

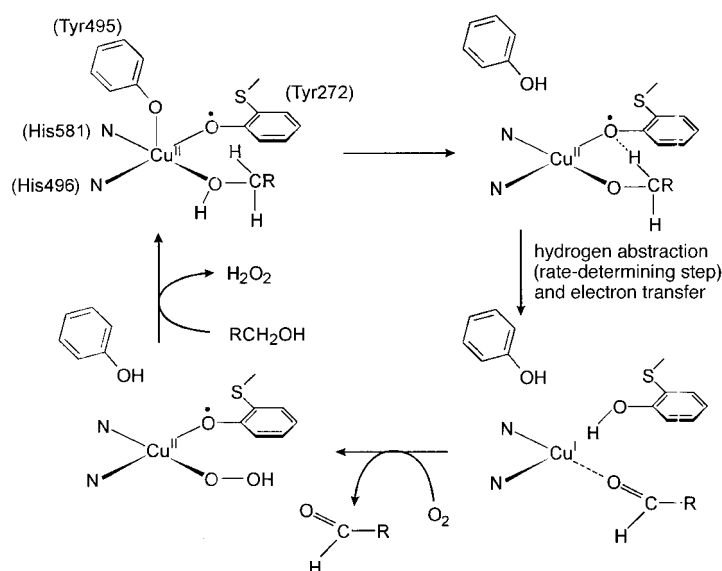
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From Structural Models of Galactose Oxidase to Homogeneous Catalysis: Efficient Aerobic Oxidation of Alcohols**

Phalguni Chaudhuri,* Martina Hess, Ulrich Flörke, and Karl Wieghardt*

Dedicated to Professor Achim Müller
on the occasion of his 60th birthday

The fungal enzyme galactose oxidase (GO) catalyzes the aerobic oxidation of primary alcohols to aldehydes and H $_2$ O $_2$.^[1] The structure^[2] of this biomolecule and its reaction mechanism^[3] are well established (Scheme 1): In its catalytically active form there is an *ortho*-S-modified tyrosyl radical (Tyr 272) coordinated to a single copper(II) ion and a unique radical cofactor. The rate-determining step of this catalysis (k_H/k_D 6–8)^[4] upon binding of the alcohol substrate to the Cu^{II} ion is the hydrogen abstraction from the α -carbon atom of the



Scheme 1. Proposed mechanism of catalysis by galactose oxidase (according to Whittaker).^[3c]

alcohol with formation of a coordinated ketyl radical anion. Rapid intramolecular electron transfer with reduction of Cu^{II} to Cu^I then leads to the formation of the unbound aldehyde. The reduced enzyme reacts with dioxygen with formation of H $_2$ O $_2$ and regeneration of the active radical cofactor.

While structural models for the active form of the enzyme containing Cu^{II}–phenoxyl moieties have been synthesized and characterized spectroscopically,^[5] it appears to be much more demanding to model the reactivity of GO.^[5a, 6] Stack et al.^[7] have reported recently mononuclear functional Cu^{II} model complexes which catalyze the aerobic oxidation of activated benzyl and allyl alcohols with concomitant formation of H $_2$ O $_2$. We describe here a novel *dinuclear* Cu^{II}–phenoxyl radical species that catalytically oxidizes primary and secondary alcohols with dioxygen (air) to the corresponding aldehyde, ketone, and/or to 1,2-glycol derivatives; the reduction product is in all cases H $_2$ O $_2$.

The reaction of Cu^{II}Cl with 2,2'-thiobis(2,4-di-*tert*-butylphenol) (LH $_2$) and triethylamine (1:1:2) in dry methanol under argon produces a yellow solution that becomes deep blue upon controlled exposure to air. From this solution microcrystalline blue [Cu^{II}L(NEt $_3$)] (**1**) is precipitated. Figure 1 displays the structure of the mononuclear neutral complex **1**: The tridentate dianion L $^{2-}$ is coordinated to a Cu^{II} ion and a fourth coordination site is occupied by an NEt $_3$ ligand; the resulting coordination polyhedron is intermediate between square planar and tetrahedral. Complex **1** is paramagnetic (1.79 μ_B ; 3–300 K). The cyclic voltammogram (CV) of **1** in CH $_2$ Cl $_2$ (0.10 M [(*n*Bu) $_4$ N]⁺PF $_6^-$; glassy carbon working electrode) at 20°C displays two quasireversible one-electron oxidation processes at $E_{1/2} = 0.52$ and 0.89 V versus ferrocene/ferrocene (Fc⁺/Fc) which are ascribed to two successive oxidations of the coordinated ligand L to generate two phenoxyl radicals.

Passing a stream of dry O $_2$ through the above yellow solution in tetrahydrofuran (THF) for 1 h induces a color change from deep blue to green and, finally, microcrystalline

[*] Priv. Doz. Dr. P. Chaudhuri, Prof. Dr. K. Wieghardt, M. Hess
Max-Planck-Institut für Strahlenchemie
Stiftstrasse 34–36, 45470 Mülheim an der Ruhr (Germany)
Fax: (+49) 208-306-3952
E-mail: chaudh@mpi-muelheim.mpg.de
wieghardt@mpi-muelheim.mpg.de

Dr. U. Flörke
Anorganische und Analytische Chemie
Universität-Gesamthochschule Paderborn (Germany)

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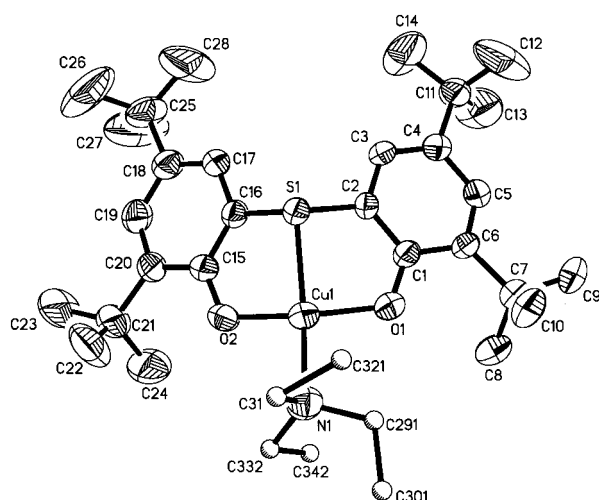
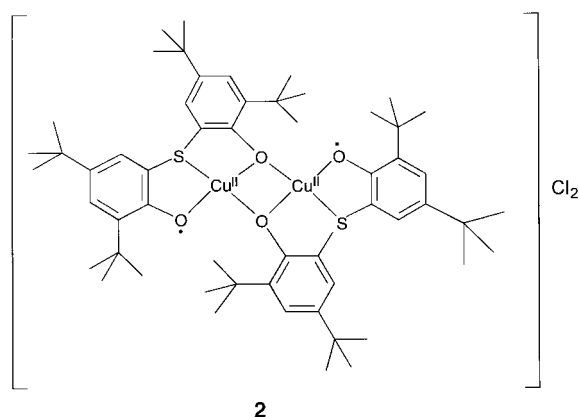


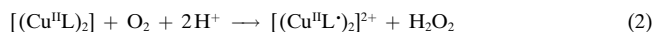
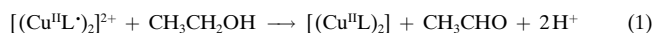
Figure 1. Crystal structure of the neutral complex $[\text{Cu}^{\text{II}}(\text{L}(\text{NEt}_3))]$ **1**. Selected bond lengths [Å] and angles [°]: Cu–O1 1.889(3), Cu–O2 1.895(3), Cu–N1 2.050(4), Cu–S1 2.290(2); O1–Cu–O2 152.2(2), O1–Cu–N1 97.9(2), O2–Cu–N1 98.0(2), O1–Cu–S1 87.6(1), O2–Cu–S1 88.0(1), N1–Cu–S1 154.0(1).

green $[(\text{Cu}^{\text{II}}\text{L}^{\cdot})_2]\text{Cl}_2$ (**2**) precipitates. Complex **2** is diamagnetic. The presence of a coordinated phenoxyl group in **2** is



evident from both the electronic spectrum in THF ($\lambda_{\text{max}} \approx 404 \text{ nm}$ ($\epsilon = 8.0 \times 10^3 \text{ L mol}^{-1} \text{ cm}^{-1}$) and the resonance Raman spectrum ($\lambda_{\text{exc}} = 458 \text{ nm}$, $\tilde{\nu}(\text{C}-\text{O}^{\cdot}) = 1451 \text{ cm}^{-1}$, $\tilde{\nu}(\text{C}=\text{C}) = 1579, 1594, 1606 \text{ cm}^{-1}$).^[5b] We propose that the structure of dinuclear **2**^[5c, d] has two bridging phenolate groups and two phenoxyl ligands. Whether the chloride anions are coordinated or not is unknown. This proposal readily explains the observed diamagnetism of **2** by an intramolecular antiferromagnetic exchange coupling between the phenoxyl groups ($S = 1/2$) and the Cu^{II} ions (d^9 ; $S = 1/2$).

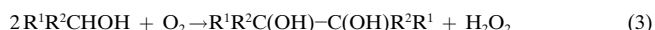
The addition of excess ethanol (10:1) to a deoxygenated green solution of **2** in THF under argon at 20°C induces a color change to blue. The formation of one equivalent of acetaldehyde [Eq. (1)] has been established photometrically (see Table 1). Subsequent exposure of this blue solution to air affords the above green solution within minutes; the electronic spectrum of this solution is nearly identical to that of a solution of **2** in THF without substrate. In this instance the formation of H_2O_2 (approximately one equivalent) has been established [Eq. (2)].



The CV of **2** in CH_2Cl_2 (otherwise the conditions are the same as above) displays two reversible one-electron reduction waves at $E_{1/2} = -1.26$ and -0.29 V versus Fc^+/Fc , which are assigned to the successive reduction of the phenoxyl radicals. These negative potentials readily account for the oxidizability of **2** by O_2 (**1** cannot be oxidized by O_2).

The combination of Equations (1) and (2) gives, in principle, the homogeneously catalyzed oxidation of ethanol with dioxygen to afford acetaldehyde and H_2O_2 . This is indeed the case, as summarized in Table 1. Remarkably, GC analysis of the products of aerobic oxidation of ethanol and benzyl alcohol reveals that in addition to the aldehydes small amounts of the corresponding 1,2-glycols, their α -hydroxyketones, and their α -diketones are formed. Mixtures of **2** in THF in the presence of H_2O_2 and a large excess of acetaldehyde or benzaldehyde are stable in air: No disproportionation of H_2O_2 , oxidation of the aldehydes to carboxylic acids, or formation of C–C coupling products is observed. Therefore, we conclude that the formation of 1,2-glycols upon oxidation of alcohols by air proceeds by a second reaction pathway which differs mechanistically from that of the aldehyde formation. This implies that secondary alcohols—in contrast to GO—can be catalytically oxidized by air with **2** as the catalyst.

Indeed, both 2-propanol and diphenylcarbinol can be employed as substrates in the above catalysis, and in both cases the corresponding 1,2-glycol derivative is the only detectable organic product (formed through oxidative C–C coupling). The simple ketones acetone and benzophenone were identified in only trace amounts^[9] or not at all. The stoichiometry of this reaction was established as that in Equation (3). On the other hand, oxidation of 2-butanol with O_2 yields the ketone 2-butanone exclusively (Table 1) and one equivalent of H_2O_2 .



The kinetics of these catalysis reactions have been measured by variation of the total concentrations of $[\text{Cu}^{\text{II}}\text{L}]$, and the alcohol. The time-dependent product formation (H_2O_2 and aldehyde, ketone, or 1,2-glycol) and the O_2 consumption (manometrically) have been measured and the two rate laws Equations (4) and (5) have been established.

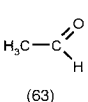
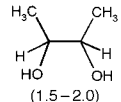
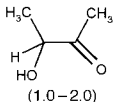
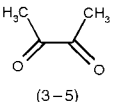
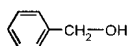
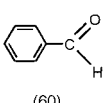
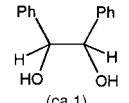
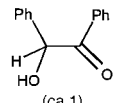
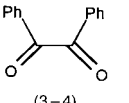
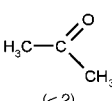
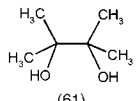
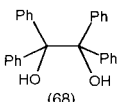
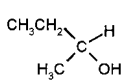
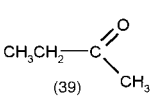
$$v = k[\text{CuL}]_i^2[\text{alcohol}] \quad (4)$$

$$v = k'[\text{CuL}]_i^2[\text{alcohol}]^2 \quad (5)$$

Thus, there are two independent pathways where aldehyde and ketone formation obey Equation (4), whereas the generation of 1,2-glycol follows Equation (5). The effect of the steric requirements of the Cu^{II} -coordinated starting materials and the electronic requirements of the putative coordinated ketyl radical anions on product formation are at present unknown.

With the selectively deuterated substrates $\text{CH}_3\text{CD}_2\text{OH}$ and $(\text{CH}_3)_2\text{CDOH}$ kinetic isotope effects $k_{\text{H}}/k_{\text{D}}$ of 8 and 10,

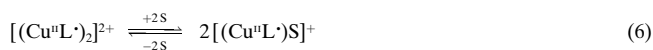
Table 1. Aerobic oxidation of primary and secondary alcohols.^[a]

Substrate	Products (yield [%]) ^[b]					Rate law
CH ₃ CH ₂ OH	 (63)	 (1.5–2.0)	 (1.0–2.0)	 (3–5)	H ₂ O ₂ (70)	Eq. (4)
	 (60)	 (ca. 1)	 (ca. 1)	 (3–4)	H ₂ O ₂ (65)	Eq. (4)
	 (< 2)	 (61)			H ₂ O ₂ (32)	Eq. (5)
	 (68)				H ₂ O ₂ (33)	Eq. (5)
	 (39)				H ₂ O ₂ (40)	Eq. (4)

[a] Experimental conditions: Cu^{II}Cl₂, LH₂ (1.25×10^{-5} mol each, NEt₃ (2.5×10^{-5} mol) in dry THF (50 mL) were heated at 50 °C under argon. After addition of the respective alcohol (6.25×10^{-3} mol) the solution was stirred at 20 °C in the presence of air for 12 h. Product analysis: the overall yield of the organic products was determined by gas chromatography; H₂O₂ was determined spectrophotometrically after complexation of the peroxide with titanium sulfate in aqueous H₂SO₄: G. M. Eisenberg, *Anal. Chem.* **1943**, *15*, 327; acetaldehyde was also determined spectrophotometrically: E. Sawicki, T. R. Hauser, T. W. Stanley, W. Elbert, *Anal. Chem.* **1961**, *33*, 93. [b] Yield of organic products: moles of C_n moieties in the product per mole of starting C_n alcohol (in percent); H₂O₂: moles of H₂O₂ per mole of starting alcohol (in percent).

respectively, have been found. This indicates that hydrogen abstraction from the α -carbon atom of the alcohols is the rate-determining step in both reaction pathways. Furthermore, it implies that the form of the catalyst prior to this step has the highest stationary concentration during catalysis. The electronic spectrum of a reaction mixture measured under turnover conditions is, therefore, very similar to that of a solution of **2** in THF (without substrate); the Cu^{II}–phenoxyl species is the dominant chromophore in both cases.

Since both rate laws display a second-order dependence on [Cu^{II}L]₂, the dinuclear form **2** constitutes the active catalyst, which is in equilibrium with its—catalytically inactive—monomeric form as shown in Equation (6). A strong donor solvent such as acetonitrile is, therefore, a very efficient inhibitor of the catalysis.



(S = solvent molecule or alcohol)

Scheme 2 exhibits two mechanistic proposals for the aerobic oxidation of primary and secondary alcohols with O₂ which is in agreement with all of the experimental results described above.

We would like to emphasize an important difference between our system and the enzymatic reaction of GO or Stack's model system.^[7] Catalyst **2** uses only the oxidation equivalents stored in the two phenoxyl radical ligands; the Cu^I oxidation state is not involved. Since two oxidation equiv-

alents are needed only the dinuclear form containing two phenoxyl ligands is catalytically relevant.

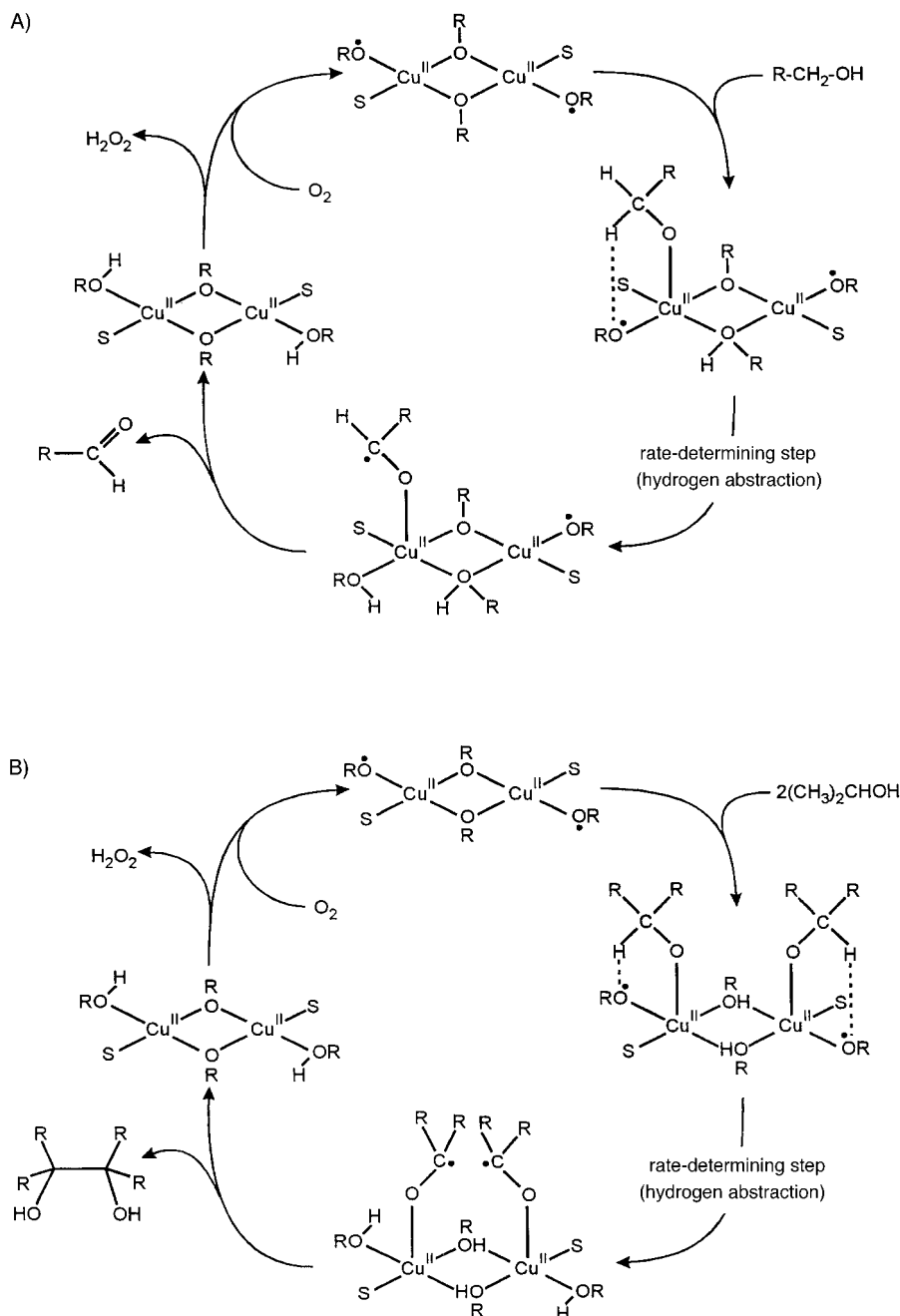
Two factors are decisive for the catalytic activity of **2**: the C–H abstraction from the coordinated alcoholate anion must be thermodynamically favorable—that is, the C–H bond should be relatively weak (therefore, methanol is *not* a substrate)—and the Cu^{II}–phenolate form must be reactive towards O₂.

Finally, the present system is not only capable of oxidizing alcohols under mild conditions, but at the same time highly concentrated H₂O₂ is formed at room temperature from air. The products are readily separated by extraction of the organic products with, for example, THF. Efficient Cu-catalyzed aerobic oxidation of alcohols has recently been described by Marko et al., but in their system water is the reduction product^[10] and oxidative C–C coupling is not observed.

Experimental Section

The ligand LH₂ has been prepared according to published procedures.^[11]

1: A suspension of CuCl (0.10 g, 1.0 mmol), LH₂ (0.44 g, 1.0 mmol), and NEt₃ (0.5 mL) in dry, deoxygenated CH₃OH (50 mL) was heated to reflux for 1 h under Ar. Careful exposure of the clear yellow solution to air at 20 °C initiated a color change to deep blue. After approximately 2 d in an open vessel at ambient temperature blue microcrystals of **1** precipitated. Recrystallization from CH₃OH:n-pentane (2:1) afforded blue rhombic crystals suitable for X-ray structure analysis. Yield: 0.48 g, 80%. Elemental analysis calcd for C₃₄H₅₅NO₂SCu: C 63.62, H 8.97, S 5.00, N 2.18, Cu 9.90;



Scheme 2. Proposed mechanisms for the catalytic oxidation of primary and secondary alcohols with **2** according to Equation (4) (A) and Equation (5) (B).

found: C 64.01, H 9.04, N 2.20, S 4.83, Cu 9.74; UV/Vis (THF): λ_{max} [nm] (ϵ [L mol⁻¹ cm⁻¹]): 400sh (ca. 370), 600sh (300), 700 (370).

2: A suspension of CuCl, LH₂, and NEt₃ (same amounts as for **1**) in dry(!) THF was heated to reflux Ar for 30 min. A stream of dry dioxygen was passed through the clear yellow solution at 20°C for 1 h (the absence of H₂O is important). The solution changed from blue to green and a green precipitate of **2** slowly formed, which was recrystallized from dry THF. Yield: 0.12 g, 11 %. Elemental analysis calcd for C₅₆H₈₀O₄S₂Cl₂Cu₂: C 62.32, H 7.47, S 5.94, Cl 6.57, Cu 11.77; found: C 61.95, H 7.48, S 5.88, Cl 6.47, Cu 11.75; UV/Vis (THF): λ_{max} , [nm] (ϵ [L mol⁻¹ cm⁻¹]): 400sh, 408 (8.0 × 10³), 424sh, 650(660).

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- [8] Crystal structure determination of **1**: blue crystal (0.65 × 0.45 × 0.12 mm³); C₃₄H₃₅CuNO₂S, *M*_r = 605.4; monoclinic, space group *P*₂₁/*n*, *a* = 15.659(3), *b* = 13.107(3), *c* = 18.321(4) (Å), β = 105.55(3)°, *V* = 3623(1) (Å³), *Z* = 4, *T* = 293(2) K; ρ_{calcd} = 1.11 g cm⁻³; μ_{Mo} = 0.687 mm⁻¹; semiempirical absorption correction, full-matrix, least-squares refinement on *F*² with 6917 reflections [*I* > 2σ(*I*)] and 348 variables, final *R* values: *R*(*F*) = 0.068 and *wR*2 = 0.135. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101165. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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