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ARTICLE

Synthesis of aliphatic polycarbonates with a tuneable thermal response.

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Thermally-responsive polymers have been widely studied, however access to materials in which both the thermal response can be tuned and in which the backbone is ultimately biodegradable is limited. To this end, a range of well-defined homopolymers of 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC) were prepared using a dual organocatalytic ring-opening polymerisation methodology. Post-polymerisation functionalisation of PAOMEC with thiols bearing a range of functional groups was optimised *via* photoinitated radical thiol-ene coupling reactions. The inclusion of thiol-terminated poly(ethylene glycol) (PEG) enabled the synthesis of polycarbonates that exhibit a lower critical solution temperature (LCST). This approach enables the facile modification of the cloud point of these materials to create a library of thermally-responsive polymers, achieved by simply varying the molecular weight of the PEG chains and grafting blends of PEG to PAOMEC.

Introduction

The use of aliphatic polycarbonates for biomedical applications has long been the subject of considerable interest, as a consequence of their low toxicity, biocompatibility and biodegradability.[1-8] In particular, recent research has focussed on the ability to vary the pendent groups on the polymer backbone, thereby providing fine control over the physical properties of the polymer and potentially enabling further functionalisations to be performed, or providing a method of generating stimuli-responsive materials for drug delivery applications.[4, 5]

Of the routes by which aliphatic polycarbonates can be accessed, the ring-opening polymerisation (ROP) of cyclic carbonate monomers, generally derived by the ring-closing of appropriate diol precursors, presents perhaps the most simple and versatile.[9-13] Importantly, functionality can be incorporated into the resultant polymers by the inclusion of a functional group in the cyclic monomer, which is then retained after ROP. In order to overcome the limitations of incompatible functional groups or low activity as a result of bulky side chain groups, the synthesis of polymers with simple pendent groups that readily undergo post-polymerisation modification is attractive.[4, 5] To this end, a wide range of polycarbonates bearing functionalities including allyl,[4, 14-19] alkyne,[20-24] azide,[25] norbornene,[26, 27] activated ester,[11, 28] and maleimide groups,[29, 30] amongst others[25, 31-34] have all been studied. Sequential post-polymerisation modifications to introduce multiple different functionalities onto a single homopolymer have also been performed, further demonstrating the power of post-polymerisation modification in the production of functional materials.[26]

Amongst the array of possible monomers, those that are accessible in the least, and most simple synthetic steps will be the most attractive to translate towards application. To this end, 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC) presents the ability to be synthesised in a single step from a commercially available diol, thus avoiding the time consuming and low yielding multistep syntheses of many analogues. First reported by Kühling *et al.*,[15, 35] Olsén and coworkers more recently demonstrated the synthesis of AOMEC by ring-closing depolymerisation of the diol precursor.[16, 36] Polymerisation by both organometallic using $SnOct_2$ and organic catalysts, using TBD, is possible in bulk to yield materials with molecular weights (M_n) of up to 15,000 g mol^{-1} and dispersities ($Đ_M$) ranging from 1.09 to 1.5. Accessibility of the alkene group for post-polymerisation functionalisation was also demonstrated by radical thiol-ene addition with 1-dodecanethiol.[16]

The ability to functionalise polycarbonates post-polymerisation offers the possibility to create advanced polycarbonate-based materials, including thermoresponsive materials. Varying the proportion of hydrophobic and hydrophilic components of a block or graft copolymer has been reported to affect the lower critical solution temperature (LCST), below which the polymer and water phases are miscible, and above which they are immiscible.[37-39] For example, work by Lutz *et al.* demonstrated that by varying the number of pendent ethylene glycol repeat units in

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poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMA), fine control could be achieved over the LCST of the polymer, with values ranging from 26 to 90 °C. Further work by the same researchers showed that by copolymerising POEGMAs possessing different numbers of ethylene glycol repeat units, the LCST of the polymers could be further tailored.[40, 41] Whilst thermoresponsive polycarbonates and polyesters possessing pendent PEG chains have been prepared both through the ring-opening of PEG-bearing monomers[42-46] and the post-polymerisation modification of functional polymers,[26, 28, 47] the ability to fully harness the tuneability in thermal properties has not been demonstrated to date.

Herein, we show that the synthesis and subsequent ROP of AOMEC using a dual organocatalytic system provides a simple two step method to present well-defined aliphatic polycarbonates bearing pendent allyl ether groups. Conditions for thiol-ene addition of less-activated thiols were optimised, enabling us to generate a thermoresponsive polycarbonate. Using a grafting-to approach presents the ability to modify the cloud point of the resulting materials, and is demonstrated by simple modification of the average molecular weight of the pendent PEG chains as well as by blending of different PEG chain lengths.

Experimental

Materials

All chemicals and solvents, unless otherwise stated, were ordered from Sigma-Aldrich or Fisher Scientific and used without further purification. Silica gel (pore size = 40 Å) was obtained from Fischer Scientific and used as received. Dry toluene, tetrahydrofuran and dichloromethane were obtained by purification over an Innovative Technology SPS alumina column and degassed by repeated freeze-pump-thawing prior to use. 3-Mercaptopropionic acid was ordered from Alfa Aesar and used as received. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was dried over CaH_2, distilled, and stored under an inert atmosphere of N_2. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was dried by sublimation and stored under an inert atmosphere of N_2. $CDCl_3$, benzyl alcohol and 1,4-butanediol were dried over 3 Å molecular sieves and stored under an inert atmosphere of N_2. 1,4-Benzenedimethanol (BDM) (Tokyo Chemical Industry) and poly(ethylene glycol) (PEG) (number-average molecular weight (M_n) = 2,000 g mol^{-1}) were dried over 3 Å molecular sieves in dry dichloromethane, and stored under an inert atmosphere of N_2 following the removal of sieves by cannula filtration and the removal of solvent under reduced pressure. Pentaerythritol dibenzyl ether (PDE) was synthesised as reported,[48] and sublimed three times before storage under an inert atmosphere of N_2. 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (TU)[49] was synthesised as previously reported and dried over CaH_2 in dry tetrahydrofuran. TU was isolated by removal of the drying agent *via* cannula filtration, followed by removal of the solvent under reduced pressure, and stored under an inert atmosphere of N_2. *L*-Lactide (Corbion Purac) was purified by passing a solution of the crude material in dichloromethane through a silica plug and recrystallising from toluene, followed by dissolution in dry dichloromethane and drying over two sets of 3 Å molecular sieves. The solution was then removed from sieves by cannula filtration, followed by removal of the solvent under reduced pressure. The *L*-lactide was recrystallised from dry toluene and the solvent removed thoroughly under reduced pressure before storage in an N_2 glovebox. Acidic Amberlyst 15 ion exchange resin was washed repeatedly with methanol and air-dried prior to use. Irgacure 369 photoinitiator was obtained from BASF and stored in a light-free environment prior to use.

General considerations

All polymerisations were performed under an inert N_2 atmosphere in an MBraun glovebox. NMR spectra were recorded on a Bruker Avance III 400 MHz, Avance III HD 400 MHz or Avance III HD 500 MHz spectrometer at 293 K. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the residual solvent signal ($CDCl_3$: ^{1}H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm, $(CD_3)_2SO$: ^{1}H, δ = 2.50 ppm, ^{13}C, δ = 39.52 ppm, $(CD_3)_2CO$: ^{1}H, δ = 2.05 ppm, ^{13}C, δ = 29.84 ppm (CD_3), 206.26 ppm (CO). High resolution mass spectrometry was performed on a Bruker UHR-Q-ToF MaXis spectrometer with electrospray ionisation. MALDI-ToF (matrix-assisted laser desorption ionisation-time of flight) mass spectrometry analysis was performed on a Bruker Daltonics Ultraflex II mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) was used as a matrix (0.6 µL of a 10 g L^{-1} solution in tetrahydrofuran), with sodium trifluoroacetate used as a cationisation agent (0.6 µL of a 10 g L^{-1} solution in tetrahydrofuran). Analyte (0.3 µL of a 5 g L^{-1} solution in tetrahydrofuran) was applied in between separate loadings of DCTB and sodium trifluoroactetate, with solvent being allowed to evaporate between applications, to form a thin matrix-analyte-matrix film. All samples were measured in reflectron mode and calibrated against a 2000 g mol^{-1} poly(ethylene glycol) standard. Size exclusion chromatography (SEC) was conducted on systems composed of a Varian 390-LC-Multi detector suite fitted with differential refractive index (RI), light scattering, and ultraviolet detectors, equipped with a guard column (Varian Polymer Laboratories PLGel 5 µM, 50 × 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 µM, 300 × 7.5 mm). The mobile phase was either $CHCl_3$ (HPLC grade) with 0.5% triethylamine, or dimethylformamide (DMF), with a flow rate of 1.0 mL min^{-1}. SEC samples were calibrated against either Varian Polymer Laboratories Easi-Vials linear poly(styrene) standards (162 – 2.4 × 10^5 g mol^{-1}) ($CHCl_3$ SEC), or linear poly(methyl methacrylate) standards (556 – 1.8 × 10^6 g mol^{-1}) (DMF SEC) using Cirrus v3.3 software. IR spectra were obtained using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Photoinitiated post-polymerisation functionalisations were carried out in a Metalight QX1 light box equipped with 12 × 9 W bulbs with a

peak output at λ = 365 nm. Samples were typically placed 10 cm away from the source with the bulbs arranged concentrically around them. Lower critical solution temperature (LCST) and cloud point measurements were recorded using a Perkin-Elmer UV-Vis Spectrometer (Lambda 35) equipped with a Peltier temperature control system, using a wavelength of 500 nm and a heating/cooling rate of 1 °C min^{-1}. Transmittance curves were normalised to 100% for clarity, and the cloud point of each sample measured at 50% of normalised transmittance.

Synthetic procedures

Synthesis of 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC). Trimethylolpropane allyl ether diol (60 mL, 348 mmol) was dissolved in dichloromethane (1 L) in a 2 L round-bottomed flask, which was cooled to 0 °C. Ethyl chloroformate (99 mL, 1.038 mol) was then added and the solution stirred at 0 °C for 30 minutes. Triethylamine (145.2 mL, 1.038 mol) was added dropwise over a period of 1 h. The reaction was then allowed to warm to room temperature and stirred for 12 h, at which point the reaction mixture was filtered and concentrated under reduced pressure. The resulting oil was dissolved in ethyl acetate (200 mL) and washed with 1 M HCl (2 × 200 mL) followed by water (2 × 200 mL). The organic fraction was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude product was purified by vacuum distillation twice to yield pure AOMEC as a colourless oil (yield = 50.9 g, 254 mmol, 73%). The product was dried over CaH_2, recovered by vacuum distillation and stored in a glovebox for use as monomer. Literature contains information on ^{1}H and ^{13}C NMR spectra only, which are in agreement with acquired data.[35] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.84-5.74 (m, 1H, CH_2-C*H*=CH_2), 5.22-5.11 (m, 2H, CH=C*H*$_2$), 4.28-4.01 (dd, $^2J_{H\text{-}H}$ = 72.9 Hz, $^3J_{H\text{-}H}$ = 10.9 Hz, 4H, O-C*H*$_2$-C-C*H*$_2$-O), 3.91 (d, $^3J_{H\text{-}H}$ = 5.6 Hz, 2H, O-C*H*$_2$-CH), 3.34 (s, 2H, C-C*H*$_2$-O), 1.49 (q, $^3J_{H\text{-}H}$ = 7.6 Hz, 2H, C-C*H*$_2$-CH_3), 0.85 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, -CH_2-C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5 (O-*C*(O)-O), 134.0 (CH_2-*C*H=CH_2), 117.4 (CH=*C*H_2), 72.8 (O-*C*H_2-C), 72.3 (O-*C*H_2-CH), 68.2 (C-CH_2-O), 35.4 (*C*$(CH_2)_4$), 23.2 (CH_3-*C*H_2), 7.3 (*C*H_3-CH_2). MS (ESI, +ve): *m/z* 200.1039 (M+). Anal. calcd for $C_{10}H_{16}O_4$: C 60.0; H 8.1; N 0.0%. Found: C 59.9; H 8.0; N 0.1%. FT-IR: max/cm^{-1} 2910 (C=*C(H)*$_2$) 1746 (O-*C(O)*-O), 1170 (H_2*C*-*O*-*C*H_2), 1109 and 1090 (C-*C(H)=C(H)*$_2$).

General procedure for the synthesis of poly(2-allyloxymethyl-2-ethyltrimethylene carbonate (PAOMEC) by DBU/TU-catalysed ring-opening polymerisation (ROP). In a typical experiment, the alcohol initiator (0.35-10 mol% to monomer dependent on $[M]_0$:$[I]_0$), 1,8-diazabicyclo[5.4.0]undec-7-ene (5 mol% to monomer) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (5 mol% to monomer) catalysts were dissolved in dry $CDCl_3$ or dichloromethane. AOMEC was dissolved separately in the same solvent and added to the initiator/catalyst solution (overall AOMEC concentration = 2 M). Conversion of monomer to polymer was monitored by ^{1}H NMR spectroscopy. At 80% monomer conversion, the polymerisation was quenched either by addition of acidic Amberlyst A15 ion exchange resin or by addition of benzoic acid (5 mg per 1 mg of DBU). Polymers were purified either by repeated precipitations into cold *n*-hexane, or by column chromatography using dichloromethane as eluent to remove trace thiourea, followed by ethyl acetate to recover the pure polymer, and subsequent precipitation into cold *n*-hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91-5.77 (m, 1H, CH_2-C*H*=CH_2), 5.28-5.08 (m, 2H, CH=C*H*$_2$), 4.13-4.05 (m, 4H, O-C*H*$_2$-C-C*H*$_2$-O), 3.91 (dd, $^3J_{H\text{-}H}$ = 5.4 Hz, $^2J_{H\text{-}H}$ = 1.7 Hz, 2H, O-C*H*$_2$-CH=CH_2), 3.31 (s, 2H, C-C*H*$_2$-O), 1.47 (q, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, C-C*H*$_2$-CH_3), 0.86 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, CH_2-C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.0 (O-*C*(O)-O), 134.6 (CH_2-*C*H=CH_2), 116.6 (CH=*C*H_2), 72.1 (O-*C*H_2-CH), 69.3 (C(O)-O-*C*H_2), 67.7 (C-*C*H_2-O), 41.8 (*C*$(CH_2)_4$), 22.5 (CH_3-*C*H_2), 7.3 (*C*H_3-CH_2). For $[M]_0$:$[I]_0$ = 24, M_n = 3,800 g mol^{-1} (DP 19, determined by ^{1}H NMR, 400 MHz, $CDCl_3$). M_n = 4,100 g mol^{-1}, $Đ_M$ = 1.09 (determined by SEC using RI detection and $CHCl_3$ as eluent).

General procedure for post-polymerisation functionalisation of PAOMEC with thiol-functional substrates. PAOMEC (20 mg, DP 20, 5 µmol) and thiol-functional substrate (2-10 equivalents to polymer alkene groups, 1-5 mmol) were dissolved in 1,4-dioxane (0.4 mL). The radical photoinitiator, 2-benzyl-2-(dimethylamino)-4'-morpholinobutyrophenone (0.37 mg, 1 µmol) was dissolved separately in the same solvent (0.1 mL) and added to the polymer/thiol solution. The solution was then transferred to an NMR tube, sealed, placed in a UV light box and irradiated with light (λ = 365 nm) for 30 minutes. The functionalised polymer was purified by repeated precipitations into cold methanol to yield the purified product. For PAOMEC grafted with 1-dodecanethiol, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (m, 4H, O-C*H*$_2$-C-C*H*$_2$-O), 3.40 (t, $^3J_{H\text{-}H}$ = 5.4 Hz, 2H, O-C*H*$_2$-CH_2), 3.25 (s, 2H, C-C*H*$_2$-O), 2.48 (t, 2H, O-CH_2-CH_2-C*H*$_2$-S), 2.42 (t, 2H, S-C*H*$_2$-CH_2-CH_2-CH_2), 1.74 (dt, 2H, O-CH_2-C*H*$_2$-CH_2-S), 1.58-1.45 (m, 2H, S-CH_2-C*H*$_2$-CH_2), 1.40 (q, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, C-C*H*$_2$-CH_3), 1.34-1.19 (m, 20H, S-CH_2-CH_2-(C*H*$_2$)$_{10}$-CH_3), 0.81 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 6H, C*H*$_3$-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3 (O-*C*(O)-O), 70.3-70.0 (C-*C*H_2-O-*C*H_2-CH_2), 68.0 (O-*C*H_2-C-*C*H_2-O), 42.0 (O-CH_2-*C*-CH_2-O), 32.3 (O-CH_2-CH_2-CH_2-S-*C*H_2-CH_2), 32.1 (O-CH_2-CH_2-*C*H_2-S-CH_2-CH_2), 29.8-28.9 (O-CH_2-*C*H_2-CH_2-S-CH_2-(*C*H_2)$_{10}$-CH_2-CH_3), 22.8 (CH_3-*C*H_2-C, S-CH_2-(CH_2)$_{10}$-*C*H_2-CH_3), 14.3 (S-CH_2-(CH_2)$_{10}$-CH_2-*C*H_3), 7.7 (*C*H_3-CH_2-C). For DP 24 polymer, M_n = 9,000 g mol^{-1} (determined by ^{1}H NMR, 400 MHz, $CDCl_3$), M_n = 10,600 g mol^{-1}, $Đ_M$ = 1.13 (determined by SEC using RI detection and $CHCl_3$ as eluent). See SI for characterising data of other substitutions.

General procedure for synthesis of thiol-functional poly(ethylene glycol) monomethyl ether (MeO-PEG-SH). The synthesis was performed according to a previously reported procedure.[47] PEG monomethyl ether (9.1 mmol) and 3-MPA (18 mmol) were weighed into a 100 mL round-bottomed flask equipped with a stirrer bar and dissolved in toluene (50 mL), with the solution heated to 80 °C to ensure complete dissolution. 2 drops of H_2SO_4 (18.4 M) were added as catalyst, and the reaction vessel connected to a Dean-

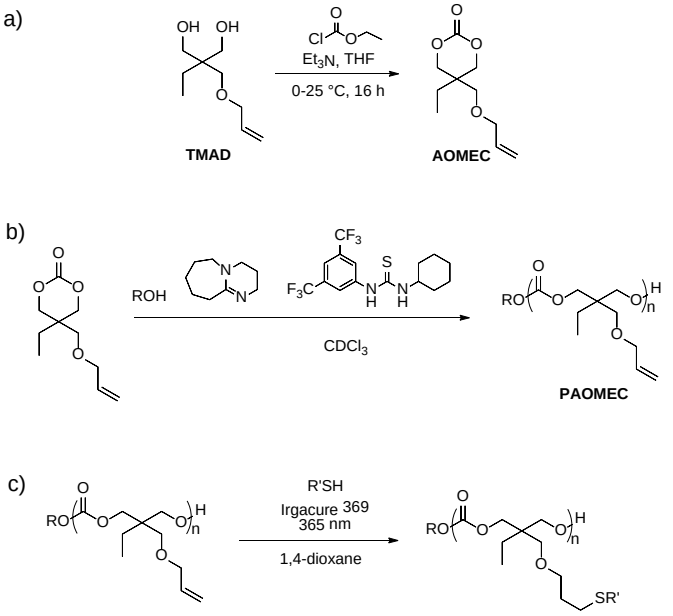
Stark trap equipped with condenser. The reaction mixture was then heated to reflux for 12 h. Upon cooling, the solvent was removed under reduced pressure, and the crude product dissolved in dichloromethane (25 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (3 × 20 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to yield the purified product as a viscous pale yellow oil (for MeO-PEG_{550}-SH, yield = 3.87 g, 6.64 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (t, $^3J_{H\text{-}H}$ = 4.8 Hz, 2H, CH_2-CH_2-O-C(O)), 3.64-3.48 (m, 44H, CH_3-O-(CH_2-CH_2-O)$_{10}$-CH_2-CH_2), 3.37 (s, 3H, CH_3-O-CH_2), 2.76 (q, $^3J_{H\text{-}H}$ = 7.3 Hz, 2H, CH_2-CH_2-SH), 2.68 (t, $^3J_{H\text{-}H}$ = 6.7 Hz, 2H, C(O)-CH_2-CH_2-SH), 1.67 (t, $^3J_{H\text{-}H}$ = 8.3 Hz, 1H, CH_2-CH_2-SH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4 (O-C(O)-CH_2), 71.8-68.9 (CH_3-O-(CH_2-CH_2-O)$_{10}$-CH_2-CH_2), 63.7 (CH_2-CH_2-O-C(O)), 58.9 (CH_3-O-(CH_2-CH_2)$_{10}$), 32.3 (C(O)-CH_2-CH_2-SH), 19.6 (C(O)-CH_2-CH_2-SH). For MeO-PEG_{550}-SH, M_n = 650 g mol^{-1} (determined by ^{1}H NMR, 400 MHz, $CDCl_3$), M_n = 1,100 g mol^{-1}, $Đ_M$ = 1.08 (determined by SEC using RI detection and $CHCl_3$ as eluent).

General procedure for functionalisation of PAOMEC with thiol-functional PEG monomethyl ether. PAOMEC (M_n = 16,400 g mol^{-1}, 40 mg, 2.44 µmol) and MeO-PEG-SH (5 eq. per PAOMEC alkene group) were weighed into a vial equipped with a stirrer bar and dissolved in 1,4-dioxane (0.9 mL). The radical photoinitiator, 2-benzyl-2-(dimethylamino)-4′-morpholinobutyrophenone (0.74 mg, 2 µmol) was dissolved separately using the same solvent (0.1 mL) and added to the polymer/thiol solution. The vial was then sealed, placed in a UV light box and irradiated with light (λ = 365 nm) for 15 minutes. The reaction mixture was then transferred to a 1 mL dialysis vessel, and the solvent allowed to evaporate. The crude product was then immersed in 18.2 MΩ cm^{-1} water, and the vessel covered with a semi-permeable membrane (molecular weight cutoff = 3,000 g mol^{-1}). The sample was then dialysed against 18.2 MΩ cm water for 10 days, with the water changed twice daily. The contents of the dialysis vessel were then transferred to a vial and the water removed under reduced pressure to yield the purified polymer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (t, $^3J_{H\text{-}H}$ = 4.8 Hz, 2H, CH_2-CH_2-O-C(O)), 4.13-4.05 (m, 4H, O-CH_2-C-CH_2-O), 3.64-3.48 (m, 44H, CH_3-O-(CH_2-CH_2-O)$_{10}$-CH_2-CH_2), 3.46 (t, $^3J_{H\text{-}H}$ = 5.4 Hz, 2H, O-CH_2-CH_2), 3.38 (s, 3H, CH_3-O-CH_2), 3.31 (s, 2H, C-CH_2-O), 2.76 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, C(O)-CH_2-CH_2-S), 2.64 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, SH-CH_2-CH_2-C(O)), 2.57 (t, $^3J_{H\text{-}H}$ = 7.2 Hz, 2H, CH_2-CH_2-CH_2-S), 1.82 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H, CH_2-CH_2-CH_2), 1.47 (q, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, C-CH_2-CH_3), 0.87 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, C-CH_2-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0 (CH_2-C(O)-O), 155.2 (O-C(O)-O), 72.3-72.0 (C-CH_2-O-CH_2-CH_2), 70.6-69.8 (O-CH_2-C-CH_2-O, CH_3-O-(CH_2-CH_2-O)-CH_2-CH_2), 63.8 (CH_2-CH_2-O-C(O)-CH_2), 59.1 (CH_3-O-(CH_2-CH_2-O)), 42.0 (O-CH_2-C-CH_2-O), 34.8 (S-CH_2-CH_2-C(O)), 29.6 (O-CH_2-CH_2-CH_2-S), 28.9 (O-CH_2-CH_2-CH_2-S), 26.9 (S-CH_2-CH_2-C(O)), 22.7 (CH_3-CH_2-C), 7.6 (CH_3-CH_2-C). For polymers grafted with MeO-PEG_{550}-SH, M_n = 68,060 g mol^{-1} (determined by ^{1}H NMR, 400 MHz, $CDCl_3$), M_n = 67,800 g mol^{-1}, $Đ_M$ = 1.17 (determined by SEC using RI detection and $CHCl_3$ as eluent).

Results and discussion

Synthesis and polymerisation of 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC)

The allyl-functional carbonate monomer, 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC) was prepared in one step from a cheap and commercially available precursor, trimethylolpropane allyl ether diol (TMAD). The synthesis of the AOMEC monomer was carried out by the ring closure of TMAD by carbonylation using ethyl chloroformate, as previously



Scheme 1. Synthesis of a) 2-allyloxymethyl-2-ethyltrimethylene carbonate (AOMEC) and b) PAOMEC by organocatalysed ROP (ROH = mono- or bifunctional alcohol initiator); c) Post-polymerisation modification of PAOMEC using photoinitiated radical thiol-ene addition chemistry (RSH = thiol-functional substituent)

reported by He *et al.* (Scheme 1a).[35] Purification of the crude liquid monomer was performed by vacuum distillation, with the pure AOMEC recovered as a colourless liquid in 73% yield (Figure S1).

Initial polymerisation studies were performed in $CDCl_3$ at 25 °C with initial monomer to initiator ratio ($[M]_0$:$[I]_0$) = 30, using a bifunctional organocatalytic system of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1 mol%) and 1-(3,5-bis(trifluoromethyl)- phenyl)-3-cyclohexylthiourea (TU, 5 mol%), with benzyl alcohol used as initiator (Scheme 1b). This dual catalyst system was selected over TBD as it has previously been shown to have good activity for the ROP of cyclic carbonates whilst still maintaining excellent control over the polymerisation.[14, 50, 51] Monomer conversion for all polymerisations was monitored by ^{1}H NMR spectroscopy, specifically the change in integral of the methylene signals on the pendent ether group of both the carbonate and polymer (at δ = 3.27 and 3.19 ppm respectively (Figure S2), with number-average molecular weight (M_n) determined by measuring the integral of the CH_2 resonance of the benzyl alcohol (**1**) against either the integral of the methylene on the

ether group (at δ = 3.19 ppm), or the integral of the alkene CH resonance (δ = 5.79 ppm). Interestingly, at [AOMEC] = 1.0 M, the polymerisation proceeded with a linear increase in monomer conversion against time up to 66% (after 45 h), at which point the polymerisation rate decreased rapidly, with no further discernible increase in monomer conversion observed by ^{1}H NMR spectroscopy. In order to increase the polymerisation rate and decrease the equilibrium monomer concentration, the concentration of the monomer in solution was increased to 2 M and the catalyst loading increased to 5 mol% DBU and 5 mol% TU. Under these conditions, ROP of AOMEC ($[M]_0$:$[I]_0$ = 30) achieved 82% monomer conversion in only 150 minutes, after which the polymerisation rate was rapidly retarded. The polymerisation was quenched by addition of acidic Amberlyst 15 ion exchange resin, with purification of the polymer performed by repeated precipitations into cold *n*-hexane. ^{1}H NMR spectroscopy and size exclusion chromatography (SEC) analysis demonstrated that the polymerisation proceeds with good control, (theoretical M_n = 5,000 g mol^{-1}, observed M_n = 5,000 g mol^{-1}, $Đ_M$ = 1.08). The polymerisation study was extended across a range of degrees of polymerisation (DPs), with a linear correlation observed for both M_n against $[M]_0$:$[I]_0$, and M_n against monomer conversion, both characteristic of a living polymerisation (Figure S3 and S4). Across the range of molecular weights and conversions, excellent control was maintained over the polymerisation of the monomer, with dispersities ranging from 1.04 for a DP 230 polymer to 1.17 for DP 10 (Figure 1 and 2).

Various mono- and bifunctional alcohols were demonstrated to be effective initiators for the polymerisation of AOMEC, including 1,4-butanediol (**2**), 1,4-benzenedimethanol (**3**) and pentaerythritol dibenzyl ether (PDE, **4**) (Table 1). The formation of block copolymers in one pot from a PEG macroinitiator, and use of PAOMEC as a macroinitator for the polymerisation of polylactide (PLA) was also demonstrated to be highly efficient (Figures S5 – S8).

Post-polymerisation modification of PAOMEC

Functionalisation of PAOMEC with a selection of thiols that possessed a range of functional groups was investigated. The photoinitiated radical addition of thiols to the pendent alkene groups of the polymer was first attempted using 2 equivalents of 1-dodecanethiol to alkene groups on the polymer backbone ([PAOMEC] = 0.01 M), with 1,4-dioxane as solvent and 2-benzyl-2-(dimethylamino)-4'-morpholinobutyrophenone (Irgacure 369) as a radical initiator (Scheme 1c). After exposure to UV light for 2 h, the reaction had reached completion (> 99.9% reduction in intensity of polymer alkene resonances observed by ^{1}H NMR spectroscopy at δ = 5.84 and 5.18 ppm (Figure S9)), with the molecular weight of the polymer observed to increase by SEC with no broadening of dispersity observed ($Đ_M$ = 1.10, Figure S10). MALDI- ToF mass spectrometry was performed on both a

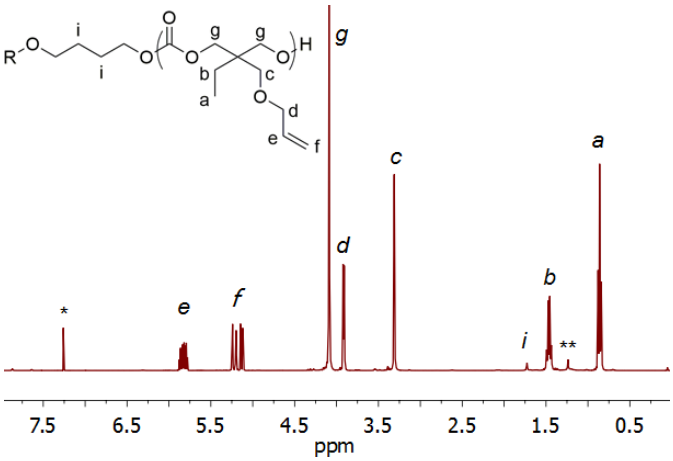


Figure 1. ^{1}H NMR spectrum of DP 42 PAOMEC initiated from 1,4-butanediol, using a catalyst system of 5 mol% DBU and 5 mol% TU (400 MHz, 293 K, $CDCl_3$; * = residual $CHCl_3$ from d-solvent, ** = residual hexane from precipitation).

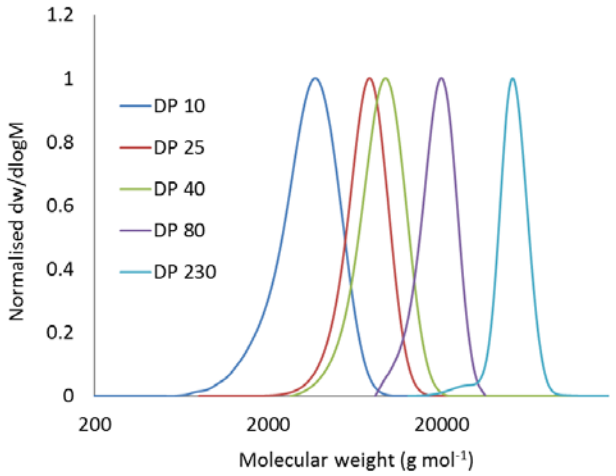


Figure 2. SEC chromatograms of polymers initiated from pentaerythritol dibenzyl ether (PDE), with $[M]_0$:$[I]_0$ ranging from 12 to 290 to give polymers with DPs of 11 to 232, and $Đ_M$ values ranging from 1.17 to 1.04. Samples measured against polystyrene standards using $CHCl_3$ as eluent.

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Table 1. Polymers of AOMEC initiated from different mono- and bifunctional alcohol initiators[a]

Initiator	$[M]_0:[I]_0$[b]	Conversion (%)[b]	Time (h)	Theor. M_n (g mol^{-1})[c]	DP[b]	M_n (g mol^{-1})[b]	$Đ_M$[d]
1	25	80	3	4,000	21	4,200	1.10
2	20	84	3	3,400	17	3,400	1.16
3	62.5	82	6	10,200	49	9,800	1.09
4	12	86	1.5	2,000	11	2,200	1.17
4	25	87	3	4,400	22	4,400	1.09
4	50	82	6	8,200	40	8,000	1.14
4	100	77	10	15,400	77	15,400	1.13
4	290	80	24	46,400	232	46,400	1.04

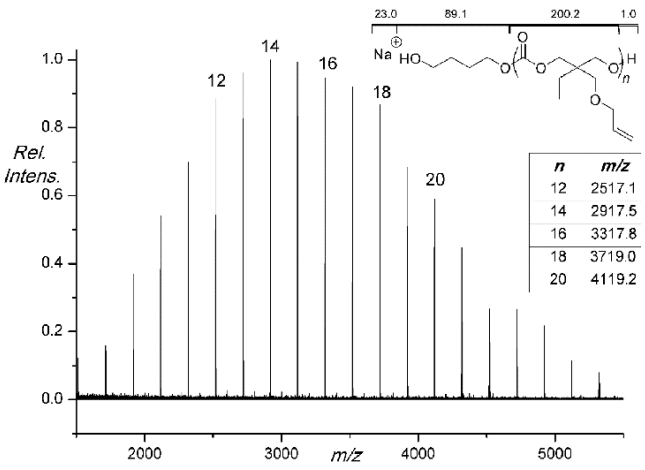
[a] Polymerisations performed in $CDCl_3$ at 25 °C, [AOMEC] = 2.0 M, using 5 mol% DBU and 5 mol% TU. [b] $[M]_0:[I]_0$, monomer conversion, degree of polymerisation and number average molecular weight determined by ^{1}H NMR spectroscopy. [c] Theoretical M_n calculated from $[M]_0:[I]_0$ × monomer conversion × molecular weight of AOMEC (200.23 g mol^{-1}). [d] Determined by SEC analysis against polystyrene standards, using $CHCl_3$ as eluent.

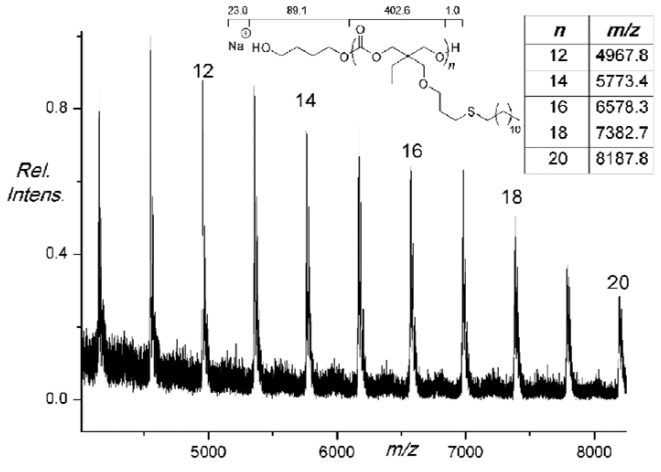
DP 20 sample of PAOMEC, and a sample of the same polymer post-functionalisation with 1-dodecanethiol. The distribution plot for the unfunctionalised polymer shows a spacing of 200 *m/z* between signals, equivalent to one AOMEC unit (Figure 3, top). The peak at *m/z* 2916 represents a DP 14 polymer chain initiated from 1,4-butanediol and carrying a charged sodium ion. The distribution for the functionalised PAOMEC has a spacing of 402 *m/z* between signals, with the peak appearing at *m/z* 5751 representative of the equivalent 1-dodecanethiol-functionalised DP 14 polymer chain (Figure 3, bottom). The absence of significant signals between distributions for the functionalised polymer further suggests that near-quantitative functionalisation takes place.

The thiol-ene reaction was also undertaken with benzyl mercaptan (BnSH) and 3-mercaptopropionic acid (3-MPA) in order to broaden the range of pendent functionalities on the polymer to include those not compatible with ROP. However, a broadening of dispersity was observed for the reactions with both BnSH and 3-MPA ($Đ_M$ BnSH = 1.54, 3-MPA = 1.23), possibly as a result of the electron-deficient nature of these thiols reducing the reactivity of the radical, thus making the radical addition less efficient and allowing cross-linking between the allyl groups on the polymer backbone to become competitive. To overcome the problem of unwanted crosslinking, the equivalents of thiol to pendent alkene groups on the polymer backbone and the exposure time to UV were varied. While varying the exposure time had no discernible effect on the degree of crosslinking taking place during the reaction (Figure S11), it did reveal that the radical addition was complete in as little as 10 minutes. Koo and co-workers have previously reported that increasing the concentration of thiol relative to alkene groups can reduce the number of side-reactions which occur in radical thiol-ene additions,[52] and indeed increasing the thiol concentration was found to greatly improve the efficiency of PAOMEC functionalisation (Figures S12 and S13). Using 10 equivalents of thiol and 30 minutes of exposure time, BnSH and 3-MPA-functionalised polymers with narrow dispersities were successfully produced (Table 2, Figures S14 – S16).

Synthesis of a PAOMEC-based thermoresponsive polymer

In order to create thermally responsive aliphatic polycarbonates, we chose to graft the hydrophilic poly(ethylene glycol) monomethyl ether (MeO-PEG-OH) (M_n = 550 g mol^{-1}) to the hydrophobic PAOMEC. The ability to graft less-activated thiols allowed the application of MeO-PEG-OH modified with 3-mercaptopropionic acid (Figure S17) to present a thiol- terminated PEG (MeO-PEG$_{550}$-SH). While SEC analysis of MeO-PEG$_{550}$-SH (Figure S18) revealed the presence of a peak at





n	m/z
12	4967.8
14	5773.4
16	6578.3
18	7382.7
20	8187.8

Figure 3. MALDI-ToF MS of PAOMEC (DP 20), measured in reflectron mode (top), and MALDI-ToF MS of PAOMEC post-functionalisation with 1-dodecanethiol, measured in linear mode (bottom).

double molecular weight of the main peak, likely indicative of the presence of a small amount of disulfide-linked PEG chains in the polymer, the low quantity present and large excess of thiol used in the functionalisation deemed it unnecessary to remove this minor disulfide impurity from the PEG-thiol. Grafting MeO-PEG_{550}-SH onto DP 82 PAOMEC by photoinitiated radical thiol-ene addition under the same conditions described above ([PAOMEC] = 0.01 M, 1,4-dioxane as solvent and Irgacure 369 as a radical initiator, 5 eq. SH) was complete after 10 minutes of exposure to UV light. The reaction mixture was dialysed against water (molecular weight cut-off = 3,500 g mol^{-1}) in order to

Table 2. Photoinitiated radical thiol-ene post-polymerisation modification of PAOMEC[a]

Polymer	Thiol	Thiol Equivalents	M_n (g mol^{-1})[b]	$Đ_M$
$PAOMEC_{19}$	-	-	3,800	1.09[c]
$PAOMEC_{24}$	-	-	4,800	1.11[c]/1.14[d]
$PAOMEC_{79}$	-	-	15,800	1.13[c]/1.12[d]
$PAOMEC_{24}$	1-Dodecanethiol	2	9,000	1.13[c]
$PAOMEC_{79}$	1-Dodecanethiol	2	30,000	1.12[c]
$PAOMEC_{19}$	3-MPA	10	6,000	1.12[d]
$PAOMEC_{79}$	3-MPA	10	24,800	1.10[d]
$PAOMEC_{19}$	BnSH	10	5,800	1.18[d]
$PAOMEC_{79}$	BnSH	10	25,600	1.16[d]

[a] [PAOMEC] = 0.01 M in 1,4-dioxane, 20 mol% Irgacure 369, exposure to UV light (λ = 365 nm) for 30 minutes. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by SEC against polystyrene standards using $CHCl_3$ as eluent. [d] Determined by SEC against poly(methyl methacrylate) standards using DMF as eluent.

remove unreacted MeO-PEG_{550}-SH. Dialysis for 10 days was found to be required to completely remove unreacted PEG. Analysis of the recovered product by ^{1}H NMR spectroscopy and SEC (Figure S19 and Figure 4) revealed that the reaction was successful, with > 99.9% reduction in intensity of polymer alkene resonances at δ = 5.84 and 5.18 ppm and the appearance of resonances corresponding to PEG (δ = 3.58 ppm). Comparison of the integrals for the PEG resonances and the methyl resonance of the PAOMEC backbone indicates an average of 11.5 ethylene glycol repeat units grafted onto each alkene functional group, corresponding closely to the average number of ethylene glycol repeat units present in the MeO-PEG_{550}-SH precursor (11.8). The slight discrepancy is most likely a result of some unfunctionalised alkene groups and the presence of a small amount of crosslinking occurring during functionalisation.

A solution of PAOMEC-*g*-PEG_{550}-OMe in water (3mg/mL) was prepared for measurement of the cloud point of the polymer by turbidimetry, using UV-Vis spectrometry (measured at 50% transmittance), scanning across a temperature range of 7 to 80 °C. Using a detection wavelength of 500 nm, the cloud point of the solution was determined to be 76 °C upon both heating and cooling, with a very low degree of hysteresis (Figure 5 and S20). This low level of hysteresis, combined with the sharp change in transmittance, indicates that the polymer undergoes rapid dehydration and rehydration above and below the LCST respectively. The effect of changing the length of the grafted PEG branches on the LCST of the polymer was also investigated. As anticipated, shorter PEG branches reduced the cloud point as a consequence of the increased hydrophobicity of the graft copolymer, thus lowering the degree of interaction between the polymer and the solvent, and consequently reducing the temperature at which the material would become immiscible in water. To this end, PAOMEC-*g*-PEG_{350}-OMe displayed a cloud point of 46 °C, while PAOMEC-*g*-PEG_{210}-OMe displayed a further reduced cloud point of just 13 °C (Figure 5).

Having successfully demonstrated that the cloud point of the graft copolymer could be varied by changing the length of the grafted PEG chains, we next attempted to precisely control the cloud point of the polymer by simultaneous grafting of PEGs with two different chain lengths to the same PAOMEC

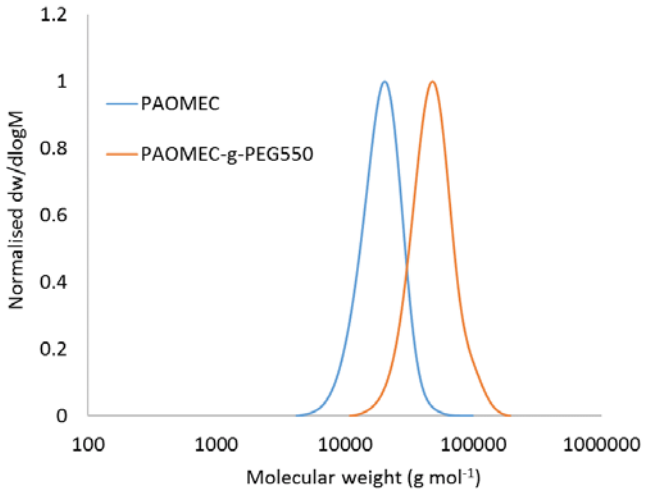


Figure 4. SEC traces of PAOMEC (M_n = 17,700 g mol^{-1}, $Đ_M$ = 1.13) and PAOMEC-*g*-PEG_{550}-OMe (M_n = 67,800 g mol^{-1}, $Đ_M$ = 1.17). Samples measured against polystyrene standards using $CHCl_3$ as eluent.

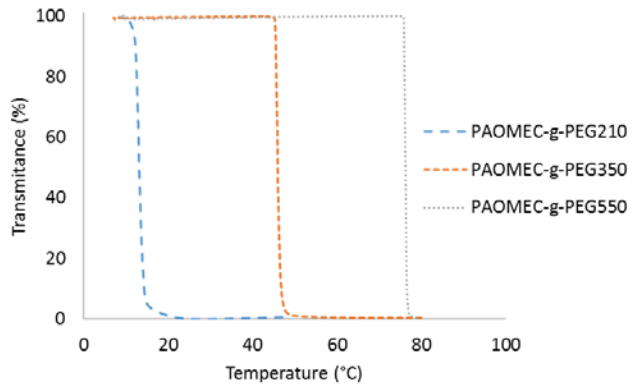


Figure 5. Plots of normalised transmittance as a function of temperature for PAOMEC-*g*-PEG-OMe with various PEG molecular weights.

backbone. Attempts to create intermediate cloud points by grafting < 1 eq. PEG to the backbone were thwarted by the low reactivity of the 3-MPA-terminated PEG that led to significant crosslinking between chains. Instead, addition of 2.5 equivalents of MeO-PEG_{550}-SH, and 2.5 equivalents of MeO-PEG_{350}-SH enabled tuning of the cloud point with a high level of control. ^{1}H NMR spectroscopic analysis confirmed that the average M_n of the PEG arms was 436 g mol^{-1} (expected M_n = 450 g mol^{-1}). The LCST of the polymer was found to be 65 °C, closely matching the trend displayed by PAOMEC grafted with only single PEG chain lengths and demonstrates the possibility to create intermediate thermal transitions by a simple blending approach (Figure 6 and S22).

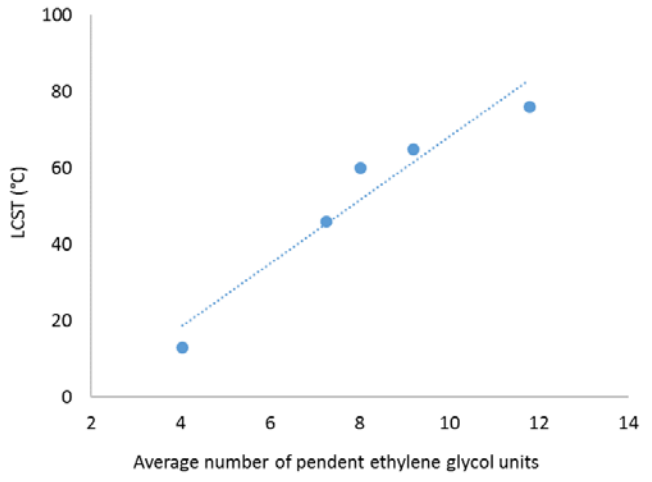


Figure 6. Plot demonstrating linear correlation between polymer LCST and average number of PEG repeat units for PAOMEC-g-PEG-OMe.

Conclusions

The synthesis and polymerisation of AOMEC and the subsequent post-polymerisation modification of the polymer provides a route to a range of polycarbonates bearing various pendent functionalities in just three steps, providing a facile and low-cost route for the synthesis of this versatile class of materials. The ROP of AOMEC by a dual organocatalytic approach provides outstanding control over the molecular parameters of the process providing high molecular weight polymers with narrow dispersities. The post-polymerisation modification methodology enables ready access to thermally-responsive degradable aliphatic polycarbonates that overcome the challenges of synthesising multiple monomers and understanding their often complex (co)polymerisation behaviour. Importantly, the versatile photoinitiated radical thiol-ene coupling chemistry provides the ability to generate a range of polycarbonates for potential drug delivery applications with predictably tuned thermal response by a simple 'mix and match' approach to PEG side-chain grafting.

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