Evidence for Termination of Intermediate Radical Species in RAFT-Mediated Polymerization

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The reversible addition−fragmentation chain transfer (RAFT) process is a highly versatile living radical polymerization technique that can be applied to most monomers that can be polymerized under free radical polymerization conditions.[1−5]

The foundations of the RAFT process rest in the rapid central addition−fragmentation equilibrium process between propagating ($P_n^{\bullet}$) and intermediate ($Y^{\bullet}$) radicals, and chain activity and dormancy, as shown in Scheme 1. The concentrations of each of the species involved in this equilibrium are dependent on the relative rate coefficients for addition of a propagating radical to the RAFT agent (k_{add}) and fragmentation of the formed intermediate radical (k_{-add}). This equilibrium only strictly holds for polymeric chains (P_n), which are only present in significant concentrations after an initialization period,[6] during which mainly shorter chains are present. A significant species in the equilibrium is the relatively stable radical intermediate that is sometimes formed in quantities that are detectable by electron spin resonance (ESR) spectroscopy.[6−12]

Two common anomalies in RAFT-mediated polymerization reactions[7,13] are "inhibition"[14,15] and rate retardation phenomena. Rate retardation is observed as a reduction in the rate of polymerization in a reaction in the presence of a RAFT agent, compared with an equivalent reaction where the RAFT agent is absent. Strong cases of both of these phenomena have been observed in dithiobenzoate-mediated polymerization reactions.[7,16,17] For this reason, the two phenomena have sometimes been linked.[14] Recent studies in our group have shown that the reasons for these phenomena appear to be independent for the dithiobenzoate systems studied.[6]

Neither inhibition nor retardation is explicitly predicted by the reactions in Scheme 1, since Scheme 1 contains no reaction that affects the propagating radical concentration and, thus, the rate of reaction. Models attempting to explain these phenomena differ significantly, which has led to debate, especially regarding rate retardation.[7,13,16,18−22] The two main models involve either slow fragmentation of intermediate radicals, leading to a lower propagating radical concentration,[2,3,14,17,19,21,23,24] or termination of intermediate radicals in addition to normal termination mechanisms.[7,16,22]

To determine whether the intermediate radical undergoes side reactions, several authors have used model systems to conclusively prove that these reactions can occur.[7,16] The reactions in those studies were performed in the absence of monomer, and thus their frequency or importance for a general RAFT-mediated polymerization was not determined. However, the study of Kwak et al.[7] provided useful equations for the estimation of the quantitative effects (on the rate of reaction) of termination of intermediate radicals and an estimate of the rate coefficient for this process for the system under investigation, although the general applicability of that rate coefficient is not yet known. ESR studies of the RAFT process[7,8,10] appear to show that the concentration of intermediate radicals is far too low to support the very slow fragmentation required to cause rate retardation, as predicted by Barner-Kowollik et al.[17]

To date, there has been no direct experimental evidence for either mechanism. Recent high-level ab initio quantum chemical calculations[25] suggest that slow fragmentation of the intermediate radical might occur in some cases, but the debate has not yet been resolved to the satisfaction of all researchers in the field.

The implication of understanding the fates of intermediate radicals lies not only in what controls the propagating radical concentration, and thus the rate of reaction, but also in synthetic limitations and possibilities. Two synthetic areas where the resolution of this question is important are the rates of reaction in (mini)-emulsion systems[26,27] and cases where the fast addition reaction becomes diffusion-controlled.[28,29] For zero-one (mini)emulsion systems, the fate of an entering radical into a particle that contains one or more intermediate radicals depends on the rate of termination between the entering species and the intermediate radical (or whether such a reaction can occur). This affects the average maximum total number of radicals (propagating and intermediate) per particle, which affects the maximum average number of propagating radical per particle and thus the rate of reaction. In cases where the fast addition reaction becomes diffusion-controlled, the equilibrium between propagating and intermediate radicals will shift toward propagating species, which will affect both the rate of reaction and extent of side reactions, both of which depend on the fates of intermediate radicals.

The current study presents data which show that termination of intermediate radicals occurs in dithiobenzoate-mediated (RAFT) polymerization of styrene and will thus cause rate retardation.

In the present study, the reactions of short-chain species during the initial periods of cumyl dithiobenzoate (CDB)-mediated polymerizations of styrene were investigated at 84 °C. High initiator and CDB concentrations were chosen such that very short chains were targeted at complete conversion, and high radical concentrations were present. It should be noted that although these concentrations are extremely high, this does not invalidate their applicability to the general RAFT mechanism, since it is not necessary to invoke

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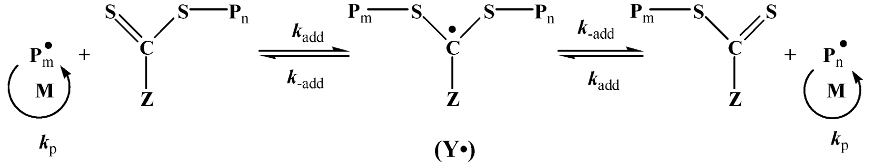
Scheme 1. The Currently Accepted Elementary Steps for the Central Equilibrium in the RAFT Process



assumptions regarding the concentrations of reactants for the mechanism to hold. The high radical and RAFT agent concentrations allowed the detailed examination of the nature and concentrations of both radical and nonradical species during the initial stages of the reaction. The probability of side reactions, such as termination of intermediate radicals, was enhanced due to the high concentrations of the potential reactants that were present.

Reactions were run under identical conditions for each of the experimental techniques.[30] The most likely site of termination reactions of intermediate radicals is at the dithioester carbon, although it has been suggested that bonding through the delocalized ring system may also be possible.[31] ^{13}C NMR spectroscopy was used to attempt direct observation of fixed and transient nonradical species in the polymerization process. ^{13}C-enriched CDB (at the dithioester carbon (from $^{13}CS_2$, 99%, Cambridge Isotope Laboratories)) was synthesized by standard procedures[1] (purity, ^{1}H NMR >95%). Analogous reactions were run with the unlabeled RAFT agent to aid peak assignment.

Polymerization experiments were monitored at 84 °C using a 600 MHz Varian ^{Unity}Inova NMR spectrometer operating at 150 MHz for the ^{13}C spectra. ^{13}C and DEPT (distortionless enhancement by polarization transfer) spectra were recorded throughout the reaction.[32] The resultant DEPT spectra, which only contain peaks belonging to protonated carbons, were used to identify quaternary carbon peaks in the ^{13}C spectra, which are potential intermediate radical termination products.

In the reaction with ^{13}C-labeled CDB, several quaternary carbon peaks were detected in the 74−78 ppm region (Figure 1) at intermediate to long reaction times. These exhibited chemical shifts that corresponded well (within uncertainties) with predictions (ACD labs 7.0 ^{13}C NMR predictor) for the signal due to the dithioester carbon of dithiobenzoate species formed by termination of intermediate radicals. The peak intensities (and implied concentrations) of the species were extremely low. Examples of species that could give these signals are shown in Figure 2. Significantly, peaks from other species expected to be present in these RAFT reactions were predicted not to occur near this region. The peaks in the 74−78 ppm region were not present during the initial stages of the reaction, but formed and increased in intensity after about 70 min, when the intermediate radical concentration was rapidly increasing (Figure 3), which will be discussed further below.

Very low concentrations of labeled impurities, which were only detectable due to the ^{13}C enrichment, were present in the ^{13}C-enriched CDB. Some of these impurities participated in the reaction, but their low concentration makes it extremely unlikely that any quaternary carbons generated by radical addition (termination) to these centers would be detectable. There was no time correlation between the disappearance of the impurity peaks and the appearance of peaks in the region from 74 to 78 ppm.

A duplicate reaction was run with unenriched CDB, and the reaction stopped at 183 min by rapid freezing in liquid nitrogen. ^{13}C spectra of the reaction mixture

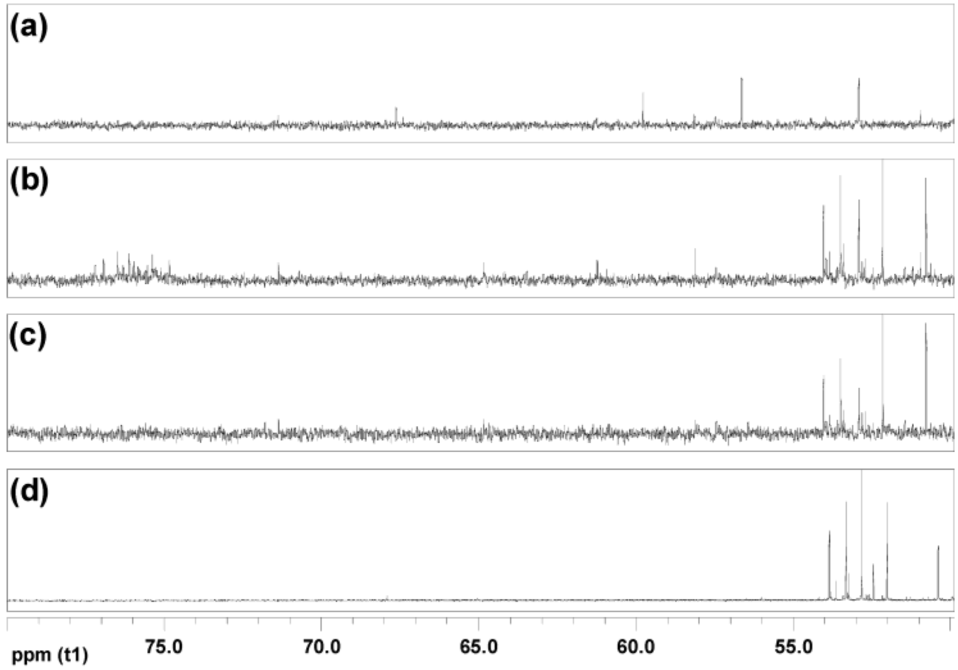


Figure 1. ^{13}C NMR spectra in the 50−80 ppm region of the solution (50 wt % in benzene or C_6D_6) free radical polymerization of styrene (0.26 g) in the presence of CDB (0.10 g) at 84 °C, using AIBN (0.010 g) as initiator: (a) ^{13}C-enriched CDB, 13 min, 128 scans; (b) ^{13}C-enriched CDB, 183 min, 128 scans; (c) ^{13}C DEPT spectrum of the enriched CDB, 183 min, 124 scans; (d) frozen sample after 183 min reaction, unenriched CDB, 17 144 scans.

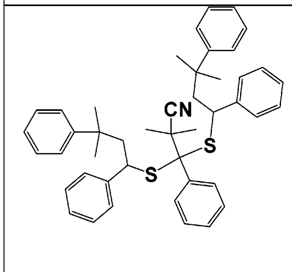
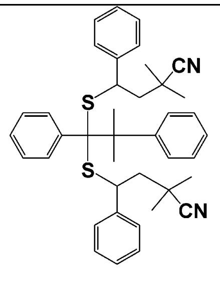
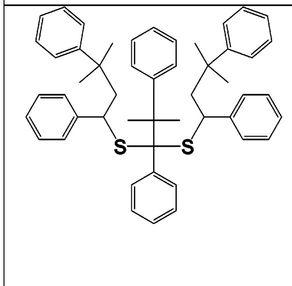
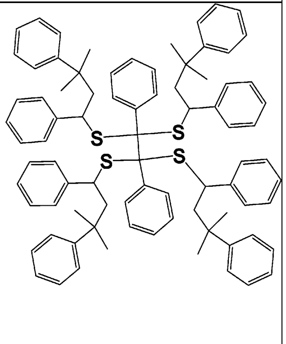
Structure/ Predicted shift of Dithioester Carbon (ppm)	Structure/ Predicted shift of Dithioester Carbon (ppm)
 68.6 (± 6.4)	 70.7 (± 6.5)
 70.7 (± 6.5)	 73.4 (± 6.5)

Figure 2. Examples of possible structures and predicted chemical shifts (and uncertainties) of species formed by the termination reactions of intermediate radicals, corresponding to the observed peaks in the 74−78 ppm region of the ^{13}C NMR spectra of the labeled CDB.

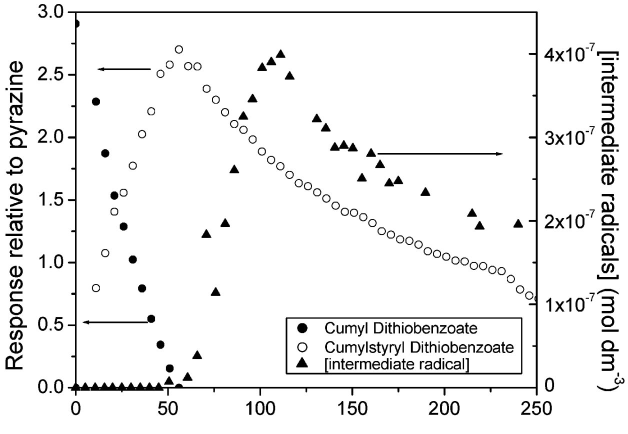


Figure 3. Intermediate radical concentration (by ESR) and CDB and CStDB (^{1}H NMR) time profiles for the solution (50 wt % in benzene or C_6D_6) free radical polymerization of styrene (0.26 g) in the presence of CDB (0.10 g) at 84 °C, using AIBN (0.010 g) as initiator.

were recorded for much longer (17 144 scans vs 128 scans for the enriched spectra), at room temperature, resulting in a much higher signal-to-noise ratio for the unenriched CDB reaction spectra than that of the enriched CDB reaction spectra. However, there were no detectable peaks in the 74−78 ppm region for the unenriched CDB spectra, indicating that the quaternary peaks detected at the same reaction time in this region using labeled CDB were due to the enriched dithioester carbon and support the assignment of terminated intermediate RAFT species. Further evidence for this assignment is now discussed in terms of both ^{1}H NMR and ESR spectroscopic observations of the reaction.

Recent ^{1}H NMR data,[6] and data from this ^{13}C study, show that the early reaction is extremely selective, particularly with respect to fragmentation, and that almost no chains reach a degree of polymerization greater than unity until all of the initial CDB adds a single monomer unit. The selectivity is directly related to the addition and fragmentation rate coefficients of the species involved in the early reaction (the "initialization" period, before all of the CDB is consumed) and is discussed in detail in a forthcoming publication.[6] The selectivity results in a succession (in time) of types of propagating and formed intermediate radicals (which will be discussed elsewhere[34]), leading to progressively greater intermediate radical stabilities, which were confirmed by in situ ESR spectra of the system.[33] The resulting intermediate radical concentrations were very low early in the reaction (0−60 min), increased rapidly (60−110 min), and reached a maximum (at 110 min) some time after the initialization period was complete (after about 55 min). The maximum concentration occurred when both growing chains attached to the dithiobenzoate contain at least one monomer unit. The reasons for the time and degree of polymerization when this maximum occurs are complex (and will be discussed in a future publication) and are mainly related to the relative stabilities of the different intermediate radicals (addition and fragmentation rate coefficients) that form as the degree of polymerization increases. The time dependencies of the intermediate radical and CDB (and the formed cumylstyryl dithiobenzoate) concentrations determined from ESR and ^{1}H NMR data, respectively, are shown in Figure 3.

Since the intermediate radical concentration is negligible during the initialization period, little termination of these species in this period is expected, which is consistent with the lack of observed peaks in the 74−78 ppm region in the ^{13}C spectra during this period. The rate of termination of intermediate radicals would be expected to be much higher once significant concentrations of intermediate radicals have formed, which occurred after about 60 min, reaching a maximum at 110 min, when most of these species will consist of two cumylstyryl chains attached to the dithiobenzoate group. It is near this time that the peaks in the 74−78 ppm region in the ^{13}C spectra appear to increase in concentration most rapidly. The correlation between intermediate radical concentration and the formation of these peaks strongly supports the hypothesis that these peaks correspond to the product of reactions of intermediate radicals.

The main reasons why species resulting from termination of intermediate radicals have been found in this study, and not in others, are the folowing:

- The concentrations of the termination products are normally extremely low with respect to other chains in a "typical" RAFT reaction, making detection difficult. Very high initiator and RAFT agent concentrations were used in this study to enhance the concentrations of products of termination reactions of both propagating and intermediate radicals, by increasing the concentrations of these species.

- This study used a ^{13}C-labeled dithioester at the carbon where the reaction of intermediate radicals is expected to occur, leading to a signal enhancement by a factor of about 88 times. Even then, the observed signals are very weak.
- Target chain lengths were very low, allowing both viscosity and the number of different species formed to be kept low, which lead to narrow, well-defined NMR signals.

The following significant observations have been made at this point:

- In situ observations of the products of the termination of intermediate radicals appear to have been made and are consistent with observations by ESR, ^{1}H NMR, and ^{13}C NMR spectroscopy.
- The reaction is very specific during these initial stages, showing a very strong preference to add a single monomer unit, followed by preferential fragmentation of the initial RAFT agent, to release the shorter (tertiary) radical, before significant numbers of longer chain species form.

The in situ observation of the formation of species by termination of intermediate radicals in CDB-mediated free radical polymerization of styrene implies that extra termination events are occurring in these reactions, other than normal combination of propagating radicals. Rate retardation will thus occur compared with an analogous conventional free radical polymerization. Precise assignments of these terminated species (and whether the reactions that form these are reversible) and relative frequency of these termination events (and the resulting degree of retardation) are currently under investigation. The possibility exists that a large fraction of the products might be due to termination by initiator fragments or other short-chain radicals due to both steric constraints and the selectivity of the fragmentation step toward producing high concentrations of the shorter, tertiary, propagating radicals (as seen by both ^{13}C and ^{1}H NMR[6]).

Although it has been shown that this reaction will lead to radical loss events and therefore rate retardation, it might not be the only such cause. The cause(s) of rate retardation can only reliably be proven by quantitative analysis of rate retardation and corresponding amounts of termination products; this work is currently in progress.

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(30) A typical reaction used a 50 wt % solution of CDB (0.10 g, 3.68×10^{-4} mol (purity, ^{1}H NMR >98%), synthesized and purified according to the method of Le et al.[1]), and AIBN (0.010 g, 3.6×10^{-5} mol), with styrene (0.26 g, 2.46×10^{-3} mol) in benzene (or C_6D_6, for NMR reactions, 0.25 g, 2.99×10^{-3} mol).

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(32) A total of 128 transients with a 6 μs (43°) pulse width, a 1.3 s acquisition time, and a 1 s pulse delay were accumulated for each ^{13}C spectrum; 124 transients were accumulated for each DEPT spectrum. The DEPT spectra were collected using a modified DEPT sequence in which a final ^{1}H decoupler pulse of 45° was used.

(33) The ESR spectra (and standards) were recorded on a Bruker Elexsys E500 spectrometer in the X-band region, with the ER4122SHQ cavity preheated to the reaction temperature. The magnetic field was modulated at 100 kHz, with amplitude 0.1 mT, and a microwave power of 2 mW was used. Spectra were recorded as single 1 min scans and adjusted by subtraction of cavity scans under identical conditions, and double integrals were compared with those of a range of TEMPO standards.

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