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Poly(pentafluorobenzyl methacrylate): Modification with
Amines, Thiols, and Carbonylthiolates**

Journal:	<i>Macromolecules</i>
Manuscript ID	ma-2017-016033.R1
Manuscript Type:	Article
Date Submitted by the Author:	25-Aug-2017
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Para-Fluoro Postpolymerization Chemistry of Poly(pentafluorobenzyl methacrylate): Modification with Amines, Thiols, and Carbonylthiolates

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KEYWORDS: para-fluoro-thiol reaction, postpolymerization modification, tacticity by ¹⁹F NMR, zwitterionic polymers, UCST in water

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 $\bar{D} \leq 1.29$ was prepared by the RAFT process. pPFBMA samples were atactic (with triad tacticity apparent in ^1H 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 thiol, base, RT, < 1h) 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 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 $(-\text{C}_6\text{F}_4)_2\text{NR}$ 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 pre-made 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 esters¹² 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 monomers¹⁸ 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-functionalised end groups were exploited for the functionalization of polythiophenes²³ and the synthesis of multi-arm copolymers.²⁴ With regards to postpolymerization functionalization of side groups, however, the literature is, with very few exceptions,^{21, 25–28} limited to the modification of 2,3,4,5,6-

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3 pentafluorostyrene-based (co)polymers with amines,²⁹ phosphite,³⁰ and thiols³¹⁻³³ (including in
4 water³⁴ and on surfaces).³⁵⁻³⁷ The thiol-*para*-fluoro substitution reaction has been combined with
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6 (and shown to be orthogonal to) pentafluorophenyl activated esters,^{25, 27} radical-mediated thiol-
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8 ene additions,^{24, 38} and Cu-catalyzed azide-alkyne cycloadditions.³⁹
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12 Herein, the Reversible Addition-Fragmentation Chain Transfer (RAFT)⁴⁰ synthesis and
13 postpolymerization modification of poly(2,3,4,5,6-pentafluorobenzyl methacrylate), pPFBMA, a
14 *methacrylic* system amenable to highly efficient *para*-fluoro substitution reactions, is presented
15 for the first time. A small number of studies have described the synthesis of this polymer through
16 anionic polymerization,⁴¹ free-radical homo-⁴² and copolymerization with styrene,⁴³ and the
17 photoinitiator-free photopolymerization⁴⁴—but not its post-modification. Acyl substitutions, key
18 to the modification of Theato's polymeric pentafluorophenyl (PFP) esters,⁴⁵ were not observed
19 on PFB esters. Instead, pPFBMA was found to react quantitatively through *para*-fluoro
20 substitution with thiols and amines, though with a certain degree of double substitution when
21 primary amines were used. Additionally, reaction with several (thio)carbonylthio reagents
22 enabled subsequent polymer analogous modification. The high selectivity of the *para*-fluoro
23 substitution was apparent by the lack of any observed reaction with bromide, iodide, thiourea,
24 and methanethiosulfonate nucleophiles. The versatility of this reactive scaffold is demonstrated
25 through the preparation of novel stimulus-responsive polymers.
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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 ($\delta_{\text{H}} = 7.26$ ppm, $\delta_{\text{C}} = 77.2$ ppm), DMSO-d_5 ($\delta_{\text{H}} = 2.51$ ppm) and HDO ($\delta_{\text{H}} = 4.79$ 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 $300 \times 7.8 \text{ mm}^2$ linear phenogel columns (10^5 , 10^4 , 10^3 , and $500 \text{ \AA}$) 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 $1,820 \text{ kg/mol}$.

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 glove box. Acetone was dried over molecular sieves (3 Å). The triethylammonium salt of *S*-carboxypropyl trithiocarbonic acid was prepared following a literature procedure.⁴⁷

Pentafluorobenzyl methacrylate (PFBMA). Potassium carbonate (anhydrous, 17.22 g, 0.125 mol, 5 eq.) was suspended in anhydrous acetone (160 mL). Methacrylic acid (3.22 g, 3.17 mL, 0.037 mol, 1.5 eq.), 2,3,4,5,6-pentafluorobenzyl bromide (6.5 g, 3.76 mL, 0.025 mol, 1 eq.) and butylated hydroxytoluene (BHT, 3 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 NaHCO₃ (3 × 150 mL, pH 9) and water (100 mL) again. The organic phase was dried over magnesium sulfate, filtered through basic aluminium oxide and the solvent was removed under reduced pressure. Three batches, yields 88%, 93%, 95%. ¹H NMR (400 MHz, CDCl₃), δ/ppm = 6.11, 5.60 (2 × 1H, *H*₂C=), 5.27 (2 H, t, ⁴*J*_{HF} = 1.4 Hz, OCH₂), 1.93 (3 H, CH₃). ¹³C NMR (101 MHz, CDCl₃), δ/ppm = 166.8 (C=O), 147.2 and 144.7 (dm, ¹*J*_{CF} = 255 Hz, 2 × *meta* C–F), 143.2 and 140.7 (dm, ¹*J*_{CF} = 255 Hz, *para* C–F), 139.0 and 136.5 (dtd, ¹*J*_{CF} = 255 Hz, ²*J*_{CF} = 17 Hz, ³*J*_{CF} = 4 Hz, 2 × *ortho* C–F), 135.7 (C(CH₃)), 126.9 (H₂C=C), 109.7 (td, ²*J*_{CF} = 17 Hz, ³*J*_{CF} = 4 Hz, CH₂C_{PFB}), 53.8 (OCH₂), 18.3 (CH₃). ¹⁹F NMR (376 MHz, CDCl₃), 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=CH₂ 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) [M¹³C + 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 approx. 1.5-fold volume of PFBMA) were mixed in a reaction vial. A stir bar was added and the vial 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 CDCl₃ (500 µL) and analysed by ¹H and ¹⁹F NMR spectroscopy to determine monomer conversion by comparison of the methylene group ¹H signals and the *para*-¹⁹F NMR signals. The polymer was precipitated twice into an excess (approx. 20–30-fold in volume) of methanol and the product was collected as a pink solid by centrifugation followed by drying in vacuum at 40 °C. ¹H NMR (300 MHz, CDCl₃), δ/ppm = 5.07 and 5.03 (2× bs, 2 H, OCH₂), 2.05–1.65 (m, 2 H, backbone CH₂), 1.20–0.65 (m, 3 H, backbone CH₃ including 1.14 (5%) *mm*, 0.96 and 0.90 (35%) *mr*, and 0.79 and 0.75 (60%) *rr* triads). ¹⁹F NMR (282 MHz, CDCl₃), 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 d and the

product was precipitated into methanol or water. See main text for details. Thiophenol-modified: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 7.29 (bs, 2 H), 7.19 (m, 3 H); Captopril-modified: ^1H NMR (300 MHz, DMSO-d_6), δ/ppm = 4.00, 3.50, 2.70, 1.99–1.88, 1.07; *n*-Octanethiol-modified: ^1H 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: ^1H 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: ^1H NMR (400 MHz, CDCl_3), δ/ppm = 3.09 (bt, 2 H, SCH_2), 2.55 (bt, 2 H, CH_2N), 2.25 (bs, 6 H, $\text{N}(\text{CH}_3)_2$). 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-propanesultone (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 $^\circ\text{C}$. The product was isolated by dialysis against ultrapure water and drying in vacuum. ^1H NMR (400 MHz, $\text{D}_2\text{O}/\text{NaBr}$), δ/ppm = 3.88 (CH_2NCH_2), 3.49 ($\text{N}(\text{CH}_3)_2$), 3.28 (SCH_2 , CH_2SO_3^-), 2.50 ($\text{CH}_2\text{CH}_2\text{CH}_2$).

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 pressurised tube and heated to 120 $^\circ\text{C}$ 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 (approx. 10 mg). Excess 1,4-butanedisulfone phase separated from the NMR sample which did not influence the measurement. The product was isolated by dialysis against ultrapure water (residual 1,4-butanedisulfone hydrolysed and dissolved slowly) and drying in vacuum. ^1H NMR (400 MHz, $\text{D}_2\text{O}/\text{NaBr}$), δ/ppm = 3.51 (CH_2NCH_2), 3.22 ($\text{N}(\text{CH}_3)_2$), 3.02 (SCH_2 , CH_2SO_3^-), 1.98, 1.89 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$).

Postmodification of pPFBMA with Sodium Hydrosulfide. 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 hydrosulfide 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 crosslinked.

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 vacuum.

Postpolymerization Modification of pPFBMA with Dithiobenzoate, Followed by Aminolysis and Thiol–ene Modification. pPFBMA (13.1 kg/mol, $\text{D} = 1.20$, 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 $^\circ\text{C}$ 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 μ L, 189 μ mol, 4.3 equiv) and *tert*-butylamine (60 μ L, 569 μ mol, 12.9 equiv) were added and the mixture stirred overnight at RT. The product was precipitated into diethyl ether–hexane (4:1) and dried in 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, $\bar{D}$ = 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 μ L)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), PEG₃₅₀ methyl ether amine, 2.5 equiv) was added. The mixture was stirred at 50 or 60 °C. Conversion was monitored by withdrawing samples (50 μ L) diluting with CDCl_3 (600 μ L) and analysing 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: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 3.38, 1.57, 1.40, 0.93; Pentylamine-modified: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 3.37, 1.59, 1.48, 1.31, 0.89; Cyclohexylamine-modified: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 3.50 (CHNH) 2.05–0.70 (CH_2); 3-(Dimethylamino)propylamine-modified: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 3.52 (NHCH_2), 2.55 (CH_2N), 2.32 ($\text{N}(\text{CH}_3)_2$), 1.83 ($\text{CH}_2\text{CH}_2\text{CH}_2$); Piperidine-modified: ^1H NMR (300 MHz, CDCl_3), δ/ppm = 3.21 ($\text{CH}_2\text{N}(\text{R})\text{CH}_2$), 1.64, 1.61 ($\text{CH}_2\text{CH}_2\text{CH}_2$); 2EG/3EG/PEG₃₅₀-modified: ^1H NMR (CDCl_3 –

CD₃OD 10:1, 400 MHz) δ /ppm = 3.55, 3.45 (OCH₂), 3.29 (OCH₃), 2.88 (NHCH₂). 4-Benzylpiperidine-modified: ¹H NMR (400 MHz, CDCl₃), δ /ppm = 7.24, 7.13 (*Ph*), 3.31, 3.02 (N(CH₂)₂), 2.54 (CH₂Ph), 1.73 (CH), 1.65, 1.36 (N(CH₂CH₂)₂); 1-(2-hydroxyethyl)piperazine-modified: ¹H NMR (400 MHz, CDCl₃), δ /ppm = 3.67 (CH₂OH), 3.34 (Ar-NCH₂CH₂), 2.64 (N(CH₂)₃). Backbone and COOCH₂ methylene resonances as above; for SEC and ¹⁹F NMR data see 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 ^1H , ^{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 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 ^1H NMR signal shifted from $\delta/\text{ppm} = 4.49$ (for the bromide) to $\delta/\text{ppm} = 5.27$ and appeared as a triplet with a $^4J_{\text{HF}}$ coupling constant of 1.4–1.5 Hz.

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**)

Table 1. Summary of measured ¹⁹F NMR chemical shifts in CDCl₃ of 2,3,4,5,6-pentafluorobenzyl derivatives (sections 1, 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 (<i>ortho</i> to benzylic)	δ _F /ppm (<i>meta</i> to benzylic)	δ _F /ppm (<i>para</i> to benzylic)
1. Small 2,3,4,5,6-Pentafluorobenzyl-functional Molecules, F₅C₆–CH₂–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. <i>para</i>-Substituted Polymers, R–F₄C₆–CH₂O–, 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 ₂ N–) ^c	–145.2	–162.8	
Dialkylamino (R ₂ N–, 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 ¹⁹F NMR resonances of *para* thiol-substituted 2,3,5,6-tetrafluorobenzyl derivatives. Assignments in this table are based on the measurement and interpretation of ¹H-decoupled and non-¹H-decoupled ¹⁹F 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 CH₃ group, see Figure S9; ^c J.-M. Noy, P. J. Roth et al. *unpublished work*

After washing and filtration over basic aluminum oxide, PFBMA was of sufficient purity for RAFT polymerization without the need for chromatography or distillation. Six 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 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 $T_g = 65\text{ }^\circ\text{C}$, higher than that of the non-fluorinated analogue poly(benzyl methacrylate) ($T_g = 54\text{ }^\circ\text{C}$),⁵⁰ but lower than that of the reactive styrenic counterpart poly(2,3,4,5,6-pentafluorostyrene) ($T_g = 95\text{ }^\circ\text{C}$).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 ^1H 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 ^1H NMR signal of the methylene side group ($\text{COO}-\text{CH}_2-\text{PFB}$) roughly reflected a similar splitting

with the main peaks ($\delta/\text{ppm} = 5.07, 5.03$) showing an approximate 60:35 integration ratio and the expected 5% component apparent as a shoulder around $\delta = 5.16$ ppm.

Table 2. List of prepared pPFBMA samples.^a

Code	Target DP	Conversion ^b (%)	DP ^{NMR,b}	M_n^{SEC} (kg/mol)	$\bar{D}^{\text{SEC}}$
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 ¹H and ¹⁹F NMR spectroscopy before purification; ^c reaction time 8 h

Figure 1. SEC traces of reactive pPFBMA species (A), and after postpolymerization *para*-fluoro substitution with thiols (B, C), 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.

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 CDCl₃ and measuring ¹⁹F NMR spectroscopy. Reactions were continued until all ¹⁹F NMR signals associated with starting material had disappeared (40 min–2 h). Isolated products were characterized by ¹H and ¹⁹F NMR spectroscopy, FT-IR spectroscopy and SEC.

Scheme 2. *para*-Fluoro Postpolymerization Modification of pPFBMA with thiols

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		after modification	
						M_n^{SEC} (kg/mol)	$\bar{D}^{SEC}$	M_n^{SEC} (kg/mol)	$\bar{D}^{SEC}$
1	Thiophenol ^c	1.1	Et ₃ N, 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 ^c	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 ¹⁹F 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

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. ¹⁹F 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*-¹⁹F signal and a downfield shift of approx. 28 ppm (*cf.* Table 1) of the *meta* fluorides, the neighbors of the functionalized position. Before purification, the replaced (former *para*) fluoride appeared as broad signal between –120 and –165 ppm in ¹⁹F NMR spectra, usually with a lower-than-expected integral. Addition of excess of DBU to NMR samples (in CDCl₃) resulted in a sharp singlet at $\delta/\text{ppm} = -123.2$ associated with the DBU hydrofluoride salt. After purification, ¹⁹F

NMR signals associated with the replaced *para*-fluoride disappeared. ^1H NMR spectroscopy confirmed the quantitative formation of functional thioether derivatives, including through the appearance of a resonance associated with $\text{R}-\text{CH}_2-\text{SC}_6\text{F}_4$ methylene groups (for $\text{R} = \text{alkyl}$, $\delta/\text{ppm} (\text{R}-\text{CH}_2-\text{SC}_6\text{F}_4) = 2.98$ (bt), compared to $\delta/\text{ppm} (\text{R}-\text{CH}_2-\text{SH}) = 2.54$ (q) for the respective thiol reagent). ^1H 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 $\text{C}=\text{O}$ stretching band ($\nu = 1735 \text{ cm}^{-1}$) was not significantly affected through the thiol-*para*-F substitution (suggesting, as desired, the absence of acyl substitution reactions), a red-shift of the $\text{C}=\text{C}$ aromatic vibrations from $\nu (\text{C}_6\text{F}_5) = 1504 \text{ cm}^{-1}$ to $\nu (\text{C}_6\text{F}_4\text{SR}) = 1472 \text{ cm}^{-1}$ 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, Figure 1BC), as to be expected for the post-polymerization 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.

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, and F, 3EG = tri(ethylene glycol) methyl ether amine, 400 MHz) and piperidine (F, 300 MHz)

Figure 3. ^1H 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.

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 ($\text{RC}_6\text{F}_5 \rightarrow \text{RC}_6\text{F}_4\text{-SR}' \rightarrow \text{RC}_6\text{F}_4\text{-SH}$), to set the stage for a range of efficient thiol-X click chemistries⁵⁸ 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 non-symmetrical disulfides ($\text{RC}_6\text{F}_5 \rightarrow \text{RC}_6\text{F}_4\text{-SSO}_2\text{R}' \rightarrow \text{RC}_6\text{F}_4\text{-SS-R}''$)⁵⁹ (Scheme 3A) with potential for drug releasing applications.⁶⁰ However, under all investigated reaction conditions (solvents *N,N*-dimethylformamide, dimethylsulfoxide, 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), ¹⁹F 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).

Scheme 3. Reaction of pPFBMA with the sulfur-based nucleophiles sodium methanethiosulfonate (**A**), sodium hydrosulfide (**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**)

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3 Reaction of pPFBMA with sodium hydrosulfide in the absence of base was successful on
4 one account (see ^{19}F NMR in Figure 2D), but led to insoluble material in other attempts (Scheme
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7 3B).
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10 Three carbonylthio reagents were used, with the aim of enabling the wide range of 'RAFT end
11 group chemistries'^{49, 61} for polymer side group modification. Potassium thioacetate showed
12 reasonably high reactivity toward pPFBMA, but the expected tetrafluorophenyl thioacetate
13 product was too reactive to be isolated with products containing about 30 mol-% of thiols
14 (Scheme 3C). A trithiocarbonate-based nucleophile, Scheme 3D, on the other hand, was less
15 reactive (presumably due to resonance stabilization of the anion) and gave 90% *para*-fluoro
16 substitution after heating to 65°C for 6 days. At a higher temperature of 80 °C, cleavage of the
17 methacrylic esters was observed and the reaction was deemed impractical for this study. A
18 dithioester-based nucleophile, however, enabled full conversion to the tetrafluorophenyl
19 benzenedithioate derivative within 24 h at 65°C, Scheme 3E, based on ^{19}F NMR spectroscopic
20 analysis (see Table 1). Among several attempts, optimal reaction conditions were an excess of
21 dithioester (1.7 equiv) and of triethylamine (2.8 equiv) in anhydrous DMF. To demonstrate the
22 potential of this benzenedithioate-functionalized species, a sample was aminolysed (releasing
23 thiolate groups) in the presence of butyl acrylate, a thiol-reactive Michael acceptor, giving the
24 ester-functional thiol-ene product in one step, Scheme 3F. ^1H NMR spectroscopic analysis
25 confirmed successful modification. SEC analysis, however, revealed a bimodal molar mass
26 distribution, Figure 1F, attributed to a small degree of crosslinking reactions, not uncommon for
27 thiol-functional polymers.⁶²
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3 It is briefly mentioned that modification attempts of pPFBMA with thiourea,
4 tetrabutylammonium bromide, and tetrabutylammonium iodide (DMF, 2.5 equiv, 80 °C, 2 days)
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6 gave no reactions, demonstrating higher selectivity and stability of pPFBMA toward
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8 nucleophiles compared to common haloalkane substrates.
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15 ***Polymer Modification: Amines***

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17 The arguably most important class of nucleophiles for polymer modification comprises
18 amines. Modification of pPFBMA was investigated with a selection of aromatic, primary, and
19
20 secondary amines. Amines were used in excess (2.5 equiv) and reactions were stirred at 50 or 60
21
22 °C in DMF until ^{19}F NMR spectroscopic analysis of a withdrawn sample indicated complete
23
24 disappearance of signals associated with the starting material. Products were isolated by
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26 precipitation or dialysis and characterized by ^1H and ^{19}F NMR spectroscopy, FT-IR spectroscopy
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28 and SEC. Reactions are summarized in Table 4 with structures of amines shown in Scheme 4.
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Table 4. Overview of reaction conditions, molar composition of products and SEC results for postpolymerization modifications of pPFBMA with amines.^a

Entry	Amine	<i>T</i> (°C)	Reaction time (h)	Disubstitution (Z) ^b (–C ₆ F ₄) ₂ NR (mol-%)	Before Modification		After Modification		Comments
					<i>M</i> _n ^{SEC} (kg/mol)	<i>D</i> ^{SEC}	<i>M</i> _n ^{SEC} (kg/mol)	<i>D</i> ^{SEC}	
1	Aniline	60	10		8.6	1.15	—	—	no reaction
2	<i>n</i> -Butylamine	50	15	8	8.6	1.15	10.0	1.11	
3	<i>n</i> -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 <i>T</i> _{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 were used in anhydrous *N,N*-dimethylformamide as solvent. With the exception of aniline, complete disappearance of PFBMA repeat units was confirmed by ¹⁹F 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.

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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 ¹H NMR spectroscopy and the percentage of *N,N*-disubstituted tetrafluoroaniline groups (= Z) from ¹⁹F NMR spectroscopy, see Table 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 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 °C overnight for reagents *n*-butylamine, *n*-pentylamine, cyclohexylamine, 3-(dimethylamino)-propylamine, piperidine, and 4-benzyl piperidine, 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 1CDE 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, ¹⁹F 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 2EF). Surprisingly, however, ¹⁹F NMR spectra also contained signals associated with *N,N*-dialkyl tetrafluoroaniline side groups. The amount of disubstituted aromatic rings ranged from 6–9 mol-% for the set of smaller primary amines (Table 4 Entries 2–5, representative ¹⁹F 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*-alkyl tetrafluoroaniline 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 derivate 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 results, Figure S13. For example, for the modification of pPFBMA with di(ethylene glycol) methyl ether amine (DEG) (Table 4, entry 6), ^1H 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 ($= 100\% - \frac{1}{2} \times 28\%$) DEG side chains per repeat unit, in excellent agreement with the ^1H 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 $\sim$ 3) did not improve solubility, suggesting no significant amount of protonation of the

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3 tetrafluoroaniline nitrogen atoms and confirming their low basicity (the conjugate acid of the
4 comparable small molecule pentafluoroaniline (*i.e.*, $\text{F}_5\text{C}_6\text{NH}_3^+$) has a reported $\text{p}K_a = -0.3$).⁶⁸ The
5 modification of pPFBMA with PEG₃₅₀ methyl ether amine, however, yielded a product with
6 temperature-dependent aqueous solubility (below a critical temperature) and measured LCST-
7 type cloud points around body temperature (Figure S14–S15). As such, this pPFBMA-derived
8 species represents a new addition to the PEG-based family of materials with similar stimulus-
9 responsive solution behavior.^{69, 70}

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11 Yet, copolymer formation and lack of compositional control make the modification of
12 pPFBMA with primary amines unideal for the preparation of well-defined polymers.
13 Gratifyingly, the modification of pPFBMA with the secondary amine piperidine (Table 4 Entry
14 9) was found to proceed without side reactions with ^{19}F NMR analysis showing only the
15 expected tertiary amine functionality (Figure 2G) and ^1H NMR measurements indicating the
16 quantitative presence of the expected cyclic substituent (Figure 3D). FT-IR analysis showed the
17 absence of N–H stretching (around $\nu = 3500\text{--}3300\text{ cm}^{-1}$) and N–H bending (around $\nu = 1640\text{--}$
18 1550 cm^{-1} , Figure 4) vibrations and a red-shift of the C=C aromatic vibrations from $\nu(\text{C}_6\text{F}_5) =$
19 1504 cm^{-1} to $\nu(\text{C}_6\text{F}_4\text{NR}_2) = 1484\text{ cm}^{-1}$ (Figure 4, inset), confirming aromatic substitution. Based
20 on these results, two further secondary amines, including an *N*-functional piperazine, (Table 4,
21 Entries 10–11; Scheme 4C) were tested and found to react quantitatively in 24–64 h without
22 observed side reactions (see ^1H NMR data in Figure 3E). By virtue of its tertiary amine
23 functionality, the 1-(2-hydroxyethyl)piperazine-functional polymer was soluble in dilute aq. HCl
24 (pH 5–6) but precipitated above pH 7 when aq. NaHCO_3 was added, demonstrating the
25 preparation of a pH-responsive polymer from the pPFPMA platform (Figure S16–17).

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 pPFBMA₇₀ (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 water, Scheme 5. Microwave heating was necessary to push the reaction with the commonly sluggish⁷⁵ 1,4-butanedisulfone to completion (Figure S18).

Scheme 5. Successive postpolymerization modification of tertiary-amine functional pPFBMA₇₀ derivative with 1,3 propanesultone (**A**) and 1,4 butanesultone (**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.

¹⁹F NMR spectroscopic analysis of the zwitterionic homopolymers in D₂O/NaBr revealed essentially no change of ¹⁹F 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-butanedisulfone 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 Figure 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 approx. 154 mM. This data demonstrates the potential in developing novel smart *homopolymers* without the need for tuning through copolymerization as was previously done to achieve UCST transitions at such high salt concentrations.

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)

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 postpolymerization 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 pentafluorophenyl 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 $\bar{D} = 1.14$ to $\bar{D} = 1.27$). 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 wide-spread applications in synthetic polymer science.

Supporting Information. Synthesis of 2,3,4,5,6-pentafluorobenzyl acrylate, ^1H , ^{13}C , ^{19}F NMR and FT-IR spectra of monomers, ^1H -coupled and ^1H -decoupled spectra of 2,3,4,5,6-pentafluorotoluene and after modification with thiophenol, ^1H - ^{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 ^1H NMR spectra of amine-modified polymers, photographs of pH-responsive polymer, ^1H NMR spectra of zwitterionic polymer and its precursor, and turbidity curves and phase diagrams of thermoresponsive polymers.

Acknowledgement. Funding for J.-M. N. from the Faculty of Engineering at the University of New South Wales is acknowledged. P.J.R. acknowledges Ms. Georgia Khinsoe (All Saints' College, Perth) for performing turbidity measurements, Mr. Elden Garrett (Curtin University) for assistance with microwave heating experiments, Mrs. Violeta Doukova (University of Surrey) for DSC measurements, and Prof. Andrew B. Lowe, Prof. Mark Buntine, the Nanochemistry Research Institute (NRI), and the Department of Chemistry at Curtin University for support.

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

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