Apple *et al*. “Biodegradable nanogel star polymers via organocatalytic ROP”

Supplementary Information:

General procedures

^{1}H NMR spectra were obtained on a Bruker Avance 2000 spectrometer (^{1}H, 400 MHz) using 5 mm o.d. tubes and were referenced to internal solvent residue ($CDCl_3$: ^{1}H = 7.26 ppm). Typical sample concentration was 20 mg / mL. All NMR spectra were recorded at ambient temperature using standard Bruker library pulse programs and are reported as the fully proton-decoupled spectra. The following abbreviations for multiplicity are used: s, singlet; m, multiplet; br, broad. Analytical Gel Permeation Chromatography (GPC) using Waters high resolution columns HR1, HR2, HR4E and HR5E (flow rate 1 mL / min, THF) in conjunction with a Waters 996 photodiode array and / or a Waters 411 differential refractometer was used to determine molecular weight distributions, M_w/M_n, of polymer samples with respect to linear polystyrene standards. Dynamic Light Scattering (DLS) measurements provided M_w, M_w/M_n, and average hydrodynamic radii, R_h, using the afore-mentioned column set with a Wyatt DAWN EOS multi-angle light-scattering detector, QELS quasi elastic light scattering detector and Optilab (intraferometric refractometer). Differential Scanning Calorimetry (DSC) was conducted using a TA Instruments Q1000 calorimeter (heating rate 5 °C / min). Thermogravimetric analyses (TGA) were conducted on using a TA Instruments TGA 2950 analyzer (heating rate 5 °C / min). Deuterated solvents were purchased from Cambridge Isotopes, Inc. and used as received. Benzyl alcohol **1**, δ-valerolactone **2**, and 1,5,7-triaza-bicyclo[4.4.0]dec-5-ene **3** were purchased from the Aldrich Chemical Co. and either used as received for **3**, purified by sublimation. Solvents were either used as obtained from a Pure Solv solvent dispenser supplied by Innovative Technology, Inc., or purchased from the Aldrich Chemical Co. and purified by standard literature procedures. All other chemicals were used as obtained from commercial sources and used as received.

General Methods:

Synthesis of 5,5’-Bis(oxepanyl-2-one) (BOP) 4.[1] 4,4’-Bicyclohexanone (20.0 g, 102.8 mmol) was slowly added over 10 minutes to a solution of urea-hydrogen peroxide ($CO(NH_2)_2.H_2O_2$) (40.0 g, 424.0 mmol) in formic acid (99%, 200 mL) and stirred at room temperature for 4 h. The solution was then diluted with water (200 mL) and extracted with chloroform (3 x 200 mL). The organic fractions were combined, washed with an aqueous solution of Na_2CO_3 (3 x 100 mL, 10 wt%), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was recrystallized (ethyl acetate) to afford the title compound as a white crystalline solid (10.0 g, 43%), m.p = 167-169 °C, lit.[1] = 174 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 4.39-4.34 and 4.21-4.15 (m, 4H, -$\underline{CH_2}$OCO- (R,R) and (R,S)), 2.78-2.72 and 2.65-2.58 (m, 4H, -$\underline{CH_2}$COO- (R,R) and (R,S)), 1.94-1.84 (m, 4H, - $\underline{CH_2}CH_2$OCO-), 1.71-1.61 (m, 4H, - $\underline{CH_2}CH_2$COO-), 1.55-1.46 (q, 2H, J = 12 Hz, -CH-). These data are consistent with lit.[1,2] values.

Preparation of Benzyl Polyester Nanogel Star Polymer 6

Route 1: A solution of δ-valerolactone **2** (10 g, 99.9 mmol) in anhydrous toluene (12.8 g) was added to a solution of benzyl alcohol **1** (0.360 g, 3.33 mmol, and TBD **3** (72 mg, 0.52 mmol) in anhydrous toluene (30 g) and stirred at room temperature under an inert atmosphere for 15 min to yield the alcohol-terminated polymer arm **5** (at this time an aliquot of the reaction mixture was taken and a sample of **5** isolated by precipitation from MeOH for analysis: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34 (br, 5H, H-Ph-), 5.1 (s, 2H, Ph-CH_2-OOC-), 4.06 (br, 58H, -CH_2-CH_2-OOC-), 3.65 (br, 2H, from the core –CH_2-OH), 2.32 (br, 60H, -CH_2-CH_2-COO-), 1.65 (br, 120H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-). GPC (RI): Mn (PDI) = 3,000 g/mol (1.05)). BOP **4** (3.762 g, 16.6 mmol) and a solution of TBD **3** (72 mg, 0.52 mmol)[3] in anhydrous toluene (96 g) were then added to the reaction mixture which was stirred at room temperature under an inert atmosphere for a further 4 h. The reaction mixture was then quenched with benzoic acid and the crude product precipitated from cold methanol, filtered, and air dried to a constant weight at room temperature. The crude polymer (10.1 g) was then dissolved in acetone (200 mL) before the slow addition of methanol (250 mL) which formed a consistently cloudy suspension which was allowed to settle overnight, forming a clear oil on the bottom of the flask. The solution was decanted off and the oil dissolved in a minimum amount of acetone before being added dropwise to cold methanol with rapid stirring. The precipitate thus formed was removed by filtration and air dried at room temperature to a constant weight to afford the polyester nanogel star polymer **6** as a white amorphous polymer (5.41 g, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34 (br, 5H, H-Ph-), 5.1 (s, 2H, Ph-CH_2-OOC-), 4.06 (br, 88H, -CH_2-CH_2-OOC-), 3.65 (br, 2H, from the core –CH_2-OH), 2.32 (br, 88H, -CH_2-CH_2-COO-), 1.65 (br, 198H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-). DLS (RI): M_n, PDI, R_h = 333 000 g/mol, 1.21, 5.0 nm respectively.

Route 2: A solution of preformed poly(δ-valerolactone) **5** (1 g, 9.9 mmol) BOP **4** (0.38 g, 1.66 mmol) and a solution of TBD **3** (7 mg, 0.05 mmol)[3] in anhydrous toluene (9 g) was stirred at room temperature under an inert atmosphere for 4 h. The reaction mixture was then quenched with benzoic acid and the crude product precipitated from cold methanol, filtered, and air dried to a constant weight at room temperature. The crude polymer (1 g) was then dissolved in acetone (2 mL) before the slow addition of methanol (25 mL) which formed a consistently cloudy suspension which was allowed to settle overnight, forming a clear oil on the bottom of the flask. The solution was decanted off and the oil dissolved in a minimum amount of acetone before being added dropwise to cold methanol with rapid stirring. The precipitate thus formed was removed by filtration and air dried at room temperature to a constant weight to afford the polyester nanogel star polymer **6** as a white amorphous polymer (0.4 g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34 (br, 5H, H-Ph-), 5.1 (s, 2H, Ph-CH_2-OOC-), 4.06 (br, 88H, -CH_2-CH_2-OOC-), 3.65 (br, 2H, from the core –CH_2-OH), 2.32 (br, 88H, -CH_2-CH_2-COO-), 1.65 (br, 198H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-). DLS (RI): M_n, PDI, R_h = 337 500 g/mol, 1.19, 5.0 nm respectively.

Preparation of core-acetylated Benzyl Polyester Nanogel Star Polymer 7: Polyester nanogel star polymer **6** (100 mg), TBD **3** (3.4 mg, 24.3 µmol), and acetic anhydride (12.5 mg, 122 µmol) were dissolved in anhydrous methylene chloride (1 mL) and stirred at ambient temperature overnight. The reaction solution was then added to cold MeOH (100 mL) with rapid stirring and the resulting precipitate isolated, filtered and air dried to a constant mass at room temperature to afford to the title compound **7** as a white amorphous powder (86 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34 (br, 5H, H-Ph-), 5.1 (s, 2H, Ph-CH_2-OOC-), 4.06 (br, 88H, -CH_2-CH_2-OOC-), 3.65 (br, 2H, from the core –CH_2-OH), 2.32 (br, 88H, -CH_2-CH_2-COO-), 2.04 (s, 3H, from the core –CO-CH_3), 1.65 (br, 198H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-). DLS (RI): M_n, PDI, R_h = 339 000 g/mol, 1.22, 5.1 nm, respectively.

Preparation of core-tosylated Benzyl Polyester Nanogel Star Polymer 8: Polyester nanogel star polymer **6** (100 mg) and *p*-toluenesulfonyl chloride (100 mg, 0.5 mmol) were dissolved in anhydrous pyridine (1 mL) before the reaction mixture was left to stand at -18 °C overnight. The reaction solution was then added to hexane (100 mL) with rapid stirring and the precipitate thus formed isolated by filtration before being redissolved in a minimal amount of acetone and reprecipitated from cold methanol. The resulting precipitate was filtered and air dried at room temperate to a constant weight, yielding the title compound **8** as a white amorphous powder (89 mg, 89 %). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.75 (d, 2H, from the core –CH-C*H*2-C-SO_2-), 7.34 (br, 7H, *H*-Ph- and from the core –C*H*-CH-C-SO_2-), 5.1 (s, 2H, Ph-CH_2-OOC-), 4.06 (br, 88 H, -CH_2-CH_2-OOC-), 2.41 (s, 3H, C*H*3-Ph-), 2.32 (br, 88H, -CH_2-CH_2-COO-), 1.65 (br, 198H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-). M_n, PDI, R_h = 330 000 g/mol, 1.24, 5.1 nm.

Synthesis of 1-*tert*-Butyldimethylsilanol-propan-3-ol: 1,3-Propanediol (15 g, 200 mmol) and imidazole (7 g, 100 mmol) were dissolved in anhydrous methylene chloride (100 mL) under a nitrogen atmosphere and cooled to 0 °C. A solution of *tert*-butyldimethylsilyl chloride (10 g, 66 mmol) in 40 mL of anhydrous methylene chloride (40 mL) was added and the reaction mixture was allowed to warm to room temperature before being stirred at room temperature for four hours. The solution was then heated to 45 °C for an additional two hours. Upon cooling the reaction mixture was washed three times with water, dried with sodium sulfate, filtered and the organic liquid concentrated under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate 80: 20, was used until the di-protected byproduct eluted and then pure ethyl acetate was used for elution of the mono-protected product). The product containing fractions were collected, concentrated, and the solvent was removed under reduced pressure yielding the title compound as a yellow oil (11.8 g, 96%). The oil was dried by stirring at room temperature under 0.02 mm Hg for 24 h before use. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.81 (m, 4H, -CH_2-OH, -CH_2-O-), 2.56 (t, 1H, *H*O-), 1.77 (m, 2H, -CH_2-CH_2-CH_2-), 0.86 (s, 9H, CH_3-C-Si-), 0.02 (s, 6H, CH_3-Si-).

Preparation of Peripherally Protected Alcohol Functionalized Polyester Nanogel Star Polymer 9: Following the general procedure for **6**, 1-tert-butyldimethylsiloxy-propan-3-ol was used in lieu of benzyl alcohol to produce the title compound **9** as a white amorphous polymer (5.3 g, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.06 (br, 118H, -CH_2-CH_2-OOC-), 3.65 (br, 4H, -CH_2-O-Si- and from the core –CH_2-OH), 2.32 (br, 118H, -CH_2-CH_2-COO-), 1.81-1.61 (br, 258H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-, Si-O-CH_2-CH_2-CH_2-OOC-), 0.86 (s, 9H, CH_3-C-Si-), 0.02 (s, 6H, CH_3-Si-). GPC (RI): PDI (1.26) DLS (RI): M_n, PDI, R_h = 376 000 g/mol, 1.32, 5.5 nm respectively.

Preparation of Polyester Nanogel Star Polymer with acetylated core and peripheral alcohol functionality 10: The nanogel star polymer **9** (2 g) was core acetylated using the same procedure as described for **7** before the core-acetylated material was dissolved in anhydrous tetrahydrofuran (5 mL) under a nitrogen atmosphere at room temperature. Anhydrous tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 5mL) was then added and the reaction mixture stirred at ambient temperature for 4 h. The reaction solution was then added to cold MeOH (100 mL) with rapid stirring and the resulting precipitate isolated, filtered and air dried to a constant mass at room temperature to afford to the title compound **10** (1.84g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.06 (br, 120H, -CH_2-CH_2-OOC-), 3.66 (t, 2H, -CH_2-OH), 2.32 (br, 118H, -CH_2-CH_2-COO-), 2.03 (s, 3H, from the core –CO-CH_3), 1.65 (br, 258H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-, HO-CH_2-CH_2-CH_2-OOC-). DLS (RI): M_n, PDI, R_h = 371 000 g/mol, 1.29, 5.5 nm, respectively.

Preparation of Polyester Nanogel Star Polymer with acetylated core and peripheral tosylate functionality 11: Nanogel star polymer **10** (1 g) and *p*-toluenesulfonyl chloride (1 g, 5 mmol) were dissolved in anhydrous pyridine (7 mL) and let to sit at -18 °C overnight. The crude polymer solution was purified by polymer precipitation from hexane. The resulting precipitate was filtered and redissolved in a minimum amount of acetone and further purified by polymer precipitation from cold methanol, filtered and dried under vacuum to produce the title compound **11** as a white amorphous polymer (0.89 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.79 (br, 2H, Ar), 7.35 (br, 2H, Ar) 4.06 (br, 120H, -CH_2-CH_2-OOC-), 3.66 (br, 2H, -CH_2-OTos), 2.44 (s, 3H, CH_3-Ph from Tos), 2.32 (br, 91H, -CH_2-CH_2-COO-), 2.03 (s, 3H, from the core -OOC-CH_3), 1.65 (br, 258H, -OOC-CH_2-CH_2-CH_2-CH_2-OOC-, Tos-O-CH_2-CH_2-CH_2-OOC-). DLS (RI): M_n, PDI, R_h = 374 000 g/mol, 1.34, 5.4 nm, respectively.

Supplement References:

(1) Nijenhuis, A. J.; Grijpma, D. W.; Pennings, A. J. *Polymer* **1996**, *37*(13), 2783.

(2) Wiltshire, J. T.; Qiao, G. G. *Macromolecules* **2006**, *39*(26), 9018

(3) The subsequent formation of the nanogel core is described as being an order of magnitude slowly that the formation of the linear arms – the additional catalyst is added to compensate for this. As the catalysts can sometimes cause a degree of transesterification if used in higher amounts, the catalyst addition is done here sequentially to avoid an unnecessarily high PDI in the linear arms.