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Insights into Relevant Mechanistic Aspects about the Induction Period of Cu^0 / Me$_6$TREN - Mediated Reversible - Deactivation Radical Polymerization

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There is a controversial debate about the mechanism of the Cu^0-catalyzed radical polymerization. Herein, a comparative analysis of a series of reactions catalyzed by different valent copper shows the induction period and the subsequent autoaccerlated polymerization of Cu^0/Me$_6$TREN - catalyzed system originate from the accumulation of soluble copper species, and Cu^I is still a powerful activator in its disproportionation favored condition.

Atom transfer radical polymerization (ATRP) is one of the most commonly used reversible-deactivation radical polymerization (RDRP) techniques for designing and synthesizing polymers with well-defined composition, functionalities, and architecture[1–3]. The key step is to establish activation-deactivation equilibrium between a lower oxidized transition metal/ligand complex (Cu^{I}X/L, X typically stands for Br or Cl) and an alkyl halide to generate a growth radical and a higher oxidized transition metal/ligand complex (Cu^{II}X$_2$/L). Due to the existence of the persistent radical effect (PRE) [4] in traditional ATRP, resulting in the loss of chain end functionalities and accumulation of copper, several alternative techniques have been developed recently, including activators regenerated by electron transfer (ARGET) ATRP[5], initiators for continuous activator regeneration (ICAR) ATRP[6], electrochemically mediated ATRP[7], and photochemically mediated ATRP[8].

Another technique, developed by Percec et al.[9], employs the metallic copper (Cu^0) as activator in presence of proper solvents and ligands, which was termed as single electron transfer living radical polymerization (SET-LRP). The detailed mechanism of SET-LRP has been the subject of controversial debate with disagreement over the pathway of the Cu^I species generated in the activation steps and the subsequent disproportionation extent. Originally, proposed by Percec et al., the activation of the dormant species occurs by Cu^0 species through an outer-sphere electron-transfer (OSET) process. The generated Cu^{I}X/L complexes disproportionate 'spontaneously'
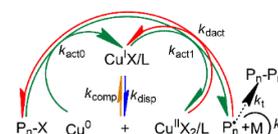
Scheme 1. Possible reactions in Cu^0-mediated RDRP

into highly reactive 'nascent' Cu^0 and Cu^{II}X$_2$/L species. The formation of deactivator does not involve bimolecular termination or PRE as reported in classical ATRP. However, another interpretation, reported by Matyjaszewski et al., is that the metallic copper acts as a supplemental activator and reducing agent (SARA), and Cu^{I}X complexes, instead of Cu^0, activate the dormant species via the inner-sphere electron-transfer (ISET) process. Cu^0 mainly acts as reducer of the comproportionation with Cu^{II}. Activation by Cu^I occurs at a slow rate and disproportionation of Cu^I is negligible[10,11]. All of the possible reactions are outlined in Scheme 1.

Continued efforts have been made to identify at which end of the spectrum the 'truth' lies. Unlike those two incompatible interpretations, some intermediate explanations have also been proposed. Harrisson et al. [12–14] concluded that both Cu^{I}X/L and Cu^0 act as activators and both disproportionation and comproportionation coexist with overall effect of disproportionation and comproportionation depending on the equilibrium constant and the concentrations of Cu^{I}X/L and Cu^{II}X$_2$/L in nonpolar and polar solvents. Wang et al.[15] proposed that the mechanism behind Cu^0/PMDETA-mediated RDRP with added CuBr$_2$ lies between the competition and equilibrium results of SET-LRP and SARA ATRP.

Remarkably, understanding the detailed process about the activation and disproportionation of the copper species in the initial stage of the Cu^0-mediated RDRP is of great interest and crucial to distinguish the mechanism[12,14]. One of the unique features in this stage is that an apparent period of slow reaction rate with few monomer conversion (similar as induction period) is observed in the early stage of various Cu^0-mediated RDRP systems[16–22]. For the extensively studied system: Cu^0(wire)/Me$_6$TREN in DMSO, Haddleton et al.[17], Percec et al.[21,23–25], Whittaker et al.[22] and Guliashvili et al.[15] independently reported the presence of the induction period (30~50min) at the initial stage of the polymerization of MA with even a rigorous deoxygenation process. Similar results are also observed

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in other solvents[26,27]. Initially, Haddleton *et al.*[17] observed the induction period was followed by an exothermic reaction due to the inefficient heat transfer, resulting in a rapid raise in temperature and a significant quick polymerization rate. Moreover, both the induction time and exothermic effect were dependent on the surface area of copper wire. Specifically, bigger surface area of copper wire leads to a shorter induction period and larger amount of generating heat. An alternative explanation for the induction time, proposed by Percec *et al.*[24,25], is the existence of the passivating layer (e.g., Cu_2O) from the surface of commercial metallic copper wire, which, thereby, can be eliminated by activating the commercial Cu^0 wire. The absence of initial induction period was reported by activating the copper wires with hydrazine hydrate[24] or acids[25].

Despite the explanation by copper oxides layer hindrance is now widely accepted, it still cannot account for all experimental phenomena. For instance, the induction period can be diminished by using larger surface area of copper wire[17] or adding a small quantity of deactivators[16,17,22]. This leads us to ask what else is occurring during the initial stage beyond the slow dissolution of copper oxides layer. To address this question, all of the relevant processes (including the activation, deactivation, disproportionation, comproportionation, propagation and termination) need to be studied and considered under a real polymerization situation, as the SET-LRP has been ascribed as a complex system where no one component can be truly viewed on its own, but only in context of its effect on other parts of the system[28]. Herein, we investigated the observed induction time by conducting a series of Cu^0-mediated RDRP of MA in DMSO at 25 °C with different valent coppers and tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as the ligand. This work aims to evoke the attention to this problem beyond the current explanation and try to shed light on the underlying mechanism involved in the Cu^0-mediated RDRP.

Followed by the copper oxides layer hindrance explanation, we tried to activate the commercial copper wire by pre-equilibration. Specifically, commercial copper wire was exposed to a degassed polymerization solution (the ratio of MA / EBriB / Me_6TREN is 100: 1: 0.18 in DMSO) for 30 min (the length of the induction period in DMSO). After a brief rinse with DMSO, the 'activated' copper wire was transferred to another freshly degassed reaction solution. With sampling the reaction at the designed time points and determining the molecular weight and conversion by SEC and NMR, we noticed the identical reaction kinetics obtained using the untreated and pre-treated copper wires and the length of the induction period was still 30 min (Figure 1). This result was unexpected, however, it was in consistent with the previous study of the activation of copper wire in MeCN[12]. One may argue that this unexpected results are originated
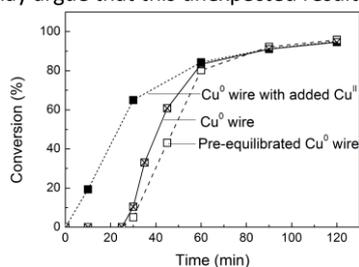
Figure 1. Kinetics plots of polymerization using untreated copper wire with and without additional Cu^{II}, and preequilibrated copper wire.

from the failure of the strict experimental operation, which initially was also one of our concern, as the induction periods in the 'activated' copper wires catalysed systems were still observed (Figure S1, Table S1). However, under the identical reaction condition except the addition of a small quantity of $CuBr_2$ (0.05 equiv. relative to initiator) at the beginning of the reaction, the absence of the induction period was observed (Figure 1) indicating that the observed induction period is stem from the internal reaction system instead of the external operation condition.

These perplexing results drove us to reconsider about all the possible reactions involved in this initial stage as outlined in Scheme 1. Considering that it is about the auto-acceleration after an induction period, our attention was therefore drawn to the mutual conversion of the catalysts (Cu^0, Cu^I and Cu^{II}) and their resulted relative concentrations. It should be noted that, under real polymerization condition, there are two equilibriums – activation / deactivation equilibrium and disproportionation / comproportionation equilibrium – coexisted. Thereby, even if the solvent and ligand thermodynamically favour disproportionation over comproportionation ($K_{disp} \gg 1$, scheme 1), the relative concentrations Cu^I and Cu^{II} species may not approach to disproportionation equilibrium ratio ($[Cu^{II}]/[Cu^I]^2 = K_{disp}$), since this ratio may far from that in the activation/deactivation equilibrium[12,16]. Although the DMSO and Me_6TREN are commonly used as solvent and ligand favouring activation with Cu^0 and disproportionation (with a relatively high k_{act0} and k_{disp}), the preferred activator (Cu^0 or Cu^I species) and extent of the disproportionation depend on both the relevant reaction rate constants and the relative concentrations of the copper species during polymerization. The synergistic effect of the two equilibriums makes the mechanism more complicated and we cannot isolate them from each other as they are in a complex system.

We start the investigation from the polymerization of MA using acid treated copper wire wrapped around the stirring bar, EBriB, Me_6TREN, and DMSO as catalyst, initiator, ligand and solvent respectively, with the feed ratio of [MA] : [EBriB] : [Me_6TREN] = 100 : 1 : 0.18 (entry 1-6 in Table S2). The polymerization is well controlled. Specifically, the recorded kinetic plot (Figure 2a) was first order with respect to monomer conversion, demonstrating a living polymerization, and the k_p^{app} was found to be 0.03 min^{-1}. 93% monomer conversion is reached within 2 h. The evolution of the number average molecular weight (M_n) and polydispersity ($Đ$) with respect to theoretical molar mass are depicted in Figures 2b. Figure 2c displays the SEC traces of the polymerization process with a narrow molecular weight distribution ($Đ$<1.1). However, the presence of a 30 min induction period was observed. Harrisson et al.[22] attributed the initial slow rate of reaction and the subsequent auto-acceleration to autocatalysis through studying the conversion of initiator. This conclusion cannot be applied directly here, since the reaction conditions are different and the conversion of monomer instead of initiators was monitored here, but it is helpful to understand the reason of the induction period.

It is obvious that the reaction must start from the activation of initiator by Cu^0 species since there is no other mechanism available to activate the initiator and produce the Cu^I species under this reaction condition without the additional Cu^{II} species. Once there are new formed copper species, it would be crucial to the reaction

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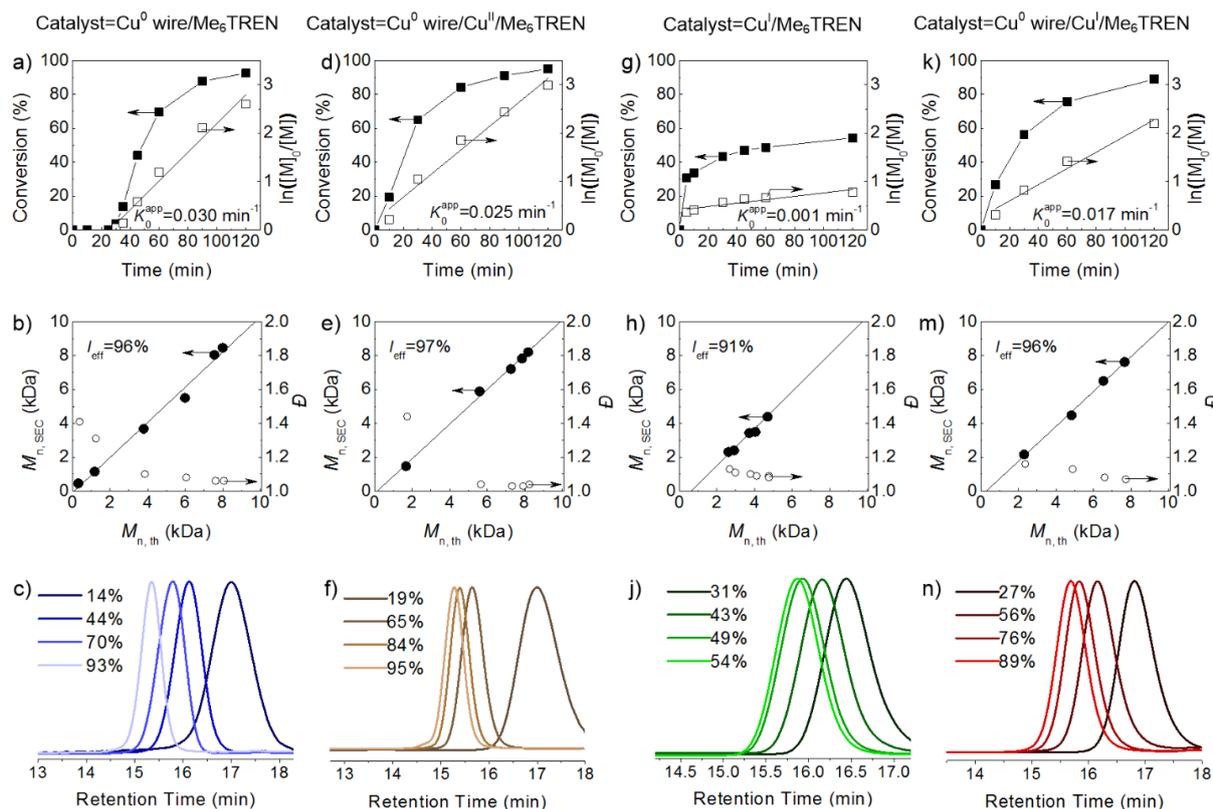
Figure 2. Kinetic plots of conversion and $\ln([M]_0/[M])$ versus time (a, d, g, k), plots of number-average molecular weights ($M_{n,\,SEC}$) and polydispersity (Đ) versus theoretical number-average molecular weights ($M_{n,\,th}$) (b, e, h, m), and the evolution of molecular weight monitored by SEC (c, f, j, n) for polymerization of MA catalyzed by Cu^0 wire(a, b, c), Cu^0 wire/Cu^{II} (d, e, f), Cu^I (g, h, j) and Cu^0 wire/Cu^I (k, m, n) with Me_6TREN as ligand in DMSO at 25 °C

process how these different valent copper species are mutually converted and which kinds of copper species are accumulated to contribute the auto-acceleration. In principle, accumulation of all of the three kinds of the copper species (Cu^0, Cu^I and Cu^{II}) produced during the reaction may have the auto-catalytic effect. Specifically, accumulation of Cu^I might accelerate the polymerization via the reaction with alkyl halide. Similarly, accumulation of Cu^{II} may result the comproportionation with metallic copper to form 2 equiv. of Cu^I which activate the reaction subsequently. Alternatively, highly reactive 'nascent' Cu^0 may also be 'accumulated' by the 'instantaneously' disproportionation of Cu^I to accelerate the reaction. But, accumulation of Cu^0 is a pseudo-concept, since the highly reactive 'nascent' Cu^0 has been assumed either to be oxidized or precipitated as soon as it formed[29]. Considering there is slow rate of polymerization occurred during the initial stage, it is reasonable to assume that the relative concentrations of different copper species are far from the polymerization equilibrium (activation/deactivation) ratio. So we hypothesized that disproportionation equilibrium dominates the mutual conversion of the different valent copper spices and accumulate the dissolved copper species in the initial stage, and once the [Cu^I]/[Cu^{II}] ratio approach to the polymerization equilibrium ratio, the polymerization would be accelerated.

We started the investigation of this hypothesis from the addition of different copper species. Firstly, a small quantity of $CuBr_2$ (0.05 equiv relative to EBriB) was added to the previous mentioned Cu^0-mediated RDRP. The polymerization is still well controlled (entry 7-

11 in Table S2 and Figure 2d-f). The living polymerization nature was demonstrated from the first order kinetic plot with respect to monomer conversion (Figure 2d), and the k_p^{app} was found to be 0.025 min^{-1}. 95% monomer conversion is reached within 2 h. The evolution of the number average molecular weight (M_n) and Đ with respect to theoretical molar mass are depicted in Figures 2e. The SEC traces of the polymerization process with a narrow molecular weight distribution (Đ<1.1) are shown in Figure 2f. Most importantly, as previously observed, the polymerization was started at the very beginning of reaction and the induction period was absent. The most likely reason is the added Cu^{II} species participate in the mutual conversion of different valent copper species at the beginning of the reaction either through the comproportionation with copper metal or deactivation. However, the latter pathway should in principle slow down the polymerization rate instead of accelerate it, since the polymerization rate is proportional to radical concentration which is decreased due to the deactivation. Therefore, the comproportionation dominates in this case. It need to be mentioned that in a real system, the preferred equilibrium direction depends not only on the absolute rate constants, but also on the relative concentrations of the different copper species. In this case, the excess Cu^{II}, ligand and copper metal shifted the disproportionation equilibrium towards the Cu^I species, In other words, the comproportionation was kinetically favoured in the initial stage and contributed positively to the build-up of polymerization equilibrium. It should be noted that the comproportionation of Cu^{II} with copper

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metal will form 2 equiv. of Cu^I, resulting the dissolved copper species are accumulated. Therefore, it can be deduced that the disappearance of induction period is because of the instant accumulation of dissolved copper species (Cu^I and Cu^{II} species). But the details about the 'actual' activator and the extent of the disproportionation of Cu^I in this unsteady initial stage still remain unclear.

Most studies devoted to clarify these details based on model experiments[30], which, to some extent, are not able to faithfully mimic the true polymerization conditions due to the nature of the complex system, and the results are conflicting. In order to further understand these unclear mechanisms based on the true polymerization conditions, the polymerization of MA initiated with EBriB in DMSO at 25 °C using Cu^I/Me_6TREN in the absence and presence of Cu^0 wire were conducted. In both cases, the initial induction period were disappeared (entry 12-21 in Table S2 and Figure 2g-n) as expected, because of the increase of dissolved copper species. However, the kinetic profiles are significantly different. For the MA polymerization catalysed by Cu^I/Me_6TREN in the absence Cu^0, the monomer conversion is *ca.* 30% within 5 min but stops with final conversion less than 60 %. Addition of fresh Cu^I/Me_6TREN solution, however, allows the polymerization proceed towards conversion as high as 86% (Figure S2), which is in agreement with previous study[16], using added Cu^0 to further increase the monomer conversion. This result indicates that the polymerization stopes should be resulted from the accumulation of Cu^{II} species by the disproportionation of Cu^I species instead of the radical termination, e.g. PRE, since the polymerization can be restarted. In contrast, for the MA polymerization catalysed by Cu^I/Me_6TREN in the presence Cu^0, the recorded kinetic plot (Figure 2k) was first order with respect to monomer conversion with the k_p^{app} of 0.017 min^{-1}, and 89% monomer conversion was achieved within 2 h. The higher monomer conversion obtained in the Cu^I/Me_6TREN catalysed system with additional Cu^0 further demonstrates the excessive accumulation of Cu^{II} is avoided due to the comproportionation with Cu^0. In other words, in the Cu^I/Me_6TREN catalysed polymerization of MA, the disproportionation effect (equilibrium shifted to Cu^{II}) on the time scale of the reaction contributes negatively to the build-up of polymerization equilibrium, but this negative effect can be avoided by adding Cu^0 to shift the equilibrium back to Cu^I. Thereby, Cu^I is still a powerful activator even in its disproportionation favoured reaction condition (in presence of Me_6TREN as ligand and DMSO as solvent) according to our investigation, indicating that both SET-LRP and SARA ATRP mechanisms are coexisted.

In summary, the current agreed hindrance of a passivating layer (Cu_2O) on commerical copper wires cannot account for the elimination of the observed induction period in the Cu^0/Me_6TREN - mediated RDRP of MA by addition of Cu^{II}. The current study proves that the induction period and the subsequent autoaccerlated polymerization orignate from the accumulation of dissolved copper speices (Cu^I and Cu^{II}) to approach the activation/deactivation equilibrium. Cu^I is verified as also a powerful activator in even its disproportionation favored condition.

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