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Radical-Catalyzed Oxidation of Thiols by Trithiocarbonate and Dithioester RAFT Agents: Implications for the Preparation of Polymers with Terminal Thiol Functionality

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Polymers with terminal thiol functionality have attracted much interest recently due to the versatile chemistry of the thiol group. Thiol-terminal polymers have been used to prepare protein−polymer conjugates by disulfide exchange with cystine residues,[1] block copolymers with reversible interpolymer disulfide bonds,[2] and end-functionalized polymers using thiol−ene reactions.[3,4] The high efficiency and robust nature of the thiol−ene reaction[5] have led to its use in the preparation of polymers with star,[6] block,[7] and macrocyclic[8] architectures from linear polymer precursors.

Thiol-terminal polymers with controlled molecular weight and architecture are typically prepared from polymers produced by reversible addition−fragmentation chain transfer polymerization (RAFT).[9] Polymers produced via RAFT carry a thiocarbonylthio end group, which may be converted to a thiol by nucleophilic cleavage. Many nucleophiles have been used to achieve this conversion, including primary amines,[2,4,6−8,10−12] hydroxide,[13] and borohydride.[3]

Unfortunately, the conversion of RAFT polymers to thiol-terminal polymers is complicated by a ubiquitous side reaction: oxidative coupling of two thiol-terminated polymers to generate a new species with twice the molecular weight of the cleaved polymer. The extent of coupling may be reduced by cleaving the RAFT agent in the presence of a reducing agent (e.g., sodium dithionite[10]), but the reaction is impossible to eliminate entirely. When sodium borohydride was used to cleave trithiocarbonate-terminated poly(*N*-isopropylacrylamide) under reducing conditions, the coupled species was the major product.[4]

The oxidation of thiols proceeds via a base-catalyzed radical mechanism, in which thiolate anions (RS^-) are oxidized to form thiyl radicals ($RS^\bullet$), which subsequently couple to form disulfides.[14] As thiyl radicals play a key role in the oxidation of thiols, it is of interest to observe their interaction with RAFT agents.

Thiyl radicals were generated in the presence of the RAFT agents dibenzyl trithiocarbonate ($BnSCS_2Bn$, 0.1 M), benzyl dodecyl trithiocarbonate ($DdSCS_2Bn$, 0.1 M), or benzyl dithiobenzoate ($PhCS_2Bn$, 0.1 M) by the thermal decomposition of 2,2′-azobis(isobutyronitrile) (AIBN, 0.02 M) at 80 °C in degassed solutions of benzyl mercaptan (BnSH, 0.1 M) or 1-dodecanethiol (DdSH, 0.1 M) in benzene-d_6. The reactions were carried out in flame-sealed NMR tubes and followed by ^{1}H NMR spectroscopy.

It was observed that the presence of an equimolar quantity of trithiocarbonate RAFT agent caused a marked increase in the rate of conversion of thiol to disulfide (Figure 1). The RAFT agent was consumed during the reaction, and toluene and carbon disulfide (detected by ^{13}C NMR) were formed, as shown in Scheme 1. No reaction of $BnSCS_2Bn$ was observed when AIBN and $BnSCS_2Bn$ were heated in the absence of thiol.

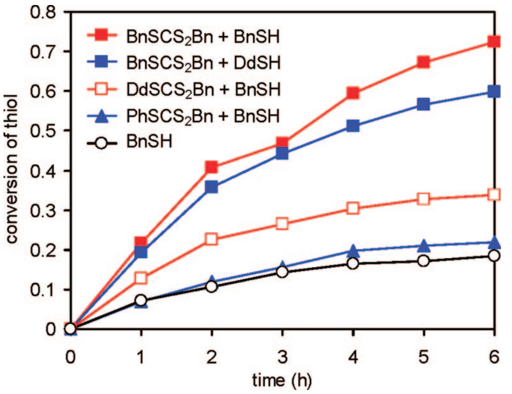
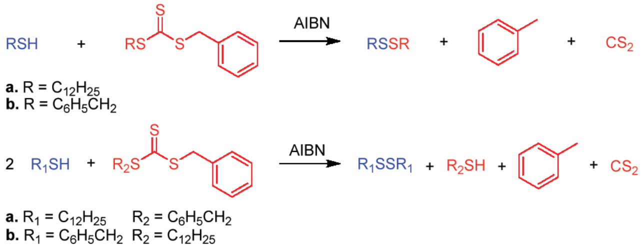


Figure 1. Reaction kinetics for the oxidation of solutions of benzyl mercaptan (BnSH) and 1-dodecanethiol (DdSH) in the presence of benzyl trithiocarbonate ($BnSCS_2Bn$), BnSH in the presence of benzyl dodecyl trithiocarbonate ($DdSCS_2Bn$), BnSH in the presence of benzyl dithiobenzoate ($PhCS_2Bn$), and BnSH alone. Reactions were carried out in degassed benzene-d_6 at 80 °C. Initial concentration of AIBN: 0.02 M. Initial concentrations of all other reagents: 0.1 M.

More disulfide was produced than could be accounted for by reaction with AIBN alone, indicating (1) that the RAFT agent itself is capable of oxidizing thiols and (2) that each radical produced by the decomposition of AIBN resulted in the production of a greater than stoichiometric quantity of disulfide (>0.5 mol disulfide/mol radical). The quantity of thiyl radicals formed during the course of the reaction was estimated from the final concentration of isobutyronitrile, which is formed when a 2-cyanopropyl radical (derived from the thermal decomposition of AIBN) abstracts a hydrogen atom from a thiol. In the oxidation of BnSH by AIBN in the absence of RAFT agent, the molar ratio of benzyl disulfide to isobutyronitrile after 6 h of reaction at 80 °C was approximately 1:2, consistent with formation of the disulfide by combination of two $BnS^\bullet$ radicals. By contrast, in the presence of $BnSCS_2Bn$ the ratio of disulfide to isobutyronitrile increased to 11:2, indicating that each thiyl radical resulted in the formation of 5.5 molecules of disulfide.

In each case investigated, the major product of the oxidation was the symmetrical disulfide derived from the thiol. In particular, the reaction of BnSH with $DdSCS_2Bn$ produced exclusively benzyl disulfide, and the reaction of DdSH with $BnSCS_2Bn$ produced dodecyl disulfide with only minor quantities of benzyl dodecyl disulfide and benzyl disulfide.[15] The failure to form significant quantities of mixed disulfides indicates

Scheme 1. Reactions of Benzyl Mercaptan and Dodecanethiol with the Trithiocarbonate RAFT Agents Benzyl Trithiocarbonate and Benzyl Dodecyl Trithiocarbonate



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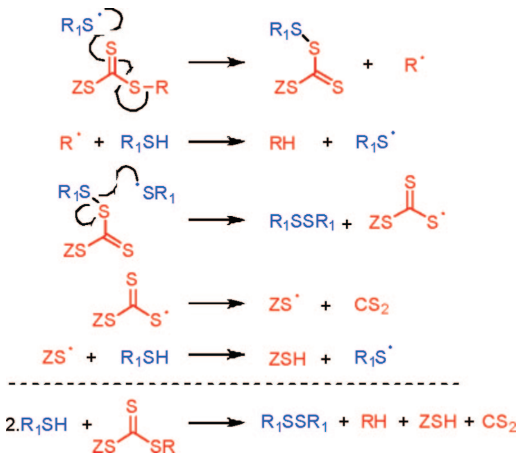
Scheme 2. Proposed Mechanism for the Radical-Catalyzed Reaction of Thiols with Trithiocarbonate RAFT Agents[a]



[a] R is a good homolytic leaving group.

that the oxidation does not proceed by a concerted reaction of the thiol with the RAFT agent but must involve the combination of two fragments derived from the thiol.

These data indicate that the reaction with trithiocarbonate RAFT agents most likely proceeds via the mechanism illustrated in Scheme 2. The thiyl radical ($R_1S^{\bullet}$) attacks the thiocarbonyl sulfur, resulting in the formation of an α-thiocarbonyl disulfide and the expulsion of a carbon-centered radical ($R^{\bullet}$), which subsequently abstracts a hydrogen atom from another thiol. The α-thiocarbonyl disulfide undergoes a disulfide exchange reaction to form the symmetrical disulfide and a trithiocarbonate radical ($ZSCS_2^{\bullet}$), which dissociates into carbon disulfide (CS_2) and a thiyl radical ($ZS^{\bullet}$). Reaction at any other sulfur atom on the RAFT agent would result in the formation of mixed disulfides, which are not observed. No net generation or consumption of radicals occurs; only catalytic quantities of radicals are required.

In the presence of a dithioester RAFT agent, $PhCS_2Bn$, formation of benzyl disulfide occurred at a rate slightly greater than that observed for BnSH alone (Figure 1). Toluene was formed during the reaction, indicating that reaction with the RAFT agent took place. This reaction is thought to proceed via a similar mechanism to that observed for trithiocarbonates.

The relative rates of reaction with BnSH were in the order $BnSCS_2Bn > DdSCS_2Bn \gg PhCS_2Bn > BnSH$. It can be deduced that trithiocarbonates are more reactive than dithioesters, and trithiocarbonates with two good homolytic leaving groups are more reactive than those carrying only one.

This reaction has strong implications for preparation of polymers with thiol functionality by nucleophilic cleavage of polymeric RAFT agents. The presence of any species capable of oxidizing a thiol to a thiyl radical may catalyze the oxidation of thiols by the RAFT agent, even though it is not present in stoichiometric quantities. The reaction of thiyl radicals with a polymeric RAFT agent will result in the creation of carbon-centered polymer radicals, which must subsequently terminate by combination, disproportionation, or chain transfer. Disproportionation and chain transfer reactions will produce saturated or unsaturated chains without thiol functionality, while combination reactions will result in irreversibly coupled chains. These products cannot be distinguished from thiol- or disulfide-functional chains by GPC analysis alone but should be detected by MALDI-TOF mass spectrometry. In fact, saturated, non-thiol-functional chains have been observed to form major components of the MALDI-TOF mass spectra of polymers formed by aminolysis or basic hydrolysis of RAFT polymers.[4,11,13]

In conclusion, it has been shown that dithioester and trithiocarbonate RAFT agents with the structure RSC(S)Z undergo a radical-catalyzed reaction with thiols which results in the oxidation of the thiol to a disulfide and concomitant reduction of the RAFT agent to RH, CS_2, and ZH. The relative rates of reaction indicate that dithioester RAFT agents should be preferred and symmetrical trithiocarbonates avoided when preparing polymers with terminal thiol functionality by RAFT polymerization followed by nucleophilic cleavage of the RAFT agent, in order to minimize the production of nonfunctional and coupled polymers.

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Supporting Information Available: Experimental details, NMR spectra, and table of disulfide:isobutyronitrile ratios. This material is available free of charge via the Internet at http://pubs.acs.org.

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