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OXIDATION CATALYSIS; A DINUCLEAR APPROACH

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Catalytic oxidation mediated by bimetallic complexes is a rapidly expanding area of chemistry due to the potential of multimetal complexes for enhanced reactivity and selectivity compared to mononuclear analogs.¹ A wealth of papers on mononuclear transition metal catalyzed oxidation reactions, using oxygen donors such as alkylhydroperoxides, hydrogen peroxide,² alkaline hypohalides or iodosylbenzene, has been reported in the last decades.³ Important goals of both academic and industrial importance are;

- i. oxidations without the production of stoichiometric amounts of salts and high atom economy conversions.
- ii. direct oxygenation of unfunctionalized hydrocarbons i.e. hydroxylations, although selective epoxidations, dehydrogenations, phenol oxidations, oxidative coupling reactions etc. are also highly warranted.

Much effort is currently devoted to develop useful catalytic systems for mild and selective oxidations with the aid of molecular oxygen.⁴ It is therefore of great interest to elucidate the factors that govern the (reversible) binding and activation of O₂ in various natural oxygen transport systems and mono- and di-oxygenases. It is not surprising that there is a major role for dinuclear copper complexes as model compounds for copper proteins.⁴ Guided by nature intriguing model systems for the active site of copper-containing O₂-binding enzymes such as hemocyanin have been developed.^{5,7} The synthesis and structural characterization of μ -1,2-(**1**) and η^2 : η^2 -(**2**) dioxygen adducts of dinuclear Cu(I) complexes, by Karlin⁶ and Kitajima and co-workers⁷ respectively, illustrate some of the most important achievements.

Figure 1   Dioxygen adducts of dinuclear copper complexes.^{6,7}

From K.D. Karlin and Z. Tyeklár, Eds., *Bioinorganic Chemistry of Copper* (Chapman & Hall, New York, 1993).

Following the pioneering work of Karlin and co-workers⁸ on arene hydroxylation by molecular oxygen in a dinuclear Cu(I) complex several groups⁹⁻¹⁴ have reported on related mimics for copper dependent monooxygenases (Scheme 1).

Scheme 1

Contrary to the successful development of oxidation catalysts based on metalloporphyrins,¹⁵ synthetically useful catalysts, based on copper complexes, that act as mimics for copper containing monooxygenases⁴ (e.g. tyrosinase dopamine- β -hydroxylase) in the oxidation of external substrates are scarce.^{1c,16,17} This is even more surprising if one realizes that selective oxidations of organic substrates mediated by copper complexes have been known over a century.¹⁸ For instance the Glaser oxidative coupling of acetylenes,¹⁹ the oxidative dimerization of naphthols²⁰ and the formation of poly(phenylene ethers) from 2,6-disubstituted phenols²¹ are all based on copper-amine complexes and molecular oxygen.

Considering bimetallic complexes that can act as catalysts for selective oxidations, the effect of the "second metal" in the catalyst complex is proposed to enhance the O₂ binding ability, to assist in oxygen-oxygen, or oxygen-R (R = alkoxide, halide, hydroxide), bond cleavage (as shown in 3) or to interfere with substrate binding (as indicated in 4).

Figure 2 Substrate and/or oxygen-donor activation in dinuclear complexes.

Two approaches for the successful development of a selective oxidation catalyst, using O₂ as the oxidant, can be envisaged;

- i. one oxygen atom of O₂ is incorporated in the substrate as in tyrosinase. These monooxygenases, with two copper ions in the active center, catalyze the incorporation of one oxygen atom into the ortho-position of phenols and an external electron and proton source is required to convert the second oxygen into water. In metalloporphyrin based catalysts this problem is circumvented using "single oxygen" donors or external reducing agents.
- ii. both oxygen atoms of O₂ are used for the oxidation as is the case with dioxygenases.

Both approaches are used in our group employing either homo- or heterodinuclear copper complexes.

In this review recent results of oxygenations with dinuclear Cu complexes will be described with main emphasis on intramolecular oxidation studies of our laboratories.

OXIDATIVE HYDROXYLATION AND METHOXYLATION

As arene hydroxylation (Scheme 1) in dinuclear Cu(I) complexes seems to depend critically on the ligands employed, we studied dinucleating 2,6-bis[N-(2-pyridyl-ethyl)-formimido]benzene (2,6-BPB) type ligands 5, which have bidentate

nitrogen-ligands available for each Cu(I) center in contrast to tridentate bis-(pyridylethyl)amine units present in Karlin's complexes.⁸ Approaches using imidazolyl alkylimine chelating group have been reported by others.^{10,11-14}

Copper(I) complex **6** (scheme 2) is extremely air sensitive in CH_2Cl_2 , CH_3OH or CH_3CN solution and rapidly oxidizes to the hydroxy-phenoxy-bridged Cu(II) complex **8**. X-ray analysis, independent synthesis and analysis of free ligand **9** confirmed the quantitative hydroxylation at the 1-position of the arene-moiety.¹⁰

Scheme 2

A number of dinuclear Cu(II) complexes, structurally related to **8**, have been reported in the literature.²² No epoxidation of external substrates, like olefins, phenols or sulfides, was found using **6** in the presence of molecular oxygen. The mild and rapid arene-oxygenation observed here may be considered a mimic for copper-dependent monooxygenases. It is conceivable that the reaction of **6** with O_2 produces a dioxygen adduct **7** as reversible O_2 binding on dinuclear copper complexes is well precedented.^{5,7,23} Furthermore we have observed reversible O_2 binding in the structurally closely related nitroaryl-substituted Cu(I) complex **10**.²⁴

The results show that arene-hydroxylation with dinuclear Cu(I) complexes and dioxygen is not specific to bidentate or tridentate ligand systems and that O_2 binding is possible with one chelating and one monodentate ligand attached to each Cu(I) center.

Figure 3 Structures of **10** and **11**

It is remarkable that no monooxygenase activity is observed when pyridine is replaced for pyrazole (tridentate) or in some cases benzimidazoles (bidentate). Minor electronic effects but perhaps more important geometrical constraints seem to prevent hydroxylation to occur. This knowledge has been successfully applied by the groups of Waegell and Casella in the design of dinuclear copper complexes for the hydroxylation of exogenous phenols.^{16,17}

In order to get more insight into the reactivity of the Cu(I) complexes and in particular in the dependency of the arene hydroxylation on the substituent pattern different X-substituents (alkoxy, halogen, alkyl) were placed at the arene-1-position in **11** which is most vulnerable to oxygenation (vide infra). Furthermore preliminary investigations show that both O₂-binding and hydroxylation are sensitive to the electronic effects of para-substituents (**11**, Y = OCH₃, CH₃, CO₂CH₃, NO₂).²⁴ When the ligand C-1 position was blocked with a methyl-substituent, as is present in complex **12**, no arene hydroxylation was observed although rapid reaction with molecular oxygen takes place. As the major part of the ligand was recovered unchanged, presumably a bis(μ -hydroxy)dicopper(II) species **13** is formed, as was observed by Sorrell and co-workers²⁵ in the reaction of a related Cu(I) complex with O₂.

Scheme 3

Partial oxygenation of the pyridylethyl unit of the ligand cannot be excluded, however. This result is remarkable in view of the fact that Karlin and co-workers²⁶ found a methyl-migration upon exposure of complex **14** to oxygen (scheme 4) resulting in complex **15**.

Scheme 4

In a different approach the bridging unit between the two Cu(I) centers was modified into a 3,6-disubstituted pyridazine leading to more rigid bis-Cu(I) complexes. Dinuclear Cu(I) complexes **17**, with both 5,5- and 5,6-chelate ring sizes, were obtained from ligand **16**. Although reversible oxygen binding to **17** was not observed, rapid oxidation and formation of H₂O₂ was found upon exposure to the air. The nature of the oxidation products has not been unraveled so far. Using

dinuclear Cu(II) complex **18** a remarkable bis- α -methoxylation at the benzylic positions, with incorporation of two methoxy-substituents from the solvent, was found.

Scheme 5

Removal of the copper ions after the oxidation reaction provided bis-methoxylated product **23** in nearly quantitative yield²⁷ (scheme 6). Hydroxylation at the benzylic position followed by H₂O elimination to acylimine intermediate **19**

Scheme 6

could be envisaged but we prefer to rationalize the methoxylation via the mechanism outlined in scheme 6. The consecutive conversions involve electron transfer to Cu(II) and deprotonation to yield acylimine bound Cu(I) complex 19 which adds either methoxide or methanol. Reoxidation of the Cu(I) centers in 20 to Cu(II) by O₂ and repetition of the cycle provides bis-methoxylated product 23 (isolated after ammonia treatment). It is intriguing that selective dimethoxylation takes place under mild conditions in particular when compared to the more severe conditions in copper-mediated α -hydroxylation of N-salicyloyl-glycine.²⁸ Further mechanistic studies will be necessary, as well as assessment of the potential of this type of conversion for selective amine α -oxidation as an alternative to electrochemical methods²⁹ and the relevance for peptidylglycine- α -hydroxylating monooxygenase (PHM) mimics. Related oxidative pathways have been found in copper-mediated N-dealkylation of peptide ligands in the presence of oxygen. Finally similar ligand oxidations might occur upon reaction of 17 with O₂.

An important observation was made when complex 18 was used in the oxidative coupling of 2,6-dimethylphenol 24. Several studies with in situ prepared Cu(II) catalysts for the PPO (25) formation have pointed to the involvement of dinuclear Cu(II) complexes in the crucial C-O coupling step, whereas PPQ formation is propose to be due to mononuclear complexes.³¹ Under basic conditions dinuclear complex 18 is not only catalytically active for PPO formation but more important only 0.14% of quinone was found. The modest yields of polymer sofar are presumably due to competing ligand methoxylation.

Scheme 7

These results experimentally confirm earlier proposals concerning activity and selectivity of dinuclear Cu(II) complexes in the formation of this important engineering polymer.

SELF-ASSEMBLY OF A HELICAL POLYNUCLEAR COPPER(I) COMPLEX

The design of self-assembling (supra)molecular structures is currently extensively studied and an important role for molecular helicity based on copper complexes has been revealed.

Using oligopyridines as ligands, spontaneous assembly of double helical polynuclear metal complexes has been demonstrated. Thus ligands with two to five 2,2'-bipyridine units separated by oxapropylene spacers form double helical Cu(I)-complexes³² whereas similar molecular topology was observed with Ni(II), Pd(II), Cd(II) and Cu(I) complexes of various oligopyridines.³³ When the 1-methoxy-substituted ligand 2,6-bis(N-(2-pyridylethyl)formimidoyl)-1-methoxybenzene (2,6-BPB-1-OCH₃, 26) was allowed to react with two equivalents of Cu(MeCN)₄BF₄ "chameleon-like" complexation behavior was observed (scheme 8). Dinuclear complexes 27a-27c are formed strongly dependent upon the amount of MeCN present. Acetonitrile complexation is reversible as heating of 27a at reflux in CH₂Cl₂ provided the acetonitrile free complex 27c whereas addition of 4 equivalents of MeCN reconverted it into 27a. Additions of excess (>10 equiv.) of MeCN to a solution of 27c in CHCl₃ provided, besides equimolar amounts of Cu(MeCN)₄BF₄, polynuclear Cu(I) complex 28.³⁴

Scheme 8

The X-ray structure (figure 4) clearly shows that each Cu(I) atom is four-coordinated with two pyridylethylimine bidentate units from different ligands in a tetrahedral geometry.

Figure 4 Molecular structure of **28** and schematic representation of the helical structure of polynuclear Cu(I) complexes

In the linear Cu(I) coordination polymer two helices are found; single stranded one of which is left handed and the other right handed with the methoxy-substituents pointing outside the helix. A comparison with the Cu(I) coordinated double stranded helicates described by Lehn and co-workers³⁵ is schematically shown (figure 4).

The ability of ligands such as 26 to assemble in the presence of Cu(I) to single stranded helical complexes offers intriguing possibilities in the area of supramolecular copper-mediated catalysis. Furthermore these complexes are still very reactive towards molecular oxygen, although initial dissociation to mono- and oligo-nuclear complexes might be essential for their reactivity.

OXIDATIVE DEMETHYLATION AND DEHALOGENATION

Various enzymes including P450 dependent monooxygenases^{36,37} ω -hydroxylases and ligninase³⁸ are known to catalyze the oxidative demethylation of arylethers. Model studies to elucidate mechanistic features as well as the development of catalysts for mild (oxidative) demethylation have been undertaken.

For this purpose 1-methoxy-substituted dinuclear Cu(I) complexes 29 and 30, which bear close structural analogies to complexes 6 and 12, were investigated.

Scheme 9

In the presence of molecular oxygen the complex Cu₂(2,6-BPB-1-OMe) 29 rapidly oxidizes to 31, with a stoichiometry of O₂ uptake; Cu:O₂ = 2:1. An oxygen-induced demethylation of the anisole moiety takes place.¹⁸ O-labeling experiments support *dual pathways* with at least 60% aryl-oxygen and approximately 20% alkyl-oxygen bond cleavage; both leading to the same phenoxy-hydroxy-bridged dinuclear Cu(II) complex 31. In the *first route* an oxidative demethoxylation takes place (CH₃OH is liberated) whereas in the *second and minor route* oxidative demethylation occurs with the formation of formaldehyde. Although the nature of the intermediates in the oxidative demethylation (demethoxylation) is still unknown, the overall conversion is reminiscent of the arene-hydroxylations following O₂ binding, reported previously. A possible mechanistic pathway is given in scheme 10. Initial (reversible) oxygen binding to form 33 is followed by nucleophilic attack of the peroxodicopper(II) at the arene-1-position. Enhanced Lewis acidity in Cu(II) complex 33 and the presence of the 2,6-imine substituents make the arene moiety more vulnerable for nucleophilic attack. It has been proposed^{23,26} that in the related arene-hydroxylations the peroxodicopper(II) entity is electrophilic in nature but it should be noted that the presence of electron withdrawing substituents and the ligating group might alter the mode of reaction in these types of complexes. The *major route* for the O₂-induced demethylation then proceeds via ipso-attack of the copper(II) peroxy species to form 35. Subsequent fragmentation and methoxide elimination from 35 results in phenoxy bridged complex 31. Consistent

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with the proposal is the slower ipso-oxidation of the more electron rich p-OCH₃ complex 30 as a result of the decreased rate of nucleophilic attack.

Scheme 10

The general accepted mechanism for demethylations based on cytochrome P450 dependent monooxygenases involves α -hydroxylation to a hemiacetal followed by fragmentation to phenol and carbonyl compounds, although other pathways have been suggested (scheme 11).³⁹

Scheme 11

The formation of 31 and formaldehyde (*minor route*) is reminiscent of such a demethylation mechanism. Furthermore an intriguing OCH₃, OCD₃ exchange was observed in complex 30 under ambient conditions in the presence of oxygen. Exclusive exchange at the 1-position, with the formation of 4-CH₃O-2,6-BPB-1-OCH₃ and 4-CH₃O-2,6-BPB-1-OCD₃ in a 1:1 ratio as well as the essential role of O₂ in the exchange process strongly point to the involvement of complex 37. Instead of attack of the peroxo-copper moiety (as in 35) ipso attack of deuteromethoxide has taken place and subsequent fragmentation provides 30 (1-OCH₃) or 38 (1-OCD₃). The significance of the experimental conditions (1h, 25 °C, CH₂Cl₂, CD₃OD 40:1 ratio) should be emphasized as generally Lewis acids or more severe conditions are essential to demethylate methoxy substituted arenes. The remarkable methoxide exchange further supports a nucleophilic mechanism. These experimental results indicate furthermore that electrophilic attack of peroxo-dicopper(II) might not be an exclusive pathway in arene hydroxylations.⁴⁰

If the dinuclear copper complexes, described here, are capable of demethoxylating anisole-moieties in the presence of O₂, it is conceivable that oxidative dehalogenation is also possible. Oxidative dechlorination during a

intramolecular hydroxylation reaction mediated by a dinuclear copper complex was reported by Karlin.⁴¹ A competing pathway to a dihydroxydicopper(II) complex was also observed, whereas highest yields of dechlorinated products were found in the presence of Zn as reductant.

Scheme 12

Dehalogenation reactions are catalyzed by various enzymes using hydrolytic, reductive or oxidative pathways.⁴² However, few enzymes are capable of oxidative dehalogenation of aromatic compounds. For instance phenylalanine hydroxylase (PAH, iron dependent) is known to defluorinate 4-fluoro-phenylalanine and converts a 4-chloro-phenylalanine to tyrosine (dechlorination) in the presence of O_2 . A bacterial copper-dependent phenylalanine hydroxylase is also known. When dinuclear copper(I) complex **40**, readily obtained from 1-bromo-substituted ligand **39**, was allowed to react with O_2 at room temperature, high yields (80%) of dinuclear Cu(II) complex **31** were obtained.⁴³ Analysis for bromide showed 72% of the theoretical amount of Br^- . In close analogy to Karlin's and our own observations with copper complexes showing monooxygenase activity is not too fetched to suggest formation of a $[\text{Cu}_2\text{O}_2]^{2+}$ complex **41** presumably followed by ipso-substitution to **42** and fragmentation with simultaneous Br^- elimination (scheme 13).

Scheme 13

Alternatively BrO^- might be formed initially with subsequent decomposition into Br^- and H_2O . It should be emphasized that an overall oxidative hydroxylation-debromination has taken place under mild conditions, i.e. room temperature and molecular oxygen. These copper containing systems can be considered interesting models to study the mechanism of metal-dependent oxidative dehalogenating enzymes.

CATALYTIC DEHYDROGENATION

During catalysis by monooxygenases, like tyrosinase, the incorporation of one oxygen atom into the ortho-position of phenols is accompanied by the formation of water involving an external electron- and proton-source. In an approach to design catalytically active complexes which could mimic tyrosinase, a copper(I)-copper(II) redox couple and a hydroquinone-quinone redox couple are incorporated in one system (scheme 14). The hydroquinone moiety should act as an electron shunt between an external reducing agent and the copper ions. As the aromatic nucleus is already hydroxylated, it might be expected that, after activation of O_2 either as a superoxo- or μ -peroxo-di-copper(II) intermediate, oxidation of an external substrate can occur.

Scheme 14

This event then leads to a hydroquinone and hydroxy-bridged dinuclear Cu(II) complex 45 and an oxygenated substrate. It can be expected that the hydroquinone bridged complex 45 undergoes an internal electron transfer process to form a quinone-di- Cu(I) complex 46. Reduction of the quinone to the hydroquinone 43 via external reducing agents, i.e. ascorbic acid, zinc or by using electrochemical methods will complete the catalytic cycle. The electron-transfer system envisaged here is reminiscent of the quinone-based systems as found in the primary photochemical step in the bacterial photosynthesis⁴⁴ and in synthetic (metallo)porphyrin-quinone electron transfer systems.⁴⁵

In order to form dinuclear copper complexes in which a hydroquinone (quinone) moiety is incorporated the new ligand 1,3-bis[N-2-(2'-pyridylethyl)-formimidoyl]-2,5-dihydroxybenzene 47 was prepared via a multistep route (scheme 15).⁴⁶ Dinuclear Cu(II) complex 48 was obtained by reaction of the bisodium

salt of 47 with $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$.

Scheme 15

Conclusive evidence for the presence of the hydroquinone and not a quinone moiety in 48 was obtained by X-ray structural analysis (figure 5).

Figure 5 Molecular structure of 48 (counter ions are omitted for clarity).

It is remarkable, and in contrast to expectation, that the hydroquinone unit in 48 is not oxidized to the corresponding quinone. Although the hydroquinone is ideally situated for electron transfer to the copper ions, this does not readily take place even in the presence of molecular oxygen. It has been suggested for related nickel complexes⁴⁷ that despite the fact that the metal ion acts as an electron sink, back-donation of electrons to the coordinated quinone might take place, strongly depending upon the redox potential of the quinone and metal and the quinone π -orbital and metal d-orbital levels. Cyclic voltametric studies under various conditions did not reveal reversible oxidation reduction patterns. As the hydroquinone oxidation in 48 does not take place a catalytic cycle as shown in scheme 14 is not feasible with the present system. Appropriate modifications in ligand 47 and complexes thereof that fulfill the requirements mentioned earlier might be obtained by reduction of the imine-functionality. It is expected that 2,6-dialkylamine-substituents will lower the oxidation potential sufficient for the quinone formation to occur. Such studies are currently in progress.

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Considering the resistance towards "internal" oxidation it is even more remarkable that dinuclear copper complex 48 is an excellent catalyst for the oxidation of "external" hydroquinones to quinones and α -hydroxyketones to diketones using O_2 as the oxidant (illustrated in scheme 16).

Scheme 16

Apparently the two-electron withdrawing imine substituents present in 47 sufficient increase the oxidation potential of the hydroquinone moiety to prevent intramolecular electron transfer to the Cu(II) ions. However, fast intermolecular electron transfer from 49 (or 51) apparently can take place. The stoichiometry with respect to substrate, base and O_2 , and the proposed consecutive binding of phenolate and oxygen in binuclear Cu(II) complexes in the first step in catalytic phenol oxidations (vide supra) suggest the following mechanistic scheme (scheme 17). Substrate binding to 53 will be followed by two-electron transfer to yield a binuclear Cu(I) complex and subsequent O_2 binding will provide 54.

Scheme 17

As addition of base is essential for the oxidation to occur deprotonation of the substrate (ROH) either before or after binding to the copper ions presumably takes place. Alter-native mechanisms as shown in scheme 17 can be proposed; for instance a redox reaction of complex 54 with deprotonated substrate is an attractive possibility.

It should be emphasized that 1 mol of O₂/mol of substrate is consumed, indicating a two-electron transfer process contrary to four electron processes that lead to H₂O as was observed in oxidative phenol coupling³¹ mediated by Cu(II) complexes. Furthermore, complex 48 catalyzes effectively the decomposition of H₂O₂ formed.

No oxygenation was achieved sofar with dinuclear hydroquinone complexes presented here as well as some structural analogs. The presence of a hydroquinone (or phenol) moiety in the ligands described here is only essential for bridging the Cu(II) ions but has as far as experimental evidence goes no role in the redox processes.

CHIRAL DINUCLEAR COPPER COMPLEXES

Besides mimicking monooxygenase activity and the important goal to achieve intermolecular oxidations of a variety of substrates with molecular oxygen a fascinating aspect is the use of chiral copper complexes for enantioselective oxidations. Enantioselective epoxidations using the Sharpless^{1a} and Jacobsen⁴⁸ procedures as well as epoxidations with chiral metallo-porphyrin enzyme mimics⁴⁹ are the most prominent examples of oxidations mediated by chiral metal complexes. Chiral dinuclear copper complexes have sofar been unexplored for these purposes, although based on the oxygenation activity of several copper complexes interesting properties in stereoselective oxidations can be expected. Starting from (S)-proline 55 the enantiomerically pure pentadentate ligand 56 was obtained in a multistep route. Reaction of 56 with Cu(ClO₄)₂ provided the phenoxy-hydroxy-bridged complex 57 with slightly distorted square planar geometry around each Cu(II) ion and a normal Cu-Cu separation of 2.971(3) Å. In accordance with a C₂-symmetric complex a trans-orientation of the N-benzyl-groups is found in 57.

Scheme 18

Reaction of ligand 56 with $\text{Cu}(\text{OAc})_2$ followed by treatment with NaClO_4 resulted in dinuclear copper complex 58. The molecular structure (figure 6) clearly shows the C_2 - symmetry in the chiral complex with a less common bis(μ -acetato)- and phenoxo-bridges. A square-pyramidal arrangement around each $\text{Cu}(\text{II})$ ion and a Cu-Cu distance of 3.296(1) Å, typically for μ -phenoxo-bis(μ -acetato) bridged dinuclear metal complexes (i.e. Fe, Mn), is observed.⁵⁰

Figure 6 Molecular structure of 58 (counter ions are omitted for clarity).

In a further extension towards chiral dinuclear copper complexes with chiral clefts additional coordinating ligands were introduced (schematically shown in figure 7).

Figure 7 Additional coordinating ligand in a C_2 -symmetric dinuclear complex.

As the N-benzyl moieties in complex 57 and 58 are rather flexible replacement of the benzyl groups by additional ligands will enforce binding in a C_2 -symmetric arrangement. Higher selectivity during the approach of a prochiral substrate to the sterically more crowded and more rigid copper-centers can be expected.

Scheme 19

Starting with (S)-prolinamide **59** the multidentate C_2 -symmetric ligand **60** was prepared in several steps. Both dinuclear Cu(II)- and Ni(II)-complexes were obtained with penta coordination around each metal ion. The molecular structure obtained for the dinuclear Ni(II) complex by X-ray analysis nicely illustrates the distorted square pyramidal arrangement (figure 8).

Figure 8 Molecular structure of dinuclear Ni(II) complex of **60** (counter ions are omitted for clarity).

Furthermore the C_2 -symmetry with trans-orientation of the ligating pyridyl-ethyl moieties is clearly shown. The synthesis and structural analysis of these chiral dinuclear copper complexes clearly demonstrates that well defined geometries, with asymmetric environments around the metal centers, can be generated. In our view the approach via these new types of chiral ligands hold promise to develop future enantioselective oxidation catalysts.

CONCLUDING REMARKS

The design and synthesis of dinuclear copper complexes, with well defined geometries, offer exciting possibilities to elucidate structure-reactivity patterns in oxidations with molecular oxygen as well as to achieve effective mimics of oxygenating enzymes. It has been demonstrated that, strictly depending upon the nature of the ligands, arene-hydroxylation, demethoxylation and demethylation of anisole moieties, oxidative methoxylation, dehalogenation and phenol coupling reactions can be mediated by dinuclear copper complexes in the presence of O_2 as the oxidant. From the various studies from our group and others on the reactivity of dinuclear copper complexes in the presence of molecular oxygen it is clear that the rates and the type of oxygenation reaction are governed by i.e. electronic effects of the ligand substituents, geometrical constraints enforced by the ligand, redox-potentials of the dinuclear copper site and the substrates, medium effects and presumably also the nature of the dicopperperoxo-species.

Apparently minor differences in steric (or electronic) effects of the dinucleating ligands and "protection" of ligand positions prone to oxygenation with

inert substituents can direct the oxygenation from an intramolecular to intermolecular mode. Furthermore oxygenations which usually require rather enforced conditions i.e. oxidative dehalogenation, hydroxylations and oxidative demethoxylation can be performed at room temperature with O₂. Although mainly intramolecular reactions were successful so far with dinuclear copper complexes and O₂ the findings above clearly indicate that a wide range of selective intermolecular substrate oxygenations should be possible, provided we are able to achieve the proper ligand framework for the dinuclear copper center. As several key features for O₂ binding and activation are now known it will be essential to study effective (and cheap) procedures for the oxygenation and simultaneous reduction of the "second" oxygen to water in order to arrive at catalytic processes. We are even further challenged by the design of chiral dinuclear copper complexes for enantioselective and catalytic oxygenations with molecular oxygen.

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