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Para-Fluoro Postpolymerization Chemistry of Poly(pentafluorobenzyl methacrylate): Modification with Amines, Thiols, and Carbonylthiolates

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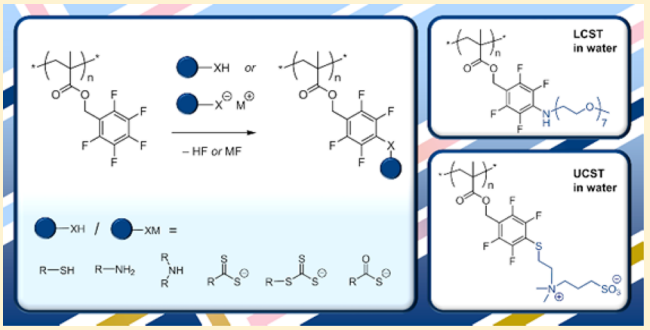
Supporting Information

ABSTRACT: A methacrylic polymer undergoing highly efficient *para*-fluoro substitution reactions is presented. A series of well-defined poly(2,3,4,5,6-pentafluorobenzyl methacrylate) (pPFBMA) homopolymers with degrees of polymerization from 28 to 132 and $Đ \leq 1.29$ was prepared by the RAFT process. pPFBMA samples were atactic (with triad tacticity apparent in ^{1}H and ^{19}F NMR spectra) and soluble in most organic solvents. pPFBMA reacted quantitatively through *para*-fluoro substitution with a range of thiols (typically 1.1 equiv of thiol, base, RT, <1 h) in the absence of any observed side reactions. *Para*-fluoro substitution with different (thio)-carbonylthio reagents was possible and allowed for subsequent one-pot cleavage of dithioester pendent groups with concurrent thia-Michael side group modification. Reactions with aliphatic amines (typically 2.5 equiv of amine, 50−60 °C, overnight) resulted in complete substitution of the *para*-fluorides without any observed ester cleavage reactions. However, for primary amines, H_2NR, double substitution reactions yielding tertiary $(-C_6F_4)_2NR$ amine bridges were observed, which were absent with secondary amine reagents. No reactions were found for attempted modifications of pPFBMA with bromide, iodide, methanethiosulfonate, or thiourea, indicating a highly selective reactivity toward nucleophiles. The versatility of this reactive platform is demonstrated through the synthesis of a pH-responsive polymer and novel thermoresponsive polymers: an oligo(ethylene glycol)-functional species with an LCST in water and two zwitterionic polymers with UCSTs in water and aqueous salt solution (NaCl concentration up to 178 mM).



INTRODUCTION

Postpolymerization modification (the introduction of chemical functionality into a premade reactive precursor) is a versatile synthetic pathway that provides unique access to functional materials and enables the study of structure−property relationships in series of functional daughter polymers with virtually identical degrees of polymerization. While the concept is as old and extensive as polymer science itself,[1] much recent work is based on vinyl systems and the architectural control offered by the suite of reversible deactivation radical polymerization (RDRP) methods.[2−5] For a reactive group to be suited for postpolymerization modification, it must (i) be compatible with polymerization conditions (or come with an easily removable protecting group) and (ii) allow for selective and efficient chemical modification, ideally under mild conditions. Commonly used chemical groups include the nucleophile-reactive epoxide,[6,7] azlactone,[8−11] and activated esters[12] as well as unsaturated groups such as dienes and alkynes which can undergo cycloadditions and reactions with thiols.[13,14]

A functional group that remains underexplored in the polymer chemistry arena is the pentafluorobenzene (PFB) motif, which undergoes selective nucleophilic aromatic substitution reactions of the *para*-fluoride (which is the most activated having two *ortho*- and two *meta*-fluoride neighbors).[15−17] Low molar mass PFB derivatives have been used for the synthesis of monomers[18] and for polymer end group modification.[19] Multifunctional PFB-functional building blocks have been condensed for the preparation of metal-containing linear polymers,[20] hyperbranched polymers,[21] and precision networks.[22] PFB-functionalized end groups were exploited for the functionalization of polythiophenes[23] and the synthesis of

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multiarm copolymers.[24] With regards to postpolymerization functionalization of side groups, however, the literature is, with very few exeptions,[21,25−28] limited to the modification of 2,3,4,5,6-pentafluorostyrene-based (co)polymers with amines,[29] phosphite,[30] and thiols[31−33] (including in water[34] and on surfaces).[35−37] The thiol−*para*-fluoro substitution reaction has been combined with (and shown to be orthogonal to) pentafluorophenyl-activated esters,[25,27] radical-mediated thiol−ene additions,[24,38] and Cu-catalyzed azide−alkyne cycloadditions.[39]

Herein, the reversible addition−fragmentation chain transfer (RAFT)[40] synthesis and postpolymerization modification of poly(2,3,4,5,6-pentafluorobenzyl methacrylate), pPFBMA, a *methacrylic* system amenable to highly efficient *para*-fluoro substitution reactions, is presented for the first time. A small number of studies have described the synthesis of this polymer through anionic polymerization,[41] free-radical homo-[42] and copolymerization with styrene,[43] and the photoinitiator-free photopolymerization[44]—but not its postmodification. Acyl substitutions, key to the modification of Theato's polymeric pentafluorophenyl (PFP) esters,[45] were not observed on PFB esters. Instead, pPFBMA was found to react quantitatively through *para*-fluoro substitution with thiols and amines, though with a certain degree of double substitution when primary amines were used. Additionally, reaction with several (thio)carbonylthio reagents enabled subsequent polymer analogous modification. The high selectivity of the *para*-fluoro substitution was apparent by the lack of any observed reaction with bromide, iodide, thiourea, and methanethiosulfonate nucleophiles. The versatility of this reactive scaffold is demonstrated through the preparation of novel stimulus-responsive polymers.

EXPERIMENTAL SECTION

Instrumentation. NMR spectroscopic measurements were performed on 300, 400, or 500 MHz Bruker instruments in 5 mm NMR tubes. Residual solvent signals of $CHCl_3$ (δ_H = 7.26 ppm, δ_C = 77.2 ppm), DMSO-d_5 (δ_H = 2.51 ppm), and HDO (δ_H = 4.79 ppm) were used as references. ^{19}F NMR chemical shifts are given relative to a $CFCl_3$ standard.

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 50 °C and a flow rate of 1 mL/min. Reported values are polystyrene (PS) equivalent molar masses based on a calibration with a series of narrow molar mass distribution PS standards with molar masses ranging from 0.58 to 1820 kg/mol.

Fourier transform infrared spectroscopy (FT-IR) was performed on a Bruker IFS 66/S instrument under attenuated total reflectance (ATR).

LCST and UCST cloud points were determined through temperature-dependent optical turbidity measurements using an Avantium Crystal16 system using heating/cooling rates of 1 °C/min. Cloud points were determined at the onset of transmittance decrease during heating (LCST type) or cooling (UCST type).

Microwave heating was done in a single-mode Anton Paar Monowave 300 reactor using an infrared temperature sensor and compressed air flow for simultaneous cooling.

Differential scanning calorimetry (DSC) was done on a DSC Q1000 by TA Instruments. The glass transition temperature, T_g, was determined from the second heating step of a heat−cool−heat cycle (rates 10 °C/min) from the intersection of extrapolated approximately straight-line portions of the thermogram before and after the onset of heat flow change.[46]

Synthesis. *General Remarks.* All reagents were purchased from Sigma-Aldrich and used without purification unless stated otherwise. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and stored in a freezer. Anhydrous *N*,*N*-dimethylformamide (DMF) was stored in a glovebox. Acetone was dried over molecular sieves (3 Å). The triethylammonium salt of *S*-carboxypropyltrithiocarbonic acid was prepared following a literature procedure.[47]

Pentafluorobenzyl Methacrylate (PFBMA). Potassium carbonate (anhydrous, 17.22 g, 0.125 mol, 5 equiv) was suspended in anhydrous acetone (160 mL). Methacrylic acid (3.22 g, 3.17 mL, 0.037 mol, 1.5 equiv), 2,3,4,5,6-pentafluorobenzyl bromide (6.5 g, 3.76 mL, 0.025 mol, 1 equiv), and butylated hydroxytoluene (BHT, three small crystals) were added. The mixture was refluxed for 3 h, and complete reaction was confirmed with TLC control (EtOAc−hexane 1:7). The mixture was filtered to remove salts, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (150 mL) and extracted with water (150 mL, pH 5), aqueous $NaHCO_3$ (3 × 150 mL, pH 9), and water (100 mL) again. The organic phase was dried over magnesium sulfate and filtered through basic aluminum oxide, and the solvent was removed under reduced pressure. Three batches: yields 88%, 93%, and 95%. ^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm = 6.11, 5.60 (2 × 1H, H_2C═), 5.27 (2 H, t, $^4J_{HF}$ = 1.4 Hz, OCH_2), 1.93 (3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm = 166.8 (*C*═O), 147.2 and 144.7 (dm, $^1J_{CF}$ = 255 Hz, 2 × *meta* *C*−F), 143.2 and 140.7 (dm, $^1J_{CF}$ = 255 Hz, *para* *C*−F), 139.0 and 136.5 (dtd, $^1J_{CF}$ = 255 Hz, $^2J_{CF}$ = 17 Hz, $^3J_{CF}$ = 4 Hz, 2 × *ortho* *C*−F), 135.7 (*C*(CH_3)), 126.9 (H_2C═*C*), 109.7 (td, $^2J_{CF}$ = 17 Hz, $^3J_{CF}$ = 4 Hz, CH_2C_{PFB}), 53.8 (OCH_2), 18.3 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$), δ/ppm = −141.9 (m, 2 F, *ortho*), −152.7 (t, 1 F, *para*), −161.7 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 2950, 2896 (w, C−H alkyl, C═CH_2 stretch), 1722 (m−s, C═O ester stretch), 1502 (s, C═C stretch), 1128 (s, C−O stretch), 1054 (s, C−F stretch). MS (ESI) *m*/*z* (%) = 289.03 (100) [M + H]$^+$, 290.03 (10) [M^{13C} + H]$^+$.

General Procedure for RAFT Polymerization. A mixture of PFBMA (varying equiv based on targeted DP), RAFT agent 2-cyano-2-propyl benzodithioate (1 equiv), AIBN stock solution (containing 0.1 equiv of AIBN in anisole), and anisole (total volume approximately 1.5-fold volume of PFBMA) were mixed in a reaction vial. A stir bar was added, and the vial was sealed with a septum and degassed for 30 min by purging with nitrogen through a needle with a shorter needle fitted for gas release. The vial was placed into a preheated oil bath (70 °C) overnight (typically 15−16 h). After cooling in an ice−water bath, a sample (100 μL) was withdrawn, diluted with $CDCl_3$ (500 μL), and analyzed by ^{1}H and ^{19}F NMR spectroscopy to determine monomer conversion by comparison of the methylene group ^{1}H signals and the *para*-^{19}F NMR signals. The polymer was precipitated twice into an excess (approximately 20−30-fold in volume) of methanol, and the product was collected as a pink solid by centrifugation followed by drying in a vacuum at 40 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 5.07 and 5.03 (2 × bs, 2 H, OCH_2), 2.05−1.65 (m, 2 H, backbone CH_2), 1.20−0.65 (m, 3 H, backbone CH_3 including 1.14 (5%) mm, 0.96 and 0.90 (35%) *mr*, and 0.79 and 0.75 (60%) *rr* triads). ^{19}F NMR (282 MHz, $CDCl_3$), δ/ppm = −141.8 (5%), −142.1 (35%), and −142.4 (60%) (3 m, 2 F, *ortho*), −152.0 (60%), −152.4 (35%), and −152.8 (5%) (3 m, 1 F, *para*), −161.5 and −161.7 (∼95%) and −162.1 (∼5%) (3 bs, 2 F, *meta*). FT-IR ν/cm^{-1} = 2995, 2935 (w, C−H stretch), 1735 (m−s, C═O ester stretch), 1504 (s, C═C stretch), 1132 (s, C−O, stretch), 1052 (s, C−F, stretch). T_g = 65 °C.

Postpolymerization Modification of PPFBMA with Thiols. Generally, pPFBMA (40 mg) was dissolved in anhydrous DMF (1−2 mL), and thiol (1.1−5 equiv) and base (triethylamine or DBU, 1.05−5.1 equiv) were added. The mixture was stirred at RT−45 °C for 40 min−1 day, and the product was precipitated into methanol or water. See main text for details. Thiophenol-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 7.29 (bs, 2 H), 7.19 (m, 3 H). Captopril-modified: ^{1}H NMR (300 MHz, DMSO-d_6), δ/ppm = 4.00, 3.50, 2.70, 1.99−1.88, 1.07. *n*-Octanethiol-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 2.97 (SCH_2), 1.60 (SCH_2CH_2), 1.40, 1.25 (CH_2), 0.86 (CH_3). *n*-Butanethiol-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 2.98 (SCH_2), 1.56 (SCH_2CH_2), 1.45 (CH_2CH_3), 0.91 (CH_3). 2-(Dimethylamino)ethanethiol-modified: ^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm = 3.09 (bt, 2 H, SCH_2), 2.55 (bt, 2 H, CH_2N)

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2.25 (bs, 6 H, $N(CH_3)_2$). Backbone and $COOCH_2$ methylene resonances as above.

Quaternization of Poly[4-(2-(dimethylamino)ethylsulfanyl)-2,3,5,6-tetrafluorobenzyl methacrylate] with 1,3-Propane Sultone. 2-(Dimethylamino)ethanethiol-modified pPFBMA (20 mg, 57 μmol of repeat units, 1 equiv) was dissolved in 2,2,2-trifluoroethanol (400 μL). A separately prepared solution of 1,3-propane sultone (14.8 mg, 121 μmol, 2.1 equiv) in 2,2,2-trifluoroethanol was added, and the resulting homogeneous mixture was stirred for 5 days at 40 °C. The product was isolated by dialysis against ultrapure water and drying in a vacuum. ^{1}H NMR (400 MHz, D_2O/NaBr), δ/ppm = 3.88 (CH_2NCH_2), 3.49 ($N(CH_3)_2$), 3.28 (SCH_2, $CH_2SO_3^-$), 2.50 ($CH_2CH_2CH_2$).

Quaternization of Poly[4-(2-(dimethylamino)ethylsulfanyl)-2,3,5,6-tetrafluorobenzyl methacrylate] with 1,4-Butane Sultone. 2-(Dimethylamino)ethanethiol-modified pPFBMA (20 mg, 57 μmol of repeat units, 1 equiv) was dissolved in 2,2,2-trifluoroethanol (400 μL). A separately prepared solution of 1,4-butane sultone (8.8 μL, 86 μmol, 1.5 equiv) in 2,2,2-trifluoroethanol was added, and the resulting homogeneous mixture was filled into a 2 mL microwaveable pressurized tube and heated to 120 °C for 15 h with stirring in a microwave reactor, reaching a pressure of 7 bar. Complete conversion was verified through ^{19}F NMR analysis of a sample (50 μL) diluted with D_2O (550 μL) containing NaBr (approximately 10 mg). Excess 1,4-butane sultone phase separated from the NMR sample which did not influence the measurement. The product was isolated by dialysis against ultrapure water (residual 1,4-butane sultone hydrolyzed and dissolved slowly) and drying in vacuum. ^{1}H NMR (400 MHz, D_2O/NaBr), δ/ppm = 3.51 (CH_2NCH_2), 3.22 ($N(CH_3)_2$), 3.02 (SCH_2, $CH_2SO_3^-$), 1.98, 1.89 ($CH_2CH_2CH_2CH_2$).

Postmodification of pPFBMA with Sodium Hydrogen Sulfide. A solution of pPFBMA (10 mg, 37.6 μmol of repeat units, 1 equiv) in anhydrous DMF (1.4 mL) was purged with nitrogen for 30 min, and sodium hydrogen sulfide hydrate (4.2 mg, 75.2 μmol, 2 equiv) was added under reverse nitrogen flow. The mixture turned light green, green-blue, then dark blue, and green again upon stirring at RT for 30 min. ^{19}F NMR analysis of a sample (100 μL) diluted with $CDCl_3$ (500 μL) confirmed complete reaction. ^{19}F NMR (282 MHz, $CDCl_3$), δ/ppm = −139.3 (s, 2 F) and −139.6 (s, 2 F), no residual starting material signals. Upon purification by dialysis against methanol, the polymer cross-linked.

Triethylammonium p-Fluorodithiobenzoate. The (unstable) acid derivative was prepared from 4-fluorophenylmagnesium bromide solution (1 M in THF) and carbon disulfide according to a literature procedure,[48] followed by addition of triethylamine and drying in a vacuum.

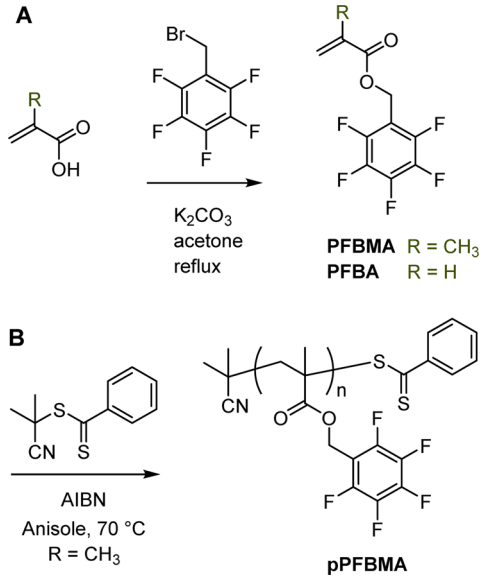
Postpolymerization Modification of PPFBMA with Dithiobenzoate, Followed by Aminolysis and Thiol–Ene Modification. pPFBMA (13.1 kg/mol, Đ = 1.20, 11.7 mg, 44 μmol of repeat units, 1 equiv) was dissolved in DMF (1.4 mL), and triethylammonium *p*-fluorodithiobenzoate (20.8 mg, 76 μmol, 1.7 equiv) and triethylamine (17 μL, 122 μmol, 2.8 equiv) were added. The pink solution was stirred at 65 °C for 24 h. ^{19}F NMR analysis of a sample (250 μL) diluted with $CDCl_3$ (350 μL) confirmed absence of starting material signals. The mixture was cooled to RT, and butyl acrylate (27 μL, 189 μmol, 4.3 equiv) and *tert*-butylamine (60 μL, 569 μmol, 12.9 equiv) were added; the mixture stirred overnight at RT. The product was precipitated into diethyl ether–hexane (4:1) and dried in a vacuum. ^{19}F NMR (282 MHz, DMSO-d_6), δ/ppm = −134.0 (bs, 2 F), − 141.6 (bs, 2 F), SEC 44.1 mg/mol, Đ = 1.56, bimodal.

Postpolymerization Modification of pPFBMA with Amines. Generally, pPFBMA (40 mg, 0.15 mmol of repeat units, 1 equiv) was dissolved in anhydrous DMF (1 mL), and butyl acrylate (to scavenge thiols release through RAFT end group aminolysis, 5 μL)[49] and amine (butylamine, pentylamine, cyclohexylamine, piperidine, 3-(dimethylamino)propylamine, aniline, 4-benzylpiperidine, 1-(2-hydroxyethyl)piperazine, di(ethylene glycol) methyl ether amine (2EG), tri(ethylene glycol) methyl ether amine (3EG), PEG_{350} methyl ether amine, 2.5 equiv) was added. The mixture was stirred at 50 or 60 °C. Conversion was monitored by withdrawing samples (50 μL) diluting with $CDCl_3$ (600 μL) and analyzing by ^{19}F NMR spectroscopy. Complete disappearance of starting material signals was achieved in 10–144 h (see details in main text). In cases where the ammonium hydrofluoride precipitated it was removed by filtration. Products were isolated by precipitation into methanol or dialysis (regenerated cellulose, MWCO 3500 Da) against methanol or water–ethanol 1:1. Butylamine-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.38, 1.57, 1.40, 0.93. Pentylamine-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.37, 1.59, 1.48, 1.31, 0.89. Cyclohexylamine-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.50 (*CH*NH) 2.05–0.70 (CH_2). 3-(Dimethylamino)propylamine-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.52 ($NHCH_2$), 2.55 (CH_2N), 2.32 ($N(CH_3)_2$), 1.83 ($CH_2CH_2CH_2$). Piperidine-modified: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm = 3.21 ($CH_2N(R)CH_2$), 1.64, 1.61 ($CH_2CH_2CH_2$). 2EG/3EG/PEG_{350}-modified: ^{1}H NMR ($CDCl_3$–CD_3OD 10:1, 400 MHz) δ/ppm = 3.55, 3.45 (OCH_2), 3.29 (OCH_3), 2.88 ($NHCH_2$). 4-Benzylpiperidine-modified: ^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm = 7.24, 7.13 (*Ph*), 3.31, 3.02 ($N(CH_2)_2$), 2.54 (CH_2Ph), 1.73 (*CH*), 1.65, 1.36 ($N(CH_2CH_2)_2$). 1-(2-Hydroxyethyl)piperazine-modified: ^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm = 3.67 (CH_2OH), 3.34 (Ar–NCH_2CH_2), 2.64 ($N(CH_2)_3$). Backbone and $COOCH_2$ methylene resonances as above; for SEC and ^{19}F NMR data see the main text.

RESULTS AND DISCUSSION

Synthesis of Monomers and Polymers. 2,3,4,5,6-Pentafluorobenzyl acrylate (PFBA) and 2,3,4,5,6-pentafluorobenzyl methacrylate (PFBMA) were prepared in high yields from (meth)acrylic acid and 2,3,4,5,6-pentafluorobenzyl bromide as confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, ESI mass spectrometry, and FT-IR spectroscopy (see Scheme 1A and Figures S1–S8 in the Supporting Information). While

Scheme 1. Synthesis of the Reactive Monomers 2,3,4,5,6-Pentafluorobenzyl Acrylate and 2,3,4,5,6-Pentafluorobenzyl Methacrylate (A) and RAFT Polymerization (B)



the ^{19}F NMR signals of the bromide starting material and the (meth)acrylate products did not differ strongly (Table 1), the benzylic methylene group ^{1}H NMR signal shifted from δ/ppm = 4.49 (for the bromide) to δ/ppm = 5.27 and appeared as a triplet with a $^4J_{HF}$ coupling constant of 1.4–1.5 Hz.

After washing and filtration over basic aluminum oxide, PFBMA was of sufficient purity for RAFT polymerization without the need for chromatography or distillation. Six

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Table 1. Summary of Measured ^{19}F NMR Chemical Shifts in $CDCl_3$ of 2,3,4,5,6-Pentafluorobenzyl Derivatives (Sections 1 and 2) and 2,3,5,6-Tetrafluorobenzyl Derivatives after Substitution of the *Para*-F with Sulfur- and Nitrogen-Based Nucleophiles (Section 3)

functional group	δ_F/ppm (*ortho* to benzylic)	δ_F/ppm (*meta* to benzylic)	δ_F/ppm (*para* to benzylic)
1. small 2,3,4,5,6-pentafluorobenzyl-functional molecules, $F_5C_6-CH_2-R$, −R =			
bromide (−Br)	−142.2	−161.2	−152.8
hydrogen (−H)	−143.3	−163.6	−158.9
acrylate (−OOC−CH=CH_2)	−141.9	−161.8	−152.7
methacrylate (−OOC−C(CH_3)=CH_2)	−141.9	−161.7	−152.7
2. poly(2,3,4,5,6-pentafluorobenzyl methacrylate)			
pPFBMA[a]	−142.4	−161.6	−152.0
3. *para*-substituted polymers, R−$F_4C_6-CH_2O$--, R− =			
alkylthio (R′S−, 7 examples)[b]	−141.6 to −142.7	−133.8 to −134.6	
carbonylthio (R′C(=X)S−; thioacetate, dithioester, trithiocarbonate)	−141.0 to −142.0	−133.9 to −134.3	
phenylthio (PhS—)	−141.7	−132.5	
sodium sulfido (NaS−)	−149.7	−139.4	
alkylamino (R′HN−, 7 examples)	−145.6 to −146.5	−160.6 to −161.8	
amino (H_2N-)[c]	−145.2	−162.8	
dialkylamino (R'_2N-, 10 examples)	−144.7 to −146.2	−151.1 to −152.3	

[a]Shift of major signal where tacticity splitting occurs. [b]There is disagreement in the literature on the assignment of ^{19}F NMR resonances of *para* thiol-substituted 2,3,5,6-tetrafluorobenzyl derivatives. Assignments in this table are based on the measurement and interpretation of ^{1}H-decoupled and non-^{1}H-decoupled ^{19}F NMR spectra of 2,3,4,5,6-pentafluorotoluene and after *para*-fluoro substitution with thiophenol. The *ortho*-fluorines of these low molar mass species can be identified by their coupling to the toluic CH_3 group; see Figure S9. [c]Noy, J.-M.; Roth, P. J.; et al. Unpublished work.

samples of poly(PFBMA), pPFBMA, with degrees of polymerization ranging from 28 to 132, and narrow, monomodal molar mass distributions were prepared using the RAFT process (see Scheme 1B, Table 2, and Figure 1A). The PFB functional

Table 2. List of Prepared pPFBMA Samples[a]

code	target DP	conv[b] (%)	DP^{NMR} [b]	M_n^{SEC} (kg/mol)	$Đ^{SEC}$
$pPFBMA_{28}$	38	74	28	8.6	1.15
$pPFBMA_{36}$	41	87	36	10.3	1.15
$pPFBMA_{63}$	68	92	63	13.1	1.20
$pPFBMA_{70}$	100	70[c]	70	16.3	1.14
$pPFBMA_{98}$	100	98	98	15.0	1.14
$pPFBMA_{132}$	197	67	132	19.8	1.29

[a]RAFT polymerizations were done using chain transfer agent 2-cyano-2-propyl benzodithioate, solvent anisole, and initiator AIBN at 70 °C overnight. [b]Determined by ^{1}H and ^{19}F NMR spectroscopy before purification. [c]Reaction time 8 h.

groups were stable during polymerization with no observed evidence of decomposition or adverse effects on the polymerization. A slight difference in ^{19}F chemical shifts between monomers and polymers enabled simple estimations of monomer conversions using ^{19}F NMR spectroscopy before polymer isolation. All samples of pPFBMA were powdery solids with a measured glass transition temperature of T_g = 65 °C, higher than that of the non-fluorinated analogue poly(benzyl methacrylate) (T_g = 54 °C)[50] but lower than that of the reactive styrenic counterpart poly(2,3,4,5,6-pentafluorostyrene) (T_g = 95 °C).[51] pPFBMA was found to be soluble in chloroform, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, dimethyl sulfoxide, acetonitrile, anisole, acetone, tetrahydrofuran, diethyl ether, pyridine, and 2,2,2-trifluoroethanol but insoluble in water, methanol, and hexane. As to be expected from radical polymerization, pPFBMA samples were atactic with a measured triad tacticity of 0.05 *mm*:0.35 *mr*:0.60 *rr* determined by ^{1}H NMR spectroscopic analysis of the backbone methyl group resonances (Figure S10). Interestingly, all three ^{19}F NMR signals of pPFBMA showed a splitting with a similar integral ratio (see Experimental Section and Figure S11), suggesting that all fluorine atoms are affected by (and can be analyzed to determine) tacticity. ^{19}F NMR spectroscopy has been shown to be a powerful tool in determining tacticity.[52−54] Notably, however, for many reported cases the decisive fluorine atoms were directly attached to the backbone.[55−57] The ^{1}H NMR signal of the methylene side group (COO−CH_2−PFB) roughly reflected a similar splitting with the main peaks (δ/ppm = 5.07, 5.03) showing an approximate 60:35 integration ratio and the expected 5% component apparent as a shoulder around δ = 5.16 ppm.

Polymer Modification: Thiols. With a series of well-defined pPFBMA polymers in hand, their reactivity toward a range of sulfur- and nitrogen-based nucleophiles was assessed. Samples of pPFBMA were first reacted with thiophenol in the presence of triethylamine and five different primary aliphatic thiols, including hydrophilic and hydrophobic species and the drug captopril, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base[25] (see Scheme 2 and Table 3). Conversions were monitored by withdrawing reaction samples, diluting with $CDCl_3$, and measuring ^{19}F NMR spectroscopy. Reactions were continued until all ^{19}F NMR signals associated with starting material had disappeared (40 min−2 h). Isolated products were characterized by ^{1}H and ^{19}F NMR spectroscopy, FT-IR spectroscopy, and SEC.

In all cases, selective substitution of the *para*-fluoride was found with no observed evidence of ester cleavage or substitution of *ortho*- or *meta*-fluorides. ^{19}F NMR spectra of pPFBMA and after modification with thiophenol and a representative aliphatic thiol are shown in Figure 2A−C. Quantitative substitution was apparent by the disappearance of the *para*-^{19}F signal and a downfield shift of approximately 28 ppm (cf. Table 1) of the *meta*-fluorides, the neighbors of the functionalized position. Before purification, the replaced

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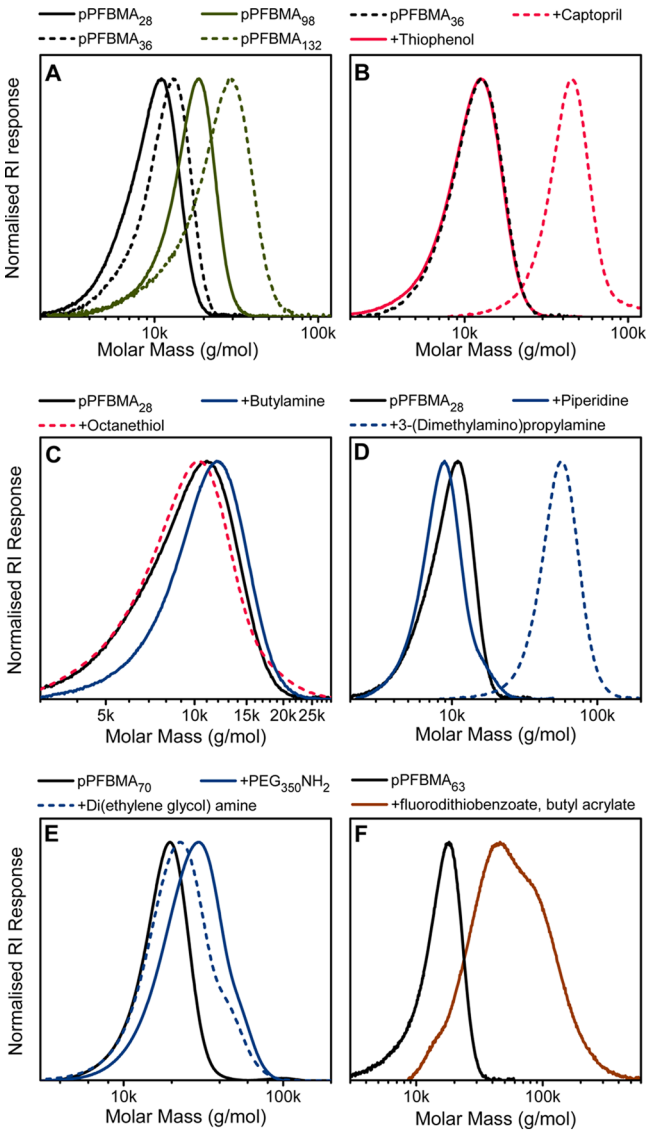
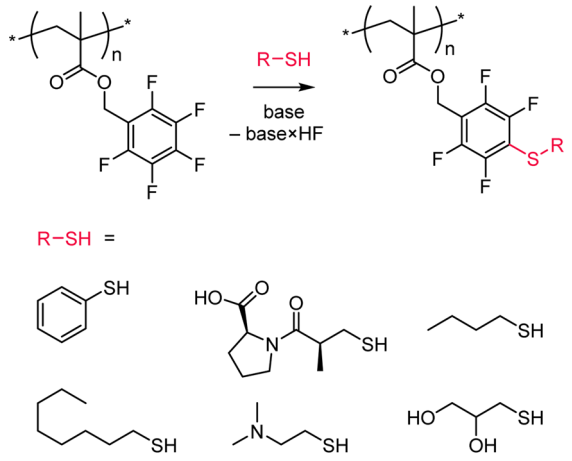


Figure 1. SEC traces of reactive pPFBMA species (A) and after postpolymerization *para*-fluoro substitution with thiols (B, C) and amines (C, D, E), and double modification with dithiobenzoate followed by aminolysis and thiol−ene modification (F). *x*-Axes are PS-equivalent molar masses in *N*,*N*-dimethylacetamide at 50 °C.

(former *para*) fluoride appeared as broad signal between −120 and −165 ppm in ^{19}F NMR spectra, usually with a lower than expected integral. Addition of excess of DBU to NMR samples (in $CDCl_3$) resulted in a sharp singlet at δ/ppm = −123.2 associated with the DBU hydrofluoride salt. After purification, ^{19}F NMR signals associated with the replaced *para*-fluoride disappeared. ^{1}H NMR spectroscopy confirmed the quantitative formation of functional thioether derivatives, including through the appearance of a resonance associated with R−CH_2−SC_6F_4 methylene groups (for R = alkyl, δ/ppm (R−CH_2−SC_6F_4) = 2.98 (bt), compared to δ/ppm (R−CH_2−SH) = 2.54 (q) for the respective thiol reagent). ^{1}H NMR spectroscopic analysis also indicated that excess reagent, base, and any other small molecules had been removed during purification (Figure 3A−C). FT-IR spectra of pPFBMA and after modification with 2-(dimethylamino)ethanethiol are shown in Figure 4. While the carbonyl C═O stretching band (ν = 1735 cm^{-1}) was not significantly affected through the thiol−*para*-F substitution

Scheme 2. *para*-Fluoro Postpolymerization Modification of PPFBMA with Thiols



(suggesting, as desired, the absence of acyl substitution reactions), a red-shift of the C═C aromatic vibrations from $\nu(C_6F_5)$ = 1504 cm^{-1} to $\nu(C_6F_4SR)$ = 1472 cm^{-1} was observed, in agreement with the change in the aromatic substitution pattern.

SEC of thiol-modified samples revealed molar mass distributions and dispersities very similar to those of the respective reactive starting materials (Table 3 and Figure 1B,C), as to be expected for the postpolymerization modification of side groups in the absence of side reactions. Apparent molar masses, however, were found to decrease slightly or increase (most significantly for the reaction with captopril, Table 3, entry 2). It is stressed that SEC separates polymers by hydrodynamic size (not molar mass). The observed changes in measured PS-equivalent molar masses thus indicated a compaction or expansion of the modified polymer chains under the measurement conditions, in agreement with their chemical modification.

Polymer Modification: Other Sulfur-Based Nucleophiles. Given the observed quantitative modification with thiols under mild conditions, modification of pPFBMA with a range of other sulfur-based nucleophiles was attempted (Scheme 3). A desired synthetic strategy was the introduction of a nucleophile that would allow for subsequent release of a tetrafluorophenylthiol (RC_6F_5 → RC_6F_4−SR′ → RC_6F_4−SH) to set the stage for a range of efficient thiol−X click chemistries[58] for further modification. To this end, reaction was first attempted using sodium methanethiosulfonate in a synthetic route that was also envisaged to provide access to functional nonsymmetrical disulfides (RC_6F_5 → RC_6F_4−SSO_2R' → RC_6F_4−SS−R″)[59] (Scheme 3A) with potential for drug-releasing applications.[60] However, under all investigated reaction conditions (solvents *N*,*N*-dimethylformamide, dimethyl sulfoxide, pyridine; without base, with DBU, with triethylamine; temperatures from RT to 80 °C), no reaction was observed. When reactions were heated to 130 °C (or 90 °C in the presence of DBU), ^{19}F NMR analysis showed multiple sharp signals suggesting the formation of small fluorinated molecules through acyl substitution (pentafluorobenzyl alcohol side product) or through nucleophilic substitution at the benzylic position (polymeric carboxylate leaving group and formation of substituted pentafluorobenzyl products).

Reaction of pPFBMA with sodium hydrogen sulfide in the absence of base was successful on one account (see ^{19}F NMR in

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Table 3. Overview of Reaction Conditions and SEC Results for Postpolymerization Modifications of PPFBMA with Thiols[a]

entry	thiol	thiol equiv[b]	base, equiv[b]	temp (°C)	reaction time (min)	before modification M_n^{SEC} (kg/mol)	before modification $Đ^{SEC}$	after modification M_n^{SEC} (kg/mol)	after modification $Đ^{SEC}$
1	thiophenol[c]	1.1	Et_3N, 1.05	45	60	10.5	1.15	10.3	1.16
2	captopril[c]	1.1	DBU, 2.1[d]	25	40	10.5	1.15	39.3	1.15
3	butane-1-thiol[c]	1.1	DBU, 1.05	25	40	8.6	1.15	10.3	1.18
4	octane-1-thiol[c]	1.1	DBU, 1.05	25	40	8.6	1.15	8.5	1.16
5	2-(dimethylamino)ethanethiol hydrochloride[e]	5.0[f]	DBU, 5.1	25	90	16.3	1.14	n.d.	n.d.
6	1-thioglycerol[g]	1.5[f]	DBU, 1.4	25	120	16.3	1.14	n.d.	n.d.

[a]In all cases, anhydrous *N*,*N*-dimethylformamide was used as solvent and quantitative conversions were confirmed by ^{19}F NMR spectroscopy. [b]With regards to 1 equiv of PFBMA repeat units. [c]The product was purified by precipitation into methanol. [d]Additional base was used due to the carboxylic acid group on captopril. [e]In the presence of DBU the tertiary amine-functional polymer is isolated (as shown in Scheme 2); the product was purified by precipitation into water. [f]Incomplete reaction when lower amount was used. [g]The product was purified by dialysis against methanol.

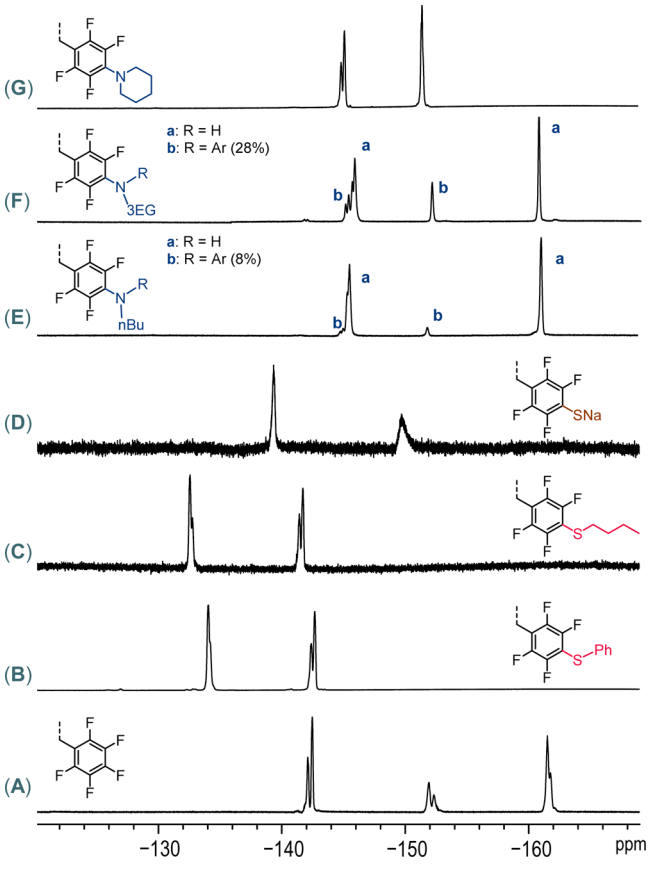

Figure 2. ^{19}F NMR spectra of pPFBMA (A, 500 MHz) and after *para*-fluoro substitution reaction with thiols (B and C, 300 MHz), sodium hydrogen sulfide (D, 300 MHz), primary amines (E, *n*-Bu = *n*-butyl, 300 MHz; F, 3EG = tri(ethylene glycol) methyl ether amine, 400 MHz), and piperidine (F, 300 MHz).

Figure 2D) but led to insoluble material in other attempts (Scheme 3B).

Three carbonylthio reagents were used, with the aim of enabling the wide range of "RAFT end group chemistries"[49,61] for polymer side group modification. Potassium thioacetate showed reasonably high reactivity toward pPFBMA, but the expected tetrafluorophenyl thioacetate product was too reactive to be isolated with products containing about 30 mol % of thiols (Scheme 3C). A trithiocarbonate-based nucleophile (Scheme 3D), on the other hand, was less reactive (presumably due to resonance stabilization of the anion) and gave 90% *para*-fluoro substitution after heating to 65 °C for 6 days. At a higher temperature of 80 °C, cleavage of the methacrylic esters was observed, and the reaction was deemed impractical for this study. A dithioester-based nucleophile, however, enabled full conversion to the tetrafluorophenyl benzenedithioate derivative within 24 h at 65 °C (Scheme 3E) based on ^{19}F NMR spectroscopic analysis (see Table 1). Among several attempts, optimal reaction conditions were an excess of dithioester (1.7 equiv) and of triethylamine (2.8 equiv) in anhydrous DMF. To demonstrate the potential of this benzenedithioate-functionalized species, a sample was aminolyzed (releasing thiolate groups) in the presence of butyl acrylate, a thiol-reactive Michael acceptor, giving the ester-functional thiol−ene product in one step (Scheme 3F). ^1H NMR spectroscopic analysis confirmed successful modification. SEC analysis, however, revealed a bimodal molar mass distribution (Figure 1F) attributed to a small degree of cross-linking reactions, not uncommon for thiol-functional polymers.[62]

It is briefly mentioned that modification attempts of pPFBMA with thiourea, tetrabutylammonium bromide, and tetrabutylammonium iodide (DMF, 2.5 equiv, 80 °C, 2 days) gave no reactions, demonstrating higher selectivity and stability of pPFBMA toward nucleophiles compared to common haloalkane substrates.

Polymer Modification: Amines. The arguably most important class of nucleophiles for polymer modification comprises amines. Modification of pPFBMA was investigated with a selection of aromatic, primary, and secondary amines. Amines were used in excess (2.5 equiv), and reactions were stirred at 50 or 60 °C in DMF until ^{19}F NMR spectroscopic analysis of a withdrawn sample indicated complete disappearance of signals associated with the starting material. Products were isolated by precipitation or dialysis and characterized by ^1H and ^{19}F NMR spectroscopy, FT-IR spectroscopy, and SEC. Reactions are summarized in Table 4 with structures of amines shown in Scheme 4.

For reactions with aniline (Table 4, entry 1), no *para*-fluoro substitution occurred, and pristine pPFBMA starting material was recovered. Being less nucleophilic than aliphatic amines, aromatic amines typically show lower reactivity in nucleophilic substitution reactions. In the case of pPFBMA, under the investigated reaction conditions this reactivity difference was sufficiently large to result in selective modification with aliphatic amines only.

For all the employed aliphatic amines, reaction rates were lower than for thiols, with reactions requiring heating to 50−60

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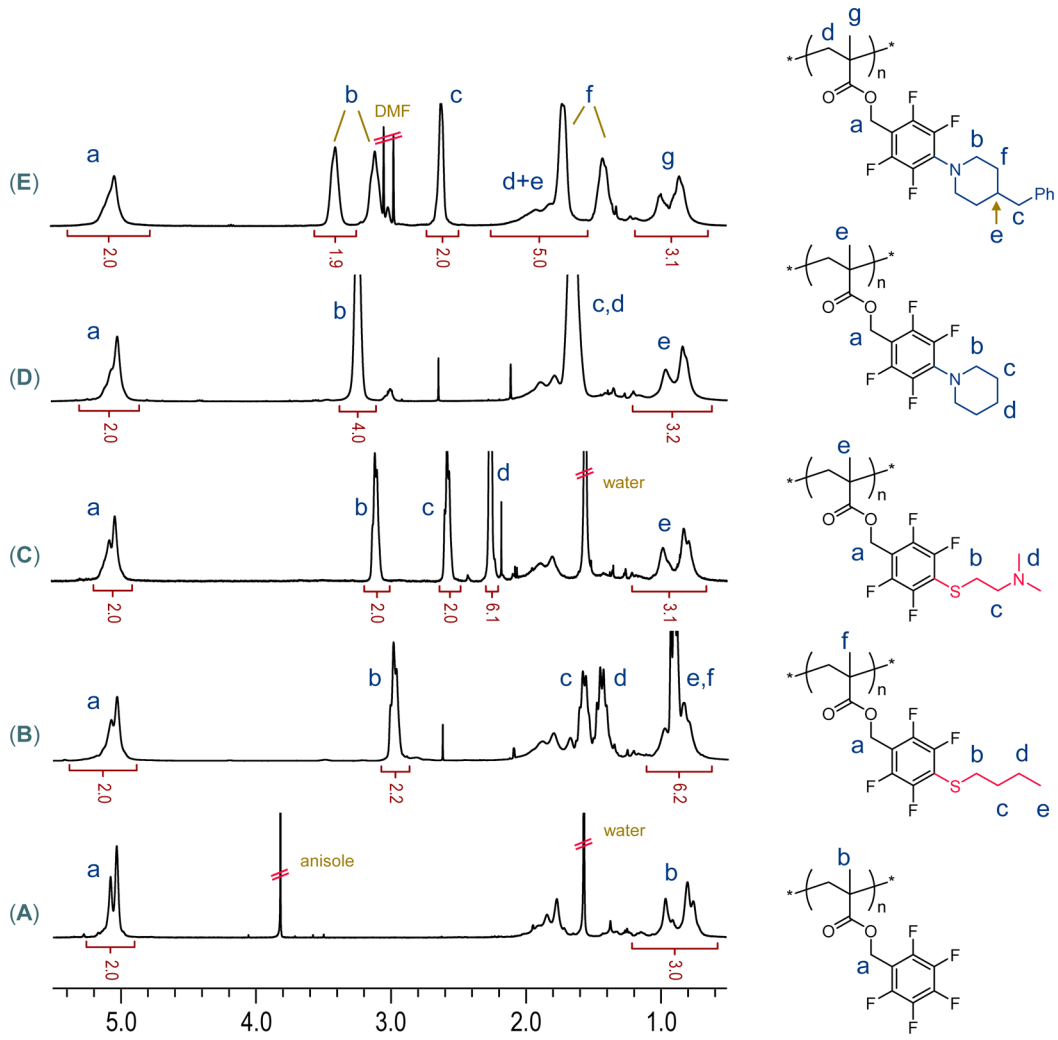

Figure 3. ^{1}H NMR spectra in $CDCl_3$ of pPFBMA (A, 500 MHz) and after modification with butane-1-thiol (B, 300 MHz), 2-(dimethylamino)ethanethiol hydrochloride (in the presence of DBU) (C, 400 MHz), piperidine (D, 300 MHz), and 4-benzylpiperidine (E, 400 MHz) with relevant signals integrated and assigned.

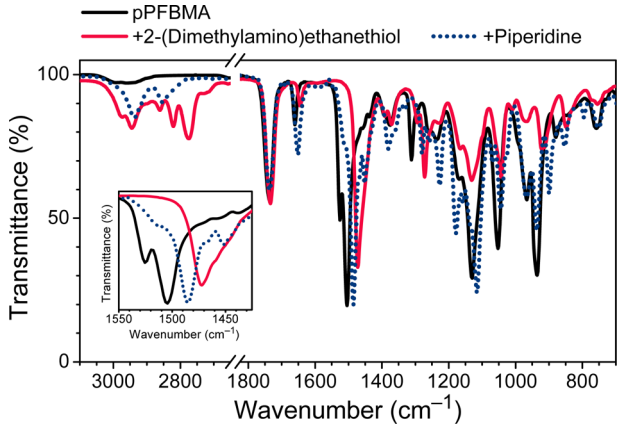

Figure 4. FT-IR spectra of pPFBMA (black) and after modification with 2-(dimethylamino)ethanethiol (red) and piperidine (dotted) with the shift of the aromatic C═C stretching vibration inset.

°C overnight for reagents *n*-butylamine, *n*-pentylamine, cyclohexylamine, 3-(dimethylamino)propylamine, piperidine, and 4-benzylpiperidine and for 3−6 days for the sterically more demanding oligo(ethylene glycol)-based amines and 1-(2-hydroxyethyl)piperazine. As such, pPFPMA appeared to show higher reactivity toward amines at 50 °C than poly(2,3,4,5,6-pentafluorostyrene), which was shown not to react at this temperature (24 h, 50 equiv of amines)[27] and to require microwave-assisted heating to 95 °C (20 min, 10 equiv of amines).[29,63] Under our reaction conditions, no evidence of acyl substitution or substitution of *ortho*- or *meta*-fluorides was observed. SEC analysis of amine-modified products yielded elugrams of similar shape and width as those of the respective pPFBMA starting materials, with the exception of modification with the oligo(ethylene glycol)-based amines, where shoulders toward higher molar masses and slightly increased dispersities were found (Figure 1C−E and Table 4). FT-IR analysis of the oligo(ethylene glycol)methyl ether amine-modified samples confirmed stronger absorbances of C−H and C−O bonds with an increasing length of the ethylene glycol-based side chains (Figure S12). For all primary amines, ^{19}F NMR spectroscopy confirmed complete modification through the disappearance of the starting material signals and the appearance of resonances characteristic of *N*-alkyl tetrafluoroaniline products (Table 1 and Figure 2E,F). Surprisingly, however, ^{19}F NMR spectra also contained signals associated with *N*,*N*-dialkyl tetrafluoroaniline side groups. The amount of disubstituted aromatic rings ranged

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Scheme 3. Reaction of PPFBMA with the Sulfur-Based Nucleophiles Sodium Methanethiosulfonate (A), Sodium Hydrogen Sulfide (B), Potassium Thioacetate (C), *S*-Carboxypropyl Trithiocarbonic Acid, Bis(triethylammonium) Salt (D), and Triethylammonium 4-Fluorodithiobenzoate (E) Followed by Aminolysis and Thia-Michael Modification with Butyl Acrylate (F)

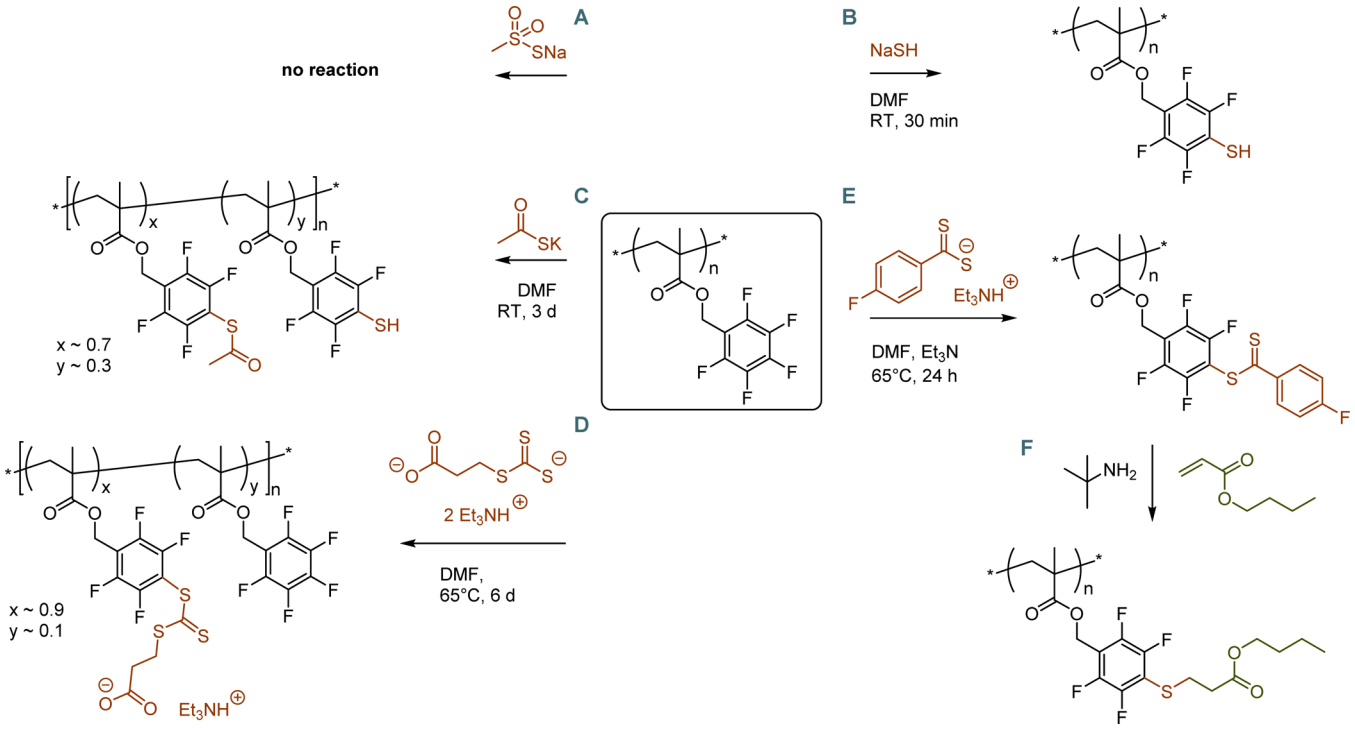

Table 4. Overview of Reaction Conditions, Molar Composition of Products, and SEC Results for Postpolymerization Modifications of PPFBMA with Amines[a]

					before modification		after modification		
entry	amine	T (°C)	reaction time (h)	disubstitution (Z)[b] $(-C_6F_4)_2NR$ (mol %)	M_n^{SEC} (kg/mol)	$Đ^{SEC}$	M_n^{SEC} (kg/mol)	$Đ^{SEC}$	comments
1	aniline	60	10		8.6	1.15			no reaction
2	*n*-butylamine	50	15	8	8.6	1.15	10.0	1.11	
3	*n*-pentylamine	60	10	6	8.6	1.15	n.d.	n.d.	
4	cyclohexylamine	60	10	9	8.6	1.15	n.d.	n.d.	
5	3-(dimethylamino)-propylamine	60	10	7	8.6	1.15	49.0	1.14	
6	di(ethylene glycol) methyl ether amine	50	69	28	16.3	1.14	19.4	1.27	water insoluble
7	tri(ethylene glycol) methyl ether amine	50	69	28	16.3	1.14	18.1	1.21	water insoluble
8	PEG_{350} methyl ether amine	50	144	26	16.3	1.14	23.7	1.25	LCST T_{CP} 40 °C[c]
9	piperidine	50	15	0	8.6	1.15	7.9	1.15	
10	4-benzylpiperidine	50	24	0	16.3	1.14	n.d.	n.d.	
11	1-(2-hydroxyethyl)piperazine	50	64	0	16.3	1.14	25.5	1.13	pH-responsive

[a]In all cases, 2.5 equiv of amine was used in anhydrous *N*,*N*-dimethylformamide as solvent. With the exception of aniline, complete disappearance of PFBMA repeat units was confirmed by ^{19}F NMR spectroscopy. [b]See Scheme 4A. [c]LCST-type cloud point (onset of transmittance decrease) of an aqueous solution at a concentration of 5 g/L.

from 6 to 9 mol % for the set of smaller primary amines (Table 4, entries 2−5, representative ^{19}F NMR spectrum in Figure 2E) to 26−28 mol % found for the oligo(ethylene glycol) methyl ether amine-modified samples (Table 4, entries 6−8, representative ^{19}F NMR spectrum in Figure 2F). Plausibly, double substitutions occurred, in which *N*-alkyltetrafluoroaniline side groups (the secondary amines formed through the intended substitution reaction) attacked another PFB group forming *N*-alkyl-*N*,*N*-bis(tetrafluorophenyl) tertiary amines (see Scheme 4B). With only small (or no) measured increases in dispersity, it is assumed that the majority of such double substitutions occurred intramolecularly, possibly, as shown in Scheme 4B, with the neighboring group. Double substitutions have previously been described for reactions of low molar mass PFB derivatives with amines.[64−67] In fact, Costa et al.[64] recently described the reaction of a primary amine with hexafluorobenzene, which produced only the doubly substituted tertiary amine derivative and recovered unreacted primary amine. The higher reactivity of the secondary amine intermediate was attributed to a higher N−H acidity caused by the fluorinated substituent. The proposed double substitution on the polymeric substrate was in agreement with ^1H NMR

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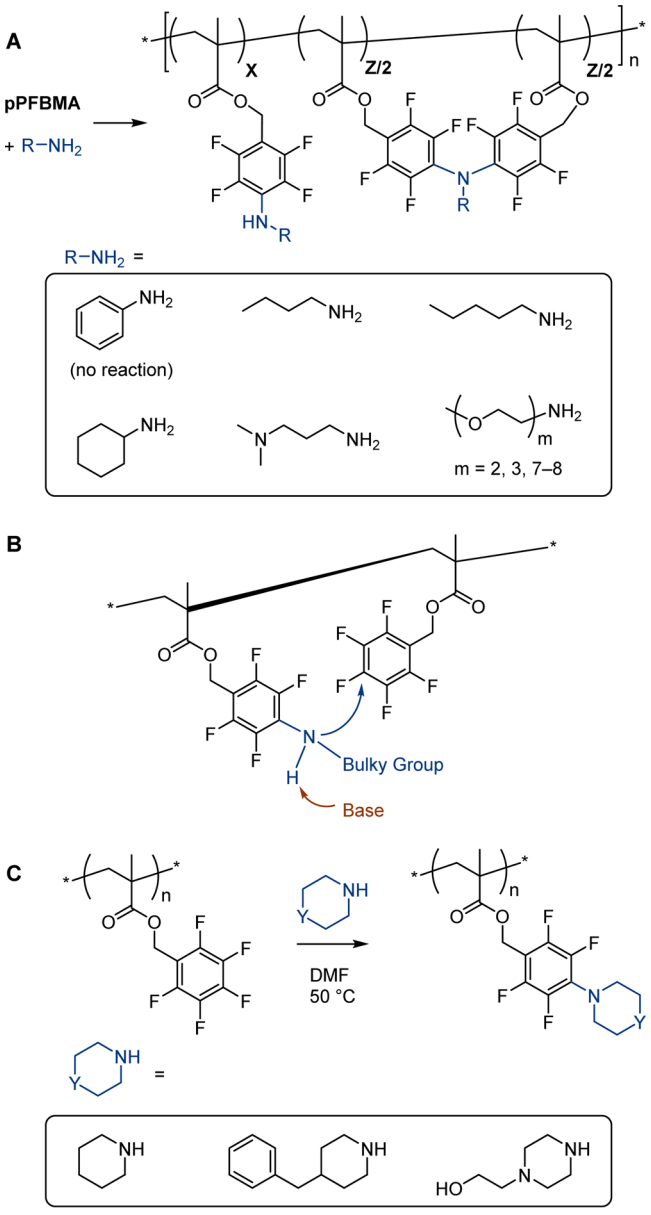
Scheme 4. *Para*-Fluoro Postpolymerization Modification of PPFBMA with Amines: Formation of Copolymers Comprising the Expected *N*-Functional Tetrafluoroaniline Side Groups (X) as Well as *N,N*-Bis(tetrafluoroaniline) Side Groups (Z) for the Reaction with Primary Amines (A);[a] Proposed Mechanism for Formation of Disubstituted Species (B); and Modification of PPFBMA with Secondary Amines in the Absence of Side Reactions (C)



[a]The molar composition (*X*, *Z*) can be estimated from the number of R groups per repeat unit (= *X* + *Z*/2) obtained from ^{1}H NMR spectroscopy and the percentage of N,N-disubstituted tetrafluoroaniline groups (= *Z*) from ^{19}F NMR spectroscopy; see Table 4.

results (Figure S13). For example, for the modification of pPFBMA with di(ethylene glycol) methyl ether amine (DEG) (Table 4, entry 6), ^{1}H NMR analysis indicated an average presence of 0.86 DEG side chains per repeat unit (Figure S13B). To reiterate, ^{19}F NMR spectroscopic analysis of this sample indicated that 28% of aryl side groups formally contributed half a functional group, equivalent to a substitution efficiency of 0.86 (= 100% − 1/2 × 28%) DEG side chains per repeat unit, in excellent agreement with the ^{1}H NMR interpretation.

Despite the unexpected side reactions, the modification of pPFBMA with amines has potential in producing "smart" polymers. The modification of pPFBMA with di- and tri(ethylene glycol) methyl ether amine (Table 4, entries 6, 7) resulted in water-insoluble products. Addition of acid (until pH ∼ 3) did not improve solubility, suggesting no significant amount of protonation of the tetrafluoroaniline nitrogen atoms and confirming their low basicity (the conjugate acid of the comparable small molecule pentafluoroaniline (i.e., $F_5C_6NH_3^+$) has a reported pK_a = −0.3).[68] The modification of pPFBMA with PEG_{350} methyl ether amine, however, yielded a product with temperature-dependent aqueous solubility (below a critical temperature) and measured LCST-type cloud points around body temperature (Figures S14 and S15). As such, this pPFBMA-derived species represents a new addition to the PEG-based family of materials with similar stimulus-responsive solution behavior.[69,70]

Yet, copolymer formation and lack of compositional control make the modification of pPFBMA with primary amines unideal for the preparation of well-defined polymers. Gratifyingly, the modification of pPFBMA with the secondary amine piperidine (Table 4, entry 9) was found to proceed without side reactions with ^{19}F NMR analysis showing only the expected tertiary amine functionality (Figure 2G) and ^{1}H NMR measurements indicating the quantitative presence of the expected cyclic substituent (Figure 3D). FT-IR analysis showed the absence of N−H stretching (around ν = 3500−3300 cm^{-1}) and N−H bending (around ν = 1640−1550 cm^{-1}, Figure 4) vibrations and a red-shift of the C═C aromatic vibrations from $\nu(C_6F_5)$ = 1504 cm^{-1} to $\nu(C_6F_4NR_2)$ = 1484 cm^{-1} (Figure 4, inset), confirming aromatic substitution. Based on these results, two further secondary amines, including an *N*-functional piperazine (Table 4, entries 10, 11; Scheme 4C), were tested and found to react quantitatively in 24−64 h without observed side reactions (see ^{1}H NMR data in Figure 3E). By virtue of its tertiary amine functionality, the 1-(2-hydroxyethyl)piperazine-functional polymer was soluble in dilute aqueous HCl (pH 5−6) but precipitated above pH 7 when aqueous $NaHCO_3$ was added, demonstrating the preparation of a pH-responsive polymer from the pPFPMA platform (Figures S16 and 17) .

Zwitterionic Temperature-Responsive Polymers. Finally, having shown selective quantitative postpolymerization modification reactions of pPFBMA with sulfur- and nitrogen-based nucleophiles, their potential in the development of novel zwitterionic polymers with upper critical solution temperature (UCST) behavior in water is presented as a proof-of-concept. This "smart" behavior involving solubility above a critical temperature is known only for very few types of polymers,[71] including some zwitterionic sulfobetaines.[72,73] Our group recently established that introduction of aromatic functionality into sulfobetaine co- and terpolymers can be beneficial in increasing UCST transition temperatures, realizing UCST transitions at physiologically relevant NaCl concentration,[74,75] and in designing terpolymers with an LCST and UCST (miscibility gap).[76] Exploiting the postpolymerization of pPFBMA, zwitterionic and aromatic functionality could easily be included into the same repeat unit.

Samples of 2-(dimethylamino)ethanethiol-modified $pPFBMA_{70}$ (Table 3, entry 5) were quaternized with 1,3-propane sultone (5 days, 40 °C) and with 1,4-butane sultone (15 h, 120 °C, microwave heating), followed by dialysis against

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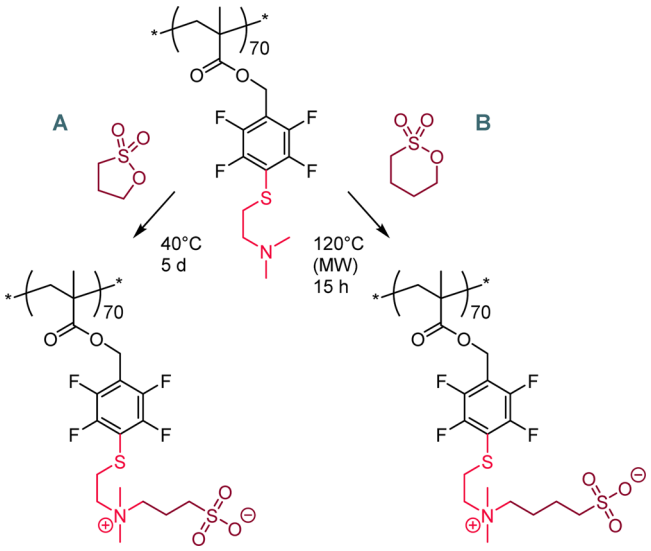
water (Scheme 5). Microwave heating was necessary to push the reaction with the commonly sluggish[75] 1,4-butane sultone to completion (Figure S18).

Scheme 5. Successive Postpolymerization Modification of Tertiary-Amine Functional $PPFBMA_{70}$ Derivative with 1,3-Propane Sultone (A) and 1,4-Butane Sultone (B) Giving the Respective Sulfopropyl- and Sulfobutylbetaine-Functional Species[a]



[a]Reactions were performed in 2,2,2-trifluoroethanol in which reagents and products were soluble.

^{19}F NMR spectroscopic analysis of the zwitterionic homopolymers in D_2O/NaBr revealed essentially no change of ^{19}F chemical shifts compared to the tertiary amine precursor, but peaks were broadened drastically which suggested poor hydration of the hydrophobic fluorinated aromatic in the aqueous solvent (Figure 5).

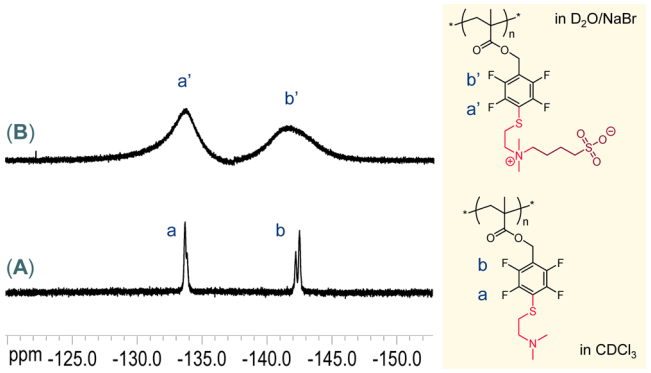


Figure 5. ^{19}F NMR spectra of the tertiary amine-functional precursor (A) and after quaternization with 1,4-butane sultone showing peak broadening (B) with solvents and peak assignments indicated.

The two novel zwitterionic homopolymers showed the desired UCST behavior in water with measured UCSTs of 56 °C (sulfopropylbetaine species) and 70 °C (sulfobutylbetaine species); see Figure 6A for temperature−concentration phase diagram and Figures S19−S21 for transmittance curves. Analogous methacrylic sulfobetaines of a similar degree of polymerization but lacking the aromatic ring can be expected to have much lower transition temperatures or to be fully soluble in water within the observable temperature range of 0−100 °C,[75] demonstrating the effect of the aromatic group on decreasing solubility. The UCST transition temperature was found, expectedly, to decrease with an increasing concentration of added NaCl (Figure 6B), with approximately linear decreases found for both species, though, surprisingly, with a larger slope for the sulfobutylbetaine homopolymer. Fortuitously, the sulfopropylbetaine derivative showed measurable cloud points up to NaCl concentrations of 178 mM, above the physiological concentration of approximately 154 mM. This data demonstrates the potential in developing novel smart *homo*polymers without the need for tuning through copolymerization as was previously done to achieve UCST transitions at such high salt concentrations.

CONCLUSION

A novel reactive polymer scaffold was introduced that benefits from high-yielding, one-step monomer synthesis, well-controlled methacrylate RAFT polymerization, polymer solubility in a wide range of organic solvents, and efficient and selective postpolymerizaton modification options. Poly(2,3,4,5,6-pentafluorobenzyl methacrylate) (pPFBMA) showed high reactivity toward thiols, comparable to that of poly(2,3,4,5,6-pentafluorostyrene), reacting to completion within an hour at room temperature. The resulting *para*-substituted aromatic structure was exploited herein for the preparation of novel zwitterionic homopolymers that showed aqueous UCST transition temperatures within a wide temperature and NaCl concentration range. Reactions of pPFBMA with various amines did not result in ester cleavage reactions common of the activated ester pentafluoro*phenyl* methacrylate analogues but proceeded with selective and quantitative substitution of the *para*-fluorides. For the use of primary amines, especially for sterically demanding reagents, a disubstitution side reaction was observed which resulted in a lower than expected presence of functional groups (minimum observed degree of functionalization 86%) and slightly increased molar mass dispersities (largest observed increase $Đ$ = 1.14 to $Đ$ = 1.27). Nonetheless, modification of pPFBMA with a PEG-based amine produced a novel species with an aqueous LCST transition. Side reactions were not observed for the reaction of pPFBMA with piperidine and piperazine derivatives for which quantitative and selective side group modification was found. For the first time, the performance of other nucleophiles in *para*-fluoro postpolymerization substitution was investigated, with pPFBMA proving to be stable toward halides, thiosulfonate, and thiourea. Modification with carbonylthio compounds, however, was successful and allowed for subsequent one-pot aminolysis, in situ release of tetrafluorophenylthiols, and their capture through thia-Michael "click" modification, albeit accompanied by a broadening of the molar mass distribution. ^{19}F NMR spectroscopy served as an expedient tool throughout the study, proving effective to determine tacticity and follow modification reactions. A reference list of ^{19}F NMR chemical shifts was compiled. Given the synthetic importance of postpolymerization modification, it is believed that this selectively reactive methacrylic system will find widespread applications in synthetic polymer science.

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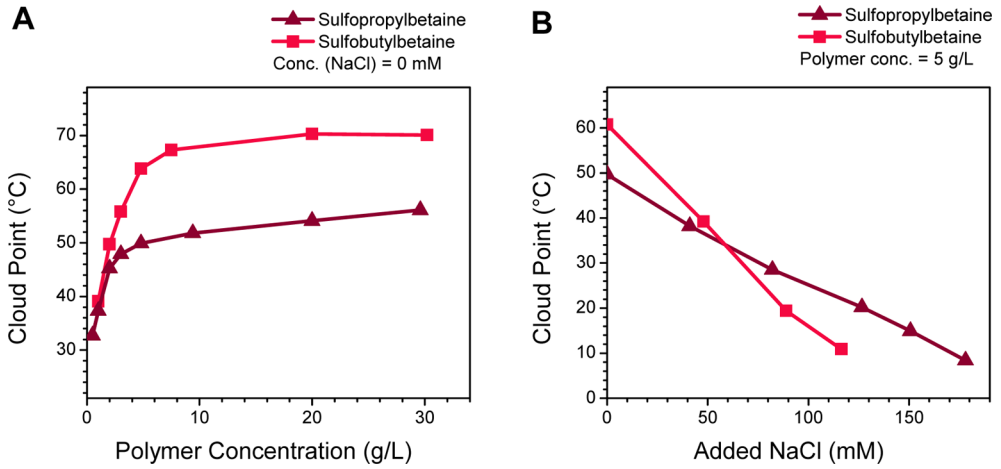

Figure 6. Temperature−concentration phase diagram indicating the temperatures above which the sulfopropylbetaine homopolymer (triangles) and the sulfobutylbetaine homopolymer (squares) were found to be soluble in pure water (A) and transition temperatures of both species in dependence of added NaCl (B).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.7b01603.

Synthesis of 2,3,4,5,6-pentafluorobenzyl acrylate, ^{1}H, ^{13}C, ^{19}F NMR, and FT-IR spectra of monomers, ^{1}H-coupled and ^{1}H-decoupled spectra of 2,3,4,5,6-pentafluorotoluene and after modification with thiophenol, ^{1}H−^{13}C HSQC and ^{19}F−^{19}F COSY NMR spectra of pPFBMA, FT-IR spectra of oligo(ethylene glycol) methyl ether amine-modified polymers, additional ^{1}H NMR spectra of amine-modified polymers, photographs of pH-responsive polymer, ^{1}H NMR spectra of zwitterionic polymer and its precursor, and turbidity curves and phase diagrams of thermoresponsive polymers (PDF)

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Notes

The authors declare no competing financial interest.

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