

RSC Advances



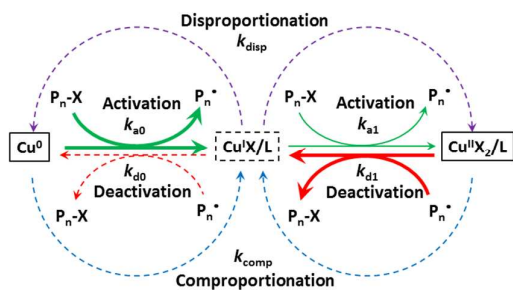
This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Table of contents:



The mechanism of Cu^0 & Cu^{II} /PMDETA catalyzed polymerization is attributed to the competition and equilibrium of the traditional ATRP and SET-LRP models.

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Cu⁰&Cu^{II}/PMDETA - mediated reversible - deactivation radical polymerization. Is it ATRP or SET-LRP?

Yongsheng Gao^{ab}, Tianyu Zhao^a and Wenxin Wang*^a

There is a controversial matter of debate as to the mechanism of the Cu⁰ catalyzed radical polymerization. Two models exist, one based upon ATRP whilst the other upon SET-LRP. Here we present new experimental results and insights into the nature of this polymerization. A good controlled/living polymerization was eventually obtained by Cu⁰&Cu^{II}/PMDETA-mediated radical polymerization. A comparative analysis shows that the mechanism behind this reaction lies between the competition and equilibrium results of SET-LRP and ATRP.

Reversible-deactivation radical polymerization (RDRP)¹ methods play an important role in the synthesis of polymers requiring well controlled structures and functionalities. The most important step for the RDRP is to establish the equilibrium between the dormant and active species. There are several methods one can use to achieve this, including nitroxide mediated polymerization (NMP)², reversible addition- fragmentation chain transfer polymerization (RAFT)³, atom transfer radical polymerization (ATRP)⁴ and single electron transfer living radical polymerization (SET-LRP)⁵.

ATRP was developed in 1995 by Matyjaszewski and coworkers^{4a}, in which equilibrium was established through a reaction of a lower oxidized transition metal, e.g. Cu^I, and an alkyl halide. The resulting higher oxidized transition metal, e.g. Cu^{II}, and the radical can also react reversely to form the alkyl halide. SET-LRP was proposed in 2006 by Percec and coworkers^{5b}, where the alkyl halides are catalyzed by Cu⁰, to generate a radical and Cu^I, which will disproportionate into Cu⁰ and Cu^{II} spontaneously. The resulting Cu^{II} will act as the deactivator to return the radical to the alkyl halide. However, there are two models, i.e. supplemental activator and reducing agent (SARA) ATRP (or previously proposed activators regenerated by electron transfer (ARGET) ATRP) and SET-LRP, gave conflicting assumptions about the mechanisms of the Cu⁰ involved RDRP.

The most controversial issues of the two mechanisms lie in these four competitions¹: (a) the activation of alkyl halides by Cu⁰, which occurs by outer-sphere electron transfer (OSET)^{5a, 6}, and Cu^I, which occurs by inner-sphere electron transfer (ISET)^{1, 7}; (b) the activation and disproportionation of Cu^I; (c) the activation and comproportionation of Cu⁰; (d) the equilibrium of disproportionation and comproportionation. The model of SARA ATRP assumes that Cu⁰ plays the role of a supplemental activator and reducing agent, whilst the activation of Cu⁰ and the disproportionation of Cu^I are negligible (Scheme S1)⁸. The model of SET-LRP determines that Cu⁰ is the major activator and the resulting Cu^I disproportionate to Cu⁰ and Cu^{II}, whilst the activation of Cu^I and comproportionation of Cu^{II} and Cu⁰ are negligible (Scheme S2)⁹. Each of these two assumptions is supported by several experiments, which make the situation more complex. Through these debates, the opportunity arises to thoroughly and carefully evaluate every detail involved in the process, and find at which end of the spectrum the 'truth' lies.

The core problems of these controversial issues are how, and to what extent, these coppers of different valences stabilize in solution and participate in the reaction; factors greatly affected by the nature of the ligand used. Much literature has reported that both tridentate nitrogen ligands: N,N,N',N',N''-pentamethyldiethylenetriamine (PMDETA)¹⁰, and tetradentate nitrogen ligands: Tris[2-(dimethylamino)ethyl]amine (Me₆TREN)¹¹, have been used in the ATRP system successfully to synthesize well-controlled polymers, such as poly(methyl acrylate) (PMA). However, to the best of our knowledge, the polymerization of methyl acrylate (MA) using PMDETA as a ligand in SET-LRP system was seldom reported, most of them were carried out using Me₆TREN as a ligand¹². Hence, if PMDETA, a commonly used ligand in the ATRP reaction system, is introduced into the SET-LRP system to polymerize MA, the results should give us a new insight into the mechanism behind the reaction and allow us to examine whether it follows an ATRP or SET-LRP mechanism. Under this hypothesis, we designed a series of experiments using PMDETA as a ligand combined with copper of

COMMUNICATION

different valences to form the catalysts, which was used to polymerize methyl acrylate (MA).

Table 1. Reaction results for the polymerization using PMDETA and Me₆TREN as ligands in presence of different valent coppers^{a)}

Catalyst ^{b)}	Ligand	Time [min]	$M_{n,th}$ [KDa]	$M_{n,SEC}^{c)}$ [KDa]	PDI ^{e)}	Conv ^{d)} [%]	
1		35	1.18	1.15	1.31	13.75	
2		45	3.79	3.68	1.10	43.97	
3	Cu ⁰	Me ₆ TREN	60	5.99	5.50	1.08	69.67
4		90	7.56	8.05	1.06	87.85	
5		120	8.00	8.46	1.06	92.57	
6		7	1.49	501.28	1.99	17.36	
7	Cu ⁰	PMDETA	10	2.47	191.74	3.31	28.74
8		20	5.04	28.66	12.05	58.50	
9		60	5.22	5.48	47.33	60.58	
10		10	2.39	2.06	1.20	27.71	
11		20	2.63	2.86	1.12	30.56	
12	Cu ^I	PMDETA	40	3.53	3.73	1.12	41.06
13		60	4.85	4.20	1.12	56.33	
14		120	5.80	5.11	1.12	67.32	
15		420	7.16	6.19	1.13	83.16	
16 ^{e)}	Cu ^{II}	PMDETA	1260	--	--	--	
17		10	0.83	0.64	1.22	9.64	
18		20	1.29	1.19	1.26	15.01	
19	Cu ⁰ &Cu ^{II}	PMDETA	40	2.92	2.62	1.25	33.92
20		60	3.79	3.60	1.16	43.97	
21		90	4.36	4.38	1.14	50.66	
22		120	5.17	5.25	1.13	60.00	

^{a)} Reaction condition: [M] : [I] : [L] = 100 : 1 : 0.18, [M] = 5.50 M; M = MA, I = EBriB, Solvent = DMSO, T = 25 °C; ^{b)} Cu⁰ = pretreated Cu(0)-wire (l = 5 cm, d = 1 mm), Cu^I = CuCl (0.18 eq), Cu^{II} = CuBr₂ (0.05 eq); ^{c)} M_n and PDI were characterized using size exclusion chromatography (SEC) equipped with an RI detector; ^{d)} Vinyl conversion was confirmed using ¹H NMR; ^{e)} No polymer was formed within 1260min.

Our first target was to identify where the difference lies between the two polymerization processes which have used PMDETA and Me₆TREN as ligands respectively. It can be clearly seen that the Cu⁰/Me₆TREN catalyzed system (entry 1-5, table 1), which is the typical SET-LRP protocol, can give a good living polymerization. The $M_{n,SEC}$ fit the $M_{n,th}$, and the conversion reached above 90% within 1.5h (Figure S1). In contrast, the Cu⁰/PMDETA catalyzed system (entry 6-9, table 1) gives an ill-controlled polymerization process (Figure S2). During the initial period, the chain propagates at an extremely high speed (the molecular weight reached to 500 KDa with 7 min), which is similar to free radical polymerization (FRP) without the deactivation of Cu^{II}. This means that the Cu⁰ can activate the initiators very fast, and hence generate radicals, which can react with monomers rapidly to form the high molecular weight polymers. From this we can decidedly draw the conclusion that no Cu^{II} species are formed either by disproportionation or by activation of Cu^I complexes at the beginning of polymerization. However, in the later stage, the $M_{n,SEC}$ decreased slowly, accompanied with the PDI growing to a very large level, suggesting that some smaller

molecules are formed during this stage. Therefore, the Cu^{II} species are formed in this period and deactivate the active species to dormant species (from R-M[•] to R-M-X). These results are in agreement with Matyjaszewski and coworkers' work¹³, despite the different reaction condition. There are only two paths to form Cu^{II} complexes from Cu^I complexes, and it appears not to be due to the rapid disproportionation proposed by SET-LRP model, because Cu^{II} complexes are formed with a lag behind the activation of Cu⁰. Hence, here we hypothesized that Cu^I complexes convert into Cu^{II} complexes though the activation of alkyl halide, namely the activation path (Scheme S3).

In order to confirm this hypothesis, we designed another experiment which used the Cu^I/PMDETA as the catalysis system, in the absence of the Cu⁰ species (entry 10-15, table 1) which is the typical ATRP protocol, and hence, polymerized via the ATRP mechanism (Scheme S4). The polymerization is well controlled but much slower than that catalyzed by Cu⁰ (Figure S3), suggesting that the activation of Cu^I complexes alone is in a much slower manner, unlike the fast catalysis speed of Cu⁰. On the other hand, the polymerization rate is faster within the first 10 min than in the later stage, which is due to the persistent radical effect (PRE)^{4b}, typical of Cu^I-catalyzed ATRP. The existence of PRE confirms that Cu^{II} species are formed by activation of Cu^I/PMDETA rather than by disproportionation of Cu^I/PMDETA.

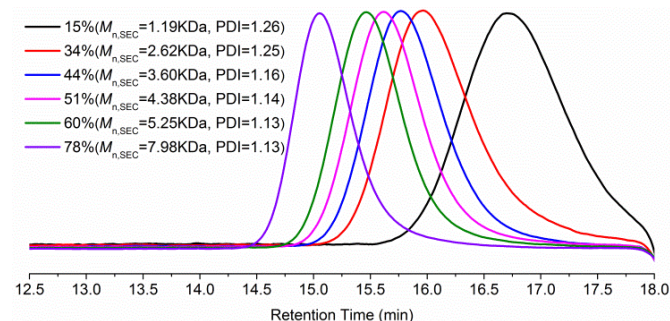


Figure 1. SEC trace of Cu⁰&Cu^{II}/PMDETA catalyzed polymerization (entry 17-22 in Table 1)

Furthermore, we aimed to confirm the role of Cu⁰ and Cu^I species in the system involving Cu⁰ catalysis and obtain a well-controlled polymerization. To this end, the Cu^{II} species was added into the initial reaction mixture. A good controlled/living polymerization process was obtained with addition of a little CuBr₂ (entry 17-22 in table 1, Figure 1). The PDIs remained low for the whole process, and the $M_{n,SEC}$ fitted well with the $M_{n,th}$ (Figure 2a). Similar with the Cu⁰/PMDETA catalyzed system, the polymerization was started at the very beginning, but in a homogeneous and slower manner in this Cu⁰&Cu^{II}/PMDETA catalyzed system (Figure 2b), and contrary to the Cu^I/PMDETA catalyzed system, the PRE effect did not occur in this Cu⁰&Cu^{II}/PMDETA system. Take both these two phenomena into consideration, we can safely deduce that Cu⁰ activates initiators directly to generate radicals and then pre-added Cu^{II} species deactivate radicals in time to form the equilibrium between the activation and deactivation. However, both the activation of Cu⁰ and the deactivation of Cu^{II} species can produce Cu^I species and hence the concentration of Cu^I species increased as the polymerization proceeded. This increase enhanced the participation of activation of the Cu^I species in the later stage. Therefore, the activation of alkyl halides by both Cu⁰ and Cu^I complexes are taking place in this Cu⁰&Cu^{II}/PMDETA system. Since some literature reports that the ligands have reducibility, and can reduce Cu^{II} to Cu^I which would

affect the mechanism of this reaction, a $\text{Cu}^{\text{II}}/\text{PMDETA}$ system was designed and no Cu^0 or Cu^{I} existed in the initial mixture (entry 16, table 1). No polymer was synthesized within 1260 min, which clearly shows that the reducibility of PMDETA is negligible.

The results in Table 1 therefore indicate that well-controlled polymerizations are obtained by both the $\text{Cu}^0/\text{Me}_6\text{TREN}$ catalyzed system and the $\text{Cu}^{\text{I}}/\text{PMDETA}$ catalyzed system, which are based on the SET-LRP and ATRP mechanism, respectively. The $\text{Cu}^0/\text{PMDETA}$ catalyzed system performed an ill-controlled polymerization, but interestingly, after the incorporation of a little amount of Cu^{II} in the initial mixture, a good controlled polymerization was obtained. It seems that Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$ catalyzed system neither obeys a typical ATRP process nor a typical SET-LRP process. This can be explained by the following three reasons. Firstly, the activation of alkyl halides by both Cu^0 and Cu^{I} are taking place in this system, which is the key difference from ARGET ATRP that claimed Cu^0 is the reduce agent to form Cu^{I} with Cu^{II} instead of the activator¹³, although Cu^0 involved ARGET ATRP was later named as SARA ATRP that claimed Cu^0 is the reduce agent and supplement activator¹. Secondly, in the early stage, Cu^0 is the primary activator and reacts with initiator, while the reaction between the initiator and the Cu^{I} generated by the comproportionation of Cu^0 and Cu^{II} is negligible. Thirdly, Cu^{I} species convert into Cu^{II} species mainly through the activation path, which occurred during the later stages, while the disproportionation is negligible, similar to the ATRP process.

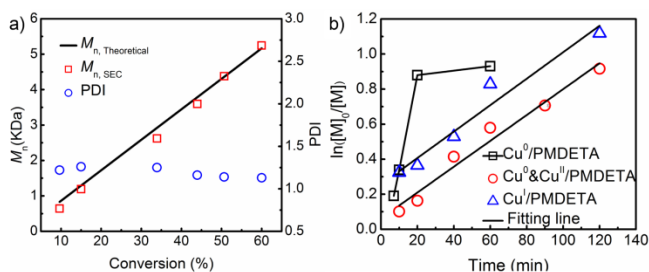
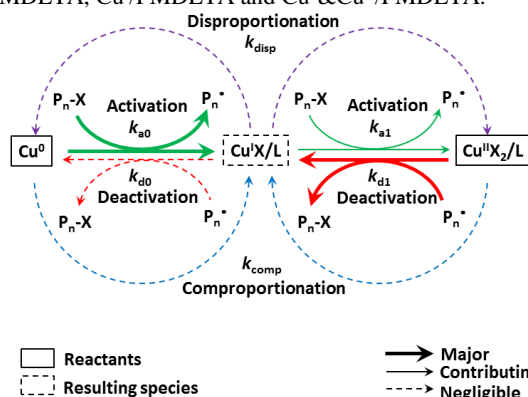


Figure 2. (a) Dependence of molecular weights and polydispersities on conversion during the Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$ catalyzed reaction, (b) Kinetics of the polymerization under three different catalyst systems: $\text{Cu}^0/\text{PMDETA}$, $\text{Cu}^{\text{I}}/\text{PMDETA}$ and Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$.



Scheme 1. The mechanism of Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$ catalyzed polymerization

The deviation of mechanism from either the typical ATRP or the typical SET-LRP is mainly attributed to the ligand. The only difference between the Me_6TREN and PMDETA is that the PMDETA is a tridentate nitrogen ligand, which forms a tetrahedral structure with Cu^{I} and square-pyramidal configuration with Cu^{II} ,¹⁰

while the Me_6TREN is a tetradentate nitrogen ligand and forms a trigonal pyramidal structure with Cu^{I} and trigonal-bipyramidal structure with Cu^{II} .^{12a} Since the tetrahedral structure of $\text{Cu}^{\text{I}}/\text{L}$ is favored to stabilize the Cu^{I} species, and Cu^{II} prefers a trigonal-bipyramidal structure¹⁰, the PMDETA is favored to stabilize Cu^{I} and Me_6TREN is favored to stabilize Cu^{II} . Hence unlike the Me_6TREN in SET-LRP, the ligand, PMDETA, changes the probability and extent of the disproportionation of Cu^{I} , and the stabilities of $\text{Cu}^{\text{I}}/\text{L}$ and $\text{Cu}^{\text{II}}/\text{L}$. This difference causes a change in the results of the competitions and equilibriums. As a result, the mechanism deviates from the traditional mechanism.

The plausible mechanism of the Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$ catalyzed system is the combination of the typical ATRP and the typical SET-LRP (Scheme 1). This mechanism is not the simple addition of these two different mechanisms. Actually, it is the result of competition and a state of equilibrium between the SET-LRP and ATRP, since the activation of alkyl halides by both Cu^0 and Cu^{I} occur in this polymerization system. It should be noted here that this mechanism is very similar to SARA ATRP. In essence, SARA ATRP is also a hybrid mechanism, since it admits that both Cu^0 and Cu^{I} complexes can activate the alkyl halide, which means that electron can be exchanged through both OSET and ISET processes, and these two processes are the main features of ATRP and SET-LRP. However, the study of the SARA ATRP is mainly focused on the Me_6TREN based system; in contrast, the PMDETA was used in our reactions. The difference between Me_6TREN and PMDETA changes all of the aforementioned competitions. Moreover, the SARA ATRP claims that Cu^0 is a supplemental activator and $\text{Cu}^{\text{I}}/\text{Me}_6\text{TREN}$ is the major activator, although it is still a controversial debate in the LRP field as mentioned previously. However, as we stated in the previous section, after comparative analysis, Cu^0 is the primary activator in the initial stage. Therefore, it would be more accurate if we describe it as the competition and equilibrium of ATRP and SET-LRP instead of SARA ATRP.

Conclusions

In conclusion, the mechanism of the good controlled/living polymerization obtained in Cu^0 & $\text{Cu}^{\text{II}}/\text{PMDETA}$ catalyzed system deviated from both the typical mechanism of ATRP and SET-LRP, which is attributed to the competition and equilibrium of those two traditional mechanisms.

The Health Research Board (HRB) of Ireland and Science Foundation Ireland (SFI), SFI Principal Investigator programme, DEBRA Ireland, National University of Ireland, Galway (Hardiman Research Scholarship to Y. Gao), are gratefully acknowledged for funding.

Notes and references

^a The Charles Institute of Dermatology, School of Medicine & Medical Science, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: wenxin.wang@ucd.ie

^b Department of Mechanical Engineering and Biomedical Engineering, College of Engineering & Informatics, National University of Ireland, Galway, Ireland.

Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data and supporting schemes and figures]. See DOI: 10.1039/c000000x/

COMMUNICATION

- 1 D. Konkolewicz, Y. Wang, M. Zhong, P. Krys, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 8749.
- 2 J. Nicolas, Y. Guillauneuf, C. Lefay, D. Bertin, D. Gigmes and B. Charleux, *Progress in Polymer Science*, 2013, **38**, 63.
- 3(a) G. Moad, E. Rizzardo and S. H. Thang, *Australian Journal of Chemistry*, 2012, **65**, 985; (b) J. Chiefari, Y. K. B. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559.
- 4(a) J.-s. Wang and K. Matyjaszewski, *Journal of the American Chemical Society*, 1995, **117**, 5614; (b) K. Matyjaszewski and J. Xia, *Chemical Reviews*, 2001, **101**, 2921.
- 5(a) B. M. Rosen and V. Percec, *Chemical reviews*, 2009, **109**, 5069; (b) V. Percec, T. Guliasvili, J. S. Ladislav, A. Wistrand, A. Stjerndahl, M. J. Sienkowska, M. J. Monteiro and S. Sahoo, *Journal of the American Chemical Society*, 2006, **128**, 14156.
- 6 N. Zhang, S. R. Samanta, B. M. Rosen and V. Percec, *Chemical Reviews*, 2014, **114**, 5848.
- 7 D. Konkolewicz, Y. Wang, P. Krys, M. Zhong, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Polymer Chemistry*, 2014, **5**, 4396.
- 8(a) M. Zhong, Y. Wang, P. Krys, D. Konkolewicz and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3816; (b) Y. Wang, M. Zhong, W. Zhu, C.-H. Peng, Y. Zhang, D. Konkolewicz, N. Bortolamei, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3793; (c) C.-H. Peng, M. Zhong, Y. Wang, Y. Kwak, Y. Zhang, W. Zhu, M. Tonge, J. Buback, S. Park, P. Krys, D. Konkolewicz, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 3803.
- 9(a) Q. Zhang, P. Wilson, Z. Li, R. McHale, J. Godfrey, A. Anastasaki, C. Waldron and D. M. Haddleton, *Journal of the American Chemical Society*, 2013, **135**, 7355; (b) N. H. Nguyen, H.-J. Sun, M. E. Levere, S. Fleischmann and V. Percec, *Polymer Chemistry*, 2013, **4**, 1328.
- 10 K. Matyjaszewski, B. Göbel, H.-j. Paik and C. P. Horwitz, *Macromolecules*, 2001, **34**, 430.
- 11 K. Matyjaszewski, S. Coca, S. G. Gaynor, M. Wei and B. E. Woodworth, *Macromolecules*, 1997, **30**, 7348.
- 12(a) B. M. Rosen and V. Percec, *Journal of Polymer Science Part A: Polymer Chemistry*, 2007, **45**, 4950; (b) N. H. Nguyen and V. Percec, *Journal of Polymer Science Part A: Polymer Chemistry*, 2011, **49**, 4227; (c) N. H. Nguyen, X. Jiang, S. Fleischmann, B. M. Rosen and V. Percec, *Journal of Polymer Science Part A: Polymer Chemistry*, 2009, **47**, 5629.
- 13 Y. Kwak, A. J. Magenau and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 811.