Supporting Information

Next generation hemostatic materials based on NHS-ester functionalized poly(2-oxazoline)s

*Marcel A. Boerman[a,b,c], Edwin Roozen[d], María José Sánchez-Fernández[c], Abraham R. Keereweer[c], Rosa P. Félix Lanao[a,c], Johan C.M.E. Bender[c], Richard Hoogenboom[e], Sander C. Leeuwenburgh[b], John A. Jansen[b], Harry Van Goor[d], Jan C.M. Van Hest[a]**

a Institute for Molecules and Materials (IMM), Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

b Department of Biomaterials, Radboudumc, Philip v. Leydenlaan 25, 6525 EX Nijmegen, The Netherlands

c GATT-Technologies BV, Toernooiveld 1 , 6525 ED, Nijmegen, The Netherlands

d Department of Surgery, Radboudumc, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands

e Supramolecular Chemistry Group, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281 S4, 9000 Ghent, Belgium

S1 Synthetic procedure for polymers (P1-P7)

Materials

All reagents (synthesis grade) for the synthesis of the monomers were purchased at Sigma Aldrich and used without further purification, unless stated otherwise. All reagents for the synthesis of the polymers were distilled twice before use in the polymerizations. Acetonitrile (obtained from Actu-all Chemicals) was dried and dispensed under nitrogen atmosphere by using an MBraun MB SPS-800 solvent dispersing system.

Characterization

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance III 500MHz spectrometer using the solvents D_2O, MeOD, $CDCl_3$ or DMSO-*d*6. FT-IR measurements were performed on a Bruker Tensor 27 IR ATR spectrometer. Microwave-assisted polymerizations were performed in a Biotage Initiator+, equipped with an autosampler. Size exclusion chromatography (SEC) was performed on an Agilent 1260 - series HPLC system equipped with a 1260 online degasser, a 1260 ISO-pump, a 1260 automatic liquid sampler, a thermostatted column compartment, a 1260 diode array detector (DAD) and a 1260 refractive index detector (RID). Analyses were performed on two Mixed-D and a guard column in series at 50 °C. As an eluent, *N,N*-dimethylacetamide (DMA), containing LiCl (concentration 50 mM), was used at a flow rate of 0.593 ml min^{-1}. The SEC traces were analyzed using the Agilent Chemstation software with the GPC add on. Number average molecular weights (M_n), weight average molecular weights (M_w), and dispersity (Đ) values were calculated against poly(methyl methacrylate) (PMMA) standards. UV was determined using a Jasco V650 spectrophotometer containing a temperature controller. NHS-ester content of the polymers was determined by measuring the absorbance of NHS using a

literature procedure based on the absorbance of the NHS anion in NH_4OH (λ 260 nm)[1] or the colored complex of iron(III)chloride with NHS (λ 505 nm)[2]. Measurements were conducted in triplo against a calibration curve (NHS-OH).

Monomers

Monomers were synthesized and distilled according to a literature procedure[3]

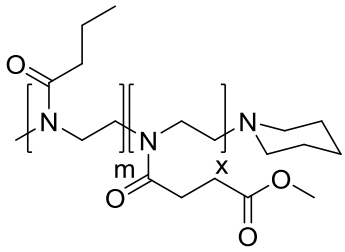
Polymers

P1a-P7a (MestOx)

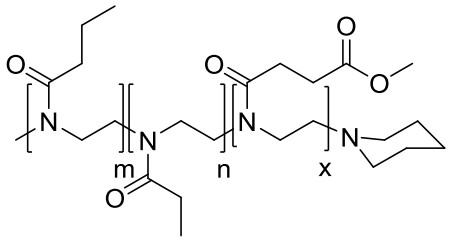
P(*n*PropOx-MestOx) and **P(*n*PropOx-EtOx-MestOx)** based copolymers were synthesized according to a literature procedure*3*.

Protocol A: General procedure polymerization (P1a-P7a)

Methyl tosylate (1 eq.), *n*Pr*o*pOx (m eq.), EtOx (n eq.), MestOx (x eq.) and acetonitrile were mixed in the desired ratios in a dry microwave vial (total monomer concentration 4M) under inert atmosphere (argon). The polymerization was heated for 30 min under microwave irradiation (140°C) after which dry piperidine (5 eq.) was added to the reaction mixture, which was stirred for another three hours. The solvent was evaporated under reduced pressure and the polymer was dissolved in DCM (100 mL) and precipitated in diethylether (DCM/Et_2O, v/v, 1:20). This procedure was performed two times. The resulting suspension was filtered and the residue dissolved in DCM (100 mL). The solvent was evaporated under reduced pressure yielding the MestOx functionalized polymers (**P1a-P7a)**.



P1a-P2a + P7a



P3a-P6a

P1a P(*n*PropOx-MestOx) 90-10 -P1a was synthesized according to protocol **A** with a monomer ratio of m/x of 90/10. **P1a** was obtained as a white foam (1.9 g, 76% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 90/10. **SEC** (PMMA) M_n 19.1 kg/mol, Đ 1.23

P2a P(*n*PropOx-MestOx) 75-25 -P2a was synthesized according to protocol **A** with a monomer ratio of m/x of 75/25. **P2a** was obtained as a white foam (19.6 g, 60% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 75/25. **SEC** (PMMA) M_n 5.3 kg/mol, Đ 1.16

P3a P(*n*PropOx-EtOx-MestOx) 40-50-10- P3a was synthesized according to the literature procedure with a monomer ratio of m/n/x of 40/50/10. **P3a** was obtained as a white foam (7.5 g, 78% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3+ CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-

C$\underline{H}_3$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 40/51/9. **SEC** (PMMA) M_n 9.5 kDa, Đ 1.16

P4a P(*n*PropOx-EtOx-MestOx) 50-40-10 - P4a was synthesized according to protocol **A** with a monomer ratio of m/n/x of 50/40/10. **P4a** was obtained as a white foam (7.8 g, 79% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3+ CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 50/41/9. **SEC** (PMMA) M_n 10.3 kDa, Đ 1.16

P5a P(*n*PropOx-EtOx-MestOx) 40-35-25 - P5a was synthesized according to protocol **A** with a monomer ratio of m/n/x of 40/35/25. **P5a** was obtained as a white foam (18.9 g, 93% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3+ CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 41/35/24. **SEC** (PMMA) M_n 11.1 kg/mol, Đ 1.19

P6a P(*n*PropOx-EtOx-MestOx) 50-25-25-P6a was synthesized according to protocol **A** with a monomer ratio of m/n/x of 50/25/25. **P6a** was obtained as a white foam (8.2 g, 78% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.60 (b, x•3H, OC$\underline{H}_3$), 3.60-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.70-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.10 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3+ CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$), 0.90-0.80 (b, m•3H,

CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 51/26/23. **SEC** (PMMA) M_n 10.8 kDa, Đ 1.24

P7a P(*n*PropOx-MestOx) 70-30-P7a was synthesized according to protocol **A** with a monomer ratio of m/x of 70/30 and 2-amino-ethanol (5 eq.) as a terminating agent. **P7a** was obtained as a white foam (27 g, 71 % yield). **^{1}H NMR** (400 MHz, D_2O) δ 3.69 (b, m•3H, CO-O-C$\underline{H}_3$), δ 3.70-3.40 (b, (m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.79-2.59 (b, x•4H, COC$\underline{H}_2$C$\underline{H}_2$CO), 2.43-2.23 (b, 2H, m•CO-C$\underline{H}_2$-CH_2-CH_3), 1.65-1.50 (b, 2H, m•CO-CH_2-C$\underline{H}_2$-CH_3), 0.98-0.85 (b, m•3H, n•CO-CH_2-CH_2-C$\underline{H}_3$) Experimentally determined monomer ratio (m/n/x): 69/31. **SEC** (PMMA) M_n 10.4 kDa, Đ 1.16

P8 (EtOx)- P8 was synthesized according to protocol **A**. **P8** was obtained as a white foam (6.9 g, 78 % yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.60-3.30 (b, n•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 2.50-2.20 (b, n•2H, CO-C$\underline{H}_2$-CH_3), 1.20-1.00 (b, n•3H, CO-CH_2-C$\underline{H}_3$), 1.00-0.90 (b, n•3H, CO-CH_2-CH_2-C$\underline{H}_3$) **SEC** (PMMA) M_n 5.1 kg/mol, Đ 1.22

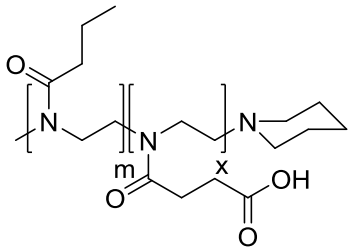
P9 (*n*PropOx)- P9 was synthesized according to protocol **A**. **P9** was obtained as a white foam (3.3g, 34% yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.48 (b, m•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 3.05 (b, 3H, C$\underline{H}_3$-NCHCH-), 2.35-2.20 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.92-1.01 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$) **SEC** (PMMA) M_n 7.7 kg/mol, Đ 1.20

P1b-P6b (COOH)

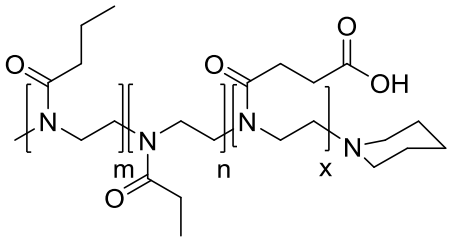
P(*n*PropOx-COOH) and **P(*n*PropOx-EtOx-COOH)** based copolymers were synthesized according to a literature procedure[3].

Protocol B: General procedure hydrolysis (P1b-P6b)

Polymers **P1a-P6a** were dissolved in a NaOH solution (0.1 M) to a polymer concentration of 1 M and this reaction mixture was stirred overnight. Afterwards, the reaction mixture was acidified to pH 4 by dropwise addition of a HCl solution (0.1 M). The reaction mixture was stirred in a heated water bath (45°C) which caused precipitation of the polymer as a sticky white precipitate. This was dissolved in cold water (100 mL) and the reaction mixture was stirred again in the heated water bath, which caused the polymer to precipitate again. The pH of the resulting solution was 4. The sticky white precipitate was either (1) dissolved again in DCM (100 mL) and concentrated under reduced pressure or (2) precipitated from DMF (20 mL) into diethyl ether (2000 mL) and subsequently filtered and dried under high vacuum, yielding the COOH functionalized polymers (**P1b-P6b**) as white fluffy powders.



P1b-P2b



P3b-P6b

P1b P(*n*PropOx-COOH) 90-10 -P1b was synthesized according to protocol **B** starting from **P1a** (10.2 g). **P1b** was obtained as a white foam (6.8 g, 69% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 92/8. **SEC** (PMMA) M_n 20.5 kg/mol, Đ 1.16

P2b P(*n*PropOx-COOH) 75-25 -P2b was synthesized according to protocol **B** starting from **P2a** (19.6 g). **P2b** was obtained as a white foam (11.8 g, 62% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 74/26.

P3b P(*n*PropOx-EtOx-COOH) 40-50-10 - P3b was synthesized according to protocol **B** starting from **P3a** (7.8 g). **P3b** was obtained as a white foam (6.5 g, 83% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3 + CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$) 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 40/49/11

P4b P(*n*PropOx-EtOx-COOH) 40-35-25 - P4b was synthesized according to protocol **B** starting from **P4a** (18.4 g). **P4b** was obtained as a white foam (10.0 g, 54% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3 + CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$) 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 40/36/24

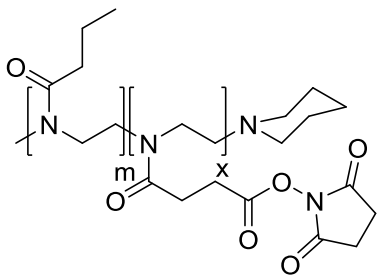
P5b P(*n*PropOx-EtOx-COOH) 50-40-10 - P5b was synthesized according to protocol **B** starting from **P5a** (7.5 g). **P5b** was obtained as a white foam (4.0 g, 52% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3 + CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-

C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$) 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 50/40/10

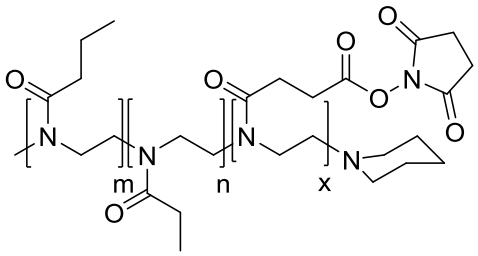
P6b P(*n*PropOx-EtOx-COOH) 50-25-25 - P6b was synthesized according to protocol **B** starting from **P6a** (8.2 g). **P6b** was obtained as a white foam (4.3 g, 54% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.60-2.50 (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3 + CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 1.15-1.05 (b, n•3H, CO-CH_2-C$\underline{H}_3$) 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 50/30/20

Protocol C: General procedure NHS-activation (P1a-P6a)

Polymers P1b-6b, *N,N′*-Diisopropylcarbodiimide (DIC) (1.1 eq. compared to COOH) and N-hydroxysuccinimide (NHS) (1.1 eq. compared to COOH) were dissolved in a mixture of solvents (DMF/DCM, v:v, 1:9) yielding a 0.1 M-solution. This mixture was stirred overnight. A white precipitate (urea byproduct of DIC) was formed which was removed by filtration of the reaction mixture over celite. Afterwards, the reaction mixture was concentrated to dryness under reduced pressure. After this, the polymers were dissolved in DCM (100 mL) and precipitated in Et_2O (DCM/Et_2O, v/v, 1:20, total volume 250 mL). This procedure was performed three times. After the final precipitation step, the polymers were collected by filtration and dried under high vacuum yielding the NHS-ester functionalized polymers (P1-P6).



P1-P2



P3-P6

P1 P(*n*PropOx-NHS) 90-10 -P1 was synthesized according to protocol **C** starting from **P1b** (6.5 g). **P1** was obtained as a white foam (1.1 g, 40% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO) + (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO (NHS))), 2.40-2.20 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 90/10. **UV (NH_4OH)** 11% NHS. **SEC** (PMMA) M_n 12.6 kg/mol, Đ 1.15

P2 P(*n*PropOx-NHS) 75-25 -P2 was synthesized according to protocol **C** starting from **P2b** (5.1 g). **P2** was obtained as a white foam (5.8 g, 95% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO + (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO (NHS))), 2.40-2.20 (b, m•2H, CO-C$\underline{H}_2$-CH_2-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/x): 71/29. **UV (NH_4OH)** 26% NHS. **SEC** (PMMA) M_n 20.9 kg/mol, Đ 1.20

P3 P(*n*PropOx-EtOx-NHS) 40-50-10 -P3 was synthesized according to protocol **C** starting from **P3b** (4.0 g). **P3** was obtained as a white foam (2.9 g, 53% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO + (b, x•4H, CO-C$\underline{H}_2$-C$\underline{H}_2$-CO (NHS))), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H}_2$-CH_2-CH_3 + CO-C$\underline{H}_2$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H}_2$-CH_3), 0.90-0.80 (b, n•3H, CO-CH_2-C$\underline{H}_3$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H}_3$). Experimentally determined monomer ratio (m/n/x): 40/49/11. **FT-IR (cm^{-1})** 1626 (C=O amide), 1738 + 1785 + 1815 (NHS-ester). **UV (NH_4OH)** 11% NHS. **SEC** (PMMA) M_n 12.5 kg/mol, Đ 1.18

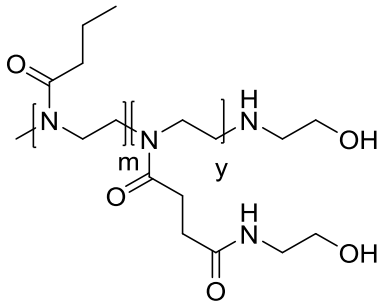
P4 P(*n*PropOx-EtOx-NHS) 40-35-25 -P4 was synthesized according to protocol **C** starting from **P4b** (10 g). **P12** was obtained as a white foam (4.7 g, 35% yield). **^{1}H NMR** (500 MHz,

D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO + (b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO (NHS))), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H_2}$-CH_2-CH_3 + CO-C$\underline{H_2}$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H_2}$-CH_3), 0.90-0.80 (b, n•3H, CO-CH_2-C$\underline{H_3}$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H_3}$). Experimentally determined monomer ratio (m/n/x): 39/33/28. **FT-IR (cm^{-1})** 1626 (C=O amide), 1738 + 1785 + 1815 (NHS-ester). **UV (NH_4OH)** 32% NHS. **SEC** (PMMA) M_n 16.8 kg/mol, Đ 1.22

P5 P(*n*PropOx-EtOx-NHS) 50-40-10 -P5 was synthesized according to protocol **C** starting from **P5b** (6.5 g). **P5** was obtained as a white foam (5.6 g, 65% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO + (b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO (NHS))), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H_2}$-CH_2-CH_3 + CO-C$\underline{H_2}$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H_2}$-CH_3), 0.90-0.80 (b, n•3H, CO-CH_2-C$\underline{H_3}$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H_3}$). Experimentally determined monomer ratio (m/n/x): 49/39/12. **FT-IR (cm^{-1})** 1626 (C=O amide), 1738 + 1785 + 1815 (NHS-ester). **UV (NH_4OH)** 9% NHS. **SEC** (PMMA) M_n 12.3 kg/mol, Đ 1.16

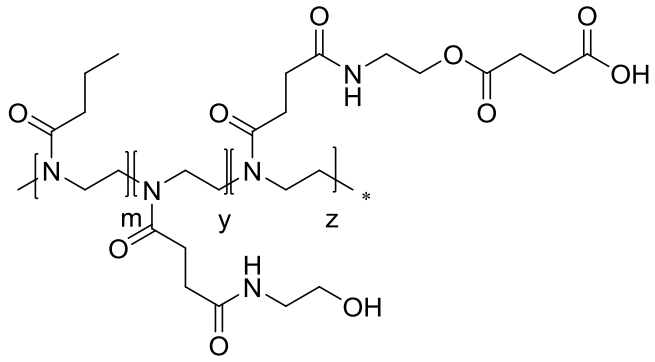
P6 P(*n*PropOx-EtOx-NHS) 50-25-25 -P6 was synthesized according to protocol **C** starting from **P6b** (5.4 g). **P6** was obtained as a white foam (4.5 g, 83% yield). **^{1}H NMR** (500 MHz, D_2O) δ 3.70-3.40 (b,(m+n+x)•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 3.00-2.60 ((b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO + (b, x•4H, CO-C$\underline{H_2}$-C$\underline{H_2}$-CO (NHS))), 2.40-2.20 (b, (m+n)•2H, CO-C$\underline{H_2}$-CH_2-CH_3 + CO-C$\underline{H_2}$-CH_3), 1.60-1.40 (b, m•2H, CO-CH_2-C$\underline{H_2}$-CH_3), 0.90-0.80 (b, n•3H, CO-CH_2-C$\underline{H_3}$), 0.90-0.80 (b, m•3H, CO-CH_2-CH_2-C$\underline{H_3}$). Experimentally determined monomer ratio (m/n/x): 50/26/24. **FT-IR (cm^{-1})** 1626 (C=O amide), 1738 + 1785 + 1815 (NHS-ester). **UV (NH_4OH)** 22% NHS. **SEC** (PMMA) M_n 14.6 kg/mol, Đ 1.18

P7b Amidation reaction



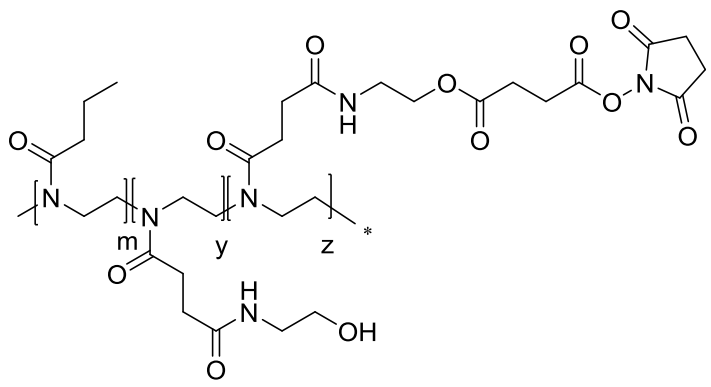
P7b- P(*n*PropOx-OH) 70-15-15- P7a (8.0 g, 0.6 mmol polymer, 18.8 mmol ester, 1 eq.) was dissolved in 2-amino-ethanol (8.4 mL, 138 mmol, 7 eq.) and the reaction mixture was allowed to reflux overnight at 60°C under reduced pressure (300 mbar). After this, 2-amino-ethanol was removed under reduced pressure and the polymer was precipitated twice from methanol (100 mL) into Et_2O (2 L). Subsequently, the precipitate was dissolved in methanol (100 mL) and the solvent was evaporated under reduced pressure. Since residual 2-amino-ethanol was present (^{1}H-NMR), the polymer was precipitated from methanol (100 mL) into Et_2O/acetone (v/v, 19:1) (2 L). Finally, the precipitate was dissolved in DCM (100 mL) and the solvent was evaporated yielding **P2** (5.1 g, 0.37 mmol) as a white foam (59% yield). **^{1}H NMR** (400 MHz, D_2O): δ 3.70-3.40 (b, (m+y)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 3.69-3.60 (b, y•2H, C=ONHCH$_2$C$\underline{H}_2$OH), 3.35-3.28 (b, y•2H, C=ONHC$\underline{H}_2$CH$_2$OH), 2.76-2.59 (b, y•2H, O=CC$\underline{H}_2$CH$_2$C=ONH), 2.60-2.48 (b, y•2H, O=CCH$_2$C$\underline{H}_2$C=ONH), 2.43-2.23 (b, m•2H, C$\underline{H}_2$CH$_2$CH$_3$), 1.65-1.50 (b, m•2H, CH$_2$C$\underline{H}_2$CH$_3$), 0.98-0.85 (b, m•3H, CH$_2$CH$_2$C$\underline{H}_3$). Experimentally determined monomer ratio (m/y): 69/31. **SEC** (PMMA) M_n 18.8, Đ 1.11

P7c-Succinic anhydride coupling



P7c - P(*n*PropOx-OH-COOH) - P7b (3.4 g, 0.3 mmol polymer, 7.8 mmol OH, 1 eq.) was dissolved in DCM (30 mL). Succinic anhydride (0.4 g; 3.9 mmol, 0.5 eq) and DMAP (0.5 g; 3.9 mmol, 0.5 eq) were added and the reaction mixture was stirred at room temperature overnight under inert atmosphere. Next, the reaction mixture was evaporated under reduced pressure to dryness. Subsequently, the polymer was precipitated twice from DCM (20 mL) into acetone (200 mL). The resulting white solid was dissolved in methanol (50 mL) and charged on a SCX-2 column (1.4 g, 0.69 mmol/g) and the loaded column was flushed twice with methanol (50 mL). After this, the combined fractions of methanol were concentrated to dryness under reduced pressure yielding **P7c** (0.515 g, 0.033 mmol) as a white solid (13% yield).**^{1}H NMR** (400 MHz, D_2O): δ 4.23-4.14 (b, z•2H, O=CNHC$\underline{H}_2$CH$_2$OC=O), 3.70-3.40 (b, (m+y+z)•4H, NC$\underline{H}_2$C$\underline{H}_2$N), 3.69-3.60 (b, (y+z)•2H, C=ONHCH$_2$C$\underline{H}_2$OH & C=ONHCH$_2$C$\underline{H}_2$OC=O), 3.35-3.28 (b, y•2H, C=ONHC$\underline{H}_2$CH$_2$OH), 2.76-2.59 (b, z•4H, O=CC$\underline{H}_2$C$\underline{H}_2$COOH & (y+z)•2H, O=CC$\underline{H}_2$CH$_2$C=ONH), 2.60-2.48 (b, (y+z)•2H, O=CCH$_2$C$\underline{H}_2$C=ONH), 2.43-2.23 (b, m•2H, C$\underline{H}_2$CH$_2$CH$_3$), 1.65-1.50 (b, m•2H, CH$_2$C$\underline{H}_2$CH$_3$), 0.98-0.85 (b, m•3H, CH$_2$CH$_2$C$\underline{H}_3$). Experimentally determined monomer ratio (m/y/z): 69/16/15. **SEC** (PMMA) no signal could be obtained

P7 NHS-ester activation



P7 - P(*n*PropOx-OH-NHS)- P7c (0.5 g, 32 µmol polymer, 0.5 mmol COOH, 1 eq.)), DIC (0.3 mL, 2.0 mmol; 3.5 eq), acetic acid (33 µL, 0.5 mmol, 1 eq.) and N-hydroxysuccinimide (0.2 g; 2.0 mmol; 3.5 eq) were dissolved in DCM (10 mL). The solution was stirred overnight at room temperature under argon. After overnight reaction, a white precipitate (urea of DIC) was formed. Subsequently, the precipitate was filtered off over cotton wool. Next, the solvent was concentrated under reduced pressure Subsequently, the polymer was precipitated twice from DCM (2.5 mL) into acetone (25 mL) and once from DCM (2.5 mL) into Et_2O (25 mL). The white fluffy precipitate was filtered off, dried under high vacuum yielding **P7** (0.2 g, 13 µmol) as a white powder (42% yield). ^{1}H NMR (400 MHz, D_2O): δ 4.23-4.14 (b, z•2H, O=CNHC$\underline{H_2}$CH$_2$OC=O), 3.70-3.40 (b, (m+y+z)•4H, NC$\underline{H_2}$C$\underline{H_2}$N), 3.69-3.60 (b, (y+z)•2H, C=ONHCH$_2$C$\underline{H_2}$OH & C=ONHCH$_2$C$\underline{H_2}$OC=O), 3.35-3.28 (b, y•2H, C=ONHC$\underline{H_2}$CH$_2$OH), 3.08-2.99 (b, z•2H, O=CC$\underline{H_2}$C$\underline{H_2}$COON), 3.01-2.90 (b, z•4H, ONO=CC$\underline{H_2}$C$\underline{H_2}$C=ONO), 2.88-2.80 (b, z•2H, O=CC$\underline{H_2}$C$\underline{H_2}$COON), 2.76-2.59 (b, (y+z)•2H, O=CC$\underline{H_2}$CH$_2$C=ONH), 2.60-2.48 (b, (y+z) •2H, O=CCH$_2$C$\underline{H_2}$C=ONH), 2.43-2.23 (b, m•2H, C$\underline{H_2}$CH$_2$CH$_3$), 1.65-1.50 (b, m•2H, CH$_2$C$\underline{H_2}$CH$_3$), 0.98-0.85 (b, m•3H, CH$_2$CH$_2$C$\underline{H_3}$). Experimentally determined monomer ratio (m/y/z): 69/16/15. **UV (Fe(III)chloride)** 15% NHS. **SEC** (PMMA) M_n 18.8, Đ 1.25

S2 ^{1}H-NMR spectra of P3-P6 and intermediate products

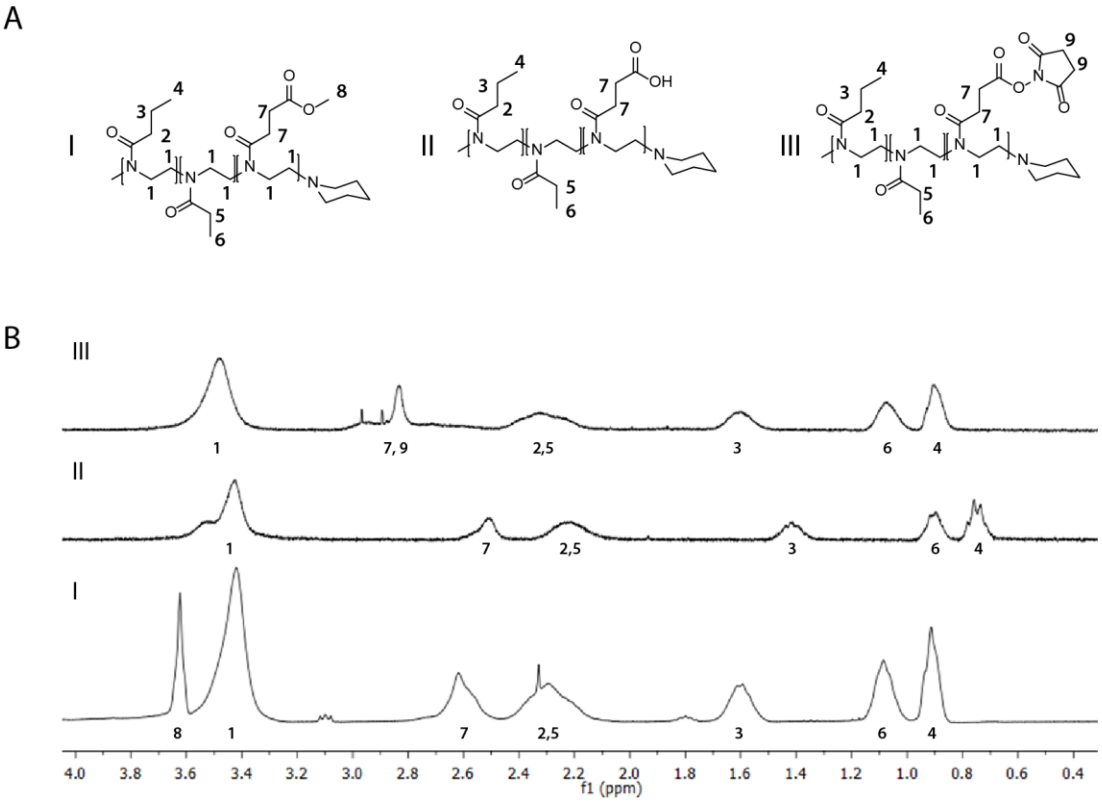


Figure S2. Representative ^{1}H-NMR spectra of P(*n*PropOx-EtOx-NHS) based polymers and intermediate products (**P3**-**P6**). A) Structural formulas of I ((P(*n*PropOx-EtOx-MestOx), II P(*n*PropOx-EtOx-COOH), III P(*n*PropOx-EtOx-NHS)), B) ^{1}H-NMR signals of I, II and III.

S3 ^{1}H-NMR spectra of P7 and intermediate products

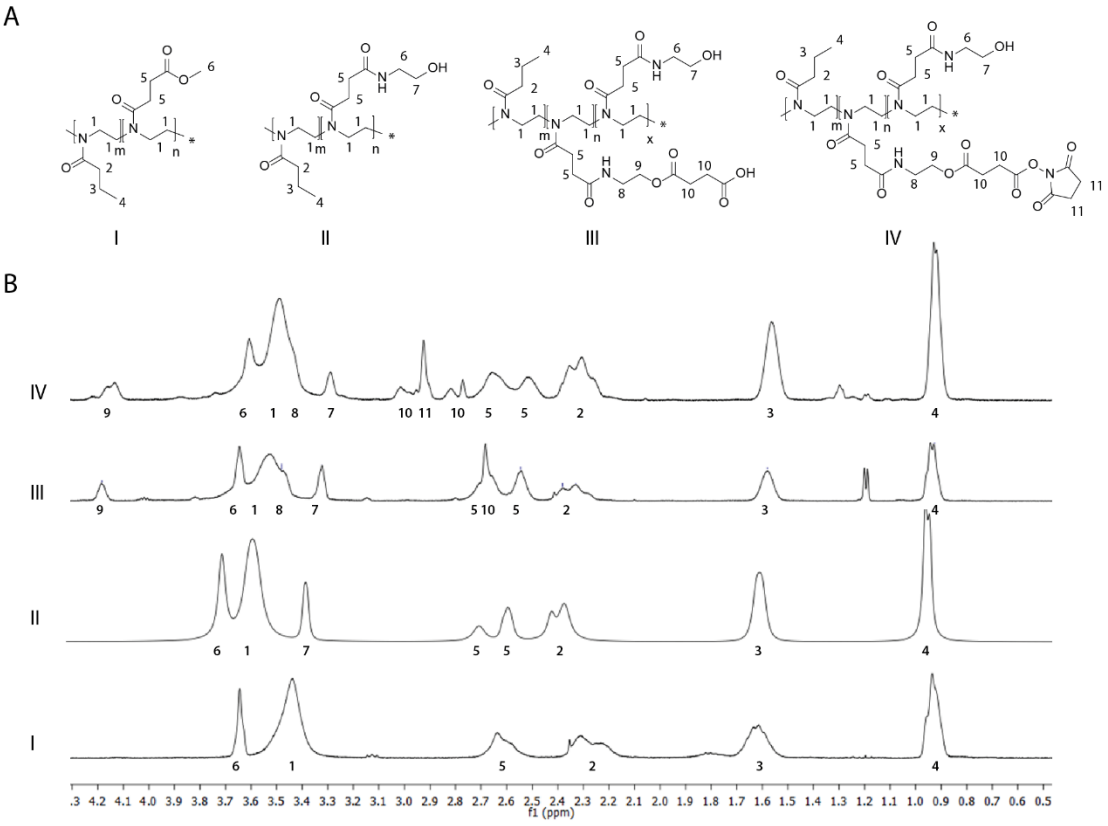


Figure S3. Representative ^{1}H-NMR spectra of P(*n*PropOx-OH-NHS) (**P7**) and intermediate products. A) Structural formulas of I (P(*n*PropOx-MestOx)), II (P(*n*PropOx-OH)), III (P(*n*PropOx-OH-COOH)), IV (P(*n*PropOx-OH-NHS)), B) ^{1}H-NMR signals of I-IV

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