Electrochemical approaches to the determination of rate constants for the activation step in atom transfer radical polymerization

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Abstract

Direct determination of ATRP activation rate constant, k_{act} , is typically limited to slow or moderately fast reactions: $k_{\text{act}} < 10^2 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ were determined by classical techniques, such as chromatography, spectrophotometry, NMR, *etc.* Therefore, these techniques are inadequate to study the fastest, and most useful, ATRP systems, such as the most frequently used Cu complexes with tris[2-(dimethylamino)ethyl]amine (Me₆TREN), tris(2-pyridylmethyl)amine (TPMA) and substituted TPMA. In this study, electrochemical methods have been used to investigate the kinetics

of activation of a series of typical ATRP initiators (RX) by $[\text{Cu}^{\text{I}}\text{L}]^+$ (L = Me₆TREN, TPMA or N,N,N',N'',N'''-pentamethyldiethylenetriamine, PMDETA) in MeCN. Both high ($>10^4 \text{ mol}^{-1}\text{dm}^3\text{s}^{-1}$) and low k_{act} values have been measured. Analysis of the collected data showed that k_{act} depends on E° of the catalyst, molecular structure of RX, and nature of the halogen atom. Although usually values of k_{act} increase with decreasing standard reduction potential of $[\text{Cu}^{\text{II}}\text{L}]^{2+}$, there is no well-defined correlation between the two parameters. Instead, k_{act} gives good and useful linear correlations with the standard reduction potential of $[\text{XCu}^{\text{II}}\text{L}]^+$, and with K_{ATRP} or Gibbs free energy of C-X bond dissociation.

Keywords: ATRP, activation rate constant, rotating disk electrode, simulation of cyclic voltammetry

1. Introduction

Atom transfer radical polymerization (ATRP) is a very important controlled radical polymerization process. It enables polymerization of a vast range of monomers for the preparation of polymeric materials with well-defined architecture, pre-determined chain length and low dispersity [1-3]. The general mechanism of atom transfer radical polymerization (ATRP) involves an equilibrium between dormant species containing a carbon-halogen bond (RX) and active, propagating radical species (R[•]) (Scheme 1). The reaction is catalyzed by transition metal complexes, mainly Cu with polydentate amine ligands [4-6]. The ATRP equilibrium is generally well-shifted toward the reagents RX and Cu^I ($K_{\text{ATRP}} \ll 1$), giving a low radical concentration in the reaction mixture and so minimizing the frequency of termination reactions between radicals [7,8]. Chains spend most of their time in the dormant state and the average life of “living” polymers is greatly extended. The

resulting controlled polymerization is characterized by linearity of $\log([M]_0/[M])$ vs. t plots (M = monomer) up to high conversions, predetermined molecular weights, preservation of most chain-end functionalities and low dispersity ($M_w/M_n < 1.3$ for a well-controlled reaction; M_w and M_n are weight average and number average molecular weights, respectively).

Although K_{ATRP} should be small to ensure low radical concentration, both activation (k_{act}) and deactivation (k_{deact}) rate constants should be high to ensure fast exchange between dormant and active species. Typically, once a radical is generated it adds only to a few monomer units before being quickly deactivated by the Cu^{II} complex. The quick activation/deactivation cycle results in simultaneous and homogenous growth of all polymer chains.

While both k_{act} and k_{deact} are important, it has been shown that k_{act} is much more sensitive than k_{deact} to the molecular structures of both catalyst and initiator (RX) [7,8]. Consequently, k_{act} is one of the main indicators of the activity of the catalyst/initiator couple and could be used alone to obtain a rough estimate of the order of magnitude of K_{ATRP} . The equilibrium constant can be used to relate the rate of polymerization, R_p , to the concentration of the propagating radicals:

$$R_p = k_p C_M C_{R\cdot} = k_p K_{\text{ATRP}} C_M C_{\text{RX}} \frac{C_{\text{Cu}^{\text{I}}}}{C_{\text{Cu}^{\text{II}}}} = k_p \frac{k_{\text{act}}}{k_{\text{deact}}} C_M C_{\text{RX}} \frac{C_{\text{Cu}^{\text{I}}}}{C_{\text{Cu}^{\text{II}}}} \quad (1)$$

where k_p is the propagation rate constant, and C_M and C_{RX} are monomer and initiator concentrations. Therefore, information on k_{act} values is important for choosing the optimal experimental conditions [9], *e.g.* for selecting the best catalyst/initiator couple in a specific polymerization system. Indeed, since some initiators mimic the dormant chain ends (*e.g.* PhCH_2X for polystyrene, $\text{CH}_3\text{CH}(\text{X})\text{CO}_2\text{CH}_3$ for poly(methyl acrylate), $\text{CH}_3\text{CH}(\text{X})\text{CN}$ for polyacrylonitrile, etc.), these data are relevant for the characterization of the activation step during polymerization. In this context, the effect of the chain length is considered to be rather weak as previously shown by Fukuda and Goto [10], although the so-called penultimate effect was observed for a few monomers such as methacrylates [11,12].

1 Recently, several efficient methods have been developed for the generation and regeneration of
2 the active Cu^{I} catalyst. Knowledge of k_{act} allows the choice of the best methodology for any
3 polymerization system. Catalysts with low activity are suitable for the normal ATRP method, where
4 Cu^{I} at a high concentration is directly injected in the reaction mixture. More active catalysts can be
5 employed at very low concentrations (ppm levels), provided that the active Cu^{I} species is
6 continuously regenerated [13] as in ARGET ATRP [14,15], SARA ATRP [16], electrochemically
7 mediated ATRP (*e*ATRP) [17-24] and photoinduced ATRP [25-27].

8 The activation rate constants of various ATRP systems have been already reported in the
9 literature. However, only in a few cases relatively fast reactions were analyzed by stopped-flow
10 [28,29] or electrochemical techniques [30-34]. In most cases, the employed methodologies (gas or
11 liquid chromatography [35-43], spectrophotometry [44-47], NMR [10,48]) were suitable only for
12 the characterization of very slow reactions. Therefore, most of the published data for the most
13 active and successful catalysts (namely, Cu complexes with PMDETA, TPMA and Me_6TREN
14 ligands) were estimated on the basis of the assumption that the k_{act} ratio of two different alkyl
15 halides (e.g. $k_{\text{act,RX}_1} / k_{\text{act,RX}_2}$) remains unaffected by changing the nature of the Cu^{I} complex, which
16 is questionable considering the inner sphere nature of the ATRP mechanism [4-6]. The currently
17 available methodologies to determine k_{act} cannot be used to investigate the kinetics of fast reactions
18 involving highly active catalysts [29,49]. Moreover, polar solvents, such as DMSO and water,
19 which are recently drawing a feverish interest in the field of ATRP, are characterized by extremely
20 high activation rate constants [34] that cannot be measured by the traditional techniques.

21 In this work, we used electrochemical methods to determine a wide range of k_{act} values,
22 including rate constants of fast reactions. The reactions between three commonly used $[\text{Cu}^{\text{I}}\text{L}]^+$
23 complexes ($\text{L} = \text{Me}_6\text{TREN}$, TPMA and PMDETA, Scheme 2a) and a set of 13 alkyl halides
24 employed as initiators (Scheme 2b) were investigated in CH_3CN . The data collected for each set of
25 catalyst/initiators were then used to build structure-reactivity correlations.

2. Experimental section

2.1. Chemicals

Acetonitrile (Carlo Erba, RS) was distilled over CaH_2 and stored under argon atmosphere. Copper(II) trifluoromethanesulfonate ($\text{Cu}(\text{OTf})_2$, Alfa Aesar, 98%) and tetrakis(acetonitrile)copper(I) tetrafluoroborate ($\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4\text{BF}_4$, Sigma-Aldrich, 97%) were used without further purification. Stock solutions of Cu^{I} were prepared in CH_3CN and standardized by spectrophotometric analysis using 2,9-dimethyl-1,10-phenantroline as a specific ligand, as described in the literature [50]. Amine ligands, tris(2-pyridylmethyl)amine (TPMA, ATRP Solutions, 98%), tris[2-(dimethylamino)ethyl]amine (Me_6TREN , Sigma-Aldrich, 97%) and N,N,N',N'',N'' -pentamethyldiethylenetriamine (PMDETA, Sigma-Aldrich, $\geq 98\%$) were used as received. All initiators in Scheme 2 were purchased from Sigma-Aldrich or Alfa-Aesar with high purity and used as received.

2.2. Instrumentation

Cyclic voltammetry (CV) was performed by an Autolab PGSTAT30 potentiostat (Eco-Chimie, Utrecht, The Netherlands) interfaced to a PC running GPES 4.9 software provided by the manufacturer. A three electrode cell with a glassy carbon (GC) working electrode (3 mm diameter disc, Metrohm) and a Pt counter electrode was used. The reference electrode was a $\text{Ag}|\text{AgI}|0.1 \text{ M } n\text{-Bu}_4\text{NI}$ in CH_3CN , separated from the working solution by a glass frit and a salt bridge. The reference electrode was calibrated after each experiment against the ferrocenium/ferrocene couple (Fc^+/Fc), which allowed conversion of all potentials to the aqueous saturated calomel electrode (SCE) scale by using $E^\circ_{\text{Fc}^+/\text{Fc}} = 0.390 \text{ V vs SCE}$ [6]. Potential step chronoamperometry under steady-state conditions was performed using a rotating disc electrode, RDE, with a glassy carbon tip of 3 mm diameter (Autolab, Eco-Chimie). Prior to each experiment, the working electrode surface

was cleaned by polishing with 0.25- μm diamond paste, followed by ultrasonic rinsing in ethanol for 5 min.

Digital simulation of voltammetric responses was performed with DigiSim 3.03 (Bioanalytical Systems, Inc.).

All experiments were performed in a jacketed cell with a fixed temperature of 25 $^{\circ}\text{C}$.

3. Results and discussion

3.1. Potential step chronoamperometry at rotating disk electrode

The rate constant, k_{act} , of the reaction between $[\text{Cu}^{\text{I}}\text{L}]^{+}$ and RX was determined by monitoring the rate of disappearance of Cu^{I} at a rotating disc electrode [5,6,51]. To extract kinetic information from the ATRP equilibrium (Scheme 1), the reaction must be made irreversible by conducting all experiments in the presence of a good radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), in a large excess with respect to $[\text{Cu}^{\text{I}}\text{L}]^{+}$ [37]. The overall reaction is shown in Scheme 3. It is known that nitroxide free radicals such as TEMPO rapidly react with alkyl radicals ($k_{\text{c}} \approx 10^9 \text{ M}^{-1}\text{s}^{-1}$) [52-54] to form relatively stable alkoxyamines [37]. Under these conditions, reaction of the radical $\text{R}^{\bullet}$ with TEMPO is much faster than deactivation, so that the whole activation reaction becomes irreversible with the initial radical generation as rate-determining step. It is therefore possible to measure k_{act} by monitoring the decrease of $C_{[\text{Cu}^{\text{I}}\text{L}]^{+}}$ with time.

Since $[\text{Cu}^{\text{I}}\text{L}]^{+}$ exhibits a well-defined anodic wave at the RDE (Fig. 1), the limiting current, I_{L} , due to oxidation of $\text{Cu}(\text{I})$, can be used to monitor $C_{[\text{Cu}^{\text{I}}\text{L}]^{+}}$ during the reaction of an initiator RX with a $\text{Cu}(\text{I})$ complex according to the Levich equation [55]:

$$I_{\text{L}} = 0.62nFAD^{2/3}\omega^{1/2}\nu^{-1/6}C_{[\text{Cu}^{\text{I}}\text{L}]^{+}} \quad (2)$$

where n is the number of exchanged electrons, F is the Faraday constant, D is the diffusion coefficient of $[\text{Cu}^{\text{I}}\text{L}]^+$, A is the area of the electrode, ω is the rotation speed and ν is the kinematic viscosity.

Slow reactions were investigated under pseudo-first-order conditions using $C_{\text{RX}}^0 \geq 20C_{[\text{Cu}^{\text{I}}\text{L}]^+}^0$, whereas equimolar quantities of Cu(I) and RX were used with $C_{[\text{Cu}^{\text{I}}\text{L}]^+}^0 = 10^{-3} - 1.3 \times 10^{-4}$ M for faster reactions [33,51]. Experimentally, a constant potential in the plateau region of the oxidation wave of Cu(I) (Fig. 1a) was applied to a solution of $[\text{Cu}^{\text{I}}\text{L}]^+$ in the presence of a radical scavenger, e.g., TEMPO. After recording the current for a short period, the initiator was injected and the current decay was monitored (Fig. 1b). Elaboration of the data according to a pseudo-first-order or second-order rate law (details in the Supporting Information), provided the rate constant, k_{act} . An illustrative example of the application of this technique for k_{act} determination is reported in Fig. 1.

The RDE technique was applied to determine activation rate constants of a large set of alkyl halides by three Cu(I) complexes, and the results are collected in Tables 1 (chlorides) and 2 (bromides). This technique is limited to measure k_{act} values below $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. In fact, if $k_{\text{act}} = 5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and $C_{[\text{Cu}^{\text{I}}\text{L}]^+}^0 = C_{\text{RX}}^0 = 1.0 \times 10^{-4} \text{ M}$, the half-life time of $[\text{Cu}^{\text{I}}\text{L}]^+$ is 2.0 s, which is close to the mixing time under the best conditions, therefore preventing the possibility of obtaining reliable results. Most of the catalyst/initiator systems reported in Tables 1 and 2 have rate constants well below the limit of the technique, but some bromides with the highly active catalyst $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ show k_{act} values greater than $5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. These values were determined by a different technique, cyclic voltammetry, which gives a much faster response than potential step chronoamperometry with RDE.

3.2. Cyclic voltammetry with digital simulation

Figure 2 illustrates a typical voltammetric pattern of copper-amine catalysts ($[\text{Cu}^{\text{II}}\text{L}]^{2+}$) in the absence and presence of RX and TEMPO. In the absence of RX, a *quasi*-reversible peak couple

with $E^\circ = -0.120$ V vs SCE is observed (for L = Me₆TREN), indicating that electrogenerated [Cu^IL]⁺ is stable in CH₃CN [56]. After addition of RX with an excess factor $\gamma = C_{\text{RX}} / C_{[\text{Cu}^{\text{II}}\text{L}]^{2+}} = 0.5$, the anodic peak of [Cu^IL]⁺ drastically decreases while a new peak couple appears at a more negative potential, $E_{1/2} = -0.307$ V vs SCE. This new peak couple is attributed to the reversible reduction of [XCu^{II}L]⁺ (see Supporting Information). Further addition of RX ($\gamma = 1$) causes a marked increase of the [XCu^{II}L]⁺ reduction peak and complete disappearance of the anodic peak of [Cu^IL]⁺. The overall reaction sequence occurring in the presence of RX and TEMPO is

where $\bullet\text{O-NR}'$ stands for the nitroxide radical TEMPO. After reduction of [Cu^{II}L]²⁺ at the first peak, electrogenerated [Cu^IL]⁺ reacts with RX to give [XCu^{II}L]⁺ and R[•], which is rapidly captured by $\bullet\text{O-NR}'$. The new Cu(II) complex has a more negative reduction potential than [Cu^{II}L]²⁺ owing to the higher stability of [XCu^{II}L]⁺ than [XCu^IL] [56]. Reduction of [XCu^{II}L]⁺, followed by dissociation of [XCu^IL], regenerates the active [Cu^IL]⁺ species [5]. Therefore, the overall reaction cascade (3)-(7) constitutes a catalytic cycle in which the active form of the catalyst is regenerated through reactions (6) and (7). Accordingly, the reduction peak of [XCu^{II}L]⁺ is expected to be catalytic with a peak current depending on γ , k_{act} and scan rate [57,58].

The rate constant of reaction (4), k_{act} , can be determined by comparing experimental CV curves with voltammograms obtained by digital simulation of the whole reaction sequence (3)-(7). This technique was used to measure k_{act} of ethyl 2-bromoisobutyrate (EBiB), 1-phenylethyl bromide (PEB) and bromoacetonitrile (BAN) with [Cu^IMe₆TREN]⁺ as catalyst. Digital simulation of CV curves required knowledge of various thermodynamic and kinetic parameters that were either taken

from the literature or determined in this work. Cyclic voltammetry was used to determine the following parameters: (i) diffusion coefficients (D) of EBiB, PEB, BAN and Cu(II) complexes; (ii) standard reduction potentials (E°) of reactions (3) and (6); and (iii) standard heterogeneous electron transfer rate constants (k^0) of reactions (3) and (6) (experimental details are reported in the Supporting Information). The values of D measured for EBiB, PEB and BAN were $3.4 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, $2.4 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ and $4.5 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, respectively, whereas other parameters used in the simulations are reported in Table 3. Coupling of $\text{R}^\bullet$ with TEMPO (Eq. 5) was considered to be an irreversible reaction with a rate constant of $10^9 \text{ M}^{-1} \text{ s}^{-1}$ [37,53,54]. ATRP equilibrium constants, K_{ATRP} , for the reaction of the three alkyl bromides with $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ were previously reported by Tang et al. [7]. Similarly, the association constant of Br^- with $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$, $K_{\text{Br}} = 186$, was already reported [56].

Besides k_{act} , also the rate constant of dissociation of $[\text{BrCu}^{\text{I}}\text{Me}_6\text{TREN}]$ to $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and Br^- ($k_{\text{d,Br}}$, Eq. 7) is unknown. $k_{\text{d,Br}}$ was estimated through simulations of the catalytic system $[\text{Cu}^{\text{II}}\text{Me}_6\text{TREN}]^{2+}$ /benzyl bromide. Indeed, in this case k_{act} was determined independently through the RDE technique ($k_{\text{act}} = 4.1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$), so that simulations could be performed with $k_{\text{d,Br}}$ as the unique fitting parameter. This gave $k_{\text{d,Br}} = 3.16 \times 10^3 \text{ s}^{-1}$ (see Supporting Information). This value allowed determination of the rate constant of association of Br^- to $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]$ as $k_{\text{a,Br}} = K_{\text{Br}} k_{\text{d,Br}} = 5.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

Figure 3 shows an example of the comparison between experimental and simulated voltammograms in the case of $[\text{Cu}^{\text{II}}\text{Me}_6\text{TREN}]^{2+}$ /BAN. For all three alkyl bromides EBiB, PEB and BAN, a set of voltammograms at different scan rates were recorded at different γ values and fitted to calculated voltammograms. All systems showed excellent fittings and the extracted activation rate constants are included in Table 2.

The k_{act} value measured for the reaction between $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and EBiB ($1.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) is comparable to the one previously obtained by Bernhardt *et al.* [30] using a similar method based on

cyclic voltammetry simulation ($3.7 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$). However, our experimental and simulated CV data were compared by a different method, which involves superimposing the two sets of data on the same graph, as shown in Figure 3. Moreover, we further refined the method by determining the rate constant of dissociation of $[\text{BrCu}^{\text{I}}\text{Me}_6\text{TREN}]$, $k_{\text{d,Br}}$, as a unique fitting parameter in a separate experiment. The obtained value ($k_{\text{d,Br}} = 3.16 \times 10^3 \text{ s}^{-1}$) is significantly higher than the previously reported value of 76 s^{-1} [30], which was obtained by determining three fitting parameters in the same experiment, and is therefore likely to be subject to a larger error.

3.3. Structure-activity correlations

The rate constants of the reaction between $[\text{Cu}^{\text{I}}\text{L}]^+$ ($\text{L} = \text{PMDETA}$, TPMA and Me_6TREN) and a series of alkyl halides (Scheme 2), commonly used as initiators in ATRP, are summarized in Tables 1 and 2. For comparison, some literature data on k_{act} , measured by non-electrochemical methods, were included in the tables. All literature data were obtained with $\text{Cu}^{\text{I}}\text{X}/\text{L}$ as activator instead of $[\text{Cu}^{\text{I}}\text{L}]^+$ used in this work (Cu^{I} was introduced as $\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4\text{BF}_4$ to avoid the presence of coordinating anions). It has been shown that $[\text{Cu}^{\text{I}}\text{L}]^+$ is the active Cu^{I} species in ATRP [5]. Instead, when equimolar amounts of $\text{Cu}^{\text{I}}\text{X}$ and an amine ligand (such as Me_6TREN) are mixed in CH_3CN , two inactive species, $[\text{XCu}^{\text{I}}\text{L}]$ and $[\text{Cu}^{\text{I}}\text{X}_2]^-$, are formed together with $[\text{Cu}^{\text{I}}\text{L}]^+$ [56]. The presence of inactive species results in a slight decrease of observed k_{act} . Although there are some differences in experimental conditions, k_{act} values obtained in this study are fairly comparable with literature data. However, as expected, in several cases our k_{act} values are slightly higher than the literature values.

3.3.1. Correlations between k_{act} and standard reduction potentials of $[\text{Cu}^{\text{II}}\text{L}]^{2+}$

The standard reduction potentials of $[\text{Cu}^{\text{II}}\text{L}]^{2+}$ complexes are -0.120, -0.015 and 0.063 V vs SCE for $\text{L} = \text{Me}_6\text{TREN}$, TPMA and PMDETA , respectively [6]. The reactivity of the Cu^{I} complexes for a given RX roughly follows their reducing power. For example, $[\text{Cu}^{\text{I}}\text{PMDETA}]^+$ is *ca.* 180 mV less

reducing than $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and this is reflected in its reactivity, which is *ca.* 2 – 4 orders of magnitude lower than that of $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$. The difference of reactivity between the complexes strongly depends on the structure of RX and on the type of halogen atom. The rate constants measured with $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and $[\text{Cu}^{\text{I}}\text{TPMA}]^+$ were normalized with respect to k_{act} values obtained with $[\text{Cu}^{\text{I}}\text{PMDETA}]^+$ and this ratio, denoted as $k_{\text{act}}/k_{\text{act,PMDETA}}$, is reported in Fig. 4. In the chloride series, $k_{\text{act}}/k_{\text{act,PMDETA}}$ varied from 2.5×10^2 to 9.0×10^3 for $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and 2.1×10^1 to 1.2×10^3 for $[\text{Cu}^{\text{I}}\text{TPMA}]^+$. A similar trend was observed for the bromide series. Again both $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ and $[\text{Cu}^{\text{I}}\text{TPMA}]^+$ were much more reactive than $[\text{Cu}^{\text{I}}\text{PMDETA}]^+$.

It is important to note that while the observed reactivity trend $[\text{Cu}^{\text{I}}\text{PMDETA}]^+ \ll [\text{Cu}^{\text{I}}\text{TPMA}]^+ < [\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ does not disagree with the E° of the complexes, which decreases in the order $[\text{Cu}^{\text{I}}\text{PMDETA}]^+ > [\text{Cu}^{\text{I}}\text{TPMA}]^+ > [\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$, the two trends do not perfectly match. Comparing $[\text{Cu}^{\text{I}}\text{TPMA}]^+$ and $[\text{Cu}^{\text{I}}\text{PMDETA}]^+$, a difference of 78 mV in their standard potentials produces k_{act} enhancement of *ca.* 10^1 – 10^3 for chlorides and *ca.* 6×10^2 – 3×10^3 for bromides. In contrast, a comparison between $[\text{Cu}^{\text{I}}\text{TPMA}]^+$ and $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$ shows that although the difference between their standard potentials (105 mV) is significantly higher than that between $[\text{Cu}^{\text{I}}\text{PMDETA}]^+$ and $[\text{Cu}^{\text{I}}\text{TPMA}]^+$, k_{act} increases less than 10 times for both alkyl halide series when passing from $[\text{Cu}^{\text{I}}\text{TPMA}]^+$ to $[\text{Cu}^{\text{I}}\text{Me}_6\text{TREN}]^+$.

Besides the redox potential, the reactivity of $[\text{Cu}^{\text{I}}\text{L}]^+$ depends on molecular structures of both Cu complex and RX, and on the nature of the halogen atom. Another important parameter, which has not been taken into account in this analysis, is the different halidophilicity of Cu complexes [56]. In conclusion, the activation-driving force relationship of the process differs from that of an outer-sphere electron transfer and it is not easy to construct simple and meaningful structure-reactivity relationships from k_{act} vs. $E^\circ_{[\text{Cu}^{\text{III}}\text{L}]^{2+}/[\text{Cu}^{\text{I}}\text{L}]^+}$ data alone.

3.3.2. Correlations between k_{act} and standard reduction potentials of $[XCu^{II}L]^+$

In ATRP experiments the catalyst is often introduced into the system as $Cu^{II}X_2/L$, which predominantly produces $[XCu^{II}L]^+$ in solution [56]. It is therefore customary to measure E° of $[XCu^{II}L]^+/[XCu^IL]$ and correlate it with thermodynamic parameters of the activation reaction [7,8,59]. To correlate k_{act} with $E^\circ_{[XCu^{II}L]^+/[XCu^IL]}$, it is necessary to consider a series of activation reactions (Eq. 12) in which only $E^\circ_{[XCu^{II}L]^+/[XCu^IL]}$ changes. The overall activation reaction can be split into four steps:

The free energy of reaction (12) is given by

$$\Delta_r G_{12}^\circ = BDFE + F \left(E^\circ_{[XCu^{II}L]^+/[XCu^IL]} - E^\circ_{X/X^-} \right) - RT \ln K_X^I \quad (13)$$

where BDFE is the R-X bond dissociation free energy. If one uses a single alkyl halide and a series of Cu complexes, BDFE and E°_{X/X^-} are fixed, but $E^\circ_{[XCu^{II}L]^+/[XCu^IL]}$ and K_X^I change with the ligand. Correlating k_{act} with $E^\circ_{[XCu^{II}L]^+/[XCu^IL]}$ could be justifiable if the effect of ligand structure on K_X^I were negligible, but experimental evidences show that this is not the case. For example, $K_{Br}^I = 1.86 \times 10^2$ and 6.61×10^1 for $[Cu^I Me_6 TREN]^+$ and $[Cu^I PMDETA]^+$, respectively. The difference is even bigger with $X = Cl$: $K_{Cl}^I = 3.72 \times 10^2$ and 5.89×10^1 for $[Cu^I Me_6 TREN]^+$ and $[Cu^I PMDETA]^+$, respectively. However, while variations of K_X^I are less than one order of magnitude, $E^\circ_{[XCu^{II}L]^+/[XCu^IL]}$ varies by *ca.* 230 mV [59], which corresponds to over 3 orders of magnitude of difference in ATRP activity [7].

It appears that the activity of $[\text{Cu}^{\text{I}}\text{L}]^+$ depends more strongly on the nature of the ligand than on halidophilicity. As a result, satisfactory correlations were obtained by plotting k_{act} versus $E^\ominus_{[\text{XCu}^{\text{III}}\text{L}]/[\text{XCu}^{\text{II}}\text{L}]}$ (Fig. 5), despite the error introduced by neglecting the role of halidophilicity on activation rate.

Figure 5 shows how activation of RX scales almost linearly for all complexes, with similar slopes for all alkyl halides. Clearly, the activation of RCl is significantly slower than that of RBr, due to higher bond dissociation energy and lower reduction potential of RCl than RBr [60].

3.3.3. Effect of RX structure on k_{act}

Interesting observations come from the analysis of the reactivity order of RX for any given catalyst. As expected, alkyl chlorides are always less reactive than the corresponding bromides, k_{act} being more than 10 times smaller for RCl than for RBr. As previously reported [43], k_{act} values for tertiary, secondary, and primary ester initiators follow the order $3^\circ > 2^\circ > 1^\circ$ (e.g., EBiB > MBP > EBA). Furthermore, within a fixed set of tertiary, secondary or primary RX ($X = \text{Cl}$ or Br), the order of reactivity follows the ability of the substituent to stabilize the radical. Thus, the general order is $\text{CN} > \text{Ph} > \text{COOR}$ (e.g., CAN > BC > ECA and BAN > BB > EBA).

3.3.4. Correlations between k_{act} and K_{ATRP}

In a well-controlled ATRP, the overall propagation rate depends on K_{ATRP} (Eq. (1)). On the other hand, the control in ATRP, in terms of molecular weight distribution (M_w/M_n), strongly depends on the deactivation rate constant (k_{deact}). In the ideal case of fast initiation and no termination M_w/M_n is expressed as [2]:

$$\frac{M_w}{M_n} = 1 + \frac{1}{DP_n} + \frac{k_p C_{\text{P}_n\text{X}}}{k_{\text{deact}} C_{[\text{XCu}^{\text{II}}\text{L}]^+}} \left(\frac{2}{p} - 1 \right) \quad (14)$$

where DP_n is the average degree of polymerization, C_{P_nX} is the concentration of dormant species, k_p is the rate constant of propagation and p is monomer conversion. A good control in ATRP requires very fast deactivation of radicals, which means k_{deact} should be as high as possible. For all investigated initiators k_{deact} was calculated from K_{ATRP} values reported in the literature and the measured k_{act} , and the results are reported in Tables 1 and 2. Figure 6 shows correlations of k_{act} and k_{deact} with K_{ATRP} . Both k_{act} and K_{ATRP} depend on the structure of RX and amine ligand and particularly on the nature of the halogen atom. Two separate plots were therefore constructed for the chloride and bromide series. As shown, $\log k_{act}$ increases with $\log K_{ATRP}$ for each series and the whole set of data obtained for different complexes can be roughly fit to a straight line. In contrast, k_{deact} is very high for all investigated systems, as required in ATRP, and is little affected by the molecular structure of RX or amine ligand. Although k_{deact} of the chloride series shows a slight tendency to decrease with increasing K_{ATRP} , on average k_{deact} of each series can be considered to be fairly constant with $\log k_{deact} = 6.2 \pm 0.9$ for RCl and $\log k_{deact} = 7.3 \pm 1.1$ for RBr. This trend is consistent with previous results [7]. It is important to stress that each set of data covers a wide range of k_{act} and K_{ATRP} values, which makes the observed trends particularly significant.

3.3.5. Correlations between k_{act} and R-X bond dissociation free energy

The $\log k_{act}$ versus $\log K_{ATRP}$ plots shown in Fig. 6 represent an important result enabling the estimation of k_{act} from experimental K_{ATRP} and vice versa. Since the mechanism of ATRP activation involves the transfer of a halogen atom from RX to a copper(I) complex, it is likely that the reaction kinetics are related to the bond energy. Indeed, if one splits the overall activation reaction (Eq. 12) into four steps (Eq (8) – (11)), $\Delta_r G^\circ_{12}$ can be obtained as the sum of the Gibbs free energies of reactions (8)-(11) (Eq. (13)). If one considers a particular copper complex and a series of chlorides or bromides, reactions (8), (10) and (11) will be the same for the whole series with a fixed

contribution to $\Delta_r G^\circ_{12}$. Therefore, k_{act} is expected to correlate with the bond dissociation free energy, BDFE, of RX.

Experimental data on BDFE of alkyl halides used as initiators of ATRP are not available, but reliable values can be obtained by computational methods. Indeed, BDFE values for a large set of initiators have recently been reported in CH₃CN [61]. Fairly linear correlations between k_{act} and BDFE were found for all three investigated complexes (Fig. 7). In each data set, k_{act} decreases with increasing BDFE. Activation of allyl bromide is a clear exception to this trend: with all three Cu complexes k_{act} for this halide is *ca.* 2 orders of magnitude lower than the value predicted on the basis of the correlations. The lowered reactivity of Cu(I) might be due to stabilization of the metal by formation of a complex with allyl bromide through π -interaction. Indeed, stable complexes between olefins and [Cu^IPMDETA]⁺ have been reported [62].

4. Conclusions

Electrochemical techniques based on direct monitoring of Cu^I species (RDE) or on digital simulation of cyclic voltammetry were used to accurately determine ATRP activation rate constants. Analysis of the measured k_{act} values ($4.3 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ – $2.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) shows that the general reactivity of copper complexes ([Cu^IL]⁺) depends on the molecular structure of the amine ligand (L) and initiator (RX). For any fixed RX, k_{act} increases in the following order: PMDETA << TPMA < Me₆TREN. Generally, alkyl bromides are more reactive than alkyl chlorides. The structure of RX influences k_{act} in terms of degree of substitution and nature of the substituent on the C-X moiety. The following trends of increasing k_{act} were observed: primary < secondary < tertiary and CO₂R < Ph < CN.

Attempts to correlate k_{act} with the standard reduction potential of the catalyst, [Cu^{II}L]²⁺, did not provide well-defined structure-activity relationships: k_{act} depends on $E^\circ_{[\text{Cu}^{\text{II}}\text{L}]^{2+}/[\text{Cu}^{\text{I}}\text{L}]^+}$ together with many other factors. Conversely, a useful empirical correlation was obtained between k_{act} and

$E^{\circ}_{[\text{XCu}^{\text{III}}\text{L}]/[\text{XCu}^{\text{I}}\text{L}]}$. Good linear correlations that could be used to predict the activity of Cu^{I} complexes or the reactivity of alkyl halide initiators were obtained by plotting k_{act} versus K_{ATRP} or versus the C-X bond dissociation free energy.

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Figure captions

Figure 1. a) Steady-state voltammetry of 5×10^{-4} M $[\text{Cu}^{\text{I}}\text{L}]^+$ in $\text{CH}_3\text{CN} + 0.1$ M Et_4NBF_4 at a GC rotating disk electrode ($\omega = 2500$ rpm). b) Potential step chronoamperometry ($E_i = -0.3$ V, $E_f = 0.15$ V) of 2.5×10^{-4} M $[\text{Cu}^{\text{I}}\text{L}]^+$ in the presence of 2.5×10^{-4} M MBP and 5×10^{-3} M TEMPO, recorded at RDE at $\omega = 5000$ rpm; inset: kinetic analysis according to a second-order rate law.

Figure 2. Cyclic voltammetry of 1.01×10^{-3} M $[\text{Cu}^{\text{II}} \text{Me}_6\text{TREN}]^{2+}$ at $v = 0.1$ V s^{-1} in $\text{CH}_3\text{CN} + 0.1$ M Et_4NBF_4 in the absence (a) and presence of (b) 1.01×10^{-2} M TEMPO + 5.05×10^{-4} M BAN or (c) 1.01×10^{-2} M TEMPO + 1.02×10^{-3} M BAN; $T = 25$ °C.

Figure 3. Background subtracted experimental (—) and simulated (○) voltammograms of $[\text{Cu}^{\text{II}}\text{Me}_6\text{TREN}]^{2+}$ in the presence of bromoacetonitrile recorded at $\gamma = C_{\text{RX}}/C_{[\text{Cu}^{\text{II}}\text{L}]^{2+}} = 0.5$ and 1 in $\text{CH}_3\text{CN} + 0.1$ M Et_4NBF_4 at 25 °C.

Figure 4. Comparison between rate constants of RX activation by different Cu^{I} complexes in $\text{CH}_3\text{CN} + 0.1$ M Et_4NBF_4 at 25 °C.

Figure 5. Correlation between $\log k_{\text{act}}$ and $E^\circ_{[\text{XCu}^{\text{II}}\text{L}]/[\text{XCu}^{\text{I}}\text{L}]}$ in $\text{CH}_3\text{CN} + 0.1$ M Et_4NBF_4 at 25 °C.

Figure 6. Correlation of k_{act} and k_{deact} with K_{ATRP} for the reaction of various alkyl chlorides (RCl) and bromides (RBr) with $[\text{Cu}^{\text{I}}\text{L}]^+$ complexes in CH_3CN : L = Me_6TREN (circles), TPMA (squares) and PMDETA (triangles). K_{ATRP} values were taken from ref. [7]. The broken lines were drawn to show the trends.

Figure 7. Correlation of k_{act} with bond dissociation free energy of RX for the reaction of various alkyl chlorides (RCl) and bromides (RBr) with $[\text{Cu}^{\text{I}}\text{L}]^+$ complexes in CH_3CN : L = Me_6TREN (circles), TPMA (squares) and PMDETA (triangles). BDFE values were taken from ref. [60].

Table 1. Rate constants of the reaction between alkyl chlorides and $[\text{Cu}^{\text{I}}\text{L}]^+$ in $\text{CH}_3\text{CN} + 0.1 \text{ M Et}_4\text{NBF}_4$ at 25°C , determined by steady state chronoampermetry at a rotating disk electrode.

L	RX	$k_{\text{act}} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{deact}} (\text{M}^{-1} \text{s}^{-1})^{\text{a}}$	$k_{\text{act}} (\text{M}^{-1} \text{s}^{-1})^{\text{lit,b}}$
Me_6TREN	BC	1.9	5.3×10^5	0.93^{c}
	ECA	0.47	1.3×10^5	
	CAN	2.3×10^2	4.8×10^5	
	MCP	1.7×10^1	8.5×10^6	
	CPN	8.1×10^2	2.4×10^6	
	PEC	7.7	5.5×10^5	
TPMA	BC	7.8×10^{-1}	1.7×10^6	1.5^{d}
	ECA	5.5×10^{-2}	1.3×10^5	
	CAN	3.8×10^1	1.2×10^6	
	MCP	1.4	3.4×10^7	
	CPN	1.1×10^2	4.9×10^6	
	PEC	3.5	4.0×10^6	
PMDETA	BC	7.3×10^{-3}	2.1×10^6	$1.5 \times 10^{-2\text{c}}$
	ECA	4.3×10^{-4}	1.3×10^5	
	CAN	4.0×10^{-2}	1.7×10^5	
	MCP	6.8×10^{-2}	2.1×10^8	
	CPN	9.0×10^{-2}	5.3×10^5	
	PEC	1.0×10^{-2}	1.5×10^6	

^aDetermined as $k_{\text{act}}/K_{\text{ATRP}}$. K_{ATRP} values at $T = 22^\circ\text{C}$ from ref. [7].

^bIn the presence of X^- with $[\text{Cu}(\text{I})]:[\text{X}^-] = 1:1$.

^cAt 22°C , from ref. [43].

^dAt 35°C , from ref. [36].

^eAt 20°C , from ref. [44].

Table 2. Rate constants of activation of alkyl bromides by $[\text{Cu}^{\text{I}}\text{L}]^+$ in $\text{CH}_3\text{CN} + 0.1 \text{ M Et}_4\text{NBF}_4$ at 25 °C.

RX		$k_{\text{act}} (\text{M}^{-1} \text{s}^{-1})$	$k_{\text{deact}} (\text{M}^{-1} \text{s}^{-1})^{\text{a}}$	Method ^b	$k_{\text{act}} (\text{M}^{-1} \text{s}^{-1})^{\text{lit,c}}$
Me ₆ TREN	EBA	2.2×10^1	1.0×10^6	CA-RDE	
	BB	4.1×10^2	4.9×10^8	CA-RDE	
	BAN	2.1×10^4	2.4×10^7	DS-CV	
	AB	3.3×10^2	1.2×10^6	CA-RDE	
	PEB	1.9×10^3	7.3×10^6	DS-CV	$8.6 \times 10^{2\text{d}}$
	MBP	2.1×10^3	7.2×10^8	CA-RDE	
	EBiB	1.2×10^4	8.0×10^7	DS-CV	$7.7 \times 10^{3\text{d}}; 3.7 \times 10^{4\text{e}}$
TPMA	EBA	2.0	6.3×10^6	CA-RDE	
	BB	1.6×10^2	2.4×10^8	CA-RDE	
	BAN	2.7×10^3	4.8×10^7	CA-RDE	
	AB	1.2×10^2	7.1×10^6	CA-RDE	
	PEB	7.7×10^2	1.7×10^8	CA-RDE	
	MBP	2.2×10^2	6.9×10^8	CA-RDE	
	EBiB	4.5×10^3	4.7×10^8	CA-RDE	
PMDETA	EBA	3.2×10^{-3}	1.3×10^6	CA-RDE	
	BB	3.4×10^{-2}	6.4×10^6	CA-RDE	
	BAN	3.4	3.9×10^5	CA-RDE	3.91^{f}
	AB	3.7×10^{-2}	2.9×10^5	CA-RDE	$3.8 \times 10^{-2\text{f}}$
	PEB	1.4×10^{-1}	4.2×10^6	CA-RDE	$9.7 \times 10^{-2\text{f}}; 0.12^{\text{g}}; 0.19^{\text{h}}$
	MBP	1.7×10^{-1}	4.3×10^7	CA-RDE	
	EBiB	2.0	2.7×10^7	CA-RDE	$2.3^{\text{d}}; 1.75^{\text{f}}; 1.7^{\text{g}}$

^aDetermined as $k_{\text{act}}/K_{\text{ATRP}}$. K_{ATRP} values at $T = 22^\circ\text{C}$ from ref. [7].

^bCA-RDE = steady state chronoamperometry at a rotating disk electrode; DS-CV = digital simulation of CV.

^cIn the presence of X^- with $[\text{Cu}(\text{I})]:[\text{X}^-] = 1:1$.

^dAt 25 °C, from ref. [28].

^eAt 25 °C, from ref. [30].

^fAt 20 °C, from ref. [44].

^gAt 35 °C, from ref. [37].

^hAt 25 °C, from ref. [45].

Table 3. Thermodynamic and kinetic parameters used in the digital simulations for k_{act} determination in $\text{CH}_3\text{CN} + 0.1 \text{ M } (\text{C}_2\text{H}_5)_4\text{NBF}_4$ at $T = 25^\circ\text{C}$.

Complex	E° (V vs SCE)	k^0 (cm s^{-1})	D ($\text{cm}^2 \text{ s}^{-1}$)	K_{Br}^{a}	$k_{\text{d,Br}}^{\text{b}}$ (s^{-1})
$[\text{Cu}^{\text{II}}\text{Me}_6\text{TREN}]^{2+}$	-0.120	3.1×10^{-2}	6.9×10^{-6}		
$[\text{BrCu}^{\text{I}}\text{Me}_6\text{TREN}]^+$	-0.341	5.1×10^{-2}	1.1×10^{-5}	1.86×10^2	3.16×10^3

^a K_{Br} is the equilibrium constant of the association of $[\text{Cu}^{\text{I}}\text{L}]^+$ with Br^- , taken from ref. [56]. ^b Rate constant of dissociation of $[\text{BrCu}^{\text{I}}\text{L}]$ (Eq. 7).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Graphical Abstract