"Green" Atom Transfer Radical Polymerization: From Process Design to Preparation of Well-Defined Environmentally Friendly Polymeric Materials

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Received August 10, 2006

Contents

1. Introduction

Virtually every branch of science, technology, and art uses a plethora of polymeric materials. These include not only "pure" linear, branched, or cross-linked (gels, rubbers, etc.) polymers but also polymer blends and composites, in which polymers are combined with other materials such as metals, metal compounds (oxides, halcogenides, etc.), clays, ceramics, biomolecules, and many others. The properties and application of these materials depend upon molecular weight and molecular weight distribution (MWD) as well as molecular structure (composition, topology, and functionality). Consequently, synthetic methods allowing control over some or all of these parameters are very desirable. Living polymerizations[1−3] are used for this purpose. The first living polymerization techniques discovered in the 1950s and 1960s were ionic processes.[4−7] The early studies on living ionic polymerizations, summarized by Szwarc,[8] revealed that, for processes in which termination and transfer are eliminated and initiation is fast,[9,10] polymers of narrow molecular weight distribution (approaching Poisson distribution[11]) could be synthesized. A drawback of the ionic techniques is their pronounced sensitivity to moisture, carbon dioxide, and numerous other acidic or basic compounds. Some improvement was achieved in systems in which propagating ionic centers were equilibrated with various types of dormant species, much less sensitive to impurities.[12−14] Ionic polymerizations can only be applied to a limited range of monomers, and due to significant differences in the reactivity ratios of the monomers, copolymerization reactions are often challenging. That limits the range of materials accessible through living ionic polymerizations.[15]

In contrast, radical polymerizations are applicable to a large number of monomers with a carbon−carbon double bond and are tolerant toward many solvents, functional groups, and impurities often encountered in industrial systems. To achieve a living-like radical polymerization, chain termination reactions should be suppressed, and a true living process in the presence of radicals is not feasible, due to the very fast (essentially diffusion-controlled) bimolecular radical termination. However, it is possible to design controlled radical polymerization (resembling living process) if propagating radicals are in dynamic equilibrium with a larger amount of dormant species. The latter cannot terminate but can be intermittently reactivated to active radicals which, after few monomer additions, are transformed back to the dormant state.[16−18] In the first living radical polymerizations, reversible radical (spin) traps, such as the trityl (triphenylmethyl) radical,[19,20] were used that formed relatively labile bonds with the propagating radical. The formed compounds could be further photochemically or thermally reactivated, and the generated polymeric radicals could continue to grow in the presence of a monomer.

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10.1021/cr050947p CCC: $65.00
Published on Web 05/27/2007

Nicolay (Nick) Tsarevsky was born in Sofia, Bulgaria, in 1976. In 1994, he won a bronze medal at the National Chemistry Olympiad for high school students and participated in the 26th International Chemistry Olympiad held in Oslo, Norway. He was then admitted to the Department of Chemistry at the University of Sofia and obtained his M.S. in theoretical chemistry and chemical physics, maxima cum laude, in 1999. His studies were on the use of hypervalent iodine compounds as polymerization initiators. He was the recipient of the "Talents" Scholarship of the Eureka Foundation (1994–99), the University of Sofia Rector's Prize for most accomplished student (1996), and the A. Wessels award (1998). He joined Professor Matyjaszewski's research group at Carnegie Mellon University as a Ph.D. student in January 2000, and he obtained his doctorate in 2005. He worked on the synthesis of functional polymers by ATRP and on the development of rules for rational selection of the catalyst for various reaction media, including aqueous solvents. He was awarded the Kenneth G. Hancock Memorial Award in Green Chemistry (2003), the Excellence in Graduate Polymer Research Award (2004), the Pittsburgh Section of ACS Polymer Group Student Award (2004), as well as the Harrison Legacy Dissertation Fellowship (2004–5). He has authored and coauthored more than 40 papers in peer-reviewed journals, 5 book chapters, and several patents. Research interests include polymerization techniques, functional materials, coordination chemistry and catalysis, and the chemistry of hypervalent compounds. He is also interested in science education and has written 2 scripts for educational TV programs, shown on National TV in Bulgaria, and 1 textbook for high school students. He was Visiting Assistant Professor at the Department of Chemistry at Carnegie Mellon University (2005–6) and is currently Associate Director of the CRP Consortium. He served as secretary (2005) and chair (2006) of the Polymer Group of the Pittsburgh Section of the ACS.

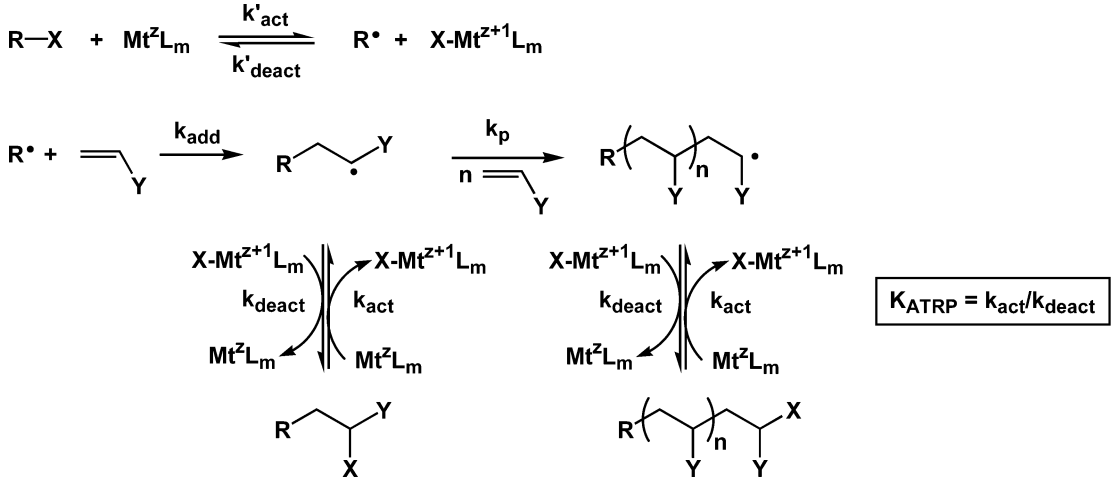
Krzysztof (Kris) Matyjaszewski was born in Konstantynow, Poland, in 1950. He obtained his Ph.D. degree in 1976 at the Polish Academy of Sciences in Lodz, Poland, working with Prof. S. Penczek. He was a postdoctoral fellow at the University of Florida, with Prof. G. B. Butler (1977–8). Since 1985 he has been at Carnegie Mellon University (CMU), where he has served as the Chemistry Department Head (1994–8) and is currently the J. C. Warner University Professor of Natural Sciences. He is also an adjunct professor at the Department of Petroleum and Chemical Engineering at the University of Pittsburgh, the Polish Academy of Sciences in Lodz, Poland, and the Department of Materials Science at CMU. He is an editor of *Progress in Polymer Science* and the *Central European Journal of Chemistry*, and he serves on the editorial boards of 14 chemistry journals. His main research interests include controlled/living polymerization, catalysis, environmental chemistry, and the synthesis of advanced materials for optoelectronic and biomedical applications. In 1995 he developed atom transfer radical polymerization (ATRP), one of the most successful methods for controlled/living radical polymerization. During the last 10 years his group has published over 400 papers on ATRP. His citation record ranked him sixth among all fields of chemistry in 2004–6. He holds over 30 U.S. patents and over 70 international patents. Close industrial interactions have been maintained via the ATRP and CRP Consortia, with over 30 industrial members. The research of Matyjaszewski group has received wide recognition, as evidenced by the ACS Carl S. Marvel Award for Creative Polymer Chemistry (1995), the ACS Award in Polymer Chemistry (2002), the ACS Cooperative Research Award in Polymer Science (2004), the ACS Hermann F. Mark Senior Scholar Award (2007), the U.K. Macro Group Medal for Outstanding Achievements in Polymer Science (2005), and the Prize of the Polish Science Foundation (2004). He received honorary degrees from the University of Ghent, Belgium, (2002) and the Russian Academy of Sciences (2006). He is a foreign member of the Polish Academy of Sciences (2005) and a member of the U.S. National Academy of Engineering (2006).

The past decade witnessed the discovery and flourishing of various methods of controlled/living radical polymerization (CRP)[21−25] that allowed for the preparation of a multitude of previously unattainable well-defined polymeric materials. The most widely used CRP methods are atom transfer radical polymerization (ATRP),[26−29] stable free radical polymerization [SFRP, the most popular of which is nitroxide-mediated polymerization (NMP),[30−34] but also including polymerizations mediated by Co/porphyrin complexes[35−37]], and degenerative transfer polymerization[38] [with reversible addition−fragmentation chain transfer (RAFT) polymerization[39−43] as the most successful example but including polymerizations in the presence of tellurium or antimony compounds[44]]. Metal complexes can mediate controlled polymerization via two mechanisms:[45] (i) the reversible formation of a metal−carbon bond upon reaction with the propagating radical (SFRP) or (ii) the reversible transfer of an atom or a group from the polymer chain end to the metal center (ATRP). Only in the latter process, the subject of this review, does the complex play the role of a catalyst.

ATRP has emerged as one of the most powerful synthetic techniques in polymer science. Similarly to the other CRP methods, it allows the synthesis of polymers with predetermined molecular weight, narrow molecular weight distribution,[46] as well as desired composition[47] and molecular architecture.[48,49] Importantly, the polymers prepared by ATRP are highly chain end-functionalized and can therefore participate in various post-polymerization modifications[50] and serve as macroinitiators in the synthesis of block copolymers.[51] A variety of organic/inorganic nanocomposites[52,53] and other complex nanostructured materials[54] have also been synthesized by this technique.

ATRP is based on the reversible reaction of a low-oxidation-state metal complex, Mt^zL_m (Mt^z represents the metal ion in oxidation state z, and L is a ligand; throughout this text, the charges of ionic species are omitted for simplicity), with an alkyl halide (RX). This reaction yields radicals and the corresponding high-oxidation-state metal complex with a coordinated halide ligand, $XMt^{z+1}L_m$. Mechanistically, ATRP is closely related to the radical addition of alkyl halides or other similar molecules across an unsaturated carbon−carbon bond, termed *atom transfer radical addition*[55] (ATRA, Scheme 1), a form of which is the synthetically appealing atom transfer radical cyclization.[56] ATRP can be viewed as a special case of ATRA, which

Scheme 1. Mechanism of Metal Complex-Mediated ATRA and ATRP



involves the reactivation of the alkyl halide adduct of the unsaturated compound (monomer) and the further reaction of the formed radical with the monomer (propagation).[57] The "livingness" of this polymerization process can be ascertained from a linear first-order kinetic plot, accompanied by a linear increase in polymer molecular weights with conversion, with the value of the number-average degree of polymerization (DP_n) determined by the ratio of reacted monomer to initially introduced initiator (i.e., $DP_n = \Delta[M]/[RX]_0$).

The ATRP equilibrium can be approached from both sides, i.e., starting either with a combination of a lower oxidation state metal complex and an alkyl halide or with a combination of a higher oxidation state complex and a radical source such as AIBN. The latter process is termed *reverse ATRP* and has the advantage of using an air-stable catalyst, which makes for easier handling.[58−60] However, block copolymers cannot be prepared using reverse ATRP, and since all halogen chain ends originate from the catalyst (initially in the form of a XMt^{z+1} complex), it has to be used in an amount equal to that of polymer chains. An improvement of this initiation technique, known as *simultaneous reverse and normally initiated* (SR&NI) ATRP,[61] uses a combination of a radical initiator and an alkyl halide in conjunction with a higher oxidation state metal halide complex, and allows for the use of a lower catalyst amount, provided that it is sufficiently active. If the alkyl halide initiator is a halogen-terminated polymer, block copolymers can be synthesized; however, they contain a certain amount of homopolymer originating from the radical initiator. SR&NI ATRP can be employed successfully in water-borne systems, and polymers with complex structures such as linear and star-shaped block copolymers can be synthesized.[62,63] Further discussion on the ways to reduce the amount of catalyst needed to mediate ATRP is presented in the following sections.

ATRP has already been employed in industry,[64] and it can be expected that in the near future it will surface as one of the processes of choice for large-scale production of specialty polymers such as thermoplastic elastomers, coatings, surfactants, and materials with medical and pharmaceutical applications, among others.

The development of "green" methods is an ongoing effort in chemistry, materials science, and industry. The term "green" implies the use of environmentally friendly (nontoxic and reusable) reagents and solvents in the processes, or the development of active catalysts, and technologies consuming less energy.[65−67] In addition, in polymer synthesis, recyclable or (bio)degradable polymeric materials are highly desirable since they provide a means to minimize environmental pollution. This paper focuses on the various efforts that are currently being made to develop environmentally friendly ATRP processes. Of major significance is the ability to remove the catalyst after completion of the procedure. The development of highly active catalysts that can be used at low concentration and/or at low reaction temperature is even more important, for it virtually eliminates the need for catalyst removal. The aforementioned catalyst-related issues are discussed first. The ability to successfully carry out ATRP reactions in "green" solvents such as water, supercritical carbon dioxide, or ionic liquids is another very important matter, and the studies in this field are also summarized. Finally, ATRP allows for the synthesis of an abundance of specialty materials that have some "environmental impact". These materials include self-plasticized polymers, (bio)-degradable polymers, solventless coatings, nonionic surfactants, etc. and are discussed in the last part of this review. Some of the environmental aspects of ATRP have been described in earlier papers.[68−70]

2. Environmentally Friendly ATRP

2.1. Toward Lowering the Concentration of Residual Catalyst in Polymeric Materials Prepared by ATRP

2.1.1. Catalyst Removal

2.1.1.1. Separation of Soluble Catalysts from the Reaction Mixture. The efficient separation of reaction products from unreacted reagents, catalysts, side reaction products, or other compounds present in the reaction mixture is of major importance in organic synthesis. Many strategies have been developed to achieve this, and the goal is to use as simple an experimental setup as possible.[71] In polymer synthesis, removal of impurities originating from the reaction medium can also be very important, particularly when the polymers are to be used for electronics or biomedical applications. ATRP is a metal complex-mediated reaction, and catalyst removal is of primary importance.

Various metal complexes have been successfully employed to mediate ATRP, including Ti,[72] Mo,[73−76] Re,[77−79] Ru,[27,80−86] Fe,[87−95] Rh[80,96−98] (for a review on the use of Rh-containing catalysts, see ref 99), Ni,[97,100−107] Pd,[108] Co,[109] Os,[110] and

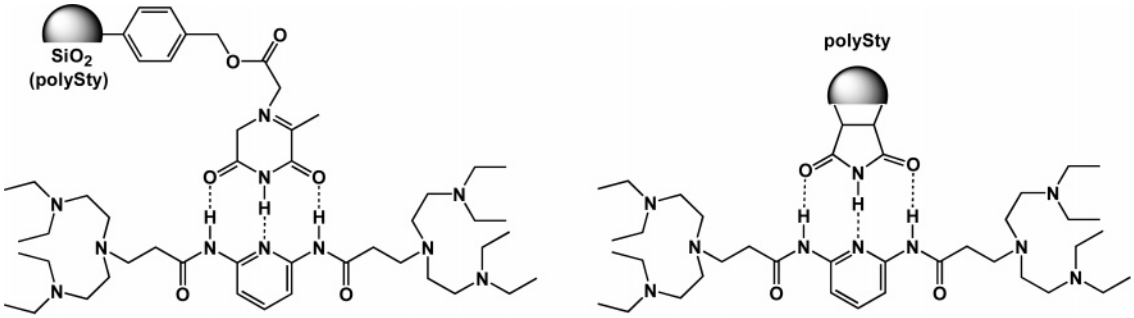


Figure 1. Ligands that can be reversibly (upon thermal treatment) attached to silica[141] or cross-linked polySty[142] surfaces and used to form ATRP catalysts.

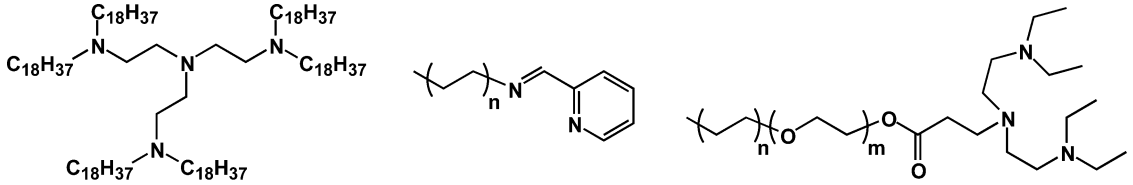


Figure 2. Ligands forming Cu-based ATRP catalysts with temperature-dependent solubility.

Cu.[26,111−120] More details are provided in review papers and monographs.[23,28,29,121−124] Dual metallic ATRP catalysts, wherein the complexes of two metals are simultaneously used to control the polymerization, have also been reported, including the combinations of $Sn^{II}Cl_2$ with $Fe^{III}Cl_3$ and N-substituted diethylenetriamine (DETA)[125] or of $Sn^{II}Cl_2$, $Mn^{II}Cl_2$, $Ni^{II}Cl_2$, and $Co^{II}Cl_2$ with $Fe^{III}Cl_3$ and Ph_3P.[126] Such systems are of fundamental interest since the presence of more than one metal complex in the reaction mixture may be beneficial, and the catalysis of more than one process may be accomplished simultaneously. More mechanistic studies are however required before such a goal is achieved. The compounds of the majority of the aforementioned metals are rather toxic and tend to accumulate in the body, where they can interact with enzymes or other biologically important molecules, or participate in various redox reactions.[127] In general, the compounds of Fe are considered least toxic, Cu compounds possess a mild toxicity, and many of the complexes of Ni and the platinum group metals are severely toxic or carcinogenic.[128]

A drawback of traditional ATRP is the relatively large amount of catalyst used, typically of the order of 0.1−1 mol % relative to monomer. For instance, in the bulk methyl acrylate ATRP with a targeted DP of 200, when the amount of CuBr-based catalyst is 1:1 relative to initiator (i.e., 0.5 mol % vs monomer), the total amount of CuBr in the system is close to 10^4 ppm. The final product contains a significant amount of metal complex, which may be hazardous or may impede specific applications. Several efficient strategies for catalyst removal have been developed.[129]

Often, simple passing of the polymer solution through a column filled with an ion-exchange resin[130,131] or absorbent such as alumina, silica,[132] or talcum is sufficient to reduce the amount of leftover catalyst. Numerous examples of absorbents are given in the patent literature. Ligands containing alkoxysilyl groups have been developed, and these form copper complexes that can react with silica and therefore be easily removed.[133]

Various forms of extraction—with water, solutions of ligands strongly binding to copper ions, or ionic liquids—are also efficient.[134] In some cases, single or multiple precipitation of the polymer produced by ATRP in a nonsolvent containing compounds able to coordinate to the metal catalyst and therefore extract it from the product has been successfully used; an example is the repeated precipitation in a mixture of methanol and a saturated aqueous NH_4Cl solution.[135]

Fluorous solvents are often well miscible with common organic solvents at elevated temperatures and phase separate upon cooling. The use of catalysts that are soluble in fluorous solvents has proved very useful in synthetic chemistry, for it allows the simple separation and often reusing of the catalyst after the reaction is completed. In other words, with fluorous solvents, the advantages of homogeneous reactions (at high temperature) are combined with the ease of product separation under biphasic conditions (lower temperature).[136−138] It was demonstrated[139] that $Cu^{I}Cl$/fluoroalkylated polyamines (derivatives of DETA and tris(2-aminoethyl)amine) (TREN) could be used in an ATRA cyclization in mixed, fluorohydrocarbon-containing, solvents. At high temperature, the reaction mixtures were homogeneous, and upon cooling, the fluorinated solvent separated and extracted almost all the catalyst. This concept was also employed in ATRP reactions. Satisfactory polymerization control was demonstrated in the ATRP of MMA in perfluoromethylcyclohexane mediated by a $Cu^{I}Br$ complex of a N-based ligand substituted with fluoroalkyl groups, although the initiation efficiency was low.[140] The reaction mixture was not entirely homogeneous at the polymerization conditions (90 °C), and efficient stirring was needed. Nevertheless, the catalyst could be separated from the produced polymer upon cooling to ambient temperature and then could be reused in subsequent polymerizations.

Complexes that possess very different solubility in the reaction medium at elevated and at low temperature can be used; these include complexes with hydrogen bond-forming groups (Figure 1)[141,142] or other complexes that precipitate upon cooling, with catalyst removal then being achieved by filtration (Figure 2).[143−146] It was demonstrated that several partially fluorinated compounds, typically used in fluorous biphasic systems, show marked solubility differences in common, nonfluorinated, organic solvents as the temperature changes.[147,148] These compounds could be used as catalysts for certain chemical transformations at high-temperature (homogeneous conditions), and upon completion of the reaction, they could be isolated by simple cooling followed

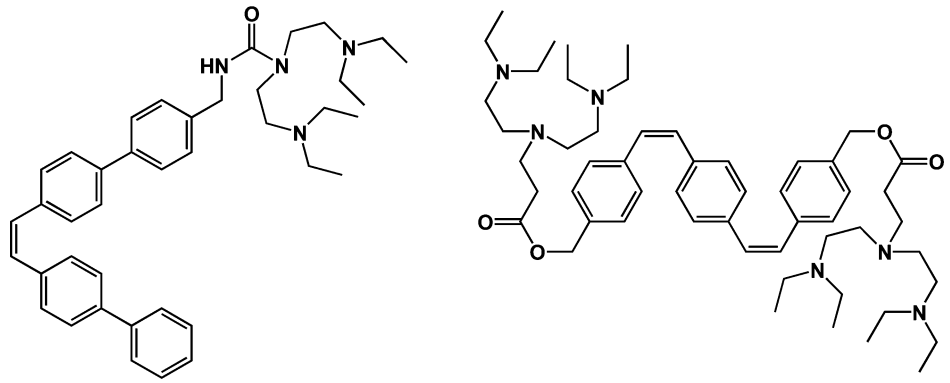


Figure 3. Stilbene-containing ligands ("precipitons"), that can form Cu-containing ATRP catalysts with altered solubility upon irradiation.

by filtration; no fluorinated solvents were required in the process. Some fluorine-free compounds are also thermomorphic. The solubility of the fluorine-free complex of $Cu^{I}Br$ and triethylenetetramine (TETA) with all four nitrogen atoms bonded to six octadecyl groups in 1,4-dioxane is strongly temperature-dependent. The ATRP of MMA in the presence of this complex was successfully conducted at 70 °C, and about 95% of the copper catalyst was recovered by cooling down the reaction mixture to 10 °C followed by filtration.[149]

There is a marked difference in the polarity and therefore the solubility of the cis- and trans-forms of stilbene, which can be interconverted using a light source of appropriate wavelength. This has been used in the preparation of "precipitons"—commonly, stilbene moiety-containing compounds that can be precipitated from a reaction mixture by simple UV-irradiation, heating in the presence of diphenyl disulfide, or irradiation in the presence of iodine with dibenzoyl peroxide.[150,151] ATRP catalysts derived from N-based ligands with stilbene group(s) have been reported (Figure 3).[146,152] When the polymerization was completed, the homogeneous reaction mixture was irradiated with UV light for 2 h, which was sufficient to convert the catalysts to the insoluble trans-form. It was shown that, after filtration, less than 1% of the original copper amount remained in the polymer.

Poly(ethylene oxide) is a hydrophilic polymer that dissolves very well in water at room temperature but becomes more hydrophobic as the temperature is raised[153] and exhibits a lower critical solution temperature (LCST) near the boiling point of water (the exact LCST value depends upon the polymer molecular weight).[154] This property was used by Sawamoto et al.[155] to prepare a phosphine-based ligand, Ph_2P-p-C_6H_4-O(CH_2CH_2O)$_{45}$-CH_3, for the Ru-mediated ATRP of MMA in a suspension consisting of an aqueous phase and the monomer in toluene as the organic phase. During the polymerization (80 °C), the catalyst partitioned in the organic phase and mediated the ATRP process. When the reaction was completed, simple cooling to room temperature led to transfer of the now hydrophilic catalyst to the aqueous phase. More than 97% of the catalyst could be removed from the polymer, and it could also be reused in subsequent polymerizations.

It was recently shown that the copper complexes of several linear aliphatic amines (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA), *N*,*N*,*N*′,*N*″,*N*‴,*N*‴-hexamethyltriethylenetetramine (HMTETA), or *N*,*N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗,*N*⁗⁗-octamethylpentaethylenehexamine) precipitated from toluene upon the addition of a sufficient amount of $Cu^{II}Br_2$ (to reach a total Cu-to-ligand ratio of 4), and the formed Cu-containing solid could be easily removed by simple filtration through a 0.1 μm PTFE filter.[156] Other approaches are also described, such as the electrochemical reduction of the copper catalyst to copper that can be removed from the reaction system in the form of amalgam.[157]

2.1.1.2. Use of Supported Catalysts in ATRP. Various supported ATRP catalysts have been utilized.[158−166] Often, the support is silica or polySty cross-linked with divinylbenzene, but JandaJel-supported pyridinemethineimine- and DETA-type ligands were also used in the ATRP of Sty, MMA, and DMAEMA.[131,146] JandaJel resins (polySty that is cross-linked with flexible oligoTHF-type linkers) have an improved swellability and site accessibility compared to their poly(Sty-co-divinylbenzene) counterparts.[167] Polyacrylate-based ion-exchange resins have also been used.[168] The accessibility of the catalytic center on the surface is crucial for achieving a well-controlled polymerization. The use of spacers between the support and the catalyst has proved beneficial in this respect. The effect of the oligo(ethylene oxide) spacer length on the performance of supported Cu^{I}-Br/triamine complexes was examined,[169] and it was shown that both the polymerization rate and the control were improved when the spacer consisted of three ethylene oxide units, compared to a single one. When the length of the spacer was increased to 10 ethylene oxide units, the catalyst performance worsened, which was attributed to potential "wrapping" of the flexible spacer around the catalyst causing the latter's "shielding". In general, the polymerization control with supported catalysts is poorer than with soluble catalysts, mainly due to inefficient reaction of the propagating radicals with the supported deactivator. However, if a small amount of very efficient deactivator such as the complex $Cu^{II}X_2$/Me_6TREN is present in solution, the produced polymers are well-defined.[163] Soluble copper-based ATRP catalyst was also used in conjunction with a supported nickel-containing catalyst to control the radical polymerization of MMA.[168] In another study, it was demonstrated that when a $Ni^{II}Br_2$/Ph_3P-type of ATRP catalyst supported on polySty was used to mediate the ATRP of MMA, the reaction was not controlled. When free Ph_3P was added, the polymerization control was improved,[164,170] probably due to the presence of a small but sufficient amount of deactivating complex in the solution.

Recently, the various scenarios for radical deactivation in ATRP mediated by supported catalysts were analyzed.[171] It was first assumed that all the catalyst was supported on particles with size of about 100 μm, and with surfaces separated by about 30 μm. The reaction of a radical (either low-molecular-weight or polymeric) with a deactivator

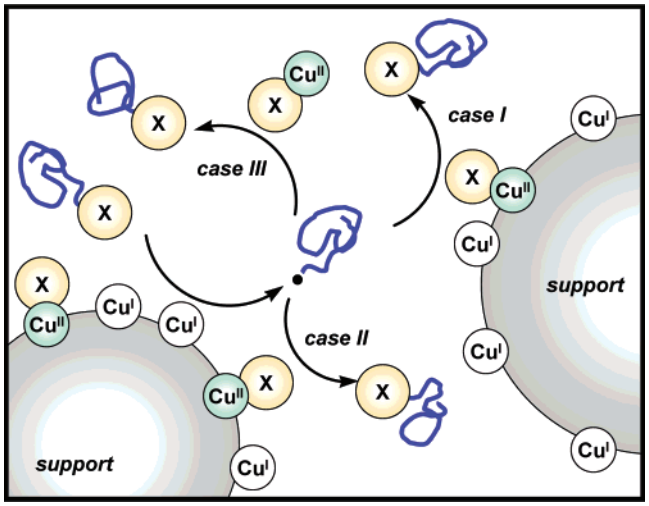


Figure 4. Mechanisms of deactivation in ATRP using supported catalysts. Adapted with permission from ref 171. Copyright 2006 American Chemical Society.

situated on a particle different from the one on which the activation process had occurred (case I in Figure 4) is improbable given the radical's short lifetime in the temporarily active state (10^{-4} to 10^{-2} s). If the particle size decreases (to <0.45 μm or so), the interparticle distance also decreases and deactivation by the discussed mechanism becomes possible. The radical deactivation at a site on the same particle on which the alkyl halide had been activated (case II) is not very likely either, since this requires that the radical remains in relatively close proximity to the particle during its lifetime (and during growth), although this mechanism cannot be fully excluded. If the system contained a small amount of soluble catalyst (not necessarily intentionally added but possibly desorbed from the support), including deactivator, its reaction with a radical (case III) would be the most probable and efficient mechanism of deactivation. Alternatively, a small amount of a very active soluble catalyst (e.g., Cu^IBr/Me_6TREN), together with a less active supported catalyst, mediates ATRP very efficiently.[172−174] The three different radical deactivation mechanisms in ATRP mediated by supported catalysts are depicted in Figure 4.[171]

Cu^IBr/HMTETA catalyst that was supported on silica gel and packed in a column was used in a continuous ATRP process.[161] The supported catalysts for ATRP can be readily reused after reduction of the higher oxidation state metal complex, accumulated due to the persistent radical effect or air-oxidation. The reduction can be carried out by heating the catalyst with a radical source such as AIBN or with other reducing agents. Unfortunately, both in continuous and batch processes where supported catalysts are employed, the catalytic performance deteriorates relatively quickly, which can be attributed to loss of catalyst due to partitioning in the liquid phase.[175]

An interesting example of supported catalyst was reported by Shen et al.[176] A triamine ligand was chemically attached to the surface of 20−30-nm-sized magnetic particles (Fe_3O_4) and reacted with Cu^IBr to yield a supported ATRP catalyst that could be easily removed after polymerization by the use of a magnet (Figure 5).

Although all described methods for catalyst removal have proved efficient in laboratory-scale reactions and deserve attention, they are not very applicable in large-scale or industrial settings. In the case of sorption/filtration techniques, this is mainly due to difficulties related to the filtration of large volumes of viscous polymer solutions and the generation of solid waste (the absorbent contaminated with metal complexes). In other cases, rather expensive and difficult to synthesize ligands are required.

2.1.2. Development of Highly Active ATRP Catalysts

The majority of publications on ATRP deal with the copper-mediated process, which seems to be the most versatile and applicable to a large number of monomers. Consequently, the discussion that follows is mostly dedicated to the performance of copper-based catalysts; however, it should be noted that the same rules for rational catalyst selection apply to all other metal complexes used in ATRP. Significant efforts have been made to develop novel catalytic systems that are very active, i.e., characterized by a large equilibrium constant $K_{ATRP} = k_{act}/k_{deact}$ (Scheme 1). Such catalysts can be used at low concentrations because the rate of polymerization in ATRP is given by[28,177]

$$R_p = K_{ATRP} k_p \frac{[RX][M][Cu^IL_m]}{[XCu^{II}L_m]} \quad (1)$$

In the very first reports on copper complex-catalyzed ATRP, 2,2′-bipyridine (bpy) was used as the ligand.[26,111] Soon, the search for more active and less expensive complexes was initiated. Ligands structurally resembling bpy,

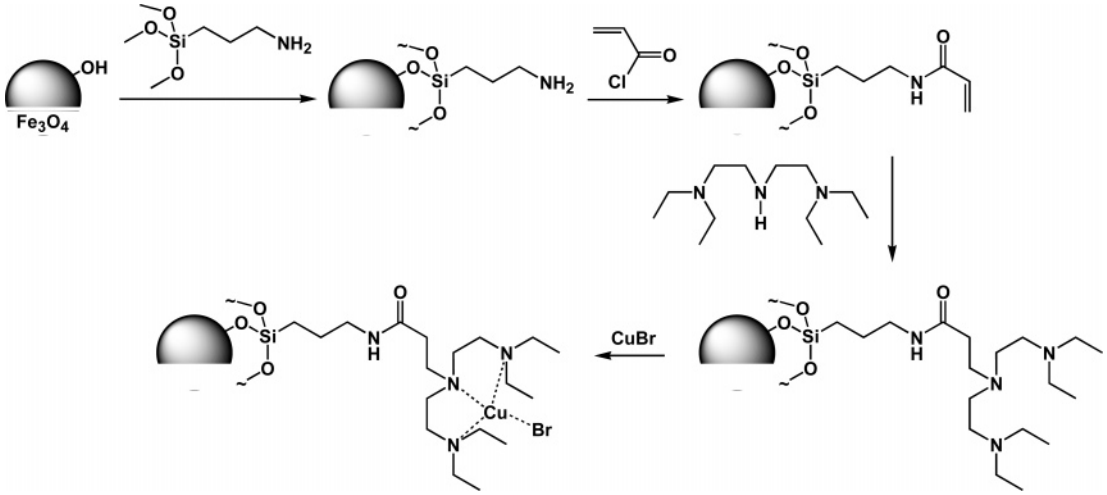


Figure 5. Preparation of a Cu^IBr/triamine-based ATRP catalyst supported on the surface of magnetic particles.[176]

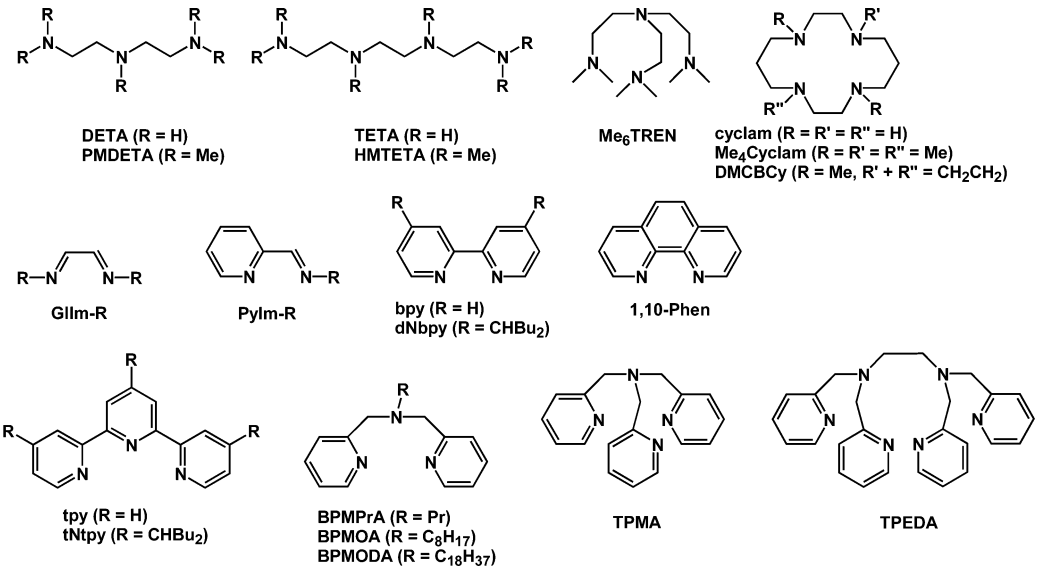


Figure 6. Examples of nitrogen-containing ligands used to form copper-based ATRP catalysts.

namely substituted bpys, 1,10-phenanthroline (1,10-phen), and its derivatives, were also studied as components of copper-based catalysts for the ATRP of Sty and (meth)acrylates.[46,178−180] Some typical ligands forming copper complexes used in ATRP are listed in Figure 6. Linear aliphatic amines such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, PMDETA, and HMTETA formed active Cu^I complexes (more active than the bpy complexes in the case of the last two amines) that could be successfully employed to control the polymerizations of Sty, MA, and MMA.[113] The PMDETA complex of Cu^ICl also proved very active (compared to the bpy complex) in the ATRA of CCl_4 to 1-octene.[181] A branched tetradentate ligand, Me_6TREN, formed a Cu^I complex so active that sufficiently fast ATRP of MA could be carried out at ambient temperature even using a molar ratio of catalyst to initiator equal to 0.1.[182,183] The activity of several successful ATRP catalysts was found to decrease in the order Cu^IBr/Me_6TREN > Cu^IBr/PMDETA > Cu^IBr/dNbpy.[182] In an attempt to polymerize substituted (meth)acrylamides in a controlled fashion, it was found that Me_4Cyclam formed a very active Cu^I complex[119] (more active than the complex of Me_6TREN[184]), which was able to mediate even the polymerization of vinyl acetate.[185] Unfortunately, although the ATRP reactions catalyzed by Cu^IX/Me_4Cyclam were very fast, the degree of control was not satisfactory due to inefficient radical deactivation by the higher oxidation state, Cu^{II}, complex. Picolylamine-based ligands, including TPMA, were shown to form Cu^ICl complexes that efficiently catalyzed ATRA and atom transfer radical cyclization reactions.[181] The Cu^I complexes of TPMA and another picolylamine-based ligand, BPMOA, were then studied as catalysts for the ATRP of Sty, MA, and MMA, and it was demonstrated that the TPMA complex possessed considerable activity (somewhat lower than that of the Me_6TREN complex).[118] Pyridinecarbaldehyde imine (PyIm-R) ligands have been successfully used in the ATRP of methacrylates.[114] The effect of the alkyl substituent at the nitrogen atom of these and glyoxal diimine-type (GlIm-R) ligands on the activity of the Cu^I-based ATRP derived therefrom was studied, and it was shown that branching in the alkyl group led to slower polymerizations.[117] In addition, it was shown that, for a series of *N*-pentyl-2-pyridylmethyl ligands, the nature of the substituent at position 5 or 6 of the pyridine ring had a pronounced effect on the rate of both ATRC and ATRP reactions.[186]

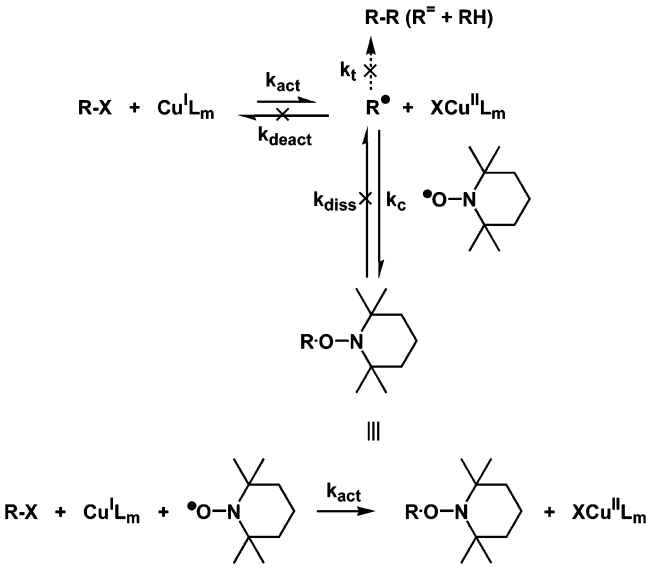
The impact of the ligand structure on the performance of Ru-based ATRP catalysts has also been demonstrated in many instances.[187−193] Clearly, a better understanding of the factors influencing the catalyst behavior was needed in order to rationally design or select the appropriate active ATRP catalyst for a given reaction system.

2.1.2.1. Evaluation of Catalyst Performance. To understand better the factors that determine the catalyst activity, as well as the polymerization control in ATRP reactions, numerous mechanistic studies employing model compounds have been carried out, as described in several review papers.[123,194,195] The purpose of these studies was to determine the accurate values of the rate constants k_{act} and k_{deact} or their ratio K_{ATRP}, which depend strongly on the nature of both the catalyst and the initiator. High catalytic activity, leading to a high polymerization rate, is related to a high K_{ATRP} value as shown by eq 1, since the equilibrium between the activation and the deactivation processes determines the radical concentration. Typically, K_{ATRP} is low ($<10^{-6}$) and a low radical concentration and therefore low radical termination rate is maintained throughout the ATRP process. In an ideal ATRP, both the rate constants k_{act} and k_{deact} should be large (with $k_{act} \ll k_{deact}$) to provide good polymerization control while keeping a reasonable polymerization rate. The experimental determination of the ATRP kinetic parameters is described in this section, and then (section 2.1.2.2) the factors affecting them are discussed.

2.1.2.1.1. Experimental Determination of Activation Rate Constants k_{act}. The rate constant k_{act} can be determined by reacting an alkyl halide with an excess of the Cu^I complex and irreversibly trapping the formed radicals by agents such as nitroxides (Scheme 2). The consumption of alkyl halide (monitored by spectroscopic or chromatographic techniques) under these conditions is directly related to k_{act}: $\ln([RX]_0/[RX]) = k_{act}[Cu^IL_m]_0 t$.[196−204]

A recent detailed study revealed that the nature of the N-donor ligand has a profound effect on the value of k_{act} in a reaction of Cu^I complexes with EBiB, with values ranging by around 6 orders of magnitude (Figure 7).[205] In general, bidentate ligands form complexes of relatively low activity,

Scheme 2. Model Reactions for Determination of k_{act} Values



although with many of them (derivatives of bpy, for instance) the polymerization control is excellent, indicating relatively high values of k_{deact} (*vide infra*). The studied tridentate ligands included both aliphatic amines and pyridine derivatives. When the aliphatic amines contained a three-carbon bridge between the nitrogen atoms, the activity of the Cu^{I}-based catalyst markedly decreased compared to those of catalysts derived from ligands with only two-carbon bridges such as PMDETA. A similar trend was observed with tetradentate aliphatic amine ligands. These results prove that the coordination angle and the mutual arrangement of adjacent chelate rings (determined by the number of C atoms linking two N-donor atoms) are important factors from the point of view of both complex stability[206] and catalytic activity (*vide infra*). Branched ligands (TREN derivatives as well as TPMA and TPEDA) formed very active catalysts. It is noteworthy that changes of the substituents at the N atoms in the TREN derivatives that seem minor at first sight (for instance, replacement of a methyl group with an ethyl) can dramatically influence the catalytic activity. This is in agreement with the observation that generally the presence of hydrophobic groups attached to N atoms in various aliphatic amine ligands makes the Cu^{I} complexes significantly less reducing (the relation between reducing power and ATRP catalytic activity is discussed below).[207] Steric and, more importantly, electronic effects of the substituents also influence the activity of the Cu^{I} complexes. Finally, the derivatives of cyclam form the most active Cu-based ATRP catalysts known to date. In particular, the highest value of k_{act} is reported for DMCBCy.[205,208]

Currently, it is difficult to predict the value of k_{act} of a certain complex based on parameters such as stability constants or redox potentials. Significantly more successful is the prediction of the values of K_{ATRP}. The experimental determination of the equilibrium constant is described followed by a discussion of the factors that affect its value.

2.1.2.1.2. Experimental Determination of the Equilibrium Constant K_{ATRP} and the Deactivation Rate Constant k_{deact}. Experimentally, the values of K_{ATRP} can be determined directly from polymerization kinetics data. In this case, an apparent value, $K_{ATRP}/[XCu^{II}L_m]$, is obtained from the slope of the time dependence of $\ln([M]_0/[M])/(k_p[Cu^{I}L_m]_0[RX]_0)$.[209] Alternatively, the classical equation describing the accumulation of deactivator due to the persistent radical effect with time was used:[177,210,211]

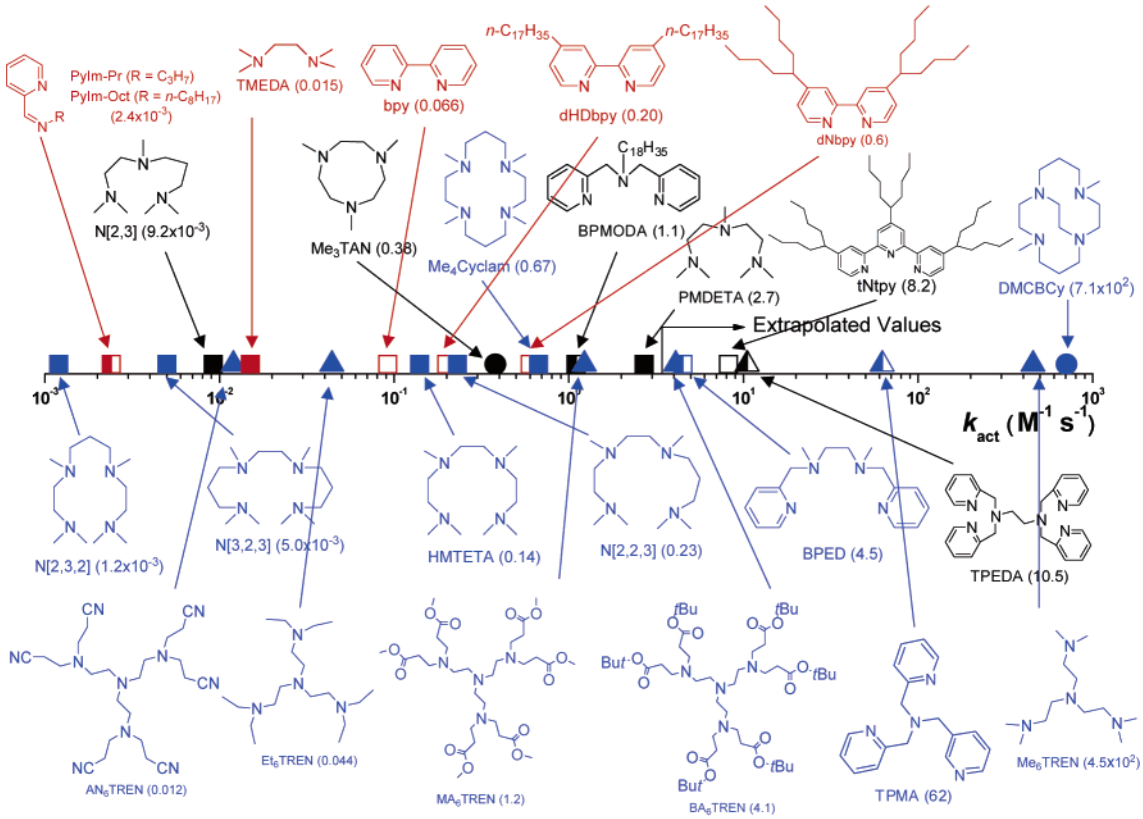


Figure 7. Activation rate constants of Cu^{I} complexes derived from various N-donor ligands in the reaction with EBiB in MeCN at 35 °C. Reprinted with permission from ref 205. Copyright 2006 American Chemical Society.

$$[XCu^{II}L_m] = (3K_{ATRP}^2 k_t [RX]_0^2 [Cu^IL_m]_0^2)^{1/3} t^{1/3} \quad (2)$$

To determine K_{ATRP}, a Cu^I complex is reacted with an alkyl halide, and the deactivator concentration (experimentally accessible through ESR or electronic spectroscopy) is monitored as a function of time. Then, a plot of $[XCu^{II}L_m]$ vs $t^{1/3}$ is constructed, and K_{ATRP} is determined from the slope, provided that the termination rate constant k_t is known.[194] This method is useful only for reactions that reach equilibrium rapidly, and then only for relatively low conversions of activator, Cu^IL_m, and alkyl halide. If these conditions are not met, the linear dependence (eq 2) is not observed. The reason is that eq 2 was originally derived with the assumption that $k_{act}[Cu^IL_m]_0[RX]_0 = k_{deact}[R^\bullet][XCu^{II}L_m]$, i.e., that the concentrations of the activator and initiator do not change significantly during the experiment. This approach is valid only for time regimes in which the product $[R^\bullet][XCu^{II}L_m]$ remains constant. This is a limitation when the values of K_{ATRP} for active catalysts should be determined.

Recently, the equations describing the persistent radical effect were modified taking into account that the concentrations of both the activator and initiator change during the experiment.[212] If the activator and initiator are mixed in a 1:1 molar ratio, the reaction stoichiometry requires that $[RX]_0 - [RX] = [Cu^IL_m]_0 - [Cu^IL_m] = [XCu^{II}L_m]$. Using the assumption (justified by simulations) that the rate of generation of deactivator exceeds significantly the rate of consumption of radicals, new equations describing the time dependence of $[XCu^{II}L_m]$ were obtained. For the simple 1:1 stoichiometry ($[Cu^IL_m]_0 = [RX]_0$), a function $F([Cu^{II}L_mX])$ is defined whose values can be plotted against time, and K_{ATRP} is obtained from the slope of the linear dependence:

$$F([XCu^{II}L_m]) \equiv \frac{[Cu^IL_m]_0^2}{3([Cu^IL_m]_0 - [XCu^{II}L_m])^3} - \frac{[Cu^IL_m]_0}{([Cu^IL_m]_0 - [XCu^{II}L_m])^2} + \frac{1}{[Cu^IL_m]_0 - [XCu^{II}L_m]} = 2k_tK_{ATRP}^2 t + \frac{1}{3[Cu^IL_m]_0} \quad (3)$$

In the case when $[Cu^IL_m]_0 \neq [RX]_0$, the time dependence of deactivator accumulation is more complex.[212]

$$F([XCu^{II}L_m]) = \left(\frac{[RX]_0[Cu^IL_m]_0}{[Cu^IL_m]_0 - [RX]_0}\right)^2 \left(\frac{1}{[Cu^IL_m]_0^2([RX]_0 - [XCu^{II}L_m])} + \frac{2}{[RX]_0[Cu^IL_m]_0([Cu^IL_m]_0 - [RX]_0)} \ln\left(\frac{[RX]_0 - [XCu^{II}L_m]}{[Cu^IL_m]_0 - [XCu^{II}L_m]}\right) + \frac{1}{[RX]_0^2([Cu^IL_m]_0 - [XCu^{II}L_m])}\right) = 2k_tK_{ATRP}^2 t + \left(\frac{[RX]_0[Cu^IL_m]_0}{[Cu^IL_m]_0 - [RX]_0}\right)^2 \left(\frac{1}{[Cu^IL_m]_0^2[RX]_0} + \frac{2}{[RX]_0[Cu^IL_m]_0([Cu^IL_m]_0 - [RX]_0)} \ln\frac{[RX]_0}{[Cu^IL_m]_0} + \frac{1}{[RX]_0^2[Cu^IL_m]_0}\right) \quad (4)$$

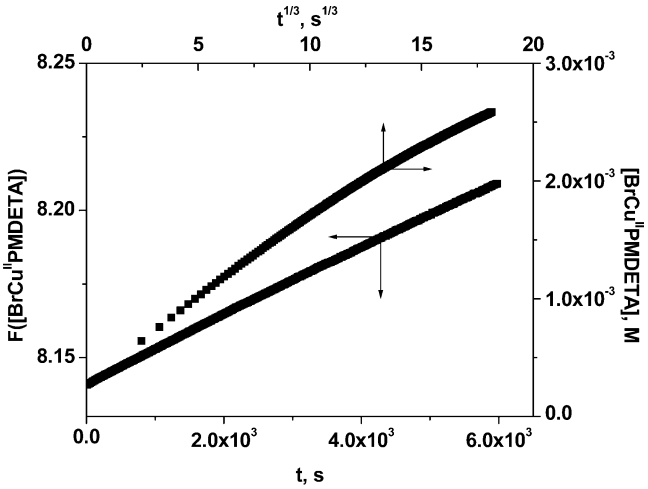


Figure 8. Experiment for the determination of K_{ATRP} via plotting $F([XCu^{II}L_m])$ against time. Reaction conditions: $[Cu^IBr/PMDETA]_0 = 5$ mM and $[1\text{-PhEtBr}]_0 = 100$ mM, in MeCN at 22 ± 2 °C. Reprinted with permission from ref 212. Copyright 2006 American Chemical Society.

Table 1. Experimental Values of K_{ATRP}[a]

no.	ligand	initiator	K_{ATRP}	ref
1	bpy	EBiB	3.93×10^{-9}	212
2	bpy	1-PhEtBr	8.5×10^{-10}	214
3	PMDETA	BPN	5.89×10^{-7}	212
4	PMDETA	EBiB	$(6.06-7.46) \times 10^{-8}$	212
5	PMDETA	1-PhEtBr	$(3.27-3.68) \times 10^{-8}$	212
6	PMDETA	MBP	3.95×10^{-9}	212
7	TPMA	EBiB	9.65×10^{-6}	212
8	TPMA	1-PhEtBr	4.58×10^{-6}	212
9	TPMA	1-PhEtCl	8.60×10^{-7}	212
10	TPMA	BnBr	6.78×10^{-7}	212
11	TPMA	MBP	3.25×10^{-7}	212
12	TPMA	MCP	$(4.07-4.28) \times 10^{-8}$	212
13	Me_6TREN	EBiB	1.54×10^{-4}	212
14	Me_6TREN	MCA	3.3×10^{-6}	208
15	DMCBCy	MCA	9.9×10^{-5}	208
16	HMTETA	EBiB	8.38×10^{-9}	195
17	HMTETA	1-PhEtBr	2.9×10^{-9}	214
18	HMTETA	1-PhEtCl	7.9×10^{-10}	214
19	BPMPrA	EBiB	6.2×10^{-8}	213
20	TPEDA	EBiB	2.0×10^{-6}	213

[a] Cu^IBr was used for alkyl bromide and Cu^ICl was used for alkyl chloride initiators, respectively. MeCN was used as the solvent; temperature = 22 ± 2 °C. [b] Concentration of initiator monitored by GC.

As the model reaction proceeds, the alkyl halide initiator is consumed, and in some instances, it is more convenient to follow the time dependence of its disappearance (for example, by GC or NMR) rather than the accumulation of deactivator. An equation describing the time dependence of the initiator consumption (for the case when $[Cu^IL_m]_0 \geq [RX]_0$) has also been derived[212] and employed.[212,213] Figure 8 shows the experimentally determined dependence of deactivator concentration, $[XCu^{II}L_m]$, on $t^{1/3}$ and also the time dependence of the function $F([XCu^{II}L_m])$ from eq 4 for the reaction of Cu^IBr/PMDETA with 1-PhEtBr (nonstoichiometric conditions) in MeCN.[212] As seen, the plot of deactivator concentration vs $t^{1/3}$ is a curved line and cannot be used to determine the value of K_{ATRP} whereas the plot of $F([XCu^{II}L_m])$ vs t is linear.

Table 1 lists experimentally determined values of K_{ATRP} for various Cu complexes using the described approaches. The values of K_{ATRP} range between 10^{-10} and 10^{-4}; that is,

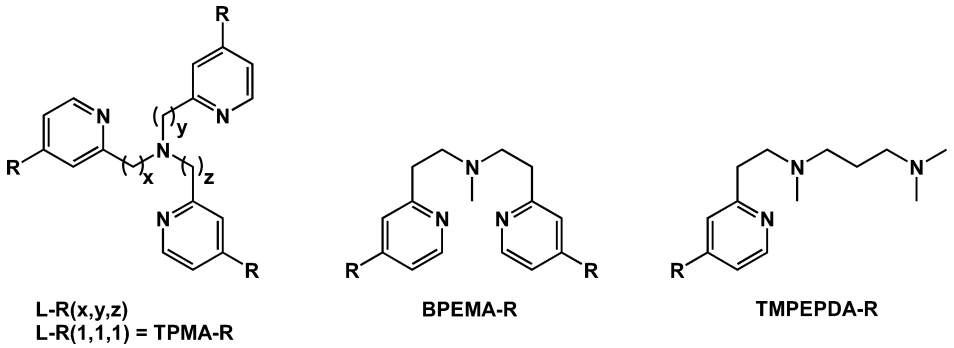


Figure 9. Substituted multidentate N-containing ligands forming O_2-binding copper complexes.

they differ by 6 orders of magnitude. Obviously, to compare the catalytic activity of two complexes, the values of K_{ATRP} in a reaction with the same alkyl halide should be compared. The ATRP catalytic activity of Cu^I complexes increases in the order bpy < HMTETA < PMDETA < TPMA < Me_6-TREN < DMCBCy. The most active complex known to date is derived from the cross-bridged cyclam ligand DMCBCy.[208] The very pronounced effect of the ligand on the ATRP catalytic activity is rationalized in the next section.

The value of K_{ATRP} depends upon the degree of substitution (primary < secondary < tertiary) of the alkyl halide initiator. This is related to the higher stability of tertiary compared to secondary and primary radicals that are formed after the hemolytic cleavage of the C−X bond. Alkyl halides with α-functional groups that stabilize radicals (such as cyano) are more active (larger K_{ATRP}) compared to those with no such substituents. Also, alkyl bromides are characterized by larger values of the equilibrium constant than those for the corresponding alkyl chlorides in reactions mediated by the same catalyst. This is related to the higher bond dissociation energy of the C−Cl bond (see Figure 11 below). However, C−Cl bonds are stronger than C−Br bonds by ca. 10 kcal mol^{-1}, and if the bond dissociation energy was the only factor determining the values of K_{ATRP}, those for alkyl bromides should be several orders of magnitude larger than those for the chlorides. According to Table 1, the difference is less than an order of magnitude, which can be attributed to the higher electron affinity of chlorine compared to bromine (i.e., larger K_{EA}(Cl) in Figure 11).[215−217] K_{ATRP} can also be viewed as the ratio of the dissociation energies of the C−X and Cu^{II}−X bonds. The lower than expected difference between K_{ATRP}(RCl) and K_{ATRP}(RBr), based only on the stability of the C−X bonds, can also be attributed to the greater stability of the Cu^{II}−Cl bond compared to the Cu^{II}−Br bond.[218]

It is possible to determine k_{act} and K_{ATRP} independently, and to calculate the values of k_{deact} from the ratio k_{act}/K_{ATRP}. Alternative experimental methods for determination of k_{deact} include the clock reaction, in which the radicals are simultaneously trapped by TEMPO and the deactivator $XCu^{II}L_m$,[200] and analysis of the initial degrees of polymerization with no reactivation, end groups, and molecular weight distributions.[219−221]

2.1.2.2. Effect of the Catalyst Nature on the Value of K_{ATRP} and Selection of Active ATRP Catalysts. Since ATRP is fundamentally a redox process, the attempt to correlate the behavior of the copper-based complexes in ATRP reactions with their redox properties is natural.[115] In a detailed study, Cu^ICl and Cu^IBr complexes of bpy, dNbpy, BPMOA, BPMODA, TPMA, PMDETA, and Me_6TREN were all characterized by CV and the measured redox potentials were correlated with the activity of the complexes in the ATRP of MA initiated by ethyl 2-bromopropionate (EBP).[209] The logarithm of the apparent ATRP equilibrium constant (determined from the slope of the time dependence of $\ln([M]_0/[M])$, divided by $k_p[Cu^IL_m]_0[EBP]_0$) was a linear function of the measured $E_{1/2}$ values. The values of either k_{act} or K_{ATRP} and the redox potential of a series of copper complexes with tridentate N-based ligands (where the nitrogen atom was amine-, imine-, or pyridine-type) were well-correlated.[200] The relatively high redox potentials (low reducing power) of Cu^I complexes of tetradentate bis-(pyridinecarbaldehyde imine) ligands was used to explain the comparatively slow MMA ATRP catalyzed by these complexes.[222] A good correlation was observed between the reducing power of several Cu^I complexes and the apparent rate constant of polymerization of OEGMEMA in aqueous media.[223] Recently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a ligand for the copper-mediated ATRP of Sty, MA, and MMA, and it was shown that the polymerizations were relatively slow, which was in good agreement with the redox potential of the copper complex (110 mV more positive than that of the bpy complex, and 220 mV more positive than that of the PMDETA complex).[224] Substituents in the ligands affect the redox properties of the complexes. For simple linear amines, the addition of more electron-donating groups stabilizes the Cu^I oxidation state, leading to lower ATRP catalytic activity. This has been observed, for instance, when hydrogen atoms from an N−H group in the ligand are replaced by alkyl[207,225] or allyl groups.[225] When a C−N fragment in a ligand molecule is substituted by C═N, usually a more pronounced relative stabilization of the Cu^I compared to the Cu^{II} complex is observed.[226,227] In summary, based on a substantial amount of data, it can be concluded that the more reducing Cu^I complexes are more active ATRP catalysts.

In light of the above discussion, it is highly desirable to be able to predict the redox properties of Cu complexes based on the nature and number of the ligand(s). For complexes of the same metal with close stereochemistry and oxidation and spin states, it is possible to use parametrization methods to predict the redox potenials.[228,229] Unfortunately, the application of these strategies is limited when multidentate ligands are employed that introduce varying degrees of distortion from ideal geometries. The electrochemical behavior of many Cu^I complexes with multidentate N-containing ligands has been studied in relation to oxygen binding by the metal center.[230] It was found that subtle changes in the ligand substituents can have a dramatic effect on the redox properties of the complexes (changes in the $E_{1/2}$ values by more than 100 mV). Some of the studied ligands are presented in Figure 9, and the measured redox potentials of their copper complexes are summarized in Table 2.[231−233]

Table 2. Redox Potentials of the Cu Complexes with the Ligands Shown in Figure 9

	$E_{1/2}$ (vs Fc/Fc^+, in V) of $Cu^IL/Cu^{II}L$ for R =				
ligand	Cl	H	tBu	MeO	Me_2N
TPMA−R[231]		−0.40[a]	−0.46[a]	−0.49[a]	−0.70[a]
BPEMA−R[232]	−0.27[b]	−0.31[b]		−0.36[b]	−0.44[b]
TMPEPDA−R[233]	−0.32[b]	−0.33[b]		−0.38[b]	−0.40[b]

[a] In MeCN. [b] In DMF.

The electrochemical properties of various Cu complexes of N-based macrocyclic ligands have also been shown to change as the electronic effect of the substituents is altered.[234,235]

As mentioned, the size of the chelate ring (determined by the number of C atoms bridging two neighboring N-donor atoms) influences significantly the values of k_{act} in Cu-mediated ATRP. It is documented that when a 5-membered chelate ring is replaced by a 6-membered one in the ligands L-R(*x*,*y*,*z*), shown in Figure 9, the Cu^I complexes become less reducing. Furthermore, the increase of the number of 6-membered rings at the expense of 5-membered rings leads to a decrease in the reducing power of the Cu^I complexes. The $E_{1/2}$ values (vs NHE in DMF) of the Cu^I/L-H(*x*,*y*,*z*) complexes are −0.386, −0.300, −0.200, and +0.115 V when the ligands change in the order L-H(1,1,1), L-H(1,1,2), L-H(1,2,2), and L-H(2,2,2), respectively.[236] Similar trends have been observed for Cu complexes with a macrocyclic ligand.[235] It can therefore be expected that Cu^I complexes of multidentate ligands containing 6-membered chelate rings should be less catalytically active in ATRP than their counterparts with 5-membered rings.

So far, only N-based ligands were discussed. The donor atoms in the ligand have a profound effect on the redox properties of complexes. For example, the very low reducing power of Cu^I complexes with thioether ligands makes these ligands inappropriate for ATRP catalysts. This is the result of the marked stabilization of the Cu^I relative to the Cu^{II} state. The redox potentials for the $Cu^{II}L/Cu^IL$ couple for several thioethers, both linear and cyclic, were in the range of 500−800 mV vs NHE.[237] It was shown that, in ligands analogous to TPMA with mixed donor atoms (N and S; Figure 10), the increase of the number of sulfur atoms led to formation of less reducing Cu^I complexes.[238] Consequently, although sulfur-only containing ligands are not appropriate as components of active ATRP catalysts, "heterodonor" ligands could possess a better catalytic activity. Such complexes are of interest because they may be sufficiently stable in the presence of acids and therefore may be used to mediate the ATRP of acidic monomers. Again, as in the case of N-donor ligands, there was a pronounced increase of the redox potential (decrease of the reducing strength) as an additional methylene group was added between the donor atoms, causing the formation of 6- instead of 5-membered chelate rings.[238] Similarly, the $E_{1/2}$ value of Cu^I complexes with N_2S_2-type ligands increases as a chelate ring in the complexes expands from 5- to 6- and then to 7-membered.[239] A detailed review on the Cu complexes with ligands containing the N_2S_2-donor set[240] demonstrates that the electrochemical properties can serve as a "probe" for the structural characteristics of the complexes. The electrochemistry of Cu^{II} complexes with N_2O_2-type heterodonor ligands has also been shown to depend upon the molecular geometry[241] and the electronic effects of the substituents.[242] A thorough review by Zanello[243] provides details about the redox potentials of numerous Cu complexes with ligands with N-, O-, and S-donor atoms. The work also discusses the influence of molecular geometry and substituent effects on the redox properties.

It should be noted that not many of the ligands discussed so far have been used as components of ATRP catalyst, but the studies that were summarized are of fundamental importance and will undoubtedly serve as an inspiration in the rational design of novel active ATRP catalysts.

A good correlation was reported between the reducing power of Ru^{II} complexes with p-substituted triphenylphosphine ligands and catalytic activity in the Kharasch addition of CCl_4 to various unsaturated compounds, namely 1-decene, Sty, and MMA.[244] Similarly, for a series of pentacoordinated $Fe^{II}Cl_2$ complexes with tridentate N-based ligands, there existed a satisfactory correlation between the redox potential and catalytic activity in ATRP.[245] However, it was noted that several tetracoordinated $Fe^{II}Cl_2$ complexes of bidentate diimine ligands showed higher catalytic activity in ATRP and were yet less reducing, in contrast to the typically observed trends.[94] On the other hand, the $Fe^{II}Cl_2$ complexes of iminomethinepyridines were less reducing than those of diimines and, as expected, showed lower ATRP catalytic activity.[246] The picture became more clouded when it was noted that, depending on the substituents at the N atoms, either ATRP or catalytic chain transfer (CCT, Scheme 3) could be mediated by the Fe^{II} complexes. It was shown that both the reversibility of the Fe^{II}-to-Fe^{III} transition[94,245,246] and the spin state of the Fe^{III} center[247] play a role in determining whether the ATRP or CCT mechanism will dominate, with the former being predominant for high-spin complexes with reversible reduction−oxidation process.

The attempt to generalize the rule that a more reducing catalyst is also more active failed in some cases, especially when trying to predict the performance of complexes of two different metals (such as Ru and Cu) or complexes of the same metal with two very different ligands (for instance, a neutral and charged one). Although Ru complexes are less reducing than the corresponding copper complexes, their catalytic activity may be similar. It was thus suggested[194] to present the overall atom transfer equilibrium as a combination of four simpler reversible reactions: (i) C−X bond homolysis (characterized by the equilibrium constant K_{BH}), (ii) oxidation (electron transfer) of the Cu^IL_m complex to yield $Cu^{II}L_m$

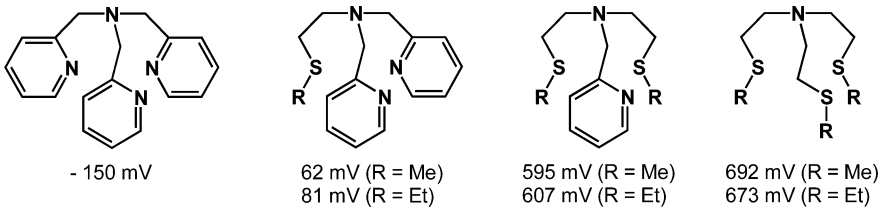
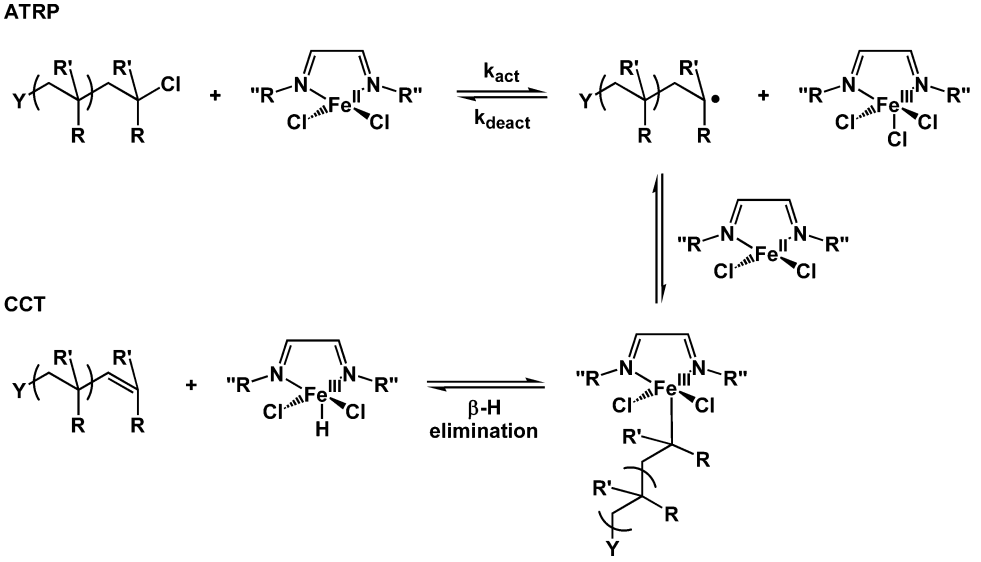


Figure 10. Ligands with similar structural features and redox potentials of their copper complexes vs NHE.[238] Note the gradual increase of the redox potential as the number of sulfur atoms is increased.

Scheme 3. Competing ATRP and CCT Mediated by Fe Complexes



(K_{ET}), (iii) reduction of a halogen atom to a halide ion (electron affinity K_{EA} of X), and (iv) association of halideion to $Cu^{II}L_m$ (termed *halidophilicity* K_X) as shown in Figure 11 and eq 5. Note that the constant K_X was previously termed

$$K_{ATRP} \equiv \frac{k_{act}}{k_{deact}} = \frac{[XCu^{II}L_m][R^\bullet]}{[Cu^{I}L_m][RX]} = K_{BH}K_{ET}K_{EA}K_X \quad (5)$$

halogenophilicity but since it reflects affinity toward halide anion rather than halogen atom, we will use from now on a more correct term halidophilicity. Although most Ru^{II} complexes are not sufficiently reducing,[187] the Ru^{III} complexes exhibit large affinity toward halide ions (i.e., large association constant K_X), which compensates for the small value of K_{ET} and leads to an acceptable overall activity of Ru^{II} in ATRP reflected by a high value of the equilibrium constant.

For a series of complexes of the same metal with structurally similar ligands, for which the halidophilicity constants are similar, the catalytic activity of a complex in ATRP can be predicted based on its redox potential. The latter, in turn, depends on the relative stability of the higher

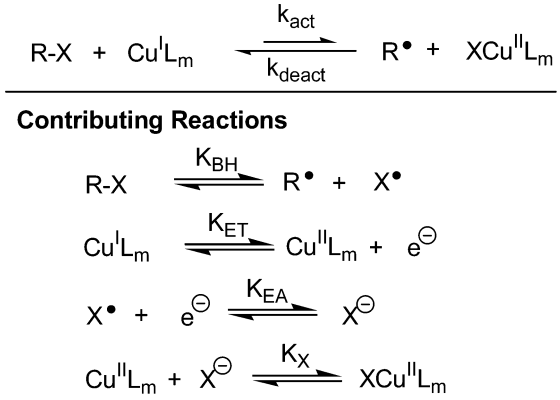


Figure 11. Representation of atom transfer as a combination of a C−X bond homolysis of an alkyl halide (RX), two redox processes, and a heterolytic cleavage of a Cu^{II}−X bond. (L represents a ligand.[194])

and lower oxidation state metal (Mt^{z+1} and Mt^z, respectively) complexes in the presence of the ligand L, according to eq 6, which is valid for one-electron-transfer processes between two complexes with the same central metal coordination number.[248−254] The overall formation (stability) constants of

$$E = E^\circ + \frac{RT}{F}\ln\frac{[Mt^{z+1}]}{[Mt^z]} = E^\circ + \frac{RT}{F}\ln\frac{[Mt^{z+1}]_{tot}}{[Mt^z]_{tot}} - \frac{RT}{F}\ln\frac{1+\sum_{j=1}^{m}\beta_j^{z+1}[L]^j}{1+\sum_{j=1}^{m}\beta_j^{z}[L]^j} \quad (6)$$

the Mt^z and Mt^{z+1} complexes containing j coordinated ligand molecules are designated by β_j^z and β_j^{z+1}, respectively. The dependence (eq 6) has been successfully used to experimentally determine the stability constants of many complexes.[255−261] For the case of relatively stable 1:1 copper complexes, eq 6 simplifies to

$$E \approx E^\circ + \frac{RT}{F}\ln\frac{[Cu^{II}]_{tot}}{[Cu^{I}]_{tot}} - \frac{RT}{F}\ln\frac{\beta^{II}}{\beta^{I}} \quad (7)$$

(Note that the subscript at the stability constant is omitted for simplicity when it is unity.) The redox potential of the $Cu^{II}L/Cu^{I}L$ couple is related to the K_{ET} value from eq 5

$$E = -\frac{RT}{F}\ln K_{ET} \quad (8)$$

Thus, by knowing the stability constants of the copper complexes with the ligand L, one should be able to predict the ATRP catalytic activity. The stability constants are readily determined either electrochemically (see the above-cited references), by potentiometric (pH) titration using a glass electrode,[262,263] or by titration calorimetry.[264−266]

Table 3 lists the experimental values of β^{II}/β^{I} (in aqueous media) for copper complexes often used as ATRP catalysts along with the measured values of K_{ATRP} in the reaction of those complexes with EBiB in MeCN. Although the two sets

Table 3. Correlation between the Ratio β^{II}/β^{I} and K_{ATRP} for Various Cu^{I} Complexes Used as ATRP Catalysts

catalyst	β^{I} [a]	β^{II} [a]	β^{II}/β^{I} [a]	ref	K_{ATRP} [b]
$Cu^{I}Br$/bpy	8.9×10^{12} [c]	4.5×10^{13} [c]	5.0	267	3.93×10^{-9} (ref 212)
$Cu^{I}Br$/HMTETA	1×10^{11}	3.98×10^{12}	39.8	225	8.38×10^{-9} (ref 195)
$Cu^{I}Br$/PMDETA	$<1 \times 10^{8}$	1.45×10^{12}	$>1.45 \times 10^{4}$	225	7.46×10^{-8} (ref 212)
$Cu^{I}Br$/TPMA	7.94×10^{12}	3.89×10^{17}	4.90×10^{4}	238	9.65×10^{-6} (ref 212)
$Cu^{I}Br/Me_6$TREN	6.3×10^{8}	2.69×10^{15}	4.3×10^{6}	268, 269	1.54×10^{-4} (ref 212)

[a] Measured in aqueous solution. [b] Reaction with EBriB in CH_3CN at 22 ± 2 °C. [c] The values of β_2^{II} and β_2^{II} and their ratio are reported.

of numbers were determined in two different solvents, the trend that higher values of β^{II}/β^{I} correspond to higher values of K_{ATRP} is clearly seen.

In a comprehensive review, Rorabacher[270] demonstrated, based on a substantial number of studies, that, as a d^{10} system, Cu^{I} has little preference for specific donor atom types, and the stabilities of Cu^{I} complexes vary much less than those of Cu^{II} complexes as the ligand structure is altered. In other words, for ligands forming very stable Cu^{II} complexes, the ratio β^{II}/β^{I} is likely to be high and the redox potential of the $Cu^{II}L/Cu^{I}L$ couple is likely to be low. Therefore, ligands forming very stable Cu^{II} complexes are likely to form active ATRP catalysts. Although it is risky to think of this as a general rule, it is useful in rapid screening of suitable ligands for the formation of catalytically active Cu^{I} complexes for ATRP. For example, both cyclam and DMCBCy form very stable Cu^{II} complexes (with log β^{II} values of 27.2 and 27.1, respectively[271]), and as expected, the catalytic activity of the Cu^{I} complexes of these ligands is exceptionally high.[208]

Several items should be borne in mind before attempting to predict the catalytic activity of a certain complex in ATRP based on literature values of stability constants. First, most of the reported stability constants were determined in aqueous medium, but ATRP reactions are often carried out in organic solvents, and like many other chemical phenomena, complexation and electron-transfer reactions are influenced very much by the nature of the solvent (its solvation and coordinating power or ability to form hydrogen bonds). Even in aqueous media, comparatively small changes in the ionic strength can affect the complex stability and therefore the redox potential.[272] Although the various effects of the solvent in chemical processes have been recognized for a long time,[273] and attempts to quantify them have been made,[274] the development of a complete theory that would allow at least semiquantitative predictions is still to be expected. Second, ATRP reactions are often conducted above the ambient temperature, and the thermal destabilization of the complexes should also be accounted for.[275,276] Finally, the halidophilicity K_X should also be determined even when structurally similar complexes are compared. It was shown that the known redox potentials alone were not sufficient to explain the catalytic activity of Ru complexes with several N-heterocyclic carbene ligands;[193] variations of the halidophilicity of the complexes as the ligand changes may be responsible for this.

It is noteworthy that an important side reaction is likely to occur if a very reducing Cu^{I} complex is used to mediate the polymerization of a monomer forming electrophilic radicals (acrylates, acrylonitrile, etc.), namely electron transfer from the complex to the radical.[277] A carbon-centered anion is formed that can be protonated, yielding dead polymer chains. Indeed, radicals with electron-withdrawing α-substituents, such as carbonyl, ester, or nitrile groups, are known to be rather oxidizing.[278] The redox process should be markedly less pronounced in the ATRP of monomers forming less electrophilic radicals, e.g., styrenes. In addition, due to the low redox potential of the active catalyst, the reaction mixtures are particularly sensitive to oxygen. These phenomena are often responsible for the limited monomer conversions often reached in the ATRP of acrylates or acrylonitrile mediated by very active Cu^{I} complexes.[269]

The driving force to develop very active ATRP catalysts is to be able to use them at low concentrations, thus making the postpolymerization catalyst removal unnecessary. However, high activity (high ratio β^{II}/β^{I}) is not sufficient to ensure that a catalyst can be used at very low concentration. If the catalyst is not stable enough (i.e., ligands forming complexes with relatively low values of β^{I} and β^{II}), it may dissociate upon dilution. Therefore, the appropriate catalysts are those for which both β^{I} and β^{II} are very high, with a high β^{II}/β^{I} ratio. A ligand that fulfills this requirement is, for example, TPEDA.[213]

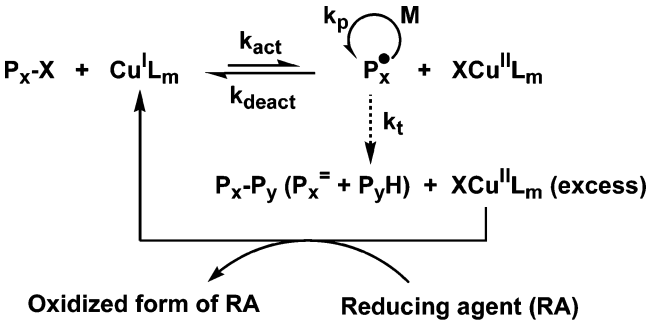
2.1.3. Decreasing the Amount of Copper in the Presence of Environmentally Benign Reducing Agents

An ATRP catalyst that is sufficiently active and stable can be used at very low concentration. The factors determining the activity of ATRP catalysts were outlined above. However, it should be borne in mind that the lower oxidation state of the catalyst (the Cu^{I} state in the case of copper-mediated ATRP) is constantly being converted to the higher oxidation state complex ($XCu^{II}L_m$) due to the occurrence of radical termination reactions and that the deactivator is accumulated in the system as the reaction proceeds—a process that was already discussed and has been dubbed the *persistent radical effect*.[177,210,211] For instance, if the catalyst is used at an amount equal to 5 mol % of the alkyl halide initiator, at the time when 5% of the polymer chains terminate, all the catalyst will be present in its higher oxidation state and the polymerization will stop. This may happen at relatively low monomer conversion. The amount of lost Cu^{I} complex due to termination is equal to the amount of terminated chains, as shown by eq 9.

$$-\Delta[Cu^{I}L_m] = \Delta[XCu^{II}L_m] = \Delta[P_{dead}] = k_t[P^{\bullet}]^2 t \quad (9)$$

In addition to the efforts to find very active ATRP catalysts, a major step toward reducing the amount of catalyst needed to mediate the polymerization was the development of a novel initiation technique named *activators generated by electron transfer* (AGET) ATRP.[279,280] This technique was a logical consequence of earlier work demonstrating that zero-valent metals could reduce the deactivator accumulated in the system[281] and that other reducing agents such as monosaccharides[282] or phenols[283] could be employed for the same purpose. AGET ATRP uses a combination of an alkyl halide (macro)initiator with an active ATRP catalyst in its higher oxidation state (Cu^{II}) in conjunction with a reducing

Scheme 4. Excess Reducing Agent (ERA) ATRP



agent such as a Sn^{II} compound,[279] ascorbic acid,[280] or phenols.[284] AGET ATRP could be successfully carried out in the presence of limited amounts of air, both in bulk and in miniemulsion.[285] Inspired by these findings, novel initiation systems were developed,[286] in which a very small amount of active copper catalyst is used, and the Cu^{II} complexes formed due to radical termination are constantly converted to the activator via a redox process. The way the new ERA (excess reducing agent) ATRP operates is sketched in Scheme 4.

In the ATRP of Sty, thermal initiation may take place and the generated radicals can reduce the accumulated deactivator. It was recently shown[286] that very low concentrations (in the ppm range) of ATRP catalyst can mediate the controlled polymerization of Sty in this manner. If the monomer does not undergo thermal initiation, a small amount of radical initiator can be added to simulate the slow thermal initiation. The process was termed *initiators for continuous activator regeneration* (ICAR) ATRP. Simulations and experimental data prove that the polymerization rate in ICAR ATRP does not depend upon the nature of the catalyst but only upon the concentration of the radical source. The steady-state radical concentration is given by the following relation, in which a slow radical generation is assumed.

$$[R^{\bullet}]_{st} = \sqrt{\frac{k_{diss}[I]}{k_t}} \approx \sqrt{\frac{k_{diss}[I]_0}{k_t}} \qquad (10)$$

In eq 10, k_{diss} is the decomposition rate of the radical source I, and the subscript "st" denotes the concentration at the steady state. These results indicate that the polymerization rate can be adjusted by selecting the proper radical initiator (k_{diss}) and by adjusting its concentration. It should be emphasized that although the rate of ICAR ATRP is catalyst-independent, the degree of polymerization control is most certainly connected to the nature of the catalyst. The ratio $k_p[M]/k_{deact}[XCu^{II}L_m]$ determines the number of monomer units added to a growing polymer chain before its deactivation. In order to achieve satisfactory polymerization control and a narrow MWD, this ratio should be low. The polymer polydispersity index (PDI), which reflects the polymerization control, is given by an equation originally derived for the case of living ionic polymerization.[287,288] The dependence was later[289] modified to describe the somewhat simpler case of controlled/living radical polymerization, and it was finally generalized for all polymerizations involving exchange reactions:[290]

$$PDI = \frac{M_w}{M_n} = 1 + \left(\frac{k_p[RX]_0}{k_{deact}[Cu^{II}L_mX]}\right)\left(\frac{2}{conv} - 1\right) \qquad (11)$$

The amount of deactivator in ICAR ATRP depends upon the value of K_{ATRP} according to eq 12.

$$[XCu^{II}L_m] = [XCu^{II}L_m]_0\left(1 - \frac{1}{K_{ATRP}\dfrac{[RX]_0}{[R^{\bullet}]_{st}} + 1}\right) \qquad (12)$$

Both the concentration of the deactivator and the value of k_{deact} are ligand-dependent. Indeed, it was demonstrated that only ligands forming Cu complexes with a high value of K_{ATRP} were successful in mediating a well-controlled ICAR ATRP. In addition, it is important to select ligands forming complexes with both Cu^{I} and Cu^{II} that are stable upon very high dilution and also in the presence of the potentially complexing or acidic reducing agents.

The amount of dissociated (and therefore "lost") complex is related to its stability and to the dilution. Equation 13 gives the dependence of the fraction of surviving complex (for the case of ligands forming 1:1 complexes) after dissociation due to dilution (j is the oxidation state and β^j is the corresponding stability constant).

$$\frac{[Cu^jL]}{[Cu^jL]_0} = 1 - \frac{\sqrt{1 + 4\beta^j[Cu^jL]_0} - 1}{2\beta^j[Cu^jL]_0} \qquad (13)$$

Obviously, only stable complexes will be appropriate for ICAR ATRP. A limitation of ICAR ATRP becomes apparent when the synthesis of block copolymers is concerned, since the radicals generated thermally (Sty) or from a radical source can initiate new polymer chains. Thus, reducing agents should be used that cannot initiate polymerization. When an excess of such a reducing agent (examples include Sn^{II} compounds, ascorbic acid, and substituted hydrazines) is added to the reaction mixture, again a ppm amount of Cu-based ATRP catalyst is sufficient to mediate the controlled polymer synthesis. This last process became known as *activators regenerated by electron transfer* (ARGET) ATRP.[286,291,292] The factors determining the polymerization rate and control in the relatively complex ARGET ATRP systems are still under investigation. There can be no doubt that both new methods (ICAR and ARGET) that allow one to perform ATRP using only very small amounts of catalyst will have a tremendous impact on the application of ATRP in industry and on making the process truly environmentally benign. In addition to the obvious advantage of using a very low catalyst amount, with the need for catalyst removal being virtually eliminated in many cases, the new ATRP initiation techniques allow for the synthesis of well-defined high molecular weight polymers (markedly higher than in conventional ATRP).[293] This is because the rates of many side reactions that limit the polymer molecular weight (such as oxidation of the propogating radicals to carbocations by the ATRP deactivator, or reduction of the radicals to carbanions by the activator) are minimized when the catalyst concentration is lowered.

2.2. ATRP in Environmentally Friendly Reaction Media

2.2.1. Water

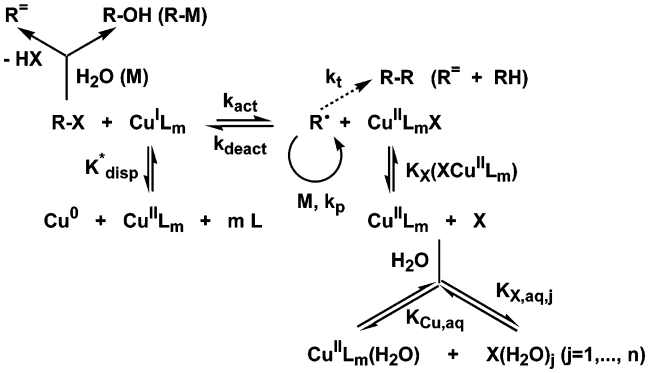
ATRP can be successfully carried out in heterogeneous aqueous systems. Details on such systems are summarized

in several review papers.[294−296] The successful suspension ATRP of 2-ethylhexyl methacrylate[297] and its copolymerization with MMA[298] mediated by $Cu^{I}Br$/dNbpy were reported. To conduct ATRP in an emulsion, efficient transport of monomer and catalyst (in both oxidation states) from large monomer droplets to the micelles through the aqueous phase is required. This is difficult to achieve, and many studies have concentrated on miniemulsion ATRP reactions.[62,63,280,299−302] The recent advances in the field include the preparation of linear and starlike block copolymers[63] by miniemulsion ATRP. Various initiation techniques have been employed including SR&NI ATRP[62] and AGET ATRP.[280] The latter has also been successfully used in stable microemulsions with well controlled size and polymer structure.[303] The microemulsion system was used as a seed for a subsequent emulsion process in which block copolymers were formed.[304]

The advances made in optimizing the conditions for conducting ATRP in aqueous homogeneous systems will be detailed. Obviously, it is very desirable to carry out well-controlled ATRP in aqueous solution. The major driving force was to successfully employ the most environmentally friendly and inexpensive solvent of all. Additionally, the research in the field is driven by the importance of the prepared polymers. Polymeric materials with hydrophilic groups, including neutral polymers, polyelectrolytes,[305−308] and ionomers,[309] are widely used in the fabrication of ion-exchange resins, superabsorbents, water-purification materials, selective membranes, etc. The physical properties, particularly the solution behavior,[305,310−312] of some of these materials can change dramatically upon changes in the environment, such as pH, ionic strength, temperature, etc., and they are thus used as "smart" or responsive materials, for instance, in controlled drug delivery, biomolecule or drug encapsulation, etc.[313] Block copolymers with two hydrophilic blocks that can act as surfactants under certain conditions are attractive materials for crystal engineering.[314,315] These polymers are also of interest for relatively large volume markets such as coatings, surfactants, adhesives, and cosmetics, to mention a few. Currently, they are mainly prepared using radical polymerization, due to its tolerance to protic solvents (including water), polar functional groups, and a variety of impurities often encountered in industrial processes. CRP of water soluble monomers in protic or aqueous media has already gained importance as a powerful synthetic tool in the preparation of various hydrophilic polymers.[316]

The first reported ATRP of a water soluble monomer, 2-hydroxyethyl acrylate, in aqueous solution employed Cu^{I}-Br/bpy as catalyst and MBP or diethyl 2-methyl-2-bromomalonate as initiator.[317] Although the M_w/M_n values of the polymers at low to moderate conversions (ca. 30−40%) were relatively high, the final products (at >80% monomer conversion) had a narrow MWD. This report demonstrating that ATRP could be successfully carried out in the presence of water was followed by a communication describing the ATRP of a charged monomer, sodium methacrylate,[318] in aqueous medium at 90 °C. The ATRP of a neutral water soluble methacrylate, poly(ethylene oxide) methyl ether methacrylate (MePEOMA),[319] in water was more successful, and it was shown that the reaction was fast even at room temperature (essentially complete monomer conversion within one to several hours). Polymers with relatively low polydispersity were obtained, plausibly due to slow termination of the sterically hindered radicals derived from MePEOMA. The polymerization of the same monomer in bulk was relatively slow, which demonstrated that water affected the polymerization rate.[320] It was also shown[320] that not only bpy but also HMTETA could be used as the ligand for the copper-based catalyst, and that the reaction was markedly faster with the latter ligand. The ATRP of sodium 4-vinylbenzoate was carried out in water at 20 °C using $Cu^{I}Br$/bpy as the catalyst and three different water soluble initiators.[321] A more detailed report on the aqueous ATRP of 2-(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA)[322] at 20 and 30 °C demonstrated that the polymerizations were fast, especially when $Cu^{I}Br$/HMTETA was used as the catalyst ($Cu^{I}Br$/bpy was the other complex studied), and that in most cases the MWD of the synthesized polyDMAEMA was rather broad. Later studies on the room-temperature ATRP of a zwitterionic monomer, 2-methacryloyloxyethyl phosphorylcholine,[323] and a neutral hydrophilic monomer, 2-hydroxyethyl methacrylate (HEMA),[324,325] demonstrated that addition of methanol to the aqueous solvent slowed down the polymerizations and improved the control. The degree of control over the polymerization was worse with $Cu^{I}Cl$/bpy than with $Cu^{I}Br$/bpy as the catalyst. Results from the ATRP of MePEOMA,[326] sodium 4-styrenesulfonate,[327,328] quaternized (alkylated) DMAEMA,[325,329] potassium 3-sulfopropyl methacrylate,[330] *N*-isopropylacrylamide,[331] and sodium 2-acrylamido-2-methylpropanesulfonate in protic media all support the idea that addition of organic solvents (methanol or DMF) leads to slower and better-controlled polymerizations and that, in order to achieve satisfactory control, the addition of a Cu^{II} halide complex to the catalyst is necessary. It was similarly shown that, in the ATRP of hydrophobic methacrylates, the addition of small amounts of water (such that a homogeneous reaction mixture was retained) enhances the polymerization rate, which can be advantageous.[332,333]

Scheme 5. Side Reactions in Copper-Mediated Aqueous ATRP (Based on Ref 334, with modifications. Copyright 2006 American Chemical Society.)



Conducting a well-controlled ATRP in aqueous media is challenging due to the occurrence of several side reactions. In water, the Cu^{I}-based ATRP activator may disproportionate, the Cu^{II}-based deactivator is likely to lose its halide ligand, and the alkyl halide initiator may hydrolyze or react with the monomer if it contains basic or nucleophilic groups, as shown in Scheme 5. These reactions are discussed in more detail below.

2.2.1.1. Dissociation of the Deactivator in Protic Media. ATRP reactions in aqueous solvents are usually fast even at ambient temperature, and the polymerizations are accelerated as the amount of water in the solvent is increased. In principle, this could be due to the effect of water or similar

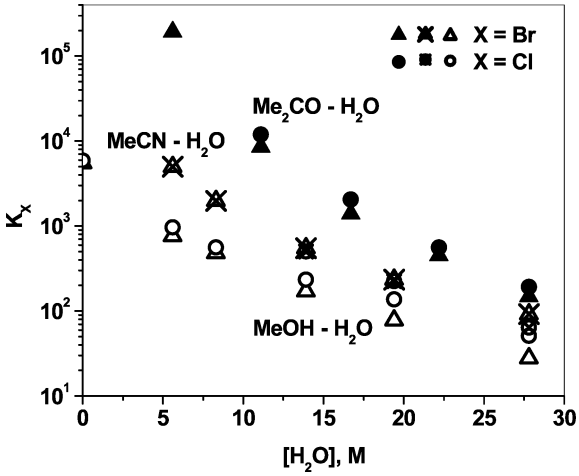


Figure 12. Dependence of halidophilicity, K_{Br} or K_{Cl}, of $[Cu^{II}(bpy)_2]^{2+}$ upon the concentration of water in mixtures of acetone (filled symbols), acetonitrile (crossed symbols), and methanol (open symbols) with water.[340,341]

protic solvents on k_p, K_{ATRP}, and/or the deactivator concentration $[XCu^{II}L_m]$ (see eq 1). Specific solvation of some polar monomers able to form hydrogen bonds with protic solvents does indeed lead to a small increase in k_p.[335−337] It was demonstrated[325] that copper-based ATRP deactivators ($XCu^{II}L_m$) are relatively unstable in protic media and tend to dissociate, forming the complex $Cu^{II}L_m$. The concentration of deactivator actually present in the system depends upon the value of the halidophilicity of the Cu^{II} complex, K_X, and on the total concentrations of Cu^{II} complexes and halide ions, according to eq 14.

$$[XCu^{II}L_m] = \frac{F - \sqrt{F^2 - 4K_X{}^2[Cu^{II}]_{tot}[X]_{tot}}}{2K_X} \qquad (F \equiv 1 + K_X[Cu^{II}]_{tot} + K_X[X]_{tot}) \quad (14)$$

The value of K_X is markedly lower in protic media than in "conventional" solvents. Typical values of K_X in aprotic solvents (hydrocarbons, ethers, ketones, DMF, etc.) are of the order of 10^4 to 10^5 M^{-1},[338] or higher, whereas in protic solvents these values are two or more orders of magnitude lower (10 to 10^3 M^{-1}).[325,339] The halidophilicity of $[Cu^{II}(bpy)_2]^{2+}$ toward both Br^- and Cl^- was studied in various water-containing mixed solvents, and it was shown that in all cases the values of K_X decreased significantly as the amount of water in the mixtures increased (Figure 12).[325,340,341]

Thus, dissociation of the $XCu^{II}L_m$ complex with the formation of $Cu^{II}L_m$ that cannot deactivate radicals is very pronounced in protic media, particularly in water-rich solvents. Lower deactivator concentration leads to increased polydispersity of the polymers produced, according to eq 11.

There are three general ways to improve the control over polymerization in protic media: (i) select ATRP catalysts that possess high values of K_X (this value should depend upon the nature of the ligand L and the metal), (ii) employ catalyst containing large initial amounts of deactivator (up to 80 mol % of the total catalyst; see Figure 13), or (iii) add extra halide salts to the system. The utility of the last two methods has been demonstrated in several systems.[325,342,343] A plot of the dependence of the fraction of "surviving" deactivator after the dissociation (i.e., $[BrCu^{II}(bpy)_2]^+/[BrCu^{II}(bpy)_2]^+_0 = [BrCu^{II}(bpy)_2]^+/[Cu^{II}]^+_{tot}$) in methanol−water mixtures as a function of the concentration of initially

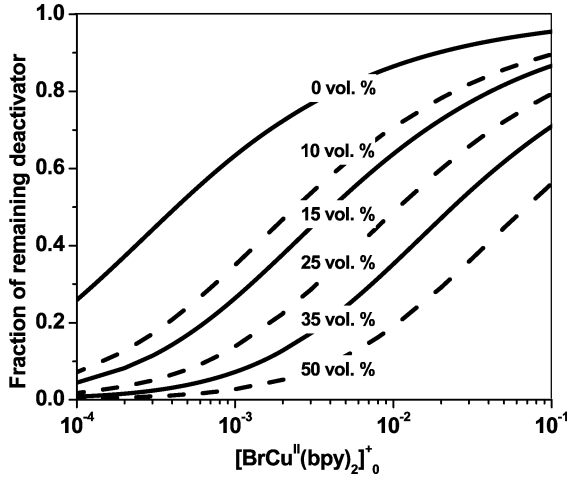


Figure 13. Relationship between the percent of deactivator remaining after dissociation and its initial concentration $[BrCu^{II}(bpy)_2]^+_0 = [Cu^{II}]_{tot}$ in methanol ($K_{Br} = 4710$) and mixtures of methanol and water containing varying amounts of water (the volume percent of water is shown at each curve): 10 vol % ($K_{Br} = 826$), 15 vol % ($K_{Br} = 486$), 25 vol % ($K_{Br} = 186$), 35 vol % ($K_{Br} = 84$), and 50 vol % ($K_{Br} = 29$). Reprinted with permission from ref 325. Copyright 2004 American Chemical Society.

present $[BrCu^{II}(bpy)_2]^+$ complex is presented in Figure 13. Clearly, more efficient radical deactivation and therefore better polymerization control in water-rich solvents can be achieved with ATRP catalysts containing a high initial amount of deactivator.

The effect of halide concentration on both the rates and control in ATRP reactions was observed when Cu^I carboxylates (acetate and 2-thiophenecarboxylate) rather than bromides were used as components of the dNbpy-based catalyst.[344] The polymerization of Sty was markedly faster with the carboxylate catalysts, and the control was poorer than with CuBr/dNbpy. The addition of $CuBr_2$ or CuBr significantly improved the control. Although it was not realized at the time when this work was published (1998), both the addition of Cu^{II} and/or extra bromide (the source could be either CuBr or $CuBr_2$) could form the deactivator that is necessary to control the polymerization. When Cu^I carboxylates were used alone, the only halide source was the ATRP initiator but, due to the presence of the coordinating carboxylate anions, significant displacement of bromide from $[Cu^{II}(dNbpy)_2Br]$ took place.

2.2.1.2. Disproportionation of Cu-Based Activating Complexes in Aqueous Media. As mentioned, the ATRP catalyst activity is mainly determined by the redox potential and the halogenophilicity of the higher oxidation state complex. However, other properties of Cu^I compounds are also determined by the nature of the ligand. The compounds of Cu^I are generally unstable in aqueous media and tend to disproportionate (eq 15 and Scheme 5). For instance, the

$$2Cu^I \underset{}{\overset{K_{disp}}{\rightleftharpoons}} Cu^{II} + Cu^0 \qquad K_{disp} = \frac{[Cu^{II}]}{[Cu^I]^2} \quad (15)$$

equilibrium constant of disproportionation of the free Cu^+ ion in water is as high as $K_{disp} = 10^6$.[345] This value is very sensitive to the solvent nature.[269] The disproportionation of the Cu^I ion is significantly less pronounced in organic solvents such as DMF ($\log K_{disp} = 4.26$[346]), methanol ($\log K_{disp} = 3.6-3.8$[347,348]), ethanol ($\log K_{disp} = 0.56$[347]), DMSO

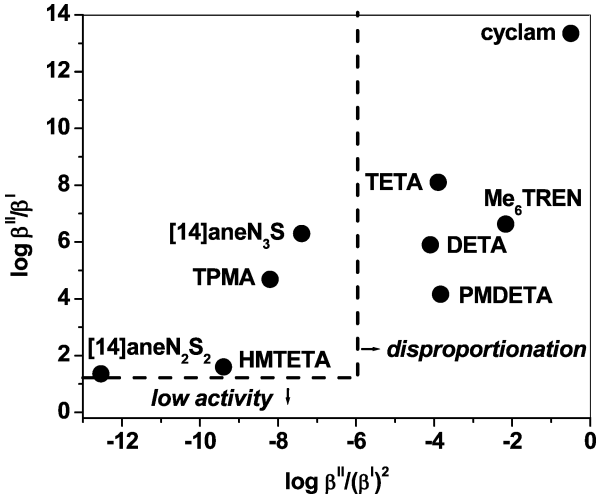


Figure 14. Correlation between ATRP catalytic activity and disproportionation ability for several Cu^I complexes.

(log $K_{disp} = 0.2-0.3$[349−351]), acetone (log $K_{disp} = -1.50$[352]), and MeCN (log $K_{disp} = -21$[353,354]). The value of the disproportionation equilibrium constant depends upon the dielectric constant[352] of the medium but mostly on its ability to preferentially solvate or coordinate to Cu^I or Cu^{II} ions.[269] In order to lower the ability of Cu^I to disproportionate in aqueous media, cosolvents such as DMSO,[351] DMF,[346] or especially MeCN[355] can be added to water.

Addition of a ligand L able to form complexes with Cu^I and Cu^{II} significantly affects the disproportionation equilibrium constant, which changes to a new value, K^*_{disp}. This can be defined with the total concentrations of Cu species, i.e., free and complexed Cu^{II} and Cu^I, and termed the *conditional disproportionation constant*, analogous to the conditional stability constants introduced by Schwarzenbach[356] and widely employed in coordination chemistry.[357] The value of K^*_{disp} is determined by the relative stabilization of the two oxidation states upon coordination according to eq 16.[195,269,334,358]

$$K^*_{disp} = \frac{[Cu^{II}]_{tot}}{[Cu^{I}]_{tot}^{\ 2}} = \frac{1 + \sum_{j=1}^{m} \beta_j^{II}[L]^j}{(1 + \sum_{j=1}^{m} \beta_j^{I}[L]^j)^2} K_{disp}$$

for a 1:1 complex: $K^*_{disp} =$

$$\frac{1 + \beta^{II}[L]}{(1 + \beta^{I}[L])^2} K_{disp} \approx \frac{\beta^{II}}{(\beta^{I})^2[L]} K_{disp} \quad (16)$$

In eq 16, K_{disp} is the disproportionation in the absence of the ligand L. Equation 16 can be used to predict whether a ligand is suitable for the formation of a Cu^I-containing catalyst for ATRP in aqueous media.

Close examination of eqs 7 and 16 leads to the conclusion that, for ligands forming 1:1 complexes with copper ions, the activity of the catalyst is proportional to β^{II}/β^I whereas the tendency of the Cu^I complex to disproportionate in aqueous solution (which should be minimized) depends on the ratio $\beta^{II}/(\beta^I)$.[2] Thus, a "map" can be constructed (Figure 14[195,269,334]) that can be used to select a ligand for aqueous ATRP that will produce a complex that is highly active, yet stable toward disproportionation. The stability constants of the Cu^I and Cu^{II} complexes of TPMA,[238] DETA,[225] PMDETA,[225] TETA,[225] HMTETA,[225] Me_6TREN,[268,269] and cyclam and its S-containing analogues[359,360] are taken from the literature. The Cu^I complexes of PMDETA and Me_6-TREN are not suitable for aqueous ATRP due to very fast disproportionation. On the other hand, ligands such as bpy, HMTETA, and TPMA can all be used in aqueous media because their Cu^I complexes are significantly less prone to disproportionate. The replacement of nitrogen with sulfur atoms, for example in cyclam, leads to a significant decrease of the catalytic activity, accompanied by a decrease in the ability of the Cu^I complex to disproportionate (see also the discussion in section 2.1.2.2). If only one of the N atoms is replaced with S, i.e., when [14]aneN_3S instead of cyclam is used, the ratio β^{II}/β^I (related to catalytic activity) is still large (larger than that of TPMA), while the disproportionation in water is very much suppressed. The use of heterodonor ligands with one or two S atoms may prove a useful strategy to stabilize the ATRP catalyst toward disproportionation and yet preserve sufficient catalytic activity. Some of the ligands shown in Figure 14 have not been used as components of Cu-based ATRP catalysts, and the future will show their applicability. It should be noted that the map in Figure 14 does not predict one very important feature of the ATRP catalyst, namely the rate of radical deactivation by the Cu^{II} halide complex. This rate is very important in order to maintain control over the polymerization. Also, strictly speaking, since K_X is responsible for the observed polymerization rate and control, its values may also be plotted on a separate axis to yield a three-dimensional catalyst selection map.

The first attempts to polymerize quaternized (alkylated) DMAEMA in a controlled fashion using ATRP in aqueous media were not successful. The catalyst (Cu^IBr/bpy) disproportionated rapidly, and precipitation of Cu^0 was observed. It is noteworthy that this catalyst does not disproportionate in aqueous solution in the presence of neutral monomers such as HEMA and DMAEMA but was unstable in the presence of charged monomers. This was most likely due to the polarity changes in the presence of large amounts of salt. When pyridine was used as a cosolvent in the polymerizations, no disproportionation took place and high monomer conversion was reached. The control over polymerization was excellent.[361]

2.2.1.3. Other Side Reactions of the ATRP Catalyst or Initiator. Although hydrolytic loss of the halide ligand from the deactivator is a major side reaction in aqueous ATRP, other interactions of reaction components with water or polar monomers can also contribute to the relatively poor control over the polymerizations. Such reactions include, *inter alia*, monomer coordination to the copper catalyst, substitution or elimination reactions of the alkyl halide initiators, and dormant chain ends in the presence of water or monomers with nucleophilic or basic groups. It was reported[326] that even relatively stable copper complexes with ligands such as pyridylmethaneimine rapidly decomposed in aqueous solution at elevated temperatures (50 °C). Some monomers can participate in side reactions during the course of the polymerization. An example is the methanolysis of tertiary amine methacrylates producing methyl methacrylate and the corresponding substituted *N*,*N*-dialkylaminoalcohol, which can coordinate to copper ions.[362]

The carbon−carbon double bond of many monomers can serve as a coordinating group that interacts with the metal

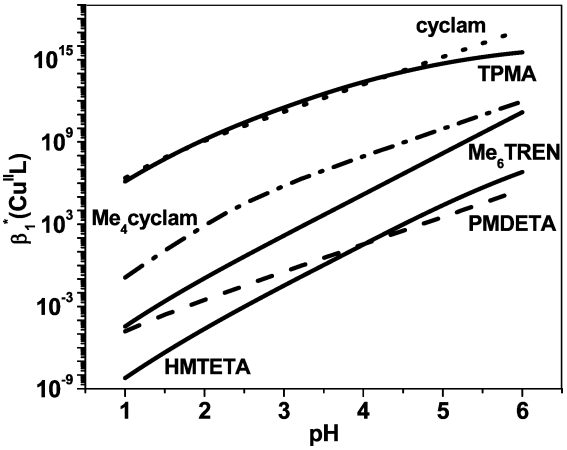


Figure 15. Dependence of the conditional stability constant of $Cu^{II}L$ complexes used as ATRP catalysts upon pH of the medium.[340] Reprinted with permission from ref 195. Copyright 2006 American Chemical Society.

center of the ATRP catalyst. For example, the complexation of Sty, MA, 1-octene, or MMA to Cu^{I} has been studied in detail and the complexes have been characterized by means of IR and variable temperature NMR spectroscopy as well as by X-ray crystallography.[363,364] In general, the coordination is relatively weak, with association or stability constants lower than 10^3. However, when the monomer contains strongly coordinating groups (e.g., amine, amide, carboxylate group, or pyridine moiety), which is often the case for water-soluble or hydrophilic monomers, the halide ligand from the Cu^{II}-based deactivator and the ligands from both the Cu^{I} and Cu^{II} complexes serving as ATRP mediators can be displaced. In many cases, this leads to partial or complete loss of catalytic activity. To prevent this reaction, ligands for the ATRP catalysts should be selected that form very stable Cu^{I} and Cu^{II} complexes. In fact, if the stability of the complex between the metal center and the monomer is known, the conditional stability of the ATRP catalyst (both the low and the high oxidation states, $\beta^{*,j}$, with j designating the oxidation state) can be calculated. If a reaction between the monomer and the ligand takes place, for instance ligand protonation by acidic monomers, the conditional stability of the ATRP catalyst can be calculated provided that the ligand protonation constants are known. As a rule, the complexes of very basic ligands are rather sensitive to the pH of the medium, although in the case when the ligand forms kinetically stable copper complexes, the complex protonation can become negligible. Equation 17 gives the dependence of the conditional stability constant $\beta^{*,j}$ of a complex as a function of acid concentration.

$$\beta^{*,j} = \frac{\beta^{j}}{\alpha_{\mathrm{L}}} \left(\alpha_{\mathrm{L}} = 1 + \frac{[\mathrm{H}^+]}{K_{a,r}} + \frac{[\mathrm{H}^+]^2}{K_{a,r}K_{a,r-1}} + \ldots + \frac{[\mathrm{H}^+]^r}{K_{a,r}K_{a,r-1}\ldots K_{a,1}}\right) \quad (17)$$

In the above equation, $K_{a,1}$, ..., $K_{a,r}$ are the acidity constants of the protonated ligand. Figure 15 is a graphical representation of eq 17 for Cu^{II} complexes of ligands for which the protonation constants and the formation constants of Cu^{II} complexes are known: PMDETA,[225] HMTETA,[268] Me_6-TREN,[268] cyclam,[268] Me_4Cyclam,[268] and TPMA.[238] As seen, the complexes of basic ligands are much destabilized in acidic media, especially when their stability constants even in the absence of protonation are relatively low (e.g., the Cu^{II} complexes of PMDETA and HMTETA). The appropriate ligand for ATRP of acidic monomers should form complexes of Cu^{I} and Cu^{II} that are both sufficiently stable in acidic media.

In summary, when side reactions with either the metal or the ligand component of the ATRP catalyst may take place, the appropriate catalyst is that for which the ratio of the conditional stability constants $\beta^{*,II}/\beta^{*,I}$ is large (to ensure sufficient catalytic activity), while the ratio $\beta^{*,II}/(\beta^{*,I})^2[\mathrm{L}]$ is low (to guarantee stability toward disproportionation). Finally, to prevent the loss of halide ligand from the deactivator, halide salts may be added to the system. Clearly, knowledge of the equilibrium constants of the side reactions is essential for evaluation of the conditional stability of ATRP catalysts, as exemplified above.

In many instances, copper bromide-based ATRP catalysts perform better (in terms of final polymer polydispersity) than the corresponding chlorides, mainly because of a larger value of k_{deact} in the former case. However, if the alkyl halide initiator or the dormant state of the polymer is prone to participate in nucleophilic substitution reactions (typical for 1-phenylethyl or polySty-like secondary alkyl halides), the use of chloride-based initiators and catalysts is necessary. The reason is that the S_N reactions that would cause "killing" of chains are slower for the alkyl chlorides compared to the bromides. For example, in the ATRP of 4VP in aqueous media, a polymer with a polymodal molecular weight distribution was obtained if a bromide-based initiator and catalyst were used. The polymodality was the result of reaction of the bromine-terminated poly4VP with either the monomer or the polymer, yielding pyridinium salts and therefore leading to branching (Scheme 6). This reaction was suppressed when $Cu^{I}Cl$ was employed as the catalyst component, and a polymer of narrower and monomodal molecular weight distribution was synthesized.[214] The importance of using a copper chloride-based ATRP catalyst has also been realized in the ATRP of 4VP in organic solvents.[365,366]

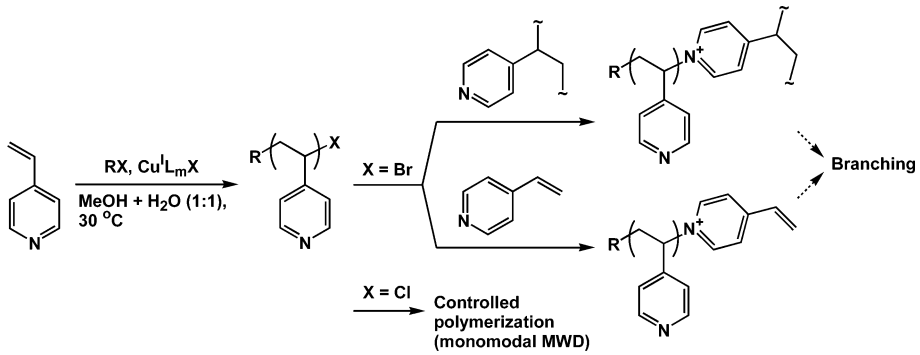
At the end of this section, it should be mentioned that the other important CRP techniques have also been successfully conducted in aqueous media. In fact, the very first work on aqueous CRP was the NMP of NaSS in water mediated by TEMPO.[367] Since this pioneering work, many reports on NMP in aqueous or protic media have been published.[368] RAFT polymerizations are also frequently conducted in aqueous media.[368−370]

2.2.2. Carbon Dioxide

Along with water, supercritical carbon dioxide ($scCO_2$) is the most environmentally friendly solvent. A multitude of chemical transformations have been successfully carried out in $scCO_2$, including polymerizations.[371−373] Most polymers are not soluble in this medium, but polymerization reactions can be conducted efficiently in it, provided that suitable surfactants[374−376] (with a CO_2-philic segment and a segment miscible with the polymer) are used to prevent flocculation. The removal of the solvent leads to a freely flowing polymer powder.

ATRP can be performed in $scCO_2$, but a special catalyst with sufficient solubility in the reaction medium has to be used. For the purpose, a partially fluorinated analogue of dNbpy, namely the compound with 4,4,5,5,6,6,7,7,8,8,9,9,9-

Scheme 6. Reaction of Bromide-Terminated Poly4VP with Pyridine Units of 4VP and/or Poly4VP Leading to Formation of Branched Structures (Reprinted with permission from ref 214. Copyright 2006 American Chemical Society.)



tridecafluorononyl groups, was employed as the ligand.[377] Well-defined acrylates and methacrylates with fluorinated alkyl groups were thus prepared in $scCO_2$. These were further chain extended with either MMA or DMAEMA. Following this first report, several works have appeared demonstrating the facility of $scCO_2$ as a reaction medium for ATRP.[378−381] The enzymatic ring-opening polymerization of ϵ-caprolactone initiated by 2-hydroxyethyl 2′-bromoisobutyrate was also successfully conducted in $scCO_2$, affording a poly(ϵ-caprolactone)-based ATRP macroinitiator. Subsequently, a semifluorinated monomer, 1H,1H,2H,1H-perfluorooctyl methacrylate, was added to the same reactor, and a block copolymer was synthesized.[382]

Other CRP procedures have also been successfully conducted in $scCO_2$, including RAFT[379] and NMP.[383] The catalytic chain transfer polymerization of MMA mediated by Co^{II}/porphyrin complexes in $scCO_2$ has also been reported.[384]

2.2.3. Ionic Liquids and Other Solvents of Low Volatility

Ionic liquids have attracted significant attention as "green" solvents mainly due to their very low volatility. They have been successfully used in polymer synthesis,[385−387] and it was reported[388] that radical polymerizations are enhanced as compared to those carried out in more conventional reaction media. MMA was polymerized in a controlled fashion using 1-butyl-3-methylimidazolium hexafluorophosphate by both normally initiated[389] and reverse[390] ATRP. The catalyst was easily separated from the product and could be reused.[390] Acrylates were also polymerized successfully in ionic liquids,[391] and the preparation of block copolymers was reported as well.[392] ATRP of acrylates was carried out in chiral ionic liquids, and it was shown that the chirality of the medium affected, although not significantly, the tacticity of the produced polymers.[393] Both copper- and iron-mediated ATRP could be conducted in ionic liquids; in the latter case, no extra ligands were needed to achieve controlled polymerization.[394]

The polymers of ethylene oxide (often referred to as PEG) of low or intermediate molecular weight are nontoxic liquids of very low volatility, which makes them very suitable as "green" reaction media.[395] The ATRP of MMA and Sty in PEG of molecular weight 400 g/mol as the nonvolatile solvent was well controlled; moreover, after precipitation of the polymers in ethanol, the amount of residual Cu from the catalyst was very low.[396]

2.2.4. Bulk Polymerizations

ATRP is often carried out in bulk, without any organic solvent. In comparison with conventional radical polymerization, bulk ATRP is easier to control, since the Trommsdorf (or gel) effect does not occur in ATRP. In conventional radical processes, the Trommsdorf effect (a result of marked reduction of the termination rate coefficients at high conversion) leads to significant polymerization rate acceleration, accompanied by heat evolution, that may lead to an explosion. The heat evolved promotes the faster descomposition of the radical initiator, and this further accelerates the polymerization because the rate of the process depends upon the ratio of the rates of initiation and termination. In ATRP, the concentration of radicals does not depend on the rates of initiation and termination but on the rates of activation and deactivation, which are much less affected by the higher viscosity of the medium reached at high monomer conversion. Thus, many bulk ATRP reactions are well controlled up to high conversion.[397]

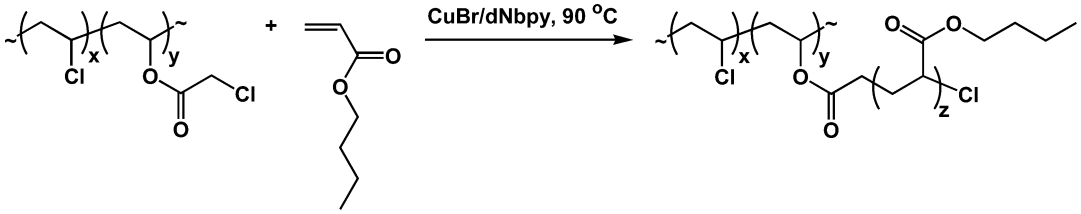
3. "Green" Polymeric Materials by ATRP

This section presents some examples of materials prepared by ATRP that have a positive environmental impact. They include various block and graft copolymers, branched and cross-linked structures, as well as hybrid materials.

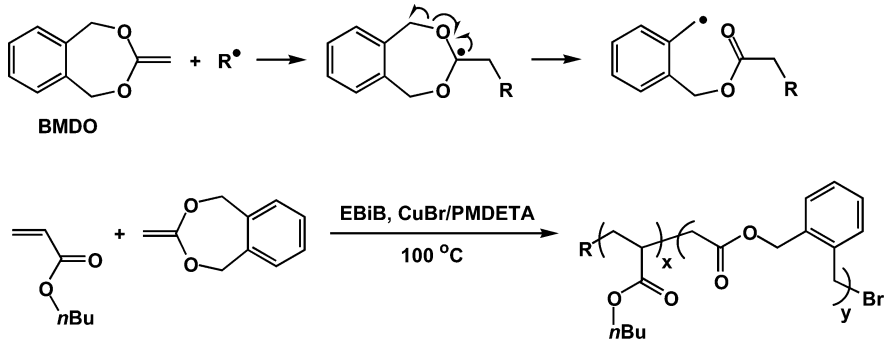
3.1. Self-Plasticized Polymers

Poly(vinyl chloride) (PVC) is brittle, which, in addition to thermal instability, limits the application of the pure homopolymer. However, PVC can be effectively plasticized using various low molecular weight plasticizers such as diisooctyl phtalate, tritolyl phosphate, and epoxidized oils.[15] These compounds can readily migrate and leach out of the product, resulting in both worsening of the material properties and contamination of the environment. Using ATRP, a rubbery polymer such as polyBA that can serve as a plasticizer can be directly grafted from PVC chains, yielding a "self-plasticized" material in which leaching of the plasticizer is essentially eliminated. The alkyl chloride groups in PVC are expected to be poor ATRP initiators, and in order to increase the initiating efficiency in the "grafting-from" process, copolymers of vinyl chloride with vinyl chloroacetate (with α-chloroesters being better initiators than chloroalkanes) were prepared. A small amount (ca. 1 mol %) of vinyl chloroacetate was copolymerized with vinyl chloride, and the copolymers served as macroinitiators in the ATRP of BA (Scheme 7) and other monomers. Spectroscopic, chromatographic, and thermal analysis of the product demonstrated efficient grafting of the rubbery polymer from the PVC chains, the lack of macroscopic phase separation, and the gradual decrease of T_g from 83 to −19 °C as the amount of incorporated polyBA in the material increased from 0 to 65 mol %.[398]

Scheme 7. Preparation of Self-Plasticized PVC by Grafting PolyBA from the Polymer Chains Using ATRP



Scheme 8. Radical Ring-Opening of BMDO with Formation of an Ester Structure (top) and Copolymerization of nBA with BMDO under ATRP Conditions Yielding a Copolymer with a Hydrolytically Degradable Ester Functionality (bottom)



Commercially available PVC always contains structural defects such as allyl chloride- and tertiary alkyl chloride-type groups that can serve as ATRP initiating sites. It was demonstrated that indeed PVC by itself can serve as macroinitiator in the ATRP of styrenes, (meth)acrylates, and (meth)acrylonitrile.[399,400] Thus, it was shown that there was no need to copolymerize vinyl chloride monomer with vinyl chloroacetate in order to carry out a grafting-from process and prepare self-plasticized PVC.

3.2. Degradable Polymers

(Bio)degradable polymers are of significant interest in soil treatment, tissue engineering, and drug delivery, which has stimulated the development of novel methods for their synthesis.[401−405] Cleavable links such as ester, amide, etc. can be generated in the backbone during polymerization, which is typical for polymers prepared by polycondensation or ring-opening processes.[406] Radical polymerization, which has wide application in industry, can also be used to synthesize degradable polymers. The incorporation of the cleavable functional group can be achieved by the use of functional monomers or initiators.

3.2.1. Introducing Degradable Functionalities by Radical Ring-Opening Polymerization

Radical ring-opening polymerizations[407−409] are quite promising in the preparation of degradable polymers. For example, hydrolytically or photodegradable α-ketoester units can be introduced in the polymer backbone by a ring-opening polymerization of cyclic ester or anhydride monomers with an exocyclic double bond, such as 5-methylene-2-phenyl-1,3-dioxolan-4-one.[410] The radical homopolymerization of a similar cyclic monomer, 5,6-benzo-2-methylene-1,3-dioxepane (BMDO),[411] which was successfully carried out under ATRP conditions,[412] affords a linear polyester (top of Scheme 8). The atom transfer copolymerization of BMDO with BA (bottom of Scheme 8) proved an efficient way to prepare hydrolytically degradable polymers which contained, at least up to moderate conversions, mostly isolated polyester units derived from BMDO.[413] The random incorporation of the degradable units was proved by means of ^{1}H NMR spectroscopy as well as by SEC studies of the alcoholysis products.

3.2.2. (Bio)degradable Polymers with Disulfide Groups

The polymers prepared by ATRP are halogen-capped, which allows for further functionalization reactions.[50] The use of functional alkyl halide initiators has been successfully applied to the preparation of various telechelic materials.[50] Disulfide is an example of a degradable group that can be cleaved reversibly upon reduction to yield a mixture of the corresponding thiols. Thiols,[414] phosphines,[415,416] metal hydrides, and various metal/acid combinations are often employed as reducing agents. The thiol−disulfide interconversion is widely utilized in nature, e.g., in the regulation of enzyme activity, in protein structure stabilization, and in various metabolic redox processes.[417,418] Polymers containing disulfide or polysulfide groups have attracted significant interest,[419] and various procedures for their synthesis have been described.[420,421] The disulfide group can be introduced in a polymer by using an appropriate sulfur-containing initiator or monomer. The preparation of polymeric materials with internal disulfide bonds such as linear polySty[422] or polymethacrylates[423−425] (including the biocompatible[426] polyHEMA[427]), polymer gels,[425] miktoarm star copolymers,[428] and hyperbranched structures[429,430] by ATRP was demonstrated. The reductive cleavage of molecules containing a disulfide link to two thiols is reversible, and it was shown[422] that the thiol-terminated polySty obtained from the corresponding disulfide upon reduction with dithiothreitol (DTT, Cleland's reagent[431,432]) could be quantitatively converted to the starting material via oxidation with $Fe^{III}Cl_3$ (Figure 16).

The disulfide-cross-linked gels prepared by ATRP retained their halogen end groups after the cross-linking and washing, which was demonstrated by their successful use as "supermacroinitiators" in a subsequent chain extension with a second monomer (Scheme 9). The degradation products of the starting gels (polyMMA-based) and of gels with grafted polySty polymer chains derived therefrom were analyzed by 2D-GPC. It was shown that, in the latter case, the degradation

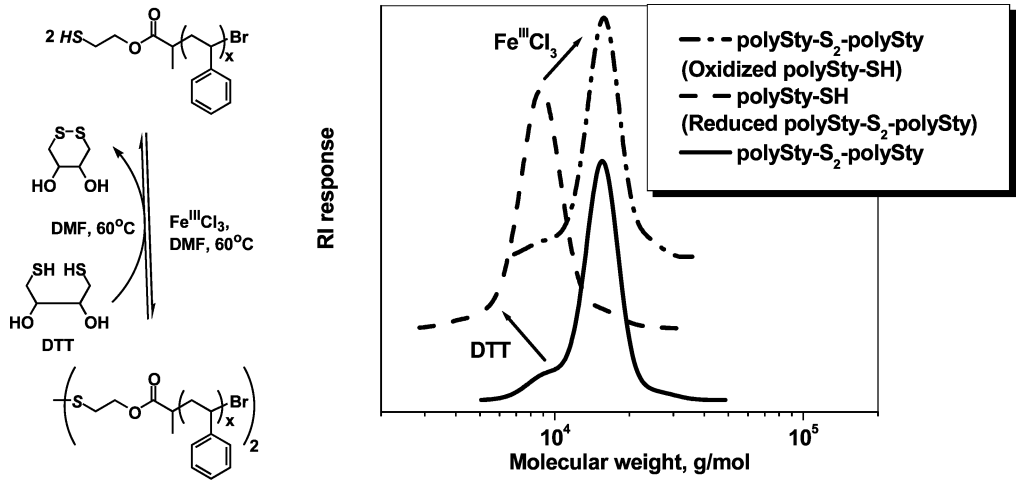
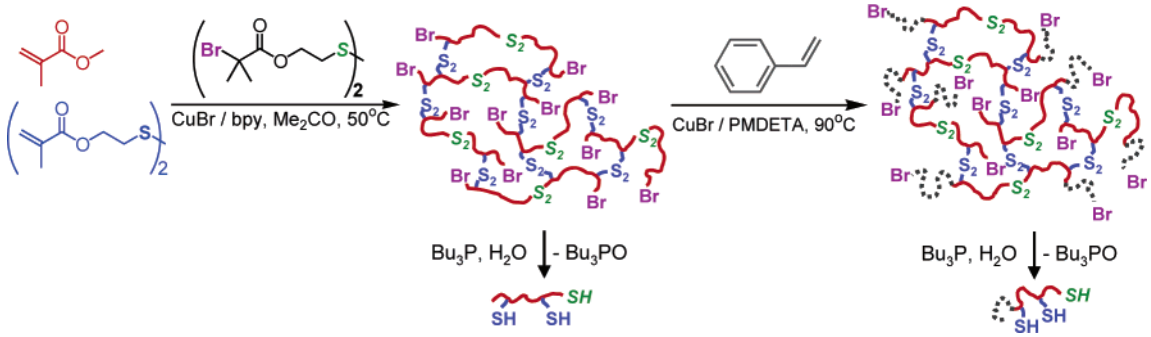


Figure 16. Reversible redox cleavage/coupling of polySty with an internal disulfide link prepared by ATRP. Modified from ref 422. Copyright 2002 American Chemical Society.

Scheme 9. Synthesis of PolyMMA-Based Disulfide-Cross-linked Gels by ATRP, and Their Chemical Modification Using a Chain Extension Reaction with a Second Monomer (Sty)[a]



[a] The degradation products of the two gels—the homopolymer from the "supemacroinitiator" and the block copolymer from the modified gel—are also presented.) Reprinted with permission from ref 425. Copyright 2005 American Chemical Society.)

products consisted of the block copolymer polyMMA-b-polySty and no homopolymer of MMA could be detected.[427]

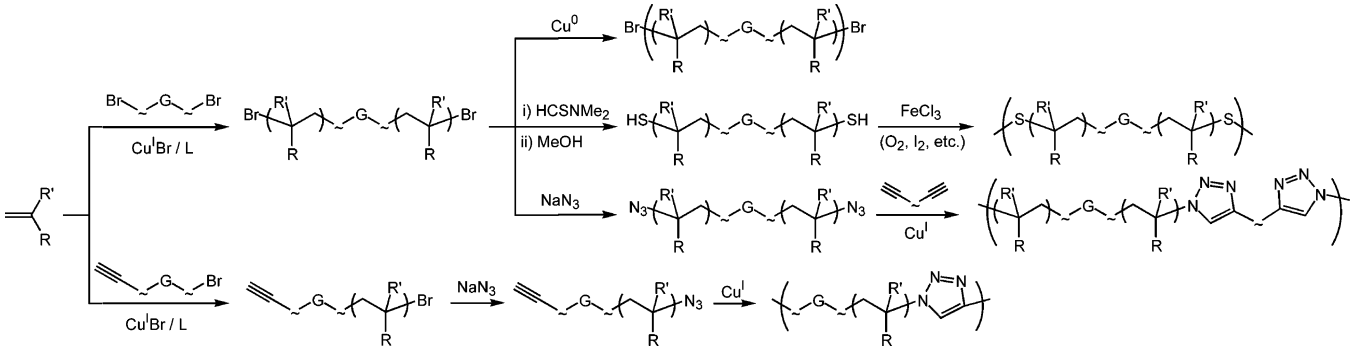
The high degree of halogen end-functionalization of the cross-linked structures prepared by ATRP could be very useful in biomedical applications, for it would allow the attachment of various functional groups to the degradable gels. For this purpose, use can be made of simple nucleophilic substitution reactions. The ATRP of MMA in the presence of a disulfide-containing cross-linker in a miniemulsion yielded a stable cross-linked polymer latex and halogen-functionalized particles that degrade in a reducing environment.[427] It was also demonstrated[433] that degradable nanometer-sized gel particles derived from biocompatible polymers such as polyOEGMEMA could be prepared by ATRP in an inverse miniemulsion.[433] Hyperbranched polymers with disulfide groups derived from 2-hydroxypropyl methacrylate could also be prepared using the same disulfide monomer as the one shown in Scheme 9, bis(2-methacryloyloxyethyl)disulfide ($(MAOE)_2S_2$), provided that the disulfide was used at low concentration (on average, less than one branching disulfide unit per polymer chain), in order to avoid formation of a macroscopic gel.[429] In analogous fashion, highly branched polyHEMA was prepared by the atom transfer copolymerization of HEMA and $(MAOE)_2S_2$ in methanol using the disulfide-containing difunctional 2-bromoisobutyrate initiator shown in Scheme 9 or 2-(*N*-morpholino)ethyl 2-bromoisobutyrate.[434]

To prove that a degradable polymer is also biodegradable, it is essential to show that the degradation experiment can be carried out at conditions mimicking the biological environment (say, aqueous medium, physiological pH and temperature, etc.) and to use the same reagents that living cells would use in the degradation. Along these lines, Armes et al. proved that a disulfide-containing block copolymer, polyNIPAAm-b-polyMPC-S_2-polyMPC-b-polyNIPAAm (MPC = 2-methacryloyloxyethyl phosphorylcholine), could easily degrade in an aqueous medium using a biological reducing agent, namely the tripeptide glutathione.[435] Since polyNIPAAm is hydrophobic above 37 °C but becomes hydrophilic below this temperature, the triblock copolymer with disulfide groups could serve as a biodegradable gelator. The highly branched polyHEMA with disulfide links mentioned above was also successfully degraded in the presence of glutathione.[434]

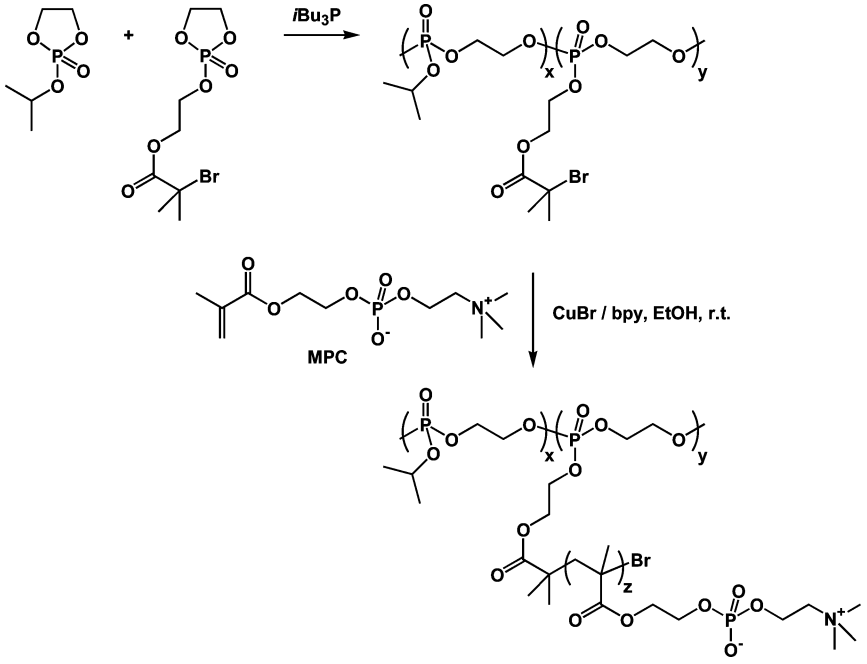
3.2.3. Coupling of Polymer Chains Prepared by ATRP as a Means To Introduce Multiple Degradable Functionalities in a Polymer Backbone

Another approach to introduce degradable groups in polymers prepared by ATRP is to use difunctional initiators that contain the degradable functionality (for example, an ester or anhydride group) and to combine the prepared well-defined polymer chains in a step-growth-type process such as atom transfer radical coupling[436,437] or click coupling[438] (Scheme 10). This yields polymers with many cleavable links.

Scheme 10. Coupling Reactions That Can Be Used to Prepare High Molecular Weight Polymers with Internal Degradable Groups (G) (The curved line represents a spacer.)



Scheme 11. Synthesis of Degradable Graft Copolymers (Polymer Brushes) with a Polyphosphate Backbone[440]



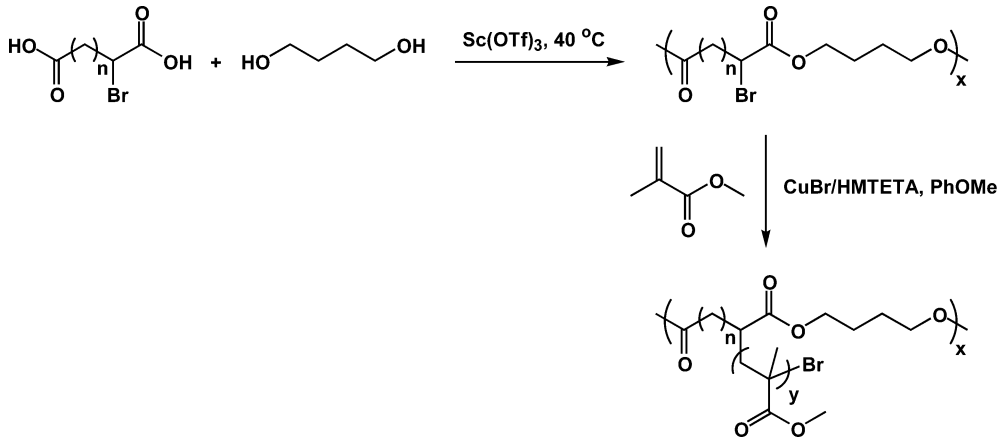
3.2.4. Polymer Brushes with Degradable Backbones

Graft copolymers with a (bio)degradable backbone (typically, polyester-type) have also been prepared by ATRP using "grafting from" techniques. The ring-opening copolymerization of ethylene-bridged cyclic phosphates containing a 2-bromoisobutyrate moiety, promoted by iBu$_3$Al, yielded linear polyphosphate esters (Scheme 11) that were further used in chain extension reactions with MPC under ATRP conditions.[439] The graft density of the synthesized polymer brushes was controlled by adjusting the ratio of the cyclic phosphate comonomers in the feed during the ring-opening reaction, and the graft length was controlled by using various MPC-to-macroinitiator ratios. The hydrolytic degradation of the backbones was studied in buffered solutions and was particularly fast in alkaline media (pH 11). Degradable polymer brushes with polyMPC grafts and containing cholesteryl groups in the backbone were prepared in a similar manner; the polymers were shown to possess virtually no cytotoxicity toward v79 cells.[440]

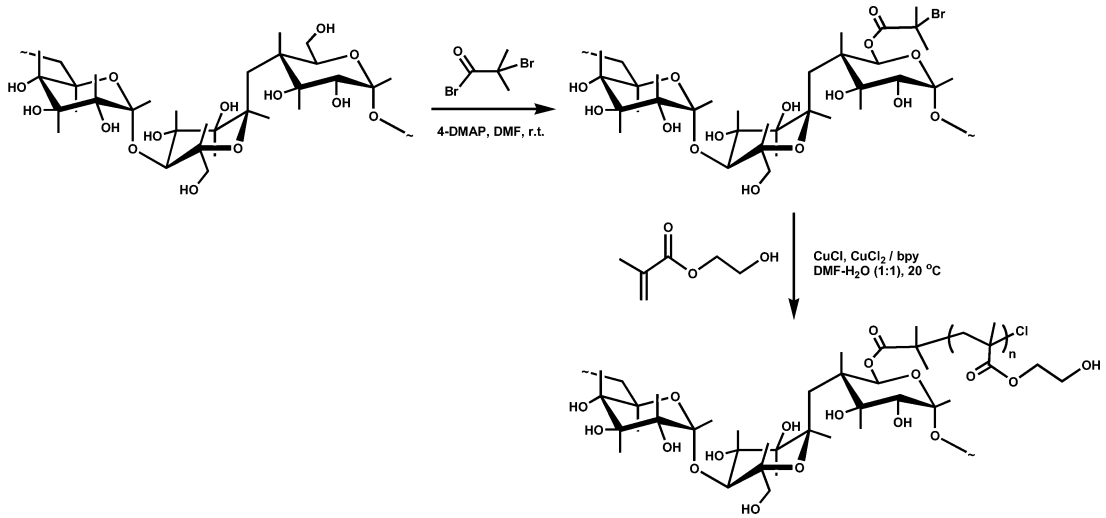
The polycondensation reactions between 1,4-butanediol and 2-bromoadipic or 2-bromosuccinic acid in the presence of $Sc^{III}(OTf)_3$ yielded bromine-containing polyesters that were used as multifunctional initiators in the ATRP of MMA to prepare polymer brushes (Scheme 12).[441] Although the hydrolytic degradation of the backbone was not demonstrated, it most likely can be easily accomplished.

Many synthetic−natural polymer bioconjugates have been synthesized by ATRP. An example is graft copolymers in which the backbone is a natural polymer, such as a polysaccharide, and the grafts are derived from a vinyl monomer. These materials are hydrolytically degradable due to the presence of labile glycoside bonds in the backbone. To accomplish the ATRP of the vinyl monomer, the hydroxy groups in the polysaccharide are converted to a 2-haloacid ester, affording a macroinitiator. Examples of polysaccharides modified with synthetic polymer side chains include cellulose[442−444] or ethylcellulose,[445] chitosan,[444,446−448] pullulan,[449] and cross-linked dextran[450] (see Scheme 13 for an example). The pullulan−polyHEMA graft copolymer conjugates obtained at different HEMA conversions were degraded in the presence of trifluoroacetic acid (at conditions at which polyHEMA itself was shown to be stable), and it was shown that the molecular weights of the yielded free polyHEMA were in agreement with the theoretically predicted ones and that the PDI values were low.[449]

Scheme 12. Synthesis of Degradable Polymer Brushes with a Polyester Backbone[441]



Scheme 13. Synthesis of a Polysaccharide (Pullulan)−Synthetic Polymer Bioconjugate by ATRP



3.3. Miscellaneous "Green" Materials Prepared by ATRP

3.3.1. Materials for Water Purification

Purification of groundwater from dense nonaqueous phase liquids (DNAPLs; mostly dense halogenated compounds) is a major challenge since the organic contaminant can often be present on the bottom of underground water sources, where it slowly dissolves and is released into the water over an extremely long period of time. It has been shown that various active metallic nanoparticles can react with chlorinated liquids and reduce them to significantly less toxic compounds.[451−454] Iron nanoparticles are very useful, but to be effective in groundwater treatment they need to be dispersable in water at a broad pH range and in the presence of various electrolytes, transportable through a water-saturated porous matrix (soil), and to have an affinity for the water−DNAPL interface. The particles should also be stable toward oxidation. A triblock copolymer, MAA_{42}-b-MMA_{26}-b-$NaSS_{462}$, was shown[455] to be a very efficient surfactant for Fe_3O_4-coated iron nanoparticles. The polyMAA block served to anchor the polymer to the magnetite shell, the hydrophobic polyMMA segment provided affinity of the particles toward DNAPL and protected the particles from oxidation, and, finally, the charged (sulfonate) block served to prevent particle aggregation and to increase the particles' affinity for water. The copolymer-coated particles, unlike the unmodified particles, were able to stabilize oil-in-water emulsions, demonstrating that DNAPLs dispersed in water could indeed be targeted.

3.3.2. Solventless Coatings

ATRP, as well as the other CRP methods, is very useful in the coatings industry.[456] Solventless coatings have attracted significant attention as the industry moves toward systems in which the amount of organic solvents is reduced. Moreover, such coatings are desirable for applications where a short curing time is needed, for instance in automotive coatings. For such applications, the replacement of organic solvents with water is inefficient due to the latter's low volatility. Powder coatings prepared by conventional radical polymerization are useful, but their broad molecular weight distribution causes nonuniform melting behavior. In addition, conventional radical polymerization does not allow good control over the architecture and functionality, which affect both the rheology and reactivity of the powder coatings prepared by this technique. Uniform reactivity in a coating material would guarantee that after curing all polymer chains are part of the same uniform material and that the amount of free polymer that may leach out over prolonged time periods is minimized. ATRP is very well suited for the fabrication of coatings, since, in addition to the control over molecular weight, it allows a control over chain end or backbone functional groups. Both functional initiators and reactions of the alkyl halide chain ends can be used to prepare a variety of functional polymeric materials by ATRP.[50] The

homo- or heterotelechelic polymers that are easily synthesized by ATRP can yield cured materials upon reaction with a multifunctional curing agent.

Functional hyperbranched polymers[457,458] can also be useful as components for coatings. Due to the compactness of their molecules, they have a significantly lower viscosity than their linear counterparts of the same molecular weight and are therefore easier to process. There are several approaches to their synthesis, but a very appealing and applicable chain-growth polymerization method is the so-termed *self-condensing vinyl polymerization* (SCVP).[459] The method uses compounds containing both a polymerizable group (such as styrene or a (meth)acrylate moiety) and a group able to initiate polymerization. Such compounds are often named *inimers* (initiator and monomer). The successful ATRP of several inimers has been reported.[460−466] Some of the prepared hyperbranched polymers contained a variety of polar functional groups such as carboxylate,[467] hydroxyl,[468] substituted amine,[469] or disulfide,[430] and they can be particularly useful for coatings applications. Other CRP techniques employing inimers have also been used.[470−475] Another useful approach to branched polymers is the copolymerization of monomers containing one double bond with a cross-linking agent (a divinyl compound, dimethacrylate, etc.) wherein the latter is used at low concentration in order to prevent the formation of a gel.[476,477] This route has also been successfully combined with CRP,[478−480] including ATRP,[429,481] to prepare hyperbranched polymers with a high degree of functionalization. The branched copolymers prepared by ATRP have the important advantage of possessing an alkyl halide end group that can be transformed into another functionality useful for curing.

Similarly, multifunctional materials can be prepared by using functional macroinitiators and cross-linkers leading to starlike polymers.[482] This approach results in stars containing functional groups derived from the end-group of the macroinitiator. In addition, the core of such stars contains potentially active groups, namely alkyl halides, that can be used in chain extension with a second monomer to yield miktoarm star copolymers, in a process dubbed *"in−out" synthesis*.[428,483,484] The halide end group can be further replaced by another functional group that makes the star polymers attractive materials for coating applications.

3.3.3. Nonionic Polymeric Surfactants

One important advantage of polymeric surfactants compared to their low molecular weight analogues is the very low critical micelle concentration.[485] This means that the micelles formed from block copolymers do not dissociate readily into unimers upon dilution, which makes them useful as stable "containers" in drug delivery.[313] Nonionic surfactants have a significantly lower toxicity than their ionic counterparts (especially cationic surfactants), and they have attracted attention.[486] ATRP is exceptionally useful in the preparation of block copolymers, including diblock copolymers with one hydrophilic and one hydrophobic segment, which can be employed as surfactants, for example in emulsion polymerization.[487] Numerous examples of surfactant block copolymers synthesized by ATRP are presented in a detailed review.[51]

4. Conclusions

All the major environmental aspects of ATRP are reviewed in this paper. The methods for catalyst removal include various sorption and extraction techniques, the use of supported catalysts, and catalysts with solubility that is influenced by the temperature. These methods have proved efficient in laboratory-scale syntheses, but they are difficult to apply in industry. Thus, active ATRP catalysts were developed that can be used at low concentration and/or at ambient temperatures while the polymerization rates are still sufficiently high. It is shown that the activity of the ATRP catalysts can be correlated to the relative stability constants of the higher and lower oxidation state metal complexes and to the affinity of the higher oxidation state metal complex for halide ions (termed halidophilicity). In order to decrease the catalyst concentration to ppm values while maintaining satisfactory reaction rates, the activating (lower oxidation state) complex has to be constantly regenerated by the use of various reducing agents, including the FDA approved Sn^{II} compounds or ascorbic acid. Various novel initiation/catalysis techniques, collectively termed ERA (excess reducing agent) ATRP were developed that provide excellent polymerization control in reactions mediated by ppm amounts of Cu-based catalyst.

ATRP can be successfully carried out in environmentally friendly reaction media such as water, supercritical carbon dioxide, and ionic liquids. The copper-based ATRP catalyst can be deactivated in protic solvents via dissociation, complexation with the solvent and/or polar monomers, or disproportionation. The addition of halide salts can largely suppress the dissociation of the ATRP deactivator. Alternatively, a large amount of deactivator (Cu^{II} complex) has to be added initially to the reaction mixture in order to achieve a well-controlled process. The addition of complex-forming agents or cosolvents that stabilize the Cu^{I} state of the catalyst relative to Cu^{II} can suppress disproportionation. All side reactions have been quantitatively described, which makes it possible to predict the reaction conditions leading to optimal results in the controlled radical polymerization of a variety of water soluble monomers in water-based or protic solvents.

Finally, the power of ATRP as a synthetic technique providing some advanced materials with a positive environmental impact is demonstrated. The examples include self-plasticized poly(vinyl chloride), (bio)degradable polymers, materials useful as solventless coatings or for the deactivation of dense nonaqueous phase (mostly chlorinated) liquids, as well as nonionic surfactants.

5. Abbreviations

α_L	alpha coefficient accounting for side reactions of a ligand L
β_j^z	stability (formation) constant of a complex of a metal ion in oxidation state z containing j coordinated ligands
AGET	activators generated by electron transfer
AIBN	azobisisobutyronitile
ARGET	activators regenerated by electron transfer
ATRA	atom transfer radical addition
ATRC	atom transfer radical coupling
ATRP	atom transfer radical polymerization
BA	*n*-butyl acrylate
BMDO	5,6-benzo-2-methylene-1,3-dioxepane
Bn	benzyl
BPMOA	bis(2-pyridylmethyl)octylamine
BPMODA	bis(2-pyridylmethyl)octadecylamine
BPMPrA	bis(2-pyridylmethyl)propylamine
BPN	2-bromopropionitrile

bpy	2,2′-bipyridine
CCT	catalytic chain transfer
CRP	controlled/living radical polymerization
CV	cyclic voltammetry
cyclam	1,4,8,11-tetraazacyclotetradecane
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DETA	diethylenetriamine
2D-GPC	two-dimensional gel permeation chromatography
dNbpy	di(5-nonyl)-2,2′-bipyridine
DMAEMA	2-(*N*,*N*-dimethylamino)ethyl methacrylate
DMCBCy	dimethylated 1,8-ethylene cross-bridged 1,4,8,11-tetraazacyclotetradecane
DMF	dimethylformamide
DNAPL	dense nonaqueous phase liquid
DP	degree of polymerization
DP_n	number average degree of polymerization
DTT	dithiothreitol (Cleland's reagent)
$E°$	standard electrode potential
EBiB	ethyl 2-bromoisobutyrate
EBP	ethyl 2-bromopropionate
ERA ATRP	ATRP with excess (with respect to catalyst) reducing agent
ESR	electron spin resonance
EtOH	ethanol
F	Faraday constant (96,500 c mol^{-1})
GC	gas chromatography
GlIm-R	substituted (R) glyoxal diimine
HEM	2-hydroxyethyl methacrylate
HMTETA	*N*,*N*,*N*′,*N*′′,*N*′′′,*N*′′′-hexamethyltriethylenetetramine
ICAR	initiators for continuous activator regeneration
$K_{a,j}$	*j*-th acidity constant of a polyprotic acid
k_{act}	activation rate constant
K_{ATRP}	ATRP equilibrium constant
K_{BH}	equilibrium constant of bond homolysis
k_{deact}	deactivation rate constant
K_{disp}	disproportionation equilibrium constant
K_{EA}	electron affinity equilibrium constant
K_{ET}	equilibrium constant of electron transfer
k_p	propagation rate constant
K_X (X =Br,Cl)	halogenophilicity (bromo- or chlorophilicity) equilibrium constant
L	ligand
LCST	lower critical solution temperature
M	monomer
M_n	number average molecular weight
M_w	weight average molecular weight
MA	methyl acrylate
MAA	methacrylic acid
$(MAOE)_2S_2$	bis(2-methacryloyloxy)ethyl disulfide
MCA	methyl chloroacetate
MBP	methyl 2-bromopropionate
MCP	methyl 2-chloropropionate
MeCN	acetonitrile
Me_2CO	acetone
Me_4cyclam	tetramethylated 1,4,8,11-tetraazacyclotetradecane
MeOH	methanol
MePEOMA	poly(ethylene oxide) methyl ether methacrylate
Me_6TREN	hexamethylated tris(2-aminoethyl)amine
MMA	methyl methacrylate
MPC	2-methacryloyloxyethyl phosphorylcholine
MWD	molecular weight distribution
NaSS	sodium 4-styrenesulfonate
NIPAAm	*N*-isopropylacrylamide
NMP	nitroxide-mediated polymerization
NMR	nuclear magnetic resonance
OEGMEMA	oligo(ethylene glycol) methyl ether methacrylate
Ph	phenyl group
1,10–phen	1,10-phenanthroline
1-PhEtBr	1-phenylethyl bromide
1-PhEtCl	1-phenylethyl chloride
PMDETA	*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine
PDI	polydispersity index (M_w/M_n)
ppm	parts per million
PTFE	polytetrafluoroethylene
PVC	poly(vinyl chloride)
PyIm-R	substituted (R) pyridinecarbaldehydeimine
R	universal gas constant (8.314 J mol^{-1} K^{-1})
R_p	rate of polymerization
RAFT	reversible addition−fragmentation chain transfer polymerization
$scCO_2$	supercritical carbon dioxide
SCVP	self-condensing vinyl polymerization
SEC	size exclusion chromatography
SFRP	stable free radical polymerization
SR&NI ATRP	simultaneous reverse and normally initiated ATRP
Sty	styrene
T	temperature (in Kelvin)
tBu	tertiary butyl group
TEMPO	2,2,6,6,-tetramethyl-1-pyperidinyloxy
TETA	triethylenetetramine
T_g	glass transition temperature
THF	tetrahydrofuran
TPEDA	tetrakis(2-pyridylmethyl)ethylenediamine
TPMA	tris(2-pyridylmethyl)amine
TREN	tris(2-aminoethyl)amine
4VP	4-vinylpyridine

6. Acknowledgments

The authors are grateful for financial support provided by the NSF (Grant CHE-04-05627) and the EPA (Grant R82958001).

7. References

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CR050947P