

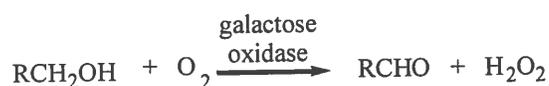
Catalysts for Alcohol Oxidation Inspired by Galactose Oxidase

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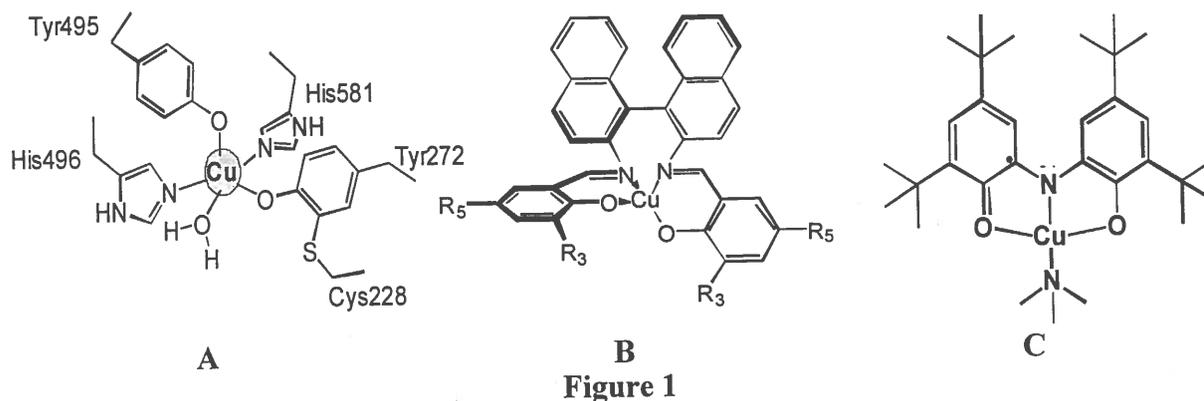
Literature Seminar

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Galactose oxidase (GO) is an enzyme excreted into the exocellular environment by root fungi. The enzyme is known to selectively catalyze the oxidation of primary alcohols to aldehydes with concomitant reduction of molecular oxygen to hydrogen peroxide, as shown below;¹ hydrogen peroxide is used outside of the cell to degrade lignin,² a dense biopolymer of tyrosine and phenylalanine. The ability to produce hydrogen peroxide in high concentrations or to oxidize alcohols to aldehydes selectively is of great interest to industry.



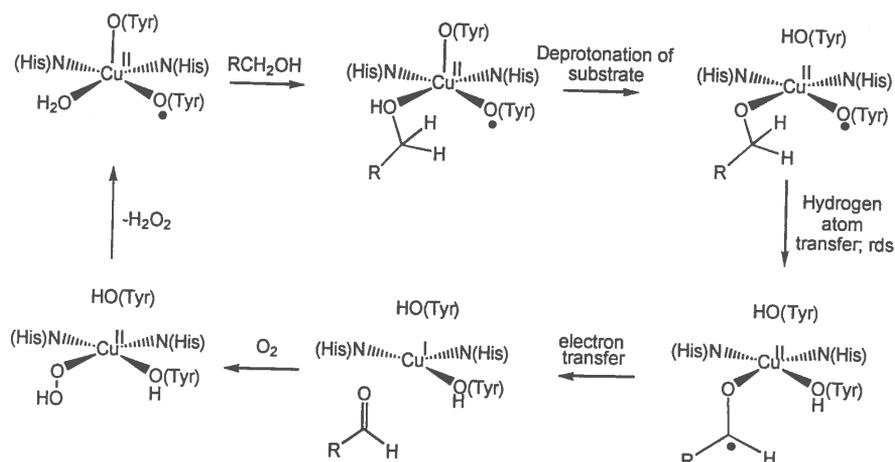
The active site of GO contains a single copper ion coordinated by two histidine imidazoles, an axial and a basal tyrosine, and a water or acetate ion in a slightly distorted square pyramidal geometry (Figure 1A).³ EPR, K-edge XANES, magnetic susceptibility, and ligand addition studies indicate that the active form of the enzyme contains an interesting Cu^{II}-phenoxyl radical species. The catalytic cycle of GO, shown in Scheme 1, is thought to start with deprotonation of the alcohol, followed by hydrogen atom transfer to the tyrosyl-radical, producing a carbon-centered radical on the substrate, and continuing with electron transfer from the substrate to the Cu^{II}. The resulting Cu^I complex is oxidized back to the resting state with O₂.⁴ Both half-reactions show kinetic isotope effects of approximately 5, indicating that a C-H or O-H bond is broken in the rate-determining step.⁵



Some of the first structural models included phenoxyl-radical complexes of copper(II)⁶ and three-coordinate copper(I) complexes.⁷ These complexes rarely showed oxidation activity but often gave mechanistic information.

Early functional models of GO, shown in Figure 1B, were based on N₂O₂ ligand sets. The ligands used by Stack and coworkers enforced a copper(II) geometry intermediate between square planar and tetrahedral and had sufficient π-conjugation to stabilize radical

species. Complexes that were EPR silent and stable at room temperature had the highest catalytic activity. Tris(4-phenyl)iminium hexachloroantimonate⁸ and also molecular oxygen⁹ were used as terminal oxidants with these catalysts. Only oxidation of activated alcohols was accomplished. Other studies used a thioether-substituted phenol ligand in a N₃O ligand set,¹⁰ eventually producing catalytic activity with (NH₄)₂[Ce(NO₃)₆] as the terminal oxidant.¹¹



Scheme 1

Weighardt and coworkers have made recent breakthroughs in this area, with the introduction of dinuclear¹² and mononuclear¹³ copper(II) catalysts that oxidize ethanol to ethanal. The mononuclear catalyst is shown in Figure 1C. The oxidation of methanol to formaldehyde has been realized with another mononuclear catalyst, shown in Figure 2. In this case, the metal center is redox inactive; the ligand has two stable radical oxidation states.¹⁴

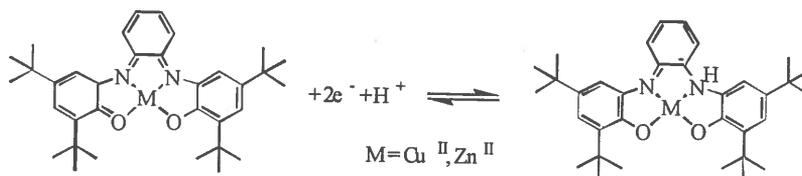


Figure 2

This body of work demonstrates that sufficient knowledge of the structure and mechanism of biological catalysts can allow chemists to produce very similar reactivity with small molecule catalysts.

References

1. Whittaker, M. M.; Whittaker, J. W. "The Active Site Of Galactose Oxidase," *J. Biol. Chem.* **1988**, *263*, 6074-6080.
2. Kirk, T. K.; Farrell, R. L. "Enzymatic 'Combustion': The Microbial Degradation Of Lignin," *Ann. Rev. Microbiol.* **1987**, *41*, 465-505.

3. Ito, N.; Phillips, S. E. V.; Yadav, K. D. S.; Knowles, P. F. "Crystal Structure Of a Free Radical Enzyme, Galactose Oxidase," *J. Mol. Biol.* **1994**, *238*, 794-814.
4. Whittaker, J. W. "The Free Radical-Coupled Copper Active Site Of Galactose Oxidase," *Metal Ions in Biological Systems*; Sigel, H.; Sigel, A., Eds.; Marcel Decker: New York, **1994**; Vol. 30, pp 315-360.
5. Whittaker, M. M.; Ballou, D. P.; Whittaker, J. W. "Kinetic Isotope Effects As Probes For the Mechanism of Galactose Oxidase," *Biochemistry* **1998**, *37*, 8426-8436.
6. (a) Halfen, J. A.; Young, Jr., V. G.; Tolman, W. B. "Modeling Of the Chemistry Of the Active Site of Galactose Oxidase," *Angew. Chem. Int. Ed.* **1996**, *35*, 1687-1689.
(b) Halfen, J. A.; Jazdzewski, B. A.; Mahapatra, S. Berreau, L. M.; Wilkinson, E. C.; Que, Jr., L.; Tolman, W. B.; "Synthetic Models Of the Inactive Copper(II)-Tyrosinate and Active Copper(II)-Tyrosyl Radical Forms of Galactose Oxidase," *J. Am. Chem. Soc.* **1997**, *119*, 8217-8227.
7. Jazdzewski, B. A.; Young, Jr., V. G.; Tolman, W. B. "A Three-Coordinate Copper(I)-Phenoxide Complex That Models the Reduced Form Of Galactose Oxidase," *J. Chem. Soc., Chem. Comm.* **1998**, 2521-2522.
8. Wang, Y.; Stack, T. D. P. "Galactose Oxidase Model Complexes: Catalytic Reactivities," *J. Am. Chem. Soc.* **1996**, *118*, 13097-13098.
9. Wang, Y.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. "Catalytic Galactose Oxidase Models: Biomimetic Cu(II)-Phenoxy Radical Reactivity," *Science* **1998**, *279*, 537-540.
10. Itoh, S.; Taki, M.; Takatama, S.; Arakawa, R.; Furuta, A.; Komatsu, M.; Ishida, A.; Takamuku, A.; Fukuzumi, S. "Active Site Models For Galactose Oxidase. Electronic Effect Of the Thioether Group In the Novel Organic Cofactor," *Inorg. Chem.* **1997**, *36*, 1407-1416.
11. Itoh, S.; Taki, M.; Takatama, S.; Nagamoto, S.; Kitagawa, T.; Sakurada, N.; Arakawa, R.; Fukuzumi, S. "Oxidation Of Benzyl Alcohol With Cu(II) and Zn(II) Complexes Of the Phenoxy Radical As a model Of the Reaction Of Galactose Oxidase," *Angew. Chem. Int. Ed.* **1999**, *38*, 2774-2276.
12. Chaudhuri, P.; Hess, M.; Weyhermüller, T.; Wieghardt, K. "From Structural Models Of Galactose Oxidase To Homogeneous Catalysis: Efficient Aerobic Oxidation Of Alcohols," *Angew. Chem. Int. Ed.* **1998**, *37*, 2217-2220.
13. Chaudhuri, P.; Hess, M.; Weyhermüller, T.; Wieghardt, K. "Aerobic Oxidation Of Primary Alcohols By a New Mononuclear Cu^{II}-Radical Catalyst," *Angew. Chem. Int. Ed.* **1999**, *38*, 1095-1098.
14. Chaudhuri, P.; Hess, M.; Müller, J.; Hildenbrand, K.; Bill, E.; Weyhermüller, T.; Wieghardt, K. "Aerobic Oxidation Of Primary Alcohols (Including Methanol) By Copper(II)- and Zinc(II)-Phenoxy Radical Catalysts," *J. Am. Chem. Soc.* **1999**, *121*, 9599-9610.

