Atom Transfer Radical Polymerization (ATRP) as a Tool for the Synthesis of Well-Defined Functional Polymeric Materials


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ABSTRACT

ATRP is one of the most powerful synthetic techniques that allows the synthesis of polymeric materials with predetermined molecular weight, composition, and molecular architecture derived from substituted styrenes, (meth)acrylates, or acrylonitrile. The polymers prepared by ATRP are chain end-functionalized and can be used as macroinitiators in chain extension reactions that yield block copolymers with excellent control over the segment size and nanophase separation. Well-defined polymers with various molecular architectures such as star- or brush-like molecules can be synthesized by ATRP, and systematic libraries are accessible, where the number and size of side chains, core functionality (in stars) or backbone length (in brushes) can be varied. Recently, new ATRP initiation techniques were developed that allow the process to be conducted using very low concentrations of Cu-based catalyst - often single-digit ppm amounts. For many applications, the polymers synthesized can be directly used and do not require further purification. A variety of previously inaccessible functional polymeric materials have been prepared by ATRP by the direct polymerization of functional monomers, the use of functional initiators, or by postpolymerization modifications. Using “universal” polymeric precursors derived from monomers containing epoxide or azide functional groups, libraries of polymers with numerous functional groups have been successfully prepared.

Keywords: ATRP, controlled radical polymerization, functional polymers, click chemistry

1 INCORPORATION OF FUNCTIONAL GROUPS IN POLYMERS PREPARED BY ATRP

Four possibilities exist to employ ATRP in the synthesis of well-defined polymers with functional groups. The most obvious is the direct polymerization of a monomer containing the desired functionality. ATRP is generally tolerant to various functional polar groups and this route has been successfully used in many instances. In some cases, polar monomers, especially strongly coordinating, basic or nucleophilic, and acidic, can react with either the ATRP catalyst (leading to its partial or complete deactivation) or the alkyl halide-type initiator or polymeric dormant species (causing “killing” of polymer chains). The synthetic strategy of choice in these cases is to use monomers with protected groups that can be transformed into the desired polar functionalities after the polymerization. The use of functional initiators makes it possible to prepare either homo- or heterotelechelic polymers.[1] Examples of the use of functional initiators and of end-group chemical transformations are presented in the following sections. The polymers produced by ATRP are halogen-terminated, and can be further used as macroinitiators in chain-extension reactions [2] or as precursors of end-functionalized polymers; a number of nucleophilic substitution reactions have been employed to achieve this goal.[1] Thus, ATRP is an attractive technique for the synthesis of well-defined end-functionalized polymers. The aforementioned methods are presented in Fig. 1.
yielding well-defined polymers containing the reactive glycidyl group, which can be used as precursors of other functional polymers. The ATRP of bio-inspired monomers, containing either short peptide chains [17, 18] or nucleobase moieties [18] has also been reported. Water-soluble monomers (both neutral and ionic) can be polymerized in a controlled fashion by ATRP directly in protic (aqueous) media.[19] Some examples of monomers with polar groups that have been polymerized by ATRP are shown in Fig. 2.

![Figure 2. Examples of monomers with polar groups that have been directly polymerized by ATRP.](image)

Monomers containing functional groups (mostly substituted amides, amines, or pyridines) can form copper complexes and to avoid competitive complexation of the monomer or polymer to the copper center of the ATRP catalyst, strongly binding ligands should be used as catalyst components.[19, 20] Although in many cases the catalyst destabilization can be suppressed by selection of the proper ligand, the ATRP of several types of polar monomers, particularly acidic ones, has proved to be quite challenging.

### 1.2 Postpolymerization Modification of Monomer Units

In many cases, due to the incompatibility of certain functional groups with the ATRP reaction components, protection group chemistry has to be employed. Phenols are known inhibitors of radical processes, and since they can also reduce the deactivating Cu(I) halide complexes [21] (which would lead to inefficient deactivation and thus to fast and poorly controlled polymerization), the direct ATRP of phenol-type monomers is complicated. The ATRP of a protected phenol, 4-acetoxy styrene, catalyzed by CuBr/bpy, however, was well-controlled [22] and some block copolymers were prepared using the bromine-terminated poly(4-acetoxy styrene) as a macroinitiator.[23] Due to the large transfer coefficient of thiols in radical processes, the direct polymerization of thiol-group-containing monomers yields only low molecular weight polymers. In addition, the thiol group is likely to interfere with the ATRP catalyst. A successful strategy to prepare thiol-containing well-defined polymers is to use monomers with a disulfide group, that can be reduced after the polymerization with Bu₃P or DTT to yield the desired product.[24]

Acidic monomers such as (meth)acrylic acid, the isomeric vinylbenzoic acids, or unsaturated sulfonic or phosphonic acids protonate and “destroy” the complexes of N-based ligands typically used as ATRP catalysts. Although some moderately successful attempts have been made to polymerize MAA by ATRP, in general, protected acids are preferred.[25] Examples of protective groups include tert-butyl [26, 27], benzyl [25, 28] (deprotection is achieved by hydrogenolysis), tetrahydropyranyl,[25, 28] 4-nitrophenyl,[29] and 1-ethoxyethyl [30] (deprotection is achieved by heating to 160 °C). The carboxylic acid functional group has also been incorporated in well-defined polymers prepared by ATRP using hydroxy group-containing polymers as precursors (poly(2-hydroxyethyl methacrylate) and its copolymers), which were reacted with succinic anhydride in anhydrous pyridine.[31]

Tetrazoles are acidic (resembling carboxylic acids) and coordinating compounds and the direct ATRP of vinyltetrazoles has not been reported. The preparation of well-defined tetrazole-containing polymers has been accomplished using the ATRP of acrylonitrile, followed by a “click” chemistry-type of chemical modification of the produced polyacrylonitrile to yield the desired materials.[32]

As mentioned above, 2-hydroxyethyl acrylate and methacrylate are easy to polymerize by ATRP, and the hydroxy group-containing polymers can be used in esterification reactions with various functionalized carboxylic acids. However, esterifications are not always very efficient, especially when a polymeric substrate is used. The glycidyl group can react with nucleophiles and thus poly(glycidyl methacrylate) prepared by ATRP can serve as a precursor of functional polymers.[16] The search for more efficient postpolymerization reactions is ongoing. With the development of the azide-alkyne click chemistry reactions which are very efficient, and especially knowing that azide-containing monomers can be successfully polymerized by ATRP, a vast number of functional polymers have become accessible.

### 1.3 Functional ATRP Initiators

Various functionalized ATRP initiators have been used to prepare telechelic polymers by ATRP. Interestingly, the acidic initiator 4-carboxybenzyl bromide was demonstrated to yield well defined polymers with a carboxylic acid group.[33] No protection-deprotection chemistry was needed. Examples of polar groups reacting specifically with protein thiol groups that have been introduced in polymers prepared by ATRP using the appropriate initiator include N-succinimidyl [34] and disulfide.[24, 35, 36] The prepared functional polymers have a great potential in the preparation of protein-polymer bioconjugates. In addition, the incorporation of disulfide groups in polymers is an efficient strategy to prepare (bio)degradable polymers.[24, 35] Biotin-containing ATRP initiator is an example of functional initiator derived from a biologically important molecule; it yields polymers reacting specifically with avidin.[37]

As mentioned in the previous section, click chemistry transformations are very efficient, and the use of ATRP initiators with either azido- [38] or alkyne-group [38, 39]
producing end-group-reactive polymers that can participate in further click-type modifications has been demonstrated. Many other functional initiators have been employed in ATRP; these are described in a review paper by Coessens et al.[1] Some representative examples of functional halides used successfully as ATRP initiators are shown in Fig. 3.

![Functional ATRP initiators](image)

**Figure 3. Functional ATRP initiators.**

### 1.4 End-group Chemistry

The halide end-functionality in polymers prepared by ATRP, particularly polystyrenes or polyacrylates, can participate in nucleophilic substitution reactions. An early example is the reaction of halogen-capped polymers with sodium azide.[40-42] Diazido-terminated polystyrene thus prepared could be further reduced with tributylphosphine in THF in the presence of water (moisture) to yield well-defined diamino-terminated polymer, that, in turn, could be used in a step-growth process with terephthaloyl chloride leading to polyamides with controlled-length polystyrene segments.[40] The azido-terminated polymers can also be used in click chemistry modifications with acetylene derivatives to incorporate various functional groups.[39, 43] Polymers with phosphonium salt end-groups were prepared from bromine-terminated polystyrene or polyacrylates, and Bu₃P.[44] Mercapto-terminated polystyrene was prepared by the reaction of the corresponding bromo-compound with either thiodimethylformamide [45] or thiourea,[46] followed by reaction with a nucleophilic compound. Some examples of end-group transformations are presented in Fig. 4.

![Examples of end-group chemistries](image)

**Figure 4. Examples of end-group chemistries used to prepare end-functional polymers by ATRP.**

### 1.5 New Advances in ATRP

Recently, two novel initiation systems were developed, named ARGET (activators regenerated by electron transfer) [47, 48] and ICAR [49] (initiators for continuous activator regeneration) ATRP, in which a very small amount of active copper catalyst is used (often in the single digit ppm amounts), and the Cu(II) complexes formed due to radical termination are constantly converted to the activator via a redox process. The amount of leftover catalyst in the polymers prepared by these techniques is very low and purification may be unnecessary for many applications.

### REFERENCES