

PRF# 58878-ND7

Project Title: Polymeric Foldamers Containing Multicopper Sites for Phenol Hydroxylation under Aerobic Conditions

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Objectives: The goal of this proposal aims at designing “type-3” multi-Cu-containing polymeric foldamers and studying the impact of polymer chain compositions/conformation on the activity of Cu sites. We hypothesize that, incorporating a large amount of “type-3” Cu sites confined in nanosized polymeric foldamers will enable the cooperative catalysis of adjacent Cu sites to activate O₂ kinetically. The roles of hydrophobicity, functional groups and hydrogen bonding of polymer frameworks in catalytic efficiency of Cu sites, including both activity and selectivity in hydroxylation of phenols, will be studied in this project.

Reports on Results

Copper (Cu)-bound metalloenzymes play an important role in biological O₂ metabolism. The geometrical organization of type-3 Cu sites and the distance of adjacent Cu sites play a key role in their activity. As we proposed in this ACS-PRF proposal, incorporating a large amount of “type-3” Cu sites confined in nanosized polymeric foldamers will enable the cooperative catalysis of adjacent Cu sites to activate O₂ kinetically. We have demonstrated the use of synthetic polymers to promote Cu-based dioxygen activation (*J. Am. Chem. Soc.* 2019, **141**, 4252–4256.). We have designed linear random copolymers of poly(N,N'-dimethylacrylamide-co-2-hydroxy-3-(dipicolylamino) propyl methacrylate) (P(DMA-co-GMADPA)) incorporated with type-3 Cu sites through Cu-dipicolylamine (DPA) co-ordination (Figure 1a). The enzyme-like activity of these Cu-polymers using O₂ as the oxidant for the oxidation of ascorbic acid (AA) and 3,5-di-tert-butylcatechol (DTBC) was studied. Compared to the monomer-ic catalyst with an identical coordination environment, polymeric catalysts are ca. 6-8 times more active due to the enhanced intramolecular cooperativity of the Cu ions within the polymers.

We established the model system to study the impact of polymer chain structures on the activity of Cu sites in the first year. We first chose AA as a model substrate to examine the catalytic

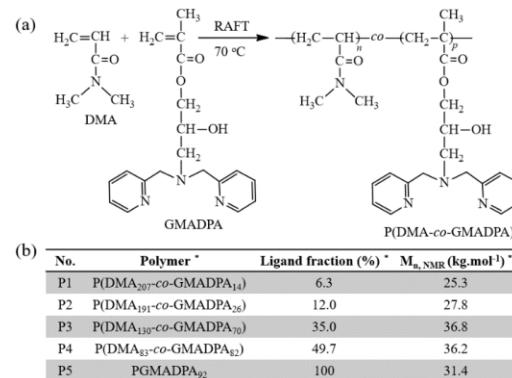


Figure 1. (a) Synthesis and the chemical structures of P(DMA-co-GMADPA). (b) Summary of the different copolymers of P(DMA-co-GMADPA).

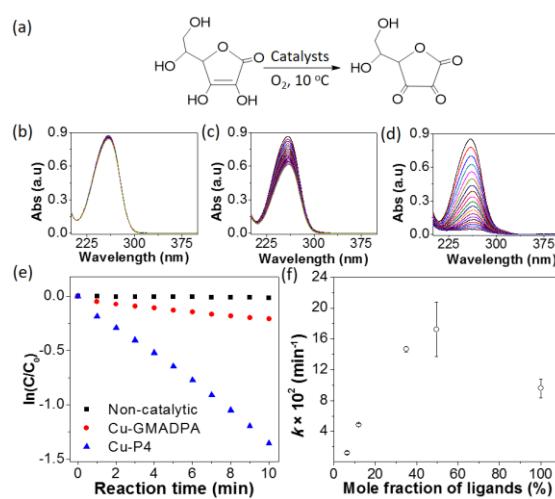


Figure 2. (a) Oxidation of AA. (b-d) UV-vis spectral changes for AA oxidation: (b) non-catalytic and catalyzed by (c) Cu-GMADPA and (d) Cu-P4. The spectra were collected every minute for 20 min. (e) The corresponded plots showing the first-order kinetics of AA oxidation. (f) The dependence of *k* vs. the molar fraction of ligands from the copolymers.

activity of Cu-polymers. The oxidation was carried out with a Cu-to-substrate ratio of 1:5 in water under saturated O₂ at 10 °C (see SI for details). As controls, the oxidation of AA without catalyst and with the Cu-GMADPA complex (or the monomeric catalyst) was also examined. The corresponding UV-vis spectral changes are plotted in Figures 2b-d. The oxidation of AA can be followed by the decrease in its absorption at 260 nm. In a non-catalytic reaction, the conversion of AA is ca. 3% after 20 min. The oxidation of AA was faster in the presence of Cu catalysts where a fast decrease in the absorbance was seen. For the monomeric catalyst Cu-GMADPA, the AA conversion reached 29% after 20 min; whereas it reached 95% with the polymeric catalyst Cu-P4. The oxidation kinetics of AA is first order with rate constants (*k*) of 0.0021, 0.02 and 0.17 min⁻¹ for the non-catalytic reaction, the reaction catalyzed by Cu-GMADPA and Cu-P4 polymer, respectively. The polymeric catalyst Cu-P4 shows 8.6 times higher activity than Cu-GMADPA and 82 times faster than the non-catalytic oxidation of AA.

To evaluate the cooperative effect of Cu sites provided by the change of the molecular state of the catalysts, we investigated the oxidation kinetics of AA using copolymeric catalysts of Cu-P(DMA-co-GMADPA). The

change in the content of catalytically active components within the polymer plays a key role in controlling the proximity of adjacent Cu sites (Figure 1c). When the concentration of the Cu sites is low, e.g., 6.3% for Cu-P1, the polymeric catalyst is less efficient with a $k = 0.0124 \text{ min}^{-1}$, compared to that of Cu-GMADPA. When increasing the concentration of the Cu sites to $> 10 \text{ mol\%}$ relative to DMA units, the cooperative catalysis is clearly seen as the polymeric catalysts become more active. The maximum k of 0.17 min^{-1} is reached for Cu-P4 with 49.7 mol\% of GMADPA. Since the concentration of polymer catalysts is $< 0.15 \text{ mg/mL}$ for all reactions, the cooperativity (referring to the promoted binding with substrates by Cu-polymers) to enhance the catalytic activity of Cu sites is from the intramolecular interaction. However, further increase in the concentration of the Cu sites is detrimental for the activity of the polymeric catalyst. Cu-P5 with 100% of Cu sites only has a k of 0.096 min^{-1} . This is presumably due to the dense packing of Cu sites that hinders the use of all Cu sites simultaneously (vide infra).

In order to gain insights into this cooperative behavior, Michaelis–Menten model was used to analyze the DTBC oxidation. The initial oxidation rate was considered when varying the DTBC concentrations from $40 \mu\text{M}$ to 0.6 mM at a constant concentration of Cu catalysts, $57 \mu\text{M}$. Figure 3 displays the dependence of the initial rate on the concentration of DTBC. The kinetic parameters were evaluated based on non-linear regression of Michaelis–Menten plots. These results are summarized in Figure 3c.

Frist, the Michaelis constant (K_M) of Cu-polymer to DTBC increases compared to Cu-GMADPA. There was also a clear trend showing the increase of K_M with a higher Cu concentration per chain. Although K_M is not a direct measure of the binding affinity of substrate-to-catalyst, it can be used to compare closely related systems. The data indicates that substrate binding is less favorable with polymeric catalysts with a high Cu concentration per random coil. These results clearly suggest that the Cu sites becomes sterically hindered. The binding of two Cu sites per substrate (O_2 and/or DTBC) will induce a “lock-in” intramolecular conformation limiting the further binding of substrate. In other words, the initial binding of the substrate will create a thermodynamic barrier for further binding. The intramolecular lock-in conformation is dependent on the localized Cu concentration per chain. A higher Cu concentration will make it thermodynamically more difficult to bind with substrates.

Second, both the maximum velocity (V_{max}) and the turnover frequency per Cu site (k_{cat}) describe the zero-order kinetics where an infinite amount substrate is available for the initial turnover. V_{max} shows a non-linear dependence on the mole fraction of ligands per polymer chain. When increasing the Cu concentration per chain, the slow saturation of V_{max} is indicative of cooperativity between Cu sites. A 7-fold increase in V_{max} when comparing Cu-GMADPA and Cu-P5 suggests the incorporation of Cu site within flexible polymer chains can dynamically modulate the activity of adjacent Cu sites to allow cooperative catalysis intramolecularly despite the thermodynamic barrier. The catalytic efficiency (k_{cat}/K_M) shows a very similar trend as observed for DTBC oxidation.

Reports on the Impact. The ACS PRF grant has supported two graduate students. The students participated this project were trained on a broad range of topics such as polymer synthesis/characterization and enzymatic kinetics. The first student graduated recently was awarded “the Connecticut Chemistry Research Award”, as one of the highest honor for the graduate student in Chemistry department at the University of Connecticut. The second graduate student taken on the project won the poster award in the annual Polymer Program Poster Session. Through the support of this ACS PRF grant, the PI was able to organize two ACS symposia this year. The first one is on “Hybrid Functional Materials from Controlled Assembly of Polymer and Inorganic Nanoparticles” in spring 2019 and the second one is on “Frontiers and Challenges in Nanoparticle-Mediated Chemical Transformations” in fall 2019. The two symposia offer a platform for the community to present new results and exchange ideas crossing disciplines.

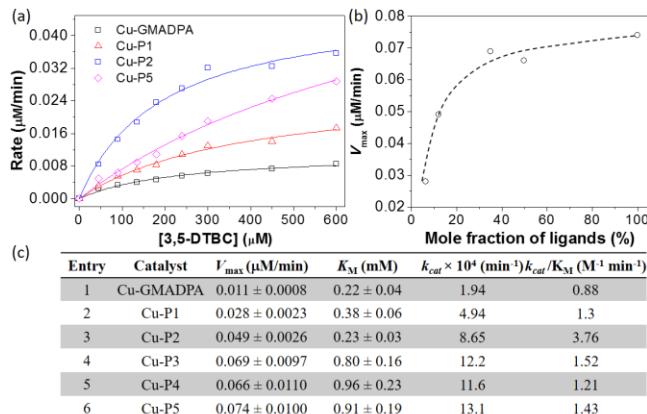


Figure 3. (a) Michaelis–Menten plots for DTBC oxidation catalyzed by Cu-GMADPA and Cu-polymers. (b) Plotting the V_{max} against the mole fraction of GMADPA within individual polymer chains. (c) The table to summarize the kinetic parameters for DTBC oxidation.