Free-Radical Intermediates in Atom Transfer Radical Addition and Polymerization: Study of Racemization, Halogen Exchange, and Trapping Reactions

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Atom transfer radical addition (ATRA) is a well-known synthetic method for carbon−carbon bond formation.[1] Recent extension of this concept to polymer synthesis, i.e., atom transfer radical polymerization (ATRP),[2,3] has opened up new possibilities to prepare various well-defined macromolecules.

The proposed mechanism for ATRA is shown in Scheme 1a. The transition metal complex (Mt^n) abstracts a halogen from an alkyl halide (RX), presumably resulting in the formation of an alkyl radical (R•) and a higher oxidation metal complex ($Mt^{n+1}X$). In the presence of unsaturated compounds (CH_2═CHY), the radical adds to a double bond. The radical adduct abstracts the halogen from the oxidized form of the metal complex, forming RCH_2CHYX. Typically, the addition step is rapid, and the radical (R•) is more stable than the radical adduct (RCH_2CHY•). The rate of monomer addition to the radical adduct is slow, and therefore the monoaddition product is predominately formed. The high chemoselectivities of these reactions have been well explained by the persistent radical effect.[4] In ATRP (Scheme 1b), the addition product can also be reactivated to re-form a radical that can add to another alkene molecule. This process can be repeated many times such that a high molecular weight polymer is obtained.[5]

The exact nature of the intermediates, however, is not fully clear. Are they radicals, or do other ionic or insertion mechanisms contribute or even dominate? Are the radicals free or interacting with the metal centers? Such questions are obviously important, especially when attempting to improve and expand the scope of ATRA and ATRP.[6]

We report here the results of the kinetic studies of three different reactions: (a) racemization of optically active methyl 2-bromopropionate (MBrP), (b) halogen exchange reaction, and (c) trapping of the intermediates with a radical scavenger in the presence of ATRA and ATRP transition-metal catalysts (Scheme 2). Racemization can occur when the intermediate allows for the inversion of the chiral center during the reversible atom transfer process. If racemization does occur, we can compare its rate with the rate of halogen exchange, where the bromine in MBrP is replaced with chlorine from Cu(I)Cl. For equimolar amounts of RBr and CuCl/2dNbpy, approximately 80−90% of the alkyl bromide transforms to the alkyl chloride.[7] Another reaction to compare is the consumption of MBrP catalyzed by copper complexes in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO), where the generated radicals are trapped with TEMPO to form an alkoxyamine.[8,9] Comparing the rates of these three reactions can elucidate the nature of the intermediates in the transition-metal-catalyzed atom transfer process.

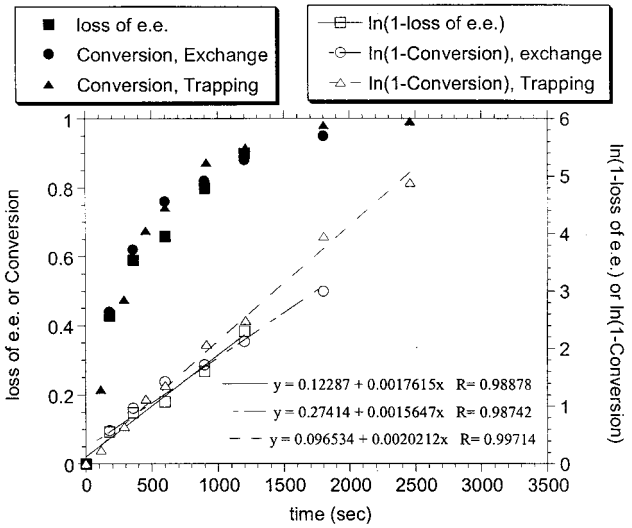

Figure 1. Comparison of the rates of racemization/exchange/trapping reactions using (−)- or (±)-MBrP/Cu(I)Cl(dNbpy)$_2$ in toluene-d_8 or toluene at 60 °C. $[MBrP]_0 = 0.0031$ mol L^{-1}, $[Cu(I)Cl]_0 = {}^1/_2[dNbpy]_0 = 0.031$ mol L^{-1}, and for the trapping experiment $[TEMPO]_0 = 0.062$ mol L^{-1}.

The catalyst used in this study was copper(I) chloride (Cu(I)Cl) complexed with 2 equiv of 4,4′-di(5-nonyl)-2,2′-bipyridine (dNbpy). Cu(I)Cl/bpy derivatives have been successfully used for both ATRA and ATRP, and the alkyl substituent on pyridine rings imparts greater solubility in relatively nonpolar media such as bulk vinyl monomer.[10] The substrate studied was MBrP, which is a model for poly(methyl acrylate) chain ends in ATRP, and it is also a widely used initiator for ATRP.

All experiments were performed under identical conditions except that TEMPO was added in the trapping experiment.[11] In each experiment, the same concentration of catalyst ($[CuCl]_0 = {}^1/_2[dNbpy]_0 = 0.031$ mol L^{-1}) and substrate ($[MBrP]_0 = 0.0031$ mol L^{-1}) were used in toluene-d_8 or toluene at 60 °C. The catalyst concentration was 10 times higher than the substrate concentration to provide pseudo-first-order kinetic conditions. The racemization reaction and exchange reactions were monitored simultaneously by polarimetry and ^{1}H NMR with optically active (*S*)-(−)-MBrP. The trapping reaction and the separate exchange reactions were carried out using GC with racemic mixture of MBrP. The results are presented in Figure 1 and summarized in Table 1.

The reasonably linear first-order plots of all three reactions confirm that the concentration of the catalyst does not vary significantly during the reactions. During the racemization and exchange reactions, the Cu(I)Br complex formed as the reaction proceeded. Cu(I)Br and Cu(I)Cl complexes have slightly different reactivities.[12] Furthermore, in the case of the halogen exchange reaction, the kinetic data should be treated globally as a reversible second-order reaction, since Cu(I)Cl is

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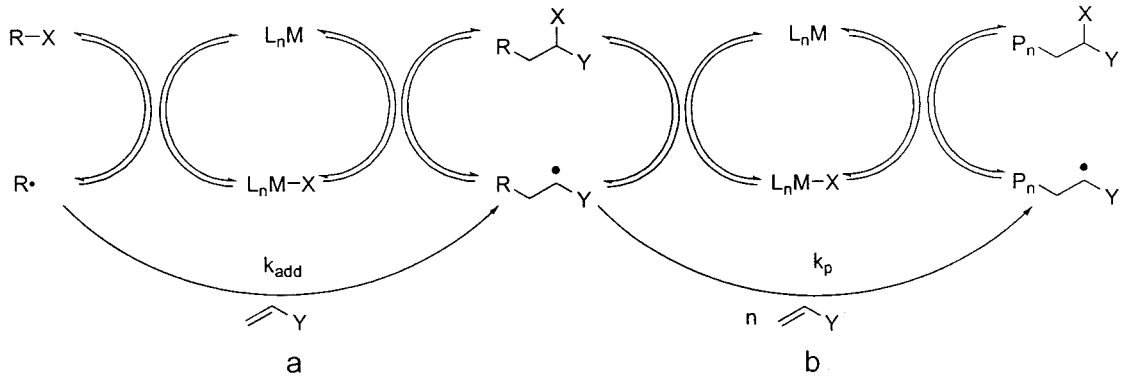
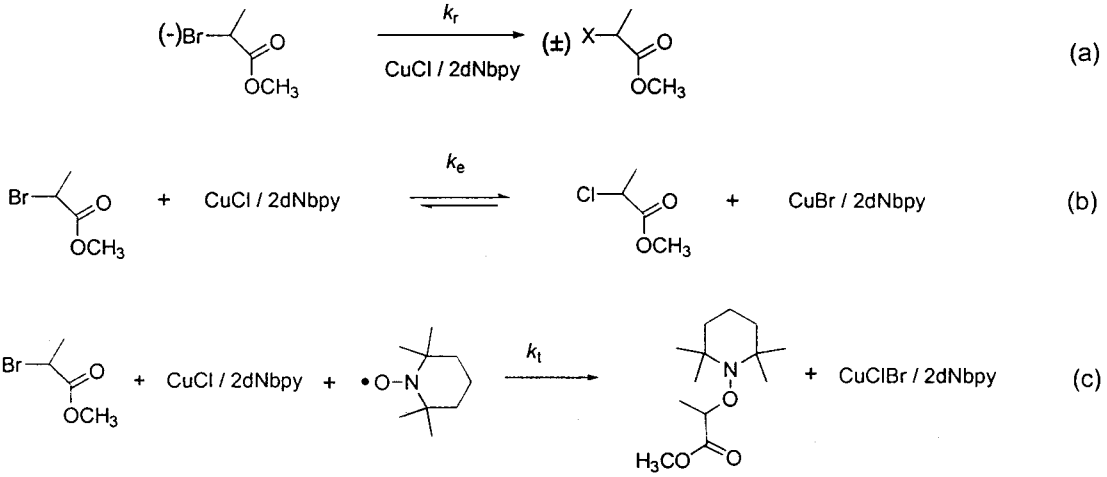
Scheme 1. Catalytic Cycles Involved in ATRA and ATRP



Scheme 2. (a) Racemization, (b) Halogen Exchange, and (c) Trapping Reactions



Scheme 3. Atom Transfer Process

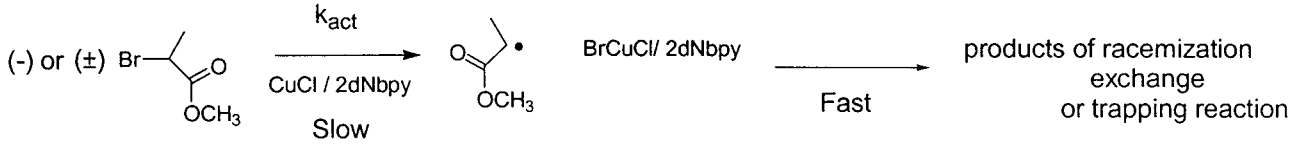


Table 1. Rate Constants of Racemization/Exchange/Trapping Reactions[a]

reactions	k (L mol^{-1} s^{-1})
racemization	$(6.0 \pm 0.3) \times 10^{-2}$
exchange[b]	$(6.6 \pm 1.1) \times 10^{-2}$
trapping	$(6.2 \pm 0.5) \times 10^{-2}$

[a] See Figure 1 caption for experimental conditions. [b] Three exchange reactions carried out simultaneously with racemization experiments using ^{1}H NMR gave $k_e = (5.6 \pm 0.4) \times 10^{-2}$ L mol^{-1} s^{-1}; the average value from all six experiments is given in Table 1.

formally consumed in the process. However, these contributions are almost negligible, owing to the use of excess catalyst relative to the substrate as confirmed by the linearity of the first-order kinetic plots in Figure 1. In the case of the trapping experiment, the catalyst is consumed by oxidation of metal center after atom transfer, but again the pseudo-first-order kinetic assumption is still valid as supported by the data in Figure 1. Similar measurements have been performed for other ATRP systems using HPLC[8,13] and NMR.[12] The pseudo-first-order rate constants ($k_{app} = k[\text{Cu(I)X}]_0$) were separated into the rate constants for the corresponding reactions (Table 1). Each experiment was repeated three times, and the average values are given in Table 1.

A potential concern in both the racemization and halogen exchange reactions is that the loss of chirality or the consumption of MBrP actually occurs via an S_N2 process, i.e., attack of chloride anion on the C−Br moiety instead of through a radical intermediate. However, contribution of this reaction is negligible on the basis of two observations. First, during the trapping experiments, no formation of an alkyl chloride by halogen exchange was observed. An S_N2 reaction would result in exchange, thus producing alkyl chlorides which should be detected during the trapping experiments, since an alkyl chloride has a slower activation rate than an alkyl bromide.[12,14]

Second, racemization and exchange occurred at the same rate. If exchange occurred via an S_N2 mechanism, the product would have inverted stereochemistry and thus would still exhibit optical activity or at least result in a different rate of racemization than exchange. The two reactions have very similar rates and yields which are very similar to that of trapping with TEMPO. These two observations indicate that the rate of nucleophilic substitution of bromide by chloride from Cu(I) or Cu(II) complex must be slower than the rate of the atom transfer reaction.

The data show that the chirality of the optically active alkyl bromide is lost relatively quickly in the presence of the Cu(I)Cl catalyst. To our knowledge, this is the first study of racemization reactions through an atom transfer process between an alkyl halide and a copper(I) complex. The similar rates of racemization, exchange, and trapping reactions in this system indicate that they proceed through the same intermediate, with formation of radicals (activation) being the rate-determining step (Scheme 3).

Some earlier indirect experiments also indicated the involvement of free radicals in ATRP.[6] The composition distributions and reactivity ratios in statistical copolymers[15] and the tacticity of polymers prepared by ATRP are similar to those in conventional radical polymerizations.[3,16,17] Reverse ATRP can be initiated by conventional radical initiators in the presence of Cu(II) complexes.[18] In addition, chiral ligands do not affect the tacticity of poly(methyl methacrylate),[19] radical scavengers inhibit ATRP,[3,16,20] and additives such as water or phenol have a minor kinetic effect.[3,10,21] Formation of persistent paramagnetic Cu(II) species has been followed by EPR,[22] and very recently, in ATRP of dimethacrylates, propagating free radicals have been directly observed by EPR.[23]

This paper has shown that, under typical ATRA and ATRP conditions, the racemization of an optically active alkyl bromide was racemized at a similar rate to those of halogen exchange and a trapping reaction, indicating that free radical intermediates form during ATRA and ATRP. However, a caveat should be placed on these studies; the reactive intermediates in metal-catalyzed reactions such as ATRA and ATRP will depend on the redox properties of the catalysts/substrates, and therefore, for some R−X/Mt^n/L systems, radicals may not be the only species present.

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References and Notes

(1) Curran, D. P. *Synthesis* **1988**, 417−439. Asscher, M.; Vofsi, D. *J. Chem. Soc.* **1963**, 1887−1896. Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827−1838. Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165−171.

(2) Wang, J. S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614−5615. Matyjaszewski, K. *Chem. Eur. J.* **1999**, *5*, 3095−3102. Patten, T. E.; Matyjaszewski, K. *Acc. Chem. Res.* **1999**, *32*, 895−903. Percec, V.; Barboiu, B. *Macromolecules* **1995**, *28*, 7970−7972.

(3) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721−1723.

(4) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925−3927.

(5) Matyjaszewski, K. *Macromolecules* **1999**, *32*, 9051−9053.

(6) Matyjaszewski, K. *Macromolecules* **1998**, *31*, 4710−4717.

(7) Matyjaszewski, K.; Shipp, D. A.; Wang, J.-L.; Grimaud, T.; Patten, T. E. *Macromolecules* **1998**, *31*, 6836−6840. Haddleton, D. M.; Heming, A. H.; Kukulj, D.; Jackson, S. G. *Chem. Commun.* **1998**, 1719−1720.

(8) Paik, H.-J.; Matyjaszewski, K. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2000**, *41*, 470−471.

(9) Matyjaszewski, K.; Woodworth, B. E.; Zhang, X.; Gaynor, S. G.; Metzner, Z. *Macromolecules* **1998**, *31*, 5955−5957.

(10) Matyjaszewski, K.; Patten, T. E.; Xia, J. *J. Am. Chem. Soc.* **1997**, *119*, 674−680.

(11) Methyl (*S*)-(−)-2-bromopropionate (MBrP) was prepared by methylation of (*S*)-(−)-2-bromopropionic acid (Aldrich) with methanol in the presence of 4-(dimethylamino)pyridine and dicyclohexylcarbodiimide in dichloromethane. 4,4′-Di-(5-nonyl)-2,2′-bipyridine (dNbpy) was prepared as previously reported.[10] Cu(I)Cl (Aldrich) was used as received. Toluene was purified and distilled under high vacuum in the presence of *n*-BuLi. Racemization was carried out in a glass tube under an atmosphere of dry nitrogen. First, Cu(I)X and dNbpy were placed in the tube, and then toluene was added with a syringe. After the addition of MBrP at −78 °C, the reaction mixture was heated at 60 °C. The reaction was followed by HPLC using a silica gel column (0.46 cm × 25 cm) on an HPLC system (JASCO PU-986) equipped with a UV detector (JASCO UV-875) and a polarimeter detector (JASCO OR-990). The intensity ratios of the chiral halides on the two detectors were used to estimate the degree of racemization. After complete racemization, the polarimeter detector showed no peak. Trapping and exchange reactions were performed in a similar way in a Schlenk flask. The reactions were monitored by the use of gas chromatography with a Shimadzu GC-17A, AOC-20i autosampler, and J &W Scientific DB 608 column (30 m × 0.53 mm) with a FID detector.

(12) Goto, A.; Fukuda, T. *Macromol. Rapid Commun.* **1999**, *20*, 633−636.

(13) Chambard, G.; Klumperman, B.; German, A. L. *Macromolecules* **2000**, *33*, 4417−4421.

(14) Paik, H.-j.; Peng, Z.; Diamanti, S. J.; Matyjaszewski, K. *Macromolecules*, submitted.

(15) Kotani, Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1998**, *31*, 5582−5587. Haddleton, D. M.; Crossman, M. C.; Hunt, K. H.; Topping, C.; Waterson, C.; Suddaby, K. G. *Macromolecules* **1997**, *30*, 3992−3998. Arehart, S. V.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 2221−2231. Matyjaszewski, K.; Ziegler, M. J.; Arehart, S. V.; Greszta, D.; Pakula, T. *J. Phys. Org. Chem.* **2000**, *13*, 775−786. Chambard, G.; Klumperman, B. *ACS Symp. Ser.* **2000**, *768*, 197−210.

(16) Wang, J.-S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7901−7910.

(17) Ando, T.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1997**, *30*, 4507−4510. Lecomte, P.; Drapier, I.; Dubois, P.; Teyssié, P.; Jérôme, R. *Macromolecules* **1997**, *30*, 7631−7633.

(18) Wang, J.-S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7901−7910. Xia, J.; Matyjaszewski, K. *Macromolecules* **1997**, *30*, 7692.

(19) Haddleton, D. M.; Duncalf, D. J.; Kukulj, D.; Heming, A. M.; Shooter, A. J.; Clark, A. J. *J. Mater. Chem.* **1998**, *8*, 1525−1532.

(20) Granel, C.; Dubois, P.; Jérôme, R.; Teyssié, P. *Macromolecules* **1996**, *29*, 8576.

(21) Haddleton, D. M.; Clark, A. J.; Crossman, M. C.; Duncalf, D. J.; Heming, S.; Morsley, S. R.; Waterson, C.; Shooter, A. J. *Chem. Commun.* **1997**, 1173.

(22) Kajiwara, A.; Matyjaszewski, K.; Kamachi, M. *Macromolecules* **1998**, *31*, 5695−5701.

(23) Yu, Q.; Zeng, F.; Zhu, S. *Macromolecules* **2001**, *34*, 1612.

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