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The synthesis and aqueous solution properties of sulfobutylbetaine (co)polymers: Comparison of synthetic routes and tuneable upper critical solution temperatures

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ABSTRACT Polysulfobutylbetaine (SBB) (co)polymers, zwitterionic species bearing ammonium and sulfonate groups separated by a butyl spacer in every repeat unit, were prepared through three different synthetic routes and their aqueous solution behaviour was studied. Postpolymerization quaternization of poly[2-(dimethylamino)ethyl methacrylate] with 1,4-butanesultone resulted in incomplete modification due to the low reactivity of this alkylating agent. RAFT radical polymerization of SBB-functional (meth)acrylate monomers and their copolymerization with a sulfopropylbetaine (SPB) methacrylate yielded well-defined (co)polymers with low dispersities $1.13 \leq Đ_M \leq 1.23$ at monomer conversions of 75–92%. For a series of SBB methacrylate homopolymers with increasing degrees of polymerization from 66–186 measured upper critical solution temperature (UCST) cloud points increased from 27–77 °C. Cloud points of statistical SPB-SBB copolymers with similar degrees of polymerization, but varying molar compositions, increased linearly with SBB content offering a simple means of UCST tuning. Additionally, novel SBB acrylamide homo- and copolymers were prepared by postpolymerization modification of poly(pentafluorophenyl acrylate) with an SBB-functional amine and in mixtures with benzylamine as a hydrophobic modifier. In all cases, the SBB (co)polymers had significantly higher UCSTs than their more common SPB counterparts, greatly extending the temperature range of tuneable UCST transitions and making the investigated SBB (co)polymers advantageous for exploiting their 'smart' behaviour. In this respect, combining SBB functionality with hydrophobic benzylacrylamide comonomers is presented as a simple means of increasing the maximum salt concentration at which UCST behaviour (which shows an antipolyelectrolyte effect) can be observed, enabling UCST transitions in aqueous solutions containing up a physiological concentration (9 g/L) of NaCl.

Introduction

Thermoresponsive polymers have been the focus of research for many decades and a range of applications including drug delivery, separation, diagnostics, and tissue engineering are based on polymers exhibiting aqueous inverse temperature solubility (lower critical solution temperature (LCST) behaviour, phase separation above a critical temperature).[1] Their counterparts, polymers with an aqueous upper critical solution temperature (UCST) which phase separate below a critical temperature, have similar potential in such applications, but only a few (co)polymers are known to exhibit this type of "smart" behaviour.[2] Sulfobetaine polymers,[3-6] which carry permanently (pH independently) charged ammonium and sulfonate groups in every repeat unit, are promising candidates for aqueous UCST behaviour because their zwitterionic side groups can cause strong inter- and intrapolymer attractions through electrostatic interlocking at low temperatures resulting in insolubility. Polysulfobetaines have additionally attracted attention because of their superior haemocompatibility and antibiofouling properties,[7, 8] which have been exploited for surface modification of ultrafiltration membranes[9] and blood-contacting devices[10, 11] and wound dressing applications.[12] Since first described in the 1950s,[13] a wide range of polysulfobetaines with various backbone types, side group geometries, ammonium alkyl substituents, and spacer lengths has been prepared.[3, 4, 6, 14-18] Notably, a large focus of past research efforts was on fully water soluble (co)polymers with miscibility gaps often being considered a nuisance rather than an opportunity. Consequently, aqueous UCST behaviour has only been reported for a small subset of zwitterionic (co)polymers.[3, 19-25] While the influence of spacer lengths, including the length of the ion bridge between the charged sites, on hydrophilicity has been investigated for small molecule (sulfo)betaines,[15, 26-29] detailed studies of aqueous solution behaviour of sulfobetaine polymers have invariably dealt with sulfo*propyl*betaine (SPB)

polymers, *i.e.* structures with three methylene groups between the charged groups.[19-21, 23, 24, 30-32] The vast majority of recent studies on polysulfobetaine UCST behaviour is, in fact, largely based on the two commercially available monomers 3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate (**MA2-3**)[21, 30, 33-35] and 3-((3-methacrylamidopropyl)dimethylammonio)propane-1-sulfonate (**MAm3-3**).[21, 31, 36, 37]

Zwitterionic monomers are typically polymerized in aqueous solution,[3, 16, 38] which poses limitations for the incorporation of hydrophobic segments including co-monomers.[39] Also, characterization of zwitterionic polymers, especially through size exclusion chromatography (SEC), suffers from limited solubility of polymers in organic solvents.[32] For these reasons, quaternization of amino groups or installation of zwitterionic segments through postpolymerization modification of (easier to characterize) precursors can be preferential.[6] Commonly, tertiary amine functional polymers, such as homo-[16, 40] or copolymers[41, 42] of 2-(dimethylamino)ethyl methacrylate (DMAEMA) are reacted with sultones, cyclic sulfonic esters, in organic solvents producing, in the case of pDMAEMA and 1,3-propanesultone, poly[3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate], **p(MA2-3)**. For reaction in most organic solvents, such as THF, the resulting partially betainized (co)polymers precipitate with reaction continuing, considerably slower,[16] under heterogeneous conditions. We recently reported[43] the postmodification of the activated ester precursor poly(pentafluorophenyl acrylate), pPFPA,[44] with a zwitterionic amine, 3-((3-aminopropyl)dimethylammonio)propane-1-sulfonate, **amine3-3**, as a novel and versatile synthetic route toward zwitterionic homo- and hydrophobically modified copolymers. Notably, also in this study only propyl-spaced derivatives were investigated.

Though promising, applications of the UCST behaviour of polysulfobetaines are limited compared to those of LCST-type polymers such as poly(*N*-isopropyl acrylamide) or non-linear poly(ethylene glycol)s for two reasons. Firstly, UCST transitions generally show a strong positive dependence on molecular weight. As the commonly studied **MA2-3** and **MAm3-3** based polysulfopropyl species can exhibit good solubility in pure water, relatively high molecular weights of several hundred kg/mol are necessary to achieve cloud points as high as 30–40 °C.[21, 35] Polymers with lower molecular weights have lower critical temperatures or may be fully soluble, not exhibiting the desired "smart" behaviour at all. Secondly, zwitterionic polymers show an antipolyelectrolyte effect: added salts screen the side chain charges from another, reducing electrostatic interlocking efficiency which results in a decrease of UCST cloud points and ultimately, at sufficiently high salt concentrations, in temperature independent aqueous solubility.[4] Consequently, it is of considerable interest to develop (co)polymers with significantly higher UCST transitions than those of comparable **MA2-3** and **MAm3-3** based polysulfopropylbetaines—possibly to an extent that polymers are insoluble in pure water over the entire temperature range up to 100 °C at 1 atm. "Smart" behaviour in a practical temperature range would then be observable for (more conveniently available) lower molecular weight samples, and, importantly, in aqueous salt solutions, most ideally extending to a physiologically relevant ion concentration (*e.g.* ~154 mM NaCl). Our previously reported postpolymerization preparation of hydrophobically modified sulfopropylbetaine copolymers represents a first study aimed at increasing UCST transitions through tuning of copolymer composition which enabled sharp transitions of a copolymer with M_n = 27 kg/mol in aqueous solutions containing up to 76 mM NaCl.[43]

Herein, we present a detailed study into the UCST behaviour of sulfo*butyl*betaine (SBB) (co)polymers and show that increasing the ion bridge by just one methylene unit represents a simple means of significantly increasing critical solution temperatures of homopolymers. SBB (co)polymers and several SPB reference samples were prepared through direct (co)polymerization of commercial and prepared zwitterionic monomers, through postmodification of pDMAEMA with sultones, and through postmodification of an activated ester precursor using a novel zwitterionic amine allowing us to compare these methods with regards to their efficiency in producing the SBB species and providing access to a library of (novel) zwitterionic acrylate, methacrylate and (hydrophobically modified) acrylamide (co)polymers with tuneable UCST transitions spanning an impressive temperature range and extending up to physiologically relevant NaCl concentrations.

Experimental Section

Materials. All reagents, including methacryloxyethyl dimethylammonio propanesulfonate (**MA2-3**) and 2-cyano-2-propyl dithiobenzoate (CPDB) were purchased from Sigma-Aldrich and were used as received unless stated otherwise. Propylene carbonate (99.7%, anhydrous) was stored in a glovebox. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and stored at −24 °C. The syntheses of the chain transfer agent (CTA) benzyl propyl trithiocarbonate (BPTC),[45] the CTA pentafluorophenyl 4-cyano-4-((phenylcarbonothioyl)thio)valerate,[46] the activated ester initiator bis(pentafluorophenyl) 4,4'-(diazene-1,2-diyl)bis(4-cyanopentanoate),[46] and the amine-functional dye 4-nitro-7-piperazin-1-yl-2,1,3-benzoxadiazole (NBD amine)[47] are described elsewhere.

Methods. NMR spectroscopic measurements in D_2O were performed on Bruker Avance 300 MHz instrument in 5 mm NMR tubes. Measurements of polymers were done on D_2O solutions containing up to 0.5 M NaCl. The internal solvent signal $\delta(D_2O)$ = 4.79 ppm was used as reference.

Size exclusion chromatography (SEC) in dimethylacetamide (DMAc) was performed on a Shimadzu system with four 300 × 7.8 mm^2 linear phenogel columns (10^5, 10^4, 10^3, and 500 Å) operating at a flow rate of 1 mL/min. The system was calibrated with a series of low polydispersity polystyrene (PS) standards with molar masses ranging from 0.58–1820 kg/mol. Aqueous SEC was performed on a Shimadzu system with two Agilent Aquagel columns with 0.2 M NaCl solution containing 0.02 mass% sodium azide as eluent at a flow rate of 1 mL/min. This system was calibrated with a series of narrow molar mass distribution poly(ethylene glycol) (PEG) standards. Chromatograms were analysed by Cirrus SEC software version 3.0.

Fourier transform infrared spectroscopy (FT-IR) was performed on a Bruker IFS 66/S instrument under attenuated total reflectance, and data was analysed on OPUS software version 4.0.

Turbidity measurements were performed on a Varian Cary 300 Scan spectrophotometer equipped with a Cary temperature controller and a Peltier heating element in quartz cuvettes of 10 mm path length at a wavelength of 520 nm with heating/cooling rates of 1 °C/min. Unless otherwise noted, polymer concentrations were 10 g/L. For clear solutions the baseline was corrected to zero absorbance, A. Transmittance, $t = 10^{-A}$, was plotted against temperature, and cloud points, T_{CP}, were determined at the onset of transmittance decrease.

Electrospray ionization (ESI) mass spectrometry was performed on a Scientific LTQ Orbitrap XL mass spectrometer operating in positive ion mode with a spray voltage of 1.2 kV, a capillary voltage of 45 V, a capillary temperature of 200 °C, and a tube lens voltage of 120 V.

Poly[2-(dimethylamino)ethyl methacrylate], **pDMAEMA**, was prepared as previously described.[48] $M_n^{theor.}$ = 31.8 kg/mol, $DP^{theor.}$ = 201, M_n^{SEC} = 22.3 kg/mol (DMAc, PS standard), $Đ_M = M_w^{SEC}/M_n^{SEC}$ = 1.14. ^{1}H NMR (D_2O, 300 MHz), δ/ppm = 4.11 (–OC<u>H</u>$_2$CH$_2$–), 2.67 (–OCH$_2$C<u>H</u>$_2$–), 2.27 (–N(C<u>H</u>$_3$)$_2$–), 2.04 (backbone –C<u>H</u>$_2$–), 1.08, 0.90 (backbone –C<u>H</u>$_3$).

Postpolymerization of pDMAEMA with sultones. Poly[3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate], **p(MA2-3)**: pDMAEMA (100 mg, 0.636 mmol of repeat units, 1 eq.) was dissolved in 2,2,2-trifluoroethanol (2 mL). In a separate vial, 1,3-propanesultone (155.4 mg, 1.272 mmol, 2 eq.) was dissolved in TFE (1 mL) and then added into the polymer solution. The mixture was stirred at 40 °C for 3 days. Brine was added to the reaction mixture and the aqueous phase was washed several times with diethyl ether, subjected to dialysis utilizing regenerated cellulose membranes with a 3500 g/mol molecular

weight cut-off in ultrapure water for 3 days followed by freeze drying, yielding 163 mg (92%) of a white solid. ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 4.54 (–OC$\underline{H}_2$CH$_2$–), 3.86 (–OCH$_2$C$\underline{H}_2$–), 3.65 (–N$^+$(CH$_3$)$_2$C$\underline{H}_2$CH$_2$–), 3.28 (–N$^+$(C$\underline{H}_3$)$_2$–), 3.03 (–C$\underline{H}_2$SO$_3^-$), 2.34 (–N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$–), 2.06 (backbone –C$\underline{H}_2$–), 1.20, 1.06 (backbone –C$\underline{H}_3$).

Poly[4-((2-(methacryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate], p(MA2-4), was prepared in an analogous procedure using 1,4-butanesultone (173.2 mg, 1.272 mmol, 2 eq.) with heating to reflux (oil bath at 103 °C) for 4 days. Workup as detailed above yielded 125 mg (67%) of a white solid. ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 4.57 (–OC$\underline{H}_2$CH$_2$–), 3.86 (–OCH$_2$C$\underline{H}_2$–), 3.56 (–N$^+$(CH$_3$)$_2$C$\underline{H}_2$CH$_2$CH$_2$–), 3.28 (–N$^+$(C$\underline{H}_3$)$_2$–), 3.03 (–C$\underline{H}_2$SO$_3^-$), 2.08 (–N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$CH$_2$– and backbone –C$\underline{H}_2$–), 1.90 (–N$^+$(CH$_3$)$_2$CH$_2$CH$_2$C$\underline{H}_2$–), 1.20, 1.06 (backbone –C$\underline{H}_3$).

Monomer 4-((2-(methacryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate (MA2-4).[49] 2-(Dimethylamino)ethyl methacrylate (DMAEMA, 4.43 mL, 26.3 mmol), 1,4-butanesultone (2.44 mL, 23.9 mmol), inhibitor 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT, 50 mg), and acetonitrile (50 mL) were combined and refluxed for 48 h. The consumption of 1,4-butanesultone was monitored by thin-layer chromatography (TLC) using *n*-hexane–ethyl acetate 50:50 as the mobile phase. The crude material which precipitated throughout the course of the reaction was filtered, washed with acetonitrile (150 mL), and dried *in vacuo* at room temperature. 5.32 g (76%) of a white solid were obtained. ^{1}H NMR (D_2O, 300 MHz), δ/ppm = 6.18 (m, 1 H, C$\underline{H}$H=C(CH$_3$)–, *cis*), 5.80 (m, 1 H, CH$\underline{H}$=C(CH$_3$)–, *trans*), 4.65 (m, 2 H, –OC$\underline{H}_2$CH$_2$–), 3.80 (m, 2 H, –OCH$_2$C$\underline{H}_2$–), 3.48 (m, 2 H, –N$^+$(CH$_3$)$_2$C$\underline{H}_2$CH$_2$CH$_2$–), 3.20 (s, 6 H, –N$^+$(C$\underline{H}_3$)$_2$–), 2.99 (t, 2 H, –C$\underline{H}_2$SO$_3^-$), 2.00 (m, 5 H, –N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$CH$_2$– and –CH$_2$C(C$\underline{H}_3$)–), 1.82 (m, 2 H, –N$^+$(CH$_3$)$_2$CH$_2$CH$_2$C$\underline{H}_2$–).

Monomer 4-((2-(acryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate (A2-4). 2-(Dimethylamino)ethyl acrylate (DMAEA, 4.19 mL, 27.6 mmol), 1,4-butanesultone (2.56 mL, 25.1 mmol), BHT (50 mg), and acetonitrile (50 mL) were combined and refluxed for 48 h. The consumption of 1,4-butanesultone was monitored by TLC with *n*-hexane–ethyl acetate 50:50 as the mobile phase. The crude material which precipitated throughout the course of the reaction was filtered, washed with acetonitrile (150 mL) and dried *in vacuo* at room temperature. 6.20 g (89%) of a white solid were obtained. ^{1}H NMR (D_2O, 300 MHz), δ/ppm = 6.49 (dd, 1 H, *trans*, $^2J_{gem}$ = 1.2 Hz, $^3J_{cis}$ = 17.4 Hz, C<u>H</u>H=CH–), 6.25 (dd, 1 H, *gem*, $^3J_{trans}$ = 17.1 Hz, $^3J_{cis}$ = 17.1 Hz, CHH=C<u>H</u>–), 6.06 (dd, 1 H, *cis*, $^2J_{gem}$ = 0.9 Hz, $^3J_{trans}$ = 10.5 Hz, CH<u>H</u>=CH–), 4.66 (m, 2 H, –OC<u>H</u>$_2$CH$_2$–), 3.79 (m, 2 H, –OCH$_2$C<u>H</u>$_2$–), 3.48 (m, 2 H, –N$^+$(CH$_3$)$_2$C<u>H</u>$_2$CH$_2$CH$_2$–), 3.20 (s, 6 H, –N$^+$(C<u>H</u>$_3$)$_2$–), 2.99 (t, 2 H, –C<u>H</u>$_2$SO$_3^-$), 2.00 (m, 2 H, –N$^+$(CH$_3$)$_2$CH$_2$C<u>H</u>$_2$CH$_2$–), 1.82 (m, 2 H, –N$^+$(CH$_3$)$_2$CH$_2$CH$_2$C<u>H</u>$_2$–).

Monomer 4-((3-methacrylamidopropyl)dimethylammonio)butane-1-sulfonate (MAm3-4). 3-(Dimethylamino)propyl methacrylamide (DMAPMAm, 3.05 g, 17.9 mmol), 1,4-butanesultone (1.67 mL, 16.3 mmol), BHT (50 mg), and acetonitrile (50 mL) were combined and heated to 45 °C for 3 days. The crude material which precipitated throughout the course of the reaction was filtered, washed with acetonitrile (150 mL) and dried *in vacuo* at room temperature. 2.63 g (53%) of a white solid were obtained. ^{1}H NMR (D_2O, 300 MHz), δ/ppm = 5.73 (m, 1 H, C<u>H</u>H=C<), 5.50 (m, 1 H, CH<u>H</u>=C<), 3.38 (m, 6 H, –NHC<u>H</u>$_2$CH$_2$C<u>H</u>$_2$–N$^+$(CH$_3$)$_2$C<u>H</u>$_2$–), 3.09 (s, 6 H, –N$^+$(C<u>H</u>$_3$)$_2$–), 2.98 (t, 2 H, –C<u>H</u>$_2$SO$_3^-$), 2.06 (m, 2 H, –NHCH$_2$C<u>H</u>$_2$CH$_2$–), 1.95 (m, 5 H, –N$^+$(CH$_3$)$_2$CH$_2$C<u>H</u>$_2$CH$_2$– and CH$_2$=C(C<u>H</u>$_3$)–), 1.81 (m, 2 H, –N$^+$(CH$_3$)$_2$CH$_2$CH$_2$C<u>H</u>$_2$–). MS (ESI) *m*/*z* (%) = 329 (100) [M + Na]$^+$, 635 (72) [2M + Na]$^+$, 941 (29) [3M + Na]$^+$, 482 (16) [3M + 2Na]$^{2+}$, 788 (11) [5M + 2Na]$^{2+}$; m.p. 117 °C.

RAFT (co)polymerization of zwitterionic methacrylate monomers (Procedure A). Zwitterionic monomer (**MA2-3** or **MA2-4**, 0.75 g, 130–300 equiv as given below), RAFT agent 2-cyano-2-propyl benzodithioate (CPDB, 1 equiv), initiator AIBN (0.1 equiv) and 2,2,2-trifluoroethanol (4 mL) were combined in a flask and degased, polymerized, analysed and purified as described above. The methacrylic copolymers **p[(MA2-3)$_x$-*co*-(MA2-4)$_y$]** were synthesized in analogy using a mixture of monomers **MA2-3** and **MA2-4** in predetermined molar feed ratios. After purification, molar compositions were determined by ^{1}H NMR spectroscopy by comparing signals at δ/ppm = 2.34 (2 H from propyl spacer of **MA2-3** repeat units) with δ/ppm = 2.20–1.50 (2 H from **MA2-3** and 6 H from **MA2-4** overlapping).

Poly[3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate], **p(MA2-3)**: ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 4.56 (–OC$\underline{H}_2$CH_2–), 3.88 (–OCH_2C$\underline{H}_2$–), 3.66 (–N$^+$(CH_3)$_2$C$\underline{H}_2$CH_2–), 3.30 (–N$^+$(C$\underline{H}_3$)$_2$–), 3.04 (–C$\underline{H}_2$SO$_3^-$), 2.34 (–N$^+$(CH_3)$_2$CH_2C$\underline{H}_2$–), 2.07 (backbone –C$\underline{H}_2$–), 1.21, 1.06 (backbone –C$\underline{H}_3$).

Poly[4-((2-(methacryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate], **p(MA2-4)**: ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 4.56 (–OC$\underline{H}_2$CH_2–), 3.85 (–OCH_2C$\underline{H}_2$–), 3.54 (–N$^+$(CH_3)$_2$C$\underline{H}_2$CH_2CH_2–), 3.27 (–N$^+$(C$\underline{H}_3$)$_2$–), 3.02 (–C$\underline{H}_2$SO$_3^-$), 2.06 (–N$^+$(CH_3)$_2$CH_2C$\underline{H}_2$CH_2– and backbone –C$\underline{H}_2$–), 1.90 (–N$^+$(CH_3)$_2$CH_2CH_2C$\underline{H}_2$–), 1.20, 1.06 (backbone –C$\underline{H}_3$).

RAFT polymerization of zwitterionic acrylate monomer (Procedure B). Zwitterionic monomer 4-((2-(acryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate (**A2-4**) (0.75 g, 2.68 mmol, 200 equiv), RAFT agent benzyl propyl trithiocarbonate (BPTC, 3.3 mg, 0.0134 mmol, 1 equiv), initiator AIBN (0.2 mg, 13.4 μmol, 0.1 equiv) and solvent 2,2,2-trifluoroethanol (4 mL) were combined in a flask equipped with a stir bar. The mixture was sealed with a rubber septum and purged with nitrogen for 20 min before being placed into a preheated oil bath at 70 °C

overnight. Polymerization was stopped by quenching the reaction with liquid nitrogen. A sample (50 μL) was withdrawn, diluted with D_2O (600 μL) and analysed by ^1H NMR spectroscopy to determine monomer conversion through quantification of residual vinyl signals and comparison with polymeric signals. The product was purified by addition of brine and washing with diethyl ether, followed by dialysis in ultrapure water for 3 days and freeze-drying. Conversion and SEC-measured M_n^{SEC} and $Đ_M$ are given below. Poly[4-((2-(acryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate], **p(A2-4)**: ^1H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 4.57 (–OC$\underline{H}_2$CH$_2$–), 3.80 (–OCH$_2$C$\underline{H}_2$–), 3.51 (–N$^+$(CH$_3$)$_2$C$\underline{H}_2$CH$_2$CH$_2$–), 3.24 (–N$^+$(C$\underline{H}_3$)$_2$–), 2.99 (–C$\underline{H}_2$SO$_3^-$), 2.55 (backbone –C$\underline{H}$<), 2.03 (–N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$CH$_2$– and backbone –C$\underline{H}_2$–), 1.85 (–N$^+$(CH$_3$)$_2$CH$_2$CH$_2$C$\underline{H}_2$–).

RAFT polymerization of MA2-3 with an activated ester end group (Procedure C). Monomer **MA2-3** (1 g, 3.58 mmol, 250 equiv), RAFT agent pentafluorophenyl 4-cyano-4-((phenylcarbonothioyl)thio)valerate (6.4 mg, 14.4 μmol, 1 equiv), activated ester-functional initiator bis(pentafluorophenyl) 4,4'-(diazene-1,2-diyl)bis(4-cyanopentanoate) (0.9 mg, 1.44 μmol, 0.1 equiv.) and anhydrous propylene carbonate (7 mL) were combined and polymerized and purified as described above. After cooling to room temperature, to 4 mL of polymer solution was added 4-nitro-7-piperazin-1-yl-2,1,3-benzoxadiazole (6.7 mg, 26.9 μmol, 3.4-fold excess with regards to PFP esters) and the mixture was stirred for 1 day at RT, followed by addition of brine and extraction with ether and dialysis in ultrapure water at 35 °C. The resulting polymer was dried yielding an orange solid that exhibited UCST behaviour in water, qualitatively confirming attachment of dye to the polymer.

Poly(pentafluorophenyl acrylate), pPFPA. Monomer PFPA (5.0 g, 21.0 mmol, 250 equiv), RAFT agent BPTC (20.4 mg, 0.084 mmol, 1 equiv), initiator AIBN (1.4 mg, 8.4 μmol, 0.1 equiv)

and acetonitrile (7 mL) were combined in a flask equipped with a stir bar. The mixture was sealed with a rubber septum and purged with nitrogen for 30 minutes before being placed into a preheated oil bath at 70 °C for 10 h. Polymerization was stopped by quenching the reaction with liquid nitrogen. A sample (100 µL) was withdrawn, diluted with $CDCl_3$ (550 µL) and analysed by ^{19}F NMR spectroscopy which indicated a monomer conversion of 71 % by comparison of the signal at −156.9 ppm (bs, polymer *para*-F) with the signal at −158.0 ppm (t, monomer *para*-F). The polymer was isolated as a slightly yellow powder (2.73 g, 55 %) by two precipitations in methanol followed by drying in vacuum. $M_n^{theor.}$ (from conversion) = 42.6 kg/mol., $DP_{theor.}$ = 178, M_n^{SEC} = 68.6 kg/mol (PS standard), $Đ_M = M_{w,SEC}/M_{n,SEC}$ = 1.23; ^{19}F NMR (282 MHz, $CDCl_3$), δ/ppm = −153.2 (bm, 2 F, *ortho*), −156.8 (bs, 1 F, *para*), −162.2 (bs, 2 F, *meta*). FT-IR: ν/cm^{-1} = 1780 (carbonyl C=O stretch), 1520 (aryl C=C bend).

3-((3-Aminopropyl)dimethylammonio)propane-1-sulfonate, (**amine3-3**) was prepared in 3 steps as previously reported:[43] (i) protection of the primary amino group of *N*,*N*-dimethylaminopropylamine with di-*tert*-butyl dicarbonate (BOC_2O) yielding *tert*-butyl (3-(dimethylamino)propyl)carbamate, which was purified by column chromatography in chloroform–methanol 6:1; (ii) quaternization of the tertiary amino group with 1,3-propanesultone and (iii) cleavage of the BOC protecting group with acid followed by treatment with base to give the free base product.

4-((3-aminopropyl)dimethylammonio)butane-1-sulfonate, (**amine3-4**) was prepared in analogy to **amine3-3** by substituting 1,3-propanesultone with 1,4-butanesultone in step (ii) under modified reaction conditions: *Tert*-Butyl (3-(dimethylamino)propyl)carbamate (2.5 g, 12 mmol, 1 equiv) was dissolved in anhydrous THF (15 mL), the flask was flushed with nitrogen, and 1,4-butanesultone (1.8 mL, 17 mmol, 1.4 eq.) was added. The mixture was stirred for 4 days at 40 °C.

The precipitated white solid was filtered off, washed with THF (100 mL), and dried in vacuum at 40°C. Yield: 1.95 g, (48 %). ^{1}H NMR (300 MHz, D_2O), δ/ppm = 3.35 (m, 4 H, –C$\underline{H}_2$N$^+$(CH$_3$)$_2$C$\underline{H}_2$–), 3.20 (t, 2 H, –CH$_2$C$\underline{H}_2$NHBOC), 3.09 (s, 6 H, –(C$\underline{H}_3$)$_2$N$^+$–), 2.99 (t, 2 H, $^-$O$_3$SC$\underline{H}_2$–), 2.02–1.46 (m, 6 H, $^-$O$_3$SCH$_2$C$\underline{H}_2$C$\underline{H}_2$–, –N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$–), 1.46 (s, 9 H, –C(C$\underline{H}_3$)$_3$). ^{13}C NMR (300 MHz, D_2O), δ/ppm = 158.14 (>$\underline{C}$=O), 81.21 (–$\underline{C}$(CH$_3$)$_3$), 63.35, 61.67 (–$\underline{C}$H$_2$N$^+$(CH$_3$)$_2$$\underline{C}H_2$–), 50.74 (–N$^+$($\underline{C}H_3$)$_2$–), 49.95 ($^-O_3S\underline{C}H_2$–), 36.82 (–CH$_2$$\underline{C}H_2$NHBOC), 27.63 (–C($\underline{C}H_3$)$_3$), 22.68 (–N$^+$(CH$_3$)$_2CH_2$$\underline{C}H_2$–), 21.06 ($^-O_3SCH_2CH_2$$\underline{C}H_2$–), 20.82 ($^-O_3SCH_2$$\underline{C}H_2$–). After treatment with aq. HCl and anion exchange beads, 0.99 g (74%) free base **amine3-4** was obtained. ^{1}H NMR (300 MHz, D_2O), δ/ppm = 3.39–3.32 (m, 4 H, –C$\underline{H}_2$N$^+$(CH$_3$)$_2$C$\underline{H}_2$–), 3.09 (s, 6 H, –N$^+$(C$\underline{H}_3$)$_2$–), 2.99 (t, 2 H, $^-$O$_3$SC$\underline{H}_2$–), 2.72 (t, 2 H, –C$\underline{H}_2$NH$_2$), 2.01–1.77 (m, 6 H, –C$\underline{H}_2$C$\underline{H}_2$CH$_2$N$^+$(CH$_3$)$_2$CH$_2$C$\underline{H}_2$CH$_2$NH$_2$). ^{13}C NMR (300 MHz, D_2O), δ/ppm = 63.47, 62.20 (–$\underline{C}$H$_2$N$^+$(CH$_3$)$_2$$\underline{C}H_2$-), 50.63 (–N$^+$($\underline{C}H_3$)$_2$–), 49.93 ($^-O_3S\underline{C}H_2$–), 37.61 (–CH$_2$$\underline{C}H_2NH_2$), 24.96 –$\underline{C}H_2CH_2NH_2$), 21.07 ($^-O_3SCH_2CH_2$$\underline{C}H_2$–), 20.80 ($^-O_3SCH_2$$\underline{C}H_2$–).

General procedure for Postpolymerization Modification of pPFPA with zwitterionic amines. pPFPA (44.7 mg, 0.188 mmol of repeat units, 1 equiv) was dissolved in anhydrous propylene carbonate (1.5 mL) at 60 °C and hydroxyethyl acrylate (5 μL) was added to scavenge thiols released from the RAFT end groups through aminolysis.[50] In parallel, 3-((3-aminopropyl)dimethylammonio)propane-1-sulfonate, (**amine3-3**, 63.2 mg, 0.282 mmol, 1.5 equiv) or 4-((3-aminopropyl)dimethylammonio)butane-1-sulfonate, (**amine3-4**, 67.1 mg, 0.282 mmol, 1.5 equiv) was dissolved in propylene carbonate (1.5 mL) with heating. After dissolving, the amine solution was quickly added into the polymer solution and the mixture stirred at 40 °C overnight. A sample (100 μL) was withdrawn, diluted with DMSO (550 μL) and analysed by ^{19}F NMR spectroscopy indicating complete conversion of PFP esters showing only signals of free

pentafluorophenol at δ/ppm = −167.4 (2 F, *ortho*), −170.2 (2 F, *meta*), −181.7 (1 F, *para*). The solution was transferred into a dialysis bag (molecular weight cut-off 3500 g/mol) and dialyzed against ultrapure water for 3 days at RT (**p(Am3-3)**) or 60 °C (**p(Am3-4)**), followed by freeze-drying.

Poly[3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate], **p(Am3-3)**: ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz) δ/ppm = 3.55 (bs, $–N^+(CH_3)_2C\underline{H}_2CH_2–$), 3.43 (bs, $–NHCH_2CH_2C\underline{H}_2–$), 3.28 (bs, $–NHC\underline{H}_2CH_2CH_2–$), 3.18 (bs, $–N^+(C\underline{H}_3)_2–$), 3.03 (bt, $–C\underline{H}_2SO_3^-$), 2.26 (bs, $–N^+(CH_3)_2CH_2C\underline{H}_2–$), 2.11, 2.07 (backbone –C<u>H</u><) and ($–NHCH_2C\underline{H}_2CH_2–$), 1.76, 1.66 (backbone $–C\underline{H}_2–$).

Poly[4-((3-acrylamidopropyl)dimethylammonio)butane-1-sulfonate], **p(Am3-4)**: ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz), δ/ppm = 3.40 (bs, $–N^+(CH_3)_2C\underline{H}_2CH_2CH_2–$, $–NHCH_2CH_2C\underline{H}_2–$), 3.28 (bs, $–NHC\underline{H}_2CH_2CH_2–$), 3.15 (bs, $–N^+(C\underline{H}_3)_2CH_2CH_2CH_2–$), 3.01 (bt, $–C\underline{H}_2SO_3^-$), 2.02 (bs, $–N^+(CH_3)_2CH_2C\underline{H}_2CH_2–$, $–N^+(CH_3)_2CH_2CH_2C\underline{H}_2–$), overlapping 2.11 (backbone –C<u>H</u><), 1.86 (bm, $–NHCH_2C\underline{H}_2CH_2–$), 1.64 (backbone $–C\underline{H}_2–$).

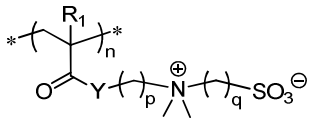
General procedure for Postpolymerization Modification of pPFPA with zwitterionic amine and benzylamine. Poly(pentafluorophenyl acrylate), pPFPA (44.7 mg, 0.188 mmol of repeat units, 1 equiv) was dissolved in anhydrous propylene carbonate (1.5 mL) at 60 °C, and hydroxyethyl acrylate (5 μL) was added. In parallel, 4-((3-aminopropyl)dimethylammonio)butane-1-sulfonate, (**amine3-4**) (x × 0.282 mmol) and benzylamine (y × 0.282 mmol, x + y = 1; 1.5 equiv of amines to PFP ester) were dissolved in propylene carbonate (1.5 mL) with heating. After dissolving, the amine solution was quickly added into the polymer solution and the mixture stirred at 40 °C overnight. Analysis of the reaction mixture was done as described above for the corresponding homopolymers. Products

were isolated by dialysis first in 500 mM aqueous NaCl solution for 2 days, then ultrapure water at 60 °C for 3 days. ^{1}H NMR (D_2O, 500 mM NaCl, 300 MHz, benzyl side groups), δ/ppm = 7.53, 7.29 (m, $–CH_2C_6\underline{H}_5$), 4.45 ($–C\underline{H}_2C_6H_5$). Molar compositions of the benzylacrylamide copolymers poly[(4-((3-acrylamidopropyl)dimethylammonio)butane-1-sulfonate)$_x$-*co*-benzylacrylamide$_y$], **p[(Am3-4)$_x$-*co*-Bz$_y$]** were determined by comparison of the aromatic peaks (5 H) to the sum of the zwitterionic group signals from 3.76–2.74 (14 H).

Results and Discussion

In this work, zwitterionic monomers and their corresponding (co)polymers are abbreviated based on their polymerizable group, *i.e.* acrylate (A), methacrylate (MA), acrylamide (Am), and methacrylamide (MAm), followed by the spacer length between polymerizable unit and ammonium group (2 or 3) and the ion bridge spacer length (3 for SPB, 4 for SBB), see Scheme 1.

Scheme 1. General structure of common sulfobetaine polymers and details and full names of polymers prepared in this study through different synthetic methods



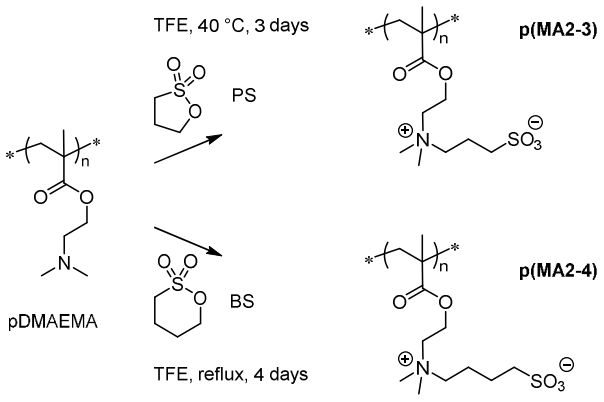
R_1 = H, CH_3 p = 2, 3
Y = O, NH q = 3, 4

Code	R_1	Y	p	q	Full Name
p(MA2-3)	CH_3	O	2	3	poly[3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate]
p(MA2-4)	CH_3	O	2	4	poly[4-((2-(methacryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate]
p(A2-4)	H	O	2	4	poly[4-((2-(acryloyloxy)ethyl)dimethylammonio)butane-1-sulfonate]
p(Am3-3)	H	NH	3	3	poly[3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate]
p(Am3-4)	H	NH	3	4	poly[4-((3-acrylamidopropyl)dimethylammonio)butane-1-sulfonate]
p(MAm3-4)	CH_3	NH	3	4	poly[4-((3-methacrylamidopropyl)dimethylammonio)butane-1-sulfonate]

Method 1: Quaternization of tertiary amine functional polymers with sultones

In order to compare the UCST behaviour of SBB with SPB polymers with identical degrees of polymerization, postmodification of tertiary amine functional species with 1,3-propanesultone (PS) and 1,4-butanesultone (BS) was considered first. Arguably the most popular tertiary amine-functional homopolymer is pDMAEMA. Notably, its acrylate sister polymer poly[2-(dimethylamino)ethyl acrylate] suffers from hydrolytic instability[51] and is far less commonly employed; this method toward SPB and SBB polymers thus primarily gives access to the methacrylic species **p(MA2-3)** and **p(MA2-4)**, see Scheme 2.

Scheme 2. Method 1: Synthesis of polysulfobetaines through post-modification of poly[2-(dimethylamino)ethyl methacrylate] (pDMAEMA) with PS and BS in 2,2,2-trifluoroethanol (TFE)



RAFT-made pDMAEMA (DP = 201, $Đ_M = M_w/M_n = 1.14$) was reacted under *homogeneous* conditions in 2,2,2-trifluoroethanol (TFE) as solvent with 2 equiv (with respect to amino groups) of PS for 3 days at 40 °C and with 2 equiv of BS for 4 days under reflux. Excess reagent was removed by adding brine and washing with diethyl ether and product polymers were isolated by

dialysis against ultrapure water and analysed by ^{1}H NMR spectroscopy, aqueous size exclusion chromatography (SEC), and turbidity measurements. While the NMR spectrum of the product from pDMAEMA and PS, Figure 1A, conformed to the expected homo-**p(MA2-3)**, suggesting quantitative conversion, the modification of pDMAEMA with the less reactive BS was found to be only 95% complete, as judged from a residual broad singlet at 2.64 ppm in the ^{1}H NMR spectrum (Figure 1B) which was assigned to the $(C\underline{H}_3)_2N$– resonance of unreacted DMAEMA segments. Aqueous SEC revealed narrow molecular weight distributions of **p(MA2-3)** and **p[(MA2-4)$_{0.95}$-*co*-DMAEMA$_{0.05}$]** predictably similar to that of the pDMAEMA parent, see Figure 2A and Table 1. The zwitterionic (co)polymers eluted at a similar time, suggesting similar hydrodynamic sizes in the 0.2 M NaCl eluent. The **p(MA2-3)** sample was found to be soluble in ultrapure water over the entire observed temperature range from 0–90 °C at a concentration of 10 g/L, not exhibiting the anticipated UCST behaviour. Presumably, in spite of the favourable ^{1}H NMR measurement (Figure 1A), the modification may not have been quantitative or the pDMAEMA precursor may have suffered hydrolysis / alcoholysis during the extended reaction time. Incomplete betainization of pDMAEMA has been shown to lead to enhanced water solubility (*i.e.* decreased UCST transitions) due to the hydrophilicity associated with the residual DMAEMA repeat units.[52] The butane-spaced sister copolymer **p[(MA2-4)$_{0.95}$-*co*-DMAEMA$_{0.05}$]**, on the other hand and regardless of its incomplete degree of betainization, exhibited a high cloud point of 77.9 °C.

Reduced solubility of SBB species compared to analogous SPBs has been documented for small molecule zwitterionic surfactants and has been speculated to be due to higher hydrophobicity imparted by the additional methylene group in the spacer,[26, 53, 54] Bredas et al.[27] found in a theoretical assessment of the aggregation of zwitterionic SPB and SBB end groups in

non-polar solvents that SBB head groups (which, same as SPP groups are usually curled as opposed to in an all-trans conformation)[28, 29] can more easily adopt an extended conformation when aggregating, which makes their dimerization (and aggregation) more favourable than that of SPB groups. To the best of our knowledge, reduced solubility of SBB-functional *polymers* compared to their SPB counterparts has only very recently been described.[22] Given the significantly higher cloud point of the (albeit incompletely modified) **MA2-4** copolymer and the resulting potential for UCST tuning (as elaborated above, a *reduction* of UCST values is easiest to achieve), other routes to SBB (co)polymers were examined.

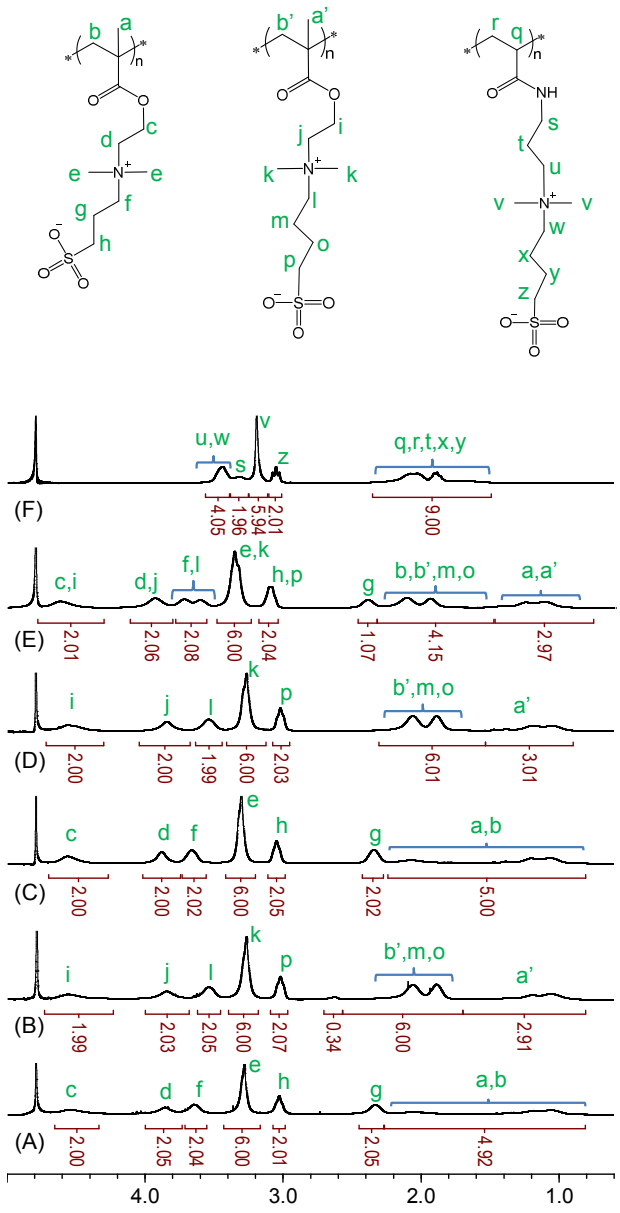


Figure 1. ^{1}H NMR spectra measured in D_2O containing 500 mM NaCl of (**A**) **p(MA2-3)** prepared from pDMAEMA (method 1); (**B**) **p(MA2-4)** prepared from pDMAEMA (method 1); (**C**) **p(MA2-3)** prepared by RAFT polymerization (method 2); (**D**) **p(MA2-4)** prepared by RAFT polymerization; (**E**) RAFT-made copolymer **p[(MA2-3)$_{0.51}$-*co*-(MA2-4)$_{0.49}$]**, and (**F**) **p(Am3-4)** obtained from postpolymerization modification of pPFPA (method 3)

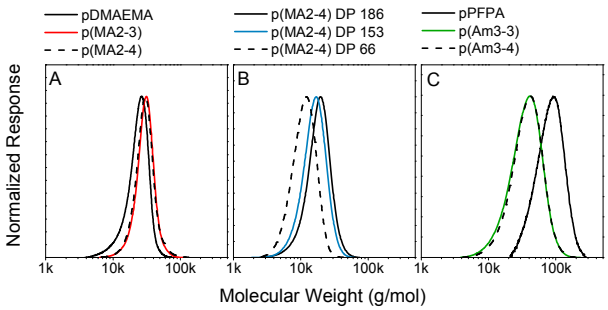


Figure 2. SEC curves of (A) pDMAEMA precursor (eluent DMAc, polystyrene standards) and its daughter homopolymers **p(MA2-3)** and **p(MA2-4)** (eluent 0.2 M aqueous NaCl, PEG standards) (method 1); (B) RAFT-made **p(MA2-4)** of different degrees of polymerization (eluent 0.2 M aqueous NaCl, PEG standards) (method 2); and (C) pPFPA precursor (eluent DMAc, polystyrene standards) and its daughter homopolymers **p(Am3-3)** and **p(Am3-4)** (eluent 0.2 M aqueous NaCl, PEG standards) (method 3).

Table 1. Homopolymers derived from pDMAEMA (DP[a] = 201, $Đ_M = M_w/M_n = 1.14$) by postpolymerization modification with sultones

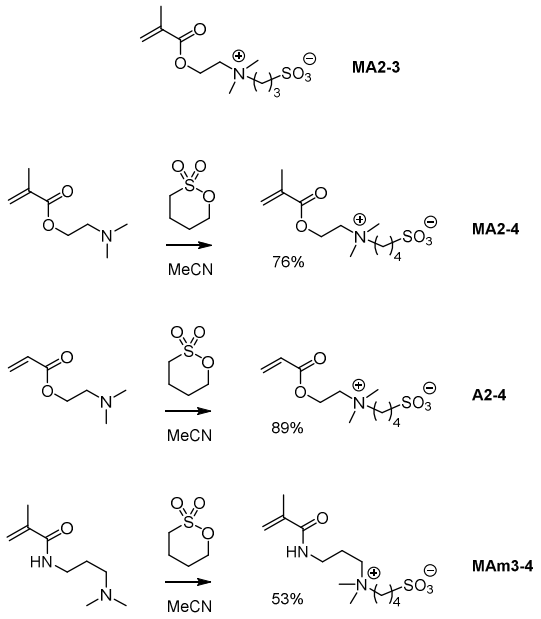
Product	Reagent	Conversion (%)[b]	DP	M_n^{theor} (kg/mol)[c]	M_n^{SEC} (kg/mol)[d]	$Đ_M$[d]	Cloud Point (°C)[e]
p(MA2-3)	1,3-propanesultone	100	201	56.4	28	1.10	S[f]
p[(MA2-4)$_{95}$-*co*-DMAEMA$_5$]	1,4-butanesultone	95	201	59.2	27	1.11	77.9

[a] degree of polymerization calculated from conversion estimated by ^{1}H NMR measurement of polymerization mixture; [b] calculated from ^{1}H NMR analysis; [c] Molar mass calculated from DP; [d] Poly(ethylene glycol) equivalent molecular weight and dispersity determined by aqueous SEC. [e] UCST cloud point measured in ultrapure water at a concentration of 10 g/L. [f] Soluble between 0 and 90 °C at a concentration of 10 g/L.

Method 2: RAFT (co)polymerization of zwitterionic monomers

Polymerization of zwitterionic monomers yields zwitterionic polymers in one step. In addition to monomer **MA2-3** used for the preparation of reference polymers, the SBB species **MA2-4**, **A2-4** and **MAm3-4** were synthesized in analogy to literature procedures[18, 49, 55] from the respective dimethylamino-functional monomers in acetonitrile with BS in moderate to high yields, Scheme 3.

Scheme 3. Overview of zwitterionic monomers including the commercially available species **MA2-3** and sulfobutylbetaine (SBB) monomers prepared in this study



RAFT polymerization[56] in homogeneous TFE solution using dithioester and trithiocarbonate chain transfer agents (CTAs) was employed to access (co)polymers with predetermined molecular weights with narrow molecular weight distributions, see Scheme 4. Table 2 summarizes conversions, degrees of polymerization (DP, calculated from feed and conversion), aqueous SEC results and cloud points for a series of **MA2-3** homopolymers (entries 1–3), a

series of **MA2-4** homopolymers (entries 5–7), a **p(A2-4)** species (entry 8), and a series of statistical copolymers **p[(MA2-3)$_x$-*co*-(MA2-4)$_y$]** with indices x and y denoting the respective measured molar percentages. Additionally, another sample of **p(MA2-3)** (entry 4 in Table 2) was prepared using a pentafluorophenyl (PFP)-functional CTA and PFP-functional initiator in propylene carbonate, structures are shown in Scheme 5.

Scheme 4. Method 2: Homo- and copolymerization of zwitterionic monomers by the RAFT process.

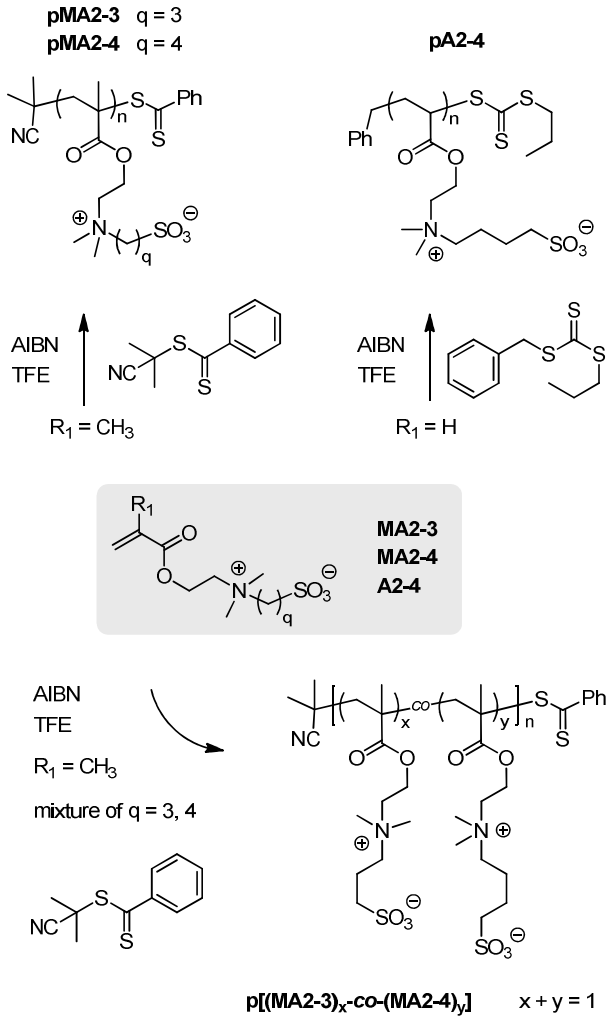
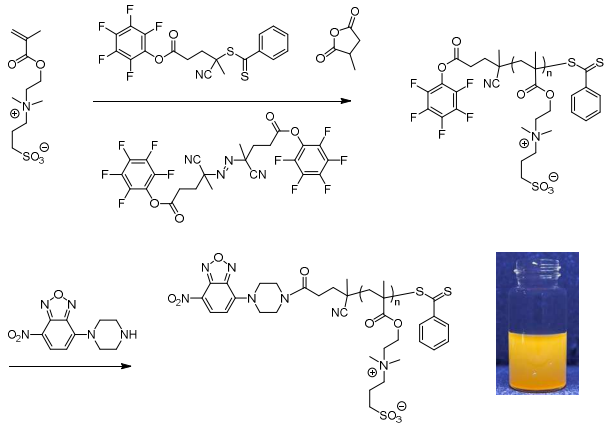


Table 2. Homo- and copolymers prepared by RAFT radical polymerization of zwitterionic monomers.

Entry	Product	procedure[a]	Comonomer feed (mol%)[b]	Target DP	Monomer Conversion (%)[c]	DP[d]	$M_{n,theor}$ (kg/mol)	$M_{n,SEC}$ (kg/mol)	$Đ_M$	Cloud Point (°C)[e]
1	**p(MA2-3)**	A	–	200	80	161	45.2	15	1.18	13.2
2	**p(MA2-3)**	A	–	230	83	191	53.6	17	1.13	18.8
3	**p(MA2-3)**	A	–	300	92	277	77.6	28	1.16	35.9
4	**p(MA2-3)**	C	–	250	99	248	69.7	24	1.37	26.9
5	**p(MA2-4)**	A	–	130	51	66	19.6	11	1.16	26.5
6	**p(MA2-4)**	A	–	200	77	153	45.1	15	1.17	64.9
7	**p(MA2-4)**	A	–	250	75	186	54.8	17	1.18	76.5
8	**p(A2-4)**	B	–	200	92	183	51.4	16	1.13	52.7
9	**p[(MA2-3)$_{0.26}$-*co*-(MA2-4)$_{0.74}$]**[f]	A	25:75	230	80	184	53.5	17	1.23	63.4
10	**p[(MA2-3)$_{0.51}$-*co*-(MA2-4)$_{0.49}$]**	A	50:50	230	82	187	53.7	18	1.20	47.8
11	**p[(MA2-3)$_{0.75}$-*co*-(MA2-4)$_{0.25}$]**	A	75:25	230	83	191	54.2	18	1.17	35.5

[a] Procedure A: CPDB in TFE; B: BPTC in TFE, C: PFP-functional CTA and initiator in propylene carbonate; [b] molar ratio of **MA2-3**–**MA2-4** in feed; [c] (global) monomer conversion determined by ^{1}H NMR spectroscopy; [d] degree of polymerization estimated from conversion; [e] UCST cloud point measured in ultrapure water at a concentration of 10 g/L. [f] molar copolymer composition determined by ^{1}H NMR spectroscopy

Scheme 5. RAFT polymerization of zwitterionic monomer **MA2-3** using a PFP activated ester-functional CTA and a PFP-functional initiator followed by attachment of the dye 4-piperidyl-7-nitrobenzofurazan with inset photograph of the purified polymer solution under UV illumination



Overall, the RAFT synthesis of zwitterionic SPB and SBB (co)polymers from **MA2-3**, **MA2-4**, and **A2-4** proceeded smoothly in TFE with conversions generally ranging between 75–92% after polymerization at 70 °C overnight. (Co)Polymer products had low measured dispersities of $Đ_M \leq 1.23$, with the exception of one **p(MA2-3)** sample that proceeded to 99% monomer conversion and had a $Đ_M$ of 1.37. Exemplary molecular weight distribution curves obtained by aqueous SEC of the series of **MA2-4** homopolymers are plotted in Figure 2B showing increasing hydrodynamic sizes with increasing DPs. Since SEC yields only apparent molecular weights, the absolute molecular weight of an exemplary sample, **p(MA2-4)** with a calculated DP of 66 (Table 2, entry 5), was estimated by end group analysis. A solution of this polymer in 2,2,2-trifluoroethanol at a concentration of 1.0 g/L was found to have an absorbance maximum of A = 0.63 at a wavelength of 308 nm which was attributed to a π–π* absorption band of the dithioester end group.[57] Using the tabulated maximum molar absorptivity of a model RAFT agent, 4-cyano-

4-(phenylcarbonothioylthio)pentanoic acid, of ε = 13,200 L mol^{-1} cm^{-1}, measured in methanol,[57] as reference, an absolute molecular weight M_n = 21.0 kg/mol was obtained, in reasonable agreement with the theoretical value of 19.6 kg/mol. Notably, this calculation assumes (i) equal absorbivities of the dithioester group of the model RAFT agent in methanol and the dithioester end group of the zwitterionic polymer in 2,2,2-trifluorethanol and (ii) no loss of RAFT end groups through hydrolysis or alcoholysis. All ^{1}H NMR spectra conformed to the expected respective homo- and copolymer structures; Figure 1 shows exemplary spectra of **p(MA2-3)** (spectrum C) and **p(MA2-4)** (spectrum D) samples and copolymer **p[(MA2-3)$_{0.51}$-*co*-(MA2-4)$_{0.49}$]**. Note the striking similarity between spectra C and A and spectra D and B, the latter with the exception of the above-mentioned residual DMAEMA resonance. RAFT polymerization of the methacrylamide derivative **MAm3-4**, however, gave only very low conversions employing BPTC or CPBP as the mediating CTAs. Low conversion of the **MAm3-3** analogue using a dithiobenzoate RAFT agent was previously observed by others;[36] while Hildebrandt et al.,[31] for example, described high conversions of **MAm3-3** using a 4-cyano-4-[(phenylethylsulfanylthiocarbonyl)sulfanyl]pentanoic acid derivative.

All RAFT-made (co)polymers showed sharp, fully reversible and reproducible UCST transitions with a hysteresis of ~3 °C, see Figure S1 in the supporting information. The significant impact of the ion bridge length on the aqueous solution behaviour was apparent from a comparison of the **p(MA2-4)** series with the homologous **p(MA2-3)** reference series. A plot of their cloud points vs their DP, shown in Figure 3, supported the following observations: Over the observed DP range, the UCST cloud point (CP) increases in a linear fashion with DP for both series. The CP increases more strongly with the DP for the SBB homopolymers, linear fits giving CP_{SBB}/°C = 0.42 × DP − 0.96 for the **p(MA2-4)** series and CP_{SPB}/°C = 0.20 × DP – 18.5 for the

p(MA2-3) series. Thus, when comparing homopolymers of the same length, **p(MA2-4)** has significantly higher cloud points than **p(MA2-3)**. The cloud point of the **p(MA2-3)** sample prepared with a different end group (entry 4 in Table 2) coincided with the trend of its sister polymers, indicating only small end group influence on the UCST transition at this DP. These observations suggest that, with regards to exploiting aqueous UCST behaviour, the investigated SBB species present a clear advantage over their SPB homologues. To reiterate, most manipulations of the aqueous solvent or the chemical structure of polysulfobetaines such as inclusion of hydrophilic (or certain hydrophobic)[43] groups bring about a decrease of UCST cloud points necessitating scaffolds with fundamentally high UCST transitions in pure water. Judging from the plot in Figure 3, aqueous UCST cloud points around body temperature can be realized with **p(MA2-4)** with an easily achievable DP of ~100, while, in agreement with literature,[21, 35] significantly higher DPs are necessary for **p(MA2-3)** to achieve as high cloud points.

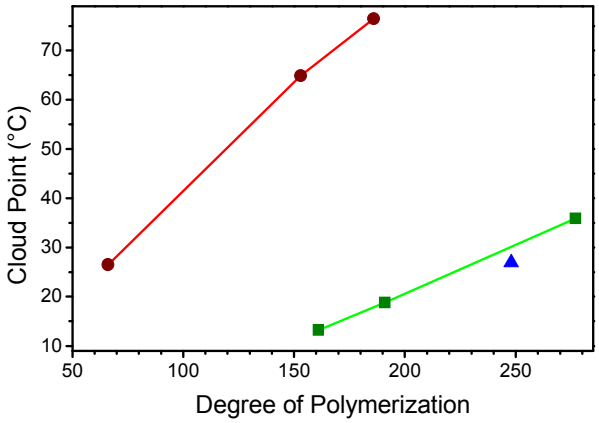


Figure 3. UCST cloud point versus degree of polymerization for **p(MA2-3)** (green squares) and **p(MA2-4)** (red circles) prepared by RAFT in 2,2,2-trifluoroethanol using CPDB as chain transfer agent and of **p(MA2-3)** made by RAFT in propylene carbonate using the activated ester CTA (Scheme 5) (blue triangle). Lines are added to guide the eye.

The aqueous solution behaviour of the SBB acrylate species **p(A2-4)** (DP = 183) was also assessed and compared to **p(MA2-4)** (DP = 186) and **p(MA2-3)** (DP = 191) with similar degrees of polymerization. A temperature–concentration phase diagram, showing the boundary between the two-phase (below the curve) and the one-phase region (above the curve), shown in Figure 4, made evident the similar shape of the phase separation boundaries with flat regions above concentrations of ~10 g/L for all three zwitterionic polymers. Of note, the acrylic polymer **p(A2-4)** exhibiting a cloud point of 52.7 °C at a concentration of 10 g/L was more water soluble than the methacrylic analog **p(MA2-4)** (CP = 76.5 °C at the same concentration) but less soluble than the SPB derivative **p(MA2-3)** (CP = 18.8 °C), indicating that the UCST is influenced much more sensitively by formal addition of a methylene segment to the ion bridge rather than to the backbone. This observation thus corroborated the notion of improved electrostatic interlocking efficiency of butyl-spaced zwitterionic groups due to higher flexibility of the of the butyl chains and their stronger tendency to adopt an extended conformation as compared to the propyl analogues.[27]

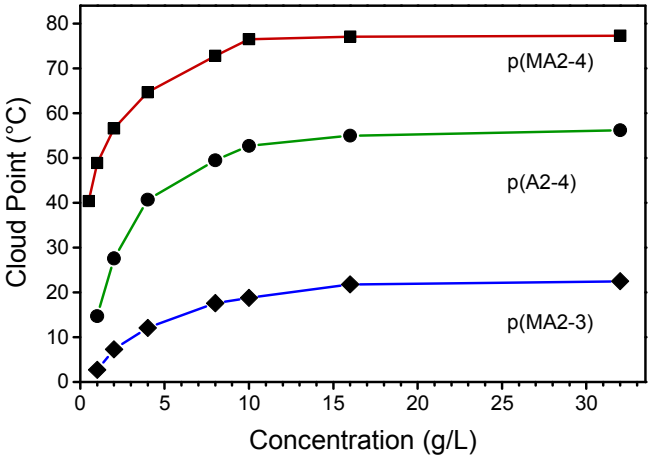


Figure 4. Temperature–concentration phase diagrams of three RAFT-made homopolymers with comparable degrees of polymerization, **p(MA2-4)** (DP = 186), **p(A2-4)** (DP = 183), and **p(MA2-3)** (DP = 191) showing a largely flat region above concentration of ~ 10 g/L.

Comparison of the RAFT-made homopolymer series with those obtained from post-modification of pDMAEMA suggested an undeniable influence of the synthetic method on the UCST behaviour. Judging from the linear fit of CP vs. DP for the RAFT-made **p(MA2-3)** series, Figure 3, the pDMAEMA-made sample with a DP of 201 would be expected to have a CP of around 22 °C, but was, as mentioned above, fully soluble. This comparison suggested that (for the chosen reaction conditions) the modification of pDMAEMA with sultones was not ideal with regards to obtaining (high) UCST transitions. In order to assess the scope and limitations of direct polymerization of zwitterionic monomers, two further experiments were conducted.

Firstly, the modification of polymer end groups is of great importance for the construction of defined polymeric architectures including diblock copolymers, surface-tethered brushes, or hybrid materials. RAFT polymerization was thus attempted with an activated ester CTA and activated ester initiator, as shown in Scheme 5. This approach produces polymers with one

activated pentafluorophenol (PFP) end group providing access to simple modification with amines.[46, 58] The reactive CTA and initiator were, however, not soluble in water and were found to react, at elevated polymerization temperatures, with TFE. Therefore, propylene carbonate was used as a non-protic solvent in which monomer **MA2-3** was moderately soluble, while, remarkably, **MA2-4**, was poorly soluble. Polymerization of **MA2-3** thus yielded a homopolymer with a reactive end group which possessed UCST characteristics with a cloud point in good agreement with those of the series polymerized in TFE, see Figure 3. Addition of an amine-functional dye to a propylene carbonate solution of the reactive end group-functional polymer followed by purification yielded an orange-coloured solid that dissolved in (warm) water with yellow colour, see Scheme 5. This experiment demonstrated successful RAFT polymerization of a zwitterionic SPB monomer with a reactive CTA in a non-protic solvent and provided qualitative evidence of successful end group modification with a hydrophobic dye. However, though advantageous with respect to higher UCST transitions, the low compatibility of the SBB **MA2-4** with non-protic solvents poses limitations for the incorporation of water / TFE sensitive or insoluble species into **MA2-4**-based (co)polymers.

Secondly, a series of copolymers of **MA2-3** and **MA2-4** with comparable DPs (184–191) and SEC-measured apparent molar masses was prepared by RAFT radical polymerization in TFE. Copolymer compositions, determined by ^{1}H NMR spectroscopy (see Figure 1E) and listed in Table 2, matched very well with the comonomer feed ratio, indicating the formation of copolymers with predetermined molar compositions. Determination of their aqueous solution behaviour revealed a linear increase of cloud points with **MA2-4** comonomer content, Figure 5, suggesting a convenient and simple methodology for tuning of UCST transitions at a constant chain length.

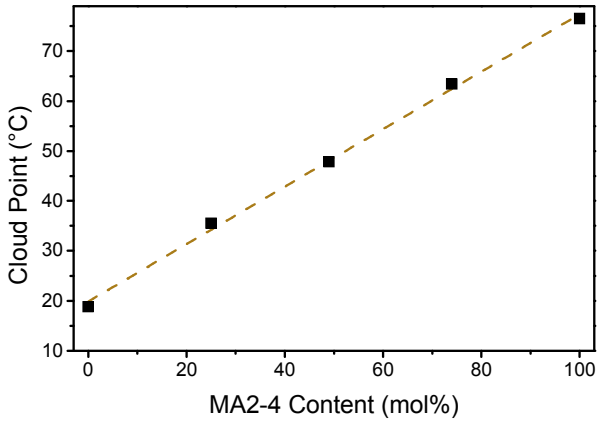
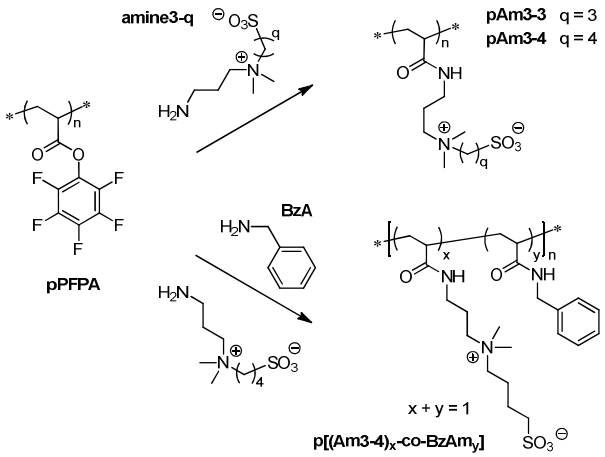


Figure 5. Cloud point versus **MA2-4** comonomer content for a series of statistical RAFT-made **p[(MA2-3)$_x$-*co*-(MA2-4)$_y$]** copolymers and the two respective RAFT-made homopolymers **p(MA2-3)** (y = 0%) and (**MA2-4)** (y = 100%). All (co)polymers had comparable DPs ranging from 184–191. A linear fit (dashed curve) was added to guide the eye.

Method 3: Post-modification of activated ester precursors with zwitterionic amines

Previously, we described the acyl substitution of poly(pentafluorophenyl acrylate) (pPFPA) with an amino-functional SPB, **amine3-3** (shown in Scheme 6), as a versatile route toward series of SPB acrylamide (co)polymers with identical DPs including hydrophobically modified copolymers with tuneable UCSTs.[43] Key to this procedure was the solubility of all involved species—pPFPA precursor, zwitterionic amine, and (co)polymer product—in propylene carbonate (PC). In this approach the introduction of zwitterionic side groups does not rely on the reactivity of different sultones (as in the non-quantitative modification of pDMAEMA with BS giving ill-defined SBB species). Therefore, we next investigated the postpolymerization synthesis of SBB (co)polymers from polymeric activated ester precursors. For this purpose, a novel zwitterionic amine, 4-((3-aminopropyl)dimethylammonio)butane-1-sulfonate, **amine3-4**, was prepared in three steps starting from *N*,*N*-dimethylaminopropylamine by (i) BOC-protection of the primary amine, (ii) quaternization of the dimethylamino group with BS in THF, followed by (iii) deprotection of the primary amine. Purification of the first intermediate, *tert*-butyl (3-(dimethylamino)propyl)carbamate by column chromatography (in spite of reasonably clean ^{1}H and ^{13}C NMR spectra of the crude product), was found to facilitate the isolation of the desired **amine3-4** reagent in high purity without the need for time-consuming recrystallization, Figure 6. Showing a similar trend as monomers **MA2-3** and **MA2-4**, this amine-functional SBB reagent was somewhat less soluble in PC than the SPB analogue necessitating heating in order to dissolve. Notably, however, unlike pPFPA, the generally less reactive[59, 60] methacrylate sister precursor poly(pentafluorophenyl methacrylate) was found to be poorly soluble in (hot) PC. This method toward zwitterionic (co)polymers thus primarily gives straightforward access to the acrylamido betaine derivatives.

Scheme 6. Method 3: Zwitterionic homo- and copolymers through postpolymerization modification of poly(pentafluorophenyl acrylate) (pPFPA) with zwitterionic amines and benzylamine



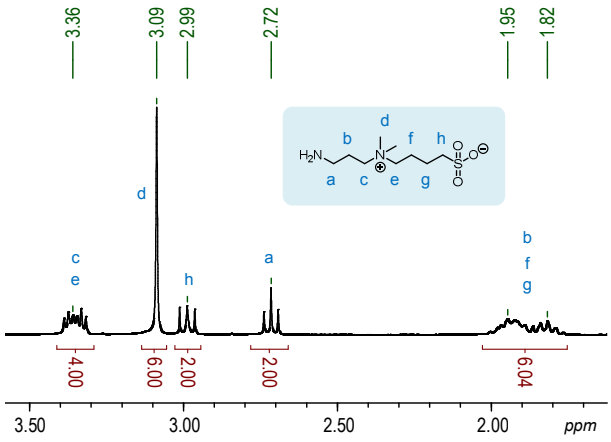


Figure 6. ^{1}H NMR spectrum of sulfobutylbetaine amine recorded in D_2O

RAFT-prepared pPFPA with a DP of 178 and $Đ_M$ = 1.23 was used as the activated precursor for all modifications. Apart from requiring more heat for initial dissolution of the small molecule reagent, the synthesis of zwitterionic homo- and copolymers from pPFPA with **amine3-4** did not differ from the previously described protocol[43] and details of the synthesis and characterization are only briefly discussed here. A 1.5-fold excess of (a mixture of) amines dissolved in PC was added to a PC solution of pPFPA and the mixture was stirred overnight. Full substitution was confirmed by ^{19}F NMR analysis (Figure S2) before product (co)polymers were purified by dialysis and isolated. In addition to a **p(Am3-3)** reference homopolymer and its SBB homologue **p(Am3-4)**, a series of copolymers containing benzylacrylamide units, **p[(Am3-4)$_x$-*co*-BzAm$_y$]**, with varying molar compositions was prepared by employing mixtures of **amine3-4** and benzylamine, see Table 3. Characterization by ^{1}H NMR (exemplary spectrum of **p(Am3-4)** shown in Figure 1F) and FT-IR spectroscopy (Figure 7) conformed to the expected zwitterionic (co)polymer structures. Aqueous SEC of **p(Am3-3)** and **p(Am3-4)**, shown in Figure 2C, revealed size distributions predictably similar to their pPFPA parent with both zwitterionic daughter homopolymers having a very similar hydrodynamic sizes in the 0.2 M aq. NaCl eluent. Due to low solubility, the BzAm copolymers were not characterized by SEC.

Table 3. Homo- and copolymers derived from pPFPA (DP = 178, $Đ_M = M_w/M_n = 1.23$) with zwitterionic amines and benzylamine (BzA)

Product, copolymer composition	DP	Amine 1 (feed, mol%)	Amine 2 (feed, mol%)	M_n^{theor} (kg/mol)	M_n^{SEC} (kg/mol)	$Đ_M^{SEC}$	Cloud Point (°C)
p(Am3-3)	178	**amine3-3** (100)	—	49.8	30	1.32	13.3
p(Am3-4)	178	**amine3-4** (100)	—	52.3	31	1.29	58.8
p[(Am3-4)$_{0.50}$-*co*-BzAm$_{0.50}$][a]	178	**amine3-4** (50)	BzA (50)	40.6	n.d.[b]	n.d.	NaCl (aq).[c]
p[(Am3-4)$_{0.38}$-*co*-BzAm$_{0.62}$]	178	**amine3-4** (35)	BzA (65)	37.8	n.d.	n.d.	NaCl (aq).[c]
p[(Am3-4)$_{0.31}$-*co*-BzAm$_{0.69}$]	178	**amine3-4** (25)	BzA (75)	36.2	n.d.	n.d.	I[d]

[a] molar copolymer composition determined by ^{1}H NMR spectroscopy; [b] not determined due to limited solubility in eluent; [c] insoluble in pure water, but UCST behaviour in aqueous NaCl solutions; [d] insoluble in pure water and in concentrated NaCl solutions between 0 and 90 °C at a concentration of 10 g/L.

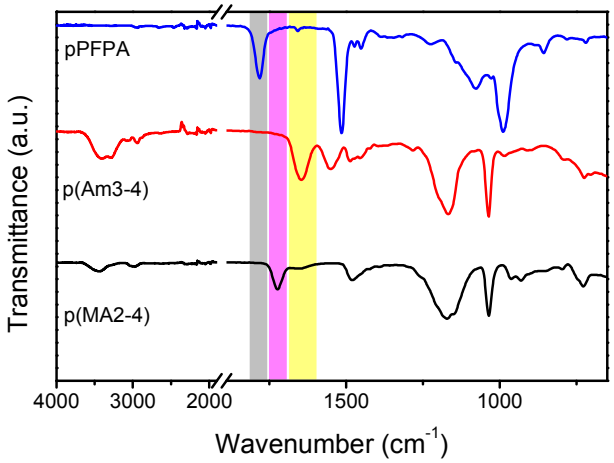


Figure 7. FT-IR spectra of the pPFPA precursor (top), a **p(Am3-4)** homopolymer prepared thereof (middle), and a RAFT-made **p(MA2-4)** homopolymer for comparison (bottom). The characteristic bands of the activated ester C=O stretching (1780 cm^{-1}, grey), the ester C=O stretching (1720 cm^{-1}, pink), and the amide C=O stretching (1650 cm^{-1}, yellow) are marked.

The SBB homopolymer **p(Am3-4)** showed a sharp, reproducible phase transition with a hysteresis of ~3 °C, similar to that of RAFT-made poly(meth)acrylates, see Figure S1. With a cloud point of 58.8 °C, this species had a considerably higher phase transition temperature than **p(Am3-3)** (cloud point 13.3 °C) suggesting again an advantage of this SBB species with regards to achieving (tuneable) UCST behaviour. Comparing samples with similar DPs (178–191) of all five zwitterionic species investigated here, we find increasing cloud points in the order: **p(Am3-3)** ≈ **p(MA2-3)** ≪ **p(A2-4)** ≈ **p(Am3-4)** ≪ **p(MA2-4)**. Cloud points found here for **p(MA2-3)** were in general agreement with recently reported values of similar homopolymers[35] while we note the similarity between the cloud points of **p(Am3-3)** (DP = 178, CP = 13.3 °C) and **p(MAm3-3)** (reported by others,[31] DP = 170, CP = 11.0 °C) suggesting a less prominent effect of the backbone methyl group in this case and/or an effect of the synthetic method.

Aside from increasing the ion bridge from a propyl to a butyl spacer, the introduction of benzylacrylamide comonomer units provides an additional handle to increase UCST transitions and the maximum salt concentration at which UCST behaviour can be observed. The cloud point dependency of the SPB copolymer **p[(Am3-3)$_{0.47}$-*co*-BzAm$_{0.53}$]** as a function of NaCl concentration, taken from the literature,[43] is plotted in Figure 8A, indicating full solubility at [NaCl] > ~80 mM. Here, a series of SBB copolymers with molar BzAm contents of 50%, 62%, and 69%, as determined by ^{1}H NMR spectroscopy in 500 mM NaCl in D_2O, was prepared. Notably, sample **p[(Am3-4)$_{0.31}$-*co*-BzAm$_{0.69}$]** with the highest BzAm content did not form a clear solution in this solvent (nor at higher NaCl concentrations)—the determined composition may thus be less accurate—indicating an upper limit of observable zwitterionic behaviour for hydrophobic modification. The remaining two samples, however, while being insoluble in pure (hot) water, did exhibit sharp, reversible UCST transitions between clear solutions and cloudy

mixtures in aqueous NaCl solution. As expected, the phase behaviour of these samples extended to higher NaCl concentrations than for the SPB copolymer, with UCST transitions measured on solutions containing up to 128 mM (7.5 g/L) NaCl for **p[(Am3-4)$_{0.50}$-*co*-BzAm$_{0.50}$]** and 154 mM (9.0 g/L, concentration of isotonic saline) NaCl for **p[(Am3-4)$_{0.38}$-*co*-BzAm$_{0.62}$]**, see Figure 8. These results demonstrate that the combination of SBB side chains with hydrophobic modification further increases the temperature/salt range in which sharp UCST transitions can be achieved. Specifically, UCST transitions of zwitterionic copolymers at a physiological NaCl concentration are promising for the exploitation of such smart materials in biomedical applications. However, the complex composition of biological fluids and the strong dependence of the UCST phase behaviour on the type of ions[20, 21, 23, 31] or, likely, other solutes needs to be considered. In the present case, for example, **p[(Am3-4)$_{0.38}$-*co*-BzAm$_{0.62}$]** was found to remain soluble in phosphate buffered saline (137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 1.8 mM KH_2PO_4) and HEPES buffer (150 mM NaCl, 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) when cooled to 0 °C. Conversely, this strong dependence of the phase behaviour on potentially minute changes of the environment may be exploited for the development of materials that respond selectively to specific biological microenvironments with (slightly) different ion concentrations.

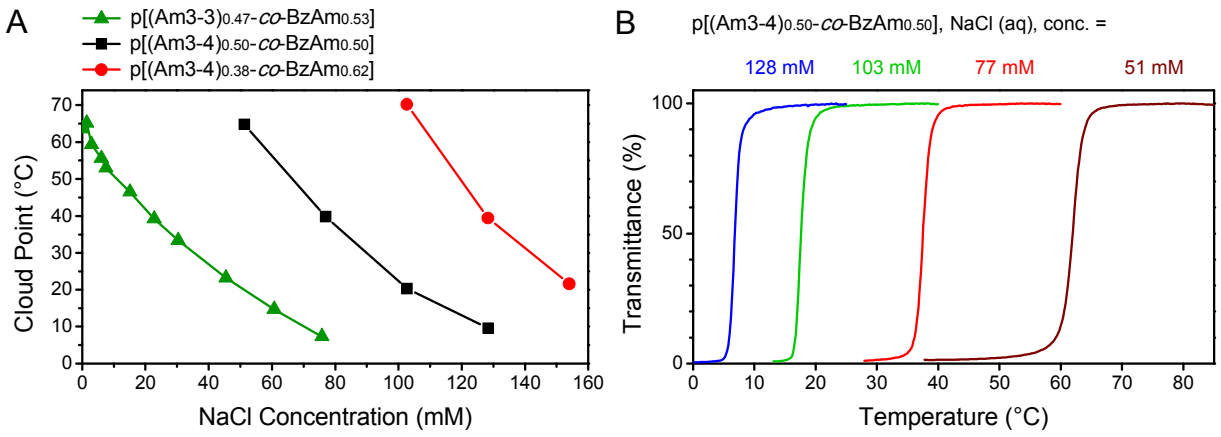


Figure 8. Influence of NaCl concentration on the phase separation temperature of **p(Am3-4)**–benzylacrylamide copolymers; (**A**) plot of UCST cloud point versus NaCl concentration for **p[(Am3-3)$_{0.47}$-*co*-BzAm$_{0.53}$]** (values taken from our previous study)[43] (green triangles), and the SBB species prepared here **p[(Am3-4)$_{0.50}$-*co*-BzAm$_{0.50}$]** (black squares) and **p[(Am3-4)$_{0.38}$-*co*-BzAm$_{0.62}$]** (red circles); (**B**) exemplary turbidity curves for **p[(Am3-4)$_{0.50}$-*co*-BzAm$_{0.50}$]** at different NaCl concentrations

Conclusion

A detailed comparative study of the aqueous solution behaviour of sulfobutylbetaine (SBB) (co)polymers was presented. In all cases, samples showed significantly higher UCST transitions, *i.e.* they were less soluble in water, than their respective sulfopropylbetaine (SPB) counterparts. Whereas the UCST transitions of the common SPB homopolymers **p(MA2-3)** and **p(MAm3-3)** are limited to relatively high molecular weight samples and/or to solutions in ultrapure water, the corresponding SBB-functional homopolymers investigated here offer a much larger temperature and salt concentration range for observing sharp, reproducible UCST transitions. Scope and limitations of three different synthetic techniques toward SBB homo- and copolymers were compared. The quaternization of pDMAEMA with 1,4-butanesultone in 2,2,2-trifluoroethanol (TFE) suffered from low reactivity of this alkylating agent resulting in incomplete modification making this procedure less advisable for the synthesis of pristine SBB species. RAFT radical polymerization of SBB-functional (meth)acrylate monomers and their copolymerization with SPB monomers in TFE proceeded smoothly with high conversions, low measured dispersities $Đ_M$, and facilitated access to a series of (co)polymers with cloud points from 13.2–76.5 °C. Low compatibility of SBB-functional monomers with non-protic solvents including propylene

carbonate (PC), however, limits the incorporation of non-polar or alcohol/water-sensitive components in this method. Post-modification of poly(pentafluorophenyl acrylate) with a SBB-functional amine in PC provided zwitterionic polyacrylamides and allowed for the introduction of hydrophobic comonomer units, but required the multi-step synthesis of the amine reagent. A SBB-functional copolymer containing 62 mol% of benzylacrylamide comonomer units showed UCST behaviour up to a physiological concentration of 9 g/L NaCl making such materials promising for exploiting their smart behaviour in the biomedical arena.

Supporting Information. Heating and cooling curves showing reproducibility and hysteresis, ^{19}F NMR measurements indicating full conversion of PFP precursors.

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References

1. M. A. C. Stuart, W. T. S. Huck, J. Genzer, M. Muller, C. Ober, M. Stamm, G. B. Sukhorukov, I. Szleifer, V. V. Tsukruk, M. Urban, F. Winnik, S. Zauscher, I. Luzinov and S. Minko, *Nat Mater*, 2010, **9**, 101-113.
2. J. Seuring and S. Agarwal, *Macromol Rapid Commun*, 2012, **33**, 1898-1920.
3. S. Kudaibergenov, W. Jaeger and A. Laschewsky, in *Supramolecular Polymers Polymeric Betains Oligomers*, Springer Berlin / Heidelberg, 2006, vol. 201, pp. 157-224.
4. A. B. Lowe and C. L. McCormick, *Chemical Reviews*, 2002, **102**, 4177-4190.
5. F. Xuan and J. Liu, *Polymer International*, 2009, **58**, 1350-1361.
6. A. Laschewsky, *Polymers*, 2014, **6**, 1544-1601.
7. G. Gunkel and W. T. S. Huck, *Journal of the American Chemical Society*, 2013, **135**, 7047-7052.
8. J. Wu, W. Lin, Z. Wang, S. Chen and Y. Chang, *Langmuir*, 2012, **28**, 7436-7441.
9. Q. Sun, Y. Su, X. Ma, Y. Wang and Z. Jiang, *Journal of Membrane Science*, 2006, **285**, 299-305.
10. Y. Chang, Y.-J. Shih, C.-J. Lai, H.-H. Kung and S. Jiang, *Advanced Functional Materials*, 2013, **23**, 1100-1110.
11. J. Yuan, X. Huang, P. Li, L. Li and J. Shen, *Polymer Chemistry*, 2013, **4**, 5074-5085.
12. R. Lalani and L. Liu, *Biomacromolecules*, 2012, **13**, 1853-1863.
13. R. Hart and D. Timmerman, *Journal of Polymer Science*, 1958, **28**, 638-640.
14. P. Köberle, A. Laschewsky and D. van den Boogaard, *Polymer*, 1992, **33**, 4029-4039.
15. P. Koeberle and A. Laschewsky, *Macromolecules*, 1994, **27**, 2165-2173.
16. V. M. Monroy Soto and J. C. Galin, *Polymer*, 1984, **25**, 121-128.
17. J. C. Salamone, W. Volksen, S. C. Israel, A. P. Olson and D. C. Raia, *Polymer*, 1977, **18**, 1058-1062.
18. D. Kratzer, L. Barner, C. Friedmann, S. Bräse and J. Lahann, *European Journal of Organic Chemistry*, 2014, **2014**, 8064-8071.
19. M. B. Huglin and M. A. Radwan, *Polymer International*, 1991, **26**, 97-104.
20. P. Köberle, A. Laschewsky and T. D. Lomax, *Die Makromolekulare Chemie, Rapid Communications*, 1991, **12**, 427-433.
21. P. Mary, D. D. Bendejacq, M.-P. Labeau and P. Dupuis, *The Journal of Physical Chemistry B*, 2007, **111**, 7767-7777.
22. J. Ning, G. Li and K. Haraguchi, *Macromolecules*, 2013, **46**, 5317-5328.
23. D. N. Schulz, D. G. Peiffer, P. K. Agarwal, J. Larabee, J. J. Kaladas, L. Soni, B. Handwerker and R. T. Garner, *Polymer*, 1986, **27**, 1734-1742.
24. V. A. Vasantha, S. Jana, A. Parthiban and J. G. Vancso, *Chemical Communications*, 2014, **50**, 46-48.
25. A. Bieglé, A. Mathis and J.-C. Galin, *Macromolecular Chemistry and Physics*, 2000, **201**, 113-125.
26. R. G. Laughlin, *Langmuir*, 1991, **7**, 842-847.
27. J. L. Bredas, R. R. Chance and R. Silbey, *Macromolecules*, 1988, **21**, 1633-1639.
28. Y. Chevalier and P. Le Perchec, *The Journal of Physical Chemistry*, 1990, **94**, 1768-1774.

29. M. Galin, A. Chapoton and J.-C. Galin, *Journal of the Chemical Society, Perkin Transactions 2*, 1993, 545-553.
30. L. Chen, Y. Honma, T. Mizutani, D. J. Liaw, J. P. Gong and Y. Osada, *Polymer*, 2000, **41**, 141-147.
31. V. Hildebrand, A. Laschewsky and D. Zehm, *Journal of Biomaterials Science, Polymer Edition*, 2014, **25**, 1602-1618.
32. V. M. Monroy Soto and J. C. Galin, *Polymer*, 1984, **25**, 254-262.
33. Y.-J. Shih, Y. Chang, A. Deratani and D. Quemener, *Biomacromolecules*, 2012, **13**, 2849-2858.
34. M. Tian, J. Wang, E. Zhang, J. Li, C. Duan and F. Yao, *Langmuir*, 2013, **29**, 8076-8085.
35. H. Willcock, A. Lu, C. F. Hansell, E. Chapman, I. R. Collins and R. K. O'Reilly, *Polymer Chemistry*, 2014, **5**, 1023-1030.
36. M. Arotcarena, B. Heise, S. Ishaya and A. Laschewsky, *Journal of the American Chemical Society*, 2002, **124**, 3787-3793.
37. Y. Pei, J. Travas-Sejdic and D. E. Williams, *Langmuir*, 2012, **28**, 8072-8083.
38. M. S. Donovan, B. S. Sumerlin, A. B. Lowe and C. L. McCormick, *Macromolecules*, 2002, **35**, 8663-8666.
39. V. Strehmel, H. Wetzel, A. Laschewsky, E. Moldenhauer and T. Klein, *Polymers for Advanced Technologies*, 2008, **19**, 1383-1390.
40. A. B. Lowe, N. C. Billingham and S. P. Armes, *Chemical Communications*, 1996, 1555-1556.
41. A. B. Lowe, N. C. Billingham and S. P. Armes, *Macromolecules*, 1999, **32**, 2141-2148.
42. J. V. M. Weaver, S. P. Armes and V. Butun, *Chemical Communications*, 2002, 2122-2123.
43. P. A. Woodfield, Y. C. Zhu, Y. W. Pei and P. J. Roth, *Macromolecules*, 2014, **47**, 750-762.
44. R. Kakuchi and P. Theato, in *Functional Polymers by Post-Polymerization Modification*, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 45-64.
45. J. Y. Quek, P. J. Roth, R. A. Evans, T. P. Davis and A. B. Lowe, *Journal of Polymer Science Part A: Polymer Chemistry*, 2013, **51**, 394-404.
46. P. J. Roth, K. T. Wiss, R. Zentel and P. Theato, *Macromolecules*, 2008, **41**, 8513-8519.
47. R. Nudelman, O. Ardon, Y. Hadar, Y. Chen, J. Libman and A. Shanzer, *Journal of Medicinal Chemistry*, 1998, **41**, 1671-1678.
48. P. J. Roth, J. Y. Quek, Y. Zhu, B. M. Blunden and A. B. Lowe, *Chemical Communications*, 2014, **50**, 9561-9564.
49. M. Gauthier, T. Carrozzella and A. Penlidis, *Journal of Polymer Science Part A: Polymer Chemistry*, 2002, **40**, 511-523.
50. P. J. Roth, C. Boyer, A. B. Lowe and T. P. Davis, *Macromolecular Rapid Communications*, 2011, **32**, 1123-1143.
51. P. van de Wetering, N. J. Zuidam, M. J. van Steenbergen, O. A. G. J. van der Houwen, W. J. M. Underberg and W. E. Hennink, *Macromolecules*, 1998, **31**, 8063-8068.
52. H.-Y. Tian, J.-J. Yan, D. Wang, C. Gu, Y.-Z. You and X.-S. Chen, *Macromolecular Rapid Communications*, 2011, **32**, 660-664.
53. P. G. Faulkner, A. J. I. Ward and D. W. Osborne, *Langmuir*, 1989, **5**, 924-926.
54. J. G. Weers, J. F. Rathman, F. U. Axe, C. A. Crichlow, L. D. Foland, D. R. Scheuing, R. J. Wiersema and A. G. Zielske, *Langmuir*, 1991, **7**, 854-867.

55. W. Ding, C. Lv, Y. Sun, X. Liu, T. Yu, G. Qu and H. Luan, *Journal of Polymer Science Part A: Polymer Chemistry*, 2011, **49**, 432-440.
56. G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2012, **65**, 985-1076.
57. K. Skrabania, A. Miasnikova, A. M. Bivigou-Koumba, D. Zehm and A. Laschewsky, *Polymer Chemistry*, 2011, **2**, 2074-2083.
58. P. J. Roth, F. D. Jochum, F. R. Forst, R. Zentel and P. Theato, *Macromolecules*, 2010, **43**, 4638-4645.
59. G. B. H. Chua, P. J. Roth, H. T. T. Duong, T. P. Davis and A. B. Lowe, *Macromolecules*, 2012, **45**, 1362-1374.
60. M. I. Gibson, E. Frohlich and H.-A. Klok, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 4332-4345.

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