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Oxygen insertion in organic substrates catalyzed by copper compounds

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CONTENTS

A. INTRODUCTION

The value of models for metalloproteins will always be relative. One of the difficulties encountered in simulating a biosite is that, as time passes, the objective may change with advancing knowledge. If the structure of the metal ion environment in the metalloprotein is unknown, the objective may be to reproduce some property of the system in a similar model coordination compound, but when the structure of the biosite is known, then the complex must be of such a nature that it reproduces, as far as possible, the known structure. A different emphasis is obtained when the action of the metal in the protein is reproduced by a model compound and the mechanism of a particular reaction is elucidated or partially explained.

A number of groups have attempted to develop chemical model systems which mimic the functional spectroscopic properties of the biological copper active sites [1–3]. Much interesting chemistry has been made available during the search for

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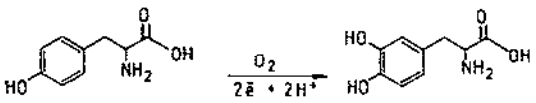
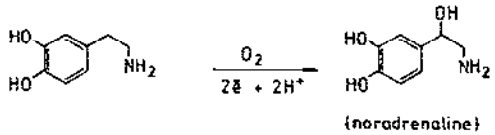
models for the copper sites of such proteins as the oxygenases. Thus, the study of oxygenation reactions, magnetic coupling, spectroscopic properties and basic ligand design has benefitted from research in this field.

This review presents the contributions that have been made in the area of oxygen insertion in organic substrates. Since copper compounds are among the most useful and versatile known oxidation catalysts, simple synthetic systems where hydroxylation occurs have been included. Oxygen activation mechanisms, related to biological systems in which the metalloenzymes are involved, are presented as models of mono-oxygenases.

The mono-oxygenases tyrosinase and dopamine β-hydroxylase are copper proteins which incorporate one oxygen atom from molecular oxygen into organic substrates [4–7]. A related system has also been reported in which the enzyme peptidylglycine α-amidating enzyme (PAM) catalyzes the transformation of a carboxyl-terminal glycine extended precursor into a carboxyl-terminal α-amidated peptide [8]. PAM gives as direct product a hydroxyl derivative at the α-carbon of the carboxyl terminal glycine [9].

Protein	Substrate	Reaction	Copper atoms	Class
Tyrosinase	Tyrosine	 (DOPA = dihydroxyphenylalanine)	2	III
Dopamine-β-Hydroxylase	Dopamine	 (noradrenaline)	? + 1	II
Peptidyl α-Amidating Monooxygenase	Glycine Extended Precursors	Pept-CONH-CH_2-COOH $\xrightarrow[\text{ascorbate}]{O_2/Cu^{2+}}$ Pept-CONH-CH(OH)-COOH $\longrightarrow$ Pept-$CONH_2$ + CHO-COOH		

B. MODEL SYSTEMS FOR TYROSINASE (AROMATIC NUCLEUS HYDROXYLATION)

The most extensively studied of the monooxygenases mentioned is tyrosinase. Tyrosinase catalyzes the orthohydroxylation of monophenols to *o*-diphenols, and the further oxidation of these to *o*-quinones. This second reaction of the tyrosinase molecule corresponds to oxidase activity. Different studies have shown that the principal difference between tyrosinase and the oxygen-carrying protein hemocyanin

is due to the fact that the active site of tyrosinase is more open and permits the approach of substrates [10,11].

Solomon and co-workers [12] have proposed a mechanism for the catalytic activity of tyrosinase in which the phenol substrate coordinates axially to one of the copper atoms of oxy-tyrosinase. In the binuclear unit, Cu_2O_2 substrate complex rearrangements through a trigonal bipyramidal intermediate is accompanied by ortho hydroxylation of the substrate followed by loss of H_2O and coordination of the diphenol product. Oxidation of the bound catechol by electron transfer regenerates the dicopper(I) deoxy-tyrosinase complex with release of the quinone product. Addition of O_2 to form oxy-tyrosinase completes the catalytic cycle [12].

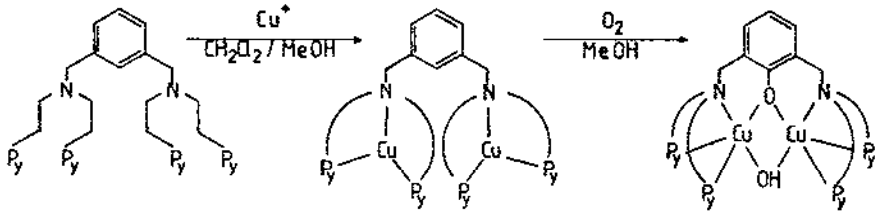
A complex similar to the catecholate intermediate postulated in the above mechanism has been isolated and characterized by X-ray diffraction. In this model system, the two copper ions are bridged simultaneously by a catecholate ion and a phenolate ion at a distance of 3.25 Å [13]. In the case of catecholase activity of tyrosinase, the type III site is geometrically correct for coordination of both phenolic oxygens in the ortho positions which are axially coordinated to both copper ions with a metal–metal distance of approximately 3.6 Å.

In the following section, the emphasis will be on binuclear copper(I) complexes, where the coordinated polydentate ligands undergo copper-mediated reactions with dioxygen. Since the ligands remain coordinated after the reaction, the transformed ligand is part of the oxidized copper(II) complex product.

(i) N_6 binuclear copper systems

The reaction that has been most thoroughly studied in relation to the oxygenation of an aromatic nucleus is that described by Karlin et al. [14,15]. The reaction of molecular oxygen with a binuclear copper(I) species derived from a *m*-xylyl binucleating hexadentate ligand *N,N,N′,N′*-tetrakis-[2-(2-pyridyl)ethyl]-α,α′-diamino-*m*-xylene (*m*-xylN$_6$ or *m*-xyl(py)) produces a binuclear copper(II) complex. The dication shows two pentacoordinated copper(II) ions bridged by a phenoxy group of the ligand and a methoxy ligand.

The crystal structure determination by X-ray diffraction of the oxidized complex



showed that the Cu_2O_2 bridging unit is planar, and that the ligand arrangement around each copper atom is square pyramidal.

When the reaction was run in the absence of methanol, the product was the analogous phenoxy- and hydroxo-bridged copper(II). Both the structure of the copper(I) and copper(II) complexes were determined [15]. The phenoxo-copper(II) charge transfer band was assigned at 450–460 nm by comparison with spectroscopic data of related complexes [16,17].

Manometric measurements of dioxygen uptake by the copper(I) complex and mass spectrometric analysis of the phenoxo-hydroxo bridged copper(II) complex, prepared by using isotopically pure $^{18}O_2$, proved that the stoichiometry of the reaction is of one molecule of dioxygen for each molecule of binuclear copper(I) complex.

$$L{-}H + 2Cu^+ + O_2 \rightarrow 2Cu^{2+} + OH^- + L{-}O^-$$

This reaction has the same stoichiometry as that observed for the oxygenases, which require that one of the two atoms of dioxygen is incorporated into the organic substrate, while the other is reduced to water [18]. This mechanism supposes the formation of a peroxo intermediate which disproportionates into an oxygen atom which is inserted into the organic substrate and an oxide which is protonated.

The first thermodynamic and kinetic data for the reversible dioxygen binding behaviour of Cu_2(*m*-xyl(py)) indicate that the copper(I) complex forms a dioxygen adduct. The dioxygen binding process is effectively a one-step process (k_1). The adduct decomposes irreversibly in a first-order process giving the hydroxylated product (k_2). The determined values for k_2 are 0.0028 s^{-1} (−80°C) and 104 s^{-1} (20°C) with $\Delta H_2^\circ = 47.6$ kJ mol^{-1} and $\Delta S_2^\circ = -44$ J mol^{-1} [19].

The fact that the copper(II) complex with this type of ligand reacts with hydrogen peroxide to give as a product the μ-hydroxo complex with the hydroxylated ligand in position 2 was considered as evidence for a peroxo intermediate [20].

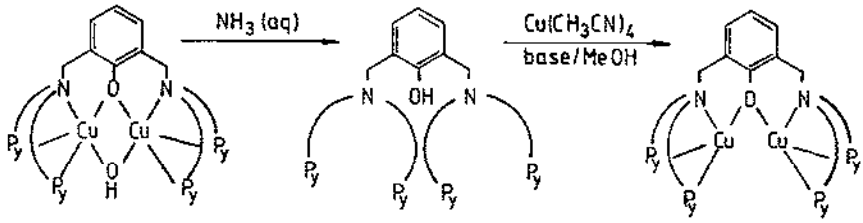
$$L{-}H + 2Cu^{2+} + H_2O_2 \rightarrow [2Cu^{2+}(LO^-)(OH^-)]$$

The kinetics of the hydroxylation reaction starting from a dicopper(II) complex was also studied [21]. These recent studies reveal that the mechanism must be different because four copper ions and hydroperoxide are involved when starting with the copper(II) dimer, whereas hydroxylation using the copper(I) complex involves only an intramolecularly bound oxygen.

The copper-mediated hydroxylation of the dinucleating ligand *m*-xyl(py) generates the *m*-xyl-OH(py) ligand. This can be simply obtained by leaching out the copper(II) ions with aqueous ammonia from the dicopper(II) μ-phenoxo μ-hydroxo *m*-xyl(py) complex.

The free phenol can then react with a copper(I) salt in the presence of a base to give the phenoxo-bridged copper(I) complex whose structure was determined by X-ray diffraction [22]. The geometry about each copper(I) atom is best described as

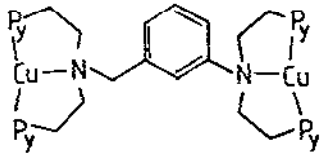
pyramidal. The basal plane is formed by two pyridine nitrogen atoms and the oxygen atom of the bridging phenoxo group.



$[Cu_2m\text{-xyl-O(Py)}]^+$

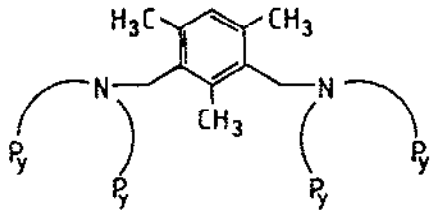
The $[Cu_2m\text{-xyl-O(py)}]^+$ complex reacts with molecular oxygen to give a peroxo-bridged species. Vibrational, electronic and resonance Raman spectral studies have been made [22,23]. EXAFS studies rule out a μ-1,1-bridged structure, but the copper–copper distance of 3.31 Å cannot distinguish between μ-1,2-bridging or terminal peroxo coordination at the dinuclear copper site [24]. If the solution is warmed up, the oxygenated derivative decomposes irreversibly to give the phenoxo-hydroxo doubly bridged dicopper(II) complex [25].

Karlin and co-workers report the synthesis and reactivity with molecular oxygen of a dinuclear copper(I) complex $[Cu_2(UN)]^{2+}$ where UN is a modified *m*-xyl N_6 ligand which permits the formation of unsymmetrically coordinated copper(I) ions [26].



Dioxygen binding to $[Cu_2(UN)]^{2+}$ is reversible at $-80°C$, and four oxygenation/deoxygenation cycles can be carried out without severe decomposition. Oxygenation of $[Cu_2(UN)]^{2+}$ at temperatures $>0°C$ in CH_2Cl_2 or DMF quantitatively produces the hydroxy-bridged copper(II) complex, with the hydroxylated aromatic ligand. In the hydroxylated copper(II) complex, the twisting of the chelating arms is such that both copper ions are on the same side of the benzene ring plane and the axial pyridine ligands are on the same side of the square-based pyramidal copper atoms. The opposite situation is true in the $[Cu_2m\text{-xyl-O(py)}]^{2+}$ complex.

A copper(I) complex with the *m*-xyl(py) binucleating ligand which has been modified by the incorporation of a methyl group in the 2 position was oxidized with molecular oxygen [27].



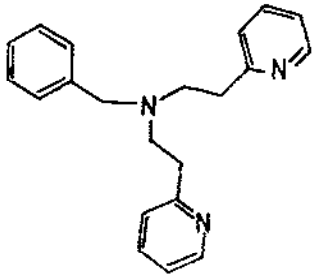
The resulting product showed the loss of one $N(py)_2$ arm, the hydroxylation of the *m*-xyl(py) ligand and the concomitant migration of the methyl group on the aromatic ring to an ortho position to the entering OH group.

The results described for this copper monooxygenase model system also provide support for previous suggestions that the catalytic action of tyrosinase proceeds via electrophilic attack on the aromatic substrate [28].

The copper(I) complex with the *m*-xyl(py) ligand in which the reactive position has been blocked by a fluorine atom in order to avoid hydroxylation gave an oxygen adduct in the form of peroxide at low temperature [29].

A modified *m*-xyl(py) ligand was synthesized with a 5-hydroxy substituent in order to study the possibility of a reaction similar to the one observed in tyrosinase. That is, the formation of the 2,5-dihydroxo dicopper(II) complex, and the further intramolecular redox process to a *p*-quinone dicopper(I) species. The reaction proved to be quite complicated with the final product corresponding to a hydroxylated species in which the initial OH group was arylated [30].

The hydroxylation reaction of the xylyl binucleating ligand in the copper(I) complex can be avoided when it is modified to a ligand containing the same aromatic substrate (benzene ring) and only one tridentate chelating group.



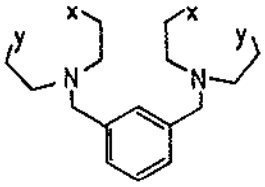
The oxidized copper(I) complex is a binuclear oxo-bridged species. This complex reacts with water to give the dihydroxo-bridged copper(II) complex which has been characterized crystallographically [31]. Since the mononuclear complex reacts with dioxygen in a 4:1 ($Cu:O_2$) ratio, and hydroxylation does not occur, this supports

the fact that a peroxo intermediate must be formed in order that arene hydroxylation reaction may occur.

Upon oxygenation, the copper(I) complexes containing the ligands NnPy2, in which the two Py2 units (Py2 = bis(2-(2-pyridyl)ethyl)amine) are connected by alkyl chains of varying lengths ($n = 3$–5) instead of the *m*-xylyl moiety, form intensely coloured solutions varying from deep purple to brown, depending on *n*. The reaction proceeds reversibly and manometric measurements at −80°C confirm the stoichiometry of the reaction to be $Cu:O_2 = 2:1$ [32,33]. EXAFS studies support a description of the oxygen adducts as four- and five-coordinated peroxo-bridged dicopper(II) complexes with copper–copper distances in the range of 3.2–3.4 Å [34].

The reaction of $[Cu_2(m\text{-xyl}N_6)](BF_4)_2$ (where the heterocycles are pyrazolyl moieties) with dioxygen gives a bis(μ-hydroxo)-bridged complex, $[Cu_2(OH)_2(m\text{-xyl}N_6)](BF_4)_2$, instead of a complex with a hydroxylated ligand. Thus, when the pyridine groups of the *m*-xyl(py) ligand are substituted by pyrazoles or by benzimidazoles, the aromatic nucleus is not hydroxylated. This fact is indicative of the importance of the electronic conditions which govern the oxygenation reaction. The much lower basicity of pyrazole relative to pyridine must substantially influence the reactivity of the complex [35].

To continue exploring the chemistry of this type of ligand, new hybrid ligands containing combinations of pyrazole, pyridine, and imidazole were prepared by Sorrell et al. [36]. All of the dinucleating ligands provide three nitrogen donors to each copper ion and each coordination unit is separated by the *m*-xylyl group.

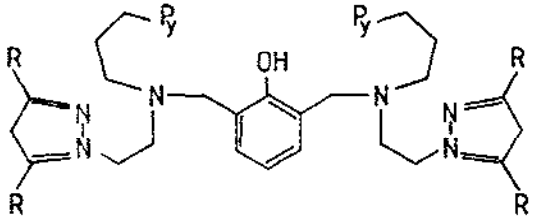


1. $x = y =$ 2-(*N*-methylimidazolyl)
2. $x =$ 2-pyridyl, $y =$ 1-pyrazolyl
3. $x =$ 2-pyridyl, $y =$ 1-(3,5-di-methylpyrazolyl)
4. $x =$ 2-pyridyl, $y =$ 2-(*N*-methylimidazolyl)
5. $x = y =$ 2-(*N*-methylbenzimidazolyl)

Hydroxylation of the arene ring was not observed since all these complexes react via four-electron reduction of the dioxygen molecule to give bis(μ-hydroxo) copper(II) dimers. These complexes are characterized by absorptions in the region at about 360 nm, typical of di(μ-hydroxo) dicopper(II) complexes [37,38]. However, the binuclear tricoordinated copper(I) complex Cu_2L (L = 5) exhibits tyrosinase-like activity on exogenous phenolic substrates [38]. Methyl-4-hydroxybenzoate was selected as exogenous phenol since the corresponding *o*-catechol is relatively stable to further oxidation. Experiments using $^{18}O_2$ yielded ^{18}O-labelled catechol.

The reaction of $Cu_2(L)^{4+}$ (L = 2) with H_2O_2 in DMF was also studied and the reactivity pattern was similar to that found for *m*-xyl(py). The spectrum resembled that for previously characterized μ-phenoxo complexes having the same nitrogen set of donor atoms. In particular, there was a new band at 380–390 nm indicative of hydroxylation of the aromatic nucleus [15,39].

The binucleating hybrid ligands containing pyrazole and pyridine, which provide three nitrogen donors to each copper(I) centre and a phenolate group to bridge the two metal ions, are oxygenated by molecular oxygen [39].

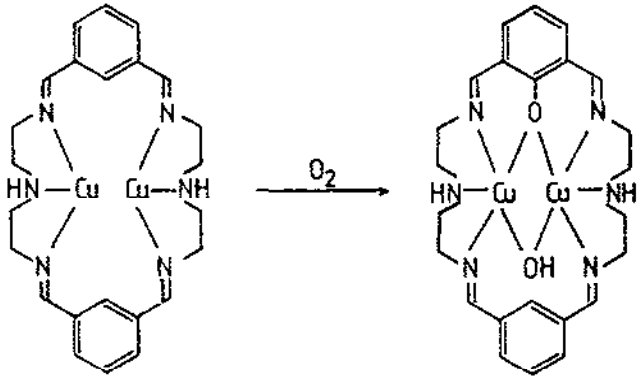


At room temperature, all the complexes (both phenolate and phenol) react with dioxygen and are oxidized to the μ-phenoxo-μ-hydroxo copper(II) species. However, at low temperatures (−78°C) in dry CH_2Cl_2, a more interesting chemistry is observed. A peroxo adduct (2:1 = Cu:O_2) characterized by an intense band at 500 nm is observed in the visible spectrum for the copper(I) phenolate complexes. The copper(I) phenol complexes also react with dioxygen at −78°C to give an hydroperoxide moiety. The final product in both cases is the hydroxo-bridged copper(II) binuclear complex. Thus, substituting pyrazole or dimethylpyrazole for one of the pyridine groups in the ligand apparently has little or no effect in the reactivity of the copper(I) complex towards molecular oxygen. This is in contrast to structurally related $Cu(I)N_6$ complexes in which the phenolate bridge is absent. The pyrazole ligated complexes react very differently from their pyridine analogues by failing to produce the hydroxylation of the aromatic nucleus.

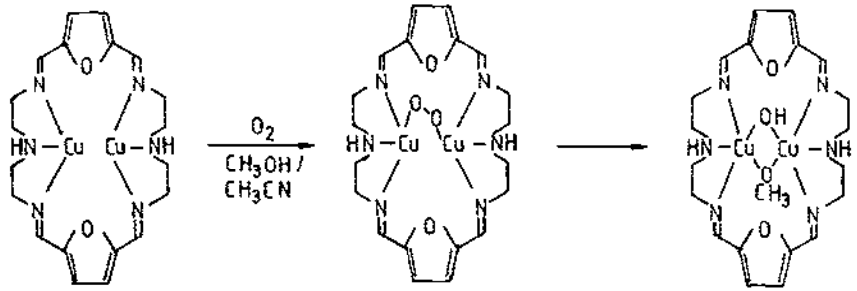
Another example which has been reported as a model system for tyrosinase, of the N_6 type, is a binuclear copper macrocyclic Schiff base complex in which the metal centres are coordinated by two imine nitrogen and one aliphatic nitrogen donor atoms [40,41]. The ligand is a 24-membered hexadentate macrocycle prepared by the non-template condensation of *m*-phthalaldehyde and triethylenetriamine.

The binuclear copper(I) complex of this ligand reacts with dioxygen to give the corresponding copper(II) complex with hydroxide and ligand-derived phenoxide bridging groups.

Martell also reported a dinuclear copper(I) complex of a modified macrocyclic Schiff-base ligand which contains two furan bridge moieties and two terdentate bis(imine)nitrogen sites [42]. The change of colour on oxygenation of a copper(I) complex in acetonitrile–methanol solution from yellow to red-brown, permits one



to postulate an intermediate dioxygen adduct with a formally peroxo bridge coordinating two copper(II) centres [43]. The spectral changes are similar to those observed by Nishida et al. [44], Karlin et al. [25,45], and Kitijima et al. [46], and are associated with peroxo species. The solution is further oxidized, and a dinuclear copper(II) complex is isolated in which the metal centres are bridged by hydroxo and methoxo groups. The copper–copper distance is 2.958(3) Å, and an unusual coordination mode which is a distorted square-planar toward a tetrahedral arrangement is formed around each copper atom. The lack of an oxygen insertion reaction is explained on the basis of the bridging oxygen-containing furan groups instead of aromatic xylyl groups, and that there is no electron-donating group nearby to react with the coordinated dioxygen.

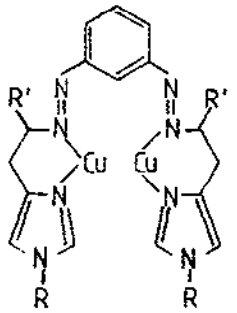


(ii) N_4 binuclear copper systems

Casella et al. have studied a series of binuclear two-coordinate copper(I) complexes with one imino and one imidazole donor nitrogen atom per metal centre as model systems of tyrosinase.

The condensation of benzene-1,3-dicarboxaldehyde and two molecules of hista-

mine or histidine gives a ligand which forms binuclear two-coordinate copper(I) complexes [47–49].



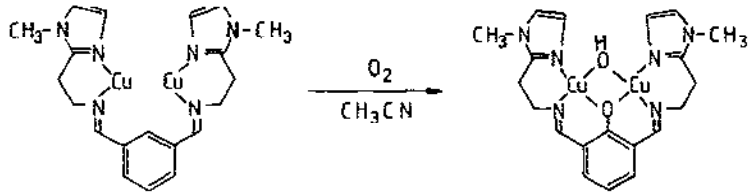
R = H, Me

R' = H, CO_2Me

The oxygenation behaviour of the complexes derived from imidazole is complicated and depends markedly upon the solvent. In dry, non-protic solvents such as acetonitrile, simple oxidation of copper(I) to copper(II) occurs. The products of the reaction can be formulated more as mono-imidazolate bridged, hydroxo copper(II) complexes. However, when the oxygenation of the complexes is carried out in a protic solvent such as methanol, copper(I) oxidation is inhibited by the hydroxylation reaction of the aromatic nucleus of the ligand at the 2 position.

The oxygenation of the N-methylated imidazole group complexes is much more rapid in a protic solvent such as methanol than in acetonitrile. Promotion of the hydroxylation reaction by $|H^+|$ suggests that a protonated dioxygen intermediate is involved as a key step. A copper-hydroperoxo species was also characterized at low temperature by Karlin et al. for the *m*-xyl(py) copper(II) complex [50,51]. A copper(II)–OOH complex generated by the one-electron reduction and protonation of a superoxo copper(II) compound has been described by Thompson [52].

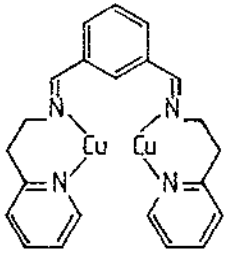
Sorrell and Garrity reported that a Schiff-base ligand derived from isophthalaldehyde and (aminoethyl)imidazole is hydroxylated when its copper(I) derivative is treated with dioxygen in acetonitrile solution [53].



This reaction permits one to conclude that the substitution of the imidazole ring in this kind of Schiff-base ligand complex has little effect on the reaction.

A similar system to the one studied by Casella et al. was obtained by the

reaction of benzene-1,3-carboxaldehyde with 2-(2-pyridyl)ethylamine. The binucleating ligand 1,3-bis[*N*-(2-pyridylethyl)formidoyl]benzene has two bidentate 2-(2-pyridyl)ethylimine units separated by a *m*-xylyl bridge [54].

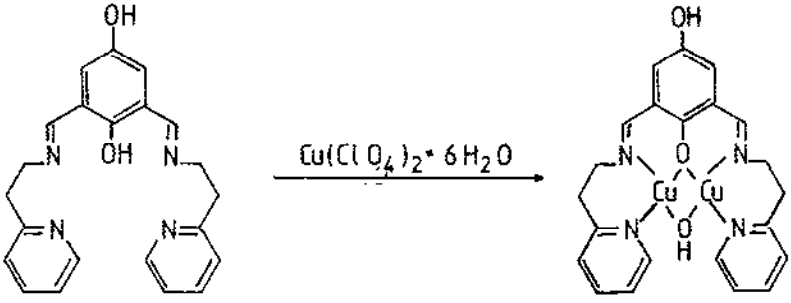


X-ray analysis of the complex revealed that each copper(I) is coordinated to three nitrogen donor atoms, two corresponding to the pyridyl ethylimine moiety and one to acetonitrile, which must be labile in solution.

The reaction of the above-mentioned copper(I) complex with molecular oxygen gives a binuclear copper(II) complex with incorporation of two oxygen atoms; one is inserted into the aryl–hydrogen bond of the initial copper(I) complex, while the other is incorporated into the hydroxo bridge. The Cu_2O_2 unit deviates from planarity with an O(1)–Cu(1)–O(2)–Cu(2) torsion angle of 9.3°.

This example of aromatic hydroxylation with binuclear copper(I) complexes and dioxygen shows that the reaction is not specific for a tridentate nitrogen ligand per copper system. In this case, the copper(I) complex contains one bidentate and one monodentate ligand attached to each metal centre.

A similar complex can be obtained with the ligand 1,3-bis[*N*-2-(2-pyridyl ethyl)-formidoyl]-2,5-dihydroxy benzene, N_4, which gives a stable hydroquinone-containing binuclear copper(II) complex [55].



The hydroquinone moiety is not oxidized to a quinone in the presence of the two copper(II) ions in the complex. Apparently the two electron-withdrawing imine substituents present in the ligand increase the oxidation potential of the hydroquinone

sufficiently to prevent intramolecular electron transfer to the copper(II) ions in the complex.

The molecular structure of this complex shows strong similarities with the previously described unsubstituted analogue which is obtained by oxygen insertion into the aryl carbon–hydrogen bond of the corresponding binuclear copper(I) complex [54].

The distances in both binuclear species for the copper–copper bond are 2.991(2) and 2.990(2) Å for the complex prepared from copper(II) perchlorate and for that obtained by reaction with dioxygen, respectively. It is a typical distance of binuclear copper complexes containing two one-atom bridging ligands [35,56].

The known binuclear tyrosinase model systems in which an aromatic nucleus is hydroxylated can be summarized as follows:

(1) Karlin reported the first tyrosinase model, which consists of a *m*-xylyl binucleating ligand which provides two pyridine nitrogens and one aliphatic nitrogen donor to each copper ion [14,15].

(2) Casella and Rigoni described a tyrosinase model consisting of a dinuclear copper complex with one imino and one imidazole donor per metal centre [47–49].

(3) Gelling described an analogous Schiff-base model complex in which the copper ions are coordinated by an imine nitrogen and a pyridine nitrogen [54].

(4) Martell reported a dinuclear copper macrocyclic Schiff-base complex in which the metal centres are coordinated by two imine nitrogens and one aliphatic nitrogen atom [40–42].

(5) Sorrell found hybrid ligands similar to those described by Karlin containing a N_6 system and a phenolate oxygen atom coordinated to the copper atoms [36,39].

All these tyrosinase models are dinuclear copper complexes in which the metal centres are coordinated by nitrogen donors supplied by pyridine, imidazole, Schiff-base imine or combinations of these donor groups.

The macrocyclic tyrosinase model makes evident that an open-chain binucleating ligand is not a prerequisite. It has also become evident that the nature of the donor groups and the number of donor atoms per copper atom are not critical.

However, the position of the copper atoms with respect to each other and to the aromatic C–H bond is of great importance since it will permit dioxygen to coordinate in the proximity of the site to be hydroxylated and will make a concerted electron-transfer process feasible. It seems that the strategy of preparing a tyrosinase mimic involves the synthesis of a binucleating ligand which can locate two copper ions within approximately 3.5 Å of each other while providing two or three nitrogen donors to each metal ion [57].

An important question which arises from the analysis of the data described in the previous section is the fact that the peroxo intermediate, which is presumably nucleophilic, seems to act as an electrophilic oxidant. Since not all the reactions analyzed seem to be proton-assisted, there may be two different mechanisms for the oxygen insertion reaction studied.

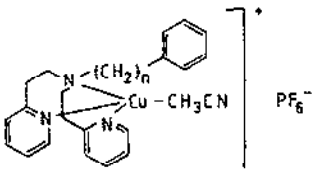
The copper(III) species Cu=O has also been postulated as being formed by homolytic scission of the μ-peroxo bridge in tyrosinase [58], and in the hydroperoxo copper group in dopamine β-hydroxylase [59,60].

(iii) Mononuclear copper systems

This section is mostly related to the oxygenation of external substrates. Substrate coordination to the copper ion(s) is most likely involved in the oxidation of external organic molecules, just as it is the case of polydentate ligand copper(I) complexes.

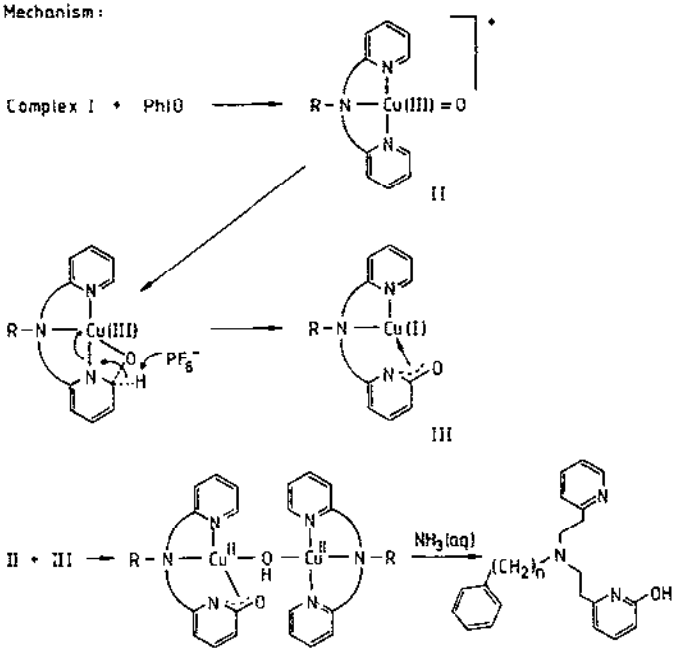
(a) Hydroxylation of pyridine

The copper(I) complex with the ligand obtained by the condensation reaction of 2-vinylpyridine with aminomethylbenzene and aminoethylbenzene can be oxygenated by iodosylbenzene [61].



Complex I (n = 1 or 2)

Mechanism:

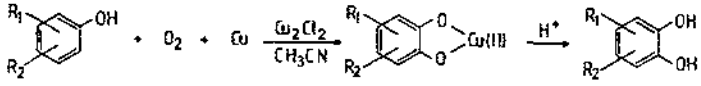


Some 50% of the monohydroxylated pyridine derivative is recovered, after leaching the copper(II) complex with NH_3. This is the first example of a copper-mediated hydroxylation of the pyridine nucleus. Hydroxylation of the $-(CH_2)_n-$ benzene side chain does not take place. An explanation could be that the $-(CH_2)_n-$ benzene side chain cannot be properly located relative to the oxo group in the copper(III) square planar complex II.

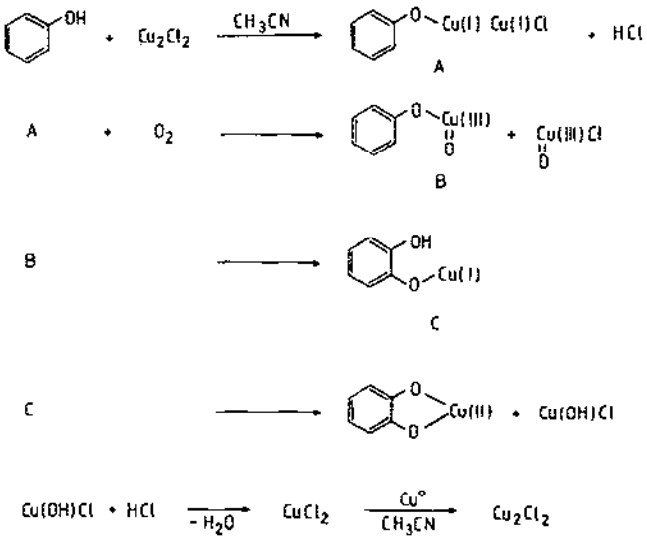
When the same reaction is done in CH_2Cl_2, instead of CH_3CN, the hydroxylation does not take place [31]. This result emphasizes the importance of the solvent in copper-mediated oxygen transfer reactions.

(b) Hydroxylation of phenol

Production of catechols. There is a catalytic system that permits one to obtain catechols from phenols without cleavage of the aromatic nucleus [62]. This system corresponds to cuprous chloride in low catalytic concentrations, metallic copper and molecular oxygen.

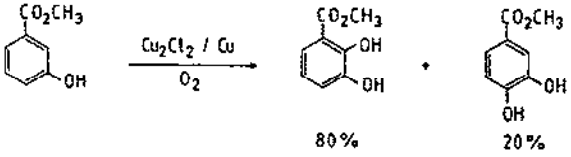


The proposed mechanism considers the formation of a cuprous phenolate as the first step. An intermediate of copper(III) is postulated; the redox reaction of this species generates the stable copper catecholate and a chlorohydroxo copper(II) salt. This salt reacts with the hydrochloric acid produced in the first step to generate cupric chloride, which is finally reduced by metallic copper.



This reaction has a high yield for phenols with substituents such as R_1 and/or $R_2 = CH_3$, *t*-butyl, or $R_1 = H$ and $R_2 = p\text{-}OCH_3$, or $R_1 = R_2 = H$. The catalytic system becomes less efficient if $R_1 = H$, $R_2 = p$-OR, *m*-CHO, –COR, –COOR.

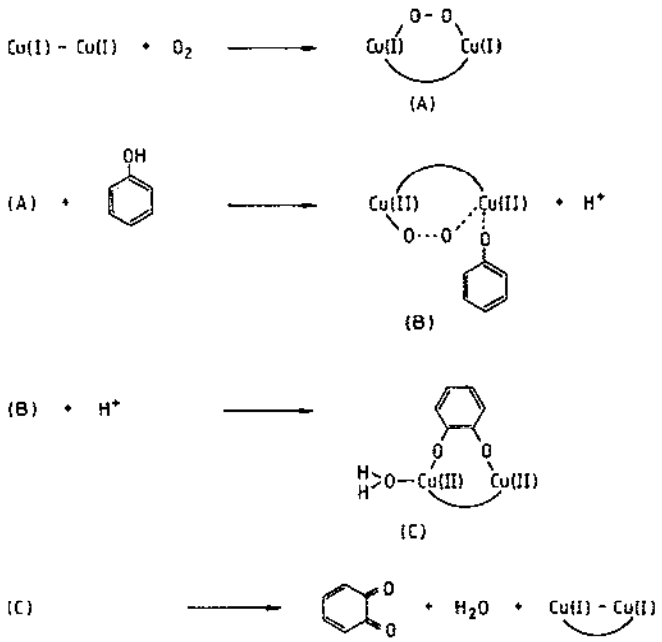
For asymmetric phenols in which the ortho positions are free, the more negative ortho position is preferentially hydroxylated.



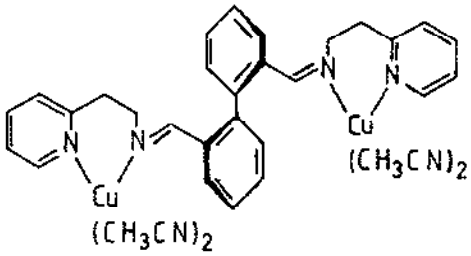
This same reaction can be accelerated by irradiating the acetonitrile solution of $CuCl_2$ in the presence of phenol by a UV mercury lamp (40% of the time of the thermal reaction is required) [63,64]. The product distribution differs from the one obtained for the thermal reaction, where less 1,4-oxygenation products are formed.

The photocatalytic oxygenation of phenols by copper(I) chloride appears to be a complex reaction which cannot be described as purely photoassisted nor as a photoinduced catalytic process.

Bulkowski and Summers reported the oxygenation of phenol to *o*-benzoquinone using a dinuclear copper complex of a macrocyclic ligand [65].



Another dinuclear copper(I) complex which exhibits both a catalytic phenolase and a catecholase activity with exogeneous 2,4-di-*t*-butylphenol and 3,5-di-*t*-butylcatechol, respectively, was prepared by Réglier et al. [66].



This chemical model is reported to be the first to present turnovers ranging from 11 to 16 h^{-1}.

A completely different system, formed by [(phen)(Ph_3P)Cu(CO_3H)] (where phen = 1,10-phenanthroline, Ph_3P = triphenylphosphine, CO_3H = bicarbonate ion) in the presence of excess phenol and O_2, generates a catecholate species [(phen)Cu(OPh)(OC_6H_4-2(OH)] (where OPh = phenolate ion and OC_6H_4-2(OH) = catecholate monoanion). The catecholate group, which is present in the copper(II) complex, originates from a phenol hydroxylation reaction assisted by the copper centre [67].

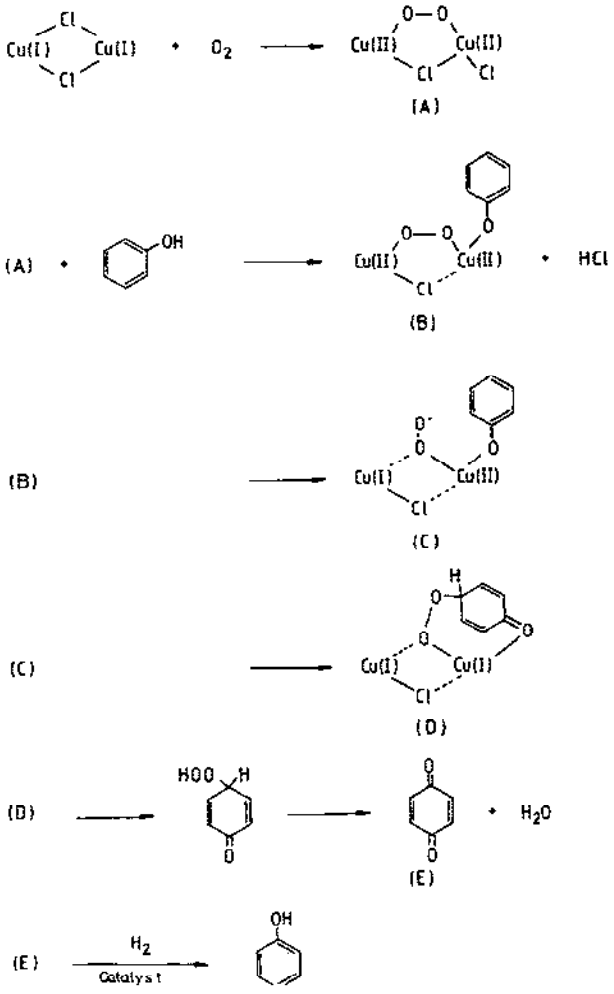
Thus the ortho-hydroxylation of phenols, stemming from the pioneering work of Brackman and Havinga, is of considerable interest in systems that are not only of commercial interest, but also as simple model systems for the action of tyrosinase [68].

Production of hydroquinones. Hydroquinone can be produced by the copper-catalyzed oxidation of phenol with O_2 to *p*-benzoquinone, followed by reduction [69,70]. The reaction, catalyzed by cuprous or cupric chloride, proceeds in acetonitrile under various conditions of temperature and pressure of dioxygen. The same catalyst is used to reduce the *p*-benzoquinone to hydroquinone using hydrogen.

Capdevielle and Maumy have shown that, by changing the catalyst to phenol ratio (catalyst = $Cu_4Cl_4O_2(CH_3CN)_3$), it is possible to obtain either oxidative coupling or para hydroxylation in a selective form, giving quinones or diphenols. For example, under stoichiometric conditions, 2,6-disubstituted or 2,3,6-trisubstituted phenols give the *p*-benzoquinones, whereas 2,4,6-trisubstituted phenols give quinols [71].

(c) Hydroxylation of benzene

The hydroxylating properties of the copper(I)–dioxygen system were discovered by Underfriend et al. in 1954 [72]. Ito and co-workers have shown that benzene is readily oxidized by dioxygen to form phenolic compounds in sulphuric acid solutions



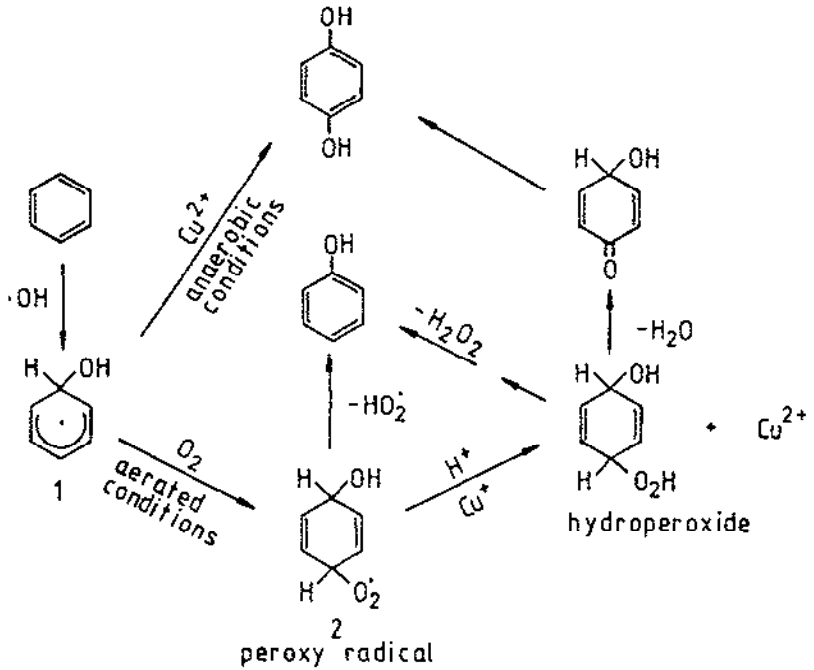
containing cuprous ions [73–76]. Arguments for and against the involvement of ·OH radicals in this reaction have been presented. Recently, new evidence has been obtained which permitted one to conclude that the reaction proceeds via ·OH radicals [77–79].

It was suggested that the H_2O_2, produced in the auto-oxidation reacts with copper(I) to give ·OH radicals in a Fenton-type reaction. The ·OH radicals that are formed react with benzene to give the hydroxycyclohexadienyl radical, which forms the phenolic products. The selectivity of phenolic products is remarkably high, and an appreciable amount of hydroquinone is produced without any complicated treatment. The formation of hydroquinone in the oxidation with copper(I)–dioxygen system has been confirmed by Weismeijer and co-workers [80]. Although the Fenton

reaction of benzene, where copper(I) is replaced by ferrous ions, has been studied extensively, the formation of hydroquinone has never been reported [81,82].

The possibility of oxidation of phenol to hydroquinone with ·OH is shown to be improbable. When phenol is oxidized as the starting material in place of benzene, the yield of catechol exceeds hydroquinone over the pH range of 1.3–3.5 [83].

The following mechanism is proposed:



The possibility of an attack of a copper(I)–dioxygen intermediate (CuO_2^+) on the hydroxycyclohexadienyl radical (I) is also considered as a possibility. Steric hindrance eliminates an attack at the ortho position of such a bulky intermediate, and thus the formation of catechol.

Using $^{18}O_2$, it was demonstrated that the two oxygen atoms in the hydroquinone are incorporated in two separate steps, and not in one step for a single oxygen molecule [84].

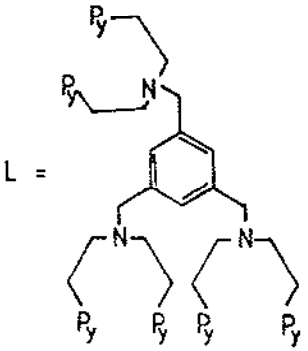
These facts are indicative of the differences that exist between the reported copper(I)–dioxygen system and the enzymatic hydroxylation of aromatic compounds.

A study was made of the hydroxylation of benzene, fluorobenzene, nitrobenzene, and anisole with copper(I)–H_2O_2, in the presence of excess copper(II). It was shown that copper(III) produced via the reaction of copper(II) and ·OH radicals does not hydroxylate these aromatic compounds in neutral or weakly acid solutions. Under

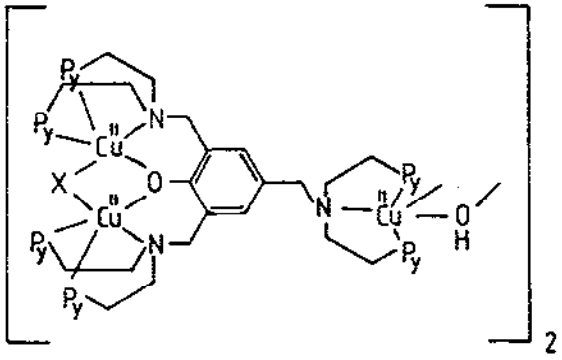
these conditions, the radical cation pathway, which is pH-dependent, does not occur. Therefore the hydroxylation reaction proceeds exclusively via ·OH radicals [83,84].

(iv) The trinuclear copper model system

The trinuclear copper(I) complex with ligand L has a behaviour reminiscent of copper monooxygenases, since the benzene ring is hydroxylated upon the reaction



of the complex with molecular oxygen. At −80°C, the hexanuclear cluster is obtained from CH_2Cl_2/CH_3CN solution. X-Ray diffraction studies confirm that this complex has two types of copper(II) environment [85].



C. REACTION OF ORGANOMETALLIC COMPOUNDS WITH DIOXYGEN

A regioselective oxygenation of aromatic compounds results from the reaction of molecular oxygen with aryl copper(I) and lithium diarylcopper(I) complexes [86]. Thus, while the reaction of R_2CuLi (R = aryl) with molecular oxygen gives the

oxidatively coupled R—R product, the bis(2,6-bis(methoxymethoxy)-4-methylphenyl) cuprate produces the corresponding phenol as the major product with the R—R as a sub-product in minor amounts.

RCu also produces phenol in the reaction with molecular oxygen. Radical inhibitors lowered the phenol/dimer ratio, thus indicating that a radical mechanism is involved.

Phenols are also formed when RCu (R = aryl) and 2, 3, or 4 tolyl-Cu react with molecular oxygen in non-polar solvents [87,88].

(i) Model systems for dopamine β-hydroxylase (aliphatic chain hydroxylation)

The monoxygenase dopamine β-hydroxyłase has been studied less than tyrosinase [89]. For dopamine β-hydroxylase, EXAFS study indicates that each of the two copper centres is coordinated to at least three imidazole groups and a solvent molecule. More recent EXAFS data on dopamine β-hydroxylase suggest the presence of a sulphur-containing ligand at a bonding distance of Cu—S = 2.3 Å [90]. EPR data are consistent with a square pyramidal site at the metal centres [91]. In contrast to tyrosinase, definitive evidence does not exist for dinuclear copper at the active site of dopamine β-hydroxylase, which catalyzes the benzilic hydroxylation of ring-substituted phenylethylamines.

In the reaction mechanism of mono-oxygenase activity, a CuOOH species has been postulated for dopamine β-hydroxylase. It is suggested that the reduction of O_2 at a copper(I) centre is accompanied by a proton transfer from a protein-derived group, leading to the copper-hydroperoxo intermediate. This is then capable of abstracting a hydrogen atom from the benzyl dopamine substrate and subsequent oxygen atom transfer leads to products [60,92–95].

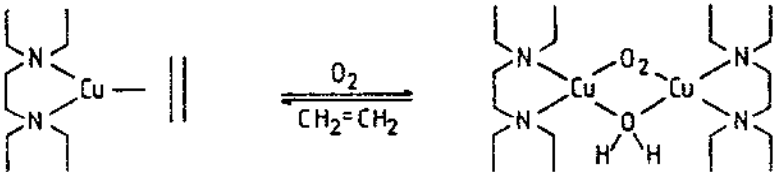
Dopamine is hydroxylated to noradrenaline, an important step in the modification of transmitter molecules [89]. There are several reports suggesting that epileptic attacks occur with depletion of norephinephine synthesis in the brain. Therefore the elucidation of the copper dependency of the synthesis and the mechanism of enzimatic activity of dopamine β-hydroxylase is very important [96–98].

D. MONONUCLEAR COPPER SYSTEMS

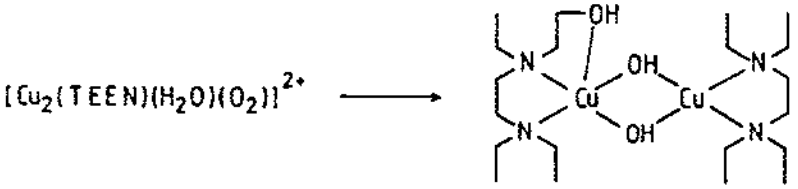
Only a few examples have been cited in the literature in which low molecular weight complexes are hydroxylated on an aliphatic group instead of the more common arene hydroxylation.

Thompson prepared a mononuclear copper(I) complex with *N,N,N',N'*-tetraethylene diamine (TEEN) and ethylene as ligands, which reacts with dioxygen at low temperature in methanol (H_2O) solution. A peroxo moiety is obtained, and the reaction can be reversed by displacement of the oxygen with ethylene [99].

The peroxo-bridged dicopper complex undergoes oxidation upon standing at

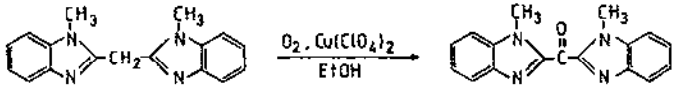


room temperature, the product containing an ethyl group of TEEN ligand which has been hydroxylated.



The hydroxylated di-μ-hydroxo dicopper(II) complex has been crystallographically characterized. Although the mechanism is not clear, the hydroxylation is most certainly derived from the cupric peroxo complex.

Alkyl monooxygenation chemistry has been described by Zuberbuhler and coworkers involving the insertion of an oxygen atom into the methylene group of di(1-methylbenzimidazole-2-yl)methane or di(2-pyridyl)methane and conversion to the ketone product [100,101]. No reductant is required, and the reaction is dependent on the metal as catalyst; this only takes place when a copper(II) salt is used.



These reactions were considered as examples of internal monooxygenase reactions since O_2 is used as oxidant, one atom from dioxygen is incorporated into the substrate (as proved by labelling experiments) and H_2O is also produced.

The corresponding alcohols have been excluded as intermediates in the direct oxidation reaction of the methylene group to ketone in aqueous solution [102].

If the bis-(di(2-pyridyl))copper(II) complex in methanol solution is made to react with dioxygen in the presence of chloride ions, the reaction product isolated corresponds to a chloro complex with one of the two coordinated ligands in the hydroxylated form, $[Cu(DPM)(DPMOH)Cl]ClO_4$. The octahedral copper(II) com-

plex, in which the hydroxylated methylene group binds the metal centre in an axial position, has been crystallographically characterized [103].

$$[Cu(DPM)_2](ClO_4)_2 \xrightarrow[CH_3OH]{O_2/Cl^-} [Cu(DPM)(DPMOH)Cl)ClO_4$$

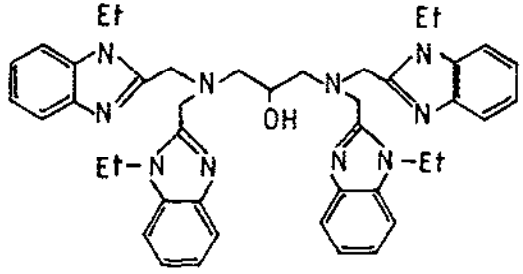
In the absence of chloride ions, the compound isolated was a dimeric copper(II) complex, the two metal centres being bridged by an OH group and by an organic molecule, L, that resulted from the reaction of the di(2-pyridyl)methane and di(2-pyridyl)ketone (L = 1,1,2,2-tetrakis(2-pyridyl)ethylene) [104]. The copper(II) complex $[Cu_2(DPM)_2L(OH)](ClO_4)_3 \cdot 2H_2O$ also contains two di(2-pyridyl)methane ligands, each bonded to a copper(II) centre in a chelating way. This dimeric complex was formed at room temperature after a long period of reaction during which the ketone was formed [105].

If the condensation reaction, which proceeds only in the presence of copper(II) ions, is done directly at room temperature, the same compound is obtained within the first 30 min of reaction. This dimeric complex was characterized by X-ray diffraction [106]. However, a mononuclear copper(II) complex $[Cu(DPM)L'](ClO_4)_2 \cdot MeOH$ ($L' = R_2{-}CH{-}COH{-}R_2$, R = pyridyl) is obtained when the reaction mixture is heated [107].

Kinetic studies indicate that the oxygenation reaction mechanism of di(2-pyridyl)methane is complicated and solvent-dependent [108].

A system that has a certain similarity with the oxygenation reaction of the methylene group of bis(1-methylbenzimidazole-2-yl)methane substrate in the presence of copper(II) ions [100] has been described by Reed and co-workers [109]. The isolation and structural characterization of bis(2-carboxy-*N*-ethylbenzimidazole) copper(II), $[Cu(2\text{-}O_2CBz{-}Et)_2]$, a copper-promoted oxidative degradation product of the binucleating ligand L, has been reported.

L =



The synthesis of $[Cu(2\text{-}O_2CBz\text{-}Et)_2]$ involves oxygenation of a copper(I) complex of the above-mentioned binucleating ligand. The oxidative degradation product is postulated to be due to the fact that the methylene group, which is adjacent to an aromatic ring and to an electronegative nitrogen atom is fairly acidic. Since the

dioxygen coordinated to copper is expected to be quite basic, the proximity of these functionalities within the coordination sphere of copper starts the oxidation reaction.

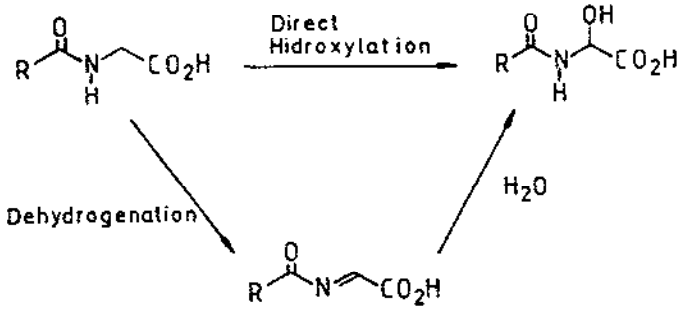
These results lead to the conclusion that the copper proteins must isolate the Cu_2O_2 moiety from close contact with highly activated C–H bonds in the polypeptide chain to avoid bond cleavage.

E. MODEL SYSTEM FOR PEPTIDYLGLYCINE α-AMIDATING MONOOXYGENASE (PAM) (GLYCINE-EXTENDED PEPTIDE HYDROXYLATION)

The enzyme peptidylglycine α-amidating monooxygenase catalyzes the production of peptide amides from their glycine-extended precursors [8,110]. However, PAM, which is a copper-dependent and ascorbate-requiring monooxygenase, apparently is not responsible for the final product. May and co-workers propose a two-step process with PAM first catalyzing the conversion of the glycine-extended peptide to the α-hydroxylglycine derivative, which is then converted to the final amide product by α-hydroxyglycine amidating dialkylase (HGAD). This last step is not copper-assisted [111].

Although the detailed mechanism of the action of PAM is yet to be established, this enzyme is strikingly similar to dopamine β-monooxygenase [112].

Two mechanisms have been proposed for the formation of the hydroxyglycine intermediate: (a) direct hydroxylation on carbon, (b) via oxidative formation of an N-acyl imine followed by stereospecific addition of water [113].

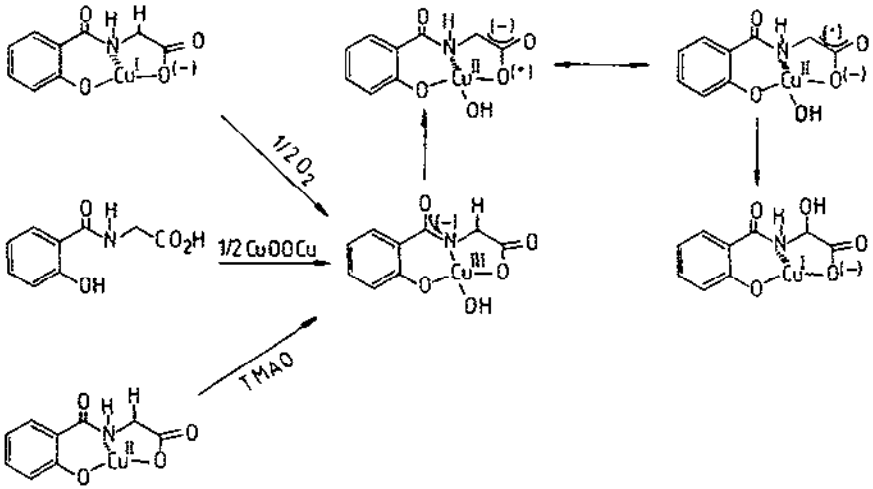


Vederas and co-workers report evidence for the direct hydroxylation mechanism based on ^{18}O labelling experiments [114].

Perkins et al. [115] have given a description of the reaction that is catalyzed by PAM, assuming that the enzyme contains two subunits with separable activities: peptidylglycine α-hydroxylating monooxygenase (PHM) requiring copper, molecular oxygen and ascorbate and producing peptidyl-α-hydroxy glycine intermediates, cleaved in a second step into COOH-amidated peptides and glyoxylic acid by peptidylhydroxy-glycine α-amidating lyase (PAL).

Capdeville and Maumy report three distinct copper-containing oxidant systems

involving dioxygen, peroxide anion or trimethylamine oxide which selectively hydroxylate the model substrate *N*-salicyloylglycine in the α position [116]. Trivalent copper is possibly the key intermediate in this first reported model for the PHM activity of PAM. The proposed mechanism is



The precise mechanism of all these reactions remains uncertain, and much remains to be done in order to have a thorough understanding of oxygen activation mechanisms. However, it is becoming increasingly clear that molecular oxygen is not involved directly in reactions with organic substrates. It is generally accepted that the required activation of molecular oxygen is achieved by reaction of the oxygen with the transition metal complex or the metal centre of the enzyme molecule. It is then the reaction of these oxygen-containing intermediates with the complexed organic substrate that brings about the observed oxygen insertion reaction.

ACKNOWLEDGEMENTS

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REFERENCES

1 K.D. Karlin and J. Zubieta (Eds.), Copper Coordination Chemistry: Biochemical and Inorganic Perspectives, Adenine Press, New York, 1983.
2 K.D. Karlin and J. Zubieta (Eds.), Biological and Inorganic Copper Chemistry, Vols. 1 and 2, Adenine Press, New York, 1986.
3 K.O. Karlin and Y. Gultneh, Prog. Inorg. Chem., 35 (1987) 219.
4 H. Sigel (Ed.), Metal Ions in Biological Systems, Vols. 13, 73, and 143, Dekker, New York, 1981.

5 S.M. Miller and J.P. Kleinman, Biochemistry, 24 (1985) 2114.
6 J.J. Villafranca, in T.G. Spiro (Ed.), Metal Ions in Biology, Vol. 3, Wiley-Interscience, New York, 1981, p. 263.
7 D.A. Robb, in R. Lontie (Ed.), Copper Proteins and Copper Enzymes, Vol. 2, CRC, Boca Raton, FL, 1984, p. 207.
8 A.F. Bradbury, M.D.A. Finnie and D.G. Smith, Nature 298 (1982) 686.
9 M. Tajima, T. Iida, S. Yoshida, K. Komatsu, R. Namba, M. Yanagi, M. Noguchi and H. Okamoto, J. Biol. Chem., 265 (1990) 9602.
10 R.S. Himmelwright, N.C. Eickman, C.D. Lubien, K. Lerch and E.I. Solomon, J. Am. Chem. Soc., 102 (1980) 7339.
11 G.L. Woolery, L. Powers, M. Winkler, E.I. Solomon, K. Lerch and T.G. Spiro, Biochim. Biophys. Acta, 788 (1984) 155.
12 M.E. Winkler, K. Lerch and E.I. Solomon, J. Am. Chem. Soc., 103 (1981) 7001.
13 K.D. Karlin, Y. Gultneh, T. Nicholson and J. Zubieta, Inorg. Chem., 24 (1985) 3725.
14 K.D. Karlin, P.L. Dahlstrom, S.N. Cozzette, P.M. Scensnny and J. Zubieta, J. Chem. Soc. Chem. Commun., (1981) 881.
15 K.D. Karlin, J.C. Hayes, Y. Gultneh, R.W. Cruise, J.W. McKnow, J.P. Hutchinson and J. Zubieta, J. Am. Chem. Soc., 106 (1984) 2121.
16 K.D. Karlin, B.I. Cohen, J.C. Hayes, A. Farooq and J. Zubieta, Inorg. Chem., 26 (1987) 147.
17 K.D. Karlin, M. Farooq, J.C. Hayes, B.I. Cohen, T.M. Rowe, E. Sinn and J. Zubieta, Inorg. Chem., 26 (1987) 127.
18 B.G. Malnström, Annu. Rev. Biochem., 51 (1981) 21.
19 R.W. Cruise, S. Kardeli, K.D. Karlin and A.D. Zuberbuhler, J. Am. Chem. Soc., 110 (1988) 6882.
20 N.J. Blackburn, K.D. Karlin, M. Concannon, J.C. Hayes, Y. Gultneh and J. Zubieta, J. Chem. Soc. Chem. Commun., (1984) 939.
21 R.W. Cruise, S. Kaderli, C.J. Meyer, A.D. Zuberbuhler and K.D. Karlin, J. Am. Chem. Soc., 110 (1988) 5020.
22 K.D. Karlin, R.W. Cruise, Y. Gultneh, J.C. Hayes and J. Zubieta, J. Am. Chem. Soc., 106 (1984) 3372.
23 J.E. Pate, R.W. Cruise, K.D. Karlin and E.I. Solomon, J. Am. Chem. Soc., 109 (1987) 2624.
24 N.J. Blackburn, R.W. Strange, R.W. Cruise and K.D. Karlin, J. Am. Chem. Soc., 109 (1987) 1235.
25 K.D. Karlin, R.W. Cruise, Y. Gultneh, A. Farooq, J.C. Hayes and J. Zubieta, J. Am. Chem. Soc., 109 (1987) 2668.
26 M.S. Nasir, K.D. Karlin, D. McGowty and J. Zubieta, J. Am. Chem. Soc., 113 (1991) 698.
27 K.D. Karlin, B.I. Cohen, R.R. Jacobson and J. Zubieta, J. Am. Chem. Soc., 109 (1987) 6194.
28 D.E. Wilcox, A.G. Porras, Y.T. Hwang, K. Lerch, M.E. Winkler and E.I. Solomon, J. Am. Chem. Soc., 107 (1985) 4015.
29 K.D. Karlin, R.W. Cruise, M.S. Haka, Y. Gultneh and B.I. Cohen, Inorg. Chim. Acta, 125 (1986) L43.
30 K.D. Karlin, B.I. Cohen, A. Farooq, S. Lin and J. Zubieta, Inorg. Chim. Acta, 153 (1988) 9.
31 K.D. Karlin, Y. Gultneh, J.C. Hayes and J. Zubieta, Inorg. Chem., 23 (1984) 519.
32 K.D. Karlin, M.S. Haka, R.W. Cruise and Y. Gultneh, J. Am. Chem. Soc., 107 (1985) 5828.
33 K.D. Karlin, M.S. Haka, R.W. Cruise, G.J. Meyer, A. Farooq, Y. Gultneh, J.C. Hayes and J. Zubieta, J. Am. Chem. Soc., 110 (1988) 1196.
34 N.J. Blackburn, R.W. Strange, A. Farooq, M.S. Haka and K.D. Karlin, J. Am. Chem. Soc., 110 (1988) 4263.

35 T.N. Sorrell, M.R. Malachovscki and D.L. Jameson, Inorg. Chem., 21 (1982) 3250.
36 T.N. Sorrell, V.A. Vankai and M.L. Garrity, Inorg. Chem., 29 (1990) 1687.
37 Y. Ishimura, Y. Nonaka, Y. Nishida and S. Kida, Bull. Chem. Soc. Jpn., 46 (1973) 3728.
38 L. Casella, M. Gulloti, R. Radaelli and P. Di Gennaro, J. Chem. Soc. Chem. Commun., (1991) 1611.
39 T.N. Sorrell and V.A. Vankai, Inorg. Chem., 29 (1990) 1687.
40 R. Menif and A.E. Martell, J. Chem. Soc. Chem. Commun., (1989) 1522.
41 R. Menif, A.E. Martell, P.Y. Squattrito and A. Clearfield, Inorg. Chem., 29 (1990) 4723.
42 M.P. Ngwenya, D. Chen, A.E. Martell and J. Reibenspies, Inorg. Chem., 30 (1991) 2732.
43 M.H. Gubelman and A.F. Williams, Struct. Bonding, 55 (1983) 1.
44 Y. Nishida, K. Takahashi, H. Kuramoto and S. Kida, Inorg. Chim. Acta, 54 (1981) L103.
45 K.D. Karlin, M.S. Haka, R.W. Cruise, G.J. Meyer, A. Farooq, Y. Gultneh, J.C. Hayes and J. Zubieta, J. Am. Chem. Soc., 110 (1988) 1196.
46 N. Kitjama, K. Fujisawa, Y. Moro-oka and K. Toyuiumi, J. Am. Chem. Soc., 111 (1989) 8975.
47 L. Casella, M. Grillotti and G. Pallanza, Biochem. Soc. Trans., 16 (1988) 821.
48 L. Casella, M. Grillotti, P. Pallanza and L. Rigoni, J. Am. Chem. Soc., 110 (1988) 4221.
49 L. Casella and L. Rigoni, J. Chem. Soc. Chem. Commun., (1985) 1668.
50 K.D. Karlin, R.W. Cruise and Y. Gultneh, J. Chem. Soc. Chem. Commun., (1987) 599.
51 K.D. Karlin, P. Ghosh, R.W. Cruise, A. Farooq, Y. Gultneh, R.R. Jacobson, N.J. Blackburn, R.W. Strange and J. Zubieta, J. Am. Chem. Soc., 110 (1988) 6769.
52 J.S. Thompson, J. Am. Chem. Soc., 106 (1984) 4057.
53 T.N. Sorrell and M.L. Garrity, Inorg. Chem., 30 (1991) 210.
54 O.J. Gelling, F. van Bolhuis, A. Meetsma and B.L. Feringa, J. Chem. Soc. Chem. Commun., (1988) 552.
55 O.J. Gelling, A. Meetsma and B.L. Feringa, Inorg. Chem., 29 (1990) 2816.
56 V.H. Crawford, H.W. Richardson, J.R. Wasson, D.J. Hodgson and W.E. Hatfield, Inorg. Chem., 15 (1976) 2107.
57 T.N. Sorrell, Tetrahedron, 45 (1989) 3.
58 P. Capdeville and M. Maumy, Tetrahedron Lett., 23 (1982) 1573.
59 L.C. Stewart and J.P. Klinman, Biochemistry, 26 (1987) 5302.
60 S.M. Miller and J.P. Klinman, Biochemistry, 24 (1985) 2114.
61 M. Reglier, E. Amadei, R. Tadayoni and B. Waegell, J. Chem. Soc. Chem. Commun., (1989) 447.
62 P. Capdeville and M. Maumy, Tetrahedron Lett., 23 (1982) 1577.
63 P. Engelbrecht, P. Thomas, H. Henning and J. Sykora, Z. Chem., 26 (1986) 137.
64 H. Henning, D. Rehorek, R. Stich and L. Weber, Pure Appl. Chem., 62 (1990) 1489.
65 J.E. Bulkowski and W.E. Summers, in K.D. Karlin and J. Zubieta (Eds.), Copper Coordination Chemistry: Biological and Inorganic Perspectives, Adenine Press, New York, 1983, 445.
66 M. Réglier, C. Jorand and B. Waegell, J. Chem. Soc. Chem. Commun., (1990) 1752.
67 G. La Monica, M.A. Angaroni, F. Cariati, S. Cenini and A. Ardizzoia, Inorg. Chem. Acta, 148 (1988) 113.
68 W. Brackman and E. Havinga, Recl. Trav. Chim. Pays Bas, 74 (1955) 1021, 1070, 1103, 1107.
69 J.E. Lyons and C.Y. Hsu, in K.D. Karlin and J. Zubieta (Eds.), Biological and Inorganic Copper Chemistry, Vol. 2, Adenine Press, New York, 1986, 57.
70 R.A. Shedon and J.K. Kochi, Metal-Catalysed Oxidations of Organic Compounds, Academic Press, New York, 1981.

71 P. Capdeville and M. Maumy, Tetrahedron Lett., 24 (1983) 5611.
72 S. Underfriend, C.T. Clark, J. Axelrod and B.B. Brodie, J. Biol. Chem., 208 (1954) 731.
73 K. Sasaki, S. Ito, Y. Sahadi, T. Kinoshita, T. Yamasaki and J. Harada, Chem. Lett., (1983) 37.
74 K. Sasaki, S. Ito, T. Kinoshita and J. Harada, Chem. Lett., (1983) 445.
75 T. Kinoshita, J. Harada, S. Ito and K. Sasaki, Angew. Chem. Suppl., (1983) 599.
76 A. Kunai, S. Hata, S. Ito and K. Sasaki, J. Org. Chem., 51 (1986) 3471.
77 S. Ito, T. Yamasaki, H. Okada, S. Okino and K. Sasaki, J. Chem. Soc. Perkin Trans., 2, (1988) 285.
78 M.K. Eberhardt, R. Colina and K. Soto, J. Org. Chem., 53 (1988) 1074.
79 M.K. Eberhardt and R. Coline, J. Org. Chem., 53 (1988) 1071.
80 J. van Gent, A.A. Weismeijer, A.W.P.G. Peter Rit and H. Bakkum, Tetrahedron Lett., 27 (1986) 1059.
81 C. Walling and R.A. Johnson, J. Am. Chem. Soc., 97 (1975) 363.
82 A. Kunai, S. Hata, S. Ito and K. Sasaki, J. Am. Chem. Soc., 108 (1986) 6012.
83 S. Ito, A. Kunai, H. Okada and K. Sasaki, J. Org. Chem., 53 (1988) 296.
84 M.K. Eberhardt, G. Ramirez and E. Ayala, J. Org. Chem., 54 (1989) 5922.
85 K.D. Karlin, Q.F. Gau, A. Farooq, S. Lui and J. Zubieta, Inorg. Chem., 29 (1990) 2549.
86 G.J. Lambert, R.P. Duffley, H.C. Dalzell and R.K. Razdan, J. Org. Chem., 47 (1982) 3350.
87 A. Camus and N. Marsich, J. Organomet. Chem., 46 (1972) 385.
88 G. van Koten, in G. Wielkinson, F.G.A. Stone and E.W. Abel (Eds.), Comprehensive Organometallic Chemistry, Pergamon, New York, 1982, p. 709.
89 N.J. Blackburn, D. Collison, J. Sutton and F.E. Mabbs, Biochem. J., 220 (1984) 447.
90 L.I. Kruse, W.E. DeWolf, P.A. Chambers and P.A. Goodhart, Biochemistry, 25 (1986) 7271.
91 S.S. Hasnain, G.P. Diakun, P.F. Knowles, N. Binsted, C.D. Garner and N.Y. Blackburn, Biochem. J., 221 (1985) 545.
92 G. Colombo, B. Rajeshekher, D.P. Giedroc and J.J. Villafranca, Biochemistry, 23 (1984) 3590.
93 P.F. Fitzpatrick, D.R. Floy and J.J. Villafranca, Biochemistry, 24 (1985) 2108.
94 P.F. Fitzpatrick and J.J. Villafranca, J. Am. Chem. Soc., 107 (1985) 5022.
95 J.P. Klinman, M. Krueger, M. Brenner and D.E. Edmondson, J. Biol. Chem., 259 (1984) 3399.
96 E.J. Underwood, Trace Elements in Human and Animal Nutrition, Academic Press, New York, 1977, p. 57.
97 W.N. Bourn, L. Chin and A.L. Picchioni, J. Pharm. Pharmacol., 30 (1978) 800.
98 P.C. Jobe, A.L. Picchioni and L. Chin, J. Pharmacol. Exp. Ther., 184 (1973) 1.
99 J.S. Thompson, J. Am. Chem. Soc., 106 (1984) 8308.
100 Ch. A. Sprecher and A.D. Zuberbuhler, Angew. Chem. Int. Ed. Engl., 16 (1977) 189.
101 F.L. Urbach, N. Knopp and A.D. Zuberbuhler, Helv. Chim. Acta, 61 (1978) 1097.
102 I.B. Lo, Thesis, University of Basel, 1980.
103 M.T. Garland, J.Y. Le Marouille, E. Spodine and J. Manzur, Acta Crystallogr. Sect. C, 42 (1986) 1720.
104 M. Vera, Thesis, University of Chile, 1990.
105 E. Spodine, J. Manzur and M.T. Garland, Proc. III Encuentro Química Inorgánica, Santiago, Chile, 1989, p. 185.
106 E. Spodine, J. Manzur, M.T. Garland, M. Kiwi, O. Peña, D. Grandjean and L. Toupet, J. Chem. Soc. Dalton Trans., (1991) 365.
107 J. Manzur, M.T. Garland, A.M. Atria, M. Vera and E. Spodine, Bol. Soc. Chil. Quim., 34 (1989) 229.

108 A.M. Atria, M. Vera and E. Spodine, Report Book XXVI, International Conference on Coordination Chemistry, Porto, Portugal, 1988.
109 M.G. Patch, V. McKee and Ch. A. Reed, Inorg. Chem., 26 (1987) 776.
110 B.A. Eipper and R.E. Mains, Annu. Rev. Phys., 50 (1988) 333.
111 A.G. Katopodis, D. Ping and S.W. May, Biochemistry, 29 (1990) 6115.
112 A.G. Katopodis and S.W. May, Biochemistry, 29 (1990) 4541.
113 K.V. Reddy, Y.J. Jin, P.K. Arora, D.S. Sfeir, S.C.F. Maloney, F.L. Urbach and L.M. Sayre, J. Am. Chem. Soc., 112 (1990) 2332.
114 T.M. Zabriskie, H. Cheng and J.C. Vederas, J. Chem. Soc. Chem. Commun., (1991) 571.
115 S.N. Perkins, E.J. Husten and B.A. Eipper, Biochem. Biophys. Res. Commun., 171 (1990) 926.
116 P. Capdeville and M. Maumy, Tetrahedron Lett., 32 (1991) 3831.