Controlled/living radical polymerization: Features, developments, and perspectives

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Abstract

Recent mechanistic developments in the field of controlled/living radical polymerization (CRP) are reviewed. Particular emphasis is placed on structure–reactivity correlations and “rules” for catalyst selection in atom transfer radical polymerization (ATRP), for chain transfer agent selection in reversible addition-fragmentation chain transfer (RAFT) polymerization, and for the selection of an appropriate mediating agent in stable free radical polymerization (SFRP), including organic and transition metal persistent radicals. Novel methods of fine tuning initiation, activation, and deactivation processes for all techniques are discussed, including activators regenerated by electron transfer (ARGET) and initiators for continuous activator regeneration (ICAR) ATRP, whereby Cu catalyst concentrations in ATRP can be lowered to just 10 ppm. Progress made in each technique related to the synthesis of both high and low molecular weight polymers, end functional polymers, block copolymers, expanding the range of polymerizable monomers, synthesis of hybrid materials, environmental issues, and polymerization in aqueous media is thoroughly discussed and compared.

Keywords: Controlled/living radical polymerization; Nitroxide-mediated polymerization (NMP); Stable free radical polymerization (SFRP); Atom transfer radical polymerization (ATRP); Degenerative transfer polymerization; Reversible addition-fragmentation chain transfer (RAFT) polymerization

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1. Introduction

The discovery of living anionic polymerization by Michael Szwarc had a tremendous effect on polymer science [1,2]. His work facilitated major developments in both synthetic polymer chemistry and polymer physics as it opened an avenue to the production of well-defined polymers with precisely designed molecular architectures and nano-structured morphologies [3–11]. His innovations are considered to be the foundation of modern nanotechnology. Additionally, his quantitative descriptions of ion pairing phenomena and electron transfer processes greatly benefited physical organic chemistry [3,12].

The elimination of transfer and termination reactions from chain growth polymerization formed the basis of Szwarc’s discovery. These chain breaking processes were avoided with the development of special high vacuum techniques to minimize traces (<1 ppm) of moisture and air in the anionic polymerization of non-polar vinyl monomers [1,3].
The techniques were first implemented in an academic setting but were quickly adapted on an industrial scale, which ultimately led to the mass production of several commercial products, most notably well-defined block copolymers capable of performing as thermoplastic elastomers [13].

The synthesis of such copolymers by living anionic polymerization demands fast initiation and relatively slow propagation in order that the distribution of block lengths be controlled. These requirements can be achieved with the use of alkyl lithium initiators in non-polar solvents via the formation of ion pairs or their aggregates. The ion pairs can essentially be considered dormant species as they have reactivities several orders of magnitude smaller than those of free ions [12]. Exchange processes between dormant and active species are fast enough in comparison with propagation to ensure the production of materials with low polydispersity [14].

Anionic polymerization was the first and only example of a living process for more than a decade after its realization, but other living techniques have since been discovered. In 1974, two types of active species were observed with spectroscopic techniques in the cationic ring-opening polymerization (CROP) of tetrahydrofuran initiated by triflate esters [15–18]. The activities and exchange dynamics among free ions, ion pairs, aggregates and significantly less active esters were quantitatively measured for growing oxonium cations and the “dormant” esters. Living CROP was subsequently extended to other heterocyclic monomers and eventually enabled the synthesis of many well-defined (co)polymers [19,20].

The possibility of a living cationic vinyl polymerization was once considered highly improbable due to dominating transfer processes and bimodal molecular weight distributions (MWD) typically observed for many systems [cf. 5]. However, it was later realized that since the reactivities of carbocations are much higher than those of carbanions, the exchange reactions were too slow relative to propagation to achieve narrow MWD and controlled MW [6]. The discovery of several techniques enabling fast exchange between growing carbocations and dormant species (esters oronium ions) enabled the development of controlled/living carboxcative polymerization [5,6,21,22]. The activities and selectivities of carbocations in these polymerizations are identical to those in non-living systems [23,24]. However, the equilibria established between growing chains and dormant species allow for a reduction of the overall polymerization rate, thereby extending the life of propagating chains from milliseconds to minutes and providing a route to low MW polymers not significantly affected by transfer processes.

Fast and adjustable equilibria between active and dormant species have enabled the development of many new controlled/living systems, which are discussed in several reviews published throughout this and other accompanying special issues. We now move our discussion from the development of ionic living polymerization methods to the realization of controlled/living radical polymerization (CRP) techniques. In light of the ever-increasing breadth of this field, our review is not intended to be comprehensive. Rather, we aim to highlight structure–reactivity correlations of the catalysts and mediating agents among the various techniques; novel methods of fine tuning initiation, activation, and deactivation processes; and recent progress made towards the synthesis of materials with designed topology, composition, and functionality, expanding the range of polymerizable monomers, environmental issues, and polymerization in aqueous media.

2. Typical features of radical polymerization (RP)

It should be mentioned that Michael Szwarc not only contributed to the development of anionic polymerization but was also involved throughout the 1950s in detailed studies of radical processes [25–32]. Indeed, while living anionic vinyl polymerization was being discovered and developed, conventional radical polymerization was already flourishing. Many new products were commercialized, and a comprehensive theory of radical polymerization was developed [33–37], including a precise characterization of the active species involved, a detailed mechanistic description of all elementary reactions, kinetic and thermodynamic parameters for the relevant rate constants, and a structure–reactivity correlation (Q–e scheme). These studies included Szwarc’s quantitative evaluation of bond dissociation energies and his investigation of the dynamics of radical exchange via a so-called methyl transfer process [29–31]. He also studied carbon–halogen bond dissociation energies [25,27], of particular relevance to atom transfer radical polymerization (ATRP). There were some attempts during this time to control the overall radical...
polymerization rate (via retardation/inhibition) \[34,38\] and molecular weights (with transfer/telemerization) \[39\], but free radical polymerization essentially could not control MW or MWD and could not yield block copolymers due to the very short lifetime of the growing chains (∼1 s).

The active species in RP are organic (free) radicals. They are typically sp² hybridized intermediates and therefore show poor stereoselectivity. However, polymers formed by RP do show good regio- and chemoselectivity, as evidenced by the high degree of head-to-tail structures in the chain and the formation of high MW polymers, respectively. Radicals can be stabilized by resonance and to a lesser degree by polar effects. They can be electrophilic or nucleophilic and in some instances possess a moderate tendency to alternate during copolymerization.

RP, like any chain polymerization, is comprised of four elementary reactions: initiation, propagation, transfer, and termination. Under steady state conditions, the initiation rate is the same as the rate of termination (i.e., ∼1000 times slower than the propagation rate). Such a slow initiation can be accomplished by using radical initiators with appropriately long half lifetimes (e.g., ∼10 h). At the end of a polymerization, unreacted initiator is often left in the reaction mixture. The chain building reaction of propagation occurs by radical addition to the less substituted C atom in a monomer (resulting in head-to-tail polymers) with rate constants \( k_p \sim 10^3 \text{ M}^{-1} \text{ s}^{-1} \) (\( k_p \) for acrylates > \( 10^4 \text{ M}^{-1} \text{ s}^{-1} \) and for butadiene < \( 10^2 \text{ M}^{-1} \text{ s}^{-1} \)). In contrast to carbocationic polymerization, transfer is \emph{not} the main chain breaking reaction in RP, and high MW polymers can be formed from most monomers. Transfer has a higher activation energy than propagation and becomes more important at higher temperatures. The bimolecular radical coupling/disproportionation termination reactions are very fast, essentially diffusion controlled (\( k_t > 10^8 \text{ M}^{-1} \text{ s}^{-1} \)), in contrast to ionic polymerization where electrostatic repulsion prevents a reaction between two cations or two anions. In order to grow long chains in RP, the termination rate \( ( \text{not rate constant}) \) must be much slower than propagation. Since termination is a 2nd-order reaction with respect to radical concentration while propagation is 1st-order, the rate of termination becomes slower than that of propagation at very low radical concentrations. Consequently, the radical concentration must be in the range of ppm or even ppb.

Because the average life of a propagating chain is ∼1 s, which constitutes ∼1000 acts of propagation with a frequency ∼1 ms, the life of a propagating chain is too short for any synthetic manipulation, end functionalization, or addition of a second monomer to make a block copolymer. The overall kinetics can be described by Eq. \((1)\), where the rate of polymerization is a function of the efficiency of initiation \( (j) \) and the rate constants of radical initiator decomposition \( (k_d) \), propagation \( (k_p) \) and termination \( (k_t) \) according to

\[ R_p = k_p[M](f k_d[I]_o/k_t)^{1/2}. \] (1)

The propagation rate scales with a square root of the radical initiator concentration and its efficiency of initiation (typically in the range of 50–80\%). Molecular weights depend on the termination (=initiation) rate as well as the rate of transfer. When the contribution of transfer can be neglected, the degree of polymerization depends reciprocally on the square root of radical initiator concentration, as shown in

\[ \text{DP}_n = k_p[M](f k_d[I]_o/k_t)^{-1/2}. \] (2)

Conventional RP can be carried out in bulk monomer, in solution, and also in dispersed media (suspension, emulsion, miniemulsion, microemulsion and inverse emulsion). Solvents should not contain easily abstractable atoms or groups, unless low MW polymers are desired. The range of reaction temperatures is quite large (−100 to >200 °C). Monomers are sufficiently reactive when the generated radicals are stabilized by resonance or polar effects (styrenes, (meth)acrylates, (meth)acrylamides, acrylonitrile, vinyl acetate, vinyl chloride and other halogenated alkenes). Due to its lower reactivity, ethylene polymerization requires high temperatures. However, it is accompanied by transfer under these conditions that leads to (hyper)branched polymers. Initiators are typically peroxides, diazenes, redox systems and high-energy sources which slowly produce initiating radicals (\( k_d \sim 10^{-5} \text{ s}^{-1} \)).

The industrial significance of conventional RP is evident in the fact that it accounts for the production of ∼50% of all commercial polymers. Low density polyethylene, poly(vinyl chloride), polystyrene and its copolymers (with acrylonitrile, butadiene, etc.), polyacrylates, polyacrylamides, poly(vinyl acetate), poly(vinyl alcohol) and fluorinated polymers comprise the most important of these materials. However, no pure block copolymers...
and essentially no polymers with controlled architecture can be produced by conventional RP.

3. New controlled/living radical polymerization (CRP)

Weak intramolecular interactions among polymer chains can be exploited to form organized nanostructured materials, provided the polymers have uniform dimensions, topologies, compositions and functionalities. Following developments in anionic polymerization by Michael Szwarc, precise control over polymeric structural parameters prepared by RP has given rise to a virtually unlimited number of new polymeric materials. The improved macroscopic properties of many of these polymers are a direct result of comprehensive structure–property investigations as well as guidelines based on theoretical and empirical predictions, as will be discussed.

3.1. Fundamentals of CRP

Such precise macromolecular synthesis employs concepts of living polymerization, in which the contribution of chain breaking reactions is minimized and the apparent simultaneous growth of all chains can be achieved via nearly instantaneous initiation. A combination of fast initiation and an absence of termination seemingly conflicts with the fundamental principles of RP, which proceeds via slow initiation and in which all chains are essentially dead at any given instant. However, the development of several controlled/living radical systems utilizing an intermittent formation of active propagating species has recently been realized concurrent with similar developments in anionic, cationic, coordination and ring-opening polymerization systems (cf. other reviews in this and other accompanying special issues).

The establishment of a dynamic equilibrium between propagating radicals and various dormant species is central to all CRP systems [40,41]. Radicals may either be reversibly trapped in a deactivation/activation process according to Scheme 1, or they can be involved in a “reversible transfer”, degenerative exchange process (Scheme 2).

The former approach relies on the persistent radical effect (PRE) [41–44]. The PRE is a peculiar kinetic feature which provides a self-regulating effect in certain CRP systems. Propagating radicals $P_n^*$ are rapidly trapped in the deactivation process (with a rate constant of deactivation, $k_{\text{deact}}$) by species $X$, which is typically a stable radical such as a nitroxide [45,46] or an organometallic species such as a cobalt porphyrin [47]. The dormant species are activated (with a rate constant $k_{\text{act}}$) either spontaneously/thermally, in the presence of light, or with an appropriate catalyst (as in ATRP) to reform the growing centers. Radicals can propagate ($k_p$) but also terminate ($k_t$). However, persistent radicals ($X$) cannot terminate with each other but only (reversibly) cross-couple with the growing species ($k_{\text{deact}}$). Thus, every act of radical–radical termination is accompanied by the irreversible accumulation of $X$. Its concentration progressively increases with time, following a peculiar $\frac{1}{3}$ power law (vide infra). Consequently, the concentration of radicals as well as the probability of termination decreases with time. The growing radicals then predominantly react with $X$, which is present at $>1000$ times higher concentration, rather than with themselves.

In systems obeying the PRE, a steady state of growing radicals is established through the activation–deactvation process rather than initiation–termination as in conventional RP. These systems include stable free radical polymerization (SFRP), or more precisely, nitroxide mediated polymerization (NMP) and cobalt mediated radical polymerization (CMRP). Such techniques require a stoichiometric
amount of mediating species, as all dormant chains are capped by the trapping agent. ATRP also operates via the PRE. However, in this catalytic process employing atom (or group) transfer between growing chains and a redox active catalyst, the amount of transition metal catalyst can often be sub-stoichiometric.

By contrast, systems employing degenerative transfer are not based on the PRE. Such systems follow typical RP kinetics with slow initiation and fast termination. The concentration of transfer agent is much larger than that of radical initiators. Thus, the transfer agent plays the role of the dormant species. Monomer is consumed by a very small concentration of radicals which can terminate but also degeneratively exchange with the dormant species.

Fast exchange among active and dormant species is required for good control over molecular weight, polydispersity and chain architecture in all CRP systems. A growing species should ideally react only with a few monomer units (within a few milliseconds) before it is deactivated to the dormant state (where it remains for several seconds). The lifetime of a chain in the active state in a CRP process is comparable to the lifetime of a propagating chain in conventional RP. However, because the whole propagation process may take \( \approx 1 \) d in CRP, there exists the opportunity to carry out various synthetic procedures, including chain-end functionalization or chain extension [48].

3.2. Similarities and differences between RP and CRP

CRP and RP proceed via the same radical mechanism, exhibit similar chemo-, regio- and stereo-selectivities, and can polymerize a similar range of monomers. However, several important differences between CRP and RP exist as summarized below.

1. The lifetime of growing chains is extended from \( \approx 1 \) s in RP to more than 1 h in CRP through the participation of dormant species and intermittent reversible activation.
2. Initiation is slow and free radical initiator is often left unconsumed at the end of a conventional RP. In most CRP systems, initiation is very fast and near instantaneous growth of all chains can be achieved, which ultimately enables control over chain architecture.
3. Nearly all chains are dead in RP, whereas in CRP the proportion of dead chains is usually \(< 10\%\).
4. Polymerization in CRP is often slower than in RP. However, the rates may be comparable in certain cases (e.g., when the targeted MW in CRP is relatively low).
5. A steady state radical concentration is established in RP with similar rates of initiation and termination, whereas in CRP systems based on the PRE, a steady radical concentration is reached by balancing the rates of activation and deactivation.
6. Termination usually occurs between long chains and constantly generated new chains in RP. In CRP systems based on the PRE, all chains are short at the early stages of the reaction and become progressively longer; thus, the termination rate significantly decreases with time. In DT processes, new chains are constantly generated by a small amount of conventional initiator, and therefore termination is more likely throughout the reaction.

4. CRP by stable free radical polymerization (SFRP)

4.1. Basic mechanism

Reports by Georges in 1993 of a controlled polymerization of styrene in the presence of benzoyl peroxide and the mediating stable free radical TEMPO (2,2,6,6-tetramethyl-1-piperidynyl-N-oxy) ushered in the dawn of modern CRP [45]. Polystyrene molecular weights evolved linearly with conversion and polydispersities were below 1.3 in this reaction, conducted at 120 °C. Despite earlier attempts reported in the patent literature [49], this was the first example of a successful CRP utilizing a nitroxide-based system.

Control in NMP is achieved with dynamic equilibration between dormant alkoxyamines and actively propagating radicals (Scheme 3). In order to effectively mediate polymerization, TEMPO (and other stable free radicals) should neither react with itself nor with monomer to initiate the growth of new chains, and it should not participate in side reactions such as the abstraction of \( \beta \)-H atoms. These persistent radicals should also be relatively stable, although their slow decomposition may in some cases help maintain appropriate polymerization rates.
TEMPO and its derivatives form a relatively strong covalent bond in alkoxyamines. The SFRP equilibrium constant (ratio of dissociation \(k_d\) to cross-coupling/association \(k_c\) rate constant) is generally very small, i.e., \(k_d/k_c = K_{eq} \approx 1.5 \times 10^{-11}\) M at 120°C for styrene [41]. The values of \(K_{eq}\) are often so low that in the presence of excess TEMPO, the equilibrium becomes very strongly shifted towards the dormant species and significantly reduces the polymerization rate. While original TEMPO-based systems were successful at controlling the polymerization of styrene and some of its copolymers, they failed to mediate polymerization of acrylates and several other monomers for this reason.

Polymerization could in principle be accelerated (i.e., the concentration of growing radicals could be increased) if the concentration of TEMPO were reduced. This might be accomplished by the slow self-destruction of nitroxide by a reaction with additives or initiating radicals [50–52]. This occurs spontaneously in the polymerization of styrene due to thermal self-initiation at elevated temperatures.

4.2. Mediating species/initiation systems

4.2.1. Nitroxides as persistent radicals

As indicated, TEMPO efficiently mediates styrene polymerization under the appropriate conditions but fails to mediate polymerization of other monomers with lower equilibrium constants. Other nitroxides were thus synthesized in an effort to provide more labile C–O bonds. Three exemplary nitroxide structures are illustrated in Fig. 1. Numerous derivatives of these structures have been successfully employed in NMP [46]. DEPN [52,53] (also known as SG-1) and TIPNO [54] contain H-atoms at the α-C. Such nitroxides were originally predicted to be very unstable and assumed to quickly decompose. However, they can both sufficiently mediate polymerization of styrene, as well as various other monomers. Bulkier nitroxides can decrease the bond dissociation energy of C–O bonds formed during polymerization, which consequently increases the proportion of radicals during a polymerization and enables lower polymerization temperatures.

Significant steric bulk was introduced to a TEMPO derivative at the 2,2,6,6- substituents with \(trans\)-2,6-diethyl-2,6-bis(1-trimethylsilanoloxylethyl)-1-(1-phenylethoxy) piperidine-N-oxyl (TEMPO-TMS) [55,56]. The steric effects of this bulk so effectively decrease the bond dissociation energy of the alkoxyamine that polymerization of butyl acrylate can be successfully mediated at temperatures as low as 70°C. However, further increasing steric hindrance by substituting the methyl group α to the TMSO unit with an isopropyl group actually significantly reduces control, likely by slowing the rate of association too much [55].

Steric effects actually prevent the successful control of methacrylate polymerization mediated by nitroxides. Reactive nitroxides prefer to abstract β-H atoms rather than form alkoxyamines. Less reactive nitroxides do not cross-couple rapidly enough with growing chains to efficiently control methyl methacrylate (MMA) polymerization [57,58]. One solution to this problem involves copolymerizing a small amount of styrene with MMA. Just 10 mol% styrene has been sufficient to control such copolymerizations [59]. However, further development of nitroxides stabilized by resonance and polar effects will be needed to
achieve control in homopolymerizations of pure methacrylates.

4.2.2. Alkoxyamine unimolecular initiators

SFRP systems can be initiated in two different ways. Conventional radical initiators can be used in the presence of persistent radicals, as discussed above. Alternatively, dormant species can be prepared in advance and used as initiators (so-called unimolecular initiators) [60,61] or macroinitiators for block copolymerization. The structure of these species is based on the alkoxyamine functionality generated at the chain end during NMP. The thermally unstable C–O bond decomposes upon heating to give the initiating species. These well-defined unimolecular initiators permit much better control over polymer molecular weight and architecture than the aforementioned nitroxide persistent radicals used in conjunction with free radical initiators [62].

The exploitation of alkoxyamines was originally limited by a lack of efficient synthetic procedures for their preparation, procedures which often resulted in low yields and a wide range of byproducts [46,60]. However, several versatile techniques have since been developed that involve the controlled generation and trapping of carbon centered radicals, including single electron transfer reactions associated with ester enolates [63] and enolate anions [64]. Another simple method involves halogen abstraction from alkyl halides by a Cu catalyst via atom transfer radical addition, and subsequent trapping of the alkyl radical by an excess of nitroxide persistent radical (Scheme 4) [65].

4.2.3. Other organic mediators

Additional organic compounds that have been used to successfully mediate SFRP of several vinyl monomers include derivatives of triazolinyl, [66] (arylazo)oxy [67], borinate [68], and verdazyl [69] radicals as well as thermolabile bulky organic alkanes [70,71] and photolabile alkyl dithiocarbamates (Fig. 2) [72].

Alkyl dithiocarbamates, originally used by Otsu, can be homolytically cleaved when irradiated by UV light [73]. Unfortunately, dithiocarbamyl radicals not only cross-couple but also dimerize and initiate extra chains in addition to mediating SFRP. However, dithiocarbamates were recently used as

![Scheme 4](image)

![Fig. 2](image)
successful moderators of vinyl acetate polymerization, although the mechanism of control is not based on the SFRP principle but rather follows a degenerative transfer mechanism (cf. below) [73–76].

4.2.4. Metal mediated polymerization

Transition metal compounds that can mediate radical polymerization include those based on Co [47], Mo [77], Os [78], and Fe [79]. Controlled polymerization of methyl acrylate with Co porphyrins is one of the most successful SFRP systems, having produced well-defined high molecular weight polyacrylates. Recently, Co(acac)$_2$ derivatives were used to control the polymerization of vinyl acetate and $N$-vinylpyrrolidone (Fig. 3a) [80–83]. Co-porphyrin and glyoxime derivatives do not control the SFRP of methacrylates but rather lead to very efficient catalytic chain transfer processes (Figs. 3b and c) [84].

4.3. Re-evaluation of the persistent radical effect

SFRP and ATRP systems are characterized by unusual non-linear semilogarithmic kinetic plots that obey a peculiar power law. These kinetics were first elegantly explained by Fischer [42], who introduced the concept of the persistent radical effect in both organic reactions and macromolecular systems. As mentioned above, stable persistent radicals do not terminate, and hence their concentration progressively increases with the reaction time, shifting the equilibrium in Scheme 3 towards the dormant species. Fischer, and later Fukuda, derived precise kinetic equations to correlate the amount of evolved persistent radical with the overall equilibrium and termination rate constants [41,42].

The essence of the PRE can be more clearly explained for systems not complicated by propagation ($k_p$). Such a system, shown in Scheme 5, is simplified into three elementary reactions: dissociation (activation) of the alkoxyamine $R-Y$ ($k_d$), cross-coupling (deactivation) of the transient radical $R$ with persistent radical $Y$ ($k_c$), and termination of two transient radicals to form product $P$ ($k_t$).

In this case, the rates of formation of the persistent radical and of loss of the transient radical are given by the expressions in Eq. (3) (where the term $2k_t$ is used because a single termination step consumes two radicals)

$$\frac{dY}{dt} = k_c I - k_c Y - 2k_t R^2,$$

$$\frac{dR}{dt} = k_d I - k_c Y = \frac{dR}{dt} + 2k_t R^2.$$  (3)

The two coupled differential equations were solved analytically by Fischer and independently by Fukuda. Both proposed that the increase in concentration of deactivator ($Y$) should be proportional to $t^{1/3}$ and the loss of transient radical ($R$) proportional to $t^{-1/3}$ according to

$$Y = (6k_t K_{eq} I_0)^{1/3} t^{1/3},$$

$$R = \left( \frac{k_{eq} I_0}{k_c} \right)^{1/3} t^{-1/3}.$$  (4)

The dependence for the persistent radical $Y$ should be valid in the time interval defined by Eq. (5), and Eq. (6) should be fulfilled

$$I_L = \frac{4\sqrt{k_t K_{eq}}}{3I_0^{1/2} k_d^{3/2}} < t < I_U = \frac{I_0}{48K_{eq} k_d},$$

$$K_{eq} < I_0 k_c / 16k_t.$$  (5)

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$$K_{eq} < I_0 k_c / 16k_t.$$  (6)
The dependences described in Eq. (3), derived independently by Fischer and Fukuda, used initial concentration of the initiator \((I_0)\) rather than the actual one, \(I\). However, initiator concentration constantly decreases with the progress of the reaction in all radical systems. It is therefore more accurate to use the actual concentration of the initiator to derive the kinetic equations for transient and persistent radicals, especially when reactions proceed to higher conversion. A new equation for the evolution of persistent radical during the quasi-equilibrium stage was therefore derived [44].

The derivation is based on the stoichiometric requirement that the amount of persistent radical is equivalent to the number of dead chains, i.e., \(I_0 - I = Y\), and the assumption that change in the persistent radical concentration is much higher than that for the propagating radicals \((dY/dt > > -dR/dt)\) after quasi-equilibrium is established.

Using variable \(I\), the integration of Eq. (3) leads to the following expression:

\[
\frac{I_0^2}{I_0 - Y} + 2I_0 \ln \frac{I_0 - Y}{I_0} - (I_0 - Y) = 2k_t K_{eq} t,
\]

where the persistent radical concentration \((Y)\) is the only variable on the left-hand side of the equation. In a new function \(F(Y)\), the only variable is \(Y\)

\[
F(Y) = \frac{I_0^2}{I_0 - Y} + 2I_0 \ln \frac{I_0 - Y}{I_0} - (I_0 - Y).
\]

A plot of \(F(Y)\) vs. \(t\) provides a straight line with a slope \(2k_t K_{eq}\). The equilibrium constants for SFRP could then be calculated as \(K_{eq} = (\text{slope}/2k_t)^{1/2}\).

The new equations were compared with Fischer’s original equations. Calculated values of \(Y\) using both equations are plotted vs. time alongside simulated values in Fig. 4. They correspond to alkoxyamine based on styrene and DEPN (1-phenylethyl-DEPN) at 120 °C [58]. The data calculated from the new equation matches perfectly the simulation once the system reaches quasi-equilibrium, while the plot from Fischer’s equation deviates from simulated values. The apparent deviation (>30%) at long reaction times is better illustrated on a linear time scale (Fig. 5).

As shown in Fig. 4, Fischer’s equation is valid only for a short time period. This period (40–400 s) is much shorter than the time range proposed by Fischer (5.9 s~1.0 × 10³) [42]. The new equation does not have an “upper time limit” and is valid from the moment the system reaches quasi-equilibrium, till essentially infinite time.

Fig. 4. Evolution of concentrations of all species (solid lines) and concentrations of persistent radical predicted from the new derivations \((\square)\) and Fischer’s equation \((\circ)\); \(k_d = 0.01 \text{s}^{-1}\), \(k_c = 5 \times 10^5 \text{M}^{-1} \text{s}^{-1}\), \(k_t = 2.5 \times 10^9 \text{M}^{-1} \text{s}^{-1}\), \(I_0 = 0.05 \text{M}\). \(K_{eq}\) (calc.) = 2.0 × 10⁻⁸ M [85].

Fig. 5. Simulated and calculated concentrations of persistent radical derived from the new equation and Fischer’s equation; \(k_d = 0.01 \text{s}^{-1}\), \(k_c = 5 \times 10^5 \text{M}^{-1} \text{s}^{-1}\), \(k_t = 2.5 \times 10^9 \text{M}^{-1} \text{s}^{-1}\), \(I_0 = 0.05 \text{M}\). \(K_{eq}\) (calc.) = 2.0 × 10⁻⁸ M. \(Y\) is the persistent radical concentration [85].

4.4. Additional considerations

Many stable free radical polymerizations are conducted in bulk or homogeneous solutions, but heterogeneous systems can also be successful. Both miniemulsion and emulsion polymerizations were well controlled with TEMPO and SG-1 [86]. While lower temperature SFRP processes have been reported (e.g., methyl acrylate can be initiated using the azo-initiator V-70 and mediated by Co-porphyrins at <60 °C), elevated temperatures are generally...
required for TEMPO mediated emulsion polymerizations (above 100 °C). As this exceeds the boiling point of water, pressurized equipment is required for such systems.

A noteworthy side reaction that occurs in NMP of styrene involves reduction of the mediating radical to give the corresponding hydroxylamine via hydrogen transfer from the chain end [87]. This reaction can affect the molecular weight distribution of the product and results in unsaturated dead polymer chains [88]. This side reaction can be minimized with the use of nitroxides such as TIPNO that do not require the long reaction times and high temperatures that TEMPO does.

5. Principles of atom transfer radical polymerization (ATRP)

5.1. Mechanism and components

The efficient ATRP catalyst consists of a transition metal species (Mt) which can expand its coordination sphere and increase its oxidation number, a complexing ligand (L), and a counterion which can form a covalent or ionic bond with the metal center. The transition metal complex (Mt/L) is responsible for the homolytic cleavage of an alkyl halogen bond RX which generates the corresponding higher oxidation state metal halide complex Mt+1X/L (with a rate constant kact) and an organic radical R• (Scheme 6) [89,90]. R• can then propagate with vinyl monomer (kp), terminate as in conventional free radical polymerization by either coupling or disproportionation (kt), or be reversibly deactivated (kdeact) in this equilibrium by Mt+1X/L to form a halide-capped dormant polymer chain. Radical termination is diminished in ATRP as a result of the PRE [42,43], and the ATRP equilibrium (KATRP = kact/kdeact) becomes strongly shifted towards the dormant species (rate constant of activation < rate constant of deactivation). Values illustrated in Scheme 6 refer to a styrene polymerization at 110 °C [91,92].

ATRP originates from a widely used reaction in organic synthesis known as atom transfer radical addition (ATRA) [93,94]. In this technique, atom transfer from an organic halide to a transition metal complex occurs to “activate” organic radicals, which are then quickly “deactivated” by back-transfer of the atom from the transition metal to the organic radical species. It has been debated whether the intermediate radicals are truly free radicals, in a solvent cage, or somehow under the influence of the metal center [95,96], all of which could have profound implications on structure–reactivity relationships in ATRP (vide infra). However, abundant support has confirmed that the dominant intermediates in these processes are indeed free radicals. This support includes: (1) similar reactivity ratios in conventional free radical and atom transfer radical copolymerization [97–101]; (2) the effects (or lack thereof) of added reagents such as protic solvents, radical scavengers, and transfer reagents [102]; (3) the atacticity of the polymers generated in ATRP [103–105]; (4) the concurrent formation of the higher oxidation state metal species during the reaction [106,107]; (5) similar rates of racemization, exchange, and trapping reactions in RP and ATRP [108,109]; (6) the direct ESR observation of radicals during ATRP gelation experiments [110]; and (7) indistinguishable 13C kinetic isotope effects between RP and ATRP [111].

ATRP has been successfully mediated by a variety of metals, including those from Groups 4 (Ti [112]), 6 (Mo [77,113,114]), 7 (Re [115]), 8 (Fe, [116–119] Ru, [120,121] Os [78]), 9 (Rh, [122] Co [123]), 10 (Ni, [124,125] Pd [126]), and 11 (Cu [89,127]). Complexes of Cu have been found to be
the most efficient catalysts in the ATRP of a broad range of monomers in diverse media. One advantage of ATRP over other CRP processes is the commercial availability of all necessary ATRP reagents (alkyl halides, ligands and transition metals). Additionally, the dynamic equilibrium between dormant species and propagating radicals can be easily and appropriately adjusted for a given system by modifying the complexing ligand of the catalyst [89]. Commonly employed nitrogen-based ligands used in conjunction with Cu ATRP catalysts include derivatives of bidentate bipyridine (bpy) [127,128] and pyridine imine [129,130], tridentate diethylenetriamine (DETA) [131], and tetradaentate tris[2-aminoethyl]amine (TREN) [132] and tetraaza-zacyclotetradecane (CYCLAM) [133], among many other multidentate ligands [134,135]. The counterion is very often a halide ion, but pseudohalides, carboxylates and non-coordinating triflate and hexafluorophosphate anions have also been used successfully [136–138].

A very important difference between SFRP and ATRP is that in the latter case, kinetics and control depend not only on the persistent radical (Mt\textsuperscript{\textit{n+1}}X/L) but also on the activator (Mt\textsuperscript{n}/L). Molecular weights are defined by the ratio \(\Delta [M]/[RX]_0\) and are not affected by the concentration of transition metal. The polymerization rate increases with initiator concentration and actually depends on the ratio of activator to deactivator concentration according to

\[
R_p = -\frac{d[M]}{dt} = k_p[M][P^*] = k_p[M]K_{\text{ATRP}}[RX][Mt^n/L]/[Mt^{n+1}X/L]).
\]  

One of the perceived limitations of metal mediated SFRP is that a stoichiometric amount of metal species is required per polymer chain. Eq. (9) suggests the absolute amount of metal catalyst in ATRP can be decreased without affecting the rate of polymerization, which is governed by a ratio of the concentrations of Mt\textsuperscript{n}/L–Mt\textsuperscript{n+1}X/L. However, the synthesis of polymers with low polydispersities and predetermined molecular weights require a sufficient concentration of deactivator according to [139]

\[
PDI = \frac{M_w}{M_n} = 1 + \frac{1}{DP_n} + \left(\frac{[RX]_0k_p}{k_{\text{deact}}[Mt^{n+1}X/L]}\right)\left(\frac{2}{\text{Conv.}} - 1\right).
\]  

Polydispersities become smaller with increasing monomer conversion, increasing deactivator concentration, and decreasing \(k_p/k_{\text{deact}}\) ratio according to Eq. (10). Catalysts with sufficiently high values of \(k_{\text{deact}}\) can therefore be used in lower concentrations and still provide control over PDI. However, the absolute amount of metal species in ATRP cannot be decreased indefinitely. The Mt\textsuperscript{n}/L deactivator accumulates as a persistent radical [140] due to unavoidable termination events, and the amount of Mt\textsuperscript{n}/L activator lost to termination reactions is equal to the amount of terminated chains according to

\[
-\Delta [Mt^n/L] = \Delta [Mt^{n+1}X/L] = \Delta [P_{\text{dead}}] = k_t\int [P^*]^2dt.
\]

If the total amount of transition metal activator does not exceed the concentration of those chains which terminate, polymerization will halt at low conversion because all of the catalyst will be present as a persistent radical.

5.2. Structure–reactivity relationships

5.2.1. Understanding the ATRP equilibrium

Understanding why some monomers such as acrylonitrile are very active in ATRP and others such as vinyl acetate are virtually inactive requires an in depth knowledge of the factors and conditions which affect \(K_{\text{ATRP}}\).

Quantifying \(K_{\text{ATRP}}\): Critical evaluation of the catalytic activity of a given complex in ATRP generally requires that the \(K_{\text{ATRP}}\) value be determined experimentally. This can accurately be accomplished for a wide range of \(K_{\text{ATRP}}\) values now that precise equations describing the PRE have been derived (vide supra) that take into account the fact that concentrations of the activator and the initiator do not remain constant throughout the reaction. A simple method for determining \(K_{\text{ATRP}}\) involves reacting an alkyl halide with the transition metal activator and monitoring the increase of deactivator concentration that accumulates as a persistent radical with time (e.g., by spectrophotometry). A plot of \(F([Mt^{n+1}X/L])\) vs. time should yield a straight line once equilibrium is reached, and \(K_{\text{ATRP}}\) can be determined from

\[
F([Mt^{n+1}X/L]) = 2k_tK_{\text{ATRP}}t + \frac{1}{3}[Mt^n/L]_0.
\]  

\(PDI = \frac{M_w}{M_n} = 1 + \frac{1}{DP_n} + \left(\frac{[RX]_0k_p}{k_{\text{deact}}[Mt^{n+1}X/L]}\right)\left(\frac{2}{\text{Conv.}} - 1\right).
\]

\[
PDI = \frac{M_w}{M_n} = 1 + \frac{1}{DP_n} + \left(\frac{[RX]_0k_p}{k_{\text{deact}}[Mt^{n+1}X/L]}\right)\left(\frac{2}{\text{Conv.}} - 1\right).
\]

\[
PDI = \frac{M_w}{M_n} = 1 + \frac{1}{DP_n} + \left(\frac{[RX]_0k_p}{k_{\text{deact}}[Mt^{n+1}X/L]}\right)\left(\frac{2}{\text{Conv.}} - 1\right).
\]
Values of $K_{\text{ATRP}}$ measured with various alkyl halide initiators and CuX/L complexes commonly employed in ATRP are provided in Table 1.

**Sub-equilibria:** $K_{\text{ATRP}}$ can be expressed as a combination of four reversible reactions: oxidation of the metal complex, or electron transfer ($K_{\text{ET}}$), reduction of a halogen to a halide ion, or electron affinity ($K_{\text{EA}}$), alkyl halide bond homolysis ($K_{\text{BH}}$), and association of the halide ion to the metal complex, or “halogenophilicity” ($K_X$) (Scheme 7) [143]. In a general effort to understand catalyst structure–reactivity relationships, many recent studies have focused on correlating these individual reactions with $K_{\text{ATRP}}$ and understanding side reactions that may affect such correlations.

These equilibrium constants, especially $K_{\text{EA}}$ and $K_X$ (and in turn, $K_{\text{ATRP}}$ [144]), are very solvent dependent. The values of $K_{\text{EA}}$ are expected to be relatively high in protic solvents as halide anions are stabilized through solvation in such media [145]. $K_X$ will likewise be affected with changes in solvent polarity. Quantification of Br$^-$/C0 coordination to CuII/L complexes with bpy, PMDETA, and Me6TREN has revealed that $K_X$ for these complexes is approximately five orders of magnitude greater in organic CH$_3$CN than in aqueous solvents where ions are more efficiently solvated [146]. This has direct implications on the degree of control attainable in aqueous media as the majority of the halogen will be dissociated from the Cu deactivating species in water. Additional studies have correlated $K_X$ measured in mixed protic solvents with polymerization rates and attainable control over molecular weights and molecular weight distributions in aqueous ATRP [147].

Catalyst activity (in terms of $K_{\text{ATRP}}$) is also intrinsically dependent upon the redox potential of the complex. A linear correlation between $K_{\text{ATRP}}$ and $E_{1/2}$ for a series of CuI complexes clearly demonstrates this facet of the ATRP equilibrium [148,149]. Recent efforts have also been made to correlate the redox potentials of Fe [118] and Ru [150,151] complexes with their ATRP catalytic activity. It should be noted that different transition metals are expected to have very different halogenophilicities, and thus redox potentials alone are not sufficient to compare $K_{\text{ATRP}}$ among different metals [143]. Additionally, such values should be very solvent dependent. However, these studies still provide a useful means for screening appropriate catalysts for a given system. Knowledge of the $E_{1/2}$ of a metal catalyst and an organic radical should also allow one to predict whether outer sphere electron transfer can occur as a side reaction to generate carbocations or carbanions during polymerization (vide infra) [102,152].

$K_{\text{ATRP}}$ should only depend upon the energetics of alkyl halide bond homolysis ($K_{\text{BH}}$) among systems

### Table 1

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Salt</th>
<th>Initiator</th>
<th>$K_{\text{ATRP}}$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>bpy</td>
<td>CuBr</td>
<td>EBriB</td>
<td>3.93 x 10^-9</td>
<td>[43]</td>
</tr>
<tr>
<td>BPMPrA</td>
<td>CuBr</td>
<td>EBriB</td>
<td>6.2 x 10^-8</td>
<td>[141]</td>
</tr>
<tr>
<td>PMDETA</td>
<td>CuBr</td>
<td>EBriB</td>
<td>7.46 x 10^-8</td>
<td>[43]</td>
</tr>
<tr>
<td>TPEDA</td>
<td>CuBr</td>
<td>EBriB</td>
<td>2.0 x 10^-6</td>
<td>[141]</td>
</tr>
<tr>
<td>TPMA</td>
<td>CuBr</td>
<td>EBriB</td>
<td>9.65 x 10^-6</td>
<td>[43]</td>
</tr>
<tr>
<td>DMCBcy</td>
<td>CuBr</td>
<td>EBriB</td>
<td>4.58 x 10^-6</td>
<td>[141]</td>
</tr>
<tr>
<td>Me6TREN</td>
<td>CuBr</td>
<td>EBriB</td>
<td>6.78 x 10^-7</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuBr</td>
<td>PEBr</td>
<td>3.25 x 10^-7</td>
<td>[141]</td>
</tr>
<tr>
<td></td>
<td>CuCl</td>
<td>PECl</td>
<td>4.28 x 10^-8</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuBr</td>
<td>BzBr</td>
<td>9.65 x 10^-6</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuBr</td>
<td>MBrP</td>
<td>8.60 x 10^-7</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuCl</td>
<td>MClP</td>
<td>6.78 x 10^-7</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuBr</td>
<td>MBrP</td>
<td>3.25 x 10^-7</td>
<td>[141]</td>
</tr>
<tr>
<td></td>
<td>CuCl</td>
<td>MClP</td>
<td>4.28 x 10^-8</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuBr</td>
<td>MClAc</td>
<td>1.54 x 10^-4</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>CuCl</td>
<td>MClAc</td>
<td>3.3 x 10^-6</td>
<td>[142]</td>
</tr>
<tr>
<td></td>
<td>CuCl</td>
<td>MClAc</td>
<td>9.9 x 10^-5</td>
<td>[142]</td>
</tr>
</tbody>
</table>

EBriB, ethyl 2-bromoisobutyrate; PEBr, 1-(bromomethyl)benzene; PECl, 1-(chloroethyl)benzene; BzBr, benzyl bromide; MBrP, methyl 2-bromopropionate; MClP, methyl 2-chloropropionate; MClAc, methyl chloroacetate.
employing the same catalyst/conditions but different monomers/initiators (where values of $K_{ET}$, $K_{EA}$, and $K_X$ remain essentially constant). Indeed, when the alkyl halide bond dissociation energies (BDE) were recently calculated for a series of ATRP monomers/initiators Fig. 6, they were found to correlate well with measured values of $K_{ATRP}$ [153]. It was proposed that such calculations could also be used to predict equilibrium constants for less reactive monomers, and in turn, polymerization rates. For example, if the ATRP of methyl acrylate would reach 90% conversion in 1 h with a given catalyst, the ATRP of styrene with the same catalyst would be expected (based on its BDE) to need 11 h and vinyl acetate 15 y to reach 90% conversion [153]. This calculation illustrates the necessity of appropriately matching a given catalyst with a specific monomer.

Relative ligand binding constants: The redox potential ($E_{1/2}$) of a transition metal catalyst, which can be correlated with its catalytic activity in ATRP reactions [148,149], also depends upon the ratio of the stability constants of the complex in its two oxidation states (i.e., $\beta^{m+1}_m$, see Eq. (13)) [154–156]. Most ligands affect the redox potential of Cu complexes through stabilization or destabilization of the CuII oxidation state [157]. Therefore, if a ligand forms a very stable CuII complex such that the ratio of $\beta^{II}/\beta^{I}$ is very large, the corresponding CuI complex should be very reducing and catalytically active in ATRP [158]. Additionally, an ATRP catalyst characterized by large values of both $\beta^{m+1}_m$ and $\beta^m$ will likely not participate in extensive ligand substitution reactions with monomer, polymer, or solvent, even in dilute solutions with respect to the catalyst. An exceptionally stable Cu complex with 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane [159,160] (or dimethyl cross-bridged cyclam, DMCBCy, see Fig. 7) was recently developed. Analysis of the redox properties of this complex revealed that the CuI species was exceptionally reducing [161]. This complex is currently the most active Cu-based ATRP catalyst known to date [142].

$$\beta^m_k = \frac{[Cu^mL_k]}{[Cu^m][L]^k}; \ m = I \ or \ II, \quad (13A)$$

$$E \approx E^0 + \frac{RT}{F} \ln \frac{[Cu^{II}]_{tot}}{[Cu^I]_{tot}} - \frac{RT}{F} \ln \frac{\beta^{II}}{\beta^I} \quad (13B)$$

5.2.2. Activation/deactivation structure-reactivity correlations

It is not possible to determine from $K_{ATRP}$ alone whether a polymerization will be well controlled or
not; fast activation and more importantly fast deactivation are required to achieve good control over polymer molecular weights and molecular weight distributions. The correlation of such reaction parameters in ATRP with catalyst, alkyl halide, and monomer structure should ultimately lead to the rational development of more efficient catalysts. These studies also serve as an excellent resource when considering appropriate ligands and conditions for a polymerization.

Quantifying $k_{\text{act}}$ and $k_{\text{deact}}$: The determination of $k_{\text{act}}$ is typically made by following the decay of $R-X$ concentration (by GC, NMR, or UV–Vis spectrophotometry) when an alkyl radical $R^\bullet$ formed by activation of an $R-X$ bond is scavenged by a chemical agent, typically a nitroxide radical present in large excess [92]. Stopped-flow techniques can also be used to measure very fast activation rate constants otherwise unattainable by “traditional” methods [162]. The rate constants of deactivation have been much less studied, owing to the lack of efficient techniques for measuring the relatively fast process ($\approx 10^{-7}$ M$^{-1}$s$^{-1}$). However, $k_{\text{deact}}$ can be directly measured when radicals are trapped simultaneously by nitroxide radicals and a transition metal deactivator in a type of clock reaction [163]. Additionally, $K_{\text{ATRP}}$ can be measured and $k_{\text{deact}}$ determined knowing independently the value of $k_{\text{act}}$ [109].

Effect of ligand structure on activation: In a recent thorough study of a wide variety of Cu complexes with nitrogen-based ligands, values of $k_{\text{act}}$ were observed to span more than six orders of magnitude under comparable conditions (representative ligands are illustrated in Fig. 7) [164]. Several “rules” pertaining to catalyst activity were derived from this study: (1) activity depends very strongly on the linking unit between the $N$ atoms (C4 $<$ C3 $<$ C2) and/or the coordination angle; (2) the topology of the ligand (cyclic $\sim$ linear $<$ branched) affects activity; (3) activity depends upon the nature of the $N$-ligand (aryl amine $<$ aryl imine $<$ alkyl imine $<$ alkyl amine $\sim$ pyridine); and (4) steric bulk around the metal center can affect the rate of activation/deactivation (e.g., the Me$_6$TREN complex is $\approx$1000 times more active than Et$_6$TREN; [165] 6,6'-diMe-2,2'-bpy is inactive in ATRP, in contrast to 2,2'-bpy and 4,4'-disubstituted 2,2'-bpy) [135].

Effect of initiator/monomer structure on activation: The broad availability of initiators provides ATRP with a significant advantage over other CRP techniques. In fact, many alkoxyamines and RAFT reagents are actually prepared from alkyl halides [65,166]. Most compounds with halogen atoms that are activated by $\alpha$-carbonyl, phenyl, vinyl or cyano groups make efficient ATRP initiators. The reactivity of these initiators depends reciprocally on the alkyl halide BDE [153]. Several rules pertaining to initiator structure that govern activation rate constants have also emerged from recent studies [167] of initiators illustrated in Fig. 8: (1) activity depends on the degree of initiator substitution (primary $<$ secondary $<$ tertiary), (2) on the leaving atom/group (for methyl 2-halopropionates: Cl $<$ Br $<$ I), and (3) on the radical stabilizing groups ($-$Ph $\sim$ $-$C(O) OR $<$ $-$CN).

The penultimate monomer unit can also have a strong effect on $k_{\text{act}}$ [168], as evidenced in measurements of $k_{\text{act}}$ for dimeric alkyl halides. This realization is of particular relevance in

Fig. 7. ATRP rate constants of activation (in M$^{-1}$s$^{-1}$) for various ligands with ethyl-2-bromoisobutyrate in the presence of Cu$^\text{I}$Br in MeCN at 35 °C [164].
copolymerization. Numerous other investigations have studied how \( k_{\text{act}} \) is affected by solvent, counterion, temperature, ligand/catalyst ratio, presence of monomer, effect of \( [\text{Cu}^{II}] \), etc. [130,169–173].

Interestingly, the order of the equilibrium constants for a series of common monomers in ATRP differs from SFRP and RAFT where steric effects are very important. In ATRP, that order is acrylonitrile > methacrylates > styrene ~ acrylates > acrylamides > > vinyl chloride > vinyl acetate. The efficient preparation of block copolymers requires this order be obeyed in the synthesis of each block to ensure near simultaneous growth from each macroinitiator (i.e., polyacrylonitrile should be chain extended with polyacrylate and not vice versa) [174,175]. However, this order can be altered in ATRP with a method known as halogen exchange. In this technique, a macromolecular alkyl bromide is extended with a more reactive monomer in the presence of a CuCl catalyst [176–178]. Because the value of the ATRP equilibrium constant for alkyl chloride-type (macro)initiators is 1–2 orders of magnitude lower than the alkyl bromides with the same structure, the C–Cl bonds formed upon deactivation of the growing chain are reactivated more slowly. The rate of propagation with respect to re-initiation is thus decreased, which effectively leads to increased initiation efficiency and lower polydispersity. In this way, block copolymers have been successfully prepared from poly(\( n \)-butyl acrylate) and chain-extended with polyacrylonitrile or poly(methyl methacrylate) (Fig. 9) [179,180].

**Deactivation:** Determination of \( k_{\text{deact}} \) is important, as the degree of control over molecular weight distribution in a controlled radical polymerization is limited by the rate of deactivation according to Eq. (10) above [173,181,182]. However, few structure–reactivity relationships have been studied for the deactivation process in ATRP. The \( \text{Cu}^{II} \)-halide bond length would be the simplest structural parameter that could be correlated with the deactivation rate. However, an analysis of this bond in complexes of \( \text{Cu}^{II} \) with dNbpy, tNtpy, PMDETA, Me4Cyclam, and Me6TREN found no direct correlation between \( \text{Cu}^{II} \)-Br bond length and values of \( k_{\text{deact}} \) for these complexes [183]. It has been proposed that the rate of structural reorganization of the \( \text{Cu}^{II} \) complex upon bromine abstraction by a radical in ATRP may be a determining factor affecting the observed rate of deactivation of the complex. However, further studies in this field will be needed to better understand these processes. Values of \( k_{\text{deact}} \) for the reaction between the 1-phenylethyl radical and \( \text{CuX}_2 \) with some commonly employed ATRP ligands are provided in Table 2.

5.3. Initiation systems

The realization of ATRP and the extraordinary control it can provide over polymer topology, composition, microstructure, and functionality has led to explosive developments in materials science over the last decade. However, despite the potential commercial application of many of the materials created with this technique, their production on an industrial scale has been rather limited for several
Table 2
$k_{\text{deact}}$ of 1-phenylethyl radicals in ATRP [41]

<table>
<thead>
<tr>
<th>Metal Salt</th>
<th>Ligand</th>
<th>$10^{-7}k_{\text{deact}}$ (M$^{-1}$ s$^{-1}$)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuBr$_2$</td>
<td><img src="image1.png" alt="Ligand" /></td>
<td>0.041</td>
<td>[149]</td>
</tr>
<tr>
<td>CuBr$_2$</td>
<td><img src="image2.png" alt="Ligand" /></td>
<td>0.31</td>
<td>[149]</td>
</tr>
<tr>
<td>CuBr$_2$</td>
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<td>0.61</td>
<td>[163]</td>
</tr>
<tr>
<td>CuBr$_2$</td>
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<td>1.4</td>
<td>[163]</td>
</tr>
<tr>
<td>CuBr$_2$</td>
<td><img src="image5.png" alt="Ligand" /></td>
<td>2.5</td>
<td>[163]</td>
</tr>
<tr>
<td>CuCl$_2$</td>
<td><img src="image6.png" alt="Ligand" /></td>
<td>0.43</td>
<td>[163]</td>
</tr>
</tbody>
</table>

Acetonitrile, 75 °C.

Fig. 9. The above illustrations and GPC traces show chain extension of a polySty-Br macroinitiator with MMA using: (a) CuBr/dNbpy, and (b) CuCl/dNbpy as the catalyst. [MMA]:[polySt-Br]:[CuX]:[dNbpy] = 500:1:1:2; 75 °C [180].
reasons: (i) special handling procedures are often required to remove all oxygen and oxidants from systems employing highly active (i.e., very reducing) ATRP catalysts; (ii) catalyst concentrations required by ATRP can approach 0.1 M in bulk monomer, and extensive post-polymerization purification of the product is often necessary and expensive; [184] and (iii) many of the transition metal species employed in this technique (i.e., Cu complexes) are generally considered mildly toxic, meaning the removal/disposal of large quantities of these catalysts can have environmental repercussions [185]. The following section details the development of several ATRP initiation systems designed to address these aforementioned limitations, including a simultaneous reverse and normal initiation procedure used to simplify the handling of catalyst precursors, hybrid and bimetallic systems designed to maximize control with economically attractive and environmentally friendly (but otherwise inefficient) catalysts, and systems employing organic reducing agents to dramatically lower the amount of required catalyst.

5.3.1. Normal/reverse/simultaneous reverse and normal initiation

A normal ATRP initiating system, consisting of an alkyl halide initiator and transition metal catalyst in the lower oxidation state, works well on an academic scale with systems that are relatively insensitive to air. However, as more and more reducing catalysts are developed in a dual effort to polymerize less reactive monomers and to employ smaller total amounts of catalyst, the systems become inherently less oxidatively stable [132,142,186,187]. Additionally, polymerization systems in large vessels and in aqueous media can be difficult to deoxygenate, which can lead to irreversible oxidation and loss of the ATRP activator.

Reverse ATRP is a convenient method for circumventing such oxidation problems. The ATRP initiator and lower oxidation state transition metal activator (i.e., CuI) are generated in situ from conventional radical initiators and the higher oxidation state deactivator (CuII) [188–190]. The initial polymerization components are thus less sensitive to oxygen in reverse ATRP and can therefore be easily prepared, stored, and shipped for commercial use. Additionally, this technique can be employed in the development of new catalysts to help verify the ATRP mechanism is operating, as it allows the ATRP equilibrium to be established from another direction.

However, because the transferable halogen atom or group is added as a part of the copper salt in reverse ATRP, the catalyst concentration must be comparable to the concentration of initiator and cannot be independently lowered. Additionally, block copolymers cannot be formed with this technique. Such is not the case with a dual initiation system comprised of both standard free radical initiators (e.g., AIBN) as well as initiators with a transferable atom or group. In this technique, simply known as simultaneous reverse and normal initiation (SR&NI), radicals generated by AIBN are subsequently deactivated by an oxidatively stable CuII salt forming CuI and some halogenated chains (Scheme 8) [191]. CuI can then reactivate alkyl halide (macro)initiator and concurrently mediate normal ATRP. In addition to bulk and solution systems, this technique can be successfully employed in emulsion and miniemulsions [192–194], where addition of the catalyst precursor as an oxidatively stable salt prior to sonication could greatly simplify commercial procedures.

5.3.2. Activators generated by electron transfer (AGET)

The limitation of both simultaneous reverse and normal initiation in ATRP is evident in the inability of these techniques to produce clean block copolymers. In AGET ATRP, reducing agents that are unable to initiate new chains (rather than organic radicals) are used to reduce the higher oxidation state transition metal complex (Scheme 8). No homopolymers are produced during block copolymerization with this technique. Many reducing agents could theoretically be used. Following early reports that zero valent Cu could be used as a
reducing agent to react with Cu$^{II}$ and enhance the rate of polymerization in ATRP [187,195], the AGET principle was demonstrated using tin$^{II}$ 2-ethylhexanoate [196], ascorbic acid [197], or triethylamine [198] as the reducing agents, which reacted with the Cu$^{II}$ complex to generate the Cu$^{I}$ ATRP activator. Normal ATRP then proceeds in the presence of alkyl halide initiators or macromonomers. The technique has proven particularly useful in aqueous and miniemulsion systems [199–201].

5.3.3. **Hybrid and bimetallic catalytic systems**

Immobilized-supported catalysts were originally developed in ATRP to aid in catalyst separation during post-polymerization purification [184,202–206]. However, ATRP conducted under these conditions is typically not well-controlled in terms of molecular weight and molecular weight distribution, a likely result of diffusion limitations of the propagating chain [163]. Controlled polymerization can be achieved with immobilized Cu$^{I}$ catalysts when a small amount of soluble efficient Cu$^{II}$ deactivator ([Cu$^{I}$]:[Cu$^{II}$] = 1: 0.03) is employed [207,208]. The soluble Cu$^{II}$ species in this hybrid system accelerates deactivation of the growing radical chain in solution and can quickly diffuse to the supported catalyst. It is reconverted to Cu$^{II}$ through a redox reaction with the immobilized Cu species. The majority of the catalyst can thus be easily removed from the product by simple filtration, leaving only residual soluble catalyst in the product [209].

This concept was also employed to improve control in ATRP catalyzed by Fe complexes with linear amines and halogen free neutral Cu$^{I}$ catalysts. These economically and environmentally attractive complexes were found to efficiently activate alkyl halides but unfortunately were very poor deactivators of propagating chains [210]. Control over molecular weights and molecular weight distributions in the homopolymerization of styrene and (meth)acrylates could be dramatically improved with the addition of 3–5 mol% of an efficient Cu$^{II}$ deactivator (relative to the Cu$^{I}$ or Fe$^{II}$ activator). The proposed mechanism is similar to that of the hybrid systems; the more reducing Cu species deactivates the majority of chains (Scheme 9) in these bimetallic or dual catalytic systems. Similar bimetallic systems have been developed to improve control over polymerizations employing Ni, Co, and Mn catalysts [211].

5.3.4. **Initiators for continuous activator regeneration (ICAR)**

As discussed, radical termination reactions lead to the irreversible accumulation of persistent radical deactivators under typical ATRP conditions. If the initial catalyst concentration employed is too low, all of the activator will eventually be consumed as a persistent radical and polymerization will only reach limited conversion. Because relatively high catalyst concentrations are thus required in ATRP, much research has been devoted to maximizing the efficiency of catalyst removal or recycling through the use of ion exchange resins [212,213], biphasic systems [214–216], and immobilized catalysts (as mentioned). However, a new technique known as initiators for continuous activator regeneration (ICAR) [217] in ATRP can be used to both scavenge oxidants and decrease the amount of catalyst needed to the point (ppm levels) where its removal or recycling would be unwarranted for many industrial applications.

In ICAR ATRP, free radicals are slowly and continuously generated by conventional radical initiators (e.g., AIBN) throughout a polymerization to constantly reduce and regenerate Cu that accumulates as a persistent radical (Scheme 10). A special case of ICAR occurs in the polymerization of styrene; thermal initiation generates a sufficient concentration of radicals for this purpose without the addition of extra free radical initiator. The development of this technique has profound industrial implications as it lowers the amount of necessary Cu catalyst from several thousand ppm under normal conditions to <50 ppm while still allowing for excellent control over molecular weights and molecular weight distribution. ICAR ATRP is distinguished from SR&NI procedures by the fact that a large excess of free radical reducing agent to catalyst is employed, and the radicals are slowly generated over the course of the reaction.
Recent mechanistic studies [217] suggest that the kinetics of ICAR very closely resemble RAFT, where a chain transfer agent is employed to reversibly transfer a labile dithioester end group among propagating radical chains (vide infra) [218]. The rate of polymerization in ICAR (as in RAFT) has been shown to depend on the rate of free radical generation, and once these initiators are consumed, ICAR (and RAFT) stop very quickly.

5.3.5. Activators regenerated by electron transfer (ARGET)

Perhaps the most recent industrially relevant development for the production of block copolymers was the realization that the relative concentration of catalyst to initiator could be significantly decreased when the reducing agent is present in excess relative to the catalyst. CuII that accumulates as a persistent radical is continuously reduced to CuI in ARGET ATRP, provided a large enough excess of reducing agent to Cu is supplied (Scheme 10) [219]. Good control over acrylate polymerization has been established with ARGET using 50 ppm of Cu and for styrene polymerization using only 10 ppm of Cu catalyst [220]. Reducing agents used in AGET ATRP can in principle be used for ARGET, including organic derivatives of hydrazine, phenol, sugar, or ascorbic acid, and inorganic species such as SnII or Cu0. The rational selection of conditions, the catalyst complexing ligand, and the reducing agent was recently discussed [217]. Well-defined block copolymers have also been synthesized employing only 50 ppm of Cu catalyst. Additionally, the catalyst and excess reducing agent can effectively work to scavenge and remove dissolved oxygen from the polymerization system.

5.3.6. Inherent differences/advantages of each system

SR&NI and AGET ATRP are used to quickly generate the CuI activator from oxidatively stable CuII catalyst precursors with nearly stoichiometric amounts of organic radicals and non-radical generating reducing agents, respectively. ICAR and ARGET differ from these techniques primarily in the ratio of catalyst to reducing agent employed and in the fact that they continuously regenerate the CuI species throughout the reaction. They have the advantage that only small amounts of catalyst are needed to mediate polymerization. Interestingly, some side reactions between the catalyst and chain end (such as outer sphere electron transfer or β-hydrogen elimination) that can affect polymer molecular weights and chain end functionality are minimized in ICAR and ARGET ATRP [221], while other side reactions that can affect catalyst performance (such as complex dissociation at low concentrations, monomer coordination to the catalyst, Lewis and protic acid evolution, etc.) create new challenges in ICAR and ARGET ATRP that were previously not an issue. ICAR has several advantages over ARGET ATRP, including a broader choice of ligand (the reductive properties of the catalyst are less important in ICAR whose kinetics are determined by thermal decomposition of the organic free radical initiator) and the fact that ligands can be used in lower concentrations (they do not compete for complexation with excess reducing agents and are not needed to trap acid). However, the reducing agents in ARGET do not generate new chains, making ARGET more applicable in the production of block copolymers. A summary of typical ratios of all reagents employed in these techniques can be found in Table 3.

5.4. Optimization of ATRP with respect to side reactions

The polymer scientist should be aware of methods which minimize a number of undesirable side reactions.
reactions that can occur in ATRP and can affect catalyst performance as well as polymer molecular weights and chain end functionality (Scheme 11). The appropriate selection of catalyst/monomer combinations and polymerization conditions is often sufficient for this purpose. The application of ICAR and ARGET ATRP can also minimize undesirable reactions between the catalyst and polymer chain end. Additionally, several efforts have been made to exploit these “side reactions” as a route to novel polymeric materials that are otherwise unattainable.

5.4.1. Avoiding side reactions

**Outer Sphere Electron Transfer (OSET):** In addition to the atom transfer redox process (which is also known as inner sphere electron transfer), OSET may occur between organic radicals and transition metal complexes whereby growing radicals are oxidized to carbocations by CuII or reduced to carbanions by CuI (Scheme 11) [222]. The extent of OSET is dictated by the relative redox potentials of the species involved. Indeed, cationic processes have been proposed or identified in attempted homopolymerizations of styrene derivatives [223–225] catalyzed by relatively oxidizing CuII complexes.

More active (i.e., reducing) catalysts have been observed to reduce electrophilic radicals to their corresponding anions, including malonate and trichloromethyl radicals [222]. This side reaction is responsible for limiting the attainable MW of polyacrylonitrile prepared by ATRP [175,226,227]. It has also been suggested that OSET may be responsible for limited conversions reached in the ATRP of electrophilic acrylates with highly active/reducing Cu catalysts [142]. These observations further suggest that attention to OSET reactions should be considered as more powerful Cu ATRP catalysts are developed, and the reducing power of the catalysts should be appropriately matched with a given monomer. Interestingly, the application of ICAR ATRP may minimize OSET between electrophilic radicals such as acrylates and acrylonitrile and extremely reducing Cu catalysts. The majority of the Cu catalyst is present as the higher oxidation state persistent radical in ICAR, in contrast to normal ATRP where the majority is in the lower oxidation state. Very little CuI would be available in such a system to reduce these radicals.

**Halide Dissociation:**

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Halide chain end functionality can also be lost during the ATRP of styrene type monomers due to electron transfer reactions catalyzed by the CuII deactivator. HBr is evolved from propagating radicals and CuIIBr2 to give unsaturated chain ends and CuIBr [228–230]. The effect of this reaction on chain end functionality becomes particularly pronounced at high conversions as the absolute time between monomer propagation events becomes longer with decreasing monomer concentration; thus, stopping a reaction at lower conversion is a simple yet effective technique for retaining high chain end functionality. However, this side reaction thwarts the production of well-defined high molecular weight polystyrene in ATRP, with upper limits between 30 and 50,000 g/mol.

The development of ARGET and ICAR ATRP which minimize Cu concentrations allowed high molecular weight styrene (co)polymers (200,000 g/mol) with narrow molecular weight distributions (PDI < 1.2) to be synthesized with just 10 ppm of Cu catalyst [221,231]. This achievement can be attributed to the fact that side reactions between the chain end and the catalyst are minimized when the catalyst concentration is dramatically lowered.

**Monomer coordination:** Several model ATRP CuI catalysts of the form \([\text{CuI(PMDETA)(\pi-M)})^+]\) (where M = vinyl monomer) have been isolated with \(\pi\)-coordinated monomers methyl acrylate
(Fig. 10a), methyl methacrylate, styrene (Fig. 10b), and 1-octene with bulky BPh$_4^-$ as the counterion [232]. Recent studies suggest that under typical ATRP conditions ([M]/[Cu] = 100/1, bulk), as much as 10% of methyl acrylate could displace Br$^-$ and coordinate to Cu$^1$(PMDETA)$^+$ at room temperature. It was ultimately concluded that monomer reactivity was not significantly affected in radical copolymerization by $\pi$-coordination to Cu$^1$ with the tridentate ligand PMDETA, and furthermore, that this coordination plays no significant role in the chain extension step of ATRP [233]. However, under ICAR and ARGET conditions where [M]/[Cu] = 20,000/1, the degree of monomer coordination to the Cu$^1$/PMDETA activator will be more significant. Detailed studies concerning how monomer coordination to Cu stabilizes the lower oxidation state and affects the redox properties of the catalyst have not yet been completed. Monomer coordination to Cu can be minimized by employing tetradeutentate ligands with very high Cu/L stability constants.

While vinyl monomers do not coordinate significantly to Cu$^1$ (a hard Lewis acid) through the alkene double bond, nitrogen containing monomers can displace halogen from the Cu$^1$ deactivator, which can result in a loss of control in the polymerization. The addition of halide salt to the reaction medium may help suppress this side reaction. Additional side reactions peculiar to nitrogen containing monomers such as 4-vinylpyridine involve reactions of the alkyl bromide polymer chain end with pyridine units in the monomer and polymer (or pyridinolysis). This can lead to the formation of branched polymeric structures. Recent studies have demonstrated the reaction evolves much slower with alkyl chloride chain ends [235]. Such studies have proven critical in preserving chain end functionality in the ATRP of these monomers.

Disproportionation: Conducting ATRP in aqueous media would allow the controlled polymerization of many hydrophilic and ionic monomers that cannot otherwise be polymerized in organic media [147]. Additionally, replacing organic solvents with aqueous media has both economic and environmental advantages. Unfortunately, the equilibrium constant for disproportionation of two Cu$^1$ centers into Cu$^1$ and Cu$^0$ is very large in water ($K_{\text{disp}} = 10^6$), and loss of the activator to this side reaction prevents the use of many Cu catalysts that are otherwise attractive for their activity or for economic reasons.

However, with knowledge of the overall stability constants of Cu/L complexes for the Cu$^1$ and Cu$^1$ oxidation states ($\beta_i^1$ and $\beta_i^1$), disproportionation can be suppressed with the choice of appropriate ligands [236]. The equilibrium constant of disproportionation can be changed with such ligands to a conditional value, $K_{\text{disp}}^*$, which is related to the concentration of ligand and the overall stability according to

$$K_{\text{disp}}^* = \frac{1 + \sum_{j=1}^{n} \beta_j^1[L]^j}{(1 + \sum_{i=1}^{m} \beta_i^1[L]^i)^{-2}} K_{\text{disp}}. \quad (14)$$

As the activity of a catalyst with ligands forming 1:1 complexes with copper ions is proportional to $\beta_i^1/\beta_j^1$, and the tendency of the Cu$^1$ complex to disproportionate depends on the ratio $\beta_i^1/([\beta_j^1]^2[L])$, knowledge of these stability constants in aqueous media would allow the controlled polymerization of many hydrophilic and ionic monomers that cannot otherwise be polymerized in organic media [147]. Additionally, replacing organic solvents with aqueous media has both economic and environmental advantages. Unfortunately, the equilibrium constant for disproportionation of two Cu$^1$ centers into Cu$^1$ and Cu$^0$ is very large in water ($K_{\text{disp}} = 10^6$), and loss of the activator to this side reaction prevents the use of many Cu catalysts that are otherwise attractive for their activity or for economic reasons.

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media can be used to select catalysts with appropriately high activity in ATRP but will also be stable towards disproportionation [185]. Knowing the appropriate binding constants of CuI and CuII complexes of Bpy [237], PMDETA [236], and TPMA [238] from literature, it can be determined that CuI complexes with Bpy are stable towards disproportionation, but are not sufficiently active for many monomers in ATRP; CuI/PMDETA is significantly more active, but is not stable towards disproportionation; and CuI/TPMA is both active and stable towards disproportionation.

The successful ATRP of several ionic monomers, which otherwise stabilized CuII relative to CuI in pure water, was also demonstrated using pyridine as a co-solvent, which significantly suppressed $K_{\text{disp}}^*$ of CuI [239].

Dissociation/solvent coordination: Hydrolysis of CuII–halide complexes occurs to a significant extent in aqueous media, as confirmed by a recent EXAFS study of typical ATRP deactivators in aqueous media [240]. Solvation of ions and, hence, dissociation of the halide anion from the metal complex will be much more significant in aqueous than in organic media. Indeed, the equilibrium constant of dissociation for CuIIBr is approximately five orders of magnitude smaller in CH3CN than in H2O [146]. Dissociation of the halide is presumably followed by coordination of water to CuII, and this ultimately lowers the available deactivator concentration during ATRP and results in faster and less controlled polymerization in aqueous and protic media. However, it has been demonstrated that control can be achieved with the addition of extra halide salts to the reaction, which suppress deactivator solvolysis [147].

5.4.2. Exploiting “side reactions”

Atom transfer radical coupling (ATRC): While every effort is often made to suppress bimolecular termination events in order to achieve near “living” conditions, these reactions have recently been exploited in a technique known as ATRC to provide an efficient route to telechelic polystyrene [241]. Macroradicals are generated in situ through the ATRP equilibrium, and the presence of a reducing agent is employed to minimize the high oxidation state transition metal deactivator. This in turn maximizes radical–radical chain coupling. While this technique is less efficient for methacrylates (where growing radicals predominantly disproportionate rather than couple) and for acrylates (where the ATRP equilibrium constant is very low), the addition of a few styrene units at the acrylate chain end is sufficient to ultimately generate poly(meth)acrylate telechelics [242]. The ATRC of difunctional chains can lead to very high MW polymers in a step-growth type process.

Radical coordination: One electron oxidative addition processes that involve alkyl radical coordination to a transition metal complex have been exploited in organic synthesis [243]. However, the formation of such an organometallic species during ATRP might be considered a side reaction as it could inhibit polymerization or greatly reduce initiation efficiency. The role of a transition metal complex in controlling a radical polymerization will ultimately be dictated by the relative BDEs of the Mt–R, Mt–X, and R–X bonds, which in turn determine whether a particular system will be controlled by SFRP only, by ATRP only, by SFRP and ATRP simultaneously, or whether polymerization can even occur or be controlled [152].

There is currently no experimental evidence to date which suggests there is any contribution from the formation of an organometallic CuII–R species during Cu mediated ATRP [244]. However, several recent elegant studies have detailed the interplay between ATRP and SFRP control mechanisms for various Mo complexes and how they relate to a one-electron oxidative addition process (Scheme 12) [77,245]. As more non-Cu based ATRP catalysts are developed, such studies will become increasingly important, and catalysts that were originally intended for ATRP might be optimized to make efficient SFRP spin traps.

$\beta$-H abstraction: The formation of a metal-hydride species during polymerization through $\beta$-H abstraction from the growing chain can inhibit the production of high molecular weight polymer. However, oligomers made by such a process are important industrial products used as building blocks in addition fragmentation processes [246]. In addition to an ATRP catalyst or an SFRP spin trap, a transition metal complex may also efficiently catalyze chain transfer to generate such oligomers through $\beta$-H abstraction and the intermittent

\[
\text{R-X} + \text{Mo}^{\text{III}} \xrightarrow{k_p} \text{Mo}^{\text{IV}} + \text{R}^* \xrightarrow{+ M} \text{Mo}^{\text{IV}} + \text{R} \quad \text{(ATRP)}
\]

\[
\text{R-X} + \text{Mo}^{\text{III}} \xrightarrow{k_p} \text{Mo}^{\text{IV}} + \text{R}^* \xrightarrow{+ M} \text{Mo}^{\text{IV}} + \text{R} \quad \text{(SFRP)}
\]

Scheme 12.
formation of a metal-hydride species \[84\]. While the contribution of SFRP and CCT pathways depend strongly on monomer (e.g., under similar conditions, polymerization of methacrylates is dominated by CCT whereas that of acrylates by SFRP \[247\]), the structure of the transition metal complex is very important. Indeed, subtle changes in the ligands of ATRP Mo-based catalysts worked to promote efficient CCT polymerization \[77\]. Slight modification of the substituents of a diimine complexing ligand can dramatically affect the role of an Fe catalyst in styrene polymerization by converting the catalyst from a successful Fe\(^{II}\) ATRP spin trap to an efficient CCT catalyst. The observed CCT phenomenon is supposedly caused by \(\beta\)-H elimination from a postulated Fe \(\text{III}\)-R intermediate (Scheme 13) \[152,248\].

**Lewis acid complexing agents:** While agents that interfere with the ATRP catalyst through complexation with the metal or reaction with the ligand can decrease attainable control during the polymerization, complexing agents are often exploited in CRP processes. For example, certain aluminum additives (e.g., aluminum isopropoxide) have been known to increase the polymerization rate in ATRP and in some cases even decrease \(M_n/M_w\) \[249\]. Recent studies suggest the nature of the catalytic effect of this additive in ATRP is the result of a more favorable Lewis acid–base interaction with the oxidized metal complex vs. the halide capped polymer chain that shifts the ATRP equilibrium more towards the active state \[250\].

While free RP is not stereoselective, the proportion of syndiotactic or isotactic triads in a polymer prepared by RP can be significantly increased in the presence of some complexing agents that strongly interact with the pendant groups of the polymer chain end and/or the monomer. This has been demonstrated for the polymerization of acrylamides in the presence of catalytic amounts of Yb(OTf)\(_3\) or Y(OTf)\(_3\) \[251\] and also in the polymerization of vinyl esters in fluoroalcohols \[252\] CRP offers the special advantage that atactic segments formed in the absence of complexing agent can be extended with regular blocks formed in the presence of such agents. Stereoblock poly(atactic-dimethylacrylamide)-block-poly(isotactic-dimethylacrylamide) was formed in such a way \[103,253,254\].

It was recently determined that monomer reactivity in a radical polymerization remains unaffected by \(\pi\)-coordination to certain transition metal species \[233\]. However, following calculations that the gas phase activation energy of methyl radical addition to ethylene could be substantially lowered though coordination with a naked alkali metal addition \[255,256\], it was demonstrated for the first time that the radical polymerization of ethylene could be induced at ambient temperatures and pressures via complexation to a Li\(^+\) salt of a highly alkylated derivative of a monocarbadodecaborate anion \[257\].

### 6. Degenerative transfer processes

Processes based on degenerative transfer (DT) operate under very different principles than either SFRP or ATRP: the latter two CRP techniques obey the PRE, as propagating radicals are reversibly trapped by persistent radicals that accumulate with time; homolytic cleavage of a dormant species occurs either spontaneously or is catalyzed by a transition metal complex; and the equilibria in both SFRP and ATRP are very strongly shifted towards the dormant species, preserving a concentration of growing radicals on the order of ppm.

CRP processes based on DT do not obey the PRE. A steady state concentration of radicals is established via initiation and termination processes as in conventional RP. These processes rely on a thermodynamically neutral transfer reaction. In contrast to systems obeying the PRE, the formal equilibrium constant should be unity. A minute amount of growing radicals undergo degenerative exchange with dormant species via a bimolecular transfer process. The exchange can proceed by atom (e.g., I) or group transfer (\(R\)-Te, \(R_2\)-Sb, etc.) or by addition–fragmentation chemistry with unsaturated...
methacrylate oligomers or dithioesters. The exchange process usually proceeds via a short lived intermediate that in some cases can be considered a transition state (iodine transfer, Scheme 14). However, in some addition–fragmentation systems, the lifetime of the intermediate may actually be long enough to either retard polymerization or participate in side reactions such as the trapping of growing radicals or initiating of new chains.

Conventional free radical initiators such as peroxides and diazenes are used in DT at temperatures typical for RP. The overall kinetics and polymerization rate resemble conventional RP, as the rate is proportional to the square root of the concentration of radical initiator and does not depend on the concentration of the transfer agent. Control over molecular weights and polydispersity is provided by transfer agents (RX), which exchange a group/atom \( X \) among all growing chains. Good control requires that exchange is fast compared to propagation \( (k_{ex} > k_p) \). The ratio of concentration of consumed monomer to the sum of the concentrations of consumed transfer agent and decomposed initiator defines the degree of polymerization

\[
DP_n = \frac{D[M]}{([RX] + f \cdot \Delta[I])}. \quad (15)
\]

Polydispersities depend on the ratio of the rate constants of propagation to exchange (Eq. (16)). Good control can be obtained if transfer is fast and the concentration of the new chains formed by decomposed initiator is much smaller than that originating from the transfer agent. Additionally, polydispersity can be lowered if monomer is slowly fed into the reaction mixture

\[
M_w/M_n = 1 + (k_p/k_{ex})(2/(p - 1)). \quad (16)
\]

6.1. Degenerative transfer by atom or group transfer

A simple example of DT occurs in the presence of conventional RP initiators and alkyl iodides (Scheme 15) [258,259]. Unfortunately, the rate constants of exchange in these systems are typically \(<3 \) times larger than rate constants of propagation for most monomers. This results in polymers with polydispersities \( >1.3 \) (cf. Eq. (16)). Exchange is faster in other DT processes employing derivatives of Te, As, Sb, and Bi [260–264]; consequently, better control can be obtained in these systems.

Interestingly, ICAR ATRP [217] kinetically resembles a DT process as polymerization rates are proportional to the square root of the concentration of radical initiator and do not depend on concentration of copper species, in contrast to typical ATRP. It should be noted that when ATRP is initiated by alkyl iodides, degenerative exchange among polymer chains occurs in addition to the ATRP process [265]. Degenerative exchange has also been proposed to occur in some SFRP systems initiated by Co porphyrins [266] and in some light initiated dithiocarbamates systems [73].
6.2. **DT via addition–fragmentation with unsaturated polymethacrylates**

Addition–fragmentation chemistry was originally applied to the polymerization of unsaturated methacrylate esters prepared by CCT [267]. The transfer reaction proceeds through an intermediate species formed by the addition of an unsaturated chain to a propagating radical. The intermediate can then either fragment back \((k_a)\) and regenerate the original chains or fragment \((k_f)\) to allow propagation from the previously unsaturated chain end. By definition, the value of equilibrium constant in these polymerizations (illustrated in Scheme 16) is unity. However, a different value may be associated between oligomers of different lengths or among chains with different substituents at the methacrylate group.

The overall exchange rate can be defined according to Eq. (17). The rate of exchange depends on the probability of the fragmentation of the resulting intermediate radical. In a truly degenerative process, the probability of fragmenting “backward” and “forward” should be the same (i.e., \(k_{ex} = k_a/2\)). However, during the actual initiation process or during crosspropagation, the rate constants of forward and backward fragmentations might be dramatically different. This can affect the efficiency of transfer, and transfer agents must therefore be carefully selected (cf. below)

\[
k_{ex} = \frac{k_a \cdot k_f}{k_a + k_f}.
\]  

(17)

In DT with unsaturated methacrylates, addition rate constants are much smaller than propagation rate constants, leading to polymers with high polydispersities. However, polymers with low polydispersities can be prepared by slowly feeding/adjusting the monomer concentration [268]. The exchange rate is not affected by this slow feeding, but the propagation rate can be greatly reduced, which ultimately leads to better control.

6.3. **DT with dithioesters and related compounds**

6.3.1. **Basic mechanism**

Reversible addition–fragmentation chain transfer, or RAFT, is among the most successful CRP processes due in large to its applicability to a wide range of monomers. Exchange reactions in this technique are also very fast, which lead to well controlled systems. Successful application of the RAFT process requires the appropriate selection of a RAFT reagent for a particular monomer. Various dithioesters, dithiocarbamates, trithiocarbonates and xanthates have been effectively used as transfer agents to control molecular weights, molecular weight distributions, and even molecular architecture [269–271].

After propagating macroradicals add to the carbon sulfur-double bond of a RAFT reagent (with a rate constant of addition \(k_a\), see Scheme 17), the radical adduct that is formed undergoes \(\beta\)-scission and either yields back the reactants \((k_{-a})\) or releases another initiating (macro)radical (with a rate constant of fragmentation \(k_f\)). In this way, an equilibrium between dormant and active species is established. However, it should be noted

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_2\text{-C} & \quad \text{CH}_2\text{-C} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_2\text{-C} & \quad \text{CH}_2\text{-C} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]
that the differences in the rate of addition/fragmentation of a propagating radical with the initial RAFT reagent and later with the polymeric RAFT reagent will impact the kinetics of the early and later phases of the RAFT polymerization. The values of these rate constants have been well studied in the initialization period, or the asymmetric “pre-equilibrium” involving an attacking macroradical and a chemically distinct leaving group radical, and can be considered independent of the “main equilibrium”, where the attacking and leaving groups are more or less symmetrical macroradicals [272]. A substantial body of work using quantum chemical calculations to assess the equilibrium constants in RAFT polymerization indicates that these equilibrium constants are large (exceeding $10^6$) and increase with increasing chain length [273–275].

6.3.2. Structure–reactivity relationships

The principles of RAFT are closely related to those of the aforementioned addition–fragmentation process with unsaturated polymethacrylates. However, the structural diversity of RAFT reagents is considerably larger, which ultimately allows for greater control over a wider range of monomers [276]. Both the $R$ and $Z$ groups of a RAFT agent should be carefully selected to provide appropriate control [277]. Generally, $R^*$ should be more stable than $P_n^*$ in order to efficiently fragment and initiate polymerization. The selection of the $R$ group should take into account the stability of the dormant species and rate of addition of $R^*$ to a given monomer.

The order of $R$ group leaving ability (illustrated in Fig. 11) reflects the importance of both steric and electronic effects. Steric effects in RAFT are much more important than in ATRP. For example, the reactivity of secondary 2-bromopropionitrile in ATRP is higher than that of the tertiary 2-bromoisobutyrate. However, the opposite trend in reactivity is observed in RAFT. Similarly, $t$-butyl halides are inactive in ATRP but are more active than benzyl derivatives in RAFT. Additionally, acrylate derivatives are not very active in RAFT, in contrast to ATRP. In the RAFT polymerization of MMA with dithiobenzoates ($S=\text{C(Ph)SR}$), the
leaving group effectiveness decreased in the order C(Alkyl)2CN ~ C(Alkyl)2Ph > C(Alkyl)2COOEt > C(CH3)2C(==O)NH(Alkyl) > C(CH3)2CH2C(CH3)3 ~ CH(CH3)Ph > C(CH3)3 ~ CH2Ph > CH(CH3)COOEt. In fact, only RAFT reagents with the first two groups were successful in preparing well-defined PMMA [278,279].

The structure of the Z group is equally important. Stabilizing Z groups such as –Ph are efficient in styrene and methacrylate polymerization, but they retard polymerization of acrylates and inhibit polymerization of vinyl esters. On the other hand, very weakly stabilizing groups, such as –NR2 in dithiocarbamates or –OR in xanthates, are good for vinyl esters but inefficient for styrene. Pyrrole and lactam derivatives occupy an intermediate position. Additional fine tuning is possible with electron withdrawing or donating substituents. For example, dithio-4-methoxybenzoate is less efficient than dithio-2,5-bis(trifluoromethyl)benzoate. A combination of resonance stabilization and polar effects contribute to the delocalization of charge and spin and stability of the intermediate. Chain transfer constants in a styrene polymerization were found to decrease in the series where Z is aryl (Ph) > > alkyl (CH3) ~ alkylthio (SCH2Ph, SCH3) ~ N-pyrrolo > > N-lactam > aryloxy (OC6H5) > alkoxy > > dialkylamino (Fig. 12) [280].

Understanding such structure–reactivity relationships has been important in the development of efficient multifunctional RAFT reagents. These reagents, often prepared from multifunctional activated alkyl bromides, can be designed in such a fashion that the leaving group following fragmentation is either bound (Scheme 18a) or detached (Scheme 18b) from the star core. The latter case results in propagation of linear chains, which can reduce cross-linking for multifunctional systems [281].

6.3.3. Retardation and termination in RAFT

The extent to which the side reactions of retardation and termination occur in RAFT depends in part upon the selection of transfer agent/monomer combinations and of the reaction conditions. One of the most extensively debated side reactions is retardation. This side reaction becomes particularly important at high concentrations of

![Scheme 18](image-url)

*Fig. 12. Rates of addition decrease and fragmentation increase from left to right for RAFT agents with these Z groups.*
RAFT agent. While retardation may be related to impurities (e.g., poor deoxygenation) or high viscosity, the full extent of its origin has been the subject of much study and debate.

Retardation may be related to the stabilization of the intermediate radical, as a highly stable intermediate radical adduct could result in slow fragmentation that would delay the establishment of a steady state of propagating radicals [282–284]. However, no further retardation would be induced by this mechanism once steady state conditions were reached. Additionally, an increased stability of the intermediate radicals could lead to an increase in their concentration, which may ultimately result in more irreversible radical–radical termination [285–287]. Other alternative models that account for retardation have been proposed that involve a reversible termination mechanism, which can help explain experimental observations of long lived intermediates [288].

Regardless of the model, rate retardation would be enhanced for an intermediate radical with enhanced stability. Indeed, significant retardation occurs in the polymerization of acrylate esters in the presence of dithiobenzoate esters, although it does not occur with dithioacetates and other alkyl dithioesters [279,289,290]. This has been attributed to the stabilization of the intermediate radical through delocalization in the aromatic group.

Termination processes can in principle lead to the formation of branched (star-like) structures. Due to delocalization of spin on the aromatic ring, the growing radicals can attack the intermediate radical at several positions, as shown in Scheme 19. Such three-arm stars have been isolated in model systems [291]. Intermediate radicals can also in principle couple to form four-arm stars [292].

6.4. Additional considerations

The dithioester group, which is responsible for color and odor if leached from the polymer chain, can be effectively removed from the product with the addition of a large excess of AIBN [271,293]. In some cases, dithioesters decompose in the presence of primary amines. Alkyl iodides may react with strong nucleophiles like amines in DMAEMA. The choice of transfer reagents is thus dictated by the monomer (according to the rules discussed above) as well as the particular synthetic target. Additional selection rules also dictate the order of monomers in a block copolymerization. For example, isobutyrate derivatives are good initiators for acrylates, but propionates are not efficient initiators for the polymerization of methacrylates in RAFT because methacrylates make much better leaving groups than acrylates. Thus, a polymethacrylate block must precede a polyacrylate segment in order to achieve controlled growth of the second block.

DT has been successfully carried out in dispersed media. Both alkyl iodide and RAFT were efficient in miniemulsions [294,295]. Some problems have been encountered using emulsion polymerization that were related to the transportation of mediating reagents through the aqueous phase. This consequently affected colloidal stability of the latexes, but
it is a common problem in all CRP systems. By using reactive macro-chain transfer agents that also can serve as surfactants, stable latexes have been prepared [296].

7. Summary and comparison of SFRP, ATRP and DT processes

The unifying element of all CRP systems is the dynamic equilibrium between propagating radicals and various types of dormant species. Radicals propagate and exchange with dormant species but can also terminate and participate in any number of other reactions typical of organic radicals (transfer, rearrangements, fragmentation, etc.). Chemoselectivity, regioselectivity and stereoselectivity in CRP and conventional RP are similar. The ability of CRP techniques to control molecular weights and polydispersities and to provide access to well-defined molecular architectures originates both in fast initiation and in limitation of the chain growth to a level where the contribution of chain breaking reactions is negligible.

There are two general approaches to establishing such an equilibrium between dormant and active species. The first relies on reversible “termination” (deactivation) whereas the second approach relies on reversible “transfer” (degenerative exchange). In both cases, the intermittent activation occurs when a radical propagates a few times before it is converted to a dormant state. Polydispersity depends upon the efficiency of initiation, the contribution of chain breaking reactions, and the dynamics of the exchange process. Polydispersities are lower when exchange is faster, i.e., less monomer units are added during each activation step.

Systems based on the PRE (ATRP and SFRP) have kinetic features distinct from DT systems. In the latter case, rates depend on the continuously supplied initiating radicals which also continuously generate new chains. End group functionalization in SFRP and RAFT generally involves radical displacement/addition chemistry. In ATRP and iodine transfer radical polymerization, nucleophilic substitution and electrophilic addition are also possible. In all systems, essentially every (dormant) chain is capped with a protecting group. Dormant species are metastable in SFRP and may be light sensitive in RAFT. The most readily available, stable, and inexpensive groups forming dormant species are alkyl halides employed in ATRP. However, ATRP also requires catalytic amounts of transition metal complexes that may need to be removed after the polymerization is completed.

The order of reactivity of dormant species dictates the order of segments to be built in block copolymer synthesis. This order generally scales with the stabilities of the resulting radicals, i.e., methacrylates > styrene > acrylates. However, this order also depends on the structure of the capping agent and is particular to each CRP mechanism. The relative rate constants of activation, the equilibrium constants between active and dormant species, and the (cross)propagation rate constants depend on three major factors: radical stability ($\sigma_{RS}$), polar effects ($\sigma_u$), and steric effects ($\nu$). These parameters are available in literature and are listed in Table 4 together with C–H bond dissociation energy values for the corresponding hydrocarbons [297–299].

A comprehensive study of the effect of these three parameters on dissociation rate constants of alkoxamines with various substituents with either TEMPO or DEPN moieties has been published [297]. The correction parameters for the radical stabilization of primary (−9.6 kJ/mol), secondary

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>BDE (C–H) kJ mol$^{-1}$</th>
<th>$\sigma_{RS}$</th>
<th>$\sigma_u$</th>
<th>$\nu$</th>
</tr>
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<tr>
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<td></td>
<td>352.8</td>
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<td>0.05</td>
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<td>0.03</td>
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<tr>
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<td>0.2</td>
<td>0.07</td>
<td>1.43</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>385</td>
<td>0.18</td>
<td>0.09</td>
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<tr>
<td>6</td>
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<td>406.3</td>
<td>0.15</td>
<td>0.15</td>
<td>0.8</td>
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<tr>
<td>7</td>
<td></td>
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<tr>
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<td>0.16</td>
<td>0.2</td>
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<td>0.54</td>
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<tr>
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<tr>
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</tr>
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<tr>
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<td></td>
<td>438.5</td>
<td>0</td>
<td>–0.01</td>
<td>0.52</td>
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</tbody>
</table>
(-14.2 kJ/mol) and tertiary (-18.0 kJ/mol) radicals were used to normalize values of \( \sigma_{RS} \). The overall rate constant can be defined by the three parameters according to

\[
\log(k_d) = a(\sigma_{RS} + b\sigma_{u} + c\sigma_{v}) + d. \tag{18}
\]

In this equation, parameters \( b \) and \( c \) illustrate the influence of polar (\( \sigma_{u} \)) and steric effects (\( \sigma_{v} \)) relative to standardized radical stabilization (\( \sigma_{RS} \)). Parameters \( a \) and \( d \) describe the overall values of rate and equilibrium constants, and their sensitivity to structural effects.

Fig. 13 illustrates the effect of \( \sigma_{u} \), \( \sigma_{v} \), and \( \sigma_{RS} \) on dissociation constants of TEMPO derived alkoxyamines. The three parameters equation shows good overall fit for 13 different species with \( R^2 = 0.94 \). A similar equation has been derived for DEPN-based alkoxyamines.

Dissociation constants for various alkyl bromides, chlorides, iodides and dithioesters have previously been computed using DFT [153,300]. It is tempting to correlate values of the dissociation equilibrium constants with the aforementioned three parameters and compare them with dissociation rate constants for alkoxyamines. All parameters are included in Table 5.

Parameters \( a \) and \( d \) for all equilibrium constants are obviously very different from those measured for the rate constants. However, parameters \( b \) and \( c \) allow comparison of the relative contribution of polar and steric effects, respectively. It appears that polar effects are more important for alkyl halides in ATRP (\( b = 2.23 \)) than TEMPO (\( b = 0.99 \)). RAFT reagents based on dithioacetate occupy an intermediate position (\( b = 1.21 \)). By contrast, ATRP shows the smallest sensitivity to steric effects (\( c = 0.14 \pm 0.02 \)), while both alkoxyamines and dithioacetate show much larger sensitivity to steric effects, \( c = 0.50 \) for TEMPO, 0.45 for DEPN and 0.48 for dithioacetate. A more comprehensive computational study is currently being conducted that will compare equilibrium constants for all processes, study the effect of stabilizing phenyl group in dithiobenzoate and other polar groups in various RAFT reagents, and expand the database for a large number of alkyl radicals.

As discussed in Sections 5.2.2 and 6.3.2, the order of segments in block copolymerization as well as efficiency of \( R \) groups in initiator/transfer agents may depend on the particular mechanism. For example, since RAFT and NMP are more accelerated by steric effects, a poly(methyl methacrylate) block can be extended with polyacrylonitrile. The opposite is true for ATRP. Similarly, tert-butyl dithioesters can efficiently control polymerization of acrylates, but tert-butyl halides are very inefficient in ATRP.

Each CRP system has some comparative advantages over as well as limitations with respect to the other techniques. The discussion now focuses on recent advances that have reduced many such limitations.

### 7.1. SFRP

Radicals are reversibly trapped to form a dormant species in SFRP that returns spontaneously (i.e. thermally) to the active state after a...
period of inactivity. The most successful traps include nitroxides (NMP) and metalloradicals (usually paramagnetic Co II species involved in SFRP). However, the trap does not have to be a radical but can also be a non-paramagnetic metal or an organic species such as thioketone [301] or phosphite [302]. The activation process is typically thermal but can be also induced by light (dithiocarbamates). There are two types of initiating systems for SFRP. The first employs preformed dormant species (e.g., alkoxyamines, or so-called unimolecular initiators). Alternatively, a binary system can be used consisting of a radical trap and any source of radicals (peroxides, diazo compound, γ-rays, etc.). The latter approach is useful in the synthesis of homopolymers but not block copolymers.

The advantages of SFRP over ATRP include that purely organic systems can be employed (NMP) and that the technique is applicable to many monomers (including acidic monomers). The limitations include that relatively expensive moderators are often used and are always required in stoichiometric amounts relative to the number of polymer chains; this large amount of species includes potentially toxic transition metal compounds; it is very difficult to control the polymerization of disubstituted alkenes such as methacrylates; it is difficult to introduce end functionality to the polymer; and relatively high temperatures are generally required.

7.2. ATRP

Both ATRP and SFRP obey the persistent radical effect. However, because activation in ATRP is a bimolecular process, the dormant species in ATRP are inherently stable and are activated only in the presence of a transition metal catalyst. Reaction rates are defined by the ATRP equilibrium constant and a ratio of concentrations of $Mt^n/L$ and $X–Mt^{n+1}/L$ species. Rules for catalyst selection have been developed to appropriately match a catalyst with a given monomer or polymerization system for optimal control. Termination coefficients in SFRP and ATRP progressively decrease with conversion and chain length, as only long chains exist after an initial period that terminate much slower than short chains and initiating radicals. Catalysis should operate via single electron transfer (inner sphere) process and ideally should not extensively participate in β-H elimination or abstraction reactions or the formation of organometallic species.

The initiation systems include normal ATRP, which starts from an appropriate alkyl halide and a transition metal complex in its lower oxidation state. Reverse ATRP employs a transition metal complex initially in its higher oxidation state together with a radical initiator. While originally less sensitive to oxidation by residual air or contaminants, the latter technique (like the binary SFRP systems) cannot be applied to the synthesis of block copolymers. Simultaneous normal and reverse initiation (SR&NI) can be used to produce block copolymers, although some homopolymer will always be formed. Pure block copolymers can be formed if the activators are generated by electron transfer (ARGET). In reverse ATRP, SR&NI and AGET systems, $X–Mt^{n+1}/L$ species are reduced at an early stage of polymerization and conventional ATRP subsequently occurs and obeys PRE kinetics. When activators are re-generated by electron transfer (ARGET), transition metal compounds can be used in truly catalytic amounts (ppm) in conjunction with benign reducing agents that compensate for any loss of activators due to biradical termination. In a similar technique, radical initiators can be used for continuous activator regeneration (ICAR), where the kinetics of this ATRP system obey that of degenerative transfer or conventional RP.

Advantages of the ATRP technique are numerous: catalytic amounts of transition metal complexes are used; many initiators are commercially available, including multifunctional and hybrid systems; a large range of monomers can be polymerized (with the exception of unprotected acids); end-functionalization is very simple; there is no Trommsdorf effect; a large range of temperatures can be employed; block copolymerization can be achieved in any order (with halogen exchange), which is not possible for other CRP methods. The limitations of ATRP include that the transition metal complex must often be removed from the product, and acidic monomers require protection.

7.3. RAFT and other DT processes

DT approaches provide the smallest perturbation to conventional RP systems. Polymerization rates usually depend on $[I]_0^{1/2}$. The degree of polymerization is defined by the ratio of concentrations of consumed monomer to that of the introduced
transfer agent (assuming the concentration of transfer agent is much higher than that of the decomposed initiator). DT systems employ either atom/group transfer or addition–fragmentation chemistry. In the latter case, intermediate radicals may participate in some side reactions, such as cross-termination. The choice of the appropriate transfer agent for a particular monomer is very critical. Weak transfer agents, such as dithiocarbamates, are efficient for vinyl acetate but fail to control RAFT of styrene or MMA. Strong transfer agents such as dithiobenzoates are efficient for MMA but can retard RAFT of styrene and acrylates and inhibit RAFT of vinyl acetate. Equally important is the structure of the leaving group \((R)\), which strongly affects initiation efficiency and is responsible for potential inhibition periods. Some functional groups in monomers or initiators are not compatible with some DT reagents. For example, dialkylamino groups are converted to ammonium in iodide transfer radical polymerization (ITRP), and primary amino groups decompose dithio compounds.

Initiation systems for DT all consist of a transfer agent and a radical initiator. In some cases, it is possible to use a precursor to a transfer agent, such as iodine (for reverse iodine transfer radical polymerization, RITRP) \([303]\), or dialkyl ditelluride (for tellurium mediated radical polymerization, TERP) \([264,304]\). DT processes require a continuous supply of new initiating radicals, which generate new polymer chains. Thus, it is not possible to prepare pure block copolymers in DT systems. Also, in contrast to SFRP and ATRP, growing long polymer chains cross-terminate faster with newly generated short chains (or initiating radicals) than with other long chains. Polydispersities in DT systems are not affected by the concentration of transfer agent but by a simple ratio of the rate constants of exchange to propagation; however, they can be reduced by slow feeding of the monomer to a polymerization mixture.

It is not clear the extent to which the Trommsdorf effect occurs in DT systems. Since termination coefficients decrease with conversion, polymerization may accelerate, increase reaction temperature and induce faster radical dissociation, as in conventional RP. However, since the amount of radical initiator is small, the magnitude of the Trommsdorf effect should be smaller. In systems based on DT, a steady state radical concentration is established through initiation/termination, as opposed to systems obeying the PRE (SFRP, ATRP), where it is established through activation/deactivation equilibria.

A very large range of monomers can be used in DT systems, there are minimal perturbations to RP kinetics in these techniques, and the systems are quite often mediated by purely organic reagents, which are important advantages of DT systems. However, limitations include the lack of commercial availability and stability of many transfer agents, the removal of dithioester and some other end groups required due to their color, toxicity, and potential odor, and the difficulty associated with end-functionalization.

7.4. Recent progress in SFRP, ATRP and DT

It is not possible to provide an absolute evaluation of these three techniques and state which one is overall most efficient. From an economic standpoint, the differences are not substantial, and on the appropriate scale, production costs among the three techniques is predominantly affected by costs associated with the particular monomer. However, one may compare the three systems from the point of view of targeted structures and particular processes. Such a comparison was attempted in 2002 and is shown in the left side of Fig. 14 \([305]\).

The figure attempts to compare NMP, ATRP and RAFT in the areas related to the synthesis of high molecular weight polymers (HMW), low molecular weight polymers (LMW), end functional polymers (End Funct), block copolymers (Blocks), range of polymerizable monomers (Mon Range), synthesis of various hybrid materials (Hybrids), environmental issues (Env) and polymerization in aqueous media (Water). The right side of the figure shows an updated situation as of 2006. All three techniques have advanced in all areas, largely a result of a more thorough mechanistic understanding of the relevant phenomena.

**High molecular weight polymers.** While linear HMW polymers can be achieved under normal ATRP conditions for a few monomers (i.e., (dimethylamino)ethyl methacrylate \([306]\)), with the majority of monomers HMW polymers are difficult to access with ATRP due to outer sphere electron transfer processes, involving oxidation or reduction of radicals, as well as \(\beta\)-H elimination reactions. However, using low concentrations of Cu catalyst in ARGET and ICAR ATRP, linear polymers with MW exceeding 200,000 g/mol were prepared \([221]\). Additionally, the application of difunctional
Initiators in NMP and ATRP can preserve functionality and increased MW by radical coupling. The synthesis of brushes from backbones with multiple initiating sites is an efficient route to HMW polymers \[307\]. In fact, MW exceeding 10,000,000 g/mol have been prepared by ATRP using multifunctional initiators \[308,309\].

Low molecular weight polymers were once difficult to prepare with RAFT due to strong retardation reactions. However, the appropriate selection of RAFT reagents has greatly alleviated this problem. The cost of the end group now remains the main issue in the synthesis of LMW polymers for all CRP techniques.

**Polymer endgroup functionality:** Several novel approaches were used to facilitate the introduction of functional groups into NMP and RAFT systems. These include the displacement of dithioesters (Scheme 20a) and reactions involving reduced thiols in RAFT \[270,271,293\]. The controlled monoaddition of maleic anhydride and maleimide derivatives in NMP to the alkoxyamine chain end ultimately allowed for the introduction of a wide variety of functional groups (Scheme 20b) \[310\].

**Block copolymers:** Block copolymerization in NMP was greatly improved with the addition of a small amount of comonomer. Halogen exchange in ATRP is now better understood, although it inherently cannot be applied to new ARGET and ICAR systems, which do not use “enough” Cu catalyst.

**Range of polymerizable monomers:** The range of monomers has been significantly extended in all CRP techniques. In NMP, MMA can now be controlled in the presence of small amounts of styrene \[59\]. In ATRP, vinyl chloride, \[311\] vinyl acetate \[265\] and some acidic monomers \[312\] can also now be controlled. New ligands have also enabled the (co)polymerization of vinyl ketones, dienes, and even maleic anhydride.

**Hybrid materials:** In the last five years, there has been an explosion of research in both organic–inorganic hybrids \[313,314\] as well as in the biohybrids area \[315,316\]. In many cases, ATRP is the method of choice due to a very facile functionalization of surfaces with activated alkyl halides. However, more inorganic substrates and biomolecules are progressively being functionalized with alkoxyamines and dithioesters, which is opening pathways to new hybrids via NMP and RAFT, respectively. Densely grafted chains form molecular brushes on inorganic surfaces. They can prevent corrosion, they have novel lubrication properties, and they cannot be compressed in the same way as less densely grafted polymers \[317\]. Novel bioconjugates prepared by all CRP techniques can be used as efficient drug carriers and components of tissue and bone engineering.

**Environmental issues:** For ATRP, a very strong reduction of the required catalyst level with the use of new ARGET and ICAR initiation systems has obvious environmental benefits. It is possible to remove dithioesters and xanthates from products.
generated in RAFT/MADIX systems. However, the cleanest systems may still be those based on nitroxides using alkoxyamines as potential polymeric stabilizers.

However, environmental issues are not only related to how environmentally benign a particular process is but also whether the preparation of materials can have any positive impact on the environment. ATRP has been successfully used to prepare self-plasticizing PVC [318,319] that can eliminate the need of using toxic phthalates as plasticizers. ATRP has been also used to prepare surfactants that can efficiently transport iron nanoparticles through ground waters to halogenated liquids (e.g. trichloroethylene) that have accumulated underground and are contaminating drinking water sources [320,321]. This system is based on a concept similar to targeted drug delivery. All CRP techniques have been used to prepare non-ionic surfactants and dispersants for pigments that increase the efficiency of these materials [322–325].

Polymerization in aqueous media: Polymerization in water has been successful under homogeneous as well as heterogeneous conditions [86,326]. Originally, only dispersion and miniemulsion processes were efficient, and true emulsions failed due to problems associated with transportation of the mediating species through the aqueous phase [327]. However, by using reactive surfactants in RAFT [296], NMP [328–330] and microemulsion [331,332] as a seed for the emulsion process, this problem has been alleviated. Additionally, inverse emulsion has been successfully carried out for water soluble monomers in the continuous organic phase [200,201]. It has been applied to prepare reversible nanogels with potential use for drug delivery and carriers for biomolecules.

8. Selected examples of controlled polymer architectures by CRP

CRP can be used to prepare well-defined polymers with predetermined molecular weights, low polydispersities, and precisely controlled architectures. In comparison with other controlled/living systems, CRP has some limitations in that termination cannot be totally eliminated. However, CRP techniques also have many advantages, including relative insensitivity to transfer and protic impurities and a very large range of (co)polymerizable monomers. The basic strategies for producing polymeric structures by CRP techniques with controlled topologies, compositions, and functionalities (illustrated in Fig. 15) are summarized below.

8.1. Topology

CRP is very well suited for the preparation of (co)polymers with controlled topologies, including star- and comb-like polymers as well as branched, hyperbranched, dendritic, network, and cyclic type structures.
Star-like polymers have been prepared using four different approaches [333]. (1) A core first approach employs multifunctional initiators from which several arms are grown simultaneously. ATRP is particularly useful with this technique due to availability of many polyols that can be subsequently converted to an initiating core with 3, 4, 6, 12 or more initiating sites [334–336]. (2) An arm first approach involves attachment of chains to a functional core. RAFT offers a unique possibility here as certain RAFT reagents can be attached to a core via the Z group [281]. "Click" chemistry can also be employed between azide functionalized chains and an acetylene functionalized core [337,338]. (3) Arms can be crosslinked in the presence of divinyl compounds (although the number of arms in the resulting stars is not precisely controlled with this technique) [339–341]. (4) Arms that are cross-linked in the presence of divinyl compounds #3 still contain active/dormant species at the core from which a second generation of arms can be grown to generate mikto-arms of different lengths or different monomers [341].

Comb-like polymers can be prepared by 3 different techniques corresponding to grafting from, onto and through. (1) **Grafting from** is similar to a core-first approach for stars as chains are grown (via CRP) from a polymer backbone prepared by RP or another method [318,342–346]. (2) **Click chemistry** can be used to efficiently attach side chains to a backbone in **grafting onto**, which is similar to an arm first approach for stars [347]. (3) **In grafting through**, vinyl terminated macromonomers are utilized as comonomers together with a low MW monomer [348–354]. Variations in grafting density enable the production of combs of different shapes, as well as gradient brushes and tadpole or dumbbell structures [355]. An interesting combination of a star-brush system is shown in an AFM image (Fig. 16) of a four arm star molecular brush with a degree of polymerization for each polymethacrylate arm DPₙ = 300 and each poly(n-butyl acrylate) side chain DPₙ = 37. The inset shows the magnification at higher resolution in which individual side chains are resolved on mica surface by tapping mode AFM [356].

Similar to RP, branching occurs in polymers made by CRP as a result of transfer to polymer. CRP can be also used to prepare hyperbranched polymers with monomers that also serve as initiators (so-called inimers) of new branches [357–359]. Hyperbranched structures can also be obtained when divinyl monomers are used in small relative concentrations or are copolymerized to relatively low conversion [360]. While these hyperbranched systems are irregular, regular dendritic structures were prepared by CRP where the degree of branching is controlled by the degree of polymerization [361,362].

CRP processes can be used to significantly improve network uniformity over structures prepared by free RP [363]. Well-defined polymers with crosslinkable pendant moieties can be prepared to form microgel networks. Degradable gels can be prepared with disulfide linkages [364]. Additionally, it is possible to use crosslinkers which can be reversibly cleaved that subsequently lead to the formation of reversible gels [201].
Anionic and/or cationic polymerizations are much better suited to make cyclic polymers than CRP processes by using complimentary reagents at very low concentrations. However, cyclization has been reported when click chemistry was used in a reaction of azido- and acetylene-terminated chains \[\text{365}\]. This process was recently optimized to provide an efficient route to polystyrene macrocycles \[\text{366}\].

\[8.2. \text{Composition}\]

The tolerance that CRP processes show toward functional groups allows for the prolific production of a vast array of statistical, segmented (blocks and graft), periodic (mostly alternating), and gradient copolymers. In addition to materials prepared by one specific CRP technique, many are prepared by a combination of radical polymerization and other techniques.

Block copolymerization has been conducted with a combination of methods through site transformation of the polymer end groups. ATRP initiators have been successfully converted to RAFT and NMP initiators \[\text{367}\] and vice versa. Polymer end groups originally prepared by cationic \[\text{368}\], anionic \[\text{369,370}\], ionic ring opening \[\text{371,372}\], ring opening metathesis \[\text{373}\], coordination \[\text{342,353,374}\], and step-growth polymerization \[\text{375–377}\] have all been converted to CRP initiating sites. Multi-segmented block copolymers are typically prepared by polycondensation processes. However, ATRP has been used to make ABC or ABCBA segments using sequential polymerization techniques. ATRP macroinitiators can also be used to create difunctional \(\pi\)-alkyne-\(\pi\)-azido-terminated blocks. Click coupling in a step growth process then affords an efficient route to multisegmented block copolymers \[\text{365}\].

Graft copolymers have been synthesized with techniques similar to those applied in the preparation of comb polymers (grafting from, onto and through) in addition to methods known for block copolymerization such as site transformation. The density of the grafts can be varied along the length of the chain to generate gradients (Scheme 21) \[\text{378,379}\], and various types of block graft-copolymers have also been created, including core-shell cylinders as well as heterografted \[\text{380}\] and double grafted \[\text{351}\] structures, etc.

When comonomers have a similar reactivity, statistical copolymers are formed. Different comonomer reactivity ratios result in copolymers with a spontaneous gradient \[\text{381,382}\]. When monomers with strong electron donor groups are copolymerized with those that have strong electron acceptors, polymerization occurs in alternating fashion to generate periodic copolymers \[\text{383}\]. Other examples of alternating copolymerizations occur with kinetically reactive but thermodynamically non-homopolymerizable monomers (e.g., maleic anhydride) \[\text{384}\] and when less reactive monomers are used in large excess to reactive monomers (e.g., olefins with acrylates) \[\text{385}\]. The addition of Lewis acids can
also affect monomer sequences [386] and polymer tacticity [103–105].

Molecular hybrids can be generated by covalently attaching synthetic polymers to inorganic materials and natural products [313]. Functional groups (NH₂ or OH) in natural products can be converted to ATRP initiators (bromoamides and bromoester) and polymerization subsequently conducted. Chains prepared by CRP containing functionalities (NH₂ or OH) can be used to grow polypeptide or DNA [387]. Biotin-avidin and click chemistry can also be used to fuse functionalized natural products together with organic polymers [316, 388–392].

8.3. Functionality

Propagating radicals are tolerant to many functionalities, which allow incorporation of functional monomers and initiators into a (co)polymer via most CRP processes. Additionally, functionality can be introduced to specific parts of a macromolecule. This includes incorporation of side functional groups directly to a polymer backbone [326] or in a protected form [393]. End groups can be incorporated by using either functional initiators or by converting a chain end to another functional group [394]. For example, dithioesters in RAFT have been converted to thiols, alkoxyamines in NMP to alkyl chlorides, and the alkyl halides in ATRP to allyl, hydroxy, amino, azido and ammonium or phosphonium groups in excellent yields (Scheme 22). The conversion of dormant species in linear chains growing in two directions leads to telechelics and in stars to multifunctional polymers. Functionalities can be also introduced to specific parts of macromolecules. This includes the functional core of stars, the centers of two-directionally grown chains, and in between periodically repeated segments prepared by ATRP or click coupling.

9. Material applications

Although the CRP processes of SFRP, ATRP and RAFT were realized in just the last decade, these techniques are already finding application in the commercial production of many new materials. A few examples of such materials already in production are highlighted hereafter, although it is anticipated that many more specialty products will become available in the relatively near future [395].

Block copolymers based on acrylates and other polar monomers may find applications as polar thermoplastic elastomers [177] similar to those for Kraton, a landmark material whose production was
enabled by Michael Szwarc’s discovery of living anionic polymerization 50 years ago. Such materials can be used as adhesives and sealants, in many compounding applications, including automotive, wire and cable, footwear, medical, soft touch overmolding, cushions, squeezables, and even toys.

They can be used as thermoplastic vulcanizates, in flexographic printing, road marking, lubricants, gels, and coatings. However, they can also be used for much more sophisticated applications such as specialized chromatographic packing [396] or controlled drug-release in cardiovascular stents [397]. They can also replace silicone and flexible PVC in several applications. These thermoplastic elastomers also have two major advantages over Kraton: they have higher UV and thermal stability and they do not swell in the presence of hydrocarbons.

Amphiphilic block copolymers with water soluble segments have been successfully used as very efficient surfactants [398] and have also been used for higher end applications including pigment dispersants, various additives, and components of health and beauty products [322,323]. Segmented copolymers with nanostructured morphologies are promising as microelectronic devices [399–402]. Graft copolymers have been used as compatibilizers for polymer blends and may be used in many applications described for block copolymers [9,342,403]. Gradient copolymers hold great promise in applications ranging from surfactants to noise and vibration dampening materials [382].

Designed branching allows precise control over melt viscosity and polymer processing. Such polymers (as well as comb and star polymers) can be used as viscosity modifiers and lubricants. An ultimate example of controlled topology might be a macromolecular bottle-brush. Such polymers, when lightly crosslinked, result in supersoft elastomers. Materials have been synthesized with moduli ~1 kPa, in the range attainable by hydrogels. However, hydrogels must be swollen 100 times by water to reach such low moduli. Molecular brushes are swollen by their own short side chains that never leach. Thus, applications are foreseen ranging from intraocular lenses and other biomedical applications requiring a soft material that does not leach to surrounding tissue, to specialty toys, adult novelty items, and even electronic applications requiring the protection of delicate components by a soft solid. These materials also show very high ionic conductivities reaching 1 mS/cm for Li cations at room temperature [404].

CRP offers unprecedented control over chain end functionality. End functional polyacrylates are excellent components of sealants for out-door and automotive applications. These functionalities can also be used for reactive blending. Multifunctional low MW polymers are desirable components in coatings with a low organic solvent content important for VOC reduction. It is also possible to design systems with two types of functionalities, curable by two independent mechanisms. Incorporation of
degradable units into the backbone of vinyl polymers allows controlled cleavage and degradation/ recycling of such polymers. Molecular hybrids with a covalent attachment of well-defined functional polymer to either an inorganic component or a natural product are currently being extensively investigated and should lead to numerous materials with previously unattainable properties. Such hybrids and nanocomposites allow better dispersability of inorganic components (pigments, carbon black, carbon nanotubes, nanoparticles), they dramatically enhance the stability of such dispersions, and they allow the formation of molecular nanocomposites. Also, dense polymer layers improve lubrication, prevent corrosion, and facilitate surface patterning. Precise grafting from chromatographic packing can enable enhanced chromatographic resolution of oligopeptides and prions not previously available [396].

Other potential applications include microelectronics, soft lithography, optoelectronics, specialty membranes, sensors and components for microfluidics. Well-defined polymers prepared by CRP are very well-suited for biomedical applications such as components of tissue and bone engineering, controlled drug release and drug targeting, antimicrobial surfaces [405], steering enzyme activity [392,406], and many others.

10. Future perspectives

Precise control over molecular architecture via controlled/living polymerization requires the suppression of chain breaking reactions. The development of such techniques has enabled the synthesis of new materials for specialty applications and has helped build a much needed correlation between molecular structure and macroscopic properties. There are several reasons why CRP is currently the most rapidly developing area of synthetic polymer chemistry. They include the large range of polymerizable monomers, the simple reaction set-up and undemanding conditions, unprecedented control for a radical polymerization, and very importantly the large potential market for products made by CRP. However, to reach its full potential, more research is needed in various areas of CRP.

Fundamental mechanistic and kinetic studies of all CRP processes are still very necessary. A deeper understanding of structure-reactivity correlation in NMP may lead to satisfactory control over polymerization of methacrylates. The proper choice of dithioesters may decrease retardation effects of RAFT reagents. A full comprehension of structural affects for ATRP catalysts could lead to the development of even more active complexes that can be used in smaller amounts. This could minimize the environmental impact of ATRP chemistry, as well as expand the range of polymerizable monomers to include (meth)acrylic acid and \( \alpha \)-olefins. Some transition metal complexes participate in both ATRP and SFRP and can potentially even be involved in coordination polymerization. This may open an efficient route to the incorporation of polar monomers into a polyolefin backbone. Model reactions with low MW analogs and oligomers are needed to evaluate penultimate effects and quantify potential chain breaking reactions. Various additives that can accelerate polymerization and provide enhanced microstructural (tacticity and sequence) control should be evaluated. They can increase stereoselectivity as well as chemoselectivity, which are relatively low for radical processes. Better cross-fertilization between synthetic organic chemistry and polymer chemistry is needed. In the past, achievements in organic chemistry were applied to polymer chemistry. However, recent advances made in polymer chemistry have now benefited organic chemistry; e.g. new catalysts developed for ATRP are used for atom transfer radical addition and cyclization and new nitroxides developed for NMP are used in organic synthesis [56,407,408].

A deeper insight into the reaction intermediates and energetic pathways will be possible using new techniques offered by computational chemistry. However, precise computational evaluation requires a large basis set, since many reaction pathways may become dramatically affected by tiny changes in the structure of the substituents. Thus, continued model studies and their correlation with macromolecular systems are very much needed to better understand and optimize the existing processes. Computational chemistry has already helped to develop new RAFT reagents and may help to discover new mediating systems for SFRP and ATRP. Although current CRP techniques seem to cover all major mechanistic approaches to equilibria between active and dormant species, it is feasible to imagine more efficient stable free radicals, more active transition metal complexes and better degenerative transfer agents than currently available. Thus, both a serendipitous and rational search (including leads from computational chemistry and model organic systems) for new mediating agents in CRP should continue.
Most CRP reactions are carried out under homogeneous conditions. However, new possibilities exist by using dispersed systems (microemulsion, inverse emulsion, precipitation polymerization, etc.). Polymerization in confined space may lead not only to new nanocomposites and hybrids but can potentially facilitate additional control over several facets of the polymerization (less termination, stereocontrol, etc.). Crosslinking reactions in CRP provide networks with very different properties than conventional RP. Higher network uniformity leads not only to better swellability but will also be very important for membranes, drug release, and special separation techniques.

CRP has provided access to nearly all macromolecular architectures available from anionic polymerization. However, there are still a few difficult and challenging structures, including heteroarm star polymers, cyclic polymers, and some others. These challenges can be resolved by using multifunctional initiators in CRP or special terminating/capping agents. Precise synthesis of polymers with complex architectures must be evaluated by accurate characterization techniques to determine quantitatively the level of functionality, detect existing imperfections, and exactly describe composition, topology, and microstructure. Novel scattering techniques, modulated thermal analysis, detailed mechanical analysis, more sensitive spectroscopic techniques, multidimensional chromatography, and visualization of individual molecules by AFM are just a few examples of techniques that help characterize the exact structure of prepared materials. There are many remaining challenges in the characterization of gradient copolymers, including measuring the profile and uniformity of the gradient. This is an important issue (from the point of view of intellectual property) since many copolymers prepared by CRP are inherently different from those prepared by RP.

New polymers with precisely controlled architecture are primarily developed to explore novel properties. Such structure–property correlation is very much needed for many applications. Since macromolecular systems are very large and complex, it is difficult to predict all properties by modeling and computational techniques without input from well-defined macromolecules. The detailed correlation of molecular structure with final properties is still not obvious since many properties will also depend on processing conditions, including the solvent used and its removal conditions, mechanical stresses, and thermal history. The incorporation of such parameters into simulations will be very beneficial.

Additionally, evaluation of all imperfections and synthetic errors on properties of prepared polymers is needed. This should include the affect of polydispersities and shape of molecular weight distribution. Polymers with higher polydispersities may form new morphologies with enhanced curvature and sponge-like systems. They can also allow more flexible processing regimes. In CRP, it will be much more economical to prepare polymers faster, with more termination, and with more errors. Therefore, it will be important to understand how these imperfections may affect material properties to optimize cost–performance ratio.

Thus, CRP has a very bright future, and it is anticipated that many new products will be introduced to the market within the next several years. The annual value of materials made by CRP was recently projected to reach as high as $20 billion, corresponding to ~10% of all materials prepared by conventional radical polymerization. However, reaching this target will require a joint effort from synthetic polymer chemists, polymer physicists, processing engineers and marketing specialists, as it happened when Michael Szwarc discovered living anionic polymerization.

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