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Structural and functional studies on model compounds of purple acid phosphatases and catechol oxidases

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Abstract

The synthesis, single crystal X-ray crystallographic, magnetic and electrochemical characterization of eight representative symmetric and unsymmetric complexes as structural model compounds for active sites in PAPs is reported. A mixed valent diiron as well as an iron(III)–zinc(II) complex as models for the active, reduced form of mammalian and plant PAPs, respectively, were synthesized and characterized. Five diiron(III) compounds as structural models for the oxidized uteroferrin-phosphato and -arsenato complex and a model for the oxidized form of PAP from beef spleen are reported. In addition to the structural relevance the catalase and peroxidase activity of one of these model complexes is introduced. Further we summarize our recent research concerning synergistic investigations on catechol oxidase and on synthetic copper coordination complexes. The catechol oxidase is an important type 3 copper protein for the activation of dioxygen. The development of low-molecular weight catalysts should facilitate the oxidation of organic substances by O_2. In particular the reported copper(II) complexes may serve as structural and functional bioinorganic model compounds for the active sites of dioxygen binding and dioxygen activating copper proteins, respectively. These investigations provided a new X-ray crystallographically characterized type of peroxo copper(II) complexes with a μ_4-$(\eta^1)_4$ coordination mode.

Keywords: Copper; Iron; Model complex; Purple acid phosphatase; Catechol oxidase; Peroxo complexes

1. Structural studies on model compounds of purple acid phosphatases

1.1. Introduction

Purple acid phosphatases (PAPs) containing a dinuclear Fe(III)–Me(II) center (where Me can be Fe or Zn) in their active sites catalyse the hydrolysis of activated phosphoric acid esters and anhydrides, like ATP, at a pH range from 4 to 7. The characteristic purple color of this subclass of acid phosphatases results from a tyrosinate → Fe(III) charge transfer transition at ca. 560 nm. PAPs differ from the metal-independent subclass of acid phosphatases in their insensitivity to tartrate inhibition (for a review see [1–4]). All mammalian PAPs characterized so far are monomeric proteins with a molecular mass of ca. 35 000 Da containing an Fe(III)–Fe(II) center in the active site. The best characterized members of this group are represented by uteroferrin and beef spleen PAP (bsPAP), which are intensively studied by Mössbauer, EPR, NMR, EXAFS, magnetic, electochemical and resonance Raman methods [5]. The most intensively studied plant enzyme from kidney bean (kbPAP) is a homodimeric Fe(III)–Zn(II) metalloprotein of molecular mass 111 000 Da [6]. In 1995, Krebs and coworkers could determine the 3D crystal structure of the kbPAP by X-ray analysis [7]. Fig. 1 shows the structure of the active site.

Local sequence similarities between the sequences of the Fe(III)–Zn(II) plant and the mammalian Fe(III)–Fe(II) PAPs, especially around the metal ligating residues,

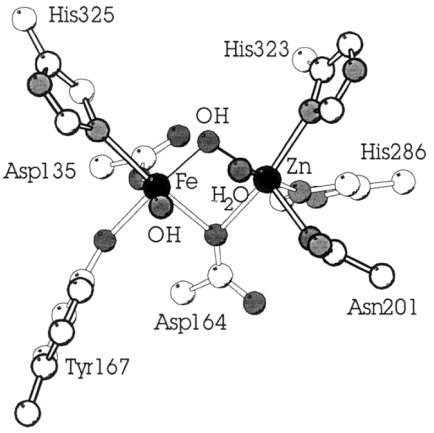


Fig. 1. Dinuclear metal center of native kbPAP.

implicate that the structurally still uncharacterized monomeric mammalian enzymes have identical active site ligands and that they also contain similar catalytical domains [8].

Phosphate and arsenate are weakly bound inhibitors of PAPs with an inhibition constant K_i in the millimolar range. Tungstate, on the other hand, is a tightly bound inhibitor with K_i in the micromolar range. Investigations on the tetraoxo complexes of PAPs and model compounds provide structural insights into the interactions of these inhibitors with the dimetal site. The physiological function of PAPs has yet to be established. In addition to a hydrolytic function, a role in the activation of dioxygen by the two-metal center has been discussed at least for the mammalian PAPs [9,10].

A mechanism of phosphate ester hydrolysis involving interaction of the substrate with Zn(II) followed by nucleophilic attack on the phosphorous by an Fe(III)-coordinated hydroxide ion was postulated based on X-ray analysis of phosphate and inhibitor complexes of kbPAP [11].

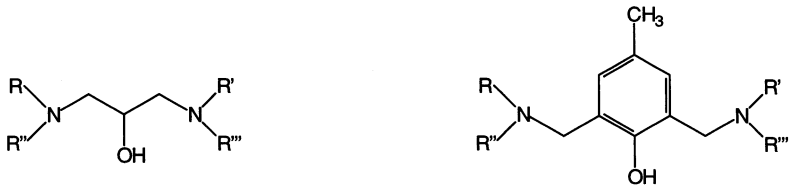


Fig. 2. General structure of dinucleating alkoxo- (A) and phenoxo-bridging (B) ligands.

Table 1
Representative diiron and iron–zinc complexes as model compounds for PAPs[a]

No.	Ligand (type)	Metal core	Bridging mode	Ref.
1	Hbpmp (B)	Fe(III)–Fe(II)	μ-phenoxo-bis(μ-diphenylphosphato)	[52]
2	Hbpmp (B)	Fe(III)–Zn(II)	μ-phenoxo-bis(μ-diphenylphosphato)	[52]
3	H_3bhpp (A)	Fe(III)–Fe(III)	μ-alkoxo-bis(μ-diphenylphosphato)	[56]
4	H_3bhpmp (B)	Fe(III)–Fe(III)	μ-phenoxo-bis(μ-diphenylphosphato)	[56]
5	Htbpo (A)	Fe(III)–Fe(III)	μ-alkoxo-bis(μ-hydrogenphosphato)	[58]
6	Htbpo (A)	Fe(III)–Fe(III)	μ-alkoxo-μ-dimethylarsinato	[59]
7	Hmtbpo (A)	Fe(III)–Fe(III)	μ-alkoxo-μ-dimethylarsinato	[61]
8	Htbpo (A)	Fe(III)–Fe(III)	μ-alkoxo	[67]

[a] Abbreviations used for ligands: Hbpmp, 2,6-bis[bis(2-pyridylmethyl)aminomethyl]-4-methylphenol; H_3bhpp, 1,3-bis[(2-hydroxybenzyl)(2-pyridylmethyl)amino)]-2-propanol; H_3bhpmp, 2,6-bis[((2-hydroxybenzyl)(2-pyridylmethyl)amino)methyl]-4-methylphenol; Htbpo, *N*,*N*,*N*′,*N*′-tetrakis(2-benzimidazolylmethyl)-1,3-diamino-2-propanol; Hmtbpo, *N*-methyl-*N*,*N*′,*N*′-tris(2-benzimidazolylmethyl)-1,3-diamino-2-propanol.

1.2. Structural model compounds for oxoanion complexes of mammalian and plant PAPs

Many groups employed tripodal ligands in diiron complex synthesis [12–46]. In most cases the use of tripodal ligands leads to μ-oxo bridged complexes. Weak antiferromagnetic coupling between the metal ions in the mixed valent PAPs indicates a μ-hydroxo or μ-alhoxo bridge and no μ-oxo bridge. The nature of the oxygen bridge in oxidised diiron PAPs is not yet fully ascertained [1]. Because of their chelating effect and the predictable formation of dinuclear centers the use of dinucleating ligands is a promising and well performed strategy for the synthesis of dinuclear iron complexes

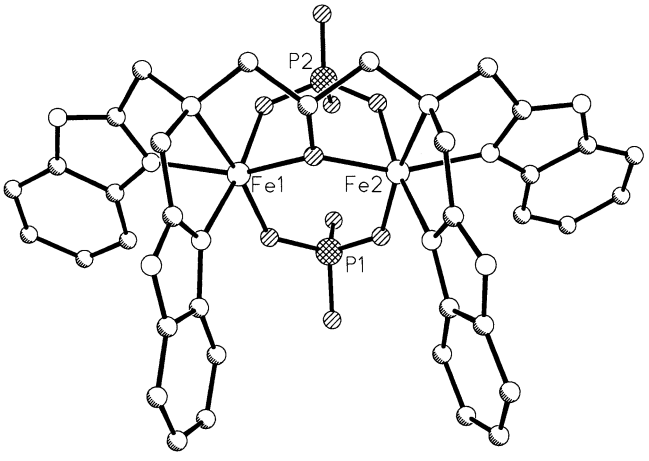


Fig. 3. Molecular structure of the cation in **5**.

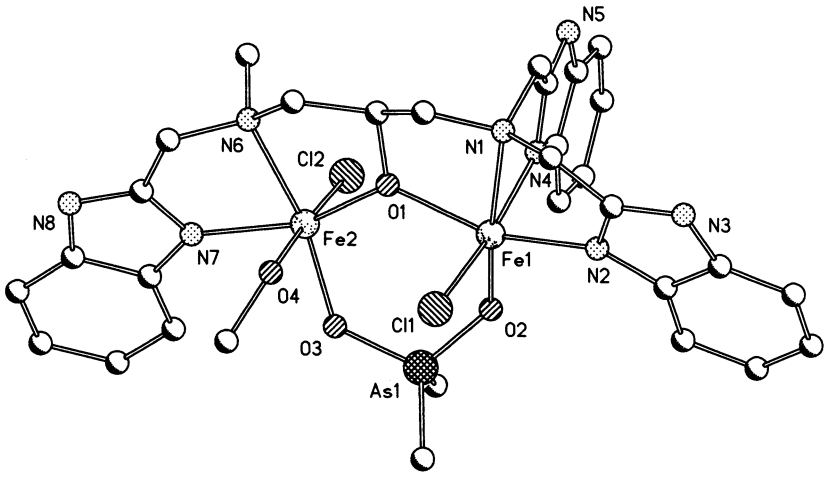


Fig. 4. Molecular structure of the cation in **7**.

[47–81]. In the case of PAP models dinucleating ligands having an oxygen/nitrogen ligand sphere are most suitable for synthesizing biomimetic model complexes. Two different backbones lead to the following general ligand types forming μ-alkoxo and μ-phenoxo bridged complexes, respectively (Fig. 2).

Variation of the residues R–R‴ leads to different Lewis acidities at the metal centers. Using benzimidazole, phenole, pyridine and alkyl groups as residues we obtained complexes **1**–**8** (Table 1).

All complexes were characterized by single crystal X-ray structure analysis and Mössbauer spectroscopy. In addition the electrochemical and magnetic properties were determined.

1.2.1. Structural model compounds for reduced PAP–tetraoxoanion complexes

$[Fe_2(bhpp)(O_2P(OPh)_2)_2](ClO_4)_2 \cdot 1.5CH_3OH \cdot H_2O$ **1** and $[FeZn(bhpp)(O_2P(OPh)_2)_2](ClO_4)_2 \cdot 1.5CH_3OH \cdot H_2O$ **2** are the first mixed valent phosphate-bridged model compounds for the reduced form of mammalian and plant PAPs, respectively [52]. Compound **1** contains a μ-phenoxo-bis(μ-diphenylphosphato)-iron(III)iron(II) unit with a metal–metal separation of 3.654 Å, which is similar to the Fe···Zn distance (3.695 Å) in the μ-phenoxo-bis(μ-diphenylphosphato)iron(III)zinc(II) center of **2**. Weak antiferromagnetic behavior was found for **1**; the coupling constant ($J = -6.2$ cm^{-1}) is in good agreement with the value determined for the reduced uteroferrin–phosphate complex. Electrochemical investigations on **1** show two reversible one-electron transfer steps to be assigned to the redox pairs Fe(III)Fe(III)–Fe(III)Fe(II) and Fe(III)Fe(II)–Fe(II)Fe(II). In the case of **2** the reversible one-electron charge transfer Fe(III)–Fe(II) can be seen. Mössbauer spectra of **1** indicate high-spin Fe(II) and high-spin Fe(III) valence states. The spectrum of **2** shows, besides the Fe(III) doublet, broad signals that can be assigned to slight contamination with Fe(II).

1.2.2. Structural model compounds for the oxidized uteroferrin–phosphato complex

Two novel ligands were used to synthesize the symmetric complexes $[Fe_2(bhpp)(O_2P(OPh)_2)_2]BPh_4 \cdot CH_3OH \cdot CHCl_3$ **3** and $[Fe_2(bhpmp)(O_2P(OPh)_2)_2]$-$ClO_4 \cdot H_2O$ **4** which contain μ-alkoxo-bis(μ-diphenylphosphato)diiron(III) and μ-phenoxo-bis(μ-diphenylphosphato)diiron(III) cores respectively [56]. The μ-alkoxo-bis(μ-hydrogenphosphato)diiron(III) core in $[Fe_2(tbpo)(O_2PO(OH))_2]ClO_4 \cdot CH_3$ $OH \cdot 8.5H_2O$ **5** is the first example for this type of 'inorganic' phosphate bridging a biomimetic Fe(III)–Fe(III) complex confirmed by single crystal X-ray analysis [58]. Therefore, **5** is the first structurally characterized model compound for the product complex of the hydrolysis. The bidentate bridging mode of the phosphate in **5** is similar to the bridging mode of phosphate in the phosphate complex in kbPAP and supports the mechanism of phosphate ester hydrolysis proposed in the literature [11,58] (Fig. 3).

The Fe···Fe distance of 3.42 Å in **5** is smaller than the metal–metal separation in **3** (3.55 Å) and **4** (3.84 Å) and in the order of the EXAFS value for the uteroferrin–phosphate complex [82]. The average Fe···P separations of 3.22 Å in **3**, 3.25 Å in **4** and 3.20 Å in **5** are in the same order of magnitude. Magnetic susceptibility measurements on the model complexes indicate the presence of weak antiferromagnetic coupling. All three Mössbauer spectra confirm the existence of octahedral high-spin Fe(III) ions. The redox properties were examined by electro-

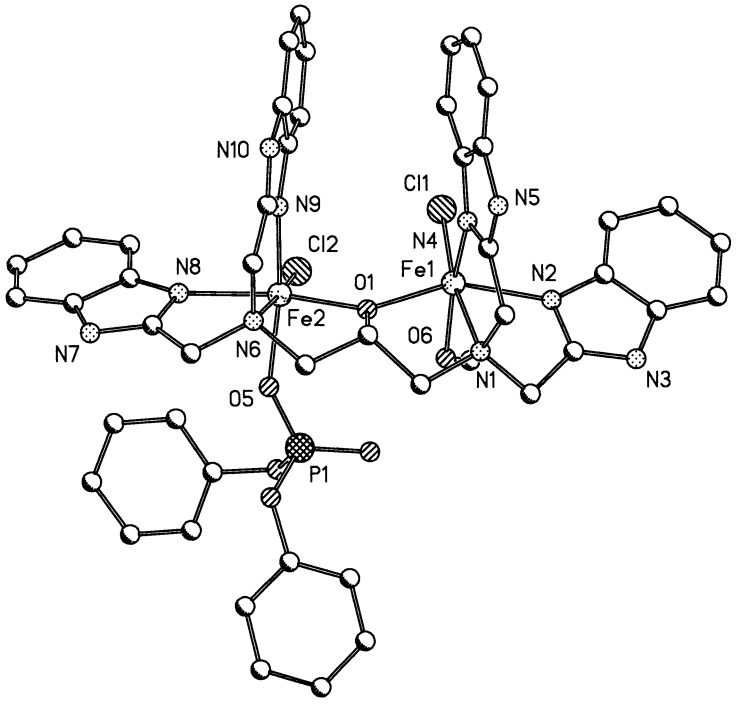


Fig. 5. Molecular structure of the cation in **8**.

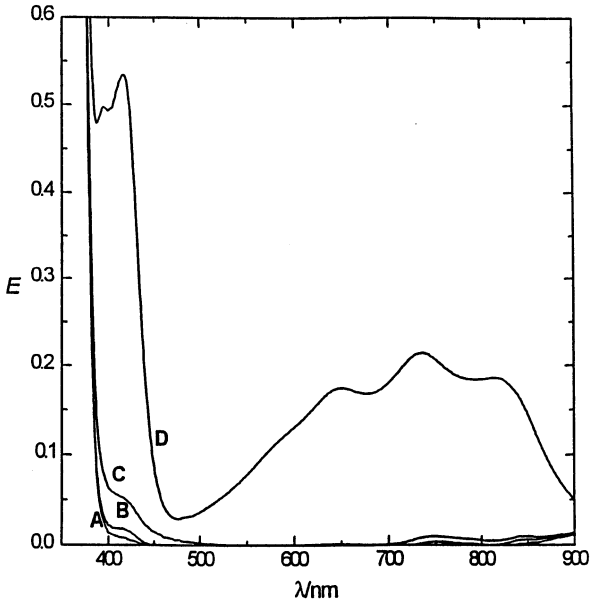
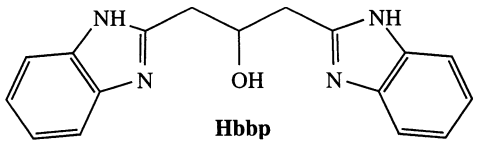


Fig. 6. UV–vis spectra of: ABTS (**A**), ABTS + H_2O_2 (**B**), ABTS + complex **7** (**C**), ABTS + complex **7** + H_2O_2 (**D**).

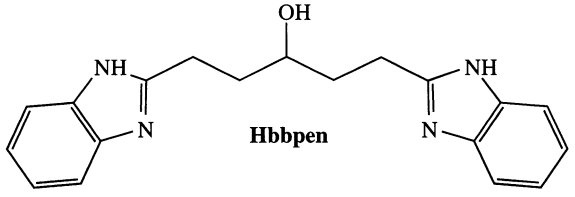
chemical investigations showing Fe(III)Fe(III)–Fe(III)Fe(II) and Fe(III)Fe(II)–Fe(II)Fe(II) transitions.

1.2.3. Structural model compounds for the oxidized uteroferrin–arsenato complex

The unsymmetrical complexes $[Fe_2(tbpo)(O_2As(CH_3)_2)(Cl)(H_2O)](ClO_4)_3 \cdot 5CH_3OH \cdot H_2O$ **6** [59] and $[Fe_2(mtbpo)(O_2As(CH_3)_2)(Cl)_2(CH_3OH)](ClO_4)_2 \cdot 4CH_3OH$



Hbbp



Hbbpen

Fig. 7. Schematic structures of the ligands 1,3-bis(2-benzimidazolyl)-2-propanol (Hbbp) and 1,5-bis(2-benzimidazolyl)-3-pentanol (Hbbpen) [103].

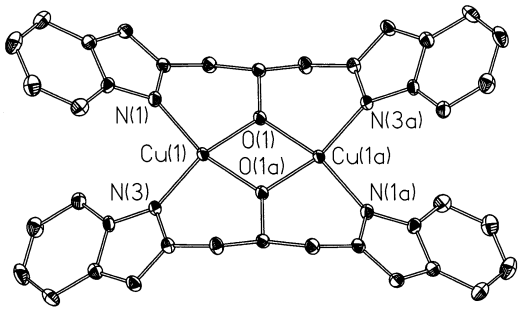


Fig. 8. Molecular structure of the cation in **9** [103].

7 [61] contain a novel (μ-alkoxo)(μ-dimethylarsinato)diiron(III) core. Both complexes contain a single bridging arsenato group which reproduces the coordination mode and the stochiometry of the PAP–oxoanion interaction proposed by Que and coworkers [82]. Therefore, **6** and **7** are good model compounds for the proposed structure of the oxidized oxoanion complex of uteroferrin. Fig. 4 shows the structure of the cation in **7**.

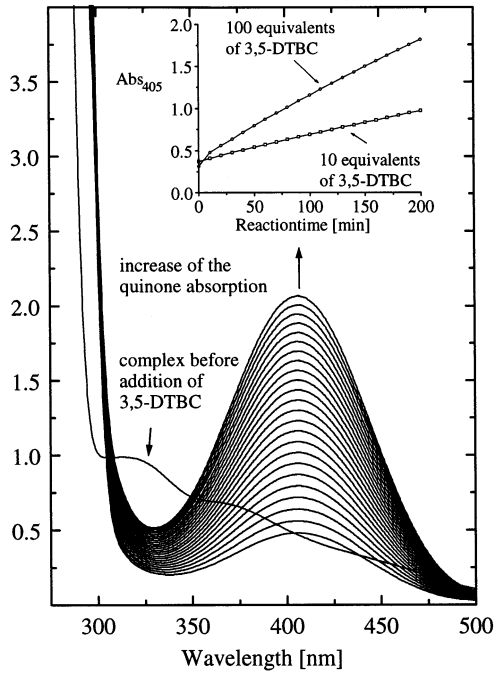


Fig. 9. Increase of the quinone band after addition of 3,5-di-*t*-butylcatechol (3,5-DTBC) (100 equivalents) to a solution of **10** (4×10^{-4} M) in methanol. The spectra are recorded every 10 min. The inset shows the course of the absorption maximum at 405 nm with time for 10 and 100 equivalents of 3,5-DTBC [103].

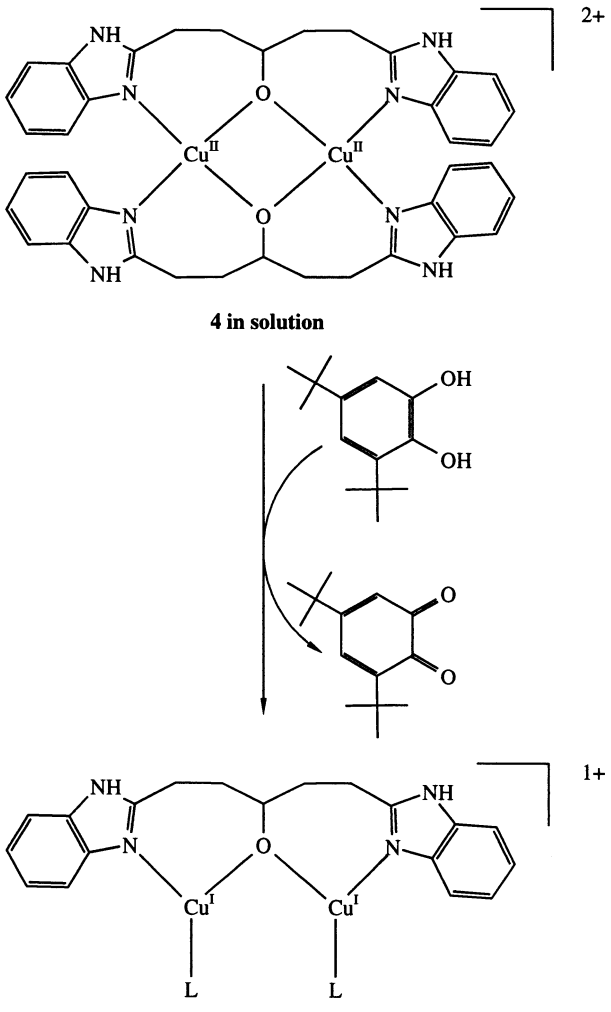


Fig. 10. Proposed course of the reaction of **10** with 3,5-DTBC in methanol [103].

EXAFS spectra on **6** were recorded and analyzed in order to get a reliable basis for the interpretation of EXAFS data for model compounds in solution and enzyme preparations. There is good agreement between the EXAFS and crystallographic results with the exception of the distance of the tertiary nitrogen atom. The Fe···Fe distance of 3.58 Å in **6** and 3.54 Å in **7** are are in accordance with the metal–metal separation found in several phosphate-bridged diiron models [13,56]. The average Fe···As distance in **6** is 3.31 Å and 3.28 Å in **7**.

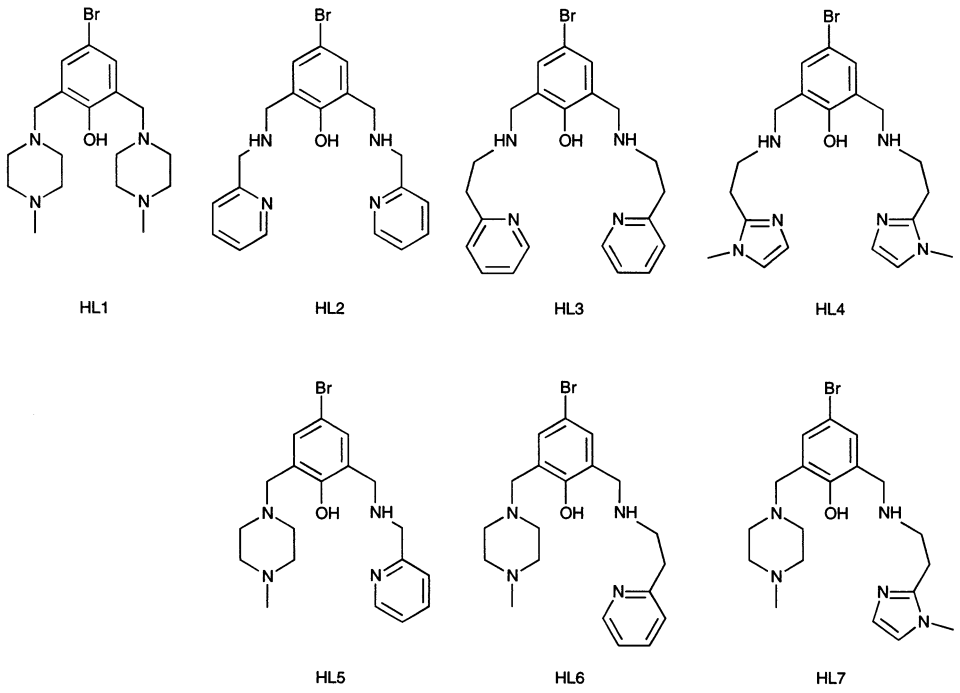


Fig. 11. Schematic structures of the pentadentate symmetric ligands HL^1 = 4-bromo-2,6-bis(4-methylpiperazin-1-ylmethyl)phenol, HL^2 = 4-bromo-2,6-bis((2-pyridylmethyl)aminomethyl)phenol, HL^3 = 4-bromo-2,6-bis((2-(2-pyridyl)ethyl)aminomethyl)phenol and HL^4 = 4-bromo-2,6-bis((2-(1-methyl-2-imidazolyl)ethyl)aminomethyl)phenol and asymmetric ligands HL^5 = 4-bromo-2-(4-methyl-piperazin-1-ylmethyl)-6-((2-pyridylmethyl)aminomethyl)phenol, HL^6 = 4-bromo-2-(4-methylpiperazin-1-ylmethyl)-6-((2-(2-pyridyl)ethyl)aminomethyl)phenol and HL^7 = 4-bromo-2-(4-methylpiperazin-1-ylmethyl)-6-((2-(1-methyl-2-imidazolyl)ethyl)aminomethyl)phenol [104].

1.2.4. A structural model compound for the oxidized form of PAP from beef spleen

$[Fe_2(tbpo)(O_2P(OPh)_2)(Cl)_2(CH_3OH)](ClO_4)_2 \cdot 3CH_3OH$ **8** is the first binuclear iron(III) complex with a terminally coordinated phosphato ligand [67] (Fig. 5). Compound **8** is a good model for the proposed structure of the inactive form of PAP from bovine spleen according to spectroscopic, magnetic and EXAFS investigations [83,84]. The metal–metal separation in **8** (3.70 Å) is larger than that found in complexes containing bridging ligands. Due to Mössbauer and magnetic investigations the core shows antiferromagnetic behavior of high-spin iron(III) ions. The monodentate terminal coordination mode of the phosphate in **8** is similar to the binding mode of phosphate ester in the initial step of a proposed mechanism of phosphate ester hydrolysis [11].

1.3. Functional studies: catalase and peroxidase activity

The non-heme diiron center in the active site of mammalian PAPs is reminiscent of the active sites in the oxygen-activating diiron enzymes methane monooxygenase

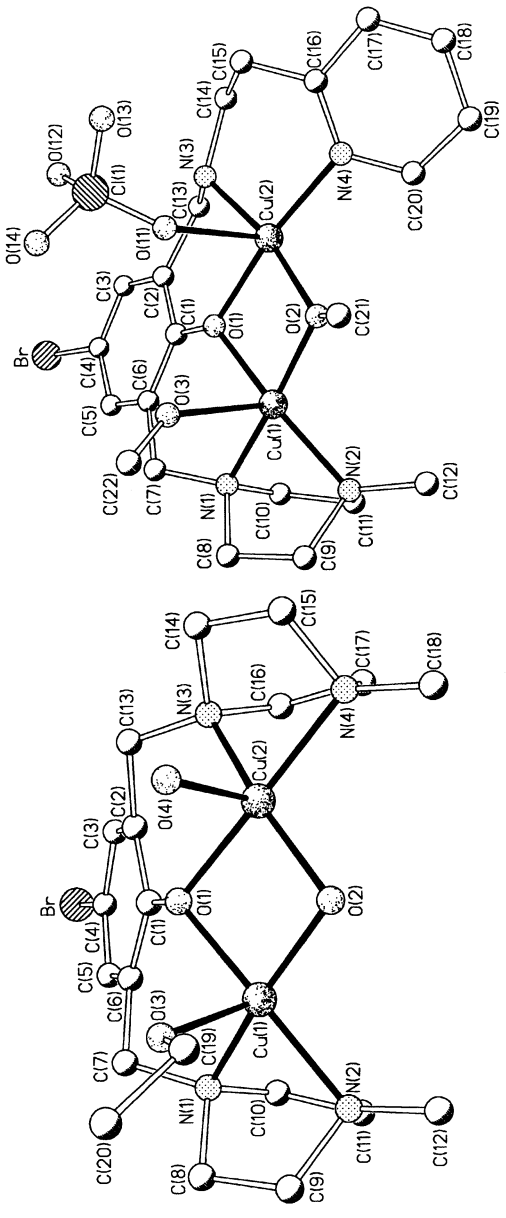
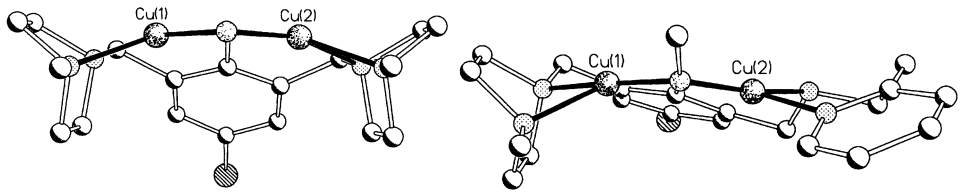


Fig. 12. Molecular structure of the cations in **11** and **16** [104].



11 **16**

Fig. 13. Cations of **11** and **16** along their O(2)–O(1) vectors (coordinating molecules or anions in axial positions are omitted) [104].

(MMO) [85,86] and ribonucleotide reductase [85,87]. A proposed mechanism of substrate hydroxylation catalysed by MMO includes a μ-peroxo diiron(III) species formed by the reaction of dioxygen and the diiron(II) form of MMO or by the reaction of hydrogen peroxide and the diiron(III) form of the enzyme [85,86].

This led to the idea to study the activation of hydrogen peroxide by diiron(III) PAP model complexes. The behavior of several diiron complexes with different ligands towards hydrogen peroxide was observed [61,88]. Some of these complexes form intensively coloured products with hydrogen peroxide showing a new absorption band at ca. 600 nm.

The catalytic properties of **6** and **7** concerning catalase and peroxidase activity were investigated [61,88]. Although iron catalases and peroxidases are heme

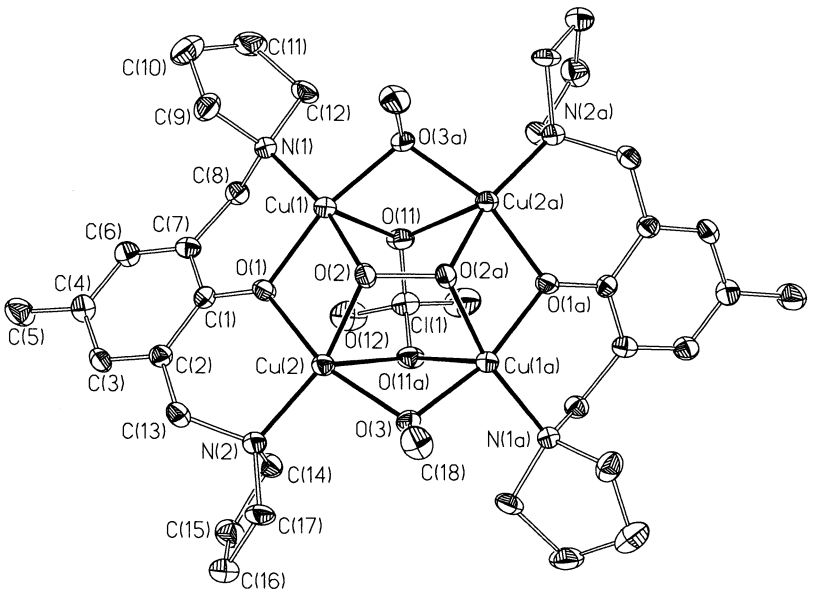


Fig. 14. Molecular structure of $[Cu_4(L^1)_2(O_2)(OMe)_2(ClO_4)]ClO_4 \cdot MeOH$ (**18**) [126].

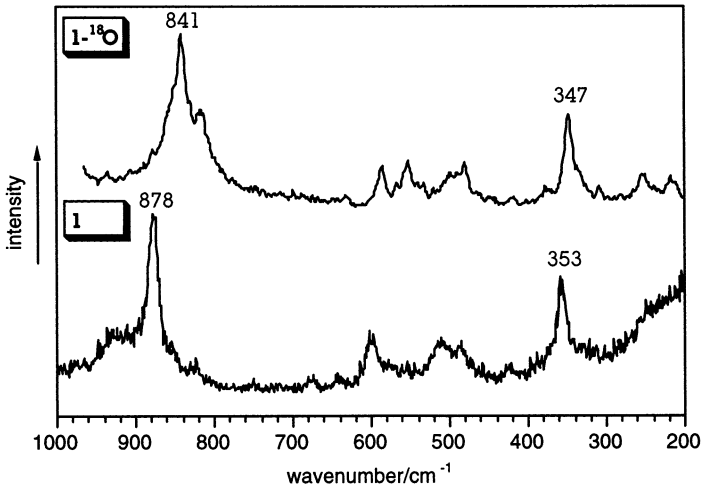


Fig. 15. Resonance Raman spectra of **18** $^{18}O_2$ (454.5 nm, 80 K) and $^{16}O_2$ (457.9 nm, 10 K) [125].

proteins their typical reactions were chosen to be investigated with PAP model complexes because they are easy to follow. The formation of a stable peroxide adduct during the reaction of H_2O_2 and the model compounds can be monitored photometrically. Compounds **6** and **7** exhibit very limited catalase properties (catalytic decomposition of H_2O_2 to O_2 and H_2O) at pH 7. In contrast, the high stability of the adduct was a reason to expect an activation of peroxides in oxidation reactions by these complexes. Diammonium 2,2′-azinobis-(3-ethylbenzothiazolin-6-sulfonic acid) (ABTS) was used as substrate. The substance is commonly applied for the quantification of the enzymatic activity of peroxidases. As with the enzyme itself, the colored oxidation product $ABTS^{\bullet+}$ is formed in the presence of **7** (Fig. 6) and it is possible to quantify hydrogen peroxide with this

Table 2
O–O stretching vibration frequencies and O–O bond lengths of some peroxo compounds

Compound	Coordination mode	ν(O–O) (cm^{-1})	d(O–O) (Å)	Ref.
$[Cu(HB(3,5\text{-}i\text{Pr}_2pz)_3]_2(O_2)$	μ-η^2:η^2	741	1.412(12)	[119]
oxyCO	μ-η^2:η^2	749		[102]
oxyHc	μ-η^2:η^2	742–752		[92], [93]a–f
oxyTyr	μ-η^2:η^2	755		[93]g
$[Cu_2(XYL–O–)(O_2)]^+$	Terminal	803		[114]b
$[[Cu(tp(a)]_2(O_2)]^{2+}$	*trans*-μ-1,2	832	1.432(6)	[118]
$[Cu(bpp(a)(OOH)]^+$	End-on	856	1.460(6)	[121]
18	μ_4	878	1.453(4)	[125]
19	μ_4	898		[125]
20	μ_4	888		[125]
$Cu(O_2)(HB(3\text{-}t\text{-Bu-}5\text{-}i\text{-Prpz})_3)$	Side-on superoxo	1112	1.22(3)	[120]

reaction [88]. An oxidation of ABTS by H_2O_2 without the presence of **7** did not occur. A further oxidation to the corresponding dication was not observed either. Compound **7** can therefore be considered as a functional model for peroxidase. The reaction rates are low when using the complex compared to those obtained with peroxidase as catalyst. The higher stability of the model compound compared to the enzyme is, however, an important advantage.

The investigation of the influence of the pH value on the catalase activity of several model complexes for PAPs showed a strong pH-dependency of the activity

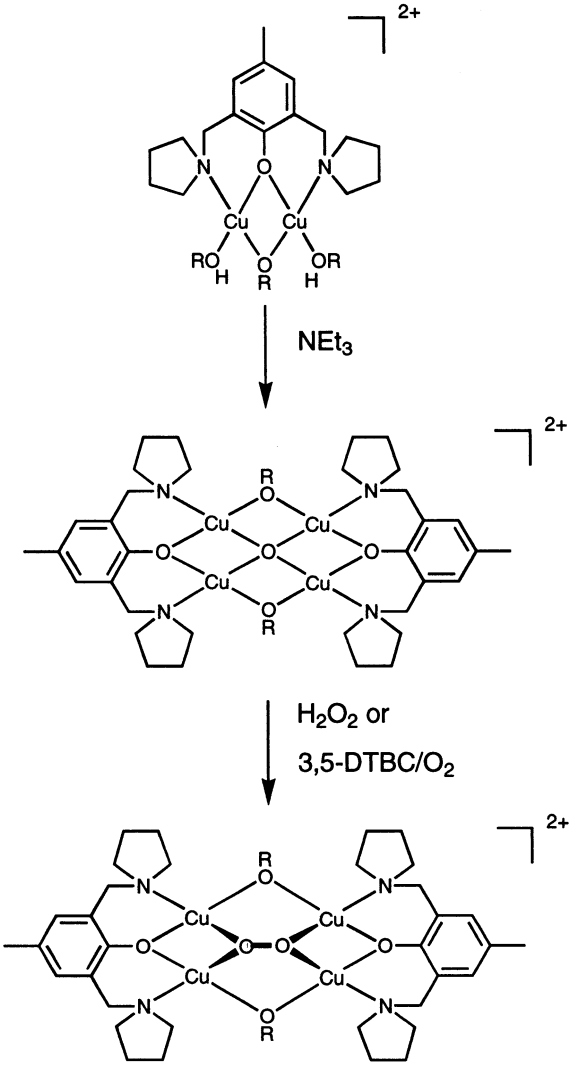


Fig. 16. Reaction of Cu_2L^1 to form tetranuclear μ_4-oxo and μ_4-peroxo complex species (R = –H, $–CH_3$) [125] (coordinating molecules in axial positions are omitted for clarity).

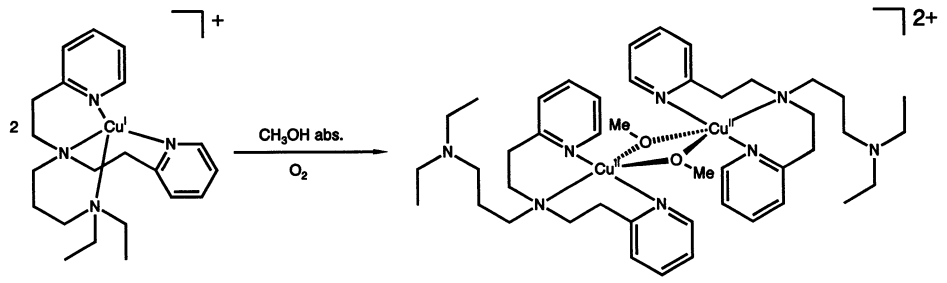


Fig. 17. Formation of the dinuclear bis-μ-methoxy copper(II) complex $[Cu_2(bpedepa)_2(\mu\text{-}OCH_3)_2](ClO_4)_2 \cdot 2CH_3OH$ (**25**) using the copper(I) precursor $[Cu(bpedepa)]ClO_4$ (**23**) [102,130].

[88]. At pH 9 a dramatic increase in the catalase activity is observed with some of the diiron complexes. These complexes show a considerable stable adduct at pH 3–7 in aqueous solution. The adduct formation of **6** was investigated as a function of $[H_2O_2]$, pH, temperature, and pressure using kinetic methods [88]. To study the influence of the cacodylate bridge in **6** on the formation of the metastable adduct an analogue hydroxo bridged complex was employed. For both complexes the first step is the addition of H_2O_2 to one of the iron centers. In the case of the hydroxo bridged complex a very fast ring closure follows. In the other case the first reaction is identical, but the following ring closure reaction is much slower, and so k_2 can be observed as $[H_2O_2]$-independent rate constant. The cacodylate bridge causes a steric

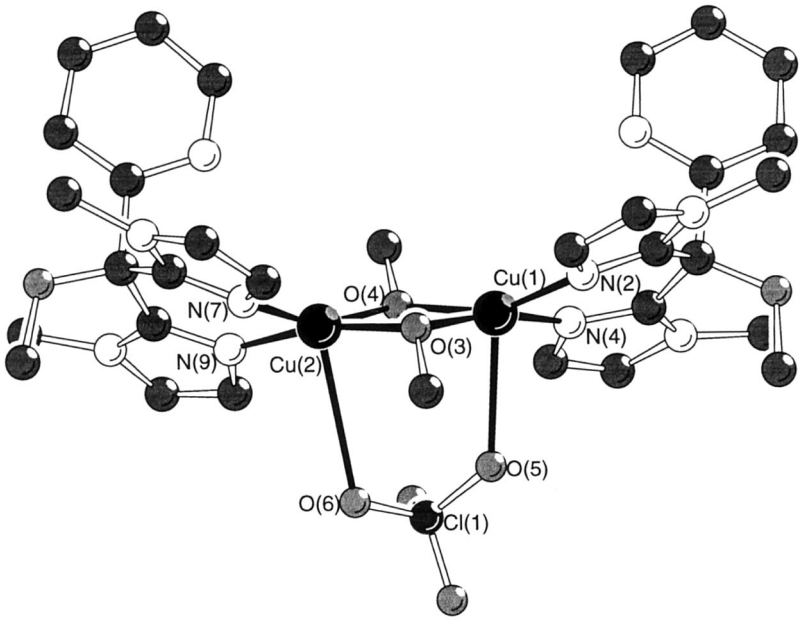


Fig. 18. Molecular structure of the cation in **27** [131].

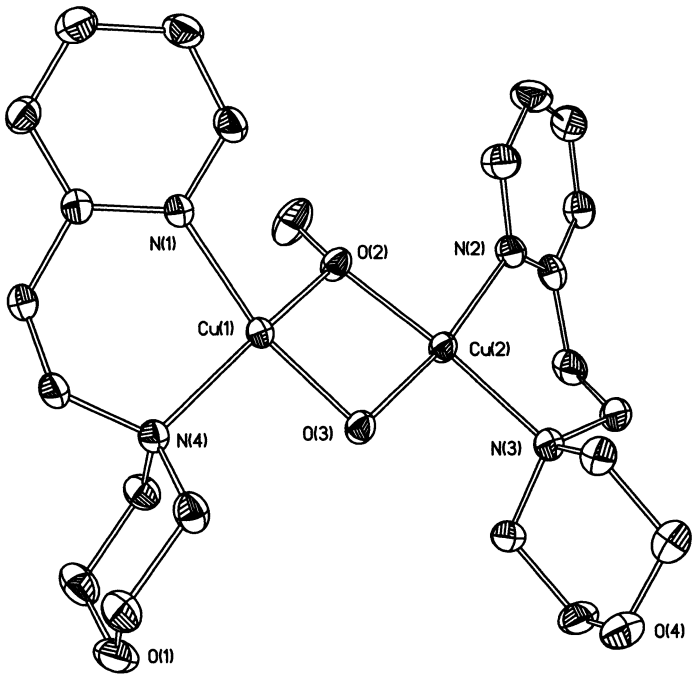


Fig. 19. Molecular structure of the cation in **28** [102].

hindrance during the ring closure reaction, so that this reaction becomes much slower. The rate constant for the first step is similar for both complexes.

The activation of hydrogen peroxide by PAP model compounds underlines the possibility of a non-hydrolytic function of mammalian PAPs.

2. Model compounds for the active site of catechol oxidase

2.1. Introduction

The oxidation of organic substrates with molecular oxygen under mild conditions is of great interest for industrial and synthetic processes from an economical and environmental point of view [89]. Although the reaction of organic substances with dioxygen is thermodynamically favored, it is kinetically hindered due to the triplet ground state of O_2. In biological systems this problem is overcome by the use of copper or iron containing metalloproteins which serve as highly efficient oxidation catalysts [90].

The catechol oxidases (EC 1.10.3.1) are type 3 copper enzymes containing a dinuclear copper center [91]. Well-known representatives of these type 3 copper proteins are hemocyanin [92,93], the dioxygen carrier for arthropods and mollusks, and tyrosinase [94]. Catechol oxidase belongs, like tyrosinase, to the polyphenol

oxidases which oxidize phenolic compounds in the presence of oxygen to quinone. Whereas tyrosinase (EC 1.14.18.1) catalyzes the hydroxylation of tyrosine to dopa (cresolase activity) and the oxidation of dopa to dopaquinone (catecholase activity) with electron transfer to dioxygen, catechol oxidase exclusively catalyzes the oxidation of catechols to quinones without acting on tyrosine [95]. This reaction is of great importance in medical diagnosis for the determination of the hormonally active catecholamines adrenaline, noradrenaline and dopa [96]. Secondary reactions (melanin formation) follow after oxidation of the substrate in the presence of polyphenol oxidases, which cause the brown color of injured plants [97].

Our investigations on the enzyme provided a detailed insight into the structure and function of catechol oxidases from different sources, isolation procedures and spectroscopic properties [98]. The copper in the isolated catechol oxidases was found to be EPR-silent and was assigned to an antiferromagnetically spin-coupled Cu(II)–Cu(II) pair [99]. The protein part of the UV–vis spectrum of the *oxy* catechol oxidase from *Ipomoea batatas* exhibits an intense absorption band at 343 nm and a weaker band at 580 nm, corresponding to the peroxo complexes of hemocyanin and tyrosinase. They were assigned to peroxo $\rightarrow$ Cu(II) charge transfer transitions [100] with an O–O stretching vibration band at 749 cm^{-1} indicating a possible μ-η^2:η^2-bridging mode of the peroxo group. XAS investigations on the native *met* forms of catechol oxidases from *Lycopus europaeus* and *I. batatas* have revealed that the active site consists of a dicopper(II) center, in which the metal atoms are coordinated by four N/O donor ligands. Multiple scattering EXAFS calculations have shown high significance for one or two coordinating histidine residues [101]. The short metal–metal distance of 2.9 Å and the results of EPR investigations indicate a μ-hydroxo bridged dicopper(II) active site in the *met* forms of the proteins [102].

Notable advances in the understanding of the structural and chemical properties of this protein have been achieved by model studies of synthetic analogues [103–108]. Present interest is focused on catecholase activity investigations of copper coordination compounds with different structural parameters and electronic features around the copper ions. In these studies, mono- or multinuclear complexes have been employed and the properties of the chelating ligands have been varied with respect to architecture, number and nature of the donor atoms. Nishida and co-workers have found that square-planar mononuclear copper(II) complexes exhibit only little catalytic activity while non-planar mononuclear copper(II) complexes show a high activity [109]. Dinuclear complexes also catalyze oxidation if the Cu···Cu distance is < 5 Å. A steric match between substrate and complex is believed to be the determining factor: two metal centers have to be located in close proximity to facilitate binding of the two hydroxyl oxygen atoms of catechol prior to the electron transfer ([109]a). This view is supported by the observation that dinuclear copper complexes are generally more reactive towards the oxidation of catechols than are the corresponding mononuclear species ([110]a). So far little is known on crystal structures of a catalytically active dinuclear copper(II) complex with a coordinated catecholato ligand ([110]b). The two mononuclear square planar copper complexes prepared very recently by Malachowski et al. ([106]f) showed to

be also effective catalysts, showing that geometrical effects are only one facet of the complex activity. The same authors pointed out that a narrow range of redox potentials for effective catalysis exists between ease of reduction by the substrate and subsequent reoxidation by molecular oxygen ([106]d). No direct correlation between the rates of reaction and the redox potentials of complexes could be determined. Although some general structure-reactivity patterns have been found, the oxidation chemistry of structurally well-characterized copper complexes is still not fully understood, especially regarding the parameters affecting the catecholase activity. In a synergistic approach, we studied potential structural and functional model complexes for catechol oxidase in addition to our investigations on the enzyme itself. Exploration of the oxidation chemistry of well-characterized copper complexes together with a detailed understanding of the function of dioxygen activating copper enzymes is expected to provide the basis for new catalytic oxidation systems for synthetic and industrial processes. In the following we summarize our approach on the synthesis of a series of mononuclear, dinuclear and tetranuclear complexes with various types of tri-, penta- and heptadentate dinucleating ligands. The design of the copper complexes is based on the natural system, that means the active site of catechol oxidase, and on the known structure-reactivity relationships.

2.2. Copper(II) complexes as structural and functional models for catechol oxidase

Dinuclear copper(II) complexes were studied as structural and functional models for catechol oxidase. For this purpose, a new type of tridentate dinucleating ligands was synthesized which is shown in Fig. 7.

Reactions of the ligands Hbbp and Hbbpen with copper(II) perchlorate in methanol lead to complexes $[Cu_2(bbp)_2](ClO_4)_2 \cdot 2MeOH$ (**9**) and $[Cu_2(bbpen)_2](ClO_4)_2 \cdot 3MeOH$ (**10**) [103]. X-ray crystal structure analysis revealed that in both complexes the cations contain a dinuclear copper(II) center in which the metal atoms are coordinated by two ligand molecules. Each copper atom is coordinated by two benzimidazole nitrogen atoms and two bridging alkoxo oxygen atoms (Fig. 8). The Cu–Cu distances were determined to be 3.033 (**9**) and 3.017 Å (**10**), respectively.

In addition, the compounds were studied by X-ray absorption spectroscopy. The Fourier-filtered EXAFS data were used for initial curve-fitting analysis of the first shell and the second shell (metal–metal contribution). Structural parameters derived from EXAFS (including multiple scattering calculations) and X-ray crystallography are in close agreement. According to the present level of knowledge, these complexes represent good model compounds for catechol oxidase. They imitate the short metal–metal distance as well as the coordination by N/O-donor ligands, especially the coordination by two imidazoles and two μ-OR bridges, which has been proposed for the enzyme [102]. This similarity between the models and the enzyme is further proven by similar EXAFS spectra.

The behaviour of **9** and **10** in solution and their reactions with 3,5-di-*tert*-butylcatechol (catecholase activity) were investigated from UV–vis and XAS spectro-

scopic studies in methanol solution. The complexes in solution have the same structures as in the crystalline state, which could be demonstrated by UV–vis spectroscopic titrations and comparisons between the XAS measurements in the solid state and in solution. The detection of the oxidation of 3,5-di-*t*-butylcatechol (3,5-DTBC) to the corresponding *o*-quinone can be followed by the development of the strong absorption band of the product at about 400 nm. No such band appears after addition of 3,5-DTBC to a solution of **9**, which means that this complex shows no activity towards the oxidation of catechols. The course of the same reaction with a solution of **10** is shown in Fig. 9.

A few seconds after addition of 3,5-DTBC to a solution of **10**, the LMCT transitions vanish, which can be explained by the formation of Cu(I). Simultaneously, the quinone absorption at 405 nm appears. Its extinction reveals a turnover of one equivalent. After this fast stoichiometric first step the quinone absorption increases linearly depending on the catechol concentration. We performed XAS measurements of complex **10** in the presence of catechol in solution. The interpretation of the XANES region suggests that after addition of 3,5-DTBC the present complex is reduced to 2- or 3-coordinated Cu(I). Due to the estimated error range of ± 1 for the coordination number, it is not possible to distinguish between 2- or 3-coordination from EXAFS. A linear 2-coordinated dinuclear Cu(I) complex bridged by the alkoxo oxygen atom of the ligand can be ruled out for sterical reasons. Therefore, in the case of a 2-coordination a mononuclear complex has to be assumed. The metal can be coordinated by the ligand Hbbpen, the solvent, the substrate or the product, but such a fit did not yield satisfactory results. A dinuclear bridged Cu(I) complex is suggested, where the copper atoms are 3-coordinated. Two coordination sites are used by the ligand Hbbpen (one alkoxo oxygen and one benzimidazole nitrogen), the third coordination site could be used by the solvent, the product, or a second ligand molecule with an uncoordinating alcohol(ate) group (named as L in Fig. 10, which is formulated for the first, fast and stoichiometric step of the reaction of 3,5-DTBC with **10** in solution). It is not possible to differentiate between these possibilities by EXAFS or UV–vis.

The further increase of the quinone band in the UV–vis spectrum after the stoichiometric first step can be explained by a slow oxidation of the Cu(I) complex to Cu(II) by oxygen from air. The Cu(II) complex is reduced immediately to the Cu(I) complex again as long as 3,5-DTBC is present. The copper complex with Hbppen is able to oxidize catechol, whereas a solution of the similar complex with Hbpp, which differs only by two CH_2 groups, cannot do so. The six-membered chelate rings formed by the ligand in **9** have a stable twisted conformation, whereas the seven-membered chelate rings in **10** should be less stable. The flexibility of the ligand Hbbpen in complex **10** becomes apparent in the disordered coordinating methanol in the crystal structure together with the large thermal ellipsoids especially of the chelate ring carbon atoms. This ligand flexibility is an essential condition for the reactivity of the complex.

Another approach we followed in modeling catechol oxidase by copper(II) complexes involved pentadentate ligands with a N_4O donor set (Fig. 11).

Crystallization experiments with the ligands HL^1–HL^7 provided the following dinuclear copper(II) complexes: $[Cu_2(L^1)(OH)(EtOH)(H_2O)](ClO_4)_2 \cdot H_2O$ (**11**), $[Cu_2(L^2)(OH)](NO_3)_2$ (**12**), $[Cu_2(L^3)(OMe)(MeOH)(ClO_4)]ClO_4$ (**13**), $[Cu_2(L^4)(OH)(MeOH)_2](BF_4)_2$ (**14**), $[Cu_2(L^5)(OMe)](ClO_4)_2 \cdot 2MeOH$ (**15**), $[Cu_2(L^6)(OMe)(MeOH)(ClO_4)]ClO_4$ (**16**) and $[Cu_2(L^7)(OMe)(MeOH)(ClO_4)]ClO_4$ (**17**) [104]. X-ray crystal structure analyses were performed for complexes **11**, **13**, **14**, **16** and **17**. These complexes all contain a dinuclear copper(II) core attached to one pentadentate ligand molecule. The copper centers are bridged by the phenolate group of the respective deprotonated pentadentate dinucleating ligand and exogenously by a μ-hydroxo or μ-methanolato anion. In terminal equatorial position each copper atom is surrounded by two nitrogen atoms of the ligand, whereby the nitrogen donor atoms are provided by the different subunits of the respective ligand. The Cu–Cu distances vary between 2.874 and 3.002 Å. One or two solvent molecules or counter anions with elongated distances occupy the axial positions. Only a few other representatives show a similar coordination sphere [111]. These complexes represent good structural model compounds for the *met* form of catechol oxidase, they simulate the short metal–metal distance as well as the N_2O_2 donor set and the Cu_2O_2 central unit (Figs. 12 and 13).

The investigation of the catecholase activity of compounds **11**–**17** in methanol solution revealed that only the symmetric complex **11** and the asymmetric complexes **15**–**17** have significant catalytic activity with respect to the oxidation of 3,5-DTBC to its corresponding *o*-quinone under aerobic conditions. The thermodynamic property determining an electron transfer reaction is the redox potential of each reactant. The electrochemical behavior of the complexes was investigated in acetonitrile solution revealing only irreversible and ill defined reduction steps. The cyclic voltammograms show cathodic reduction peaks in the range from -0.37 to -0.96 V and a broad anodic oxidation peak in the range from $+0.06$ to $+0.18$ V. The potentials for the oxidation of 3,5-DTBC to its corresponding semiquinone and quinone are very sensitive to the degree of protonation and/or the number of transferred electrons [112]. No clear relationship between the electrochemical properties of the complexes and the reported data for 3,5-DTBC exists. It may be that the poorly defined redox chemistry of this class of complexes will never allow such a correlation to be established.

Binding of catechol was proven by spectroscopic titration with TCC. In contrast to this, complexes **12**–**14** are completely indifferent towards catechol. Even with a large excess of 3,5-DTBC no binding is observed. The μ-hydroxo and μ-alkoxo bridged dicopper(II) centers are obviously more stable than a bridging catechol coordination. However, coordination of catechol is a necessary condition for electron transfer to the copper centers. The common characteristic of the active complexes is the coordinating piperazine group within their ligand framework. This distinguishes the active complexes from the inactive ones. Obviously, this structural unit is essential for catecholase activity of the studied series of complexes. The X-ray structures have revealed that the square-pyramidal coordination geometry of the copper ions in **11**, **15**, **16** and **17** are strongly distorted, and a strained structure results. On the contrary, the symmetric complexes **12**–**14** are present in a relaxed, energetically favored conformation. This leads to the assumption that the differ-

ences in reactivity are primarily based on geometric factors. The distinct trend of oxidation rates of the active compounds is in accord with the amount of strain within the complexes. The most strained conformation, caused by the exogenous μ-hydroxo bridge, and the most reactive system of all of the complexes synthesized in this work is **11**. In the presence of alternative bridging coordination partners with a larger bite distance, the complex will change into a more relaxed conformation ([111]a). Therefore, **11** is able to give up the μ-hydroxo bridged structural motif in favor of a bridging catechol coordination. This is surely also valid for complexes **15**–**17**, although in a lesser degree of strain and reactivity.

2.3. Stable μ_4-(η^1)$_4$ peroxo copper(II) complexes

In the field of copper coordination chemistry the synthesis and characterization of peroxo complexes is of particular interest and subject of intensive research [113]. Copper dioxygen complexes are suggested as key intermediates not only in enzymatic reactions but also in catalytic synthetic oxidation reactions. In this context investigations were directed towards the stabilization and characterization of synthetic copper–dioxygen compounds. Detailed descriptions of the kinetic and thermodynamic properties of discrete CuO_2 and Cu_2O_2 adducts, their formation as well as of their spectroscopic characteristics were achieved in the last decade [114–126] Most copper–dioxygen adducts were characterized as solution species in aprotic solvents at low temperatures and were thermally unstable [114–117]. Only five well-characterized peroxo copper(II) complexes with different binding modes have been structurally described by X-ray crystallography. The complex synthesized by Karlin et al. [118] consists of two mononuclear copper(II) units bridged by a *trans*-μ-1,2-peroxo unit. The Cu···Cu distance is 4.36 Å and the O–O bond length is 1.432 Å. Kitajima et al. [119] synthesized a planar side-on ligated μ-η^2:η^2-peroxo dicopper(II) complex with a sterically hindered tridentate ligand sharing a Cu···Cu distance of 3.56 Å and a O–O distance of 1.412 Å. This model compound closely matches the spectroscopic, magnetic and structural properties of oxyhemocyanin [92]. By the same group the only X-ray structure of a mononuclear side-on superoxo copper(II) complex [120] has been synthesized (O–O 1.22 Å). Recently a new mononuclear hydroperoxocopper(II) complex was structurally characterized by Harata et al. [121] exhibiting a O–O bond length of 1.460 Å. Only a few papers describe peroxo copper complexes showing considerable stability at ambient temperature [122]. Very recently new types of synthetic copper complexes containing dioxygen were studied X-ray cristallographically [123] and in solution [124].

We were able to generate an extraordinarily stable novel type of peroxo copper(II) complexes [125]. Isolation and structural characterization revealed an unusual end-on fourfold bridging μ_4-(η^1)$_4$ new peroxo copper coordination mode (Fig. 14) [126]. On treatment of two equivalents of copper(II) perchlorate and trietylamine with the tridentate ligand 2,6-bis(pyrrolidinomethyl)-4-methylphenol (HL^1), $[Cu_4(L^1)_2(O_2)(OMe)_2(ClO_4)]ClO_4 \cdot MeOH$ (**18**) precipitates in the presence of air from a methanolic solution to which either 3,5-di-*t*-butylcatechol (3,5-DTBC) or hydrogen peroxide was added [126].

Alternatively, **18** is available by reaction of copper(I) perchlorate with HL^1 under argon in basic methanol followed by exposure to air. The average interatomic Cu···Cu distance is 4.25 and 1.453 Å for the O–O distance. Other μ_4-$(\eta^1)_4$ peroxo complexes $[Cu_4(L^2)_2(O_2)(OMe)_2(ClO_4)]ClO_4 \cdot MeOH$ (**19**) and $[Cu_4(L^3)_2(O_2)(OMe)_2(ClO_4)]ClO_4 \cdot MeOH$ (**20**) are accessible using the tridentate amino alcohol ligands 2,6-bis(piperidinomethyl)-4-methylphenol (HL^2) and 2,6-bis(morpholinomethyl)-4-methylphenol (HL^3), respectively [125]. The spectroscopic properties of these peroxo complexes are very similar. The UV–vis spectrum contains a broad intense band at about 390 nm ($\varepsilon \sim 9500\ M^{-1}\ cm^{-1}$) with a shoulder around 430 nm and a band at about 580 nm ($\varepsilon \sim 600\ M^{-1}\ cm^{-1}$). While the first feature can be interpreted as a superposition of a phenolato to Cu(II) and peroxo to Cu(II) charge transfer transition, the second may be assigned to a superposed d–d and a less intense peroxo to Cu(II) charge transfer band. Resonance Raman experiments of solid samples of **18** and of the analogous $^{18}O_2$ labeled compound were performed [127]. Fig. 15 displays the Raman features at 878 and 353 cm^{-1} which shift to 841 and 347 cm^{-1} upon $^{18}O_2$ substitution.

The frequencies are assigned to ν(O–O) and ν(Cu–O), respectively. The observed isotopic frequency shift [$\Delta\nu(^{18}O-^{18}O) = 37\ cm^{-1}$] is not in agreement with the expected shift for a diatomic harmonic oscillator [$\Delta\nu(^{18}O-^{18}O) = 50\ cm^{-1}$]. This indicates a coupling of the O–O stretching vibration with another vibration within the Cu_4 moiety resulting the highest ν(O–O) reported so far in peroxo copper(II) compounds. Indeed, comparison of the FT Raman spectra of both samples reveals an isotopic shift of the band at 823–817 cm^{-1}. In the resonance Raman spectra of **19** and **20** two characteristic Raman features are found as well which were accordingly assigned to the O–O stretching and a Cu–O peroxide vibration. Whereas the frequencies of the metal–donor vibrations are essentially identical (352 cm^{-1} in **19**, 353 cm^{-1} in **20**) for all three peroxo complexes, the peroxide vibrations differ remarkably. In the spectrum of **19** this band is located at 898 cm^{-1} and in the spectrum of **20** it is found at 888 cm^{-1}.

The magnetic moment of complex **18** decreases by lowering the temperature while the magnetic susceptibility shows a minimum at 80 K. The room temperature values for μ_{eff} per copper center is 0.80 μ_B showing strong antiferromagnetically coupling. The theoretical fitting procedure using the Bleaney–Bowers [128] equation gives $2J = -510 \pm 20\ cm^{-1}$ which confirms the magnetic susceptibility measurements (Table 2).

The synthesis of the μ_4-peroxo complexes is relevant to our studies on the preparation of new functional models for the active site of catechol oxidase. The O_2^{2-} ion has been formed by a copper mediated reduction of O_2 with 3,5-DTBC as electron donor which itself is oxidized to quinone. Under basic reaction conditions in methanol, a planar tetranuclear μ_4-oxo species $[Cu_4(L^1)_2(O)(OH)_2(MeOH)_2(ClO_4)_2]$ (**21**) crystallizes on treatment of the corresponding tridentate ligand HL^1 with two equivalents of copper(II) perchlorate. This fully spectroscopic and structurally characterized tetranuclear μ_4-oxo copper(II) complex **21** can be converted into the μ_4-peroxo complex **18** by addition of H_2O_2 or 3,5-DTBC/O_2 in solution (Fig. 16).

In the presence of coordinating anions an aggregation of complexes of this type is favored reaction leading for example with halide or carboxylate groups, to similar tetrahedral tetranuclear μ_4-oxo complexes [129].

2.4. Mononuclear copper(I) complexes as precursors for modeling the active site of catechol oxidase

An accurate structural model for the dinuclear active site of catechol oxidase might be generated by bringing two monomer copper(I) complexes in the presence of dioxygen together. We have undertaken reactions of O_2 with mononuclear copper(I) complexes containing di- and tripodal ligands having only nitrogen donors to mimic the protein.

Particularly the group of Karlin has synthesized various dicopper complexes utilizing neutral ligands with tridentate Py_2(bis[2-(2-pyridyl)ethylamine]) units, especially the mentioned peroxo species [118]. We also use ligands predominantly with pyridine and imidazole units and incorporated *N*-donors such as morpholine or substituted aliphatic nitrogen atoms. These hindered tripodal ligands provide the formation of copper(I) complexes with a distorted tetrahedral geometry which is believed to increase the reactivity towards dioxygen. Cationic copper(I) complexes can be isolated as stable compounds of the new tripodal tetradentate ligands bpepa {[(bis(2-(2-pyridyl)ethyl))-(3-*N*,*N*-dimethylpropylamino)]amine}, bpedepa {[(bis(2-(2-pyridyl)ethyl))-(3-*N*,*N*-diethylpropylamino)]amine} and pmpempa {[((2-pyridyl)methyl)-(2-(2-pyridyl)ethyl)(*N*-morpholino-propylamino)]amine} with $[Cu(CH_3CN)_4]Y$ ($Y = ClO_4/PF_6/BF_4$) in methanol under argon. The X-ray structures of the tetrahedral distorted complexes $[Cu(bpepa)]PF_6$ (**22**) and $[Cu(bpedepa)]ClO_4$ (**23**) were determined [102,130]. Fig. 17 represents a general scheme of the preparation of the dinuclear bis-μ-methoxy copper(II) complexes using a copper(I) precursor.

We could isolate and characterize the dinuclear bis-μ-methoxy copper(II) complexes $[Cu_2(bpepa)_2(\mu\text{-}OCH_3)_2](PF_6)_2$ (**24**), $[Cu_2(bpedepa)_2(\mu\text{-}OCH_3)_2](ClO_4)_2 \cdot 2CH_3OH$ (**25**), $[Cu_2(pmpempa)_2(\mu\text{-}OCH_3)_2](PF_6)_2$ (**26**) and $[Cu_2(bmipmm)_2(\mu\text{-}OCH_3)_2(ClO_4)][ClO_4] \cdot CH_3OH$ (**27**) (bmipmm = di-(1-methyl-1*H*-2-imidazolyl)(2-pyridyl)methyl-methylether) [131] from a methanolic solution of the precursors in the presence of dioxygen. X-ray crystal structure analysis indicates the cations to contain a dinuclear copper(II) center coordinated by one ligand molecule to each copper. The central atoms are in distorted square pyramidal coordination by two aromatic nitrogen atoms and two bridging alkoxy oxygen atoms in the plane and the central ligand nitrogen or anion on the apex of the pyramid. The Cu–Cu distances of the antiferromagnetically coupled centers were determined to be 3.070(3) (**24**), 3.104(2) (**25**), 3.070(3) (**26**) and 2.954(1) Å (**27**), respectively. Fig. 18 gives an example of the structural properties of the characterized bis-μ-methoxy copper(II) cations with tripodal ligands.

The dinuclear metal center in $[Cu_2(bmipmm)_2(\mu\text{-}OMe)_2(ClO_4)][ClO_4] \cdot MeOH$ (**27**) is bridged by a perchlorate anion. This structural motif is rather unusual and has been found in only a few dinuclear copper(II) complexes [104,132].

The synthesis of a μ-peroxo dinuclear copper(II) complex by Thompson ([117]b) via treatment of the copper(I) ethylene complex with the dipodal ligand *N*,*N*,*N*′,*N*′-tetraetylenediamine prompted us to try dipodal nitrogen containing ligands such as mpe (*N*-morpholino-2-(2-pyridyl)ethane (mpe)) and tben (*N*,*N*,*N*′,*N*′-tetrakisbenzylethylenediamine) [133] hoping for similar results. The copper(II) complexes can be isolated by oxygenation of the in situ prepared copper(I) precursors of equimolar amounts of ligand and $[Cu(CH_3CN)_4]ClO_4$ in methanol or acetone. From X-ray crystal data of the μ-hydroxy-μ-methoxy bridged complex $[Cu_2(mpe)_2(\mu\text{-}OH)(\mu\text{-}OCH_3)](ClO_4)_2$ (**28**) and the bis-μ-hydroxy complex $[Cu_2(tben)_2(\mu\text{-}OH)_2](ClO_4)_2 \cdot 2CH_3COCH_3$ (**29**) the Cu–Cu distances of the antiferromagnetically coupled centers are determined to be 2.967(1) (**28**) and 3.014(2) Å (**29**), respectively. Fig. 19 gives the structures of the in situ prepared hydroxy bridged copper(II) complexes.

All prepared complexes have an antiferromagnetically coupled dinuclear copper(II) center with a Cu–Cu distance of about 3 Å. Including the nitrogen coordination sphere and the structural analogy of the complexes, they are model compounds for the active site of catechol oxidase. Also some important parameters for molecular modeling concerning different copper coordination polyhedra were developed by our group [134].

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