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Atom Transfer Radical Polymerization

Controlled Aqueous Atom Transfer Radical Polymerization with Electrochemical Generation of the Active Catalyst**

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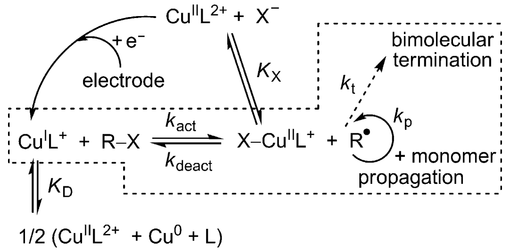
Controlled/living radical polymerizations (C/LRPs) in aqueous media are attractive from both economic and environmental points of view. Aqueous media can be used for the synthesis of a vast array of hydrophilic and hydrophobic polymers, through homogenous and heterogeneous (e.g. suspension and (mini)emulsion) polymerization systems, respectively.[1] Moreover, efficient C/LRPs conducted in aqueous saline buffers can be crucial for the preparation of polymer–biomolecule conjugates under biologically relevant conditions.[2]

Atom transfer radical polymerization (ATRP) is one of the most commonly employed C/LRP techniques, enabling the synthesis of polymers with predetermined molecular weights, narrow molecular weight distributions, and specific compositions and architectures. ATRP is often catalyzed by a Cu^{II}/Cu^{I} system in which the success of this process relies on a rapid and reversible activation/deactivation step. In this dynamic equilibrated system, activators ($Cu^{I}L^{+}$) react with dormant macromolecular species (RX) to produce propagating radicals ($R^{\bullet}$) and deactivators ($X\text{-}Cu^{II}L^{+}$; Scheme 1, region delimited by the dashed line). In nonaqueous solvents the equilibrium constant, $K_{ATRP} = k_{act}/k_{deact}$, is usually small ($<10^{-4}$)[3] resulting in a dramatic decrease of [$R^{\bullet}$] which consequently suppresses bimolecular termination reactions.

In contrast to the success of ATRP in organic solvents, aqueous ATRP has been found to suffer from some limitations, specifically with regard to achieving polymerization control and the targeted degree of polymerization (DP).[4] These observed limitations in aqueous ATRP may result from three main phenomena. First, aqueous ATRP has a relatively large K_{ATRP} providing a high [$R^{\bullet}$] and usually fast polymerizations.[5] Second, the halidophilicity (K_X) of $Cu^{II}L^{2+}$, that is, association of X^- to $Cu^{II}L^{2+}$, is small therefore diminishing the concentration of deactivator $X\text{-}Cu^{II}L^{+}$.[6a] Third, $Cu^{I}L^{+}$ may be unstable in water and may undergo disproportionation.



Scheme 1. Mechanism of conventional (delimited by dashed line) and aqueous electrochemical ATRP.

Developing a successful aqueous ATRP requires consideration of all the previously mentioned issues.[6a] In fact, improved polymerization control was found by using a high [X^-], which helps to suppress deactivator dissociation.[6] Further development of the process has been recently achieved through AGET (activators generated by electron transfer) ATRP.[7] Although this process provides good results in terms of both control and DP, the correct [Cu^{II}]/[reducing agent] ratio and appropriate reducing agent are critical for success.[7b] The ideal process should have a constant and high Cu^{II}/Cu^{I} ratio, which is difficult to achieve over the whole polymerization by addition of a single reducing agent.

Herein we describe an electrochemical ATRP method (*e*ATRP), aimed to fulfill these criteria. The overall mechanism of *e*ATRP is depicted in Scheme 1. Initially, the reaction mixture contains solvent, monomer, initiator, and $Cu^{II}L^{2+}$ (or $Cu^{II}L^{2+} + X\text{-}Cu^{II}L^{+}$). Under these conditions, $Cu^{I}L^{+}$ activator is absent in solution, and hence, no polymerization occurs. The onset of polymerization begins only when a sufficient potential (E_{app}) is applied to the cathode so that reduction of $Cu^{II}L^{2+}$ to $Cu^{I}L^{+}$ occurs at the working electrode. The magnitude of E_{app} can be appropriately chosen to achieve a continuous (re)generation of a small quantity of $Cu^{I}L^{+}$ and consequently dictate the [$R^{\bullet}$]. A living polymerization process is ensured by the combination of a low [$R^{\bullet}$] and high [$Cu^{II}L^{2+}$]/[$Cu^{I}L^{+}$] ratio. Furthermore, the polymerization rate and degree of control can be tuned by adjusting the E_{app}. The first example of ATRP under electrochemical generation of activator has been recently reported for the successful polymerization of methyl acrylate in acetonitrile.[8]

Herein, we describe *e*ATRP of oligo(ethylene glycol) methyl ether methacrylate ($OEOMA_{475}$) in water. As a catalyst system, $Cu^{II/I}$TPMA (TPMA = tris(2-pyridylmethyl)-amine) was selected, which is one of the most active

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complexes used in ATRP.[9] Cyclic voltammetry (CV) of this $Cu^{II}L^{2+}$ complex exhibits a reversible peak couple at $E^{o\prime} = -0.245$ V versus the standard calomel electrode (SCE) (Figure 1). Addition of a large excess of Br^- to the solution had no significant effect on the CV response, indicating that the K_X of $Cu^{II}L^{2+}$ is small (see Figure S1 in the Supporting Information). The full reversibility of this response at low scan rates also indicated that $Cu^{I}L^{+}$ is quite stable in H_2O with a lifetime of at least a few seconds (duration of CV). In fact, we estimated a K_D value of 6.8×10^{-3} for the disproportionation of $Cu^{I}L^{+}$ (see the Supporting Information).

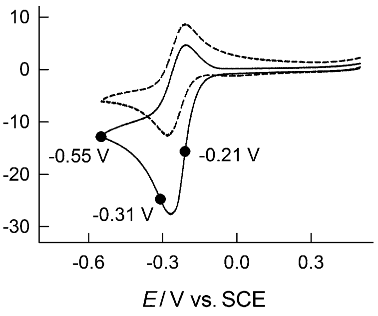

Figure 1. Cyclic voltammograms of 1 mм $Cu^{II}L^{2+}$ in H_2O/$OEOMA_{475}$ (9:1 v/v) + 0.1 м Et_4NBF_4 recorded at $v = 0.1$ V s^{-1} in the absence (-----) and presence (——) of 1 mм HEBriB; the three dots on the CV trace correspond to the E_{app} values used in the polymerization experiments.

The CV response of $Cu^{II}L^{2+}$ drastically changed when an equimolar amount of initiator (2-hydroxyethyl 2-bromoisobutyrate, HEBriB) was added; the cathodic peak approximately doubled in height while the anodic one decreased, clearly indicating that $Cu^{I}L^{+}$ rapidly reacted with HEBriB. On the basis of thermodynamic data available in the literature, we estimated a K_{ATRP} value of 1.5×10^{-1} for this system (see the Supporting Information), which is 4 orders of magnitude higher than that measured for an analogous system in CH_3CN.[3a] An estimate of the activation rate constant based on voltammetric analysis of the system (i.e. $Cu^{II}L^{2+}$ + HEBriB) at different concentration ratios (see Figure S3 in the Supporting Information) and scan rates provided a very large $k_{act} \geq 2.5 \times 10^{6}$ м$^{-1}$ s^{-1}.

These voltammetric analyses have shown that the system under investigation has all the characteristics (low K_X, high K_{ATRP}, and rapid activation) expected to result in an uncontrolled polymerization. Therefore, this system represents an ideal candidate to test the ability of the proposed electrochemical method to control aqueous ATRP. Electrogeneration of the active catalyst was carried out under potentiostatic conditions starting from the catalytic system $Cu^{II}L^{2+}$/HEBriB 1:1 in H_2O + 10% $OEOMA_{475}$ (molecular weight, MW = 475). The effect of E_{app} on the degree of polymerization control was first investigated. Three E_{app} values around $E^{o\prime}$ (see Figure 1) were applied and the results are summarized in Table 1 (entries 1–3).

The driving force of the electrochemical process is given by $\Delta G^{o} = F(E_{app} - E^{o\prime})$ and the $[Cu^{II}L^{2+}]/[Cu^{I}L^{+}]$ ratio at the electrode surface is closely related to that dictated by the Nernst equation. At the beginning of electrolysis there is only $Cu^{II}L^{2+}$ present in solution, so the current must decay as Cu^{II} is converted to Cu^{I}, thereafter approaching zero as the $[Cu^{II}L^{2+}]/[Cu^{I}L^{+}]$ ratio approaches the value required by E_{app}. However, $Cu^{I}L^{+}$ also participates in a reversible reaction with alkyl halides (i.e. dormant species), which represents a perturbation to the equilibrium concentrations imposed by E_{app}. Therefore, whether a constant $[Cu^{II}L^{2+}]/[Cu^{I}L^{+}]$ ratio can be imposed in the bulk solution depends on the mutual rates of electrogeneration and disappearance of $Cu^{I}L^{+}$ and therefore will depend on E_{app}. Actually, the current decreases to a small constant value rather than to zero (see Figure S4 in the Supporting Information) because of the dynamic ATRP equilibrium and the termination reactions.

At $E_{app} = -0.55$ V, which is $\ll E^{o\prime}$, the electrode process is under diffusion control and $Cu^{II}L^{2+}$ is almost quantitatively converted to $Cu^{I}L^{+}$ in a relatively short time; this behavior is exemplified by the rapidly decreasing current to a minimal value (see Figure S4 in the Supporting Information). The overall rate of polymerization was rather high, and 79% monomer conversion was achieved in less than 30 min (Figure 2a), however, at the expense of polymerization control. The plot of ln([monomer]/[monomer]$_0$) versus time deviated significantly from linearity, while the distributions of MW, expressed as M_w/M_n (where M_w and M_n are the weight-average and number-average molecular weights, respectively) were broad (Figure 2b). These features are typical of an

Table 1: Electrochemical aqueous ATRP of $OEOMA_{475}$ at 25 °C.

Entry	Monomer [% v/v]	[monomer]/[RX]/[Cu^{II}L]	Electrolyte[c]	E_{app} [V vs. SCE]	t [h]	Q [C]	Conv. [%][e]	$M_{n,theor}$ [10^{-3}]	$M_{n,app}$ [10^{-3}][f]	M_w/M_n
1	10	200/1/1[a]	Et_4NBF_4	−0.550	0.5	3.05	79	75.1	71.6	1.58
2	10	200/1/1[a]	Et_4NBF_4	−0.310	1.8	4.34	88	83.2	74.8	1.53
3	10	200/1/1[a]	Et_4NBF_4	−0.210	3.0	2.65	98	93.1	54.1	1.22
4	10	200/1/1[a]	Et_4NBr	−0.210	2.5	2.32	99	94.0	56.8	1.16
5	10	200/1/1[a]	PBS buffer[d]	−0.275	3.0	1.94	98	93.1	58.2	1.15
6	5.0	1000/1/1[b]	Et_4NBr	−0.210	2.0	0.175	84	399	202	1.25
7	2.5	500/1/1[b]	Et_4NBr	−0.210	2.0	0.210	72	171	106	1.19
8	1.0	200/1/1[b]	Et_4NBr	−0.210	2.5	0.267	77	73.2	61.3	1.35
9	5.0	1000/1/1[b]	PBS buffer[d]	−0.275	2.0	0.179	79	375	177	1.20

[a] $[Cu^{II}L^{2+}] = 1$ mм. [b] $[Cu^{II}L^{2+}] = 0.1$ mм. [c] 0.1 м. [d] 0.137 м NaCl + 2.7 mм KCl + 11.9 mм ($Na_2(HPO_4)$ + KH_2PO_4) in H_2O; pH 7.4. [e] Determined by ^{1}H NMR analysis. [f] Determined by GPC with linear PMMA calibration.[10]

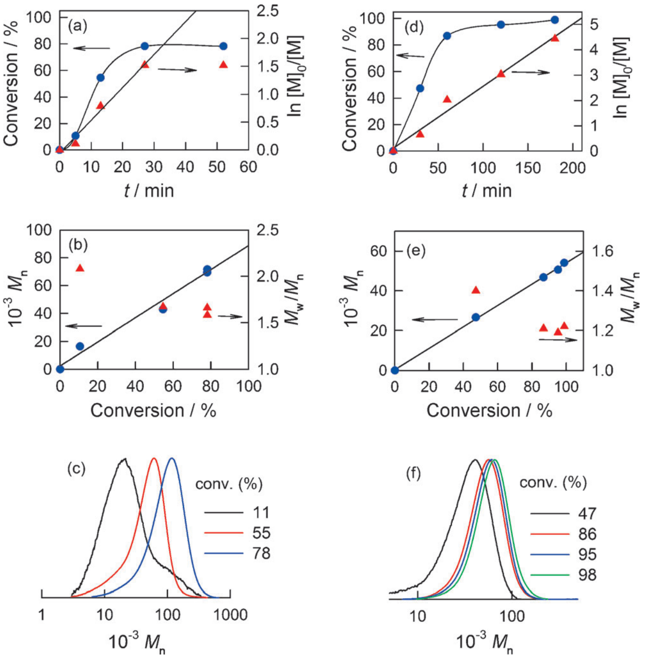

Figure 2. First-order kinetic plots (a, d; M = monomer), evolution of molecular weight and molecular-weight distribution (b, e), and GPC traces (c, f) as a function of conversion for *e*ATRP of OEOMA$_{475}$ performed in H_2O at $E_{app} = -0.55$ V (a–c) or -0.21 V (d–f). Conditions: [monomer]/[RX]/[$Cu^{II}L^{2+}$] = 200:1:1, [$Cu^{II}L^{2+}$] = 1 mM, $T = 25$ °C.

uncontrolled polymerization dominated by termination reactions, such as bimolecular radical–radical coupling as shown in Figure 2c (conv. ≈ 11 %).

With $E_{app} = -0.31$ V, the current decays slower than in the case of -0.55 V, but also reaches a constant value except after a longer duration (see Figure S4 in the Supporting Information). Under these conditions, the rate of polymerization decreased without significant improvement in polymerization control (Table 1, entry 2). However, utilizing $E_{app} = -0.21$ V, the current decays very slowly, approaching a constant value (≈ −250 μA) within a short period (Figure S4). Note that $E_{app} > E^o$, which implies an equilibrium ratio $[Cu^{II}L^{2+}]/[Cu^{I}L^{+}] \gg 1$. In this case, the polymerization was observed to be under control ascertained by the linearity of the first-order kinetic plot (Figure 2d and Table 1, entry 3). Nearly quantitative monomer conversion was attained; furthermore, M_n increases linearly as a function of monomer conversion and low M_w/M_n values (ca. 1.2) were realized. This improvement in polymerization control was achieved through low charge consumption (Q), which serves as evidence of a drastic decrease in termination events due to an appropriately supplied balance between [$Cu^{I}L^{+}$] and [$Cu^{II}L^{2+}$].

To promote the formation of X-$Cu^{II}L^{+}$, additional experiments were performed in the presence of a large excess of X^- (Table 1, entries 4 and 5). As shown, the presence of X^- resulted in a significant improvement to the MW distribution without any loss to the final monomer conversion. Furthermore, the overall rate does not decrease as a result of the formation of inactive $Cu^{I}X_n$ species, as previously demonstrated in organic solvents.[11]

In an effort to expand the utility of this *e*ATRP process, we carried out polymerizations under biologically relevant conditions using a PBS buffer. In this medium $E^{o\prime}$ shifts to -0.326 (see Figure S5 in the Supporting Information), therefore requiring an adjustment of the E_{app} to -0.275 V, which provides an effective E_{app} similar to that used in the previous experiments (Table 1, entries 3 and 4). Although several interferences perturbing the ATRP equilibrium are plausible (e.g., formation of insoluble $Cu^{II}_3(PO_4)_2$, stable $Cu^{I}(H_2PO_4)_2^-$, and/or $Cu^{I}Cl_2^-$ [11,12]), excellent results were observed both in terms of conversion and M_w/M_n values (Table 1, entry 5). Indeed, neither displacement of the ligand nor loss of catalysis was observed by CV analysis.

Last, different targeted DPs were explored (Table 1, entries 6–8) using 0.1 mM $Cu^{II}L^{2+}$ (6.4 ppm with respect to medium) and different concentrations of monomer. All polymerizations resulted in linear plots of ln([monomer]/[monomer]$_0$) versus time (Figure S6 in the Supporting Information), which together with low M_w/M_n, values, are indicative of a well-controlled *e*ATRP. Good results were obtained also in the PBS buffer (Table 1, entry 9).

In conclusion, this work illustrates that *e*ATRP overcomes many of the drawbacks typically associated with conventional aqueous ATRP. The $Cu^{II}L^{2+}$ to $Cu^{I}L^{+}$ ratio, which is crucial to accomplish a well-controlled polymerization, can be easily regulated by the appropriate selection of E_{app}. The best results were observed at $E_{app} > E^0_{Cu^{II}L/Cu^{I}L}$, providing excellent control over MW and MW distribution, accompanied by a fast polymerization rate and low charge consumption. Furthermore, *e*ATRP was demonstrated to be tolerant to both phosphates and halide ions, which additionally served to provide reduced M_w/M_n values. The presented aqueous *e*ATRP system may also provide an attractive polymerization system for the synthesis of biologically relevant materials.

Experimental Section

Electrochemical measurements were performed on a PARC 263A potentiostat in a thermostatted three-electrode cell under N_2 atmosphere, using Pt working electrodes, Pt counter electrode, and saturated calomel reference electrode (SCE).

Monomer conversions were measured by ^{1}H NMR analysis in D_2O using a Bruker 500 MHz spectrometer. Relative molecular weights and M_w/M_n values were determined by gel-permeation chromatography (GPC), using a Waters 2414 RI detector and PSS columns (Styrogel 10^5, 10^3, 10^2 Å) with a calibration based on PMMA standards (in THF at 35 °C).

Purification of materials as well as procedures and further experimental details are reported in the Supporting Information.

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