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Hydrophobically Modified Sulfobetaine Copolymers with Tunable Aqueous UCST through Postpolymerization Modification of Poly(pentafluorophenyl acrylate)

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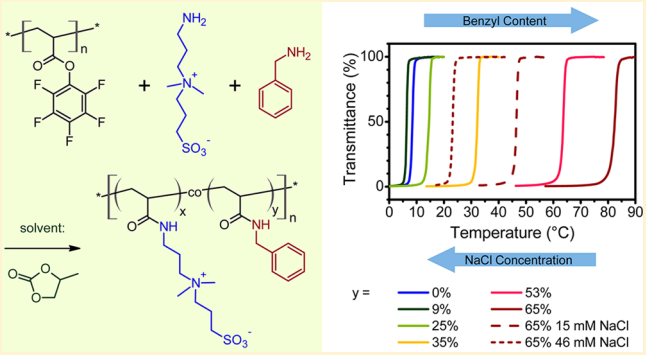
Supporting Information

ABSTRACT: Polysulfobetaines, polymers carrying highly polar zwitterionic side chains, present a promising research field by virtue of their antifouling properties, hemocompatibility, and stimulus-responsive behavior. However, limited synthetic approaches exist to produce sulfobetaine copolymers comprising hydrophobic components. Postpolymerization modification of an activated ester precursor, poly(pentafluorophenyl acrylate), employing a zwitterionic amine, 3-((3-aminopropyl)dimethylammonio)propane-1-sulfonate, ADPS, is presented as a novel, one-step synthetic concept toward sulfobetaine (co)polymers. Modifications were performed in homogeneous solution using propylene carbonate as solvent with mixtures of ADPS and pentylamine, benzylamine, and dodecylamine producing a series of well-defined statistical acrylamido sulfobetaine copolymers containing hydrophobic pentyl, benzyl, or dodecylacrylamide comonomers with well-controllable molar composition as evidenced by NMR and FT-IR spectroscopy and size exclusion chromatography. This synthetic strategy was exploited to investigate, for the first time, the influence of hydrophobic modification on the upper critical solution temperature (UCST) of sulfobetaine copolymers in aqueous solution. Surprisingly, incorporation of pentyl groups was found to increase solubility over a wide composition range, whereas benzyl groups decreased solubility—an effect attributed to different entropic and enthalpic contributions of both functional groups. While UCST transitions of polysulfobetaines are typically limited to higher molar mass samples, incorporation of 0–65 mol % of benzyl groups into copolymers with molar masses of 25.5–34.5 kg/mol enabled sharp, reversible transitions from 6 to 82 °C in solutions containing up to 76 mM NaCl, as observed by optical transmittance and dynamic light scattering. Both synthesis and systematic UCST increase of sulfobetaine copolymers presented here are expected to expand the scope and applicability of these smart materials.



INTRODUCTION

Polybetaines—electrically neutral polymers carrying positive and negatives charges in every repeat unit—have been known for several decades[1−6] and have been receiving increased attention in recent years as a very promising class of materials. An important subclass of polybetaines is constituted by polysulfobetaines, featuring a sulfonate anion and typically a quaternary ammonium cation, affording a largely pH-independent zwitterionic character.[7] A very tightly bound hydration layer around each zwitterionic group has been proposed to be the reason for the material's exceptional nonspecific protein absorbance and hemocompatibility,[8] which has been applied in antibiofouling surfaces,[9−14] e.g. for medicinal purposes,[15−17] in separation science,[18,19] as well as for gene[20] and drug[21,22] delivery. Moreover, sulfobetaine-based zwitterionic conjugated polyelectrolytes have been shown to improve the performance of optoelectronic devices.[23,24] A further intriguing aspect of these materials is that certain polysulfobetaines, predominantly the methacroyloxyethyl dimethylammonio propanesulfonate[25−27] and methacrylamidopropyl dimethylammonio propanesulfonate[26] derivatives, have been shown to display an upper critical solution temperature (UCST) in water—a phenomenon known only for very few types of water-soluble (co)polymers.[28,29] Because of strong intra- and interpolymer attractions (in polybetaines: electrostatic interactions), these hydrophilic polymers are insoluble in water below a critical solution temperature but become soluble when the temperature-weighed entropy of mixing (which favors

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a single phase) outbalances these enthalpic attractions. For polysulfobetaines, this positive thermoresponsive behavior is accompanied by an antipolyelectrolyte effect:[26,27,30] addition of electrolytes, e.g. sodium chloride, screens the charges of the zwitterionic side chains from one another, reducing their interactions, thereby increasing solubility (decreasing the UCST). Exhibiting double responsiveness (temperature and salt), the polysulfobetaine family offers great potential in the smart materials arena, and several polysulfobetaine species have been used to produce thermoresponsive gels,[31] mechanically tough, highly stretchable thermoresponsive nanocomposite gels,[32] schizophrenic diblock copolymers[1,5,33] with temperature-independent hemocompatibility,[34] thermoresponsive hybrids containing biological materials,[35] surfaces with thermoswitchable wettability,[36,37] and surfaces with switchable wettability triggered by an electrical stimulus (exploiting the antipolyelectrolyte effect).[38]

Though of great interest,[28,29] the responsive behavior of polysulfobetaine suffers from two major drawbacks, limiting applicability: (i) As with most UCST systems, the phase separation temperature depends strongly on the molar mass of polymers, with transition temperatures decreasing with decreasing molar masses.[26,27] A recent study by Willcock et al.[39] demonstrated that for linear chains of poly(methacroyloxyethyl dimethylammonio propanesulfonate), the most commonly described polysulfobetaine, relatively high molar masses of M_w = 258 and 448 kg/mol were necessary to reach cloud points (optically observed transition temperatures) of 26 and 43 °C, respectively, with lower molar mass samples displaying lower cloud points and a sample of M_w = 29 kg/mol having no measurable cloud point. (ii) The antipolyelectrolyte effect typically requires working under strictly salt-free conditions in order to observe UCST transitions. Because of these influences, UCSTs of polysulfobetaines of lower molar masses (e.g., <50 kg/mol) and/or in solutions containing electrolytes may be impractically low or may not be observable at all. In order to widen the applicability of these "smart" materials, it would therefore be of considerable interest to be able to tune the UCST, especially to *increase* the phase separation temperature, so as to enable UCST transitions for lower molar mass polysulfobetaines and in solutions containing salts, e.g., physiological environment.

Tuning of aqueous UCST transitions was recently described for polyacrylamide and poly(*N*-acryloyl glycinamide) for which copolymerization with the (more) hydrophobic monomers acrylonitrile and styrene or *n*-butyl acrylate, respectively, was found to increase the phase separation temperatures.[40] Hydrophobic modification of poly(methyl methacrylate)-based copolymers,[41] poly(ethylene glycol (meth)acrylate)-based copolymers,[42] and certain poly(2-alkyl-2-oxazoline)s[43] has been successfully applied to increase their respective UCST transition temperatures in ethanol–water mixtures. Likewise, increasing the content of hydrophobic segments in polymers displaying a lower critical solution temperature (LCST, soluble–insoluble transition upon heating) is known to decrease their solubility (observable through *decreasing* LCSTs). This method is well-established in the literature, and both postpolymerization modification[44−48] and (azeotropic) copolymerization[49−52] have lent themselves perfectly to the production of libraries of well-defined copolymers comprising varying amounts of hydrophobic comonomer units displaying tunable LCST transitions.

Hydrophobic modification of polysulfobetaines can therefore be assumed to bring about the desired increase of UCST cloud points. Because of the strongly polar nature of sulfobetaine monomers, however, their copolymerization with hydrophobic comonomers poses synthetic challenges. While many copolymers of sulfobetaine monomers with hydrophilic comonomers such as acrylamide,[53−55] methacrylamide,[56] *N*-isopropylacrylamide,[31,57,58] *N*,*N*-dimethylacrylamide,[18,32] and acrylic acid[17,54] have been reported (and some of which were shown to—expectedly—have increased solubility, i.e. *lower* UCST transitions, than comparable homopolymers),[31,57,59] the literature on hydrophobically modified sulfobetaine copolymers is sparse. In a considerable synthetic effort, Köberle and Laschewsky[60,61] prepared a series of acrylic and methacrylic sulfobetaine monomers carrying alkyl substituents of varying lengths on the quaternary nitrogen atom in varying geometrical configurations. Several of the corresponding homopolymers, including several propanesulfonate derivatives, were found to be soluble only in (hot) water. Direct copolymerization of sulfobetaine monomers with hydrophobic comonomers has only been described for very few systems: free radical polymerization with ethyl acrylate in ethanol (found to precipitate most copolymers),[62−64] or with vinyl acetate in an aqueous emulsion polymerization,[22,65] and with *n*-butyl acrylate.[66−70] The copolymerization behavior of latter system, sulfobetaine monomer–*n*-butyl acrylate, has been investigated by several research groups in ethanol (becomes heterogeneous),[68] trifluoroethanol,[69] and acetonitrile–water 96:4.[70] Strehmel et al.[70,71] found that using ionic liquids as solvents significantly improved the copolymerization behavior of this system, though isolation of pure zwitterionic homopolymers from the ionic liquid was not possible.[70] Different strategies toward hydrophobically modified polysulfobetaines have included copolymerization of a tertiary amine functional monomer with *n*-butyl acrylate,[72] ethyl acrylate,[73] or acrylonitrile[19] followed by quaternization of the tertiary amines to give sulfobetaine species, and copolymerization of styrene and *N*-vinylpyrrolidone with the reactive monomer phthalimido acrylate, which was converted, in two steps, into a tertiary amine species and then a sulfobetaine by quaternization.[74] While sulfobetaine copolymers comprising larger amounts of *N*-vinylpyrrolidone,[74] ethyl acrylate,[64] *n*-butyl (meth)acrylate,[66−68,72] and acrylonitrile[19] were reported to be insoluble in water, a temperature-dependent solubility or a potential increase of a UCST transition was, however, not investigated in these studies.

Herein, we present a simple one-step synthesis of sulfobetaine copolymers incorporating different hydrophobic comonomers through postpolymerization modification[75,76] of an activated ester precursor.[77] We optimized reaction conditions to convert poly(pentafluorophenyl acrylate), in homogeneous solution, with a zwitterionic amine and with mixtures of the zwitterionic amine and hydrophobic amines producing well-defined sulfobetaine acrylamido copolymers incorporating a controllable amount of hydrophobic comonomers. In a first description of this synthetic strategy, we investigated the influence of hydrophobic comonomers on the UCST phase behavior and found that while alkyl functional comonomers—counterintuitively—increased solubility over a wide composition range, aromatic comonomers brought about the desired decreased solubility, enabling sharp, reproducible UCST transitions of lower molar mass (~30 kg/mol) copolymers between 6 and 82 °C and in aqueous solutions

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containing up to 76 mM sodium chloride. We envisage that these findings will increase the scope of polysulfobetaines in the smart materials arena, and setting the stage for contact angle tuning of polysulfobetaine surfaces[38] and for the incorporation of zwitterionic segments into more complex polymeric architectures[78] will advance many of the aforementioned applications.

EXPERIMENTAL SECTION

Materials. All reagents were purchased from Sigma-Aldrich and were used as received unless stated otherwise. Propylene carbonate (99.7%, anhydrous) and dimethylformamide (DMF, 99.8%, anhydrous) were stored in a glovebox. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and stored at −24 °C. Amberlyst A26 anion exchange resin was washed with mQ water three times prior to use. The synthesis of benzyl propyl trithiocarbonate (BPTC) was described elsewhere.[79]

Methods. NMR spectroscopic measurements in D_2O and $CDCl_3$ were performed on Bruker Avance 300 MHz and Bruker Avance III 500 MHz instruments in 5 mm NMR tubes. The internal solvent signals were used as reference ($\delta(CDCl_3)$ = 7.26 ppm, $\delta(D_2O)$ = 4.79 ppm). Measurements on copolymers containing 35, 53, and 65 mol % of benzylacrylamide were measured on D_2O solutions containing 0.1, 0.2, and 0.5 M NaCl, respectively. A copolymer containing 85 mol % of pentylacrylamide was measured in $CDCl_3$ solution. NMR spectroscopic measurements in trifluoroethanol-d_3 were performed on a Bruker Avance III 600 MHz instrument in 3 mm NMR tubes. The internal solvent signal was used as reference ($\delta(CF_3CD_2O\underline{H})$ = 5.22 ppm).

Size exclusion chromatography (SEC) in tetrahydrofuran (THF) 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 narrow molar mass distribution polystyrene (PS) standards with molar masses ranging from 0.58 to 1820 kg/mol. Aqueous SEC was performed on a Shimadzu system with two Agilent Aquagel columns with 0.1 M NaCl solution containing 0.2 mass % sodium azide as eluent at a flow rate of 0.8 mL/min. This system was calibrated with a series of narrow molar mass distribution poly(ethylene glycol) (PEG) standards. Chromatograms were analyzed 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 (ATR), and data were analyzed on OPUS software version 4.0.

Inductively coupled plasma atomic emission spectroscopy (ICP-OES) was performed on a PerkinElmer OPTIMA 7300 ICPOES instrument after sample digestion in concentrated nitric acid.

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 were determined at 50%.

Dynamic light scattering (DLS) measurements were performed on a Malvern Zetasizer Nano ZS at a scattering angle of 173° and were analyzed by Malvern Zetasizer Software version 6.20.

Pentafluorophenyl Acrylate, PFPA. Pentafluorophenol (18.4 g, 100 mmol), triethylamine (14.6 mL, 105 mmol), and dichloromethane (500 mL) were mixed and cooled to 0 °C. Acryloyl chloride (8.94 mL, 110 mmol) was added dropwise, and the mixture was stirred and let warm to room temperature overnight. 18.9 g (80%) of product was obtained after washing the organic phase with water (5 × 400 mL). ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 6.67 (dd, 1 H), 6.31 (dd, 1 H), 6.12 (dd, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm = 161.8 (C═O), 142.9, 141.1, 139.8, 137.6, 135.6 (5 m (large $^1J_{C-F}$ coupling), 5 F), 135.6, 125.4 (C═C). ^{19}F NMR (282 MHz, $CDCl_3$), δ/ppm = −152.7 (m, 2 F, *ortho*), −158.1 (t, 1 F, *para*), −162.5 (m, 2 F, *meta*).

Poly(pentafluorophenyl acrylate), pPFPA. Monomer PFPA (4.5 g, 18.9 mmol, 130 equiv), RAFT agent BPTC (35.2 mg, 0.145 mmol, 1 equiv), initiator AIBN (2.4 mg, 0.015 mmol, 0.1 equiv), and acetonitrile (6 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 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 analyzed by ^{19}F NMR spectroscopy which indicated a monomer conversion of 90% by comparison of the signal at −157.1 ppm (bs, polymer *para*-F) with the signal at −158.1 ppm (t, monomer *para*-F). The polymer was isolated as a slightly yellow powder (3.78 g, 84%) by two precipitations in methanol followed by drying in vacuum. $M_{n,theor}$ (from conversion) = 28.1 kg/mol, DP_{theor} = 117, $M_{n,NMR}$ (by end-group analysis) = 25.7 kg/mol, DP_{NMR} = 107, $M_{n,SEC}$ (THF) = 13.8 kg/mol, $Đ_M = M_{w,SEC}/M_{n,SEC}$ = 1.40. ^{19}F NMR (282 MHz, $CDCl_3$), δ/ppm = −153.2 (bm, 2 F, *ortho*), −157.1 (bs, 1 F, *para*), −162.4 (bs, 2 F, *meta*). FT-IR: ν/cm^{-1} = 1780 (carbonyl C═O stretch), 1520 (aryl C═C bend).

***tert*-Butyl (3-(Dimethylamino)propyl)carbamate.** was prepared in analogy to a literature procedure.[80] Briefly, *N*,*N*-dimethylaminopropylamine (9.125 mL, 72.5 mmol) was dissolved in methanol (38 mL), and the mixture was cooled to 0 °C. Di-*tert*-butyl dicarbonate (15.0 g, 68.8 mmol) was added, and the mixture was stirred overnight while warming to room temperature. After evaporating the solvent, water (60 mL) was added, and the product was extracted with ethyl acetate (4 × 70 mL) yielding 8.7 g (78%) of a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.02 (t, 2 H, $-C\underline{H}_2NH-$), 2.27 (t, 2 H, $(CH_3)_2NC\underline{H}_2-$), 2.17 (s, 6 H, $(C\underline{H}_3)_2N-$), 1.61 (m, 2 H, $-CH_2C\underline{H}_2CH_2-$), 1.37 (s, 9 H, $-C(C\underline{H}_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm = 156.6 (C═O), 78.8 ($-\underline{C}(CH_3)_3$), 56.5 ($(CH_3)_2N\underline{C}H_2-$), 44.4 ($(\underline{C}H_3)_2N-$), 38.2 ($-\underline{C}H_2NH-$), 27.8 ($-C(\underline{C}H_3)_3$), 27.0 ($-CH_2\underline{C}H_2CH_2-$).

3-((3-((*tert*-Butoxycarbonyl)amino)propyl)dimethylammonio)propane-1-sulfonate. *tert*-Butyl (3-(dimethylamino)propyl)carbamate (8.6 g, 42.5 mmol), propane sultone (7.3 g, 60 mmol), and anhydrous DMF (50 mL) were combined in a round-bottom flask and stirred at room temperature for 5 days. The product was precipitated into diethyl ether (300 mL) and isolated by centrifugation and drying in vacuum. The product was used in the next step without further purification. ^{1}H NMR (300 MHz, D_2O), δ/ppm = 3.40, 3.28 (2 m, 2 × 2 H, $-C\underline{H}_2N^+(CH_3)_2C\underline{H}_2-$), 3.11 (t, 2 H, $-NHC\underline{H}_2CH_2CH_2N^+-$), 3.03 (s, 6 H, $-N^+(C\underline{H}_3)_2-$), 2.91 (t, 2 H, $-C\underline{H}_2SO_3^-$), 2.14, 1.89 (2 m, 2 × 2 H, $-C\underline{H}_2CH_2N^+(CH_3)_2CH_2C\underline{H}_2-$), 1.36 (s, 9 H, $(C\underline{H}_3)_3O_2CNH-$).

3-((3-Aminopropyl)dimethylammonio)propane-1-sulfonate Hydrochloride, ADPS·HCl. The product of the previous step, 3-((3-((*tert*-butoxycarbonyl)amino)propyl)dimethylammonio)propane-1-sulfonate, was dissolved in mQ water (32 mL) in a beaker, and concentrated hydrochloric acid (15 mL) was added. The mixture was stirred overnight, and water and excess acid were evaporated. The product was recrystallized from water−ethanol. ^{1}H NMR (300 MHz, D_2O), δ/ppm = 3.55, 3.49 (2 m, 2 × 2 H, $-C\underline{H}_2N^+(CH_3)_2C\underline{H}_2-$), 3.18 (s, 6 H, $-N^+(C\underline{H}_3)_2-$), 3.13 (t, 2 H, $H_3N^+C\underline{H}_2-$), 3.03 (t, 2 H, $-C\underline{H}_2SO_3^-$), 2.56 (m, 4 H, $-C\underline{H}_2CH_2N^+(CH_3)_2CH_2C\underline{H}_2-$). ^{13}C NMR (75 MHz, D_2O), δ/ppm = 62.4, 60.6 (2 t, $-\underline{C}H_2N^+(CH_3)_2\underline{C}H_2-$), 50.8 (t, $-N^+(\underline{C}H_3)_2-$), 47.1 ($-\underline{C}H_2SO_3^-$), 36.3 ($H_3N^+\underline{C}H_2-$), 20.5 ($H_3N^+CH_2\underline{C}H_2-$), 18.1 ($-\underline{C}H_2CH_2SO_3^-$).

3-((3-Aminopropyl)dimethylammonio)propane-1-sulfonate, ADPS. The corresponding hydrochloride, ADPS·HCl, was dissolved in mQ water and treated with Amberlyst A26 anion exchange resin until a pH of ∼11 was reached. The resin was filtered off, and the aqueous solution was freeze-dried. Yield based on *tert*-butyl (3-(dimethylamino)propyl)carbamate (product of step 1) = 61%. ^{1}H NMR (300 MHz, D_2O), δ/ppm = 3.52, 3.42 (2 m, 2 × 2 H, $-C\underline{H}_2N^+(CH_3)_2C\underline{H}_2-$), 3.16 (s, 6 H, $-N^+(C\underline{H}_3)_2-$), 3.03 (t, 2 H, $-C\underline{H}_2SO_3^-$), 2.75 (t, 2 H, $H_2NC\underline{H}_2-$), 2.26 (m, 2 H, $-C\underline{H}_2CH_2SO_3^-$), 1.96 (m, 2 H, $NH_2CH_2C\underline{H}_2-$). ^{13}C NMR (75 MHz, D_2O), δ/ppm = 62.3, (m, 2 C,$-\underline{C}H_2N^+(CH_3)_2\underline{C}H_2-$), 50.6 (t, 2 C,$-N^+(\underline{C}H_3)_2-$), 47.3 (1 C, $-\underline{C}H_2SO_3^-$), 37.6 (1 C, $H_2N\underline{C}H_2-$),

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25.1 (1 C, $H_2NCH_2\underline{C}H_2-$), 18.1 (1 C, $-\underline{C}H_2CH_2SO_3^-$). FT-IR: ν/cm^{-1} = 3350 (amine N−H stretch), 2990−2870 (C−H stretch), 1490 (CH_2 bend), 1210 (C−N stretch), overlapping with 1170 (S═O stretch), 1035 (S═O stretch).

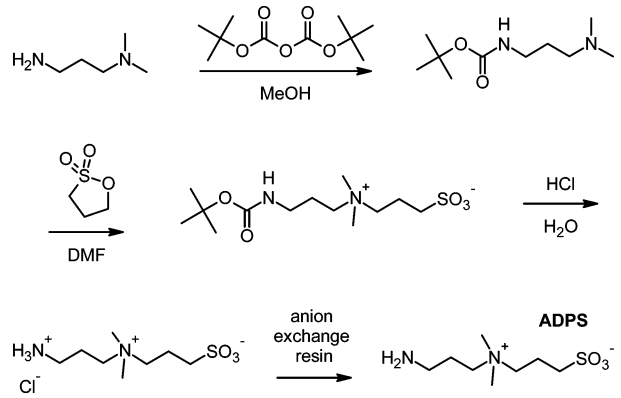
Poly[(3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate)], pADPS. The target homopolymer was prepared as follows. pPFPA (44.6 mg, 0.188 mmol of PFP units, 1 equiv) was dissolved in propylene carbonate (1.5 mL) at 60 °C, and hydroxyethyl acrylate (5 μL) was added. In parallel, zwitterionic amine ADPS (63.1 mg, 0.281 mmol, 1.5 equiv) was dissolved in propylene carbonate (1.5 mL) at 60 °C. After dissolving, the amine solution was quickly added into the polymer solution, and the mixture was stirred at 40 °C overnight. The solution was transferred into a dialysis bag (MWCO 3500 Da) and dialyzed against mQ water for 3 days. The product (48.2 mg, 92%) was isolated by freeze-drying as a fluffy white solid and was kept in a tightly sealed container to avoid moisture uptake. ^{1}H NMR (500 MHz, D_2O), δ/ppm = 3.53 (bs, 2 H, $-C\underline{H}_2CH_2CH_2SO_3^-$), 3.40 (bs, 2 H, $-NHCH_2CH_2C\underline{H}_2-$), 3.27 (bs, 2 H, $-NHC\underline{H}_2-$), 3.16 (bs, 6 H, $-N^+(C\underline{H}_3)_2-$), 3.01 (bt, 2 H, $-CH_2\underline{H}_2SO_3^-$), 2.24 (bs, $-CH_2\underline{C}H_2CH_2SO_3^-$), 2.04 (bs, $-NHCH_2C\underline{H}_2-$) overlapping 2.11 (backbone $-CH_2C\underline{H}R-$), 1.74, 1.64, 1.50 (backbone $-C\underline{H}_2CHR-$). ^{13}C NMR (75 MHz, D_2O), δ/ppm = 176.6 ($-\underline{C}ONH-$), 62.1, ($-\underline{C}H_2N^+(CH_3)_2\underline{C}H_2-$), 61.6 ($-CONH\underline{C}H_2-$), 50.9 ($-N^+(\underline{C}H_3)_2-$), 47.4 ($-\underline{C}H_2SO_3^-$), 42.4 (backbone $-CH_2\underline{C}HR-$), 36.4 (backbone $-\underline{C}H_2CHR-$), 22.1 ($-CONHCH_2\underline{C}H_2-$), 18.2 (1 C, $-\underline{C}H_2CH_2SO_3^-$). FT-IR: ν/cm^{-1} = 1650 (amide C═O stretch), 1550 (amide N−H bend), 1170 (side chain C−N stretch and S═O stretch), 1035 (S═O stretch).

Statistical Copolymers p(ADPS-*co*-pentylacrylamide), p(ADPS-*co*-benzylacrylamide), and p(ADPS-*co*-dodecylacrylamide) (p($ADPS_x$-*co*-$Pent_y$), p($ADPS_x$-*co*-Bz_y), and p($ADPS_x$-*co*-$Dodec_y$)). A general procedure is given. pPFPA (44.6 mg, 0.188 mmol of PFP units, 1 equiv) was dissolved in propylene carbonate (1.5 mL) at 60 °C, and hydroxyethyl acrylate (5 μL) was added. In parallel, zwitterionic amine ADPS ($x \times 0.281$ mmol) and a hydrophobic amine (pentylamine, benzylamine, or dodecylamine) ($y \times 0.281$ mmol, $x + y = 1$; 1.5 equiv of amines to PFP ester) were dissolved in propylene carbonate (1.5 mL) at 60 °C. After dissolving, the amine solution was quickly added into the polymer solution, and the mixture was stirred at 40 °C overnight. *Purification*: Pentylacrylamide copolymers p($ADPS_x$-*co*-$Pent_y$) with $y \leq 0.65$ and benzylacrylamide copolymers p($ADPS_x$-*co*-Bz_y) with $y \leq 0.25$ were purified by dialysis (MWCO 3500 Da) against mQ water for 3 days, followed by freeze-drying. Copolymer p($ADPS_{0.15}$-*co*-$Pent_{0.85}$) containing 85 mol % of pentylacrylamide comonomer units was purified by two precipitations from propylene carbonate into water, followed by centrifugation, washing with water, and drying. Benzylacrylamide copolymers p($ADPS_x$-*co*-Bz_y) with $y > 0.25$ were purified by dialysis (MWCO 3500 Da) in warm (up to 70 °C) water in a beaker heated by a hot plate and equipped with a stirrer bar and temperature controller and closed with an inverted plastic funnel connected to a reflux condenser. Samples were isolated by freeze-drying. Elemental analysis by inductively coupled plasma atomic emission spectroscopy (ICP-OES) run on select samples confirmed a very low concentration of sodium (below 0.01 mass %) and potassium (below detection limit) after purification by (warm) dialysis. Dodecylacrylamide copolymer p($ADPS_{0.60}$-*co*-$Dodec_{0.40}$) was purified by dialysis in ethanol and then dialysis in water, during which the polymer precipitated inside the dialysis bag. Yields of all copolymers were typically between 85 and 90%. ^{1}H NMR (300 MHz, D_2O, pentyl side chains), δ/ppm = 1.54 ($-NHCH_2C\underline{H}_2CH_2CH_2CH_3$), 1.34 ($-NHCH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.93 ($-NHCH_2CH_2CH_2$ $CH_2C\underline{H}_3$). ^{1}H NMR (300 MHz, D_2O, benzyl side groups, 0−0.5 M NaCl), δ/ppm = 7.65, 7.53 (m, $-CH_2C_6\underline{H}_5$), 4.45 ($-C\underline{H}_2C_6H_5$). ^{1}H NMR (300 MHz, trifluoroethanol-d_3, dodecyl side chains), δ/ppm = 1.57 ($-NHCH_2C\underline{H}_2-$), 1.35 ($-C\underline{H}_2-$), 0.94 ($-C\underline{H}_3$). Molar compositions of pentylacrylamide and dodecylacrylamide copolymers were determined by comparison of the alkyl $-C\underline{H}_3$ signal (0.9 ppm, 3 H) to the broad triplet of the $-C\underline{H}_2SO_3^-$ (3.0 ppm, 2 H) segment. Molar compositions of the benzylacrylamide copolymers were determined by comparison of the aromatic peaks (5 H) to the sum of the zwitterionic group signals from 3.75−2.65 (12 H).

RESULTS AND DISCUSSION

Synthesis of Zwitterionic Amine. In order to incorporate sulfobetaine functionality into an activated ester precursor, the zwitterionic amine 3-((3-aminopropyl)dimethylammonio)-propane-1-sulfonate, ADPS, was synthesized from *N*,*N*-dimethylaminopropylamine in three synthetic steps—BOC protection of the primary amine, quaternization with propane sultone, and BOC deprotection—followed by treatment with hydroxide loaded anion exchange resin to yield the free base (Scheme 1). ^{1}H and ^{13}C NMR spectra of ADPS hydrochloride

Scheme 1. Synthesis of Amine-Functional Sulfobetaine ADPS



and ADPS are shown in Figures S1−S4 of the Supporting Information. ADPS was found to be soluble in water, acetic acid, trifluoroethanol, warm dimethylformamide (DMF), warm dimethyl sulfoxide (DMSO), warm propylene carbonate (PC), and warm *N*-methylpyrrolidone (NMP) and was insoluble in methanol, ethanol, 2-propanol, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, triethylamine, and dichloromethane.

Synthesis of Sulfobetaine Homopolymer. With the zwitterionic amine ADPS in hand, we investigated its reaction with an activated polyacrylate precursor with the aim of producing the sulfobetaine homopolymer poly[(3-((3-acrylamidopropyl)dimethylammonio)propane-1-sulfonate], pADPS (Scheme 2, top). Based on the poor solubility of the zwitterionic amine in solvents of medium polarity and the highly polar nature of the target polysulfobetaine product, the use of a water-soluble activated ester precursor, such as the (meth)acrylate derivatives of *N*-hydroxysulfosuccinimide sodium salt, sodium 4-hydroxy-3-nitrobenzenesulfonate, or sodium 2,3,5,6-tetrafluoro-4-hydroxybenzenesulfonate,[81] in aqueous solution would have seemed reasonable. Because of the poor availability and higher cost of these materials, however, we sought to employ a common, well-established activated ester, poly(pentafluorophenyl acrylate), pPFPA, in spite of its apparent hydrophobicity. pPFPA with a degree of polymerization of 117, a molar mass of $M_{n,theor}$ = 28.1 kg/mol, and a polydispersity index of 1.40 was prepared by RAFT polymerization[82] using a trithiocarbonate chain transfer agent. This reactive precursor was insoluble in water, alcohols (including longer chain alcohols), and DMSO, dissolved in warm DMF and warm propylene carbonate, while it was well-soluble in solvents of lower polarity, e.g. THF and chloroform. We initially explored the reaction of pPFPA with ADPS in DMF−

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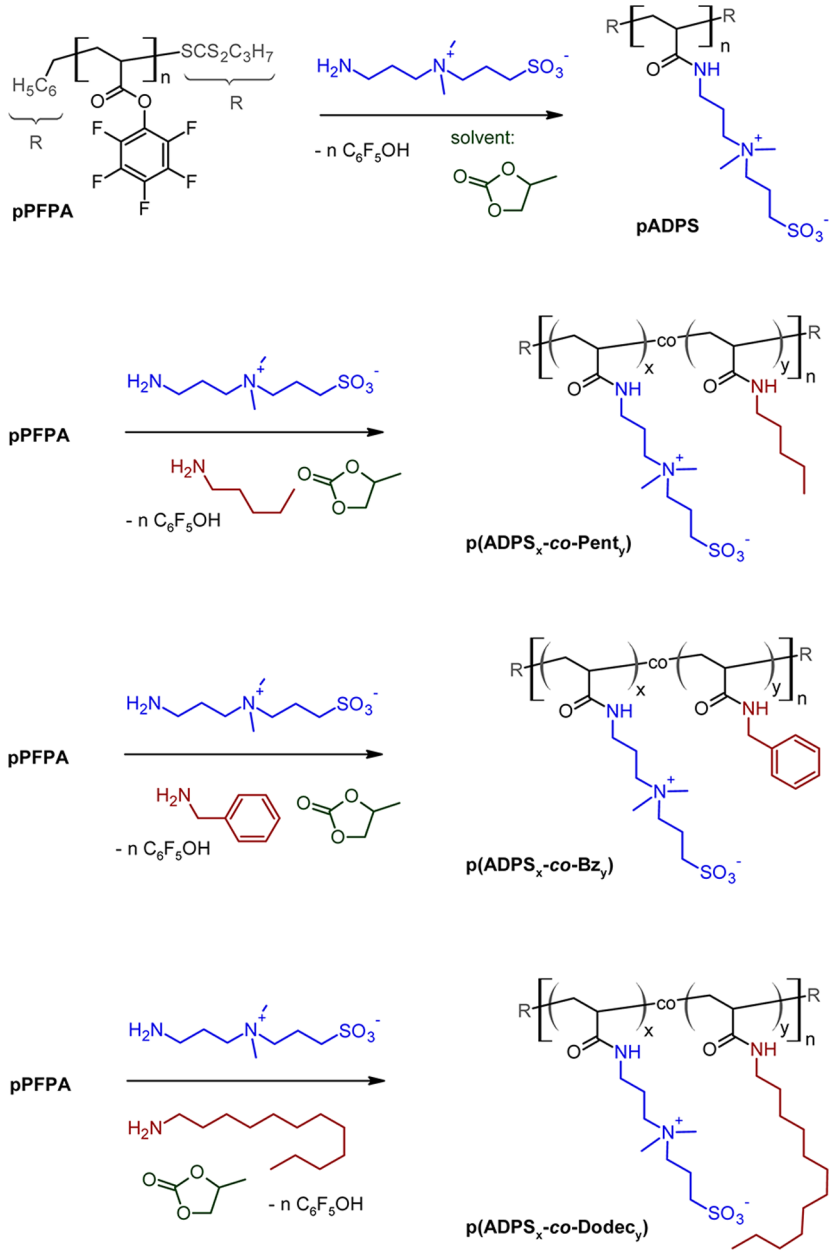
Scheme 2. Synthesis of Hydrophobically Modified Sulfobetaine (Co)polymers in Propylene Carbonate



water, adding an aqueous solution of ADPS into a DMF solution of pPFPA. Precipitation occurred within seconds, and a polymeric material was isolated by dialysis in water. FT-IR analysis (not shown) revealed hydrolysis of pentafluorophenyl (PFP) esters as a main reaction pathway yielding a poorly defined sulfobetaine–acrylic acid copolymer that was not further analyzed. Further experiments involving water or trifluoroethanol likewise resulted in solvolysis of the activated ester precursor, suggesting protic solvent systems to be less ideal and implying a need for optimization. Further experiments revealed propylene carbonate to be an expedient solvent for this problem. A highly polar aprotic solvent, propylene carbonate, has previously been employed in sulfobetaine synthesis,[3,83] and we found it to enable a homogeneous reaction between pPFPA and ADPS. Reactions were carried out in anhydrous propylene carbonate (to avoid hydrolysis) by stirring overnight at 40 °C with a 1.5-fold excess of amines to activated ester groups. A small amount of hydroxyethyl acrylate was added to scavenge any thiols released by aminolysis of the trithiocarbonate RAFT end groups in a thiol–Michael addition reaction.[84] Products were isolated by excessive dialysis in ultrapure water and subsequent lyophilization. The success of the reaction was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, FT-IR spectroscopy, and size exclusion chromatography.

A ^{19}F NMR spectroscopic measurement of a reaction sample withdrawn before purification showed only the sharp signals of released pentafluorophenol and complete disappearance of the broad PFP ester signals of the pPFPA precursor, indicating complete reaction of the PFP esters and suggesting a quantitative integration of sulfobetaine side groups into the backbone (Figure 1).

FT-IR measurements were performed of the pPFPA precursor, the ADPS reagent and the sulfobetaine (co)polymer products. Representative curves are shown in Figure 2. The spectrum of the pPFPA precursor showed the characteristic

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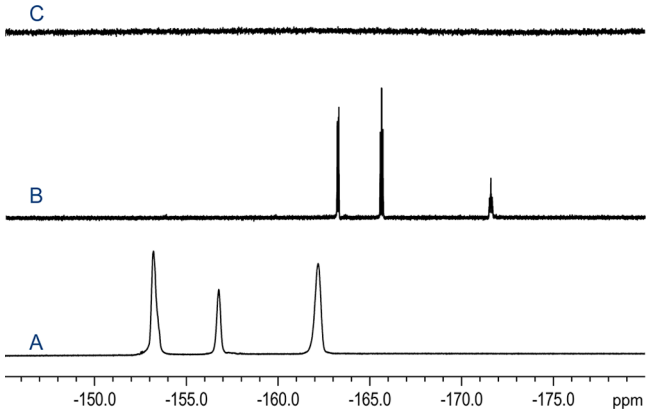

Figure 1. ^{19}F NMR spectra of pPFPA (A), after reaction with ADPS before purification showing the signals of free pentafluorophenol (B), and of a sulfobetaine polymer after purification indicating complete removal of pentafluorophenol by dialysis (C).

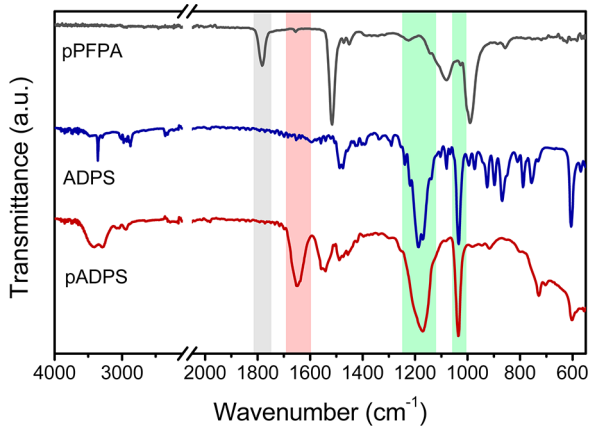

Figure 2. FT-IR spectra of the pPFPA precursor (top), the ADPS reagent (middle), and the pADPS homopolymer product (bottom). The characteristic bands of the activated ester C═O stretch (gray), the amide C═O stretch (red), and the C−N stretch (left green) and S═O stretch (two bands, one overlapping with C−N, green) are marked.

absorption bands of the activated carbonyl group and the perfluorinated aromatic at 1780 and 1515 cm^{-1}, respectively. Strong bands in the spectrum of ADPS were assigned to C−N stretching vibrations of the quaternary ammonium group (1210 and 1170 cm^{-1}) and the S═O stretching vibrations of the sulfonate groups (1170 cm^{-1}, overlapping with C−N band, and 1035 cm^{-1}). Most characteristically, a spectrum of the product pADPS showed amide bands at 1650 cm^{-1} (C═O stretch) and 1550 cm^{-1} (N−H bend), with no remaining signals of the activated ester carbonyl group discernible, suggesting a complete conversion of esters into amides. Additionally, signals assigned to the ammonium and sulfonate groups (see above) were clearly visible, indicating the presence of zwitterionic groups in the polymeric product. An absorbance ∼3400 cm^{-1} was assigned to traces of water due to the hygroscopic nature of the zwitterionic product.

Further evidence of complete conversion of the pPFPA precursor and conversion into the target polysulfobetaine pADPS was obtained by NMR spectroscopic measurements. A section of a ^{1}H NMR spectrum of pADPS in D_2O solution is shown in Figure 3 (bottom). The observed signals and their integration conformed to the expected structure (as assigned in

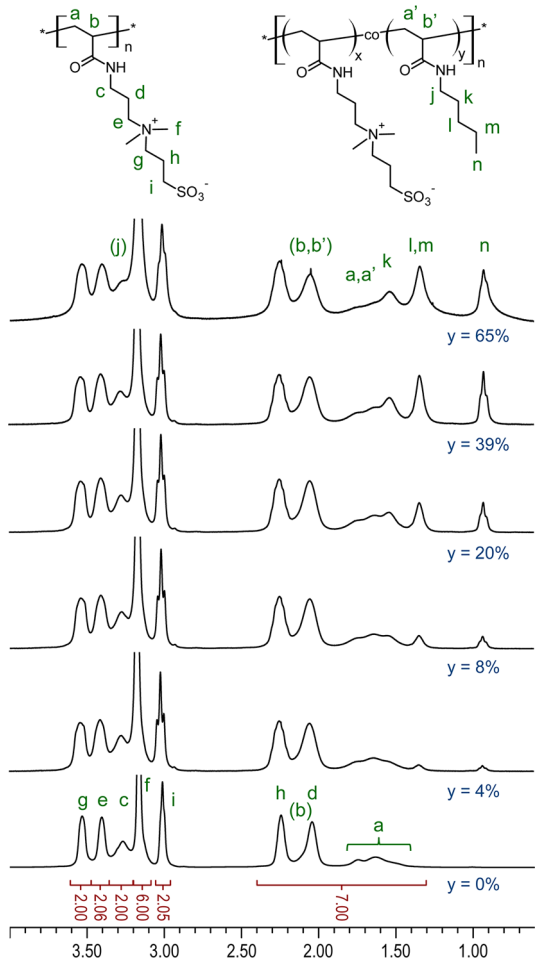

Figure 3. ^{1}H NMR spectra of homopolymer pADPS (500 MHz, D_2O) and of pentylacrylamide copolymers p(ADPS$_x$-*co*-Pent$_y$) (300 MHz, D_2O) with peak assignments.

Figure 3), suggesting successful preparation of pADPS. Noteworthy, the signals originating from groups furthest from the backbone showed best resolution, with the methylene group adjacent to the sulfonate (marked i in Figure 3) appearing as a broad triplet, while groups closer to the backbone, most notably the methylene segment adjacent to the amide functionality (denoted c in Figure 3), gave rise to broader signals. This was interpreted to reflect a somewhat poorer hydration around the hydrophobic backbone. ^{13}C NMR spectroscopy (chemical shifts given in the Experimental Section) likewise conformed to the targeted structure.

Size exclusion chromatograms of pPFPA (measured in THF, polystyrene standard) and pADPS (measured in 0.1 M aqueous NaCl, poly(ethylene glycol) standard) are shown in Figure 4 (bottom). Both curves were of very similar shape, being monomodal with light tailing toward lower molar masses and had similar polydispersity indices (both 1.40, see Table 1), as to be expected from a quantitative postpolymerization modification reaction. Coincidentally, both polymers had comparable apparent molar masses, in spite of the different calibrations used. Additionally, the curve of pADPS did not show any shoulder toward higher molar masses, suggesting that unwanted thiol−thiol coupling reactions following an aminolysis of RAFT end groups had not occurred.[84]

Synthesis of Sulfobetaine Copolymers. After successful synthesis of the sulfobetaine homopolymer pADPS by way of

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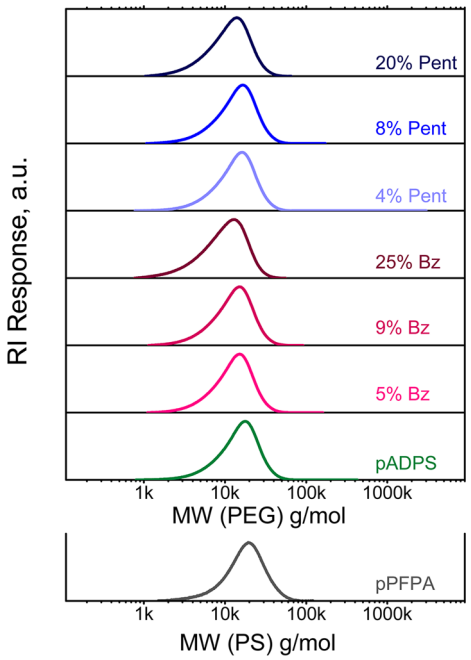

Figure 4. SEC curves of pPFPA precursor (eluent THF, polystyrene standard, bottom curves), and sulfobetaine homo- and copolymers (eluent 0.1 M aqueous NaCl, poly(ethylene glycol) standard).

postpolymerization modification of pPFPA in propylene carbonate, we next took advantage of this synthetic approach to prepare a library of statistical hydrophobically modified sulfobetaine copolymers. Expecting different behavior of alkyl versus aromatic functionality within a zwitterionic copolymer, we first chose pentylamine and benzylamine as hydrophobic modifiers. Reactions were carried out by adding mixtures of benzylamine (5−60 mol % of total amines in feed) or pentylamine (5−85 mol % of total amines in feed) and ADPS dissolved in propylene carbonate to solutions of pPFPA in propylene carbonate, followed by stirring overnight and dialysis in water. The resulting copolymers of the series containing pentylacrylamide and benzylacrylamide comonomers are denoted p(ADPS$_x$-*co*-Pent$_y$) and p(ADPS$_x$-*co*-Bz$_y$), respectively, where y defines the molar ratio of hydrophobic comonomers, as determined by ^{1}H NMR spectroscopy. For most copolymers ^{1}H NMR analysis was performed on solutions in D_2O and confirmed on solutions in trifluoroethanol-d_3 (TFE-d_3), with excellent agreement between both measurements (see Table 1). ^{1}H NMR spectra of the p(ADPS$_x$-*co*-Pent$_y$) series measured in D_2O are plotted in Figure 3 showing the characteristic signals of the zwitterionic and the pentyl side chains with ratios changing with molar composition. ^{1}H NMR spectra of both series measured on TFE-d_3 solutions are shown in Figures S5 and S6 of the Supporting Information. Simple linear regression (not shown) with high correlation (R_{pent}^2 = 0.986; R_{Bz}^2 = 0.993) between the molar percentage of hydrophobic amines in feed and the molar percentage of hydrophobic amide comonomer units in the products (from ^{1}H NMR spectroscopy in D_2O) was found for both series, signifying the high amount of control over copolymer composition that this method offers. Postpolymerization modification with mixtures of reagents is generally considered to yield statistical copolymers,[83] though we note that recent research on effects of neighboring groups to cause nonstatistical incorporation of functionality is limited. As thermoresponsive copolymers prepared herein displayed sharp transitions without evidence of micellization (*vide infra*), we excluded the presence of block-like segments within the products and assumed a largely statistical distribution of hydrophobic and zwitterionic side chains along the copolymer backbones. SEC was measured of copolymers containing 4, 8, and 20 mol % of pentylacrylamide and of those containing 5, 9, and 25 mol % of benzylacrylamide in 0.1 M aqueous NaCl solution (see Figure 4). Very similar shapes, similar apparent molar masses, and similar polydispersity indices (see Table 1) were found for all copolymers, indicating that the characteristic molar mass distribution of the pPFPA precursor was retained in the modified copolymers. We noted, however, a more pronounced

Table 1. Homo- and Copolymers Derived from pPFPA (DP = 117, $Đ_M = M_w/M_n$ = 1.40) with ADPS and Hydrophobic Coamines

	coamine					
code	type	feed[a] (mol %)	found[b] (mol %)	$M_{n,theor}$[c] (kg/mol)	$Đ_M$[d]	cloud point[e] (°C)
pADPS	none	0	0 (D_2O)	34.5	1.40	8.5
p(ADPS$_{0.96}$-*co*-Pent$_{0.04}$)	pentyl	5	3.7 (D_2O); 3.8 (TFE-d_3)	33.9	1.41	2.5
p(ADPS$_{0.92}$-*co*-Pent$_{0.08}$)	pentyl	10	8.3 (D_2O); 8.3 (TFE-d_3)	33.1	1.42	s[g]
p(ADPS$_{0.80}$-*co*-Pent$_{0.20}$)	pentyl	20	19.7 (D_2O); 19.3 (TFE-d_3)	31.3	1.44	s
p(ADPS$_{0.61}$-*co*-Pent$_{0.39}$)	pentyl	30	38.7 (D_2O); 37.7 (TFE-d_3)	28.2	n.d.[f]	s
p(ADPS$_{0.35}$-*co*-Pent$_{0.65}$)	pentyl	60	65.3 (D_2O); 70.7 (TFE-d_3)	24.0	n.d.	s
p(ADPS$_{0.15}$-*co*-Pent$_{0.85}$)	pentyl	85	84.6 ($CDCl_3$)	20.9	n.d.	ins[h]
p(ADPS$_{0.95}$-*co*-Bz$_{0.05}$)	benzyl	5	5.2 (D_2O); 4.6 (TFE-d_3)	33.7	1.38	7.2
p(ADPS$_{0.91}$-*co*-Bz$_{0.09}$)	benzyl	10	9.2 (D_2O); 8.2 (TFE-d_3)	33.2	1.40	6.4
p(ADPS$_{0.75}$-*co*-Bz$_{0.25}$)	benzyl	20	24.7 (D_2O); 23.2 (TFE-d_3)	31.1	1.47	14.5
p(ADPS$_{0.65}$-*co*-Bz$_{0.35}$)	benzyl	30	34.8 (D_2O, 0.1 M NaCl); 36.8 (TFE-d_3)	29.7	n.d.	32.2
p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$)	benzyl	45	52.8 (D_2O, 0.2 M NaCl); 53.5 (TFE-d_3)	27.2	n.d.	63.6
p(ADPS$_{0.35}$-*co*-Bz$_{0.65}$)	benzyl	60	65.3 (D_2O, 0.5 M NaCl); 72.5 (TFE-d_3)	25.5	n.d.	82.4
p(ADPS$_{0.60}$-*co*-Dodec$_{0.34}$)	dodecyl	33	34.3 (TFE-d_3)	32.6	n.d.	ins

[a]Amount of coamine in reaction. [b]Amount of coacrylamide in copolymer determined by ^{1}H NMR spectroscopy, solvent given in parentheses; TFE = trifluoroethanol. [c]Molar mass of copolymer calculated from DP of precursor and copolymer composition from NMR assuming full conversion. [d]Polydispersity index determined by aqueous size exclusion chromatography. [e]Cloud point measured in mQ water at a concentration of 10 g/L. [f]Not determined. [g]Soluble between 0 and 90 °C at a concentration of 10 g/L. [h]Insoluble between 0 and 90 °C at a concentration of 10 g/L.

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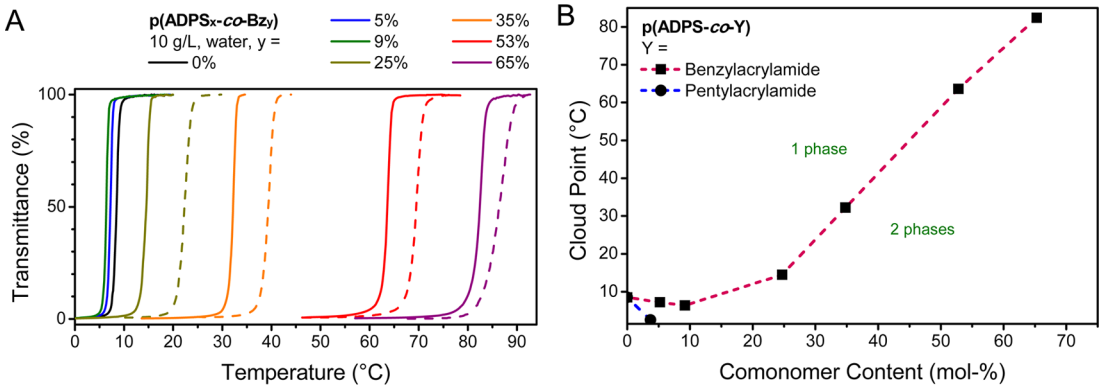

Figure 5. Influence of hydrophobe type and content on aqueous solution properties of sulfobetaine copolymers. (A) Turbidity curves for homopolymer pADPS and benzylacrylamide copolymer series. Solid lines are cooling curves, and dashed lines are heating curves. (B) Phase diagram of cloud point vs hydrophobe content.

tailing toward lower molar masses for the measured copolymers containing the highest amount of hydrophobic groups, i.e., p(ADPS$_{0.80}$-*co*-Pent$_{0.20}$) and p(ADPS$_{0.75}$-*co*-Bz$_{0.25}$), resulting in slightly higher polydispersity indices ($Đ_M$ = 1.44 and 1.47, respectively), possibly due to interactions with the column material, accompanied by an overall shift toward lower apparent molar masses, reflecting lower absolute molar masses of copolymers with higher hydrophobe content. Absolute molar masses of the (co)polymers were estimated from the degree of polymerization of the pPFPA precursor and from molar compositions determined by ^{1}H NMR spectroscopy. Values, given in Table 1, ranged from 20.9 kg/mol for p(ADPS$_{0.15}$-*co*-Pent$_{0.85}$) to 34.5 kg/mol for the pADPS homopolymer.

With sulfobetaine copolymers containing varying (small) amounts of pentyl- and benzylacrylamide successfully prepared through postpolymerization modification of pPFPA in propylene carbonate, we additionally investigated the scope of this synthetic method to produce two further copolymer species: (i) Hydrophobic copolymers containing minor amounts of zwitterionic side chains. Combining improved antifouling properties imparted by the zwitterionic segments with the mechanical properties of a hydrophobic matrix, such materials have recently gained interest in the production of fibers[67] and ultrafiltration membranes.[19,66] We thus prepared p(ADPS$_{0.15}$-*co*-Pent$_{0.85}$) by the same method as described above, using precipitation into water for purification. ^{1}H NMR spectroscopy in $CDCl_3$ confirmed successful synthesis and the targeted molar composition (see Table 1). The copolymer was soluble in methanol, ethanol, propylene carbonate, THF, and chloroform and was insoluble in water (swelling slightly after prolonged heating to 95 °C and also when cooled to 0 °C), acetone, and hexane. These observations suggested successful synthesis of a hydrophobic copolymer comprising zwitterionic functionality using our protocol. (ii) Copolymers containing larger hydrophobic groups. In order to investigate whether the synthesis would also allow for the production of copolymers containing larger hydrophobic groups, the synthesis of a copolymer containing 33 mol % of dodecylacrylamide was investigated (see Scheme 2, bottom). After adding a mixture of ADPS and dodecylamine dissolved in propylene carbonate to a solution of pPFPA in propylene carbonate, clouding (but no precipitation) occurred, suggesting limited solubility of the copolymer product in propylene carbonate. The reaction mixture was then subjected to dialysis in ethanol and then water. In both cases, precipitation occurred inside the dialysis bag, indicating insolubility in both solvents. The dried polymeric material was found to be insoluble in chloroform, to dissolve partially in DMSO−water 5:1, and to dissolve well in trifluoroacetic acid−H_2O 10:1 and trifluoroethanol-d_3. A ^{1}H NMR spectrum measured of the latter solution conformed to a sulfobetaine copolymer containing 34 mol % of dodecylacrylamide. Though no signals of lower molar mass impurities were discernible, the purity of this product was, however, questionable, due to precipitation during dialysis. While a copolymer containing both zwitterionic and dodecyl side chains may have limited applicability due to poor solvent compatibility, our observations nevertheless indicated that the synthetic method presented here allows also for the preparation of copolymers with strongly disparate side chains including larger hydrophobic groups.

Aqueous Phase Behavior of Hydrophobically Modified Sulfobetaine (Co)polymers. The homopolymer pADPS dissolved quickly in ultrapure water at room temperature and showed a cloud point of 8.5 °C at a concentration of 10 g/L (see Table 1 and black curve in Figure 5A). This low cloud point was in agreement with cloud points measured for similar (methacrylato)sulfobetaine copolymers,[39] taking into account that the molar mass of pADPS of 34.5 kg/mol was considerably lower than that of literature examples.[26,27,31,85] With postpolymerization modification producing (co)polymers with identical degrees of polymerization (and thus comparable molar masses), the p(ADPS$_x$-*co*-Pent/Bz$_y$) series presented an ideal platform to investigate the influence of statistically distributed hydrophobic moieties on the phase behavior with the goal of increasing the UCST transition to a more practical range while keeping the main chain degree of polymerization constant. The aqueous solution behavior of sulfobetaine copolymers containing between 4−65 mol % of pentylacrylamide and 5−65 mol % of benzylacrylamide comonomers was investigated by turbidity (at a concentration of 10 g/L) and dynamic light scattering. Consider first the pentylacrylamide series. p(ADPS$_{0.94}$-*co*-Pent$_{0.04}$) had a cloud point of 2.5 °C, 6 °C lower than the homopolymer (see Table 1 and Figure 5B). p(ADPS$_{0.92}$-*co*-Pent$_{0.08}$) was soluble in water upon cooling to 0 °C. However, below 2 °C the transmittance of this sample decreased very slightly to 98.5%, suggesting the presence of a theoretical cloud point below 0 °C (see Figure S7 in Supporting Information). These observations indicated that, surprisingly, incorporation of pentyl side chains into polysulfobetaines increased their solubility, in contrast to the well-

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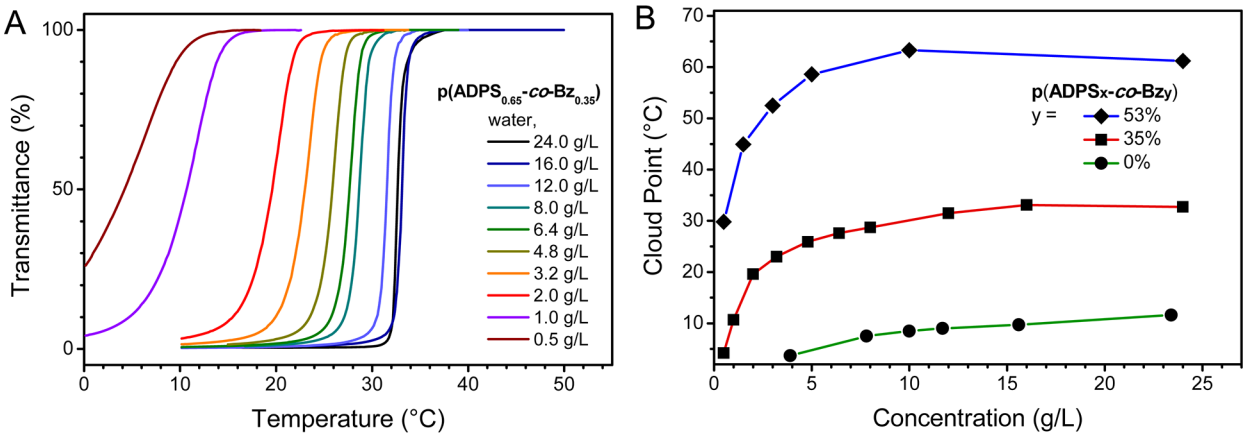

Figure 6. Concentration influence on the cloud point: (A) turbidity curves of p($ADPS_{0.65}$-*co*-$Bz_{0.35}$) in water at varying concentration and (B) temperature−concentration phase diagrams of three (co)polymers showing a largely flat region above concentrations of ∼10 g/L.

established effect of hydrophobic modification to decrease the solubility of polymers with an LCST in water.[44−52] Copolymers containing up to 65 mol % of pentylacrylamide comonomers were found to be soluble in water over the entire temperature range between 0 and 90 °C, showing an increased solubility over a wide composition range. As mentioned above, the sister copolymer comprising 85 mol % of pentylacrylamide was found to be insoluble over the entire investigated temperature range, with thermal phase behavior possibly occurring at molar compositions between these two values.

A very different behavior was observed for the benzylacrylamide copolymer series—turbidity measurements are shown in Figure 5A, cloud points are listed in Table 1, and a plot of cloud points vs benzylacrylamide content is presented in Figure 5B. Incorporation of small amounts of benzylacrylamide, i.e., 5 and 9 mol %, were found to slightly decrease the transition temperature, resulting in cloud points of 7.2 and 6.4 °C, respectively. Higher content of benzyl groups, however, caused the UCST transition temperature to *increase*, as intended, with cloud points increasing in an almost linear fashion from 14.5 °C found for p($ADPS_{0.75}$-*co*-$Bz_{0.25}$) to 82.4 °C observed for p($ADPS_{0.35}$-*co*-$Bz_{0.65}$) (Figure 5B). Of note, a similar trend—slightly increased solubility at low hydrophobe content—was found by Seuring et al.[40] for the variation of UCST cloud points of poly(*N*-acryloylglycinamide) with increasing butyl acrylate content. Transitions observed for benzylacrylamide−sulfobetaine copolymers occurred sharply and were fully reversible and reproducible, with a hysteresis of ∼7 °C between cooling and heating curves observed at cooling/heating rates of 1 °C/min (see Figure S8 in Supporting Information). For the sample of highest benzyl content, 65 mol %, complete redissolution was slow during heating, with small aggregates remaining in an otherwise clear solution until the sample was annealed to 90 °C (∼8 °C above the cloud point) for 15 min, after which a reproducible cooling curve was obtained.

The difference between benzyl and pentyl side chains within pADPS was striking. While benzylacrylamide units expectedly decreased solubility—that is, above a content of ∼9 mol %, incorporation of pentyl groups increased the solubility of sulfobetaine copolymers over a composition range from 0 to at least 65 mol %, though both acrylamide units are hydrophobic, their respective homopolymers polypentylacrylamide and polybenzylacrylamide being insoluble in water. It is conceivable that the pentylacrylamide copolymers might self-assemble into micellar structures with the hydrophobic chains segregated in the cores. Previous research on LCST-type polymers demonstrated a reduced influence of hydrophobic end groups on lowering the solubility if the end groups self-assembled and were thus not exposed to the solvent.[47] In the current case, however, there was no evidence of such self-assembly. Notably, the ^{1}H NMR signals of the pentyl side groups were quite well resolved in D_2O (Figure 3), showing solvation of the hydrophobic groups. An excellent agreement between molar compositions determined through NMR analysis in D_2O and TFE-d_3 (and the feed ratios of pentyl vs zwitterionic groups, Table 1) suggested that the pentyl groups were not segregated in D_2O solution. Additionally, DLS of pentylacrylamide copolymers in aqueous solution gave no evidence of self-assembled structures, suggesting unimerically dissolved copolymers (see Figure S9 in the Supporting Information). With no previous systematic studies on UCST behavior of hydrophobically modified sulfobetaine copolymers available, we propose the following explanation. (i) Thermodynamic considerations. As mentioned in the Introduction, UCST behavior relies on a balance between enthalpic polymer−polymer interactions favoring phase separation and mixing entropy favoring dissolution. Entropic and enthalpic contributions from the incorporated pentyl and benzyl side groups can thus be expected have an influence on the phase separation temperature. In a recent study on entropic trends during hydration of common functional groups,[86] the authors described that rigid molecules (such as benzyl groups) cause a higher *loss* of water orientational entropy during hydrophobic hydration compared to flexible groups, while alkyl chains have *higher* rotational entropy and can, in fact, experience an increase in internal entropy through hydration by stabilization of higher energy gauche transformations in solution. This would suggest a higher gain in entropy during the dissolution of a pentyl-functional copolymer compared to a similar benzyl-functional copolymer, thus making the pentyl-modified species more soluble than the corresponding benzyl analogue. It should also be considered that the aromatic benzyl groups have the potential to form attractive interactions with each other ($\pi-\pi$),[87] as well as with the ammonium groups (cation−π),[88] and, though less likely, the sulfonate groups (anion−π).[89] Such enthalpic interactions—granted, their experimental observation may be difficult—would likewise suggest a decreased solubility of the benzyl-functional polymers compared to their pentyl counter-

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parts. (ii) Kinetic considerations. Insolubility of sulfobetaine (co)polymers at low temperature and in the absence of electrolytes is based on an interlocking of zwitterionic side groups of different polymer chains, creating a semicrystalline structure. The presence of flexible pentyl chains can be assumed to sterically interrupt this interlocking to a higher extent than the presence of rigid benzyl groups, thereby reducing the crystallinity and increasing the solubility of pentyl-functional copolymers. We therefore hypothesize that incorporation of any rigid hydrophobic functionality into sulfobetaine copolymers will decrease their solubility, allowing for a tuning of their UCST cloud points. If, on the other hand, temperature-independent water solubility of a hydrophobically modified sulfobetaine copolymer is desired, flexible functionality that does not contribute to polymer−polymer attractions would appear to be the appropriate choice.

Having successfully increased the UCST of polysulfobetaines enabling tunable, sharp transitions of copolymers with molar masses ranging from 25.5 to 34.5 kg/mol (see Table 1), we next investigated the phase behavior of the p(ADPS$_x$-*co*-Bz$_y$) series in more detail. Temperature−composition phase diagrams were measured for three (co)polymers with benzyl contents of 0, 35, and 53 mol % (see Figure 6). With very low transition temperatures, the homopolymer pADPS only had measurable cloud points above a concentration of 4 g/L, while the benzyl-modified copolymers with higher transition temperatures showed the expected cloud point decrease with decreasing concentration, measured down to 0.5 g/L, demonstrating again the benefit of hydrophobic modification. An "inverted LCST" around 10 g/L as previously described for similar systems[27] was not observed for the present (co)polymers. The phase diagrams had largely flat regions above a concentration of ∼10 g/L, offering a reliable phase behavior above this concentration. The concentration coordinate of the UCSTs (maxima of the binodal curves) decreased with increasing benzyl content lying at or above 24 g/L for the homopolymer, at ∼16 g/L for p(ADPS$_{0.65}$-*co*-Bz$_{0.35}$) and at ∼10 g/L for p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$).

Dynamic light scattering (DLS) was used as a further method to characterize the phase transition. In Figure 7, the temperature-dependent derived count rate of a sample of p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$) in water at a concentration of 1.5 g/L is shown together with the optical transmittance of the same sample. By turbidity, a cloud point (50% transmittance) of 44.9 °C was found with an onset of transmittance decrease just around 55 °C. By DLS, an increase of count rate, i.e. increased scattering, was found to occur in the same temperature range, agreeing well with the turbidity measurement. DLS analysis also confirmed that the polymer chains appeared to be unimerically dissolved just above the phase transition having volume-average diameters of 9.40 and 9.25 nm at temperatures of 60 and 55 °C, respectively (see inset of Figure 7). This is in contrast to amide-based polymers with aqueous UCSTs, such as poly(*N*-acryloyl glycinamide), which are known to contain aggregates above the UCST, in spite of appearing as clear solutions.[28]

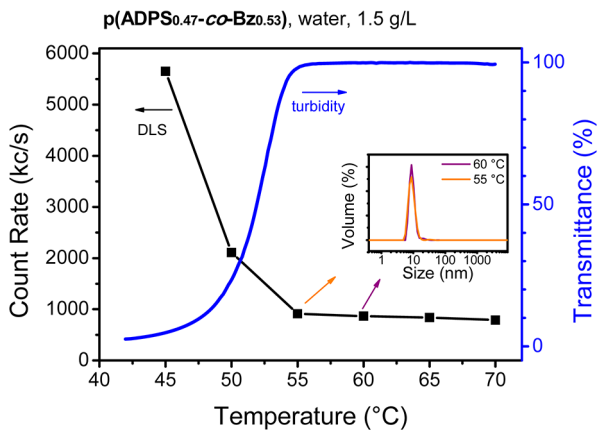

Figure 7. Scattering intensity (by dynamic light scattering, black curve) and transmittance (by turbidity, blue curve) for a sample of a benzylacrylamide−sulfobetaine copolymer showing concurrent decrease of transmittance and increase of scattering count rate and volume-average diameter of scatterers (inset) suggesting unimers and absence of aggregates just above the UCST transition.

As mentioned in the Introduction, zwitterionic (co)polymers are known to display an antipolyelectrolyte effect—addition of electrolytes increasing solubility—which has been exploited in applications[38] but which also poses limitations to applicability of polysulfobetaines, typically necessitating working in ultrapure water. We therefore probed the tolerance of the phase transition of a sample with a UCST increased through benzylacrylamide incorporation, p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$), toward the presence of a model electrolyte, sodium chloride, at constant polymer concentration of 10 g/L. In pure water, this copolymer had a cloud point of 63.6 °C. At a NaCl concentration of 1.5 mM the cloud point *increased* slightly to 65.2 °C. This effect has been shown to occur at salt levels below a threshold concentration, when the amount of added salt is not sufficient to completely screen the attractions between the positive and negative charges in the polymers, with reported NaCl concentrations at maximum solubility being between 0.7 and 2 mM—consistent with our observation.[26] It is, at this stage, important to note that the amount of electrolyte contamination within the (co)polymer samples after exhaustive dialysis in ultrapure water was lower than the lowest added concentration of NaCl, with the sodium concentration of a (co)polymer solution at a concentration of 10 g/L estimated to be 0.06 mM from elemental analysis. At higher added NaCl concentrations, the cloud point of p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$) was found to decrease, showing the expected antipolyelectrolyte effect. Turbidity curves are shown in Figure 8A, and the trend of cloud point vs NaCl concentration is plotted in Figure 8B. While the cloud point of p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$) initially showed a rather steep decline, decreasing by 5.8 to 59.4 °C at a salt concentration of 3.0 mM, the influence became somewhat less pronounced at higher salt concentrations, with cloud points of 14.7 and 7.3 °C measured at salt concentrations of 60.7 and 75.8 mM (corresponding to 3.55 and 4.43 g/L), respectively. A cloud point of 39.2 °C, close to body temperature, was found for a salt concentration of 22.8 mM. Phase separations of p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$) in salt water were fully reversible and reproducible with a hysteresis of ∼7 °C, similar to that found in pure water (see Figure S8 in Supporting Information). These measurements illustrated the potential of tuning the phase separation temperature of hydrophobically modified sulfobetaine copolymers through the addition of salt, showing that the incorporation of benzyl groups can enable sharp, reproducible phase transitions in aqueous salt solutions. Yet, the salt tolerance of p(ADPS$_{0.47}$-*co*-Bz$_{0.53}$) is unquestionably not high enough for an exploitation of the UCST transition under physiological conditions, typically involving (among many other components) salt concentrations of ∼154 mM (9 g/L)

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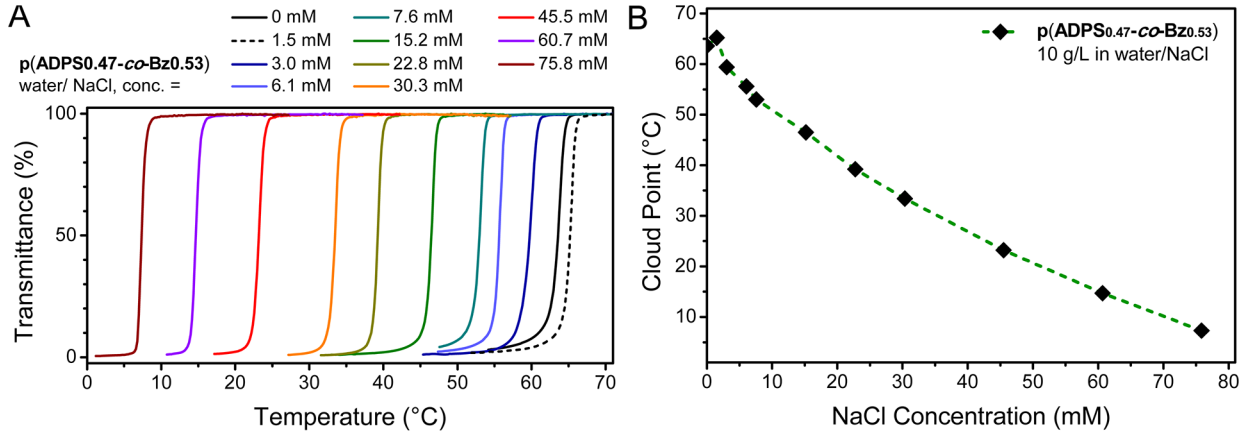

Figure 8. Influence of salt concentration on the phase separation temperature of a benzylacrylamide–sulfobetaine copolymer: (A) turbidity curves for increasing NaCl concentration; (B) variation of cloud point with increasing NaCl concentration, showing an initial increase below the threshold salt concentration[26] and a decrease above enabling UCST transitions up to a NaCl concentration of 75.6 mM (4.43 g/L).

NaCl. Nonetheless, this first detailed study into tuning the UCST transition of sulfobetaine copolymers offers the necessary understanding and tools to further develop zwitterionic copolymers and to extend the scope of these smart, blood-compatible materials into other realms of science.

CONCLUSION

We expanded the scope of activated esters in the polymer chemistry arena by optimizing reaction conditions for converting poly(pentafluorophenyl acrylate) with a zwitterionic amine, thus providing simple synthetic access to a library of well-defined hydrophobically modified zwitterionic (co)-polymers. This strategy was applicable to copolymers over the full range of molar compositions including hydrophobic copolymers comprising minor amounts of zwitterionic functionality, as well as copolymers containing large hydrophobic moieties, providing excellent control over the molar composition of copolymers. In spite of hydrophobic modification, a copolymer series containing varying amounts of pentylacrylamide showed temperature-independent water solubility over a wide compositional range, which was attributed to an entropic contribution of the flexible pentyl chains. Conversely, a copolymer series comprising varying amounts of benzylacrylamide expectedly exhibited decreased water solubility with increasing benzyl content, manifested in increasing UCST transition temperatures. Benzylacrylamide incorporation thus allowed, for the first time, a precise tuning of the UCST cloud point of sulfobetaine copolymers and made this rare phase behavior much more accessible with polymer samples of intermediate molar masses (~30 kg/mol) exhibiting UCST cloud points in the range of 6–82 °C. Addition of electrolytes had the opposite effect, causing decreasing cloud points with increasing NaCl concentration. Both effects—antipolyelectrolyte effect and increased UCST by virtue of benzyl incorporation—were found to compensate each other well, allowing for sharp, fully reversible and reproducible UCST transitions of benzyl-modified sulfobetaine copolymers in salt solutions. The synthetic approach described here, moving UCST transitions of polysulfobetaines into a much more accessible temperature/molar mass range, is envisaged to allow for exploitation of the full plethora of advantages that postpolymerization modification offers including incorporation of smart/biological functionality into polybetaines and construction of complex polymeric architectures containing zwitterionic segments, thus significantly widening the applicability of these smart materials.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of the zwitterionic amine and its hydrochloride, ^{1}H NMR spectra of pentylacrylamide and benzylacrylamide copolymers in TFE-d_3, turbidity curves of pentylacrylamide copolymers, reproducibility measurements of copolymers in pure water and in NaCl solution, DLS measurements of pentylacrylamide copolymers This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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