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Preparation of Well-Defined Polymers and DNA−Polymer Bioconjugates via Small-Volume eATRP in the Presence of Air

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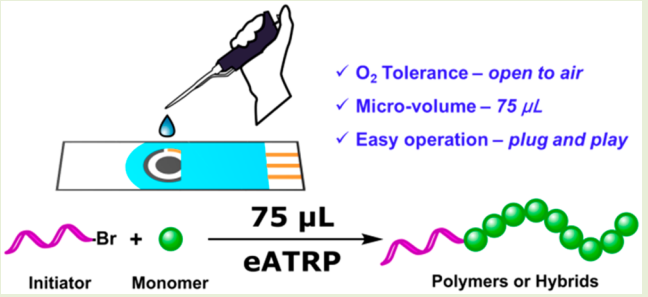
Supporting Information

ABSTRACT: An aqueous electrochemically mediated atom transfer radical polymerization (eATRP) was performed in a small volume solution (75 μL) deposited on a screen-printed electrode (SPE). The reaction was open to air, thanks to the use of glucose oxidase (GOx) as an oxygen scavenger. Well-defined poly(2-(methylsulfinyl)ethyl acrylate) (PMSEA), poly(oligo(ethylene oxide) methyl ether methacrylate) (POEOMA), and corresponding DNA−polymer biohybrids were synthesized by the small-volume eATRP at room temperature. The reactions were simplified and polymerization rates increased by the application of the enzyme deoxygenating system and the compact electrochemical setup. Importantly, the volume of polymerization mixture was lowered to microliters, which not only decreases the cost for each reaction, but can also be potentially implemented in combinatorial chemistry and electrode-array configurations for high-throughput systems.



Atom transfer radical polymerization (ATRP) is one of the most widely used techniques to generate polymers with narrow molecular weight distributions and predetermined architectures.[1] With the development of active catalyst systems, ATRP can now be conducted at parts per million (ppm) levels of transition metal using activators regenerated by electron transfer (ARGET),[2] initiators for continuous activator regeneration (ICAR),[3] supplemental activator and reducing agent (SARA),[4] photoinduced (photo-ATRP),[5] electrochemically mediated ATRP (eATRP),[6] and mechanically induced (mechano-) ATRP.[7]

eATRP and other electrochemical polymerizations[8] receive an increasing attention due to low catalyst loading, improved tolerance toward oxygen, elimination of chemical reducing agents, capability of copper removal through electrodeposition, and fabrication of functional surfaces.[9] Also, eATRP allows precise selection and control of the ratio of activator to deactivator, and the polymerization can be stopped and restarted by changing the applied current (I_{app}) or applied potential (E_{app}).[10] eATRP was previously used to prepare various functional polymers. For example, Li et al.[11] conducted eATRP on nonconducting substrates, and they controlled brush growth through catalyst diffusion between the working electrode and the initiator-anchored substrate. Sun et al.[12] prepared a hemoglobin (Hb) imprinted polymer by eATRP in which Hb was used as the catalyst via electrochemical reduction of methemoglobin (Hb-Fe(III)) to Hb-Fe(II). De Bon et al.[13] carried out eATRP of methyl acrylate (MA) in an ionic liquid without a supporting electrolyte.

eATRP is generally carried out in a traditional three-electrode system, which includes a working electrode (WE), a counter electrode (CE), and a reference electrode (RE).[8a,14] The WE is used to generate the active Cu(I) catalysts from air-stable Cu(II) complexes.[15] The setup requires quite large volumes (∼10 mL) to ensure appropriate stirring and contact of all electrodes with the polymerization solution. It would be beneficial to reduce the volume of an eATRP polymerization in order to employ scarce or expensive materials such as proteins or DNA or for high-throughput synthesis with microelectrode arrays. A small-volume polymerization (<100 μL) not only reduces the cost for each reaction, but also has a positive environmental impact, generating less waste and contamination.

We employed a compact and very simple electrochemical setup consisting of a screen-printed electrode (SPE) in order to decrease the typical reaction volume of an eATRP by over 100× (down to 75 μL). SPEs are disposable and inexpensive electrode substrates, which contain the WE, CE, and RE in an all-in-one package and in a small footprint of <1 cm^2.[16] SPEs can avoid traditional preparation and polishing of solid electrodes, thus, making the operation drastically easier. Moreover, in an SPE, the surface area of the working electrode is very large compared to the tiny polymerization volume, which is a fundamental prerequisite to efficiently reduce Cu(II) species to active Cu(I) complexes.

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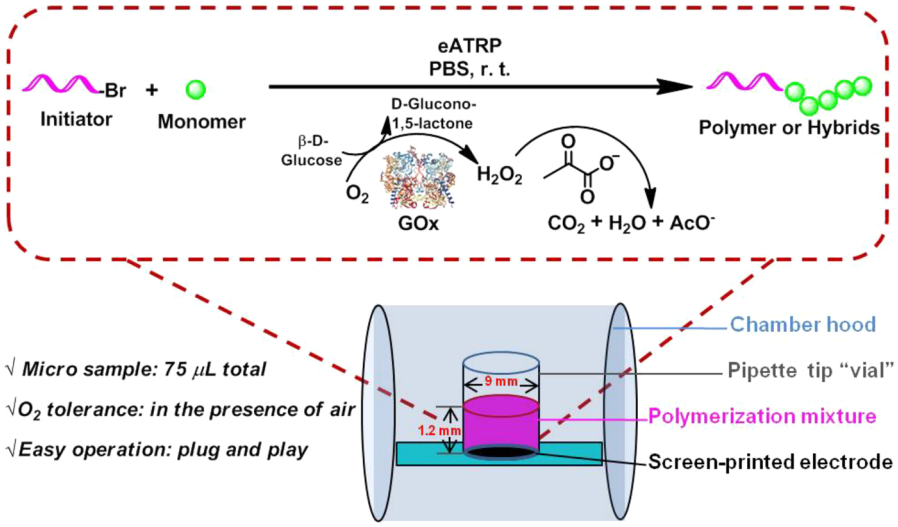
Scheme 1. Preparation of DNA–Polymer Hybrids by Small-Volume eATRP



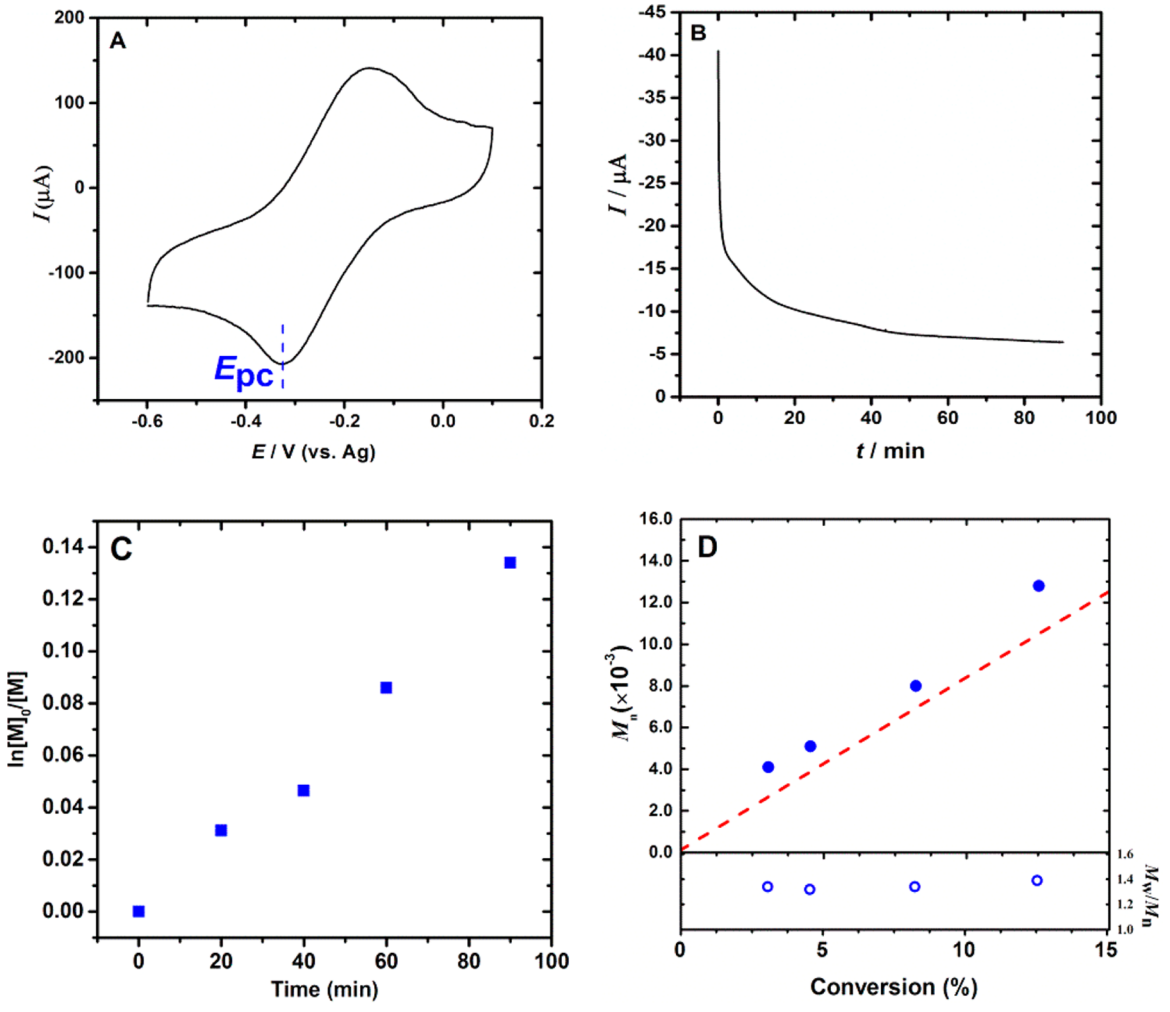


Figure 1. eATRP of MSEA. (A) CV of $CuBr_2/Me_6TREN$ in the presence of HOiBBr, MSEA, and EDS at 0.1 V/s. (B) $I-t$ curve. (C) Kinetics and (D) evolution of M_n and M_w/M_n with conversion of MSEA. Reaction conditions: MSEA (monomer, M; 50% m/v), [M]/[I]/[$CuBr_2$]/[Me_6TREN] = 500:1:2.5:5. I = initiator (HOiBBr). [Glucose] = 0.2 M, [GOx] = 2 μM, [SP] = 0.1 M. $E_{app} = E_{pc} = -0.32$ V (vs Ag pseudoreference electrode). SPE = DS110 (Metrohm Dropsens), WE: Carbon, CE: Carbon, RE: Silver.

However, such a drastic cut of the reaction volume exacerbates the challenge of deoxygenation of the reaction mixture. Radical polymerizations are typically performed in anaerobic environments because propagating radicals react with oxygen to form stable peroxy radicals and hydroperoxides, thus quenching chain growth.[17] Commonly used techniques for

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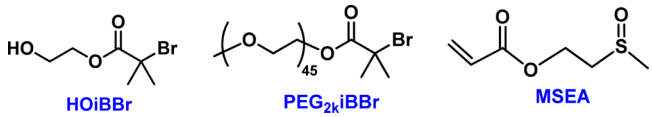
Table 1. Small-Volume eATRP of MSEA[a]



entry	EDS	E_{app} (mV)	initiator	M/I/$CuBr_2$/Me_6TREN	t (min)	k_p^{app}[b] (h^{-1})	conv.[c] %	$M_{n,Th}$[d] ($\times10^{-3}$)	$M_{n,GPC}$[e] ($\times10^{-3}$)	M_w/M_n[e]
1	×	E_{pc}	HOiBBr	500:1:2.5:5	60	0.051	5	4.3	5.2	1.37
2	√	E_{pc}	HOiBBr	500:1:2.5:5	60	0.083	8	6.8	8.0	1.34
3	√	E_{pc}-40	HOiBBr	500:1:2.5:5	60	0.105	10	8.3	9.0	1.44
4	√	$E_{1/2}$[f]	HOiBBr	500:1:2.5:5	60	0.073	7	5.9	6.4	1.34
5	×	E_{pc}	PEG_{2k}iBBr	500:1:2.5:5	120	0.047	9	9.4	12.1	1.27
6	√	E_{pc}	PEG_{2k}iBBr	500:1:2.5:5	60	0.073	7	7.9	10.0	1.33

[a][M] = 50 vol %, total volume = 75 μL, T = rt, SPE = DS110 (Metrohm Dropsens), WE: carbon, CE: carbon, RE: silver, [glucose] = 0.2 M, [GOx] = 2 μM, [SP] = 0.1 M. [b]Calculated from the slope of the $\ln([M]/[M]_0)$ vs time plot. [c]Conversion determined by ^{1}H NMR using <2% DMF as internal standard. [d]$M_{n,Th}$ calculated based on equation ($M_{n,Th} = M_{MSEA} \times [MSEA]_0 \times conv/([I]_0) + M_I$. [e]$M_{n,GPC}$ and M_w/M_n were determined by GPC in DMF, based on poly(methyl methacrylate) (PMMA) as the calibration standards. GPC traces are shown in Figure S5. [f]The half wave potential of the catalysts.

degassing polymerization solutions are freeze−pump−thaw cycles, purging with inert gas, and working in a glovebox or Schlenk line.[18] However, these methods are time-consuming, difficult to scale up, challenging for nonexperts, and may lead to significant evaporation of some volatile reagents, especially in the case of low-volume reactions.[19] Moreover, freeze−pump−thaw cycles are not compatible with most electrochemical instruments. Enzyme degassing, on the other hand, does not require any applied vacuum or inert gas, because the enzyme glucose oxidase (GOx) creates an in situ anaerobic environment by the continuous conversion of oxygen to carbon dioxide in the presence of glucose and sodium pyruvate (SP).[18d,19b,20] It is a very convenient, fast, and efficient deoxygenation method for controlled radical polymerizations, and it is especially suitable for electrochemistry setups.

Considering the advantages of eATRP and small volume reactions, this paper describes the preparation of well-defined polymers and DNA−polymer biohybrids via small-volume eATRP. As shown in Scheme 1, eATRP was conducted using 75 μL samples on SPEs with an enzyme degassing system (EDS; glucose + SP + GOx).

The reaction setup for small-volume eATRP is shown in Figure S1. A pipette tip was cut and placed on the surface of SPE to confine the polymerization solution, thus, acting as a vial open to air (diameter 9 mm). A small volume of polymerization solution (75 μL) was mixed and put into the pipette-tip "vial". A small, nonairtight chamber hood covered the electrode setup to slow down solvent evaporation and oxygen diffusion.

To investigate the effect of the EDS on eATRP, we conducted cyclic voltammetry (CV) of the polymerization mixture in the presence, or in the absence, of EDS. As shown in Figure S2, the CV of the ATRP catalyst $CuBr_2$/Me_6TREN (Me_6TREN = tris[2-(dimethylamino)ethyl] amine) was similar in the presence or in the absence of EDS, which showed that the enzyme degassing system had no effect on the electron transfer on the surface of a SPE and, thus, can be used in an eATRP process .

We first tested the small-volume eATRP of the monomer 2-(methylsulfinyl)ethyl acrylate (MSEA) due to its biocompatibility.[21] The catalyst was $CuBr_2$/Me_6TREN and the initiator 2-hydroxyethyl α-bromoisobutyrate (HOiBBr).

Figure 1 shows the eATRP results of MSEA. Figure 1A illustrates the CV of $CuBr_2$/L (L = Me_6TREN) in the presence of HOiBBr, MSEA, and EDS at 0.1 V/s. The cathodic peak potential (E_{pc}) is selected to conduct the polymerization.[22] Figure 1B shows the typical I−t curve. The current decays rapidly as $[XCu^{II}L]^+$ is converted to $[XCu^{I}L]$ with time. Afterward, the current approaches a low and constant value as the system tends toward a fixed $[XCu^{II}L]/[XCu^{I}L]$ ratio, determined by the selected applied potential (E_{app}). Figure 1C shows the polymerization kinetics for the eATRP of MSEA after application of a potential of E_{pc}. Cu(I)/L was generated at the working electrode and diffused into the small solution volume, triggering polymerization. Figure 1C shows a linear semi-logarithmic kinetic plot. Figure 1D shows the evolution of the number-average molecular weight ($M_{n,GPC}$) and dispersity values with conversion of MSEA (GPC traces can be seen in Figure S3). The $M_{n,GPC}$ values of the polymers increased linearly with monomer conversion. The experimental molecular weights were a little higher than the theoretical values, which could be attributed to the difference between PMSEA and the GPC calibration standards (PMMA).

After this first successful microscale electropolymerization, several eATRP parameters were studied, such as the effect of enzyme degassing, E_{app}, and nature of the initiator, Table 1.

When the polymerization was conducted in the absence of EDS, the reactions reached 5% conversion in 60 min with the dispersity ($Đ$) of 1.37. This indicated that this low volume eATRP is itself oxygen tolerant. The presence of EDS, however, accelerated the polymerization: the conversion was 8%, with a slightly lower $Đ$ = 1.34 (Table 1, entries 1 and 2). The reaction rate increased more than 60% in the presence of the degassing enzyme (apparent propagation rate constant, k_p^{app}, increased from 0.051 to 0.083 h^{-1}). Figure S4 further showed the effect of EDS on the kinetics of the low volume eATRP of MSEA.

Three E_{app} values were selected to perform the polymerization (entries 2−4), thus, altering the Cu(I)/Cu(II) concentration at the surface of the SPE. The reaction rate increased with the application of a more negative potential, in agreement with increasing [Cu(I)] at the working electrode. The polymer prepared at the most negative potential, E_{pc} − 40 mV, showed the highest dispersity, which could be due to too low [Cu(II)] and, thus, insufficient deactivation. Conversely, the polymer prepared at both E_{pc} and $E_{1/2}$ (half-wave potential of the redox couple) had the same low $Đ$ value of 1.34. Since the polymerization at E_{pc} was faster than at $E_{1/2}$, E_{pc} was used as the E_{app} in the following experiments.

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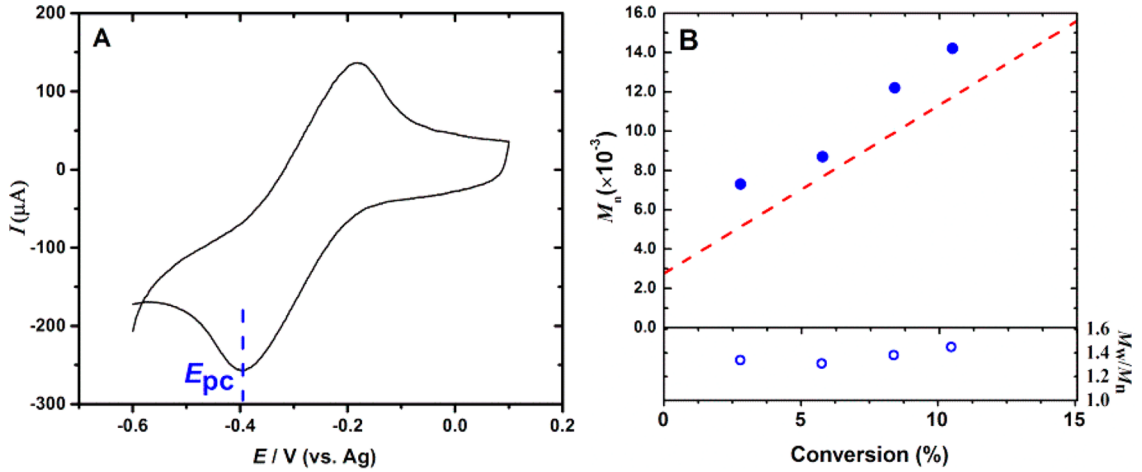

Figure 2. (A) CV of $CuBr_2/Me_6TREN$ in the presence of DNA initiator, MSEA, and EDS at 0.1 V/s. (B) Evolution of M_n and M_w/M_n with conversion of MSEA using modified-DNA as the initiator. Reaction conditions: MSEA (M) (50% m/v), [M]/[I]/[$CuBr_2$]/[Me_6TREN] = 500:1:0.25:5, SPE = DS110 (Metrohm Dropsens), WE: carbon, CE: carbon, RE: silver.

Table 2. eATRP Results for Polymerization of $OEOMA_{300}$ under Various Conditions[a]

entry	EDS	E_{app} (mV)	initiator	M/I/$CuBr_2$/TPMA	t (min)	k_p^{app} (h^{-1})	conv.[b] %	$M_{n,Th}$[c] (×10^{-3})	$M_{n,GPC}$[d] (×10^{-3})	M_w/M_n[d]
1	√	E_{pc}	PEG_{2k}iBBr	500:0.5:1:5	5	0.35	2	10.4	7.8	1.37
2	√	E_{pc}	PEG_{2k}iBBr	500:0.25:1:5	30	0.31	12	74.6	63.2	1.39
3	√	E_{pc}	PEG_{2k}iBBr	500:0.25:0.5:2.5	10	0.26	4	24.2	18.4	1.36
4	√	E_{pc}	PEG_{2k}iBBr	500:0.25:0.2:1	20	0.22	6	38.0	27.0	1.59

[a][M] = 50 vol %, total volume = 75 μL, T = rt, SPE = DS550 (Metrohm Dropsens), WE: platinum, CE: platinum, RE: silver, [glucose] = 0.2 M, [GOx] = 2 μM, [SP] = 0.1 M. [b]Conversion determined by ^{1}H NMR. [c]$M_{n,Th}$ calculated based on equation ($M_{n,Th} = M_{OEOMA} \times [OEOMA]_0 \times conv/([I]_0) + M_I$. [d]$M_{n,GPC}$ and M_w/M_n were determined by GPC in DMF, based on PMMA as the calibration standards. GPC traces can be seen in Figure S10.

The macroinitiator poly(ethylene glycol)$_{45}$ modified with an α-bromoisobutyrate end group (PEG_{2k}iBBr) was also tested for the small-volume eATRP of MSEA. The polymer's $Đ$ was low whether it was prepared in the presence or in the absence of the EDS (Table 1, entries 5−6). The M_n values estimated from GPC were slightly higher than the theoretical values, which could be due to either incomplete initiation or the difference in hydrodynamic volume between the PMMA standards and PMSEA.[21a]

The bioconjugates of synthetic polymers with DNA, that is, DNA−polymer hybrid materials,[23] have been considered for drug delivery,[24] as scaffolds for directing organic reactions,[25] or models of virus-like particles.[26] Herein, a 6-mer DNA macroinitiator (cf. Figures S6A and S7A) was synthesized with a preattached α-bromoisobutyrate group on the 5′-end, as previously reported.[18c,27] Figure 2A presents the CV of $CuBr_2/Me_6TREN$ in the presence of DNA initiator, MSEA, and enzyme degassing system. According to the results of Table 1, eATRP was conducted at E_{pc}, which gave a successful grafting from DNA with linear polymerization kinetics (Figure S8A). The evolution of $M_{n,GPC}$ and dispersity values versus MSEA conversion are shown in Figure 2B. The polymerization was stopped when the dispersity increased to higher than 1.45, which may be due to not homogeneous stirring conditions. The GPC traces can be seen in Figure S8B. In order to confirm that the DNA remained intact after the polymerization, a DNA initiator with Cyanine3 dye on the 3′-end (Cy3-DNA-iBBr) was synthesized for the polymerization (cf. Figures S6B,C and S7B). As shown in Figure S9, the characteristic fluorescent peak of the dye at 585 nm was observed on both the Cy3-DNA and Cy3-DNA-poly(MSEA), which indicated the successful preparation of the DNA−polymer conjugates.

Polymerization of the commercially available monomer oligo(ethylene oxide) methyl ether methacrylate (M_n = 300, $OEOMA_{300}$) was also conducted on the SPEs. A catalyst with lower activity was selected, $CuBr_2$/TPMA (TPMA = tris(2-pyridylmethyl)amine), due to the higher activity of this methacrylate monomer in ATRP. First, in order to optimize the conditions for the preparation of DNA−$POEOMA_{300}$ hybrids, a PEG_{2k}iBBr macroinitiator was used. The effects of a targeted degree of polymerization (DP_T) and Cu catalyst concentrations were studied. As shown in Table 2, for different DP_T, all the experiments exhibited relatively narrow molecular weight distributions (M_w/M_n < 1.40). When DP_T = 1000 or 2000 (Table 2, entries 1−2), the polymerization rate decreased when targeting higher DP. Different loadings of Cu catalyst were then tested at DP_T = 2000. Initially 2000 ppm of Cu(II) catalytic complex (vs monomer) was utilized and then gradually decreased to 400 ppm (Table 2, entries 2−4). Although, with a reduced rate of reaction, eATRP provided good control with 1000 ppm of Cu catalyst. When 400 ppm of Cu was used, only 6% of conversion was reached in 20 min, and the polymer had a broader molecular weight distribution (M_w/M_n = 1.59). The limited control was possibly due to the low deactivator concentration at lower ppm of Cu. The polymerization rate increased at increasing Cu concentration, in agreement with previous reports.[28]

The molar ratio of [M]/[I]/[$CuBr_2$]/[TPMA] = 500:0.25:0.5:2.5 was used to prepare DNA−$POEOMA_{300}$ hybrids because of the low concentration of DNA initiator and catalyst. Figure 3A shows the CV of $CuBr_2$/TPMA in the

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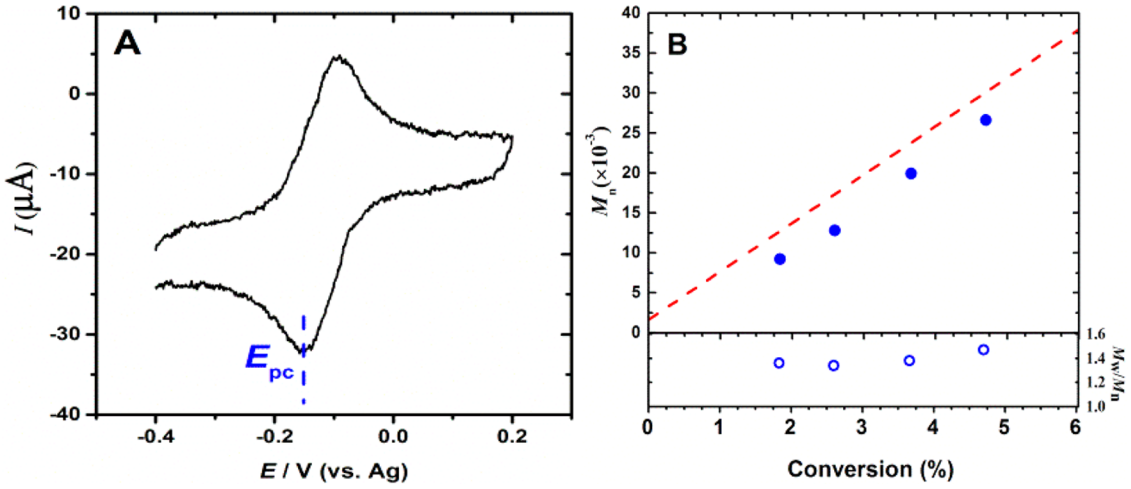

Figure 3. eATRP of $OEOMA_{300}$. (A) CV of $CuBr_2$/TPMA in the presence of DNA initiator, $OEOMA_{300}$, and EDS at 0.1 V/s. (B) Evolution of M_n and M_w/M_n with conversion of $OEOMA_{300}$. Reaction conditions: $OEOMA_{300}$ (M) (50% m/v), [M]/[I]/[$CuBr_2$]/[TPMA] = 500:0.25:0.5:2.5, E_{app} = Epc, SPE = DS550 (Metrohm Dropsens), WE: platinum, CE: platinum, RE: silver.

presence of DNA initiator, $OEOMA_{300}$, and enzyme degassing system. After the eATRP of $OEOMA_{300}$, conducted at E_{pc} for different times, a linear semilogarithmic kinetic plot versus time was observed, Figure S11A. The evolution of the number-average molecular weight ($M_{n,GPC}$) and dispersity values with conversion of OEOMA are shown in Figure 3B; the $M_{n,GPC}$ values of the polymers increased linearly with monomer conversion. Despite the low monomer conversion, a well-defined polymer with a molecular weight >25000 was grafted from DNA in less than 30 min. The GPC traces can be seen in Figure S11B.

In conclusion, the first example of small-volume eATRP using GOx as oxygen scavenger was conducted in aqueous media. Well-defined polymers and DNA hybrids were synthesized, with reaction times varying from a few minutes to hours at room temperature. The reactions benefitted from the simple setup and were accelerated by the application of a Glu + GOx + SP deoxygenating system.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.9b00159.

Experimental details and GPC traces of DNA−polymer hybrids (PDF)

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Notes

The authors declare no competing financial interest.

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