Macromolecules **2004,** *37,* 2383−2394

Beyond Inhibition: A ^{1}H NMR Investigation of the Early Kinetics of RAFT-Mediated Polymerization with the Same Initiating and Leaving Groups

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Received October 1, 2003; Revised Manuscript Received January 27, 2004

ABSTRACT: In situ ^{1}H nuclear magnetic resonance (NMR) spectroscopy has been used to directly investigate the processes that occur during the early stages (typically the first few monomer addition steps) of an AIBN-initiated reversible addition−fragmentation chain transfer polymerization of styrene in the presence of the RAFT agent cyanoisopropyl dithiobenzoate at 70 and 84 °C. The change in concentration of important dithiobenzoate species as a function of time has been investigated. It was found that the reaction was extremely selective during the period of consumption of the initial RAFT agent (defined as the initialization period), with almost no production of RAFT-capped chains of degree of polymerization greater than unity until all of the cyanoisopropyl dithiobenzoate was converted to its single monomer adduct. The rate-determining step for this process was found to be the addition (propagation) of the cyanoisopropyl radicals to styrene. During the period where the initial RAFT agent was consumed, fragmentation of formed intermediate radicals strongly favored the production of the tertiary cyanoisopropyl radicals, which were the only significant propagating species during that period. This led to a greater rate of propagation during that period, since the propagation rate coefficient for the cyanoisopropyl radical is greater than that of polystyryl radicals. It was found that inhibition effects can occur in the presence of RAFT agents in homogeneous media when the k_p for initiator fragments is smaller than for long chain radicals, which is a result of this aspect of the RAFT mechanism.

Introduction

Nuclear magnetic resonance spectroscopy is a powerful tool for product analysis. In situ NMR is an elegant way to investigate the kinetics of free radical polymerization reactions. Some pioneering work has been carried out,[1−4] but the limitations of kinetic experiments are usually associated with the complexity of the system to be investigated.

In situ NMR investigation of free radical polymerization is normally extremely complicated due to the nature of a conventional free radical polymerization reaction. High molecular weight polymer forms very rapidly, resulting in peak broadening (two factors often contribute to this: overlap of peaks of many slightly different species and high system viscosities) and difficulty in identifying and examining specific species (usually for the same reasons and also because the very low concentrations of polymer end groups are often below the detection limit of NMR spectroscopy).

In living radical polymerization this situation is significantly different. Living radical polymerization is characterized by a linear increase in molecular weight with monomer conversion and consequently does not usually involve high molecular weight polymer formation early in the reaction.

There are a number of living radical polymerization techniques that are commonly used, each having its own unique characteristics and specific advantages and/or disadvantages. Two of the most well-established techniques are stable free radical mediated polymerization (SFRP)[5,6] and atom transfer radical polymerization (ATRP),[7−10] both of which are reversible end-capping techniques. Recently, there has been a renewed interest in transfer methodology.

Reversible addition−fragmentation chain transfer, or RAFT,[11−16] is a living radical polymerization technique that is extremely versatile and robust. It is compatible with almost all monomers and most conditions that are applicable to conventional free radical polymerization. The RAFT process and its benefits are achieved simply by the addition of a suitable RAFT agent to the polymerization mixture.

In Scheme 1 the elementary reactions for the central exchange process of the RAFT mechanism are depicted. (The main focus of this paper will be on the reactions preceding the central RAFT exchange process, but the central exchange process is used to demonstrate the importance of considering the transfer reactions as bimolecular processes.) The process requires the interaction of two species. The first species is the incoming radical, which adds to the sulfur, across the carbon−sulfur double bond of the thiocarbonyl species. The second species is the thiocarbonyl thio compound, the

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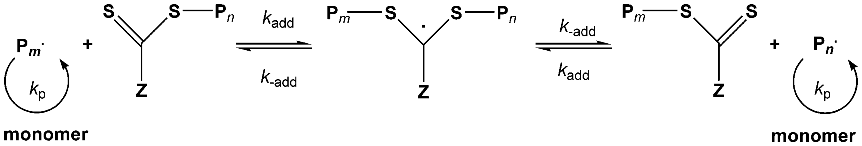
10.1021/ma035478c CCC: $27.50

Scheme 1. Elementary RAFT Process as Commonly Accepted in the Literature[11]



mediating species in the polymerization, which is referred to as the RAFT agent.

There are a number of mysteries regarding the details of the mechanism of the RAFT process. If the central exchange process is all that controls the RAFT-mediated polymerization reaction, then there are some common observations that cannot easily be explicitly explained by this mechanism. The most significant anomalies in RAFT systems are the inhibition and retardation phenomena that occur in many polymerizations.[17−19] These anomalous phenomena have been investigated by a number of authors, including ourselves, and most investigations have focused on the fate of the intermediate radical species that is formed in the RAFT process and its effects on polymerization kinetics. In this paper the issue of inhibition is addressed directly, with focus on the cause and length of the observed inhibition period with reference to the reaction temperature. In the first part of the study, a system in which both the initial RAFT agent leaving group and the initiator-derived radical are the same will be considered.

The relatively stable intermediate radical (which will be referred to as $Y^\bullet$) that is formed by the addition process can fragment to release one of two radical species, namely, the original incoming radical species ($P_m^\bullet$, a propagating radical of degree of polymerization m) or the homolytic leaving group ($P_n^\bullet$) that was previously a part of the RAFT agent.

The rate of polymerization in a radical polymerization is a function of the concentration and type of radical available for propagation and is a function of all radical generation and loss mechanisms. If an equilibrium exists in a RAFT system, then

$$K_{eq} = \frac{k_{add}}{k_{-add}} = \frac{[Y^\bullet]}{[P^\bullet][PX]} \qquad (1)$$

Here K_{eq} is the equilibrium constant, k_{add} and k_{-add} are the rate coefficients for addition and fragmentation, $[Y^\bullet]$ and $[P^\bullet]$ are the concentrations of the intermediate and propagating radicals, and [PX] is the concentration of RAFT-capped chains. K_{eq} should be constant for a particular RAFT agent/monomer combination at a particular temperature and independent of other conditions. In previous studies[20] it was observed that, early in the reaction, the apparent K_{eq} varies with time and overall degree of polymerization of propagating chains. This implies that the rate coefficients of addition and fragmentation vary significantly with propagating chain type and degree of polymerization during the first few monomer additions per growing chain in the RAFT polymerization process.

Previously,[20] it was suggested that this could be due to a number of possibilities, including chain length dependence of the addition and fragmentation rate constants and possibly termination of the intermediate radical species, either reversibly or irreversibly. The possibility of termination of the intermediate radicals has also been investigated by Monteiro et al.[17] and Kwak et al.[18] Barner-Kowollik et al.[19] have approached the problem by discounting the possibility of intermediate radical termination and suggesting that the inhibition period that is observed in some particular RAFT polymerizations, which is reported as being RAFT agent dependent, could be explained (from modeling results) by the concept of slow fragmentation. Most recently, Barner-Kowollik et al.[21] proposed a reduced irreversible termination and a potential reversible termination of the intermediate radical.

The models provided by these previous studies do not fully explain all the phenomena that have been observed or have not been experimentally validated. The slow fragmentation approach is contradictory[22] to published ESR experimental data,[20] and the products of the termination of the intermediate radical have only very recently been shown to form during the course of a polymerization,[23] although the relative probability of those termination events has not yet been determined.

To fully understand the RAFT process, it is important to examine the nature of the radical species that are present in each reaction. Radical reactivities for addition and radical leaving group stabilities are very important factors that, together with reactant concentrations, determine the rates of polymerization in a RAFT-mediated polymerization. Moad and Solomon's review provides a deeper examination of the general factors that affect radical stabilities and reactivities.[24] It is instructive to consider that, within a series, tertiary radicals are typically more stable and less reactive than secondary radicals, and by the same token, primary radicals are more reactive than secondary radicals. Within the three classes of radicals, the substituents play a crucial role in determining radical behavior. Both steric and electronic effects are important to determine rates of reactions with specific molecules.[25,26]

The current study addresses the early reaction (the first few monomer addition steps) of AIBN-initiated styrene polymerization in the presence of the RAFT agent cyanoisopropyl dithiobenzoate at 70 and 84 °C. The early reaction period before complete conversion of the initial RAFT agent to include growing polymer chains is addressed, i.e., the first monomer addition step(s). In situ ^{1}H NMR spectroscopy was used to directly investigate the concentration of several characteristic species, and thus the rate of polymerization, in the first steps of dithiobenzoate-mediated polymerizations.

Experimental Section

Chemicals. Styrene monomer (Plascon Research Centre, University of Stellenbosch, estimated purity ~99% ^{1}H NMR) was washed with 0.3 M KOH and then distilled under vacuum prior to use to remove inhibitor and polymer. Azobis(isobutyronitrile) (AIBN, Riedel De Haen) was recrystallized from AR grade methanol and found to be ~99% pure by ^{1}H NMR. Deuterated solvents (C_6D_6 99.6%, 0.1% TMS, both from Sigma-Aldrich) and pyrazine (99%, Sigma-Aldrich) were used as received.

Sample Preparation. Samples were prepared by weighing out the masses as given in Table 1. The samples were then transferred to NMR tubes. The tubes were flushed with

Table 1. Composition of Reaction Mixtures for in Situ NMR Analysis[a]

	solvent		initiator		styrene		RAFT agent			
sample	mass (g)	mol ($\times 10^{-3}$)	mass (g)	mol ($\times 10^{-5}$)	mass (g)	mol ($\times 10^{-3}$)	mass (g)	mol ($\times 10^{-4}$)	ratio monomer to RAFT agent $[M]_0/[R]_0$	RAFT agent: initiator $\times$ 2 ($[R]_0/2[I]_0$)
1[b]	0.300	3.56	0.010	6.75	0.25	2.40	0.107	4.84	4.96	3.96
2[c]	0.300	3.56	0.010	6.10	0.24	2.31	0.100	4.52	5.10	3.70
3[b]	0.365	4.34	0.011	6.71	0.38	3.68	0	0	0	0
4[c]	0.300	3.56	0.010	6.10	0.38	3.68	0	0	0	0

[a] The solvent used was deuterated benzene (99.6%), and the initiator used was AIBN. The RAFT agent is cyanoisopropyl dithiobenzoate (AD). [b] Reaction carried out at 70 °C. [c] Reaction carried out at 84 °C.

ultrahigh-purity nitrogen for 10 min. At this point a sealed glass insert containing the integration reference standard (pyrazine dissolved in C_6D_6) was inserted, and the tubes were sealed. The use of the reference standard was solely for integration purposes.

Analysis. NMR spectra were recorded on a 600 MHz Varian $^{\text{Unity}}$Inova spectrometer. A 5 mm inverse detection PFG probe was used for the experiments, and the probe temperature was calibrated using an ethylene glycol sample in the manner suggested by the manufacturer using the method of Van Geet.[27] ^{1}H spectra were acquired with a 3 μs (40°) pulse width and a 4 s acquisition time. The chosen pulse angle allowed complete relaxation of all relevant peaks in the sample, the T_1's of the system having been measured and taken into account. For the ^{1}H kinetic experiments, samples were inserted into the magnet at 25 °C, and the magnet was fully shimmed on the sample. A spectrum was collected at 25 °C to serve as a reference. The sample was then removed from the magnet, and the cavity of the magnet was raised to the required temperature (70 or 84 °C). Once the magnet cavity had stabilized at the required temperature, the sample was reinserted (time zero) and allowed to equilibrate for approximately 5 min. Additional shimming was then carried out to fully optimize the system, and the first spectra were recorded approximately 10 min after the sample was inserted into the magnet.

Integration of spectra was carried out both manually and automatically to allow identification of species during formation. Automated integration was carried out using an ACD labs 7.0 ^{1}H processor.

Synthesis of Transfer Agents. The synthesis of bis(thiobenzoyl) disulfide was carried out following the method of Thang et al.,[28] with the modifications of de Brouwer et al.[29] The synthesis of cyanoisopropyl dithiobenzoate was carried out according to the method of Le et al.[11] and purified by liquid chromatography on a silica column using a 4.5:4.5:1 ratio of pentane:heptane:diethyl ether. The product was dried under vacuum to provide the compound with a ^{1}H NMR purity estimated at ~98%.

Results and Discussion

The NMR data that were obtained during the investigation provide instantaneous concentrations of detectable nonradical species in the RAFT reactions. The effect of chemically induced nuclear polarization on the apparent concentrations of the observed NMR signals in the experiments was found to be minimal under the conditions used.

The concentrations and molar ratios of the reaction components used in all of the reactions in this study are summarized in Table 1. A representative selection of ^{1}H NMR peaks that were integrated for this study can be found in Table 2, and a sample spectrum showing the most important peaks after initialization (see below) was completed is shown in Figure 1. Although the styrene peaks in the spectra collected were large in comparison to the species forming, no dynamic range problems were experienced. As can be seen from Figure 1, a good signal-to-noise ratio was achieved, allowing for integration of the smaller peaks in the spectrum.

Table 2. ^{1}H NMR Chemical Shifts of a Representation of Integrated Species Relevant to the Investigation of Initialization in the Cyanoisopropyl Dithiobenzoate-Mediated Polymerization of Styrene[a]

methyl peaks of R groups δ (ppm)	ortho protons of corresponding dithiobenzoate ring δ (ppm)	species
singlet 0.93	N/A	AA
singlet 1.45	doublet 7.71	AD
two peaks 1.01, 0.87	doublet 7.85	ASD
two peaks 0.81, 0.65	doublet 7.90	AS_2D[b]
two peaks 0.89, 0.72	doublet 7.79	

[a] Species AA is tetramethylsuccinonitrile, AD is cyanoisopropyl dithiobenzoate, and AS_nD are the styrene adducts of AD containing *n* styrene units. [b] Note stereochemistry.

Figure 2 shows the chemical structures of the primary species of interest for this study. For convenience, the following naming convention will be used. Species AD is the initial RAFT agent containing the dithiobenzoate species (D) and the initial cyanoisopropyl leaving group (A), and ASD is the dithiobenzoate species formed by the single styrene (S) adduct of a cyanoisopropyl radical ($A^\bullet$), while AS_2D and AS_3D species are formed by the respective second and third styrene adducts of the cyanoisopropyl radicals. Note that ASD contains one chiral center, and the resonances of the diasterotopic groups in this molecule can be clearly observed (Figure 1). AS_2D is a diastereomer, and consequently while ASD has only two methyl resonances in the ^{1}H NMR spectrum, AS_2D has four.

The assignments of the ^{1}H NMR peaks were confirmed in a number of ways. Initially, the ^{1}H NMR spectrum of each component in the reaction mixture was obtained to ensure the peaks belonging to each component were unambiguously assigned. Observation of AIBN decomposition at 70 and 84 °C by ^{1}H NMR spectroscopy allowed for the assignment of the peak due to tetramethylsuccinonitrile (AA), which forms during this process. Once the reaction had started, AIBN was consumed to produce AA and initiate polymerization. Styrene was consumed to primarily produce ASD, and AD was consumed to produce ASD. The assignment of the ASD peaks was confirmed by comparing the rates of consumption of AD and styrene and the production of the ASD peaks. There was very good agreement in the time evolution of integrated areas of all corresponding peaks. Additionally, it was found that when all of the AD peaks (both methyl and ortho phenyl protons) disappeared, the assigned ASD peaks reached a maximum, and the amount of monomer consumption according to the assigned styrene peaks was in good agreement with the amount required for complete consumption of the AD species. Thus, all assigned peaks showed good consistency in the time dependences of their intensities, and the rate of monomer consumption was internally verified. The assignments of the peaks for AS_2D were similarly made. Further verification of the peak assign-

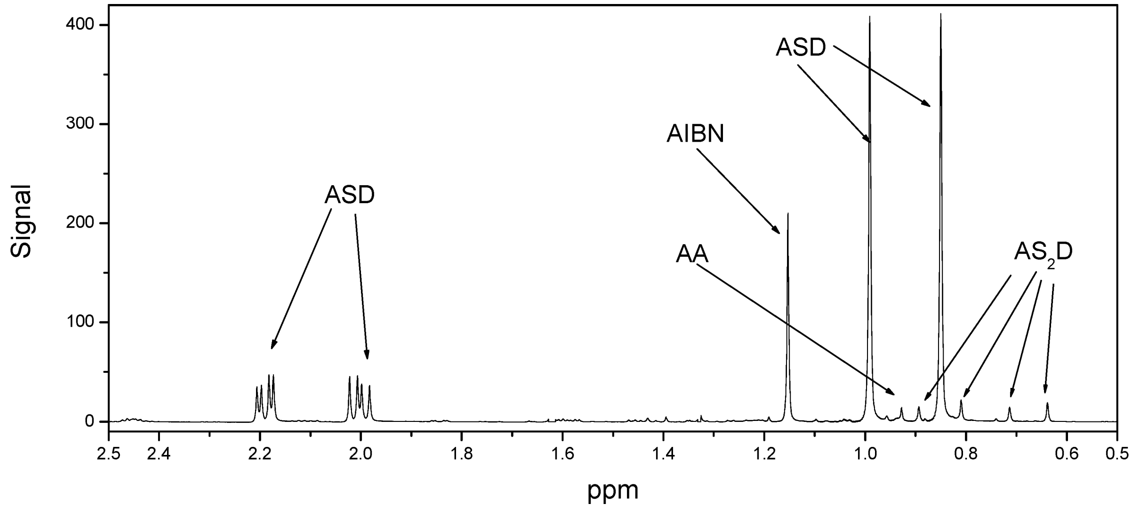


Figure 1. Typical ^1H NMR spectrum between 2.5 and 0.5 ppm, directly after initialization, at 70 °C, showing the peaks corresponding to several of the important species studied here. AS_nD are the peaks for the *n*-meric styrene adducts of the cyanisopropyl dithiobenzoate, AA is the product of the termination reaction between two cyanoisopropyl radicals, and AIBN is the initiator. Reactants (reaction 1): 3.56×10^{-3} mol of C_6D_6, 6.75×10^{-5} mol of AIBN, 2.40×10^{-3} mol of styrene, 4.84×10^{-4} mol of cyanoisopropyl dithiobenzoate.

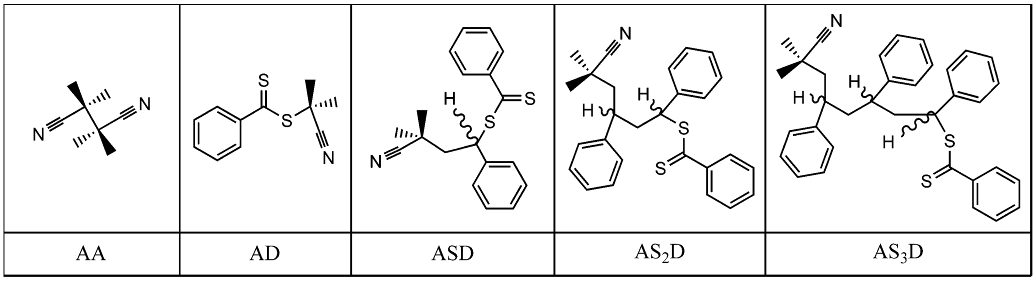


Figure 2. Predominant nonradical species of interest for the investigation of the early period of the free radical polymerization of styrene in the presence of cyanoisopropyl dithiobenzoate, using AIBN as an initiator.

ments was carried out using various NMR experiments on the samples after reaction at room temperature. 2D NMR techniques were investigated, but the most information in regards to confirmation of the peak assignments was obtained by carrying out 1D TOCSY and 1D NOESY experiments. In this way it was possible to identify peaks belonging to a single species and confirm the asssignments. Especially valuable was that the 1D NOESY experiments made it possible to identify the two diastereomers of AS_2D.

This paper addresses, for simplicity, the use of cyanoisopropyl dithiobenzoate as the RAFT agent. The use of this agent, styrene monomer and AIBN as initiator, results in a single active tertiary radical species in the system. This system is far less complex than in the case in which two different tertiary radical species are present, which is discussed in a companion paper.[30] It should be noted that the choice of styrene as a monomer means that the vast majority of radicals formed from propagation reactions should be secondary radicals.

Temperature plays an important role in the rate of reactions in a RAFT-mediated polymerization. For that reason two different temperatures were used to determine whether the results could be explained by the same arguments.

The first experiment was carried out for a period of 4 h at 70 °C, with a reaction mixture containing styrene monomer, cyanoisopropyl dithiobenzoate (species AD), and AIBN initiator (reaction 1, Table 1). Figure 3 shows the time dependence of the concentrations of dithiobenzoate species during this reaction. A rapid decrease in concentration of the species AD and a buildup of the species ASD until the cyanoisopropyl dithiobenzoate had been completely consumed (after 50 min) were observed. At this point the concentration of species ASD reached a maximum. The nearly linear decrease of [AD] with reaction time is indicative of a pseudo-zero-order reac-

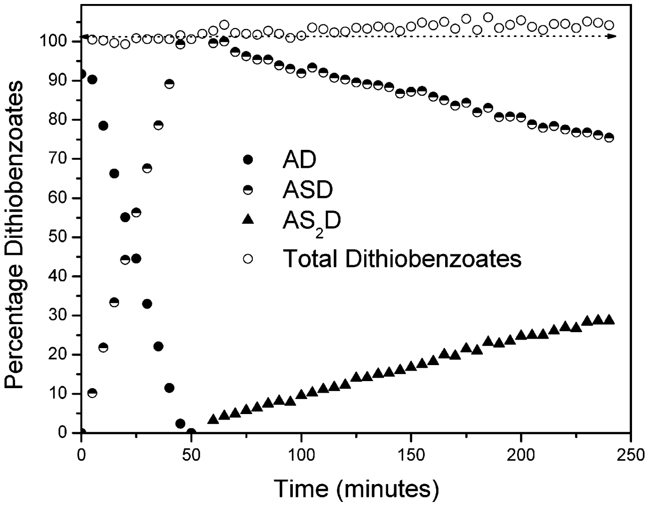
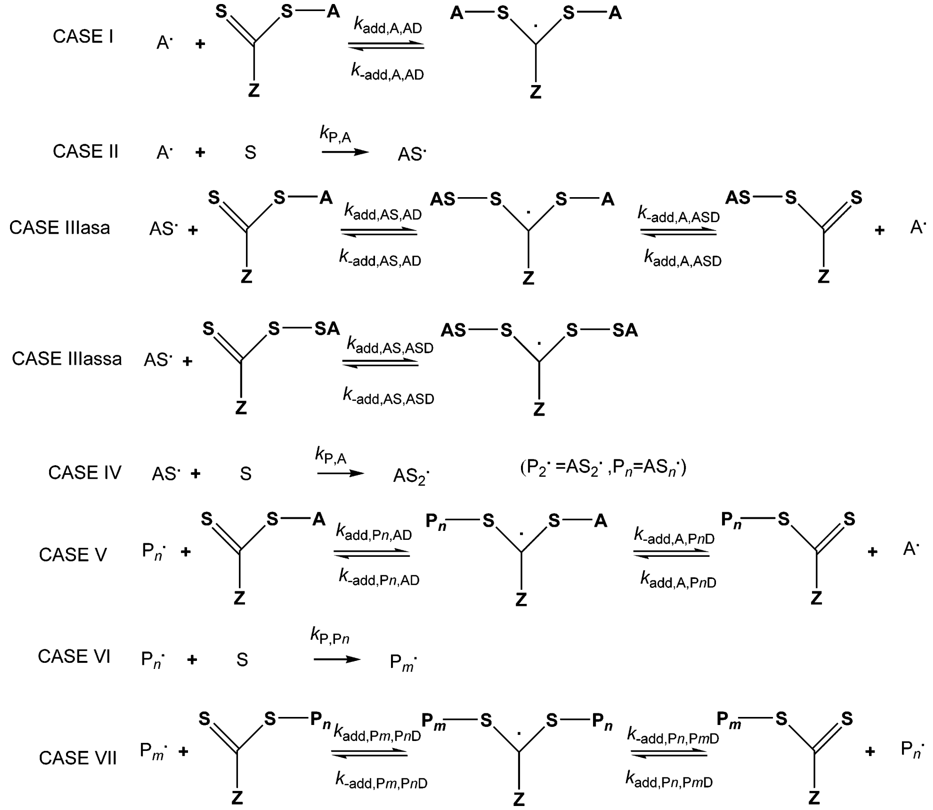


Figure 3. Relative concentrations of methyl protons of dithiobenzoate species vs time in the free radical polymerization of styrene in the presence of cyanoisopropyl dithiobenzoate using AIBN as an initiator polymerized in situ at 70 °C (Table 1, reaction 1: 3.56×10^{-3} mol of C_6D_6, 6.75×10^{-5} mol of AIBN, 2.40×10^{-3} mol of styrene, 4.84×10^{-4} mol of cyanoisopropyl dithiobenzoate).

Scheme 2. Steps Involved in the Initialization Period of the RAFT Reaction of Cyanoisopropyl Dithiobenzoate, Styrene Monomer, and AIBN Initiator[a]



[a] The subcases of case III are variants of reactions of AS• radicals with the two different forms of the RAFT-capped species that are present at that stage of the reaction.

tion in [AD]. Once all of the cyanoisopropyl dithiobenzoate had been converted to ASD (and a very small amount of higher species), the second monomer additions to the radical species begin to increase in frequency (to form species AS_2D). Note that almost no formation of this species occurred before this stage; i.e., the reaction is extremely (although not completely) selective. This will be explained below.

There are several important points to note here. The first is that the conversion of the species AD to ASD is complete, with no detectable "loss" of dithiobenzoate groups to side reactions or the formation of high (detectable) concentrations of intermediate radical species. The termination products for such reactions could not be detected during the course of the reaction (or were below the detection limits of the instrument used), implying that the concentrations of such species were below 10^{-3} M during this reaction. The same was observed for all reactions in this study. The second point to note is that the early reaction is extremely selective. Only one type of radical addition reaction appeared to occur to any significant extent during this initial period (before 50 min), i.e., the propagation of cyanoisopropyl radicals. Very little propagation of longer chain radicals occurred until after this initial period. This also implies that the concentrations of these other propagating radicals and the corresponding thiocarbonylthio-functional dormant chains were very low during this period.

On the basis of the above observations, to facilitate discussion, the following terms are defined: *Initialization* is the process by which the starting RAFT agent is consumed. *Initialization period* is the period in which the starting RAFT agent is consumed. *Initialization time* is the time required for the starting RAFT agent to be completely consumed (converted to other forms). A point to note is that the initialization period is not necessarily the same as a preequilibrium period. "Equilibrium" is not necessarily (probably not) attained immediately following initialization. Also, there are cases where the system might reach a steady state long before initialization is completed. The key point in the current system is that the behavior of the reaction is very different before and after initialization.

Reactions of Radical Species during Initialization. In Scheme 2, the relevant reactions during the polymerization are represented in a way that allows a qualitative discussion on the rate-determining step; termination events are not displayed. The relative probabilities of competing reactions occurring are proportional to their overall rates, which are proportional to the concentrations of reactants and the rate coefficients for the competing processes. The reagent concentrations for this system are a function of a combination of the addition, fragmentation, and propagation rates of the species shown in Scheme 2. It is important to note that there are several different types of intermediate radical species in this period, each of which has different stabilities and (asymmetric) fragmentation rate coefficients. The apparently large differences in addition and fragmentation rate coefficients for the different species involved in this initial period are key to understanding the behavior of the reaction during this period. The most important of these differences is the much faster (preferred) fragmentation rate of intermediates containing a potential tertiary leaving group, to form a RAFT agent and a tertiary radical. This will be discussed in more detail later. The competing processes and fates of each of the important species in this initial period are now described in detail.

Cyanoisopropyl radicals ($A^•$) generated in the system will undergo one of three main reactions: first, addition to a RAFT agent (relative frequency = k_{add}[RAFT], e.g., $k_{add,AD}$[AD]), for each type of RAFT agent, to form an intermediate radical (these reactions are depicted in cases I, IIIasa, and V; note that case I gives a degenerate product after fragmentation of the formed intermediate radical); second, addition to monomer (propagation, with relative frequency = $k_{p,A}$[M], case II) to give radical species $AS^•$; or third, termination with other radical species.

The radical species $AS^•$ can participate in reactions that are similar to the reactions undergone by the $A^•$ radicals. These reactions are as follows: first, addition (with different addition rate coefficients) to the RAFT agents (cases IIIasa, IIIassa, or VII); second, propagation with the relevant propagation rate coefficient to form radical species $AS_2^•$ (case IV); or third, termination. The products of these processes will be described below.

For the RAFT process to be efficient, propagating radicals must display higher addition rates to the RAFT agent than to monomer.[11] This prevents a possible scenario of rapid propagation to form long chains before the addition−fragmentation process can allow exchange (via the intermediate radical species) between growing chains. Depending on the monomer concentration, a portion of initiator-derived radicals adds directly to the RAFT agent. These reactions cannot be distinguished in the reaction under discussion since when $A^•$ adds to AD, eventually resulting in fragmentation to form $A^•$, the overall result is degenerate, and there is no effect on the NMR spectrum. A fraction of $A^•$ species will eventually add to a styrene monomer, leading to the formation of $AS^•$ in the reaction mixture. The degenerate type of interchange will become evident if the initiating radical is different from the RAFT leaving group (as seen in the second paper of this series[30]).

The fragmentation behavior of each of the formed intermediate radical species is key to the behavior of the early reaction. If the possibility of termination reactions of the intermediate radicals is neglected (probably a good approximation here, since their concentrations during initialization are very small[31]), then each of these intermediate radicals will soon undergo fragmentation, to again produce a propagating radical and RAFT agent. The fragmentation reaction is generally very asymmetric, with a very strong preference to form the more stable propagating radical.

Secondary radical species are more reactive than tertiary radical species with the same substituents (as the reactivity of radical species is inversely related to their stability) when comparing reactions with the same reagents. When radical species with varied substituents are compared, however, care must be taken when making generalizations. Cyanoisopropyl (and cumyl, see the second part of this series[30]) radicals have higher addition rate constants to styrene than the long chain propagation rate constant for styryl radicals.[32,33] These radicals are tertiary and are superior leaving groups and are thus more likely to fragment when attached to a RAFT agent than their respective styryl adducts. For example, in the case of $ASDA^•$, the fragmentation rate, $k_{-add,ASD,A}$, of the tertiary cyanoisopropyl radicals will be much larger than the fragmentation rate, $k_{-add,AD,AS}$, of the secondary $AS^•$ radical species (case IIIasa in Scheme 2) due to their higher radical stabilities.[24] This difference in leaving ability generates a large asymmetry in fragmentation rate coefficients for the same intermediate radical (e.g., $ASDA^•$), with the much greater rate coefficient being for the formation of the more stable leaving radical. This implies that the lifetime of intermediate radicals containing at least one tertiary radical will be shorter than for equivalent secondary species, with the large asymmetry in fragmentation rate coefficients leading to a preference for the tertiary radical to result from the fragmentation step. The generated $AS^•$ radical species will therefore quickly become end-capped as a thiocarbonyl thio species (ASD) because addition is very fast and will displace tertiary radicals ($A^•$ in this case) that are attached to the RAFT agent (case IIIasa). The expelled tertiary radicals can then undergo addition (case I, IIIasa, V) or propagation (case II).

The tertiary radicals ($A^•$) will be unlikely to displace the secondary radical species (e.g., $AS^•$) that are trapped in the dormant state (e.g., case IIIasa) (since the rate coefficient for fragmentation to form the secondary species is much lower than that to form the tertiary species). In such a case, they ($A^•$) will instead begin to behave in a fashion similar to a reversible end-capping reaction such as ATRP or SFRP until such time as they encounter a monomer and propagate, encounter an AD species to form an intermediate radical, before again fragmenting (which has a degenerate end-product after fragmentation), or undergo termination. This means that it is still possible to have a controlled process occurring in the system, but the mechanism by which chains are being activated to allow propagation is different than that of the normal RAFT process.

Almost every cyanoisopropyl dithiobenzoate molecule (AD) in the system is converted to an ASD dormant species before significant concentrations of $AS_2^•$ radicals (and therefore any AS_2D or higher dormant species) have the opportunity to develop in the system. This selectivity results from a combination of the fast rates of addition of propagating radicals to the RAFT agent and the extreme asymmetry of the fragmentation step. Accordingly, the formation of $AS^•$ radicals (which quickly form the ASD species) becomes the rate-determining step in the process of the formation of ASD from AD. It has been mentioned above that the decrease in RAFT agent concentration initially occurs according to a pseudo-zero-order reaction. ASD cannot form until $AS^•$ radicals are formed, which implies that the rate-determining step is the propagation of $A^•$ to form $AS^•$ (with rate = $k_{p,A}$[M][$A^•$]), since this is much slower than the addition of $AS^•$ to AD. The result of this propagation step is visible as the formation of ASD from AD.

As it is unlikely that a secondary radical will be displaced by the addition of a tertiary radical to ASD, the probability of the secondary radical species being reactivated by a transfer step (i.e., case IIIassa, an addition of and then fragmentation to form a secondary species) is dependent on the active concentration of the aforementioned secondary radical species. Since radicals are first formed as tertiary species in this system, which will not activate the secondary radical species by addition to RAFT agents, reactivation of those species depends on both propagation of the cyanoisopropyl radicals and their consequent addition to a RAFT agent that already contains a dormant secondary species. This will only occur when there is a significant concentration of RAFT agents containing dormant secondary species, which is not the case during the early stages of the initialization period. In the early stages of this period, the rate of addition of AS• to the initial RAFT agent (containing tertiary species) is too high to allow significant concentrations of AS• to exist. Thus, the dominant propagating radical will be A•, and the concentration of the secondary radical species (and ASD) will increase until it reaches a maximum after the end of the initialization period (when no AD remains). This has a significant effect on the total concentration of intermediate radical species in the system, since only intermediate radicals with at least two secondary species will be relatively stable. Once a significant concentration of RAFT agents containing dormant secondary species (ASD) is formed at the end of this period, and a significant fraction of secondary radicals are present (AS•), longer chains may form in significant concentrations, and more stable intermediate radicals will form. This should lead to a buildup in intermediate radical concentration, reaching a maximum some time after initialization has been completed. This has indeed been observed in recent ESR spectroscopic studies of this system.[31]

The most prominent criteria for the extremely selective and stepwise behavior in the initialization period, as observed here, are first that the fragmentation of the formed intermediate radicals is very selective toward radicals that have not yet undergone propagation and second that addition of propagating radicals of degree of polymerization of at least unity to the RAFT agent is much faster than to monomer. The first of these criteria will usually hold if the initial leaving group on the RAFT agent is a much better leaving group than that formed after one propagation step, as is the case here. The second criterion will hold if $k_{\mathrm{add}}[\mathrm{RAFT}] \gg k_{\mathrm{p},1}[\mathrm{M}]$ (with the appropriate k_{add} for the incoming radical and for all forms of the RAFT agent), which will typically be the case when efficient RAFT agents are used. $k_{\mathrm{p},1}$ (the propagation rate coefficient for a monomeric radical) is chosen here since $k_{\mathrm{p},1}$ is typically greater than k_{p}. In these systems, most oligomeric radicals will consist of a single monomer unit added to an initiator or RAFT leaving group fragment. If $k_{\mathrm{add}}[\mathrm{RAFT}] \ll k_{\mathrm{p},1}[\mathrm{M}]$, then the selective and stepwise behavior will probably not occur since chains of degree of polymerization greater than unity will form before all of the initial RAFT agent has been consumed. Scenarios in which this is likely are when k_{add} (e.g., a low activity RAFT agent, such as a MADIX agent) is small, [RAFT]/[M] is small (e.g., a very high target molar mass), or $k_{\mathrm{p},1}$ is very large (which might occur for some initiators and/or very active monomers). Note that the [RAFT]/[M] ratio can be kept high during initialization, and further monomer added, if this problem arises.

Effects of Temperature. A duplicate reaction was carried out at 84 °C (reaction 2, Table 1). The time dependence of the concentrations of important species is shown in Figure 4. As expected, the reaction rate is substantially faster than in the case of the reaction carried out at 70 °C. In fact, the reaction proceeds so rapidly that the cyanoisopropyl dithiobenzoate is consumed prior to the time the first spectrum was collected. This is presumably due to both the higher radical flux due to initiator decomposition and the higher propagation rate coefficient for the cyanoisopropyl radicals.

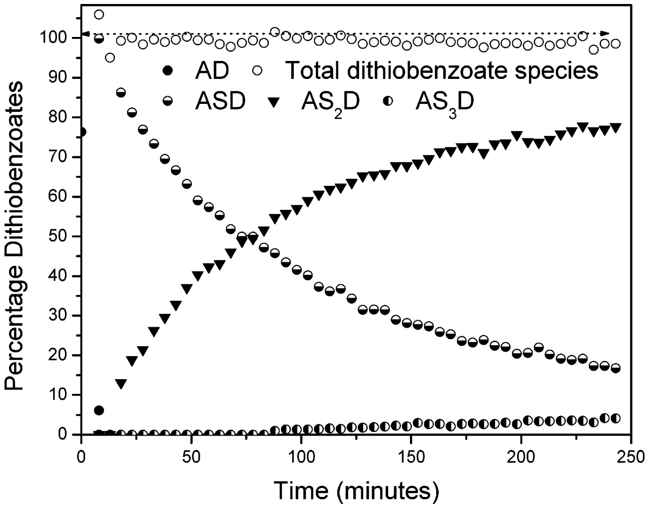


Figure 4. Relative concentrations of ortho protons of the dithiobenzoate rings vs time in the free radical polymerization of styrene in the presence of cyanoisopropyl dithiobenzoate using AIBN as an initiator polymerized in situ at 84 °C (reaction 2, Table 1: 3.56 × 10^{-3} mol of C_6D_6, 6.1 × 10^{-5} mol of AIBN, 2.31 × 10^{-3} mol of styrene, 4.52 × 10^{-4} mol of cyanoisopropyl dithiobenzoate).

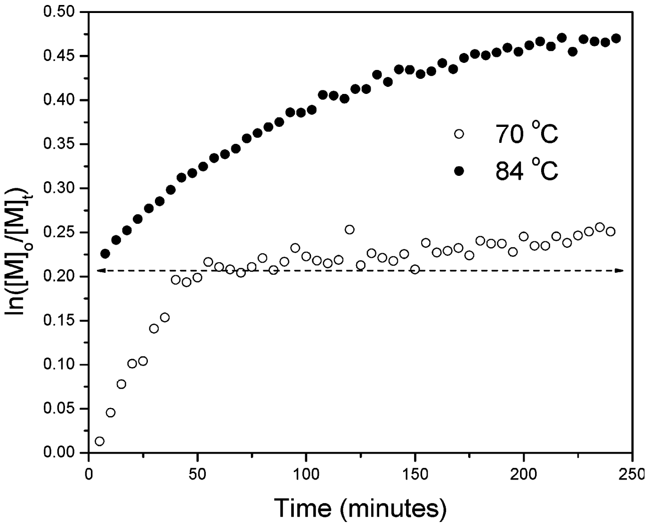


Figure 5. Logarithmic plot of conversion vs time in the reactions of cyanoisopropyl dithiobenzoate with AIBN and styrene in deuterated benzene at 70 and 84 °C. Reactions 1 and 2, Table 1. Reaction 1: 3.56 × 10^{-3} mol of C_6D_6, 6.75 × 10^{-5} mol of AIBN, 2.40 × 10^{-3} mol of styrene, 4.84 × 10^{-4} mol of cyanoisopropyl dithiobenzoate. Reaction 2: 3.56 × 10^{-3} mol of C_6D_6, 6.1 × 10^{-5} mol of AIBN, 2.31 × 10^{-3} mol of styrene, 4.52 × 10^{-4} mol of cyanoisopropyl dithiobenzoate.

Overall, the same characteristics were observed at this higher temperature. The reaction showed similar selectivity, with no significant concentrations of AS_2D or higher dormant species formed until after the end of the initialization period, followed by a decrease in rate after the end of the initialization period.

Monomer Consumption. Some interesting observations can be made when comparing the fractional conversion for reactions 1 and 2 in the first-order kinetic plot in Figure 5. The rate of monomer consumption is substantially higher during the initialization period than after this period.

The substantial decrease in rate of reaction after the initialization period at 70 °C is so extreme that after the initialization period polymerization appears to cease (though it must be noted that it does not, the rate is just so slow that it would not be noticed by most analysis techniques). This is consistent with reports of systems that show little polymerization especially at lower temperatures, even though radicals are being generated in the system.[34]

The rates of polymerization in the reactions, normalized to monomer concentration, are equal to the sum of $k_p[P^\bullet]$ for all propagating species present. The dominant propagating species in the two periods of the polymerization (i.e., initialization and equilibrium) are quite different, namely $A^\bullet$ (cyanoisopropyl radicals) during initialization and $AS_n^\bullet$ (oligostyryl or polystyryl radicals) after initialization. The propagation rate coefficient for the addition of cyanoisopropyl radicals to styrene is 5200 L mol^{-1} s^{-1} at 70 °C,[33] and the propagation rate coefficient for addition of polystyryl radicals to styrene is 480 L mol^{-1} s^{-1} at 70 °C[35] and possibly higher for short oligomeric radicals. The decrease in rate immediately following the end of the initialization period is by a factor of approximately 20. The difference in propagation rate coefficients alone is unable to account for the difference in rates. The only other possibility is that the propagating radical concentration must also have decreased rapidly after initialization, leading to rate retardation that was not present during the initialization period.[23] Thus, the decrease in rate is probably due to a decrease in both the propagating radical concentration (corresponding to the rate retardation commonly observed in dithiobenzoate-mediated free radical polymerization reactions) and the propagation rate coefficient for the dominant propagating radicals in the system. It is important to note that for this reaction there was no apparent inhibition period at the beginning but that the rate of reaction was much higher in the initialization period. This will be discussed further below.

One of the consequences of the initialization period is that the rate of monomer consumption is governed by the rate of conversion of the starting RAFT agent (AD) into the single monomer adduct analogue (ASD). The rate of RAFT agent conversion controls the amount of time taken to change the dominant type of propagating species from that during the initialization period ($A^\bullet$ here) to a different dominant form ($AS_n^\bullet$ here) later. This in turn is governed by the addition rate constants of the R-derived radical (or initiator fragment radical, which is the same in this case) groups to monomer.[32,33] Here it becomes clear that much experimental evidence that has been presented for inhibition in RAFT polymerization[21,36,37] is actually evidence of a slower rate of reaction due to a smaller k_p (than that of the long-chain polymeric radical value) for the R-derived radicals during the initialization period.

In free radical polymerizations, the propagating radical concentration is dependent on the overall rates of initiation and termination and rapidly reaches equilibrium. In a RAFT system there is an extra radical species (intermediate radicals) whose concentration is potentially very significant.[17,20,38] The potential for termination of the intermediate radical, whether reversible or irreversible, is discussed elsewhere.[23] For the purposes of simplification it is assumed that the termination of the intermediate radicals does not significantly change the equilibrium concentration of propagating radicals. This simplification is valid during the initialization period due to the very low concentrations of intermediate radicals in the initialization period; after initialization this assumption may be poor, dependent on the RAFT agent concentration.[23] The discussion will also only consider the case in which the intermediate radical lifetime is not so extensive as to cause rate retardation.

As mentioned earlier, the rate of reaction is significantly faster in the initialization period than after the initialization period for styrene. In contrast, some of the most significant inhibition times that have been reported have been in methyl acrylate (MA) systems.[36] If the methyl acrylate RAFT system using the same RAFT agents used in this study is examined, the following relationship can be derived from literature values:[32,33,39]

$$\frac{k_{p,MA}}{k_{p,A,MA}} \gg 1 \gg \frac{k_{p,STY}}{k_{p,A,STY}} \tag{2}$$

Here $k_{p,MA}$ and $k_{p,STY}$ refer to the long-chain propagation rate coefficients for MA and STY, and $k_{p,A,MA}$ and $k_{p,A,STY}$ refer to the rate coefficients for the addition of the cyanoisopropyl radical to MA and STY. Assuming, as a first approximation, similar propagating radical concentrations before and after initialization (this is apparently not true here, and usually the propagating radical concentration will be lower after initialization), the relative reaction rates will be primarily dependent on the relevant k_p values. For styrene, this gives a higher rate during initialization than for the period afterward. For MA, a somewhat different rate behavior is predicted, as $k_{p,MA}$ is 13 100 L mol^{-1} s^{-1} [40] at 25 °C and $k_{p,A,MA}$ is 367 L mol^{-1} s^{-1} at 42 °C;[33] i.e., the rate of reaction will be much slower during initialization.

When there is a relatively small amount of RAFT agent present in a reaction (i.e., long chains are targeted), then a very small percentage of the monomer will be consumed during the initialization period. This would be difficult to distinguish from complete inhibition if the target molar mass is high. Monomer to RAFT agent concentration ratios that have been used in the literature are commonly very high,[36] often of the order of a thousand to one. Figure 6 demonstrates this point for both cases where $k_p/k_{p,I}$ (where I is the initiating radical) is greater and less than unity, for different target molar masses. In Figure 6a,b molar ratios of 1:10 RAFT agent to monomer are presented and in Figure 6c,d molar ratios of 1:100 RAFT agent to monomer, assuming constant propagating radical concentrations, in which case the relative reaction rates are proportional to the relevant k_p value. For systems in which the monomer to RAFT agent ratio is not so extreme as to allow for the addition of two monomer units per transfer and in which the transfer rate constant is sufficiently greater than the propagation rate constant, approximately 1 mol of monomer is consumed per mole of RAFT agent during the initialization period. This would be almost indistinguishable from total inhibition (i.e., less than 0.1% conversion would occur during this time), as would cases in which there are oligomers present; e.g., four monomer additions prior to transfer would still be substantially less than 1% of conversion in many systems. It is important to note that examples of systems in which there is supposed to be total inhibition are reported to show color change, which is a well-known indication of polymerization in RAFT-mediated polymerizations. This is consistent with the suggestion

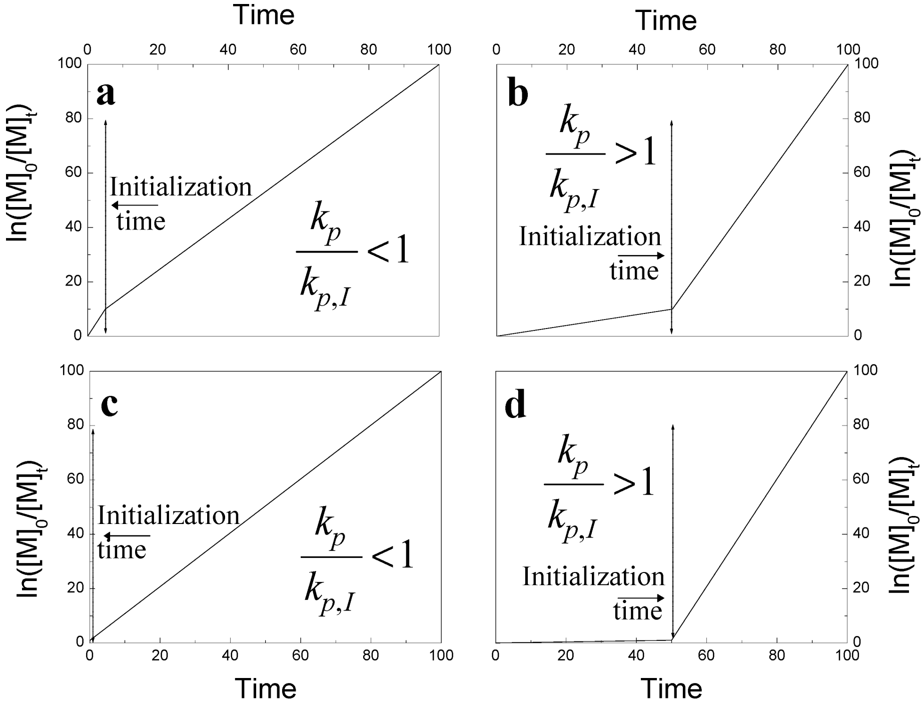


Figure 6. Relationships of the rate of monomer consumption in the two phases of the reaction is indicated in the figures with subscript I referring to equilibrium and initialization, respectively. (a) Case in which the rate of monomer consumption in the equilibrium part of the reaction is higher than in the initialization period (monomer to RAFT agent molar ratio 10:1). (b) Case in which the rate of monomer consumption in the equilibrium part of the reaction is lower than in the initialization period (monomer to RAFT agent molar ratio 10:1). (c) Case in which the rate of monomer consumption in the equilibrium part of the reaction is higher than in the initialization period (monomer to RAFT agent molar ratio 100:1). (d) Case in which the rate of monomer consumption in the equilibrium part of the reaction is lower than in the initialization period (monomer to RAFT agent molar ratio 100:1).

that these systems have an initialization period.[34] Because of the ratios of reagents used in the present study, the initialization period is accentuated.

Radical Generation and Termination Products. The formation of the AA (tetramethyl succinonitrile, TMSN) species in the studied systems was examined in the context of a conventional free radical reaction and initiator (AIBN) decomposition. The AA product is formed by mutual termination of cyanoisopropyl radicals. In Figure 7, the time dependences of the concentrations of AA and AIBN at 84 °C are presented. In reaction 2, the concentration of the AA product shows a slight increase when compared to a control polymerization (reaction 4). The concentration difference appears to be due to an event that generated significant amounts of this product prior to the time of the first scan. This deduction can be made, as the formation of the AA product in reaction 2 appears to be occurring at a slower rate than in reaction 4, suggesting that some event prior to observation caused the different initial concentrations. The higher initial concentration was probably due to the termination behavior of cyanoisopropyl radicals in the initialization period, which could not be examined at the reaction temperature, since initialization was completed before the first scan could be made. The results suggest that the presence of the RAFT agent does not increase the amount of TMSN formation after initialization is complete; i.e., the RAFT agent does not directly promote termination in the system (although it alters the relative populations of propagating radicals, which can change the termination kinetics). The difference in the formed amounts of AA (TMSN) in the RAFT-mediated polymerization and the control lies in the nature of the radical species and the length of the initialization period.

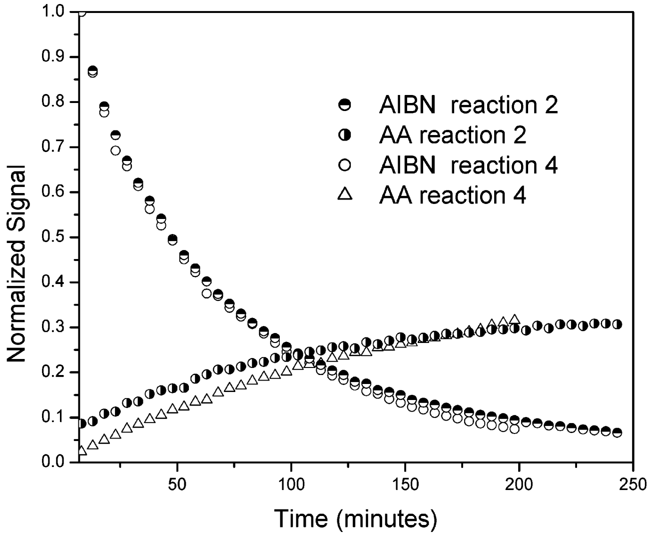


Figure 7. Concentrations of AIBN and AA of reactions 2 and 4 carried out in deuterated benzene at 84 °C. Reaction 2 contains RAFT agent cyanoisopropyl dithiobenzoate, and reaction 4 is a conventional free radical polymerization. Reaction 2: 3.56 × 10^{-3} mol of C_6D_6, 6.1 × 10^{-5} mol of AIBN, 2.31 × 10^{-3} mol of styrene, 4.52 × 10^{-4} mol of cyanoisopropyl dithiobenzoate. Reaction 4: 3.56 × 10^{-3} mol of C_6D_6, 6.1 × 10^{-5} mol of AIBN, 3.68 × 10^{-3} mol of styrene.

Comparisons between the RAFT-mediated reaction (reaction 2) and the control (reaction 4) at 84 °C (Figure 7) also indicate that the presence of a RAFT agent does not increase the rate of AIBN decomposition.

Figure 8 presents the AIBN and AA product concentrations as determined at 70 °C. The formation of the AA product in reaction 1 occurs at an increased rate throughout the initialization period (lasting approxi-

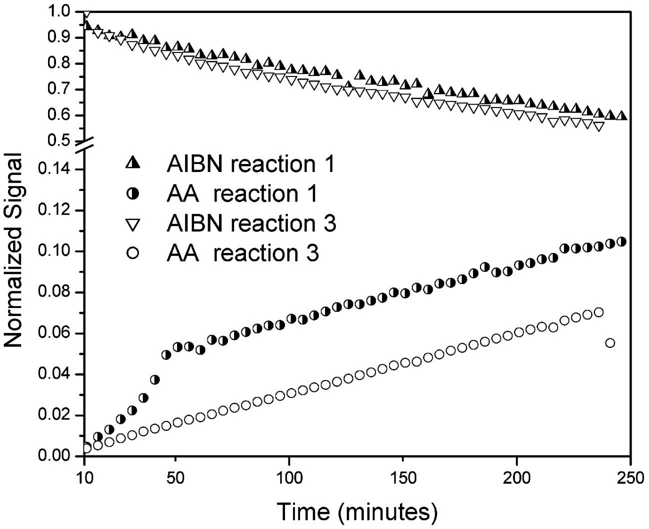


Figure 8. Concentrations of AIBN and AA of reactions 1 and 3 carried out in deuterated benzene at 70 °C. Reaction 1 contains RAFT agent cyanoisopropyl dithiobenzoate, and reaction 3 is a conventional free radical polymerization. Reaction 1: 3.56×10^{-3} mol of C_6D_6, 6.75×10^{-5} mol of AIBN, 2.40×10^{-3} mol of styrene, 4.84×10^{-4} mol of cyanoisopropyl dithiobenzoate. Reaction 3: 4.34×10^{-3} mol of C_6D_6, 6.71×10^{-5} mol of AIBN, 3.68×10^{-3} mol of styrene.

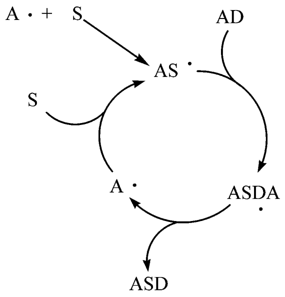


Figure 9. Cycle by which cyanoisopropyl radicals ($A^•$) are rapidly regenerated by addition–fragmentation through a dithioester mediating species, during the early stages of the cyanoisopropyl dithiobenzoate-mediated polymerization of styrene. ($A^•$) adds to styrene (S) to form $AS^•$. $AS^•$ adds to AD to generate intermediate radical $ASDA^•$ that rapidly fragments to produce $A^•$, which is then once again able to cycle through by adding to styrene.

mately 60 min). This substantiates the above argument presented for the reactions at higher temperatures, namely that the excess AA product is produced during initialization. Following the initialization period the AA product is formed at a similar rate as in a conventional free radical polymerization as evident from comparisons of reactions 1 and 3.

The increased concentrations of the respective termination products in the RAFT-mediated polymerizations are due to an unusual process, in which active chains are kept short (see Figure 9) that occurs during the initialization period. During the initialization period, the $A^•$ will add to a monomer unit to form $AS^•$. When these species undergo efficient transfer, a short $A^•$ will be expelled. This means that, unlike a conventional radical polymerization, the initialization period replaces the slower terminating $AS^•$ species with faster terminating $A^•$ radical species. There are significantly higher concentrations of their termination products compared with those in a control reaction because of this replacement during the initialization period. After the initialization period the usual geminate recombination process dominates the formation of the AA species, as can clearly be observed in Figures 7 and 8. The concentration curves for AA are roughly parallel in Figure 8, although in Figure 7 there is a deviation at higher temperature. The reactions at higher temperatures will result in higher conversions and viscosities in the control reaction, leading to a decrease in initiator efficiency and an increase in the geminate recombination product being produced at longer reaction times in reaction 4. A weaker corresponding increase in viscosity is expected in the RAFT system, since both overall conversion and average chain length (on which viscosity depends) are both much lower than in the conventional system.

The chain length dependence of the termination rate coefficients[41–45] means that short species will have a higher rate of termination. The overall termination rate will be higher during initialization than that in a control reaction in which the short chains are quickly converted into longer chains. The higher rate of radical loss through termination implies that reactions with longer initialization periods will consequently have a lower propagating radical concentration after the initialization period, leading to a slower rate of reaction after the initialization period than comparable reactions with shorter initialization periods.

Beyond Initialization. To minimize the length of the initialization period, it is important that the propagation rate constant of the homolytic leaving group of the original RAFT agent with respect to the monomer in use be as high as possible. The only caution is that it should remain a better leaving group than the incoming monomer adduct radicals. To minimize the effect of propagation rate constant differences between initialization and the equilibrium phase of the reaction, a polymeric RAFT agent of the same monomer can be used. In this case the propagation of the initiator fragment, which is unable to displace the polymeric chain until it has propagated, will result in an immediate increase in intermediate radicals equivalent to the end of initialization, as has been seen by ESR spectroscopy.[31] The experimental implication of using the polymeric agent is that the RAFT equilibrium period should be reached very quickly.

Conclusions

This study has provided direct evidence for details of the mechanism of the initialization period of the RAFT process. It was found that the addition–fragmentation process was extremely selective during this period, and because of this, significant quantities of RAFT adducts of degrees of polymerization greater than unity were formed only after complete conversion of the initial RAFT agent to its monomeric adducts. The critical process in the initialization of a dithiobenzoate (RAFT)-controlled polymerization was found to be the formation of the single monomer adduct dithiobenzoate species and, by implication, the propagation of the initial leaving group radicals and the initiator-derived radicals (which are both the cyanoisopropyl radical here).

In situ ^1H NMR spectroscopy shows that the first interval of polymerization that could be observed in the studied systems is an initialization period, which has been defined as the period prior to the complete consumption of the initial RAFT agent. In the case of styrene this initialization period shows a more rapid rate of reaction than during the RAFT equilibrium. The rate of polymerization is a function of the values of the propagation rate constants for the initiator and leaving group fragments. It has been shown that a slower rate of reaction during the initialization period compared to the equilibrium period is expected in the case of methyl acrylate, which is currently under investigation. The initialization period has largely been mistaken for inhibition in the RAFT literature for homogeneous reactions. The lack of previous reports of the rapid rate of reaction during this period is suggested as being due to the long chain lengths targeted in other studies, which means that the initialization period would have been completed before significant conversion had occurred, and thus this period may have gone unnoticed in many systems.

In the system studied, the poorest leaving group was the cyanoisopropylstyryl (i.e., $AS^{\bullet}$) radical although the "long chain" value of addition, propagation, and fragmentation rate coefficients need to be achieved before the system is at equilibrium. This could be for species containing two or more monomer units for both addition and propagation.

The reasons for the behavior observed for the RAFT system are suggested as being dependent on the relative reactivities and radical stabilities and therefore the related addition and fragmentation rate coefficients of the tertiary radical species and their monomer adducts in the system. This can be extended to all efficient RAFT systems, even those where multiple radical species are present and should not be considered as solely an explanation of the cyanoisopropyl dithiobenzoate system.

The main reasons for the extremely selective and stepwise behavior observed in the initialization period are that the fragmentation of the formed intermediate radicals is very selective toward tertiary radicals and that addition of propagating radicals of degree of polymerization of at least unity to the RAFT agent was much faster than to monomer. Cases where this behavior might not occur include the use of RAFT agents with low addition rate coefficients, the use of very high initial ratios of [M]/[RAFT], or systems in which $k_{p,1}$ is very large.

The second part of this investigation addresses the same reaction using cumyl dithiobenzoate, where the initiating and leaving groups are different, and illustrates the similarities and differences in observed behavior.[30]

Acknowledgment. The authors acknowledge the financial assistance of the National Research Foundation of South Africa and the Dutch Polymer Institute. The NMR facilities of the Central Analytical Facility at the University of Stellenbosch are acknowledged for the extensive machine time and expertise required for conducting the experiments.

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MA035478C