

HIGHLIGHT

Macromolecular Design via Reversible Addition–Fragmentation Chain Transfer (RAFT)/Xanthates (MADIX) Polymerization

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ABSTRACT: Among the living radical polymerization techniques, reversible addition–fragmentation chain transfer (RAFT) and macromolecular design via the interchange of xanthates (MADIX) polymerizations appear to be the most versatile processes in terms of the reaction conditions, the variety of monomers for which polymerization can be controlled, tolerance to functionalities, and the range of polymeric architectures that can be produced. This review highlights the progress made in

RAFT/MADIX polymerization since the first report in 1998. It addresses, in turn, the mechanism and kinetics of the process, examines the various components of the system, including the synthesis paths of the thiocarbonyl-thio compounds used as chain-transfer agents, and the conditions of polymerization, and gives an account of the wide range of monomers that have been successfully polymerized to date, as well as the various polymeric architectures that have been produced. In the last

section, this review describes the future challenges that the process will face and shows its opening to a wider scientific community as a synthetic tool for the production of functional macromolecules and materials. © 2005 Wiley Periodicals, Inc. *J Polym Sci Part A: Polym Chem* 43: 5347–5393, 2005

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Dr. Sébastien Perrier was born in Saint-Malo, France, in 1974. He undertook his undergraduate studies in France, at the Ecole Nationale Supérieure de Chimie de Montpellier, a French Grande Ecole, and obtained his 'Diplome d'Ingenieur' in 1998. He received a Ph.D. degree in the field of transition metal mediated living radical polymerization from the University of Warwick, England, in 2001. He then moved to Sydney, Australia, to work on RAFT polymerization as a research fellow at the University of New South Wales. In October 2002, Dr. Perrier was appointed Lecturer at the University of Leeds and was promoted to Senior-Lecturer in August 2005. He is currently heading a team of 10 researchers, working at the interface of organic chemistry, polymer synthesis (with a strong specialization in RAFT/MADIX polymerization), and material science.

Pittaya Takolpuckdee was born in Bangkok, Thailand in 1975. He completed his undergraduate studies in chemistry from Chulalongkorn University, Thailand. He obtained his master's degree in polymer science from the Petroleum and Petrochemical College, Chulalongkorn University under the supervision of Assoc. Prof. Suwabun Chirachanchai. He received the Royal Thai Government scholarship to continue his Ph.D. in the Department of Colour and Polymer Chemistry, University of Leeds, U.K. His Ph.D. research involved the progress in RAFT polymerization, design, application, and recovery of chain transfer agents under the supervision of Dr. Sébastien Perrier. He is now a lecturer in chemistry at Valaya Alongkorn Rajabhat University, Thailand. His research interests have included natural adhesives and modification of natural products using living radical process, i.e., RAFT polymerization.

INTRODUCTION

Research in the field of controlled/living radical polymerizations has increased significantly over the last few decades. The term *living polymerization* originally described a polymerization in which the chain could only propagate and not undergo chain transfer or irreversible termination.¹ Thus, in an ideal living polymerization system, each chain should maintain its ability to further propagate in the presence of the monomer.

The concept of living radical polymerization (LRP) was originally introduced by Otsu in the early 1980s through his extensive investigation of iniferters.^{2,3} The term *iniferters* was adopted to describe such compounds that could *initiate*, *transfer*, and *terminate* a radical polymerization by analogy to the inifers used by Kennedy⁴ in cationic polymerization. Numerous studies led to the synthesis of efficient iniferters, among which those based on organosulfur radicals such as

dithiuram sulfides are the most successful. However, because of slow initiation, these systems lead to high polydispersity and poor control over the molecular weight of the products (discussed further in the Mechanism of RAFT/MADIX Polymerization section).

In recent years, LRP has seen increasing interest from industry and academia as it gives similar control of polymer architectures to that observed with more drastic systems (complex experimental procedures and limited polymerizable monomers) such as living anionic polymerization, living cationic polymerization, and coordination polymerization. LRP generates well-defined architectures, such as polymers with well-known degrees of polymerization, molecular weight distributions, end functionalities, chain architectures, and compositions. To date, the major processes of LRP are nitroxide-mediated polymerization (NMP),^{5,6} atom transfer radical polymerization (ATRP),⁷⁻¹⁰ reversible addition-

fragmentation chain transfer (RAFT),^{11,12} and macromolecular design via the interchange of xanthates (MADIX)^{13,14} polymerization. As shown in the next section, RAFT and MADIX follow the same mechanism and differ only by the polymerization mediator used. In this review, we adopt the term *RAFT/MADIX* when acknowledging the general concept of polymerization, and we only differentiate the two systems when dealing with points specifically related to one or the other. Despite being one of the most recent of the LRP systems, the RAFT/MADIX process is attracting increasing interest from both academia and industry, with over 400 publications and patents published in the last 7 years (see Fig. 1).

The concept of RAFT/MADIX finds its source in two different pieces of work first reported in the late 1980s. In 1986, the Commonwealth Scientific and Industrial Research Organisation (CSIRO) group reported the use of poly(methyl methacrylate) (PMMA) macromonomers as chain-transfer agents (CTAs) in radical polymerization. They called the process addition fragmentation chain transfer (AFCT) and described how a propagating radical would add onto a PMMA macromonomer and, by a chain-transfer reaction, would form a new propagating chain and a new alkene-terminated macromonomer.^{15,16} A variety

of AFCT^{15,17–19} agents were reported later, all with the general structure outlined in Scheme 1; for instance, in compound **2**, X is a good leaving group by homolysis (e.g., SR',^{20,21} Br,^{18,19} and SnR'^{19,22}), Z is an activating group, and the C–X or O–X bond is a weak single bond. However, in most cases, the polymers prepared from these processes show high polydispersity under homogeneous reaction conditions, the exception being when a thiocarbonyl-thio group is used (**3**, Scheme 1).^{11,12} In the latter case, the CSIRO group found that polymers with predictable molecular weights and very narrow polydispersities could be achieved for a wide range of monomers [$1.05 < \text{polydispersity index (PDI)} < 1.40$] while their end groups were kept active at the end of the reaction—this is an essential feature of a living polymerization system. The authors called the system a RAFT polymerization, for which thiocarbonyl-thio groups are the most efficient CTAs.

At a similar time, Zard's group developed a new technique to facilitate radical to double-bond addition while limiting side-product formation (by the quenching of the formed radical by its precursor, or by radical–radical interactions), using a degenerative transfer of radical species to a xanthate (Scheme 2).²³ The radical (benzyl

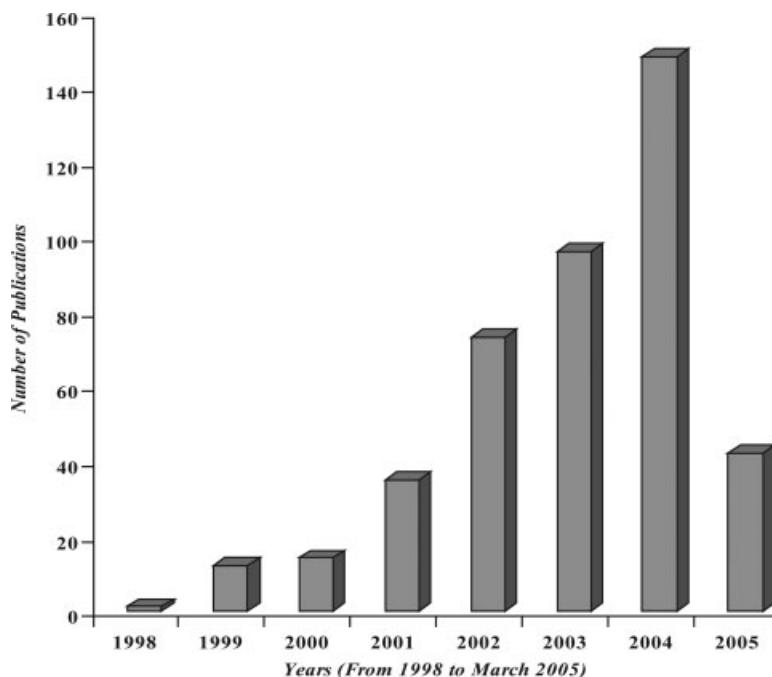
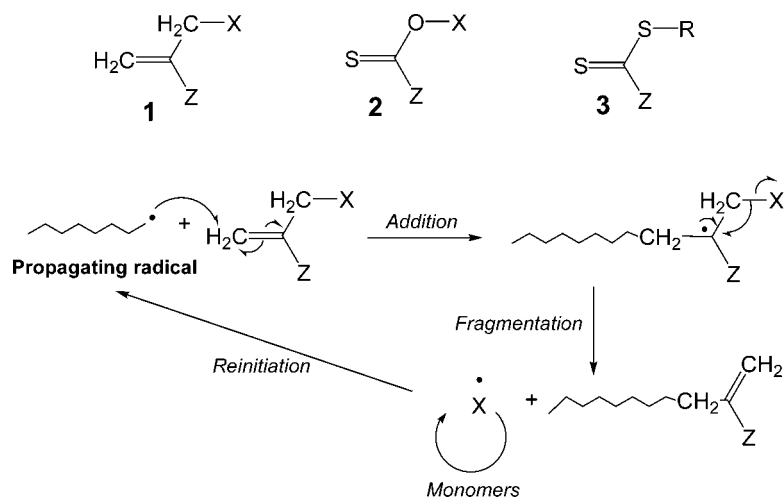


Figure 1. Number of scientific publications on RAFT/MADIX (search performed by Scifinder with the following keywords: reversible addition fragmentation chain transfer and/or MADIX and/or RAFT).



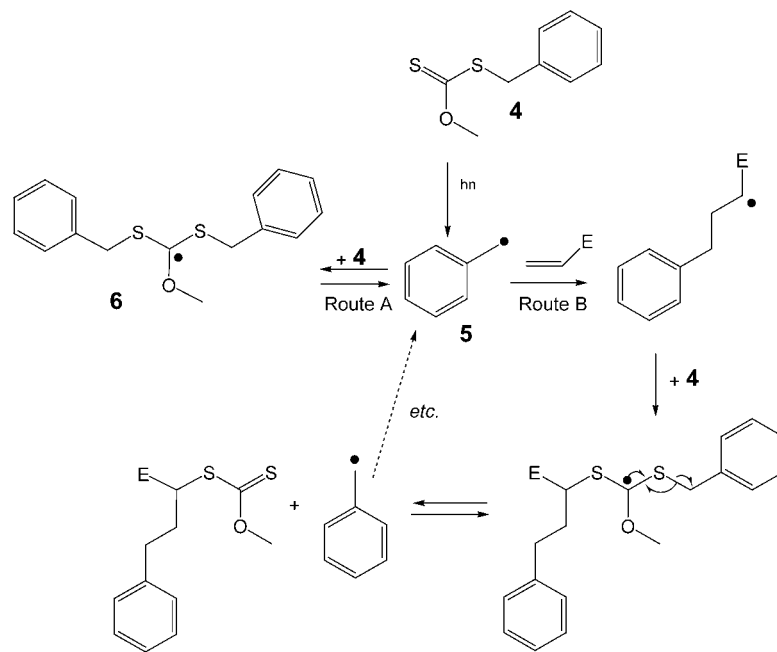
Scheme 1. Common structures of AFCT agents and general mechanism of AFCT with I as a CTA (X is a good leaving group by homolysis, e.g., SR',^{20,21} Br,^{18,19} and SnR';^{19,22} Z is an activating group).^{15,16}

radical **5** in the example of Scheme 2) can add either to the alkene (route B) or to the thiocarbonyl group of xanthate **4** (route A) to give symmetrical intermediate **6** (Scheme 2). The radical formed can then only fragment to give back the benzyl radical and the xanthate, and the reaction is overall degenerate. This technique was then exploited in the area of organic synthesis²² before being adapted to polymer synthesis.¹³ Indeed,

by introducing an excess of compounds with a double bond (i.e., monomers), Zard, in collaboration with the Rhodia research group, produced polymers that displayed living properties.¹³

General Remarks for This Review

To give a clear account of the work published to date, we have tried as much as possible to favor



Where E = electron withdrawing group

Scheme 2. Proposed degenerative transfer mechanism in the presence of xanthates.²³

peer-refereed publications as references, rather than conference proceedings or patents. However, the latter are referenced in those cases for which the work is not reported in peer-refereed publications.

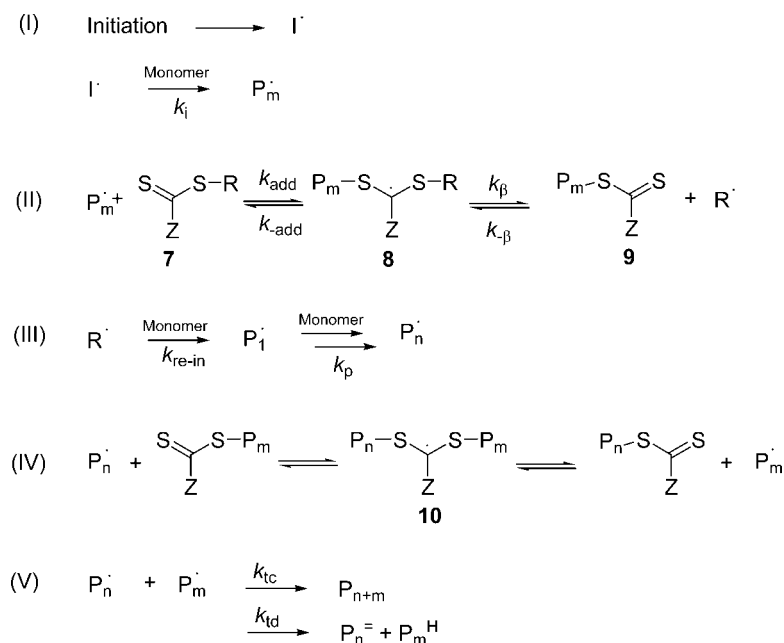
The first part of this review (this section to the Polymerization Processes section) describes the polymerization technique and addresses the mechanism and kinetics of the polymerization, and then each compound involved in the reaction is reviewed: CTAs (their synthetic paths and removal from the polymeric chains after polymerization), free-radical sources, and polymerization conditions and processes. The second part (the Monomers section and the Molecular Architectures Prepared from RAFT/MADIX section) gives an overview of the monomers that have been polymerized via RAFT/MADIX, and this is followed by a review of the various architectures achievable by the process.

MECHANISM AND KINETICS OF THE RAFT/MADIX PROCESS

Mechanism of RAFT/MADIX Polymerization

RAFT and MADIX are based on a similar process that consists of the simple introduction of a small amount of dithioester of generic formula **7** (CTA; Scheme 3) in a conventional free-radical

system (monomer + initiator). The transfer of the CTA between growing radical chains, present at a very low concentration, and dormant polymeric chains, present at a higher concentration, will regulate the growth of the molecular weight and limit the termination reactions. The mechanism of RAFT/MADIX polymerization, as it is generally accepted, is depicted in Scheme 3.^{24–26} The radical species issued from the decomposition of the radical initiator reacts with the monomer (k_i). This growing polymer chain rapidly adds to the reactive C=S bond of the CTA (**7**) (k_{add}) to form a radical intermediate (**8**; the radical initiator may add directly onto the CTA, before reacting with any monomer). Step II shows the fragmentation of the intermediate occurring reversibly either toward the initial growing chain (k_{add}) or to free the re-initiating group (R) and a macro chain-transfer agent (macro-CTA; **9**) (k_{β}). The R group can then re-initiate polymerization ($k_{\text{re-in}}$) by reacting with the monomers and start a new polymer chain, which will propagate (k_p) (III) or react back on the macro-CTA (k_{β}) (II). Once the initial CTA has been entirely consumed, the macro-CTA agent is solely present in the reaction medium and enters equilibrium (IV). This equilibrium is considered the main equilibrium, and a rapid exchange between active and dormant (thiocarbonyl-thio capped) chains ensures equal probability for all chains to grow, therefore leading to



Scheme 3. Proposed general mechanism of RAFT/MADIX polymerization.

the production of polymers of narrow molecular weight distribution. The intermediate radicals **8** and **10** were first observed via electron spin resonance (ESR) by the CSIRO group²⁷ and have since been confirmed by many other research groups.^{27–35} Such radical intermediates may also be involved in a variety of side reactions during polymerization, including termination with a propagating polymeric chain (see the Side Reactions Involving the Intermediate Radicals section). Step V describes the unavoidable reactions of termination present in all free-radical polymerization systems, by either combination (k_{tc}) or disproportionation (k_{td}). However, as the termination reactions are kept to a minimum, the final product consists of a large majority of polymeric chains showing the re-initiating group (R) at one end and the thiocarbonyl-thio group at the other. There have been many reports confirming such structures via a variety of analytical techniques, including ¹H NMR and UV spectroscopy. Mass spectroscopy has also been used to prove the presence of both groups, either via matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)^{36–54} or by electrospray ionization (ESI) mass spectroscopy.^{37,47,55–58} These studies have also shown that a small number of chains terminated by the thiocarbonyl-thio moiety have been initiated by the free-radical initiator.

From this mechanism, the following remarks can be drawn:

1. The mechanism of RAFT/MADIX differs greatly from that of ATRP or NMP, as chain growth is based on the cooperative chain transfer between polymeric chains (bimolecular reactions), instead of reversible radical capping (monomolecular reactions).
2. The source of radicals triggers the degenerative chain transfer, which allows polymeric chains to grow. An increase in the radical concentration will increase the rate of polymerization but will increase the probability of chain termination, leading to polymers with higher polydispersities.
3. The majority of the polymeric chains are initiated by the CTA re-initiating group

(R group) and terminated by the thiocarbonyl-thio group (Scheme 4).

4. The molecular weight increases linearly with conversion and can be predicted, if we assume that all CTAs have reacted and neglect the chains initiated by the source of radicals, by the following equation:

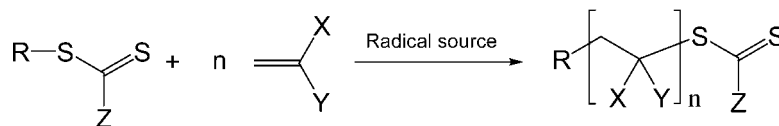
$$M_{n,theo} = \frac{[\text{Monomer}]}{[\text{CTA}]} \times \text{FW}(\text{M}) \times c + \text{FW}(\text{CTA})$$

where $M_{n,theo}$ is the theoretical number-average molecular weight; [Monomer] and [CTA] are the concentrations of the monomer and CTA, respectively; FW(M) and FW(CTA) are the monomer and CTA formula weights, respectively; and c is the fractional conversion (see Fig. 2).

Effect of the Z Group

The Z group strongly influences the stability of the thiocarbonyl-thio radical intermediate. Therefore, strong stabilizing groups will favor the formation of the intermediate and hence enhance the reactivity of the S=C bond toward radical addition. However, the stability of the intermediate needs to be finely tuned, to favor its fragmentation, which will free the reinitiating group (R·). Numerous groups have investigated the effect of the Z group on the polymerization of a variety of monomers.^{41,42,59–64} From these studies, one can identify the phenyl group as the ideal candidate for most monomers as it balances the stability of the radical intermediate and its reactivity toward fragmentation.

In the case of the benzyl group, the intermediate is less stable, and the fragmentation step occurs more easily; this leads to almost no retardation in the polymerization of styrene (see the Kinetics of the RAFT/MADIX Process section)⁶² and faster polymerizations for more reactive monomers such as *N*-isopropyl acrylamide,⁵² acrylamide,⁶⁵ and methyl acrylate.⁶⁰ In the latter case, it is even possible to reach quantitative conversion, with good control over the molecular weight, at room temperature.⁶⁰ On the other



Scheme 4. Overall reaction in RAFT/MADIX polymerization.

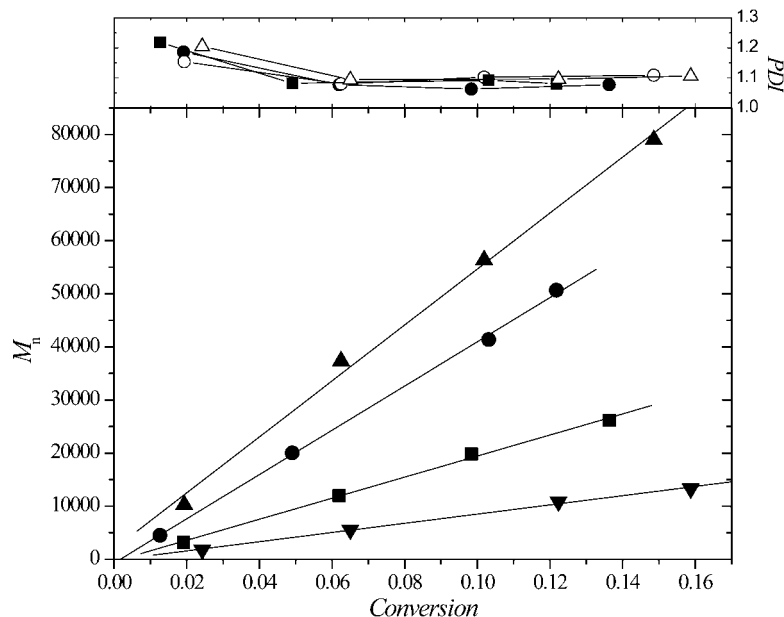


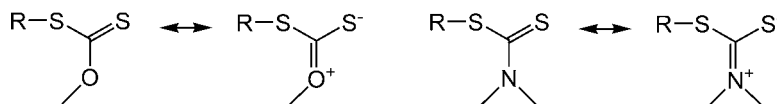
Figure 2. Evolution of M_n and PDI with the monomer conversion in the bulk polymerization of methyl acrylate at 60 °C mediated by PEDB in the following concentrations: (▲) 1.9×10^{-3} , (●) 3.8×10^{-3} , (■) 7.7×10^{-3} , and (▼) 17.4×10^{-3} mol L⁻¹.

hand, this less stable intermediate leads to poor control over the polymerization of bulkier propagating radicals such as methyl methacrylate (MMA).⁶²

Alkyl Z groups also give reasonable control over the polymerization of styrene,^{63,66} butyl acrylate,^{12,25} and MMA.⁶⁷

In the case of Z = O or N, the nonbonded electron pair on the heteroatom is delocalized with the S=C double bond (Scheme 5). This lowers the reactivity of the double bond toward radical addition, and therefore the rate of addition of the propagating radical on the sulfur atom is decreased; this leads to poor control over the molecular weight of the growing polymeric chains. For instance, in the specific case of methacrylates, the rate of addition of a bulky methacrylate radical on the sulfur atom will be greatly reduced, and this will result in a final polymer with poorly controlled molecular weight.^{13,67,68} However, in the case of fast propagating monomers (e.g., vinyl acetate), CTAs with C=S bond of a lower reactivity are desirable, as they permit the addition of poorly stabilized

propagating radicals on the C=S bond and give some control over the molecular weight of the polymer. Indeed, vinyl acetate polymerization can be successfully controlled in the presence of xanthates, whereas it is strongly inhibited by dithiobenzoates.^{56,69,70} Xanthates (Z = O-Z') have been used with styrene^{14,25,41,42,63,71,72} (the best control was achieved with Z' = -CH[P(O)(OEt)₂]CF₃⁴² or -CH₂CF₃,⁷² PDI = 1.2–1.4), acrylic acid,^{73,74} methyl acrylate,¹⁴ ethyl acrylate,^{14,42} butyl acrylate,⁶⁸ and *tert*-butyl acrylate,^{67,68} and acrylamide⁷³ to give polymers with PDIs typically ranging from 1.2 to 2.0. Finally, xanthates offer excellent control over vinyl acetate^{13,14,67,75} and permit the production of living poly(vinyl formamide) with PDIs around 1.7.⁷⁶ Dithiocarbamates (Z = NR₁R₂) have also been used with styrene,⁶¹ ethyl acrylate,⁶¹ and vinyl acetate.^{61,67} Once again, the delocalization of the lone electron pair from the nitrogen atom led to poor control over styrene and acrylate polymerization, while giving low-PDI poly(vinyl acetate). Using structures in which the nonbonded electron pair is conjugated with another elec-



Scheme 5. Canonical forms of xanthates and dithiocarbamates.

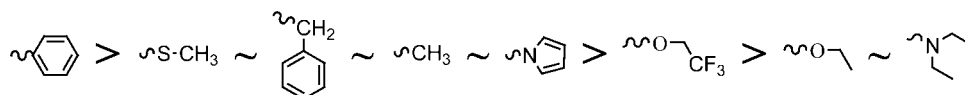
tron-withdrawing group, or part of an aromatic structure, will on the other hand increase the reactivity of the C=S bond and the overall rate of chain transfer.^{59,61,77} Styrene,^{42,59,61,63,67,68} methyl acrylate,^{42,59,61,67,68} ethyl acrylate,⁶¹ MMA,^{59,61,68} and *N*-isopropyl acrylamide⁵³ have all been polymerized in a controlled manner in the presence of such CTAs. This marks a key difference between polymerizations based on iniferters and via RAFT/MADIX.

The specific case of Z being a sulfur is worth considering. In this case, the C=S bond is reactive enough to ensure rapid chain-transfer reactions, leading to efficient transfer agents, while minimizing polymerization retardation (see the Kinetics of the RAFT/MADIX Process section). Such CTAs can be obtained via a straightforward forward one-step reaction, and their yellow color does not affect the final product color as much as their dithiobenzoate counterparts (which usually show a red-orange color).^{63,78} Finally, the Z group can be functionalized to produce a variety of architectures (see the Molecular Architectures Prepared from RAFT/MADIX section). A range of monomers have been successfully polymerized in a controlled manner with trithiocarbonates, including styrene,^{11,63,67,78–82}

acrylic acid,^{74,79,83} methyl acrylate,^{67,78,82} ethyl acrylate,⁷⁹ butyl acrylate,^{47,79,80} hydroxy ethyl acrylate,⁷⁹ acrylamide,⁸⁴ dimethyl acrylamide,^{82,85} *N*-*tert*-butyl acrylamide,⁷⁹ *N*-isopropyl acrylamide,⁸⁶ MMA,^{67,78,79,82} dibutyl itaconate, and dicyclohexyl itaconate.⁸⁷

Other Z groups that have been investigated include (diethoxyphosphoryl)dithioformate (I) and (diethoxythiophosphoryl)dithioformate (II) in the polymerization of styrene.^{29,33} Such CTAs, although mediating a living polymerization, did not offer good control over the molecular weight.

In conclusion, a general classification of Z groups that allow good control over the majority of monomers is as follows: dithiobenzoates > trithiocarbonates ~ dithioalkanoates > dithiocarbamates (where the nonbonded electron pair on N is conjugated with another electron-withdrawing group) > xanthates > dithiocarbamates. The polymerization of methacryloyl derivatives is better controlled by dithiobenzoates, whereas the polymerization of vinyl acetate and derivatives is better controlled by xanthates. More specifically, experimental data^{41,42,59–64,72} and *ab initio* calculations⁹⁸ suggest the following guideline for the selection of a CTA Z group:



Effect of the R Group

The R group is required to be a good leaving group in comparison with the growing polymeric chain and a good re-initiating species toward the monomer used. It also contributes toward the stabilization of the radical intermediate, although to lesser extent than the Z group. Parameters such as the stability of the expelled radical, steric bulk, and polarity need to be considered for the choice of the R group. Previous studies have shown the importance of this group when monomers are polymerized with a high rate of propagation.^{53,88,89,90} To date, cumyl and cyanoisopropyl groups seem to be the most efficient for the reinitiation step.⁶¹ Chong et al.⁹⁰ showed that when a CTA of structure S=C(Ph)S—R is used for MMA polymerization at 60 °C, the efficiency depends strongly on R in the following order: —C(alkyl)₂CN ~ —C(Me)₂

Ar > —C(Me)₂C(O)O(alkyl) > —C(Me)₂C(O)NH(alkyl) > —C(Me)₂CH₂C(Me)₃ ≥ —C(Me)HPh > —C(Me)₃ ~ CH₂Ph.

Several groups have investigated the use of R groups that mimic the propagating polymeric radical. This approach has been successful in the polymerization of styrene,^{66,90} dimethyl acrylamide,⁸⁹ and methyl acrylate and other acrylates,⁸⁸ although the polymerization of fast propagating monomers has shown some degree of inhibition at the start of the polymerization. On the other hand, this approach has not been successful with methacrylate derivatives, as the penultimate unit effect favors fragmentation of the polymethacrylate radicals in comparison with the single methacrylate unit.^{90,91} Figure 3 illustrates the rates for the polymerization of methyl acrylate mediated by CTAs with changing R groups. Note the inhibition/induction observed for the various R groups, including one

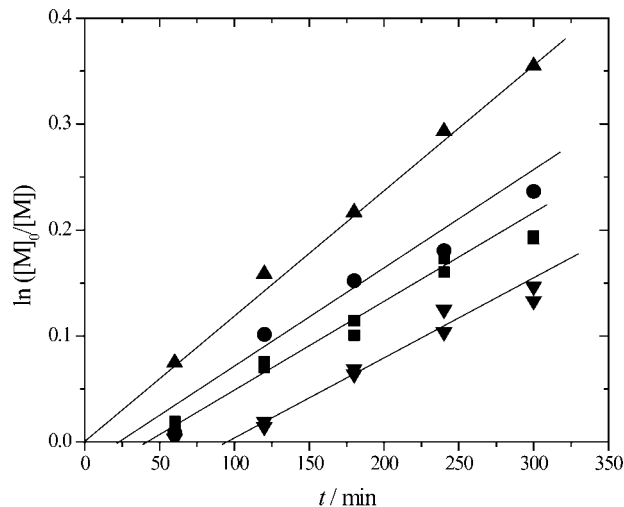


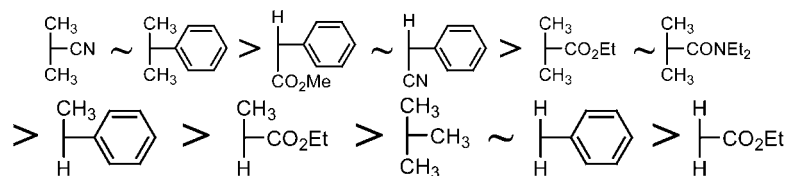
Figure 3. Pseudo-first-order rate plot for the bulk polymerization of methyl acrylate at 60 °C mediated by (●) 1-methoxycarbonyl ethyl dithiobenzoate, (■) cyanoisopropyl dithiobenzoate, (▼) PEDB, and (▲) poly(methyl acrylate) dithiobenzoate at an initial concentration of $7.7 \times 10^{-3} \text{ mol L}^{-1}$.

mimicking the methyl acrylate propagating radical, whereas no inhibition is observed when the R group is a poly(methyl acrylate) chain.

The specific case of ester/amide leaving groups is noteworthy, as their synthesis is straightforward and they allow the easy introduction of functionalities at the polymeric chain end.^{82,89,90,92–94} The substituent variation at the α -carbon of the carbonyl group leads to generated radicals of various stabilities. When R = $\text{C}(\text{CH}_3)_2\text{CO}_2\text{R}'$, a reasonably well controlled

polymerization can be achieved with styrene and acrylate derivatives, but poor control is observed with methacrylates. This effect is due to the low capacity of these R groups to act as leaving groups in comparison with polymethacrylate radicals, forcing the equilibrium (II, Scheme 3) to be strongly shifted to the left.⁹¹ If R = $\text{CHCH}_3\text{CO}_2\text{R}'$, the control of the polymerization of styrene and acrylates is still achievable, but again a poor efficiency toward methacrylate derivatives is observed.^{88,93} In the case of R = $\text{CH}_2\text{CO}_2\text{R}'$, the generated radical is not very stable, and poor control over the polymerization of styrene and acrylates is observed, whereas no control whatsoever is observed for the polymerization of methacrylates.⁹³ Our group recently reported a CTA with R = $\text{CH}(\text{C}_6\text{H}_5)\text{CO}_2\text{Me}$: the presence of a phenyl group increased the stability of the generated radical, whereas H reduced its bulkiness. The CTA offered very good control over the polymerization of styrene, MMA, methyl acrylate, and dimethyl acrylamide.⁸² We made similar observations when using a CTA with R = $\text{CH}(\text{C}_6\text{H}_5)\text{CON}(\text{Et})_2$.⁹⁴ Following a similar trend of thought, Li et al.⁹⁵ reported very recently a CTA with R = $\text{CH}(\text{C}_6\text{H}_5)\text{CN}$ that controlled the polymerization of styrene, acetoxy-styrene, *n*-butyl acrylate, *tert*-butyl acrylate, and MMA, giving polymers with a PDI around 1.1 and block copolymers of MMA and styrene with a PDI around 1.2.

Experimental data and *ab initio* calculations⁹⁸ provide the following general guidelines for the selection of the R group for a CTA:



General Comments on the Combined Effects of the Z Group and the R Group on a CTA

It is clear that in most cases, the effects of both the R and the Z groups need to be considered to design the most efficient CTA to control the polymerization of a specific monomer. The CSIRO group has worked extensively on the determination of chain-transfer constant (C_{tr}) values for specific RAFT agents.^{25,63,90} As for conventional chain transfer, C_{tr} of a RAFT/MADIX agent can

be calculated by the ratio of the rate constant for chain transfer to the rate constant for propagation ($k_{\text{tr}}/k_{\text{p}}$). However, in the case of reagents that react by addition–fragmentation, k_{tr} depends on the rate constant for addition to the thiocarbonyl-thio group (k_{add}) and the partitioning of the fragmentation of the intermediate radical toward either an attacking radical or a re-initiating radical [$k_{\text{tr}} = k_{\text{add}}[k_{\beta}/(k_{-\text{add}} + k_{\beta})]$; Scheme 3]. The transfer constants of various thi-

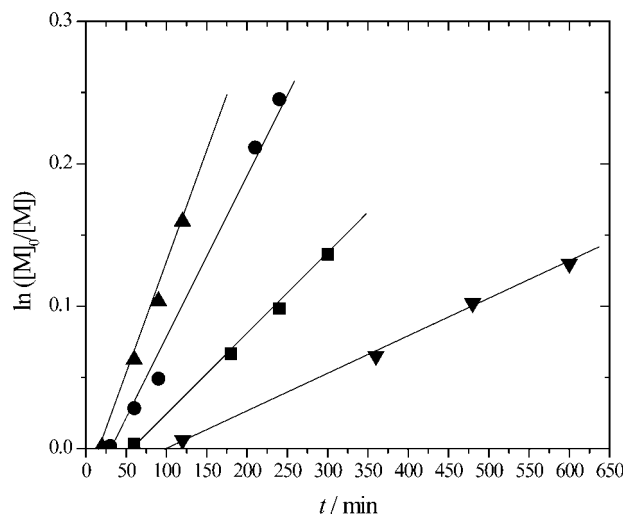


Figure 4. Pseudo-first-order rate plot for the bulk polymerization of methyl acrylate at 60 °C mediated by PEDB in the following concentrations: (▲) 1.9×10^{-3} , (●) 3.8×10^{-3} , (■) 7.7×10^{-3} , and (▼) 17.4×10^{-3} mol L⁻¹. Note the decrease in the polymerization rate and the increase in the inhibition/induction period as the CTA concentration increases.

ocarbonyl-thio compounds have been found to range from below 0.01 to above 1000, depending on the Z and R substituents and the specific monomer to be polymerized.^{25,63,90} Even at low monomer conversions (required for the calculations of C_{tr}), the procedure does not yield conventional C_{tr} values, and these values must be treated with caution as they are only valid as comparative data between RAFT/MADIX agents, under specific conditions, for specific monomers. Transfer coefficients can also be estimated by the analysis of the dependence of the molecular weight distribution on the monomer/CTA conversion.^{62,63,66,96,97} Recently, Coote et al.⁹⁸ published an excellent review on the use of high-level *ab initio* molecular orbital calculations to assess the effect of both R and Z groups on RAFT/MADIX polymerizations. *Ab initio* calculations are emerging as a very promising technique to predict CTA reactivity, but, as this technique is still relatively unexplored in the area of RAFT/MADIX polymerization, it requires further work to correlate calculations with empirical data.⁹⁹

In conclusion, although there is a wide range of CTAs available, the living polymerization of most common monomers can be controlled by a choice of four CTAs. We would acknowledge cumyl dithiobenzoate,⁶⁷ cyanoisopropyl dithiobenzoate,⁶⁷ methoxycarbonylphenylmethyl dithiobenzoate,⁸² and α -cyanobenzyl dithiobenzoate⁹⁵

as the most versatile of all CTAs for controlling the living polymerization of the most commonly used monomers [i.e., styrene, (meth)acrylate, and (meth)acrylamide derivatives] and a cyanoalkyl xanthate for controlling the polymerization of vinyl acetate and its derivatives [see the Vinyl Acetate (and Derivatives) and Vinyl Formamide section].

Kinetics of the RAFT/MADIX Process

Rate Retardation

In ATRP and NMP, the propagation of the polymeric chains occurs via a series of activation–deactivation equilibria, during which a radical is formed that can react with one monomer, or many, before undergoing reversible termination. In RAFT/MADIX, the activation–deactivation equilibrium is a chain-transfer reaction, and for each radical consumed by a reversible termination reaction, a new radical is formed. As the chain-transfer reactions have no effect on the overall polymerization rate,¹⁰⁰ the kinetics of a RAFT/MADIX polymerization should, therefore, follow those of a conventional free-radical polymerization, and the rate of polymerization should be half-order with respect to the initiator and independent of the CTA. It is therefore surprising to observe slower kinetics of polymerization for RAFT/MADIX systems, in comparison with a conventional free-radical polymerization system under similar conditions. Furthermore, it is common in RAFT polymerization to observe a decreasing rate of polymerization, a retardation effect, when the concentration of the CTA is increased (see Fig. 4 for an example of methyl acrylate polymerization). The retardation effect in RAFT polymerization has been studied by many research groups and appears more pronounced with the use of dithiobenzoates,^{27,67,96,97,101,102} as opposed to aliphatic dithioesters^{60,62,67} or trithiocarbonates.⁷⁸ Very little, or in some cases, no retardation is usually observed in MADIX polymerization (xanthates as CTAs).⁵⁶ The cause for the retardation effect is still the subject of an ongoing international debate. This review does not aim to describe in great detail the issues attached to the ongoing discussion, and we will limit ourselves to presenting only the arguments put forward by the research groups active in this area. For a deeper understanding of the debate, one can refer to a number of high-quality publications.^{35,103,104}

There are two main justifications for the rate retardation in RAFT polymerization.

Side Reactions Involving the Intermediate Radicals. The intermediate radical may be involved in a variety of side reactions during polymerization. Monteiro and de Brouwer¹⁰⁵ first proposed the termination of intermediate **4** (Scheme 3) with a propagating polymeric chain to generate a three-arm star structure. Later, Fukuda's group^{48,66,96,102,106,107} confirmed Monteiro's observation by isolating and characterizing via a variety of analytical techniques three-arm stars formed during the RAFT-mediated polymerization of styrene. In a recent piece of work, Venkatesh et al.⁵⁴ also observed the formation of three-arm and four-arm stars (the latter being produced by the coupling of two intermediate radicals, **4**; Scheme 3) from butyl acrylate in a model system, but the authors could not isolate such architectures when undertaking a RAFT polymerization. Similar observations on the formation of three-arm and four-arm star polymers were made by other research groups in the polymerization of styrene, mediated by cumyl dithiobenzoate,¹⁰⁸ and butyl acrylate, mediated by *tert*-butyl dithiobenzoate.³² On the other hand, the Centre for Advanced Macromolecular Design (CAMD) team could not isolate any three-arm or four-arm stars by analyzing the product of the RAFT polymerization of methyl acrylate mediated by cumyl dithiobenzoate, via online coupling of size exclusion chromatography with ESI mass spectrometry. However, the authors could clearly isolate the products corresponding to the polymeric CTA and the combination and disproportionation termination products, along with side products generated by oxidation of the polymeric CTA.⁵⁷ The authors also noted a peak corresponding to intermediate radical **10** (Scheme 3), within experimental error, although they were cautious to assign it as the stable radical + H.⁵⁷ It is noteworthy that most reactions describing the occurrence of three-arm and four-arm stars were set as model systems, in the presence of a high concentration of free radicals, and to date there is no direct evidence of such reactions occurring during a conventional RAFT polymerization.

Other side reactions that may cause the observed retardation include a potential reaction of intermediate **4** (Scheme 3) with oxygen or other impurities during polymerization¹⁰⁹ and the addition of the intermediate onto a monomer to re-initiate polymerization.

Slow Fragmentation of the Intermediate Radical. The CAMD team has developed computer

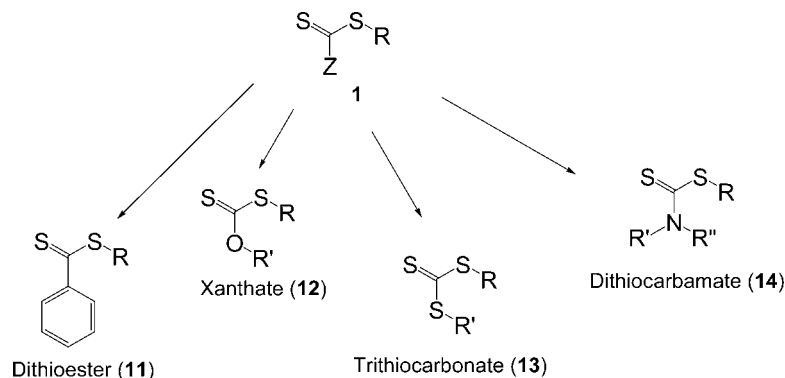
simulations for the polymerization of styrene mediated by cumyl dithiobenzoate which suggest that the intermediate radical is a stable species with a lifetime longer than 10^{-5} s, especially in the case of dithiobenzoates for which the intermediate radical is stabilized by a phenyl group.^{62,97,104,110–113} Such observations suggest a very high concentration of the intermediate radical (10^{-4} M for the polymerization of styrene mediated by cumyl dithiobenzoate), which is in direct contradiction to the experimental ESR data reported to date, which all suggest a concentration of the intermediate radical lower than 10^{-7} M.^{27–35} In a later paper, the CAMD team suggested such discrepancy could be explained by the possibility of a reversible radical sink.⁶² Wang and coworkers^{35,114–116} and other research groups¹¹⁷ have also described the RAFT polymerization via a computer simulation based on a different model and concluded that the concentration of the intermediate radical is closer to 10^{-7} M than to 10^{-4} M. Such reports have led to an open debate that is, as yet, unsolved.^{35,104}

To prove the stability of the intermediate radical, CAMD used γ radiation to generate the intermediate radical and showed a significant free-radical storage effect for the RAFT polymerization mediated by cumyl dithiobenzoate. The free radicals generated by γ irradiation at ambient temperatures were stored in the system, with the occurrence of little or no polymerization. After an extensive period of time, these free radicals were released in the presence of monomer and, with an increase in the temperature, led to polymers with controlled molecular weights.^{112,118}

Recently, the use of high-level *ab initio* molecular orbital calculations has shown that dithiobenzoates generate intermediate radicals that are more stable than aliphatic dithioesters and trithiocarbonates.^{70,98,103,119} Similar calculations also suggest that the retardation observed in the polymerization of methyl acrylate⁹⁹ and styrene¹⁰¹ mediated by cumyl dithiobenzoate may be attributed to the slow fragmentation of the CTA intermediate radical.

Inhibition/Induction

Slow fragmentation of the intermediate radical may also affect the very start of the polymerization. Indeed, a certain degree of inhibition/induction is often observed in RAFT polymerization, and the effect is enhanced for fast propa-



Scheme 6. General structures of RAFT/MADIX agents and examples of the different functional groups on the Z positions: dithioester (**11**),^{11,12} xanthate (**12**),^{13,14,42} trithiocarbonate (**13**),^{78,123} and dithiocarbamate (**14**).^{53,59,61}

gating monomers such as vinyl acetate, acrylates, and acrylamides (see Fig. 4). This effect may be due to slow fragmentation of intermediate radical **2** (Scheme 3), as evidenced by experimental data^{32,88} and *ab initio* calculations¹⁰¹ in the RAFT polymerization of methyl acrylate. An alternative explanation of inhibition is the slow re-initiation of the initiating and leaving group radicals during the early part of the polymerization (the period of consumption of the initial RAFT agent, called initialization), which has been observed in the polymerization of acrylamides^{53,89} and characterized by NMR spectroscopy in the polymerization of styrene and methyl acrylate.^{120–122} However, as both fragmentation and slow initiation are intrinsically related to the stability of the R radical, it is difficult to favor one or the other hypothesis. One can, however, clearly observe that inhibition increases with the concentration in CTA, as is observed for retardation (see Fig. 4). Finally, inhibition may also be due to impurities present in the solution, as shown by the CAMD team in the MADIX polymerization of vinyl acetate.⁷⁵

CTA

CTA Synthesis

CTAs can be categorized into four classes, depending on their activating Z group (Scheme 6): dithioesters (**11**),^{11,12} xanthates (**12**),^{13,14,42} trithiocarbonates (**13**),^{78,123} and dithiocarbamates (**14**).^{53,59,61} The few RAFT/MADIX agents that are commercially available are not efficient enough to control the polymerization of most monomers, but fortunately, there is a variety of routes for their synthesis (Table 1, Scheme 7).

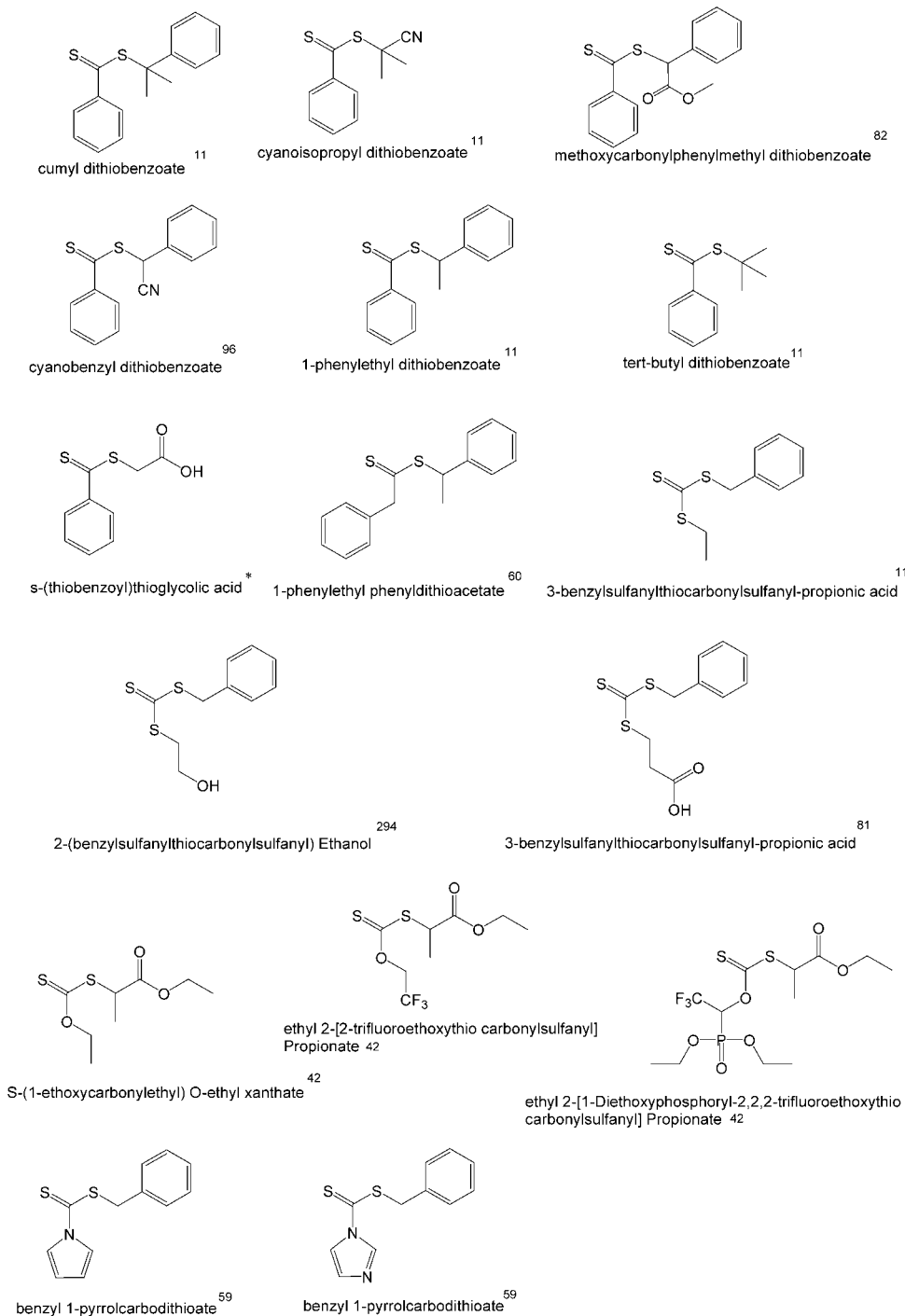
The synthesis of CTAs often requires the preparation of a dithiocarboxylic acid; the next three subsections present general techniques for its production. The seven subsections following them outline the various synthetic techniques that have been reported for the synthesis of RAFT/MADIX agents.

Synthesis of Dithiocarboxylic Acid from CS₂

An alkoxide, a thiolate salt, or an amine is reacted with CS₂ under reflux to produce a xanthate salt,¹³ trithiocarbonate,¹²⁴ or dithiocarba-

Table 1. Summary of References for the Relevant CTAs and Their Relevant Synthetic Methodologies

	Dithioesters	Xanthates	Trithiocarbonates	Dithiocarbamates
Cyclic tetrathio phosphate	125	—	—	—
Alkylation	62, 87, 138	56, 139–141	79, 80, 124, 142, 143	53, 144
Via bis(thiocarbonyl) disulfide	25, 145–148	129, 130	129, 130	129, 130
Markovnikoff addition	25, 60, 145, 149	—	—	—
Michael addition	125, 132	—	—	—
Via TCDI	—	136	136	136
Via ATRP	137	—	—	—

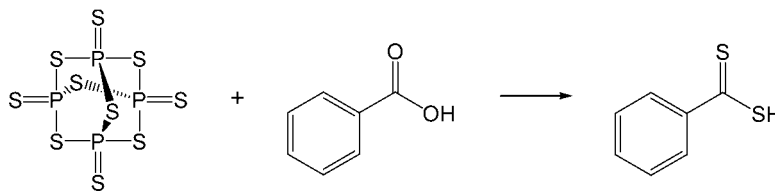


Scheme 7. Main CTAs discussed in this review (the references describe the syntheses; the asterisk indicates commercial availability).

mates,⁶¹ respectively. Alternatively, a Grignard reaction can be applied to an alkyl/aryl halide and reacted with CS₂ to produce the corresponding thiocarbonyl-thio salt.^{62,88}

Synthesis of Dithiocarboxylic Acid from S₈

The addition of sodium methanolate to elemental sulfur and alkyl/aryl halide under reflux also leads to the formation of a thiocarbonyl-thio salt.¹¹



Scheme 8. Use of P_4S_{10} with benzoic acid to prepare dithiobenzoic acid.

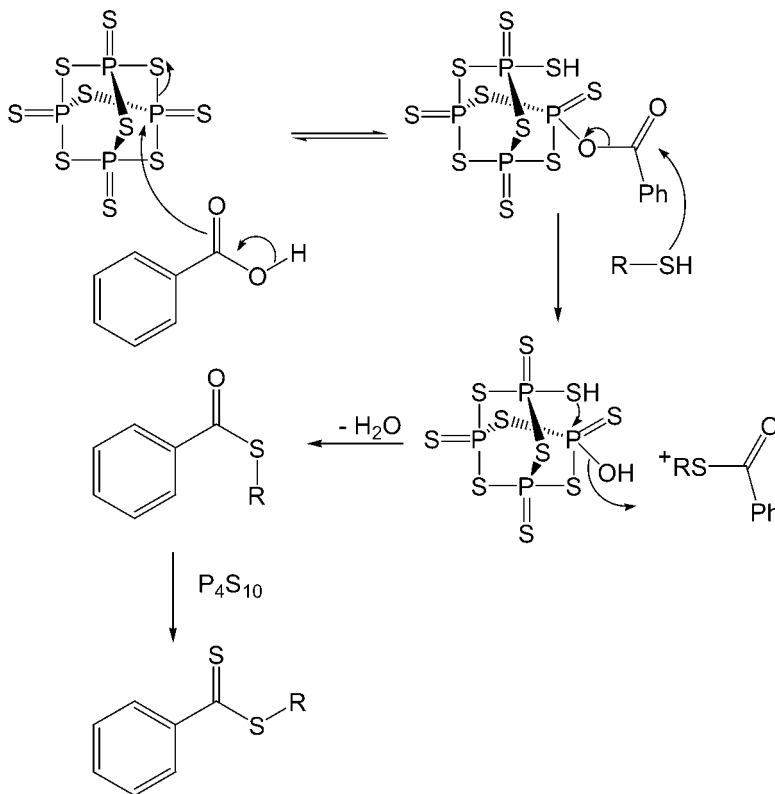
Thionation on a Carbonyl Group Catalyzed by Cyclic Tetrathio phosphates

Dureault et al.¹²⁵ first reported the use of cyclic tetrathio phosphates to prepare thiocarbonyl-thio compounds (see Scheme 9 for the general mechanism of reaction). Dithiobenzoic acid is synthesized from P_4S_{10} and benzoic acid (Scheme 8) and then further reacted, *in situ*, with the relevant chemicals to introduce the R substituents. In addition, P_4S_{10} can react with a carboxylic acid in the presence of a relevant thiol to form a dithioester (Scheme 9).¹²⁶

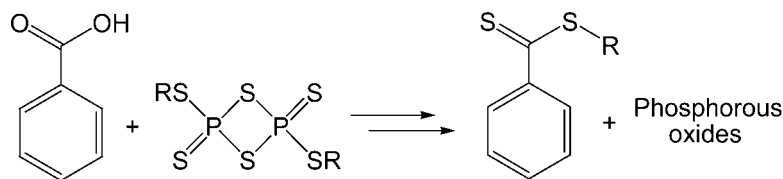
The same group also reported the use of the Davy reagent^{125,127} to react the desired R substituent with benzoic acid to form a thiocarbonyl-thio CTA (Scheme 10).

Preparation via Alkylation

One of the most widely used synthetic pathways to prepare a CTA is the alkylation of a thiocarbonyl-thio group. Generally, a dithio salt is reacted with an alkyl halide. The key to this synthesis depends on the choice of the thiocarbonyl-thio salt counterions (Na^+ , K^+ , NH_4^+ , Cu^{2+} , or Mg^{2+}) and the appropriate alkyl halide.¹²⁸ To achieve a MADIX agent,¹³ an alkoxide is chosen as a precursor to react with carbon disulfide, followed by the addition of an alkyl halide, whereas trithiocarbonates¹²⁴ and dithiocarbamates⁶¹ can be prepared with a thiolate salt or an amine, respectively. Grignard reactions can also be applied to an alkyl/aryl halide to convert it into a magnesium salt, which is further reacted with carbon disulfide to form a



Scheme 9. Use of P_4S_{10} to prepare dithioesters.



Scheme 10. Reaction of Davy reagents with benzoic acid.

thiocarbonyl-thio salt and reacted further with an alkyl halide to yield a CTA (Scheme 11).^{62,88} This method is suitable for preparing dithioesters, xanthates, trithiocarbonates, and dithiocarbamates. The preparation reported by Lai et al.⁷⁹ is also noteworthy. The authors found that the reaction of 1 equiv each of alkylmercaptan and carbon disulfide with hydroxide ions, followed by alkylation with chloroform and acetone in a phase-transfer-catalyzed reaction, led to the production of a monocarboxyl-terminated trithiocarbonate derivative in a very good yield.

Preparation from a Bis(thiocarbonyl) Disulfide or via a Radical Addition–Fragmentation

This process requires the formation of bis(thiocarbonyl)disulfides, which can be prepared from the oxidative coupling of the relevant thiocarbonylthio salts.^{129,130} These compounds can be further reacted with a free-radical initiator via radical addition-fragmentation, leading to the CTA (Scheme 12). The yields obtained with this procedure are moderate to good. This compound has also been used in the polymerization of styrene to generate the CTA *in situ*.¹³¹

An alternative technique is the addition of a free radical onto a pre-existing CTA, followed by fragmentation of its leaving group. To obtain a good yield, the precursor CTA must have a good leaving group with respect to the CTA product, or an excess of the radical must be used.¹¹ Our group has used this technique to recycle CTAs following RAFT/MADIX polymerization (see the End-Group Modification by Radical Addition–Fragmentation and Recovery of CTA section).

Exchange between Carboxymethyl Dithiocarboxylates and Thiols

This synthetic route is based on the transesterification between a carboxymethyl dithiocarboxylate and a thiol to yield a new dithioester (Scheme 13).^{125,132} The yield of this reaction is relatively low because of the reactivity limitations of the starting materials and the genera-

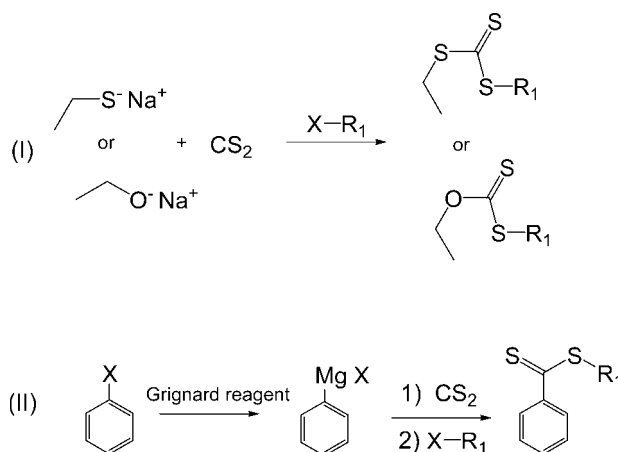
tion of undesirable byproducts, but it has the advantages of using commercially available S-(thiobenzoyl)thioglycolic acid to synthesize dithiobenzoate derivatives.

Markovnikoff Addition-Type Mechanism

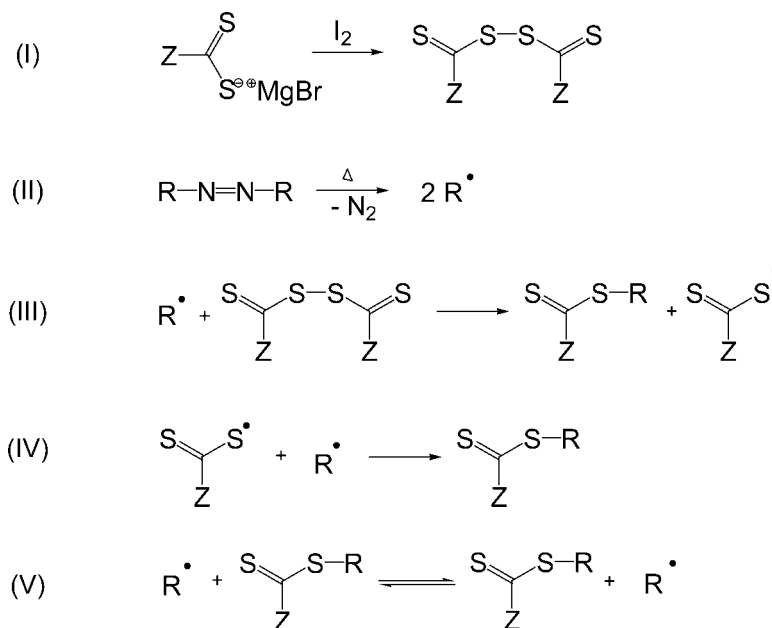
The Markovnikoff addition is triggered by the ability of the substituents to stabilize the carbocation formed by initial protonation and depends on the electron density on the alkene. An example of the synthesis of cumyl dithiobenzoate from α -methyl styrene via this process is shown in Scheme 14.^{125,132}

Michael Addition-Type Mechanism

This type of addition was invented by Michael in 1887 and is now one of the most popular mechanisms for the addition of alkenes onto carbonyl groups.^{133–135} For the synthesis of CTAs, a 1,4-addition between alkenes and dithiocarboxylic acid is performed, as shown in Scheme 15.^{125,132} It is worth mentioning that the Markovnikoff addition (see the Markovnikoff Addition-Type Mechanism section) cannot be applied to methacrylate derivatives to produce methacrylate radicals as leaving groups.



Scheme 11. Several examples of the alkylation of the thiocarbonyl-thio group (X = Cl or Br).



Scheme 12. Suggested mechanism for the formation of RAFT/MADIX CTAs via bis(thiocarbonyl) disulfide and an azo compound.

Reaction with 1,1'-Thiocarbonyl Diimidazole (TCDI)

Recently, our group developed the use of TCDI as a precursor to react with primary and secondary alcohols, thiols, and amines to form xanthates, trithiocarbonates, and dithiocarbamates, respectively (Scheme 16).¹³⁶ This method avoids the use of CS₂ (volatile, toxic, and flammable), can be achieved in a one-pot reaction, and provides the opportunity to easily design symmetric or/and asymmetric CTAs.

Transformation from ATRP initiators to RAFT CTAs

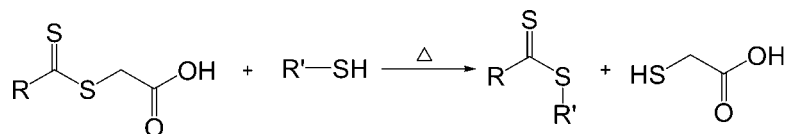
This technique was reported by Wager et al.¹³⁷ to convert ATRP initiators into CTAs. In this technique, an ATRP initiator is reacted with a copper complex, formed from Cu(I)Br/Cu(0) with *N-n*-pentyl-2-pyridylmethanimine, to produce a

radical that can add onto the bis(thiobenzoyl) disulfide.

Methodologies To Remove Thiocarbonyl-Thio End Groups

Although RAFT/MADIX polymerizations have been intensively studied over the last 5 years, the use of the process for industrial applications is still limited by the relatively high cost of CTAs, the color of the polymer product conferred by the thiocarbonyl-thio end group, and the presence of sulfur at the chain end of the polymer.^{12,13,150}

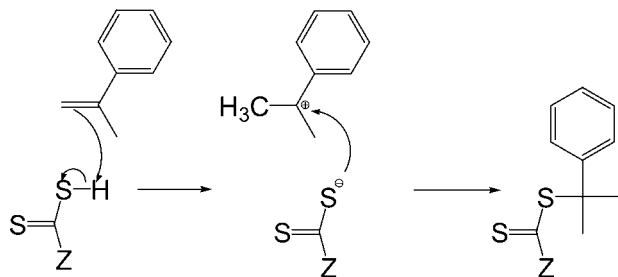
There are, however, a number of examples in the literature for the removal of the thiocarbonyl-thio end group, reported first by Rizzardo et al. in 1999.¹⁵⁰ Several methodologies to remove the dithiocarbonyl-thio chromophore end groups are reviewed next.



Where R = alkyl or aryl group

R' = primary or secondary thiol

Scheme 13. Reaction between carboxymethyl dithiocarboxylates and thiols.



Scheme 14. Synthesis of cumyl dithiobenzoate from α -methyl styrene via a Markovnikoff-type addition reaction.

Hydrolysis

Hydrolysis, under basic or acidic conditions, is a commonly used reaction for the conversion of a thioester to a related thiol. CAMD reported the base-catalyzed hydrolysis on a polymer containing dithiocarbonyl-thio. They prepared star polymers derived from the hydrolysis of poly(vinyl acetate) with potassium hydroxide in methanol. Poly(vinyl alcohol) was achieved with the removal of the thiocarbonyl-thio moiety.¹⁵¹ Around the same time, Llauro et al.⁸³ gave an account of the preparation of low-molecular-weight poly(acrylic acid) with trithiocarbonic acid dibenzyl ester as a CTA. After neutralization with sodium hydroxide, the polymeric chain end groups were hydrolyzed into thiols. However, the same authors observed side reactions leading to disulfide, base-catalyzed elimination to form vinyl end groups, and cyclization to form cyclic lactones or thiolactones (Scheme 17), as characterized by negative-ion MALDI-TOF mass spectroscopy and NMR spectroscopy.

Hruby et al.¹⁵² reported the acid hydrolysis of polymers containing a dithiocarbonate as a pendant group on the main chain. After acid-catalyzed hydrolysis at 90 °C for several hours with 35% hydrochloric acid, the final hydrolyzed

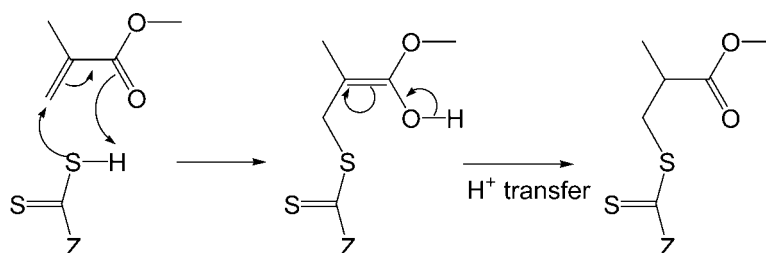
polymer showed thiol end groups corresponding to a quantitative reduction of the thiocarbonyl-thio groups (Scheme 18).

Metal-Assisted Elimination

In 1963, Ferris and Schutz¹⁵³ reported the preparation of carbodiimides, isocyanates, and isothiocyanate by metal-ion-assisted elimination of mercaptan compounds (e.g., xanthate). Scheme 19 shows the reaction of thiocarbonyl-thio compounds to form a thiocarbonyl-thio end-functionalized polymer and an isothiocyanate for which the Z group is a carbamate group. Unfortunately, this type of metal-catalyzed elimination reaction is limited to *N*-alkyl or *N*-aryl dithiocarbamate (**15**, Scheme 19), and both silver and mercury salts are toxic, carcinogenic, and expensive; this makes their industrial application difficult.¹⁵⁴

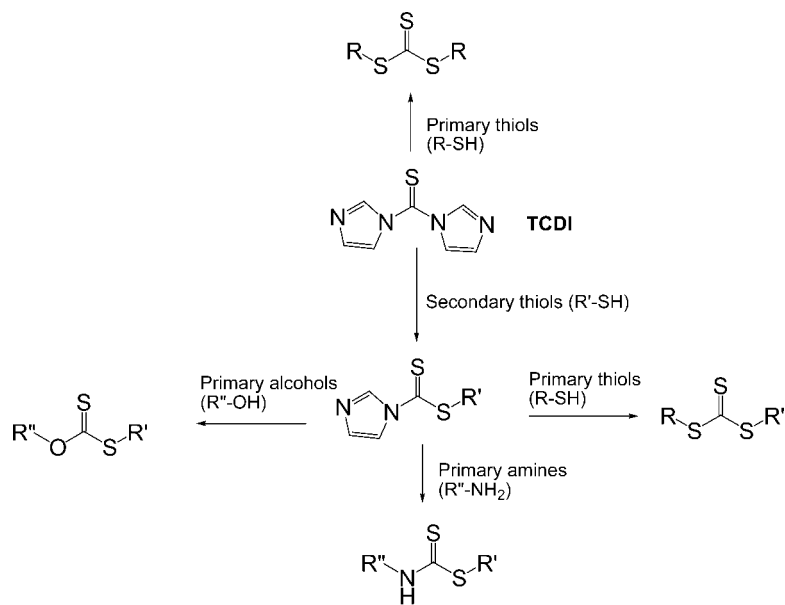
Pyrolysis

The thermal decomposition of dithioesters occurs via a syn elimination (or cis elimination) to yield an alkene for which β -hydrogens are required. The syn or suprafacial character of these eliminations is enforced by the five- or six-membered cyclic transition state. Although a six-membered transition state is relatively unstrained, esters and thioesters of alcohols require higher temperatures for elimination reactions because of the stronger C—O bond and the lower polarity of C=O. On the other hand, the thioester function of xanthate derivatives undergoes elimination at much lower temperatures than carboxylic esters because of a favorable bond energy change from O—C=S in the xanthate to S—C=O C=O in the eliminated fragment. Xanthate pyrolysis is known as the Chugaev (or Tschugaev) reaction (Scheme 20).^{155,156}



Where Z = alkyl or aryl group

Scheme 15. Mechanism of CTAs prepared via a Michael addition-type reaction.

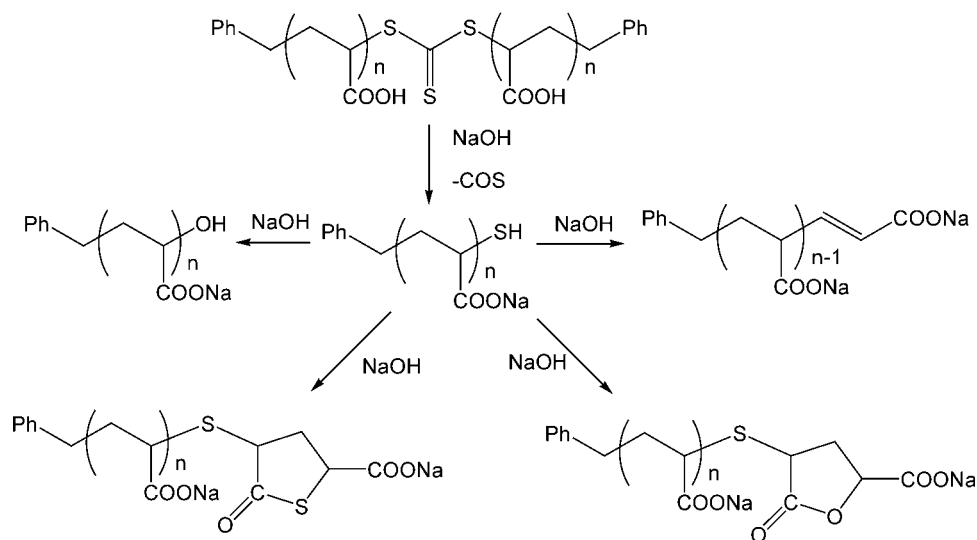


Scheme 16. Preparation of xanthates, trithiocarbonates, and dithiocarbamates with TCDI.

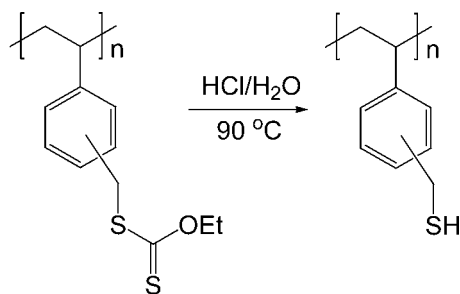
Transesterification by an Amine (Aminolysis)

Initially, the reaction between amines and a thiocarbonyl-thio compounds was limited to the area of organic synthesis.¹⁵⁷⁻¹⁵⁹ Recently, there have been several publications reporting the reaction of an amine with a dithioester group on a polymeric chain. Both primary and secondary amines, acting as nucleophiles, can convert a thiocarbonyl-thio moiety to a thiol.^{78,150} Polystyrene containing

dithiocarbonate groups as pendant sites was reacted with aqueous ammonium hydroxide (7.5% NH_3) to cause aminolysis at the ambient temperature, modifying the thiocarbonyl-thio group into a thiol with 94% conversion (Scheme 21, reaction I).^{152,158} This method was also used to prepare a mercapto-terminated polymer from a thiocarbonyl-thio group on the main chain.¹⁶⁰ Moreover, aminolysis of a resin containing dithiocarbamate



Scheme 17. Base hydrolysis of trithiocarbonic acid dibenzyl ester and poly(acrylic acid) prepared from acrylic acid.



Scheme 18. Acid hydrolysis of polystyrene at 90 °C containing a dithiocarbamate as a pendant group.

groups was also studied by the heating of the supported resins with a secondary amine to yield a thiourea and mercaptomethylated resin (Scheme 21, reaction II).¹⁵⁴

Peroxide Treatment

In organic synthesis, the removal of thiocarbonyl-thio groups via cyclization can be achieved by treatment with peroxide.^{161–168} Dilauroyl peroxide induces radical cleavage of the C–S bond to generate a radical intermediate, which can undergo either intramolecular cyclization or intermolecular addition, under suitable conditions. The CAMD team used this approach to modify the end group of a RAFT polymer from C=S to C=O and characterized the resulting product by mass spectroscopy.⁵⁸

Reduction

Another classical methodology used to modify the thiocarbonyl-thio group on the polymeric chain is achieved by reduction via metal hydride compounds (e.g., LiAlH₄ or NaBH₄). McCormick and coworkers^{169,170} reported the use of a 0.01 wt % solution of an appropriate salt and a 1.0 M aqueous solution of NaBH₄ as a reducing agent at the ambient temperature for 1 h to form thiol end-functionalized polymers, which were further used for the stabilization of gold nanoparticles.

End-Group Modification by Radical Addition–Fragmentation and Recovery of CTA

In a recent communication,¹⁷¹ we reported a straightforward forward technique to cleave the thiocarbonyl-thio end group of a polymer produced by RAFT polymerizations by mixing the polymeric chains with an excess source of radicals. The *in situ* addition of a radical to the reactive C=S

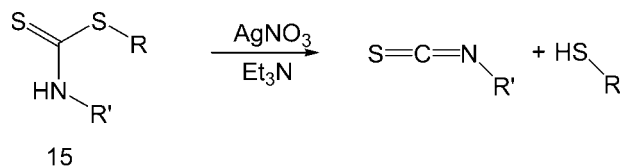
bond of the thiocarbonyl-thio polymer end group leads to the formation of an intermediate radical, which can then fragment either back to the original attacking radical or toward the polymeric chain radical. In the presence of an excess of free radicals, the equilibrium is displaced toward the formation of the polymeric chain radical, which can then recombine irreversibly with one of the free radicals present in excess in solution, thus forming a dead polymeric chain. This method eliminates all sulfur compounds from the polymeric chain end, removes the color from the polymer (Figure 5), introduces a new functionality at the end of the polymeric chain, and permits the recovery of the CTA, as shown in Scheme 22.

SOURCE OF RADICALS

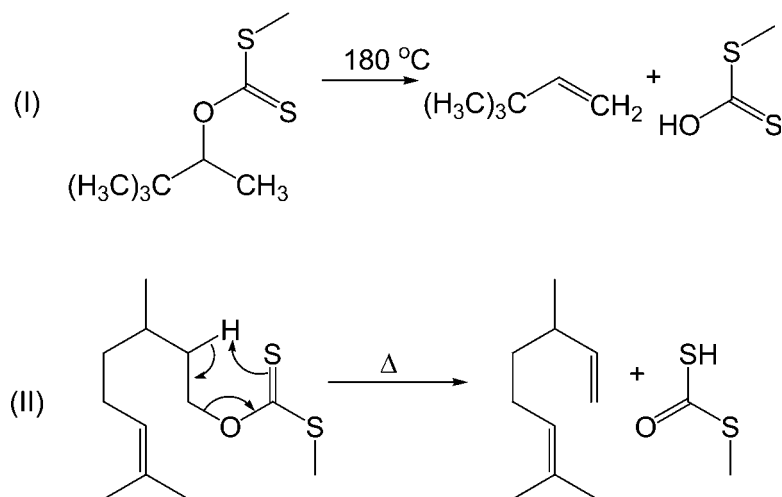
RAFT/MADIX polymerization requires the introduction of radicals at the very start of the polymerization to trigger the degenerative chain-transfer reactions that dominate the polymerization. The presence of free radicals in the system not only influences the molecular weight distribution of the polymer (as it generates dead polymeric chains of uncontrolled molecular weight) but also affects the rate of polymerization. Therefore, the concentration of free radicals introduced in the system needs to be carefully balanced. Radicals generated in RAFT/MADIX polymerization can be classified into three classes: (1) decomposition of organic initiators, (2) initiation via an external source (UV–vis or γ -ray), and (3) thermal initiation.

Radicals Generated by an Organic Initiator

The most commonly used sources of radicals in RAFT/MADIX polymerization are organic initiators. Over 80% of the publications to date use a thermal initiator to introduce radicals in the RAFT/MADIX system, and most of them rely on azo compounds (for temperatures ranging 25–80 °C) or peroxides (for temperatures above



Scheme 19. Metal-assisted elimination of *N*-alkyl or *N*-aryl dithiocarbamate with silver salt.



Scheme 20. Pyrolysis of xanthates.

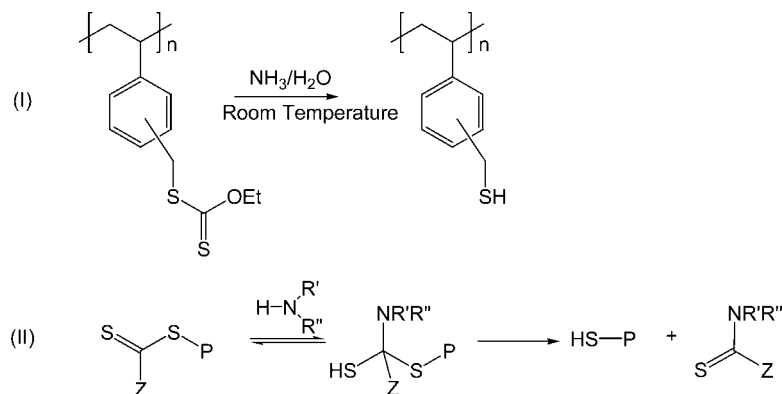
90 °C) because of their commercial availability, the wide range of thermal decomposition to generate radicals, and the stability of the formed radicals.^{172,173} Azobisisobutyronitrile (AIBN) is a commonly encountered source of radicals as its half-lifetime is ideal for the range of temperatures used in the RAFT/MADIX process (typically 50–80 °C). Typically, a CTA/free-radical initiator ratio of 1:1 to 10:1 is used to produce polymers of narrow molecular weight distributions in a reasonable reaction time.

As seen previously, the free-radical initiators will produce polymeric chains that do not contain the thiocarbonyl-thio end group. The total number of chains produced in RAFT will be equal to the number of radicals derived from the initiator and CTA leaving group (R), but the maximum number of living chains will be equal

to the number of CTAs. Therefore, the proportion of dead chains (*Dc*) is given by the ratio of the number of initiator-derived radicals $\{2f([\text{I}]_0 - [\text{I}]_t)\}$, where *f* is the initiator efficiency, $[\text{I}]_0$ is the initial initiator concentration, $[\text{I}]_t$ is the initiator concentration at time *t*, and $[\text{I}]_t$ is equal to $[\text{I}]_0 e^{-k_d t}$ to the number of CTAs ($[\text{CTA}]$) plus the initiator-derived radicals (the number of dead chains is halved if terminations occur by combination):¹⁷⁴

$$Dc = \frac{2f([\text{I}]_0 - [\text{I}]_t)}{[\text{CTA}] + 2f([\text{I}]_0 - [\text{I}]_t)}$$

In practice, the concentration of dead chains in RAFT/MADIX polymerization can be kept below 5%. For instance, in the polymerization of methyl acrylate at 60 °C mediated by cyanoisopropyl dithiobenzoate with the ratio MA/CTA/



Scheme 21. Aminolysis of pendant dithioester groups on a polymeric chain (I) or on a solid support material (P; II).



Figure 5. Picture of PMMA synthesized by the RAFT process (a) before and (b) after the reaction with AIBN at 80 °C for 2.5 h.

AIBN = 1230:1:0.1, only 1.1% of the chains are dead at 75% conversion [number-average molecular weight (M_n) = 97,000 g/mol, PDI = 1.04]. In the case of a more slowly propagating monomer such as MMA, for similar molecular weights and conversions, the proportion of dead chains will be higher.¹⁷⁴

It is noteworthy that the number of dead chains decreases when the concentration of the CTA increases, and this results in low-molecular-weight polymers having a smaller number of dead chains; RAFT/MADIX is therefore effective for the production of low-molecular-weight polymers with narrow polydispersities.¹⁷⁴

Radicals Generated by UV and γ Radiation

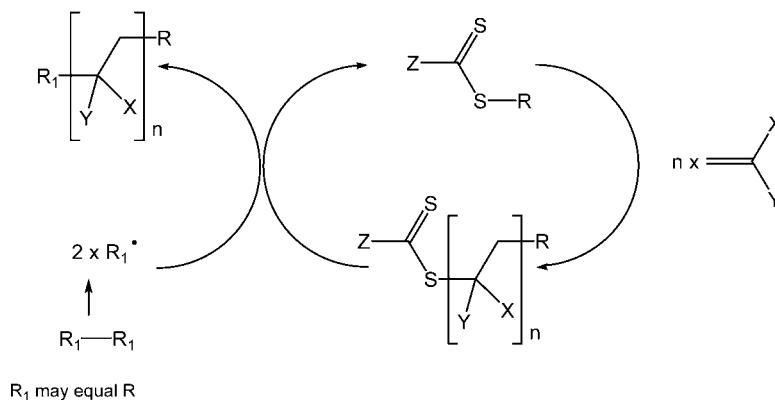
The major advantage of using UV and γ radiation to introduce radicals into the system is to allow the polymerization to be performed at the ambient temperature with shorter reaction times. In addition, γ -ray irradiation has the advantage over UV light of being more penetrating, and

therefore commercial-scale production is feasible.^{175,176} RAFT polymerization performed under ^{60}Co γ -ray irradiation was reported first by Pan's group in the presence of dibenzyl trithiocarbonate,^{175,177,178} dithiobenzoic acid¹⁷⁹ and a variety of dithiocarbamates^{180,181} and xanthates.¹⁸² More recently, the same group reported the polymerization of acryloyl azide under similar conditions.¹⁸³ The CAMD team also reported the successful RAFT polymerization of styrene¹⁸⁴ and MMA¹⁸⁵ and the graft polymerization of styrene onto a propylene solid support.^{176,186} Furthermore, the same group used γ -ray irradiation to generate *in situ* and at room temperature the intermediate radical observed in RAFT polymerization (**10**, Scheme 3) and stored it for a length of time, before raising the temperature in the presence of the monomer, to perform the polymerization. Under these conditions, γ -ray irradiation allowed the production of remarkably low PDI polymers.^{112,118}

The use of UV at 365 nm to initiate RAFT polymerization was simultaneously reported by the CAMD team¹⁸⁷ and You et al.¹⁸⁸ in 2002. Both groups obtained well-defined polymers with molecular weights close to theory, but CAMD observed a loss of control over the molecular weight for conversions higher than 30%, as the CTAs decompose under UV light.¹⁸⁷

Radicals Generated by Plasma Initiation

Plasma initiation was used for the RAFT polymerization of MMA mediated by cyanoisopropyl 1-dithionaphthalate, and narrow-molecular-weight polymers were obtained. Chain exten-



Scheme 22. Reaction cycle to produce chain-end functional polymers via RAFT/MADIX, with recovery of the CTA.

sions with MMA and styrene were performed to obtain higher molecular weight polymers.¹⁸⁹

Radicals Generated Thermally

RAFT/MADIX polymerizations of styrene undertaken at temperatures above 100 °C may use the thermal self-initiation of the monomer as a source of radicals.^{11,190–192} Even though the polymerization is initiated thermally, the number of living propagating chains remains constant, and the number of terminations by combination are kept low.¹⁹²

POLYMERIZATION PROCESSES

The process of polymerization is one of the major advantages of the RAFT/MADIX technique, as the system only requires the introduction of a CTA to an otherwise conventional free-radical polymerization. It is therefore possible, in theory, to perform RAFT/MADIX polymerization under the exact same conditions as those for conventional free-radical polymerization, and the system does not require any modification of existing setups; this makes large-scale production a more realistic ambition. RAFT/MADIX polymerization has, to date, been performed in a variety of processes, including bulk, solution, emulsion, and miniemulsion, in ionic liquids and supercritical carbon dioxide, and at high pressure.

Bulk

Bulk polymerization is by far the simplest process for RAFT/MADIX polymerization and is routinely used by researchers working in this area. However, the associated increase in viscosity when the polymerization proceeds to high conversions may cause problems for the processing of the final product. Polymerizations in bulk are generally faster than those in solution [e.g., Zhu et al.¹⁹³ showed that the polymerization of glycidyl methacrylate at 60 °C reached 96.7% conversion in bulk and 64.3% in benzene—50% (v/v) with respect to the monomer—for the same reaction time], but they do not necessarily lead to higher polydispersity (e.g., the polymerization of 4-acetoxystyrene and isobutyl methacrylate in bulk gives polymers with narrower polydispersities than those obtained from solution or emulsion, with the same reaction conditions^{194,195})

Solution

Solution polymerization, although slower than bulk polymerization, solves the viscosity problems encountered for high glass-transition temperature polymers at high conversions. The polydispersities, however, are also slightly broader than those in bulk polymerization, especially at high conversions.^{194,195} One major advantage of solution polymerization is that it allows the copolymerization of monomers that are not miscible; for instance, copolymers of vinylidene chloride and methyl acrylate were successfully prepared in a controlled/living manner in benzene at 70 °C.¹⁹⁶

Aqueous RAFT/MADIX polymerization deserves a special mention. McCormick and coworkers^{197–199} have devoted much effort in studying RAFT polymerization under aqueous conditions and have authored excellent reviews in the field. It is noteworthy that to date only Donovan et al.⁸⁹ and Baussard et al.²⁰⁰ have synthesized fully water-soluble CTAs. Other CTAs used in aqueous RAFT/MADIX are usually only partially water-soluble but dissolve in water/monomer mixtures. A variety of monomers have been (co)polymerized via aqueous RAFT, including acrylamides,^{73,84,86,198,199,201–205} methacrylamides,²⁰⁶ styryl derivatives,¹⁴⁶ vinyl pyridine,²⁰⁷ glycomonomers,²⁰⁸ acrylic acid,⁷³ and 2-(dimethylamino)ethyl methacrylate.²⁰⁹ A recent study by Thomas et al.¹⁴⁷ showed that dithioesters are susceptible to hydrolysis at high pHs during polymerization.

Emulsion

Emulsion polymerization is a well-studied process for the industrial-scale production of polymers and provides good heat transfer as the viscosity of the system remains low, even at high polymer loadings.²¹⁰ Emulsion polymerization mediated by the RAFT process was first reported by the CSIRO group, with the polymerization of butyl methacrylate,¹² and was further applied to the polymerization of styrene and MMA.²⁵ Monteiro and coworkers used both RAFT²¹¹ and MADIX²¹² to mediate the emulsion polymerization of styrene and butyl acrylate, respectively, but they obtained ill-defined polymers. Further work was undertaken by various research groups on the polymerization of styrene^{141,211–218} and styrene derivatives,¹⁹⁴ MMA,^{219–222} butyl acrylate,^{139,141} and vinyl ace-

tate,²¹⁹ but all highlighted considerable difficulties in controlling the molecular weight growth or the colloidal stability. A number of issues in implementing the RAFT system to emulsion polymerization were encountered, including the occurrence of two or even three phases in the reaction mixture leading to phase partitioning of the CTA, rate retardation, water sensitivity of some RAFT agents, transport of the controlling agent between phases, surface activity of some RAFT agents, and particle nucleation.^{14,194,213,219,223–225} Monteiro and coworkers showed that MADIX polymerization, which uses a less reactive CTA than RAFT, allows the production of controlled molecular weight polymers with PDIs ranging from 1.6 (in the case of *n*-butyl acrylate²¹²) to 2 (for styrene²¹³), a fast rate of polymerization, and controlled particle size distributions.^{71,141,211,213} Narrower polydispersities could be achieved by the feeding of the monomer into the reaction to keep a low local monomer concentration.¹⁴¹ However, in a recent communication, the same group reported the use of a fluorinated xanthate [ethyl 2-(*O*-trifluoroethylxanthyl)propionate] to mediate the *ab initio* emulsion polymerization of styrene and to control both the particle size and molecular weight of the polymer, with polydispersities lower than 1.5.²¹⁷ In RAFT polymerization, the ill-defined polymers were explained by the transport of the CTA across the aqueous phase.^{214,226} Prescott et al.²¹⁴ offered a solution by ensuring that all CTAs are located in seed emulsion particles before the polymerization is started. However, this technique is limited to seeded emulsion and cannot be applied to *ab initio* emulsion polymerization, in which most of the polymerization occurs from the seed and is, therefore, not controlled by the CTA. To avoid problems related to the transfer of the CTA in the aqueous phase and the loss of colloidal stability in *ab initio* RAFT emulsion polymerization, surface-active CTAs were designed and used as both surfactant and CTA.^{220–222} Vosloo et al.¹³¹ used the same principle and designed polystyrene oligomers terminated by a thiocarbonyl-thio group, which were dispersed in an aqueous solution and used to mediate polymerization. Ferguson and coworkers^{139,216} developed further the idea of surface-active RAFT oligomers by producing *in situ* low-molecular-weight amphiphilic block copolymers of poly(acrylic acid-*b*-butyl acrylate) that can self-assemble in micelles, which in turn are used as surface-active CTAs controlling the poly-

merization of hydrophobic monomers. Another elegant solution to the problem of the transfer of the CTA in the aqueous phase was proposed by Apostolovic et al.,²²⁷ who used cyclodextrins to encapsulate the hydrophobic CTA and facilitate its transport across the water phase to the polymer particles. RAFT/MADIX-mediated emulsion polymerization has also been used to produce latexes^{71,212,215,228} and core-shell particles.^{213,216} Recently, the CAMD team reported the successful use of RAFT in the suspension polymerization of MMA mediated by 2-cyanoprop-2-yl dithiobenzoate. A good control of the molecular weight and polydispersity was achieved, and the authors observed that the particle size and PDI of the produced polymer decreased with increasing cyanoisopropyl dithiobenzoate (CPDB) concentration.³⁵⁴

Miniemulsion polymerization has also been adapted to the RAFT process. The use of a miniemulsion removes the need for the CTA to migrate across the aqueous phase, as the particles form from the droplets initially present in the emulsion. In the initial reports on RAFT miniemulsion, although successful, the polymerizations suffered from stability issues and a slow rate of polymerization.^{226,229–237} The retardation of the rate was reduced by the use of aliphatic dithioesters²³⁸ or trithiocarbonates.²³⁹ To improve particle stability, Xiong et al.²⁰⁹ used a macro-CTA based on dimethyl amino ethyl methacrylate to mediate the miniemulsion polymerization of styrene and MMA. Furthermore, to avoid issues attached to the use of surfactants present at high concentrations in a miniemulsion, Pham et al.²³⁹ used a nonlabile amphiphilic macro RAFT agent as a sole stabilizer in their miniemulsion to emulsify the dispersed phase, stabilize the particles, and control the molecular weight of the polymer. In their system, the authors observed that the formation of secondary nucleation of new particles could be neglected, with good particle size control, and they obtained a final product free of surfactant and with a controlled molecular weight. Russum et al.²⁴⁰ investigated miniemulsion on a multi-tube reaction system for continuous RAFT polymerization with styrene and observed that M_n increased linearly with conversion, although the polydispersities were higher in tube reactors than in batch reactors. Another study on continuous miniemulsion polymerization by RAFT was also reported by Smulders et al.,²⁴¹ who used a train of continuously stirred tank reactors. They

observed a decrease in the polydispersity when the number of continuously stirred tank reactors in a train was increased. Very recently, the CAMD team reported the use of MADIX polymerization to facilitate the LRP of vinyl acetate in a miniemulsion.³⁵⁶

Finally, microemulsion polymerization mediated via RAFT was reported by Hermanson et al.,²⁴² with the polymerization of *n*-hexyl methacrylate yielding polymers with well-controlled molecular weights.

Ionic Liquids

Ionic liquids not only provide a green alternative to high volatile organic chemical (VOC) solvents, but they have also been shown to enhance the rate of reaction in radical polymerization. Perrier et al.²⁴³ demonstrated the use of a room-temperature ionic liquid (butylmethylimidazolium hexafluorophosphate), as an alternative to traditional organic solvents, in the RAFT polymerization of MMA and methyl acrylate; this led to polymers with controlled molecular weights and narrow polydispersities, with a higher rate of polymerization than the equivalent reaction in toluene.

Supercritical CO₂

Supercritical CO₂ is another environmentally friendly alternative to high VOC solvents. Arita et al. first reported the RAFT polymerization of styrene²⁴⁴ and methyl acrylate³⁵⁵ in supercritical carbon dioxide. They obtained polymers with well controlled molecular weights, but they observed that the polymerization rates were slower in supercritical CO₂ in comparison with toluene.

High Pressure

The use of high pressure (up to 1.8 kbar) for the RAFT polymerization of styrene was found to give higher reaction rates and a lower number of dead polymeric chains than those observed at atmospheric pressure, but retardation was still observed.²⁴⁵ When an even higher pressure (5 kbar) is used, very high molecular weight PMMA ($M_n > 10^6$ g/mol) can be achieved in solution polymerization (toluene or methyl ethyl ketone). The polydispersities, especially in toluene, are as low as 1.03, and the theoretical and

experimental M_n values are very close.²⁴⁶ At a similar time, the bulk polymerization of styrene at a high pressure (up to 2.5 kbar), mediated by cumyl dithiobenzoate, was also reported.²⁴⁷ The overall rate of polymerization could be increased by nearly a factor of three, with a reduction of polydispersity from 1.35 to 1.10. No significant effect of increased pressure on the rate retardation effect was observed.

High-Throughput Polymer Synthesis

As the RAFT/MADIX process does not require stringent conditions or a catalyst and can be very easily set up, it is the technique of choice for the high-throughput synthesis of living polymers with controlled molecular weights. There have been a few reports on the use of RAFT⁴⁵ and MADIX^{248,249} as combinatorial polymerization techniques to produce a range of polymers with slight variations in their structures, and there is no doubt that this promising route will be developed further in the near future.

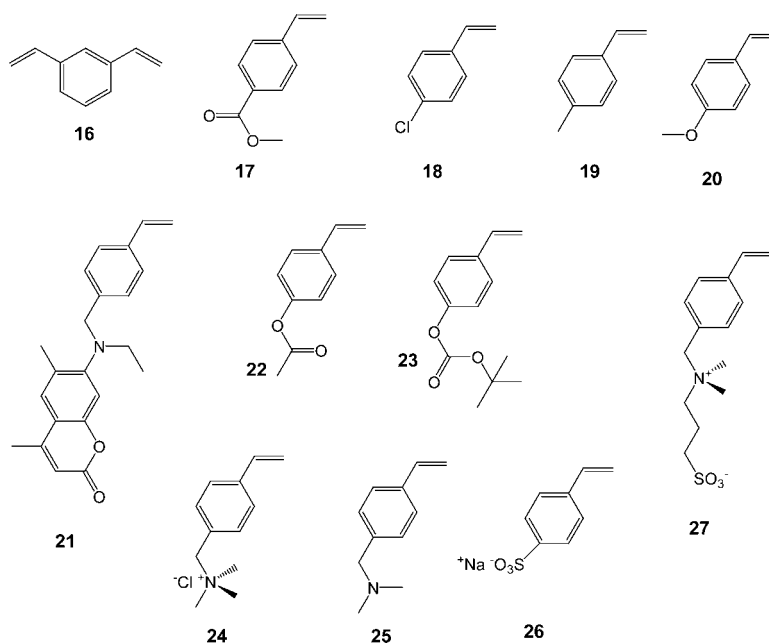
MONOMERS

The RAFT/MADIX process has been applied successfully to a wide range of monomers.

Styrenes

The control of the living polymerization of styrene has been studied via both MADIX and RAFT processes by the variation of the structure of the CTA (dithioesters, trithiocarbonates, xanthates, and dithiocarbamates).^{12,24,33,41,148,149,170,194,197,206,209,250-257}

The lower propagation rate and low steric bulk of the styryl radical allow the RAFT polymerization of styrene to be controlled by most CTAs (PDI = 1.03–1.25), the exception being xanthates, because of the poor stability of their intermediate radical (PDI = 1.2–2.2).^{14,41} However, PDIs as low as 1.2 can be obtained from polymerizations mediated with a xanthate substituted with *O*-trifluoroethyl as the *Z* group.^{72,217} The relative stability of its propagating radical makes styrene one of the slowest monomers to polymerize. Nevertheless, styrene is by far the most studied monomer in RAFT/MADIX polymerization (over 160 publications report the use of styrene via RAFT or MADIX polymerization) for the investigation of the kinetics and mechanism of the system,



Scheme 23. Examples of styrene derivatives polymerized by RAFT/MADIX.

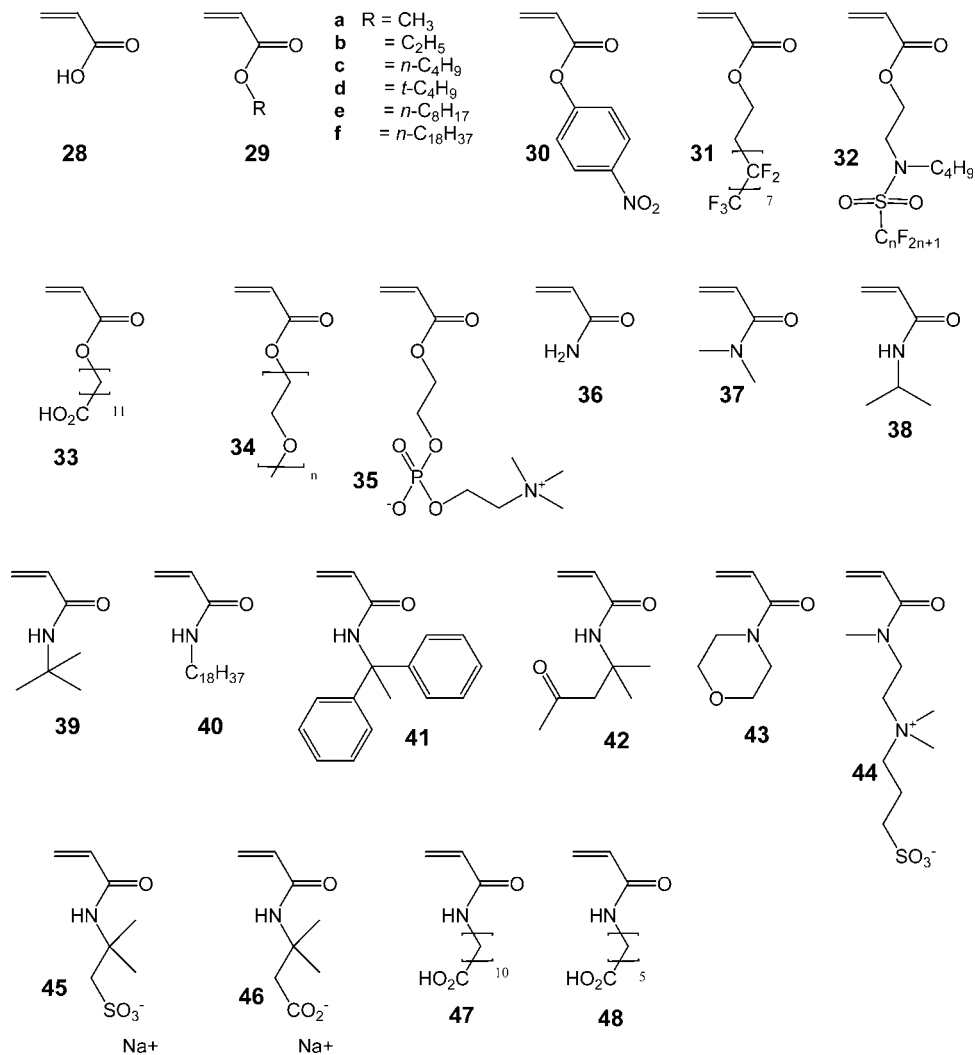
the polymerization processes, or the reaction conditions.

Functional polymers have also been produced via RAFT/MADIX from styrene derivatives (Scheme 23), including divinylbenzene (**16**),^{251,256,258} *p*-vinyl benzoate (**17**),¹⁴⁶ *p*-chlorostyrene (**18**),^{174,252} *p*-methylstyrene (**19**),^{174,252} *p*-methoxystyrene (**20**),^{95,174,252} *p*-(coumarin)styrene (**21**),²⁵⁹ *p*-acetoxystyrene (**22**),^{95,194} and *p*-*tert*-butoxycarbonyloxystyrene (**23**),²⁶⁰ and water-soluble monomers such as *p*-(vinylbenzyl) trimethylammonium chloride (**24**),^{146,209} *N,N*-dimethylvinyl benzylamine (**25**),^{146,261} sodium styrenesulfonate (**26**),¹⁴⁶ and 3-(*N,N*-dimethylvinyl benzylammonio)-propanesulfonate (**27**).²⁰² Also, it has been shown that alternating copolymers of styrene and maleic anhydride can be achieved with reasonable control over their molecular weights,^{252,262,263} whereas well-defined alternating 1:1 copolymers of styrene and MMA can be produced in the presence of a Lewis acid (diethyl aluminum chloride).²⁶⁴

Acrylates and Acrylamides

Acrylates and acrylamides have also been widely studied, and their polymerization via RAFT usually leads to very well controlled polymers. Both monomers have a very reactive propagating radical with low steric bulk, which leads to fast polymerizations, although an inhibition/induction

period is observed at the start of the polymerization.^{32,53,88,89,101,120–122} Polymerizations mediated by dithiocarbamates and most xanthates generally lead to broader molecular weight distributions (although living polymers are achieved with PDIs between 1.2 and 2.3), whereas trithiocarbonates and dithioesters produce living polymers with low polydispersities (PDI ranges from 1.06 to 1.25).^{14,61} The room-temperature RAFT polymerization of methyl acrylate⁶⁰ and *N*-isopropylacrylamide⁸⁶ was shown to be controlled when mediated by an aliphatic dithioester (1-phenylethyl phenyldithioacetate) and a trithiocarbonate (2-dodecylsulfanylthiocarbonylsulfanyl-2-methyl propionic acid), respectively. It is also noteworthy that the living polymerization of acrylic acid (**28**), although straightforward by RAFT,^{73,74,83,139,216,239,265–269} is difficult to achieve via ATRP as the carboxylic acid functionality tends to deactivate the catalyst.²⁷⁰ Furthermore, both monomers allow the introduction of a wide range of functionalities into the polymer backbone, as illustrated by Scheme 24. To date, the following monomers have been reported: methyl acrylate (**29a**),^{36,57,58,60,82,88,90,118,120–122,142,143,182,196,243,271–275} ethyl acrylate (**29b**),¹⁹⁰ *n*-butyl acrylate (**29c**),^{32,36,54,80,90,139,212,239,241,266,274,276–281} *tert*-butyl acrylate (**29d**),²⁸² octyl acrylate (**29e**),²⁷⁵ octadecyl acrylate (**29f**),²⁸³ *p*-nitrophenyl acrylate (**30**),²⁸⁴ 1,1,2,2-tetrahydroperfluorodecyl

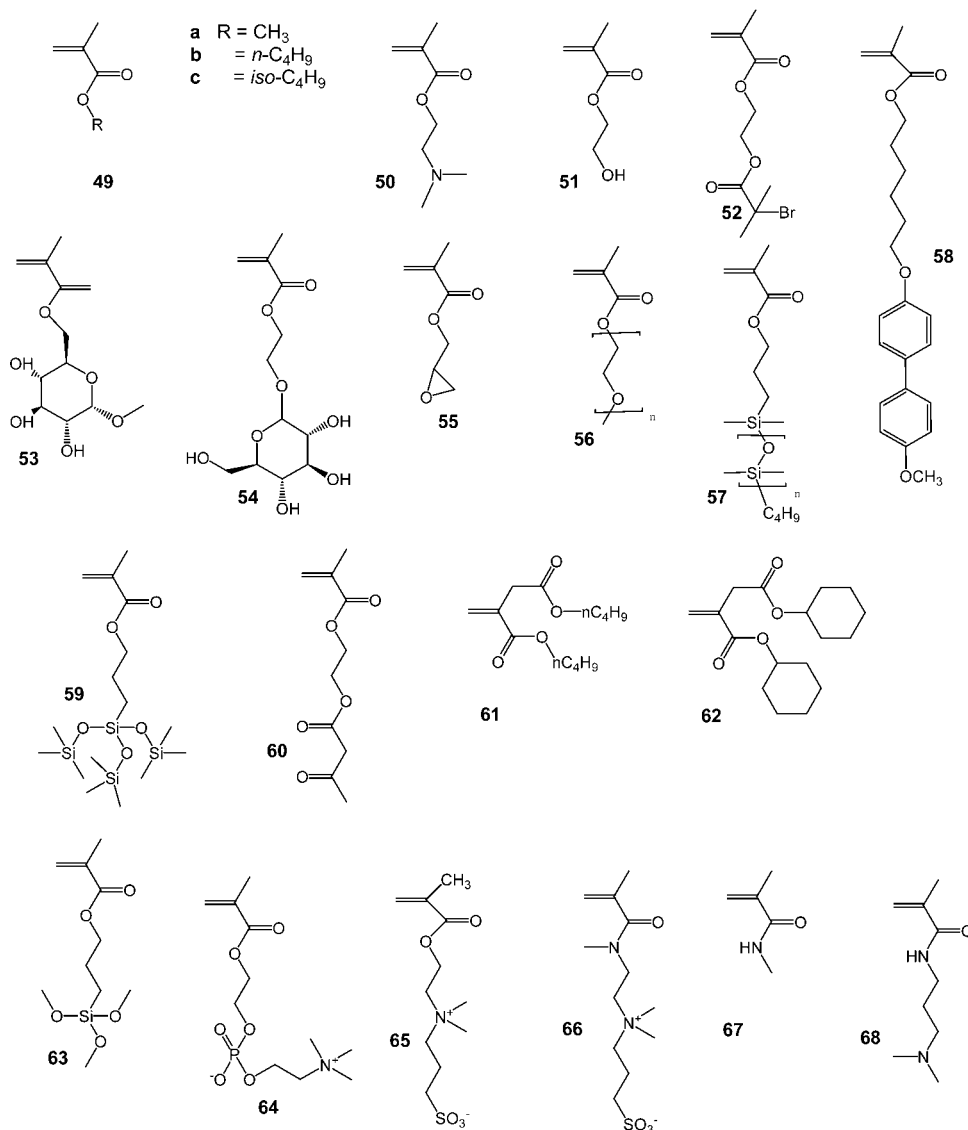


Scheme 24. Various acrylate/acrylamide derivatives prepared by RAFT/MADIX.

acrylate (**31**),²⁸⁵ 2-(*N*-butyl perfluorooctane-fluorosulfonamido) ethyl acrylate (**32**),⁸⁵ 12-acryloyloxydodecanoic acid (**33**),²¹⁵ poly(ethylene oxide) methyl ether acrylate (**34**),²⁸⁶ 2-acryloyloxyethyl phosphorylcholine (**35**),^{280,287} acrylamide (**36**),^{65,73,84,288} *N,N*-dimethylacrylamide (**37**),^{82,85,89,203,289–291} *N*-isopropylacrylamide (**38**),^{46,51–53,86,267,269,272,292–301} *N*-*tert*-butyl acrylamide (**39**),^{39,302} *N*-octadecyl acrylamide (**40**),^{39,215} *N*-diphenylmethylacrylamide (**41**),³⁹ diacetone acrylamide (**42**),²⁶⁹ *N*-acryloylmorpholine (**43**),^{38,43,44,302–305} 3-[2-(*N*-methylacrylamido)-ethyl]dimethylammonio] propane sulfonate (**44**),^{202,204,306} sodium 2-acrylamido-2-methylpropanesulfonate (**45**),^{201,205,300} sodium 3-acrylamido-3-methylbutanoate (**46**),^{201,205} 11-acrylamidoundecanoic acid (**47**),²¹⁵ and sodium 6-acrylamidohexanoate (**48**).³⁰⁷

Methacrylates and Methacrylamides

Steric hindrance makes it difficult for the bulky tertiary propagating radical generated from methacrylate and methacrylamide derivatives to add to the C=S of the CTA. To favor the addition–fragmentation equilibrium toward the formation of intermediate **4** (Scheme 3), strongly stabilizing *Z* groups are required,⁶⁷ and dithiobenzoates are the best CTAs to control polymerization. Certain aliphatic dithioesters,⁶⁷ trithiocarbonates,⁶⁷ and dithiocarbamates⁵⁹ also lead to reasonably well controlled polymeric architectures (PDI = 1.1–1.3), whereas xanthates, although producing living polymeric chains, offer very poor control. The R group also requires careful selection as the stability of the generated radical (to favor



Scheme 25. Various methacrylate/methacrylamide derivatives used in RAFT/MADIX polymerization.

preferential fragmentation with respect to that of the propagating polymeric radical) needs to be balanced with its reactivity, to favor addition to the monomer. For instance, using a re-initiating group that mimics the methacrylic propagating radical does not lead to narrow polydispersities, as the rate of fragmentation of the leaving radicals varies between a polymeric chain and a single molecule, because of the penultimate unit effect.⁹⁰ To date, there are only a few CTAs that produce polymers of methacryloyl derivatives with narrow molecular weight distributions. Cumyl dithiobenzoate⁶⁷ and cyanoisopropyl dithiobenzoate⁶⁷ are the best mediators for such polymerizations, whereas methoxycarbonylphenylmethyl

dithiobenzoate⁸² and α -cyanobenzyl dithioester⁹⁵ are the only CTAs with an R substituent generating a secondary radical that gives good control over methacrylic polymers. A recent publication by Benaglia et al.⁹¹ gives an excellent account of the factors to consider for methacrylate polymerization via RAFT. An original feature of methacryloyl polymerization is its faster rate of polymerization than that observed for the polymerization of acryloyl monomers, although the rate of propagation of the latter is higher than that of the former. Methacrylates and methacrylamides can also introduce a variety of functionalities into the polymer structure, and there has been a wide range of methacrylate and methacryla-

amide derivatives polymerized by RAFT/MADIX (Scheme 25): MMA (**49a**),^{45,47,50,59,62,66,78,82,88,90,92,93,189,219,221,222,236,237,246,264,266,274,275,281,291,308–314} *n*-butyl methacrylate (**49b**),^{27,140,231,275,281,301,308} isobutyl methacrylate (**49c**),¹⁹⁵ 2-(dimethylamino)ethyl methacrylate (**50**),²⁰⁹ hydroxyethyl methacrylate (**51**),^{64,315} 2-(2-bromoisobutyryloxy)ethyl methacrylate (**52**),³¹⁶ methyl 6-*O*-methacryloyl- α -D-glucoside (**53**),³¹⁷ 2-methacryloxyethyl glucoside (**54**),²⁰⁸ glycidyl methacrylate (**55**),¹⁹³ poly(ethylene glycol) methyl ether methacrylate (**56**),^{316,318–320} poly(dimethylsiloxane) methacrylate (**57**),^{321,322} [6-[4-(4'-methoxyphenyl)phenoxy]hexyl methacrylate] (**58**),^{323,324} 3-[tris(trimethylsilyloxy) silyl] propyl methacrylate (**59**),¹⁴⁵ 2-acetoacetoxyethyl methacrylate (**60**),^{71,325,326} dibutyl itaconate (**61**) and dicyclohexyl itaconate (**62**),⁸⁷ γ -methacryloxypropyltrimethoxysilane (**63**),⁵⁰ 2-methacryloxyethylphosphorylcholine (**64**),³²⁷ 3-[*N*-(3-methacrylamidopropyl)-*N,N*-dimethyl]ammoniopropane sulfonate (**65**),³²⁸ 3-[*N*-(2-methacryloylethyl)ethyl]dimethylammonio]propanesulfonate (**66**),²⁰² *N*-methyl methacrylamide (**67**),³¹² *N*-[3-(dimethylamino)propyl methacrylamide] (**68**),²⁰⁶ and dendronized methacrylate macromonomers.³²⁹

Crescenzi et al.³³⁰ also used RAFT to partially crosslink methacrylated pullulan and showed that the hydrogels produced via RAFT swelled to a greater extent than gels synthesized via conventional free-radical polymerization at the same double-bond conversion.

Vinyl Acetate (and Derivatives) and Vinyl Formamide

The polymerization of vinyl acetate is challenging to control because of the high reactivity and low steric bulk of the propagating radical. MADIX is, to date, the only polymerization technique to produce poly(vinyl acetate)s of reasonably narrow polydispersities.^{13,14,55,56,61,67,68,70,75,151,219,331} For a CTA to react rapidly with the propagating radical, intermediate **4** (Scheme 3) needs to be less stable than in the polymerizations of most other monomers. Therefore, although most thiocarbonyl-thio compounds retard considerably the polymerization of vinyl acetate (dithiobenzoates inhibit completely vinyl acetate polymerization), xanthates (MADIX) allow reasonably good control of the polymerization with a molecular weight distribution around 1.2–1.4 (e.g., with Z = OEt and R = CH₂CN, a polydispersity of 1.37 was obtained, whereas for R = CH₂CO₂CH₃,

polydispersities below 1.2 can be achieved⁵⁶). The CAMD team published an excellent study on the influence of the Z group on the MADIX polymerization of vinyl acetate and found that a xanthate with R = CH₂CO₂CH₃ and Z = OCH₃, OCH₂CH₃, OCH(CH₃)₂, or OC₆H₄OCH₃ could yield poly(vinyl acetate) of a predictable molecular weight and with a PDI below 1.2.⁵⁶ Dithiocarbamates [R = CH₂CN and Z = N(Ph)(CH₃)] permit us to obtain polymers with PDIs as low as 1.24.⁶⁷

Boschmann and Vana⁵⁵ also reported the polymerization of poly(vinyl propionate) mediated by a tetrafunctional xanthate to produce four-arm star polymers with polydispersities as low as 1.2. Functional vinyl acetate derivatives were also investigated, and CAMD reported the synthesis of polymers from the glycomonomer 6-*O*-vinyladipoyl-D-glucopyranose) with PDI below 1.1 and controlled molecular weights, mediated by both xanthate and dithiocarbamate.³¹⁷

A similar monomer to vinyl acetate, vinyl formamide, a precursor for preparing polyamine, was also successfully polymerized with a poly(ethylene)glycol macro-CTA. However, the polydispersity of the final block copolymer was slightly higher than expected (PDI = 1.7).⁷⁶

Miscellaneous Monomers

RAFT/MADIX has also been used to mediate the polymerization of a range of vinyl monomers (Scheme 26). *N*-Acryloxysuccinimide (**69**) was copolymerized via RAFT with *N*-acryloylmorpholine (**43**),³⁰⁵ *N,N*-dimethylacrylamide,²⁹⁰ butyl methacrylate,¹⁴⁰ a mixture of *N*-*tert*-butyl acrylamide and *N*-acryloylmorpholine,³⁰² and *N*-isopropylacrylamide,²⁹⁷ and polydispersities below 1.1 were achieved when *tert*-butyl dithiobenzoate³⁰⁵ or cyanoisopropyl dithiobenzoate²⁹⁷ was used as the CTA.

Schilli et al.²⁶⁹ showed that 2-vinyl-4,4-dimethyl-5-oxazolone (**70**) and *N*-methacryloxy-succinimide (**71**) could be homopolymerized via RAFT with cyanoisopropyl dithiobenzoate as a CTA, and they obtained well-controlled polymers with polydispersities equal to or below 1.1 for the former and higher-than-predicted molecular weights, with PDI around 1.5, for the latter. The polymeric chains were reacted further with *N*-isopropylacrylamide and tested for their response to combined external stimuli.

2-Vinylpyridine and 4-Vinylpyridine (**72** and **73**, respectively) have been homopolymerized

and block copolymerized with cumyl dithiobenzoate as a CTA in bulk at 60 °C to yield very well controlled polymers with PDI in the range of 1.1–1.25.²⁰⁷ 4-Vinylpyridine has also been homopolymerized with dibenzyl trithiocarbonate, and ABA block copolymers poly(styrene-*b*-4-vinyl pyridine-*b*-styrene) and poly(4-vinyl pyridine-*b*-styrene-*b*-4-vinyl pyridine) with polydispersities below 1.25 have been produced.³³²

The polymerization of acenaphthylene (**74**) mediated by 4-cyano-4-[(thiobenzoyl)sulfanyl]pentanoic acid, which was esterified by 9-anthracenemethanol, produced light-harvesting polymers of well-controlled molecular weights and polydispersities below 1.1.²⁵⁵

Lacroix-Desmazes et al.^{196,273} reported the copolymerization of vinylidene chloride (**75**) with methyl acrylate. The authors found that the use of 1-methoxycarbonyl ethyl dithiobenzoate offered the best control over the polymerization, with polydispersities around 1.5, and made possible the extension of the polymeric chains after further monomer addition. Transfer to vinylidene chloride, however, was thought to be the main limitation of the system.

The polymerization of acrylonitrile (**76**) mediated by cyanoethyl dithiobenzoate, in ethylene carbonate at 60 °C, although rather slow (40% conversion in 7 h), led to polymers with molecular weights close to the theoretical values and polydispersities below 1.3. The polyacrylonitrile chains were successfully extended with *n*-butyl acrylate.³³³

The copolymerization of 1-hexene (**77a**), 1-octene (**77b**), and 1-decene (**77c**) with methyl acrylate mediated by benzyl 1-pyrrolcarbodi-thioate was reported by Liu et al.,¹⁴² and the polymerizations of 1-octene (**77b**) with methyl acrylate mediated by *S,S'*-bis(α,α' -dimethyl- α'' -

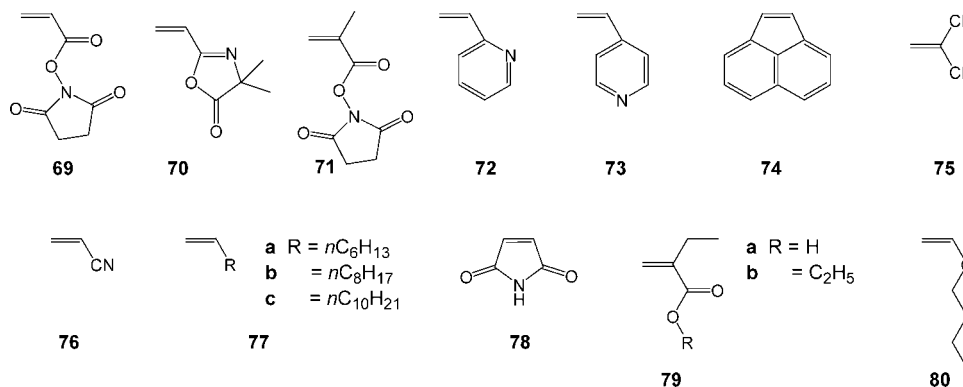
acetic acid)trithiocarbonate and butyl acrylate mediated by cyanoisopropyl dithiobenzoate were studied by Venkatesh et al.³³⁴ Both systems led to polymers of molecular weights close to the theoretical values and polydispersities ranging from 1.1 to 1.5. Chain extension with methyl acrylate was also successful.¹⁴²

Ren et al.³⁴ attempted to control the copolymerization of maleimide (**78**) with ethacrylic acid (**79a**) using cumyl dithiobenzoate as a CTA. The authors obtained ill-defined copolymers, and they attributed their observation to the inhibition of the re-initiating radical by the association of ethacrylic acid in a polar solvent and the strong interaction of the imino group of maleimide with the carboxyl group of α -ethacrylic acid. However, the copolymerization of maleimide with ethyl ethacrylate (**79b**) led to alternating copolymers with controlled molecular weights. The authors observed that good control was achieved up to 30% conversion, but they obtained retardation at higher conversions and temperatures.

The copolymerization of allyl butyl ether (**80**) with methyl acrylate or butyl acrylate mediated by RAFT with *S,S'*-bis(α,α' -dimethyl- α'' -acetic acid)trithiocarbonate resulted in excellent control over the molecular weight with a significant incorporation of allyl butyl ether within the copolymer chains (Scheme 26).³⁶

MOLECULAR ARCHITECTURES PREPARED FROM RAFT/MADIX

In addition to allowing for the introduction of a wide range of functionalities through the variety of monomers available to the process, RAFT/MADIX polymerization also permits the design



Scheme 26. Various monomers prepared by RAFT/MADIX.

of polymers of specific macromolecular architectures by the variation of the monomer composition and topology. End-functional polymeric chains [including telechelic (co)polymers] can be prepared, as well as statistical, gradient, block, and comb/brush copolymers and a variety of (functional) architectures such as star, hyperbranched, and network (co)polymers.

Block Copolymers

Block copolymers are the simplest polymeric architectures achievable via RAFT/MADIX. There are two routes to their synthesis, depending on whether all comonomers can be polymerized via RAFT/MADIX.

Block Copolymers Generated from Sequential Monomer Addition

One of the major direct applications of living polymerization is the synthesis of block copolymers via the sequential addition of monomers. In this approach, monomer A is initially polymerized quantitatively, and either by direct addition of a second monomer to the reaction system or after purification, the polymer is used as a macro-CTA to mediate the polymerization of monomer B. If monomer B is added directly to the system when the polymerization of monomer A has reached a high conversion, the final polymeric chain will show a middle section composed of a gradient polymer between A and B, separating the block rich in monomer A from the block rich in monomer B. The production of block copolymers from sequential monomer addition requires that the first block retains its chain-end functionality, and this is generally achieved by the polymerization of the first monomer being stopped at a conversion below 90%. In RAFT/MADIX polymerization, the radical source introduced to the system to trigger the degenerative chain transfer also leads to the formation of homopolymer side products with uncontrolled chain length. Therefore, a low concentration of the radical source should be used to maintain a high ratio of living chains to dead/uncontrolled chains. The sequence of the monomer addition also needs careful consideration. One requirement for forming a narrow-polydispersity AB block copolymer is that the first formed polymeric thiocarbonyl-thiol compound should have a high transfer constant to the

monomer in the subsequent polymerization. This requires that the leaving ability of the first block is comparable to, or greater than, that of the propagating radical of the second block under the reaction conditions (i.e., greater stability of the re-initiating radical).^{67,150}

There have been extensive studies for the production of block copolymers by RAFT/MADIX, either to prove the efficiency of the system in generating well-controlled polymeric structures or to generate self-assembly structures. Listing all the structures that have been reported would be impossible, but there have been specific studies using the original procedure to obtain (multi)block copolymers, and these are highlighted next.

A very elegant and original reaction was reported by both Lutz et al.²⁸⁹ and Ray et al.⁵² to produce stereoblock [atactic-*b*-isotactic] polymers in the presence or absence of Lewis acid yttrium trifluoromethanesulfonate [Y(OTf)₃] via RAFT polymerization. Both Lutz et al. and Ray et al. obtained atactic-*b*-isotactic poly(*N,N*-dimethylacrylamide) and poly(*N*-isopropylacrylamide), respectively, via a one-pot synthetic procedure including the synthesis of the atactic block in the absence of the Lewis acid followed by the addition of the Lewis acid to synthesize the isotactic block. Ray et al. also successfully synthesized diblock copolymers of poly[*N*-isopropylacrylamide (atactic)-*b*-styrene] and poly[*N*-isopropylacrylamide (isotactic)-*b*-styrene], starting with the atactic and isotactic poly(*N*-isopropylacrylamide) macro-RAFT agents, respectively.⁵²

Of specific interest is the use of multiple sequential additions to generate multiblock copolymers. Monteiro and de Barbeyrac²¹³ used the surface activity in the emulsion polymerization of the MADIX agent 1-(*O*-ethylxanthyl) ethylbenzene to produce core-shell latex particles consisting of either ABC triblock copolymer poly(styrene-*b*-acetoacetoxyethyl methacrylate-*b*-butyl acrylate) or poly(styrene-*b*-butyl acrylate-*b*-acetoacetoxyethyl methacrylate) and AB diblock copolymers poly[styrene-*b*-(acetoacetoxyethyl methacrylate-*co*-butyl acrylate)].

The specific case of ABA block copolymers is worth mentioning. There are two techniques used to obtain ABA triblock copolymers.

Difunctional R Groups. By the use of a CTA with a difunctional R group, telechelic homopolymers and triblock copolymers of type ABA with

the thiocarbonyl-thio functionality as an end group can be obtained.

Donovan et al.²⁰⁴ used the CTA *N,N'*-ethylenbis[2-(thiobenzoylthio)propionamide] (**81**) to produce diblock copolymers poly(*N,N*-dimethylacrylamide-*b*-3-[2-(*N*-methylacrylamido)-ethyl-dimethylammonio] propane sulfonate), poly(3-[2-(*N*-methylacrylamido)-ethyl-dimethylammonio] propane sulfonate-*b-N,N*-dimethylacrylamide-*b*-3-[2-(*N*-methylacrylamido)-ethyl-dimethylammonio] propane sulfonate), and poly(3-[2-(*N*-methylacrylamido)-ethyl-dimethylammonio] propane sulfonate-*b-N,N*-dimethylacrylamide) with polydispersities around 1.3–1.4 and characterized their self-assemblies in water.

Bussels and coworkers^{234,335} proposed an original technique based on RAFT miniemulsion polymerization to produce triblock and multi-block copolymers. The authors synthesized a linear multi-RAFT agent (**82b**) based on *N,N*-butoxycarbonylmethyl-dithiocarbamate (**82a**) and used it to mediate the polymerization of butyl acrylate in a first step, reacted further with isooctyl acrylate.

Taton et al.⁷³ used a difunctional xanthate (**83**) to produce triblock copolymers of type ABA from acrylamide and acrylic acid with controlled molecular weights and polydispersities in the range of 1.2–1.5.

Symmetrical Trithiocarbonates and Difunctional Z Groups. An alternative technique is the use of symmetrical trithiocarbonates, which contain two re-initiating R groups and lead to the production of triblock copolymers of type ABA with the re-initiating group at the chain end. One of the drawbacks of this technique is the presence of the thiocarbonyl-thio moiety in the middle of the chain, which might be a weak bond depending on the applications of the structures and confers color to the final product (although trithiocarbonates are usually yellow and lead to polymers of a very pale-yellow color). Mayadaune et al.⁷⁸ applied this technique to produce poly(styrene-*b-n*-butyl acrylate-*b*-styrene) with polydispersities as low as 1.16, with dibenzyl trithiocarbonate (**84**) as the CTA. Yuan et al.³³² used the same CTA to produce poly(styrene-*b*-4-vinyl pyridine-*b*-styrene) and poly(4-vinyl pyridine-*b*-styrene-*b*-4-vinyl pyridine) with molecular weight distributions below 1.25, and they varied their chain lengths and block length ratios to test their aggregation in water. Liu et al.³³⁶ used *S,S'*-bis(2-hydroxyethyl-2'-butyrate)

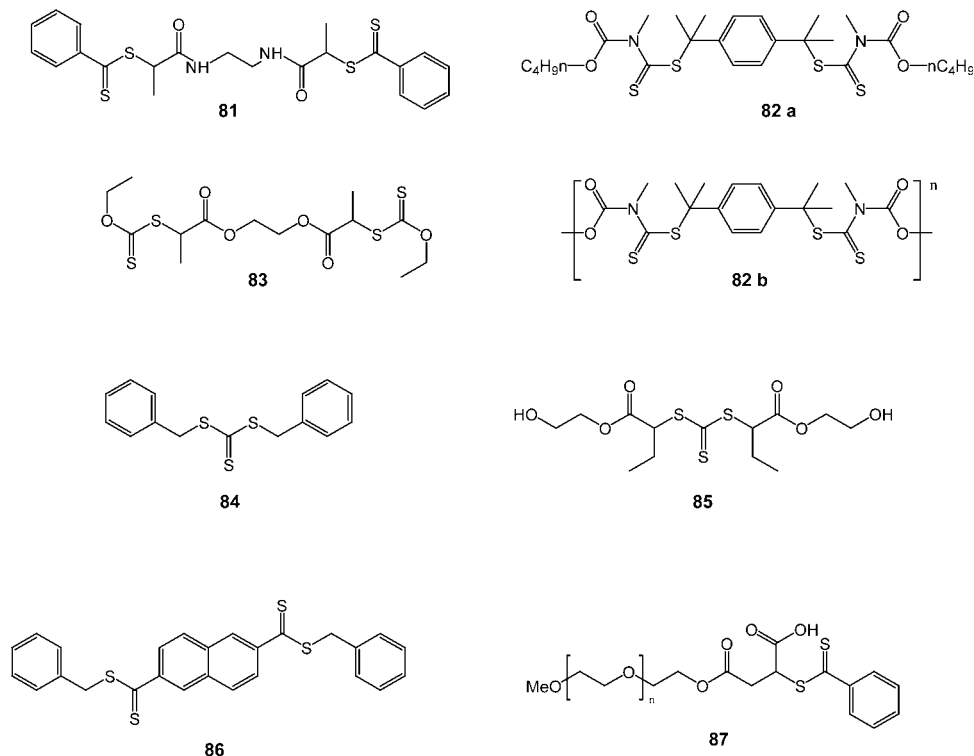
trithiocarbonate (**85**) to mediate the polymerization of styrene followed by *n*-butyl acrylate and yielded hydroxyl-terminated telechelic triblock copolymers of molecular weights around 20,000 g/mol and polydispersities around 1.1.

This technique can be extended to other non-trithiocarbonate CTAs by the use of CTAs with a difunctional Z group (bearing two R groups). Dureault et al.²⁸² used a difunctional CTA obtained from the reaction of tetraphosphorus decasulfide with 2,6-naphthalene carboxylic acid (**86**; see the Thionation on a Carbonyl Group Catalyzed by Cyclic Tetrathiosphosphates section) to synthesize a poly(*tert*-butyl acrylate-*b*-styrene-*b-tert*-butyl acrylate) with overall values of $M_n = 20,200$ g/mol and PDI = 1.20 (Scheme 27).

Block Copolymers Generated from Macro-CTAs

A second approach for the production of block copolymers consists of preparing a polymeric CTA (macro-CTA) from an already existing polymeric chain via organic synthetic transformation. By this process, block copolymers with polymers formed by other (nonradical) mechanisms can easily be synthesized. If the initial polymeric chains are modified at both chain ends, triblock (or multiblock) copolymers of type ABA (or CBABC, etc.) can be obtained.

The CSIRO group first suggested the esterification of 4-cyano-4-[(thiobenzoyl)sulfanyl]pentanoic acid with poly(ethylene glycol) methyl ether (750 g/mol) to produce a polymeric CTA that mediated the RAFT polymerization of styrene or benzyl methacrylate to yield block copolymers with PDI < 1.1.²⁶ Poly(ethylene glycol) has since been used as a CTA by a variety of research groups. Hong et al.²⁹⁵ produced block copolymers based on poly(ethylene glycol) (5000 g/mol) by the modification of monohydroxy and dihydroxy poly(ethylene glycol)s into monofunctional and difunctional CTAs, respectively, followed by transesterification with maleic anhydride. The aforementioned reaction on dithiobenzoic acid led to the macro-CTA (**87**), which was used to mediate the polymerization of *N*-isopropylacrylamide to yield poly(*N*-isopropylacrylamide-*b*-ethylene glycol-*b-N*-isopropylacrylamide) with a controlled molecular weight and PDI < 1.2. Following the same process, Shi et al.⁷⁶ used a poly(ethylene glycol)-modified xanthate (2000 g/mol) to mediate the MADIX polymerization of *N*-vinyl formamide and obtained high-polydispersity block copolymers (PDI = 1.7). Poly(ethy-



Scheme 27. Functional CTAs for the production of block copolymers.

lene glycol) (2000 g/mol) was reacted with *S*-(thiobenzoyl)thioglycolic acid to form a CTA that mediated the RAFT polymerization of 1,1,2,2-tetrahydroperfluorodecyl acrylate to synthesize hydrophilic/ CO_2 -philic poly(ethylene oxide)-*b*-poly(1,1,2,2-tetrahydroperfluorodecyl acrylate) block copolymers used as surfactants for the formation of water-in- CO_2 emulsions²⁸⁵ and for the dispersion polymerization of 2-hydroxyethyl methacrylate in supercritical CO_2 .³³⁷

Our group also synthesized a poly(ethylene glycol) methyl ether CTA based on the structure of methoxycarbonylphenylmethyl dithiobenzoate (5000 g/mol) and mediated the polymerization of MMA (PDI = 1.28).⁸² Following the same approach, we also produced poly(L-lactic acid-*b*-methyl methacrylate), with a molecular weight distribution of 1.33.⁸²

The modification of polyolefins such as Kraton was performed by De Brouwer et al.²⁶³ to produce diblock copolymers with a first block of Kraton and a second block of either polystyrene or poly(styrene-*co*-maleic anhydride).

Pai et al.⁸⁵ modified a dihydroxy poly(dimethyl siloxane) into macro-CTA by esterification with 3-benzylsulfanylthiocarbonylsulfanyl-propionic acid and polymerized *N,N*-dimethylacrylamide and 2-(*N*-butylperfluorooctanefluorosulfonamido)ethyl

acrylate to form ABA triblock copolymers with the molecular weight increasing linearly with conversion and polydispersities below 1.25.

Lebreton et al.⁹² studied the RAFT polymerization of styrene, MMA, ethyl acrylate and 1,3-butadiene mediated by five dithiobenzoates with a fluorinated chain of 6–8 carbons to produce block copolymers with a short fluorinated block. They also reported the synthesis of triblock copolymers with the second and third block being PMMA and polystyrene or poly(ethyl acrylate) and polystyrene.

Block copolymers of 2-vinyl-4,4-dimethyl-5-oxazolone, *N*-hydroxysuccinimide methacrylate diacetone acrylamide, *N*-isopropylacrylamide, or acrylic acid with short blocks of oligo(active ester)s were also synthesized with narrow polydispersities in most cases, and their conjugation to model peptides was assessed.²⁶⁹

Block Copolymers Generated from the Combination of RAFT/MADIX Polymerization with Other Polymerization Techniques

You et al.²⁹⁹ and CAMD²⁹⁴ offered a very original process to access block copolymers from both vinyl and lactide monomers by combining a

ring-opening polymerization initiated by the RAFT agent, followed by RAFT polymerization. You et al. used the hydroxyl functionality of the R group from *S,S'*-bis(2-hydroxyethyl-2'-butyrate) trithiocarbonate (**85**) to initiate the ring-opening polymerization of lactide, followed by the RAFT polymerization of *N*-isopropylacrylamide to obtain poly(lactide-*b*-*N*-isopropylacrylamide) with a molecular weight in good agreement with theory and polydispersities of around 1.2. The CAMD team initiated the ring-opening polymerization of *D,L*-lactide with the hydroxyl group from 2-(benzylsulfanylthiocarbonylsulfanyl) ethanol, followed by polymerization of *N*-isopropylacrylamide to yield narrow-molecular-weight block copolymers. The authors observed the formation of vesicles when the diblock copolymers were placed in an aqueous solution. An additional feature of this approach was the possibility of stabilizing the vesicles formed by the crosslinking of the interface poly(*D,L*-lactide)/poly(*N*-isopropylacrylamide). Indeed, chain extension by the polymerization of hexamethylene diacrylate from the trithiocarbonate group located between the poly(*D,L*-lactide) and poly(*N*-isopropylacrylamide) blocks resulted in a crosslinked layer between the core and the corona of the vesicles.

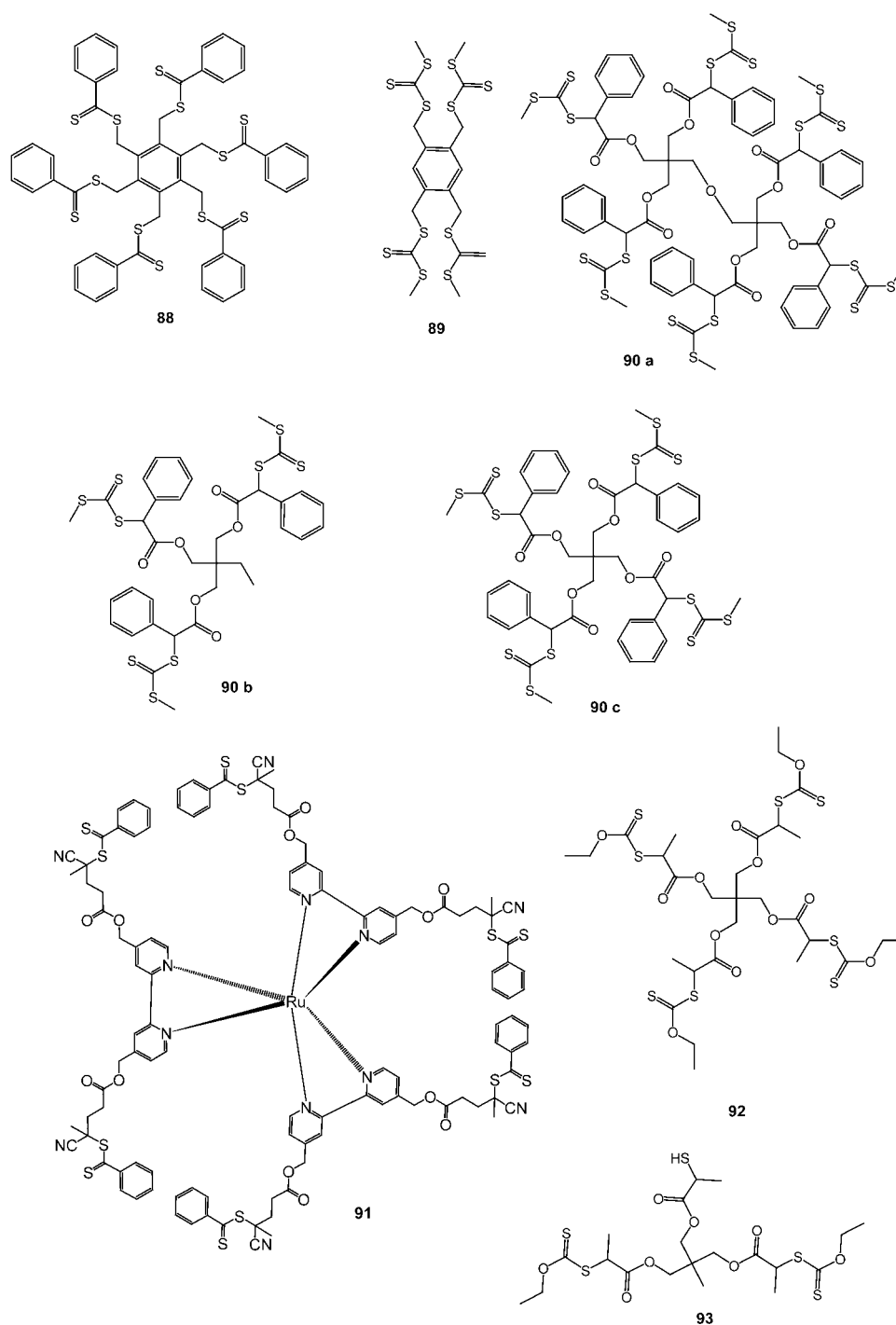
Star (Co)polymers

The preparation of star (co)polymers via RAFT/MADIX polymerization is well documented, and a variety of multifunctional CTAs have been used. However, the RAFT/MADIX process differs from all other LRP techniques such as ATRP or NMP by the fact that the core of the star can be introduced via functionalization of either R substituents (Scheme 28) or the Z substituents (Scheme 29).

The polymerization from a multifunctional CTA from its R group gives results similar to those obtained from ATRP or NMP (the so-called attached-to or R approach technique, as the polymeric arms grow away from the core). As a general rule, for the polymerization of monomers for which the main termination route is by combination, conversions should be kept low to limit star–star coupling. Furthermore, the radicals used to trigger the AFCT reactions should be kept at a very low concentration to minimize the number of dead linear polymeric chains. When these considerations are followed, polydispersities ranging from 1.1 to 1.4 can be achieved. A variety of molecules have been modified into

multifunctional CTAs. They include hexakis(thiobenzoylthiomethyl) benzene (**88**) to mediate the polymerization of styrene (six arms)^{191,250} and 2,4,5-tris([methylsulfanyl]-carbonothioyl)sulfanyl)methyl)benzylmethyl trithiocarbonate (**89**), prepared from 1,2,4,5-tetrakis(bromomethyl)benzene, to mediate the polymerization of methyl acrylate and styrene (four arms).³³⁸ The syntheses of dipentaerythritolhexakis(phenyl-*S*-methyl trithiocarbonyl methanoate) (**90a**; six arms) and its three- (**90b**, Scheme 28), four- (**90c**), and eight-arm equivalents were also reported, but these CTAs were not used in polymerization.¹²⁴ Short chains of poly(vinylbenzyl chloride) ($M_n = 900$ and 1800 g/mol) were modified into poly(vinylbenzyl dithiobenzoate) to mediate the polymerization of styrene.²⁵³ Ru(II) complexes bearing thiobenzoylsulfanyl-functionalized 2,2'-bipyridine ligands were used in the polymerization of styrene-functionalized coumarin monomers, and the resulting macromolecular architectures were used as light-absorbing antenna chromophores for the ruthenium complex (**91**).³³⁹ Finally, pentaerythritol and 1,1,1-tris(hydroxymethyl)propane were modified with a xanthate group to form the core of four- (**92**) and three-arm (**93**) stars, respectively, and used to mediate the polymerization of vinyl acetate.¹⁵¹

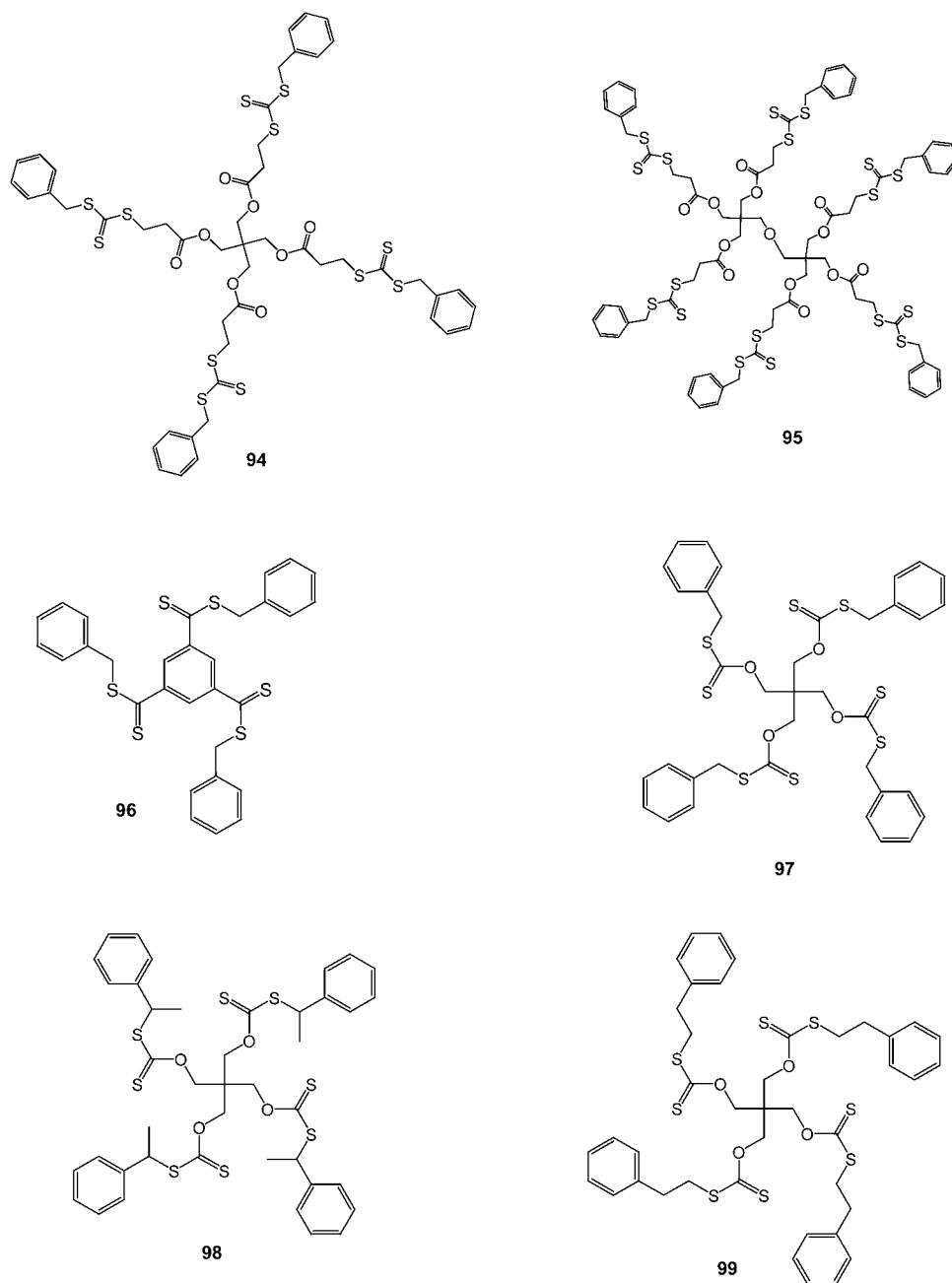
The use of the Z group as a core for star polymers is an original feature specific to RAFT/MADIX polymerization. Indeed, in this case, the polymeric arms are detached from the core while they grow, and they react back onto the core for the chain-transfer reaction (the technique is called the away-from process or Z approach): coupling occurs only between arms and not between stars. Therefore, very narrow polydispersity polymeric stars can be obtained, often with PDIs as low as 1.1. The polymerization can be taken to a higher conversion than that in the growing-from approach, but steric hindrance may affect arms with a high molecular weight (the chain has more difficulty to react back on the thiocarbonyl-thio moiety attached to the core). Also, it is noteworthy that in this type of architecture, the thiocarbonyl-thio moiety is the point of attachment of the arms to the core and is therefore integrally part of the polymeric structure. Examples of these architectures include pentaerythritoltetrakis[3-(*S*-benzyltrithiocarbonyl)propionate] (**94**) to mediate the polymerization of methyl acrylate, styrene, and their block copolymers^{124,338} and dipentaerythritolhexakis[3-(*S*-benzyltrithiocarbonyl) propionate] (**95**; six arms), although it was not used in poly-



Scheme 28. Functional CTAs for the production of star (co)polymers: the R approach.

merization.¹²⁴ β -Cyclodextrin was modified into a trithiocarbonate heptafunctional β -cyclodextrin to mediate the polymerization of styrene.^{81,340} Tri(thiobenzoylthiomethyl)benzene (**96**) was used as a CTA in the polymerization of styrene.^{125,282} Xanthates tetrakis(benzyl-sulfanyl-thiocarbonyl-

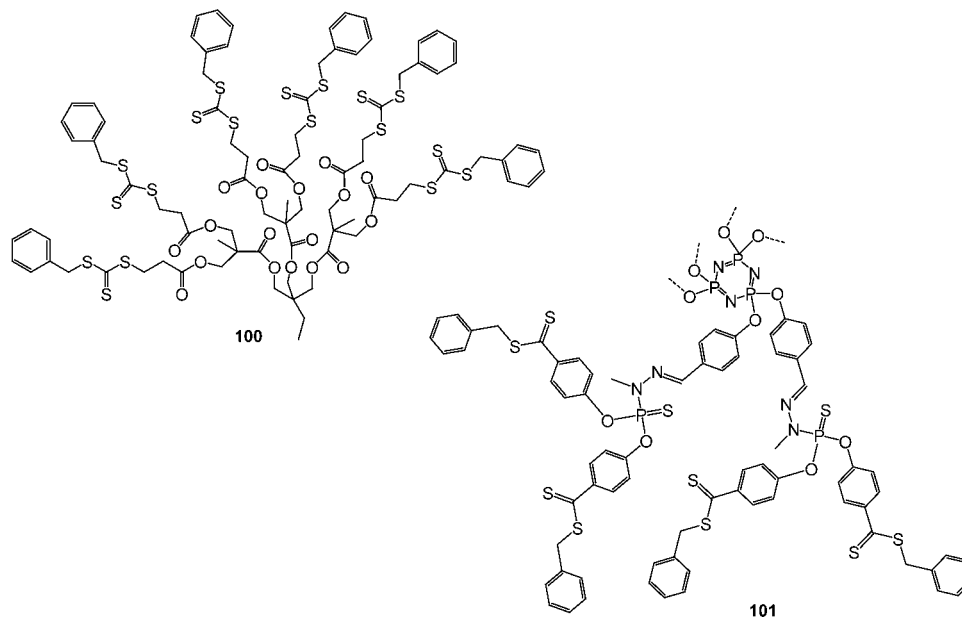
oxymethyl)methane (**97**), [1-(phenyl-ethyl)-sulfanyl-thiocarbonyl-oxymethyl]methane (**98**), and tetrakis[2-(phenyl-ethyl)-sulfanyl-thiocarbonyl-oxymethyl]methane (**99**) were all used to mediate the polymerization of vinyl acetate and vinyl propionate.⁵⁵



Scheme 29. Functional CTAs for the production of star (co)polymers: the Z approach.

Multiarm star polymers were also generated from dendritic cores (Scheme 30). The CAMD team used first- and second-generation dendritic CTAs showing 6 and 12 pendant 3-benzylsulfanylthiocarbonylsulfanylpropionic acid RAFT end groups, respectively, with a Z group architecture based on 1,1,1-hydroxyphenyl ethane and trimethylolpropane cores (**100**) to mediate the polymerization of butyl acrylate, styrene, and their block copolymer.^{80,277} You et al.²⁹⁸ used a similar

dendrimer and esterified the terminal hydroxyl group with maleic anhydride and further reacted the double bond of maleic anhydride with dithiobenzoic acid. The authors used the newly formed CTA to mediate the polymerization of *N*-isopropylacrylamide. Darcos et al.³⁴¹ used a first-generation phosphorus-containing dendrimer with 12 terminal benzyl dithiobenzoate functionalities (**101**) to mediate the polymerization of styrene (Scheme 30).



Scheme 30. Functional CTAs for the production of star (co)polymers from dendrimers as the core.

The CAMD group also generated multiarm stars by the sequential polymerization of styrene and divinylbenzene, the latter generating cross-linking to form a microgel core with polystyrene arms (the technique is called the arms-first approach). After characterization, the authors found that each star had, on average, 16 arms.^{251,253} Our group used an intermediate approach between dendritic and crosslinked microgel cores, using a branched PMMA, synthesized by RAFT copolymerization of MMA with ethylene glycol dimethacrylate, as a macro-CTA and polymerizing styrene (see the Dendrimer and Hyperbranched Polymers section). Note that in the two last cases, the polydispersities were very high as the number of arms per star varied to a great extent.³¹⁴

Pan and coworkers used RAFT polymerization for the synthesis of miktoarm ABC star copolymers. In their initial work, the authors re-initiated a polystyrene prepared via RAFT polymerization in the presence of maleic anhydride. As maleic anhydride does not homopolymerize, a polystyrene chain end-capped by a maleic anhydride functionality was obtained. The macro-CTA was then reacted further with either methyl acrylate (respectively *N*-isopropyl acrylamide) to yield a diblock copolymer. Finally, the anhydride functionality at the junction of the two blocks was reacted with the terminal hydroxyl group of a poly(ethylene glycol) methyl ether to yield a

poly(styrene-*b*-methyl acrylate-*b*-ethylene glycol) respectively poly(styrene-*b*-*N*-isopropyl acrylamide-*b*-ethylene glycol) miktoarm star copolymer.²⁷² In some later work, the same group reacted a polystyrene chain produced by RAFT with hydroxyethylene cinnamate to introduce a hydroxyl pendant group between the polystyrene chain and the terminal dithiobenzoate moiety. The hydroxyl group was used to initiate the cationic ring-opening polymerization of 1,3-dioxepane to produce a diblock copolymers of poly(styrene-*b*-1,3-dioxepane). Finally, MMA polymerization was mediated by the dithiobenzoate present at the junction of the two blocks to yield poly(styrene-*b*-1,3-dioxepane-*b*-methyl methacrylate) miktoarm star copolymers.³¹⁰ In a recent publication, the same group reported an alternative route by first producing a macro-CTA via organic synthesis: the reaction of the chain-end hydroxyl group to form a poly(ethylene glycol) methyl ether with maleic anhydride followed by the addition of dithiobenzoic acid led to a poly(ethylene glycol) macro-CTA with a pendant carboxylic acid group. The macro-CTA was then reacted with ethylene glycol to introduce a pendant hydroxyl group at the chain end. The macro-CTA mediated styrene polymerization to yield poly(ethylene glycol-*b*-styrene) diblock copolymers, and the pendant hydroxyl groups were used to initiate the ring-opening polymerization of *L*-lactide in the presence of Sn(OOct)₂. The resulting poly(ethylene glycol-*b*-styrene-*b*-*L*-

lactide) was characterized by NMR spectroscopy and GPC.³⁴²

Finally, a recent article by the CAMD team proposed a first attempt at modeling the process of polymerization for star production via RAFT/MADIX polymerization.³⁵⁷

Branched (Co)polymers

The synthesis of branched polymers can be achieved by two routes.

Grafting from the Polymeric Backbone

This approach uses a polymeric chain as a support from which to grow polymers. As in polymeric star synthesis, one can differentiate between the attached-to approach and away-from approach. The away-from approach uses polymeric chains that are bonded to the thiocarbonyl-thio moiety through its R substituent. CAMD illustrated this approach by synthesizing a branched polystyrene from poly(styrene-*co*-vinyl benzene chloride); the benzyl chloride functionality had been modified into a dithiobenzoate with a phenyl leaving group (pendant functionality from the polystyrene chain).²⁵³ A similar route was used by Vosloo et al.¹⁴⁰ when they copolymerized *n*-butyl acrylate with *N*-acryloxysuccinimide via RAFT and substituted the succinimide pendant group with benzyl 2-(2-hydroxyethylamino)-1-methyl-2-oxoethyl trithiocarbonate to mediate the RAFT polymerization of *n*-butyl acrylate from the poly(*n*-butyl acrylate-*co*-*N*-acryloxysuccinimide) backbone. A different route to the production of polymers with branches of controlled molecular weight is the thermal initiation of polymerization from a polymer backbone (the polymer acts then as a source of radicals and not as a CTA, as seen previously). This approach produced poly(vinylidene fluoride) grafted with poly[poly(ethylene glycol) methacrylate] chains initiated by radicals formed on ozone-pretreated poly(vinylidene fluoride), for which the polymerization is controlled by RAFT.^{268,318} A similar route was applied to produce poly(imide) grafted by poly[poly(ethylene glycol) methacrylate].^{319,320} Pan's group also reported the control of the branch spacing of poly(ethylene glycol) or poly(tetrahydrofuran) grafted on polystyrene. The authors polymerized styrene via RAFT and isolated the polymer. Re-initiation of the polystyrene in the presence of maleic anhydride introduced one maleic anhy-

dride unit per polystyrene chain (as maleic anhydride does not homopolymerize), and re-initiation of this new macro-CTA in the presence of styrene, targeting the same degree of polymerization as that used previously, produced a homopolymer showing the maleic anhydride functionality in the middle of the backbone. The reiteration of these steps on the same polymeric chain led to the production of polystyrene chains with maleic anhydride functionalities regularly spaced along the backbone. The further reaction of these functionalities with the terminal hydroxy group of poly(ethylene glycol) or poly(tetrahydrofuran) gave the grafted copolymer.¹⁴⁴

Macromonomer Approach

An alternative technique for obtaining branched (co)polymers involves the use of macromonomers; that is, polymeric chains end-functionalized with a vinyl group are homopolymerized or copolymerized. Examples of this process include the homo- or copolymerization of poly(ethylene glycol) methyl ether methacrylate,^{316,318–320} and poly(dimethylsiloxane) methacrylate^{321,322} to yield graft (co)polymers with the corresponding pendant chain.

Dendrimer and Hyperbranched Polymers

Styrene radical polymerization was carried out in the presence of a polymerizable dithioester (benzyl 4-vinyldithiobenzoate) after the reaction of a self-condensing vinyl polymerization, first reported by Fréchet et al.³⁴³ The polymerization displayed a living character and led to highly branched polystyrene. Analyses revealed that the primary chains had a narrow molecular weight distribution.¹⁹²

Our group polymerized MMA in the presence of an ethylene glycol dimethacrylate brancher, and we observed that CTA/brancher ratios less than 2 did not lead to crosslinking, as observed in conventional free-radical polymerization, but we obtained branched PMMA. The branched polymers retained their chain-end thiocarbonyl-thio moieties, as established by chain extension with styrene, to produce a macro star polymer with branched PMMA as the core and polystyrene as the arms.³¹⁴

Control over Tacticity

Several research groups have investigated the stereocontrol, in addition to molecular weight

control, of polymers generated via RAFT/MADIX polymerization.^{52,264,289,292,311,312} Kirci et al.²⁶⁴ reported the use of Lewis acid diethyl aluminum chloride as a chelating agent to prepare the alternating copolymer poly(methylacrylate-*co*-styrene). Ray and coworkers^{52,292} reported the synthesis of isotactic poly(*N*-isopropylacrylamide) and their block copolymers (see the Block Copolymers Generated from Sequential Monomer Addition section) using 1-phenylethyl phenyldithioacetate as a CTA in the presence of Lewis acid Y(OTf)₃ or ytterbium trifluoromethanesulfonate [Yb(OTf)₃], and they obtained polymers for which the dyad isotacticity reached 87%. Recently, Lutz and coworkers^{289,311,312} studied the use of various types of Lewis acids and the impact of their concentration to control the tacticity of poly(*N*-dimethyl methacrylamide) and its block copolymers produced by RAFT (see the Block Copolymers Generated from Sequential Monomer Addition section).

Surface-Grafted Polymers

Surface-grafted polymerization is currently attracting growing interest from the scientific community,^{344–346} and the RAFT/MADIX process has been used in a variety of studies to produce surface-grafted polymeric chains showing living character and/or controlled molecular weight. This area of research was pioneered by Tsuji et al.,³⁴⁷ who first studied the use of RAFT to grow polymers from a silica surface. The research group modified polystyrene oligomers, grown from the silica surface by ATRP into macro-CTAs with 1-phenyl ethyl dithiobenzoate (leading to a CTA attached to the surface via its R moiety), and mediated the polymerization of styrene, in the presence of an additional free CTA in solution. They observed that termination reactions by combination were enhanced specifically in the case of the RAFT system, and this was attributed to radical migration on the surface by sequential degenerative exchange chain transfer. The CAMD team grew polystyrene from crosslinked core poly(divinyl benzene) microspheres produced via RAFT and used the residual 1-phenylethyl dithiobenzoate (PEDB) CTA end groups on the surface and within the particle to grow polystyrene chains.²⁵⁸ A surface-immobilized dithiobenzoate, attached to the solid support via its R substituent (isobutyrate group), was also used for the growth of polystyrene chains from multi-walled carbon nanotubes to improve their solu-

bility.³⁴⁸ Homopolymers, random copolymers, and block copolymers were also grown from trithiocarbonate-covered CdSe nanoparticles, and this led to good nanoparticle dispersion in a wide range of polymers, while maintaining the photophysical properties of the nanoparticles.³⁴⁹ Our group used a CTA based on methoxycarbonylphenylmethyl dithiobenzoate attached to a cellulose substrate via its R group to mediate the controlled polymerization of styrene, methyl acrylate, and MMA.⁸² In some of our most recent work, we report the growth of polymeric chains from polystyrene crosslinked resins or silica surfaces via CTAs that are immobilized on the support through their Z group. This route can be used to produce true living polymeric chains, as such CTAs permit separation between pure living polymeric chains, which are attached to the support, from nonliving chains, as well as non-reacted monomers and other side products from the reaction that remain free in solution.³⁵⁰

A different approach is the use of the surface as a source of radicals to initiate RAFT polymerization. Several research groups have used this approach, with polypropylene, with radicals generated by γ radiation,^{186,351} or with silica, using an immobilized free-radical initiator.^{291,306,352}

A third route to surface grafting is to use vinyl groups present on the surface. CAMD copolymerized pendant vinyl functionalities on a crosslinked poly(divinyl benzene) with styrene in the presence of PEDB as a CTA.

We can also include in this section the use of polymers obtained from RAFT/MADIX polymerization as stabilizers (or ligand) for metal particles. RAFT permitted the synthesis of poly(*N*-isopropylacrylamide), which was then used to passivate gold nanoparticles either via its terminal dithiobenzoate group or via a thiol end group obtained from hydrazinolysis of the dithioester.²⁹³ The same approach was used to produce poly(sodium 4-styrene sulfonate), poly[(vinylbenzyl) trimethylammonium chloride], poly(*N,N*-dimethylacrylamide), and poly(3-[2-(*N*-methylacrylamido)-ethyl]dimethyl ammonio] propane sulfonate-*b-N,N*-dimethylacrylamide), which were immobilized onto gold films after the reduction of the terminal dithioester into a thiol.^{169,170}

CONCLUSIONS

LRP has revived the field of free-radical polymerization over the last 20 years. It is now possible to produce polymeric architectures (from

block copolymers to more complex structures such as star polymers) with a good-to-excellent degree of control, without the requirement of expensive equipment and stringent reaction conditions; thus this area is rendered more accessible to a wider scientific community. RAFT and MADIX polymerizations are among the youngest and yet most promising LRP techniques. This is due to the versatility of the system, the simple setup, the wide range of functionalities and monomers (this extends to vinyl esters), and the variety of macromolecular structures achievable.

For the nonexpert, the process is simple to undertake and does not require specialist equipment, and the polymerization mediator now has well-documented synthetic paths. Among the variety of structures that have been reported to date, block copolymers and star polymers are the most significant. RAFT/MADIX presents a simple approach for the production of block copolymers from a variety of functional monomers and should allow laboratories that do not possess in-house expert knowledge of living polymerization to synthesize their own products. The polymerization of star polymers is equally easy to achieve, although this requires more specific polymerization mediators. The material produced, especially when the Z group approach is used, is very close to that obtained from the more demanding ionic polymerization systems in terms of architectural control. The potential to introduce functionalities as part of either the R group or the Z group is an additional feature of RAFT/MADIX that is not available through other living polymerization techniques. Reports are increasingly emerging that highlight the potential outcomes of such an approach. At present, these are largely focused on the synthesis of star polymers, although it may be anticipated that further work will be developed in this area. RAFT/MADIX mediators may be offered to nonexperts. Finally, the RAFT/MADIX process has been taken beyond the synthesis aspect, as it has also been used as a tool to determine kinetic parameters in free radical polymerization.³⁵³ There is no doubt that this approach will be exploited further in the future.

The RAFT/MADIX process does not stop in the laboratory. One only needs to refer to the increasing number of patent applications on the use of RAFT/MADIX to appreciate that the system offers real potential for the large-scale production of living polymers with controlled structures, perhaps for the first time. The production

of block copolymers on an industrial scale has never before been within such close reach.

However, the RAFT/MADIX process remains full of challenges. A clear understanding of the mechanism and kinetics of polymerization is still lacking. The system has yet to be tested in the full range of processes that are applied to conventional radical polymerization, particularly within the context of ever-increasing environmental awareness. The range of monomers that can be polymerized by the process has not yet been fully explored, and the versatility of the system requires a broader chemical community to test specialist monomers and functionalities. The CTA structure requires further improvement to enable polymerization of the widest possible range of monomers. The synthesis of CTAs needs to be optimized so that simple routes for the production of RAFT/MADIX mediators may be offered to nonexperts.

RAFT and MADIX polymerizations are currently entering a new phase in their development. The system is now sufficiently well understood to attract the attention of a wide scientific community, and publications that use RAFT as a tool for the production of specific materials are on the increase. However, there is still scope for research groups to contribute to a more comprehensive understanding of the RAFT/MADIX system to facilitate the delivery of an accessible tool for the production of well-designed polymers.

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