

## Recent Dioxygen Dicopper Models of Hemocyanin and Tyrosinase

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One goal of inorganic chemists has been the modeling of both the coordination and the function of metalloproteins. Two such enzymes that have been studied are hemocyanin and tyrosinase. Hemocyanin is an oxygen-carrying enzyme found in mollusks and arthropods and is generally made up of six to as many as forty-eight subunits.<sup>1</sup> What makes hemocyanin interesting is its oxygen binding site. It consists of two monovalent copper ions coordinated by the three imidazoles each from histidine residues.<sup>2</sup> Recently an X-ray crystal structure for subunit II of *Limulus polyphemus* hemocyanin determined that oxygen was bound to the copper ions in a  $\mu\text{-}\eta^2\text{:}\eta^2$  peroxy mode creating a distorted square pyramidal coordination for the divalent copper centers (Figure 1).<sup>3,4,15</sup>

Tyrosinase is found more widely in nature than hemocyanin and serves as a mono-oxygenase. It also contains two monovalent copper ions in its active site. The oxygenated form has very similar characteristics to oxyhemocyanin, supporting a similar oxygen binding mode.<sup>5,6,16</sup>

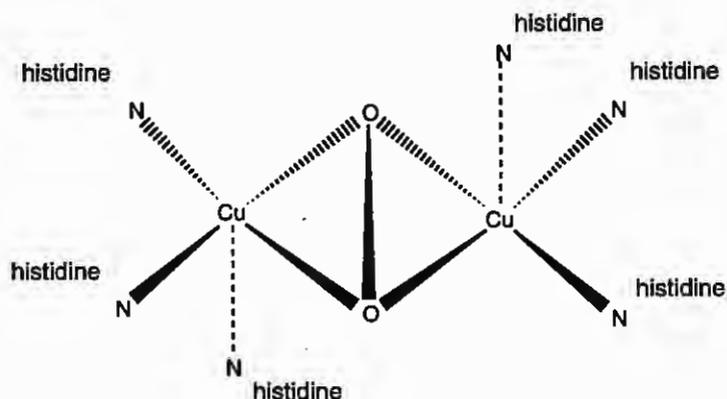


Figure 1. Representation of the O<sub>2</sub> in oxyhemocyanin.

The first fully structurally characterized dicopper peroxy model was developed by Karlin and coworkers using the tetradentate tris(2-pyridylmethyl)amine ligand. An X-ray crystal structure of the peroxy complex showed a  $\mu\text{-}1,2$  *trans* peroxy structure, different from what was later discovered for oxyhemocyanin (Figure 2). Though the model complex was not structurally similar, it served as a functional analogue.<sup>7</sup> It was found that dioxygen could be removed from the complex by rapidly warming under vacuum and then replaced after rapidly cooling to  $-78^\circ\text{C}$ , the temperature at which the complex was originally formed.<sup>7,8,15,17</sup>

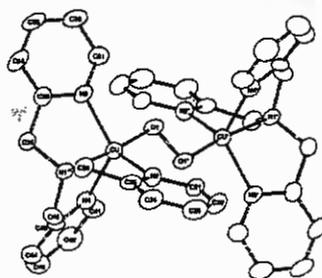
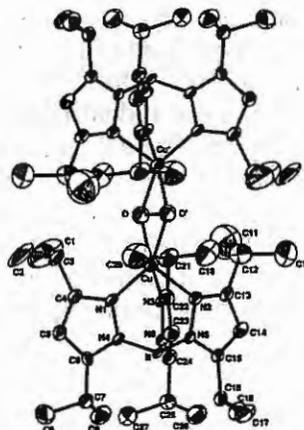


Figure 2. ORTEP diagram of  $[\{\text{CuTMPA}\}_2(\text{O}_2)]^{-2}$   
 TMPA=tris(2-pyridylmethyl)amine

Work by Kitajima *et al* produced the first structurally characterized model complex with structural features similar to oxyhemocyanin. The use of the tridentate hydrotris(3,5-diisopropylpyrazolyl)borate ligand allowed for dioxygen to bind in the  $\mu\text{-}\eta^2\text{:}\eta^2$  manner creating a distorted square pyramidal coordination of the divalent copper ions (Figure 3).<sup>9</sup> Despite being similar to hemocyanin structurally,  $\text{O}_2$  binding can not be cycled as in Karlin's complex, but it does have oxidative capabilities that may be similar to that of tyrosinase.<sup>6,17</sup>

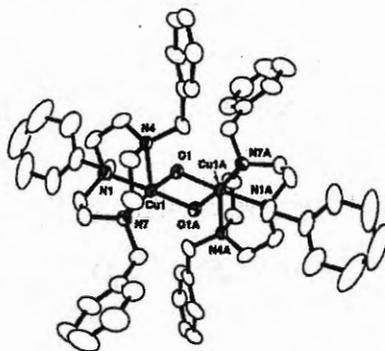


**Figure 3.** ORTEP diagram of  $[\text{Cu}(\text{HB}(3,5\text{-iPrpz})_3)_2(\text{O}_2)]$ .  
 $\text{HB}(3,5\text{-iPrpz})_3 =$  hydrotris(3,5-diisopropylpyrazolyl)borate

An interesting discovery was recently made by Karlin and coworkers concerning the formation of peroxo compounds using the tethered twin tridentate ligand, 1,4-di(bis(2-pyridylethyl)amine)-butane.<sup>10</sup> Previously it had been determined, based on spectroscopy, that this system had a  $\mu\text{-}\eta^2\text{:}\eta^2$  peroxo structure. However, recent low temperature kinetics experiments with UV-vis spectroscopy indicated the initial formation of what is believed to be a  $\mu\text{-}1,2$  *trans* peroxo binding mode, which then rearranges to form the more thermodynamically stable  $\mu\text{-}\eta^2\text{:}\eta^2$  peroxo form.<sup>11</sup> This may demonstrate how dioxygen initially binds to hemocyanin.

An attempt at more closely mimicking the binding in the hemocyanin protein was made by Kurtz and coworkers with tridentate 1,4 disubstituted tris(imidazolyl)phosphines. Spectroscopic data support a  $\mu\text{-}\eta^2\text{:}\eta^2$  peroxo binding mode because of similarities with data from oxyhemocyanin and Kitajima's model compound. The isopropyl substituted adduct demonstrated a temperature dependent oxygen binding cycling ability that could be repeated several times with little decomposition.<sup>12</sup>

The only other dicopper dioxygen complex that has been structurally characterized was achieved by Tolman *et al* and may help elucidate the oxidative processes of tyrosinase. The oxygen bridged dicopper complex using the tridentate 1,4,7-trisbenzyl-1,4,7-triazacyclononane shows a novel bis  $\mu\text{-oxo}$  structure achieved by oxygen-oxygen bond homolysis (Figure 4).<sup>13,14</sup> A formal plus three oxidation state was proposed for the copper ions based on comparison of bond lengths with characterized structures containing both divalent and trivalent copper.<sup>14</sup>



**Figure 4.** ORTEP diagram of  $[d_{21}\text{-L}^{\text{Bn}^3}\text{Cu}]_2(\mu\text{-O})_2(\text{SbF}_6)_2 \cdot 7(\text{CH}_3)_2 \cdot 2 \text{CH}_3\text{CN}$   
 $d_{21}\text{-L}^{\text{Bn}^3}$  = deuterated 1,4,7-trisbenzyl-1,4,7-trisazacyclononane

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