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Direct Synthesis of Pyridyl Disulfide-Terminated Polymers by RAFT Polymerization

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Materials and Methods

Materials

Hydroxyethyl disulfide (Sigma), tris(2-carboxyethyl)phosphine hydrochloride (TCEP.HCl) (99.5%, Sigma), 2,2'-dithiodipyridine (Sigma), thionyl chloride (>98%, Riedel-DeHaen), 2,2'-azobis(isobutyronitrile) (AIBN, 98%, Sigma-Aldrich), polyethylene glycol acrylate (PEG-A, average molecular weight 454, n=8–9, Aldrich) n-butyl acrylate (BA), 11-mercapto-1-undecanol (MU) (>97%, Aldrich), carbontetrachloride (Aldrich), dichloromethane (>99.5%, Univar), tetrahydrofuran (THF, >99.7%, Unichrom), hexane (>95%, Univar), anhydrous sodium sulphate (>99%, Unilab), diethyl ether (>99%, Univar), ethyl acetate (>99.5%, Univar), Milli Q water (>18 mΩ). Deuteriumoxide (D_2O) and deutarated-dimethylformamide (d7-DMF) were from Aldrich. The synthesis of 3-benzylsulfanylthiocarbonylsulfanyl propionic acid (BSTP)[1] and its chloride derivative[2] (Scheme 1) was carried out following the method reported elsewhere.[S1,S2]

Experimental Method

Synthesis of the Biadduct Product[3] *of BSTP Chloride with 2-Hydroxyethyl Disulfide*. To a solution of BSTP chloride (0.21 g, 0.8 mmol) in 2 ml THF was slowly added 2-hydroxyethyl disulfide (63 mg, 0.41 mmol) solution in 1ml THF. The resulting mixture was stirred overnight at room temperature. After removal of the solvent under vacuum, the resulted mixture was subjected to silica gel chromatography using hexane/EtOAc (40/60) as eluent to obtain the biadduct product[3] (200 mg, yield 81%).

Biadduct Product[3] *of BSTP Chloride with 2-Hydroxyethyl Disulfide* 300 MHz ^{1}H NMR ($CDCl_3$) δ: 7.28–7.33 (m, 10H, 2 × $C_6\boldsymbol{H_5}$), 4.60 (s, 4H, 2 × C_6H_5-C$\boldsymbol{H_2}$), 4.34–4.38 (t, 4H, 2 × C$\boldsymbol{H_2}$O), 3.61–3.65 (t, 4H, 2 × S–C$\boldsymbol{H_2}$), 2.90–2.94 (T, 4H, 2 × S–S–C$\boldsymbol{H_2}$), 2.77–2.82 (t, 4 H, 2 × C$\boldsymbol{H_2}$–CO). 300MHz ^{13}C NMR ($CDCl_3$) δ: 31.18 (CH_2), 32.99 (CH_2), 37.06 (CH_2), 41.44 (CH_2S), 62.61 (CH_2CO), 127.73 (***C***H=CH), 128.63 (***C***H=CH), 129.16 (***C***H=CH), 134.75 (CH_2–***C***H=CH), 171.06 (***C***=O), 222.77 (C=S).

Cleavage of Biadduct to BSTP Thiol.[4] To a deoxygenated solution of biadduct (72 mg, 0.12 mmol) in 2 ml THF was added TCEP.HCl (66 mg, 2.3 mmol). The resulting mixture was stirred for one hour under nitrogen atmosphere, and then transferred to a separating funnel and added deoxygenated 10 ml of dicholoromethane and 20 ml distilled water. Following mixing the phases, the organic phase was collected and washed three times with deoxygenated water. The organic phase was then dried over anhydrous sodium sulphate and filtered. Upon the removal of the solvent, 65 mg of product[4] was obtained and used immediately for the next step without further purification.

Synthesis of BSTP Pyridyl Disulfide.[5] To a solution of BSTP thiol (65 mg, 0.22 mmol) in 2 ml THF was added 2,2'-dithiodipyridine (100 mg, 0.45 mmol). The mixture was stirred overnight. After removal of THF, the product[5] was isolated through column chromatography using hexane/EtOAc (50/50) as eluent (69 mg, yield 78%).

BSTP Pyridyl Disulfide,[5] 300 MHz ^{1}H NMR ($CDCl_3$) δ: 8.47–8.48 (d, 1H, C***H***-N), 7.64–7.66 (m, 2H, S–C***H***=C***H***), 7.28–7.33 (m, 5H, phenyl group), 7.09–7.12 (t, 1H, C***H***=CH–N), 4.60 (s, 2H, 2 × C_6H_5–C***H*****$_2$**), 4.34–4.48 (t, 2H, C***H***$_2$O), 3.59–3.64 (t, 2H, S–C***H***$_2$), 3.02-3.07 (t, 2H, S–S–C***H***$_2$), 2.73–2.78 (t, 2 H, C***H***$_2$–CO). 300MHz ^{13}C NMR ($CDCl_3$) δ: 31.13 (CH_2), 32.94 (CH_2), 37.30 (CH_2), 41.42 (CH_2S), 62.52 (CH_2CO), 120.21 (***C***H=CH), 120.99 (***C***H=CH), 127.72 (***C***H=CH), 128.63 (***C***H=CH), 129.16 (***C***H=CH), 134.75 (CH_2–***C***H=CH), 137.59 (S–***C***H=CH), 149.04 (N–***C***H=CH), 159.36 (N=***C***H-S), 170.98 (***C***O), 222.77 (***C***=S).

RAFT Polymerization of PEG-A with Pyridyl disulfide Modified RAFT A*gent.* A solution of PEG-A (1.75 g, 3.85 x 10^{-3} mol), pyridyl disulfide modified RAFT agent[5] (15.4 mg, 3.76 × 10^{-5} mol), and AIBN (1.6 mg, 9.75 × 10^{-6} mol) were dissolved in DMF (4.2 ml) to obtain a homogeneous solution. Aliquots were transferred to six different vials, which were then sealed with rubber septa. Each vial was deoxygenated for 30 min prior, followed by the placement in a preheated water bath at 65 ºC. The vials were removed at 0.5, 1.5, 3.5, 5.5, 6.5, and 7.5 h. Immediate cooling with ice and exposure to air halted the polymerisation. The monomer conversion for each polymerization sample was determined by H NMR after the removal of DMF from polymerization mixtures under vacuum. The polymers[6] were collected after precipitation in diethyl ether and then dried under vacuum.

RAFT Copolymerization of n-BA with Pyridyl Disulfide-Terminated Poly(PEG-A)[6] *as Macro-RAFT Agent***.** A solution of pyridyl disulfide-terminated poly(PEG-A)[6] (0.361 g, 1.76 × 10^{-5} mol, M_n 20 500 g·mol^{-1}, PDI 1.17, at 58% monomer conversion), BA (1.27 g, 9.9 × 10^{-3} mol), and AIBN (1.02 mg, 6.2 × 10^{-6} mol) in DMF was mixed thoroughly to obtain a homogeneous solution. Aliquots were transferred to four different vials, which were then sealed with rubber septa. Each vial was deoxygenated for 30 min prior to incubation in a preheated water bath at 65 ºC. The vials were removed from the water bath at 1, 2, 4 and 6 h. Immediate cooling with ice

and exposure to air halted the polymerisation. The monomer conversions were determined gravimetrically after removing the unreacted monomer and the solvent under vacuum. The copolymers were collected after the precipitation of the polymerization mixtures in diethyl ether followed by drying.

Coupling Reaction of Pyridyl Disulfide-Terminated Poly(PEG-A)-b-poly(BA) with a Thiol-Compound. 85 mg poly(PEG-A)-b-poly(BA) (3×10^{-6} mole, M_n 27 700 g·mol^{-1}, PDI 1.26) was reacted with 5 equivalent 11-mercapto-1-undecanol (MU) (3 mg, 1.5×10^{-5} mole) in 10 ml DMF. After 3 h, the UV absorption of the reaction solution was measured using a UV-visible spectrophotometer (Cary 1E). The reaction solution was diluted 10 times with DMF to measure the absorbance values in the spectrophotometer`s detection range. In order to ensure that the coupling reaction was completed, 5 equivalent of MU (3 mg, 1.5×10^{-5} mole) was added to the reaction solution after 3 hours and the final solution was let to react overnight. After the incubation time, the reaction solution was diluted 10 times with DMF and the UV absorption of the diluted solution was recorded. To determine the extinction coefficient of 2-pyridinethione in DMF, known concentrations of 2,2'-dithiodipyridine were reacted with the excess of 2-mercaptoethanol in DMF for 3 h. A calibration curve was built from the absorbance of the reaction mixtures and the concentrations of 2,2'-dithiodipyridine.

Characterization

^{1}H NMR spectra were obtained using a Bruker AC300F (300 MHz) Spectrometer or a Bruker DPX300 (300 MHz) Spectrometer. Data were reported as follows: chemical shift (δ) measured in ppm downfield from TMS; multiplicity; proton count. Multiplicities were reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), and multiplet (m). ^{13}C spectra were obtained on Bruker AC300F (300 MHz) Spectrometer. ^{13}C chemical shifts (δ) were reported in parts per million

(ppm) downfield from TMS and identifiable signals were given. The protons and carbons relevant to the response in NMR spectra are highlighted in bold and italic character. Gel permeation chromatography (GPC) analysis of poly(PEG-A) and poly(PEG-A)-*b*-poly(BA) was performed in N,N-dimethylacetamide (DMAc) (0.03% w/v LiBr, 0.05% BHT stabilizer) at 50 °C (flow rate: 0.85 mL·min^{-1}) using a Shimadzu modular system comprising a DGU-12A solvent degasser, an LC-10AT pump, a CTO-10A column oven, and an RID-10A refractive index detector. The system was equipped with a Polymer Laboratories 5.0 mm bead-size guard column (50 × 7.8 mm^2) followed by four 300 × 7.8 mm^2 linear PL columns (10^5, 10^4, 10^3, and 500). Calibration was performed with low polydispersity polystyrene standards ranging from 500 to 10^6 g·mol^{-1}.

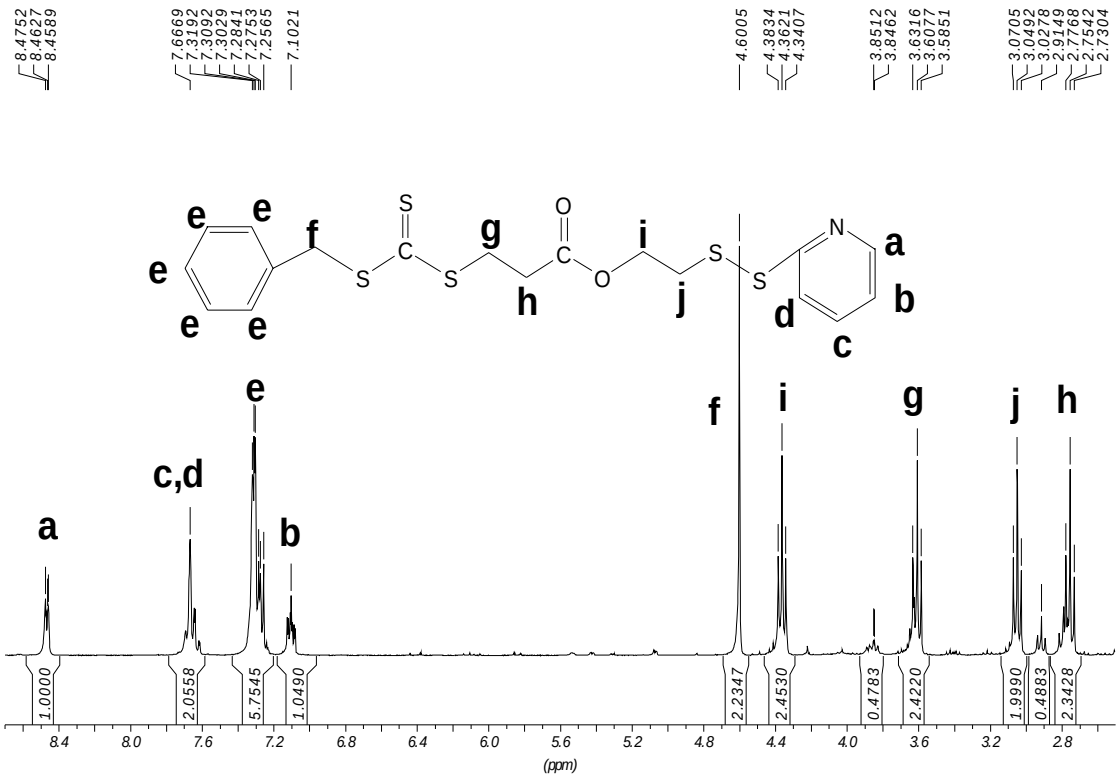

Figure S1. The H NMR spectrum of the modified RAFT agent in $CDCl_3$ (the peaks at 2.9 and 3.85 were caused by the THF residue).

[S1] M. H. Stenzel, T. P. Davis, *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 4498.

[S2] J. T. Lai, D. Filla, R. Shea, *Macromolecules* **2002**, *35*, 6754.