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A Guide to the Synthesis of Block Copolymers using Reversible-Addition Fragmentation chain Transfer (RAFT) Polymerization

Daniel J. Keddie*^a

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The discovery of reversible-deactivation radical polymerization (RDRP) has provided an avenue for the synthesis of a vast array of polymers with a rich variety of functionality and architecture. The preparation of block copolymers has received significant focus in this burgeoning research field, due to their diverse properties and potential in a wide range of research environments. This tutorial review will address the important concepts behind the design and synthesis of block copolymers using reversible addition-fragmentation chain transfer (RAFT) polymerization. RAFT polymerization is arguably the most versatile of the RDRP methods due to its compatibility with a wide range of functional monomers and reaction media along with its relative ease of use. With an ever increasing array of researchers that possess a variety of backgrounds now turning to RDRP, and RAFT in particular, to prepare their required polymeric materials, it is pertinent to discuss the important points which enable the preparation of high purity functional block copolymers with targeted molar mass and narrow molar mass distribution using RAFT polymerization. The key principles of appropriate RAFT agent selection, the order of monomer addition in block synthesis and potential issues with maintaining high end-group fidelity are addressed. Additionally, techniques which allow block copolymers to be accessed using a combination of RAFT polymerization and complementary techniques are touched upon.

Key learning points

The mechanistic principle of degenerative chain transfer in the RAFT process

Identify important factors for the selection of an appropriate RAFT agent to control the polymerization of a given monomer

The importance of the relative homolytic leaving group ability of propagating radicals in block copolymer synthesis

Importance of maintaining end-group fidelity for efficient formation of block copolymers

Introduction

The advent of reversible deactivation radical polymerization (RDRP),^{1,2} initiated through the discovery of nitroxide mediated polymerization (NMP)^{2,3} and furthered through the development of atom transfer radical polymerization (ATRP)⁴ and reversible-addition fragmentation chain transfer (RAFT) polymerization,⁵⁻⁸ has instigated a renaissance in the use of free radical polymerization for the preparation of functional polymeric materials. RDRP techniques have provided access to functional polymers with targeted molar mass, narrow molar mass distributions and defined molecular architecture (e.g. block copolymers, gradient copolymers, graft copolymers and stars); properties once thought impossible to obtain via free radical processes.

RDRP allows for the preparation of a broad suite of new polymeric materials due to significantly less stringent reaction conditions than those required for anionic or cationic polymerization techniques, compatibility with a much broader range of functional monomers and reaction conditions. With this,

RDRP has brought renewed focus to the synthesis of block copolymers which, due to the covalent attachment of two (or more) distinctly different polymeric segments, display the microphase separation that gives rise to their unique properties. The applications for block copolymers are diverse with examples including use as surfactants, dispersants, surface modifiers, compatibilizers in polymer melt processing and drug delivery vehicles.^{9,10}

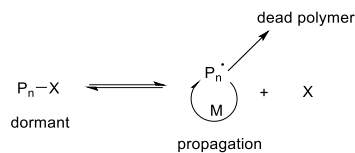
Reversible Deactivation Radical Polymerization

The essence of a RDRP process lies within the partitioning of propagating polymer radicals between active and dormant states through a reversible activation/deactivation equilibrium.

In NMP and ATRP this equilibrium is established through a mechanism of reversible termination of the propagating chain (Scheme 1), through either nitroxide capping (NMP) or via a redox process with a metal halide salt (ATRP), in which the equilibrium strongly favours the dormant species. As radical formation occurs only upon activation of the dormant species, at any given time the concentration of propagating radicals remains low. This

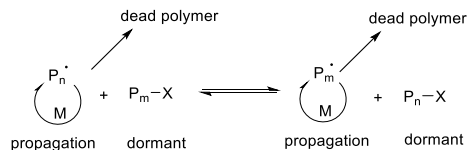
significantly reduces formation of dead polymer by irreversible termination. The random statistical probability of chain activation per active cycle provides the control over molar mass and dispersity observed for these techniques, with the rate of polymerization dictated by the position of the activation/deactivation equilibrium

Scheme 1: Reversible-Deactivation Radical Polymerization by Reversible Termination



The mechanism in which RAFT provides control over a radical polymerization fundamentally differs from that of NMP and ATRP. RAFT proceeds via a degenerative chain transfer process, where the propagating species equilibrate with dormant species (Scheme 2). Other RDRP methods, such as organotellurium-mediated polymerization (TERP),¹¹ also operate via a degenerative chain transfer mechanism. As degenerative chain transfer does not create radicals, the reaction requires addition of an external source of radicals to maintain a constant rate of polymerization. This is commonly in the form of an azo initiator, such as 2,2'-azobisisobutyronitrile (AIBN).

Scheme 2: Reversible-Deactivation Radical Polymerization by Degenerative Chain Transfer



RAFT Polymerization

The Mechanism of the RAFT Process

Degenerative chain transfer in RAFT polymerization is facilitated by a thiocarbonylthio chain transfer (or RAFT) agent **1**, with the RAFT process effectively a swapping of the thiocarbonylthio functionality (ZC(=S)S-), between growing polymer chains.

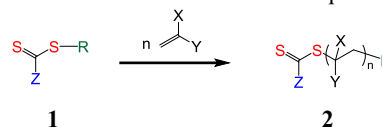


The control over molar mass and dispersity arises through rapid equilibration of chains with respect to the polymerization rate where all chains are apportioned an equal opportunity to grow ($k_{\text{addP}} \gg k_p$ and $k_{\beta} \gg k_p$; see Scheme 4 for definitions of rate constants).

Upon completion of a RAFT polymerization the vast majority of chains will possess a thiocarbonylthio end-group, with the overall process able to be viewed as an insertion of monomer units between the S-R bond of the RAFT agent **1** (Scheme 3) to give a polymer **2**. The (largely) conserved RAFT end-group of **2**, itself a macro-RAFT agent, facilitates the synthesis of block copolymers

through the subsequent polymerization of a second monomer (*vide infra*). Additionally the thiocarbonylthio group provides a functional handle for a variety of post-polymerization modifications.^{12, 13}

Scheme 3: The overall outcome of the RAFT process

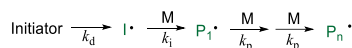


RAFT polymerization is arguably the most versatile of the RDRP processes, with most monomers that polymerize radically able to be controlled via the RAFT process. RAFT controls the polymerization of a broader range of functional monomers than do competing techniques, providing good control over the polymerization of vinyl esters (e.g. vinyl acetate) and vinylamides (e.g. *N*-vinylpyrrolidone), where NMP and ATRP typically provide minimal control. Additionally, RAFT is compatible with a wide variety of reaction media, being routinely applied in organic solution, aqueous solution¹⁴ and in dispersed phase.¹⁵

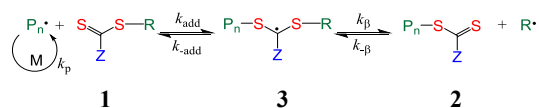
RAFT typically requires minimal process development, with the inclusion of a RAFT agent often the sole deviation from a typical conventional radical polymerization protocol. Indeed the equilibria of the RAFT process (see Scheme 4) are superimposed upon the regular processes of conventional free radical polymerisation. This is a distinct advantage of RAFT over competing technologies and has no doubt contributed to its adoption by industry.

Scheme 4: Equilibria of Reversible-Addition Fragmentation Chain Transfer (RAFT) Polymerization

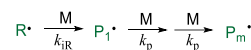
Initiation:



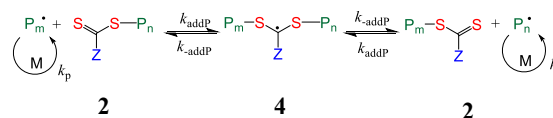
Initialization/Pre-equilibrium:



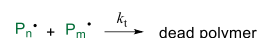
Reinitiation:



Main equilibrium:



Termination:



The RAFT process does not prevent the formation of dead chains formed through termination or irreversible chain transfer but suppresses their significance through the formation of many more, shorter chains compared to a conventional radical polymerization performed under similar conditions.

Since the RAFT process does not alter the radical concentration, the rate of polymerization need not differ from that of conventional free radical polymerization. However, most RAFT agents

generally stray from that ideal, with polymerization often being retarded somewhat, the magnitude of which is dictated by the specific RAFT agent, monomer and reaction conditions used.

The RAFT mechanism begins through the formation of an initiator derived radical (I·) that propagates with monomer (M) to give a polymeric radical (P_n·). In an ideal RAFT polymerization P_n· reacts efficiently with the RAFT agent **1** after which the intermediate **3** fragments to quantitatively give the macro-RAFT agent **2** and the expelled RAFT agent-derived radical (R·), which re-initiates polymerization. In practice however the undesired reverse reaction, which reforms the starting materials P_n· and **1**, occurs to a degree determined by the structure of the RAFT agent **1** and the monomer being polymerized. This can be defined in terms of a partition coefficient (ϕ) which relates to the relative rates of fragmentation of the intermediate **3** to the starting materials, P_n· and **1** (k_{add}), or the products, R· and **2** (k_{β}), through the equation 1,¹⁶⁻¹⁸ the rate constants for which are defined in Scheme 4.

$$\phi = \frac{k_{\beta}}{k_{\text{add}} + k_{\beta}} \quad (1)$$

For the preparation of polymers of low dispersity R· must be a good homolytic leaving group with respect to P_n· (i.e. $\phi \geq 0.5$) and be able to reinitiate polymerization efficiently to prevent rate retardation. The leaving group ability of P_n· is related to the structure of the monomer (M) being polymerized, with k_{add} decreasing in the following order: methacrylates ~ methacrylamides >> styrenics ~ acrylates ~ acrylamides > *N*-vinyl heteroaromatics > vinyl amides ~ vinyl esters. Due to steric factors polymeric R groups are typically better homolytic leaving groups than their monomeric analogues.¹⁸ For example 2-ethylpropionate (C(CH₃)₂CO₂Et), a monomeric analogue of poly(methyl methacrylate) (PMMA), is a poor R group for controlling the polymerization of methyl methacrylate (MMA). General guidelines for the selection of the R group, adapted from previous publications,¹⁸ are shown below (Figure 1).

The pre-equilibrium (or initialization) of the RAFT process concludes when the original RAFT agent **1** (and the derived radical, R·) has been fully consumed. In a well-controlled RAFT polymerization $k_{\beta} > k_{\text{add}}$ and the pre-equilibrium is completed rapidly. The system moves into the main equilibrium relatively early in the reaction, allowing for maximal equilibration of the growing chains, giving polymers of low dispersity.

When developing reaction conditions for a RAFT polymerization, three stoichiometric ratios influence the reaction:

- [M]/[RAFT]: As the amount of RAFT agent determines the number of polymer chains formed, the molar ratio of monomer to RAFT agent determines the theoretical number average

degree of polymerization X_n (calc.) and theoretical number average molar mass M_n (calc.). M_n (calc.) is the theoretical mass that would be obtained in the absence of any undesired reactions, such as termination or irreversible chain transfer. A defined [M]/[RAFT] ratio allows the preparation of polymers with targeted molar mass.

- [RAFT]/[I]: The relative ratio of RAFT agent to initiator influences the functionality at both α and ω chain-ends. That is, at the α chain-end, the number of R-derived chains to initiator-derived chains, and at the ω chain-end the number of thiocarbonylthio-functional dormant chains to dead chains and hence the degree of control over the polymerization. Due to low initiator efficiency and slow rate of initiator decomposition the ratio of dormant thiocarbonylthio chain-ends to dead chains will be greater than that of the initial ratio. Therefore polymers obtained through a RAFT polymerization process will display a higher ratio of dormant chains to dead chains than predicted from [RAFT]/[I].
- [M]/[I]: As with conventional radical polymerization, the ratio between monomer and initiator influences the rate of polymerization.

Many articles in the literature report reaction conditions in terms of these ratios (i.e. [M]/[RAFT]/[I]) but do not give the concentrations of each species in solution. This fails to acknowledge the influence absolute concentration has on the rate of polymerization. Clearly for a given [M]/[RAFT]/[I] ratio a higher absolute monomer (and initiator) concentration will result in a higher rate of polymerization.

Overall the theoretical molar mass, M_n (calc.), of a RAFT synthesized polymer can be calculated using equation 2.¹⁷

$$M_n(\text{calc.}) = \frac{([M]_0 - [M]_t)}{([RAFT]_0 + d f ([I]_0 (1 - e^{-k_d t})))} \times M_M + M_{\text{RAFT}} \quad (2)$$

Where [M]₀ and [M]_t are the concentration of monomer at $t=0$ and $t=t$; [RAFT]₀ is the initial RAFT agent concentration; [I]₀ is the initial initiator concentration; M_M is the molar mass of the monomer; and M_{RAFT} is the molar mass of the RAFT agent.

$d f ([I]_0 (1 - e^{-k_d t}))$ corresponds to the number of initiator-derived chains produced, where d is the average number of chains formed from each radical-radical termination event (determined by the relative prevalence of termination by combination or disproportionation), f is the initiator efficiency (f = rate of initiation of propagating radicals/rate of initiator derived radical formation), t is time in seconds, and k_d is the rate coefficient for initiator decomposition.

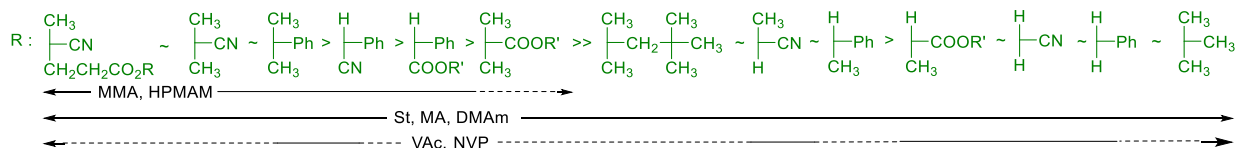


Figure 1: Guidelines for selection of RAFT agent R groups for the polymerization of monomers. Dashed lines indicate partial control over polymerization is achieved (i.e., control over molar mass but poor dispersity control due to inferior homolytic leaving group ability (MMA, HPMAM) or substantial retardation due to slow reinitiation of polymerization (VAc, NVP)). Figure adapted from reference 18.

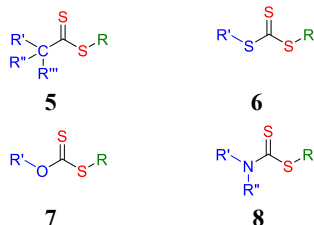
Abbreviations: MMA – methyl methacrylate, HPMAM – *N*-(2-hydroxypropyl) methacrylamide, St – styrene, DMAM – *N,N*-dimethylacrylamide, VAc – vinyl acetate, NVP – *N*-vinylpyrrolidone

For a well-controlled RAFT polymerization, the number of initiator derived chains is low in comparison to [RAFT] and the contribution of the $df([I]_0(1-e^{-k_{tr}}))$ can be neglected, giving the more commonly used expression for the theoretical molar mass, equation 3.

$$M_n(\text{calc.}) \approx \frac{([M]_0 - [M]_t)}{[\text{RAFT}]_0} \times M_M + M_{\text{RAFT}} \quad (3)$$

RAFT Agents: Structural Design and Monomer Compatibility

To obtain optimal control over a RAFT polymerization, selection of a RAFT agent **1** possessing appropriate Z and R group functionality for the monomer in question is of prime importance. The Z-group modifies the reactivity of the thiocarbonyl group towards radical addition and the rate of fragmentation of the RAFT intermediate radical **3**. RAFT agent activity is able to be tuned by varying the Z group, with the most reactive having carbon (dithioesters **5**) or sulphur (trithiocarbonates **6**) adjacent to the thiocarbonyl moiety. RAFT agents possessing oxygen (xanthates **7**) or nitrogen (dithiocarbamates **8**) next to the thiocarbonyl group are typically less reactive towards radical addition.



The activity of a RAFT agent can be defined in terms of a chain transfer coefficient (C_{tr})^{‡‡} which relates to the relative rates of chain transfer (k_{tr}) and propagation (k_p), through equations 4 and 5.¹⁶⁻¹⁸ More active RAFT agents have a higher C_{tr} corresponding to more chain transfer events per propagation cycle. This leads typically to narrower molar mass distributions than less active RAFT agents. For a RAFT polymerization to display a linear increase of M_n with conversion and give polymers of low molar mass dispersity ($D < 1.2$), factors often associated with a well-controlled RDRP process, C_{tr} should be at least 10; the most active RAFT agents have $C_{tr} > 100$.

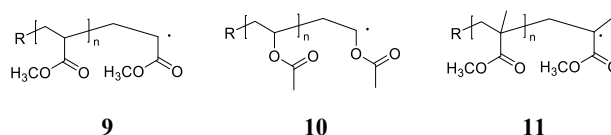
$$k_{tr} = \phi k_{add} \quad (4)$$

$$C_{tr} = \frac{k_{tr}}{k_p} \quad (5)$$

Radically polymerizable monomers can nominally be divided into two general classes; “more-activated monomers” (MAMs) where the vinylic group is conjugated to a neighbouring functionality such as a carbonyl group (i.e. (meth)acrylates, (meth)acrylamides) or an aromatic ring (i.e. styrenes); and the “less-activated monomers” (LAMs) where the vinylic group is adjacent to an electron rich atom, such as oxygen or nitrogen (i.e. vinyl esters, vinylamides)^{‡‡‡}.¹⁹ The classification of a monomer as a MAM or LAM reflects its ability to react in a free radical process; MAMs react more readily with radicals than do LAMs. In this context the relative reactivity of the propagating radicals derived from these

monomers are at odds with these classifications. Due to the enhanced electronic stabilization and often coupled with additional steric factors MAMs produce more-stabilized, less reactive macro-radicals than LAMs. For example, the secondary MAM derived poly(methyl acrylate) propagating radical **9** is less reactive than the LAM derived poly(vinyl acetate) propagating radical **10** (Scheme 5), due to the presence of resonance stabilization of the radical centre of **9** by the proximal carbonyl group. The acetate group adjacent to the radical centre of **10** provides significantly less stabilization, solely through inductive effects, hence **10** is a more reactive radical. Additional steric stabilization on the tertiary MAM-derived poly(methyl methacrylate) propagating radical **11** results in further reduced reactivity when compared to **9**. Understanding the reactivity of the propagating radical formed from a given monomer is key in the selection of an appropriate RAFT agent for control over its polymerization.

Scheme 5. The propagating radicals of methyl acrylate, vinyl acetate and methyl methacrylate



The polymerization of MAMs are generally well controlled through the use of active RAFT agents (high C_{tr}), such as dithioesters **5** (typically dithiobenzoates, PhC(=S)S-R) or *S*-alkyl trithiocarbonates (**6**; $\text{R}'=\text{alkyl}$), as these provide a high rate of reversible chain transfer via addition-fragmentation with respect to propagation. This allows for rapid equilibration of growing polymer chains. Attempts to use these more active RAFT agents to control the polymerization of LAMs generally results in complete inhibition of polymerization as propagation is encumbered by the high rate of addition of reactive propagating radicals, such as **10**, to the thiocarbonyl, coupled with their slow fragmentation from the intermediate **3**. For this reason the RAFT polymerization of LAMs typically uses less active (low C_{tr}) RAFT agents such as *O*-alkyl xanthates (**7**; $\text{R}'=\text{alkyl}$) or *N*-alkyl-*N*-aryldithiocarbamates (**8**; $\text{R}'=\text{alkyl}$, $\text{R}''=\text{aryl}$) as the control agent. The electron rich Z-groups in these RAFT agents donate electrons into the thiocarbonyl group which can be qualitatively rationalised by the zwitterionic resonance contributors **12** and **13** in Scheme 6. This both deactivates the thiocarbonyl towards radical addition and destabilises the RAFT intermediate radical **3**, promoting both monomer propagation and intermediate fragmentation. This results in improved control over the polymerization of LAMs. *O*-alkyl xanthates and *N*-alkyl-*N*-aryldithiocarbamates tend to be relatively inert to MAMs derived propagating radicals, such as **9**, rendering them poor control agents for these monomers. The activity of xanthates and dithiocarbamates in MAMs polymerization may be improved through incorporation of an aromatic ring (i.e. *N*-heteroaromatic dithiocarbamates)²⁰ or electron withdrawing group on the heteroatom.^{21, 22} However these structural alternations may compromise their ability to control LAMs polymerization. General guidelines for the selection of the Z groups, adapted from previous publications,¹⁸ is shown in Figure 2.

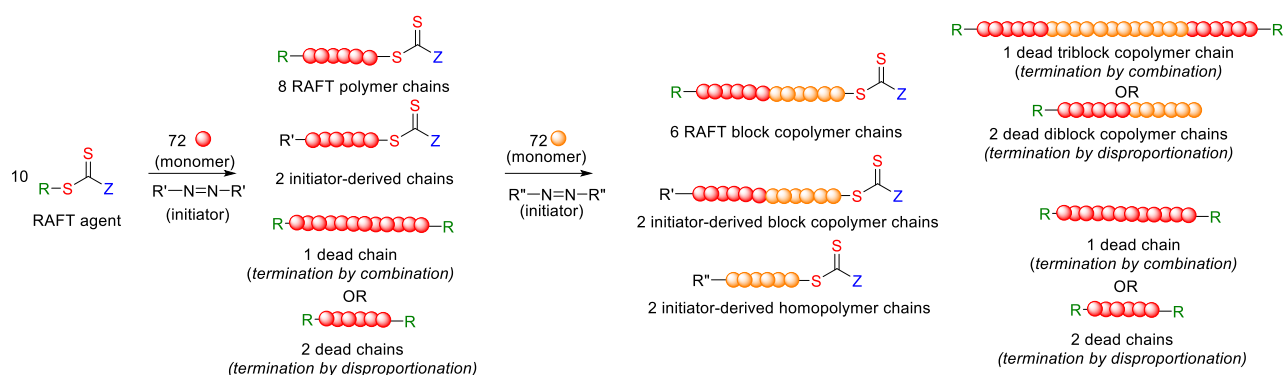


Figure 3: The various polymer species formed during synthesis of block copolymers via stepwise RAFT polymerization ($[M]/[RAFT]/[I]$ for homopolymer and block copolymer synthesis selected as 72/10/1 at full monomer and initiator conversion with initiator efficiency of 1 for illustrative purposes only, typically the defects are in much smaller proportions than shown).

5

there are strict limitations in the range of block copolymers that can be prepared using sequential RAFT polymerization techniques. These limitations are also present when using NMP or ATRP for block copolymer synthesis. The monomer order requirement dictates which materials can be successfully prepared and which cannot. The general requirements for order of monomer addition for successful synthesis of well-defined block copolymers (macro-R group selection) are illustrated in Figure 4.

The radical initiator used to drive RAFT polymerization gives rise to two types of polymer defects that present as impurities in the block copolymer upon chain-extension of the macro-RAFT agent.²⁵ The prevalence of these defects is heavily influenced by the initiator concentration. The use of a low concentration of radical initiator with respect to RAFT agent concentration reduces the incidence of these defects; however a sufficiently high concentration of initiator is required to obtain acceptable rates of polymerization. This varies depending on the identity of the monomer.

The first of these defects is the generation of initiator-derived chains, rather than those generated from the R group. Whilst this can be addressed fairly easily in the synthesis of homopolymers through the use of an initiator that generates the same radical as the R group (i.e. $R=R'$ in Figure 3), it is unavoidable during block copolymer synthesis (i.e. the macro-R group cannot equal R') (see Figure 3).

The second type of defect arising from the initiator is the formation of dead polymer. As decomposition of a radical initiator liberates two radicals, for each radical that escapes the solvent cage and initiates polymerization there is a second radical that forms a

dead chain through irreversible radical termination by either combination or disproportionation (see Figure 3). Dead chains are unable to undergo chain extension and thus remain as impurities in the block copolymer unless they can be removed through purification processes.

To reduce the prevalence of dead chain contaminants in macro-RAFT agents, it is best practice to keep monomer well below full conversion (ca. 70%). As the monomer is depleted and fewer radicals are consumed through initiation, the radicals formed via continued initiator decomposition instead promote more termination. This is exemplified by the process of initiator promoted thiocarbonylthio end-group removal,²⁶ which is akin to conducting a RAFT polymerization at full monomer conversion.

Dead polymer may also form via degradation of the thiocarbonyl group. This can occur during storage and through excessive post-polymerization handling (i.e. hydrolysis during purification), particularly for polymers derived from more active RAFT agents. For this reason it is generally advised that macro-RAFT agents be stored at low temperatures and used for block synthesis as soon as practicable after preparation.

The influence of the dead chains formed during the RAFT process increases with the addition of successive blocks to such a degree that reports of block polymers of low dispersity from more than three successive RAFT polymerizations are rare; the highest number of successive RAFT polymerizations resulting in block copolymers of relatively low dispersity appearing in the literature is currently five.^{27, 28}

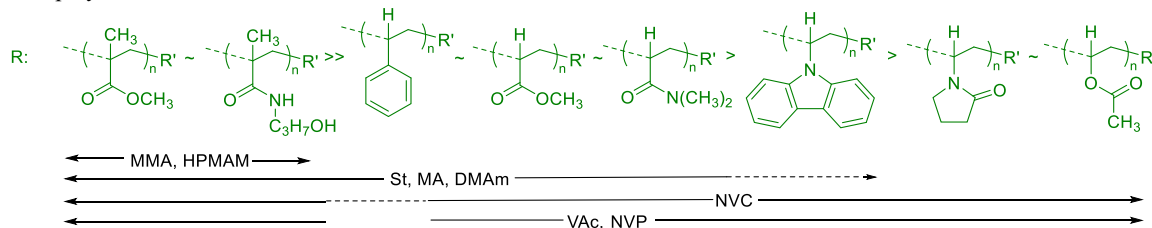
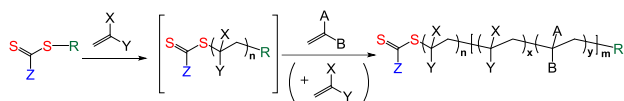


Figure 4: Guidelines for selection of macro-R group for the preparation of block copolymers. Dashed lines indicate partial control over polymerization is achieved (i.e., control over molar mass but poor dispersity control due to inferior homolytic leaving group ability (St, MA, DMAm) or retardation due to slow re-initiation of polymerization (NVC). Abbreviations: MMA – methyl methacrylate, HPMAM – *N*-(2-hydroxypropyl) methacrylamide, St – styrene, DMAm – *N,N*-dimethylacrylamide, NVC – *N*-vinylcarbazole, Vac – vinyl acetate, NVP – *N*-vinylpyrrolidone

Synthesis of Quasi-Block Copolymers by RAFT

Recently, one-pot processes have been developed to prepare quasi-block copolymers with view to industrial application. These processes involve the subsequent addition of a second monomer after an initial RAFT polymerization, without purification of the macro-RAFT agent (Scheme 8). The one-pot protocol has proved successful for the preparation of polymer materials in organic solution,^{29, 30} sequential aqueous solution/emulsion^{30, 31} and in supercritical carbon dioxide.³² The amount of residual monomer from the initial polymerization and the copolymerization reactivity ratios dictate how each of the two monomers are consumed in the second step of quasi-block synthesis (i.e. the formation of a gradient or statistical copolymer as the second block). Defects of the first monomer in the second block may alter the properties of the quasi-block copolymers compared to their pure block counterparts, particularly if the properties of the two monomers vary substantially. Because of this a relatively high conversion of the first monomer, desirable to eliminate structural defects in the second block, must be balanced against the formation of dead chains during the initial polymerization step.

Scheme 8: Synthesis of quasi-block copolymers



Synthesis of Block Copolymers using “Universal” RAFT Agents

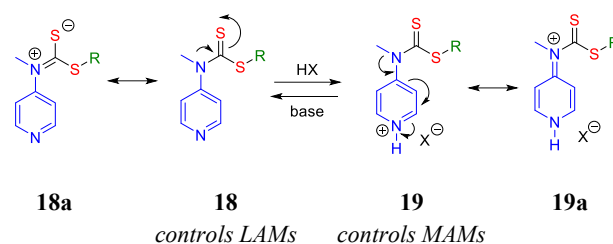
The Z group of RAFT agents determines which monomers they can adequately control (see Figure 2) and therefore the block copolymers they can be used to prepare. The more active dithioesters and trithiocarbonates control the polymerization of MAMs allowing for synthesis of poly(MAM)-*block*-poly(MAM) whilst the less active xanthates and dithiocarbamates control the polymerization of LAMs providing a route to poly(LAM)-*block*-poly(LAM). A drawback to this however is that well-defined block copolymers which display unimodal molar mass distributions whilst incorporating both MAM and LAM units cannot easily be prepared using conventional RAFT agents.

In this context, high level *ab initio* molecular orbital calculations have predicted that a fluorine Z group (F-RAFT agents; **17**) should provide good control over the polymerization of both MAMs and LAMs.³³ Unlike conventional RAFT agent the fluorine Z-group is predicted to destabilize the RAFT intermediate radical **3** promoting its fragmentation, whilst not detrimentally affecting the reactivity of the thiocarbonyl group of the RAFT agent towards radical addition. To date however, experimentation with this class of RAFT agent has been limited, perhaps in part to their challenging synthesis, to the polymerization of styrene³⁴ and ethylene at high temperature and pressure.³⁵ To confirm unequivocally whether F-RAFT agents indeed have the ability to deliver good control over the polymerization of both MAMs and LAMs further experimentation is required.



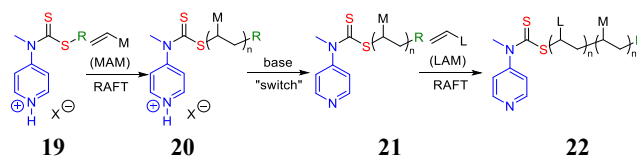
Another approach to the same problem was recently reported where a switchable Z-group, based upon an *N*-methyl-*N*-4-pyridyl dithiocarbamate **18**,^{19, 36-38} was shown to control over the polymerization of both MAMs and LAMs. This new protocol provides a convenient avenue to poly(MAM)-*block*-poly(LAM) block copolymers.^{19, 36, 37} This is achieved through switching the reactivity of the thiocarbonyl group towards propagating radicals between an activated pyridinium form **19** and a deactivated pyridine form **18**. This change in reactivity can be qualitatively rationalized by inspection of the resonance contributors **18a** and **19a** shown in Scheme 9. In the neutral pyridine form **18** the dithiocarbamate nitrogen lone pair donates its electrons into the thiocarbonyl group (**18a**), similar to that shown in Scheme 6.

Scheme 9: Acid/base switchable dithiocarbamate RAFT agents



Thus **18** acts as a typical *N*-alkyl-*N*-aryl dithiocarbamate offering control over the polymerization of LAMs. Upon conversion to the protonated pyridinium form **19**, the lone pair on the dithiocarbamate nitrogen is instead delocalized onto the pyridinium nitrogen (**19a**). This increases the reactivity of the thiocarbonyl group toward radical addition, allowing for the control over MAM polymerization. For successful synthesis of block copolymers using switchable RAFT blocks derived from MAMs must first be polymerized due to the relative homolytic leaving group ability of MAMs and LAMs derived propagating radicals as discussed above (see Figure 4). Experimentally the RAFT agent **19** is formed *in situ* through protonation of **18** with a stoichiometric amount of strong acid. Following MAM polymerization, neutralization of the macro-RAFT agent **20** to **21** with a base allows for the control over the polymerization of a LAM (Scheme 10) to give the desired block **22**. After incorporation of a LAM block, subsequent switching of the Z-group back to the pyridinium form does not allow for addition of further MAM blocks as the LAM-derived macro-R group is a poor radical leaving group in MAMs polymerization. As such the current protocol is effectively a one-way switch.

Scheme 10: Synthetic protocol for block copolymer synthesis via Switchable RAFT

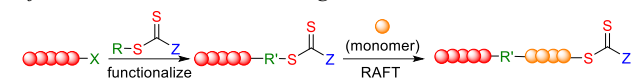


Block Copolymer Synthesis by a Combination of RAFT Polymerization and Complementary Polymerization Techniques

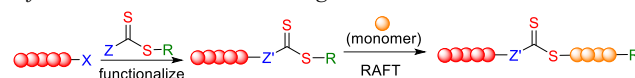
Block copolymers may also be prepared that incorporate a RAFT synthesized block and a block prepared via an alternate synthetic technique. These often arise from complementary non-radical processes. Typically these block copolymers are prepared by thiocarbonylthio functionalization of a pre-synthesized polymer to form a macro-RAFT agent which is subsequently used in a RAFT polymerization. The thiocarbonylthio group may be installed through either the R or Z group (see Scheme 11), with the more hydrolytically stable R-group linkage preferred as hydrolysis of a Z linked system will result in cleavage of the block into its constituent homopolymers. Some typical examples include the chain extension of poly(ethylene glycol), poly(dimethylsiloxane) and polylactide macro-RAFT agents. Specific examples can be found in the comprehensive reviews of Moad et al.⁶

Scheme 11: Synthesis of block copolymers by RAFT polymerization from R or Z thiocarbonylthio functionalized polymers

R-functionalized macro-RAFT agent:



Z-functionalized macro-RAFT agent:



Recently a related one-pot process has been developed where, following anionic polymerization, a macro-RAFT agent is prepared and used to control a RAFT polymerization.³⁹ Examples of a mechanistic change of polymerization for the preparation of block copolymers, where RAFT is used in the synthesis of the first block, have also been recently reported.^{40, 41} These new developments illustrate the complementarity of RAFT with other polymerization techniques, allowing for the precise preparation of new polymer materials.

Preparation of Block Copolymers through Post-RAFT Polymerization Modular Approaches

The synthesis of complex polymeric materials including block copolymers via post-polymerization coupling chemistries, has recently garnered significant research interest in the literature.⁴²⁻⁴⁴ Several quality articles address this topic from a RAFT perspective.⁴⁵⁻⁴⁷

In the broader scientific literature the copper catalyzed azide-alkyne cycloaddition (CuAAC) is seen as the quintessential reaction of this type and it has been broadly applied within a RAFT context.⁴⁵ However, due to the presence of the thiocarbonylthio group which can act as a masked thiol, RAFT polymers lend themselves more specifically towards thiol-based coupling chemistries, such as those shown in Figure 5.^{45, 48} A key advantage of thiol-based chemistries for post-polymerization conjugation is that additional functionality need not be carried through the polymerization process as is the case for the CuAAC. The RAFT-based thiol (R-P_n-SH) is easily accessible by treatment of the

thiocarbonylthio RAFT group with a range of nucleophilic reagents, most commonly an aliphatic amine (see Figure 5). The reaction of the R-P_n-SH with a polymer possessing a thiol-reactive group results in the synthesis of a block copolymer.

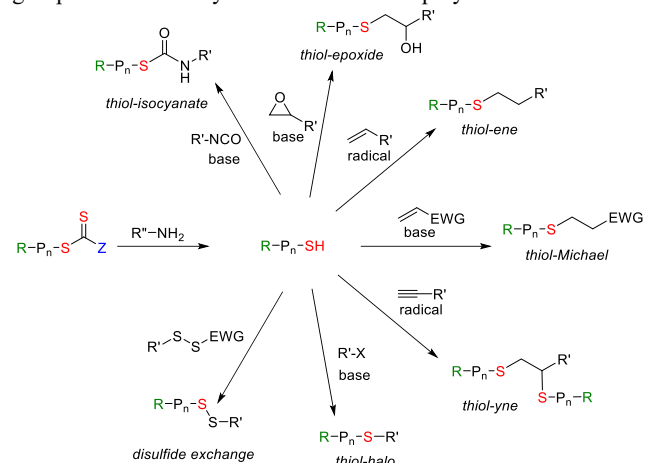
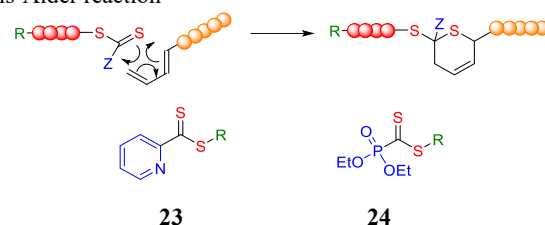


Figure 5: Highly efficient thiol-based coupling chemistries. Abbreviations: EWG – electron-withdrawing group. Figure adapted from references 45 and 46.

An example of a RAFT specific coupling process that can be utilized for the formation of block copolymers is the RAFT hetero Diels-Alder reaction developed by Barner-Kowollik, Stenzel and co-workers.^{49, 50} The process involves the thiocarbonyl group of a RAFT agent reacting in a [4+2]-cycloaddition with a diene (Scheme 12).^{49, 50} For RAFT polymers to successfully undergo this reaction they require a highly electron-deficient thiocarbonyl group, such as is present in the RAFT agents **23** and **24**. This requirement limits the variety of polymers applicable to the process as these RAFT agents are too active to give control over the polymerization of LAMs.

Scheme 12: Formation of block copolymers via the RAFT hetero Diels-Alder reaction



Conclusions

The preparation of well-defined polymers via RAFT demands judicious selection of the RAFT agent R and Z groups. This requires informed correlation of the RAFT agent to the structure of the monomers to be polymerized. Fortunately this information has been accumulated through the combined efforts of many research groups and it is summarised in the guidelines to R and Z selection presented herein.

This tutorial review has addressed several key factors that influence the controlled synthesis of block copolymers using sequential RAFT polymerization. The order in which the monomers are incorporated into the polymer is of prime

importance, with the relative leaving group ability of polymeric radicals dictating which monomer must be introduced first. To best maintain high fidelity of the thiocarbonylthio functionality taking a polymerization to high monomer conversion is strongly discouraged and the use of the lowest practical amount of radical initiator is advised.

Block copolymers may also be prepared by combining a RAFT polymerization with other complementary polymerization techniques, where the RAFT block may be synthesised as either the first or second block. Additionally blocks may be accessed via conjugation of RAFT polymers using various coupling chemistries. Furthermore the recent development of switchable RAFT, which provides a route for synthesis of block copolymers containing both MAM and LAM functionality, has placed RAFT polymerization firmly at the forefront of precision polymer synthesis.

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Notes and references

^a Chemistry, School of Science and Technology, University of New England, Armidale, New South Wales, 2351, Australia.

Fax: +61 2 6773 3268; Tel: +61 2 6773 2912;

E-mail: daniel.keddie@une.edu.au

‡ IUPAC recommendations indicate that the term “living polymerization” be reserved for polymerization processes free from irreversible chain termination or irreversible chain transfer. As such the IUPAC recommended term reversible-deactivation radical polymerization is used throughout this manuscript when referring to radical polymerization processes where the effect of these processes is minimised.

‡‡ There is another transfer coefficient, C_{-tr} ($C_{-tr} = k_{-tr}/k_{tr}$ and $k_{-tr} = k_p\phi(1-\phi)$), which relates to the reverse reaction. During the pre-equilibrium $C_{tr} \neq C_{-tr}$. During the main equilibrium $C_{tr} = C_{-tr}$ and $\phi = 0.5$.

‡‡‡ N-Vinylcarbazole has previously been classified as a LAM, however recent results as per references 29 and 38 indicate it is of intermediate reactivity, being considerably more activated than typical LAMs but less active than typical MAMs.

‡‡‡‡ The overall dispersity of a block copolymer is weighted with respect to the size of each of the blocks which comprise it. Care should be taken when attributing good control over dispersity in a block copolymer synthesis if the mass of the second block is significantly lower than the macro-RAFT agent used during its preparation. Poor control over the polymerization of the second monomer may be masked by the large molar mass discrepancy between the two blocks.

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