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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.

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 crosslinkages. 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 crosslinked 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 crosslinking 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 10^7–10^8 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

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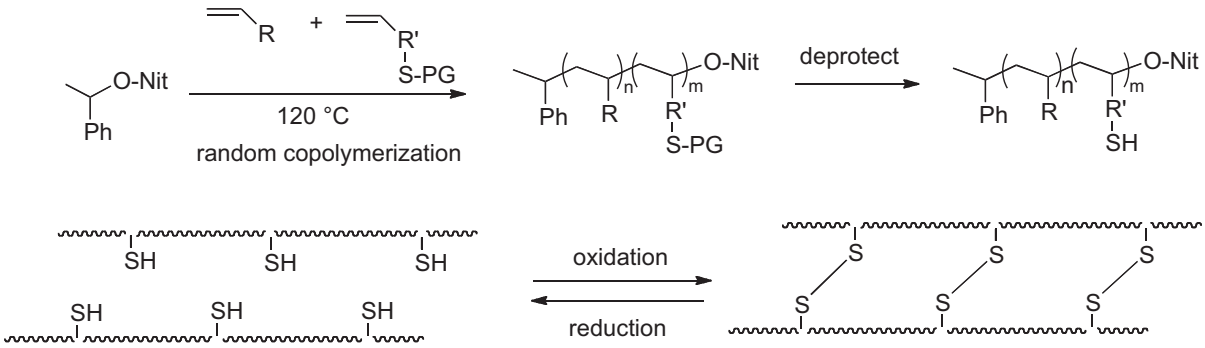
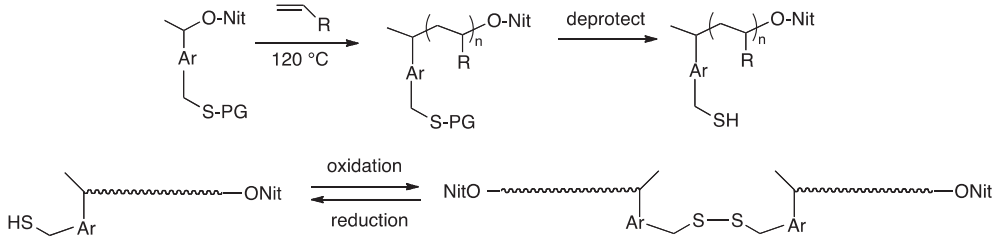


Scheme 1. Preparation of random co-polymers containing pendant thiol sidechains: redox control of crosslinking.



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

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).

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.

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 et al. [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 × 4.6 mm, 5 μm 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, 50–1,000,000 Da), HR 5E (linear bed, mixed pore sizes, 2000–4×10^6 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) isothiourea 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