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## Radical Havoc

# Impact of Catalyzed Radical Termination (CRT) and Reductive Radical Termination (RRT) in Metal-Mediated Radical Polymerization Processes

Lucas Thevenin,<sup>[a]</sup> Christophe Fliedel,<sup>[a]</sup> Krzysztof Matyjaszewski,<sup>[b]</sup> and Rinaldo Poli\*<sup>[a]</sup>

**Abstract:** Atom Transfer Radical Polymerization (ATRP), a metal-catalyzed process, is a most powerful method for macromolecular engineering, producing polymers with targeted and low-dispersity molar masses and with high chain-end fidelity. This is due to the persistent radical effect, which dramatically reduces the spontaneous radical terminations, prolonging the lifetime of radical chains and the concurrent growth of all polymer chains. Two additional reaction modes that involve metals

and organic radicals, however, may negatively affect the controlled polymerization. These are the Catalyzed Radical Termination (CRT) and the Reductive Radical Termination (RRT) and were shown to be particularly important for the polymerization of acrylate monomers. The scope and the mechanistic investigations carried out to elucidate how these processes interplay with ATRP and with each other are outlined in this Minireview.

## 1. Introduction

Coordination chemistry has had, and continues to have, enormous impact on controlled radical polymerization, which has revolutionized polymer science over the last 25 years, especially through the implication of metal complexes in the controlling mechanism widely known as “Atom Transfer Radical Polymerization” (ATRP).<sup>[1]</sup> Metal complexes, however, may react with the growing radical chains in various ways,<sup>[2]</sup> each one affecting the control of chain growth either positively or negatively. The positive interplay between ATRP and a second method of metal-mediated radical polymerization, known as “Organometallic-Mediated Radical Polymerization” (OMRP) has been highlighted in a number of previous contributions.<sup>[3]</sup> This Minireview will focus on the negative impact of two specific phenomena, one of which (Catalyzed Radical Termination, CRT) was discovered recently and the second one (Reductive Radical Termination, RRT), although well-known in stoichiometric radical reactions, was only recently shown to interfere in ATRP-type systems. A previous account on the effect of CRT in metal-mediated polymerization is available,<sup>[4]</sup> but more recent progress is also included here, whereas the effect of RRT on radical polymerization has not been previously highlighted in a review article. Learning how these reactions take place and how to minimize them or completely stop them is of crucial impor-

tance to improve the quality of polymeric materials made by metal-mediated processes. Before describing the current state of understanding of how CRT and RRT affect a metal-mediated radical process, it is necessary to briefly recall a few principles in controlled radical polymerization, in metal-mediated polymerization and in metal-radical interactions.

## 2. General Principles

### 2.1. Controlled Radical Polymerization

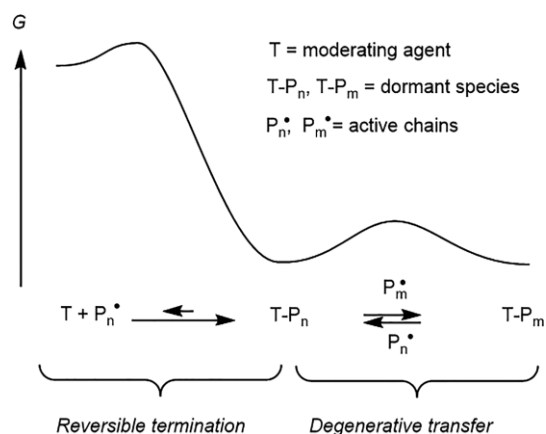
Taming radical reactivity and achieving controlled/living chain growth requires the use of a mediating agent, but radical terminations by bimolecular radical combination (Comb) and/or disproportionation (Disp) can never be totally suppressed. All methods, differing by the nature of the mediating agent, can be grouped into two general families, commonly termed “reversible termination” and “degenerative transfer” methods (Scheme 1).

In the first family, the reactive radical chain ( $P_n^*$ ) is dissociatively and reversibly liberated from a dormant species ( $P_n-T$ ), in which it is bonded to the mediating agent, or deactivator (T). The dissociation equilibrium dramatically lowers the free radical concentration, thereby reducing the rates of terminations, which are second order in radical, relative to that of propagation (first order in radical). This is also known as “persistent radical effect”.<sup>[5]</sup> Additionally, the intermittent dormancy extends the overall life of the growing chains from ca. 1 s to a few hours and provides concurrent growth of all chains. The second family of methods is based on an associative and degenerative exchange between a large amount of dormant chains and a tiny amount of free ones. The dormant species acts in this case as a transfer agent and the best control is

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Scheme 1. Energy profiles for reversible termination and degenerative transfer processes implicated in controlled polymerizations.

obtained when the exchange rate is greater than the propagation rate. An important difference between the two families is that  $[T]$  is much greater than the free radical concentration in the reversible termination methods whereas the reverse is true (free  $T$  is not required) in degenerative transfer polymerization. In both of these systems the growing radical concentration is much lower than that of the dormant species. A degree of control (low dispersity, i.e. uniformity of chain length) depends on

how many times a radical propagates before it is either converted to a dormant state by a mediating agent or it exchanges degeneratively. Only reversible termination methods will be of concern in this article, although metal complexes with a suitable coordination sphere may also operate by degenerative transfer. Starting from either  $R_0\cdot$  or from a conventional source of a primary radical  $R_0\cdot$  in the presence of  $T$  as initiator, plus  $n$  equivalents of monomer ( $M$ ) per  $R_0$ , polymer chains with average composition  $R_0\cdot(M)_n\cdot T$  can be recovered with high chain-end fidelity (e.g. low levels of unwanted bimolecular terminations) and narrow molecular weight distributions if initiation is fast and if the rate of terminations can be made very small relative to the rate of propagation.

## 2.2. ATRP and OMRP

Both ATRP and OMRP are reversible termination methods. In OMRP,  $T$  is a metal complex ( $L/Mt^x$ , where  $L$  represents the coordination sphere and  $x$  is the formal oxidation state). The dormant species ( $L/Mt^{x+1}\cdot P_n$ ) is a higher-valent organometallic complex with the metal atom covalently linked to the chain end. In ATRP, the function in the dormant species chain end (a halogen atom  $Y$ ) does not directly dissociate. Rather, it is transferred to a metal complex  $L/Mt^x$ , which acts as activator, to yield a higher oxidation state complex  $L/Mt^{x+1}\cdot Y$ , which acts as the



Lucas Thevenin graduated from Strasbourg University and he is currently completing his PhD at the Paul Sabatier University supervised by Dr. Fliedel and Prof. Poli. His current research field is controlled radical polymerization (ATRP and OMRP). He is specifically investing the termination mechanisms during metal-mediated radical polymerization.



Christophe Fliedel obtained his Ph.D. from the University of Strasbourg (France) in 2010 under the supervision of Dr. Pierre Braunstein. He then moved to the New University of Lisbon (Portugal), where he was awarded a postdoctoral fellowship from the Fundação para a Ciência e a Tecnologia (FCT, Portugal) in 2011, to conduct research in the groups of Prof. Teresa Avilés (Universidade Nova de Lisboa) and Dr. Samuel Dagorne (Université de Strasbourg). Early in 2016, he joined the group of Prof. Rinaldo Poli at the Laboratoire de Chimie de Coordination (LCC) in Toulouse, France, as a CNRS researcher. His research interests are mainly focused on organometallic and coordination chemistry and controlled radical polymerization.

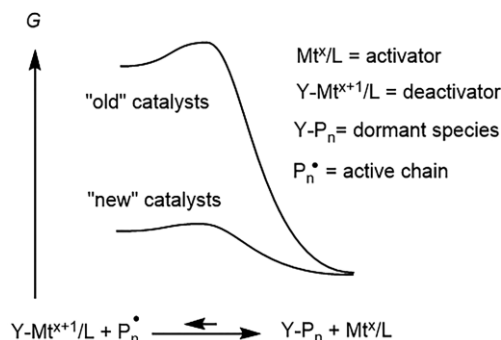


Krzysztof (Kris) Matyjaszewski received his Ph.D. from Polish Academy of Sciences under Stan Penczek. After 1 year postdoctoral stay with George Butler at the University of Florida, he returned to Poland and got his habilitation from Lodz Polytechnic. After 1 year stay as invited professor at University of Pierre et Marie Curie and CNRS in Paris, he moved to Carnegie Mellon University in Pittsburgh, where he is currently J. C. Warner University Professor of Natural Sciences and Director of Center for Macromolecular Engineering and Director of Controlled Radical Polymerization Consortium that has included 60 international corporations. His main research interests include controlled/living ionic and radical polymerizations, especially ATRP and preparation of various advanced materials for applications related to energy, environment and biomedicine.



Rinaldo Poli received his Ph.D. from Scuola Normale Superiore, Pisa (Italy) under Fausto Calderazzo with a 1-year internship with Geoff Wilkinson at Imperial College London, followed by a post-doc with Al Cotton at Texas A&M University. His academic career started at the University of Maryland College Park, where he rose the ranks to Full Professor, then continued in France, first in Dijon and now in Toulouse where he leads a research group at the Laboratoire de Chimie de Coordination. His current research interests span the reactivity of coordination/organometallic compounds, especially those with an open-shell configuration and/or involving carbon-based radicals, the investigation of reaction mechanisms, homogeneous catalysis and the catalytic applications of hierarchically organized metal-decorated polymers.

deactivator. Thus, while ATRP still belongs to the “reversible termination” family because it rests on the same moderating principle and energy profile, the moderating equilibrium is slightly more complex, Scheme 2.



Scheme 2. Energy profile for the ATRP moderating equilibrium.

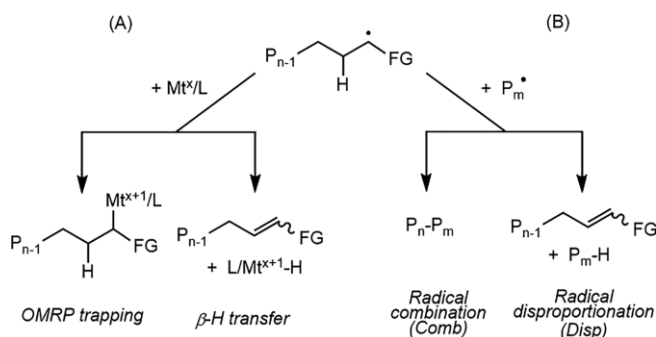
OMRP requires one metal complex per polymer chain, whereas ATRP is catalytic because the  $L/Mt^x$  complex is not incorporated in the produced macromolecules and may be recovered. During an ATRP process, the active radical may be trapped not only by the ATRP deactivator ( $L/Mt^{x+1}-Y$ ) but also by the ATRP activator ( $L/Mt^x$ ), which now becomes also the OMRP deactivator. This leads to a potential ATRP/OMRP interplay with simultaneous presence of two mediating equilibria. Therefore, control is improved because the two equilibria work together to reduce the active radical concentration. When a radical polymerization is carried out using a halide-free  $L/Mt^x$  mediator, on the other hand, no ATRP may occur and any control is solely ensured by OMRP.<sup>[3a]</sup>

The most successful metal used in ATRP is undoubtedly copper, shuttling between the oxidation states I and II in the mediating equilibrium, although several other metals can provide suitable control for many monomers. For copper complexes, the coordination sphere tremendously influences the atom transfer equilibrium, tuning the activation equilibrium constant (cf. Scheme 2), for the same radical species, over more than 9 order of magnitude.<sup>[6]</sup> The  $Cu^{II}-C$  bond is generally too weak to lead to a significant contribution of OMRP trapping (except for the most active ATRP catalysts, see below). There is also a strong interest in iron-based ATRP catalysts ( $Fe^{II}/Fe^{III}$ ), because of the low cost and toxicity of this element.<sup>[7]</sup> The dominating element in OMRP, on the other hand, is cobalt.<sup>[8]</sup>

### 2.3. Catalytic Chain Transfer (CCT)

In addition to forming a direct bond with each other to yield the OMRP dormant species  $P_n-Mt^{x+1}/L$ , the active radical chain  $P_n^\bullet$  and the  $L/Mt^x$  species may also react by  $\beta$ -H transfer, yielding a dead chain with an unsaturated chain end and a hydride complex,  $L/Mt^{x+1}-H$  (see Scheme 3A). This event may be followed by an H atom transfer from the hydride complex to a monomer molecule, leading to a metal-catalyzed chain transfer to monomer. This phenomenon negatively interferes with controlled chain growth in an OMRP or ATRP/OMRP system but, when very efficient, can be exploited to yield short-chain mac-

romonomers, which are also valuable materials.<sup>[9]</sup> Therefore, considerable attention has been devoted to this phenomenon. The two competing reaction pathways involving  $P_n^\bullet$  and  $L/Mt^x$  (OMRP trapping and  $\beta$ -H transfer in CCT) parallel the two competing modes of radical termination (Comb and Disp), Scheme 3B. The dichotomy between controlled OMRP and CCT is a very interesting phenomenon that would merit a separate review article, but will not be further discussed here. Like for OMRP, cobalt is the most commonly employed element in CCT and its complexes give the highest catalytic activities.<sup>[9]</sup>

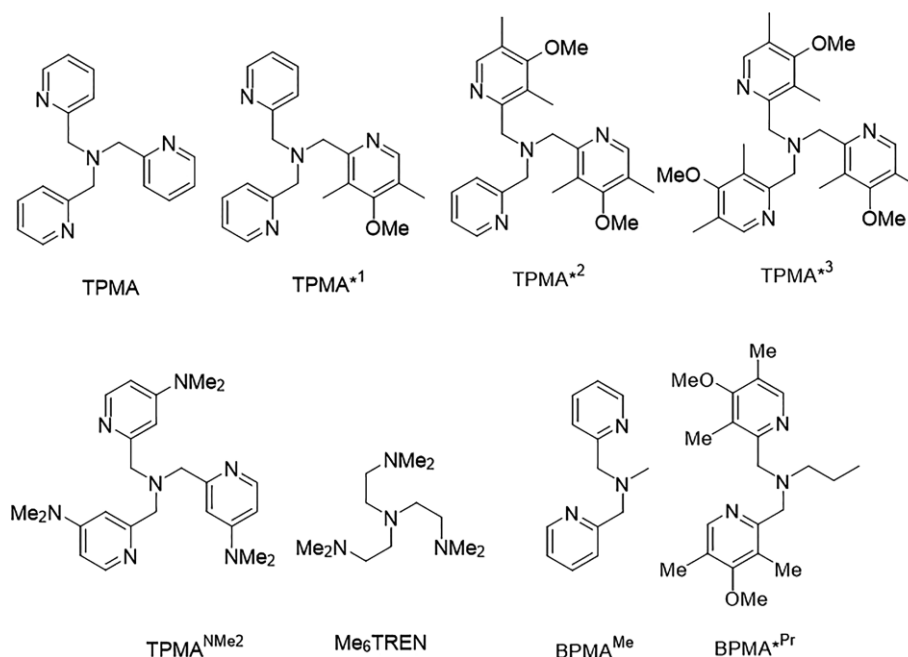


Scheme 3. Parallel between the combination and  $\beta$ -H transfer processes in the reactions between a radical chain and (A)  $L/Mt^x$  or (B) a second radical chains.

## 3. Metal-Catalyzed Radical Termination (CRT)

### 3.1. Discovery and Scope

The atom transfer equilibrium constant, which is experimentally available from the analysis of the mediating species accumulation kinetics,<sup>[10]</sup> together with all other kinetic parameters (propagation and termination rate constants) and the concentrations of all species, allows the estimation of the molar percentage of dead chains (i.e. the chain end fidelity) for an ATRP process. However, running the ATRP of acrylates with very active catalysts gave a much greater percentage of dead chains than predicted. For instance, a methyl acrylate (MA) polymerization carried out at 40 °C with the  $CuBr/TPMA$  catalyst ( $TPMA = \text{tris}(2\text{-pyridylmethyl})\text{amine}$ , Scheme 4) gave a 62.5 % conversion after 6.5 h with 1.9 % of dead chains, while the predicted value under the employed operating conditions was only 0.05 %.<sup>[11]</sup> This phenomenon raised a red flag about the presence of additional termination pathways. The addition of substoichiometric amounts of  $CuBr$  and  $\text{tris}((4\text{-methoxy-3,5-dimethylpyridin-2-yl})\text{methyl})\text{amine}$  ( $TPMA^{*3}$ , Scheme 4), which yields a ca. 1000 times more active system than  $TPMA$ , significantly retarded the radical polymerization of *n*-butyl acrylate (*n*BA) in anisole initiated by azobisisobutyronitrile (AIBN) at 60 °C, while the molecular weights decreased. These phenomena, which scaled with the amount of added  $Cu$  complex, clearly suggested that radical termination is accelerated by the catalytic action of the  $Cu^I$  complex.<sup>[12]</sup> The  $Cu^I/TPMA^{*3}$  system, which is present in the reaction medium mostly as the  $[Cu^I(TPMA^{*3})]^+$  complex, may yield either the organometallic  $[PnBA-Cu^{II}(TPMA^{*3})]^+$  (OMRP dormant species) or the hydride complex  $[H-Cu^{II}(TPMA^{*3})]^+$ , as



Scheme 4. Ligands used in combination with CuBr for the investigation of acrylate radicals CRT.

shown in Scheme 3A. One of these two products must therefore be able to quench a second radical to yield one or two dead chains and regenerate the Cu<sup>I</sup> catalyst. If CRT transits through the hydride system, it must necessarily lead to disproportionation products, whereas transit through the OMRP dormant species may lead to either Comb or Disp, depending on the intimate mechanism of the complex-radical interaction.

A subsequent study showed the same phenomenon with the less active TPMA ligand and also with tris[2-(dimethylamino)ethyl]amine (Me<sub>6</sub>TREN, Scheme 4).<sup>[13]</sup> This study also established the CRT rate law as first order in radical and first order in catalyst and provided EPR evidence for the formation of an unstable Cu<sup>II</sup> intermediate, although the identity of the latter could not be determined. The retardation of the polymerization of acrylates (but not of styrene) by addition of a Cu<sup>I</sup> complex was actually already shown in a previous contribution,<sup>[14]</sup> which made use of stoichiometric amounts of copper(I) triflate in combination with a substituted bipyridine, but the intervention of CRT was not suggested. More recently, Cu<sup>0</sup> has also been found to promote radical termination.<sup>[15]</sup> Another contribution has revealed a similar catalytic action on radical termination by FeBr<sub>2</sub>.<sup>[16]</sup> To date, to the best of our knowledge, no other metals have been highlighted as capable of leading to CRT. In terms of monomers, on the other hand, only acrylates have been clearly shown to suffer from this phenomenon. The polymerizations of styrene and methacrylates do not appear to be affected, at least not to a detectable level and detailed investigations on other monomers have not yet been carried out.

### 3.2. Hydride or Organometallic Intermediate?

A computational study, carried out for the TPMA system with  $\cdot\text{CH}(\text{CH}_3)\text{COOCH}_3$  as model radical for a PMA chain, showed that

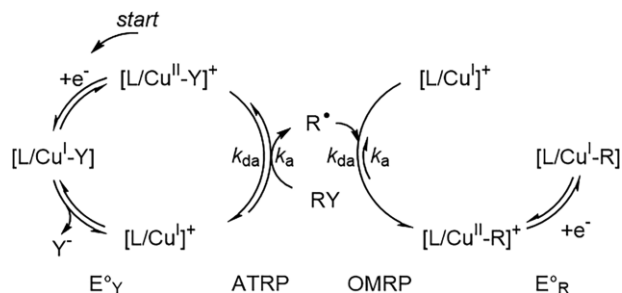
the formation of the Cu<sup>II</sup>-C bond is exoergic whereas H-atom transfer leading to the Cu<sup>II</sup>-H bond and MA is endoergic. This strongly suggested that OMRP trapping is the key step leading to CRT.<sup>[17]</sup> This conclusion was also supported by the experimental comparison of CRT activities for a series of systems with various ligands (Scheme 4) of different donor power (TPMA < TPMA\*<sup>1</sup> < TPMA\*<sup>2</sup> < TPMA\*<sup>3</sup>; BPMA<sup>Me</sup> < BPMA\*<sup>Pr</sup>) and denticity (tridentate, bidentate). The observed CRT activity scaled with the Cu<sup>II</sup>-C bond dissociation enthalpy (BDE), as estimated by DFT calculations.<sup>[18]</sup> These calculations also showed that the aptitude to engage in OMRP trapping, for copper complexes, scales with the ATRP activity. The key role of the organometallic species is also consistent with the observation of CRT for acrylates but not for methacrylates, the latter being bulkier and therefore presumably forming a weaker bond with copper. On the other hand, methacrylates are more prone than acrylates to CCT, where the H-atom transfer to produce the hydride complex is the rate-determining step.

### 3.3. Detection and Stability of the Organometallic Intermediate

Stable organocopper(II) compounds are rare, although not unprecedented.<sup>[19]</sup> The isolation and characterization of a model organocopper(II) system of the OMRP dormant species has not been possible so far, even for the most active ATRP catalysts. However, direct evidence for formation of these species during the ATRP with very active catalysts has been possible through electrochemical studies.<sup>[20]</sup> Starting from the ATRP mediating complex [L/Cu<sup>II</sup>-Y]<sup>+</sup> and in the absence of initiator, the reduction at potential E<sup>o</sup><sub>v</sub> (Scheme 5) is electrochemically reversible. However, in the presence of a haloalkane RY (a suitable ATRP initiator), the reduction is followed by the ATRP activation atom



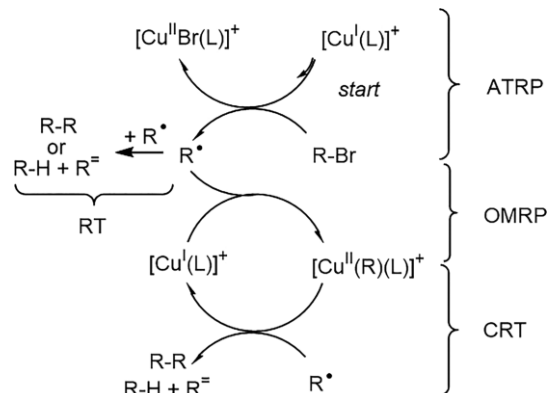
transfer step with formation of  $R^\bullet$  and regeneration of the mediating complex. Then, the radical is trapped by the electrogenerated  $[L/Cu^I]^+$  (ATRP activator and OMRP deactivator) to afford the organometallic species  $[L/Cu^{II}-R]^+$ . Formation of the latter can be evidenced by the appearance of a new wave at  $E^\circ_R$ , which is at lower potential than  $E^\circ_Y$  as expected from the greater donor power of  $R$  relative to  $Y$ . This behavior was observed for the electrochemical investigation of  $[Cu^{II}(TPMA)Br]^+$  and  $[Cu^{II}(Me_6TREN)Br]^+$  in the presence of  $YCH_2CN$  ( $Y = Cl, Br$ ).<sup>[20]</sup> The resulting organometallic complexes,  $[L/Cu^{II}-CH_2CN]^+$ , are not very good models of an OMRP dormant species because they contain a primary radical. However, a subsequent similar study of  $[Cu^{II}(Me_6TREN)Br]^+$  in the presence of the homologous series or bromoesters  $Br-CH_nMe_{2-n}COOMe$ , revealed that a copper-radical adduct forms not only for the primary radical ( $n = 2$ ), but also for the secondary one ( $n = 1$ ), which is a model of a polyacrylate chain. The tertiary radical ( $n = 0$ , model of a polymethacrylate chain), on the other hand, yields no detectable reduction wave at  $E^\circ_R$ , suggesting that this radical does not bind strongly enough to the  $[Cu^I(Me_6TREN)]^+$  complex.<sup>[21]</sup>



Scheme 5. Formation of  $[L/Cu^{II}-R]^+$  species by electrochemically-induced radical generation from ATRP initiators.

In a more recent investigation, the same electrochemical method, as well as the chemical method shown in Scheme 6, for generation of the radical and of the organometallic species were applied to a wider range of initiators, namely primary, secondary and tertiary bromides,  $X-CH_nMe_{2-n}-Br$  with  $X = CN, COOMe$  or  $Ph$ .<sup>[22]</sup> The chemical method allowed the reaction to be investigated by stopped-flow kinetics in the sub-second timescale. For the very active complexes investigated in this study ( $[Cu^I(L)]^+$  with  $L = TPMA, TPMA^{*3}$  and  $TPMA^{NMe_2}$ , Scheme 4) and using a  $[Cu^I(L)]^+/R-Br$  ratio of 2:1 to ensure quantitative trapping of the generated radicals, the build-up of the  $[Cu^{II}(L)Br]^+$  and  $[Cu^{II}(L)(CH_nMe_{2-n}-X)]^+$  products proceeds at the same rate, showing that the ATRP activation is rate-limiting and that the follow-up OMRP trapping is favorable and very fast. The stability and decomposition rate of the organometallic species were investigated by a combination of the chemical and electrochemical methods. The stability of  $[Cu^{II}(L)(CH_nMe_{2-n}-X)]^+$  decreases with  $X$  in the order  $CN > COOMe > Ph$  and in the order primary > secondary > tertiary. No  $[Cu^{II}(L)(CH_nMe_{2-n}-X)]^+$  species could be detected for tertiary radicals with any  $X$  functionality, or for  $X = Ph$ , even in the primary case, e.g. benzyl. The solvent nature is also important, DMF stabilizing the organometallic species more than MeCN. The electronic properties of the ligand  $L$  affect the  $[Cu^{II}(L)(CH_nMe_{2-n}-X)]^+$  stability much less than they affect the  $[Cu^I(L)]^+$  ATRP activity. Importantly, the

kinetics of the  $[Cu^{II}(L)(CH_nMe_{2-n}-X)]^+$  disappearance, which was accurately measured for  $[Cu^{II}(TPMA)(CHMeCOOMe)]^+$  in DMF at 25 °C, could only be correctly simulated by taking the CRT pathway into account. These experiments, however, could not provide information about the nature of the termination products (coupling or disproportionation).



Scheme 6. Chemical activation of ATRP initiators and decomposition pathways of the produced free radicals.

### 3.4. Nature of the CRT Products

A few investigations have targeted the identification of the CRT-generated product(s) and the intimate reaction mechanism. These studies have mostly dealt with polyacrylate radicals, e.g.  $PMA^\bullet$ , and small models such as  $\bullet CH(CH_3)COOCH_3$ , because CRT appears to be more or less restricted to these radical chains. However, these studies have led to some debate and are complicated by the presence of RRT (vide infra). Unfortunately, a full understanding of this point has not yet been achieved.

In one of the first reports of CRT, already highlighted above,<sup>[13]</sup> Br-terminated polystyrene (PSt-Br) and poly(methyl acrylate) (PMA-Br) samples, made by ATRP, were activated by  $Cu^I/TPMA$  in MeCN at 25 °C in the absence of monomer, according to Scheme 6, and the terminated chains were analyzed by size exclusion chromatography (SEC). PSt-Br gave, as expected, a predominant distribution of double molar mass relative to the macroinitiator, because this radical does not engage in CRT and because the bimolecular termination of PSt $^\bullet$  is known to yield mostly Comb. On the other hand, PMA-Br led to a product where the double molar mass distribution was not detected, showing a negligible contribution of Comb. Since the literature indicates that the bimolecular termination of PMA $^\bullet$  leads predominantly to Comb,<sup>[23]</sup> it was then suggested that CRT promotes Disp. As will be shown later, this result may be affected by the presence of RRT.

A subsequent investigation, however, has challenged this conclusion. Using the same strategy of Scheme 6, PMA-Br, PMMA-Br and PSt-Br macroinitiators were activated by  $CuBr/Cu^0/Me_6TREN$  in toluene at 70 °C.<sup>[24]</sup> The  $Me_6TREN$  ligand yields a more active ATRP catalyst than TPMA, and  $Cu^0$  ensures reduction of the ATRP activation product (the  $L/Cu^{II}-Br$  ATRP mediator) back to  $L/Cu^I$  by comproportionation. The termina-

tion of PMMA<sup>•</sup> and PSt<sup>•</sup> gave molar mass distributions for the products in agreement with the absence of CRT and with the known bimolecular termination pathways of these radicals. On the other hand, the SEC analysis of the isolated polymer obtained from PMA-Br indicated a bimodal distribution with a 73:27 ratio of identical and double average molar mass, respectively, relative to that of the macroinitiator. These authors were prejudiced by one of their own previous studies, where PMA<sup>•</sup> generated by photolytic activation of PMA-TePh was found to give predominantly Disp (>98:2 under similar conditions of solvent and temperature), which led them to challenge the literature dogma and to conclude that PMA<sup>•</sup> spontaneously terminates preferentially by Disp.<sup>[25]</sup> Therefore, the minority double molar mass (Comb) distribution was attributed to CRT.<sup>[24]</sup> In addition, the polymer analysis by NMR and MALDI-TOF-MS revealed that the majority distribution contains only saturated chain ends (PMA-H), with no detectable unsaturated chains (PMA<sup>•</sup>). Furthermore, when the same study was conducted in the presence of CH<sub>3</sub>OD (10 equiv.), the product was fully deuterated (PMA-D). This revealed the intervention of RRT (vide infra) with the H chain end being attributed to the adventitious water present in the solvent (toluene).

A subsequent investigation,<sup>[26]</sup> however, revealed that part of the above conclusions were based on a wrong assumption. This new investigation made use of TPMA, TPMA<sup>\*3</sup> and Me<sub>6</sub>TREN in carefully dried MeCN at room temperature and in the absence of Cu<sup>0</sup>, in order to avoid any possible contribution of Cu<sup>0</sup>-CRT<sup>[15]</sup> and to allow an accurate determination of the extent of terminations by measurement of [Cu<sup>II</sup>] (halogen conservation principle<sup>[27]</sup>). Furthermore, compound [Cu<sup>I</sup>(MeCN)<sub>4</sub>][BF<sub>4</sub>]<sup>-</sup> was used rather than Cu<sup>I</sup>Br, in order to obtain a well-defined [Cu<sup>I</sup>/L]<sup>+</sup> activating species. In this study, preset amounts of the [Br-Cu<sup>II</sup>(L)]<sup>+</sup> deactivator were also added. While the deactivator plays no direct role in CRT, it lowers the radical concentration by shifting the ATRP activation equilibrium and thus skews the termination process in favor of CRT.<sup>[26]</sup> Using the Me<sub>6</sub>TREN system, while the product distribution obtained in the absence of Cu<sup>II</sup> essentially matched the previously published one,<sup>[24]</sup> an incremental addition of Cu<sup>II</sup> *decreased* the double mass distribution, unambiguously proving that the Comb product derives predominantly from the spontaneous bimolecular termination and not from CRT. The TPMA and TPMA<sup>\*3</sup> systems led to the same results (less Comb in the presence of more Cu<sup>II</sup>, hence more CRT). The double molar mass distribution was much less prominent for the TPMA system, which is a less active ATRP catalyst, and substantial again for the more active TPMA<sup>\*3</sup> system. This also agrees with the notion that bimolecular termination prevalently leads to Comb, because a greater ATRP activity results in a greater initial radical concentration. Simulations of the [Cu<sup>II</sup>] accumulation kinetics gave an excellent fit when considering that bimolecular termination gives Comb and CRT gives Disp, and a very poor one when using the opposite assumption.

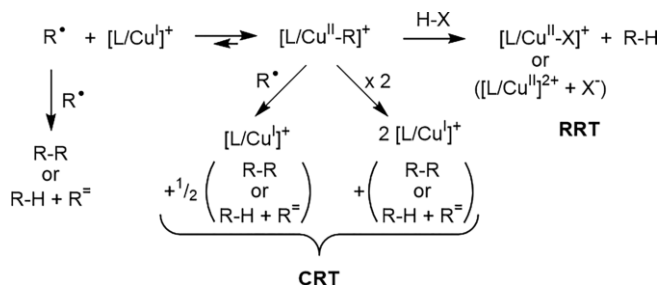
In light of this study, it is quite clear that the spontaneous termination of acrylate radicals proceeds primarily by Comb. The observation of prevalent Disp when these radicals were generated from photolysis of PhTe-PMA<sup>[25]</sup> is an interesting

phenomenon and a possible interpretation has been advanced.<sup>[28]</sup> However, the nature of the product(s) derived from CRT is still uncertain, because all the above studies were carried out using an over-stoichiometric amount of L/Cu<sup>I</sup>. While this ensured an efficient radical trapping with minimization of the competing bimolecular termination process, it also evidenced the presence of reductive radical termination (see next section), which, like Disp, yields a molar mass distribution identical to that of the macroinitiator. A mass spectrometric analysis of the terminated chains was not carried out in this study. At the present stage, the formation of Disp products by CRT seems likely, but the possibility that the main molar mass distribution, identical to that of the macroinitiator, is entirely due to RRT cannot be completely excluded. Further investigations will be necessary to clarify this point.

## 4. Reductive Radical Termination (RRT)

### 4.1. Background from Coordination Chemistry Studies

The Mt-C bond in alkyl complexes is polarized with a partial negative charge on the C atom and alkyl anions are amongst the strongest bases known. Hence, these compounds are typically quite sensitive to protonolysis, although the late transition metal systems yield bonds with a lower Mt-C electronegativity difference that are less proton-sensitive and even water-stable in certain cases. The addition of radicals to Cu<sup>I</sup>, to produce alkyl-copper(II) systems and the subsequent protonolytic decomposition of the latter in water have been thoroughly studied.<sup>[19]</sup> From the point of view of the radical, the overall process (addition of one electron from copper and a proton from the medium) constitutes a reductive radical termination. This reaction (Scheme 7) competes with the spontaneous radical termination (especially when the Cu-R bond is homolytically weak).



Scheme 7. Interplay of bimolecular radical termination, catalysed radical termination (CRT) and reductive radical termination (RRT) by the action of a copper(I) complex in the presence of a proton donor.

For instance, the (H<sub>3</sub>C-Cu<sup>II</sup>)<sub>aq</sub><sup>+</sup> aqua ion was produced very rapidly [ $k = (3.5 \pm 0.4) \cdot 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ] by reacting Cu<sup>+</sup><sub>aq</sub> with the CH<sub>3</sub><sup>•</sup> radical produced by pulse radiolysis of aqueous DMSO.<sup>[29]</sup> This organometallic transient decomposes according to different mechanisms depending on pH. At pH ≤ 1.5, only methane is produced by RRT with a first-order rate law, whereas ethane becomes the predominant product at pH ≥ 2.5 and the rate law becomes second order in metal complex. Thus, the preferred pathway at higher pH involves a bimolecular interaction between two transients. The two alternative pathways involving

homolytic dissociation followed by bimolecular radical combination, or interaction between  $\text{CH}_3^\bullet$  and a second transient, were excluded on the basis of the absence of a  $[\text{Cu}_{\text{aq}}^{+}]$ -dependence in the rate law. The observed high pH pathway also represents a CRT from the point of view of the methyl radical, although it is probably not relevant for the catalyzed termination of the radical chains that are typically involved in metal-mediated radical polymerization. This is because the radical functions associated to these chains are generally more stabilized and thus form weaker bonds with the metal center, relative to the methyl radical. On the other hand, the decomposition of other  $(\text{R-Cu}^{\text{II}})_{\text{aq}}^{+}$  aqua ions by CRT has not been clearly highlighted. This is because the aqueous medium used for these studies renders RRT by and large the preferred decomposition pathway. Other minor pathways generally involve the  $\text{Cu}_{\text{aq}}^{2+}$  ions that are present in the reaction medium or that are produced by the main RRT pathway.<sup>[19]</sup> It is also relevant to point out that most of these transients involve primary non-stabilized radicals, which form relatively strong  $\text{R-Cu}^{\text{II}}$  bonds. Studies of transients where  $\text{Cu}^{\text{II}}$  is bonded to a resonance-stabilized radicals have been very limited.<sup>[19]</sup>

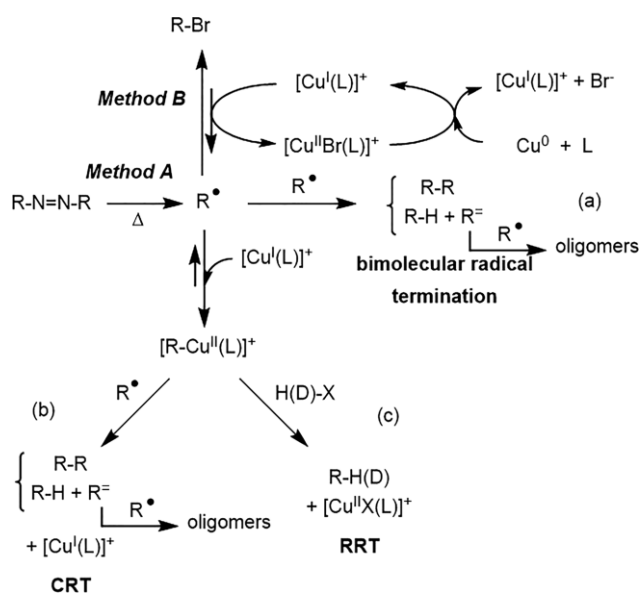
Complexes of  $\text{Cu}^{\text{I}}$  with neutral polyaza ligands, i.e. having electronic properties similar to those of the typical ligands used in ATRP, also yield  $(\text{L/Cu}^{\text{II}}\text{-R})_{\text{aq}}$  systems upon reaction with  $\text{R}^\bullet$ . For  $\text{L} = 2,5,8,11$ -tetramethyl-2,5,8,11-tetraazadodecane, the  $(\text{L/Cu}^{\text{II}}\text{-R})_{\text{aq}}$  transient with  $\text{R} = \text{CH}_3$  decomposes by a clean second order rate law at high pH yielding ethane, like the corresponding aqua complex.<sup>[29b]</sup> However, the decomposition rate law of the corresponding transient with  $\text{R} = \text{CH}_2\text{CH}_2\text{COOH}$  also exhibits, in addition to the second-order dependence on the organocopper species, an inverse dependence on  $[\text{L/Cu}^{\text{I}}]$  and the observed product is  $(-\text{CH}_2\text{CH}_2\text{COOH})_2$ . This behavior agrees with bond homolysis, followed by either bimolecular radical coupling or by the interaction of the free radical with an organocopper(II) species.<sup>[29b]</sup> When  $\text{R} = \text{CH}_2\text{COOH}$ , the decomposition occurs solely by the first-order protonolytic pathway (RRT), even at high pH (7 to 10).<sup>[29b]</sup> The transient with  $\text{R} = \text{CH}(\text{CH}_3)\text{COOH}$ , which is the closest model of a polyacrylate chain, unfortunately, could only be obtained together with the  $\text{R} = \text{CH}_2\text{CH}_2\text{COOH}$  derivative already mentioned above (40:60 ratio) by pulse radiolysis of a propionic acid solution. Its decomposition also appears to follow solely the RRT pathway.<sup>[29b]</sup> The two important conclusions of that study are that (i) steric hindrance enhances  $\text{L/Cu}^{\text{II}}\text{-R}$  bond homolysis and (ii) electron withdrawing substituents on the  $\alpha$ -C atom (e.g. a COOMe group) enhance the protonolytic decomposition. Hence, acrylate type radicals are particularly sensitive to RRT.

#### 4.2. RRT for Radical Chains and Models Thereof

Evidence that RRT can take place for radical polymer chains in the presence of  $\text{L/Cu}^{\text{I}}$  complexes was shown by the CRT study of Br-terminated poly(methyl acrylate), already mentioned in section 3.4.<sup>[24]</sup> Just to recall the salient points of that study, a bimodal distribution resulted from PMA $^\bullet$  chains obtained by activation of PMA-Br with  $\text{Me}_6\text{TREN/CuBr}$  in toluene at 70 °C. The main distribution has the same average molar mass as the

macroinitiator and was identified as essentially only PMA-H from the simulation of the MALDI-TOF mass spectrum, without a significant contribution by the unsaturated chain-end product expected from Disp. Therefore, it must result from RRT and was attributed to adventitious water in the toluene solvent. The occurrence of RRT was confirmed by the production of PMA-D when the experiment was repeated in the presence of  $\text{CH}_3\text{OD}$ . The minor distribution (27 %) has a double molar mass (hence, it corresponds to PMA-PMA resulting from Comb) and was attributed by these authors to CRT,<sup>[24]</sup> but a later study<sup>[26]</sup> reasigned it to spontaneous bimolecular termination.

Quantification of any Disp requires the precise determination of the amount of unsaturated chains, which is difficult from the simulation of the isotopic distribution in the mass spectrum of the polymer mixtures. Therefore, additional studies have been carried out on model systems with  $^1\text{H}$  NMR analysis of the product distribution. In addition, identification of the CRT products requires removal of the interfering RRT process, hence the use of thoroughly dehydrated solvents. Two strategies were used to generate radicals, followed by the investigation of their interaction with  $\text{L/Cu}^{\text{I}}$  systems either in the absence or in the presence of strictly controlled amounts of proton donors  $\text{H-X}$  (water, methanol, and the deuterated analogues), see Scheme 8. A first method (A) consists of the thermal decomposition of a diazo initiator,  $\text{R-N=N-R}$ . This method has the advantage of allowing a comparison with control experiments carried out in the absence of  $\text{L/Cu}^{\text{I}}$ . However, it is not available for all possible R groups. For instance, a suitable diazo initiator is not available for the 1-carbomethoxyethyl radical,  $\text{R} = \text{CH}(\text{CH}_3)\text{COOMe}$  (a poly(methyl acrylate) model). On the other hand, this method can be used to generate tertiary radicals, e.g. the cyano- and carbomethoxy-substituted isopropyl radicals,  $^\bullet\text{C}(\text{CN})\text{Me}_2$  from azobisisobutyronitrile (AIBN) and  $^\bullet\text{C}(\text{COOMe})\text{Me}_2$  from dimethyl 2,2'-azobis(2-methylpropionate) (V-601). A second method (B) is atom transfer activation of  $\text{R-Br}$  by a  $\text{L/Cu}^{\text{I}}$  complex, which is



Scheme 8. Generation and further evolution of radicals in the absence or presence of  $\text{L/Cu}^{\text{I}}$  complexes and proton donors  $\text{HX}$ .

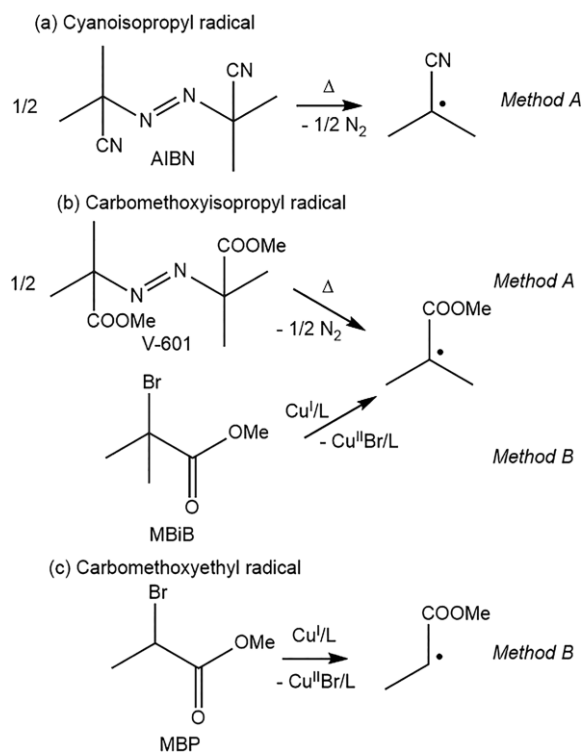


possible for all radicals (tertiary, secondary and even primary) but allows investigations only in the presence of the copper complex.

The product analysis and the determination of the percent radicals undergoing bimolecular termination, CRT and RRT ((a), (b) and (c) in Scheme 8, respectively) is complicated by the possible subsequent oligomerization of the unsaturated product from Disp ( $R^=$ ), which may be produced by processes (a) and (b), in the presence of radicals. The control experiments run in the absence of  $L/Cu^I$  and HX (method A) yield the natural distribution of bimolecular radical terminations for the corresponding radical, where the % radicals leading to Comb and Disp can be calculated respectively from the mol of R–R (times 2) and R–H (times 2). Any change from this distribution caused by the presence of  $L/Cu^I$  and/or H–X can be attributed to either CRT or RRT.

A study of the cyanoisopropyl radical generated from AIBN (Scheme 9a) in either  $CD_3CN$  at 80 °C or  $C_6D_6$  at 75 °C<sup>[30]</sup> gave results in agreement with previous investigations<sup>[31]</sup> for the control experiment, namely Comb is the major bimolecular termination mode (Disp/Comb = 10.0:90.0 or 0.11 in  $CD_3CN$ , 6.5:93.5 or 0.07 in  $C_6D_6$ ). The presence of H–X or D–X (X = OH or  $OCH_3$ , up to 200 equiv.) did not alter this ratio in the absence of copper complex. Obviously, no RRT is possible in the absence of the metal reductant. Neither did this Disp/Comb ratio change significantly in the presence of  $[Cu^I(Me_6TREN)]^+$  (in  $CD_3CN$ ) or  $CuBr/Cu^0/Me_6TREN$  (in  $C_6D_6$ ), when no H–X was present. The molar amounts used in these experiments were chosen to mimic those of the previous CRT studies in MeCN<sup>[26]</sup> and toluene,<sup>[24]</sup> respectively, but in addition, these experiments were done in thoroughly dehydrated solvents. This result is not surprising, because the stabilized tertiary cyanoisopropyl radical should not favourably interact with  $L/Cu^I$  to generate a sufficiently stable  $L/Cu^{II}-C(CN)Me_2$  intermediate, thus no significant impact of CRT is anticipated. However, the observed distribution of R in the R–H and R–R products dramatically changed in the presence of both  $L/Cu^I$  and H–X. For instance, in the simultaneous presence of  $[Cu^I(Me_6TREN)]^+$  and H–X (200 equiv.) in  $CD_3CN$ , the R ratio jumped from 10.0:90.0 (0.11) to 81.2:19.8 (4.28) (HX =  $H_2O$ ) or 76.0:24.0 (3.17) (HX =  $CH_3OH$ ) and a deuterium kinetic isotope effect (KIE) was observed (ratios of 1.09 or 0.94 were obtained in the presence of the same amounts of  $D_2O$  or  $CD_3OD$ , respectively, with a large % of D incorporation in R–H(D)). Even greater changes were measured with  $CuBr/Cu^0/Me_6TREN$  in  $C_6D_6$  (from 0.07 to 7.81 with 100 equiv. of  $CH_3OH$  and 4.36 with the same amount of  $CD_3OD$ ).<sup>[30]</sup> Similar trends (though the changes for the R–H/R–R ratio were smaller) were observed using TPMA in place of  $Me_6TREN$ , whereas the R ratio was essentially unaltered when the ligand used was 2,2'-bipyridine (BIPY), which yields the activator complex  $[Cu^I(BIPY)_2]^+$ . For instance, in  $C_6D_6$  the  $R_{R-H}/R_{R-R}$  ratio increased from 0.07 for the control experiment to only 0.13 in the presence of 100 equiv. of either  $CH_3OH$  or  $CD_3OD$ . However, a significant fraction (38.2 %) of R–D product in the experiment with  $CD_3OD$  suggested a slight contribution of RRT.

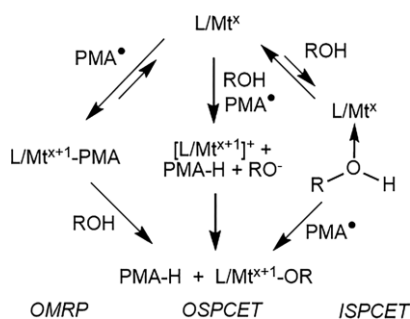
The above results demonstrate the predominance of RRT, even though the radical is not expected to form a very stable



Scheme 9. Methods used for the generation of cyanoisopropyl (a), carbomethoxyisopropyl (b) and carbomethoxyethyl (c) radicals.

organocopper(II) derivative. Actually, alternative pathways that do not require the formation of a radical complex adduct exist for RRT. These are the outer-sphere and inner-sphere proton-coupled electron transfer (OS-PCET and IS-PCET), Scheme 10, and have ample precedents in transition metal chemistry.<sup>[32]</sup> The first one involves an elementary termolecular reaction between the reductant, the proton donor and the radical, while the second one is a two-step process with coordination of the proton donor to the reducing metal complex, followed by simultaneous transfer of a proton and an electron to the external radical in the second step. However, these pathways could be discarded in the cyanoisopropyl/copper study on the basis of electrochemical considerations and of the observation of a high R–H/R–R ratio in the presence of a non-coordinating proton donor ( $Et_3NH^+$ ). DFT calculations suggested that the coordination of water to the  $L/Cu^I$  complexes is unfavourable (hence confirming that an IS-PCET pathway is unlikely) whereas addition of the  $\cdot C(CN)Me_2$  radical provides a certain stabilization, particularly for the  $Me_6TREN$  and TPMA systems. However, somewhat surprisingly, the most favoured addition mode is not the  $Cu^{II}-C$  bond formation, but rather formation of a  $Cu^{II}-N$  bond to yield  $[(L)Cu^{II}-N=C(CN)Me_2]^+$ .<sup>[30]</sup> This brings the interesting question whether (meth)acrylates radicals might also prefer to bind to the copper ion through the oxygen atom as enolates rather than form organometallic derivatives. Investigations on the carbomethoxy-isopropyl and -ethyl radicals (Scheme 9b and Scheme 9c), which are respectively models of the poly(methyl methacrylate) and poly(methyl acrylate) chains, are currently ongoing in our laboratories and full details will be published in due course. The most relevant findings, however, will be high-

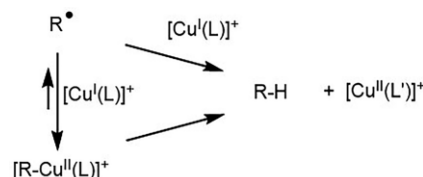
lighted here. For the methacrylate radical, the control experiment from the V-601 decomposition, both in  $\text{CD}_3\text{CN}$  at 80 °C and in  $\text{C}_6\text{D}_6$  at 75 °C, yields Disp/Comb = ca. 50:50 in agreement with the literature.<sup>[33]</sup> Like for the cyanoisopropyl radical, the product distribution is not significantly affected by the presence of proton donors in the absence of copper complex, or by the copper complex in the absence of proton donor. The product distribution is also grossly unaffected in the presence of both  $\text{Cu}^{\text{I}}/\text{Me}_6\text{TREN}$  and a large excess of  $\text{CD}_3\text{OD}$ , although a slight increase of the R-H (methyl isobutyrate) amount with slight D incorporation at the  $\beta$ -C atom indicates the intervention of a bit of RRT. However, relative to the cyanoisopropyl radical, RRT is less important. We recall that this type of radicals is also not affected by CRT. Essentially the same behaviour is shown when using the Br atom transfer activation method from methyl 2-bromoisobutyrate, MBiB, to  $\text{Cu}^{\text{I}}/\text{Me}_6\text{TREN}$  (Scheme 9b).



Scheme 10. Different pathways leading to RRT.

The termination products of the carbomethoxyethyl radical, produced by atom transfer activation of methyl 2-bromopropionate (MBP) as show in Scheme 9c, however, gave unexpected results. In strictly dehydrated solvents and without added proton donor, the termination gave a significant amount of the R-R product dimethyl 2,3-dimethylsuccinates (*meso* and *dl* mixture) but also a large amount of the saturated R-H product methyl propionate, (ca. 45 % in  $\text{CD}_3\text{CN}$  at 80 °C, ca. 80 % in  $\text{C}_6\text{D}_6$  at 75 °C) plus only a very small amount of methyl acrylate (ca. 2 % in  $\text{CD}_3\text{CN}$ , undetectable in  $\text{C}_6\text{D}_6$ ). This R-H product cannot derive from Disp (either bimolecular or CRT), because otherwise the same amount of  $\text{R}^=$  product (MA) should be formed. The only possible explanation of a strong methyl acrylate consumption could be the formation of oligomeric products by further reaction with free radicals as shown in Scheme 8, however such species were not detected. The R-H product must result from RRT, but the amount of residual water in the dehydrated solvents (which could be assessed by a Karl-Fischer titration) accounts only for a few percent, at the most, of this product. The source of the H atom cannot be the solvent itself (no D incorporation). This suggests the implication of ligand H atoms. The termination may occur either directly or via the radical-copper adduct (Scheme 11). Studies involving selectively deuterated ligands are currently ongoing. The addition of a proton donor (water, methanol) up to 200 equiv. per radical to the system does not significantly change the relative amount of R-H, but a large fraction of R-D is obtained when using  $\text{D}_2\text{O}$  or  $\text{CD}_3\text{OD}$ , showing that external proton sources compete effec-

tively in RRT. The DFT calculations indicate a preference for the formation of a  $\text{Cu}^{\text{II}}\text{-C}$  bond relative to a  $\text{Cu}^{\text{II}}\text{-O}$  bond for both tertiary and secondary carbomethoxy-substituted radicals.



Scheme 11. RRT with implication of the ligand H atoms.

These observations lead to a number of considerations and questions. It now seems quite well established that the atom transfer activation of a  $\text{R-CH}_2\text{-CHBr-COOMe}$  function ( $\text{R} = \text{H}$  or PMA), for very active catalysts such as  $\text{Cu}^{\text{I}}/\text{Me}_6\text{TREN}$ , leads to a significant fraction of spontaneous bimolecular terminations for the resulting secondary radical and that this occurs mostly by combination.<sup>[26]</sup> Indeed, the combination product was observed in significant amounts from the activation of MBP (Scheme 9c). The presence of a CRT mechanism in this model system could not be clearly established. If it occurs, it seems likely that it also leads to the Comb product. Rather, the major additional termination pathway is RRT, even in the absence of an external proton source, but the H atom is apparently provided by the ligand. This obviously opens the question of whether the observed CRT phenomenon in the presence of monomer<sup>[12–13,18]</sup> is real or whether the additional terminations may just be the result of RRT. While CRT is catalytic in copper, RRT is stoichiometric and leads to ligand modification (Scheme 11), but a continuous flux of new radicals may serve the purpose of regenerating the  $\text{Cu}^{\text{I}}$  species, making the stoichiometric process look like a catalytic one. Further studies aiming at a better understanding of this complex system are ongoing.

## 5. Conclusions

We may only draw partial conclusions on this ongoing and complex mechanistic study of the metal effect on termination in radical polymerization processes. They allow, however, to highlight the intricate occurrence of various phenomena and to argue about the conditions that may allow reducing their incidence on the quality of metal-mediated chain growth for macromolecular engineering.

A first and most important conclusion is that, although metal complexes are a most powerful tool to reduce the impact of terminations in a radical polymerization system and to allow controlled chain growth, they can also promote a number of side reactions, most of them negatively affecting the quality of this control. This is at least true for copper, one of the most investigated metals so far. Iron-mediated CRT was also reported in one contribution,<sup>[16]</sup> but whether ATRP catalysts based on other metals are also able to promote CRT, and why, are questions remaining without answer for the moment and further investigations are needed. Catalyzed radical termination (CRT) can play a significant role in the controlled polymerization of

acrylate monomers.<sup>[12–13,18]</sup> One well-established fact is that CRT involves an organometallic intermediate, i.e. an organocopper(II) complex for a copper(I)-catalyzed process, but the intimate mechanism and even the nature of the products resulting from this reaction is not yet fully established. Indeed, the most recent results highlighted in section 4.2 open the question of whether the phenomenon results from reductive radical termination (RRT) instead. While RRT was (initially) supposed to occur only in the presence of an external H donor source such as water, very recent results have highlighted the fact that the ligand itself may be involved as proton donor. Additional studies are necessary in order to bring full light onto this system. These will involve structural variations on the ligand, including selective deuteration, elucidation of the nature of the termination products for other radicals, isolation and characterization of the copper(II) complexes with modified ligands (i.e. L' in Scheme 11) and possibly also isolation and reactivity studies of the proposed organocopper(II) intermediate. Once the nature of the occurring phenomena are completely elucidated, new ligands capable of blocking the CRT and RRT pathways, while still leading to high ATRP activity, may be developed. For the moment, the simplest and most effective strategy to minimize the impact of unwanted additional terminations is to use very active ATRP catalysts at reduced concentration levels. Under these conditions, the Cu<sup>II</sup> deactivator that stoichiometrically forms for every radical termination event is continuously reduced back to the activator complex (i.e. "activator regenerated by electron transfer",<sup>[34]</sup> known as ARGET-ATRP, "supplemental activator and reducing agent"<sup>[35]</sup> known as SARA-ATRP, or other low ppm Cu systems<sup>[36]</sup>). This is because the ATRP rate scales with the [Cu<sup>I</sup>]/[Cu<sup>II</sup>] ratio and is independent on [Cu<sup>I</sup>]. Hence, for very active catalysts (large values of K<sub>ATRP</sub>), [Cu<sup>I</sup>] can be kept very small. This minimizes all Cu-induced radical termination (CRT or RRT) that are first-order in respect to [Cu<sup>I</sup>] and consequently diminish [R-Cu<sup>II</sup>(L)].

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**Keywords:** Copper · Catalysis · Controlled radical polymerization · Radical termination

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