5642 *Inorg. Chem.* **2010**, *49*, 5642–5649
DOI: 10.1021/ic100540q

Inorganic Chemistry
Article

Kinetic Studies of the Initiation Step in Copper Catalyzed Atom Transfer Radical Addition (ATRA) in the Presence of Free Radical Diazo Initiators as Reducing Agents

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Received March 22, 2010

Kinetic parameters for the reduction of copper(II) complexes in atom transfer radical addition (ATRA) in the presence of free-radical diazo initiator (AIBN) were determined using both experimental and kinetic modeling techniques. The rate constant of decomposition of AIBN (k_{dc}) in various solvents was determined at 60 °C using UV−vis spectroscopy. Rate constants of deactivation ($k_{d,AIBN}$) of [Cu^{II}(TPMA)Cl][Cl] (TPMA = tris(2-pyridylmethyl)amine), [Cu^{II}(Me$_6$TREN)Cl][Cl] (Me$_6$TREN = tris[2-(*N*,*N*-dimethylamino)ethyl]amine), [Cu^{II}(PMDETA)Cl$_2$] (PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine), and [Cu^{II}(bpy)$_2$Cl][Cl] (bpy = 2,2′-bipyridine) complexes by radicals generated from the decomposition of AIBN were measured using the TEMPO-trapping method in a competitive clock reaction. Activation rate constants ($k_{a,AIBN}$) were finally estimated from kinetic modeling utilizing the experimentally determined rate constants of decomposition of AIBN and deactivation. The effect of $k_{a,AIBN}$, $k_{d,AIBN}$, k_{dc} and initial AIBN concentration on the overall copper(I) and copper(II) concentrations in the initiation step of the ATRA process was also evaluated through kinetic modeling.

Introduction and Background

Transition metal catalyzed atom transfer radical addition (TMC ATRA) is a very useful synthetic tool for carbon−carbon bond formation utilizing alkyl halides and alkenes.[1−7] The reaction can be conducted in both inter- and intramolecular fashion (also commonly known as atom transfer radical cyclization or ATRC), and it is typically catalyzed by copper,[1,8−11] ruthenium,[12−16] iron,[8,17−20] and nickel[21−23] complexes. Until recently, the major drawback of this versatile tool remained the large amount of metal catalysts required to achieve quantitative yields and high selectivity toward the desired monoadduct.[1,4,6,7,9,24−27] The principal reason for high catalyst loading was the inevitable accumulation of the higher-oxidation-state metal complex as a result of unavoidable

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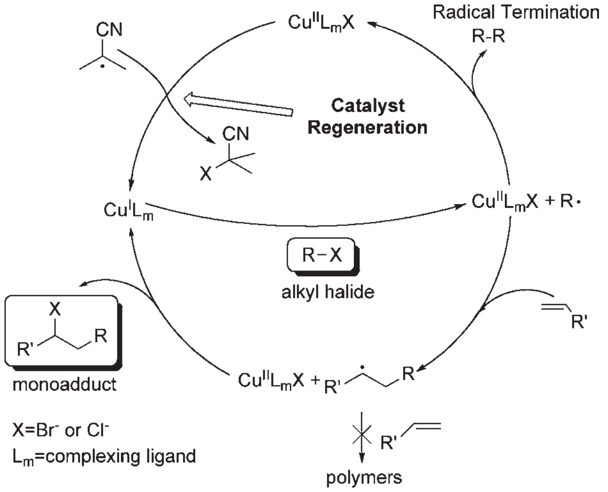
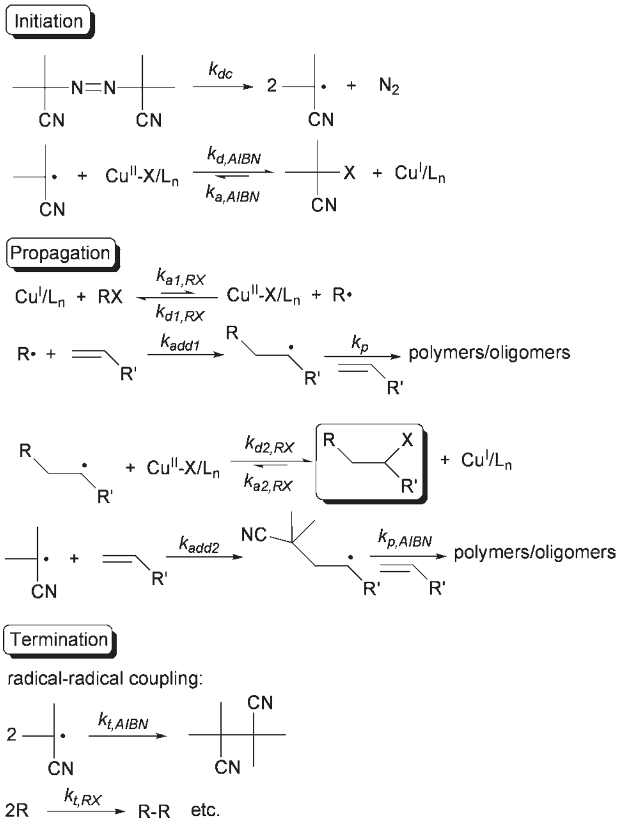
Scheme 1. Proposed Mechanism for Copper(I) Regeneration in ATRA in the Presence of Free Radical Diazo Initiator AIBN



radical—radical termination reactions. Recent research in this area has been geared toward finding alternative methods for making TMC ATRA more economically and environmentally friendly process. One such methodology, originally developed for mechanistically similar atom transfer radical polymerization (ATRP),[28] involves a catalyst regeneration in the presence of reducing agents such as free radical diazo initiators.[7,29] As indicated in Scheme 1 for copper catalyzed ATRA, homolytic cleavage of an alkyl halide bond by a copper(I) complex generates a radical and the corresponding copper(II) complex. Although the latter is needed to complete the catalytic cycle by deactivating the radical formed in the first addition to alkene, every termination step in the reaction (which is often diffusion controlled, $k_t \approx 10^9$ M^{-1} s^{-1}) will result in its accumulation. To compensate for this side reaction, a reducing agent such as free radical diazo initiator AIBN (2,2′-azobis(2-methylpropionitrile)) is added to the reaction mixture. The radicals generated from thermal decomposition of AIBN constantly reduce copper(II) to the copper(I) complex. As a result, ATRA reactions can be conducted using significantly lower amounts of metal catalysts, which in some cases approach parts per million levels.[4,6,7,30-34] Since the seminal reports by our,[32] and the research group of Severin,[30] this method of catalyst regeneration in ATRA has attracted considerable academic interest.[7,33-56] This is a visible indicator that this methodology is on a potential trajectory to become a "greener" alternative to currently available synthetic processes for such organic transformations.[4,6,7]

Scheme 2. Initiation, Propagation, and Termination Steps in Copper Catalyzed ATRA in the Presence of Free Radical Diazo Initiator AIBN



In our previous report, the rate law for copper catalyzed ATRA in the presence of AIBN as a reducing agent was derived taking into account the reaction steps involving

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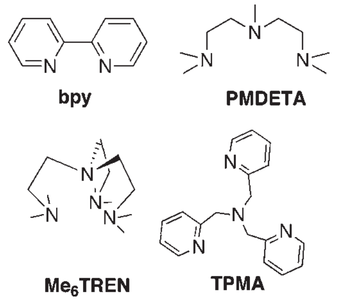
Scheme 3. Structures of Nitrogen Based Ligands Commonly Used in Copper Catalyzed ATRA



decomposition of AIBN (k_{dc}), the reduction of Cu^{II} to Cu^{I} in the presence of radicals generated from AIBN ($k_{a,AIBN}$ and $k_{d,AIBN}$), and the AIBN-initiated free radical polymerization ($k_{p,AIBN}$).[45] These steps are shown in Scheme 2. The rate of alkene consumption was found to depend on the initial concentration of the radical initiator and its decomposition (k_{dc}) and termination (k_t) rate constants, but not on the concentrations of either Cu^{I} or Cu^{II} complex, which was contrary to the derived rate law for copper-catalyzed ATRA in the absence of a reducing agent.[7] Further kinetic experiments have confirmed that the observed rate constant for ATRA (k_{obs}) was indeed not dependent on the concentration of the catalyst. However, product selectivity was found to be highly reliant on the nature of the catalyst, that is, active catalysts with higher equilibrium constants ($K_{ATRA} = k_{a1,RX}/k_{d1,RX}$, Scheme 2) such as $[Cu^{II}(Me_6TREN)Cl][Cl]$ (Me_6TREN = tris[2-(*N*,*N*-dimethylamino)ethyl]amine) and $[Cu^{II}(TPMA)Cl][Cl]$ (TPMA = tris(2-pyridylmethyl)amine) produced higher yields of the monoadduct compared to the less active catalyst such as $[Cu^{II}(PMDETA)Cl_2]$ (PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) and $[Cu^{II}(bpy)_2Cl][Cl]$ (bpy = 2,2′-bipyridine, Scheme 3).

Results from UV−vis experiments of model reaction systems containing only AIBN and a Cu^{II} complex also revealed that the amount of Cu^{II} was governed by deactivation ($k_{d,AIBN}$) and activation ($k_{a,AIBN}$) rate constants, and that the highly active catalysts $[Cu^{II}(TPMA)Cl][Cl]$ and $[Cu^{II}(Me_6TREN)Cl][Cl]$ had higher overall Cu^{II} concentrations at the equilibrium than the less active $[Cu^{II}(bpy)_2Cl][Cl]$ and $[Cu^{II}(PMDETA)Cl_2]$. Determination of the kinetic parameters for the reduction of the deactivator species in copper-catalyzed ATRA in the presence of AIBN is therefore highly crucial in the quantification of the efficiency of various copper(II) complexes in ATRA systems. Several research groups have extensively studied and measured activation (k_a) and deactivation (k_d) rate constants for a number of Cu^{I}/Cu^{II} complexes and alkyl halides using different techniques and methods.[57] However, to the best of our knowledge, k_a and k_d values for copper-catalyzed ATRA systems containing highly active alkyl halides (e.g., 2-chloro-2-methylpropanenitrile or chlorine trapped radical generated from the decomposition of AIBN) have not yet been determined. In this article, we report on the kinetic studies of the initiation step in copper catalyzed ATRA in the presence of free radical diazo initiators as reducing agents using a combination of spectroscopic and kinetic modeling techniques.

Experimental Section

General Procedures. All reagents were obtained from commercial sources. 2,2′-Azobis(2-methylpropionitrile) (AIBN) was recrystallized from cold methanol and dried at room temperature under vacuum. Solvents (acetonitrile and methanol) were degassed and deoxygenated using Innovative Technology solvent purifier. Tris(2-pyridylmethyl)amine (TPMA),[58] tris-[2-(*N*,*N*-dimethylamino)ethyl]amine (Me_6TREN),[59] and copper(II) complexes $[Cu^{II}(TPMA)Cl][Cl]$,[32] $[Cu^{II}(Me_6TREN)Cl][Cl]$,[60] $[Cu^{II}(PMDETA)Cl_2]$[61] (PMDETA = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine), and $[Cu^{II}(bpy)_2Cl][Cl]$[62] (bpy = 2,2′-bipyridine) were synthesized according to published procedures. All other reagents were used as received. Manipulations were performed under argon in a drybox (< 1.0 ppm of O_2 and < 0.5 ppm of H_2O) or using standard Schlenk line techniques. ^1H NMR spectra were obtained at room temperature on a Bruker Avance 400 MHz spectrometer with chemical shifts given in parts per million relative to the residual solvent peak ($CDCl_3$, 7.26 ppm). UV−vis spectra were recorded using Beckman DU-530 spectrometer. Kinetic modeling was performed using the Chemical Kinetics Simulator CKS (IBM's Almaden Research Center).[63]

Measurement of the Rate of Decomposition of 2,2′-Azobis(2-methylpropionitrile) (AIBN). 2,2′-Azobis(2-methylpropionitrile) (AIBN) solutions (0.08 M) were prepared by dissolving AIBN (39.5 mg, 0.24 mmol) in 3.0 mL of acetonitrile or methanol. Deuterated solvents were used for ^1H NMR measurements with anisole (26 μL, 0.24 mmol) and/or *p*-methoxybenzene (33.0 mg, 0.24 mmol) as internal standards. The solutions were then placed in an airtight 10 mm quartz cell (UV−vis) or a Schlenk flask (^1H NMR), purged with argon, capped, and heated at 60 °C in an oil bath. Samples were taken at timed intervals, and the absorbance of AIBN at λ_{max} = 345 nm or the ^1H NMR peak at 1.65 ppm monitored. The concentration of AIBN in the case of UV−vis measurements was determined using the extinction coefficient value calculated from Beer−Lambert's law ($\varepsilon = 11.9\ L\ mol^{-1}\ cm^{-1}$).

Deactivation Rate Constant Measurements. A stock solution of AIBN (17.0 mg, 0.10 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (47.6 mg, 0.3 mmol) was prepared in methanol. Copper(II) catalyst solutions (0.025 M) were prepared in situ by dissolving the appropriate ligand and $CuCl_2$ in methanol. The desired amount of copper(II) catalyst was then added to 0.15 mL of the AIBN/TEMPO stock solution, and the reaction mixture was stirred at 40 °C for 5 days. The amounts of 2-chloro-2-methylpropanenitrile (chlorine trapped radical generated from the decomposition of AIBN, ClMPN) and 2-methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanenitrile (TEMPO trapped radical generated from the decomposition of AIBN, $(CH_3)_2C(CN)$-TEMPO) were monitored using ^1H NMR. ^1H NMR ($CDCl_3$, 400 MHz, RT): δ1.72 (s, ClMPN adduct) and δ1.52 (s, $(CH_3)_2C(CN)$-TEMPO adduct).

Reduction of Copper(II) Complexes in the Presence of AIBN. Copper(II) solutions were prepared with the following initial concentrations using methanol as solvent: $[Cu^{II}(Me_6TREN)Cl][Cl]_0 = 0.0028$ M, $[Cu^{II}(TPMA)Cl][Cl]_0 = 0.0045$ M, $[Cu^{II}(PMDETA)Cl_2]_0 = 0.0045$ M and $[Cu^{II}(bpy)_2Cl][Cl]_0 = 0.01$ M. Catalyst solution (3 mL) and AIBN (10 equiv relative to copper(II) complex) were placed in an airtight 10 mm quartz cell. The reaction mixture was heated at 60 °C for 3 h, and the absorbance

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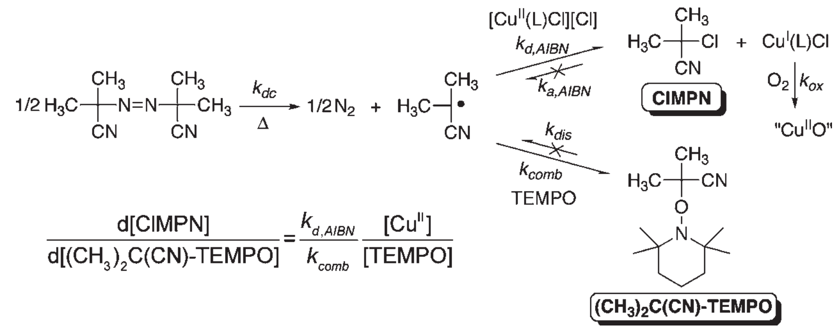
[63] CKS can be obtained from the IBM Research Center web site: http://www.almaden.ibm.com/st/msim/ckspage.html.

Scheme 4. Model Reactions for Determination of the Deactivation Rate Constant ($k_{d,AIBN}$)



at λ_{max} ([Cu^{II}(Me$_6$TREN)Cl][Cl] = 938 nm, [Cu^{II}(TPMA)Cl][Cl] = 967 nm, Cu^{II}(PMDETA)Cl$_2$ = 698 nm, and [Cu^{II}(bpy)$_2$Cl][Cl] = 736 nm) monitored at timed intervals. The concentration of Cu^{II} was determined using extinction coefficient values at λ_{max} calculated from Beer−Lambert's law: ε([Cu^{II}(Me$_6$TREN)Cl][Cl]) = 413.9 L mol^{-1} cm^{-1}, ε([Cu^{II}(TPMA)Cl][Cl]) = 192.1 L mol^{-1} cm^{-1}, ε(Cu^{II}(PMDETA)Cl$_2$) = 214.3 L mol^{-1} cm^{-1} and ε([Cu^{II}(bpy)$_2$Cl][Cl]) = 179.0 L mol^{-1} cm^{-1}.

Results and Discussion

Kinetic Studies. The initiation step in copper catalyzed ATRA in the presence of AIBN is a very important part of the reaction mechanism because it regulates the amounts of copper(I) and copper(II) complexes present in the reaction mixture (Scheme 2). In this step, radicals generated from thermal decomposition of AIBN (k_{dc}) reduce copper(II) to the corresponding copper(I) complex. The equilibrium between copper(II) complex/2-methylpropanenitrile radicals and copper(I) complex/2-chloro-2-methylpropanenitrile is governed by the deactivation ($k_{d,AIBN}$) and activation ($k_{a,AIBN}$) rate constants, which are in turn strongly dependent on the complexing ligand. Thermal decomposition of AIBN in various solvents has been widely studied, and it usually follows first order kinetics.[64−66] Furthermore, the rate of AIBN decomposition at a given temperature depends on the nature of the reaction medium because of the cage effect.[67] In this study, the rate of decomposition of AIBN (k_{dc}) at 60 °C was determined using acetonitrile and methanol as solvents, and also in the presence of additives such as anisole and *p*-methoxybenzene (commonly used internal standards for ATRA reactions). The consumption of AIBN was monitored using ^{1}H NMR or UV−vis spectroscopy, and the rates were determined from first order kinetic plots. The rates of decomposition of AIBN in acetonitrile and methanol were determined to be 3.8×10^{-6} s^{-1} and 2.7×10^{-6}, respectively. This is in good agreement with other literature values which range from 2.0×10^{-6} to 1.0×10^{-5} s^{-1}.[68,69] Addition of additives such as anisole ($k_{dc} = 1.2 \times 10^{-5}$ s^{-1}) or *p*-methoxybenzene ($k_{dc} = 1.2 \times 10^{-5}$ s^{-1}) slightly increased the decomposition rate constant of AIBN, which could be attributed to the disruption of the solvent cage.

Deactivation rate constants in copper catalyzed ATRA and mechanistically similar ATRP (atom transfer radical polymerization) are difficult to measure directly because they are typically very fast (on the order of 10^8 M^{-1} s^{-1}).[57] One of the methods includes a clock reaction in which the generated radicals are simultaneously trapped with TEMPO and the deactivator or copper(II) complex.[70,71] Model reactions for determination of $k_{d,AIBN}$ are illustrated in Scheme 4. Thermal decomposition of AIBN generates tertiary 2-methylpropanenitrile radicals, which are either trapped by TEMPO or copper(II) complex. Dissociation rate constants of TEMPO adducts are typically very low (10^{-4}−10^{-7} s^{-1})[72] compared to the combination rate constants (~10^8 M^{-1} s^{-1}) but, nevertheless, an excess of TEMPO (3 equiv relative to AIBN) was used to shift the equilibrium toward the formation of 2-methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanenitrile (TEMPO trapped radical generated from the decomposition of AIBN, (CH$_3$)$_2$C(CN)-TEMPO). Similarly, excess of copper(II) complex (6−10 equiv relative to AIBN) was utilized. Furthermore, to minimize the possibility for the consumption of 2-chloro-2-methylpropanenitrile (chlorine trapped radical generated from the decomposition of AIBN, ClMPN) by the activation process, reactions were performed in the presence of air to continuously oxidize copper(I) complex. By determining the ratio of ClMPN and (CH$_3$)$_2$C(CN)-TEMPO adducts produced at various copper(II)/TEMPO ratios, the rate constant can be calculated using the combination rate constant $k_{comb} = 4.0 \times 10^8$ M^{-1} s^{-1} of a similar O-substituted hydroxylamine (1-(2′-cyano-2′-propoxy)-4-oxo-2,2,6,6-tetramethylpiperidine).[73] The equation indicated in Scheme 4 does not take into account any potential side reactions occurring in the system. In particular, of concerns are the presence of oxygen, as well as dissociation of the (CH$_3$)$_2$C(CN)-TEMPO adduct. Oxygen is well-known to react with free radicals, which would result in lower yield of (CH$_3$)$_2$C(CN)-TEMPO if the dissociation occurs to a significant extent. Alternatively, even in the absence of oxygen, the same dissociation would give rise to an increase in

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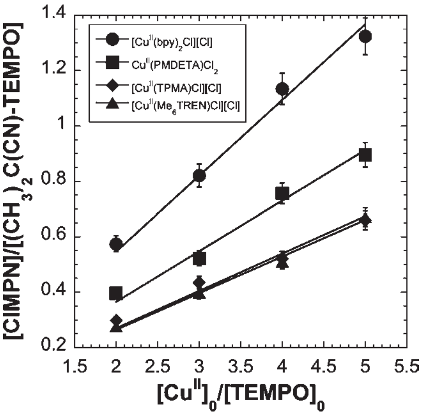

Figure 1. Plots of mole ratio of [ClMPN]/[$(CH_3)_2C(CN)$-TEMPO] adducts versus initial [Cu^{II}]$_0$/[TEMPO]$_0$ ratio at 40 °C in methanol for a series of copper(II) complexes with neutral nitrogen based ligands.

Table 1. Rate Constants of Deactivation of 2-Methylpropanenitrile Radicals by Various [Cu^{II}(L)Cl][Cl] Complexes[a]

ligand (L)	$k_{d,AIBN}$ (M^{-1} s^{-1})
Me_6TREN	5.3×10^7
TPMA	5.4×10^7
PMDETA	7.3×10^7
bpy[b]	1.1×10^8

[a] [AIBN]$_0$ = 0.05 M, [AIBN]$_0$/[TEMPO]$_0$ = 1:3, solvent = MeOH, T = 40 °C. [b] Two equivalents relative to $Cu^{II}Cl_2$ were used.

[ClMPN]/[$(CH_3)_2C(CN)$-TEMPO] ratio over time. However, the ratio of [ClMPN]/[$(CH_3)_2C(CN)$-TEMPO] remained nearly constant for all complexes investigated over a period of 12 h at 40 °C, indicating that oxygen and/or $(CH_3)_2C(CN)$-TEMPO dissociation had negligible effect on the reaction kinetics. This was not observed in a related study of trapping of 1-phenylethyl radical at 75 °C in the absence of oxygen, in which case the relative amounts of the two products did not remain constant after prolonged reaction times (as a result of TEMPO adduct dissociation and additional formation of styrene via proton abstraction).[70,71] The plots of [ClMPN]/[$(CH_3)_2C(CN)$-TEMPO)] at various copper(II)/TEMPO ratios for [Cu^{II}(TPMA)Cl][Cl] (TPMA = tris(2-pyridylmethyl)amine), [Cu^{II}(Me_6TREN)Cl][Cl] (Me_6TREN = tris[2-(N,N-dimethylamino)ethyl]amine), [Cu^{II}(PMDETA)Cl_2] (PMDETA = N,N,N',N'',N''-pentamethyldiethylenetriamine), and [Cu^{II}(bpy)$_2$Cl][Cl] (bpy = 2,2′-bipyridine) complexes are shown in Figure 1 and the results summarized in Table 1. The deactivation rate constants ($k_{d,AIBN}$) were found to decrease in the order bpy > PMDETA > TPMA ≈ Me_6TREN, which was similar to 1-phenylethyl radical determined previously.[70,71] Furthermore, as expected, $k_{d,AIBN}$ values were in the range 10^7−10^8 M^{-1} s^{-1}, which was also consistent with earlier studies on the deactivation rate constant measurements for 5-hexenyl and cyclopropylmethyl radicals by simple copper(II) salts.[74−76]

So far, we have successfully determined kinetic parameters for thermal decomposition of AIBN (k_{dc}) and deactivation ($k_{d,AIBN}$) of generated radicals by a series of copper(II) complexes with neutral nitrogen based ligands.

The only parameter that remains in the initiation step of copper catalyzed ATRA is the activation rate constant ($k_{a,AIBN}$). The activation step in atom transfer radical processes is known to be controlled by a number of factors, such as the structure of the radical initiator or alkyl halide, nature of the complexing ligand, reaction temperature, and so forth. The k_a values for primary, secondary, and tertiary alkyl halides are known to follow the order of 3° > 2° > 1°.[77,78] Alkyl bromides are generally more active than alkyl chlorides because the C−Br bond is much weaker than the C−Cl bond.[57,79] The general order of activities for copper complexes with neutral nitrogen based ligands is as follows: tetradentate (cyclic-bridged) > tetradentate (branched) > tetradentate (cyclic) > tridentate > tetradentate (linear) > bidentate ligands.[57] Also, the nature of the nitrogen atoms present in the ligand is important and usually follows the order alkylamine ≈ pyridine > alkylimine > arylimine > arylamine.[80] Activation rate constants are typically determined from model studies in which the activation process is kinetically isolated from the deactivation step by trapping the generated radical with a radical scavenger such as TEMPO. This method has been widely used in determination of activation rate constants for various radical initiators and copper(I) complexes commonly employed in ATRP.[70,81−83] However, the method is limited in measuring fast activation rate constants with the maximum upper limit of approximately 2 M^{-1} s^{-1}. Other methods, such as the stopped-flow technique, were also successfully employed for measuring activation rate constants as high as 10^2 M^{-1} s^{-1}.[81] 2-Chloro-2-methylpropanenitrile (chlorine trapped radical generated from thermal decomposition of AIBN) is a highly active alkyl halide, and we were unable to accurately measure the activation rate constant under pseudo-first order conditions using either excess copper(I) complex or alkyl halide. Therefore, we reverted to kinetic modeling.

Kinetic modeling is a widely popular alternative method for examining very fast and complicated chemical reactions. In particular, it has been extensively used to model radical reactions, including ATRP.[84−86] In our previous report, we performed UV−vis experiments at 60 °C for model ATRA systems containing only copper(II) catalyst and AIBN.[45] The amount of copper(II) in the reaction was found to be governed by $k_{a,AIBN}$ and $k_{d,AIBN}$, and was strongly dependent on the complexing ligand. By using previously obtained data, in conjunction with experimentally determined values of the deactivation ($k_{d,AIBN}$, Table 1) and AIBN decomposition (k_{dc}) rate

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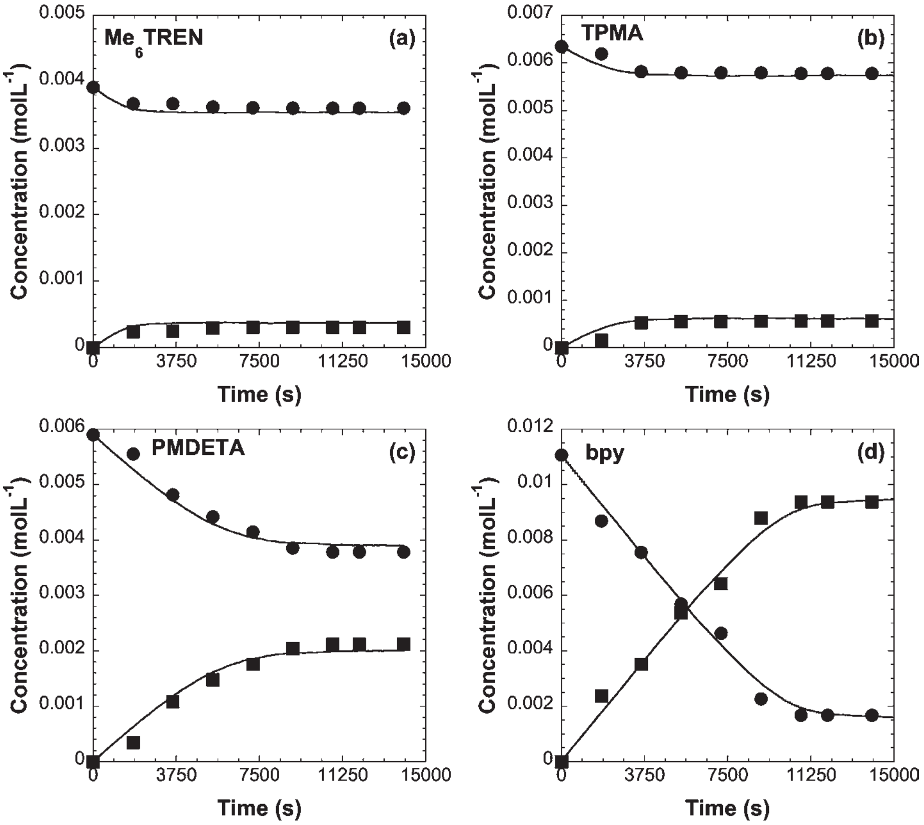

Figure 2. Reduction of copper(II) complexes with Me_6TREN (a), TPMA (b), PMDETA (c), and bpy (d) ligands in the presence of AIBN as a reducing agent in CH_3OH at 60 °C. Data points for Cu^{II} (●) and Cu^{I} (■) complexes show experimental concentrations from UV−vis data, and solid lines are plotted from kinetic modeling. $[Cu^{II}]_0/[AIBN]_0 = 1{:}10$.

constants, kinetic modeling can be used to estimate the activation rate constants ($k_{a,AIBN}$). Kinetic simulations of the initiation step in copper catalyzed ATRA in the presence of AIBN (Scheme 2) were performed using the Chemical Kinetics Simulator CKS (IBM's Almaden Research Center).[63] In addition to initiation steps (radical decomposition, activation, and deactivation), radical termination reactions were also taken into account and assumed to be diffusion controlled (k_t = 2.0 × 109 M^{-1} s^{-1}). Simulations were done systematically by varying the activation rate constants ($k_{a,AIBN}$) for a particular complexing ligand until the reasonable fit to the experimental data was obtained. The relative errors in conducting such optimizations could not be obtained using the CKS chemical kinetics simulator. However, such parameters are easily accessible using programs with more advanced algorithms, which are currently being pursued in our laboratories. The results are shown in Figure 2, and the activation rate constants, as well as equilibrium constants for ATRA, are summarized in Table 2. As expected, the activation rate constants for 2-chloro-2-methylpropanenitrile estimated from kinetic modeling were very high and ranged between 3.0×10^2 M^{-1} s^{-1} ($[Cu^{II}(bpy)_2Cl][Cl]$) and 6.0×10^4 M^{-1} s^{-1} ($[Cu^{II}(Me_6TREN)Cl][Cl]$). Furthermore, the values for $k_{a,AIBN}$ and K_{ATRA} increased in the order $[Cu^{II}(bpy)_2Cl][Cl] < [Cu^{II}(PMDETA)Cl_2] < [Cu^{II}(TPMA)Cl][Cl] \approx [Cu^{II}(Me_6TREN)Cl][Cl]$, which was in good agreement with that in previously reported studies.[77,78,87,88] Interestingly, the value for K_{ATRA} on going from less active 2,2′-bipyridine to most active Me_6TREN ligand increased approximately 400 times. The increase of nearly 40000 times was observed in the case of ethyl-2-bromoisobutyrate, which is a common initiator for copper catalyzed ATRP of (meth)acrylates.[88]

Table 2. Activation Rate Constants for 2-Chloro-2-methylpropanenitrile

Cu^{II} complex[a]	$k_{a,AIBN}$ (M^{-1} s^{-1})[b]	K_{ATRA}[c]
$[Cu^{II}(Me_6TREN)Cl][Cl]$	6.0×10^4	1.1×10^{-3}
$[Cu^{II}(TPMA)Cl][Cl]$	5.8×10^4	1.0×10^{-3}
$[Cu^{II}(PMDETA)Cl_2]$	5.0×10^3	6.8×10^{-5}
$[Cu^{II}(bpy)_2Cl][Cl]$[d]	3.0×10^2	2.7×10^{-6}

[a] $[Cu^{II}]_0/[AIBN]_0$ = 1:10, T = 60 °C. [b] Determined from kinetic modeling. [c] $K_{ATRA} = k_{a,AIBN}/k_{d,AIBN}$, $k_{d,AIBN}$ values were taken from Table 1. [d] Decomposition rate constant for AIBN of 4.5×10^{-6} s^{-1} was used in kinetic simulations.

Kinetic Modeling. In the previous section, we have successfully demonstrated that kinetic modeling can be used to estimate very fast activation rate constants in copper catalyzed ATRA in the presence of free radicals as reducing agents. To further understand the role of free radical diazo initiator in copper-catalyzed ATRA, additional modeling for the reduction of copper(II) to copper(I) in the presence of free radicals generated by thermal decomposition of AIBN was performed. In particular, the effect of the activation ($k_{a,AIBN}$), deactivation ($k_{d,AIBN}$), and AIBN decomposition (k_{dc}) rate constants, as well as the initial concentration of AIBN in the system, was investigated. The corresponding plots for the effect of AIBN

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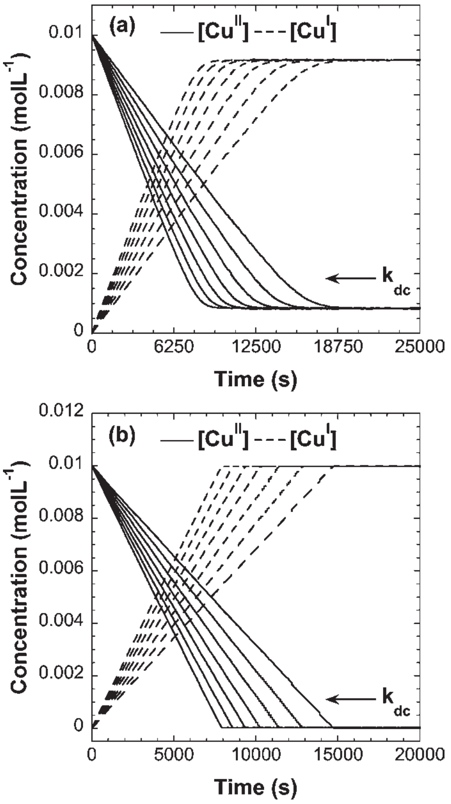

Figure 3. Kinetic modeling of the effect of decomposition rate constant (k_{dc}) of free radical diazo initiator on the reduction of Cu^{II} to Cu^{I} complexes, k_{dc} values range from 3.5 to 6.5 × 10^{-6} s^{-1} with $k_{a,AIBN} = 1.0 \times 10^{2}$ M^{-1} s^{-1} (a) and 1.0×10^{-1} M^{-1} s^{-1} (b). $k_{d,AIBN} = 1.0 \times 10^{8}$ M^{-1} s^{-1}, $k_t = 2.0 \times 10^{9}$ M^{-1} s^{-1}, [Cu^{I}]$_0$ = 0.01 M, [AIBN]$_0$ = 0.1 M.

decomposition rate constant (k_{dc}), which was varied from 3.5 to 6.5 × 10^{-6} s^{-1}, are shown in Figures 3a and 3b for catalysts with two different activation rate constants ($k_{a,AIBN} = 1.0 \times 10^{2}$ M^{-1} s^{-1} and 1.0×10^{-1} M^{-1} s^{-1}, respectively). It is evident from the kinetic plots presented in Figure 3 that the decomposition rate constant of AIBN does not have an effect on the extent of copper(I) regeneration, and hence does not control the concentrations of copper(I) and copper(II) at the equilibrium $k_{a,AIBN}$[Cu^{I}][RX] = $k_{d,AIBN}$[Cu^{II}][R•]). However, the rate of decomposition of AIBN controls the time at which the ATRA equilibrium is being established. Increasing the decomposition rate constant by a factor of 2 reduced the time to establish equilibrium by approximately half.

Kinetic simulations of the effect of radical initiator concentration on the initiation step in copper catalyzed ATRA are shown in Figure 4. Concentrations of AIBN were ranged from 5 to 20 equiv relative to copper(II) complex (corresponding to 5−20 mol % if the reaction mixture contained 1 M alkene). For the catalyst with smaller activation rate constant ($k_{a,AIBN} = 1.0 \times 10^{2}$ M^{-1} s^{-1}, Figure 4a), increasing the AIBN concentration allowed for the equilibrium between copper(I) and copper(II) to be established in a shorter period of time. Also, the equilibrium concentrations of copper complexes were different. With 20 equiv of AIBN, approximately 98% of copper(II) was reduced to copper(I) in 10000 s (2.7 h). The corresponding number decreased to 60% with 5 equiv of AIBN, and the time required to reach equilibrium increased to nearly 40000 s (11 h). However, the concentration of AIBN did not significantly affect the extent of copper(I) regeneration when the kinetic parameters for more active catalyst ($k_{a,AIBN} = 1.0 \times 10^{4}$ M^{-1} s^{-1} and $k_{d,AIBN} = 1.0 \times 10^{8}$ M^{-1} s^{-1}, Figure 4b) were used. While increasing the relative concentration of AIBN from 5 to 20 equiv (relative to copper(II) complex) still decreased the time span for the equilibrium to be established, the concentrations of copper(I) and copper(II) remained very similar. These simulation results indicate that the extent of copper(I) regeneration in ATRA systems can be controlled by the initiator concentration for less active catalysts such as [Cu^{II}(bpy)$_2$Cl][Cl], but its effect is not as significant for highly active catalysts (e.g., [Cu^{II}(TPMA)Cl][Cl]). Also, caution needs to be exercised when increasing free radical initiator concentration relative to copper(II) complex because of the occurrence of free radical polymerization, which will compete with monoadduct formation.[45]

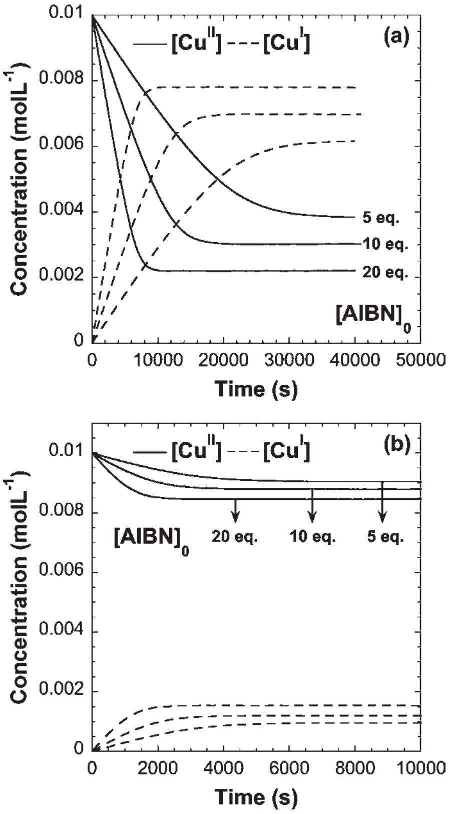

Figure 4. Kinetic modeling of the effect of AIBN concentration on the regeneration of Cu^{I} from Cu^{II} complexes, AIBN concentrations range from 0.05 to 0.20 M (5.0−20 equiv relative to Cu^{II}) with $k_{a,AIBN} = 1.0 \times 10^{2}$ M^{-1} s^{-1} (a) and 1.0×10^{4} M^{-1} s^{-1} (b). $k_{dc} = 3.0 \times 10^{-6}$ s^{-1}, $k_{d,AIBN} = 1.0 \times 10^{8}$ M^{-1} s^{-1}, $k_t = 2.0 \times 10^{9}$ M^{-1} s^{-1}, [Cu^{I}]$_0$ = 0.01 M, [AIBN]$_0$ = 0.1 M.

Lastly, the effect of $k_{a,AIBN}$ (Figure 5a) and $k_{d,AIBN}$ (Figure 5b) on the copper(I) and copper(II) concentrations in the initiation step of ATRA was evaluated. For catalysts with smaller activation rate constants, a significant reduction of copper(II) to copper(I) was observed. For example, when $k_{a,AIBN} = 1.0$ M^{-1} s^{-1}, nearly quantitative conversion of copper(II) was achieved. The extent of copper(I) regeneration decreased by increasing the activation rate constant and reached approximately 10% when $k_{a,AIBN} = 1.0 \times 10^{4}$ M^{-1} s^{-1}. The deactivation rate constant ($k_{d,AIBN}$) was also found to affect the concentrations of copper(I) and copper(II) at the equilibrium.

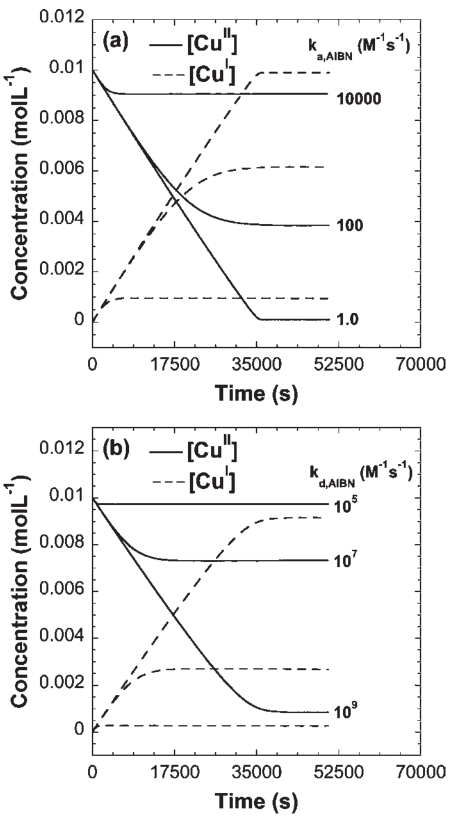

Figure 5. Kinetic modeling of the effect of activation (a) and deactivation (b) rate constants on the reduction of Cu^{II} to Cu^{I} complexes. $k_{a,AIBN}$ values range from 1.0 to 1.0×10^4 M^{-1} s^{-1} with $k_{d,AIBN} = 1.0 \times 10^8$ M^{-1} s^{-1} (a). $k_{d,AIBN}$ values range from $1.0 \times 10^5 - 1.0 \times 10^9$ M^{-1} s^{-1} with $k_{a,AIBN} = 1.0 \times 10^2$ M^{-1} s^{-1} (b). $k_{dc} = 3.0 \times 10^{-6}$ s^{-1}, $k_t = 2.0 \times 10^9$ M^{-1} s^{-1}, $[Cu^{I}]_0 = 0.01$ M, $[AIBN]_0 = 0.1$ M.

As shown in Figure 5b, decreasing the deactivation rate constant significantly lowers the amount of copper(I) generated from copper(II). Deactivation rate constant of 1.0×10^9 M^{-1} s^{-1} allowed for nearly complete regeneration of the copper(I). Lowering the rate constant to 1.0×10^5 M^{-1} s^{-1} resulted in the reduction of only less than 5% of copper(II). The results of kinetic simulations presented in Figures 4 and 5 indicate that the reduction of copper(II) to copper(I) in the initiation step of ATRA process greatly depend on the activation and deactivation rate constants, which can be controlled through ligand design and the choice of the radical initiator.

Conclusions

In summary, kinetic studies of the initiation step in copper catalyzed ATRA in the presence of free radical diazo initiators as reducing agents were reported using a combination of spectroscopic and kinetic modeling techniques. The decomposition rate constant of AIBN at 60 °C was determined to be approximately 3.0×10^{-6} s^{-1}. Deactivation rate constants ($k_{d,AIBN}$) were successfully measured for copper(II) complexes with bpy (1.1×10^8 M^{-1} s^{-1}), PMDETA (7.3×10^7 M^{-1} s^{-1}), TPMA (5.4×10^7 M^{-1} s^{-1}), and Me_6TREN (5.3×10^8 M^{-1} s^{-1}) ligands using TEMPO-trapping method along with ^1H NMR spectroscopy. Kinetic modeling was used to estimate the activation rate constants ($k_{a,AIBN}$), which were found to range between 3.0×10^2 M^{-1} s^{-1} ($[Cu^{II}(bpy)_2Cl][Cl]$) and 6.0×10^4 M^{-1} s^{-1} ($[Cu^{II}(Me_6TREN)Cl][Cl]$). Simulation results indicated that the extent of copper(I) regeneration in the initiation step of ATRA process increased by decreasing the activation or increasing the deactivation rate constant. Furthermore, the rate of AIBN decomposition only controlled the time to establish equilibrium, but it did not affect the concentrations of copper(I) and copper(II). ATRA equilibrium was reached faster at higher mol % of AIBN relative to copper(II) complexes; however, the copper(I) and copper(II) concentrations at the equilibrium were greatly affected only when a less active catalyst (lower $k_{a,AIBN}$) was used.

Acknowledgment. Financial support from a National Science Foundation Career Award (CHE-0844131) is gratefully acknowledged.