Polymer Chemistry

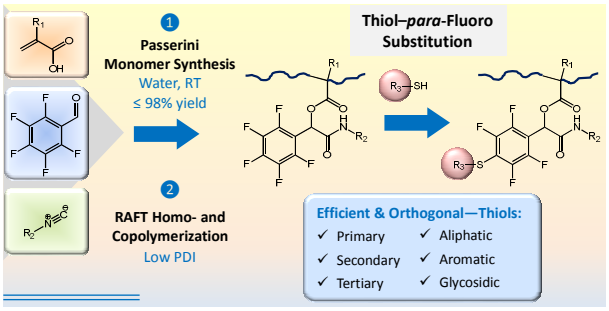
Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/polymers

Janina-Miriam Noy, Miriam Koldevitz, Peter J. Roth*

Thiol-reactive Functional Poly(meth)acrylates: Multicomponent Monomer Synthesis, RAFT (Co)polymerization and Highly Efficient Thiol–*para*-Fluoro Postpolymerization Modification



Journal Name

RSCPublishing

ARTICLE

Thiol-reactive Functional Poly(meth)acrylates: Multicomponent Monomer Synthesis, RAFT (Co)polymerization and Highly Efficient Thiol–*para*-Fluoro Postpolymerization Modification†

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Janina-Miriam Noy,[a‡] Miriam Koldevitz,[a‡] and Peter J. Roth[a]*

A novel class of thiol-reactive (meth)acrylate monomers and the quantitative postpolymerization modification of their RAFT-made (co)polymers with aromatic, glycosidic, and aliphatic thiols are presented. A set of 6 different *N*-functional 2-(meth)acryloyloxy-2-(pentafluorophenyl)acetamide monomers bearing pentafluorophenyl groups was prepared by a Passerini three-component reaction of (meth)acrylic acid, 2,3,4,5,6-pentafluorobenzaldehyde, and various isocyanides in water in up to near-quantitative isolated yields. RAFT polymerization was used to produce well-defined homopolymers and copolymers with methyl methacrylate, *tert*-butyl methacrylate, poly(ethylene glycol methyl ether) (meth)acrylate, and pentafluorophenyl acrylate, with low polydispersity indices of generally $Đ_M \leq 1.23$. In the presence of base, (co)polymers underwent selective *para*-fluoro substitution reactions with thiols in the absence of any side reactions observable by ^{1}H and ^{19}F NMR spectroscopy and size exclusion chromatography. The selection of employed thiols included various alkanethiols, a thiolated glucose derivative, mercaptopropionic acid, L-cysteine and the drug captopril. ^{19}F NMR kinetic measurements indicated quantitative thiol–*para*-fluoro substitutions after <3–80 min at 25–45 °C using 1–1.1 equiv of thiol, depending on the reactivity of the employed thiol (aromatic, glycosidic > primary aliphatic > secondary aliphatic > tertiary aliphatic) and the choice of a suitable base (triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)). The versatility of thiol-reactive (meth)acrylate species is demonstrated by the examples of a thermoresponsive copolymer showing a thiol-sensitive lower critical solution temperature (LCST) and the selective sequential modification with thiols and amines of a doubly reactive copolymer containing activated pentafluorophenyl esters.

Introduction

Thiols represent an extremely versatile class of synthetic reagents, undoubtedly due to the high commercial and synthetic availability of functional thiols and the extensive range of highly efficient thiol–X reactions.[1-8] Arguably the most prominent examples of thiol–X reactions are the thiol–ene and thiol–yne addition reactions. Their success in the synthesis of dendrimers, branched macromolecules, crosslinked materials, in polymer end group (bio-)modification, surface functionalization, the preparation of functional films, and many other aspects of synthetic materials science can be followed in recent reviews and scholarly books.[1-4, 9-15]

There has been long-standing interest in the chemical modification of repeat units of pre-made (co)polymers as a means to produce new types of macromolecules. The scope of postpolymerization modification advanced significantly with the development of controlled radical polymerization techniques suitable for preparing polymers with predetermined molecular weights and low molecular weight distributions from a wide variety of functional and reactive vinyl monomers.[16-19] The combination of reversible addition–fragmentation chain transfer (RAFT) polymerization[20] with the amine-reactive monomers pentafluorophenyl acrylate (PFPA)[19] or vinyldimethylazlactone, for example, has been used to generate a suite of well-defined homo- and copolymers with tailored properties and behavior, including bio-compatibility[21] and responsiveness to (multiple)[22-24] external stimuli[25] including temperature,[26-28] pH,[29] CO_2,[30] light,[22, 23] or agitation.[31] There are, however, some limitations to the side-group modification of pre-made vinyl polymers with thiols, as many thiol-reactive groups inherently have low compatibility with radical polymerization processes resulting in side reactions and higher polydispersities.[32-37] In particular, while side reactions of alkene-functional vinyl monomers in a radical polymerization may be suppressed to some degree for specially designed monomers[38, 39] or under carefully controlled (co)polymerization conditions,[34, 40, 41] incorporation of alkene side groups through an additional postpolymerization step can be preferable.[42] Radical (co)polymer synthesis from triple-bond functional

monomers suitable for thiol–yne reactions, on the other hand, typically requires the use of protecting groups to avoid side reactions.[37] In this context, thiol–halo substitution reactions are attractive,[43, 44] especially on the pentafluorophenyl (PFP) functionality. This aromatic is stable during (radical) polymerization processes and, under mild conditions, undergoes selective nucleophilic aromatic substitution reactions with thiols in the *para* position (which experiences the largest activation from its two *ortho* and two *meta* fluorine neighbours).[45, 46] Of note, this reactivity applies to aliphatically connected PFP groups, in most instances pentafluorobenzyl derivatives and homologs, and should be distinguished from the carbonyl reactivity of PFP esters.[19] In the polymer chemistry arena the *para*-fluoro substitution reaction has been exploited exclusively in the modification of 2,3,4,5,6-pentafluorostyrene (PFSty)-based homo- and copolymers with nucleophiles including primary thiols[47-51] and, at elevated temperatures, amines.[52-54] Bearing perfluorinated side groups, however, the PFSty homopolymer, pPFSty, has limited solubility in more polar solvents, including ethers and especially alcohols.[55] In addition, as a styrene derivative, PFSty is not readily available for copolymerization with the larger (meth)acrylic family of monomers, likewise limiting versatility.

Recently,[56, 57] the Passerini multicomponent reaction[58, 59] has been exploited for the synthesis of novel multifunctional (meth)acrylic monomers.[60, 61] In one study, we demonstrated successful RAFT (co)polymer synthesis of several reactive Passerini-made monomers, including a PFP-functional species, but did not address thiol–*para*-fluoro substitution modifications.[56] Herein, we firstly expand the portfolio of Passerini-made PFP-functional monomers to a total of six (meth)acrylate monomers prepared from (meth)acrylic acid, 2,3,4,5,6-pentafluorobenzaldehyde, and different isocyanides in a single step. After RAFT-synthesis of well-defined homo- and copolymers, we highlight extremely efficient thiol–*para*-fluoro substitution reactions (reaching completion in >3–80 min) with a range of aromatic, glycosidic, and primary, secondary, and tertiary aliphatic thiols producing, in the absence of any observable side reactions, well-defined functional products. We demonstrate the versatility of this synthetic strategy toward tailored materials through the preparation of copolymers of a PFP-functional acrylate (i) with a poly(ethylene glycol) acrylate yielding thermoresponsive copolymers with a thiol-tunable aqueous lower critical solution temperature (LCST) and (ii) with the amine-reactive PFP acrylate yielding a dual-functional polymer with orthogonally reactive PFP groups.

Experimental Section

Instrumentation

Size exclusion chromatography (SEC) was performed on a Shimadzu system equipped with four 300 × 7.8 mm^2 linear phenogel columns (10^5, 10^4, 10^3 and 500 Å) operating at a flow rate of 1 mL/min using dimethylacetamide as eluent. Reported molar masses are apparent values with regards to a polystyrene calibration based on a series of narrow molar mass distribution polystyrene standards (0.58–1820 kg/mol).

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

Turbidity measurements were performed on a Varian Cary 300 Scan spectrophotometer equipped with a Cary temperature controller and a Peltier heating element in quartz cuvettes of 10 mm path length at a wavelength of 520 nm with heating / cooling rates of 1 °C/min. Polymer concentrations were 10 g/L. For clear solutions the baseline was corrected to zero absorbance, A. Transmittance, $T = 10^{-A}$, was plotted against temperature and cloud points were determined at $T = 50$ %.

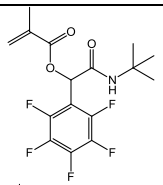
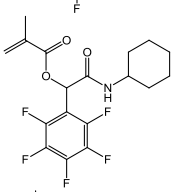
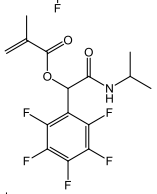
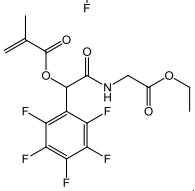
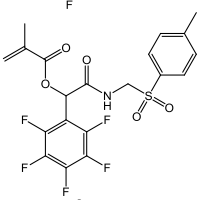
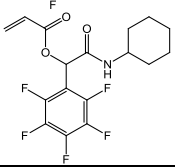
NMR spectroscopic measurements were performed on a Bruker Avance 300 MHz instrument (282 MHz for ^{19}F nuclei). The internal solvent signal of $CDCl_3$ (δ = 7.26 ppm) was used as reference. Kinetic measurements over a period of 24 h (thiophenol without base and 1-octanethiol with triethylamine) were performed by withdrawing samples (50 µL) from reactions, diluting with $CDCl_3$ (600 µL) and measuring a ^{19}F NMR spectrum. Kinetic measurements within a time frame of 1.5 h (thiophenol with triethylamine and 1-thio-β-D-glucose tetraacetate with triethylamine) were performed in an NMR tube. A solution of PFP-functional polymer (44.5 µmol of PFP groups) in DMF (580 µL) and acetone-d_6 (50 µL) (for locking and shimming purposes) was added into an NMR tube which was heated to 45 °C inside the spectrometer. After locking, shimming, and matching the sample was taken from the spectrometer and poured into a glass vial. Stock solution containing triethylamine in DMF (10 µL, containing 44.5 µmol of triethylamine) and thiol (thiophenol or 1-thio-β-d-glucose tetraacetate, 44.5 µmol, together with 10 µL of DMF) were added quickly, the sample was shaken, filled into the NMR tube and transferred back into the spectrometer. After adjusting the receiver gain, measurements (delay time D1 = 0.5 s, sweep width = 237 ppm centered on −150 ppm, 78 scans) were run every 3 minutes for ~ 1.5 h. The temperature stabilized at 45 ± 1 °C within several minutes. A kinetic measurement of a reaction with 1-octanethiol and DBU was performed in analogy to the previous procedure at room temperature. Conversions for all kinetic measurements were determined by comparison of integrals of phase- and baseline-corrected spectra of the signals at δ / ppm = −132.3 (bs, 2 F (*meta* to backbone) of product) and −163.1 (bs, 2 F (*meta*) of starting material).

Materials

All reagents were purchased from Sigma-Aldrich and were used as received unless stated otherwise. Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and stored at −24 °C. Comonomers methyl methacrylate (MMA), *tert*-butyl methacrylate (*t*BuMA), poly(ethylene glycol) methyl ether methacrylate (PEGMA, monomer molecular weight 360 g/mol), and poly(ethylene glycol) methyl ether acrylate (PEGA, monomer molecular weight 480 g/mol) were passed through basic Al_2O_3 to remove inhibitors before polymerization. Comonomer pentafluorophenyl acrylate,[26] and the RAFT agents 4-cyano-4-[(phenylcarbonothioyl)thio]pentanoic acid (CPADB)[62] and benzyl propyl trithiocarbonate (BPTC)[30] were prepared as described elsewhere. The Passerini monomer *N*-*tert*-butyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide, ***t*Bu-MA-PFP**, was prepared in water according to our previously published procedure[56] and purified by column chromatography using *n*-hexane–ethyl acetate 4:1 as eluent.

Multicomponent Monomer Synthesis. Pentafluorophenyl (PFP) functional monomers were prepared by a Passerini reaction according to the following general procedure. 2,3,4,5,6-Pentafluorobenzaldehyde (1.00 g, 0.63 mL, 5.1 mmol) and milliQ water (1.7 mL) were mixed in a 10 mL round bottom flask. Methacrylic acid **1a** (0.439 g, 0.432 mL, 5.1 mmol) or acrylic acid **1b** (0.367 g, 0.350 mL, 5.1 mmol) was added and the mixture was stirred for several minutes at room

Table 1. Summary of Synthetic Details of PFP-functional Monomers

Entry	Name, Abbreviation	Structure	Acid reagent	Isocyanide reagent	Isolated Yield (%)
1	*N*-*tert*-butyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide **tBu-MA-PFP**		1a	2a	96
2	*N*-cyclohexyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide **cHex-MA-PFP**		1a	2b	98
3	*N*-isopropyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide **iPr-MA-PFP**		1a	2c	98
4	*N*-(2-ethoxy-2-oxoethyl)-2-methacryloyloxy-2-(pentafluorophenyl)acetamide **EE-MA-PFP**		1a	2d	93
5	*N*-tosylmethyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide **Tos-MA-PFP**		1a	2e	62
6	*N*-cyclohexyl-2-acryloyloxy-2-(pentafluorophenyl)acetamide **cHex-A-PFP**		1b	2b	94

temperature. Isocyanide (*tert*-butyl isocyanide **2a**, cyclohexyl isocyanide **2b**, isopropyl isocyanide **2c**, ethyl isocyanoacetate **2d**, or *p*-toluenesulfonylmethyl isocyanide **2e**, 5.1 mmol) was added slowly and the mixture was stirred at room temperature overnight. Water was decanted and remaining solvent was removed under reduced pressure. Products were isolated as white solids by column chromatography on silica gel using eluents as specified below. Yields are given in Table 1.

N-cyclohexyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide, **cHex-MA-PFP** (hexane–ethyl acetate 3:2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm = 6.45 (s, 1 H, –COOC*H*PFP–), 6.29 (1 H, –N*H*–), 6.20 (s, 1 H, *H*HC=C(CH_3)–), 5.74 (t, 1 H, H*H*C=C(CH_3)–), 3.85 (m, 1 H, –NHC*H*<), 1.99 (s, 3 H, H_2C=C(C*H*$_3$)–), 1.94–1.16 (m, 10 H, cyclohexyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm = 164.85, 164.71 (–COO–, –CONH–), 135.00 (H_2C=*C*(CH_3)–), 127.90 (H_2*C*=C–), 65.36 (–COO*C*HPFP–), 48.37 (–NH*C*H<), 32.72, 32.65 25.41, 24.59, 24.51 (cyclohexyl), 18.20 (H_2C=C(*C*H$_3$)–); ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −141.36 (m, 2 F, *ortho*), −151.92 (t, 1 F, *para*), −161.39 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 3363 (w, N−H, stretch), 2939, 2860 (w, C−H stretch), 1736 (m–s, ester C=O stretch), 1655 (s, amide C=O stretch), 1505 (s, PFP C=C bend), 1129 (s, C–N stretch), 997 (s, C–F stretch); MS (ESI) *m/z* (%) = 414.11 (100) [M+Na]$^+$.

N-isopropyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide, **iPr-MA-PFP** (hexane–ethyl acetate 3:2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm = 6.44 (s, 1 H, –COOC*H*PFP–), 6.25 (bs, 1 H, –N*H*–), 6.21 (q, 1 H, *H*HC=C(CH_3)–), 5.76 (q, 1 H, H*H*C=C(CH_3)–), 4.14 (m, 1 H, –NHC*H*(CH_3)$_2$), 1.98 (s, 3 H, H_2C=C(C*H*$_3$)–), 1.22 (m, 6 H, –C(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm = 165.05, 164.79 (–COO–, –CONH–), 134.85 (H_2C=*C*(CH_3)–), 128.26 (H_2*C*=C–), 65.15 (–COO*C*HPFP–), 41.95 (–*C*(CH_3)$_2$), 22.56 (–C(*C*H$_3$)$_2$), 18.35 (H_2C=C(*C*H$_3$)–); ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −140.86 (m, 2 F, *ortho*), −151.94 (t, 1 F, *para*), −161.13 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 3318 (w, N–H stretch), 2971 (w, C−H stretch), 1730 (m–s, ester C=O stretch), 1657 (s, amide C=O stretch), 1509 (s, PFP C=C bend), 1131 (s, C–N stretch), 1000 (s, C–F stretch); MS (ESI) *m/z* (%) = 352.10 (89) [M+H]$^+$, 374.08 (100) [M+Na]$^+$

Table 2. Summary of PFP-functional (Meth)acrylate Homo- and Copolymers Prepared by the RAFT Process.

Entry	Polymer Code[a]	Comonomer (mol% in feed)	solvent (reaction time /h)	Conversion (%)[b]	$M_n^{theor.,c}$ (kg/mol)	$M_n^{SEC,d}$ (kg/mol)	$Đ_M^{SEC,d}$
1	p(*t*Bu-MA-PFP)	—	PhOMe (15)	65	24.0	46.8	1.19
2	p(*t*Bu-MA-PFP$_{0.51}$-*co*-MMA$_{0.49}$)	MMA (60)	PhOMe (15)	90/76	19.4	14.1	1.10
3	p(*t*Bu-MA-PFP$_{0.40}$-*co*-tBuMA$_{0.60}$)	*t*BuMA (60)	PhOMe (15)	74/74	15.5	36.0	1.18
4	p(*t*Bu-MA-PFP$_{0.18}$-*co*-PEGMA$_{0.82}$)	PEGMA (83)	PhOMe (15)	100/95	34.9	32.3	1.48
5	p(*t*Bu-MA-PFP$_{0.11}$-*co*-PEGMA$_{0.89}$)	PEGMA (89)	PhOMe (8)	81/77	28.1	23.3	1.20
6	p(cHex-MA-PFP)	—	PhOMe (15)	93	35.2	27.6	1.19
7	p(cHex-MA-PFP$_{0.73}$-*co*-MMA$_{0.27}$)	MMA (25)	PhOMe (15)	96/97	30.3	10.1	1.12
8	p(iPr-MA-PFP)	—	PhOMe (15)	98	34.7	17.0	1.12
9	p(iPr-MA-PFP$_{0.43}$-*co*-MMA$_{0.57}$)	MMA (55)	PhOMe (15)	95/91	19.6	16.9	1.12
10	p(EE-MA-PFP)	—	PhOMe (15)	92	36.6	16.4	1.16
11	p(EE-MA-PFP$_{0.56}$-*co*-MMA$_{0.44}$)	MMA (40)	PhOMe (15)	92/90	24.4	12.8	1.16
12	p(Tos-MA-PFP)	—	PhOMe (15)	87	41.8	32.0	1.18
13	p(cHex-A-PFP)	—	MeCN (16)	99	37.6	9.7	1.37
14	p(cHex-A-PFP)	—	MeCN (9)	67	25.6	12.2	1.23
15	p(cHex-A-PFP$_{0.31}$-*co*-PEGA$_{0.69}$)	PEGA (69)	MeCN (6)	82/77	35.4	31.0	1.36
16	p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$)	PFPA (55)	MeCN (7)	47/43	13.4	60.7	1.22

[a] molar composition as measured by ^{1}H NMR spectroscopy on purified product; [b] conversion of monomers (PFP-functional monomer/comonomer) determined by ^{1}H NMR spectroscopy before purification by quantification of residual monomers; [c] calculated from conversion and composition; [d] determined by size exclusion chromatography (PS calibration) in DMAc

N-(2-ethoxy-2-oxoethyl)-2-methacryloyloxy-2-(pentafluorophenyl)acetamide, **EE-MA-PFP** (hexane–ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm = 7.06 (m, 1 H, –N*H*–), 6.52 (s, 1 H, –COOC*H*PFP–), 6.27 (s, 1 H, *H*HC=C(CH$_3$)–), 5.76 (t, 1 H, H*H*C=C(CH$_3$)–), 4.26 (q, 2 H, –COOC*H*$_2$CH$_3$), 4.12 (q, 2 H, –NHC*H*$_2$CO–), 2.01 (s, 3 H, H$_2$C=C(C*H*$_3$)–), 1.30 (t, 3 H, –CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm = 169.16, 166.11, 164.76 (2 × –COO–, –CONH–), 134.80 (H$_2$C=*C*(CH$_3$)–), 128.27 (H$_2$*C*=C–), 65.25 (–COO*C*HPFP–), 61.96 (–COO*C*H$_2$CH$_3$), 41.45 (–NH*C*H$_2$COO–), 18.16 (H$_2$C=C(*C*H$_3$)–), 14.08 (–COOCH$_2$*C*H$_3$); ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −140.61 (m, 2 F, *ortho*), −151.85 (t, 1 F, *para*), −161.20 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 3343 (w, N–H stretch), 2956 (w, C–H stretch), 1760, 1731 (m–s, esters C=O stretch), 1660 (s, amide C=O stretch), 1510 (s, PFP C=C bend), 1190 (s, C–O–C, stretch), 1125 (s, C–N, stretch), 1000 (s, C–F, stretch); MS (ESI) *m/z* (%) = 396.09 (27) [M+H]$^+$ 418.07 (100) [M+Na]$^+$.

N-tosylmethyl-2-methacryloyloxy-2-(pentafluorophenyl)acetamide, **Tos-MA-PFP** (hexane–ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm = 7.76 (d, 2 H, *ortho* –SO$_2$(C$_6$H$_4$)CH$_3$), 7.46 (t, 1 H, –N*H*–), 7.34 (d, 2 H, *meta* –SO$_2$(C$_6$H$_4$)CH$_3$), 6.37 (s, 1 H, –COOC*H*PFP–), 6.22 (s, 1 H, *H*HC=C(CH$_3$)–), 5.71 (t, 1 H, H*H*C=C(CH$_3$)–), 4.79 (m, 2 H, –NHC*H*$_2$SO$_2$–), 2.43 (s, 3 H, –SO$_2$(C$_6$H$_4$)C*H*$_3$), 1.95 (s, 3 H, H$_2$C=C(C*H*$_3$)–); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm = 165.88, 164.84 (–COO–, –CONH–), 145.84 (Ar-*C*–CH$_3$), 134.56 (Ar-*C*–SO$_2$), 133.42 (Ar-*C meta*), 129.99 (H$_2$C=*C*(CH$_3$)–), 128.75 (H$_2$*C*=C–), 128.64 (Ar-*C ortho*), 65.06 (–COO*C*HPFP–), 60.11 (–NH*C*H$_2$SO$_2$–), 21.65 (–Ar*C*H$_3$), 18.09 (H$_2$C=C(*C*H$_3$)–); ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −140.29 (m, 2 F, *ortho*), −151.48 (t, 1 F, *para*), −161.10 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 3338 (w, N–H, stretch), 2926 (w, C–H stretch), 1732 (m–s, ester C=O stretch), 1705 (s, amide C=O stretch), 1508 (s, PFP C=C bend), 1322 (s, SO$_2$), 1129 (s, C–N stretch), 1005 (s, C–F stretch); MS (ESI) *m/z* (%) = 500.05 (100) [M+Na]$^+$.

N-cyclohexyl-2-acryloyloxy-2-(pentafluorophenyl)acetamide, **cHex-A-PFP** (hexane–ethyl acetate 3:2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ/ppm = 6.51 (dd, 1 H, *H*HC=CH–), 6.45 (s, 1 H, –COOC*H*PFP–), 6.34 (d, 1 H, –N*H*–), 6.20 (dd, 1 H, H$_2$C=C*H*–), 5.99 (dd, 1 H, H*H*C=CH–), 3.82 (m, 1 H, –NHC*H*<), 1.97–1.88, 1.73–1.60, 1.43–1.12 (3 m, 10 H, cyclohexyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ/ppm = 164.70, 163.63 (–COO–, –CONH–), 133.74 (H$_2$C=*C*H–), 126.58 (H$_2$*C*=CH–), 65.12 (–COO*C*HPFP–), 48.58 (–NH*C*H<), 32.72, 32.68, 25.37, 24.72, 24.65 (cyclohexyl); ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −140.65 (m, 2 F, *ortho*), −151.98 (t, 1 F, *para*), −161.52 (m, 2 F, *meta*). FT-IR ν/cm^{-1} = 3307 (w, N–H, stretch), 2930, 2860 (w, C–H stretch), 1737 (m–s, ester C=O stretch), 1654 (s, amide C=O stretch), 1506 (s, C=C bend), 1128 (s, C–N stretch), 1000 (s, C–F stretch); MS (ESI) *m/z* (%) = 378.11 (34) [M+H]$^+$, 400.09 (100) [M+Na]$^+$.

General Procedure for RAFT (Co)polymerization. PFP-functional monomer (100 equiv) or a mixture of PFP functional monomer and a comonomer (100 equiv in total), RAFT agent BPTC (for acrylate monomers) or CPADB (for methacrylate monomers) (1 equiv), AIBN (0.1 equiv) and solvent (acetonitrile or anisole, approx. 0.8 mL/mmol of monomers) were mixed in a glass flask which was sealed with a rubber septum, purged with nitrogen for 25 min and placed into a preheated oil bath at 70 °C for 6–15 h. After cooling, polymers were isolated by precipitation into diethyl ether–hexane (4:1) or by dialysis against methanol (regenerated cellulose membranes, 3500 g/mol molecular weight cut-off). Details on comonomers, solvents, polymerization times, and polymer characterization by SEC are summarized in Table 2.

Postpolymerization Thiol–*para*-Fluoro Substitution Reactions. Procedure for more S–H acidic thiols (thiophenol or 1-thio-β-D-glucose tetraacetate): PFP-functional (co)polymer (1 equiv of PFP groups) was dissolved in DMF (0.8–1.5 mL per 100 mg of PFP-functional polymer), triethylamine (1.05 equiv) and thiol (1.1 equiv) were added. The mixture was stirred for 1.5 h at 45 °C. Full conversion was confirmed by a ^{19}F NMR measurement of a reaction sample (50 µL) diluted with $CDCl_3$ (600 µL) (product signals (using thiophenol) at δ/ppm = −131.8 (2 F) and −140.1 (2 F), signal of Et$_3$N·HF around −167 ppm (varied between reactions)). Polymers were isolated by precipitation into diethyl ether–hexane or by dialysis in methanol (regenerated cellulose membranes, 3500 g/mol molecular weight cut-off).

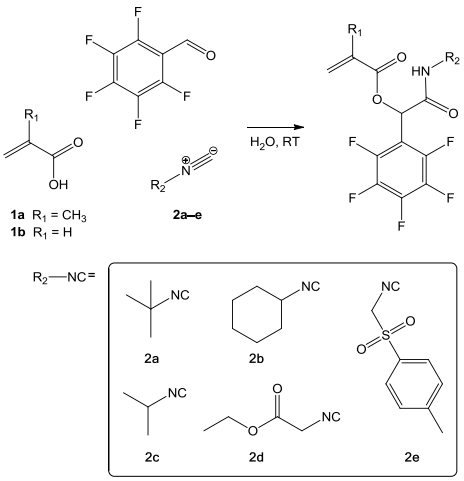
Procedure for alkanethiols (1°, 2°, and 3°): PFP-functional (co)polymer (1 equiv of PFP groups) was dissolved in DMF (0.8–1.5 mL per 100 mg of PFP-functional polymer), 1,8-diazabicycloundec-7-ene (DBU, 1.05 equiv) and thiol (1.1 equiv) were added. The mixture was stirred for 30–45 min at room temperature. Full conversion was confirmed by a ^{19}F NMR measurement of a sample (50 µL) diluted with $CDCl_3$ (600 µL) (product signals (using 1-octanethiol) at δ/ppm = −135.3 ppm (2 F) and −141.2 (2 F), signal of DBU·HF around −148 ppm (varied between reactions)). Polymers were isolated by precipitation into diethyl ether–hexane or by dialysis in methanol (regenerated cellulose membranes, 3500 g/mol molecular weight cut-off). For thiols containing acidic groups (mercaptopropionic acid, cysteine), a total of 2.1 equiv of DBU was used with otherwise unchanged conditions.

Sequential Postpolymerization Modification of a Copolymer Containing PFP groups and activated PFP esters. Double-reactive copolymer p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$) was prepared according to the above general procedure using PFPA as comonomer. ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −141.08 (cHex-A-PFP *ortho*), −152.07 (cHex-A-PFP *para*), −153.49 PFPA *ortho*), −156.29 (PFPA *para*), −161.76 (cHex-A-PFP *meta*, PFPA *meta*). p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$) (60 mg, containing approx. 0.11 mmol of amine-reactive PFP esters and 0.09 mmol of thiol-reactive aliphatic PFP groups) was dissolved in acetonitrile (0.4 mL). Butyl acrylate (6 µL, to scavenge thiols released by aminolysis of RAFT end groups)[4] and isopropylamine (13.9 mg, 20 µL, 0.24 mmol, 2.2 equiv with regards to PFP esters) were added followed by stirring at room temperature overnight. A sample (50 µL) was withdrawn, diluted with $CDCl_3$ (600 µL) and analyzed by ^{19}F NMR spectroscopy showing remaining broad signals of unmodified cHex-A-PFP repeat units at δ/ppm = −140.74 (2 F, *ortho*), −152.40 (1 F, *para*), −161.49 (2 F, *meta*) and sharp signals of released pentafluorophenol at δ/ppm = −167.28, 168.01 (4 F, *ortho, meta*), −180.96 (1 F, *para*). The solution was subsequently dialyzed against methanol to yield p(cHex-A-PFP$_{0.45}$-*co*-NIPAM$_{0.55}$), M_n^{SEC} = 34.2 kg/mol, $Đ_M$ = 1.26. ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −140.73 (2 F, *ortho*), −151.85 (1 F, *para*), −161.17 (2 F, *meta*). The product was subsequently modified with thiophenol according to the above procedure yielding p(cHex-A-PhS$_{0.45}$-*co*-NIPAM$_{0.55}$) with M_n^{SEC} = 26.0 kg/mol, $Đ_M$ = 1.30. ^{19}F NMR ($CDCl_3$, 282 MHz) δ/ppm = −132.53 (2 F, cHex-A-PhS, *meta to acrylate side*), −140.16 (2 F, cHex-A-PhS, *ortho to acrylate side*).

Results and Discussion

Monomer Synthesis

The Passerini multicomponent reaction produces an α-acyloxycarboxamide as the single product from the reaction of a carboxylic acid, an aldehyde or ketone, and an isocyanide.[58] In order to prepare PFP-functional (meth)acrylate monomers, we chose as reagents (meth)acrylic acid and 2,3,4,5,6-pentafluorobenzaldehyde in combination with a selection of isocyanides, including the alkyl-functional isocyanides **2a**–**2c**, the ester-containing species **2d** and tosylmethyl isocyanide **2e**, see Scheme 1. The resulting *N*-functional 2-(meth)acryloyloxy-2-(pentafluorophenyl)acetamides featured, in addition to a polymerizable (meth)acrylate handle, a pentafluorophenyl group and an *N*-functional amide moiety carrying the residue of the employed isocyanide component (labelled R_2 in Scheme 1). In total, one acrylate and five methacrylate monomers were prepared; Table 1 gives a summary of all monomers with their names, abbreviations (which reflect the respective synthetic reagents in the order isocyanide–carboxylic acid–aldehyde), structures and yields. Reactions were carried out in water at room temperature. In all instances, products separated as a white solid allowing for isolation of crude product by decanting and drying. PFP-functional monomers were then purified by column chromatography with isolated yields of 93–98% in all cases except for the tosylmethyl-functional monomer **Tos-MA-PFP**, whose synthesis suffered from lower conversion resulting in an isolated yield of 62%. ^{1}H, ^{13}C, and ^{19}F NMR spectra of all monomers conforming to the expected structures and confirming high purity are shown in the supporting information. Apart from ***t*Bu-MA-PFP**, the preparation of which we recently reported,[56] these monomers have, to the best of our knowledge, not been previously described.

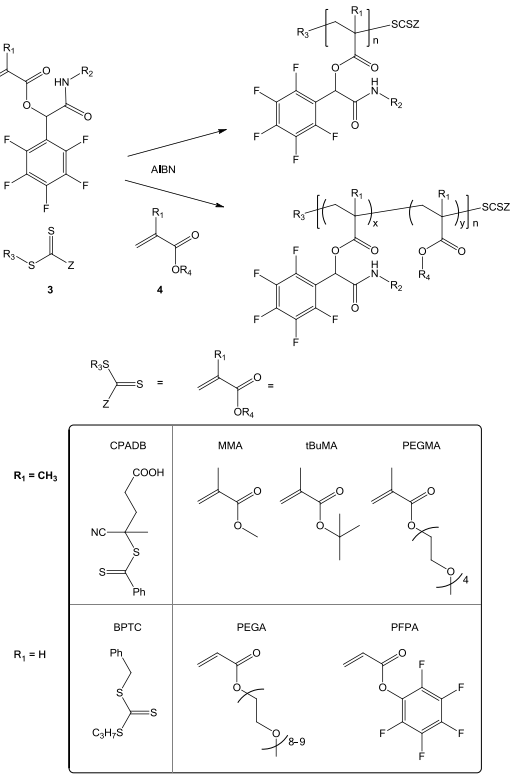


Scheme 1. Multicomponent monomer synthesis with structures of employed isocyanide reagents

Polymer Synthesis

With a series of novel PFP-functional (meth)acrylate monomers in hand, we next subjected them to RAFT (co)polymerization in anisole or acetonitrile mediated by dithioester (for methacrylate systems), or trithiocarbonate (for acrylate systems) chain transfer agents (CTAs), at a feed concentration ratio [monomers]:[CTA]:[AIBN] of 100:1:0.1. As comonomers methyl methacrylate (MMA), *tert*-butyl methacrylate (*t*BuMA), poly(ethylene glycol methyl ether) methacrylate (PEGMA), poly(ethylene glycol methyl ether) acrylate (PEGA), and pentafluorophenyl acrylate (PFPA) were used, see Scheme 2. Polymer products were isolated by several precipitations into diethyl ether–hexane. Reaction solvents and times, monomer conversions, comonomer feed ratio, measured molar copolymer compositions, and measured and calculated molecular weight characteristics of all (co)polymers are compiled in Table 2. In most cases, copolymerizations proceeded with similar conversions of PFP-functional monomers and comonomers (determined by a combination of ^{1}H and ^{19}F NMR spectroscopy on polymerization mixtures before purification), resulting in copolymers with molar compositions predetermined through the comonomer feed ratio. Somewhat high molecular weight dispersities were measured for copolymers containing PEG(M)A comonomers (entries 4 and 15 in Table 2, $Đ_M$ = 1.48

and 1.36, respectively), presumably due to crosslinker impurities in the comonomers, and for the homopolymerization of **cHex-A-PFP** when allowed to proceed to full monomer conversion (entry 13, 16 h, $Đ_M$ = 1.37). Stopping this polymerization after 9 h, however, resulted in a lower dispersity sample (entry 14, $Đ_M$ = 1.23). In all other cases, dispersities were low with $Đ_M \leq 1.22$ and SEC-measured molecular weight distributions were monomodal and nearly symmetrical. Representative curves for (meth)acrylate homo- and copolymers are shown in Figure 1 (black curves).



Scheme 2. Synthesis of (meth)acrylic homo- and copolymers by the RAFT process with structures of chain transfer agents and comonomers

While the hydrophobic PFP group may suggest limited polymer solubility, PFP monomer-derived homopolymers **p(*t*Bu-MA-PFP)**, **p(cHex-MA-PFP)**, **p(iPr-MA-PFP)**, and the ethyl ester side chain-functional species **p(EE-MA-PFP)** were, in fact, soluble in many common organic solvents of medium polarity including chloroform, anisole, tetrahydrofuran, dimethylformamide, dimethylacetamide, and acetonitrile, but were insoluble in water. Homopolymers **p(*t*Bu-MA-PFP)**, **p(iPr-MA-PFP)**, and **p(EE-MA-PFP)**, but not **p(cHex-MA-PFP)**, were additionally soluble in ethanol, suggesting larger versatility compared to pPFSty, and highlighting the influence of the isocyanide-originating amide residue in tuning the behaviour of the derived materials.

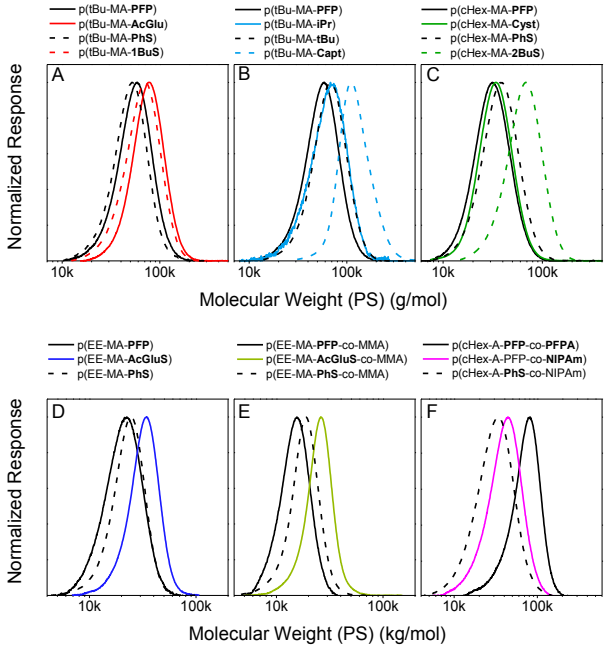


Figure 1. (A–E) Representative SEC traces of PFP-functional (co)polymer precursors (solid black lines) and after modification with different 1°, 2°, and 3° thiols (coloured and dashed lines) and (F) SEC traces of PFP–PFP ester double functional copolymer p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$) (black curve) and after modification with isopropylamine (pink curve) and thiophenol (dashed black curve)

Thiol–*para*-Fluoro Postpolymerization Modification

In order to determine the amenability of the PFP-functional (co)polymers to thiol–*para*-fluoro substitution reactions, we exposed **p(*t*Bu-MA-PFP)** as a model homopolymer dissolved in DMF (at a concentration of 25 g/L, resulting in [PFP groups] = 68 mM) to model aromatic, glycosidic and aliphatic thiols (thiophenol, 1-thio-β-D-glucose tetraacetate, or 1-octanethiol; 1 equiv.) in the presence of different bases (Et_3N, 1,8-diazabicycloundec-7-ene (DBU), or no base; 1 equiv.) at 45 °C. Conversions after predetermined reaction times between 1–24.5 h were determined by ^{19}F NMR measurements on withdrawn reaction samples. For reactions which had proceeded to (near) completion within 1 h, kinetic measurements were repeated in NMR tubes with ^{19}F NMR spectroscopic measurements run every 5 minutes. Results are plotted in Figure 2. The reaction of **p(*t*Bu-MA-PFP)** with thiophenol in the absence of base reached a conversion of 35% after 22 h. In the presence of 1 equiv of triethylamine however, the reaction proceeded to 99% conversion after 69 min. The thio-sugar derivative 1-thio-β-D-glucose tetraacetate exhibited similar reactivity in the presence of triethylamine modifying 99% of PFP groups in 72 min. In contrast, the reaction with 1-octanethiol with triethylamine at 45 °C was the slowest reaction we observed reaching a conversion of only 28% after 24.5 h. Assuming that the reactive species in the thiol–*para*-fluoro substitution reaction is the thiolate, and that the slow reaction of 1-octanethiol was due to a higher pK_a of the aliphatic RS–H dissociation, we repeated a

reaction with the stronger base DBU instead of triethylamine. This reaction was complete (> 99% conversion) within 3 minutes at room temperature. In analogy to the (better documented) pK_a values of the homologous alcohol series, we expected secondary and tertiary thiols to be even less acidic and initially performed test reactions. We found homopolymer **p(*t*Bu-MA-PFP)** to be quantitatively modified after exposure to 1 equiv of the secondary thiol isopropanethiol in DMF at room temperature when analysed after 35 min. The tertiary reagent *tert*-butanethiol was indeed somewhat less reactive; a similar reaction with 1 equiv reached ~95% conversion after 35 min. However, employing 1.1 equiv. of *tert*-butanethiol, we found **p(*t*Bu-MA-PFP)** to be quantitatively converted to **p(*t*Bu-MA-*t*BuS)** after 45 min at room temperature. Reactions reaching completion with 1 (or for tertiary reagents 1.1) equiv of thiols in as little time as 3 min are, especially in consideration of the fairly bulky nature of the ester-amide side groups extremely fast and occur, to reiterate, on groups that are very robust during radical polymerization processes. While thiol–*para*-fluoro postpolymerization modifications of pPFSty are typically done with primary thiols, we here further expanded this efficient reaction to secondary and tertiary thiol reagents, signifying its versatility.

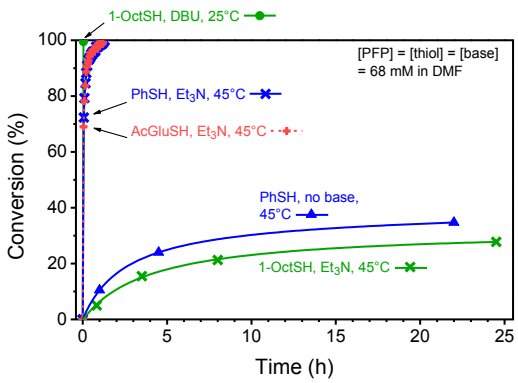
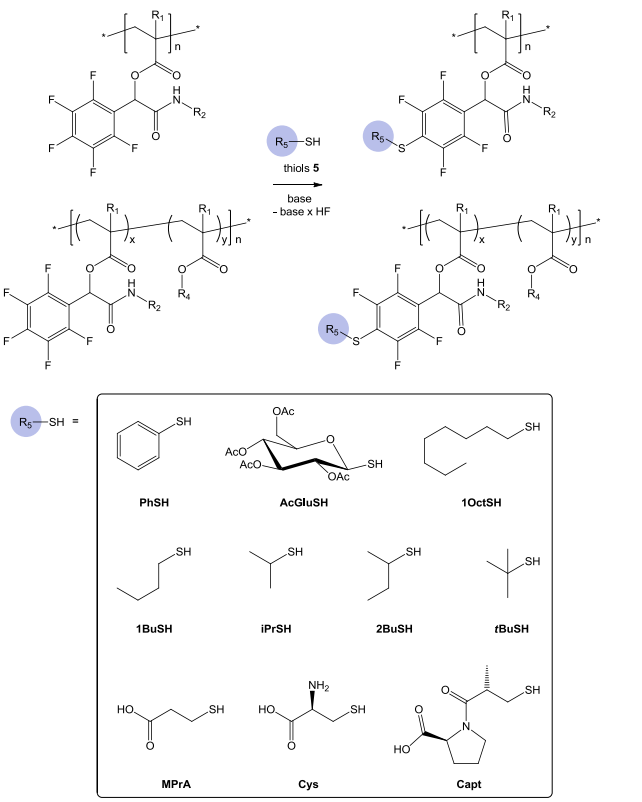


Figure 2. Kinetics of thiol–*para*-fluoro substitution reactions for different combinations of thiols (aromatic, glycosidic, aliphatic) and bases (none, triethylamine, DBU) at equimolar concentrations of PFP groups, thiols and base in DMF measured by ^{19}F NMR spectroscopy. Fitted curves are added to guide the eye

Subsequently, all PFP-functional homo- and copolymers were reacted with a range of functional thiols, see Scheme 3. The selection of thiols included the above-mentioned thiophenol, 1-thio-β-D-glucose tetraacetate, 1-octanethiol, isopropanethiol, and *tert*-butanethiol, and additionally 1-butanethiol and 2-butanethiol as further primary and secondary alkanethiols, as well as mercaptopropionic acid as a functional thiol and the amino acid L-cysteine and the enzyme inhibiting drug captopril as biologically relevant thiols. In order to assure complete conversion all reactions were done with 1.1 equiv of thiols in DMF—for 1.5 h at 45 °C for the aromatic and glycosidic thiols with triethylamine as base; for 30–45 min at room temperature for all other, aliphatic thiols. For these reaction parameters no differences in reactivity between homo- and copolymers or between (co)polymers with different amide residues were observed; complete modification was confirmed for all reactions by ^{19}F NMR spectroscopy prior to workup. Modified polymers were isolated either by precipitation into diethyl ether–hexane or by dialysis against methanol. Table 3 provides a summary of all reactions with employed thiols and base, product abbreviations, and SEC-measured molecular weight characteristics before and after thiol modification.



Scheme 3. Thiol–*para*-fluoro postpolymerization substitution reactions on PFP-functional homo- and copolymers with structures of employed 1°, 2°, and 3° thiols (AcGluSH = 1-thio-β-D-glucose tetraacetate; MPrA = mercaptopropionic acid, Cys = L-cysteine, Capt = captopril)

In all cases, well-defined thiol-modified homo- and copolymer products were obtained. Representative SEC traces are plotted in Figure 1; molecular weights and polydispersities of all reactions are compiled in Table 3. The thiol–*para*-fluoro substitution caused the SEC-measured size distributions to shift to higher or lower apparent molecular weights, without significant changes in width or shape, as to be expected for the quantitative modification of the repeat units. We also interpreted the well-defined unimodal SEC traces of thiol-modified products as evidence for the absence of side reactions, in particular such of thiols released from RAFT end groups. In this context, it is worth mentioning that a thiol modification reaction performed accidently with a shortage of thiol and an excess of DBU yielded a product with a higher polydispersity showing multiple overlapping higher apparent molecular weight peaks in an SEC measurement. This result was presumably due to base-mediated cleavage of RAFT

Table 3. Summary of Thiol–*p*-Fluoro Postpolymerization Modifications conducted in DMF with 1.1 equiv of Thiol (1.5 h at 45 °C for reactions with Et_3N; 30–45 min at RT for reactions with DBU). Complete Substitution was Confirmed for all Reactions by ^{19}F NMR spectroscopy.

Entry	PFP-functional Precursor			Thiol	Base	Thiol-modified Product			
	Code	$M_n^{SEC,a}$ (kg/mol)	$Đ_M^{SEC,a}$			Code	$M_n^{theor.,b}$ (kg/mol)	$M_n^{SEC,a}$ (kg/mol)	$Đ_M^{SEC,a}$
1	p(*t*Bu-MA-PFP)	46.8	1.19	PhSH	Et_3N	p(*t*Bu-MA-PhS)	29.9	43.9	1.20
2				AcGluSH	Et_3N	p(*t*Bu-MA-AcGluS)	60.1	65.1	1.12
3				1BuSH	DBU	p(*t*Bu-MA-1BuS)	28.6	56.5	1.20
4				1OctSH	DBU	p(*t*Bu-MA-1OctS)	32.3	n.d.	n.d.
5				iPrSH	DBU	p(*t*Bu-MA-iPrS)	27.7	55.6	1.19
6				*t*BuSH	DBU	p(*t*Bu-MA-*t*BuS)	28.6	56.4	1.19
7				Capt	DBU	p(*t*Bu-MA-Capt)	37.0	103.3	1.16
8	p(*t*Bu-MA-$PFP_{0.40}$-*co*-*t*$BuMA_{0.60}$)	36.0	1.18	PhSH	Et_3N	p(*t*Bu-MA-$PhS_{0.40}$-*co*-*t*$BuMA_{0.60}$)	17.9	59.6	1.22
9				AcGluSH	Et_3N	p(*t*Bu-MA-$AcGluS_{0.40}$-*co*-*t*$BuMA_{0.60}$)	30.2	54.7	1.20
10	p(cHex-MA-PFP)	27.6	1.19	PhSH	Et_3N	p(cHex-MA-PhS)	43.3	32.6	1.21
11				AcGluSH	Et_3N	p(cHex-MA-AcGluS)	84.6	50.4	1.16
12				2BuSH	DBU	p(cHex-MA-2BuS)	41.5	56.1	1.19
13				Cys	DBU	p(cHex-MA-Cys)	44.3	30.2	1.16
14	p(cHex-MA-$PFP_{0.73}$-*co*-$MMA_{0.27}$)	10.1	1.12	AcGluSH	Et_3N	p(cHex-MA-$AcGluS_{0.73}$-*co*-$MMA_{0.27}$)	69.2	20.5	1.11
15	p(iPr-MA-PFP)	17.0	1.12	iPrSH	DBU	p(iPr-MA-iPrS)	40.2	27.6	1.15
16				MPrA	DBU	p(iPr-MA-MPrA)	43.2	110.4	1.18
17	p(iPr-MA-$PFP_{0.41}$-*co*-$MMA_{0.59}$)	16.9	1.12	PhSH	Et_3N	p(iPr-MA-$PhS_{0.41}$-*co*-$MMA_{0.59}$)	23.2	20.7	1.11
18	p(EE-MA-PFP)	16.4	1.16	PhSH	Et_3N	p(EE-MA-PhS)	44.9	20.9	1.13
19				AcGluSH	Et_3N	p(EE-MA-AcGluS)	87.5	29.1	1.12
20	p(EE-MA-$PFP_{0.54}$-*co*-$MMA_{0.46}$)	12.8	1.16	PhSH	Et_3N	p(EE-MA-$PhS_{0.54}$-*co*-$MMA_{0.46}$)	29.0	17.4	1.10
21				AcGluSH	Et_3N	p(EE-MA-$AcGluS_{0.54}$-*co*-$MMA_{0.46}$)	52.3	23.3	1.10
22	p(cHex-A-PFP)	12.2	1.23	AcGluSH	Et_3N	p(cHex-A-AcGluS)	62.9	26.8	1.18
23				2BuSH	DBU	p(cHex-A-2BuS)	30.4	33.0	1.21
24	p(cHex-A-$PFP_{0.31}$-*co*-$PEGA_{0.69}$)	31.0	1.36	PhSH	Et_3N	p(cHex-A-$PhS_{0.31}$-*co*-$PEGA_{0.69}$)	37.6	30.3	1.33
25				AcGluSH	Et_3N	p(cHex-A-$AcGluS_{0.31}$-*co*-$PEGA_{0.69}$)	48.9	31.5	1.33
26	p(cHex-A-$PFP_{0.45}$-co-$NIPAM_{0.55}$)	34.2	1.26	PhSH	Et_3N	p(cHex-A-$PhS_{0.45}$-*co*-$NIPAM_{0.55}$)	12.4	26.0	1.30

[a] determined by size exclusion chromatography in DMAc; [b] calculated from conversion and composition

thiocarbonylthio end groups producing terminal thiols[4] which would cause crosslinking by reacting with remaining PFP groups of other polymer chains. When modifications were performed under the above-described conditions, however, no such side reactions were observed. The shift of apparent molecular weights measured by SEC with thiol–*para*-fluoro modification depended on the type of (co)polymer used. For example, while introduction of the sugar derivative caused all (co)polymers to shift to higher apparent molecular weights, polymers modified with thiophenol had either higher or lower apparent molecular weights compared to their PFP-functional precursors, depending on the chemical nature of the *N*-functional amide group. This observation highlighted again the influence of the isocyanide component on the physical behaviour of the derived functional materials.

Product (co)polymers were further characterized by ^1H and ^{19}F NMR spectroscopy, representative examples are shown in Figures 3 and 4. For the ^1H NMR spectra of **p(cHex-A-AcGluS)** as an acrylate example (shown in Figure 3A) and **p(iPr-MA-iPrS)** as a methacrylate example (shown in Figure 3B) integration of relevant signals indicated quantitative introduction of the respective sugar and isopropyl groups. The ^{19}F NMR spectra of **p(cHex-A-PFP)** and its sugar-modified sister polymer **p(cHex-A-AcGluS)**, shown in Figure 4, showed the complete disappearance of the *para*-F resonance at δ = −152.5 ppm, a shift of the *meta* fluorine signals from δ =

−161.6 ppm to −131.8 ppm, and a less pronounced shift of the *ortho* fluorine peaks from δ = −140.6 ppm to −140.1 ppm, likewise indicating quantitative thiol–*para*-fluoro modification.

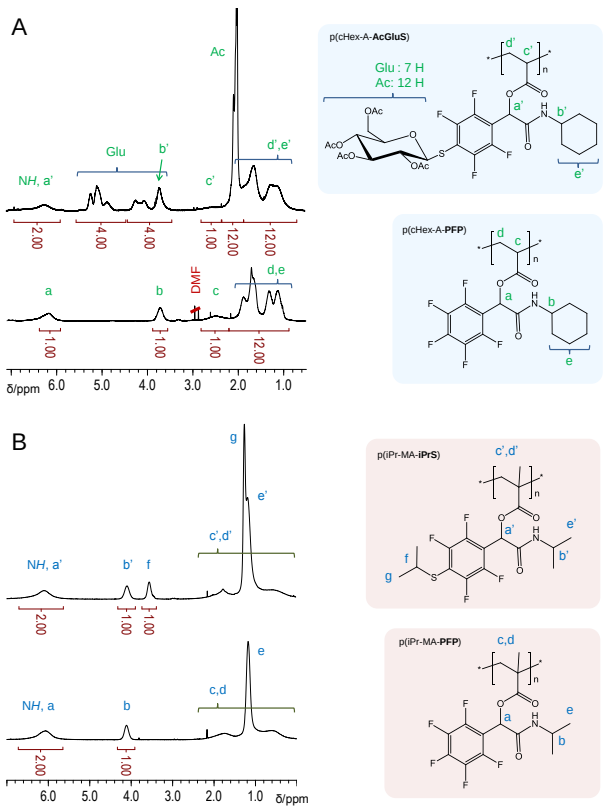


Figure 3. Exemplary ^{1}H NMR spectra of PFP-functional precursors (bottom spectra) and thiol-modified products (top spectra) for the modification of (A) p(cHex-A-PFP) with a thio-glucose derivative and (B) p(iPr-MA-PFP) with isopropanethiol with peak assignments showing well-defined, quantitatively converted polymers

Smart / Doubly Reactive Copolymers

Finally, we highlighted the versatility of thiol-reactive (meth)acrylate monomers in the examples of two acrylic copolymers. Firstly, **p(cHex-A-PFP$_{0.31}$-co-PEGA$_{0.69}$)** containing 69 mol% of the thermoresponsive PEG-based comonomer showed lower critical solution temperature (LCST) behaviour in water, i.e. insolubility above a critical temperature. An aqueous solution of the reactive precursor with a concentration of 10 g/L exhibited a phase transition upon heating with a sharp decrease of optical transmittance (occurring over a range of ~1.2 °C) with a measured cloud point (50% transmittance), T_{CP}, of 68.9 °C, see Figure 5. After thiol–*para*-fluoro substitution using thiophenol the cloud point shifted to T_{CP}, = 70.1 °C suggesting a slightly higher water solubility of the resulting copolymer **p(cHex-A-PhS$_{0.31}$-co-PEGA$_{0.69}$)**. Interestingly, however, the transition for this modified species was markedly broader occurring over a range of ~9 °C, and starting at ~66°C, below that of its reactive precursor suggesting a potentially different mechanism during the dehydration of the 2,3,5,6-tetrafluoro-4-(phenylthio)phenyl derivative compared to the pentafluorophenyl parent species. A sample modified with the sugar derivative AcGluSH, **p(cHex-A-AcGluS$_{0.31}$-co-PEGA$_{0.69}$)**, exhibited a similarly broad phase transition with a measured T_{CP} of 64.1 °C, suggesting that this copolymer was less water soluble. These two instances of tuning an aqueous thermal response by means of thiol–*para*-fluoro substitution show the potential for the development of novel smart thiol-responsive materials beyond the scope of the current work.

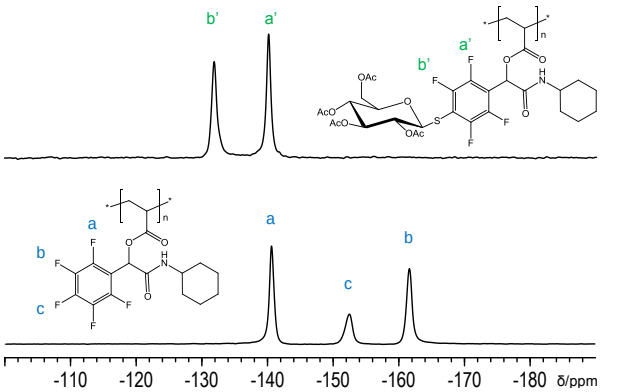


Figure 4. Representative example of ^{19}F NMR spectra of a PFP-functional precursor (bottom) and after thiol–*para*-fluoro substitution (top) with peak assignments showing the complete disappearance of the *para* resonance (marked c) and downfield shift of the *meta* fluorines (marked b, b')

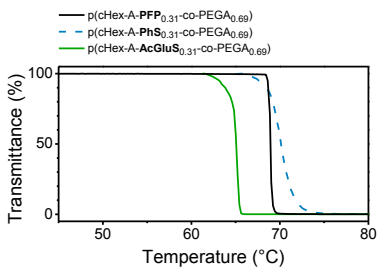


Figure 5. Transmittance vs. temperature for a **cHex-A-PFP**–PEGA copolymer in water showing LCST behaviour and transition temperature shifts through thiol–*para*-fluoro substitution reactions

Secondly, we prepared copolymer **p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$)** which contained, in addition to the thiol-reactive Passerini-made monomer **cHex-A-PFP**, the active ester comonomer pentafluorophenyl acrylate which undergoes acyl-substitution reactions with amines, see entry 16 in Table 2. The copolymer showed the characteristic resonances of the two different PFP groups in a ^{19}F NMR spectroscopic measurement with overlapping of the *meta* signals, but clearly distinguishable *ortho* and *para* peaks, see top spectrum in Figure 6 with assignments. In a first step, **p(cHex-A-PFP$_{0.45}$-*co*-PFPA$_{0.55}$)** was reacted with an excess of isopropylamine at room temperature converting the PFPA repeat units to *N*-isopropylacrylamide (NIPAM) segments. After removal of the pentafluorophenol leaving group ^{19}F NMR spectroscopy showed a complete disappearance of the PFP ester signals suggesting complete conversion, unchanged signals of the thiol-

reactive PFP units, and no evidence of modification of the Passerini-made repeat units with amines, see middle spectrum in Figure 6. Subsequently, the resulting copolymer **p(cHex-A-PFP$_{0.45}$-co-NIPAM$_{0.55}$)** was modified with thiophenol as described above (see also entry 26 in Table 3), which resulted in the expected *para*-F resonance disappearance and pronounced *meta*-F shift in a ^{19}F NMR spectroscopic measurement, see bottom spectrum in Figure 6. SEC curves of the double-reactive precursor and after each modification with isopropylamine and thiophenol are plotted in Figure 1F showing a shift of apparent molecular weight with each step without strong changes in peak width or shape, as to be expected for quantitative postpolymerization modification. These experiments demonstrate selective reactivity of the (non-ester) PFP groups towards thiols under the employed reaction conditions with no observable reaction occurring with amines, and the resulting orthogonality of the two different PFP-functional acrylate repeat units. The addition of the set of Passerini-made thiol-reactive species to the extensive family of (meth)acrylic monomers can thus be expected to widen the horizon of robust, efficient, and orthogonal conjugation chemistries in the design of multifunctional tailored materials.

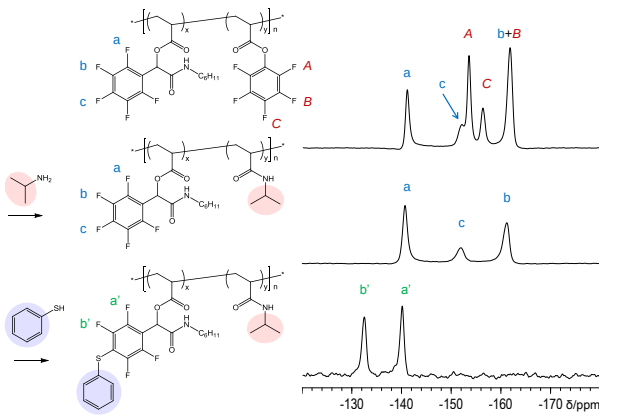


Figure 6. Double postpolymerization modification of a copolymer bearing thiol-reactive PFP groups and amine-reactive PFP esters with ^{19}F NMR spectroscopic evidence of selective and orthogonal functionalization

Conclusions

Novel acrylate and methacrylate monomers containing pentafluorophenyl groups amenable to nucleophilic aromatic substitution reactions with thiols were prepared by the Passerini reaction of 2,3,4,5,6-pentafluorobenzaldehyde, acrylic or methacrylic acid, and various isocyanides. These one-step reactions of commercially available starting materials gave excellent isolated yields in water at room temperature. Superior, in this regard, to common unsaturated thiol-reactive groups, the PFP functionality is compatible with radical polymerization processes, as substantiated here in the synthesis of well-defined PFP-functional homo- and copolymers by the RAFT technique. Thiol-reactive homopolymers were soluble in many organic solvents of medium polarity including, for most species, ethanol. Conditions for thiol–*para*-fluoro substitution reactions with a variety of thiols, including secondary and tertiary species, were optimized; fast and efficient conversion depended on the addition of base capable of forming thiolates, as, for example, in the quantitative thiol–*para*-fluoro reaction of 1 equiv of primary alkanethiol in less than 3 minutes at room temperature in the presence of DBU. This series of multicomponent reaction-made monomers combines the reactivity, selectivity, and robustness of PFP *para*-fluoro chemistry (as known for pentafluorostyrene (co)polymers) with the versatility and diversity of the (meth)acrylic family of monomers. In two brief examples of the manifold opportunities these monomers offer beyond the scope of this initial study, thermoresponsive copolymers and doubly reactive copolymers allowing for orthogonal modification were presented.

Acknowledgements

The authors acknowledge Ms. Sonja Schmidt and Mr. Joseph Tannous for synthetic assistance. The Mark Wainwright Analytical Centre is acknowledged for performing mass spectrometry experiments. P.J.R. acknowledges the Australian Research Council (ARC) for funding through a Discovery Early Career Researcher Award (DE120101547).

Notes and references

[a] Centre for Advanced Macromolecular Design (CAMD), School of Chemical Engineering, University of New South Wales, UNSW Sydney NSW 2052, Australia

‡ These authors contributed equally.

† Electronic Supplementary Information (ESI) available: ^{1}H, ^{13}C, and ^{19}F NMR spectra of all monomers.. See DOI: 10.1039/b000000x/

1. N. t. Brummelhuis and H. Schlaad, in *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, Ltd, 2012.
2. C. E. Hoyle, A. B. Lowe and C. N. Bowman, *Chem. Soc. Rev.*, 2010, **39**, 1355-1387.
3. A. B. Lowe and C. N. Bowman, *Thiol-X Chemistries in Polymer and Materials Science*, The Royal Society of Chemistry, Cambridge, UK, 2013.
4. P. J. Roth, C. Boyer, A. B. Lowe and T. P. Davis, *Macromol. Rapid Commun.*, 2011, **32**, 1123-1143.
5. P. Espeel and F. E. Du Prez, *Eur. Polym. J.* (http://dx.doi.org/10.1016/j.eurpolymj.2014.07.008)
6. M. T. Gokmen, J. Brassinne, R. A. Prasath and F. E. Du Prez, *Chem. Commun.*, 2011, **47**, 4652-4654.
7. A. Musa, B. Kiskan and Y. Yagci, *Polymer*. (http://dx.doi.org/10.1016/j.polymer.2014.06.076)
8. L.-T. T. Nguyen, M. T. Gokmen and F. E. Du Prez, *Polym. Chem.*, 2013, **4**, 5527-5536.
9. A. Dondoni, *Angew. Chem. Int. Ed.*, 2008, **47**, 8995-8997.
10. A. Dondoni and A. Marra, *Chem. Soc. Rev.*, 2012, **41**, 573-586.
11. C. Hoyle and C. Bowman, *Angew. Chem. Int. Ed.*, 2010, **49**, 1540-1573.
12. M. J. Kade, D. J. Burke and C. J. Hawker, *J. Polym. Sci. Pol. Chem.*, 2010, **48**, 743-750.
13. A. B. Lowe, *Polym. Chem.*, 2010, **1**, 17-36.
14. A. B. Lowe, *Polym. Chem.*, 2014. DOI: 10.1039/c4py00339j
15. A. B. Lowe, C. E. Hoyle and C. N. Bowman, *J. Mater. Chem.*, 2010, **20**, 4745-4750..

16. H. Durmaz, A. Sanyal, G. Hizal and U. Tunca, *Polym. Chem.*, 2012, **3**, 825-835.
17. K. A. Günay, P. Theato and H.-A. Klok, *J. Polym. Sci. Pol. Chem.*, 2013, **51**, 1-28.
18. K. A. Günay, P. Theato and H.-A. Klok, in *Functional Polymers by Post-Polymerization Modification*, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 1-44.
19. R. Kakuchi and P. Theato, in *Functional Polymers by Post-Polymerization Modification*, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 45-64.
20. G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2012, **65**, 985-1076.
21. G. B. H. Chua, P. J. Roth, H. T. T. Duong, T. P. Davis and A. B. Lowe, *Macromolecules*, 2012, **45**, 1362-1374.
22. F. D. Jochum and P. Theato, *Chem. Commun.*, 2010, **46**, 6717-6719.
23. P. Schattling, F. D. Jochum and P. Theato, *Chem. Commun.*, 2011, **47**, 8859-8861.
24. P. Schattling, F. D. Jochum and P. Theato, *Polym. Chem.*, 2014, **5**, 25-36.
25. P. J. Roth, *Macromol. Chem. Phys.*, 2014, **215**, 825-838.
26. P. A. Woodfield, Y. C. Zhu, Y. W. Pei and P. J. Roth, *Macromolecules*, 2014, **47**, 750-762.
27. Y. Zhu, A. B. Lowe and P. J. Roth, *Polymer*, 2014, **55**, 4425-4431.
28. Y. Zhu, J. Y. Quek, A. B. Lowe and P. J. Roth, *Macromolecules*, 2013, **46**, 6475-6484.
29. J. Y. Quek, Y. Zhu, P. J. Roth, T. P. Davis and A. B. Lowe, *Macromolecules*, 2013, **46**, 7290-7302.
30. J. Y. Quek, P. J. Roth, R. A. Evans, T. P. Davis and A. B. Lowe, *J. Polym. Sci. Pol. Chem.*, 2013, **51**, 394-404.
31. P. J. Roth, J. Y. Quek, Y. Zhu, B. M. Blunden and A. B. Lowe, *Chem. Commun.*, 2014, **50**, 9561-9564.
32. J. D. Flores, J. Shin, C. E. Hoyle and C. L. McCormick, *Polym. Chem.*, 2010, **1**, 213-220.
33. S. Ghosh, S. Basu and S. Thayumanavan, *Macromolecules*, 2006, **39**, 5595-5597.
34. Z. Jia, J. Liu, T. P. Davis and V. Bulmus, *Polymer*, 2009, **50**, 5928-5932.
35. N. K. Singha and H. Schlaad, in *Functional Polymers by Post-Polymerization Modification*, Wiley-VCH Verlag GmbH & Co. KGaA, 2012, pp. 65-86.
36. M. H. Stenzel, in *Thiol-X Chemistries in Polymer and Materials Science*, The Royal Society of Chemistry, 2013, pp. 236-258.
37. W. Zhang, W. Zhang, Z. Zhang, J. Zhu and X. Zhu, *Macromol. Rapid Commun.*, 2010, **31**, 1354-1358.
38. J. Ma, C. Cheng, G. Sun and K. L. Wooley, *Macromolecules*, 2008, **41**, 9080-9089.
39. J. Ma, C. Cheng and K. L. Wooley, *Aust. J. Chem.*, 2009, **62**, 1507-1519.
40. L. M. Campos, K. L. Killops, R. Sakai, J. M. J. Paulusse, D. Damiron, E. Drockenmuller, B. W. Messmore and C. J. Hawker, *Macromolecules*, 2008, **41**, 7063-7070.
41. F. Heatley, P. A. Lovell and J. McDonald, *Eur. Polym. J.*, 1993, **29**, 255-268.
42. G. Chen, S. Amajjahe and M. H. Stenzel, *Chem. Commun.*, 2009, 1198-1200.
43. B. M. Rosen, G. Lligadas, C. Hahn and V. Percec, *J. Polym. Sci. Pol. Chem.*, 2009, **47**, 3931-3939.
44. J. Xu, L. Tao, C. Boyer, A. B. Lowe and T. P. Davis, *Macromolecules*, 2009, **43**, 20-24.
45. P. Battioni, O. Brigaud, H. Desvaux, D. Mansuy and T. G. Traylor, *Tetrahedron Lett.*, 1991, **32**, 2893-2896.
46. R. D. Chambers, D. Close and D. L. H. Williams, *J. Chem. Soc. Perk. T. 2*, 1980, 778-780.
47. V. Atanasov, M. Bürger, S. Lyonnard, L. Porcar and J. Kerres, *Solid State Ionics*, 2013, **252**, 75-83.
48. K. Babiuch, C. R. Becer, M. Gottschaldt, J. T. Delaney, J. Weisser, B. Beer, R. Wyrwa, M. Schnabelrauch and U. S. Schubert, *Macromol. Biosci.*, 2011, **11**, 535-548.
49. C. R. Becer, K. Babiuch, D. Pilz, S. Hornig, T. Heinze, M. Gottschaldt and U. S. Schubert, *Macromolecules*, 2009, **42**, 2387-2394.
50. A. S. de Leon, A. d. Campo, C. Labrugere, M. Fernandez-Garcia, A. Munoz-Bonilla and J. Rodriguez-Hernandez, *Polym. Chem.*, 2013, **4**, 4024-4032.
51. M. Riedel, J. Stadermann, H. Komber, F. Simon and B. Voit, *Eur. Polym. J.*, 2011, **47**, 675-684.
52. D. Gan, A. Mueller and K. L. Wooley, *J. Polym. Sci. Pol. Chem.*, 2003, **41**, 3531-3540.
53. C. Ott, R. Hoogenboom and U. S. Schubert, *Chem. Commun.*, 2008, 3516-3518.
54. C. Ott, C. Ulbricht, R. Hoogenboom and U. S. Schubert, *Macromol. Rapid Commun.*, 2012, **33**, 556-561.
55. W. A. Pryor and T.-L. Huang, *Macromolecules*, 1969, **2**, 70-77.
56. S. Schmidt, M. Koldevitz, J.-M. Noy and P. J. Roth, *Polym. Chem.* , 2014, *accepted*, DOI: 10.1039/C1034PY01147C
57. A. Sehlinger, O. Kreye and M. A. R. Meier, *Macromolecules*, 2013, **46**, 6031-6037.
58. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168-3210.
59. R. Kakuchi and P. Theato, *ACS Macro Lett.*, 2013, **2**, 419-422.
60. R. Kakuchi, *Angew. Chem. Int. Ed.*, 2014, **53**, 46-48.
61. J. G. Rudick, *J. Polym. Sci. Pol. Chem.*, 2013, **51**, 3985-3991.
62. P. J. Roth, M. Collin and C. Boyer, *Soft Matter*, 2013, **9**, 1825-1834.