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Radical Nature of Cu-Catalyzed Controlled Radical Polymerizations (Atom Transfer Radical Polymerization)

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ABSTRACT: Copper-catalyzed atom transfer radical polymerization (ATRP) is one of the most robust and precise techniques for controlling radical polymerization. The very good control of molecular weights, polydispersities, functionalities, chain composition, and topologies unusual for radical systems combined with the application of transition metals as catalysts requires more detailed mechanistic studies and proof of the radical nature of active species. The following results are in agreement with the radical nature of ATRP: reverse ATRP, chemoselectivities similar to those for conventional radical polymerization (effect of additives and inhibitors/scavengers, reactivity ratios, transfer coefficients), regioselectivities similar to those for conventional radical polymerization (low proportion of head-to-head units and expected structure of both tail and head end groups), stereoselectivities (tacticities) similar to that in conventional radical polymerization, EPR detection of X−Mt^{n+1} species resulting from the persistent radical effect, and confirmation of the termination by doubling molecular weights as well as cross-linking with multifunctional initiators and inimers. In addition, it seems that, in most ATRP systems, the contribution of degenerative transfer and reversible formation of organometallic intermediates is small and a halogen atom is transferred in the concerted process rather than in a two-step process with the involvement of radical anions.

Introduction

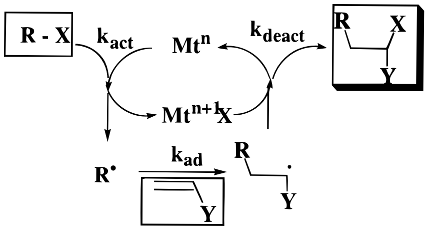
Several methods have been developed to prepare well-defined (co)polymers by radical means.[1] All of these systems employ a dynamic equilibrium between low concentrations of propagating free radicals with various types of dormant species such as alkoxyamines (in nitroxide-mediated polymerizations), alkyl halides (in either degenerative transfer processes or transition metal-catalyzed reactions), and organocobalt derivatives (in systems with labile bonds between growing chain and organometallic species).[1−3] These systems have many features typical of controlled/living polymerizations and are very different from conventional radical polymerizations. For example, molecular weights increase linearly with conversion, polydispersities are relatively low (well below $M_w/M_n < 1.5$), and block copolymers as well as end-functional polymers are efficiently formed.[1] Some of these features are so unusual for radical processes that the radical nature of these polymerizations may be questioned, especially those polymerizations catalyzed by transition metals.

This paper summarizes the evidence supporting radical mechanisms for these reactions. It must be stressed that none of the experiments discussed below provides a single, unambiguous, and undeniable argument for a radical process. However, when considered together, they strongly indicate that nearly all monomer is consumed (or nearly all polymer chains are formed) by free radicals.

Background

Controlled Organic Radical Reactions. It has long been difficult to control organic reactions proceeding by free radical intermediates. However, the Kharasch addition of alkyl halides to alkenes initiated by small amounts of peroxides (or light)[4] and atom transfer additions of alkyl halides to alkenes catalyzed by transition metals led to 1:1 adducts in high yields.[5] Although observed regioselectivities, stereoselectivities, additive effects, and trapping reagents strongly indicated radical intermediates, it was difficult to rationalize the absence of products expected for coupling/disproportionation of organic radicals. Therefore, involvement of coordinated radicals or even organometallic species was considered.[6]

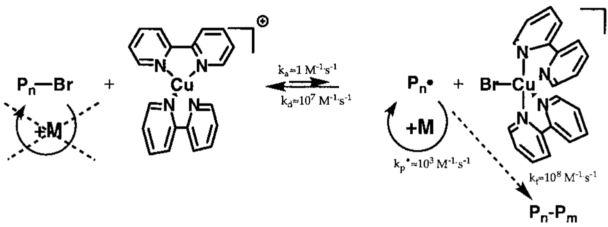
High chemoselectivities were later explained through a persistent radical effect (PRE),[7] resulting from the coupling of organic radicals at the initial stages of the reaction. This leads to an excess of persistent radicals and consequently the reduced probability of reaction between two organic radicals in comparison with that for the reaction between persistent radicals and organic radicals. This process reduces the concentration of free radicals and directs the entire process to the desired addition products which are formed in high yields:



This process occurs in many atom transfer radical reactions and is currently used in organic synthesis of both simple and complex molecules and macromolecules.[1]

Controlled Radical Polymerization. An analogous PRE is responsible for controlled radical polymerizations.[8−11] However, there are additional prerequisites for synthesizing well-defined polymers. Because the kinetic processes occurring during a polymerization influence the molecular weight (and compo-

Scheme 1



sition) distribution, it is necessary to initiate all chains simultaneously and ensure the same probability of growth for all chains in order to obtain uniform macromolecules.[1,12] Moreover, separating a few percent of the undesired termination products from the desired adduct is difficult. Therefore, the proportion of termination/transfer should be reduced to below a few percent, which can be accomplished by targeting polymers with lower molecular weights.[1,12]

Below, a typical copper-catalyzed atom transfer radical polymerization (ATRP) is described. Nitroxide-mediated polymerizations are similar, but the activation process is unimolecular (no catalysts involved) and free nitroxide, rather than X−Cu(II), is the deactivator.[13,14] Cobalt-mediated polymerization of acrylates is mechanistically more similar to nitroxide systems than to ATRP, since no catalysis is involved and the activation occurs unimolecularly (Scheme 1).[8]

According to model mechanistic studies, alkyl halides react with transition metals in a concerted fashion by bridged transition-state intermediates.[15] This inner sphere electron transfer process (or atom transfer, however, groups such as the pseudohalogens N_3, SCN, CN, etc. can also be transferred)[15] results in the cage consisting of a higher oxidation state metal and a radical. The radical quickly diffuses out of the cage and reacts with monomer (propagates). After a certain time, the radical abstracts a halogen atom from the transition metal at a higher oxidation state (X−Cu(II)), reforming the dormant alkyl halide.

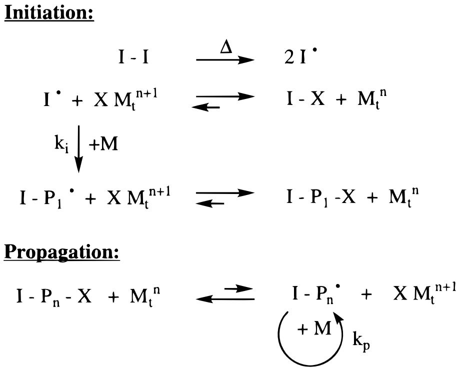
Various alkyl halides and pseudohalides as well as compounds with weak heteroatom−halogen bonds can be used as ATRP initiators.[16−20] Various types of monomers have been successfully polymerized by ATRP: styrenes,[21] acrylates,[16,22,23] methacrylates,[17,24,25] and acrylonitrile.[26] Not only copper but also other transition metals have been used as efficient catalysts.[27−33] The activity of the catalyst depends dramatically on the nature of the ligands, which are preferably polydentate N-, P-, S-, or O-containing compounds.[16,34−36]

It must be stressed that the cationic nature of the tetrahedral structure of Cu(I) species is oversimplified and used only as a potential structure, since it was established either in aqueous solutions or in the solid state.[37] Other structures can exist in nonpolar organic solvents. Similarily, the trigonal bipyramidal structure of cationic Cu(II) has only been established in the solid state or in polar solvents.[38]

The number of monomer units added during one activation step (n) depends on the concentration of monomer and deactivator ([D]) and on the relative values of the rate constants of deactivation (k_d) and propagation (k_p):

$$n = k_p[M]/k_d[D] \tag{1}$$

Scheme 2



For well-defined polymers this number should be very low, meaning that the rate of deactivation should be larger than or comparable to the rate of propagation.

An additional requirement for preparing well-defined polymers is that the contribution of transfer and termination should be very low. This can be accomplished by limiting degrees of polymerization (predefined by the ratio of the consumed monomer to the introduced initiator), since the proportion of chains marked by both chain-breaking reactions increases with chain length and conversion. For example, in the case of transfer to monomer, the degrees of polymerization should be lower than[12]

$$\mathrm{DP} = \Delta[M]/[I]_0 < 0.1k_p/k_{trM} \tag{2}$$

If all of the four discussed prerequisites are fulfilled (fast initiation and deactivation, low contribution of transfer and termination), polymers with low polydispersities ($M_w/M_n < 1.1$), predetermined degrees of polymerization (DP $= \Delta[M]/[I]_0$), and controlled end functionalities can be and have been prepared.[1]

ATRP usually follows first-order kinetics in monomer, initiator, and Cu(I) and negative first-order kinetics with respect to Cu(II), the apparent rate constant being the product of the absolute rate constant of propagation and the equilibrium constant:

$$R_p = k_pK_{eq}[M][RX]_0[Cu(I)]/[Cu(II)] \tag{3}$$

However, precise reaction orders depend strongly on the solubilities of and interactions between the catalyst and the deactivator, depend on the efficiency of initiation, chain length, and may be much more complex than eq 3. Therefore, it seems that the kinetic studies alone cannot provide the proof for the radical process.

Results and Discussion

1. Reverse ATRP. In a typical ATRP, the initiation system consists of a suitable alkyl halide such as a primary/secondary benzyl halide, an α-haloester, α-haloketone, α-halonitrile, or sulfonyl halide[18] and a transition metal compound in its lower oxidation state such as Cu(I), Fe(II), Ru(II), or Ni(II). According to Scheme 1 the alkyl halide and Mt^n species reversibly form alkyl radicals and $X-Mt^{n+1}$ species.

It is also possible to approach the same type of equilibrium starting from conventional radical initiators such as peroxides or diazo compounds and $X-Mt^{n+1}$ species (Scheme 2).

As illustrated in Figure 1, when 1.6 equiv of $CuBr_2$/2dNbipy per AIBN molecule is used, polymers with good

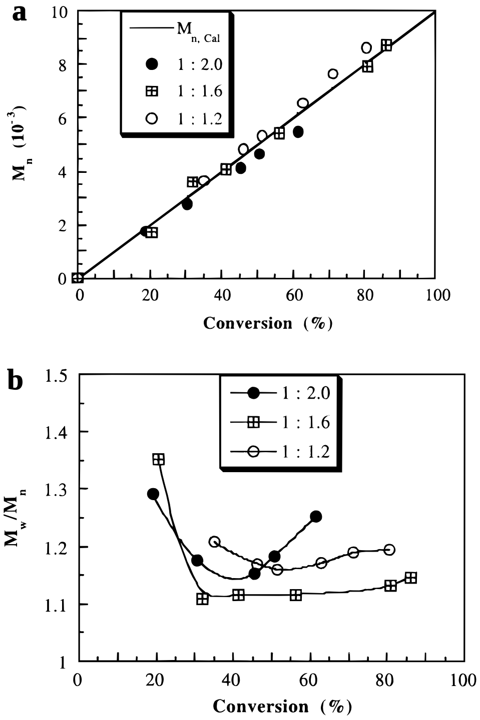


Figure 1. Dependence of molecular weight, M_n, (a) and polydispersities (b) on monomer conversion for the homogeneous reverse ATRP of styrene at 110 °C in bulk varying $[CuBr_2/2dNbipy]_0$, $[styrene]_0 = 8.7$ M; $[AIBN]_0 = 0.045$ M; $[CuBr_2]_0 = [dNbipy]_0/2 = 0.090$ M (1:2.0), 0.073 (1:1.6), 0.054 M (1:1.2).[39]

control of molecular weights and polydispersities lower than those with either 1.2 or 2 equiv are obtained. This observation indicated that the efficiency of AIBN initiation at 110 °C in bulk polystyrene is approximately 80%.

Similar behavior was also observed for the reverse ATRP for methyl acrylate and methyl methacrylate.[39] Efficient reverse ATRP requires sufficiently soluble Cu(II) species. When the heterogeneous $CuBr_2$/bipy system was used, a larger excess of deactivator was needed.[40] This system has been recently extended to Fe-based catalysts.[41]

Thus, successful reverse ATRP experiments demonstrate that the ATRP equilibrium can be approached from either side and that free radicals are efficiently scavenged by $X-Mt^{n+1}$ species.

2. Scavengers and Additives. Adding scavengers or inhibitors selective for a particular active site is often used to distinguish between ionic, radical, or coordination mechanisms. For example, most ionic and coordination polymerizations cannot be carried out in the presence of water and other protonogenic species. Cations are also scavenged by strong nucleophiles whereas anions are scavenged by electrophiles. Many coordination polymerizations are terminated by esters, ketones, and aldehydes. In contrast, radical polymerizations are insensitive to water and compounds with carbonyl groups but require the absence of oxygen due to rapid formation of relatively unreactive peroxy radicals. Radical polymerizations can also be scavenged/inhibited under appropriate conditions by many paramagnetic species such as galvinoxyl, DPPH, TEMPO, and CuX_2. It must be recognized that some stable radicals can also terminate ionic reactions, for example by electron-transfer reactions.

Several scavengers and additives were used in ATRP to test the nature of the growing species. Some results are summarized below.

(i) Addition of a large excess of galvinoxyl and TEMPO stops Cu-catalyzed polymerization of styrene and (meth)acrylates.[16,17] Similar observations were reported for Ru-catalyzed polymerization of methacrylates.[24] TEMPO reacts directly with radicals, forming alkoxyamines in high yields.[42]

(ii) Both Cu- and Ru-catalyzed polymerizations were successful in the presence of either small amounts of water or even directly in aqueous solutions or suspensions. This observation excludes cationic or anionic intermediates and probably also organocuprates.[10,23,43,44]

(iii) Adding small amounts of nucleophiles does not interfere with Cu-based ATRP. This excludes cationic intermediates.[10]

(iv) Phosphines inhibit Cu-based ATRP, probably because phosphines coordinate strongly to Cu(I) and block the coordination side required for the atom transfer to occur.[10]

(v) Phenols have a small effect on Cu-based ATRP of methacrylates. The latter observation was previously used to question the radical intermediates of ATRP.[45] However, several earlier studies clearly demonstrated that although phenols do affect the polymerization of styrene, their action on radical polymerization of (meth)acrylates in the absence of oxygen is very weak. For example, less than 1% retardation was observed for MMA polymerization with 0.2 M hydroquinone. 4-Methoxyphenol even increased the polymerization rate initiated by AIBN at 45 °C. In the latter case the transfer coefficient is $k_{tr}/k_p < 0.0005$.[46] A similar observation was made for methyl acrylate, where inhibition was again insignificant at 50 °C, $k_x/k_p < 0.0002$.[47] Thus, the weak retardation/transfer effect of phenols on polymerization of (meth)acrylates does not contradict the radical mechanism. Phenols may even accelerate polymerization of MMA.[45] This can be ascribed to higher activity of catalysts (larger equilibrium constants) with phenoxy ligands at the Cu center. A similar effect was observed for Cu carboxylates and $CuPF_6$.[19,48] It must be also recognized that because neither $Cu(II)(OPh)_2$ nor $Cu(II)(OAc)_2$ can deactivate polymerization due to a lack of radically transferable halogen atoms, they should not be considered as deactivators and could not reduce polymerization rates.

3. Reactivity Ratios. Another important mechanistic criterion is chemoselectivity. For polymerizations, chemoselectivity determines the activity of transfer agents for a given monomer and reactivity ratios in copolymerizations. Reactivity ratios are very sensitive to the nature of the active centers. For example, radical copolymerization of styrene and MMA results in a nearly random copolymer, in contrast to nearly exclusive polystyrene formed under cationic and pMMA formed under anionic conditions.

The reactivity ratios measured in Cu-based ATRP are nearly identical to those reported for conventional radical polymerization but very different from those for anionic, group transfer, and cationic systems. For example, ATRP copolymerization of MMA and *n*-butyl methacrylate provides $r_{MMA} = 0.98$ and $r_{BMA} = 1.26$, which are very close to the values reported for the conventional radical process (0.93 and 1.22, respectively) and very different from those for group transfer polymerization (1.76 and 0.67), as well as anionic polymer-

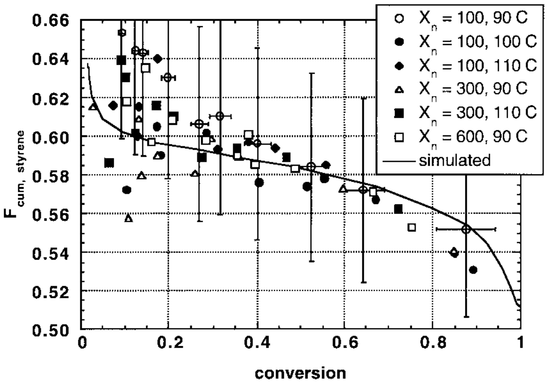


Figure 2. Dependence of cumulative copolymer composition on conversion in copolymerization of styrene and butyl acrylate ($[S]_0 = [BA]_0$) at variable temperatures and variable initiator concentrations using $[\text{methyl 2-bromopropionate}]_0 = [\text{CuBr/2dNbipy}]_0$.

ization carried out with Li as counterion (1.04 and 0.81).[43] Similar observations were reported for copolymerization of styrene and methyl acrylate, styrene and acrylonitrile, and MMA and methyl acrylate.[49,50]

Figure 2 presents the observed cumulative composition of the formed copolymer in styrene/butyl acrylate ATRP.[51] The solid lines are calculated values using $r_{ST} = 0.69$ and $r_{BA} = 0.17$, according to the literature.[52] The agreement is good, although the reaction temperature was different (110 and 60 °C, respectively).

It must be noted that some discrepancies between reactivity ratio values in ATRP and conventional radical processes are expected due to the following:

(i) differences in reaction temperatures

(ii) differences in reaction solvents

(iii) differences in polymerization degrees. In a conventional process, a high polymer is formed at very low conversion and the polymer composition is determined at low conversion. It was previously reported that reactivity ratios depend strongly on polymerization degree.[53] Such an effect may originate in different chemoselectivities of initiating and propagating species.

(iv) the “bootstrap” effect.[54] This effect can even be magnified in systems based on reversible activation processes. Polymer chains in the dormant form can be preferentially solvated by one monomer and after activation react with this monomer preferentially and convert to the dormant state before the second monomer can diffuse to the reaction site. A similar effect can operate for the catalyst which can be preferentially solvated by one monomer and increase the probability of its reaction with the newly generated radical.

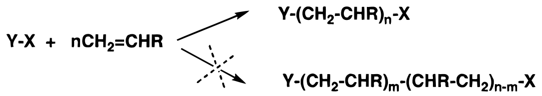
(v) activation of one comonomer by complexation with Lewis acids.[55] Transition metal catalysts are weak Lewis acids and may affect reactivities of some monomers (e.g. (meth)acrylates) by complexation.

(vi) measurement methodologies which involve cumulative compositions in ATRP in the continuously evolving monomer feed versus instantaneous composition measured at low conversion and variable monomer feed in conventional processes.

Considering all of these differences, the agreement of the reactivity ratios in controlled radical polymerizations and conventional processes is remarkable.

4. Chemoselectivity and Regioselectivity. So far, no significant improvements in chemoselectivities were observed regarding transfer to polymer, monomer, or transfer agents. However, additional research is needed. This behavior is similar to those of many other new “living” reactions such as carbocationic processes in which molecular weights are usually lower than those in conventional processes.[56] Thus, the key approach in all controlled/“living” reactions is to limit molecular weights below the level at which chain breaking reactions become noticeable rather than to extend the accessible ranges of molecular weights. In some cases, more complex initiating/catalytic systems may provide additional pathways for side reactions, as reported for styrene ATRP.[57]

All polymers formed by ATRP have regular head-to-tail structures with the growing species of the typical secondary/tertiary structures, as evidenced by NMR.[17,20] Neither head-to-head defects nor primary alkyl halides at growing chain ends have been detected. The latter could be expected for some coordination mechanisms based on insertion.



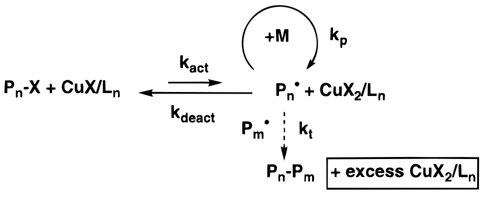
(4)

The observed regio- and chemoselectivities are typical for conventional free radical systems and do not indicate any new features expected for coordinated or ionic species.

5. Tacticity. Stereoselectivity is often used as an important mechanistic criterion for many organic reactions. In polymerization stereoselectivity defines chain microstructure, that is, tacticity. Polymers formed in many anionic and coordination polymerizations have tacticities substantially different from those for polymers formed in radical polymerizations, due primarily to a nearly planar structure of radicals (sp^2-like) in contrast to sp^3 hybridization of carbanions and organometallic derivatives.

We and others have analyzed the microstructure of poly(methyl methacrylates) (PMMAs) formed in Cu-based as well as Ru-, Ni-, Fe-, Pd-based ATRPs and concluded that polymers have the same tacticity as PMMA prepared by a conventional free radical process.[16,17,24,28−31,43,58] It has to be again noted that some anionic polymerizations, carried out in the presence of bulky counterions, lead also to tacticities similar to those of radical systems.[59] However, any tight association of the growing chain and metal center, like in lithium enolates, cannot happen in ATRP; this rather excludes the coordination mechanism for Cu-catalyzed systems.

6. Formation of Cu(II) via Persistent Radical Effect and Cross-linking. A consequence of the equilibrium between growing radicals and dormant chains is unavoidable termination between free radicals. This termination leads to the irreversible formation of excess Cu(II) and slows the reaction.



(5)

Simultaneously, the Cu(II) acts as a deactivator and is responsible for the polymerization control. Usually,

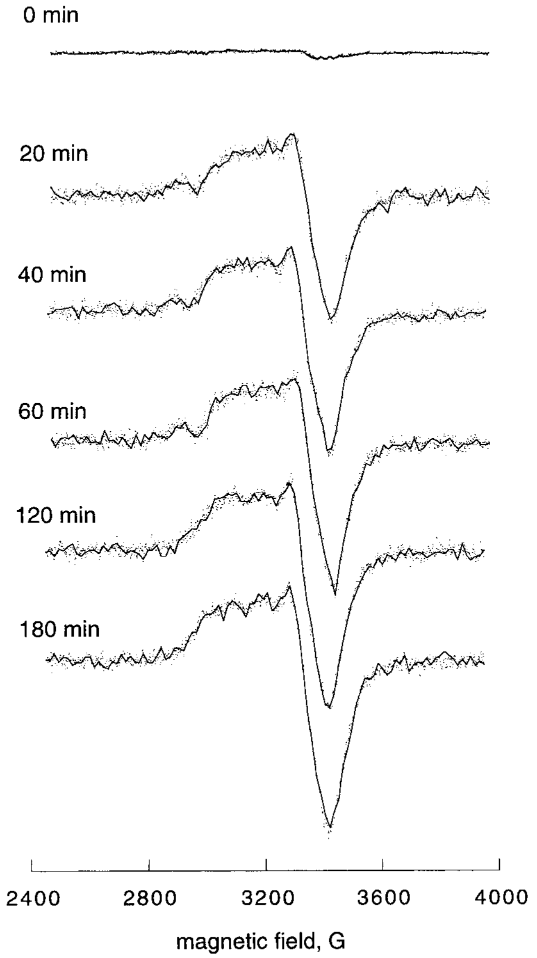


Figure 3. EPR spectra of the polymerization mixture measured at 25 °C after 0, 20, 40, 60, 120, and 180 min at 110 °C. Styrene/1-phenylethyl bromide/CuBr/dNbipy (= 100/1/1/2) in toluene (50 vol %).[60]

this termination happens early in the polymerization because termination coefficients are inversely proportional to chain length. They are additionally reduced due to the increasing viscosity resulting from monomer consumption, that is, less solvent (monomer in bulk systems) in the reaction mixture, as well as formation of the larger amount of polymer with progressively increasing molecular weight. The initially formed Cu(II) species are sufficient for control of the polymerization by the PRE, and their formation is strongly reduced at later stages, leading to a small variation of Cu(II) and nearly constant concentration of growing radicals.

Figure 3 presents EPR spectra recorded in the bulk ATRP of styrene at 110 °C using 1-phenylethyl bromide (0.09 M) and CuBr/2dNbipy (0.09 M) as the initiating system. After a relatively short time, Cu(II) reaches nearly a stationary concentration, corresponding to approximately 5 mol % from the initial Cu(I) species.[60] This also means that 95% of the chains are still controlled and carry the halogen atoms at the chain ends. Because termination in styrene polymerization is predominantly by coupling, some chains may have double molecular weight.

The proportion of Cu(II) species formed depends on the equilibrium constant but also increases with higher initial concentrations of both initiator and Cu(I). Thus, in some systems with high concentration of radicals (polymerization of acrylates with $CuPF_6$ or in polar solvents (ethylene carbonate)), doubling of molecular weights has been detected at high conversions.[19,61]

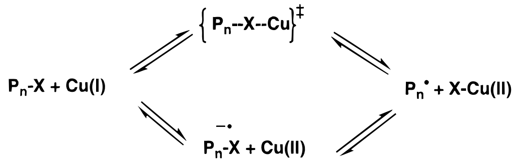
In addition, when hyperbranched polymers were prepared using inimers (initiator and monomer being the same molecule) such as *p*-chloromethylstyrene or 2-(2-bromopropionyloxy)ethyl acrylate, cross-linking was detected when large amounts of catalysts were used.[62] In these bulk polymerizations, the concentration of the initiator (= monomer) is >100 times higher than that in conventional ATRP and, therefore, the termination rate increases substantially.

It has been observed that the polymerization rate is significantly reduced in the presence of externally added Cu(II) species[10] and accelerated when the concentration of Cu(II) is decreased, for example in the presence of Cu(0).[63] Both observations are in agreement with Schemes 1 and 2.

Thus, direct observation of Cu(II) species by EPR and UV, doubling of molecular weights, and cross-linking using inimers and multifunctional initiators provide additional evidence for radical intermediates, since ionic/polar species cannot couple due to electrostatic repulsions.

7. Possibilities of Other Mechanisms. The experimental evidence presented above for Cu-catalyzed ATRP (and presumably other transition metals) is consistent with a free radical mechanism. However, control can be ascribed not only to the reversible transfer of halogen atoms between growing chains and transition metals via an inner sphere electron transfer process but also to some other reactions.

An alternative to the inner sphere process may be an outer sphere electron transfer proceeding by the formation of the intermediate radical anions followed by halogen *anion* transfer to the oxidized metal. This would result in a two-step rather than a concerted inner sphere process.

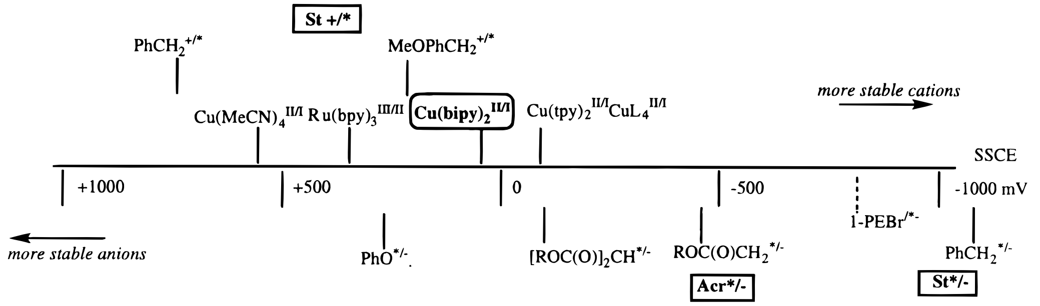


(6)

The results of the preliminary studies of correlations between rates of atom transfer reactions and R−X bond energies and electron affinities suggest the concerted process for many initiating and propagating species. Thus, for adducts with the same radical-stabilizing substituent, tertiary alkyl halides are typically better initiators than secondary ones, which are better than primary alkyl halides.[64] However, unexpectedly high rates even at the low temperatures found for some alkyl halides (haloacetonitrile) could indicate an outer sphere electron transfer process. This may happen for initiators with very high electron affinities (bromomalonates, CCl_4) and may sometimes lead to side reactions reducing initiation efficiency. Nevertheless, the formation of radical anions by the outer sphere electron transfer process from Cu(I) to 1-phenylethyl bromide and other similar dormant species has low probability due to the unfavorable redox potentials (cf. also Scheme 3).[65]

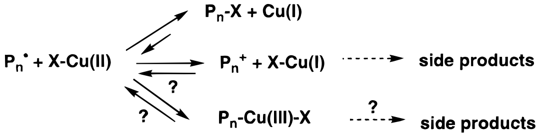
Polymerization control may also be due to a degenerative transfer process, previously reported for styrene and acrylates using suitable alkyl iodides and conventional radical initiators.[66] However, degenerative transfer was found to be inefficient for alkyl bromides and

Scheme 3



chlorides due to extremely slow exchange in comparison with propagation.[67] Thus, degenerative transfer contributes negligibly to Br- and Cl-based ATRP. In contrast, I-based ATRP may be additionally moderated by the degenerative transfer process.

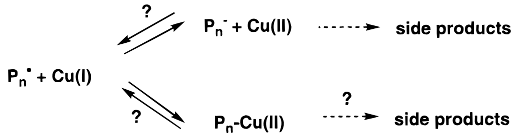
It has been previously reported that some radicals may react with metal centers, reversibly forming organometallic species.[8,68] In principle, this could also happen with either Cu(I) or Cu(II) species, leading to R−Cu(II) and R−Cu(III) species, respectively.[69] It seems that these reactions are not very important for styrene polymerization, since the rates of conventional radical polymerization initiated by AIBN or peroxides are not affected by addition of CuBr/2dNbipy or Cu(OTf)$_2$/2dNbipy.[10] Cupric triflate was used in these experiments instead of cupric bromide because the latter acts as an efficient inhibitor in reverse ATRP (cf. previous sections). However, adding larger amounts of cupric triflate reduces the molecular weight and terminates the reaction, presumably by the oxidation of growing radicals via an outer sphere electron transfer process, as suggested previously.[57]



(7)

Methyl acrylate behaves differently. Addition of cupric salts has no effect on rates and molecular weights for conventional initiators. However, reactions are decelerated in the presence of CuBr and CuOTf (Figure 4).

This observation can be explained either by the formation of organometallic R−Cu(II) species, providing an additional pathway of control and supplementing the atom transfer process, or by the reversible reduction of growing radicals to the enolate anions via an outer sphere electron transfer process. The contribution of these reactions is, however, relatively low, since polymerization of 2-hydroxyethyl acrylate is well controlled either in bulk or even in aqueous solution.[23]



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We have presented many experimental data against involvement of carbocations and carbanions in the polymerization of several substituted styrenes and (meth)acrylates in typical ATRP catalyzed by Cu(I) complexed by bipy derivatives. However, oxidation of growing radicals to carbocations or reduction to carbanions may happen under appropriate conditions and sometimes can become the dominant pathway. This depends on the redox properties of both the transition metal complex and the corresponding organic radicals. For example, ATRP of *p*-methoxystyrene with Cu(I)/2dNbipy is unsuccessful and cationic intermediates are responsible for the elimination process.[70] This could be due to a much easier oxidation of the *p*-methoxystyryl radical ($\Delta E_{1/2} = 0.4$ V for the corresponding unsubstituted and *p*-methoxybenzyl radicals).[71]

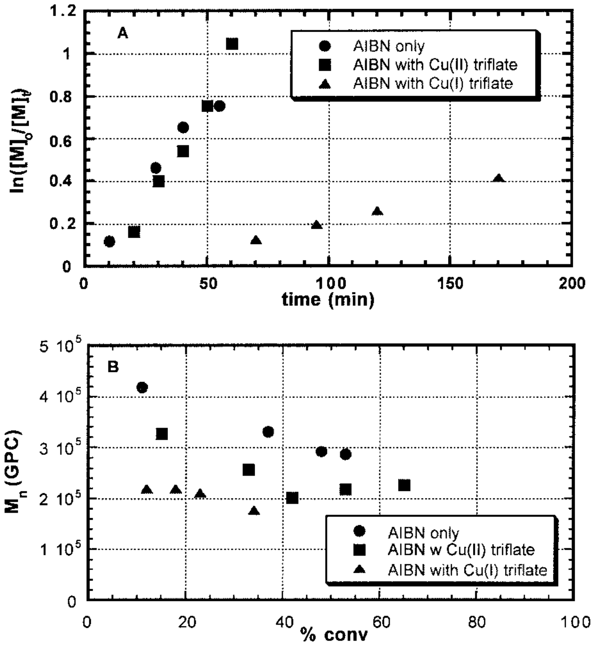

Figure 4. Kinetic plots and dependence of molecular weights on conversion in the polymerization of methyl acrylate initiated by AIBN alone ([AIBN]$_0$ = 0.013 M) at 60 °C and in the presence of [CuOTf/2dTbipy]$_0$ = 0.011 M and [Cu(OTf)$_2$/2dTbipy] = 0.005 M.

Similarly, using CuPF$_6$/(CH$_3$CN)$_4$ complexes for styrene polymerizations resulted in a cationic process.[72] This can be ascribed to a much stronger oxidation power for this complex in comparison with the Cu(I)/2bipy complex ($\Delta E_{1/2} = 0.6$ V).[73] Similar reactions are possible for radicals which can be easily reduced, such as malonates or trichloromethyl radicals. Under homogeneous conditions they are readily reduced to carbanions with CuBr/2dNbipy complexes. The interrelations between the electrochemical potentials of copper complexes and organic radicals as well as propagating radicals in styrene and acrylate polymerizations are illustrated in Scheme 3.

It seems that the Cu/bipy complex is well-suited for most styrenes and (meth)acrylates, but other metals or other ligands may open the possibility for either cationic or anionic processes which can be formed by the reactions shown in eqs 7 and 8. However, under typical conditions of ATRP (high temperatures, presence of moisture) the carbocations and carbanions will be involved in many side reactions interfering with the polymerization control. These reactions may take place even if ions are formed in a small proportion (but continuously) due to the presence of moisture and relatively high temperature; therefore, differences between redox potentials should be larger than $\Delta E_{1/2} = 0.3$ V, corresponding to $K = 10^{-5}$ at ambient temperature.

It must be stressed that electron transfer reactions are additionally affected by solvent and temperature and may be quite different from those estimated at room temperature in acetonitrile (Scheme 3).

Summary

Many features of copper-catalyzed atom transfer radical polymerization resemble closely those of other controlled radical systems such as nitroxide-mediated, degenerative transfer or those proceeding with organometallic intermediates. Molecular weights increase linearly with conversion, polydispersities initially decrease with conversion, an excess of persistent radicals reduces polymerization rates, oxygen inhibits polymerization, and water generally does not affect polymerization. In addition, chemoselectivity (reactivity ratios and transfer coefficients), regioselectivity, and stereoselectivity (tacticity) are similar to those in conventional radical polymerizations. However, the presence of transition metals in the reaction requires very careful examination of the reactive intermediates and the mechanism of propagation.

We described the following experiments which either support or do not contradict the radical mechanism for ATRP:

(i) reverse ATRP leading to the same products as the classic ATRP

(ii) inhibition/termination by typical radical inhibitors such as oxygen and stable radicals and no affect of protonogenic compounds and either nucleophiles or electrophiles

(iii) reactivity ratios very similar to those in conventional radical polymerizations

(iv) regio- and chemoselectivities typical for conventional radical polymerizations

(v) tacticities identical to those in conventional radical polymerizations

(vi) direct observations of Cu(II) species resulting from the coupling of growing radicals via the PRE and cross-linking found for AB* systems

(vii) negligible effect of Cu(I) or Cu(II) species on rates and molecular weights in AIBN-initiated polymerization of styrene and acrylates.

None of these experiments proves unambiguously and unequivocally a radical process. However, when taken together they very strongly indicate that the majority of the monomer is consumed and that the polymer is predominantly formed by free radicals. Even if propagating free radicals could be observed directly, the contribution of other species could not be completely excluded.

It is possible that, under certain conditions, ATRP can be supplemented by degenerative transfer and reversible formation of organometallic intermediates. It is also possible that it may sometimes occur not via a concerted process with bridged intermediates but by the two-step process with the involvement of radical anions. For some monomers and some metal complexes, either oxidation or reduction of growing radicals to ionic species is possible, which will usually induce loss of control due to high reaction temperature and the presence of adventitious water.

In conclusion we would like to propose that, for any metal catalyzed radical polymerization such as Cu-based ATRP, it is necessary to verify the following criteria to prove the radical nature of polymerization:

(1) approaching ATRP equilibria from both sides: radicals/X$-$Mt^{n+1} species (reverse ATRP) and RX/Mt^{n}

(2) chemoselectivities similar to those for conventional radical polymerization: (a) effect of additives and inhibitors/scavengers; (b) reactivity ratios; (c) transfer coefficients

(3) regioselectivities similar to and not exceeding those for conventional radical polymerization: (a) head-to-head structures; (b) end groups (both tail and head groups)

(4) stereoselectivities (tacticity) similar to those for conventional radical polymerization

(5) detection of X$-$Mt^{n+1} species resulting from the PRE and confirmation of the termination by doubling molecular weight or cross-linking for multifunctional initiators and inimers

(6) detection of growing free radicals if they resonate in frequencies sufficiently separated from those of the persistent radicals present in excess in controlled radical systems.

Cu-based ATRP fulfills the first five criteria for a radical process. Unfortunately, the *g*-values for propagating free radicals and Cu(II) species are too close to enable direct detection of growing radicals.[60]

To answer the question if the control is ascribed to a ATRP process, degenerative transfer, or reversible formation of organometallic intermediates, additional experiments must be performed using conventional radical initiators in the presence of initiating alkyl halides and transition metal catalysts (both Mt^{n} and Mt^{n+1}).

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