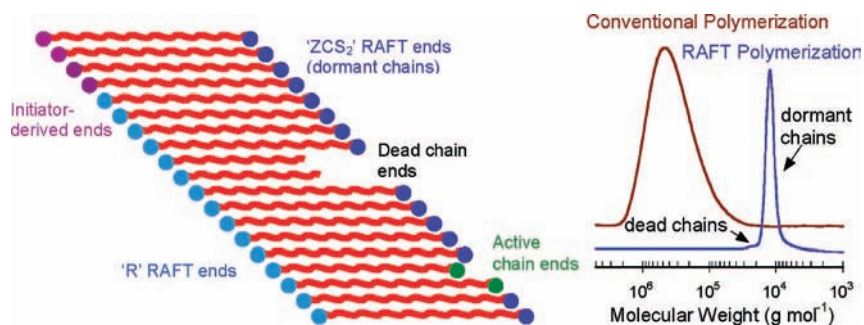


Toward Living Radical Polymerization

GRAEME MOAD,* EZIO RIZZARDO,* AND SAN H. THANG*
Commonwealth Scientific and Industrial Research Organisation (CSIRO)
Molecular and Health Technologies, Bayview Avenue, Clayton, Victoria 3168,
Australia

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CON SPECTUS



Radical polymerization is one of the most widely used processes for the commercial production of high-molecular-weight polymers. The main factors responsible for the preeminent position of radical polymerization are the ability to polymerize a wide array of monomers, tolerance of unprotected functionality in monomer and solvent, and compatibility with a variety of reaction conditions. Radical polymerization is simple to implement and inexpensive in relation to competitive technologies. However, conventional radical polymerization severely limits the degree of control that researchers can assert over molecular-weight distribution, copolymer composition, and macromolecular architecture.

This Account focuses on nitroxide-mediated polymerization (NMP) and polymerization with reversible addition–fragmentation chain transfer (RAFT), two of the more successful approaches for controlling radical polymerization. These processes illustrate two distinct mechanisms for conferring living characteristics on radical polymerization: reversible deactivation (in NMP) and reversible or degenerate chain transfer (in RAFT). We devised NMP in the early 1980s and have exploited this method extensively for the synthesis of styrenic and acrylic polymers. The technique has undergone significant evolution since that time. New nitroxides have led to faster polymerization rates at lower temperatures. However, NMP is only applicable to a restricted range of monomers.

RAFT was also developed at CSIRO and has proven both more robust and more versatile. It is applicable to the majority of monomers subject to radical polymerization, but the success of the polymerization depends upon the selection of the RAFT agent for the monomers and reaction conditions. We and other groups have proposed guidelines for selection, and the polymerization of most monomers can be well-controlled to provide minimal retardation and a high fraction of living chains by using one of just two RAFT agents. For example, a tertiary cyanoalkyl trithiocarbonate is suited to (meth)acrylate, (meth)acrylamide, and styrenic monomers, while a cyanomethyl xanthate or dithiocarbamate works with vinyl monomers, such as vinyl acetate or *N*-vinylpyrrolidone. With the appropriate choice of reagents and polymerization conditions, these reactions possess most of the attributes of living polymerization. We have used these methods in the synthesis of well-defined homo-, gradient, diblock, triblock, and star polymers and more complex architectures, including microgels and polymer brushes. Applications of these polymers include novel surfactants, dispersants, coatings and adhesives, biomaterials, membranes, drug-delivery media, electroactive materials, and other nanomaterials.

Introduction

This Account focuses on two of the more successful approaches to living radical polymerization. Namely, nitroxide-mediated polymerization (NMP),

which was developed at CSIRO in the mid-1980s,¹ and radical polymerization with reversible addition–fragmentation chain transfer (RAFT) also invented at CSIRO a decade later.² The Account

will concentrate on work carried out at CSIRO and, for the most part, will be illustrated with examples from research carried out in our laboratories. It will focus on the selection and design of reagents that control radical polymerization by conferring the attributes of living polymerization.

Toward Living Radical Polymerization

Radical polymerization is one of the most widely used processes for the commercial production of high-molecular-weight polymers. The main factors responsible for the preeminent position of radical polymerization are³ (i) the ability to polymerize a wide variety of monomers, including (meth)acrylates, (meth)acrylamides, acrylonitrile, styrenes, dienes, and vinyl monomers; (ii) tolerance of unprotected functionality in monomer and solvent (e.g., OH, NR₂, COOH, CONR₂, and SO₃H) (polymerizations can be carried out in aqueous or protic media); (iii) compatibility with reaction conditions (e.g., bulk, solution, emulsion, mini-emulsion, and suspension); and (iv) it is simple to implement and inexpensive in relation to competitive technologies.

However, conventional radical polymerization has severe limitations with respect to the degree of control that can be asserted over molecular-weight distribution, copolymer composition, and macromolecular architecture. This situation has been redressed with the advent of processes that provide the attributes of living polymerization, such as NMP, atom transfer radical polymerization (ATRP), and RAFT.

Conventional radical polymerization is a chain reaction.³ Chains are initiated by radicals formed from an initiator adding to monomer. Chain propagation then involves sequential addition of monomer units to form propagating radicals. Chain termination occurs when these propagating radicals self-react by combination or disproportionation.

The steady-state concentration of propagating species is only $\sim 10^{-7}$ M, and the lifetime of individual chains is ~ 5 – 10 s. The ultimate length of chains formed during the early stages of polymerization is high and, notwithstanding the gel or Trommsdorf effect, should reduce with conversion because of monomer depletion. The breadth of the molecular-weight distribution and polydispersity is governed by statistical factors, and the ratio of weight/number average molecular weights (\bar{M}_w/\bar{M}_n) is typically > 2.0 , if termination is by disproportionation or chain transfer, or > 1.5 , if termination is by combination.

In marked contrast, in an ideal living polymerization, all chains are initiated at the beginning of the process, grow at a similar rate, and survive the polymerization (there is no irreversible chain transfer or termination). If initiation is rapid with

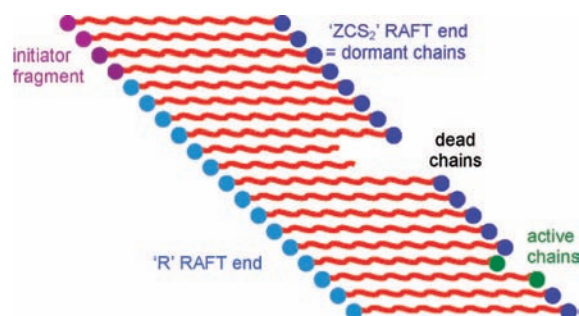


FIGURE 1. RAFT polymerization schematic. Initiator fragments = (dead chains + active chains). The number of chains of each type is not in proportion to that expected for a well-designed experiment. Ideally, the fraction of dormant chains is much greater than that shown. On average, all living chains grow simultaneously (have equal chain length) because equilibration of dormant and active chain ends is rapid with respect to propagation.

respect to propagation, the molecular-weight distribution is very narrow, approaching a Poisson distribution, and chains can be extended by the provision of further monomer.

In a radical polymerization, the propensity of radicals to undergo self-termination means that all chains cannot be simultaneously active. Living attributes are only displayed in the presence of reagents that are capable of reversibly deactivating propagating radicals ($P_n\bullet$), such that the majority of living chains are maintained in a dormant form (P_n-X), and reaction conditions that support a rapid equilibrium between the active and dormant chains (Figure 1).

The rate of termination scales as the square of the total radical concentration $[P_n\bullet]^2$, while the rate of propagation is directly proportional to $[P_n\bullet]$. Thus, a first strategy for suppressing termination is to lower the steady-state radical concentration. Application of this strategy necessarily also results in a lowered rate of polymerization.

It is possible to achieve a high fraction of living chains while maintaining an average concentration of active propagating species similar to or higher than that in a conventional radical polymerization. This requires that the total number of living chains ($=P_n\bullet + P_n-X$) is much higher than would be obtained in a conventional polymerization with a similar rate of initiation and that the molecular weight of the chains formed is correspondingly lower.

A third strategy for simultaneously achieving high rates of polymerization and a high degree of livingness is to make use of compartmentalization phenomena, as exist in some forms of heterogeneous polymerization, to effectively isolate individual propagating radicals.

Whichever strategy is employed, rapid equilibration of the active and dormant forms of the propagating species is essential to ensure that all chains possess an equal chance for

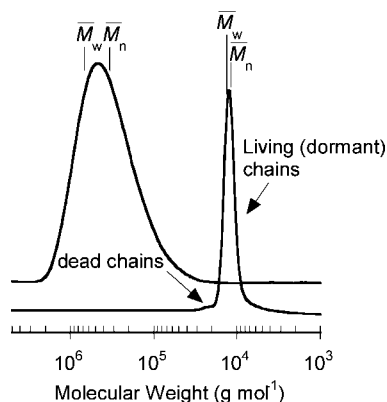


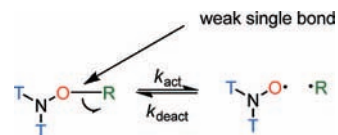
FIGURE 2. Typical molecular-weight distributions for a conventional and RAFT polymerization of styrene under similar experimental conditions. Data shown are for polystyrene prepared by thermal polymerization of styrene at 110 °C for 16 h ($\bar{M}_n = 324\,000$; $\bar{M}_w/\bar{M}_n = 1.74$; 72% conversion) and a similar polymerization with added cumyl dithiobenzoate (0.029 M) ($\bar{M}_n = 14\,400$; $\bar{M}_w/\bar{M}_n = 1.04$; 55% conversion).⁴

growth and that all chains will grow, albeit intermittently. Under these conditions, molecular weights can increase linearly with conversion, molecular-weight distributions can be very narrow (Figure 2), and the polymerization product should comprise overwhelmingly dormant chains that can be extended by the provision of further monomer and the reaction conditions that support chain growth.⁴

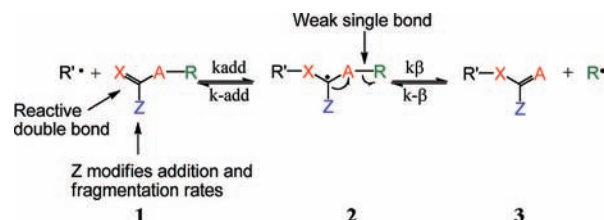
Terminology. Currently, there is some controversy over the use of the terms “living” and “controlled” in the context of describing radical polymerizations.⁵ The International Union of Pure and Applied Chemistry (IUPAC) recommendation, that a living polymerization is “a chain polymerization from which irreversible chain transfer and irreversible chain termination (deactivation) are absent”, generally precludes use of “living” in referring to these processes.⁶ The use of “controlled” by itself is also contrary to IUPAC recommendations. It is incorrect to use “controlled” in an exclusive sense to mean a particular form of polymerization because the word has an established, much broader, usage. The adjectives “controlled living”, “controlled/living”, “pseudo-living”, and “quasi-living” are also discouraged. An IUPAC task group has recommended the term (controlled) reversible deactivation radical polymerization (RDRP) to describe those polymerizations (such as NMP or RAFT) that entail equilibria between active and dormant chains. This term is not intended to have any connotations to the fraction of living chains that might be present in a particular polymerization process.

We have used the term living radical polymerization in the title of this Account. It relates to approaches to living radical polymerization, a hypothetical process in which termination is indeed absent. We do not imply that termination is absent

SCHEME 1. Reversible Coupling–Dissociation Mechanism for NMP



SCHEME 2. Mechanism for Addition–Fragmentation Chain Transfer



^a R is a homolytic leaving group. R• must also be able to re-initiate polymerization. For reversible chain transfer (RAFT), groups A and X should be the same. from any polymerizations described herein. Many systems do display the observable characteristics normally associated with living polymerization, and in a few cases, termination, while undeniably present, is undetectable.

Techniques. The techniques for imparting living behavior to polymerization through reversible deactivation include the iniferter method first described by Otsu,⁷ NMP, ATRP, RAFT, and other degenerative chain-transfer methods.^{8,9}

NMP was devised at CSIRO in the early 1980s¹ and has been exploited extensively for the synthesis of styrenic and acrylic polymers.^{10–12} A generic mechanism for chain activation/deactivation in NMP is shown in Scheme 1.

ATRP is substantially more versatile and is currently the most widely applied method for controlling radical polymerization.^{13,14} The mechanism of chain activation/deactivation is analogous to that for NMP but requires a bimolecular activation step.

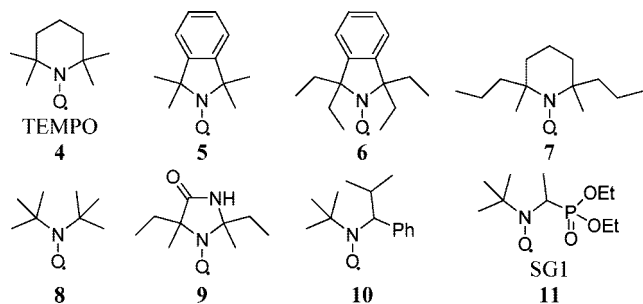
RAFT polymerization^{2,15} is arguably the most convenient and versatile in allowing the use of reaction conditions more typical of the conventional process.^{16–18} The mechanism of chain activation/deactivation is shown in Scheme 2. Cobalt-mediated polymerization is also believed to involve a form of addition–fragmentation chain transfer. Other degenerative transfer techniques, such as iodine transfer polymerization (ITP) and tellurium-mediated radical polymerization (TERP), involve atom or group transfer by reversible homolytic substitution.^{8,9}

Nitroxide-Mediated Polymerization (NMP)

The development of NMP at CSIRO had its origin in studies of initiation mechanisms. Prior to the development of NMP, nitroxides were well-known as radical scavengers, and various derivatives were widely used in polymer stabilization.

These applications were based on the property of nitroxides to efficiently trap carbon-centered radicals by combining them at near diffusion-controlled rates to form alkoxyamines.

In the period 1979–1990, a large number of studies of the reactions of initiator-derived radicals with monomers were carried out, in which a nitroxide (e.g., **4** and **5**) was used as a radical trap.^{19,20} In the course of that work, it was observed that under some conditions the trapping of propagating radicals by the nitroxide was reversible, an observation that ultimately led to the development of NMP. The exploitation of alkoxyamines as polymerization initiators and the use of NMP for producing block and end-functional polymers were first described in a CSIRO patent application in 1985.¹ In this patent, NMP was described as a method of living radical polymerization. In 1990, Johnson et al.²¹ described what is now known as the persistent radical effect²² and showed theoretically that NMP could provide narrow polydispersity polymers. The early work focused on polymerization of (meth)acrylates with nitroxides, such as **6–8**, being preferred control agents.¹ However, NMP only received significant attention in the wider literature following the demonstration by Georges et al.²³ in 1993 that NMP with **4** as the control agent allowed for preparation of polystyrene with a relatively narrow molecular-weight distribution.



Two strategies have been applied to initiate NMP. In the first, the initiator is an alkoxyamine. This approach was used in the original CSIRO work.¹ Hawker and co-workers²⁴ also exploited this method and coined the term “unimer” to describe these initiators. In the second approach, the alkoxyamine is formed *in situ* from the nitroxide and radicals generated using a conventional initiator. Dibenzoyl peroxide was used in the work of Georges et al.²³

A wide range of nitroxide and derived alkoxyamines has now been exploited in NMP. Experimental work and theoretical studies have related nitroxide/alkoxyamine structure to polymerization outcome and provided further understanding of the kinetics and mechanism. Important parameters are the activation–deactivation equilibrium constant K and the values of k_{act} and k_{deact} (Scheme 1).²⁵ However, the success of

NMP also depends upon the significance of side reactions. Thus, the combination/disproportionation ratio for the reaction of the nitroxide with the propagating radical and the intrinsic stability of the nitroxide under the polymerization conditions are also important. This leads to two strategies to improve the rate of polymerization in NMP: (1) One is to decrease the incidence of side reactions. Imidazolinone-derived nitroxides (e.g., **9**) provide substantially better control than TEMPO, particularly for polymerizations of (meth)acrylates.²⁶ This is attributed to the higher combination/disproportionation ratio with the five-membered ring nitroxides. With methyl methacrylate (MMA), limiting conversion behavior is, nonetheless, observed with the final product being the macromonomer formed by disproportionation.^{26,27} Even though these polymerizations yield “dead” polymer, very close correspondence of found and calculated molecular weights^{26,27} demonstrates that the polymer is formed by NMP and that there is little chain transfer or other initiation mechanisms. (2) The second strategy is to use nitroxides that are sufficiently unstable that an excess of nitroxide does not build up during polymerization. The open-chain nitroxides (**10**)²⁸ and SG1 (**11**)²⁹ provide good examples of this approach. These nitroxides are also very effective at relatively low temperatures.

Radical Polymerization with Reversible Addition–Fragmentation Chain Transfer (RAFT)

The first reports of radical addition–fragmentation processes appeared in the organic chemistry literature in the early 1970s. However, the direct use of addition–fragmentation transfer agents to control molecular weight and end group functionality in polymers was not reported until the mid-1980s.³⁰ The RAFT process using thiocarbonylthio compounds, including dithioesters and trithiocarbonates, was reported by CSIRO in early 1998.² Researchers from France reported a process with an analogous mechanism but using xanthate RAFT agents (MADIX) in late 1998.³¹ A CSIRO patent claiming the use of xanthate and dithiocarbamate RAFT agents appeared in early 1999.³² The historical development of the process is described in a recent review.¹⁸

Unsaturated compounds of general structure **1** can act as transfer agents by a two-step addition–fragmentation mechanism. Such transfer agents possess a C=X double bond that is reactive toward radical addition, groups A and X that are most often CH₂ or S, a substituent Z that is chosen to give the transfer agent an appropriate reactivity toward propagating radicals and convey appropriate stability to the intermediate

radicals **2**, and a group R that is a homolytic leaving group and such that R• is capable of efficiently re-initiating polymerization. Reversible chain transfer requires that both **1** and **3** are active transfer agents under the polymerization conditions. This means that the groups A and X should be the same (both CH₂ or both S) and R must have similar or better homolytic leaving group ability than the propagating radical.

In addition–fragmentation chain transfer, the rate constant for chain transfer (k_{tr}) is defined in terms of the rate constant for addition (k_{add}) to the transfer agent and a partition coefficient (ϕ) defined as follows:³³

$$k_{tr} = k_{add} \frac{k_{\beta}}{k_{-add} + k_{\beta}} = k_{add} \phi$$

$$\phi = \frac{k_{\beta}}{k_{-add} + k_{\beta}}$$

The transfer constant is then defined in terms of k_{tr} and the propagation rate constant (k_p) in the usual way ($C_{tr} = k_{tr}/k_p$).

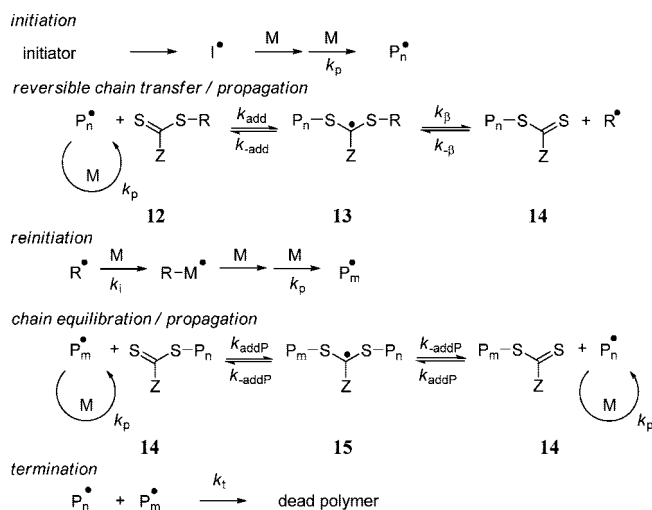
Efficient transfer requires that the radical intermediates formed by addition undergo facile β -scission. The driving force for fragmentation of the intermediate radical is provided by cleavage of a weak A–R bond. If both addition and fragmentation are rapid and irreversible with respect to propagation, the polymerization kinetics should differ little from those seen in polymerization with conventional chain transfer. If the overall rate of β -scission is slow relative to propagation, then retardation is a likely result. If fragmentation is slow, the adducts **2** also have a greater potential to undergo side reactions, such as radical–radical termination. In designing transfer agents and choosing a R group, a balance must also be achieved between the leaving group ability of R and re-initiation efficiency of R• because, as with conventional chain transfer, the rate constant for re-initiation by R• (k_i) should be $\geq k_p$. If fragmentation leads preferentially back to starting materials, the transfer constants are lowered.

RAFT polymerization shows the same wide tolerance of reaction conditions as the conventional process. This makes RAFT polymerization particularly suited to aqueous solution³⁴ and emulsion polymerization,³⁵ and this has led to the rapid development of these areas.

RAFT Agent Design

The mechanism of RAFT polymerization comprises a sequence of addition–fragmentation equilibria shown in Scheme 3.¹⁵ Initiation and radical–radical termination occur as in conventional radical polymerization. In the early stages of the polymerization, the addition of a propagating radical ($P_n\bullet$) to the

SCHEME 3. Mechanism of RAFT Polymerization



initial RAFT agent **12** and fragmentation of the intermediate formed provides a polymeric RAFT agent **14** and a new radical (R•). Re-initiation by R• forms a new propagating radical ($P_m\bullet$). Rapid equilibrium between the active propagating radicals ($P_n\bullet$ and $P_m\bullet$) and the corresponding dormant species **14** provides equal probability for all chains to grow and allows for the production of narrow polydispersity polymers. When the polymerization is complete (or stopped), the vast majority of chains will retain the thiocarbonylthio end group. The reactions associated with RAFT equilibria shown in Scheme 3 are in addition to those (i.e., initiation, propagation, and termination) that occur during conventional radical polymerization. In an ideal RAFT process, the RAFT agent should behave as an ideal transfer agent. Thus, as with radical polymerization with conventional chain transfer, the kinetics of polymerization should not be directly influenced beyond those affects attributable to the differing molecular weights of the reacting species. Radical–radical termination is not directly suppressed by the RAFT process.

A summary of RAFT agents (ZC(=S)SR, **12**) and the factors that should influence choice of the RAFT agent for a particular polymerization can be found in recent reviews.^{16–18,34,36} The effectiveness of RAFT agents is determined by the substituents R and Z. A guide to the suitability of RAFT agents for controlling polymerization of particular monomers is provided in Figure 3.^{16,18}

Monomers are broadly divided into two categories: (1) “More-activated” monomers include vinyl aromatics (styrene and vinylpyridine), methacrylics, e.g., MMA, methacrylic acid, and methacrylamide (MAM), and acrylics, e.g., methyl acrylate (MA), acrylic acid, acrylamide (AM), and acrylonitrile (AN). (2) “Less-activated” monomers include vinyl esters, e.g., vinyl

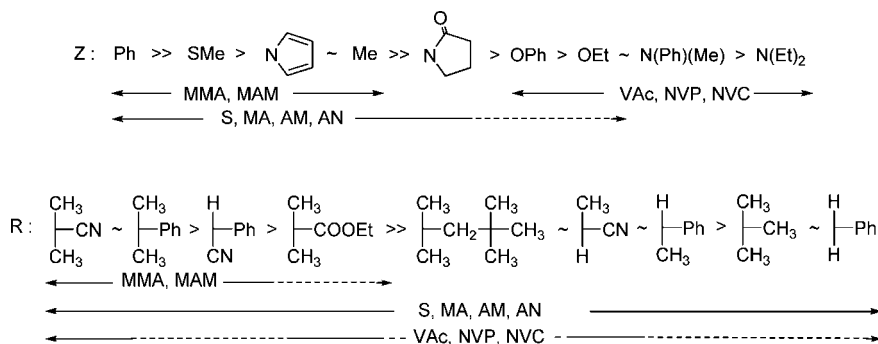


FIGURE 3. Guidelines for selection of RAFT agents for various polymerizations.^{16,18} For Z, addition rates decrease and fragmentation rates increase from left to right. For R, fragmentation rates decrease from left to right. A dashed line indicates partial control.

acetate (VAc), and vinyl amides, e.g., *N*-vinylpyrrolidone (NVP) and *N*-vinylcarbazole (NVC).

A key feature of RAFT polymerization is that the thiocarbonylthio groups are retained in the polymeric product. This is responsible for the living character of RAFT polymerization and renders the process suitable for synthesizing block copolymers and end functional polymers. However, the presence of the thiocarbonylthio groups is detrimental to some applications. Removal or transformation of the thiocarbonylthio group therefore forms an integral part of many polymer syntheses.^{37–42}

RAFT Polymerization of “More-Activated” Monomers

The “more-activated” class may be further divided into those that generate tertiary propagating radicals (i.e., 1,1-disubstituted olefins) and secondary propagating radicals (i.e., monosubstituted olefins). To understand retardation or inhibition, phenomena sometimes associated with RAFT polymerization of activated monomers that have high ($k_p > 1000 \text{ M}^{-1} \text{ s}^{-1}$; e.g., acrylates and acrylamides) and low propagation rate constants ($k_p < 1000 \text{ M}^{-1} \text{ s}^{-1}$; e.g., vinyl aromatics and methacrylates) should also be distinguished.

The order of activity as a function of “Z” shown in Figure 3 is predicted by orbital calculations (Figure 4).⁴³ The apparent transfer constant correlates with the calculated heat of reaction, the lowest unoccupied molecular orbital (LUMO) energy, and the partial charge on sulfur. Even though values predicted by semi-empirical calculations were substantially in error, the trend in values was similar to those predicted by *ab initio* methods using various basis sets.

Dithiobenzoates and other aromatic dithioesters (Z = aryl, e.g. **16** and **17**) are among the most active RAFT agents and have general utility in the polymerization of the “more-activated” monomers class.^{16,17} However, reasonable control over polymerization is also observed with trithiocarbonates (Z = S-alkyl), aromatic dithiocarbamates (e.g., Z = pyrrole), and

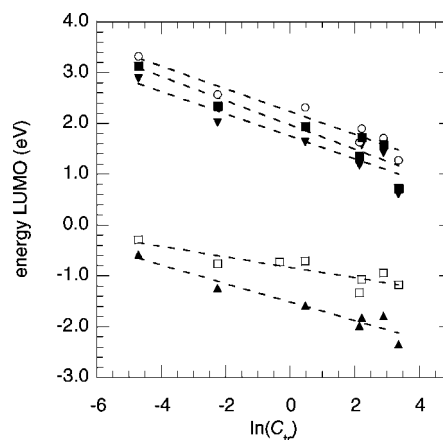


FIGURE 4. Plot of the logarithm of the apparent transfer coefficient for $ZC(=S)S-CH_2Ph$ in styrene polymerization versus calculated LUMO energy for $ZC(=S)S-CH_3$. Values from AM1 (\square) or *ab initio* calculations with Gaussian 98 and 3/21G* (\circ), 6/31G* (\blacktriangle), MP2/D95 (\blacktriangledown), and B3LYP/6-31G* (\blacksquare) basis sets.⁴³

dithioesters (e.g., Z = alkyl or aralkyl). The latter RAFT agents, while slightly less active than the aromatics dithioesters, are also less sensitive to hydrolysis and decomposition induced by Lewis acids.^{44,45}

R must efficiently re-initiate polymerization and must be a good homolytic leaving group with respect to the propagating radical.⁴⁶ The choice of “R” is critical in the case of methacrylates (Figure 6). In the most effective RAFT agents, R is tertiary cyanoalkyl (e.g., **17**) or cumyl (**16**). That only poor control is seen with **18**, where “R” is a monomeric model for the propagating radical, and indicates that the penultimate unit effects are important.⁴⁶ The apparent transfer constant for **18** is lower than that for **22** by almost 2 orders of magnitude. RAFT agents with R = tertiary alkyl (e.g., $-C(Me)_2CH_2C(Me)_3$, **19**) offer essentially no control. Agents with R = $-CHPh(CO_2Me)$,⁴⁷ $-CHPh(CO_2H)$,¹⁷ or $-CHPh(CN)$ ^{44,48} also have some utility in controlling RAFT polymerization of methacrylates. However, an inhibition period is observed, which is attributed to slow re-initiation by $R\cdot$.

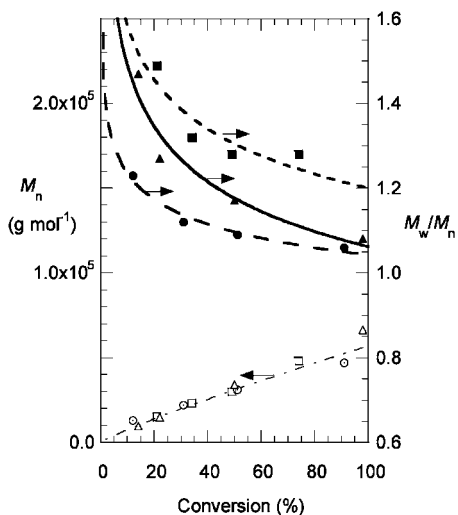
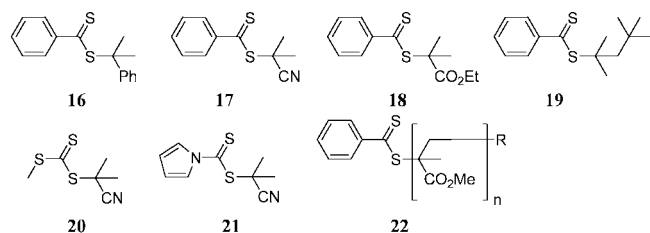


FIGURE 5. Evolution of the molecular weight (open symbols) and polydispersity (closed symbols) with conversion for polymerization of methyl methacrylate (7.02 M in benzene) at 60 °C with AIBN initiator (0.0070 M) in the presence of dithiobenzoate esters $ZC(=S)SC(Me)_2CN$ (0.0010 M), where $Z = Ph$ (**17**; ●, ---), $Z = SMe$ (**20**; ▲, ---), and $Z = N$ -pyrrolo (**21**; ■, ---). Calculated molecular weight (---).⁴⁵

Electron-withdrawing groups can enhance the activity of dithiobenzoate RAFT agents. For ring-substituted cyanoisopropyl dithiobenzoate RAFT agents in MMA polymerization electron-withdrawing groups, which render the thiocarbonyl sulfur more electrophilic, enhance the rate of addition to the $C=S$ double bond and provide narrower polydispersities from the early stages of polymerization.^{16,49}

However, the use of dithiobenzoates can retard polymerization particularly when they are used in high concentrations to provide lower molecular-weight polymers. This is particularly noticeable with cumyl dithiobenzoate. An IUPAC task group *Toward a Holistic Mechanistic Model for RAFT Polymerizations: Dithiobenzoates as Mediating Agents* was formed in 2005. The first output of that working party has recently been published. This is a *dilemma paper* that summarizes the current situation with respect to the polymerization kinetics, possible side reactions, and mechanisms for retardation.⁵⁰

Retardation observed during polymerization of methacrylates and styrene is strongly dependent upon the RAFT agent concentration and can be directly correlated with consumption of the initial RAFT agent. Retardation is most pronounced

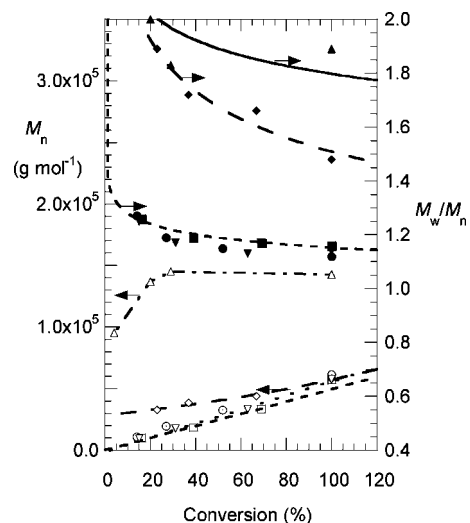


FIGURE 6. Evolution of the molecular weight (open symbols) and polydispersity (closed symbols) with conversion for methyl methacrylate polymerization (7.02 M in benzene) at 60 °C with azobisisobutyronitrile initiator (0.0061 M) in the presence of dithiobenzoate esters $PhC(=S)SR$ (0.0116 M), where $R = -C(Me)_2Ph$ (**16**; ■), $R = -C(Me)_2C_6H_4Cl$ (●), $R = -C(Me)_2CN$ (**17**; ▼), $R = -C(Me)_2CO_2Et$ (**18**; ◆), and $R = -C(Me)_2CH_2C(Me)_3$ (**19**; ▲).⁴⁶ Calculated molecular weight assuming no initiator-derived chains (---) or including initiator-derived chains (---).

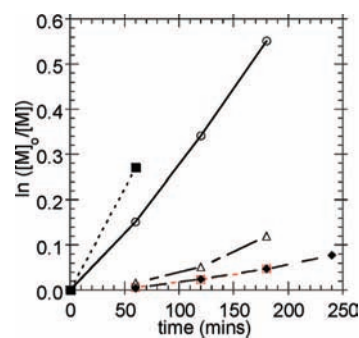


FIGURE 7. Pseudo-first-order rate plot for methyl acrylate polymerization (4.45 M in benzene) at 60 °C with $\sim 3.3 \times 10^{-4}$ M azobisisobutyronitrile in the absence (■, ---) or presence of 0.00306 M $MeC(=S)CH_2Ph$ (○, ---), 0.0306 M $MeC(=S)SCH_2Ph$ (Δ, ---), 0.00366 M $PhC(=S)SCH_2Ph$ (red □, red ---), or 0.00366 M $PhC(=S)SC(Me)_2CN$ (◆, ---) (data points for the latter two RAFT agents are almost coincident).⁴⁶

with cumyl dithiobenzoate.^{51,52} Dithioesters with different R and/or Z substituents (e.g., cyanoisopropyl dithiobenzoate) and aliphatic dithioesters (e.g., cumyl dithiophenylacetate) display less retardation.⁵²

Retardation tends to be more pronounced with high k_p monomers (acrylates and acrylamides). For the case of acrylates, retardation with dithiobenzoate RAFT agent is not directly related to consumption of the initial RAFT agent, which is rapid, with the initial dithiobenzoate being completely consumed at very low monomer conversion. Use of aliphatic

TABLE 1. RAFT Polymerization of Vinyl Acetate⁵⁶

monomer (M)	RAFT agent (M × 10 ²)	initiator ^a (M × 10 ³) conditions	conversion (%)	\bar{M}_n (g mol ⁻¹)	\bar{M}_w/\bar{M}_n
10.86	25 (9.96)	ACHN (8.7) 100 °C 4 h	66	7000	1.18
10.86	27 (4.98)	AIBN (6.1) 60 °C 16 h	96	22700	1.24

^a AIBN, 2,2'-azobis(isobutyronitrile); ACHN, 1,1'-azobis(cyclohexanecarbonitrile).

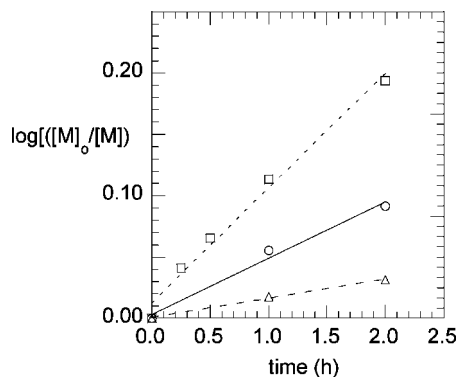


FIGURE 8. Plot of the logarithm of the monomer concentration versus time to 2.5 h for polymerization of *N*-vinylpyrrolidone [~50% (v/v) NVP/toluene] in the presence of **26** at 60 °C with [NVP]/[RAFT] = 71 (□, ---), 92 (○, ----), and 151 (△, ---); [azobisisobutyronitrile] = 1.28×10^{-2} , 4.42×10^{-3} , 8.82×10^{-4} M, respectively.⁴⁰

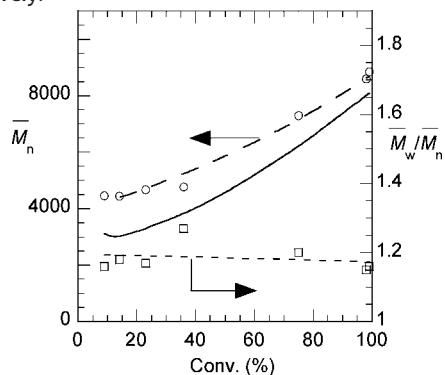


FIGURE 9. Evolution of the number average molecular weight (\bar{M}_n , polystyrene equivalents, ○, ----) and polydispersity (\bar{M}_w/\bar{M}_n , □, ---) with conversion during polymerization of *N*-vinylpyrrolidone [~50% (v/v) NVP/toluene] in the presence of **26** [NVP]/[RAFT] = 71 and azobisisobutyronitrile (1.28×10^{-2} M) at 60 °C. The solid line is the calculated molecular weight based on RAFT agent consumed.⁴⁰

dithioesters or trithiocarbonates provides substantially less retardation.^{4,46,52–55} Quinn et al.⁵⁴ observed that 1-phenylethyl dithiophenylacetate enabled RAFT polymerization of MA at ambient temperature, whereas 1-phenylethyl dithiobenzoate strongly retarded polymerization under the same conditions.

The form of retardation is illustrated in Figure 7.⁴⁶ The rate of polymerization in the presence of dithiobenzoate derivatives does not depend upon R and is strongly retarded with

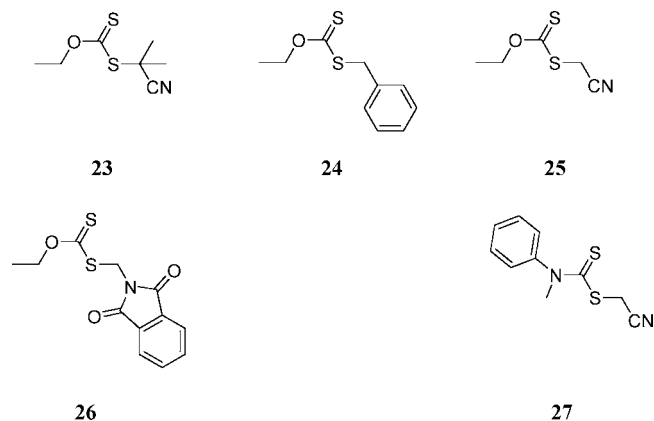
respect to that observed in the absence of the RAFT agent.^{4,46,52} While the dithioacetate also retards polymerization, the extent is substantially less than that observed with the dithiobenzoates even with a 10-fold higher RAFT agent concentration. All polymerizations ultimately gave high conversions and narrow (yet bimodal) molecular-weight distributions. These retardation issues do not, by themselves, prevent the formation of low polydispersity or block polymers.

RAFT Polymerization of “Less-Activated Monomers”

Controlled radical polymerization of the less-activated monomers (e.g., VAc, NVP, and NVC) are often problematic; ATRP and NMP are not generally effective with this monomer class. The more active RAFT agents (dithioesters and trithiocarbonates) also strongly inhibit polymerization, such that even after extended reaction times little polymerization may be observed. This inhibition is attributed to the propagating radicals generated from these monomers being poor homolytic leaving groups and the consequent stability and side reactions undergone by the intermediate formed by addition to the RAFT agent.⁵⁶

The less active RAFT agents, such as xanthates and dithiocarbamates, provide control over molecular weight and polydispersities for VAc, NVP, and NVC. Examples of VAc polymerizations are shown in Table 1. Polymerization of VAc is complicated by transfer to the monomer and polymer. The incidence of these processes is not directly influenced by the RAFT process. A frequently observed trend for an increase in polydispersity at high monomer conversion can be largely attributed to this. An example of NVP polymerization with **26** is shown in Figures 8 and 9.⁴⁰ Good control is achieved, and no inhibition period is evident.

The choice of R group is critical because most monomers in the class have a high k_p ($> 10^3$). The rate constants for benzyl, cyanoisopropyl, and cyanomethyl adding to VAc are reported as 46, 79, and 1×10^4 M⁻¹ s⁻¹, respectively (298 K).⁵⁷ Thus, inhibition periods because of slow re-initiation are expected for RAFT agents, such as **23** and **24**.



Conclusions

Nitroxide-mediated polymerization (NMP) and polymerization with reversible addition–fragmentation chain transfer (RAFT) have emerged as two of the most important methods for controlling radical polymerization.

RAFT has been shown to be robust and versatile and applicable to the majority of monomers subject to radical polymerization. However, selection of the RAFT agent for the monomers and choice of reaction conditions is crucial for success. Most polymerizations can be controlled using one of just two RAFT agents: one suited to (meth)acrylate, (meth)acrylamide, and styrenic monomers, for example, a tertiary cyanoalkyl trithiocarbonate, and another suited to vinyl monomers, such as VAc, for example, a cyanomethyl xanthate or dithiocarbamate. Requirements for specific end-functionality or architecture may dictate the use of other RAFT agents.^{37,58}

NMP and RAFT (and ATRP) are being used in the synthesis of well-defined homo-, gradient, diblock, triblock, and star polymers and other architectures, including microgels and polymer brushes. New materials that have the potential of revolutionizing a large part of the polymer industry are beginning to appear. Much research has been redirected from fundamental understanding to applications. Our first NMP¹ and RAFT patents² are among the most cited in the field of chemistry and related science.⁵⁹ Many reviews^{16–18,34} and a book³⁶ describe the RAFT process. Notwithstanding these comments, there remains significant scope for process improvement. Many features of the kinetics and mechanism remain to be unraveled, and a significant part of current research remains directed to this end.

BIOGRAPHICAL INFORMATION

Graeme Moad obtained his Ph.D. in 1977 from the University of Adelaide in the field of organic free-radical chemistry. In 1977, he undertook postdoctoral research at Pennsylvania State University. He joined CSIRO in 1979 and is currently a chief research

scientist and also a project leader in the Cooperative Research Centre (CRC) for Polymers. Dr. Moad is author or co-author of more than 120 papers in refereed journals, co-inventor on more than 25 patent families, and co-author of the book *The Chemistry of Radical Polymerization*. His research interests lie in the fields of polymer design and synthesis (free-radical polymerization and reactive extrusion), polymerization kinetics and mechanism, and most recently polymer nanocomposites.

Ezio Rizzardo was born in Italy in 1943. He was awarded a Ph.D. by the University of Sydney in 1969 for his studies on the photochemistry of organic nitro compounds. He joined CSIRO in 1976 after postdoctoral research on the synthesis of biologically active organic compounds at Rice University, RIMAC, and the Australian National University. His CSIRO research has focussed on developing methods for understanding and controlling free-radical polymerization. He is a CSIRO Fellow, the recipient of the Australian Polymer Medal, and a Fellow of both the Australian Academy of Science and the Australian Academy of Technological Sciences and Engineering.

San H. Thang obtained his Ph.D. in 1987 from Griffith University in the field of organic chemistry. In 1986, he joined CSIRO as a Research Fellow and then moved to Imperial Chemical Industries (ICI) Australia Research Group in late 1987 to undertake the challenge of industrial research in UV sunscreens and agrochemicals. He rejoined CSIRO in late 1990 and is currently a Senior Principal Research Scientist, where his research focuses on the interface between organic and polymer chemistry. Dr. Thang has about 100 papers in refereed journals and is responsible for several key inventions in the area of controlled/living radical polymerization. Significantly, he is a co-inventor of the reversible addition–fragmentation chain transfer (RAFT) process.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: graeme.moad@csiro.au (G.M.); ezio.rizzardo@csiro.au (E.R.); san.thang@csiro.au (S.H.T.).

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