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Macromolecular Salen Catalyst with Largely Enhanced Catalytic Activity

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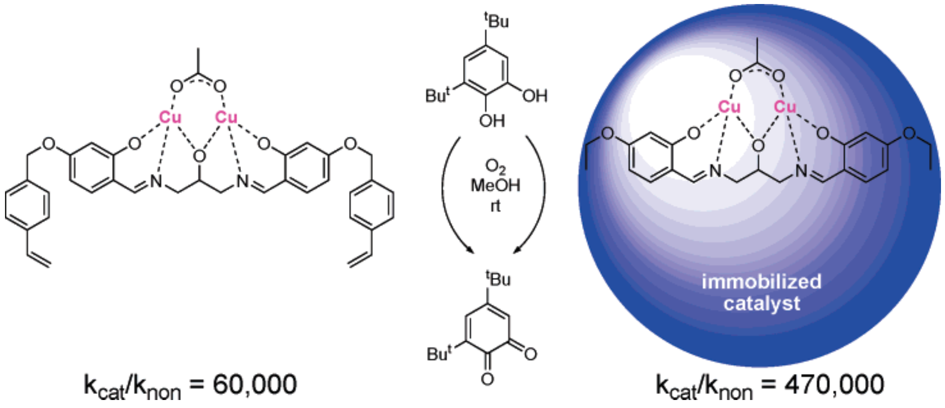
ABSTRACT



A dinuclear copper(II) Schiff-base complex was immobilized in a poly(acrylate) matrix by emulsion polymerization. The spheric microbeads were used for aerobic catalytic oxidation of 3,5-di-*tert*-butylcatechol into 3,5-di-*tert*-butylquinone in methanol at ambient temperature to study the contribution of the macromolecular matrix to the overall rate acceleration of the reaction. The polymeric catalyst catalyzes the oxidation about 1 order of magnitude faster (k_{cat}/k_{non} = 470 000) than its low molecular weight analogue (k_{cat}/k_{non} = 60 000).

Enzymes are macromolecules, while many enzyme mimics are not.[1] The macromolecular structure of an enzyme, however, contributes to the overall catalytic activity. Enhanced catalytic turnover was achieved in a predominantly linear macromolecular enzyme mimic compared to a small molecular weight entity.[2] Along these lines, we and others[2] hypothesize that a reagent immobilized in a polymer matrix will support selective interactions between a catalytic site and a substrate due to the rigidity imposed by the polymer backbone. This might be achieved by appropriate building blocks of the macromolecular matrix that enable hydrophobic interactions, $\pi-\pi$ stacking, and/or hydrogen bonding in addition to the coordinative bonds at a metal complex-containing active site. The immobilization of a well-explored catalyst in a polymeric environment lends itself as a promising strategy toward this goal.

In view of the great importance of oxidation reactions for industrial and synthetic processes and the ongoing search for new and efficient oxidation catalysts,[3] we chose the catalytic oxidation of catechol as a model reaction to test our hypothesis. Quite a number of mono- and dinuclear copper coordination compounds have been investigated as

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(3) (a) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343. (b) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (d) Marko, I. E.; Gautier, A.; Dumeunier, R.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1588. (e) Zhang, C. X.; Liang, H.-C.; Humphreys, K. J.; Karlin, K. D. In *Catalysis by Metal Complexes*; ACS Symp. Ser. 26; American Chemical Society: Washington, DC, 2003; p 79. (f) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774.

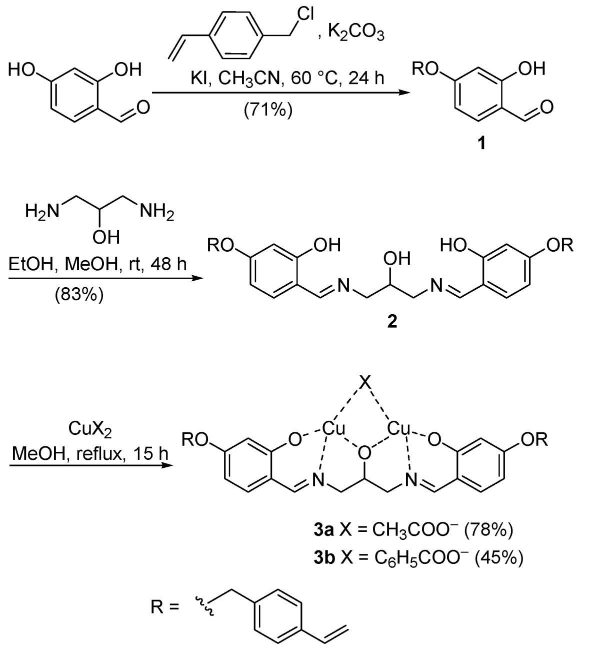
10.1021/ol702672k CCC: $40.75

biomimetic catalysts toward this end.[4] While no clear relation between the catalytic activity and the redox potential of the copper species has emerged,[5] dinuclear copper complexes are generally found to be more reactive than mononuclear compounds.[4]

Keeping all these factors in mind, we herein report the synthesis of a polymerizable dinuclear copper(II) complex, its composition in methanolic solution, and its catalytic activity in comparison to a nonpolymerizable analogue and a macromolecular catalyst.

For preparation of the complex, commercially available 4-hydroxysalicylaldehyde was reacted with *p*-vinylbenzyl chloride in a Williamson ether synthesis yielding 2-hydroxy-4-[(4-vinylbenzyl)oxy]benzaldehyde **1** in high purity and more than 70% yield after modification of a reported procedure.[6] Consecutive condensation of **1** with 1,3-diaminopropanol at ambient temperature afforded polymerizable *N*,*N*′-1,3-bis[(2-hydroxy-4-vinylbenzyloxy)benzylideneamino]propan-2-ol (**2**, bssdpo) in good yields and high purity after recrystallization from ethyl acetate. Ligand **2** was reacted with copper(II) acetate or copper(II) benzoate to obtain the new {*N*,*N*′-1,3-bis[(2-hydroxy-4-vinylbenzyloxy) benzylideneamino]propan-2-ol}ato (*μ*-acetato) (or *μ*-benzoato) dicopper complexes **3a** [Cu_2(bssdpo)(Ac)] and **3b** [Cu_2(bssdpo)(benzoato)] (Scheme 1).[7]

Scheme 1. Synthesis of Polymerizable Ligand **2** and Related Dinuclear Copper(II) Complexes **3a** and **3b**



Attempts to prepare dinuclear copper(II) complexes containing other bridging anions, including gluconate, gallate, anthracene-9-carboxylate, terephthalate, formate, or malate, have failed so far. Similar observations were reported for the preparation of the nonpolymerizable dinuclear copper(II) complex {*N*,*N*′-1,3-bis[(2-hydroxy)benzylideneamino]-propan-2-ol}ato (*μ*-acetato) dicopper(II) diperchlorate [**4**, Cu_2(bsdpo)(Ac)],[8] derived from *N*,*N*′-1,3-bis[(2-hydroxy)-benzylideneamino]propan-2-ol (**5**, bsdpo) (Figure 1).[9]

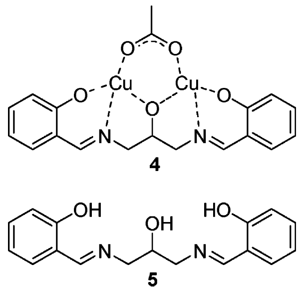


Figure 1. Structures of nonpolymerizable backbone ligand **5** and the dinuclear copper(II) complex **4** derived thereof.

The composition of complexes **3a** and **3b** in the solid state is confirmed by elemental analysis and mass spectrometry. Coordination of **2** to copper(II) acetate resulting in complex **3a** is indicated by IR spectroscopy. The asymmetric (and symmetric) C−H valence bond vibrational bands are shifted from 1446 cm^{-1} (1420 cm^{-1}) in copper acetate to 1424 cm^{-1} (1397 cm^{-1}) in **3a**. The C−O valence bond vibrational band of the aliphatic hydroxyl group at 1116 cm^{-1} in **2** is located at 1123 cm^{-1} in **3a**. Similar alterations are observed upon coordination of copper(II) benzoate to ligand **2** resulting in complex **3b** (see the Supporting Information).

A single-crystal X-ray structure analysis of complex **3a** reveals a nearly planar N_1O_3 coordination environment for each of the metal centers in **3a** and **3b**. The interatomic Cu···Cu distance in **3a** of 3.51(5) Å and in **3b** of 3.50(1) Å is comparable to that of nonpolymerizable analogue **4** (3.49(5) Å).[10] The X-ray structure analyses of various dinuclear copper(II) salen complexes will be discussed in detail elsewhere.[11]

We then explored the composition of **3a** in solution to determine whether or not the bridging acetate anion is abstracted in methanol by using the spectrophotometric titration method developed by Zuberbühler.[12] The nonpolymerizable backbone ligand **5** was used instead of polym-

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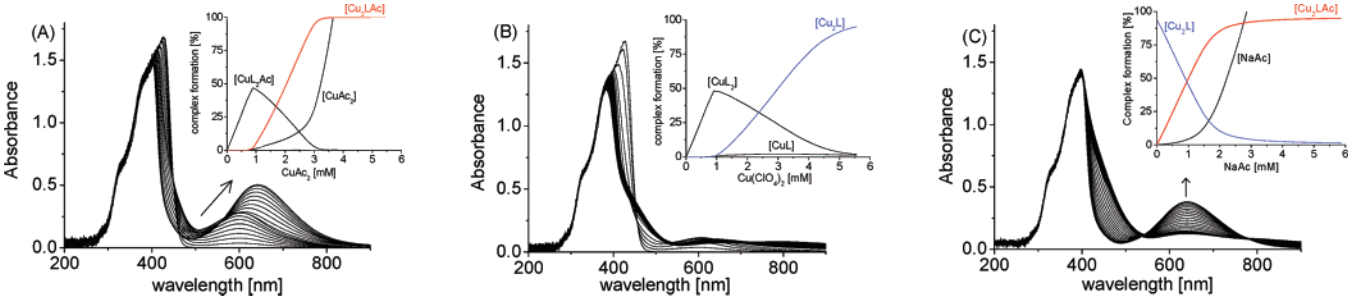


Figure 2. UV/vis spectra and corresponding distribution of species obtained during titration of 2 mM L (L = bsdpo; **5**) with (A) copper(II) acetate monohydrate, (B) copper(II) perchlorate hexahydrate, and (C) sodium acetate in the presence of excess copper(II) perchlorate hexahydrate in methanol, 25 °C.

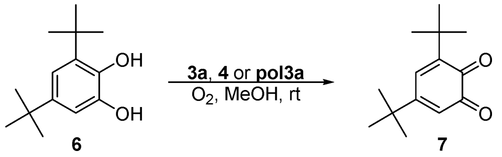
erizable **2** for these titrations assuming that the polymerizable substituent in **4** has no pronounced electronic effect on the metal core.[13] First, titrating **5** with copper(II) acetate in methanol reveals formation of a dinuclear copper(II) complex with UV/vis absorption spectra identical to **4** (λ_{max}= 640 nm, Figure 2A). Second, titrating **5** with copper(II) perchlorate results in formation of a complex with significantly different UV/vis absorption spectra compared to **4** (Figure 2B). Third, titration of **5** with sodium acetate in the presence of 2 equiv of copper(II) chloride results in the same UV/vis absorption spectra as are observed for **4** (Figure 2C), when equimolar amounts of sodium acetate and **5** are present.

If the acetate anion were abstracted from the complex and exchanged by coordinating solvent molecules upon solvation of **4**, the titration of **5** with copper(II) perchlorate should show an UV/vis spectrum identical with that of dissolved **4**. As this is clearly not observed (Figure 2B), the bridging acetate anion is crucial for the formation of the dinuclear copper(II) complex **4** and remains coordinated to the metal core, even in methanol. The complex composition is therefore identical in solid state and solution.

By analogy, we assume the same coordination behavior of the counteranion for the dinuclear copper(II) complexes **3a** and **3b**. A coordinated counteranion, however, does not prevent bidentate substrate coordination to the dinuclear metal core in a catalytic transformation due to the overall planar complex structure.

The synthesized dinuclear copper(II) complexes **3a** and **4** were initially employed as catalysts for the oxidation of 3,5-di-*tert*-butylcatechol (3,5-DTBC, **6**) to 3,5-di-*tert*-butylquinone (**7**, 3,5-DTBQ) (Scheme 2). Various groups have used this procedure to establish catechol oxidase-like activity for structurally related dinuclear copper(II) complexes.[14]

Scheme 2. Model Reaction



The reaction proceedings were followed by UV/vis spectroscopy at 420 nm. The reaction rates at constant substrate concentration increase in a linear fashion with increasing catalyst concentration, and the kinetic data of the oxidation can be analyzed using the Michaelis−Menten model. The initial rates of product formation revealed a rate constant k_{cat} of 0.04 min^{-1} and a Michaelis constant K_m of 40 mM in the presence of 200 μM dinuclear copper(II) complex **4** at 30 °C.

The rate constant of the spontaneous reaction k_{non} is 7×10^{-7} min^{-1} at 30 °C and corresponds to the self-oxidation of the substrate under aerobic conditions without catalyst.[15] The rate acceleration of the oxidation by catalyst **4** is calculated from these values as 60 000 (k_{cat}/k_{non}).

Performing the oxidation in the presence of 200 μM polymerizable complex **3a** yields a k_{cat} of 0.04 min^{-1} and a K_m of 37 mM at 30 °C. Derivatization of the ligand backbone

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(12) Binstead, R. A.; Jung, B.; Zuberbühler, A. D. *SPECFIT/32 Global Analysis System*, 3.0 ed.; Spectrum Software Associates: Marlborough, MA, 2000.

(13) Typical procedure for spectrophotometric titrations: All experiments were performed in methanol at 25.0 ± 0.1 °C. The pH value was measured with a Beckman Φ 250 pH meter equipped with a refillable long combination Futura pH electrode of 0.7 mm thickness. Typically, 2 mL of stirred ligand solutions (2 mM) was titrated with methanol solutions of copper acetate monohydrate, copper perchlorate hexahydrate, or sodium acetate (c = 10 mM) by addition of 25 μL portions. The UV/vis spectra were recorded independent of the pH value measured in the reaction vessel after equilibration in a range of 200−900 nm. The spectral data were computed by the fitting procedures provided by the program Specfit.[12]

(14) Selected reviews for dinuclear metal complexes with catechol oxidase-like activity may be found in: (a) Belle, C.; Selmeczi, K.; Torelli, S.; Pierre, J.-L. *C. R. Chim.* **2007**, *10*, 271. (b) Koval, I. A.; Gamez, P.; Belle, C.; Selmeczi, K.; Reedijk, J. *Chem. Soc. Rev.* **2006**, *35*, 814. (c) Chaudhuri, P.; Wieghardt, K.; Weyhermueller, T.; Paine, T. K.; Mukherjee, S.; Mukherjee, C. *Biol. Chem.* **2005**, *386*, 1023. (d) Selmeczi, K.; Reglier, M.; Giorgi, M.; Speier, G. *Coord. Chem. Rev.* **2003**, *245*, 191. (e) Kaim, W. *Dalton Trans.* **2003**, 761.

(15) Control reactions were performed (a) without oxygen and (b) without copper(II) complex. While the oxidation was completely inhibited in a sealed cuvette containing degassed, nitrogen-purged methanol, slow spontaneous oxidation of 3,5-DTBC to 3,5-DTBQ was observed in the presence of oxygen. The rate constant was determined from spectral data collected over a 1 h period.

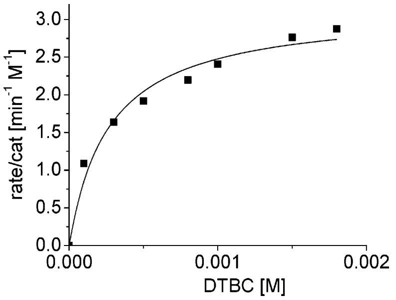

Figure 3. The oxidation of 3,5-DTBC by **pol3a** follows Michaelis−Menten kinetics and is more than 470 000-fold accelerated over background; $k_{cat} = 3.3$ min^{-1}, $K_M = 200$ μM.

with a *p*-vinylbenzyloxy group consequently does not alter the catalytic activity. The rate constant k_{cat} for the catalytic oxidation of DTBC by other dinuclear copper(II) complexes with similar Cu(II)···Cu(II) distances of 3.50 Å is reported to be in the same order of magnitude ($k_{cat} = 0.04$ min^{-1}).[14]

Subsequently, complex **3a** was immobilized in a poly(acrylate) matrix by microemulsion polymerization.[16] As radical polymerizations are inhibited in the presence of paramagentic metal ion radicals, such as Cu(II) ions, we copolymerized the ligand **2** into a poly(acrylate) matrix, and activated the catalyst by addition of metal ions afterward. Elemental analysis of the dried beads confirmed quantitative incorporation of the polymerizable ligand **2** into the poly(acrylate). TEM imaging revealed formation of spherical particles with 50 nm diameter on average. Isothermal titration calorimetry disclosed accessibility of the copper(II) ions to the ligand core and quantitative complex formation with immoblized **2** in a 2:1 molar ratio (see the Supporting Information). The addition of appropriate amounts of copper(II) acetate solution activated the dormant catalyst **pol3a** that was then used for transformation of the model substrate **6** into **7** under the described conditions (see Scheme 2).

The initial rates of product formation promoted by **pol3a** were analyzed using the Michaelis−Menten model (Figure 3). The reaction proceeds in the presence of 1.5 μM **pol3a** with a rate constant k_{cat} of 3.3 min^{-1} and a Michaelis−Menten constant K_m of 200 μM.[17] The acceleration of the reaction by **pol3a** over background is deduced from these values as 470 000, which is almost 10-fold faster than for the low molecular weight salen analogues **3a** or **4**. The macromolecular structure of **pol3a** does therefore significantly contribute to its overall catalytic activity. A thorough investigation of this effect to the catalytic oxidation and a detailed physical characterization of the polymeric catalyst will be reported in due course.

Acknowledgment. Partial support of this project by an award to S.S. in the Competitive Research Grant Program at Auburn University is gratefully acknowledged.

Supporting Information Available: Representative experimental procedures and full characterization of all new compounds and a table with selected bond lengths and angles of complexes **3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Typical procedure for emulsion polymerization: Poly(acrylate) beads were prepared by mixing of 3 g of butyl acrylate and 3 g of styrene in 500 mg of decane with 48 mL of water containing 144 mg of sodium dodecyl sulfate (SDS). Ligand **2** (144 mg, 0.26 mmol) dissolved in 1 g of DMSO was then added and the resulting mixture was stirred vigourously for 1 h followed by sonication for 2 min. The polymerization was initiated by addition of aqueous potassium peroxysulfate at 72 °C and allowed to proceed for 3 h. The polymer particles obtained were purified by ultracentrifugation using micropore filters with a 10 000 MW cutoff. A sample aliquot of the aqueous polymer solution was dried for elemental analysis.

[17] The kinetic experiments were conducted after addition of appropriate amounts of aqueous copper(II) acetate solution to prepare a 0.09 mM aqueous catalyst stock solution that was subsequently diluted into methanol to yield a final 1.5 μM concentration of catalyst **pol3a**.