

Cleaning the Click: A Simple Electrochemical Avenue for Copper Removal from Strongly Coordinating Macromolecules

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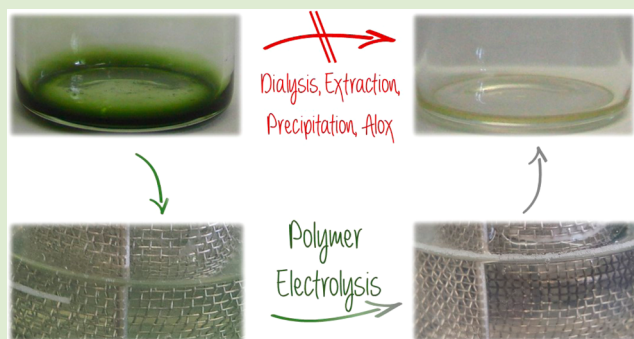
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S Supporting Information

ABSTRACT: We introduce a novel electrochemical method for the purification of complex water-soluble functional polymers contaminated with copper salts originating from copper-catalyzed azide/alkyne ligation chemistry, for which no standard purification protocol is suitable. A triethylene glycol methyl ether methacrylate (TEGMA) star polymer with 2-ureido-4*H*-pyrimidone (UPy) end groups was prepared via an activator generated by electron transfer atom transfer radical polymerization (AGET ATRP) and copper-catalyzed azide/alkyne cycloaddition (CuAAC) and selected as a model system for electrolysis of an aqueous polymer solution. We systematically investigate the influence of sample concentration, voltage, and time of electrolysis on the quality of the purification. Atom emission spectroscopy (AES) reveals almost quantitative removal of copper, and size exclusion chromatography (SEC) as well as proton nuclear magnetic resonance spectroscopy (¹H NMR) ensure the full integrity of the polymer under all selected conditions.



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Copper halides are important reagents in organic and polymer chemistry. The two most important reactions relying on copper halides are atom transfer radical polymerization (ATRP) for the construction of complex polymer architectures and copper-catalyzed azide/alkyne cycloaddition (CuAAC), which is frequently utilized in organic and polymer chemistry, e.g., in polymer end group modification, conjugation of polymer blocks, and surface modification.^{1–4} Due to its high reaction rate, its orthogonality, and high yield, CuAAC can often be considered as the ligation technique of choice in material science. Typically, only catalytic amounts of copper salt are necessary, and most of the copper (Cu) can be removed by standard polymer purification protocols such as precipitation, extraction, dialysis, or filtration over aluminum oxide. However, these methods fail for systems which exhibit high affinity towards Cu⁺/Cu²⁺, e.g., by complexation. Due to the toxicity of copper, its electrochemical properties, and its color, even trace amounts can have a detrimental impact on the material properties.^{5,6} Thus, there exists an intense need to reduce the

amount of Cu required (e.g., for ATRP) or to develop Cu-free reaction protocols as a substitute for the copper-catalyzed azide/alkyne conjugation.^{5–9} For CuAAC, the standard protocol employing Cu salt is in most of the cases the method of choice compared to Cu-free alternatives.^{7,9} In many complex systems such as PEGylation reactions or β -cyclodextrin modifications, however, the amount of copper halide has to be increased to (over)stoichiometric amounts.^{10–19} Thus, purification is extremely important since otherwise the high amount of remaining Cu salt affects the material properties. Depending on the specific system, standard (polymer) purification protocols might not be suitable. An example for such a system, in which Cu halide has to be employed in a stoichiometric amount, are 2-ureido-4*H*-pyrimidone (UPy) units, which are dimerizing hydrogen bonding motifs, frequently applied in supramolecular

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polymers or single-chain nanoparticle formation.^{20–22} UPy end groups are well-known to strongly complex copper.¹⁵

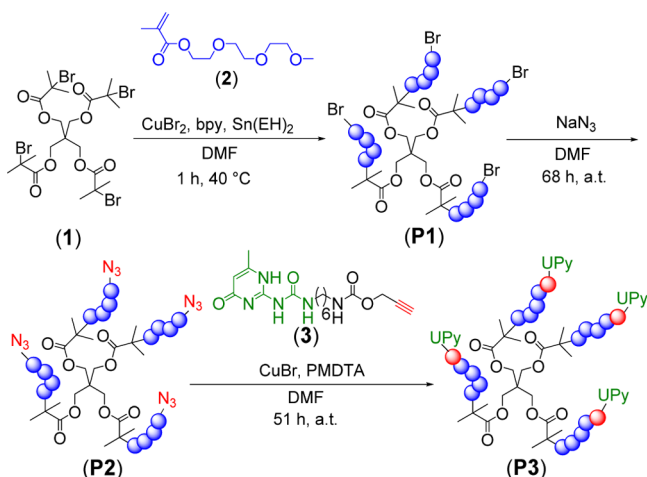
Herein, we critically enlarge the toolbox of polymer purification methods by electrolysis of aqueous polymer solutions that not only enables an efficient purification of the functional polymer but also recycles the added Cu.

The method is related to eATRP (electrochemically mediated ATRP),^{23,24} where electrodeposition from organic media can be employed for the quantitative removal of relatively low amounts of copper from an ATRP reaction. Another related electrochemical method reduces copper ions from noncomplexing polymers via zinc, which is rather a substitution than a purification and introduces issues with the end group stability.²⁵

However, we demonstrate the successful purification of a highly Cu-contaminated polymer with high affinity toward Cu ions via simple electrolysis in a neutral aqueous solution without further purification steps, without sacrificial molecules, and in the absence of any degradation events. In addition—to broaden the study—the stability of other end groups such as aliphatic alcohols and azides under electrolytic conditions was investigated.

To demonstrate the applicability of the electrolysis method, we prepared a four-arm star polymer functionalized with UPy end groups, which are introduced via CuAac (Scheme 1, P3).

Scheme 1. Synthetic Route for the Preparation of P3, Starting with AGET ATRP of 4f-Bib (1) with TEGMA (2) Yielding P1 ($M_n = 5500 \text{ g}\cdot\text{mol}^{-1}$, $\mathcal{D} = 1.2$)^a



^aThe bromine end groups are substituted with NaN_3 , yielding P2, followed by CuAac with alkyne-functionalized UPy (3).

Since triethylene glycol methyl ether methacrylate (TEGMA) is soluble in water, it was chosen as the monomer for our study. The synthesis route starts from commercially available pentaerythritol tetrakis(2-bromoisobutyrate) (4f-Bib (1)). The ATRP initiator **1** is used for the activator generated by electron transfer atom transfer radical polymerization (AGET ATRP) employing triethylene glycol methyl ether methacrylate (TEGMA (2)), yielding the bromine-terminated star polymer P1 ($M_n = 5500 \text{ g}\cdot\text{mol}^{-1}$, $\mathcal{D} = 1.2$). The monomer TEGMA (2) was prepared according to a literature procedure.²⁶ The bromine end groups of P1 were substituted with azides using NaN_3 resulting in the precursor polymer P2. The N_3 -functionalized star polymer (P2) was finally functionalized via CuAac, employing four equivalents of alkyne-functionalized

UPy (3) and four equivalents of CuBr under inert conditions resulting in the UPy-functionalized four-arm star polymer (P3) dialyzed in water before further electrolysis. The alkyne-functionalized UPy (3) was prepared according to a literature procedure.¹⁵

The entire reaction sequence was monitored by size exclusion chromatography (SEC) in THF at 35 °C (Figure 2, see below), which indicates no significant changes in molecular weight or distribution during end group modification. The FT-IR spectra of P1–3 and 3 are given in Figure S1 (Supporting Information) and the $-\text{N}_3$ signal of the reactant P2 at a wavenumber of 2120 cm^{-1} , and the alkyne band of 3 at a wavenumber of 2120 cm^{-1} disappears completely after CuAac, indicating that both functionalities have reacted quantitatively. ^1H NMR was employed for the polymers P1 and P3, revealing the protons at 13.0, 11.8, and 10.1 ppm assigned to UPy moieties and the signal at 7.8 ppm resulting from triazoles within P3 (Figure 3).

Prior to the electrochemical purification approach, Cu removal was attempted via dialysis (in neutral water or EDTA solution), precipitation, or passing over an aluminum oxide column. However, no Cu salt removal was achieved due to the high affinity of Cu to the UPy end groups. Finally, the Cu salt was simply removed from the polymer by aqueous electrolysis with a Pt electrode (>98%) (P3*). All electrolysis procedures were carried out with an identical Pt electrode at ambient temperature in deionized water. For the electrolysis, a stock solution of 754 mg P3 in 10 mL of deionized water was prepared. From this solution 950 μL was taken (475 μL for (P3*E)) and further diluted to the specific concentrations given in Table 1. A detailed procedure is given in the Supporting Information.

Table 1. Summarized Data for the Electrochemical Removal of Cu from P3^a

sample	$c(\text{poly})^b/\text{g}\cdot\text{L}^{-1}$	voltage/V	time/h	res $\text{Cu}^c/\text{wt } \%$	removed $\text{Cu}^d/\%$
P3	-	-	-	2.895	-
P3*A	9.0	9	5.5	1.726	40.4
P3*B	9.0	12	5.5	1.315	54.6
P3*C	9.0	12	24	0.096	96.7
P3*D	9.0	7.5	24	2.854	1.4
P3*E	4.8	12	24	0.042	98.6
P3*F	9.0	12	44	0.047	98.4
P3*G	18.1	12	24	0.060	97.9

^aSamples are dissolved in deionized water at the specified concentration and electrolyzed with Pt electrodes for the given time applying the given voltage. The purity of the isolated polymers is assessed via AES. ^bThe polymer concentration was adjusted by defined dilution of the stock solution. ^cWt % of Cu of each sample was measured by AES. ^dThe percentage of recovered Cu was calculated by comparison of the wt % Cu of each sample with the initial Cu contamination of P3.

To gain a full understanding of the system, we systematically varied the concentration of the polymer (in the range of 4.8–18.1 $\text{g}\cdot\text{L}^{-1}$), voltage (7.5–12 V), and time of electrolysis (5.5–44 h).

The initial weight percentage of the Cu contamination before purification and the remaining amount after electrolysis were assessed via atom emission spectroscopy (AES). Figure 1 depicts the evolution of removed Cu with time for voltages of

7.5 V (blue), 9 V (red), and 12 V (black) at a constant polymer concentration of $9.0 \text{ g}\cdot\text{L}^{-1}$.

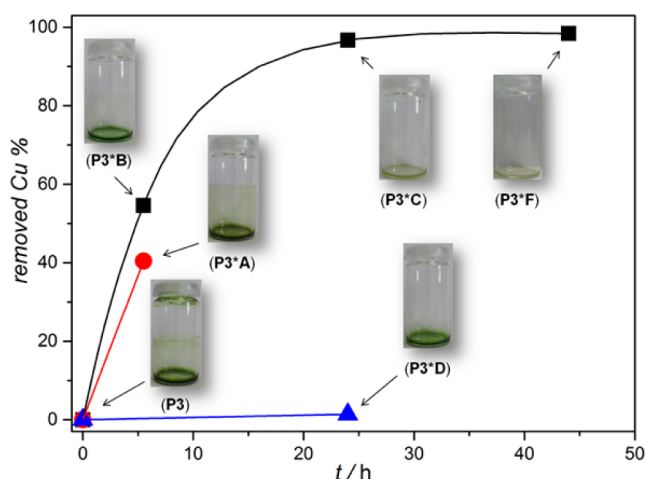


Figure 1. Removed weight percentage of Cu, calculated relative to the initial contamination of P3 measured by AES versus electrolysis time. Voltages of 7.5 V (blue), 9 V (red), and 12 V (black) are employed. All samples feature a concentration of $9.0 \text{ g}\cdot\text{L}^{-1}$. Longer electrolysis times and higher voltages result in an increased purity.

A voltage of 7.5 V was insufficient to remove a significant amount of Cu salt from the polymer P3*D. Higher voltage in general increased the quality of purification at constant times (P3*A and P3*B). To remove 96.7% of the initial Cu contamination, 12 V and 24 h were required (P3*C). A longer electrolysis time (44 h) resulted in a better polymer purity with 98.4% of removed Cu salt (P3*F). We find that the concentration of the polymer does not have a decisive influence on the observed concentration regimes (P3*E, P3*C, and P3*G). The best obtained purity for P3* featured a residual copper content of 42 ppm for sample P3*E (resulting in its slightly green color), starting from 2895 ppm for P3 (calculated from the corresponding wt % Cu from AES). Comparative UV–Vis spectra of P3 and P3* in water are given in Figure S2 (Supporting Information).

In the following, we demonstrate the stability of the investigated polymer (P3) during electrolysis. For convenience—and since all electrochemically treated polymer samples exhibit similar analytical data with respect to polymer stability—a representative sample (P3*) is discussed and compared to the polymer before electrochemical purification (P3). To exclude degradation of the polymer arms and end groups, each sample (P3*) was analyzed via nuclear magnetic resonance (^1H NMR) as well as size exclusion chromatography (SEC) and compared to the reference polymer before electrolysis (P3). Three degradation events during electrolysis of polymer P3 are possible: (i) degradation of the ATRP initiator 1 forming the core of the polymer star, (ii) degradation of the polymer arms poly(TEGMA) (2), and (iii) degradation or cleavage of the UPy end groups. The electrolysis was conducted with voltages ranging from 7.5 to 12 V, times from 5.5 to 44 h, and sample concentrations from 4.8 to $18 \text{ g}\cdot\text{L}^{-1}$ (Table 1). However, in the investigated interval, none of these degradation events (i–iii) are observed. We employed SEC for an initial assessment of the polymer stability during electrolysis. The SEC traces of P3 before electrolysis and of the purified material P3* as well as the precursor polymers P1 and P2 are

depicted in Figure 2. Inspection of Figure 2 indicates that only slight differences in the molecular weight distributions are

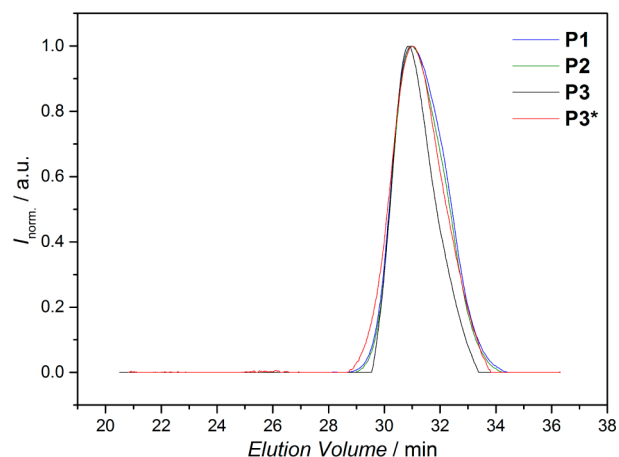


Figure 2. SEC traces of P1, P2, and the final four-arm star polymer P3 in THF at 35°C . The four-arm star polymer after electrolysis (P3*) exhibits the same molecular weight distribution compared to the nonpurified product P3.

visible, which are well below the SEC error and are not indicative of degradation.

Furthermore, the ^1H NMR spectrum for P3 and a characteristic spectrum of the electrochemically cleaned material (P3*) are given in Figure 3. The proton resonances

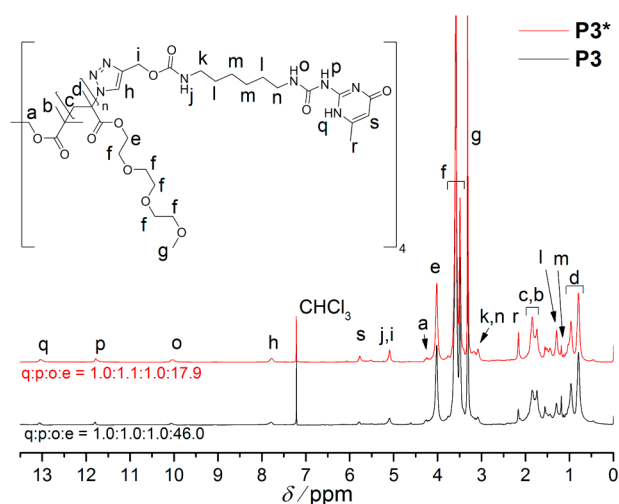


Figure 3. ^1H NMR spectra of the star polymer before (P3) and after electrolysis (P3*). The UPy end groups stay intact during electrolysis, as is evident from the labeled protons h, o, p, q, and s. The ratios of integrals q:p:o:e are given in the spectrum and indicate an increase of free UPy relative to the backbone after electrolysis.

assigned to the UPy end groups are labeled in the spectrum. Both spectra are identical, indicating neither degradation events of the end groups (iii) nor degradation of the polymer arms (ii). However, the ratio of the integrals of q:e (UPy to backbone) increases after electrolytic purification which is an indication for the removal of complexed Cu ions from these groups.

The stability of functional groups (aliphatic alcohols, azides) under the electrolytic conditions was additionally investigated. Therefore, a new star polymer (P6) without any complexing

groups was prepared, where only a quarter of all azide groups had been purposefully ligated with propargyl alcohol, thus generating a star polymer featuring azide as well as alcohol termini. The primary data and synthesis protocol of **P6** are available in the Supporting Information. We found that these noncomplexing groups (including azides) are not only stable under the applied conditions but also purification is faster than for materials having UPy end groups (2 h, 5 V, >98% Cu removal). Substrate integrity was verified via ¹H NMR, SEC, and FT-IR (Figures S3–5, Supporting Information). The copper contamination was quantified via AES.

In summary, we introduce a novel and efficient tool for the purification of complex water-soluble polymeric systems with a strong tendency to complex copper, for which standard polymer purification procedures fail (precipitation, extraction, dialysis, and filtration over aluminum oxide). The polymer is electrolyzed in neutral, aqueous solution without additional sacrificial molecules. Voltage (7.5–12 V), time (5.5–44 h), and concentration (4.8–18.1 g·L⁻¹) are investigated systematically. We find longer times and higher voltages to result in better polymer purity (>98% removed Cu for 12 V and 44 h). An influence of concentration was not detected. However, polymers featuring noncomplexing end groups can be purified faster and under milder conditions. The integrity of electrolyzed polymers (**P3***, **P6***) was monitored by SEC and ¹H NMR analysis and no degradation events could be detected under the investigated conditions. The established polymer electrolysis is thus a highly attractive candidate for large-scale purification since the utilized Cu salts can simply be removed from the polymer (>98%) and the copper can be recovered from the system for further usage.

■ ASSOCIATED CONTENT

● Supporting Information

All synthesis protocols, experimental characterization methods, and instrumental data and the spectra that were referred to in the main text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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