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NMR Spectroscopy in the Optimization and Evaluation of RAFT Agents

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Summary: The selection of a suitable mediating agent in Reversible Addition-Fragmentation Chain Transfer (RAFT) mediated polymerization is crucial to the degree of control that can be achieved. An overview of work from the Stellenbosch group is presented in which the use of NMR spectroscopy as a tool for evaluating RAFT-agents is highlighted. The occurrence of selective initialization, *i.e.* the selective conversion of a RAFT-agent into its single monomer adduct is discussed for various classes of monomers, as well as for copolymerization. One of the general rules for living polymerization is that chains should start growing early in the polymerization reaction. Selective initialization is claimed to be the extreme case where all chains have begun growing after the conversion of only one monomer equivalent per RAFT-agent.

Keywords: dithiobenzoates; dithioesters; initialization; NMR Spectroscopy; RAFT-mediated polymerization; xanthates

Introduction

Reversible Addition-Fragmentation Chain Transfer (RAFT) mediated polymerization is among the most versatile living/controlled radical polymerization techniques.[1] It allows for the controlled polymerization of virtually any monomer that can be polymerized via conventional radical polymerization. However, the selection of a suitable RAFT-agent is of extreme importance in order to obtain a high degree of control. The inventors of RAFT-mediated polymerization at CSIRO (Australia) have drawn up a scheme of so-called leaving (R) groups, and activating (Z) groups that are expected and/or found to be suitable for various classes of monomers.[1] In general one can say that an R-group should be a good homolytic leaving group and a good re-initiating radical for a particular monomer. The Z-group should activate the C=S bond sufficiently to obtain a high addition rate of propagating radicals to the C=S bond. It should also stabilize the intermediate radical that is formed upon addition of the propagating radical to the RAFT-agent. In the present publication we will summarize some of our findings and discuss the results in terms of the mechanism underlying the phenomenon of initialization.

Results and Discussion

It was shown previously that some monomer – RAFT-agent combinations lead to induction periods and retardation phenomena.[3] A lively discussion in the literature has resulted on the origin of these observations. This discussion largely focused on the retardation phenomena. A few years ago the Stellenbosch group started to use *in situ* ^{1}H-NMR spectroscopy to investigate the

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induction period during the early stages of dithiobenzoate-mediated polymerizations of styrene (STY).[2] After assignment of the signals, concentration profiles of the relevant species can be recorded as a function of time. In doing so, it was found that the RAFT-agent is selectively converted into the so-called single monomer adduct, a process for which the name *initialization* was coined. In the cyanoisopropyl dithiobenzoate (CiPDB) mediated polymerization of styrene at 70 °C with [STY]:[CiPDB]:[AIBN] = 5:1:0.1 [mol] an initialization period of circa 40 minutes was observed (see Figure 1). Recently, these results were modeled in two independent publications. Coote and co-workers used *ab initio* quantum chemical calculations to predict equilibrium constants for the various equilibriums involved in the early stages of the polymerization.[4] They were able to show a fairly good agreement between experimental and predicted data, without using any adjustable parameters. In a publication from the Stellenbosch group, it was shown that both, the slow fragmentation model and the intermediate radical termination model are able to provide a good fit with the experimental data.[5] A similar experiment in which the CiPDB was replaced by cumyl dithiobenzoate (CDB) showed an initialization period of circa 240 minutes (see Figure 2).[6] On the basis of the close to linear conversion of the RAFT-agent as a function of time in the CiPDB experiment (see Figure 1) a mechanistic interpretation was proposed. It was concluded that the RAFT-agent cannot be involved in the rate-determining step, or otherwise the observed pseudo-zero order kinetics would not be observed. In other words, if the RAFT-agent would were involved in the rate-determining step, a first order decay of the RAFT-agent concentration should be observed. Hence, a curved RAFT-agent concentration *versus* time profile would be obtained. The fragmentation reaction cannot be rate-determining either, since this would lead to unrealistically high intermediate radical concentrations. Hence, the only remaining explanation is that the rate-determining step is the addition of the primary radical (or leaving group radical) to the first monomer unit. This explanation is in contradiction with the slow fragmentation model, and the *ab initio* quantum chemical calculations by Coote and co-workers.[4] A simple model, in which primary radical addition as the rate-

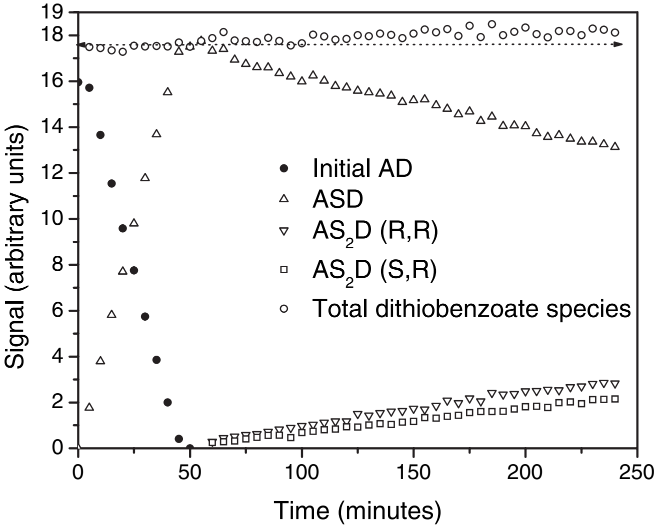

Figure 1.

Relative concentrations of relevant species as a function of time determined via *in situ* ^{1}H-NMR spectroscopy during the CiPDB-mediated polymerization of styrene at 70 °C, where A = CiP fragment, S = styrene, D = dithiobenzoate. [STY]:[CiPDB]:[AIBN] = 5:1:0.1 [mol].[2]

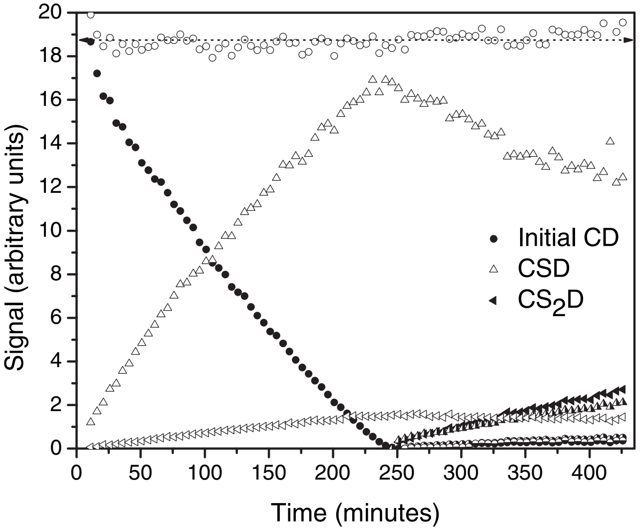

Figure 2.
Relative concentrations of relevant species as a function of time determined via *in situ* ^{1}H-NMR spectroscopy during the CDB-mediated polymerization of styrene at 70 °C, where C = cumyl fragment, S = styrene, D = dithiobenzoate. The non-assigned symbols are CiP-initiated chains as indicated in the CiPDB study (see Figure 1). [STY]:[CDB]:[AIBN] = 6.7:1:0.2 [mol].[6]

determining step is implemented, shows a good fit of the concentration profile of the RAFT-agent concentration for the CiPDB and CDB experiments. This observation points at a significant difference in addition rate constant of the cyanoisopropyl radical to styrene compared to the cumyl radical to styrene or the bimolecular combination rates of the respective radicals. These rate constants have been calculated[7] based on Arrhenius parameters that were determined independently.[8,9] The differences observed in initialization behavior between the CiPDB and CDB case have been discussed using these previously reported rate constants.[6] In a qualitative sense the results were in agreement, and a more quantitative assessment was hampered by the inaccuracies in the rate constants due to extrapolations over large temperature intervals.

The same experimental approach was chosen for the investigation of methyl acrylate (MA) polymerization, mediated by CDB and by cumyl phenyl dithioacetate (CPDA)[10]. The purpose was to check the degree to which selective *initialization* is a general phenomenon. Figure 3 shows the concentration profiles of RAFT-agent and monomer. It is immediately evident that there is a large difference in initialization behavior between CDB and CPDA as the mediating agent. It is noteworthy to point at the great similarity in experimental data between the work presented here, and that of Vana and co-workers on CDB-mediated MA polymerization.[11] They explain the occurrence of initialization by a combination of intermediate radical termination and equilibrium constants that differ between pre-equilibrium and main equilibrium.

CPDA mediated polymerization of MA behaves in a fashion somewhat similar to the situation of styrene polymerization mediated by dithiobenzoates as shown in Figure 1 and 2. The decrease of the RAFT-agent concentration with time is nearly linear, and growth of the polymer chains beyond single monomer adduct formation only commences after all RAFT-agent is converted. On the other hand, in the case of CDB-mediated polymerization

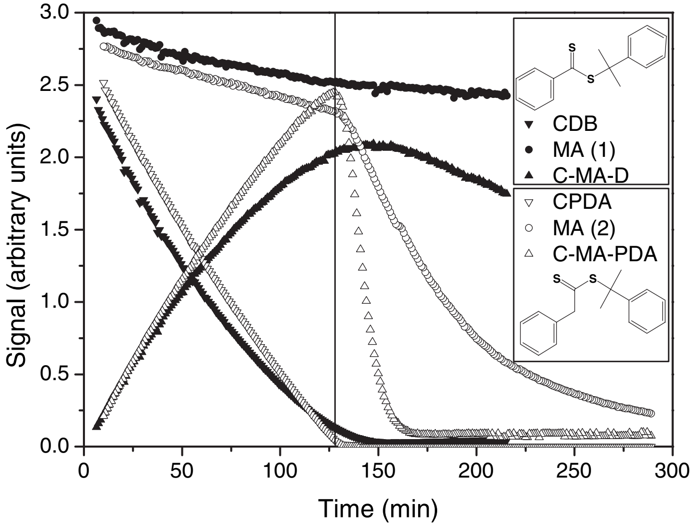

Figure 3.

Relative concentrations of relevant species as a function of time determined via *in situ*^{1}H-NMR spectroscopy during the polymerization of methyl acylate mediated by CDB and by CPDA $[MA]_0/[RAFT\text{-}agent]_0 = 7.5$ at 70 °C.[10]

of MA, significant curvature of the RAFT-agent conversion as a function of time is observed. The curvature is due to the buildup of intermediate radical species within the reaction system, due to the formation of longer lived intermediate radicals derived from MA and the concomitant rate retardation that occurs. In other words, CDB-mediated polymerization of MA does not show as clean an initialization behavior as observed in the earlier discussed situations. *In situ* ESR measurements with similar time resolution as in the NMR studies are presently being investigated by different groups in order to confirm the abovementioned buildup of intermediate radical species. At this point it is good to comment on the statistical nature of the process. The whole process of RAFT-mediated polymerization is governed by probabilities, as is conventional radical polymerization. This means that very reactive radicals, *i.e.* radicals that exhibit a high propagation rate constant, may experience competition between addition to the RAFT agent providing selective initialization and addition to monomer providing chain growth at an earlier stage than the less reactive ones. The radical addition to the RAFT agent is inherently dependent on the RAFT-agent and the susceptibility of the specific thio-carbonyl thiol moiety to radical addition, which means that a selective initialization can only be obtained if the RAFT-agent is properly designed for the specific monomer. This will be further exemplified below.

For further insight into the initialization process, the focus is shifted to a copolymerization system. The copolymerization of styrene and maleic anhydride (MAh) was investigated using CDB and CiPDB as the RAFT-agents.[12] This provides an excellent opportunity to investigate the effect of an electron-deficient comonomer on the initialization behavior of styrene as an electron-rich monomer. As indicated above, under certain conditions, the initialization time for the CiPDB-mediated polymerization of styrene is approximately 40 minutes. An experiment was conducted under comparable conditions, where styrene is now replaced by a 1:1 [mol] mixture of styrene and maleic anhydride. Despite the slightly different reactant concentrations it is interesting to notice that the initialization time is virtually identical to the styrene homopolymerization case. Closer inspection of monomer conversion and the nature of the single monomer adducts reveals that the cyanoisopropyl radical adds almost exclusively to styrene. This is not too surprising as the cyano-isopropyl radical is electron-deficient, which leads to a higher affinity for an electron-rich monomer (styrene). Figure 4 shows the concentration profiles of the relevant species. Since the majority of CiP radicals add to styrene it is logical that the initialization time quite closely resembles that of styrene homopolymerization.

Figure 5 shows the concentration profiles of the relevant species in the CDB-mediated copolymerization of styrene and maleic anhydride. This experiment was conducted at 70 °C, in the same fashion as the previously discussed experiments. The initialization in this experiment was extremely fast in comparison to the homopolymerization of styrene. Where the initialization period for a CDB-mediated styrene homopolymerization was 240 minutes, here the initialization period is less than 5 minutes, again with slightly different reactant concentrations. In the first NMR spectrum acquired, which was recorded after 5 minutes, no CDB remained. Assignment of the peaks indicates that the single maleic anhydride adduct is formed virtually exclusively. Again, this is no surprise if one considers the electron-rich nature of the cumyl radical, and the electron-deficient nature of maleic anhydride. However, the overwhelming increase in conversion rate of the RAFT-agent of more than 50 times is surprising. The finding confirms the hypothesis that the addition of the leaving group radical to the monomer is rate-determining during the initialization process.

Interesting phenomena are observed in this copolymerization if one looks beyond the initialization period. In the case of cumyl as the leaving group, exclusive addition to maleic anhydride takes place. Maleic anhydride does not undergo homopropagation, which means that after initialization styrene consumption starts, whereas the maleic anhydride consumption rate reduces to virtually zero. The behaviour visually resembles a second initialization, but the

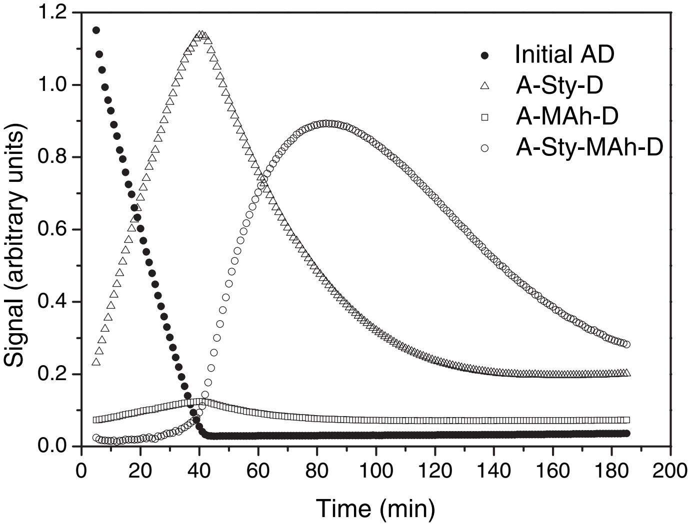

Figure 4.

Relative concentrations of relevant species as a function of time determined via *in situ* ^{1}H-NMR spectroscopy during the CiPDB-mediated copolymerization of styrene and maleic anhydride at 70 °C. [STY]:[MAh]:[CiPDB]:[AIBN] = 4.1:3.8:1:0.20 [mol].[12]

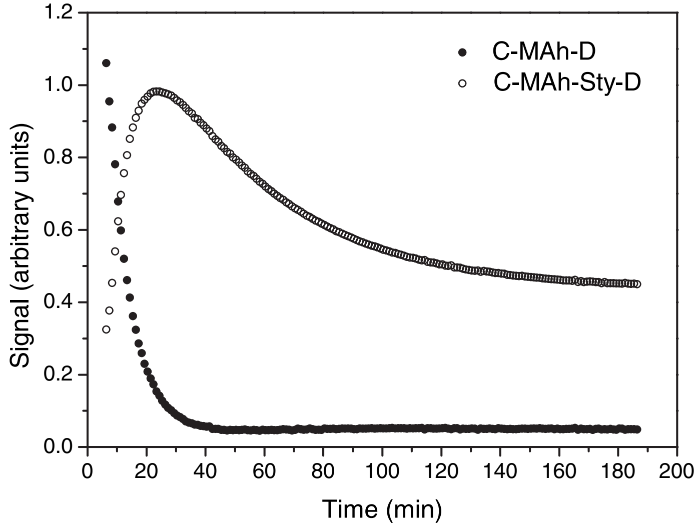

Figure 5.
Relative concentrations of relevant species as a function of time determined via *in situ* ^{1}H-NMR spectroscopy during the CDB-mediated copolymerization of styrene and maleic anhydride at 70 °C. [STY]:[MAh]:[CDB]:[AIBN] = 3.6:3.6:1:0.2 [mol].[12]

specificity is lower in this case. In additional experiments (not shown), temperature was decreased to 60 °C, which reduces the rate of initialization sufficiently to be monitored accurately by NMR spectroscopy.

Until recently only stabilized monomers, carrying an electron-withdrawing substituent, were investigated in terms of initialization behavior. In order to explore the general applicability of the concept, poorly

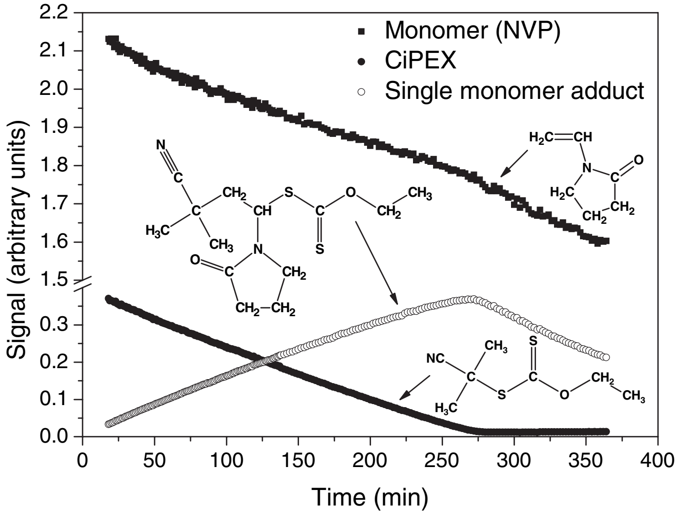

Figure 6.
Relative concentrations of relevant species as a function of time determined via *in situ* ^{1}H-NMR spectroscopy during the CiPEX-mediated polymerization of *N*-vinyl pyrrolidone at 70 °C in C_6D_6, [Monomer]$_0$/[Xanthate]$_0$ = 5.[13]

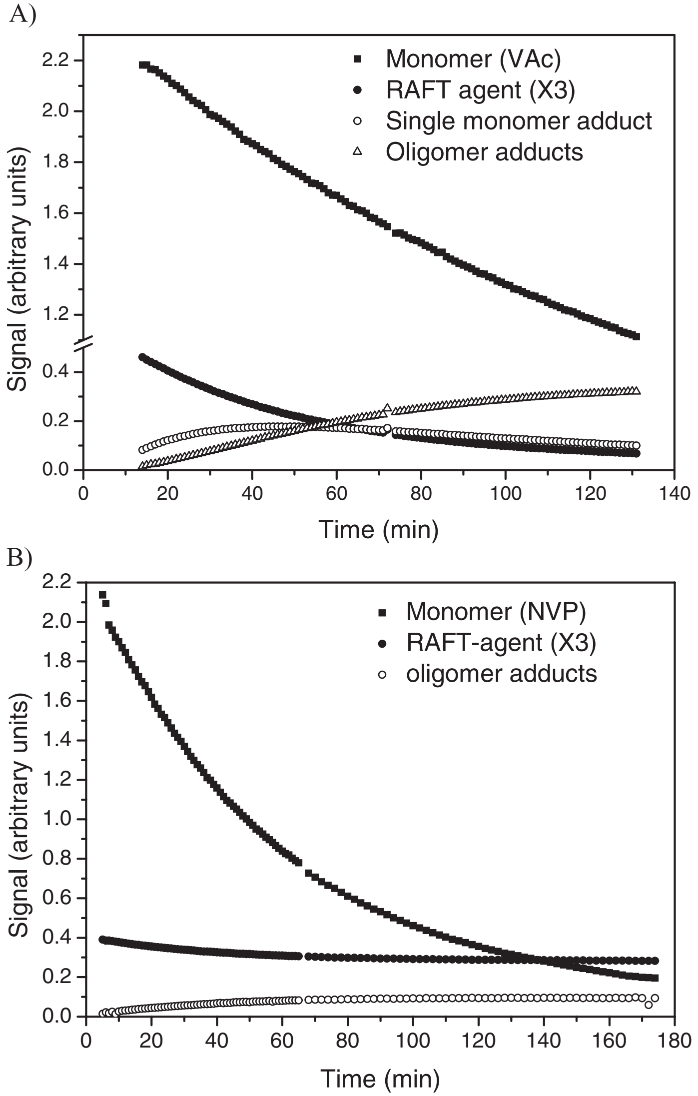

Figure 7.

A and 7B. Relative concentrations of relevant species as a function of time determined via *in situ*^{1}H-NMR spectroscopy during the *tert*-butyl ethyl xanthate (X3)-mediated polymerization of vinyl acetate (A) and of *N*-vinyl pyrrolidone (B) at 70 °C in C_6D_6, $[\text{Monomer}]_0/[\text{Xanthate}]_0 = 5$.[13]

stabilized monomers were recently subjected to *in situ* NMR studies. *N*-vinyl pyrrolidone (NVP) and vinyl acetate (VAc) were investigated in RAFT-mediated polymerization. It is reasonably well-documented that dithiocarbamates and xanthates are the RAFT-agents of choice for the controlled polymerization of these classes of monomers.[14–16] After preliminary experiments that will not be detailed here, it was decided to implement *O*-ethyl xanthates as the RAFT-agents to control NVP and VAc polymerization.[13] The leaving groups were varied in order to judge their effect on the initialization behavior. Figure 6 shows the concentration profiles of relevant species for the cyanoisopropyl *O*-ethyl xanthate (CiPEX) mediated polymerization of NVP. It is clearly visible that an initialization process takes place that is not too dissimilar from what was observed for styrene and MA. In the first 270 minutes of the reaction exclusively the single monomer adduct of CiPEX and NVP is formed. Only after complete conversion of CiPEX, does further polymerization commence in a similar fashion as previously observed for styrene and MA. The initialization process in the case of CiPEX-mediated polymerization of NVP is fairly slow, which is expected to be due to the low rate constant of addition of the CiP radical to NVP. However, if the same experiment is repeated with VAc, it is observed that initialization is even much slower than in the case of NVP. It looks as if initialization is highly selective, but the estimate of the length of the initialization period is around 22 hours extrapolated from the first 3 hours of the reaction. Despite the fact that VAc and NVP are often considered as similar monomers in terms of their reactivity, this seems to point at a large difference in the rate coefficient of CiP radical addition. A leaving group that shows very selective initialization behavior for VAc appeared to be 2-propionic acid (results not shown). The initialization time for the 2-propionic acid ethyl xanthate-mediated polymerization of VAc is only 20 minutes under comparable conditions as the abovementioned systems.

Inspection of the scheme of leaving groups for the various monomer classes as mentioned above reveals that *tert*-butyl should be an appropriate leaving group for VAc.[1] For this reason, *tert*-butyl ethyl xanthate (X3)-mediated polymerizations of VAc and of NVP were investigated. Figures 7A and 7B show the concentration profiles of the relevant species of VAc and of NVP polymerizations respectively. It is immediately clear that neither of these two systems undergoes selective initialization. After 130 minutes close to 50% VAc conversion is observed, while there is still a significant fraction of the original RAFT-agent present. In the case of NVP, after 170 minutes some 90% monomer conversion has taken place, where only approximately 25% of the RAFT-agent is converted. Both results point at a poor leaving group quality, *i.e.* the asymmetrical intermediate radical that carries an oligomeric fragment on one side and the original leaving group on the other side fragment preferentially on the oligomeric side. Note that this is a different scenario from the slow re-initiating leaving group radical as was observed for the CiPEX-mediated polymerization of VAc, where the fragmentation rate was appropriate, but the reinitiation rate was extremely slow. The two different modes of failure for appropriate initialization point at the subtle optimization of RAFT-agents suitable for a specific monomer system.

Conclusions

Initialization is frequently observed in RAFT-mediated polymerization. The selective transformation of the initial RAFT-agent into its single monomer adduct is commonly observed for RAFT-agents that possess a good leaving group that also yields an effective re-initiating radical. The process of initialization is observed for homopolymerizations of various monomers including poorly stabilized monomers such as vinyl acetate and *N*-vinyl pyrrolidone. It is also observed in copolymerizations, where the specificity of the formation of the single monomer adduct is directly related to the addition rate constants of the leaving group radical to the two monomers.

NMR spectroscopy is an efficient tool to monitor the quality of the R-group as a leaving group, and as a reinitiating fragment. As such it can be used for the selection and optimization of RAFT-agents for specific monomer systems.

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