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Living Radical Polymerization

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Free radical polymerization processes are used to produce approximately 50% of polymer products worldwide and are therefore of great industrial importance [1]. However, many product properties cannot be controlled precisely using conventional free radical polymerization techniques due to the fundamental reaction mechanism. Whereas general bulk properties of polymers can be controlled to some extent with conventional processes, structural control at the molecular level cannot be achieved.

Over the past 15 years, new free radical polymerization techniques have been developed which allow significantly improved control over polymer structure at the molecular level. By using these techniques, customized polymeric materials can be produced which are not possible using conventional methods of the past. These new techniques are typically termed *living* or *controlled* free radical polymerization. There is some debate over the semantic use of these terms [2, 3], but the term “living radical polymerization” (LRP) will be used here for simplicity.

The purpose of this chapter is to give a basic overview of the living radical polymerization field, along with a survey of work that has been carried out specific to microreactors. First there is a general definition of living polymerization processes and a description of why they are useful. This is followed by details of the mechanistic differences between conventional free radical polymerization and three general classes of living radical polymerization. A more detailed overview is then given of the three most common living radical polymerization techniques: nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP) and reversible addition–fragmentation chain transfer (RAFT) polymerization. Finally, there is a discussion about living radical polymerization techniques that have been investigated in the microreactor field.

13.1

Living Polymerization

The term “living” polymerization was coined by Szwarc in 1956 during the development of the anionic polymerization process [4, 5]. For a polymerization process to be

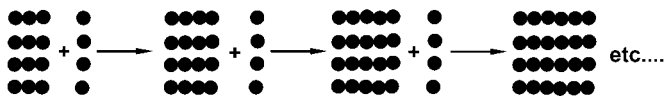


Figure 13.1 Idealized living polymerization: one monomer unit adds to the end of each polymer chain during each reaction step. Each black dot is a single monomer molecule and a string of black dots is a polymer chain.

considered living, it is necessary to suppress all chain-breaking reactions such as termination and chain transfer [6]. In other words, a living polymer chain should always have the ability to grow further under appropriate circumstances.

An *ideal* living polymerization process would consist of the following conditions (see Figure 13.1):

1. Each polymer chain in a system starts to grow at the same time.
2. A monomer unit is added to every polymer chain endgroup in the system during each growth (propagation) step of the reaction.
3. No unwanted side-reactions occur.

In addition to the above, there are two further requirements for an ideal living polymerization process:

1. The reaction only stops when there is no more monomer present in the system or when the conditions are adjusted to force the reaction to stop.
2. The polymerization reaction can be restarted at any time. One interesting aspect of this condition is that a block copolymer can be formed if a different monomer is added to the system before restarting the reaction (see Figure 13.2).

Note that the term “living” arises from the fact that the polymer chain never “dies” via a termination reaction or other side-reaction and it can start to grow again if new monomer “food” is added to the system [5]. In principle, one should be able to stop and restart the process at will and polymers can be tailored to any molecular weight and structure desired for a given application [7] (see Figure 13.3 for examples).

This idealized process is not possible using current methods, but there has been much progress towards approaching the ideal. Until the early 1990s, the most successful living polymerization work was in the area of anionic, cationic and group transfer polymerization processes [8]. However, although these techniques have been heavily studied in academia, they have not been implemented in industry as widely as conventional processes due to a number of drawbacks such as sensitivity to impurities, inability to react in the presence of water and undesirably low reaction

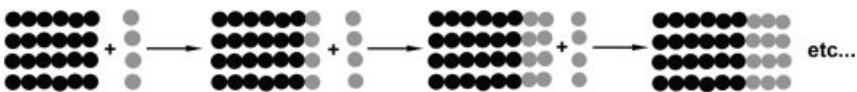


Figure 13.2 Idealized living polymerization: Reaction can be restarted using a different monomer, thus creating a block copolymer.

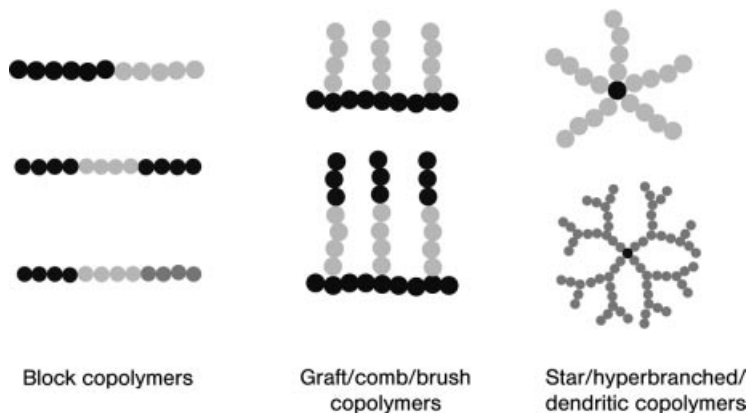


Figure 13.3 Examples of structures that have been prepared by LRP.

temperatures [9]. Free radical polymerization processes are not affected by these issues to the same extent, so there has always been interest in developing living polymerization techniques that work for free radical systems.

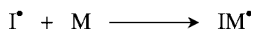
Studies as early as 1955 hinted at methods by which living radical polymerization (LRP) could be performed [10] and a number of studies over the years also suggested that it should be feasible [11]. One of the first major breakthroughs occurred in 1982, when Otsu and coworkers demonstrated the concept of the “iniferter” (*initiator transfer agent terminator*) and first used the term *living* radical polymerization [12–14]. Some living polymer characteristics were demonstrated at this time (i.e. linear increase in molecular weight with time), but non-living characteristics were also observed (i.e. broad molecular weight distribution). Other promising results were shown in 1986, but only low molecular weight materials could be obtained [15]. Major breakthroughs began in the early 1990s, when several techniques were demonstrated that clearly approached the concept of a living radical polymerization process. Since this time, three general LRP mechanisms have been developed into practical processes that improve control significantly compared with conventional processes. The following sections will describe how these new processes differ mechanistically from conventional free radical processes and how they control the polymerization reaction.

13.1.1

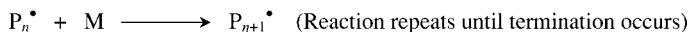
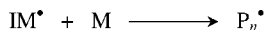
Free Radical Polymerization Mechanism

All conventional free radical polymerization processes contain three basic mechanistic steps, along with various potential side-reactions. Living radical polymerization processes share the first two steps and aim to eliminate the third step and side-reactions.

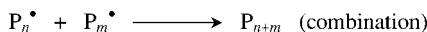
- *Step 1. Initiation* (start of a polymer chain). An initiator molecule (I_2) decomposes into two primary free radicals ($2I^*$). The primary free radicals can then react with



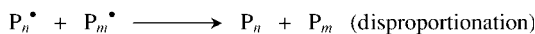
Scheme 13.1 Initiation.



Scheme 13.2 Propagation.



OR



Scheme 13.3 Termination.

the double bond of a monomer molecule (M). This forms the initiating radical, which is the first unit in a polymer chain (IM^\bullet) (Scheme 13.1).

- *Step 2. Propagation* (growth of a polymer chain). The initiating radical reacts with the double bond of another monomer molecule, creating a new free radical, and this process repeats in a chain reaction to create a polymer chain (P_n) (Scheme 13.2).
- *Step 3. Termination* (end of polymer chain growth). The radical endgroups of two growing chains meet and termination of the chains occur via a combination or disproportionation reaction (Scheme 13.3).

This initiation–propagation–termination cycle occurs within about 5–10 s during a conventional free radical polymerization, resulting in a long polymer chain which cannot react further (i.e. it is “dead”) [16]. Initiation occurs throughout the reaction, so that new polymer chains are continually growing and “dying” over the course of the reaction. The polymer chains grow to different lengths throughout the reaction, depending on factors such as monomer concentration, termination mechanism and viscosity. The molecular weight and polymer structure are also affected by number of side-reactions, particularly chain transfer to monomer, solvent or impurities. This overall process results in a mixture of polymer chains of varying length and structure (e.g. linear, branched).

There are two main changes to this mechanism that are required for an ideal living radical polymerization process:

1. Initiation should only occur at the start of the reaction so that all chains start to grow at the same time. This is not achievable in practice, but it is approached by applying fast initiation at the start of the reaction and minimizing initiation throughout the remainder of the reaction.
2. Termination and side-reactions must be eliminated completely. This is also not achievable in practice, but these reactions can be minimized to an acceptable level and this is the key to the different LRP mechanisms.

In practice, the termination reactions are minimized by reducing the overall concentration of free radicals in the system at any given time, which reduces the probability of two radicals meeting and terminating. In basic terms, this is done by placing removable “caps” on the ends of the polymer chains. When the cap is present on the chain endgroup, the polymer is “dormant” and it does not propagate. The cap can be released from the chain endgroup for a short period during which the polymer becomes “active” and a few monomer units are added to the chain, then the cap is replaced. Most of the polymer chains are in the dormant state at any given time during the reaction. Therefore, relatively few active chains are growing at a given time, which in turn results in a low probability that two chains will meet and terminate. The process of reverting between dormant and active states is termed “reversible activation” or “activation–deactivation” and it is the basis for all current successful living radical polymerization techniques. The type of cap, or *controlling agent*, that is used dictates the reversible activation mechanism that will occur.

13.2 Living Radical Polymerization General Mechanisms

There are three general classifications of living radical polymerization based on differences in the reversible activation reaction step described in the previous section. These three mechanisms are termed dissociation–combination, atom transfer and degenerative chain transfer, respectively [17, 18].

13.2.1

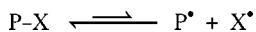
Dissociation–Combination (Scheme 13.4)

In this case, the controlling species (X) is released from the endgroup of the dormant polymer chain ($P-X$). When this occurs, the polymer becomes activated (P^*) and the radical at the end of the polymer chain can propagate in the presence of monomer. The propagating radical readily deactivates back to the dormant state ($P-X$) by reacting with the controlling species (X^*) after only a short period of propagation. Nitroxide-mediated polymerization (NMP) is the most extensively studied example of dissociation–combination and this will be discussed in more detail in the next section. Other examples of this mechanism involve the use of quinones [19] and boroxyls [20] as the controlling species.

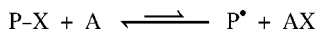
13.2.2

Atom Transfer (Scheme 13.5)

This is similar to the dissociation–combination scheme, but the release and return of the controlling species (X) are catalyzed by an activator (A) which is a transition metal complex. The controlling species is a halide radical in the most common form of this reaction, atom transfer radical polymerization (ATRP), and this technique will be described further in Section 13.5. It is also possible to use a quinone instead of a



Scheme 13.4 Reversible activation step for dissociation–combination reactions.



Scheme 13.5 Reversible activation step for atom transfer reactions.

halide as the controlling species in atom transfer reactions, in a process termed quinone transfer radical polymerization (QTRP) [21].

13.2.3

Degenerative Chain Transfer (Scheme 13.6)

Degenerative transfer is the third general LRP mechanism. In this case, activation and deactivation occur as the controlling agent (X) is exchanged between an active and dormant polymer chain (P and P'), thus activating one chain and deactivating the other. The most commonly studied type of this reaction is the reversible activation–fragmentation transfer (RAFT) method, which will be described in more detail in Section 13.6 along with a variant that has been termed MADIX. Other examples of degenerative chain transfer include the use of controlling agents such as 1,1-diphenylethylene (DPE) [22], alkyl iodides [23–25] and organotellurium (TERP) and organostibine (STBP) [26].

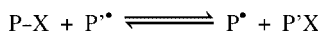
The next three sections will describe in more detail the three most common examples of the above general mechanisms.

13.3

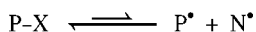
Nitroxide-mediated Polymerization

Since its discovery in 1993 [27], nitroxide-mediated polymerization (NMP) has been the most extensively studied technique from the dissociation–combination class of LRP mechanisms (Scheme 13.7). This method is also commonly termed *stable free radical polymerization* (SFRP). NMP reactions are distinguished by the use of stable free radical nitroxide molecules (N*) as the controlling agent [e.g. 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), (1-diethylphosphono-2,2-dimethyl)propyl nitroxide (DEPN)].

Many different nitroxide molecules can be used successfully for NMP reactions and the reaction conditions and kinetics have been studied extensively [28]. Nitroxide selection is important in determining the specific conditions under which the NMP



Scheme 13.6 Reversible activation step for degenerative chain transfer reactions.



Scheme 13.7 Reversible activation step for NMP reactions.

reaction will control the polymerization successfully [29]. Numerous tailored structures can be prepared using the NMP method and general strategies for achieving various structures have been developed [30].

NMP reactions are not usually done by simply adding a nitroxide molecule to a conventional free radical polymerization formulation and running under conventional conditions. Usually, NMP reactions are run at elevated temperatures (e.g. 115–135 °C), compared with conventional systems which are run at temperatures well below 100 °C. Progress has been made in this area, however, and controlled NMP reactions have been demonstrated below 100 °C by using nitroxides that have been designed for lower temperature reactions [31].

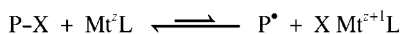
Most polymerization schemes can easily be performed using NMP (e.g. bulk, solution, miniemulsion), with a notable exception being emulsion polymerization. In fact, none of the LRP techniques are easily performed via emulsion polymerization and it is common to observe colloidal instability and loss of polymerization control in all cases. The general cause of these problems involves mass transfer limitations of the controlling species which are usually not soluble in water and recent reviews describe in detail the mechanisms that cause these problems [32–35]. However, some recent progress has been made in developing emulsion systems for NMP reactions, typically by using water-soluble nitroxides [36, 37].

NMP is somewhat limited in the selection of monomers that can be polymerized under controlled conditions compared with the other LRP techniques. Most work to date has been done in the area of styrene, acrylates and their copolymers. A number of other monomers have been demonstrated, but there are some monomers that cannot be easily polymerized controllably by NMP, notably methacrylates. However, there has been some recent progress in preparing copolymers of styrene with methyl methacrylate [38, 39] and butyl methacrylate [40], and research remains active in this area.

13.4 Atom Transfer Radical Polymerization

In terms of the atom transfer reversible activation mechanism, the most actively studied method is *atom transfer radical polymerization* (ATRP), which was first demonstrated in 1995 [41–43]. ATRP reactions use a halogenated initiator (e.g. alkyl halide) to start the polymerization and the halide becomes the removable controlling agent on the polymer chain endgroup. A transition metal complex is present in the formulation to mediate the removal of the halide radical from the polymer chain. The general atom transfer reversible activation scheme shown previously can be represented in more detail for ATRP by the reaction shown in Scheme 13.8.

In this case, X is a halide, Mt^z is a transition metal ion in oxidation state z and L is a ligand that is complexed with the metal to impart solubility in the polymerization medium. Numerous transition metals, halide initiators and ligands can be used to



Scheme 13.8 Reversible activation step for ATRP reactions.

facilitate ATRP reactions and the reaction conditions are more similar to conventional systems than in NMP reactions, particularly in terms of reaction temperature [44, 45]. Similarly to NMP however, ATRP reactions cannot be done easily in emulsion polymerization systems, although specialized techniques have been developed using modified emulsion methods [46, 47].

Monomer selection for ATRP reactions is more flexible than with NMP reactions. Specifically, methacrylate monomers are significantly easier to polymerize and homopolymers can be synthesized readily [48]. However, polymerization of protic monomers such as acrylic acid can be problematic [49].

One of the primary drawbacks of ATRP involves residual catalysts in the final product which can be toxic and/or can cause discoloration issues. However, recent progress has been made in this area through several different strategies, such as improving catalyst removal and recycling techniques and reduction of catalyst concentration by improving activity [50].

13.5

Reversible Addition–Fragmentation Chain Transfer

Reversible addition–fragmentation chain transfer (RAFT) polymerization is the third LRP method which has been developed to a relatively mature state since its first demonstration in 1998 [51] (Scheme 13.9). RAFT is a specialized case of the degenerative transfer LRP mechanism in which the controlling agent (X) is a thiocarbonylthio molecule (e.g. dithio esters, dithiocarbamates, trithiocarbonates).

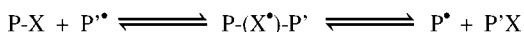
The generic structure for thiocarbonylthio RAFT agents is $Z-C(=S)SR$, where Z is a functional group which dictates the reactive properties of the agent and R is the free radical leaving group (a polymer chain once the reaction is up and running). Numerous different initiators and controlling agents can be used for RAFT reactions and the reaction conditions are similar to those used for conventional systems [52, 53]. One specific subclass of RAFT is macromolecular design via interchange of xanthates (MADIX), where the controlling agent is a xanthate molecule [54].

Similarly to NMP and ATRP, emulsion polymerization reactions are challenging for RAFT systems. Recently however, techniques have been developed that enable this type of reaction to be performed [55–59].

13.6

NMP, ATRP and RAFT Summary

NMP, ATRP and RAFT currently are the most commercially promising LRP techniques and many of the fundamental kinetic mechanisms and issues have been elucidated [60–66]. These processes are now at the stage where companies are actively pursuing



Scheme 13.9 Reversible activation step for RAFT reactions.

commercial applications and building larger scale production capabilities [67]. Each of the processes have certain advantages and limitations which must be considered when choosing which method is best for a particular application [68]. Recent demonstrations have shown that it is useful to use various combinations of NMP, ATRP and RAFT reactions to capitalize on the specific advantages of each process [69–72].

13.7

Living Radical Polymerization in Tubular Reactors

Most of the foundation research for LRP reactions has been done using batch processes. As the development of these methods progresses towards commercialization, some scoping work has been done to investigate using continuous reactors which could offer some economic benefits. A number of these studies have been done in continuous tubular reactors which approach the size scale of microreactors.

Homogeneous bulk ATRP of methyl methacrylate homopolymer and block copolymers can be achieved with some success in a continuous packed-bed tubular reactor using a supported catalyst [73–75]. The metal catalyst can be adsorbed on the silica gel column packing material instead of dissolving the catalyst in the bulk of the reaction medium. Some control can be achieved, but it is not as effective as more typical reactions using soluble catalysts. This is typical of ATRP systems that use supported catalysts and is attributed to inefficient reaction of the propagating radicals with the supported deactivator [76]. Also, it has been speculated that the activation–deactivation reaction does not actually occur at the supported catalyst site, but rather occurs with a trace amount of free catalyst that is present in the system [77].

RAFT miniemulsion reactions can be carried out successfully in a continuous tubular reactor [78, 79]. In the reported experiments, the tubing i.d. was 1.6 mm, which is slightly larger than the typical microreactor size regime. Stable latexes can be produced in the tubular reactor and the polymerization exhibits a living nature. However, the tubular reactor produces polymer with a slightly higher molecular weight distribution than comparable samples produced in a batch reactor. This is attributed to back-mixing or axial dispersion effects in the tubular reactor that would broaden the residence time distribution of particles within the reactor.

Nitroxide-mediated miniemulsion polymerization reactions can also be performed successfully in a tubular reactor [80]. The demonstrated case used a tubular reactor with an i.d. of 2 mm and a length of 170 m. Samples prepared in the tubular reactor are comparable to those made in a batch reactor in terms of kinetics and molecular weight characteristics.

13.8

Living Radical Polymerization in Microreactors

A fairly limited number of studies have been carried out to date using LRP reactions in microreactors, but it seems that interest in this area is starting to grow.

Before discussing LRP reactions *within* microreactors, it is interesting to point out that LRP methods can be used to *fabricate* microfluidic devices. Surface-bound iniferters can be used to graft polymers on surfaces in directed micropatterns using a degenerative transfer living radical polymerization method [81–83]. This method can be used to pattern and build microfluidic devices that have varying grafted functionalities on the surface. Different physical and chemical properties can therefore be patterned on the surface, such as varying hydrophobicity. These devices have been demonstrated for uses such as direction of fluid flow and surface-assisted cell patterning applications [84]. The same technique can be used in conjunction with a salt leaching process to build macroporous polymer networks within microfluidic devices. These porous networks can be used for applications such as static mixers, high surface area-to-volume reactors and rapidly responding hydrogel valves [85].

Several recent studies have demonstrated ATRP reactions within microfluidic devices. An initial study demonstrates the use of a thiolene polymer based reactor with rectangular microchannels ($500 \times 600 \mu\text{m}$) [86]. The device consists of two inlet channels, an active mixing chamber containing a magnetic stir bar and one outlet channel. Homopolymerization of 2-hydroxypropyl methacrylate (HPMA) by ATRP was demonstrated in this device and it was shown that the kinetics and product properties were similar to those for experiments performed in a batch reactor. This technique provides a fast way of screening various ATRP reaction conditions while using a minimum of raw materials.

The above study was expanded to investigate block copolymerization via ATRP in a similar device containing three inlet channels [87]. Block copolymers of poly(ethylene oxide-block-2-hydroxypropyl methacrylate) (PEO-b-HPMA) were successfully demonstrated with varying block lengths. This technique provides a rapid method for screening various block copolymer compositions.

ATRP can also be used to graft polymer chains on surfaces within microchannels [88]. The surface of a microreactor channel can be functionalized with the ATRP initiator, then polymer grafts form and grow from the surface initiator sites as reactants flow through the reactor. Gradients form based on the exposure time to reactants, with the longest grafts at the inlet of the reactor and shortest grafts at the outlet. This demonstrates the unique topologies that can be built within devices using these techniques.

Initial work with NMP reactions in microreactors has shown some promise for product improvements due to the improved heat transfer characteristics of the reactor. It is well known that the molecular weight of polymers is affected by the reaction temperature. This can be problematic when exothermic polymerization reactions cause the temperature within the reactor to drift, thus causing deviations from the desired molecular weight. Since microreactors improve heat removal due to the large surface area-to-volume ratio, they should theoretically permit improvements in molecular weight control for exothermic polymerization reactions. Living radical polymerization of *n*-butyl acrylate in a microtube reactor of $900 \mu\text{m}$ i.d. does indeed show significantly narrower polydispersity than comparable reactions in a batch reactor [89]. Similar experiments with styrene do not show the same degree of

polydispersity improvement, which is as expected since it is significantly less exothermic.

Micromixers in conjunction with serial microreactors can also be used effectively for LRP reactions, particularly for mixing viscous living polymer melts with non-viscous monomer for block copolymer production. For example, poly(*n*-butyl acrylate) can be synthesized in a microtube reactor via an NMP reaction, then the viscous homopolymer melt can be efficiently mixed with low-viscosity styrene monomer via a micromixer [90]. This can then be followed by NMP of the styrene on to the poly(*n*-butyl acrylate) chains in a second microtube reactor, thus creating a block copolymer. This technique gives a narrower molecular weight distribution product than comparable batch reactions.

13.9

Conclusion

Living radical polymerization has seen much research activity over the past fifteen years, and it has reached the point where commercialization activities are in progress. The fundamental mechanisms of three different LRP techniques (NMP, ATRP, and RAFT) are well understood, and many different unique materials can be prepared using these methods. While these three processes are developed to the commercial scale, newer LRP techniques are being discovered and investigated in the hopes of developing even better processes and materials. The use of LRP methods in the area of microprocessing and microreactors is in the very early stages. It has been shown that LRP techniques can be used to fabricate unique microreactor devices, and controlled structures can be grown within microreactors. Also, microreactors have been demonstrated as an interesting tool for rapid screening of different LRP structures such as block copolymers. Finally, there has been some indication that the improved heat transfer characteristics of microreactors can enable a further improvement in polymerization control for LRP reaction, particularly for more exothermic reactions.

Overall, the combined area of living radical polymerization and microreactors remains a fairly wide open field. Presumably more activity will be seen over the next few years and into the future as microreactor technology is introduced into more LRP-based research groups and the inherent benefits of this technology become better known.

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