_2 or anhydride to produce graft or hyperbranched copolymers.

School of Chemistry, University of Nottingham, University Park, Nottingham, UK. E-mail: steve.howdle@nottingham.ac.uk; Fax: +44 (0)115 9513058; Tel: +44 (0)115 9513486

† Electronic supplementary information (ESI) available: Experimental details, NMR spectra, SEC traces. See DOI: 10.1039/b810297j

Table 1 CALB-catalysed ring-opening polymerisation of ε-CL using glycidol as initiator[a]

Entry	Glycidol/ mmol	Conversion of ε-CL[b]	$M_{n,SEC}$[c]/ Da	PDI[c]	M_n[d]/Da
1	3.75	95%	7300	1.67	2729
2	7.5	87%	3240	1.80	1250
3	15	90%	3100	1.43	646
4	30	95%	1570	1.67	341

[a] 94.5 mmol ε-CL in 20 ml toluene, 0.5 g Novozyme-435 (0.5 wt% CALB to ε-CL). 90 °C, 3 h. [b] By ^{1}H NMR. [c] By SEC with RI detector calibrated by polystyrene standards. [d] Calculated from glycidol stoichiometry. M_n = [ε-CL]/[glycidol] × $M_{W,\varepsilon\text{-CL}}$ × conversion of ε-CL.

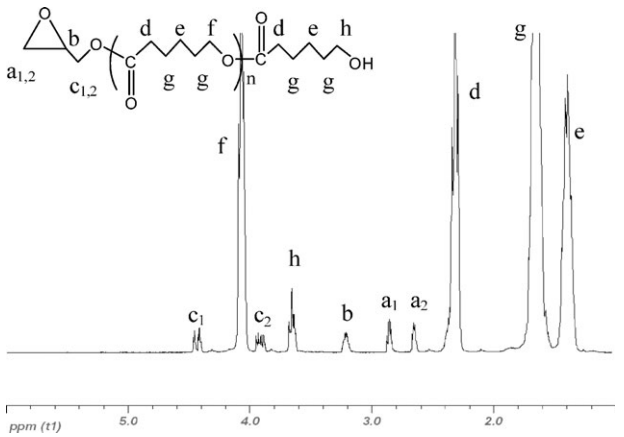


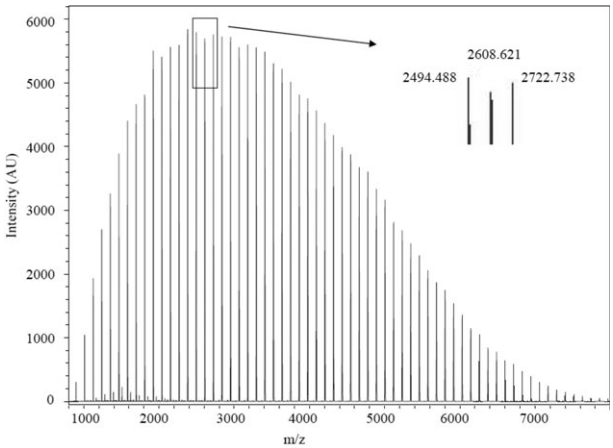
Fig. 1 ^{1}H NMR spectrum of glycidol-initiated PCL (entry 3 in Table 1) clearly demonstrating that the epoxy group remains intact in the final polymer product.

unused. This unused glycidol also explains why the M_n of PCL does not decrease linearly with increasing glycidol concentration.

^{1}H NMR data clearly show the epoxy ring was intact in the polymer product (Fig. 1).

MALDI-TOF MS provided an insight into the molecular structure of the glycidol-initiated PCL (Gly-PCL) (Fig. 2). The masses in the MALDI-TOF MS spectrum were used to determine the end-groups that were present in the polymer. The distribution clearly showed a separation of 114.144 (equivalent to the mass of an ε-CL unit), while the peak masses can be assigned to linear PCL with a glycidol end-group. Importantly, no peaks were found that could be attributed to ether end groups from the epoxy ring-opening of glycidol. Therefore, CALB seems to have selectively catalysed the ring opening of ε-CL, whilst the epoxy ring was not affected. However, when an organometallic species such as $Sn(Oct)_2$ was used, not only was the ring-opening polymerisation of ε-CL observed, but also the epoxy group is ring opened leading to a much more complex MALDI-TOF spectrum with multiple series of masses (see S2.2, ESI†). Therefore, enzymatic polymerisation shows significant advantages over the organometallic route when epoxy functional groups are desired in the final polyester product. This is the first time glycidol has been used as an initiator for the ring-opening polymerisation of ε-CL to yield epoxy-functionalised PCL.

The successful introduction of an epoxy functional group into the PCL chain allows further reaction with CO_2 or anhydride to produce novel copolymers.



m/z values of glycidol initiated PCL with various DP

DP	21	22	23
m/z calculated[a]	2494.094	2608.238	2722.382
m/z detected	2494.488	2608.621	2722.738

[a] $m/z = MW_{CL} \times DP + MW_{Na^+} + MW_{glycidol}$
$= 114.144 \times DP + 22.99 + 74.08$

Fig. 2 MALDI-TOF MS spectrum of glycidol-initiated PCL (entry 2 in Table 1). The peak separation of 114.144 is highlighted (inset). The precise m/z values by theoretical calculation and experimental detection are listed in the table below the figure.

The copolymerisation of epoxides with CO_2 is well known,[6–9] and we now show that Gly-PCL can be copolymerised with CO_2 at 60 °C, 1500 psi for 6 h using ZnO/Glutaric acid as catalyst. The coupling of CO_2 with the epoxy ring should yield polycarbonates, in this case a poly(ethylene carbonate)-graft-poly(ε-caprolactone) (polymer (**1**) in Scheme 1. See ESI† for ^{1}H NMR spectrum (Fig. S-5) and SEC trace (Fig. S-6)).

The copolymersiation of Gly-PCL with succinic anhydride (SA) is a typical A3-B2 polymerisation, which leads to branching. Here, the epoxy ring on the Gly-PCL can be regarded as two –OH groups, with the –OH end group at the PCL chain end being considered as the third –OH site. Therefore, the A3-B2 (3 –OH, 2 –COOH) reaction should lead to a hyperbranched polyester (polymer (**2**) in Scheme 1. See ESI† for ^{1}H NMR spectrum (Fig. S-7) and SEC trace (Fig. S-8)). In this study, the Gly-PCL and SA were copolymerised in bulk at 160 °C with benzyl dimethyl amine (BDMA) as catalyst.

Molecular weight and structure analysis of Gly-PCL, polymer (**1**) and (**2**) was performed by SEC with an RI detector and multi-angle light scattering (MALS) detector. It is well known that calibration by polystyrene (PS) standards can overestimate the M_W of PCL, because linear PCL has a larger hydrodynamic volume than PS at the same M_W. On the other hand, the MALS detector can determine the absolute M_W without calibration. The increase in M_W following copolymerisation was confirmed by both RI and MALS (Table 2), and clearly showed the copolymerisations were successful (the SEC chromatographs can be found in the ESI†, S2.3).

SEC-MALS also provided information on the conformation of the polymer (Fig. 3). The conformation plot compares the root mean square (RMS) radius *versus* the molecular weight obtained by MALS on a logarithmic scale. The slope of the subsequent line gives information on the conformation of the polymer.[23–25]

Table 2 Copolymerisation of epoxy-functionalised PCL with CO_2 (polymer (**1**)) or succinic anhydride (polymer (**2**)): the increase of molecular weight upon copolymerisation is clearly shown

	SEC-RI[a]		SEC-MALS[b]	
Polymer	M_n /Da	PDI	M_n /Da	PDI
Gly-PCL[c]	3 240	1.80	1880	1.40
Polymer (**1**)	10 840	1.69	7030	1.36
Polymer (**2**)	10 390	3.20	11 920	2.03
Gly-PCL[d]	1570	1.67	950	1.33
Polymer (**1**)	5510	1.99	3480	1.68
Polymer (**2**)	8110	2.49	8960	1.74

[a] Calibrated using polystyrene standards. [b] The dn/dc value for PCL is 0.075 ml g^{-1}. Because the copolymer samples measured here consist of over 90% PCL in molar ratio, the dn/dc value of PCL was also used for the copolymers as a simplification. [c] Entry 2 in Table 1. [d] Entry 4 in Table 1.

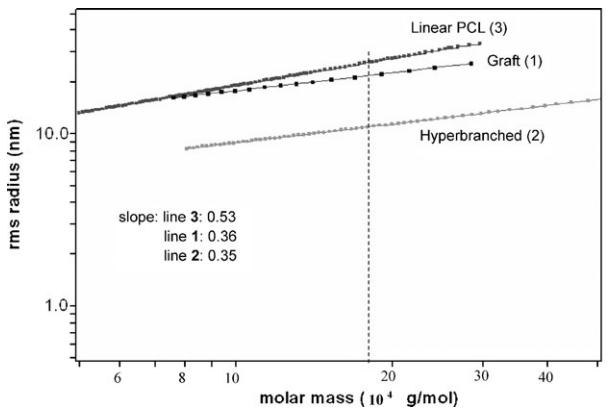


Fig. 3 Conformation plot of linear PCL (**3**), graft copolymer (**1**) and hyperbranched copolymer (**2**).

Generally, linear polymers exhibit a slope of 0.5–0.6; and spherical molecules such as hyperbranched polymers have slopes around 0.33. In the conformation plot (Fig. 3), the linear PCL has a slope of 0.53, which indicates the expected random coil, while polymers (**1**) and (**2**) have values of 0.35 and 0.36, respectively, suggesting that graft polymer and hyperbranched polymer have been formed.

A further interesting observation from the conformation plot is seen if we draw a vertical line to intersect the three conformation curves (1, 2 and 3). These crosspoints have the same M_W, while the RMS radius or the size of the molecules are clearly different. The order of RMS radii of linear polymer (**3**) > graft polymer (**1**) > hyperbranched polymer (**2**) is exactly what we would predict from the conformations of these molecules in solution. Spherical molecules have a smaller RMS radius than the random coil counterpart at the same M_W (see S2.3, ESI†). Furthermore, the closer to spherical the molecule, the smaller the RMS radius, and again we predict that at the same M_W the hyperbranched polymer (**2**) would be more spherical than the graft polymer (**1**), which should also be more spherical than the linear (**3**). These trends again would seem to reinforce our conclusions that graft and hyperbranched polymer have been successfully synthesised from the intact epoxy moiety on the enzymatically synthesised linear PCL chains.

In conclusion, we present the first example of the successful use of glycidol as an initiator for ring-opening polymerisation of ε-caprolactone, where the epoxy ring remains intact, whilst the ring-opening polymerisation of ε-CL successfully yields epoxy-functionalised poly(ε-caprolactone). The epoxy-functionalised PCL was subsequently copolymerised with CO_2 or anhydride to produce novel graft or hyperbranched copolymers. The structure of the epoxy-functionalised PCL was analysed by ^{1}H NMR and MALDI-TOF MS, and the formation of graft or hyperbranched copolymers was confirmed by ^{1}H NMR and SEC-MALS.

This research was funded by Marie Curie Research Training Network (BIOMADE, Contract no. MRTN-CT-2003-505147) (JZ and SV). KJT acknowledges the Royal Commission for the Exhibition of 1851 for a research fellowship. The suggestions and advice from Dr A. Heise and Prof. C. E. Koning are highly appreciated. We thank Dr K. Jackson of Wyatt Technology for the help on the SEC-MALS analysis.

Notes and references

1 W. Hartmeier, *Trends Biotechnol.*, 1985, **3**, 149–153.
2 E. Katchalskikatzir, *Trends Biotechnol.*, 1993, **11**, 471–478.
3 R. Marie, S. Schmid, A. Johansson, L. E. Ejsing, M. Nordstrom, D. Hafliger, C. B. V. Christensen, A. Boisen and M. Dufva, *Biosens. Bioelectron.*, 2006, **21**, 1327–1332.
4 R. Murugan and S. Ramakrishna, *Biomaterials*, 2004, **25**, 3073–3080.
5 C. Preininger, L. Bodrossy, U. Sauer, R. Pichler and A. Weilharter, *Anal. Biochem.*, 2004, **330**, 29–36.
6 D. J. Darensbourg, *Chem. Rev.*, 2007, **107**, 2388–2410.
7 G. W. Coates and D. R. Moore, *Angew. Chem., Int. Ed.*, 2004, **43**, 6618–6639.
8 D. J. Darensbourg and M. W. Holtcamp, *Coord. Chem. Rev.*, 1996, **153**, 155–174.
9 D. J. Darensbourg, R. M. Mackiewicz, A. L. Phelps and D. R. Billodeaux, *Acc. Chem. Res.*, 2004, **37**, 836–844.
10 R. Tadros and D. C. Timm, *Macromolecules*, 1995, **28**, 7441–7446.
11 S. Vyazovkin and N. Sbirrazzuoli, *Macromol. Chem. Phys.*, 1999, **200**, 2294–2303.
12 A. Olsson, M. Lindstrom and T. Iversen, *Biomacromolecules*, 2007, **8**, 757–760.
13 A. Finne and A. C. Albertsson, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 444–452.
14 X. H. Chen, S. P. McCarthy and R. A. Gross, *Macromolecules*, 1998, **31**, 662–668.
15 D. Mecerreyes, R. Jérôme and P. Dubois, in *Macromolecular Architectures*, ed. J. G. Hilborn, Springer, Berlin/Heidelberg, 1999, pp. 1–59.
16 A. C. Albertsson and I. K. Varma, *Biomacromolecules*, 2003, **4**, 1466–1486.
17 R. A. Gross, A. Kumar and B. Kalra, *Chem. Rev.*, 2001, **101**, 2097–2124.
18 S. Kobayashi, H. Uyama and S. Kimura, *Chem. Rev.*, 2001, **101**, 3793–3818.
19 S. Matsumura, in *Enzyme-Catalyzed Synthesis of Polymers*, ed. S. Kobayashi, H. Ritter and D. Kaplan, Springer, Berlin/Heidelberg, 2006, pp. 95–132.
20 A. Duda, A. Kowalski, S. Penczek, H. Uyama and S. Kobayashi, *Macromolecules*, 2002, **35**, 4266–4270.
21 S. Namekawa, S. Suda, H. Uyama and S. Kobayashi, *Int. J. Biol. Macromol.*, 1999, **25**, 145–151.
22 L. van der Mee, F. Helmich, R. de Bruijn, J. Vekemans, A. R. A. Palmans and E. W. Meijer, *Macromolecules*, 2006, **39**, 5021–5027.
23 S. Podzimek and T. Vlcek, *J. Appl. Polym. Sci.*, 2001, **82**, 454–460.
24 S. Podzimek, *Am. Lab.*, 2002, **34**, 38.
25 S. Grcev, P. Schoenmakers and P. Iedema, *Polymer*, 2004, **45**, 39–48.

