Title

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Reversible Crosslinking of Polymers bearing Pendant or Terminal Thiol Groups Prepared by Nitroxide-Mediated Radical Polymerization

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Abstract

Monomers or *N*-alkoxyamine initiators containing protected thiol groups are utilized to prepare polymers via nitroxide-mediated radical polymerization. Following thiol deprotection, the macromolecular properties of these polymers are manipulated, by adjusting the redox conditions to either form or cleave disulfide bonds, or irreversibly cap free thiols by the rapid addition to a maleimide Michael acceptor. Formation of disulfide bonds under dilute conditions results in intramolecular disulfide formation, resulting in internal polymer collapse. Alternatively, disulfide formation under high concentration results in intermolecular crosslinking of polymers to form networked macromolecular assemblies.

Keywords: Disulfide, Thiol, Nitroxide-mediated free radical polymerization, Reversible, Crosslink

1. Introduction

Disulfide crosslinking of polymers is a ubiquitous theme in the macromolecular world. Functional proteins utilize strategic cysteine-based disulfides to lock in critical tertiary structure, whereas disulfide linkages in structural proteins such as α-keratin control the attributes of straight or curly hair. Vulcanization of natural and synthetic rubber imparts rigidity via di, tri and higher order sulfide cross-linkages. Using conventional

(uncontrolled) free radical polymerization, a number of synthetic polymers containing disulfide crosslinks have been prepared. For example, crosslinked polyacrylamide hydrogels have been prepared by polymerization of acrylamides mixed with acrylamide-disulfide crosslinking agents [1]. Cysteine-functionalized polymethacrylamide formed an insoluble crosslinked material [2]. Polyvinylidene fluoride containing pendant protected thiol side groups was vulcanized by deprotection to the free thiols and cured with 1,5-hexadiene [3]. Uncontrolled free radical polymerization of substituted styrenes with and without pre-formed disulfide crosslinkers formed extensively cross-linked networks, in which the reversibility of disulfide formation was examined as a function of proximal cooperativity or site isolation [4]. Emulsion copolymerization of styrenes with vinylbenzyl *S*-thioacetate gave thiol-substituted microgels: disulfide crosslinks were avoided by the use of reducing agents during deprotection of the thiol groups, although undesired cross-linking was observed under bulk polymerization conditions [5]. Free radical polymerization of acrylates bearing acetate-protected thiol sidechains followed by amine deprotection and Michael trapping has been demonstrated [6]. Using cationic polymerization, gelation of disulfide crosslinked polyoxazoline was studied: reductive cleavage returned the material to a soluble polymer [7]. In the self-assembly of liposomes, thiol-substituted phosphatidylcholine species formed bilayer vesicles that could be crosslinked reversibly under redox control [8]. Rotaxanes with cleavable disulfide spindles [9] have been developed, and dynamic disulfide exchange has been studied in the formation of supramolecular hydrogen bonded systems [10]. Thus disulfides are effective and reversible crosslinking agents [11]. However thiol groups are incompatible with free radical polymerization, as they act as chain transfer agents, rapidly donating a hydrogen atom to carbon radicals with rate constants typically on the order of 10^7 to 10^8 M^{-1} s^{-1} [12]. Thus protected thiols or disulfides

must be utilized when carrying out radical polymerization. A number of groups have investigated the use of thiol crosslinking following ATRP (Atom Transfer Radical Polymerization) [13-19] or RAFT (Reversible Addition Fragmentation Transfer) polymerization [20-28]. There is one report of the conversion of polymers prepared by Nitroxide-Mediated Radical Polymerization (NMRP) [29] to RAFT, followed by thiol crosslinking [30]. However, there are two papers utilizing this strategy in manipulating polymers prepared by NMRP: earlier work by our group employing a thiol-terminated polymer [31], and a paper utilizing NMRP or RAFT of thiolactone-substituted styrenes [32]. In addition to applications in preparing reversible crosslinks, thiols and disulfides form bonds to metal surfaces such as gold, silver, and CdSe and related quantum dots. Thiols are have also become popular in appending groups to organic molecules utilizing the thiol-ene [33] and thiol-yne [34] “click” reactions to unactivated terminal olefins.

In this work, vinyl monomers containing protected thiol groups were prepared and subjected to NMRP mixed with non-thiolated monomers, followed by deprotection of the thiols to provide polymer chains with intermittent pendant thiol groups (Scheme 1).

Scheme 1.

Alkoxyamine initiators bearing protected thiols were also prepared. Polymerization, followed by deprotection, yielded thiol-terminated polymer chains (Scheme 2). The redox control of polymers bearing pendant thiols or a terminal thiol was adjusted by oxidation to form disulfides, or reduction to cleave the disulfides. Thus the macromolecular properties can be manipulated following polymerization.

Scheme 2.

2. Experimental

2.1. Materials and Instrumentation

Styrene (99%, Acros Organics) and *t*-butyl acrylate (98%, Aldrich) were distilled under vacuum immediately before use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Acetonitrile, dichloromethane, methanol and toluene were obtained from a PureSolv solvent purification system (SPS) manufactured by Innovative Technologies, Inc. when anhydrous conditions were required. All other solvents were used as received. Water was deionized. Manganese(salen) catalyst was prepared following the procedure of Choudary [35]. All other reagents were used without further purification. The following reagents were purchased from Sigma-Aldrich: *tert*-butyldimethylsilyl chloride (TBDMS) (97%), DL-dithiothreitol (DTT) (99%), *N*-phenylmaleimide (97%), acryloyl chloride (96%), and acrylic acid. The following reagents were purchased from Acros Organics: L-cysteine methyl ester hydrochloride (98%), 4-vinylbenzyl chloride (90%, tech.), thiourea (reagent grade, ACS), sodium hydride (60% dispersion in mineral oil), copper chloride (99%), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (98+%), and *N*,*N*'-dicyclohexyl dicyclocarbodiimide (DCC) (99%). The following reagents were purchased from Fisher Scientific: sodium hydroxide (ACS certified), trifluoroacetic acid (reagent grade), sodium borohydride (98%), and triethylamine. Trityl chloride was purchased from EMD. Tri*iso*propylsilane was purchased from Oakwood Products, Inc. Granular copper (20-30 mesh) was purchased from J. T. Baker. Flash chromatography was performed using EM Science Silica Gel 60. Analytical TLC was performed using commercial Whatman plates coated with silica gel (0.25 mm thick). PAA TLC stain was made from a mixture of ethanol (37.5 mL), concentrated sulfuric acid (2.08 mL),

glacial acidic acid (0.427 mL), and *p*-anisaldehyde (2.5 mL). Polymerizations were carried out in sealed ampoules under argon. NMR spectra were recorded at ambient temperature in $CDCl_3$ or CD_3OD on either a Varian UNITY plus 500 MHz or INOVA 600 MHz spectrometer as noted. Size exclusion chromatography (SEC) was performed using a Waters apparatus equipped with five Styragel columns (300 x 4.6 mm, 5 □m bead size), HR 0.5 (pore size 50 Å, 0-1000 Da), HR 1 (pore size 100 Å, 100-5000 Da), HR 2 (pore size 500 Å, 500-20,000 Da), HR 4 (pore size 10,000 Å, 50-1000,000 Da), HR 5E (linear bed, mixed pore sizes, 2000-4 x 10^6 Da). Tetrahydrofuran (THF) was used as the eluent at a flow rate of 0.35 mL/min at ambient temperature. A refractive index detector was used, and the molecular weights were calibrated against seven polystyrene standards ranging from 2000 to 156,000 Da. SEC traces are shown with absorbance on the y-axis, and minutes on the x-axis.

2.2. Synthesis and characterization of monomers and initiators

2.2.1. Synthesis of 2-(4-vinyl-benzyl) *iso*thiourea hydrochloride [36] (**1**)

Thiourea (3.517 g, 46.20 mmol) was dissolved in methanol (15 mL) in a flask containing 4-vinylbenzyl chloride (7.077 g, 46.37 mmol). The reaction was heated at 60 °C overnight. Upon cooling, diethyl ether was added to the reaction mixture until a constant turbidity was observed; this solution was left in the freezer overnight. The next day, the *iso*thiouronium salt was filtered, and rinsed with diethyl ether to give 9.728 g (92% yield) of the title product as a white powder. ^{1}H NMR (600 MHz, CD_3OD): δ 7.45 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 6.74 (dd, 1H, *J* = 17.4, 10.8 Hz), 5.81 (dd, 1H, *J* = 17.4, 0.6 Hz), 5.27 (dd, 1H, *J* = 10.8, 0.6 Hz), 4.42 (s, 2H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ□172.2, 139.4, 137.5, 134.8, 130.6, 127.9, 115.2, 36.3 ppm.

2.2.2. Synthesis of 4-vinyl-phenyl methanethiol [37] (**2**)

Following a modified procedure from Yamaguchi [37], 2-(4-vinyl-benzyl) *iso*thiourea hydrochloride **1** (3.000 g, 13.12 mmol) was dissolved in DMF (5 mL). This system was purged with N_2 before adding 2 N NaOH (19.8 mL); a white precipitate formed immediately. The solution was stirred at room temperature under N_2 for 2 hours. To this was added 2 N HCl (19.8 mL) and the solution was stirred for 5 minutes. Ether (20 mL) was added and the solution was washed with H_2O (4 X 60 mL) and brine (1 X 60 mL), and then dried over $MgSO_4$. The solid was removed by filtration and the volatiles were removed in vacuo to afford 1.601 g (10.66 mmol, 91%) of a yellow oil which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 8.4 Hz), 6.73 (dd, 1H, *J* = 17.5, 10.5 Hz), 5.76 (dd, 1H, *J* = 17.5, 1.0 Hz), 5.26 (dd, 1H, *J* = 10.5, 1.0 Hz), 3.75 (d, 2H, *J* = 7.5 Hz), 1.77 (t, 1H, *J* = 7.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.9, 136.6, 129.7, 128.8, 126.6, 114.0, 28.9 ppm.

2.2.3. Synthesis of 1, 2-bis(4-vinyl-benzyl) disulfide [4] (**3**)

The synthesis began by adding 2N NaOH (5mL) to a solution of 4-vinyl-phenyl methanethiol (1.000 g, 4.372 mmol) in H_2O (9.9 mL). This solution was heated to 50 ^{o}C and air was bubbled through the reaction mixture overnight. The reaction was quenched with a saturated solution of NH_4Cl (5 mL) before being extracted with ether (3 X 20 mL). The solution was dried over $MgSO_4$, filtered and concentrated to give 503 mg (65%) of the desired product as a yellowish oil. IR: (neat) 1445, 759, 699, 638 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38-7.20 (m, 8H), 6.71 (dd, 1H, *J* = 17.4,

10.8 Hz), 5.75 (dd, 1H, *J* = 17.4, 2.4 Hz), 5.25 (dd, 1H, *J* = 10.8, 2.4 Hz), 3.63 (s, 1H) ppm. ^{13}C-NMR, DEPT (125 MHz, $CDCl_3$): δ 146.8 (C), 136.9 (C), 136.4 (CH), 129.6 (CH), 127.9 (CH), 127.2(CH), 126.4 (CH), 114.0 (CH_2), 43.1 (CH_2) ppm.

2.2.4. Synthesis of 4-*t*-butyldimethylsilylthiomethylstyrene (**4**)

Following a modified procedure from Yamaguchi [37], a solution of 60% NaH in mineral oil (611 mg, 15.3 mmol) and THF (20.4 mL) was cooled to 0 °C under N_2 before adding freshly prepared 4-vinyl-phenyl methanethiol. Effervescence was observed. This mixture was allowed to warm to room temperature before adding a solution of *t*-butyldimethylsilyl chloride (2.303 g, 15.28 mmol) in THF (14 mL). The reaction mixture was allowed to stir at room temperature under N_2 overnight. The THF was removed and the remaining oil was taken up in CH_2Cl_2 and washed with a 5% solution of NaOH (75 mL) followed by brine (75 mL). The combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a yellow oil. This crude product was run through a short chromatography column of silica using hexanes as the eluent to yield 1.497 g (56%) of the product as a colorless oil. R_f = 0.6 (hexanes:ethyl acetate, 20:1, UV, I_2, PAA). ^{1}H NMR (500 MHz, $CDCl_3$):): δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.69 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.77 (d, *J* = 17.5 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 2H), 0.97 (s, 9H), 0.26 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.51, 136.70, 136.37, 128.83, 126.51, 113.73, 30.61, 26.53, 19.21, -3.38 ppm.

2.2.5. Synthesis of (4-vinyl-benzyl)-trityl sulfide (**5**)

Following a modified literature procedure [38], to a solution of freshly prepared 4-vinyl-phenyl methanethiol (2.407 g, 16.02 mmol) in DMF (9.6 mL) was added trityl chloride (5.359 g, 19.23 mmol). This solution was stirred overnight. The next day, CH_2Cl_2 (50 mL) was added and the mixture was washed with H_2O (4 X 50 mL), brine (1 X 50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated to give a yellow solid. This was dissolved in a minimal amount of CH_2Cl_2 and recrystallized from diethyl ether to give 5.317 g (85%) of the title compound. Mp = 91-95 ^oC. IR ($CDCl_3$) 699 (S-C). R_f = 0.38 (hexanes:ethyl acetate, 20:1, UV, I_2, PAA). ^1H NMR (500 MHz, $CDCl_3$): δ 7.47-7.26 (m, 19H), 6.64 (dd, *J* = 14.5, 9.0 Hz, 1H), 5.68 (d, *J* = 14.5 Hz, 1H), 5.18 (d, *J* = 9.0 Hz, 1H), 3.30 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 136.6, 136.5, 136.5, 129.7, 129.3, 128.0, 126.8, 126.4, 113.7, 67.5, 36.8 ppm.

2.2.6. Synthesis of *S*-trityl-L-cysteine methyl ester hydrochloride (**6**)

Following the literature procedure [38], to a solution of L-cysteine methyl ester hydrochloride (300 mg, 1.76 mmol) in DMF (2 mL) was added trityl chloride (735 mg, 2.64 mmol). The reaction mixture was allowed to stir for three days at room temperature. An aqueous solution of 10% sodium acetate (10 mL) was added and a white precipitate formed. The sticky white mass was isolated by filtration. Column chromatography (hexanes:ethyl acetate, 1:1) afforded 653 mg (90%) of the title compound as a white solid. ^1H NMR (600 MHz, CD_3OD): δ 7.41 (d, *J* = 4.0 Hz, 6H), 7.27 (dd, *J* = 4.0, 4.0 Hz, 6H), 7.20 (t, *J* = 4.0 Hz, 3H) 3.65 (s, 3H), 3.14 (dd, *J* = 5.4, 5.4 Hz, 1H), 2.59 (dd, *J* = 6.6, 5.4 Hz, 1H), 2.49 (dd, *J* = 6.6, 5.4 Hz, 1H) ppm.

2.2.7. Synthesis of L-cysteine-*N*-acryl-*S*-(triphenylmethyl)-methyl ester (**7**)

Following the literature procedure [39], a flame-dried 250 mL round bottom flask was charged with dry methylene chloride (106 mL), S-trityl-L-cysteine methyl ester hydrochloride **6** (3.945 g, 9.530 mmol), acryloyl chloride (0.85 mL, 949 mg, 10.5 mmol), and triethylamine (2.80 mL, 2.02 g, 20.0 mmol). The solution was stirred at room temperature overnight. The reaction mixture was washed with water (1 x 100 mL). The aqueous layer was extracted with methylene chloride (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and then concentrated to give the title product in quantitative yield (4.336 g). ^{1}H NMR (500 MHz, CD_3OD): δ 7.39-7.20 (m, 15H), 6.28 (dd, J = 14.3, 1.0 Hz, 1H), 6.06 (dd, J = 14.3, 8.5 Hz, 1H), 5.67 (dd, J = 8.5, 1.0 Hz, 1H), 4.69 (ABX, J_{AX} = 4.6, J_{BX} = 3.9 Hz, 1H), 2.89 (ABX, J_{AB} = 10.5, J_{AX} = 4.6 Hz, 1H), 2.51 (ABX, J_{AB} = 10.5, J_{BX} = 3.9 Hz, 1H) ppm.

2.2.8. Synthesis of *N*-[1-(4-tritylthiomethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine (**8**)

Following a modified procedure of Hawker [40], 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO, 43 mg, 0.20 mmol) was dissolved in 2:3 v/v of toluene (0.70 mL) and ethanol (0.95 mL) followed by the addition of (4-vinyl-benzyl)-trityl sulfide (**5**, 150 mg, 0.38 mmol). Manganese(salen) catalyst [35] (17 mg, 0.048 mmol) was then added followed by sodium borohydride (23 mg, 0.61 mmol) and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated, combined with dichloromethane (10 mL), water (10 mL), and a few drops of 10% hydrochloric acid was added (until pH~7) to break the resulting emulsion. The aqueous layer was extracted with dichloromethane (3 $\times$ 10 mL). The combined organic layer was washed with saturated sodium bicarbonate (30 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 231 mg of a

brownish oil. The resulting oil was purified by silica gel column chromatography with 3:2 hexanes/dichloromethane to give 69 mg (58% yield) of the title product as a white solid, as a mixture of two diastereomers. TLC: 3:2 hexanes/dichloromethane, UV, *p*-anisaldehyde stain, R_f = 0.67. Melting point: 62-63 ^oC. IR: (neat) 2973, 1489, 1444, 1361, 1206, 1061, 740, 700 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, diastereomers): δ 7.50-7.07 (m, 40H), 4.87 (q+q, 2H, *J* = 6.6 Hz), 3.40 (d, 1H, *J* = 10.8 Hz), 3.33 (s, 2H), 3.29 (s, 2H), 3.29 (d, 1H, *J* = 10.8 Hz), 2.32 (m, 1H), 1.58 (d, 3H, *J* = 6.6 Hz), 1.51 (d, 3H, *J* = 6.6 Hz), 1.37 (m, 1H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.03 (s, 9H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.76 (s, 9H), 0.54 (d, 3H, *J* = 6.6 Hz), 0.22 (d, 3H, *J* = 6.6 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, two diastereomers): δ 144.8, 144.7, 143.9, 142.5, 142.4, 135.9, 135.2, 131.0, 131.0, 129.7, 128.9, 128.9, 128.0, 127.4, 127.3, 127.2, 126.8, 126.4, 126.3, 126.2, 83.2, 82.4, 72.1, 67.4, 60.5, 60.4, 59.3, 36.8, 36.8, 32.0, 31.6, 28.3, 28.2, 24.6, 23.1, 22.1, 21.9, 21.1, 21.0 ppm. HRMS: M+1 ($C_{42}H_{48}NOS^+$) 614.3451 calcd; 614.3436 obsd.

2.2.9. Synthesis of *N*-*tert*-Butyl-*O*-{1-[4-(4-{1-[*N*-*tert*-butyl-*N*-(2-methyl-1-phenyl-propyl)-aminooxy] ethyl}-benzyldisulfanylmethyl)-phenyl]-ethyl}-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine [31] (**9**)

Following a modified procedure of Hawker [40] 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO, 72 mg, 0.33 mmol) was dissolved in 2:3 v/v of toluene (0.45 mL) and ethanol (0.65 mL) followed by the addition of 4-vinyl benzyl disulfide (**3**, 38 mg, 0.13 mmol). Manganese(salen) catalyst [35] (11 mg, 0.030 mmol) was then added followed by sodium borohydride (22 mg, 0.58 mmol), and the reaction was allowed to stir open to the atmosphere overnight. The reaction mixture was concentrated, combined with dichloromethane (10 mL), water (10 mL), and a few

drops of 10% hydrochloric acid was added (until pH~7) to break the resulting emulsion. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with saturated sodium bicarbonate (30 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give 64 mg of a brownish oil. The resulting oil was purified by silica gel column chromatography with 3:2 hexane/dichloromethane to give 39 mg (41% yield) of the title product as a yellowish oil, as a mixture of diastereomers. TLC: 3:2 hexanes/dichloromethane, UV, *p*-anisaldehyde stain, R_f = 0.52. ^{1}H-NMR (600 MHz, $CDCl_3$, two diastereomers): δ 7.48-7.12 (m, 36H), 4.91 (q+q, 4H, *J* = 6.6 Hz), 3.68 (s, 4H), 3.57 (s, 2H), 3.56 (s, 2H), 3.42 (d, 1H, *J* = 10.8 Hz), 3.40 (d, 1H, *J* = 10.8 Hz), 3.31 (d, 1H, *J* = 10.8 Hz), 3.30 (d, 1H, *J* = 10.8 Hz), 2.34 (m, 2H), 1.62 (d, 3H, *J* = 6.6 Hz), 1.61 (d, 3H, *J* = 6.6 Hz), 1.54 (d, 3H, *J* = 6.6 Hz), 1.53 (d, 3H, *J* = 6.6 Hz), 1.40 (m, 2H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.30 (d, 3H, *J* = 6.6 Hz), 1.06 (s, 9H), 1.05 (s, 9H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 0.76 (s, 9H), 0.75 (s, 9H), 0.56 (d, 3H, *J* = 6.6 Hz), 0.55 (d, 3H, *J* = 6.6 Hz), 0.21 (d, 3H, *J* = 6.6 Hz), 0.20 (d, 3H, *J* = 6.6 Hz) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 145.2, 145.1, 144.3, 144.2, 142.4, 142.2, 136.3, 136.2, 135.8, 135.6, 131.0, 130.9, 129.2, 127.4, 127.2, 127.1, 126.3, 126.2, 126.1, 83.3, 82.5, 82.4, 72.2, 60.5, 60.4, 43.2, 43.1, 43.0, 32.1, 31.7, 28.4, 28.2, 24.8, 24.7, 23.3, 23.2, 22.2, 22.0, 21.2, 21.1 ppm.

2.2.10. Synthesis of *N*-*tert*-butyl-*O*-[1-(4-mercaptomethyl-phenyl)-ethyl]-*N*-(2-methyl-1-phenyl-propyl)-hydroxylamine [31] (**10**)

Following the procedure of Hill [31], disulfide initiator (**9**, 95 mg, 0.13 mmol) was dissolved in dimethylformamide (2 mL) followed by the addition of dithiothreitol (DTT, 41 mg, 0.27 mmol). The reaction flask was subjected to three freeze/pump/thaw

cycles to remove oxygen, and then stirred at 60 °C overnight under N_2. Upon cooling, the reaction mixture was taken up in dichloromethane (10 mL), washed five times with water (10 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 40 mg (85% yield) of the title product as a yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$, two diastereomers): δ 7.50-7.10 (m, 18H), 4.89 (q+q, 2H, *J* = 6.5 Hz), 3.75 (d, 2H, *J* = 7.5 Hz), 3.72 (d, 2H, *J* = 7.5 Hz), 3.41 (d, 1H, *J* = 10.5 Hz), 3.29 (d, 1H, *J* = 10.5 Hz), 2.30 (m, 1H), 1.74 (td, 2H, J_t = 7.5 Hz, J_d = 2.5 Hz), 1.60 (d, 3H, *J* = 6.5 Hz), 1.52 (d, 3H, *J* = 6.5 Hz), 1.40 (m, 1H), 1.29 (d, 3H, *J* = 6.5 Hz), 1.03 (s, 9H), 0.91 (d, 3H, *J* = 6.5 Hz), 0.77 (s, 9H), 0.52 (d, 3H, *J* = 6.5 Hz), 0.21 (d, 3H, *J* = 6.6 Hz) ppm.

2.3. Polymerization: the following procedure is representative: trityl-protected thiol terminated polystyrene (**P9**)

Following the procedure of Hawker [41], to a 5 mL ampule was added *N*-[1-(4-tritylthiomethyl-phenyl)-ethoxy]-*N*-*tert*-butyl-2-methyl-1-phenylpropan-1-amine (**8**, 25 mg, 0.040 mmol), and styrene monomer (913 mg, 8.77 mmol). The ampule was subjected to three freeze/pump/thaw cycles, sealed under argon and heated in an oil bath at 120 °C for 3.25 hours. After cooling, an aliquot was analyzed by ^{1}H NMR to determine the percent monomer conversion: 52%. The reaction mixture was dissolved in tetrahydrofuran, and methanol was added dropwise to precipitate a white polymer. The polymer was filtered and dried *in vacuo* to afford 480 mg (50% yield) of the title product as a white powder. The GPC trace showed M_n = 12700 amu, PDI = 1.08. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.2-6.9 (br, aromatic H), 6.7-6.3 (br, aromatic H), 2.0-1.7 (br, *PhC*<u>*H*</u>), 1.7-1.3 (br, *PhCHC*<u>H_2</u>) ppm.

2.4. Post-polymerization modification of polymers

2.4.1. Deprotection of thiotrityl terminated polymer (**P9**) and disulfide formation to form central disulfide polystyrene (**P10**)

Following the procedure of Wang [42], trityl-protected thiol terminated polystyrene (**P9**, 100 mg, 0.8 mmol) was dissolved in tetrahydrofuran (2 mL) followed by the addition of copper (I) chloride (22 mg, 0.22 mmol) and water (0.1 mL) as a co-solvent. The reaction was conducted under ultrasonic irradiation open to the atmosphere for 3 days. Tetrahydrofuran was added regularly to maintain the original volume; and the reaction flask was capped each night without ultrasonication. The reaction mixture was taken up in dichloromethane (5 mL) and water (5 mL), and then the aqueous layer was extracted with dichloromethane (2 $\times$ 5 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 89 mg of a yellowish powder as a mixture of starting material and product. The GPC trace showed M_n = 19900 amu, PDI = 1.23.

2.4.2. Disulfide cleavage of central disulfide polymer (**P10**) and trapping of the terminal thiol to prepare *N*-phenylmaleimide sulfide terminated polystyrene (**P11**)

Following the procedure of Hill [31], central disulfide polystyrene (**P10**, 26 mg, 0.0010 mmol) was dissolved in dimethylformamide (3 mL) followed by the addition of dithiothreitol (DTT, 25 mg, 0.16 mmol). The reaction flask was subjected to three freeze/pump/thaw cycles and then heated at 60 ^{o}C for 2 days. After cooling, *N*-phenylmaleimide (34 mg, 0.20 mmol) was added, and the reaction mixture was stirred for an additional 7 hours. The solution was taken up in tetrahydrofuran (1 mL), and methanol was added dropwise to precipitate a white polymer. The polymer was

collected by centrifugation to afford 15 mg of a white powder. The GPC trace showed M_n = 16600 amu, PDI = 1.24. There was a small shoulder of high molecular weight polymer in GPC trace, so the polymer was subjected to further reduction using the same conditions for 2 additional days. The resulting GPC trace showed no shoulder: M_n = 12800 amu, PDI = 1.10.

3. Results and discussion

3.1. Sulfur-containing monomers to provide pendant thiol functionality

3.1.1. Thiol-substituted styrene monomers

The first thiol-substituted monomer investigated was as styrene derivative, prepared from the vinyl benzyl chloride via the isothioruronium salt [43] **1** (Scheme 3). This polar salt was insoluble with styrene, however copolymerization with the alkoxyamine derived from TIPNO [41] was carried out using DMF as a co-solvent, with poor control over polydispersity at 9:1 or 1:1 styrene:isothioruronium salt **1** ratios. The isothioruronium salt was hydrolyzed to prepare the benzylic thiol **2** in excellent yield, which was reprotected using three different strategies. Mild oxidation of the sodium salt with air provided the disulfide **3**, whereas protection with tributyldimethylsilyl (TBDMS) or trityl gave the substituted styrene monomers **4** and **5** (Scheme 1). The tritylated vinyl monomer **5** was a stable, slightly yellow solid.

Scheme 3.

Copolymerizations of derivatives **4** and **5** with styrene (9:1 styrene:protected benzyl thiol derivative) were carried out at using 0.5% of the alkoxyamine initiator (Scheme 4). The trityl protected monomer gave rise to random copolymer **P2** with excellent control over polydispersity (M_n=20,800, PDI=1.15), whereas the TBDMS-protected monomer gave rise to random copolymer **P1** with a GPC trace showing a larger molecular weight shoulder, that

Scheme 4.

indicated a small amount of disulfide incorporated into each chain (M_n=14,600, PDI=1.44). For the clean tritylated random co-polymer **P2** (the GPC peak was symmetric, with no visible shoulders, Figure 1), the trityl group was removed by deprotection with trifluoroacetic acid [44] (TFA), followed by concentration, and precipitation upon addition of cold methanol. This material was then dissolved in THF, and basified by addition of aqueous sodium hydroxide while bubbling air through the sample to promote disulfide formation (**CAUTION: do not concentrate solution in case of peroxide formation**). The resulting GPC trace of **P3** (Figure 1) illustrates the formation of large cross-linked networks, probably formed during concentration of the free thiol in the presence of air, however a significant amount of uncrosslinked polymer (presumably **P2**) remained (M_n=20,800).

Scheme 5.

Fig. 1.

Varying the conditions, deprotection with TFA in THF was repeated with a new sample of **P2**, after which the volatiles were removed to provide a concentrated sample. After dilution with dichloromethane to 6 x 10^{-4} M, copper granules were added and air bubbled through the mixture overnight. A crosslinked network of polymers **P4** was formed, indicating that significant disulfide formation occurred upon exposure to air in the concentrated sample, prior to dilution and treatment with Cu and air. Again, a shoulder to the right on the GPC trace of **P4** indicated incomplete deprotection (Figure 2).

Scheme 6.

Fig. 2.

Cleavage of the disulfide linkages by treatment with dithiolthreitol [45] (2,3-dihydroxy-1,4-butanethiol, DTT), followed by capping the free thiol groups by Michael addition to *N*-phenylmaleimide (NPM) returned most of the crosslinked material **P4** to the lower molecular weight polymer **P5** (Scheme 7, Figure 3). Thus one can manipulate the crosslinking by controlling the redox properties of thiol/disulfide functionalities.

Scheme 7.

Fig. 3.

3.1.2. Thiol-substituted acrylamide monomers

Following the work of Endo [2], tritylated L-cysteine methyl ester **6** was coupled to acrylic acid to provide trityl-protected thiol-substituted acrylamide **7** (Scheme 8). Use of standard coupling agents EDC or DCC provided only moderate yields of the desired acrylamide. Alternatively, a stoichiometric yield of acrylamide **7** was obtained using acryloyl chloride.

Scheme 8.

Copolymerization with nine equivalents of *tert*-butyl acrylate (TBA) to every one equivalent of tritylated cysteine-derived acrylamide **7** (Scheme 9) provided random copolymer **P6**

Scheme 9.

(M_n=12,800, PDI=1.55). Instead of allowing the sample to concentrate, deprotection and crosslinking of the thiol group was carried out under dilute conditions to enhance intramolecular disulfide formation. To optimize trityl group removal, deprotection using tri*iso*propyl silane/TFA (5% v/v with respect to dichloromethane) [46] was first examined on monomer **7** at room temperature overnight in dichloromethane. After work-up, complete removal of the trityl group was observed by TLC and NMR. Thus random copolymer **P6** was dissolved in dichloromethane at 3.7 x 10^{-3} M, and then exposed to tri*iso*propyl silane/TFA to remove the trityl group overnight. Upon exposure to air under these dilute conditions, intramolecular disulfide formation occurred (Scheme 10). This was evident from the GPC trace of **P7** (M_n=8,700, PDI=1.50), which reflected a polymer of apparent size 68% of that of the trityl-protected

Scheme 10.

linear polymer **P6**, indicative of a collapsed nanoparticle. Work by Harth [47,48] has demonstrated collapsed nanoparticles with apparent masses of 62% and 68% of the weight of the linear polymer precursors, respectively. ^{1}H NMR indicated that most of the *t*Bu groups remained intact. Partial reduction of the disulfide bonds by treatment with DTT followed by capping the free thiols with *N*-phenylmaleimide (Scheme 11) provided a mixture of the collapsed nanoparticle, the linear polymer **P8**, and a

Scheme 11.

higher weight component indicating cross-linking between two or more polymer chains. Apparently the DTT reagent was unable to access some of the more deeply buried disulfide crosslinks within **P7**. There was also a high molecular weight shoulder, indicating intermolecular crosslinking prior to capping the free thiol groups with *N*-phenylmaleimide (Figure 4).

Fig. 4.

3.2. Sulfur-containing *N*-alkoxyamine initiators to provide thiol-functionalized polymer termini

The use of functionalized azo initiators, [49,50], or pre-formed *N*-alkoxyamine initiators provides the opportunity to functionalize the phenethyl “foot” of the polymer [51]. Given the robust nature of the trityl protecting group in forming thiol-bearing monomers **5** and **7**, we decided to re-visit our preparation of a thiol functionalized *N*-alkoxyamine initiator, in which TBS had been the protecting group [31]. In that previous work, polystyrene prepared from the TBS-protected thiol initiator showed a high molecular weight shoulder in the GPC trace, even though the initiator had been purified by flash column chromatography, indicating that a small amount of disulfide initiator was a contaminant. Thus rigorous chromatography by HPLC was needed to prepare clean TBS-thiol substituted initiator. To avoid this need for extensive purification, the trityl-protected analogue **8** was prepared. Thus styryl benzyl tritylthiol **5** was converted to the *N*-alkoxyamine **8** following a modified procedure of Hawker

[40], utilizing TIPNO nitroxide, Mn(salen) reagent [35], sodium borohydride and air (Scheme 12). This *N*-alkoxyamine was easily handled and purified by simple column chromatography, with no lability of the protecting group. Polymerization of styrene (219 equivalents of styrene to 1 equivalent of *N*- alkoxyamine **8** for 3.25 hours at 120 °C) provided polystyrene **P9** bearing a terminal *S*-trityl group (M_n=12,279, PDI=1.08). Removal of the trityl protecting group and disulfide formation was carried out by simultaneous detritylation and oxidation using a catalytic amount of copper(I) chloride and air under sonication

Scheme 12.

for 3 days. The resulting polymer **P10** (M_n=19,900, PDI=1.23) showed a small low molecular weight shoulder, indicating deprotection or oxidation did not go to completion (see Figure 5).

Fig. 5.

Disulfide cleavage with DTT, and capping of the free thiol groups with *N*-phenylmaleimide to prevent reoxidation to disulfide provided polymer **P11** of similar molecular weight (M_n=12,800, PDI=1.10) (Figure 6) to that of the trityl-protected polymer **P9**, demonstrating the reversibility of the disulfide forming process.

Fig. 6.

The bidirectional initiator **9** was prepared from vinyl benzyl disulfide **3**, again using the Mn(salen) procedure (Scheme 13). This material was identical to that prepared in our previous publication by a different route [31]. Reduction of the disulfide with DTT gave the free thiol initiator **10**. Although the free thiol **10** cannot be

used directly in free radical polymerizations, it should be useful for anchoring the initiator to a variety of metal surfaces, or adding to olefins via the versatile thiol-ene or yne “click” reactions.

Scheme 13.

4. Conclusion

In summary, NMRP with protected thiol functionalities on either the monomer or *N*-alkoxyamine initiator provides polymers that can be manipulated by deprotection and redox control between thiol and disulfide. The trityl protecting group was found to be superior to the TBDMS protecting group for both applications. For pendant thiol groups, crosslinking under concentrated conditions resulted in the formation of crosslinked polymer aggregates, whereas crosslinking under dilute conditions (10^{-3} M) provided collapsed nanoparticles. Reduction of the disulfide bonds and capping of the free thiol groups by Michael addition to *N*-phenylmaleimide was effective in preventing reformation of disulfide linkages. The synthesis of an initiator bearing a free thiol is presented, providing access to an *N*-alkoxyamine with potential applications to bonding to a variety of metal surfaces, as well as thiol ene “click” reactions to unactivated terminal olefins prior to NMRP.

Acknowledgements

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Figure Captions

Scheme 1. Preparation of random co-polymers containing pendant thiol sidechains: redox control of crosslinking.

Scheme 2. Preparation of polymers containing a thiol terminus: redox control of crosslinking to prepare linear polymers of double the molecular weight.

Scheme 3. Preparation of protected benzylic thiol derivatives of styrene.

Scheme 4. Random copolymerization of protected benzylic thiol styrene derivatives **4** and **5** with styrene by NMP.

Scheme 5. Partial deprotection of tritylated random copolymer **P2**, followed by crosslinking to form **P3**.

Fig. 1. Overlay of GPC chromatographs of protected random tritylated copolymer **P2** [(---) PDI=1.15, M_n=20,800] and partially deprotected, oxidized polymer network **P3** (—).

Scheme 6. Deprotection of tritylated random copolymer **P2**, concentration of the sample, and crosslinking to form **P4**.

Fig. 2. GPC chromatograph of the cross-linked polymer **P4** (M_n=33,300).

Scheme 7. Disulfide reduction with DTT, followed by capping the free thiol groups with NPM to reform linear polymer.

Fig. 3. Overlay of GPC chromatographs of cross-linked polymer **P4**
(---, M_n=33,300) and reduced and NMP-capped polymer **P5**
(—, PDI=1.44, M_n=28,100).

Scheme 8: Preparation of trityl protected cysteine derived acrylamide **7**.

Scheme 9. Random copolymerization of protected cysteine acrylamide **7** with TBA by NMP to form **P6**.

Scheme 10. Deprotection of tritylated random copolymer **P6** and crosslinking under dilute conditions to form a collapsed nanoparticle **P7**.

Scheme 11. Deprotection of collapsed nanoparticle **P7** by cleavage of solvent accessible disulfide bonds by DTT, followed by capping with NPM.

Fig. 4. Overlay of GPC chromatographs of tritylated random co-polymer **P6** (black line, PDI=1.55, M_n=12,800), deprotected, intramolecular cross-linked collapsed

nanoparticle **P7**(grey line, PDI=1.50, M_n=8,700), and reduction and capping to give a mixture of linear capped polymer **P8 (**M_n=12,800), collapsed nanoparticle, and a higher molecular weight crosslinked polymer network (dashed line).

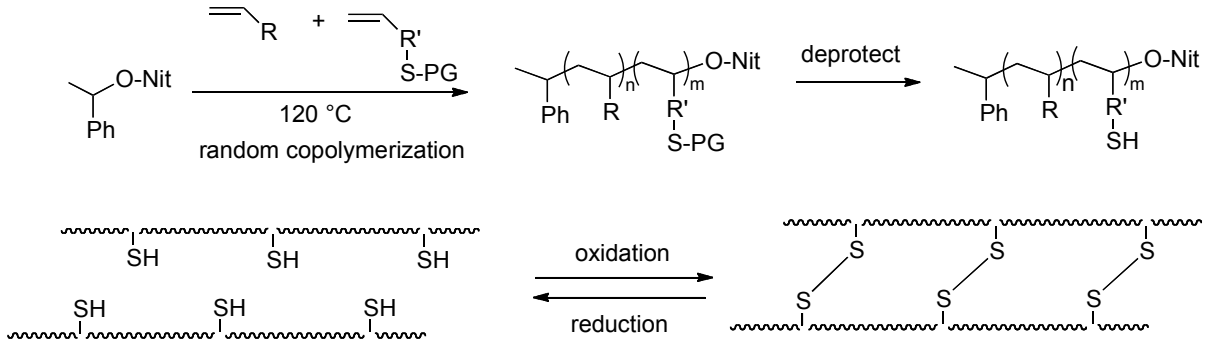
Scheme 12. Preparation of *N*-alkoxyamine initiator **8** bearing a trityl-protected thiol, NMP polymerization of styrene, one-pot trityl deprotection and disulfide formation, and cleavage of the central disulfide bond by DTT, followed by capping with NPM.

Fig. 5. Overlay of GPC chromatographs of trityl-protected polystyrene **P9** (right, M_n=12,700, PDI=1.08) and the resulting disulfide linked polystyrene **P10** (left, M_n=19,900, PDI=1.23).

Fig. 6. Overlay of GPC chromatographs of disulfide linked polystyrene **P10** (left, M_n=19,900, PDI=1.23) and maleimide-trapped thiol terminated polystyrene **P11** following disulfide cleavage (right, M_n=12,800, PDI=1.10).

Scheme 13. Preparation of *N*-alkoxyamine free thiol initiator **10** via the disulfide **3**.

Schemes and Figures



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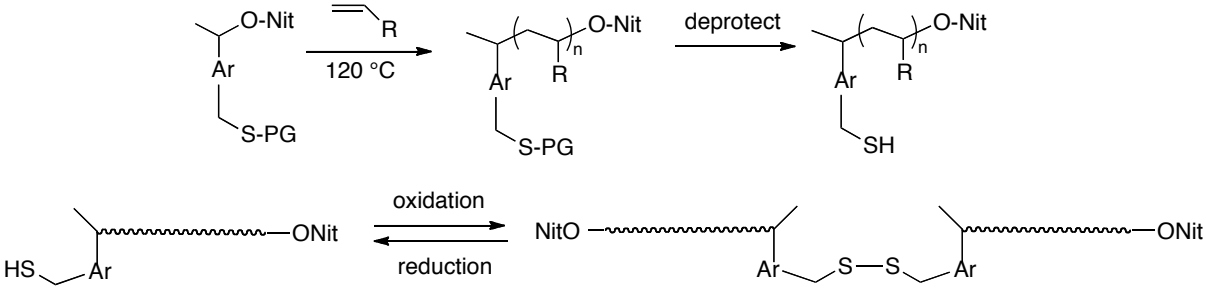

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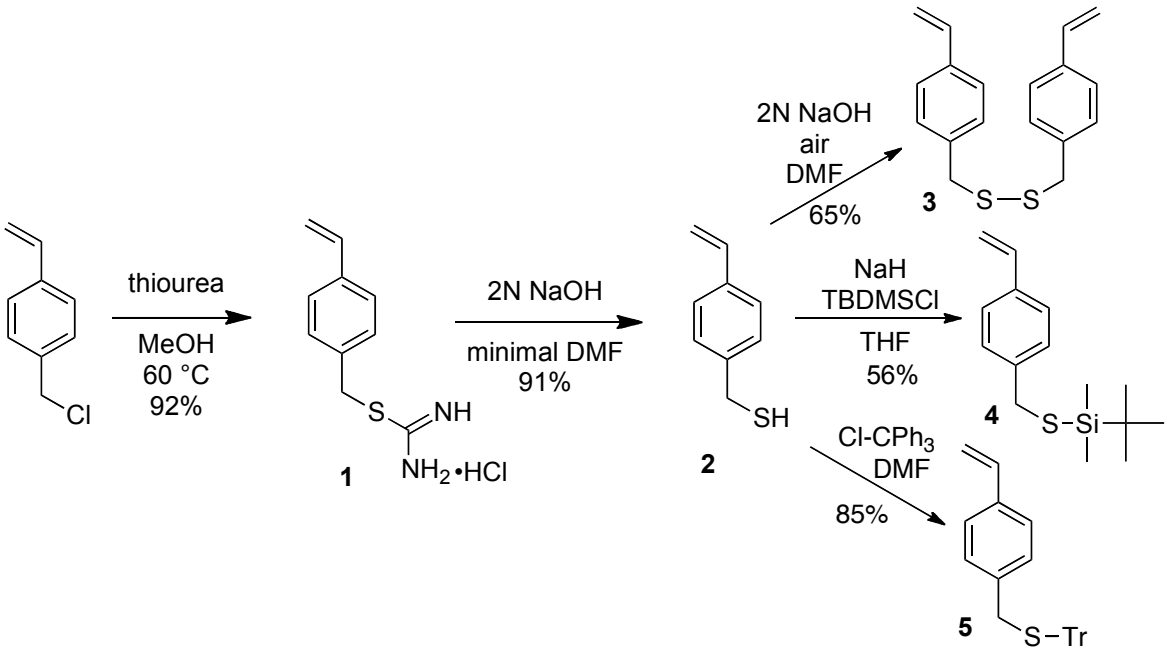

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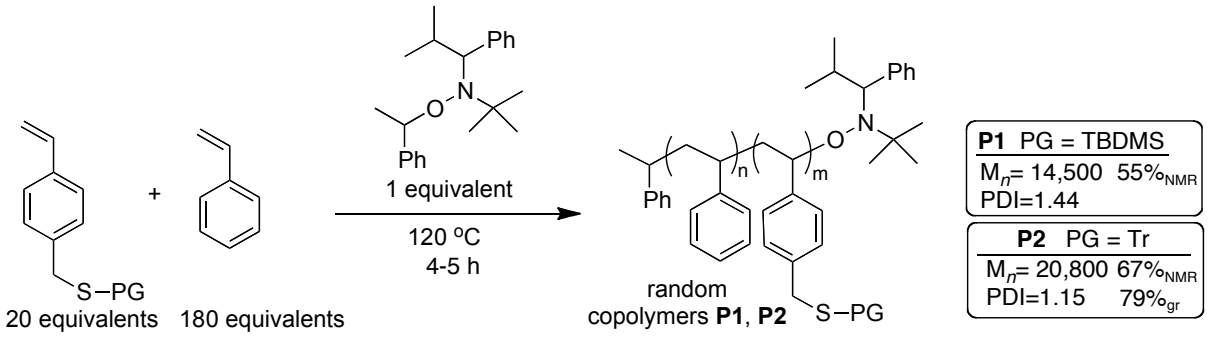

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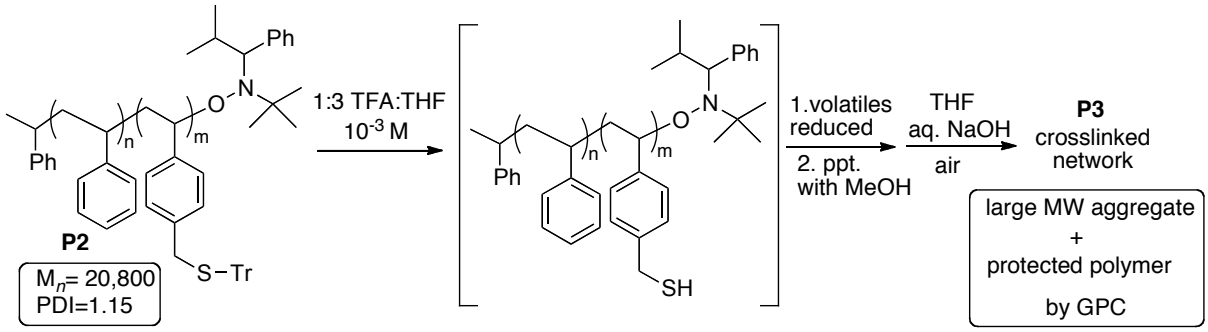

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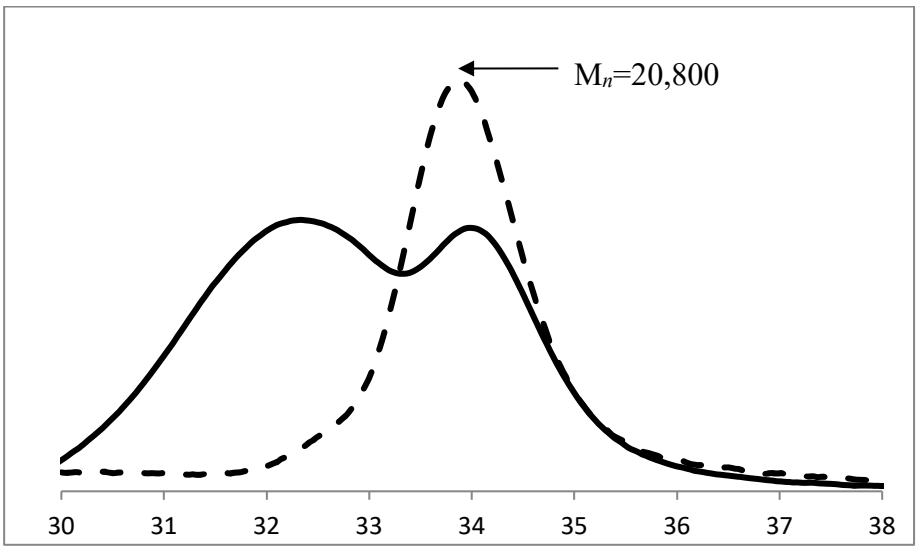

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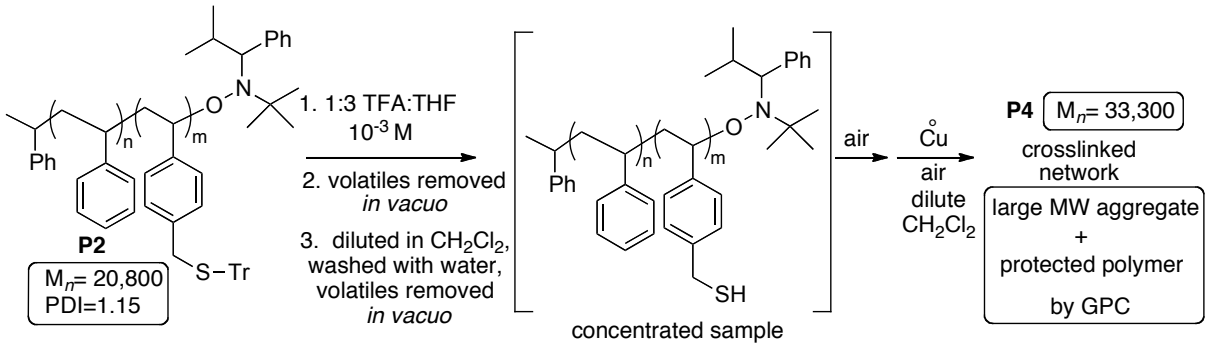

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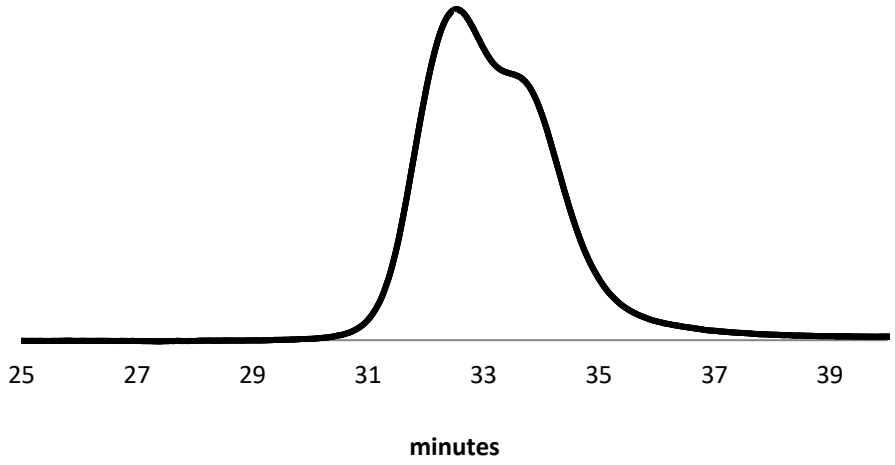

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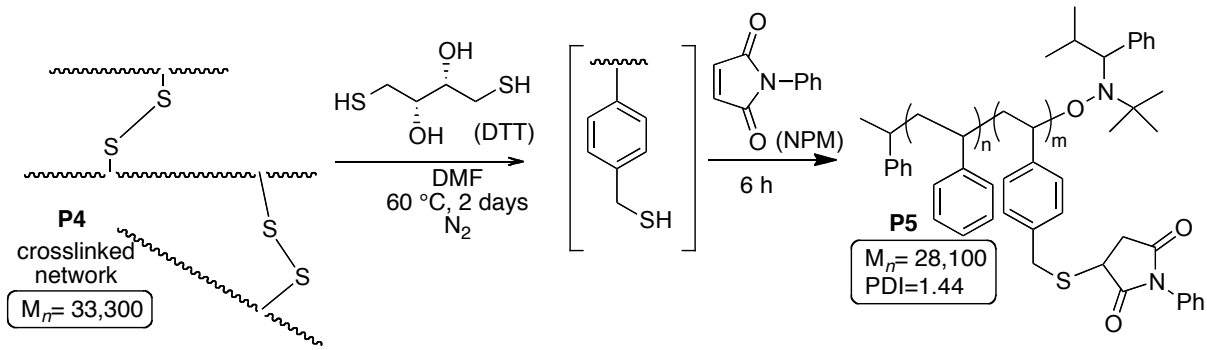

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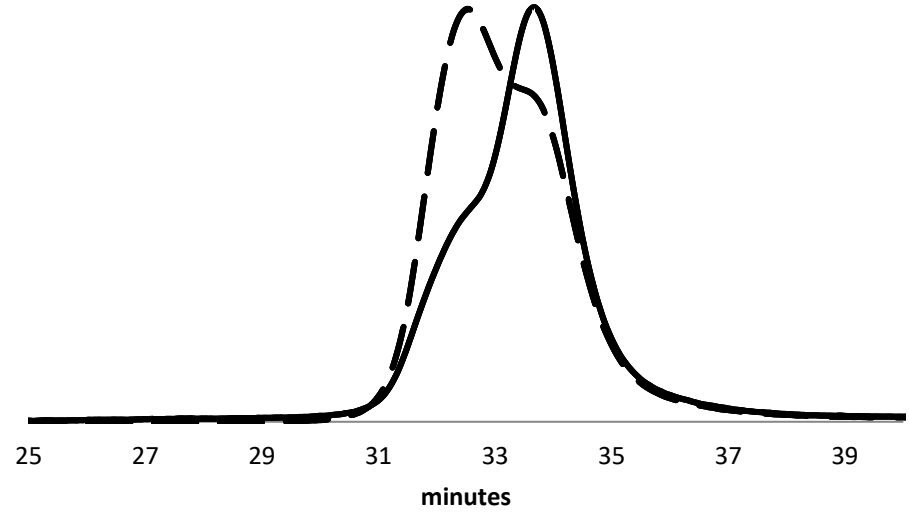
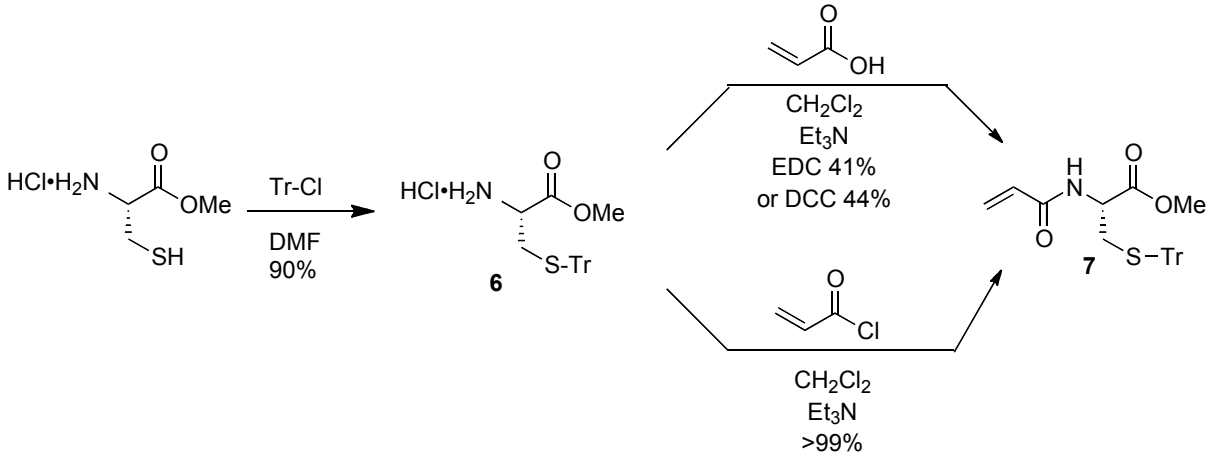


Fig. 3.



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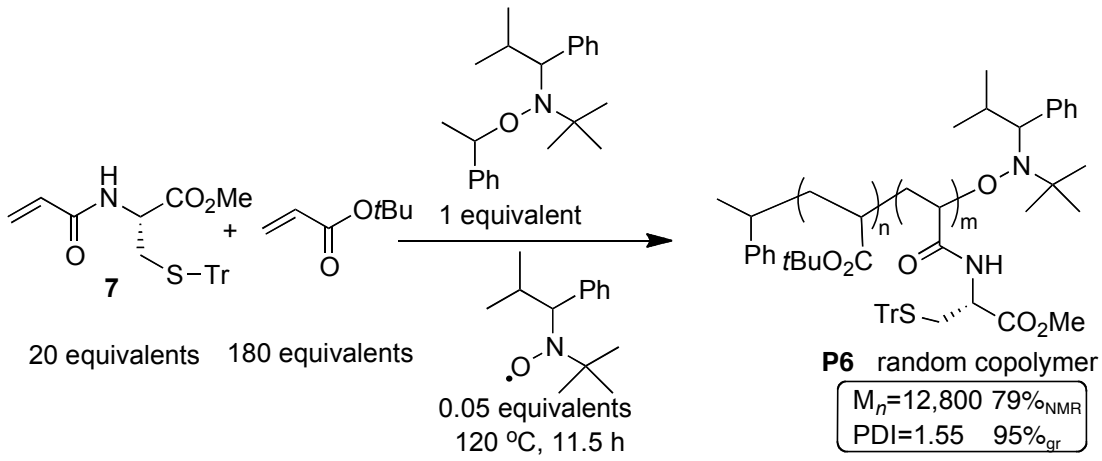

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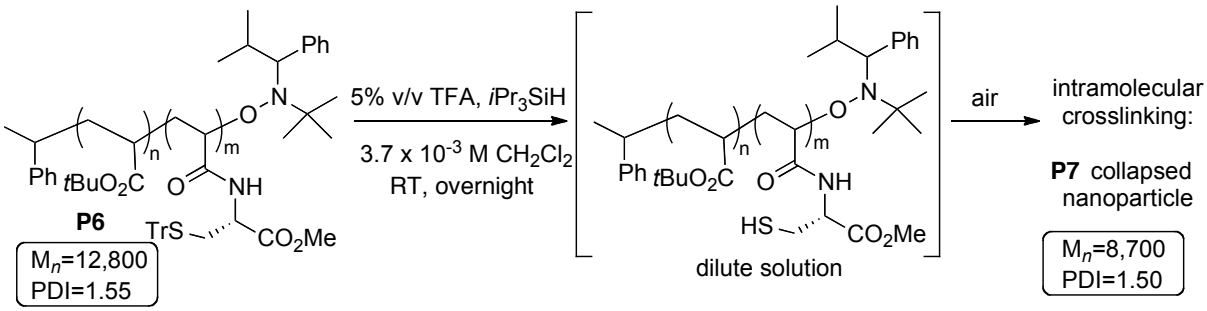

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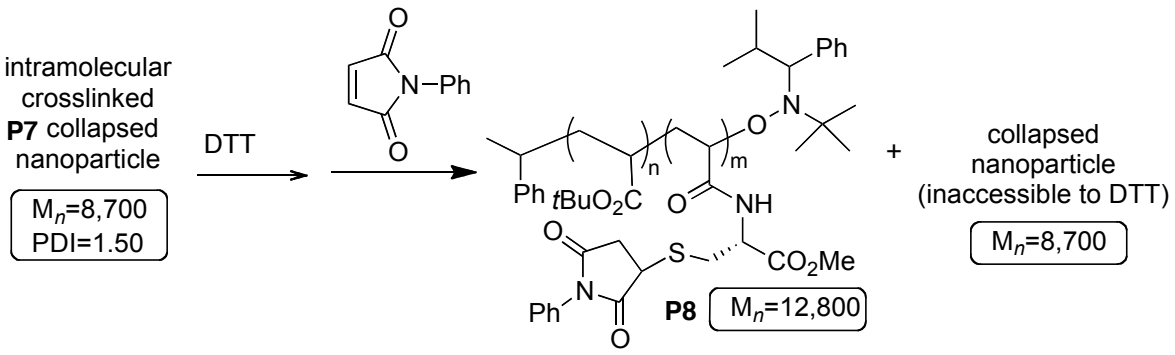

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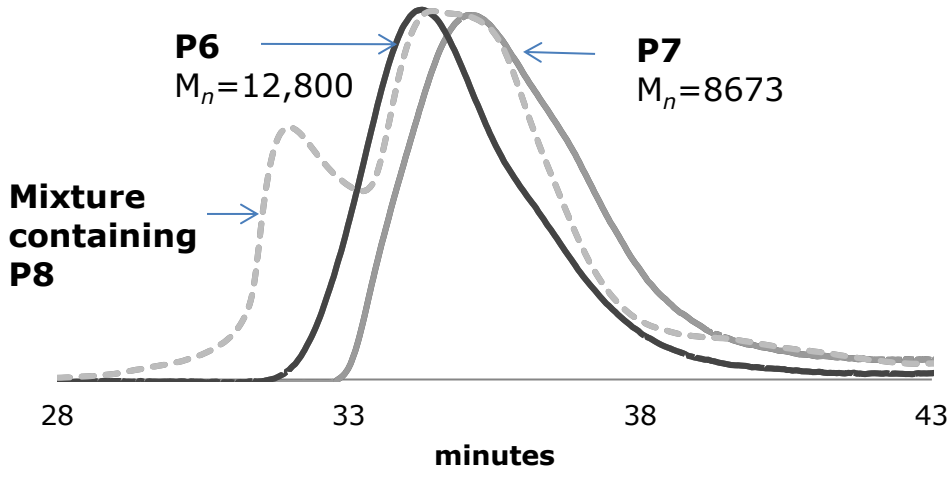
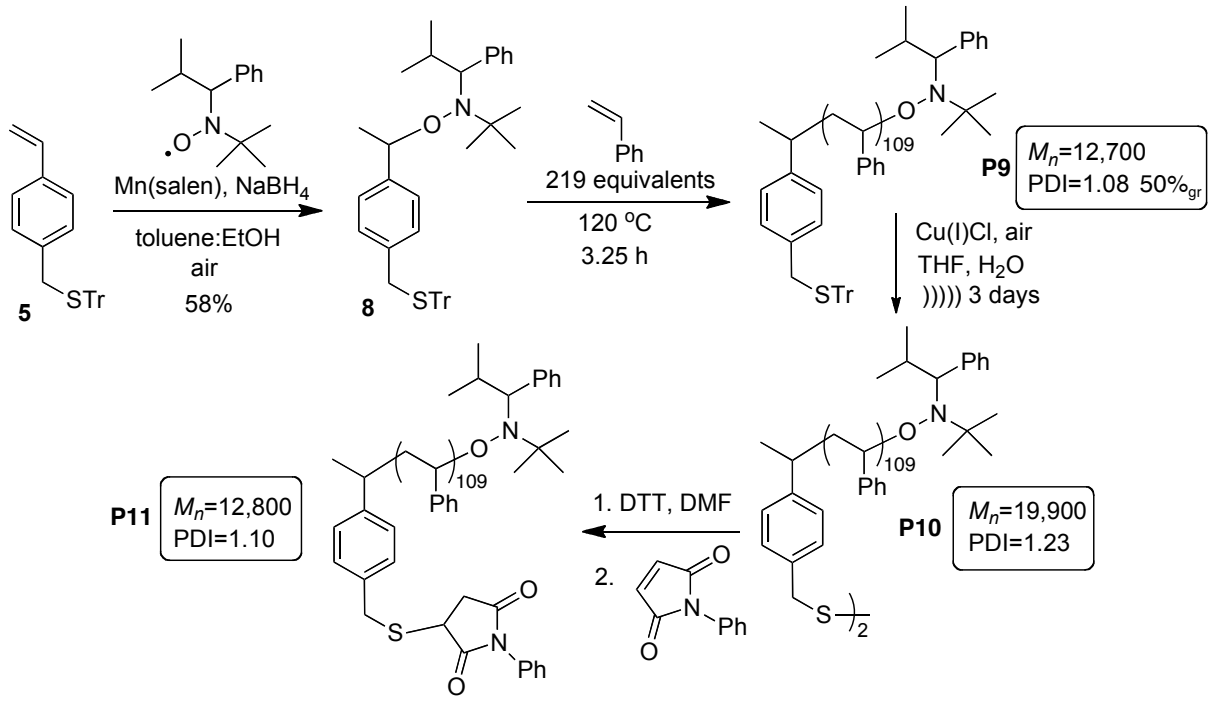


Fig. 4.



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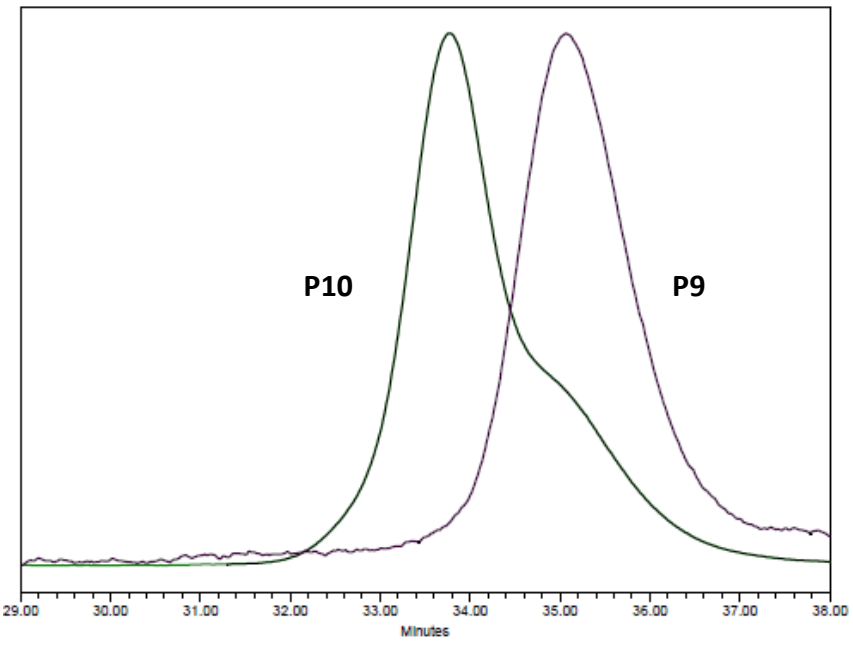


Fig. 5.

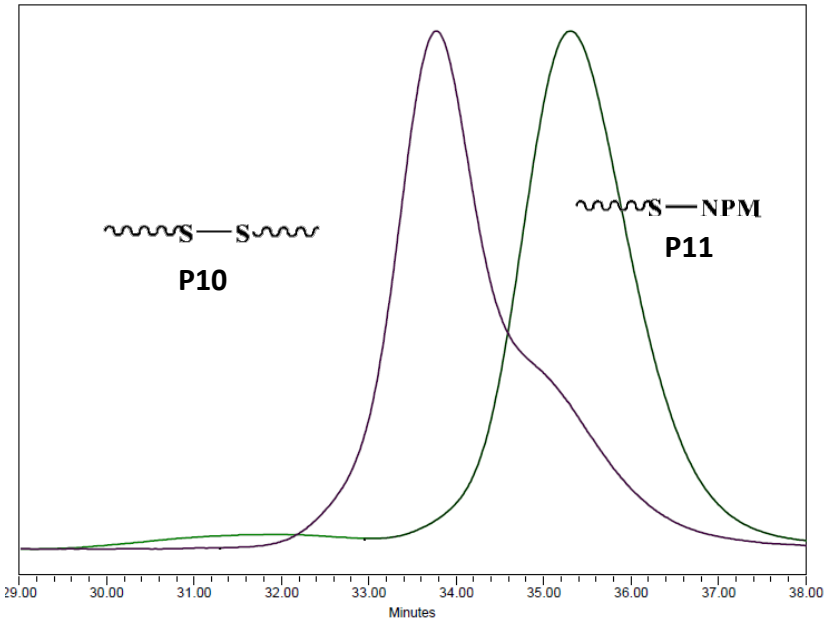
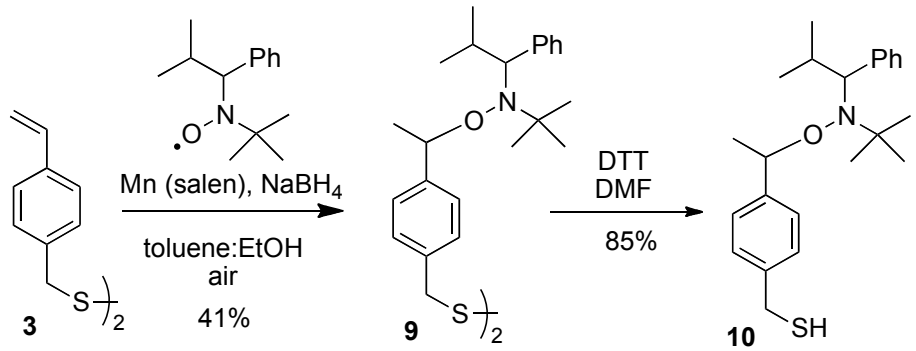


Fig. 6.



Scheme 13.