J|A|C|S
ARTICLES

# Effect of Water on the Catalytic Oxidation of Catechols

Moses G. Gichinga and Susanne Striegler*

*Department of Chemistry and Biochemistry, Auburn University, 179 Chemistry Building, Auburn, Alabama 36849-5123*

Received October 23, 2007; E-mail: susanne.striegler@auburn.edu

***Abstract:*** A dinuclear copper(II) complex derived from a new water-soluble pentadentate Schiff base backbone ligand has been prepared and characterized in solution and in the solid state. The complex has been found to accelerate the aerobic oxidation of 3,5-di-*tert*-butylcatechol (DTBC) into 3,5-di-*tert*-butylquinone (DTBQ) by 5 orders of magnitude, compared to the background reaction in aqueous methanol ($k_{cat}/k_{non}$ = 160 000) at 30 °C. The transformation of the model substrate is considerably slower in pure methanol ($k_{cat}/k_{non}$ = 60 000) under otherwise identical conditions. In-depth investigation of the catalytically active species revealed different structures for the copper(II) complex in methanol and in methanol/water mixtures.

## Introduction

The oxidation of alcohols is an important reaction in organic chemistry. While this transformation is traditionally performed in organic solvents, the use of aqueous organic solutions has become a field of intense study[1–3] after Breslow first pointed out a hydrophobic effect of water on the acceleration of the Diels–Alder reaction[4–6] and the benzoin condensation.[7] Extensive kinetic measurements on the higher reaction rates for the Diels–Alder reaction and other types of organic reactions in water have been reported since and have increased the knowledge about the hydrophobic effect in organic reactions.[3,8] The effect of water on transition-metal-catalyzed reactions, however, remains widely unexplored as most of these reactions need to be conducted in absolute organic solvents to avoid decomposition of the transition-metal catalyst, water-sensitive reagents, or intermediates by nucleophilic attack of water.[2] *Comparative* studies focusing on the effect of water as a cosolvent on the catalyst and the reaction proceedings are therefore rare.[9]

In our ongoing efforts to develop oxidation catalysts that are functional in water as environmentally benign solvent, we synthesized a water-soluble pentadentate Schiff base ligand with polyethylene glycol side chains. After coordination of copper(II) ions, a dinuclear copper(II) complex **1** is obtained that is soluble in water, methanol, and mixtures of both solvents. A fair number of dinuclear copper complexes with a Schiff base ligand backbone have been prepared as functional mimics for catechol oxidase or as new biomimetic catalysts for oxidation reactions.[10–15] Typically, the aerobic oxidation of 3,5-di-*tert*-butylcatechol (DTBC) into 3,5-di-*tert*-butylquinone (DTBQ) is used as a model reaction to demonstrate catalytic oxidation activity in *predominantly organic solvents*. Due to the structural similarity of complex **1** to the functional catechol oxidase mimics known, we used the same substrate (DTBC) in our initial studies to focus on the effect of water on the catalytic activity of the prepared complex in *aqueous organic solution*. The oxidation of the model substrate DTBC into DTBQ is accelerated by 5 orders of magnitude over background in aqueous methanol (MeOH/$H_2O$ = 60/40, v/v; $k_{cat}/k_{non}$ = 160 000), which is unexpectedly high for a dinuclear copper(II) complex with a Cu···Cu distance of 3.5 Å ($k_{cat} = 0.16\ \text{min}^{-1}$). Complexes with comparable intermetallic distance are usually so slow in their reactions that the rate constant is not determined.[16]

## Results and Discussion

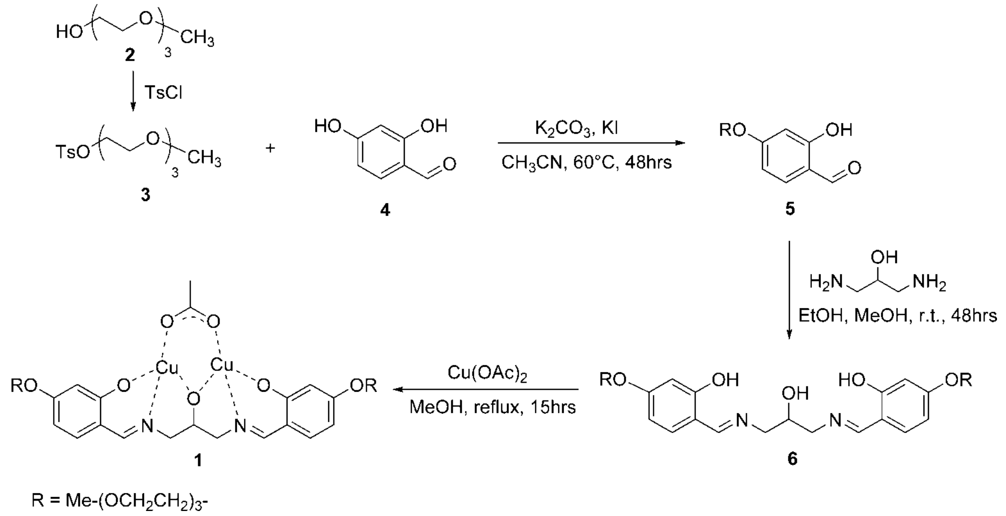
**Synthesis of a Water-Soluble Pentadendate Ligand and a Related Copper(II) Complex.** Initially, the terminal hydroxyl group of 2-[2-(2-methoxyethoxy)ethoxy]ethanol **2** was activated with tosyl chloride yielding **3**.[17] A Williamson ether synthesis of commercially available 2,4-dihydroxybenzaldehyde **4** and compound **3** afforded monosubstituted salicylaldehyde **5** after chromatographic purification. Compound **5** serves as a new building block for the synthesis of water-soluble Schiff base ligands after adequate modification of the procedure for the

---

(1) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820.
(2) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114–120.
(3) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
(4) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
(5) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239–1240.
(6) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901–1904.
(7) Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 1596–1597.
(8) Garner, P. P. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; pp 1–46.
(9) Butler, R. N.; Cunningham, W. J.; Coyne, A. G.; Burke, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 11923–11929.
(10) Thomas, F. *Eur. J. Inorg. Chem.* **2007**, 2379–2404.
(11) Chaudhuri, P.; Wieghardt, K.; Weyhermueller, T.; Paine, T. K.; Mukherjee, S.; Mukherjee, C. *Biol. Chem.* **2005**, *386*, 1023–1033.
(12) Selmeczi, K.; Reglier, M.; Giorgi, M.; Speier, G. *Coord. Chem. Rev.* **2003**, *245*, 191–201.
(13) Koval, I. A.; Gamez, P.; Belle, C.; Selmeczi, K.; Reedijk, J. *Chem. Soc. Rev.* **2006**, *35*, 814–840.
(14) Sprakel, V. S. I.; Feiters, M. C.; Meyer-Klaucke, W.; Klopstra, M.; Brinksma, J.; Feringa, B. L.; Karlin, K. D.; Nolte, R. J. M. *Dalton Trans.* **2005**, 3522–3534.
(15) Zhang, C. X.; Liang, H.-C.; Humphreys, K. J.; Karlin, K. D. *Catal. Met. Complexes* **2003**, *26*, 79–121.
(16) Ackermann, J.; Meyer, F.; Kaifer, E.; Pritzkow, H. *Chem.—Eur. J.* **2002**, *8*, 247–258.
(17) Kocian, O.; Chiu, K. W.; Demeure, R.; Gallez, B.; Jones, C. J.; Thornback, J. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 527–535.

10.1021/ja078057+ CCC: $40.75

***Scheme 1.*** Synthesis of Water-Soluble Ligands **6** and Dinuclear Copper(II) Complex **1**



reaction of **4** with benzyl tosylate described by Dewick et al.[18] Subsequent condensation of **5** with 1,3-diaminopropanol yielded water-soluble ligand **6** in sufficient purity and 89% yield after aqueous workup.[19] The formation of the azomethine bond is indicated by a shift of the $^{13}$C NMR signal for the carbonyl carbon from 194.4 ppm in aldehyde **5** to 166.4 ppm for the imino carbon in **6**. The pentadentate ligand **6** was then treated with copper(II) acetate in methanol to obtain the dinuclear copper(II) complex **1** as a green solid (Scheme 1).[19]

The use of alkyl halogenides instead of the tosylate **3** did not result in any reaction with **4** to obtain **5**, even after allowing prolonged reaction times (24–72 h), using elevated reaction temperatures (60 °C to reflux), or increasing the amount of the potassium iodide catalyst up to 1 molar equiv. Control experiments of **4** with benzyl halides promoted the reaction as described in the literature.[20]

**Composition of Complex 1 in the Solid State.** The composition of complex **1** in the solid state was confirmed by elemental analysis. Coordination of **6** to copper(II) acetate resulting in complex **1** was followed by IR spectroscopy. The C═N stretching vibration is shifted from 1622 cm$^{-1}$ in ligand **6** to 1629 cm$^{-1}$ in complex **1**. Similarly, the C−O stretching vibration of the phenoxy and alkoxy groups is shifted from 1115 cm$^{-1}$ in **6** to 1122 cm$^{-1}$ in **1** (see Supporting Information). All attempts to obtain a single crystal of **1** suitable for X-ray structure analysis have failed so far. For the planned study of the oxidation ability of **1**, however, we focused on its composition in aqueous organic solution to identify the catalytically active species.

**Composition of Complex 1 in Solution.** The composition of the copper complex **1** may differ in solution from that in the solid state. The solvent and/or hydroxyl ions in aqueous organic solution might exchange the bridging acetate in **1**, yielding the actual catalytically active species for the oxidation reaction. To clarify the composition of **1** *in solution*, we investigated the complex formation by a series of UV/vis spectroscopic titrations as developed by Zuberbühler and co-workers.[21]

The distribution of species related to **1** was determined in pure methanol and methanol/water mixtures (80/20 and 60/40, v/v, respectively) by computing multiwavelength spectroscopic UV/vis data (Figure 1), which were recorded as a function of the amount of copper salt added to the ligand **6** at constant ionic strength.

The titration of **6** with copper(II) acetate in methanol initially shows formation of an absorption band at 600 nm and then a shift of the absorbance maximum from 600 to 650 nm (Figure 1). This is characteristic for a $^2T_{2g} \rightarrow {}^2E_g$ (G) transition of square-planar copper(II) complexes.[22] The distribution of species derived from the titration data indicates 100% formation of a dinuclear copper(II) complex species above a 1:2 molar ratio of ligand **6** to copper(II) acetate (Figure 2). A mononuclear copper(II) species $CuL_{-2H}$ (**7**) dominates at a 1:1 molar ratio of **6** and copper(II) acetate (Figure 3). Control experiments for the assignment of putative structures based on the obtained spectroscopic data included a UV/vis spectroscopic titration of **6** with anhydrous sodium acetate in the presence of copper(II) chloride and revealed that acetate is necessary for the formation of a copper (II) complex in methanol (see Supporting Information). The composition of **1** in methanol is therefore the same as in the solid state.

The composition of a dinuclear complex derived from ligand **6** and copper(II) acetate is drastically altered in *aqueous* methanol ($MeOH/H_2O$ = 80/20 and 60/40, v/v, respectively). The bridging acetate anion in **1** is exchanged by water and hydroxyl ions under these conditions as concluded from spectrophotometric and calorimetric titration experiments (see Supporting Information). The resulting dinuclear copper(II) species $Cu_2L_{-3H}(OH)$ (**8**) (Figure 4) is consequently described with a $\mu^1$-coordinating or $\eta^2$-bridging hydroxyl group in equilibrium structures.

The amount of **8** formed at a 2:1 molar ratio of copper(II) acetate and **6** is diminished in $MeOH/H_2O$ to 59% (80/20, v/v) and 72% (60/40 (v/v), respectively, of the theoretical value due to the presence of mononuclear complex **7** (Figure 5).

The apparent concentration of **8** used for the determination of kinetic parameters for the oxidation of DTBC was therefore

---

(18) Dewick, P. M. *Synth. Commun.* **1981**, *11*, 853–857.
(19) Fallon, G. D.; Murray, K. S.; Mazurek, W.; O'Connor, M. J. *Inorg. Chim. Acta* **1985**, *96*, L53–L55.
(20) Maslak, V.; Yan, Z.; Xia, S.; Gallucci, J.; Hadad, C. M.; Badjic, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 5887–5894.
(21) Binstead, R. A.; Jung, B.; Zuberbühler, A. D. *SPECFIT*, 3.0 ed.; Spectrum Software Associates: Marlborough, MA, 2000.
(22) Tas, E.; Aslanoglu, M.; Guler, M.; Ulusoy, M. *J. Coord. Chem.* **2004**, *57*, 583–589.

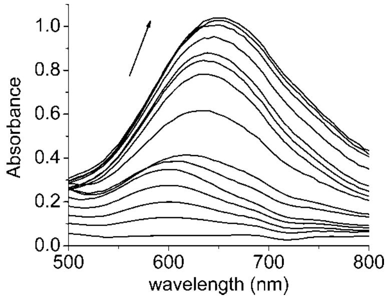


***Figure 1.*** Electronic spectra obtained from titration of ligand **6** with copper(II) acetate in methanol.

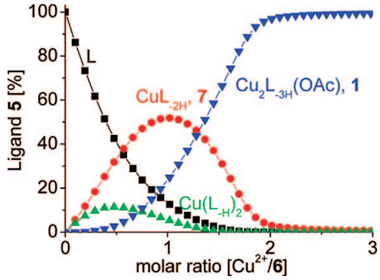


***Figure 2.*** Distribution of species derived from spectrophotometric titration of ligand **6** with copper(II) acetate in methanol.

adjusted accordingly. The contribution of **7** to the catalytic transformation of DTBC into DTBQ was negligible (see Supporting Information). A structurally related *planar* mononuclear copper(II) complex has been previously described to be catalytically inactive.[23] Due to the higher concentration of **8** in 60% MeOH compared to a system with 80% MeOH, we hypothesized that the rate acceleration of the reaction will be higher in solutions with higher water content.

**Catalytic Transformation of the Model Substrate DTBC.** In view of the great importance of oxidation reactions for industrial and synthetic processes and the ongoing search for new and efficient oxidation catalysts that are functional in water, we chose the catalytic oxidation of 3,5-di-*tert*-butylcatechol, DTBC (**9**), to 3,5-di-*tert*-butylquinone, DTBQ (**10**), as a model reaction to test our hypothesis and establish the catalytic abilities of **1** and **8** (Scheme 2) in organic and aqueous organic solution. Substrate **9** has a low redox potential and high stability against ring-opening reactions.[24] Various groups have used **9** as a model substrate to investigate catechol oxidase-like activity for dinuclear copper(II) complexes.[12,13]

The catalyst **1** (or **8**) was prepared by mixing solutions of copper(II) acetate and ligand **6** in 2:1 molar ratio and adjusting the concentration of **8** as described above. The reaction was monitored by UV/vis spectroscopy by following the formation of **10** at a wavelength of 420 nm. The initial rates were used for analysis of the catalyzed oxidation of **9** into **10** that follows Michaelis–Menten kinetics (Figure 6). A control experiment shows that the reaction rates at constant substrate concentration increase linearly with the catalyst concentration (see Supporting Information).

First, the substrate concentration was varied from 15 to 50 mM at a 200 $\mu$M concentration of **1** for the determination of kinetic parameters for the transformation of **9** into **10** *in pure methanol*. The catalytic rate constant $k_{cat}$ was determined to be 0.04 $min^{-1}$, and the Michaelis–Menten constant $K_m$ was determined to be 40 mM at 30 °C. The rate constant is comparable to those reported for other dinuclear Cu(II) complexes with a comparable Cu $\cdots$ Cu distance of 3.5 Å but about one magnitude lower than those observed for complexes with a shorter intermetallic distances, for example, 2.9 Å ($k_{cat} = 0.21$ $min^{-1}$)[25] or 3.075 Å ($k_{cat} = 0.32$ $min^{-1}$).[25–27] The rate constant $k_{non}$ for the spontaneous (uncatalyzed) oxidation of **9** into **10** was determined to be $6 \times 10^{-7}$ $min^{-1}$ and corresponds to the oxidation without catalyst under otherwise identical conditions. The rate acceleration ($k_{cat}/k_{non}$) deduced from these values is 60 000-fold.

Second, the transformation of **9** into **10** was monitored in 80% aqueous MeOH for substrate concentrations between 0.05 to 0.4 mM and 12 $\mu$M of apparent concentration of **8**. Unbuffered nanopure water was always used, as the addition of base accelerates the uncatalyzed oxidation of **9** by air significantly. The catalytic rate constant $k_{cat}$ in 80% aqueous MeOH was determined to be 0.13 $min^{-1}$. The Michaelis–Menten constant $K_m$ was determined to be 0.07 mM, which refers to a higher affinity of the substrate to the metal complex in aqueous methanol than in pure methanol. The rate constant for the spontaneous reaction $k_{non}$ was determined to be $1 \times 10^{-6}$ $min^{-1}$ in 80% aqueous MeOH. The transformation of **9** into **10** is 140 000-fold accelerated over background under these conditions and is thus about twice as fast accelerated than the reaction in pure methanol.

Finally, the oxidation of **9** into **10** in 60% aqueous MeOH was determined by varying the substrate concentration from 0.1 to 0.8 mM at 15 $\mu$M of apparent catalyst concentration of **8**. The catalytic rate constant $k_{cat}$ was determined as 0.16 $min^{-1}$ and the Michaelis–Menten constant $K_m$ as 0.41 mM. The rate constant for the spontaneous reaction $k_{non}$ was determined as $1 \times 10^{-6}$ $min^{-1}$. The rate acceleration ($k_{cat}/k_{non}$) was deduced from these values as 160 000, which indicates that the transformation of **9** into **10** in 60% aqueous MeOH is accelerated almost 3 times faster than the reaction in pure methanol ($k_{cat}/k_{non} =$ 60 000; see above and Table 1).

The catalytic proficiency $(k_{cat}/K_m)/k_{non}$ of the oxidation in the three different solvents can be calculated from the values derived above to provide a measure of the affinity that the catalyst develops for a given substrate as passing through the transition state.[28] The proficiency of the oxidation is $1.7 \times 10^6$ $M^{-1}$ in pure MeOH, $1.9 \times 10^9$ $M^{-1}$ for 80% MeOH, and $0.4 \times 10^9$ $M^{-1}$ in 60% MeOH. The catalytic proficiencies of the reactions in aqueous MeOH are comparable but 3 orders of magnitude larger than in pure MeOH. The transition state in aqueous solution is therefore better stabilized in aqueous solution than in pure MeOH, which is in agreement with the observed different rate accelerations.

**Proposed Mechanism of Oxidation.** Reduction of dioxygen into hydrogen peroxide is often proposed for catecholase-like

---

(23) Oishi, N.; Nishida, Y.; Ida, K.; Kida, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2847–2850.

(24) Monzani, E.; Battaini, G.; Perotti, A.; Casella, L.; Gullotti, M.; Santagostini, L.; Nardin, G.; Randaccio, L.; Geremia, S.; Zanello, P.; Opromolla, G. *Inorg. Chem.* **1999**, *38*, 5359–5369.

(25) Rey, N. A.; Neves, A.; Bortoluzzi, A. J.; Pich, C. T.; Terenzi, H. *Inorg. Chem.* **2007**, *46*, 348–350.

(26) Peralta, R. A.; Neves, A.; Bortoluzzi, A. J.; dos Anjos, A.; Xavier, F. R.; Szpoganicz, B.; Terenzi, H.; de Oliveira, M. C. B.; Castellano, E.; Friedermann, G. R.; Mangrich, A. S.; Novak, M. A. *J. Inorg. Biochem.* **2006**, *100*, 992–1004.

(27) Belle, C.; Beguin, C.; Gautier-Luneau, I.; Hamman, S.; Philouze, C.; Pierre, J. L.; Thomas, F.; Torelli, S.; Saint-Aman, E.; Bonin, M. *Inorg. Chem.* **2002**, *41*, 479–491.

(28) Miller, B. G.; Wolfenden, R. *Annu. Rev. Biochem.* **2002**, *71*, 847–885.

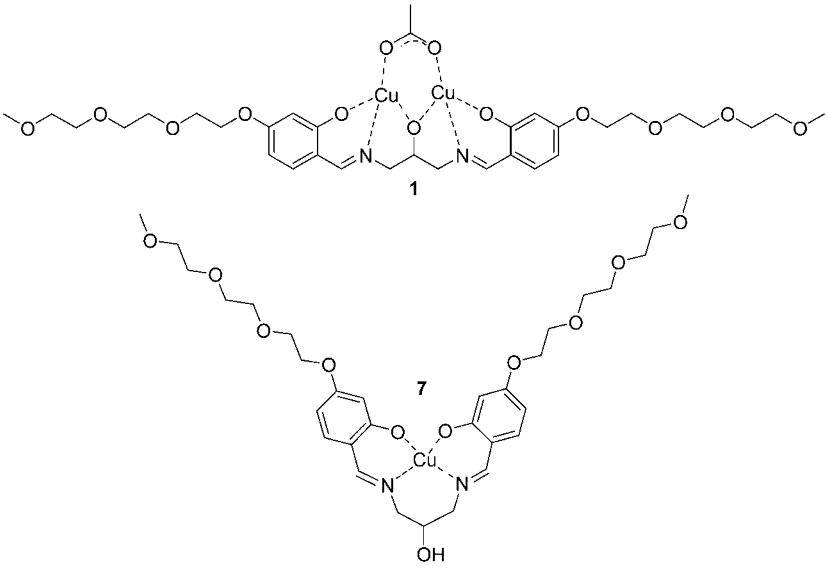


***Figure 3.*** Putative structures for the di- and mononuclear species $Cu_2L_{-3H}(OAc)$ (**1**) and $CuL_{-2H}$ (**7**).

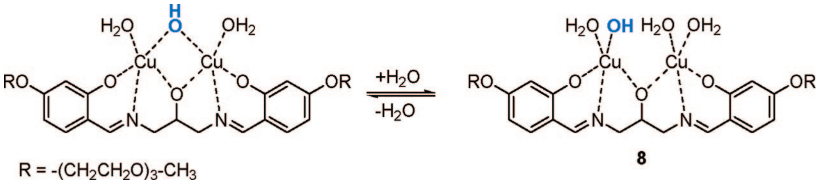


***Figure 4.*** Equilibrium structures of $Cu_2L_{-3H}(OH)$ (**8**) derived from backbone ligand **6** and copper(II) acetate in aqueous methanol.

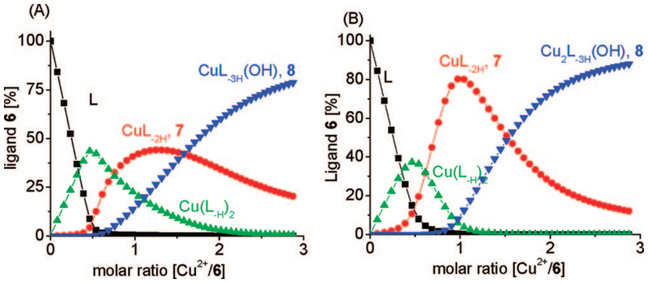
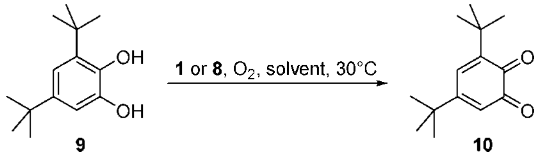


***Figure 5.*** Distribution of species derived from spectrophotometric titration data of ligand **6** with copper(II) acetate in (A) MeOH/$H_2O$ 80/20 (v/v) and (B) MeOH/$H_2O$ 60/40 (v/v).

***Scheme 2.*** Model Reaction



**9** **10**

oxidation reactions with dinuclear copper(II) complexes. A very sensitive test for the presence of hydrogen peroxide is based on the spectrophotometric detection of the triiodide ($I_3^-$) anion as triiodide−molybdate complex at 352 nm ($\epsilon = 26\,400$ $M^{-1}$ $cm^{-1}$) that is formed from potassium iodide in the presence of $H_2O_2$.[29] The detection limit for the presence of hydrogen peroxide is $10^{-6}$ M.[29] Hydrogen peroxide was not detected in the product solutions for both the catalytic and the noncatalytic aerobic oxidation reaction in aqueous MeOH (see Supporting Information). We therefore conclude that dioxygen is reduced to water as final product and not to $H_2O_2$.

We subsequently analyzed the dependence of the reaction on the presence of dioxygen. The formation of **10** from **9** is negligible under anaerobic conditions (see Supporting Information). The reaction does, however, proceed when the degassed solution is exposed to dioxygen in an open flask resulting in the formation of **10** (see Supporting Information) after a short lag time that stems from the slow dissolution of oxygen gas into the solution. These results imply that a spontaneous two-electron transfer from substrate **9** to catalyst **8**, yielding stoichiometric quantities of **10**, does not take place prior to coordination of oxygen to **1** or **8**. The formation of a dicopper−catecholate intermediate as a first step of the reaction is thus rather unlikely,[30–33] although this has been frequently described for the oxidation of catechols by dinuclear Cu(II) complexes.[13,34–40]

On the basis of our results, we propose the addition of two molecules of DTBC to **1** or **8** resulting in dicatechol adduct **I**.

---

(29) Kormann, C.; Bahnemann, D. W.; Hoffmann, M. R. *Environ. Sci. Technol.* **1988**, *22*, 798–806.

(30) Habermehl, N. C.; Angus, P. M.; Kilah, N. L.; Noren, L.; Rae, A. D.; Willis, A. C.; Wild, S. B. *Inorg. Chem.* **2006**, *45*, 1445–1462.

(31) Casella, L.; Monzani, E.; Gullotti, M.; Cavagnino, D.; Cerina, G.; Santagostini, L.; Ugo, R. *Inorg. Chem.* **1996**, *35*, 7516–7525.

(32) Karlin, K. D.; Gultneh, Y.; Nicholson, T.; Zubieta, J. *Inorg. Chem.* **1985**, *24*, 3725–3727.

(33) Demmin, T. R.; Swerdloff, M. D.; Rogic, M. M. *J. Am. Chem. Soc.* **1981**, *103*, 5795–5804.

(34) Belle, C.; Selmeczi, K.; Torelli, S.; Pierre, J.-L. *C. R. Chim.* **2007**, *10*, 271–283.

(35) Kim, E.; Chufan, E. E.; Kamaraj, K.; Karlin, K. D. *Chem. Rev.* **2004**, *104*, 1077–1133.

(36) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047–1076.

(37) Mukherjee, R. *Comp. Coord. Chem. II* **2004**, *6*, 747–910.

(38) Halcrow, M. A. *Comp. Coord. Chem. II* **2004**, *8*, 395–436.

(39) Itoh, S. *Comp. Coord. Chem. II* **2004**, *8*, 369–393.

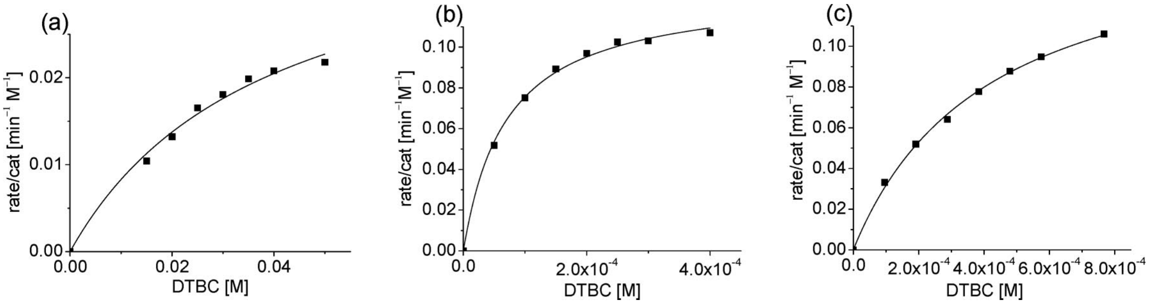


***Figure 6.*** Kinetic profile for the aerobic oxidation of **9** into **10** promoted by **1** (or **8**) in (a) MeOH, (b) MeOH/$H_2O$ (80/20, v/v), and (c) MeOH/$H_2O$ (60/40, v/v) follows the Michaelis–Menten kinetic model and is (a) 60 000-fold, (b) 140 000-fold, and (c) 160 000-fold accelerated over background.

***Table 1.*** Summary of kinetic parameters for oxidation of **9** into **10**

| solvent | $k_{cat}$ (min$^{-1}$) | $K_m$ (mM) | $k_{non}$ (min$^{-1}$) | $k_{cat}/k_{non}$ | $(k_{cat}/K_m)k_{non}$ (M$^{-1}$) |
|---|---|---|---|---|---|
| 100% MeOH | 0.04 | 40 | $6 \times 10^{-7}$ | 60000 | $1.7 \times 10^6$ |
| 80% MeOH | 0.13 | 0.07 | $1 \times 10^{-6}$ | 140000 | $1.9 \times 10^9$ |
| 60% MeOH | 0.16 | 0.41 | $1 \times 10^{-6}$ | 160000 | $0.4 \times 10^9$ |

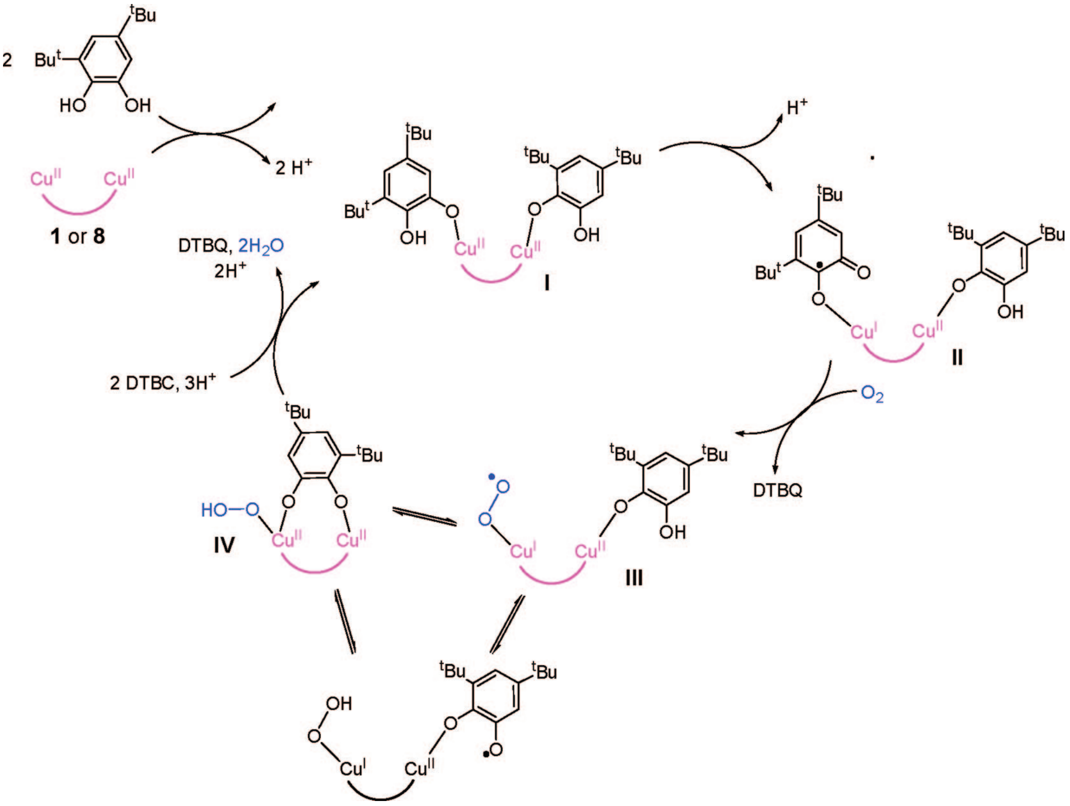
The catalytic transformation of **9** into **10** will then proceed via a one-electron transfer from the catechol to the copper(II) core of **1** or **8**, resulting in a semiquinone intermediate species **II** that is known to be stable only in the absence of dioxygen (Scheme 3).[41] As the anaerobic oxidation does not result in stoichiometric formation of DTBQ, the addition of oxygen to intermediate species **II** is very likely the rate-determining step and results in release of 1 mol of DTBQ and a mixed Cu(I)•••Cu(II) species **III** that undergoes rapid hydrogen radical transfer forming the catecholate−dicopper(II) adduct **IV**. A two-electron transfer reaction of intermediate **IV** will result in formation of another mol of **10** and the release of 2 mol of water. The coordination of two additional molecules of DTBC results in re-formation of intermediate **I** and allows repetition of the catalytic cycle.

## Conclusions

The introduction of PEG side chains into the ligand backbone affords a water-soluble complex **1** that preserves its composition in the solid state and in pure MeOH but exchanges the bridging acetate anion in aqueous MeOH with water and hydroxyl ions forming **8** as a new catalytic species. The catalytic aerobic oxidation of 3,5-DTBC (**9**) into 3,5-DTBQ (**10**) is about 3 times faster in aqueous solvent (MeOH/$H_2O$ = 60/40, v/v) than in pure MeOH and is 5 orders of magnitude accelerated over background. To the best of our knowledge, complex **8** promotes one of the highest accelerations of the aerobic catechol oxidations by a dinuclear copper(II) complex with a 3.5 Å Cu−Cu distance that is due to the formation of a hydroxyl-ion-containing catalytically active species in aqueous solution.

Our results highlight the pronounced effect of water as a co-solvent on the composition of a catalytically active species and

***Scheme 3.*** Putative Mechanism for the Aerobic, Catalytic Oxidation of DTBC (**9**) into DTBQ (**10**) with **1** or **8**



indicate that catechol oxidations can be conducted in aqueous solution, which will largely impact the design of catalysts aimed at promoting the hydrolysis of catechol-like fragments in lignin. Lastly, our results emphasize the importance of a carefully conducted characterization of a catalytically active species that may vary depending on the solvent system used. Current efforts focus on the transformation of water-soluble catechols in aqueous solution and on the variation of the intermetallic Cu···Cu distance to accelerate the reaction even further.

## Experimental Section

**Instrumentation.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon). Chemical shifts ($\delta$) in $^1$H NMR are expressed in parts per million and coupling constants ($J$) in hertz. Signal multiplicities are denoted as s (singlet), d (doublet), t (triplet), and m (multiplet). Deuterated chloroform was used as solvent, and chemical shift values are reported relative to the residual signals of this solvent ($\delta = 7.24$ for $^1$H and $\delta = 77.0$ for $^{13}$C). UV–vis spectra were recorded at 30 °C over a range of 200–900 nm on a Varian Cary 50 with WinUV Analysis Suite software, version 3.0, using Suprasil standard cells (200–2000 nm) of 1 cm thickness and 4.5 mL volume for the determination of the distribution of species. Disposable 1.5 mL semimicro Brandtech UV cuvettes (220–900 nm) of 10 mm light path with caps were used for the oxidation studies. The IR spectra were obtained on a Shimadzu IR Prestige-21 FT-IR spectrophotometer with IR solution software version 1.10 as thin films or KBr pellets ($\nu$ in cm$^{-1}$). Samples for elemental analysis were sent to Atlantic Microlab Inc., Atlanta, GA. ESI-MS data were obtained on a VG Trio-2000 Fisons Instruments mass spectrometer with VG MassLynx software, version 2.00, or sent to the Laboratory for Biological Mass Spectrometry, Texas A&M University, College Station, TX, for analysis.

Thin layer chromatography (TLC) was done using silica gel TLC plates from SORBENT Technologies, 200 $\mu$m, 4 × 8 cm, aluminum backed, with fluorescence indicator $F_{254}$ with detection by charring with anthrone sulfate, and by UV light when applicable. Column chromatography was carried out using silica gel 60 as stationary phase from Silicycle (40–63 $\mu$m, 230–240 mesh). All melting points were recorded on a Mel-Temp melting point apparatus, and the values are uncorrected.

**Reagents.** 3,5-Di-*tert*-butylcatechol (3,5-DTBC, **9**) was purchased from Aldrich and recrystallized twice from *n*-pentane under argon before use. Nanopure water obtained from an EASYpure II water system from Barnstead (18.2 MΩ/cm) and HPLC grade methanol (purchased from Aldrich, 99.93%) were used for all UV/vis experiments. All other reagents were used as received from commercial suppliers.

**2-(2-(2-Methoxyethoxy)ethoxy)ethyl-*p*-toluenesulfonate (3).** The title compound was prepared by adoption of a method described by McCairn et al. for the ditosylation of polyethylene glycol.[42] A solution of tosyl chloride (3.62 g, 22 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise over 2 h to an ice-cooled solution of 2-[2-(2-methoxyethoxy)ethoxy]ethanol (**2**) (4.32 g, 22.3 mmol) and triethylamine (6.2 mL, 22 mmol) in $CH_2Cl_2$ (50 mL), and the resulting solution was stirred overnight while warming to ambient temperature. The reaction mixture was treated with 20 mL of distilled water; the organic layer was separated, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. Column chromatography of the residue on silica gel using cyclohexane/ethyl acetate (1:1, v/v) gave a pale yellow oil (5.01 g, 15.72 mmol, 71%). The NMR data obtained match the literature data reported for the title compound:[43] $\delta_H$ (400 MHz, $CDCl_3$) 7.77 (d, 2H, 7.58), 7.32 (d, 2H, 8.08), 4.13 (t, 2H, 4.67, $OCH_2$), 3.66 (t, 2H, 4.17, $OCH_2$), 3.53–3.61 (m, 6H, $OCH_2$), 3.48–3.52 (m, 2H, $OCH_2$), 3.34 (s, 3H, $OCH_3$), 2.42 (s, 3H, $ArCH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 144.9, 133.0, 129.9, 128.0, 72.0, 70.8, 70.6, 70.5, 69.4, 68.7, 59.1, 21.7.

**4-{2-[2-(Methoxyethoxy)ethoxy]ethoxy}salicylaldehyde (5).** A mixture of 2.1 g (15 mmol) 2,4-dihydroxybenzaldehyde (**4**), 3.2 g (10 mmol) of **3**, and 2 g (15 mmol) of potassium carbonate was stirred in 150 mL of acetonitrile at 60 °C for 36 h. The reaction mixture was then cooled to room temperature and filtered, and the solvent was evaporated to obtain a brownish residue. The crude product was purified by column chromatography on silica gel with ethyl acetate/cyclohexane (1:1). Yield: 900 mg (3.17 mmol, 32%), yellow oil. Found: C, 58.85; H, 7.24. $C_{14}H_{20}O_6$ requires: C, 59.14; H, 7.09; $\delta_H$ (400 MHz, $CDCl_3$) 11.46 (1H, s, OH), 9.71 (1H, s, CHO), 7.43 (1H, d, ArH), 6.56 (1H, dd, 8.72, 2.15, ArH), 6.43 (1H, d, 2.27, ArH), 4.17 (2H, m, $ArOCH_2-$), 3.87 (2H, m, $CH_2$) 3.73 (2H, m, $CH_2$), 3.67 (4H, m, $CH_2$), 3.37 (3H, s, $-CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 194.4, 166.0, 164.4, 135.3, 115.2, 108.8, 101.3, 71.9, 70.9, 70.6, 70.5, 69.3, 67.9, 59.0; $\nu_{max}$ (thin film)/cm$^{-1}$) 3497br (OH), 3074w (=CH), 2877s (C−H), 1725m (C=O), 1112s (C−O); HRMS calcd for $(C_{14}H_{20}O_6 + Li)^+$ 291.1420; found 291.1417.

***N,N′*-1,3-Bis[{2-hydroxy-4-[2-(2-methoxyethoxy)ethoxy]ethoxy}-benzylideneamino]propan-2-ol, TEGbsdpo, (6).** A solution of 1,3-diamino-2-propanol (158 mg, 1.75 mmol) in 10 mL of ethanol was added to a solution of **5** (1 g, 3.5 mmol) in 150 mL of ethanol/methanol (1:1, v/v) at ambient temperature and allowed to stir for an additional 48 h. The solvents were then evaporated to give a crude residue, which was dissolved in 20 mL of water and extracted using chloroform (2 × 100 mL). The combined organic layers were dried using anhydrous sodium sulfate and evaporated, yielding a yellow solid that was used without further purification. Yield: 90% (1.03 g, 1.58 mmol). Found: C, 59.09; H, 7.35; N, 4.42. $C_{31}H_{46}N_2O_{11}\cdot½H_2O$ requires: C, 58.92; H, 7.44; N, 4.42; $\delta_H$ (400 MHz, $CDCl_3$) 8.14 (s, 2H, $-CH{=}N-$), 7.04 (d, 2H, 8.84, ArH), 6.36 (d, 2H, 2.53, ArH), 6.33 (s, 2H, ArH), 4.14 (m, 1H, $-CHOH-$), 4.09 (m, 4H, $ArOCH_2-$), 3.82 (t, 4H, 4.80, $ArOCH_2CH_2-$), 3.74 (dd, 6H, 3.28, 5.84, $-CH_2-$), 3.71–3.56 (m, 10 H, $-CH_2-$), 3.55–3.50 (m, 4H, $-CH_2-$), 3.35(s, 6H, $-OCH_3$); $\delta_C$ (400 MHz, $CDCl_3$) 166.4, 165.9, 163.3, 133.1, 112.2, 107.0, 101.9, 71.9, 70.8, 70.6, 70.5, 70.2, 69.5, 67.5, 61.2, 59.0; $\nu_{max}$ (KBr)/cm$^{-1}$ 3573 (br, OH), 3073w (=CH arom), 2871s (C−H), 1622v (C=N), 1115s (C−O); positive ion ESI MS, calcd for $(C_{31}H_{46}N_2O_{11} + H)^+$ 622.31, found 622.81.

**{*N,N′*-1,3-Bis[{2-hydroxy-4-[2-(2-methoxyethoxy)ethoxy]}-benzylideneamino]propan-2-ol}ato (*μ*-acetato) Dicopper Complex 1.** To obtain an analytically pure sample for the characterization of complex **1** in the solid state, a solution of 125 mg (0.2 mmol) of backbone ligand **6** in 50 mL of ethanol was added to copper(II) acetate monohydrate (80 mg, 0.44 mmol) dissolved in 10 mL of methanol. The green solution was stirred at 60 °C for 24 h. Subsequently, the solution was concentrated to dryness and the resulting green solid purified on Sephadex LH-20-100 to remove excess acetate using methanol as solvent. The fraction with an $R_f$ value of 0.69 was collected and evaporated to dryness to obtain the analytically pure sample of complex **1** as a green-black solid. Yield: 20 mg, 0.023 mmol, 12%. Found: C, 48.29; H, 5.77; N, 3.58. $C_{33}H_{47}Cu_2N_2O_{13}\cdot H_2O$ requires: C, 48.05; H, 5.99; N, 3.40; $\nu_{max}$ (KBr)/cm$^{-1}$ 3466br (OH), 2894s (C−H), 1629v (*C*=N), 1122s (C−O); HRMS calcd for $(C_{33}H_{46}Cu_2N_2O_{13} + K)^+$ 843.1429, found 843.1126.

**General Procedure for Conducting Species Distribution Experiments.** All experiments were done in thermostatted 4 mL UV–vis cuvettes in (a) MeOH, (b) MeOH/$H_2O$ 80/20 (v/v), or (c) MeOH/$H_2O$ 60/40 (v/v) at constant ionic strength (0.1 M $NaClO_4$)

---

(40) Fabian, I.; Csordas, V. *Adv. Inorg. Chem.* **2003**, *54*, 395–461.

(41) Thompson, C.; Calabrese, J. *J. Am. Chem. Soc.* **1986**, *108*, 1903–1907.

(42) McCairn, M. C.; Tonge, S. R.; Sutherland, A. J. *J. Org. Chem.* **2002**, *67*, 4847–4855.

(43) Yamazaki, K.; Yokoyama, A.; Yokozawa, T. *Macromolecules* **2006**, *39*, 2432–2434.

at 30 ± 0.1 °C. Aliquots (10 μL) of 0.3 M copper(II) acetate solutions were added to 2 mL (initial volume) of a 2 mM (initial concentration) solution of ligand **6**. After mixing the solution with a pipet, UV–vis spectra were recorded as a function of the total concentration of copper(II) acetate, and the spectral data of complex formation computed by fitting procedures provided by the program SPECFIT.[21]

**General Procedure for Conducting Kinetic Experiments.** The experiments were conducted in three different solvent systems: (a) MeOH, (b) MeOH/$H_2O$ (80/20), and (c) MeOH/$H_2O$ (60/40) at 30 ± 0.1 °C using 1.5 mL disposable UV–vis cuvettes.

**MeOH Solution.** Typically, a 2 mM catalyst stock solution was prepared by mixing a solution of 8 mg (40 μmol) copper(II) acetate monohydrate and 12.5 g (20 μmol) of ligand **6** and adjusting the total volume to 10 mL. A 0.125 M DTBC stock solution was prepared by dissolving 222 mg of **9** in 8 mL of MeOH. Aliquots of this DTBC stock solution (120–400 μL) were pipetted into the cuvettes, and 780–500 μL of MeOH was added and thermostated at 30 °C. Subsequently, aliquots of the thermostated catalyst stock solution (100 μL) were pipetted into these substrate solutions, resulting in a total substrate concentration of 15−50 mM **9** in methanol and a total 0.2 mM catalyst concentration. The formation of DTBQ (**10**) was followed by UV/vis spectroscopy, observing the development of an absorbance band at 420 nm. The molar absorbance of **10** at that wavelength was determined to be 1670 $M^{-1}$ $cm^{-1}$ by using a commercial sample. The self-oxidation of **9** into **10** was determined without catalyst under otherwise identical conditions.

**MeOH/$H_2O$ (80/20, v/v).** The concentration of the substrate **9** was varied from 50 to 400 μM at a 12 μM apparent catalyst concentration. The self-oxidation of **9** in air was observed for 15–50 mM solutions of **9** without catalyst under otherwise identical conditions.

**MeOH/$H_2O$ (60/40, v/v).** The concentration of substrate **9** was varied from 100 to 800 μM at a 14 μM apparent catalyst concentration. The self-oxidation of **9** in air was observed for 15–50 mM solutions of **9** without catalyst under otherwise identical conditions.

**Supporting Information Available:** Extensive UV/vis titrations and ITC experiments to clarify the composition of complex **1** in solution and to study the catalytic transformation promoted by mononuclear complex **7**; NMR, IR, and mass spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA078057+