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SELF-ASSEMBLY OF MONO- AND DINUCLEAR METAL COMPLEXES; OXIDATION CATALYSIS AND METALLOENZYME MODELS

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ABSTRACT. In this chapter several approaches to achieve assembly of mono- and dinuclear metal complexes, which can be considered structural and functional models for metalloenzymes, are described. The emphasis lies on oxidation chemistry, summarizing O₂ binding, hydroxylation, demethylation, dehalogenation and dehydrogenation. Furthermore self-assembly of chiral mono- and dinuclear complexes is illustrated.

1. Introduction

Nature has provided a plethora of self-assembled mono- and multinuclear metalloproteins. At the heart of the supramolecular assemblies are the active site structures situated, which involve metal ion coordination by a variety of ligands. In recent years we have seen a tremendous activity towards synthesis of metal containing molecules that resemble the active sites of metalloproteins.¹ It is essential that key features of the metal coordination sites and their physical (spectroscopic) properties are present in these structural mimics. A second aspect is the design of multidentate ligand systems, which upon metal binding, preorganize for selective recognition and binding of substrate molecules.² More recently increased emphasis has been on functional modeling of metalloenzymes, in order to unravel the molecular mechanisms of catalysis. This information can be used in the design of new synthetic catalysts.^{1,3,4} This chapter focuses on oxidation chemistry summarizing both structural and functional models for mono- and dinuclear metalloenzymes as well as new oxidation catalysts. The activation of dioxygen in biological systems is intriguing in particular with respect to selective oxygenation of arenes, alkanes and alkenes (scheme 1).^{3,5}

scheme 1

The development of efficient catalysts for such processes is highly warranted with major goals⁶ being:

1. oxidations without the production of stoichiometric amounts of salts and high atom economy conversions.
2. direct oxygenations of hydrocarbons, i.e. hydroxylation and epoxidation.

The efficiency and selectivity of enzymes,^{1,3} i.e. tyrosinase, Cytochrome P-450 or methane monooxygenase, in these oxygenations offer a challenge to mimic the catalytically active metal site and to design self-assembling supramolecular coordination complexes. Besides mimicking monooxygenase activity a fascinating aspect is the design of chiral complexes for enantioselective catalysis.⁷ Prominent examples of oxidations mediated by chiral metal complexes are the enantioselective epoxidation of alkenes using the titanium tartrate based catalyst developed by Sharpless *et al.*⁸ and the metallo-porphyrin enzyme mimic designed by Groves and co-workers⁹ (figure 1). In the Sharpless system self assembly of a chiral dinuclear titanium(IV) complex **1** results in a highly enantioselective catalyst for the formation of epoxides of homoallyl alcohols. Preorganization of a porphyrin with chiral appendages leads, upon binding of iron(III), to catalyst **2** which epoxidizes unfunctionalized olefins with modest enantioselectivities.

figure 1

We will show that metal coordination, both in mono- and dinucleating ligand systems can enforce chiral cleft formation. A summary of approaches towards O₂-binding and activation, catalytic oxygenations and self-assembly of dinuclear and chiral oxidation catalysts is presented.

2. Dioxygen binding to dinuclear copper and iron complexes

An important aspect of dioxygen metabolism is the reversible binding and activation of O₂ on heme-¹⁰ and non-heme-iron¹¹ and copper^{12,13,14} proteins. Hemocyanins (scheme 2) are dinuclear copper containing proteins used in anthropods and molluscs for O₂-transport. The X-ray structure of the deoxy-form of spiny lobster hemocyanin¹⁵ revealed a dinuclear copper(I) binding site (Cu-Cu distance 3.5-3.6 Å). Each copper ion is coordinated tightly by two imidazole ligands (Cu-N ≈ 1.96 Å) and one more weakly bound imidazole ligand (Cu-N ≈ 2.5 Å).

scheme 2

Although various binding modes of O_2 to dicopper centers were proposed based on extensive spectroscopic analysis of oxyhemocyanin and synthetic analogues,¹⁴ it was not until recently that an X-ray analysis of the oxyhemocyanin of the horseshoe crab (*limulus polyphemus*) revealed the true O_2 -binding mode being a $\mu\text{-}\eta^2\text{:}\eta^2$ coordination at the peroxo-dicopper(II) center **4**.¹⁶ It is remarkable to note that this *side-on* O_2 -coordination was proposed only following the X-ray characterization by Kitajima and co-workers¹⁷ in 1989 of the dicopper(II)peroxo model complex **5** ($\text{Cu}[\text{hydrotris-}((3,5\text{-diisopropyl-1-pyrazoyl})\text{borate})_2(\text{O}_2)]$) (Cu-Cu distance 3.56 Å, O-O distance 1.41 Å) with similar properties as observed in oxyhemocyanin. Following the early report by Karlin¹⁸ on reversible O_2 -binding with complex **6**, presumably involving unsymmetrical coordinated dioxygen (end-on peroxo intermediate), various reversible $[\text{Cu}_2\text{O}_2]$ -species have been described.^{12,19}

Generally a multidentate ligand is designed that upon binding of two copper(I) atoms and O_2 assembles into a macrocyclic $[\text{Cu}_2\text{O}_2]$ -complex (scheme 3a). Alternatively a preorganized dinuclear metallomacrocycle can reversibly bind O_2 (scheme 3b).

scheme 3

Typical examples, employing two bis(2-(2-pyridylethyl)amine) units linked through a hydrocarbon spacer **7** (Karlin *et al.*)²⁰ or dinucleating 2,6-bis(N-(2-pyridylethyl)-formimidoyl)arene type ligands **9** (Feringa *et al.*)²¹ are shown in scheme 4.

scheme 4 (py = 2-pyridyl)

Dioxygen binding in a dinuclear copper(I)-complex, based on a macrocyclic tetra Schiff base ligand **11**, was reported by Martell and co-workers²² (scheme 5).

scheme 5

It should be noted that O_2 -binding mode, stability, reversibility and oxygenation activity strongly depend on ligand properties. In order to bind O_2 geometrical constraints seem to be most important and a dinuclear (macrocyclic) copper system is not required. This is clearly illustrated in structure **5**¹⁷ ($\mu-\eta^2:\eta^2-O_2$ binding) and the first characterized Cu_2O_2 structure **13**²³ (a *trans*- μ -1,2-peroxo complex). In both cases association of two mononuclear copper(I) centers takes place. These functional mimics of O_2 activating systems provide the key information for further design of dinuclear copper complexes with oxygenase activity.

Dinuclear iron metalloproteins^{3,11} have a diversity of functions in nature, i.e. reversible O_2 -binding (hemerythrin), DNA synthesis (ribonucleotide reductase) and alkane hydroxylation (methane monooxygenase). The iron atoms are bridged by oxo (O^{2-}), hydroxo (OH^-) or carboxylato (RCO_2^-) groups, whereas protein derived ligands terminally coordinate to the iron centers. The bridging μ -oxo-bis- μ -carboxylato-diiron(III) core, for instance found in the oxidized form of hemerythrin, was assembled using tris(pyridazolyl)borate ($HBpz_3$) or TACN ligands as is shown in complexes **14** and **15** described by the groups of Wieghardt²⁴ and Lippard.²⁵

figure 3

Hemerythrin, the O_2 -transport protein in marine invertebrates contains a dinuclear iron(II) binding site ($Fe-Fe$ distance 3.2 Å), with bridging hydroxo and μ -carboxylato groups. X-ray analyses²⁶ of the non oxygenated and oxygenated forms revealed two distinct iron centers and the formation of a hydroperoxo-dinuclear iron(III) complex **17** upon O_2 binding to the pentacoordinated $Fe(II)$ center in **16** (scheme 6).

scheme 6

Dinuclear iron(II) model complexes for the deoxyhemerythrin active site have been structurally characterized. i.e. $[Fe_2(OH)(OAc)_2L_2]^+$ with $L = TACN, Me_3TACN$ ²⁷ and $Fe_2(BiPhMe)_2(O_2CH)_4$.²⁸ The latter complex contains a $(\mu$ -formato-O)-bis(formato-O,O'-formato)diiron core with a six coordinate and a five coordinate iron center as present in deoxyhemerythrin **16**. Oxygen binding has been reported for both mononuclear and

dinuclear iron(II) complexes. Six coordinated complex **18** (Fe(Obz)(MeCN)(HB(3,5-*i*Pr₂pz)₃)²⁹ binds O₂ reversible at -20 °C, presumably *via* loss of acetonitrile (scheme 7a). In the second case (complex **19**) dinucleating ligand N,N,N',N'-tetrakis(2-benzimidazoymethyl)-1,3-diamino-2-propanol was employed to achieve the μ -alkoxy- μ -carboxylate diiron core.³⁰ The alkoxy-carboxylate bridged five coordinated iron(II) complex **19** binds O₂ irreversibly at -60 °C. Based on spectroscopic data a symmetric μ -1,2-peroxide structure **20** is proposed (scheme 7b).

scheme 7

With the purpose to design alkoxy bridged dinuclear metal complexes in which the presence of five and six coordinated metal centers is enforced by the ligand in the assembly process, new routes to multidentate ligands were developed.³¹ The first method (scheme 8) is based on sequential aromatic Mannich reactions of para-substituted phenols. In this way dinucleating ligand **22**, which can bind two metal atoms in chemical or geometrical distinct environments, is accessible.

scheme 8

In the second approach (scheme 9), a Mannich condensation on a substituted salicylaldehyde is followed by a two step or a single step reductive amination. Both yields and flexibility towards a diversity of non symmetric dinucleating ligands, such as **26** and **27**, are greatly improved.

scheme 9

As expected, assembly of the phenolate-bridged non-symmetric dinuclear metal core readily takes place, as is illustrated for the dicopper(II) complex **28** (figure 4).³²

figure 4

Although iron binding to these ligands readily takes place definite proof for dinuclear iron(II) sites with different coordination spheres awaits further structural characterization. We need to emphasize that symmetrical ligands can also enforce non-symmetric coordination geometries on the dinuclear centers.³³ A pertinent example is the dinickel complex **29**,³⁴ based on 2,6-bis(N-2-(2'-pyridylethyl)formido)-1-hydroxybenzene as a dinucleating ligand. In the latter case a remarkable difference in coordination of the two acetate groups is observed as well as methanol binding to one of the nickel centers.

3. Oxygenation, a dinuclear approach

3.1 HYDROXYLATION

Tyrosinase is a dinuclear copper monooxygenase which catalyzes the *ortho*-hydroxylation of phenols to catechols (scheme 10).³⁵

scheme 10

Following the pioneering work of Karlin and co-workers³⁶ on arene hydroxylation in a dinuclear copper(I)-complex, a number of related mimics for copper dependent monooxygenases have been developed.^{21,37,38,39,40,41} C-H activation of xyl-yl-moieties was achieved with dinucleating ligands, with either bidentate or tridentate units available for each copper(I) center, as is seen in complexes **10**²¹ and **32**³⁶ (scheme 11). Rapid reversible O₂ binding under mild conditions (1 atm, rt), is followed by quantitative hydroxylation at the 1-position of the arene moiety, resulting in hydroxy phenoxy bridged copper(II) complexes **33** and **34**.

scheme 11

X-ray analysis of both copper(I) (e.g. **9**) and copper(II) complexes, independent synthesis, and ammonolysis to the free ligands **35** and **36**, confirmed the hydroxylation pathway.^{19,21,42} O₂-binding and hydroxylation in complex **10** were shown to be sensitive to electronic effects of the para-substituent (X = OMe, Me, CO₂Me, NO₂).²¹ Tyrosinase, which contains a dinuclear copper active site strongly resembling the hemocyanine active site, binds O₂ reversibly and activates O₂ for arene hydroxylation (stoichiometry Cu : O₂ = 2 : 1).⁴² These are key features observed in the dinuclear copper complexes shown in scheme 11, which can be considered functional mimics for tyrosinase. It is intriguing to unravel the mechanism(s) of the oxygen insertion under mild conditions into unactivated C-H bonds. A key feature is the positioning of the peroxo-group in a very favourable position to the arene C-H group. Furthermore, the nature of the Cu₂O₂-moiety apparently strongly depends on the ligand environment. Reactivity studies revealed that *side-on* peroxo-dicopper complexes behave as electrophilic peroxides whereas *end-on* peroxo-dicopper complexes show nucleophilic reactivity (figure 5).^{19,42}

figure 5

Hydrogen peroxide formation upon protonation and oxidative demethoxylation or dehalogenation reactions (see following section), support the nucleophilic nature of *end-on* Cu_2O_2 -complexes. Oxygenation of triphenylphosphine supports electrophilic reactivity of *side-on* Cu_2O_2 -complexes. Further mechanistic information was obtained from oxygenation experiments with a methyl-substituent placed in the arene-1-position, e.g. **37** ($\text{R} = \text{Me}$) and **38** ($\text{R} = \text{Me}$), emphasizing the sensitivity of the Cu_2O_2 -reactivity for ligand effects. Although rapid O_2 -uptake (to form **37**) was observed in the first case, no hydroxylation was found. Apparently four-electron reduction to bis(μ -hydroxy)dicopper(II) complexes **39** takes place; a reaction path also found by Sorrell *et al.*⁴³ in related copper(I) complexes.

figure 6

However, Karlin *et al.*⁴⁴ found arene hydroxylation in **38** ($\text{R} = \text{Me}$), which is accompanied by 1,2-migration of the methyl group. Apparently attack of an electrophilic μ - η^2 - η^2 peroxo moiety on the arene 1-position to yield **40**, is followed by deprotonation to **34** (in the case of $\text{R} = \text{H}$), or methyl migration and fragmentation to form **41** (in the case of $\text{R} = \text{Me}$). The electrophilic process in **38** is strongly reminiscent of the "NIH-shift" mechanism.¹⁹ It is remarkable that no monooxygenase activity is observed with dinuclear copper(I) complexes such as **7** and **9**, when pyridine is replaced for pyrazole (tridentate) or (benz)imidazole (bidentate).^{37,41} Minor electronic effects, but perhaps more important geometrical constraints seem to prevent hydroxylation. This knowledge has been successfully applied by the groups of Waegell⁴¹ and Casella³⁷ in the design of dinuclear copper complexes for the hydroxylation of exogeneous phenols. For instance methyl-4-hydroxybenzoate was oxygenated to catechol **44**, employing the copper(I) complex of ligand **42** (scheme 12).

scheme12

In a different approach,⁴² as shown with ligand **45**, we modified the bridging unit between the two copper(I) centers into a 3,6-disubstituted pyridazine. Although reversible O₂-binding has not been observed, rapid oxidation and formation of H₂O₂ were found upon exposure to air. Dinuclear copper(II) complex **46** undergoes a remarkable quantitative bis- α -methoxylation at the benzylic positions, with incorporation of two methoxy substituents from the solvent.

figure 7

Benzylic hydroxylation, analogous to the oxygenations described above, followed by water elimination and subsequent methanol addition to the resulting acyl imine could be envisaged. We propose the formation of dinuclear copper(I) complex **47**. Subsequent steps from **46** involve electron transfer to copper(II), deprotonation to acyl imine and methanol addition to provide **47**. This is followed by reoxidation to a dicopper(II) complex with O₂ and repetition of the cycle to provide bismethoxylated ligand **48** (after removal of copper(II)). Related oxidative pathways have been found in copper mediated N-dealkylation of peptide ligands in the presence of oxygen.⁴⁵ The relevance of these oxygenations for peptidylglycine- α -hydroxylating monooxygenase (PHM mimics) has to be examined further.

3.2 DEMETHYLATION, DEHALOGENATION AND DEHYDROGENATION

The use of ligand systems, which allow for synergetic action of the metal centers, provides a valuable tool to study such delicate mechanisms as the binding and activation of small molecules on dinuclear metal sites. Systematic ligand variation can reveal effects of active site environment on substrate recognition and binding. The knowledge how O_2 can be activated forms a basis for the development of new catalysts for mild and selective oxidation processes.

Various enzymes including P-450 dependent monooxygenases,⁴⁶ ω -hydroxylases and ligninases⁴⁷ are known to catalyze demethylation of aryl ethers. The general accepted mechanism for demethylation with Cytochrome P-450 dependent monooxygenase involves α -hydroxylation to a hemiacetal, as shown in scheme 13, although other pathways have been suggested.⁴⁸

scheme 13

To increase our understanding of oxidative demethylation processes dinuclear copper(I) complexes **49** $Cu_2(2,6-BPB-1-OMe)$ and **50** were investigated. In the presence of O_2 complex **49** rapidly oxidizes to **33** (a, X = H) with a stoichiometry of $Cu : O_2 = 2 : 1$. An oxygen induced demethylation of the anisole moiety takes place. ^{18}O -Isotope labelling experiments with ^{18}O -ligands and $^{18}O_2$ support *dual pathways*, with at least 60% aryl-oxygen bond cleavage and approximately 20% alkyl-oxygen bond cleavage. Both routes lead to the same phenoxy-hydroxy bridged dinuclear copper(II) complex **33** (scheme 14).⁴⁹

scheme 14

The overall conversion is strongly reminiscent of the O_2 -binding and arene hydroxylation described in the previous section. Demethylation presumably proceeds *via* methyl-hydroxylation (see scheme 13). A mechanism for the demethylation is given in scheme 14. Initial O_2 -binding, to form **51**, is followed by ipso-nucleophilic attack of the peroxo-dicopper(II) species at the arene 1-position. Subsequent fragmentation and elimination results in the formation of hydroxy-phenoxy bridged complex **33a**. Consistent with this scheme, involving a nucleophilic end-on peroxo- Cu_2 species, is the slower oxidation of the more electron rich para-methoxy substituted complex **50**. The synergetic effect of the copper centers upon O_2 -binding is further illustrated by an intriguing OCH_3/OCD_3 exchange in complex **52** in CD_3OD at $20^\circ C$, in the presence of molecular oxygen (scheme 15). The exclusive exchange at the 1-position and the essential role of O_2 are strong indications for the involvement of complex **55**.

scheme 15

The dinuclear copper complexes, which are described here, are capable of demethoxylating anisole moieties in the presence of O_2 . Therefore, it is conceivable that oxidative dehalogenation is possible. Dehalogenation reactions are catalyzed by various enzymes using hydrolytic, reductive or oxidative pathways.⁵⁰ Few enzymes are capable of oxidative dehalogenation of aromatic compounds.⁴² For instance, phenylalanine hydroxylase (PAH, iron dependent) converts a 4-chlorophenylalanine to tyrosine (dechlorination), while a bacterial (copper dependent) phenylalanine hydroxylase also is known.⁵⁰ An example of a facile dehalogenation with O_2 at room temperature is shown in scheme 16.⁵¹ Dinuclear copper(II) complex **33** is readily obtained in 80% yield (72% Br^- formed). O_2 -binding to **56** is followed by ipso-substitution involving peroxo complex **57**. It should be emphasized that the hydroxylation-dehalogenation proceeds under very mild conditions which allows important features of enzymatic oxidative dehalogenation to be studied.^{51,52}

scheme16

In an alternative approach to mimic tyrosinase activity a copper(I)-copper(II) redox couple and a hydroquinone-quinone redox couple were incorporated in one complex (scheme 17).⁵³ The hydroquinone moiety should act as an electron shunt between an external reducing agent, i.e. ascorbic acid, zinc or electrochemical reduction, and the copper ions. Catalytic oxygenation by monooxygenases is usually accompanied by the formation of water, with the aid of an external electron and proton source.^{35,46} Activation of O_2 by dinuclear copper(I) complex **58** results in superoxo- or μ -peroxo-dicopper(II) complex **59**, which oxygenates an external substrate molecule. Internal electron transfer to quinone dicopper(II) complex **60** is followed by quinone to hydroquinone reduction. The electron transfer system shown here is reminiscent of the quinone based systems found in the primary photochemical step of bacterial photosynthesis, and in (metallo)porphyrin quinone electron transfer systems.⁵⁴ In contrast to expectation, the hydroquinone dinuclear copper(II) complex **60** ($L = (2\text{-pyridylethyl})\text{formidoyl}$, scheme 17), designed to mimic step c in this cycle, is a stable system in which the hydroquinone moiety is not oxidized to a quinone structure **61**.

scheme 17

Although the hydroquinone is ideally situated for electron transfer to the copper(II)-ions, this event does not take place, even in the presence of O_2 . It is remarkable that complex **60** is an excellent catalyst for the oxidation of external hydroquinone to quinone, and the dehydrogenation of α -hydroxy ketones, with excellent turnover numbers in both cases (t.o. $> 1000\text{ h}^{-1}$, scheme 18).⁵³ In these catalytic processes the stoichiometry (substrate : $O_2 = 1 : 1$) indicates a two electron transfer process, contrary to the four electron processes leading to water.

scheme 18

So far emphasis has been on the design of ligands, which are able to position the metal atoms in such a way that they cooperate in binding and activating small molecules like O_2 . Control of substrate binding is essential to achieve, for instance, selective hydroxylation. An important approach is the introduction of (chiral) cleft forming units or receptors to the dinuclear metal-site to enforce selective binding (and positioning) of neutral molecules (figure 8).

figure 8

4. Self-assembly of mono- and polynuclear helical complexes

Numerous metal complexes are known that adapt helical shaped structures and the stereochemical information is crucial to the design of chiral metal complexes for enantioselective catalysis or chiral recognition.⁷ However, effectiveness as a chiral catalyst requires the substrate to be brought in close proximity to the metal center without major disturbance to the helical structure. This condition is often not fulfilled.⁷ By employing bis-imines, such as **62**, which contain either achiral ($R = H$), or chiral N, N' -bridging units ($R = \text{alkyl, aryl}$), helical shaped complexes are spontaneously formed upon metal binding.⁵⁵ In the bis-imines, which preferentially adopt an *E*-configuration, the large naphthyl moieties are folded away from each other due to steric effects. Complexation of the imine-nitrogen atoms assembles the structure as the naphthyl "wings" are forced together creating a helical shaped chiral cleft (**63**).

scheme 19

Binding of the reactants or substrate molecules to the metal center will hardly disturb the helicity. A large number of bis-imines of type **62** was synthesized⁵⁵ and the X-ray structure of complex **63** ($M = \text{ZnCl}_2$) confirms the folding process shown in scheme 19.

The design of ligands for the spontaneous assembly of helical oligonuclear complexes has recently attracted much attention.^{56,57,58,59} For instance, oligopyridines have been used as ligands for the formation of double helical metal complexes.⁵⁶ With oligo-2,2'-bipyridines double helical copper(I) complexes were formed, whereas several helical complexes with a variety of metal ions were prepared using oligo-pyridyl ligands.⁵⁷ Bridging of two 2-pyridylethylimine ligands by a 1,3-aryl group, also provides a useful structural motive for the assembly of helical shaped supramolecular structures.⁵⁸

When 2,6-bis[N-(2-pyridylethyl)formimidoyl]-1-methoxybenzene (2,6-BPB-1-OMe, **64**) was allowed to react with two equivalents of $\text{Cu}(\text{BF}_4) \cdot (\text{MeCN})_4$, in the presence of excess (> 10 equiv.) acetonitrile in chloroform, a polynuclear copper(I)-complex **65** was obtained. The X-ray structure of **65** (figure 9) clearly shows that each copper(I) atom has a four coordinated tetrahedral geometry binding two pyridylethylimine units from different ligands.⁵⁸

scheme 20

In the linear copper(I) coordinated polymer two helices are found. These are single stranded, one is left handed and one right handed with the methoxy substituents pointing outside the helix. A comparison with the copper(I) based double stranded helicates reported by Lehn and co-workers⁵⁹ is schematically shown in figure 9.

figure 9

5. Chiral mono- and dinuclear complexes

Currently much effort is devoted to the development of chiral metal complexes for enantioselective catalytic transformations.⁷ Fundamental questions are associated with absolute stereocontrol of the geometry at the catalytically active site. Again, nature provides impressive examples how to deal with the spontaneous assembly of catalytic sites and secondary structures that enables chiral recognition to take place. We focused on new chiral mono- and dinuclear complexes, in particular aiming at the generation of a chiral C_2 -symmetric environment at the catalytically active site. C_2 -symmetric ligands have been shown to be extremely successful in transition metal catalyzed enantioselective transformations.⁷ For this purpose (S)-proline **66** was converted in several steps into enantiomerically pure pentadentate ligand **67**. Complexation with two equivalents of $\text{Cu}(\text{ClO}_4)_2$, or $\text{Ni}(\text{ClO}_4)_2$ provided phenoxy-hydroxy bridged complexes **68** and **69**, with distorted square planar geometry around each metal center (scheme 21).³⁴ The Ni-Ni separation (2.849(1) Å) is slightly shorter than the Cu-Cu distance (2.97(3) Å), as expected in view of the smaller ion radius of Ni(II) compared to Cu(II).

scheme 21

The X-ray structure of **69** clearly shows the *trans*-arrangement of the N-benzyl groups and the pyrrolidine rings. When **67** was treated with $\text{Cu}(\text{OAc})_2$ or $\text{Ni}(\text{OAc})_2$, followed by anion exchange, C_2 -symmetric dinuclear Cu(II) (**70**) and Ni(II) (**71**) complexes were obtained. In the X-ray structure of **70**, the C_2 -symmetry of the complex is nicely seen. The chiral environment, after assembly of the dinuclear site, is imposed by the design of the ligand. It should be noted that a square pyramidal arrangement around each metal is found (Cu-Cu distance 3.296(1) Å). Moreover, the two copper(II)-ions are bridged by the two acetate units in the exposed site of the dicopper center.

figure 10

Chiral "cleft"-formation can be enforced by the introduction of additional coordinating ligands **72** as is schematically shown in figure 11. In a second approach "fences" are assembled, close to a catalytically active metal site (structure **73**), in a C_2 -symmetric arrangement.

figure 11

Higher selectivity during the approach of a prochiral substrate to the mono- or dinuclear metal sites can be expected as the more rigid C_2 -symmetric geometry allows introduction of groups that enforce substrate complexation in a well-defined manner. Examples of both types of complexes are shown in scheme 22 and figure 12. Starting with (S)-prolinamide the multidentate C_2 -symmetric ligand **75** was prepared. Dinuclear copper(II) and nickel(II)-complexes were obtained with pentacoordinated metal ions. The molecular structure of nickel complex **76** clearly shows the distorted square pyramidal arrangement (scheme 21). Also the folding of the ligand around the di-Ni(II) center, with *trans*-orientation of the pyridylethyl moieties can be observed.

scheme 22

In the second approach the manganese(III)salen unit is used as the catalytically active center whereas binaphthol derivatives are introduced as "fence" forming units. Chiral manganese(III)salen complexes are intriguing mono-oxygenase model systems, as has been demonstrated by Jacobsen and co-workers⁶⁰ in the highly enantioselective epoxidation of *cis*-alkenes. The C_2 -symmetric (S,S)-binaphthol-(S,S)-salen ligand **77** readily forms nickel(II) and manganese(III) complexes, e.g. **78** (figure 12). The molecular structure of **78** shows the square pyramidal geometry of the catalytically active manganese(III)-site and the pseudo C_2 -symmetric arrangement of the 2-methoxynaphthyl moieties. High activity and selectivity in enantioselective epoxidation have been found with this complex.

These examples clearly demonstrate that well-defined geometries, with asymmetric environments around the active site, can be generated. Combination of the experimental information summarized here with the extensive knowledge currently available on synthetic receptors for selective substrate binding, opens intriguing possibilities for the design of sophisticated supramolecular catalysts.

6. Conclusions

The variety of coordination geometries that can be envisaged by metal complexation together with the flexibility offered by the synthesis of multidentate ligands holds enormous potential for the design of new supramolecular structures. Besides developing new supramolecular architecture and receptors the design of supramolecular catalysts is a major goal in supramolecular chemistry based on metal complexes. Two main approaches are usually followed. First the assembly of receptor molecules and combining these with catalytic centers or alternatively, assembly of catalytically active mono- or multinuclear metal centers and subsequent elaboration of receptor units. In this chapter various examples of the second approach are summarized with a strong emphasis on oxidation catalysts. A major challenge is to "extent" the structural assembly for selective substrate binding retaining all functional properties. The structural and functional assembly of catalytically active mono- and dinuclear complexes elucidated key features, for instance with respect to O_2 -binding and activation. It is particular interesting to note that processes that usually require forced conditions like hydroxylation, oxidative dehalogenation or demeth(ox)ylation can be performed at ambient conditions with e.g. O_2 . Besides redox potentials of the metals and electronic effects, geometrical constraints enforced by the ligands are essential to achieve these catalytic effects.

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