ELSEVIER

Coordination Chemistry Reviews
190–192 (1999) 855–869

COORDINATION CHEMISTRY REVIEWS

www.elsevier.com/locate/ccr

Dioxygen activation by copper sites: relative stability and reactivity of (μ-η^2:η^2-peroxo)- and bis(μ-oxo)dicopper cores

Patrick L. Holland, William B. Tolman *

Department of Chemistry and Center for Metals in Biocatalysis, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455, USA

Accepted 6 April 1999

Contents

Abstract

Investigations of complexes comprising the title cores are summarized with a view toward understanding their interconversion and possible implications in metallobiochemistry. Detailed studies on the solvent and concentration dependence of the equilibrium between (μ-η^2:η^2-peroxo)dicopper(II) (**A**) and bis(μ-oxo)dicopper(III) (**B**) cores using mono- and binucleating ligands have elucidated the effects of ligand geometry, solubility, solvent donor ability and temperature on O–O bond cleavage and formation. These effects suggest that similar environmental influences may be significant in metalloenzymes and in particular, raise the possibility of either core being responsible for arene hydroxylation by tyrosinase. Recent

* Corresponding author. Fax: + 1-612-624-7029.
E-mail address: tolman@chem.umn.edu (W. B. Tolman)

PII: S0010-8545(99)00125-3

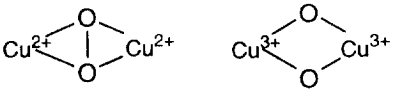
studies on a synthetic system composed of a $[Cu_2(\mu\text{-}O)_2]^{2+}$ unit ligated to a mixed imine/amine ligand with an appended arene substituent substantiate the notion that core **A** or **B** may be competent in performing arene hydroxylation chemistry.

Keywords: Copper; Dioxygen; Tyrosinase; Synthetic models

1. Introduction

The important biological functions and fundamentally interesting chemistry of metalloproteins that bind or activate dioxygen for substrate functionalization have inspired much research into the nature of the metal–dioxygen adducts and derived reactive intermediates [1].

One of the most thoroughly characterized metal–dioxygen species within the growing class of proteins with nonheme active sites is the planar (μ-η^2:η^2-peroxo)dicopper(II) unit **A** that was identified in the reversible dioxygen-binding protein hemocyanin [2,3], the arene-oxidizing protein tyrosinase [3,4], and, more recently, the *o*-quinone-generating catechol oxidase [5]. Our understanding of the structure, bonding, and aspects of the reactivity of **A** has been informed by studies both of the proteins [2–5] and of synthetic model complexes [1f,6,7]. Recently, an isomer of **A**, the bis(μ-oxo)dicopper(III) core **B**, was characterized in several synthetic systems [8,9], and the facile interconversion of **A** and **B** was observed in a specific instance [10]. Several important questions were raised by these findings that relate to the possible viability of **B** as a reactive intermediate in biology. What controls the relative stability of isomers **A** and **B**? Is intermediate **B**, which heretofore has remained unobserved in studies of tyrosinase, capable of performing tyrosinase reactions (e.g. hydroxylating an arene)? In this brief review, work aimed at characterizing **A** and **B** in synthetic systems will be summarized and recent efforts in our laboratory to address the above questions will be presented.



A **B**

2. (μ-η^2:η^2-Peroxo)dicopper(II) complexes

Since the initial discovery of core **A** in Cu/O_2 chemistry by Kitajima, Moro-oka, and coworkers using sterically hindered tris(pyrazolyl)hydroborate supporting ligands [1f,6], several other groups have observed this core in low temperature reactions of Cu(I) precursors with dioxygen [7,11]. In general, tridentate, facially coordinating N-donor ligands have enabled access to isolable (μ-η^2:η^2-per-

Table 1
Structural and spectroscopic parameters for planar (μ-η^2:η^2-peroxo)dicopper(II) complexes and bis(μ-oxo)dicopper(III) complexes

Compound	Cu···Cu (Å)	O–O (Å)	Cu–O (Å)	UV–vis (nm), ε (M^{-1} cm^{-1})	RR (cm^{-1})[a]	$\Delta^{18}O$ (cm^{-1})[b]	Ref.
Oxyhemocyanin	3.6[c] 3.7[d]	1.4[c]	1.7–2.2[c]	345, 20 000 570, 100	744	39	[3]
Oxytyrosinase	–	–	–	345, 17 000 590, 1000	755	41	[3]
Oxy-catechol oxidase	3.8[d]	–	–	345, strong 575, weak	750	–	[5]
$[\{P(im^{iPr_2})Cu\}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$[e]	–	–	–	343, 19 500 549, 790	750	–	[76]
$[\{(bpepe)Cu\}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$[f]	–	–	–	362, ~3200 526, ~200	737	42	[11]
$[(FD_2DIEN_2)Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$[g]	–	–	–	360, large 504, 1000	–	–	[7e]
$[(T1Et_4MeIPCu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$[h]	3.5[d]	–	1.9[d]	338, 19 000 521, 1000	740	38	[7a]
$(Tp^{iPr_2}Cu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)$[i]	3.56[c]	1.41[c]	1.90–1.93[c]	349, 21 000 551, 790	741	43	[6a]
$[(L^{iPr_3}Cu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$	–	–	–	366, 22 500 510, 1300	713	41	[10]
$[(L^{iPr_3}Cu)_2(\mu\text{-}O)_2]^{2+}$	2.88[d]	–	1.89[d]	324, 11 000 418, 13 000	589	22	[10,12]
$[(L^{Bn_3}Cu)_2(\mu\text{-}O)_2]^{2+}$	2.79[c]	2.29[c]	1.80–1.81[c]	318, 12 000 430, 14 000	603/595	23	[14,12]
$[(iPr_4dtne)Cu_2(\mu\text{-}O)_2]^{2+}$	2.78[c]	2.35[c]	1.82–1.84[c]	316, 13 000 414, 14 000	585	21	[15,12]
$[(L_{ME}Cu)_2(\mu\text{-}O)_2]^{2+}$[j]	2.74[c]	2.34[c]	1.79–1.82[c]	306, 21 000 401, 28 000	610	23	[9a]
$[\{(PhPyNEt_2)Cu\}_2(\mu\text{-}O)_2]^{2+}$	–	–	–	404, 13 000	607	27	[18]

[a] O–O or Cu_2O_2 vibration in resonance Raman spectrum.
[b] Raman shift of $^{16}O_2$ compound–Raman shift of $^{18}O_2$ compound.
[c] Distance from X-ray crystal structure.
[d] Distance from EXAFS.
[e] $P(im^{iPr_2})$ = tris[2-(1,4-diisopropylimidazolyl)]phosphine.
[f] dpepe = *N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenylethylamine.
[g] FD_2DIEN_2 = 3,6,9,16,19,22-hexaaza-27,28-dioxatricyclo[22.2.1.1^{11,14}]octacosa-1(26),2,9,11,13,15,22,24-octaene.
[h] $T1Et_4MeIP$ = tris(1-ethyl-4-methylimidazolyl)phosphine.
[i] Tp^{iPr_2} = hydrotris(3,5-diisopropylpyrazolyl)borate.
[j] L_{ME} = *N*,*N*′-diethyl-*N*,*N*′-dimethyl-*trans*-(1*R*,2*R*)-diaminocyclohexane.

oxo)dicopper(II) cores, as long as bulky substituents are incorporated in order to encapsulate the reactive unit in a hydrocarbon sheath and inhibit decomposition reactions enough to allow its characterization. Structural features of **A** available from the X-ray crystal structure of $[(Tp^{iPr2}Cu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]$ (Fig. 1; Tp^{iPr2} = tris(3,5-diisopropylpyrazolyl)hydroborate) and various EXAFS studies are summarized in Table 1, alongside data from the oxy forms of hemocyanin, tyrosinase, and catechol oxidase. Notable aspects include the Cu–Cu distance of ca. 3.6 Å and the planar and symmetrical $\mu\text{-}\eta^2\text{:}\eta^2$ binding mode of the O_2^{2-} ligand that has an O–O distance of ca. 1.4 Å typical for peroxide. Spectroscopic signatures of **A** include a diagnostic pattern of peroxo → Cu(II) charge-transfer features in the optical absorption spectrum (λ_{max} ca. 350 nm (ε ca. 20 000 $M^{-1}cm^{-1}$) and ca. 550 nm (ε ca. 1000)), EPR silence due to antiferromagnetic coupling between the Cu(II) ions, and a low O–O stretching frequency observed by resonance Raman spectroscopy ($\nu_{O\,O}$ ca. 750 cm^{-1}). A bonding description was developed through a detailed correlation of spectral features, structural parameters and theoretical calculations [3,6]. Several key aspects of this description are reproduced in pictorial fashion in Fig. 2; significantly, back-donation of electron density from the Cu(II) $d_{x^2-y^2}$ orbitals into the peroxide σ^* orbital in the HOMO rationalizes the weak O–O bond, among other properties.

The characteristics of the product of oxygenation of solutions of $[L^{iPr3}Cu(CH_3CN)]^+$ (L^{iPr3} = 1,4,7-triisopropyl-1,4,7-triazacyclononane) in CH_2Cl_2 are typical of the ($\mu\text{-}\eta^2\text{:}\eta^2$-peroxo)dicopper(II) core [7d]. Thus the oxygenation product is EPR silent, exhibits the appropriate CT features in the UV–vis spectrum and has a 2:1 Cu/O_2 stoichiometry as measured by manometry. Interestingly, however, the O–O stretching vibration in the resonance Raman spectrum of this compound is 713 cm^{-1} [7d,12], to our knowledge the lowest value for a metal–peroxide complex. Although caution must be exercised in correlating this low $\nu_{O\,O}$ with

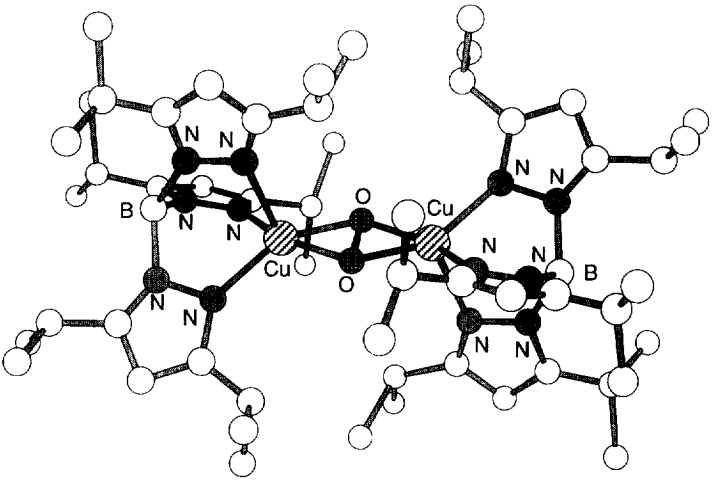


Fig. 1. CHEM3D representation of the X-ray crystal structure of $[(Tp^{iPr2}Cu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]$ [6], with non-carbon atoms labeled and H atoms omitted for clarity.

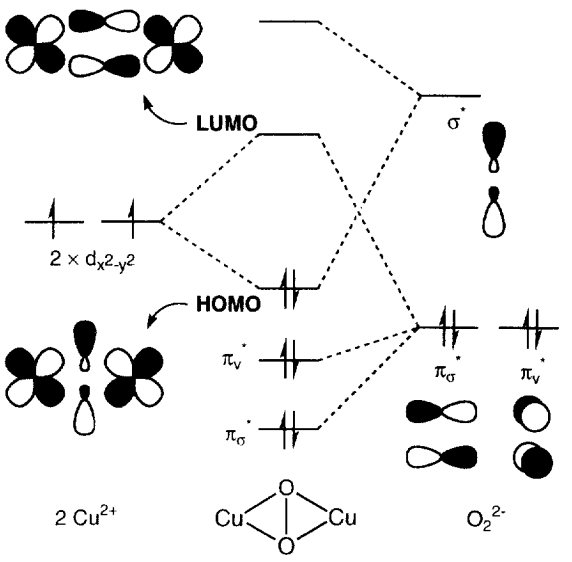


Fig. 2. Partial molecular orbital diagram showing the frontier orbitals of the (μ-η^2:η^2-peroxo)dicopper(II) core, adapted from [3,6].

the O–O bond strength [3,6b,13], the existence of a particularly weak O–O bond in this complex is consistent with the strong σ-donor characteristics of the L^{iPr3} ligand which would be expected to increase the amount of electron density in the peroxide σ* orbital (HOMO in Fig. 2). Most importantly, the attribution of a weak O–O bond to the core helps to rationalize the observed propensity of its (μ-η^2:η^2-peroxo)dicopper(II) core to undergo O–O bond scission, as described below.

3. Bis(μ-oxo)dicopper(III) complexes

Oxygenation of the Cu(I) complex of a 1,4,7-triazacyclononane ligand with benzyl rather than isopropyl substituents (L^{Bn3} = 1,4,7-tribenzyl-1,4,7-triazacyclononane) resulted in the formation of a new species with spectroscopic properties clearly different from the (μ-η^2:η^2-peroxo)dicopper(II) species capped by L^{iPr3} [8,10,14]. Detailed spectroscopic and structural studies revealed that the new species contained a bis(μ-oxo)dicopper(III) core (**B**), and there are now several crystallographically characterized examples of similar compounds that are capped by various bi- and tridentate tertiary amine ligands (Fig. 3) [8,9,14,15]. The geometries of the $[Cu_2(\mu\text{-}O)_2]^{2+}$ cores of these molecules are similar to each other, and diverge significantly from those characteristic of the isomeric $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ unit (Table 1). Overall, the bis(μ-oxo)dicopper(III) core is more compact; the Cu–Cu mdistance (2.8 Å) and Cu–O bond length (1.8 Å) are shorter than in the (μ-η^2:η^2-peroxo)dicopper(II) compounds. Diagnostic spectral properties include a pair of intense, apparently CT features in the absorption spectrum (ca. 320 and ca. 420 nm, ε ca. 14 000 M^{-1}

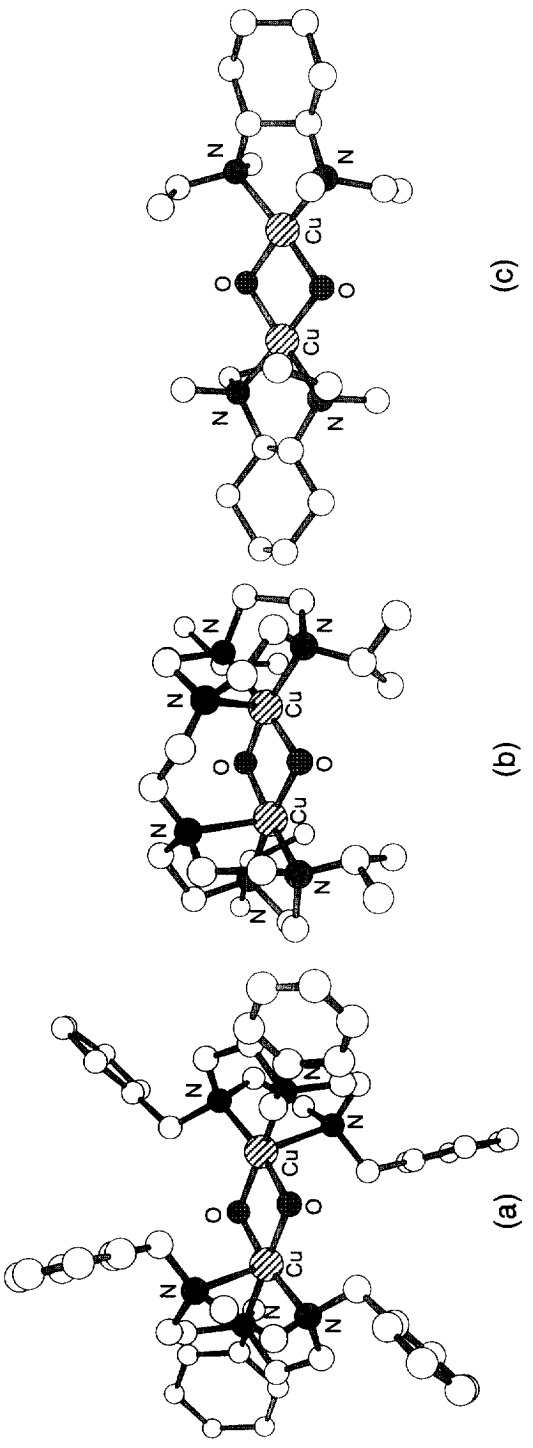


Fig. 3. CHEM3D representations of the cationic portions of the X-ray crystal structures of: (a) $[(L^{Bn3}Cu)_2(\mu\text{-}O)_2](SbF_6)_2$ [10,14]; (b) $[(iPr_4dtne)Cu_2(\mu\text{-}O)_2](SbF_6)_2$ [iPr_4dtne = bis(1,4-diisopropyl-1,4,7-triazacyclonon-7-yl)ethane]; and (c) $[(L^{ME}Cu)_2(\mu\text{-}O)_2](CF_3SO_3)_2$ [9a] [L^{ME} = *N,N''*-dimethyl-*N,N'*,-diethyl-(1*R*,2*R*)-diaminocyclohexane]. Non-carbon atoms are labeled and H atoms are omitted for clarity.

cm^{-1} for each), EPR silence and NMR spectral features in the 0–10 ppm region indicative of diamagnetism and an ^{18}O-sensitive feature in the resonance Raman spectrum at ca. 600 cm^{-1} ($\Delta^{18}O = 14–27$ cm^{-1}) that is due to a symmetric vibration of the tetra-atomic $[Cu_2(\mu\text{-}O)_2]^{2+}$ core [12]. These features are notably different from those of the $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ unit, thus allowing the two cores to be readily differentiated. Finally, XAS studies [9b] and theoretical calculations [14,16] support a dicopper(III) ground state electronic structure description for the $[Cu_2(\mu\text{-}O)_2]^{2+}$ species, but with a high degree of covalency in the core Cu–O bonding indicated by the extensive overlap between the Cu $d_{x^2-y^2}$ and the antibonding combination of O p orbitals in the HOMO (Fig. 4). Comparison of the HOMOs of the $[Cu_2(\mu\text{-}O)_2]^{2+}$ and $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ cores (Figs. 2 and 4) reveals a relationship between them; both involve interactions between Cu $d_{x^2-y^2}$ orbitals and antibonding combinations of O p (or hybrid) orbitals, but with different orbital coefficients that are consistent with their respective Cu^{III} and Cu^{II} formal oxidation state assignments. Indeed, this relationship implies that the cores may smoothly interconvert in a symmetry-allowed process [16], experimental support for which will be discussed below.

4. What controls the relative stability of the (μ-η^2:η^2-peroxo) and bis(μ-oxo)dicopper cores?

A comparison of the various ligands that were used in Cu^I/O_2 reactivity studies reveals that ligand structural effects are dominant in controlling which of the isomeric cores are generated [8,9,17]. The key ligand structural elements are ligand substituent size and disposition and, in binucleating ligands containing linked macrocyclic donors, the geometry enforced by the particular linker. Thus, bidentate amine ligands and triazacyclononanes with at least one alkyl substituent that is not

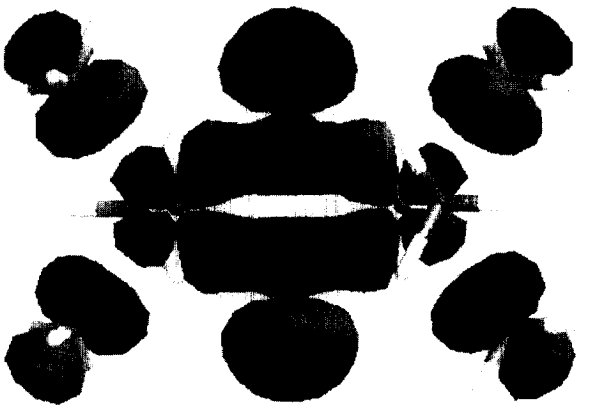


Fig. 4. The calculated HOMO of $[(NH_3)_6Cu_2(\mu\text{-}O)_2]^{2+}$, adapted from [16a].

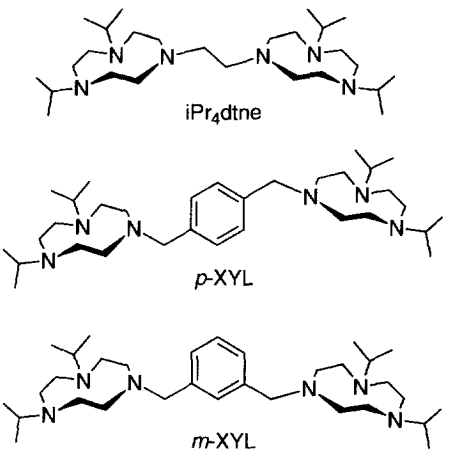


Fig. 5. Binucleating ligands used to explore Cu^{I}/O_2 chemistry [15,17].

branched at the position α to a N atom comprise a class that are relatively sterically unhindered, and thus upon reaction of their Cu(I) complexes with O_2 are capable of collapsing to the compact bis(μ-oxo)dicopper(III) core. The tris(pyrazolyl) and -(imidazolyl) ligands used to date support only the (μ-η^2:η^2-peroxo)dicopper(II) core [6,7], apparently because the large size and orientation of their ligand substituents inhibits approach of the Cu atoms to a distance less than 3 Å. The donor groups in these ligands also are weaker σ donors (i.e. are 'softer') than the amines that are capable of supporting the Cu^{III} ions in the oxo-bridged core, suggesting that this electronic effect (and possibly others, as noted in [16b]) may also be important. However, recently uncovered evidence for the production of $[Cu_2(\mu\text{-}O)_2]^{2+}$ complexes using ligands with relatively soft pyridyl donors indicates that the electronic effect is not as important in determining the choice of isomers (vide infra) [18,19].

In binucleating ligands, a short tether such as the ethyl linker in iPr_4dtne (Fig. 5) inhibits (μ-η^2:η^2-peroxo)dicopper(II) core formation by preventing the Cu atoms from achieving the required ca. 3.6 Å separation; only a bis(μ-oxo)dicopper(III) complex was generated with this constrained ligand system [15]. On the other hand, the *p*-xylyl bridge in *p*-XYL (Fig. 5) keeps the Cu sites far apart, yet bis(μ-oxo)dicopper(III) core formation was observed [17]. With the *m*-XYL system, both isomeric cores formed, but in ratios that were dependent on the Cu^{I} complex concentration (low concentration favoring peroxo). These results, in conjunction with those from detailed stopped-flow kinetics studies of the oxygenation process, suggested that intramolecular and intermolecular pathways are followed to yield $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ or $[Cu_2(\mu\text{-}O)_2]^{2+}$ units, respectively. Only the latter was seen with *p*-XYL because the Cu sites are kept distant, thus 'dimer-of-dimers' or higher order oligomers were seen. Both types of cores were observed with *m*-XYL, which in an intramolecular reaction can accommodate a (μ-η^2:η^2-peroxo)dicopper(II) core, but can only support a bis(μ-oxo)dicopper(III) unit by reacting in an intermolecular sense. Consistent with these findings are recent results that showed that

a different *m*-xylyl-bridged ligand with bis(pyridyl)amine caps was unable to allow access to a constrained $[Cu_2(\mu\text{-}O)_2]^{2+}$ core, and supported a (μ-peroxo)dicopper core with a 'bent' geometry instead [20].

In a simple, yet interesting system capped by L^{iPr3}, the two cores **A** and **B** have similar thermodynamic stability, with evidence for the existence of a rapid equilibrium between them under certain conditions. Previously reported observations [10] that supported the ability of the isomers to interconvert included the conversion of 1.2 mM solutions of $[(L^{iPr3}Cu)_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)](ClO_4)_2$ in CH_2Cl_2 to $[(L^{iPr3}Cu)_2(\mu\text{-}O)_2](ClO_4)_2$ by dilution with > 50-fold excess (v/v) of THF, as well as the opposite reaction via dilution of a 1.2 mM THF solution of the bis(μ-oxo) compound with CH_2Cl_2. In acetone, both isomers were present as shown by UV–vis and Raman spectroscopy. Moreover, stopped-flow kinetics studies showed that the oxygenation reaction in acetone involved rate-controlling 1:1 Cu/O_2 adduct formation and that the $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ and $[Cu_2(\mu\text{-}O)_2]^{2+}$ complexes formed at identical rates. Rapid equilibration of the two isomers is required to explain these kinetic results. While equilibration of the isomers was apparent in acetone solution, the situation in CH_2Cl_2 and/or THF was less clear, as only discontinuous interconversion was observed in solvent mixing experiments using ratios of these solvents intermediate between those used in the originally reported protocols. This finding contradicts what would be expected if the two species were in equilibrium.

This complication in conjunction with others, such as the observation of large differences in λ_{max} for the bis(μ-oxo)dicopper complex in acetone and THF and observations of turbidity in solutions with the latter, led to a recently completed series of experiments in which the oxygenation of $[L^{iPr3}Cu(CH_3CN)]X$ (X = PF_6^-, ClO_4^-, or SbF_6^-) in THF and various THF/CH_2Cl_2 mixtures was re-examined [21]. In an important discovery, the oxygenation of concentrated THF solutions (> 2 mM in Cu^I precursor) was found to first give a solution with UV–vis and Raman features indicative of a mixture of the isomeric cores similar to that seen in acetone (Fig. 6a). Within minutes, however, the spectral features due to the (μ-η^2:η^2-peroxo)dicopper species disappeared, the λ_{max} for the bis(μ-oxo)dicopper core shifted (from 418 to 448 nm), and the baseline absorbance in the UV–vis spectrum increased (Fig. 6b). The results of conductivity measurements, the finding of a dependence of the time of onset of the aforementioned spectral changes on the nature of the counterion and the concentration (faster at higher concentration with X = ClO_4^-), and the observation of precipitate in some instances were all indicative of aggregation/precipitation phenomena that accompanied the spectral changes. To explain all of these results, it was postulated that selective aggregation/precipitation of the bis(μ-oxo)dicopper isomer occurs, and this drives an initially homogeneous equilibrium between the two cores toward the $[Cu_2(\mu\text{-}O)_2]^{2+}$ form (Fig. 7).

By avoiding this aggregation/precipitation phenomenon through use of low concentrations of Cu^I precursor and appropriate choice of counterion, further evidence in support of the **A**/**B** equilibrium was obtained. The ratio of the two cores in THF was found to smoothly and reversibly vary with temperature, and a peak-fitting protocol gave thermodynamic parameters for the peroxo/bis(oxo) equilibrium: $\Delta H = 0.9(2)$ kcal mol^{-1} and $\Delta S = 6(1)$ cal mol^{-1} K^{-1}. These values are in agreement

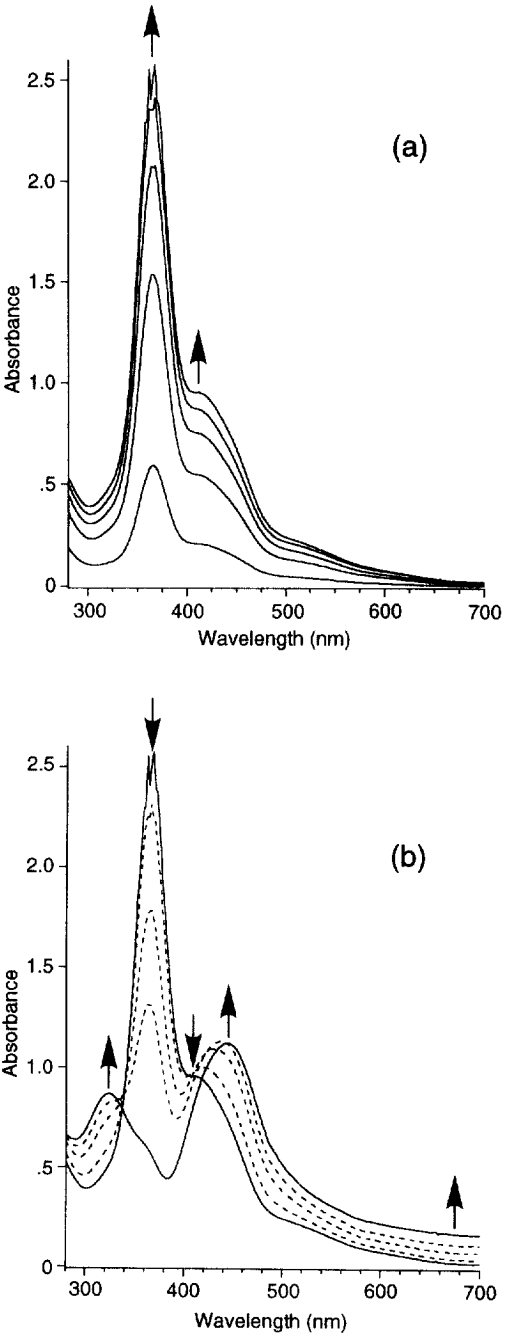


Fig. 6. UV–vis spectral monitoring of the oxygenation of $[L^{iPr3}Cu(CH_3CN)]PF_6$ (0.28 mM) in THF at −60°C, (a) every 40 s for the initial 4 min, and (b) after 4 (solid line), 5, 6, 7 (all dashed lines) min, and 20 min (solid line). Adapted from [21].

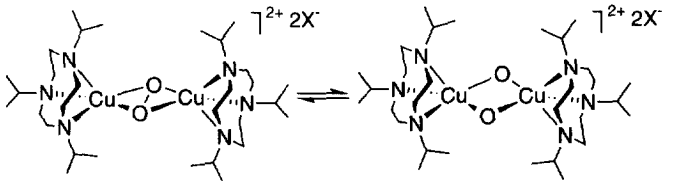


Fig. 7. Equilibrium between (μ-η²:η²-peroxo)dicopper(II) and bis(μ-oxo)dicopper(III) complexes that is shifted to the right by selective precipitation/aggregation of the latter under certain conditions (*e.g.* $X = ClO_4^-$, THF solvent).

with the small energetic differences between analogous isomers calculated theoretically [16]. In addition, when aggregation/precipitation was avoided, the ratio of the two cores was found to vary smoothly with the proportion of the solvents in CH_2Cl_2/THF mixtures (more **B** as THF:CH_2Cl_2 ratio increased). It is difficult to explain the preference for the bis(μ-oxo)dicopper isomer as the relative amount of THF increases, but the large difference in the electron pair donor ability of these two solvents that have similar polarities [22] suggests that coordination of THF and/or the counterions to the bis(μ-oxo)dicopper complex is involved.

In any case, the change in the proportions of the two isomeric cores as a function of solvent and temperature are clear indications that, in this particular system capped by L^{iPr3}, environmental factors subtly influence their relative energies. An important implication of this finding is that in biological or catalytic systems, minor changes in ligand environment, solvent, temperature, or other factors may induce the interconversion of the two isomeric cores. In particular, while the only observable intermediate in tyrosinase is the (μ-η²:η²-peroxo)dicopper unit in oxy-tyrosinase, one may readily envisage that a transient bis(μ-oxo)dicopper isomer may be generated as a result of some minor active site structural perturbation or substrate binding, and that the latter species may attack the substrate arene ring. Before this notion will be accepted, however, the capability of the bis(μ-oxo)dicopper core to hydroxylate an arene ring must be demonstrated.

5. Is the bis(μ-oxo)dicopper core capable of hydroxylating an arene?

The important arene hydroxylation step performed biologically by tyrosinase has been modeled successfully with coordination compounds. For example, many dicopper(I) complexes of binucleating ligands containing a bridging *m*-xylyl group react with dioxygen to hydroxylate the arene ring [23]. Although the intermediates in most of these reactions are unknown, Karlin and coworkers were able to observe a dioxygen adduct in one case that they postulated is a 'bent' (μ-η²:η²-peroxo)dicopper(II) species on the basis of extensive spectroscopic studies (Fig. 8) [24]. This butterfly core geometry is distinguished from the planar variant **A** discussed above by the presence of an additional charge transfer band at 435 nm [20,24]. The similarity of this electronic transition to the characteristic band in bis(μ-oxo)dicopper

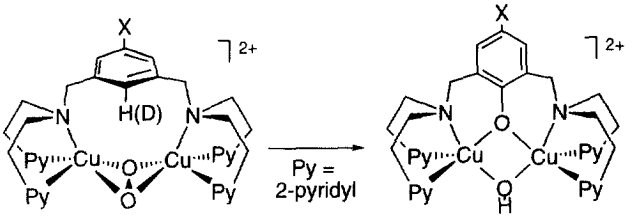


Fig. 8. Hydroxylation of an arene by a bent (μ-η²:η²-peroxo)dicopper complex [24].

complexes initially suggested that the O–O cleaved isomer could be present, but subsequent resonance Raman studies verified that the amount of bis(μ-oxo)dicopper complex (if any) was less than 0.1% [20]. Mechanistic studies of the hydroxylation reaction showed that it was slowed by electron-withdrawing substituents X on the phenyl ring and that there was an insignificant deuterium kinetic isotope effect. These data are consistent with rate-controlling electrophilic attack on the arene π-electrons, and it was proposed that the oxygen of an (μ-η²:η²-peroxo)dicopper(II) core directly attacks the arene ring in a process concurrent with O–O cleavage. The plausibility of this pathway was supported further by calculations [20].

When it became clear that the O–O bond in some (μ-η²:η²-peroxo)dicopper complexes could break spontaneously to form a bis(μ-oxo)dicopper core, the possibility was raised that the above aromatic hydroxylations could proceed via a small equilibrium concentration of highly reactive bis(μ-oxo)dicopper complex. However, attempts to demonstrate aromatic hydroxylation activity like that of tyrosinase with complexes containing core **B** were frustrated by the tendency of the tertiary amine ligands to undergo *N*-dealkylation, even in the presence of aryl substituents. For example, kinetic studies showed that the decomposition of $[(L^{Bn^3}Cu)_2(\mu\text{-}O)_2]^{2+}$ (Fig. 3a) proceeded by aliphatic hydrogen atom abstraction from the benzylic C–H bond (leading to *N*-dealkylation) despite the presence of a nearby phenyl group [25]. In an even more striking example, ligand recovery studies on the decomposition of the mixture of planar (μ-η²:η²-peroxo)dicopper and bis(μ-oxo)dicopper complexes with the *m*-XYL ligand (vide supra) showed that the (μ-η²:η²)-peroxodicopper complexes derived from intramolecular O_2 binding (low-concentration conditions) gave aromatic hydroxylation as in Karlin's complexes, while the bis(μ-oxo)dicopper complexes derived from intermolecular O_2 binding (high-concentration conditions) gave only *N*-dealkylation [17]. Thus, it appeared that bis(μ-oxo)dicopper complexes decayed in a different way than (μ-η²:η²-peroxo)dicopper complexes, preferring aliphatic to aromatic hydroxylation.

It must be noted, however, that geometric constraints are important controlling factors in these oxygenation and subsequent hydroxylation reactions. The X-ray crystal structures of $[(L^{Bn^3}Cu)_2(\mu\text{-}O)_2]^{2+}$ and $[(dtne)Cu_2(\mu\text{-}O)_2]^{2+}$ (Fig. 3a and b) each displayed weak C–H···O bonds from ligand α C–H units to the oxo bridges, showing that interaction of the α hydrogen atom with the bis(μ-oxo)dicopper core requires little reorganization and suggesting that the observed attack at this position is due to the orientation of the hydrocarbyl group. In the *m*-XYL system, the results were also ambiguous with respect to the ability of the bis(μ-oxo)dicopper core to react

with an appropriately poised aryl ring, because in the polynuclear bis(μ-oxo)dicopper complexes the bis(μ-oxo) cores linked different ligands and the necessary geometry for aryl group attack was no longer present.

In an attempt to provide a phenyl group in an appropriate orientation to interact with a bis(μ-oxo)dicopper core, the ligand $PhPyNEt_2$ (Fig. 9) was utilized [18]. This ligand features an arene that can make an extremely close approach to the core and bidentate ligation that should favor bis(μ-oxo)dicopper(III) complex formation. Indeed, oxygenation of the copper(I) complex $[(PhPyNEt_2)Cu(NCCH_3)](SbF_6)$ at $-70°C$ led to formation of the anticipated species with core structure **B**, as shown by the optical absorption (λ_{max} ca. 404 nm), EPR (silent), and resonance Raman (Cu_2O_2 vibration at 607 cm^{-1}) characteristics of the yellow solutions (Table 1). Decomposition of this intermediate and recovery of the ligand showed roughly 30% hydroxylation at the position *ortho* to the pyridine (Fig. 9), the oxygen atom in the product being derived from molecular oxygen as shown from isotope labeling experiments. Kinetic studies of the disappearance of the bis(μ-oxo)dicopper intermediate showed effects similar to that of the system in Ref. [24]: an electron-withdrawing substituent slowed the decomposition substantially, and there was little effect from substituting hydrogen for deuterium in the phenyl ring. Thus, it is evident that when a phenyl group is presented to the bis(μ-oxo)dicopper core in an appropriate orientation, electrophilic attack on the arene π-system can be observed (but see Section 6).

6. Summary and conclusions

Studies of the reactivity of Cu^I complexes with dioxygen have led to the thorough characterization of cores **A** and **B** in synthetic complexes. Through the variation of capping N-donor ligands and examination of effects of solvent, temperature, and counterions, the factors that control the relative stabilization of these cores have begun to be elucidated. These factors are quite subtle in some instances, particularly for the compounds capped by L^{iPr3} where equilibration between cores **A** and **B** wa scharacterized experimentally. Importantly, the identification of the **A**/**B** equilibrium

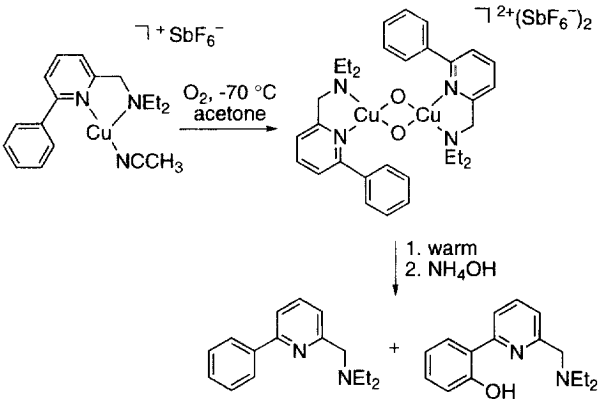


Fig. 9. Hydroxylation of an arene by a bis(μ-oxo)dicopper complex [18].

in synthetic complexes raises the question: Which species is responsible for the C–O formation step in the hydroxylation reaction catalyzed by tyrosinase? At the present time, aromatic hydroxylation reactions have been observed from one bent (μ-η^2:η^2-peroxo)dicopper complex (Fig. 8), one planar (μ-η^2:η^2-peroxo)dicopper complex (with the *m*-XYL ligand), and one bis(μ-oxo)dicopper complex (with the $PhPyNEt_2$ ligand, Fig. 9). Each of the three cores might react directly with aryl groups in different ways; however, because these cores can interconvert with small energetic cost, it is also possible that they all isomerize to one form (which may not have been observed yet!) that is most reactive toward arene π-electrons.

If one isomer is most reactive toward aromatic hydroxylation, which one is it most likely to be? Solomon and coworkers pursued a molecular-orbital analysis of this problem [20], and concluded that the appropriate acceptor orbitals of (μ-η^2:η^2-peroxo)dicopper and bis(μ-oxo)dicopper cores are at similar energies (within 0.4 eV), but that the lesser electron density on oxygen in a (μ-η^2:η^2-peroxo)dicopper complex makes it more likely to display electrophilic reactivity. On the other hand, for the sake of simplicity it is preferable that O–O cleavage should only occur once, and that the bis(μ-oxo)dicopper complexes in Fig. 9 would not reform the O–O bond in order to break it again by reacting with an arene ring. Thus, generalizations are difficult to draw at this point, and only further detailed kinetic, spectroscopic, and reactivity studies will resolve the issue and provide a clear underpinning for mechanistic understanding of arene hydroxylations by Cu/O_2 systems.

Acknowledgements

We thank the contributors to the work described here that are cited in the references; their efforts are greatly appreciated. Financial support was provided by the National Institutes of Health, the National Science Foundation, the Searle Scholars—Chicago Community Trust, the Alfred P. Sloan and Camille & Henry Dreyfus Foundations, and the University of Minnesota.

References

[1] (a) J.T. Groves, Y.-Z. Han, in: P.R. Ortiz de Montellano (Ed.), Cytochrome P450: Stucture, Mechanism and Biochemistry, Plenum Press, New York, 1995. (b) A.L. Feig, S.J. Lippard, Chem. Rev. 94 (1994) 759. (c) L. Que Jr., Y. Dong, Acc. Chem. Res. 29 (1996) 190. (e) K.D. Karlin, S. Kaderli, A.D. Zuberbühler, Acc. Chem. Res. (1997) 139. (f) N. Kitajima, Y. Moro-oka, Chem. Rev. 94 (1994) 737.

[2] (a) K.A. Magnus, H. Ton-That, J.E. Carpenter, Chem. Rev. 94 (1994) 727. (b) K.A. Magnus, B. Hazes, H. Ton-That, C. Bonaventura, J. Bonaventura, W.G.J. Hol, Proteins 19 (1994) 302. (c) M.E. Cuff, K.I. Miller, K.E. van Holde, W.A. Hendrickson, J. Mol. Biol. 278 (1998) 855.

[3] (a) E.I. Solomon, U.M. Sundaram, T.E. Machonkin, Chem. Rev. 96 (1996) 2563. (b) E.I. Solomon, F. Tuczek, D.E. Root, C.A. Brown, Chem. Rev. 94 (1994) 827.

[4] A. Sánchez-Ferrer, J.N. Rodríguez-López, F. García-Cánovas, F. García-Carmona, Biochim. Biophys. Acta 1247 (1995) 1.

[5] (a) C. Eicken, F. Zippel, K. Büldt-Karentzopoulos, B. Krebs, FEBS Lett. 436 (1998) 293. (b) B.

Krebs, in: D.P. Kessissoglou (Ed.), Bioinorganic Chemistry: An Inorganic Perspective of Life, Kluwer Academic, Dordrecht, The Netherlands, 1995.
[6] (a) N. Kitajima, K. Fujisawa, C. Fujimoto, Y. Moro-oka, S. Hashimoto, T. Kitagawa, K. Toriumi, K. Tatsumi, A. Nakamura, J. Am. Chem. Soc. 114 (1992) 1277. (b) M.J. Baldwin, D.E. Root, J.E. Pate, K. Fujisawa, N. Kitajima, E.I. Solomon, J. Am. Chem. Soc. 114 (1992) 10421.
[7] (a) W.E. Lynch, D.M. Kurtz Jr., S. Wang, R.A. Scott, J. Am. Chem. Soc. 116 (1994) 11030. (b) T.N. Sorrell, W.E. Allen, P.S. White, Inorg. Chem. 34 (1995) 952. (c) W.E. Allen, T.N. Sorrell, Inorg. Chem. 36 (1997) 1732. (d) S. Mahapatra, J.A. Halfen, E.C. Wilkinson, L. Que Jr., W.B. Tolman, J. Am. Chem. Soc. 116 (1994) 9785. (e) M.P. Ngwenya, D. Chen, A.E. Martell, J. Reibenspies, Inorg. Chem. 30 (1991) 2732.
[8] W.B. Tolman, Acc. Chem. Res. 30 (1997) 227.
[9] (a) V. Mahadevan, Z. Hou, A.P. Cole, D.E. Root, T.K. Lal, E.I. Solomon, T.D.P. Stack, J. Am. Chem. Soc. 119 (1997) 11996. (b) J.L. DuBois, P. Mukherjee, A.M. Collier, J.M. Mayer, E.I. Solomon, B. Hedman, T.D.P. Stack, K.O. Hodgson, J. Am. Chem. Soc. 119 (1997) 8578.
[10] J.A. Halfen, S. Mahapatra, E.C. Wilkinson, S. Kaderli, V.G. Young Jr., L. Que Jr., A.D. Zuberbühler, W.B. Tolman, Science 271 (1996) 1397.
[11] S. Itoh, H. Nakao, L.M. Berreau, T. Kondo, M. Komatsu, S. Fukuzumi, J. Am. Chem. Soc. 120 (1998) 2890.
[12] P.L. Holland, C.J. Kramer, E.C. Wilkinson, S. Mahapatra, K.R. Rodgers, S. Itoh, M. Taki, S. Fukuzumi, L. Que Jr., W.B. Tolman, unpublished results.
[13] T.C. Brunold, N. Tamura, N. Kitajima, Y. Moro-oka, E.I. Solomon, J. Am. Chem. Soc. 120 (1998) 5674.
[14] S. Mahapatra, J.A. Halfen, E.C. Wilkinson, G. Pan, X. Wang, V.G. Young Jr., C.J. Cramer, L. Que Jr., W.B. Tolman, J. Am. Chem. Soc. 118 (1996) 11555.
[15] S. Mahapatra, V.G. Young Jr., S. Kaderli, A.D. Zuberbühler, W.B. Tolman, Angew. Chem. Int. Ed. Engl. 36 (1997) 130.
[16] (a) C.J. Cramer, B.A. Smith, W.B. Tolman, J. Am. Chem. Soc. 118 (1996) 11283. (b) X.-Y. Liu, A.A. Palacios, J.J. Novoa, S. Alvarez, Inorg. Chem. 37 (1998) 1202. (c) A. Bérces, Inorg. Chem. 36 (1997) 4831.
[17] S. Mahapatra, S. Kaderli, A. Llobet, Y.-M. Neuhold, T. Palanché, J.A. Halfen, V.G. Young Jr., T.A. Kaden, L. Que Jr., A.D. Zuberbühler, W.B. Tolman, Inorg. Chem. 36 (1997) 6343.
[18] P.L. Holland, K.R. Rodgers, W.B. Tolman, Angew. Chem. Int. Ed. Engl. 38 (1999) 1139.
[19] (a) S. Itoh, H. Nakao, S. Fukuzumi, in: Proceedings of the 216th National American Chemical Society Meeting, Boston, MA, August 1998, American Chemical Society, Washington, DC, Abstract # 299. (b) H.V. Obias, Y. Lin, N.N. Murthy, E. Pidcock, E.I. Solomon, M. Ralk, N.J. Blackburn, Y.M. Neuhold, A.D. Zuberbühler, K.D. Karlin, J. Am. Chem. Soc. 120 (1998) 12960. (c) H.V. Obias, Y. Lin, N.N. Murthy, E. Pidcock, E.I. Solomon, M. Ralle, N.J. Blackburn, Y.M. Neubold, A.D. Zuberbühler, K.D. Karlin, J. Am. Chem Soc. 120 (1998) 12960.
[20] E. Pidcock, H.V. Obias, C.X. Zhang, K.D. Karlin, E.I. Solomon, J. Am. Chem. Soc. 120 (1998) 7841–7847.
[21] J. Cahoy, P.L. Holland, W.B. Tolman, Inorg. Chem. 38 (1999) 2161.
[22] C. Reichardt, Solvents and Solvent Effects in Organic Chemistry, 2nd ed., VCH, Weinheim, Germany, 1988.
[23] (a) O.J. Gelling, F. van Bolhuis, A. Meetsma, B.L. Feringa, J. Chem. Soc. Chem. Commun. (1988) 552. (b) M. Réglier, C. Jorand, B. Waegell, J. Chem. Soc. Chem. Commun. (1990) 1752. (c) R. Gupta, R. Mukherjee, Inorg. Chim. Acta 263 (1997) 133. (d) L. Casella, M. Gullotti, G. Pallanza, L. Rigoni, J. Am. Chem. Soc. 110 (1988) 4221. (e) T.N. Sorrell, V.A. Vankai, M.L. Garrity, Inorg. Chem. 30 (1991) 207. (f) T.N. Sorrell, M.L. Garrity, Inorg. Chem. 30 (1991) 210. (g) S. Ryan, H. Adams, D.E. Fenton, M. Becker, S. Schindler, Inorg. Chem. 37 (1998) 2134. (h) G. Alzuet, L. Casella, M.L. Villa, O. Carugo, M. Gullotti, J. Chem. Soc. Dalton Trans. (1997) 4789.
[24] (a) R.W. Cruse, S. Kaderli, K.D. Karlin, A.D. Zuberbühler, J. Am. Chem. Soc. 110 (1988) 6882. (b) K.D. Karlin, M.S. Nasir, B.I. Cohen, R.W. Cruse, S. Kaderli, A.D. Zuberbühler, J. Am. Chem. Soc. 116 (1994) 1324. (c) E. Pidcock, H.V. Obias, M. Abe, H.-C. Liang, K.D. Karlin, E.I. Solomon, J. Am. Chem. Soc. 121 (1999) 1299.
[25] S. Mahapatra, J.A. Halfen, W.B. Tolman, J. Am. Chem. Soc. 118 (1996) 11575.