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Biomimetic Applications of Metal Systems Supported by Scorpionates

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1. Introduction

It is well established that a number of metal ions are essential to life (Fraústo da Silva & Williams, 2001; Bertini et al., 2006). A major determinant of their functional relevance in living systems is that a substantial fraction of enzymes requires metal for its catalytic activity. A wide variety of metal-dependent enzymes is found in nature which acts in fundamental biological processes, including photosynthesis, respiration and nitrose fixation (Bertini et al., 2001). Over the years, a wealth of knowledge on enzymes has been accumulated, including data on three-dimensional structures, kinetic and biochemical properties, and reaction mechanisms (Andreini et al., 2008). As metalloprotein chemistry is governed by the environment close to the metal center(s), a fertile field of investigation is concerned with the preparation of low molecular weight complexes that mimic the structural or functional features of protein active sites. The synthetic analogue or model approach provides insights into bioinorganic systems through the synthesis and study of closely related 'model' compounds. It garners structural, electronic, spectroscopic, and chemical information crucial to a complete understanding of enzyme behavior. Scorpionates have been extensively used in biomimetic chemistry as "spectator ligands" but are not directly involved in the metal-based reactivity. A common approach for obtaining synthetic analogs of the type $[\{XYZ\}M-L]$ (M = metal; L = OH, H₂O, Cys, etc.) involves the application of tridentate ligands which incorporate the requisite X, Y, and Z donor groups to mimic the protein residues that bind metals at the active site. In particular, tripodal ligands in which the X, Y, and Z groups are attached to a common tetrahedral (or trigonal pyramidal) center have proven to be of particular benefit for several reasons: a) tripodal ligands enforce the "facial" binding that is required to create a tetrahedral metal center, b) tripodal ligands typically possess only a single relevant binding conformation, c) as a consequence of the directional nature of tripodal ligands, it is possible to incorporate substituents that directly influence the steric environment about the metal center, and d) the substituents on these ligands can be readily modified to provide a mean to influence both the size of the coordination pocket and the electronic properties of the metal center. One of the most versatile tripodal ligand typology that can be utilized for biomimetic purposes is represented by the scorpionates. Theazole rings of these ligands can in fact be considered as good models of the histidine residues of proteins, and their spatial disposition provides the steric arrangements found in many active sites. In addition, from a synthetic point of view,

the steric and electronic properties of these ligands can be easily modulated by placing appropriate substituents in close proximity of the N donor atoms. In recent years, complexes of scorpionate ligands were successfully used to mimic the activity of enzymes containing metals. With this ever-growing wealth of scorpionate-supported coordination and bioinorganic chemistry, this issue would provide a valuable resource for chemists and biologist, clarifying the properties of metal complexes with scorpionate ligands with biological activity or used as models for active sites of enzymes and proteins.

This Chapter analyzes the chemical diversity exhibited by some metal complexes (such as copper and zinc complexes) supported by scorpionate ligands and the overall progress on synthetic analogs of enzyme centers, focusing primarily on systems in which coordination spheres contain poly(pyrazolyl)borate ligands.

2. Poly(pyrazolyl)borate ligands

Since poly(pyrazolyl)borate ligands were discovered in 1966 by Trofimenko (Trofimenko, 1966), their coordination chemistry has been extensively developed with particular interest arising out of the ability of this class of ligands to modify or control the steric and electronic environment about the metal center by variation of the pyrazolyl groups (Trofimenko, 1999). Apart Trofimenko's papers (Trofimenko, 1971; Trofimenko, 1972; Niedenzu & Trofimenko, 1986; Trofimenko, 1986; Trofimenko, 1993), a number of reviews and chapters were devoted to chemistry of poly(pyrazolyl)borate ligands (Edelmann, 2001; Ward et al., 2001; Webster & Hall, 2003; Pettinari & Santini, 2004; Dias & Fianchini, 2007; Spicer & Reglinski, 2009; Pellei et al., 2010; Santini et al., 2010) and related metal complexes. In 2003 the scorpionate ligands and their father Trofimenko were guests of honor at a symposium to celebrate 35 years of chemistry with poly(pyrazolyl)borates and related ligands (Ritter, 2003). The special issues 2-3 (Vol. 23, 2004) of *Polyhedron* were dedicated to this topic, the first paper being presented by Trofimenko on development of scorpionate ligands system from its genesis (Trofimenko, 2004). In 2008 a book dedicated to Swiatoslaw Trofimenko has been published by the Imperial College Press (Pettinari, 2008). The special issue 12 (Vol. 362, 2009) of *Inorganica Chimica Acta* was dedicated to Dr. Swiatoslaw Trofimenko to honour and remember his strong contribution to chemistry and 40 years of work accomplished with the poly(pyrazolyl)borates and related tripodal ligands.

2.1 Poly(pyrazolyl)borate properties

The fundamental feature in all poly(pyrazolyl)borate complexes is the six-membered ring within a more general structure $RR'B(\mu\text{-pz})_2M(L)_n$ (Fig. 1). For these ligands and their constituents we adopt an extensive nomenclature based on the abbreviation proposed in ref. (Pellei et al., 2010).

Because of the bond angles and distances involved, the $B(\mu\text{-pz})_2M$ ring has almost nearly a boat conformation. In Fig. 1a, R and R' are different: the pseudoequatorial R' is pointing away from the metal roughly along the B-M axis, but the pseudoaxial R is directed towards the metal, and may bond to it, interact with it, or simply screen it towards other ligands. R may be H, alkyl, aryl, OR, SR, NMe₂ or another pyrazolyl group with unspecified substituents (pz^x). It was this feature that prompted Trofimenko to coin the term "scorpionates" for polypyrazolylborates, as the coordination behavior of the $RR'B(\mu\text{-pz})_2$ ligands closely resembles the hunting habits of a scorpion: this creature grabs its prey with

two identical claws (coordination of M through the two 2-N atoms of the B(μ -pz)₂ groups), and then may, or may not, proceed to sting it with its overarching tail (the R' group).

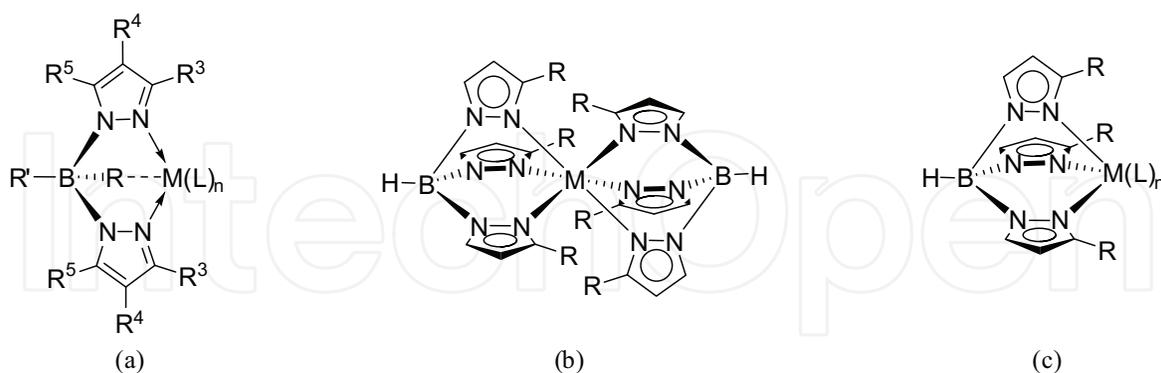


Fig. 1. General structure of: a) poly(pyrazolyl)borate complexes $RR'B(pz^{R^3,R^4,R^5})_2M(L)_n$; b) $[HB(pz^R)_3]_2M$ complexes; c) $[HB(pz^R)_3]M(L)_n$ complexes

Tris(pyrazolyl)borates generally coordinate as tridentate ligands κ^3-N,N',N'' (Fig. 1b and 1c), through three nitrogen atoms of the pyrazole rings thereby providing effective steric shielding of the metal center. In a $M[HB(pz^R)_3]$ fragment the R substituents protrude in space past the metal, enveloping it, and forming a protective pocket of varying size and shape. The evaluation of the size of the variously substituted $[HB(pz^R)_3]$ ligands is more important for developing an understanding the influence of pyrazolyl ring substituents on the chemistry of their metal complexes. Ligand size can be evaluated by the concept of *cone angle* (θ), which was originally introduced for phosphine ligands (Tolman, 1977). The smaller the cone angle, and the larger the wedge angle, the easier it is for other ligands coordination to the metal. Because of this feature, the proper choice of 3-R substituents does adjust the steric accessibility of the coordinated metal, in this fashion controlling the coordination chemistry of the $[HB(pz^R)_3]M$ species (Trofimenko, 1999). All of the $[HB(pz^R)_3]$ ligands have a cone angle (θ) larger than 180° , and the trends in the values of these angles were consistent with the trends in the coordination chemistry of the $[HB(pz^R)_3]$ ligands. Indeed, the ligands of small cone angle (i.e. $[HB(pz)_3]$, $[HB(pz^{Me})_3]$, etc.) are characterized by a strong tendency to form $[HB(pz^R)_3]_2M$ (Fig. 1b) complexes with divalent first row transition metals, and the inability to form stable $[HB(pz^R)_3]M(L)_n$ species (Fig. 1c) (Trofimenko, 1999; Pettinari & Santini, 2004; Pellei et al., 2010; Santini et al., 2010). Ligands having an intermediate cone angle (i.e. $[HB(pz^{iPr})_3]$, $[HB(pz^{Ph})_3]$, etc.) are capable of forming both $[HB(pz^R)_3]_2M$ and $[HB(pz^R)_3]MX$ species. The most sterically demanding ligands (i.e., $[HB(pz^{tBu})_3]$, $[HB(pz^{Ms})_3]$, etc.) inhibit formation of $[HB(pz^R)_3]_2M$ and heavily favour four-coordinate compounds $[HB(pz^R)_3]MX$ with C_{3v} -distorted tetrahedral geometries (Trofimenko et al., 1992). The cone angles depend not only on the ligand itself, but also on the length of the N-M bond. The combined results from experimental studies in which the structures, spectroscopic properties, and reactivity of a number of metal complexes were examined and in some cases directly compared, were summarized in a series according to effective steric bulk at a complexed metal center. Analogously, comparison of the structure, physical and spectroscopic properties of similar compounds with homologous ligands provides insight into the relative electron-donating or electron-withdrawing capabilities of $[HB(pz^R)_3]$ ligands (Kitajima & Tolman, 1995).

3. Biomimetic chemistry of Scorpionates

In the last decades the comprehension of the molecular mechanisms behind crucial enzymatic reaction has considerably advanced. The increasing number of available protein structures has allowed to elucidate many metal-based catalytic sites responsible of specific enzymes activity. In parallel with this, the employment of synthetic analogues (Holm & Solomon, 2004), such as small molecular weight complexes that reproduce not only the structural aspects of the metals sites, but also their functioning, has permitted a better understanding of many biological processes. In addition, this has resulted also in the potential exploitation of these models in stoichiometrically simple but fundamental catalytic reactions such as nitrogen activation (Yandulov & Schrock, 2003) or oxygen-evolving from water (Kanan & Nocera, 2008). The design and synthesis of specific ligands that confer to the resulting complex desired structural and, possibly, functional properties is therefore of fundamental importance, and many new ligand systems were produced with this specific intent.

Scorpionate ligands have been extensively used in biomimetic chemistry as *spectator ligands*, which modulate the electronic and steric properties of the metal ion and of the co-ligands or actor ligands, but are not directly involved in the metal-based reactivity. Poly(pyrazolyl)borates can in many ways mimic histidine nitrogen ligation, so, it is possible to synthesize simple models for active sites of bio-organic macromolecules such as enzymes (Parkin, 2004). In addition, from a synthetic point of view, the steric and electronic properties of these ligands can be easily modulated by placing opportune substituents in close proximity of the N donor atoms. Different steric hindrance produces in some cases complexes that exhibit different nuclearity.

3.1 Copper biomimetic systems

The biological role of copper is made evident by its involvement in many crucial biological functions. These can be classified as follows: dioxygen activation and transport (Solomon et al., 1994; Solomon et al., 1996; Solomon et al., 2001), electron transfer (Colman et al., 1978; Durley et al., 1993; Hart et al., 1996; Shibata et al., 1999), nitrite reduction (Wasser et al., 2002) and copper delivery, storage and detoxification (Henkel & Krebs, 2004; Calderone et al., 2005). In most cases copper exerts its function by means of its redox properties, *i.e.*, the ability to cycle between +1 and +2 oxidation states. The geometry and the type of donor atoms surrounding the metal are fundamental in determining the functional properties of the Cu-proteins (Holm et al., 1996). The copper centers can be classified according to their geometry, donor set and nuclearity. At present, at least seven structural motives have been recognized (Koval et al., 2006), among which are the classical T1 (plastocyanin), T2 (copper nitrite reductase), and T3 (oxy-hemocyanin, oxy-Hc) arrangements (Fig. 2).

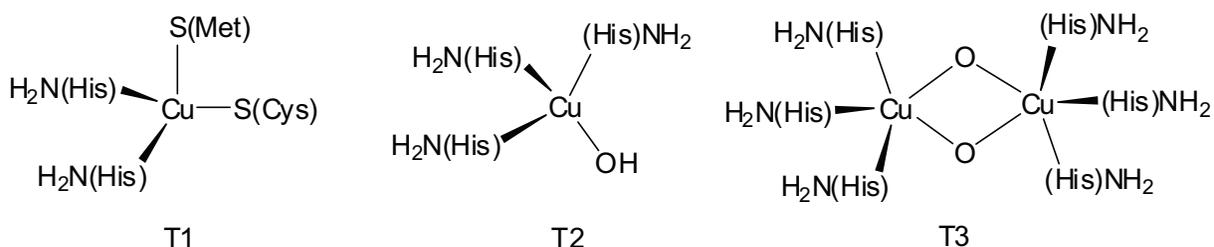


Fig. 2. Some examples of T1, T2 and T3 copper sites.

Model chemistry has been decisive in identifying the mode of peroxide coordination in oxy-hemocyanin (oxy-Hc). Better spectroscopic models of oxy-Hc were obtained by using sterically encumbered tris(pyrazol-1-yl)borates as supporting ligands in Cu(I) complexes that can bind dioxygen. The peroxo complex $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]_2\text{Cu}_2(\text{O}_2)$ represents the first X-ray characterized model of the oxy-Hc metal site that mimics well the spectral properties of the protein (Kitajima et al., 1989; Volbeda & Hol, 1989; Hazes et al., 1993; Magnus et al., 1994; Cuff et al., 1998) (Fig. 3a).

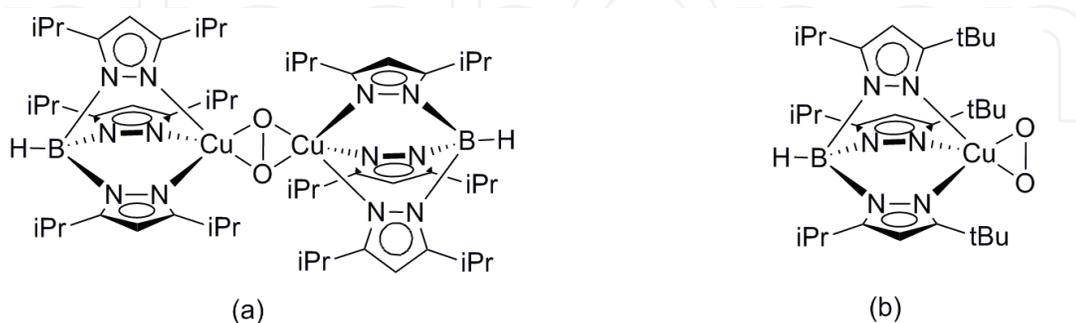


Fig. 3. Structure of: a) $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]_2\text{Cu}_2(\text{O}_2)$; b) $[\text{HB}(\text{pz}^{\text{tBu,iPr}})_3]\text{Cu}(\text{O}_2)$.

The complex displayed an unprecedented coordination mode of the bridging peroxo anion, with a planar arrangement of the $\text{Cu}-\text{O}_2-\text{Cu}$ moiety and with the peroxo group bridging side-on two metal centers ($\mu-\eta_2:\eta_2-\text{O}_2^{2-}$ or $^{\text{SP}}$ coordination mode). It is notable that the reaction between $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]_2\text{Cu}_2(\text{O}_2)$ and $\text{NaN}_3\cdot\text{H}_2\text{O}$ gave $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]_2\text{Cu}_2(\mu-\text{OH})(\mu-\text{N}_3)$, a dinuclear copper(II) complex containing (μ -hydroxo)(μ -1,3-azido) bridges (with the bridging hydroxide originating from water) (Kitajima et al., 1993), which mimics the physico-chemical properties of metazido-hemocyanin (Himmelwright et al., 1980; Pate et al., 1986). As for the functional properties of hemocyanin, the Cu-site allows a reversible and fast O_2 -binding that renders O_2 -transport possible, while the Cu(I) model complexes with tris(pyrazolyl)borates bind O_2 irreversibly to yield the $^{\text{SP}}$ species (Kitajima et al., 1988; Kitajima et al., 1989; Hu et al., 2000). On the other hand, O_2 -reactivity is modified when employing neutral tris(pyrazolyl)methanes ($[\text{HC}(\text{pz}^{\text{R,R}})_3]$) as supporting ligands in Cu(I) models. For example, the pseudo-tetrahedral complex $\{[\text{HC}(\text{pz}^{\text{Me,Me}})_3]\text{Cu}(\text{MeCN})\}^+$ binds O_2 as a $^{\text{SP}}$ species in a reversible manner (Cvetkovic et al., 2001).

Oxytyrosinase (oxy-Tyr) has an active site very similar to oxy-Hc (Matoba et al., 2006). Models of oxy-Hc ($^{\text{SP}}$ peroxo complexes) have been tested as models for tyrosinase activity, in order to verify whether they are able to incorporate an oxygen atom into a substrate such as phenol. The model compound $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]_2\text{Cu}_2(\text{O}_2)$ reacts with hindered phenols, but yields diphenoquinones instead of benzoquinones (Kitajima et al., 1990). However, this behavior is not in contrast with tyrosinase biomimetics, because this enzyme also gives primarily diphenoquinones when hindered phenols are used as substrates (Pandey et al., 1990). Two mechanisms can explain this reactivity of $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]_2\text{Cu}_2(\text{O}_2)$: 1) the spontaneous O-O bond cleavage of the peroxide to give a Cu(II)-O-species that abstracts a hydrogen atom from phenol; 2) the acid/base substitution between the acidic phenol and the basic peroxide, affording a Cu(II)-phenoxo species (equivalent to a Cu(I)-phenoxy one) that undergoes reductive Cu-O bond cleavage. In both the cases a phenoxyl radical is generated, which easily reacts to yield diphenoquinones. The alkylperoxo complex $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{tBuOO})$ models the supposed hydroperoxo intermediate (Kitajima et al., 1993).

A successful strategy to isolate Cu(II)-O₂^{·-} complexes has been developed by employing sterically hindered tris(pyrazolyl)borates as supporting ligands. The steric hindrance and the anionic character of these ligands contribute to diminish the oxidizing ability of the mononuclear species towards the second equivalent of Cu(I), such that 1:1:1 [HB(pz^{R,R'})₃]:Cu:O₂ complexes could be isolated. In particular, by reacting the mononuclear complex [HB(pz^{tBu,iPr})₃]Cu(DMF) with dioxygen, a diamagnetic mononuclear side-on superoxo complex (^sS) (Fig. 4) [HB(pz^{tBu,iPr})₃]Cu(O₂), was crystallized (Fujisawa et al., 1994).

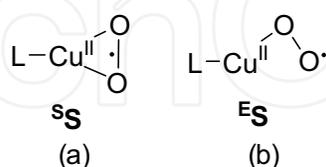


Fig. 4. a) Diamagnetic mononuclear side-on superoxo complex (^sS); b) dioxygen in an end-on coordinated superoxo form (^eS).

A more hindered *t*-butyl group in place of a *i*-propyl group was decisive in defining the nuclearity of the product of oxygenation (Kitajima & Tolman, 1995). As shown by spectroscopic measurements, solutions of [HB(pz^{tBu,iPr})₃]Cu(O₂) (Fujisawa et al., 1994) (Fig. 3b) contain small amounts of the corresponding binuclear ^sP species. When a bulkier R substituent such as an adamantyl group was introduced on the pyrazolic arms of the scorpionate, in place of *t*-butyl, only the ^sS species [HB(pz^{Ad,iPr})₃]₂Cu₂(O₂) was detected, without any trace of the ^sP form (Chen et al., 2003).

Fungal galactose oxidase (GOase) is an extracellular copper enzyme that catalyzes the oxidation of various primary alcohols to aldehydes (Whittaker & Whittaker, 1998; Whittaker, 2003; Whittaker, 2005). The crystal structure of the protein (Ito et al., 1994) reveals a mononuclear copper site, with two N-donor histidines, two O-donor tyrosines (one axial and one equatorial) and an exogenous ligand (water or acetate) in a distorted square-pyramidal coordination. The catalytically active group is the modified tyrosine in the equatorial position (cofactor), which is covalently linked to a cysteine residue. Three oxidation levels of the metal site are involved in the mechanism of the enzyme: 1) the oxidized Cu(II)-tyrosyl radical (GOase^{OX}), which is responsible for the two-electron oxidation of the substrate, 2) the Cu(I)-tyrosine form (GOase^{RED}) that reduces O₂ to H₂O₂, and 3) the Cu(II)-tyrosine form (GOase^{SEMI}), which is considered as an intermediate between the previous states. The related enzyme glyoxal oxidase, which catalyzes the oxidation of aldehydes to carboxylic acids, has a similar reactivity and active site composition (Chaudhuri & Wieghardt, 2001). Modeling the Cu(II)-phenoxo state (GOase^{OX}) in order to improve our understanding of the mechanistic details of the first rate-determining step of the catalytic cycle has been a challenge for biomimetic chemists (Wang et al., 1998; Thomas, 2007). Chelate effect, sulfur involvement and steric shielding have been employed to mimic the stability of the Cu(II)-phenoxo moiety. In this context, tris(pyrazolyl)borates were used as supporting ligands in ternary complexes to mimic the diradical Cu(II)-phenoxo state. The complex [HB(pz^{Cum,Me})₃]Cu(O(MeS)C₆H₄) (Cum = cumenyl, C₆H₄(SMe)OH = 2-(methylsulfanyl)phenol) of Fig. 5a, is a structural model of GOase^{SEMI} (Ruf & Pierpont, 1998). The irreversible behavior of the phenoxo/phenoxy radical couple in [HB(pz^{Cum,Me})₃]Cu(O(MeS)C₆H₄) is attributed to sulfur decoordination during the oxidative process. Also the complex [HB(pz^{Ph})₃]Cu(L) (L = 2-hydroxy-3-methylsulfanyl-5-methylbenzaldehyde, Fig. 5b) can be considered as a model of GOase^{SEMI}, wherein the co-

ligand L mimics the thioether-substituted Tyr272 of the enzyme (Halcrow et al., 1998; Halcrow et al., 1999).

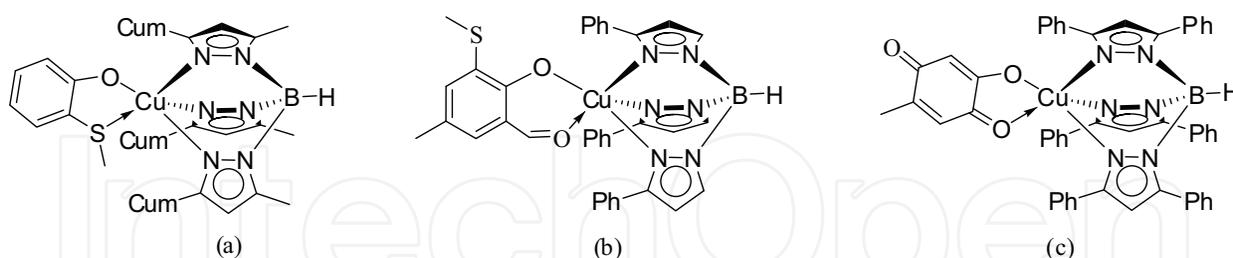


Fig. 5. Molecular structure of: a) $[\text{HB}(\text{pz}^{\text{Cum,Me}})_3]\text{Cu}(\text{O}(\text{MeS})\text{C}_6\text{H}_4)$; b) $[\text{HB}(\text{pz}^{\text{Ph}})_3]\text{Cu}(\text{L})$ ($\text{L} = 2\text{-hydroxy-3-methylsulfanyl-5-methylbenzaldehyde}$); c) $[\text{HB}(\text{pz}^{\text{Ph,Ph}})_3]\text{Cu}(\text{L})$ ($\text{HL} = 2\text{-hydroxy-5-methyl-1,4-benzoquinone}$).

Other $[\text{HB}(\text{pz}^{\text{Ph}})_3]\text{Cu}^{\text{II}}$ complexes containing chelate phenolates exhibit a similar arrangement around the copper center (Halcrow et al., 1999). $[\text{HB}(\text{pz}^{\text{Ph}})_3]\text{Cu}(\text{L})$ was electrochemically oxidized to $\{[\text{HB}(\text{pz}^{\text{Ph}})_3]\text{Cu}(\text{L})\}^+$, which is a good spectroscopic model of the diradical $\text{Cu}(\text{II})$ -phenoxo moiety of GOase^{OX} , being EPR silent and presenting comparable visible-NIR features (Whittaker et al., 1996). The electrochemical reversibility of the phenoxo/phenoxy radical redox process, not observed in the aforementioned $[\text{HB}(\text{pz}^{\text{Cum,Me}})_3]\text{Cu}(\text{O}(\text{MeS})\text{C}_6\text{H}_4)$ model, probably implies conservation of the square pyramidal geometry also in the oxidised form $\{[\text{HB}(\text{pz}^{\text{Ph}})_3]\text{Cu}(\text{L})\}^+$, even though there is no structural evidence to support this hypothesis. Interestingly, by introducing bulky substituents such as *t*-butyl group in the *para* position of the phenolic co-ligand, a decrease in the kinetic stability of the electrochemically generated diradical $\text{Cu}(\text{II})$ -phenoxo species is observed (Sylvestre et al., 2005). The heteroscorpionate ligand (2-hydroxy-3-*t*-butylmethylphenyl)bis(3,5-dimethylpyrazolyl)methane (L1O) gave the ternary complex $[\text{Cu}(\text{L1O})(\text{OAc})]$ where the acetate ion is bound to the metal with both oxygen atoms. It has been proposed that the N_2O donor set provided by L1O ligand serves as a mimic for two histine and the tyrosine residues (Warthen & Carrano, 2003).

Copper amine oxidases (CuAOases) catalyze the aerobic oxidation of primary amines to aldehydes in some bacteria, yeasts, plants and mammals (Klinman, 1996; Mure et al., 2002). The catalytic site contains a T2 copper center, $[\text{Cu}(\text{His})_3(\text{OH}_2)_n]^{+/2+}$ ($n = 0$ or 2), and the organic cofactor 2-(1-amino-1-carboxyethyl)-5-hydroxy-1,4-benzoquinone (TPQ). CuAOases were crystallized in two forms, TPQ-on (Parsons et al., 1995) and TPQ-off (Li et al., 1997) exhibiting the TPQ cofactor bound to the metal or 3-5 Å distant from it, respectively. The complex $[\text{HB}(\text{pz}^{\text{Ph,Ph}})_3]\text{Cu}(\text{L})$ ($\text{HL} = 2\text{-hydroxy-5-methyl-1,4-benzoquinone}$, Fig. 5c) (Foster et al., 2000) was synthesized and electrochemically characterized in order to model Cu/TPQ interactions in CuAOases . In the structure of $[\text{HB}(\text{pz}^{\text{Ph,Ph}})_3]\text{Cu}(\text{L})$, copper adopts a distorted square-pyramidal geometry, with a longer Cu-N interaction in axial position, as was previously found for similar complexes (Li et al., 2000) and in TPQ-on CuAOases (Nakamura et al., 1992; Speier et al., 1994).

Model complexes have been reported to reproduce the peculiar structure and spectroscopic features of blue copper proteins (Kitajima et al., 1990; Kitajima et al., 1992; Holland & Tolman, 1999; Holland & Tolman, 2000; Randall et al., 2000), or the function of these biological electron carriers (Rorabacher, 2004). The major synthetic challenges to yield structural/spectroscopic models have been: 1) obtain $\text{Cu}(\text{II})$ -thiolate species, without the

concomitant formation of disulfides and Cu(I) (Mandal et al., 1997), and 2) provide complexes exhibiting distorted tetrahedral coordination of Cu(II), which mostly prefers a tetragonal environment. Substituted tris(pyrazolyl)borate ligands were originally employed in order to fulfil these requirements (Kitajima & Tolman, 1995), since they are tetrahedral enforcers and furnish enough electron density to copper to disfavor oxidation of thiolate co-ligands (Bruce & Ostaszewski, 1973; Churchill et al., 1975). Moreover, steric hindrance on $[\text{HB}(\text{pz}^{\text{R,R'}})_3]^-$ prevents (a) the formation of $[\text{HB}(\text{pz}^{\text{R,R'}})_3]_2\text{Cu}$ complexes and (b) the occurrence of direct Cu(II)-thiolate-Cu(II) bridges, which may be involved in the mechanism of disulfide formation (Lappin & McAuley, 1978).

The complexes $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]\text{Co}^{\text{II}}(\text{SR})$ ($\text{SR} = p$ -nitrobenzenethiolate or O-ethylcysteinate), which are stable in solution only at low temperatures, represent the first spectroscopic models of the Co(II)-substituted blue Copper proteins active site (Thompson et al., 1979). Cu(II) complexes with $\text{N,N',S}(\text{SR}')$ coordination motif, as commonly found in T1 sites, were isolated by using the N,N',S -donor scorpionate ligand $[\text{H}(\text{SPh}^{p\text{-Me}})\text{B}(\text{pz}^{\text{Me,Me}})_2]^-$ instead of $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]^-$ (Thompson et al., 1980). The complexes exhibit similar spectroscopic features to the aforementioned $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]\text{Cu}(\text{SR})$ species. An increase in the steric bulk of the scorpionate substituents (*i*-propyl groups in place of methyl groups) allowed for the crystallization of a model of an oxidized T1 site in the form of the complex $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SR})$ ($\text{SR} = \text{SC}_6\text{F}_5$, Fig. 6a) (Kitajima et al., 1992).

The $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SR})$ complexes ($\text{SR} = \text{SC}_6\text{F}_5$, SCMe_3 , SCPh_3 , S-tBu) are good spectroscopic models for the oxidized T1 sites (Kitajima et al., 1990; Kitajima et al., 1992; Qiu et al., 1994). Spectroscopic measurements and DFT calculations on $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SCPh}_3)$ have led to the following observations (Randall et al., 2000): 1) there is a stronger and more covalent thiolate-Cu donor interaction in $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SCPh}_3)$ than in the T1 site of plastocyanin; 2) there is a weaker ligand field in the model, consistent with a more regular tetrahedral geometry around the metal; 3) an increase in the effective nuclear charge of copper from plastocyanin to $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SCPh}_3)$, which implies a weaker donor set in the model (N,N,N from $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]$) relative to the $\text{N}(\text{His})_2\text{S}(\text{Met})$ donor set in plastocyanin.

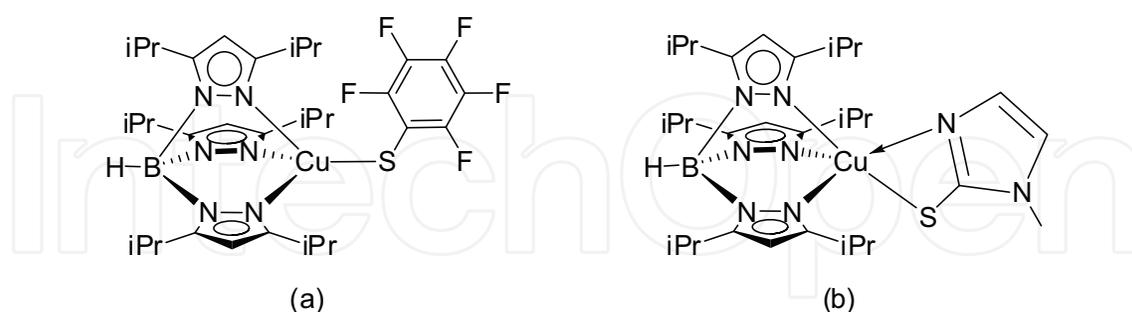


Fig. 6. Molecular structure of: a) $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SC}_6\text{F}_5)$; b) $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{tim}^{\text{Me}})$.

A further Cu(II) complex with the $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]^-$ supporting ligand was synthesized, using a thioxo-imidazole (tim^{Me}) as co-ligand (Basumallick et al., 2002). The resulting complex $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{tim}^{\text{Me}})$ exhibits a square-pyramidal geometry around the copper ion, with a N_4S donor set (Fig. 6b). $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{SMelM})$ can be considered a structural model of some mutant azurins (Canters & Gilardi, 1993; Den Blaauwen & Canters, 1993; den Blaauwen et al., 1993) and nitrosocyanin (a red copper protein) (Whittaker et al., 2000; Lieberman et al., 2001), both involving a pentacoordinated Cu(II) ion. The effect of the

increase of the coordination number was investigated by comparing the structural/spectroscopic properties of $[\text{HB}(\text{pz}^{\text{iPr},\text{iPr}})_3]\text{Cu}(\text{SMelM})$ with those of $[\text{HB}(\text{pz}^{\text{iPr},\text{iPr}})_3]\text{Cu}(\text{SCPh}_3)$.

The metalloenzyme copper nitrite reductase (CuNIR) plays a key role in the nitrogen cycle since it reduces nitrite ions (NO_2^-) to nitric oxide (NO). The resting state active site of CuNIR consists of a Cu(II) ion tetrahedrally coordinated by three N-donor histidines and a water molecule (T2 site) (Godden et al., 1991). This site is connected to a T1 electron transfer site by a His-Cys bridge. A first hypothesis of the enzyme's catalytic mechanism, proposed by Averill (Hulse et al., 1989; Averill, 1996), contemplates the initial reduction of the metal center (with electrons shuttled from the T1 site) and subsequent binding of nitrite to Cu(I) by means of the N atom ($\eta^1\text{-N}$ coordination). This $\eta^1\text{-N}$ coordination is supported by experimental evidence on model complexes (Halfen & Tolman, 1994; Mahapatra et al., 1996). Subsequent protonation of the substrate would give water and a copper-nitrosyl complex, presumably an unstable $\{\text{CuNO}\}^{10}$ species (Enemark & Feltham, 1974), wherein NO is reasonably considered to be $\eta^1\text{-N}$ end-on coordinated to the metal. The copper-nitrosyl intermediate is crucial for the catalytic mechanism of CuNIR, and for this reason some mononuclear Cu-NO complexes were prepared to model this species. Copper complexes as models for nitrite reductase were examined in ref. (Wasser et al., 2002). The complex $[\text{HB}(\text{pz}^{\text{tBu}})_3]\text{Cu}(\text{NO})$ is the first structurally characterized mononuclear copper-nitrosyl complex (Fig. 7a) (Carrier et al., 1992; Ruggiero et al., 1993).

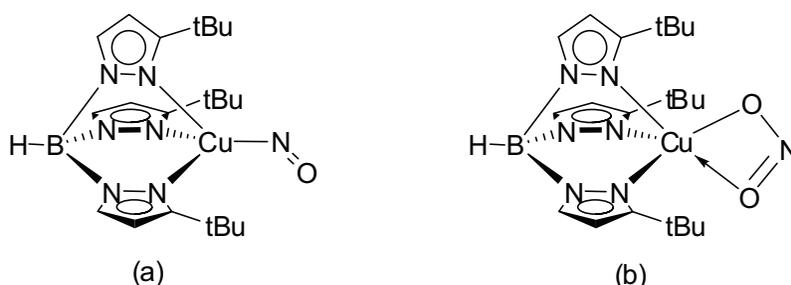


Fig. 7. Molecular structure of: a) $[\text{HB}(\text{pz}^{\text{tBu}})_3]\text{Cu}(\text{NO})$; b) $[\text{HB}(\text{pz}^{\text{tBu}})_3]\text{Cu}(\text{NO}_2)$.

The metal presents a pseudotetrahedral geometry and a $\eta^1\text{-N}$ end-on NO coordination, supporting indirectly the $\eta^1\text{-NO}$ end-on hypothesis for the $\{\text{CuNO}\}^{10}$ species of CuNIR. Nitric oxide binding is reversible, since it is lost upon application of a vacuum or when purging with argon. Two other Cu-nitrosyl complexes with scorpionates as supporting ligands, namely $[\text{HB}(\text{pz}^{\text{tBu},\text{iPr}})_3]\text{Cu}(\text{NO})$ and $[\text{HC}(\text{pz}^{\text{tBu},\text{iPr}})_3]\text{Cu}(\text{NO})$, have been characterized in the solid state (Fujisawa et al., 2008). Both these species are structural analogues of $[\text{HB}(\text{pz}^{\text{tBu}})_3]\text{Cu}(\text{NO})$, exhibiting tetrahedral coordination of the metal, with a $\eta^1\text{-N}$ end-on NO. Spectroscopic evidence and *ab initio* calculations have revealed that all the three complexes have a $\{\text{CuNO}\}^{11}$ electronic structure, better described with a Cu(I)-NO· radical interaction characterized by a significant covalency. The sterically hindered scorpionate ligand $[\text{HB}(\text{pz}^{\text{tBu}})_3]^-$, as well as being a pseudotetrahedral enforcer, has the important role of stabilizing NO coordination, by protecting it from possible disproportionation into N_2O and NO_2^- . A similar NO decomposition pathway occurs even in the enzyme, under conditions of high NO concentration (Jackson et al., 1991). NO dismutation in model complexes is strongly influenced by the nature of the substituents R and R' on the $[\text{HB}(\text{pz}^{\text{R,R'}})_3]^-$ ligand. Interesting, not only steric bulk (e.g., tBu group), but also the electron withdrawing

character (e.g., CF_3 group) of the $[\text{HB}(\text{pz}^{\text{R,R'}})_3]$ -substituents tends to slow the rate of NO disproportionation. Mechanistic investigations suggest that the process occurs by an electrophilic attack of a second NO molecule on the initial Cu-NO adduct, thus yielding a $[\text{HB}(\text{pz}^{\text{R,R'}})_3]\text{Cu}(\text{NO})_2$ adduct. Following N-N coupling and O-atom transfer, N_2O and $\text{Cu}(\text{II})-(\text{NO}_2^-)$ are generated.

The Cu(II)-nitrito form of CuNIR, which exhibits $\eta^2\text{-O,O}'$ coordination of NO_2^- to copper (Murphy et al., 1997; Veselov et al., 1998), is stabilized by hydrogen bond interactions with the protein-matrix side chains. A few Cu(II)-nitrito model complexes with hydrotris(pyrazolyl)borate co-ligands have been structurally characterized, showing either a symmetric or asymmetric $\eta^2\text{-O,O}$ coordination mode of NO_2^- , depending on the pyrazolyl substituents. Bulky R substituents, such as *t*-butyl groups, favor an asymmetric array as found in the active site of CuNIR. This is observed in the complexes $[\text{HB}(\text{pz}^{\text{tBu}})_3]\text{Cu}(\text{NO}_2)$ (Fig. 7b) (Tolman, 1991) and $[\text{HB}(\text{pz}^{\text{tBu,iPr}})_3]\text{Cu}(\text{NO}_2)$ (Lehnert et al., 2007), whereas $[\text{HB}(\text{pz}^{\text{iPr,iPr}})_3]\text{Cu}(\text{NO}_2)$ (Lehnert et al., 2007), $[\text{HB}(\text{pz}^{\text{CF}_3,\text{Me}})_3]\text{Cu}(\text{NO}_2)$ and $[\text{HB}(\text{pz}^{\text{Me,Me}})_3]\text{Cu}(\text{NO}_2)$ (Schneider et al., 1998) show a symmetric bidentate nitrite coordination. When using a neutral tris(pyrazolyl)methane as a co-ligand, two NO_2^- ions are coordinated to Cu(II): one nitrite is $\eta^1\text{-O}$ and the second one is $\eta^1\text{-N}$ bound (Lehnert et al., 2007).

Recently it has been discovered that the nitrite ion is bound in a tridentate fashion in the reduced form of CuNIR, with its oxygen atoms coordinated to Cu(I) and an additional weak Cu-N interaction (Antonyuk et al., 2005). This binding mode would allow minimal structural rearrangements between the reacting $\eta^2\text{-O,O}'$ NO_2^- and the incipient side-on coordinated NO ($\{\text{CuNO}\}^{10}$ species). The spectroscopic properties of the model complexes $[\text{HB}(\text{pz}^{\text{tBu,iPr}})_3]\text{Cu}(\text{NO})$ and $[\text{HC}(\text{pz}^{\text{tBu,iPr}})_3]\text{Cu}(\text{NO})$, in which NO is end-on bound to the metal, were compared to those of CuNIR (Usov et al., 2006). This has allowed for the determination of the binding mode of the $\{\text{CuNO}\}^{11}$ species in protein solutions as strongly bent end-on but not side-on (Fujisawa et al., 2008).

Comprehensive reviews describing structural and functional aspects of copper dioxygen models have been reported (Kitajima & Moro-oka, 1994; Lewis & Tolman, 2004; Mirica et al., 2004). The employment of scorpionate ligands in copper biometics (Kitajima, 1992; Kitajima & Tolman, 1995; Gennari & Marchiò, 2009) and to understand copper protein active-sites chemistry (Tolman, 2006) was reviewed in the past.

3.2 Zinc biomimetic systems

Zinc is essential to all forms of life and it is probably the most bio-relevant metal. Human beings contain an average of approximately 2 to 3 g of zinc and it has been found that 3% of the human genome contain the code for zinc finger proteins (Klug, 1999). There are about 400 three-dimensional structures for zinc proteins, representing all six fundamental enzyme classes: oxidoreductases (alcohol dehydrogenase family), transferases, hydrolases (carboxypeptidase family), lyases (carbonic anhydrase family), isomerases, and ligases (Auld, 2006). Thus, zinc is involved in a wide variety of metabolic processes including carbohydrate, lipid, protein, and nucleic acid synthesis and degradation. Mononuclear zinc enzymes were currently studied by several bioinorganic research groups with biomimetic complexes. Recent and substantial reviews by G. Parkin (Parkin, 2000; Parkin, 2004; Parkin, 2007), H. Vahrenkamp (Vahrenkamp, 2007) and N. Burzlaff (Fischer et al., 2009) cover almost all aspects of synthetic zinc enzyme analogues. Thus, here we will summarise some aspects of synthetic analogues of zinc enzymes that feature scorpionate ligands.

The molecular characterization of zinc sites in biological systems came first through replacing the spectroscopically silent zinc with the chromophoric metal cobalt. In particular, Co(II) substitution has been widely employed as a tool for conversion of spectroscopically silent Zn(II)-containing proteins into still-functioning enzymes, but for which optical (absorption, magnetic circular dichroism (MCD)) and magnetic resonance (nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), electron nuclear double resonance (ENDOR)) spectroscopic techniques all can be productively applied to understand enzyme structure and function (Maret & Vallee, 1993; Bertini et al., 2001). Recent examples involved high-frequency and -field electron paramagnetic resonance (HF-EPR) investigation of cobalt-substituted zinc enzymes (Krzystek et al., 2010), EPR/ENDOR studies of a Co-substituted Zn finger protein, TF IIIA (Walsby et al., 2003), MCD studies of a variety of Co-substituted Zn enzymes and model compounds (Larrabee et al., 1997). In the past the substitution of zinc in enzymes by cadmium was also attempted, in an effort to take advantage of ^{113}Cd NMR spectroscopy in gaining structural and mechanistic information (Coleman, 1992). These efforts were abandoned because it became too obvious that cadmium and zinc have essentially nothing in common in terms of ligand preferences, coordination numbers or stabilities.

Zinc enzymes in the resting state almost without exception contain zinc-bound water (Vallee & Auld, 1993). The tetrahedral $[\{\text{XYZ}\}\text{Zn}-\text{OH}_n]$ zinc centre is the most common structural feature found for the active site of zinc enzymes. In these enzymes zinc is bound to the protein by three amino acid residues. The zinc binding residues X, Y and Z are either histidine, glutamate, aspartate or cysteine.

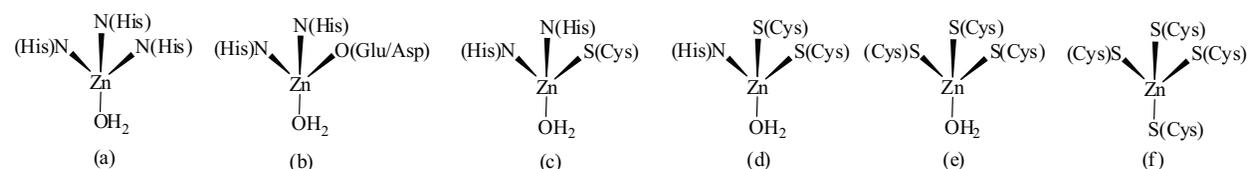


Fig. 8. Coordination motifs in mononuclear zinc enzymes: a) carbonic anhydrase, matrix metalloproteases; b) thermolysin, carboxypeptidase A; c) plant peptide deformylases (PDFs); d) alcoholdehydrogenase, cobalamine independent methionine synthase; e) 5-aminolevulinate dehydratase; f) Ada DNA repair protein.

Almost all triple combinations of these residues are found in zinc enzymes. During the resting state, the fourth position of the $[\{\text{XYZ}\}\text{Zn}-\text{OH}_n]$ active site is usually occupied by water or a hydroxido ligand (Fig. 8) (Parkin, 2004; Kraatz & Metzler-Nolte, 2006). In many cases, characteristically in the alcoholdehydrogenase (ADH) and cobalamine independent methionine synthase (CAIMS) group, the water molecule only represents the vacant coordination site which during catalysis is occupied by the substrate. More importantly, though, and exclusively in the carbonic anhydrase (CA) and matrix metalloproteases (MMP) group, the water ligand is the functional reagent which is deprotonated to become the powerful Zn-OH nucleophile which is responsible for the efficiency of the hydrolytic zinc enzymes. In fact, during their catalytic cycle the tetrahedral or pseudotetrahedral geometries of these zinc enzymes are quite flexible and change between a tetra-coordinated and a penta-coordinated zinc centre. Especially the coordination of a carboxylate donor e.g. a glutamate can easily vary in the so called carboxylate shift between a monodentate and a bidentate coordination. This flexibility is thought to be essential for the hydrolytic activity of many of the zinc enzymes.

Bioinorganic coordination chemists who are trying to model such active sites by simple ligands and zinc complexes are therefore facing several problems: a) the flexibility mentioned above is difficult to mimic without a surrounding protein pocket; b) amino acids on their own coordinate zinc ion not only via the amino acid residue but also via the N- or C-terminus of the sequence; c) protected amino acids or small oligopeptides are often not bulky enough to prevent the formation of bisligand complexes or hydroxido bridged dinuclear zinc complexes, this is also the case for imidazoles or thiols, which tend to form oligo- or poly-nuclear complexes. During studies by coordination chemists aimed at the modelling of zinc enzymes, many polydentate ligands have been designed which leave room for just one water ligand in the coordination sphere of zinc (Parkin, 2004). In those cases where the acidities of these complexes have been determined they provide evidence for the coordination number/ pK_a relationship. In particular, $LZn(OH_2)$ complexes with L being a tetradentate ligand have pK_a values at or above 8 (Mareque-Rivas et al., 2004). But, most strikingly, all attempts to prepare $LZn(OH_2)$ complexes with tripodal scorpionate ligands have resulted in the isolation of their deprotonated derivatives, the $LZn-OH$ complexes.

Tripodal scorpionate ligands have been applied successfully in zinc model complexes. Their key advantages are a "facial" binding causing tetrahedral to octahedral zinc centre and a rather rigid geometry compared to the often very flexible macrocyclic ligands. As Figure 9 shows, they can form 4-, 5-, or 6-coordinate zinc complexes depending on the counteranions present (Rombach et al., 1999).

Basing on borderline properties of zinc, mixed hard and soft ligand environments make for perfectly stable complexes, purely hard or soft ligand environments making zinc unwilling to accept the ligand thiolate. This is one of the most important properties governing the biological chemistry of zinc (Vahrenkamp, 2007). Modifications regarding the sterical hindrance can easily be employed to many scorpionate ligands to prevent dimer formation e.g. by attachment of bulky residues (R groups) to the ligands. In recent studies functional groups are attached to the ligands to mimic the enzyme pockets more closely. This allows the stabilisation of coordinated substrates, water or hydroxido ligands by hydrogen bridges. Similar interactions are found in enzymes.

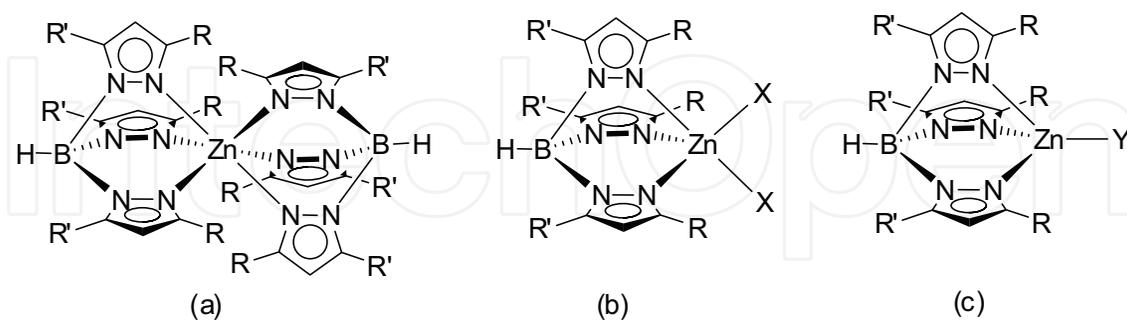


Fig. 9. Pyrazolylborate zinc complexes with 4-, 5-, and 6-coordinated zinc: a) with non coordinating anions; b) with hard coligands X; c) with soft coligands Y.

Most models for mononuclear zinc enzymes described so far consist of tripod ligands with three or four N donors to mimic mononuclear zinc enzymes with three zinc binding histidine residues (e.g. the matrix metalloproteases or carbonic anhydrase) (Parkin, 2000; Parkin, 2004). Often sterically hindered hydrotris(pyrazol-1-yl)borate ligands are used to mimic this tris(histidine) motif by three pyrazol-1-yl donors. Especially the works of H.

Vahrenkamp and G. Parkin have helped to elucidate several biocatalytic mechanisms with poly(azolyl)borate-zinc models. Scorpionate zinc complexes have been recognised by various research groups as versatile tools in the quest for new zinc binding groups suitable for enzyme inhibitors. The synthesis of such structural enzyme (inhibitor) models usually starts from the hydroxido complexes.

The most difficult task, which is not fully achieved as yet, is the isolation of a $\{[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}(\text{OH}_2)\}^+$ cation (Ruf et al., 1996; Bergquist & Parkin, 1999) ($[\text{HB}(\text{pz}^{\text{R}})_3]$ denotes any one substituted tris(pyrazolyl)borate ligand), the main reason for which is the hydrolytic destruction of the $[\text{HB}(\text{pz}^{\text{R}})_3]^-$ ligands in acidic media. In all cases studied, the $[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}-\text{OH}$ complexes are the easiest to prepare (Alsfasser et al., 1993; Ruf et al., 1996; Ruf & Vahrenkamp, 1996). In just a few cases they could be induced to release water and form the dinuclear complexes $\{[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}-\text{OH}-\text{Zn}[\text{HB}(\text{pz}^{\text{R}})_3]\}^+$ (Ibrahim et al., 2006); full deprotonation with formation of the neutral molecular species $\{[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}-\text{O}-\text{Zn}[\text{HB}(\text{pz}^{\text{R}})_3]\}$ have been achieved in one case (Ruf & Vahrenkamp, 1996).

The $[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}-\text{OH}$ complexes owe their stability both to the fact that the sterically laden $[\text{HB}(\text{pz}^{\text{R}})_3]^-$ ligands enforce a low coordination number and that they create a hydrophobic pocket and an encapsulation of the Zn-OH unit. Increasing the polarity (hardness) near zinc (e.g. by a pyridyl substituted ligand) allows the coordination number to be increased; as a result, observed in the enzyme-substrate model complex $[\text{HB}(\text{pz}^{\text{Py,Me}})_3]\text{Zn}(\text{OH}_2)\text{OPO}(\text{OPh})_2$ (Weis et al., 1998), the hydrolytic agent water and the organophosphate (employed to model the substrate) are attached to zinc at the same time.

The $[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}-\text{OH}$ complexes were shown to be able to perform, in a stoichiometric way, all hydrolytic reactions catalyzed by zinc enzymes (Vahrenkamp, 1999; Parkin, 2004). Bearing voluminous organic substituents, they suffer from two limitations with respect to catalytic action. They are hydrophobic and do not dissolve in water, thereby rendering the reagent H_2O unavailable, and they form very stable complexes with the carboxylates and phosphates resulting from hydrolysis. On one hand this is unfavourable and still requires efforts in order to overcome it, but on the other hand it has provided important compounds for the structure correlation based mechanistic findings.

The $[\text{HB}(\text{pz}^{\text{R,R'}})_3]\text{Zn}(\text{OH})$ complexes ($\text{R} = \text{tBu}, \text{Ph}, \text{Cum}, \text{R}' = \text{H}, \text{Me}, \text{tBu}$) (Fig. 10a) (Alsfasser et al., 1991; Kitajima et al., 1993; Looney et al., 1993; Ruf & Vahrenkamp, 1996), including $[\text{HB}(\text{pz}^{\text{R}})_3]^-$ incorporating hydrogen bonding accepting ester substituents, react as functional models according to the carbonic anhydrase mechanism (Looney et al., 1993; Rombach & Vahrenkamp, 2001; Hammes et al., 2002; Bergquist et al., 2003; Lipton et al., 2003; Lipton & Ellis, 2007) and form bicarbonate from CO_2 . Hydrogensulfido, thiolato, phenolato and alcoholato $[\text{HB}(\text{pz}^{\text{R}})_3]^-$ complexes are accessed by substitution reactions with H_2S , thiols, phenols or alcohols (Ruf & Vahrenkamp, 1996; Bergquist et al., 2000; Brand et al., 2001).

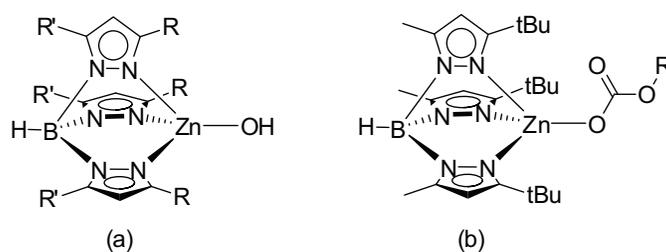


Fig. 10. Structure of: a) hydroxido complexes $[\text{HB}(\text{pz}^{\text{R,R'}})_3]\text{Zn}(\text{OH})$; b) $[\text{HB}(\text{pz}^{\text{tBu,Me}})_3]\text{Zn}(\text{OCOR})$ as a carbonic anhydrase model.

The complex $\{[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]_2\text{Zn}_2(\text{H}_3\text{O}_2)\}\text{ClO}_4$ (Puerta & Cohen, 2002) is important for the relevance of its structure in terms of hydrolytic zinc enzymes, that use hydrogen-bond stabilized water nucleophiles to perform peptide bond cleavage.

With dialkyl carbonate the hydroxido complexes form monoalkyl carbonato complexes (Fig. 10b) (Ruf et al., 1996; Vahrenkamp, 1999). These are also accessible by a reaction of alcoholato complexes with CO_2 , a reaction that is analogous to the carbonic anhydrase catalysis. This even allows the catalytic formation of dialkyl carbonate from alcohols and CO_2 under pressure (Vahrenkamp, 1999). Binding studies with sulfonamide inhibitors have also been described (Hartmann & Vahrenkamp, 1994; Brombacher & Vahrenkamp, 2004).

The protective pocket provided by the pyrazolylborate ligands $[\text{HB}(\text{pz}^{\text{Cum,Me}})_3]^-$ and $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]^-$ has made it possible to obtain stable and inert zinc complexes $[\text{HB}(\text{pz}^{\text{R}})_3]\text{Zn}$ -base of the anionic nucleobases (i.e. thymine, uracil, dihydrouracil, cytosine, adenine, guanine, diaminopurine, xanthine, hypoxanthine) in their deprotonated forms (Badura & Vahrenkamp, 2002) and to investigate the reactivity of aminoacids toward zinc (Rombach et al., 2002). The complex $[\text{HB}(\text{pz}^{\text{Cum,Me}})_3]\text{Zn}(\text{OH})$ has been reported to cleave activated amides and esters (Ruf & Vahrenkamp, 1996). Other hydroxido complexes, e.g. $[\text{HB}(\text{pz}^{\text{Cum,Me}})_3]\text{Zn}(\text{OH})$, are able to hydrolyse amides (Vahrenkamp, 1999; Parkin, 2004). This indicates that such model complexes are also structural and functional models for matrix metalloproteases (MMPs). Therefore, matrix metalloproteases model properties are also utilised for binding studies with protease inhibitors (Ruf et al., 1996; Vahrenkamp, 1999). In these binding studies the coordination properties of the zinc binding groups of MMP inhibitors are investigated. In particular the pioneering work of Cohen (Puerta & Cohen, 2002; Puerta & Cohen, 2003; Jacobsen & Cohen, 2004; Puerta et al., 2004; Puerta et al., 2005; Puerta et al., 2006; Jacobsen et al., 2007) and Vahrenkamp (Ruf et al., 1996; Tekeste & Vahrenkamp, 2006; Tekeste & Vahrenkamp, 2006) in this field has to be highlighted.

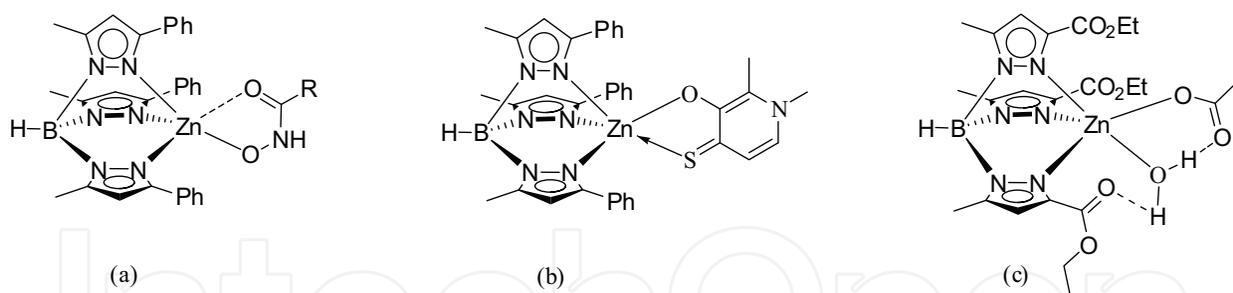


Fig. 11. a) Model complex for MMPs with bound hydroxamate inhibitor; b) Bidentate k^2 -coordination of pyridinethione in biomimetic zinc complex $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]\text{ZnL}$; c) structure of $[\text{HB}(\text{pz}^{\text{CO}_2\text{Et,Me}})_3]\text{Zn}(\text{H}_2\text{O})(\text{OAc})$.

Common zinc binding groups applied successfully in peptidase inhibitors have been either a carboxylic acid, a hydroxamic acid or a thiol functionality. Reactions of $[\text{HB}(\text{pz}^{\text{R,R}})_3]\text{Zn}(\text{OH})$ complexes with carboxylic acids, hydroxamic acids or thiols yield carboxylato, hydroxamato (Fig. 11a) and thiolato complexes (Ruf et al., 1996; Parkin, 2004). These complexes may be understood as biomimetic complexes that model the coordination environment of these zinc binding groups bound to the catalytic zinc ion in the matrix metalloproteases. Cohen and coworkers first utilized coordination complexes to model drug-protein interactions of inhibitors to MMPs of which the binding mode was not known so far. The focus of this work was to predict the drug-protein interaction of non-

hydroxamate inhibitors without the need for elaborate drug synthesis or protein structure determination. They reported the binding of β -mercaptoketone and β -mercaptoamide drugs in a bidentate fashion, while β -mercaptothiols bound exclusively in a monodentate manner, contrary to prior expectations (Puerta & Cohen, 2002). A whole series of publications by the same authors extended this concept to four different groups of chelators: hydroxypyridinones, pyrones, hydroxypyridinethiones and thiopyrones (Puerta & Cohen, 2003; Puerta et al., 2004; Puerta et al., 2005; Puerta et al., 2006; Jacobsen et al., 2007). Each of the tested small molecules was able to displace the hydroxide ligand in the $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]\text{ZnOH}$ model complex of the active site and to coordinate the zinc(II) in a bidentate fashion (Puerta & Cohen, 2003; Puerta et al., 2004; Puerta et al., 2006; Jacobsen et al., 2007) (Fig. 11b). These compounds represented the zinc chelating portion of new MMP inhibitors (MPIs), lacking the critical peptidomimetic backbone. The zinc binding groups (ZBGs) listed above were found to have a greater affinity than acetohydroxamic acid (AHA) for the zinc(II) ion the model complex. Furthermore, the inhibitory activity of these ZBGs was compared with that of AHA (Puerta et al., 2006). All the new compounds were found to be more potent inhibitors of MMP-3 than AHA (Puerta et al., 2004). This finally resulted in the development of potent and selective pyrone-based inhibitors (Puerta et al., 2005).

Other binding studies by the Cohen group reported on κ^1 -coordination for zinc complexes $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]\text{ZnL}$ bearing 2-thenylmercaptan, salicylamide and thiosalicylic acid, but on κ^2 -coordination in case of methyl salicylate, methyl thiosalicylate or 2-hydroxyacetophenone ligands. Thus, it was possible to reveal the mode of binding of many ZBGs (Jacobsen & Cohen, 2004). Interesting, Cohen and coworkers applied the $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]\text{ZnOH}$ -fragment to identify ZBGs for the lethal factor of anthrax (Jacobsen et al., 2006). Vahrenkamp and coworker observed both, a bidentate and a monodentate coordination to a $[\text{HB}(\text{pz}^{\text{Ph,Me}})_3]\text{ZnOH}$ fragment, in case of 2-mercaptophenol (Tekeste & Vahrenkamp, 2006). Vahrenkamp also reported on further studies regarding the coordination manner of α -keto carboxylic acids, α - and β -diketones, β -mercapto amines and alcohols as well as mercaptopropionic acid (Tekeste & Vahrenkamp, 2006).

Recent studies try to attach functional groups to the scorpionate ligands of the zinc models, in order to mimic the catalytically important glutamic acid of the HExxH zincin sequence. In some examples, the carboxylate complex $[\text{HB}(\text{pz}^{\text{CO}_2\text{Et,Me}})_3]\text{Zn}(\text{H}_2\text{O})(\text{OAc})$ and the amidate complex $[\text{HB}(\text{pz}^{\text{Fu,Me}})_3]\text{Zn}(\text{H}_2\text{O})(\text{NHCOCF}_3)$, ester or furyl functionalities form hydrogen bridges to water or an amidate, respectively (Fig. 11c) (Hammes et al., 2002; Maldonado Calvo & Vahrenkamp, 2006).

Chelating ligands belonging to the poly(pyrazolyl)borates can be regarded as relatively *hard* donor ligands having two or three azole nitrogen atoms that can be involved in metal coordination. The analogous poly(methimazolyl)borate anions (methimazole = 1-methyl-1*H*-imidazole-2(3*H*)-thione) have recently been reviewed by Reglinski and Spicer (Spicer & Reglinski, 2009) in order to explore the properties of a softer coordination environment in an anionic ligand, provided in this case by thione sulfur atoms of the methimazole rings. The two ligand systems also differ fundamentally in the number of atoms linking the central boron atom to the donor atoms. The structural consequences of this difference are displayed in the dimensions of the chelate rings formed upon metal complex formation and the molecular symmetry generated as a consequence of the conformations adopted by these rings. Thus, complexes of the tris(pyrazolyl)borates contain three six-membered chelate rings and the resulting complexes exhibit a local coordination environment of C_{3v} symmetry, while poly(methimazolyl)borates complexes contain three eight-membered chelate rings,

thus generating a more flexible twisted or propeller-like ligand conformation and local C_3 symmetry.

The $[\text{HB}(\text{tim}^{\text{R}})_3]$ ligand systems (Fig 12a) provide a useful platform for obtaining synthetic analogues of zinc enzymes and proteins that have sulfur rich active sites such 5-aminolevulinate dehydratase (ALAD) and the Ada DNA repair protein (Penner-Hahn, 2007) (Fig 8f).

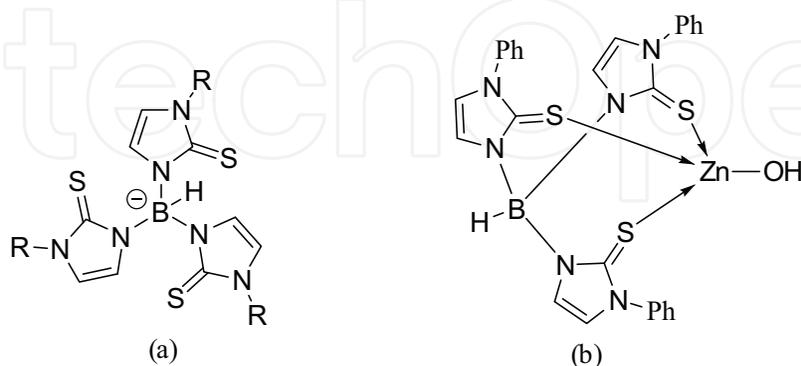


Fig. 12. Structure of: a) $[\text{HB}(\text{tim}^{\text{R}})_3]$ ligands; b) $[\text{HB}(\text{tim}^{\text{Ph}})_3]\text{ZnOH}$ complex, synthetic analogue of ALAD.

The three sulfur donors of the $[\text{HB}(\text{tim}^{\text{R}})_3]$ ligand system may be used to emulate the three cysteine residues in ALAD. In particular, the zinc hydroxide complex $[\text{HB}(\text{tim}^{\text{Ph}})_3]\text{ZnOH}$ complex (Bridgewater & Parkin, 2001) (Fig 12b) is the first tetrahedral zinc hydroxide complex supported by a $[\text{S}_3]$ donor ligand to be structurally characterized by X-ray diffraction.

The mechanism of action of ALAD involves displacement of the aqua ligand by the substrate 5-aminolevulinic acid (ALA). A simple indication that displacement of the aqua ligand in such a coordination environment is facile is provided by protonation of $[\text{HB}(\text{tim}^{\text{Ph}})_3]\text{ZnOH}$ with HClO_4 in acetonitrile, in which the incipient aqua ligand is displaced by MeCN to give $\{[\text{HB}(\text{tim}^{\text{Ph}})_3]\text{Zn}(\text{NCMe})\}^+$ (Bridgewater & Parkin, 2000; Bridgewater & Parkin, 2001).

Simple synthetic analogues for the $[(\text{Cys})_4\text{Zn}]$ motif of the Ada protein (Penner-Hahn, 2007) are provided by the thiolate complexes $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnSPh}$ ($\text{R} = \text{Ph}$ or tBu), in which the $[\text{HB}(\text{tim}^{\text{R}})_3]$ ligand serves the role of the three cysteine residues that remain bound to zinc during the course of the alkylation reaction (Bridgewater et al., 2000; Ibrahim et al., 2005; Melnick et al., 2006). The thiolate complexes $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnSCH}_2\text{C}(\text{O})\text{N}(\text{H})\text{Ph}$ ($\text{R} = \text{Ph}$, tBu), which incorporate an N-H hydrogen bonding functionality, provide a more refined structural analogue for the Ada protein (Morlok et al., 2005).

Alkylation of a zinc-cysteine thiolate residue is the key step in the mechanism of action of the Ada DNA repair protein and may be modeled by the reactivity of $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnSR}$ towards alkylating agents such as MeI. Indeed, $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnSR}$ complexes react rapidly with MeI to yield $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnI}$ and RSMel (Bridgewater et al., 2000; Ibrahim et al., 2005; Melnick et al., 2006). A comprehensive evaluation of the reactivity of a series of zinc thiolate complexes, namely $[\text{HB}(\text{pz}^{\text{R,R'}})_3]\text{ZnSR}$, $[\text{HB}(\text{pz})_2(\text{tim}^{\text{R}})]\text{ZnSR}$, $[\text{HB}(\text{pz}^{\text{R}})(\text{tim}^{\text{R}})_2]\text{ZnSR}$, and $[\text{HB}(\text{tim}^{\text{R}})_3]\text{ZnSR}$, in which the supporting ligand presents $[\text{N}_3]$, $[\text{N}_2\text{S}]$, $[\text{NS}_2]$ and $[\text{S}_3]$ donor arrays, demonstrates that the reactivity towards thiolate alkylation increases by four orders of magnitude across the series (Rombach et al., 2006).

In addition to the widespread use of tris(pyrazolyl)hydroborato ligands, their bis(pyrazolyl)hydroborato counterparts, $[\text{H}_2\text{B}(\text{pz}^{\text{R,R'}})_2]$, were employed to prepare three-

coordinate derivatives, e.g. $[\text{H}_2\text{B}(\text{pz}^{\text{R,R'}})_2]\text{ZnR}$, (Gorrell et al., 1990; Looney et al., 1995) that may be functionalized by insertion of unsaturated molecules (e.g. R_2CO , CO_2 and R_2CS) into the B-H group to obtain compounds that feature new facially tridentate $[\text{N}_2\text{O}]$ and $[\text{N}_2\text{S}]$ donor ligands that have potential for modeling certain zinc enzymes (Gorrell et al., 1990; Dowling & Parkin, 1996; Ghosh & Parkin, 1998). Vahrenkamp synthesized the bis(pyrazolyl)(thioimidazolyl)borate ligands, as $[\text{N}_2\text{S}]$ donor ligands namely $[\text{HB}(\text{pz}^x)_2(\text{tim}^x)]^-$ (Fig. 13a) (Benkmil et al., 2004).

The $[\text{NS}_2]$ donor bis(thioimidazolyl)(pyrazolyl)borate ligands (Santini et al., 2010), $[\text{HB}(\text{pz}^x)(\text{tim}^x)_2]^-$, can be prepared essentially by the same procedure used for the species $[\text{HB}(\text{pz}^x)_3]^-$ and $[\text{HB}(\text{tim}^x)_3]^-$, which consists of the high-temperature reaction between KBH_4 and a stoichiometric amount of the pyrazole and/or thioimidazole. The ligand $\text{Li}[\text{HB}(\text{pz})(\text{tim}^{\text{Me}})_2]$ (Fig. 13b) has been prepared by Parkin and applied successfully for modeling aspects of the bioinorganic chemistry of zinc enzymes. The molecular structure of $[\text{HB}(\text{pz})(\text{tim}^{\text{Me}})_2]\text{ZnI}$ was determined by X-ray diffraction, thereby demonstrating that the complex is indeed mononuclear with a distorted tetrahedral coordination geometry that resembles the active site of LADH (Kimblin et al., 1997; Kimblin et al., 1999; Kimblin et al., 2000).

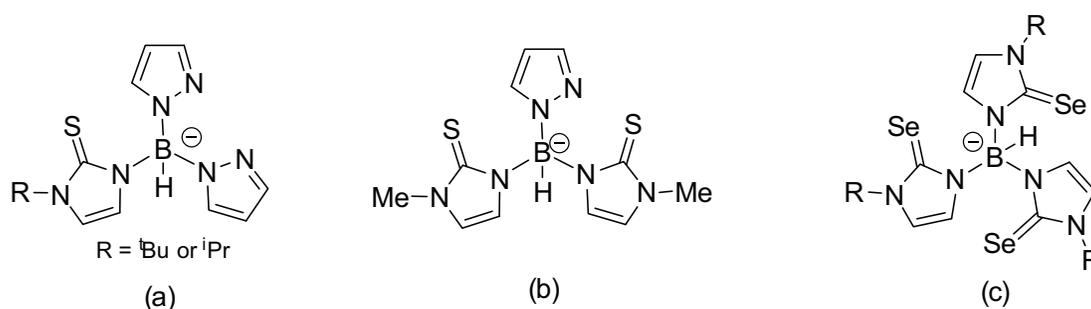


Fig. 13. Structure of a) $[\text{HB}(\text{pz})_2(\text{tim}^{\text{R}})]^-$, b) $[\text{HB}(\text{pz})(\text{tim}^{\text{Me}})_2]^-$ and c) $[\text{HB}(\text{Seim}^{\text{R}})_3]^-$ ligands.

An important development with respect to the use of this class of $[\text{NS}_2]$ donor ligands was provided by isolation of the ethanol complex, $\{[\text{HB}(\text{pz}^{\text{Ph,Me}})(\text{tim}^{\text{o-An}})_2]\text{Zn}(\text{HOEt})\}\text{ClO}_4\cdot\text{EtOH}$ (Seebacher et al., 2001; Shu et al., 2003; Ibrahim et al., 2005) ($\text{tim}^{\text{o-An}} = 1\text{-}(o\text{-anisyl})\text{-}2\text{-thioimidazole}$) which provides the best structural model to date for LADH. Interestingly, the sulfur rich coordination environment provided by poly(thioimidazolyl)borate ligand stabilizes coordination of the alcohol to zinc, thereby suggesting that one of the reasons why LADH utilizes a sulfur rich coordination environment is to promote coordination of the alcohol relative to that of water. A recent and substantial review by J. Reglinski and M. D. Spicer (Reglinski & Spicer, 2009) covers almost all aspects of chemistry of methimazole based soft scorpionate ligands with special reference to their use in biomimetic chemistry (alc. dehydrogenase, Ada repair proteins, 5-aminolevulinic acid dehydratase, sulfite oxidase, hydrogenase, MerB) and their emerging use as radiopharmaceuticals (rhenium, technetium). Since the poly(thioimidazolyl)borate ligands (Garner et al., 1996) have proven to be versatile, with a large variety of $[\text{HB}(\text{tim}^{\text{R}})_3]^-$ derivatives having been prepared, Parkin et al. envisioned that a similar series of ligands that features an Se_3 -donor or Se_2 -donor array should be accessible and thereby provide a set of ligands with modified electronic properties (Minoura et al., 2006). Indeed, the tris(2-seleno-1-R-imidazolyl)borate ligands, $[\text{HB}(\text{Seim}^{\text{R}})_3]$ (Guziec & Guziec, 1994) ($\text{R} = \text{Me}, \text{Mes}$), have been obtained (Fig. 13c) and used to synthesize a variety of metal (zinc, cadmium and mercury) complexes (Landry et al.,

2007). The related $[\text{Se}_2]$ -donor bis(2-seleno-1-methylimidazolyl)hydroborato ligand, $[\text{H}_2\text{B}(\text{Seim}^{\text{Me}})_2]$, has also been synthesized and investigated (Landry et al., 2007; Landry & Parkin, 2007). Interesting, whereas $\{[\text{H}_2\text{B}(\text{Seim}^{\text{Me}})_2]\text{ZnI}\}_2$ exists as a dimer, the sulfur counterpart $[\text{H}_2\text{B}(\text{tim}^{\text{Me}})_2]\text{ZnI}$ is a monomer (Kimblin et al., 1997; Kimblin et al., 2000). Another interesting aspect of $\{[\text{H}_2\text{B}(\text{Seim}^{\text{Me}})_2]\text{ZnI}\}_2$ is that the bridging entity is one of the 2-seleno-1-methylimidazolyl groups rather than the halide ligands.

Several attempts to model the mononuclear active site with small biomimetic zinc complexes ended either in bisligand complexes $[\text{ZnL}_2]$ or the formation of oligo- or poly-nuclear complexes (Parkin, 2004). C. J. Carrano and B. S. Hammes applied bulky *tert*-butyl groups in *ortho* position to a phenolate donor to overcome these problems. With their anionic tripodal *N,N,O* ligand (3-*tert*-butyl-2-hydroxy-5-methylphenyl)bis(3,5-dimethylpyrazol-1-yl)methane, $[\text{HC}(\text{pz}^{\text{Me}_2})_2(\text{C}_6\text{H}_2\text{OH}(\text{tBu})\text{Me})]$, they obtained several tetrahedral zinc complexes with halogeno, acetato or thiolato ligands (Fig. 14a) (Hammes & Carrano, 1999). With two nitrogen donors and an oxygen donor this ligand is well suited to mimic the active sites of thermolysin or carboxypeptidase A, although the zinc(II) in these models is bound by a phenolato donor instead of a carboxylato donor (Smith et al., 2003; Smith et al., 2005).

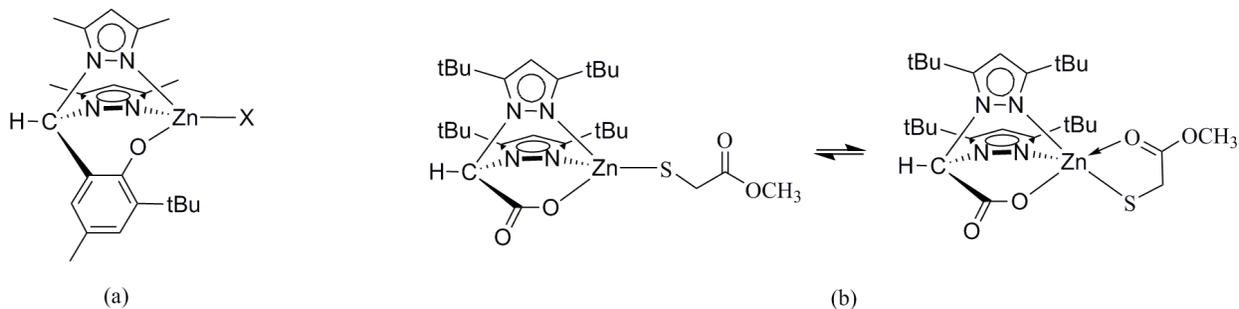


Fig. 14. a) Structure of $[\text{HC}(\text{pz}^{\text{Me}_2})_2(\text{C}_6\text{H}_2\text{O}(\text{tBu})\text{Me})]\text{ZnX}$ complexes; b) κ^1/κ^2 equilibrium in hydroxamato complexes.

Alkyl zinc complexes bearing various bis(pyrazol-1-yl)acetato ligands $(\text{HC}(\text{pz}^{\text{R,R'}})_2(\text{COO})^-)$ offer an easy access to better structural model complexes for zinc peptidases with a 2-His-1-carboxylate motif. Starting from methyl complexes $[(\text{HC}(\text{pz}^{\text{R,R'}})_2(\text{COO})\text{ZnCH}_3)]$ so far several complexes with carboxylato-, thiolato- and also hydroxamato-ligands have been obtained by methane releasing reactions with carboxylic acids, thiols and hydroxamic acids (Beck et al., 2001; Hegelmann et al., 2003; Smith et al., 2003; Smith et al., 2005). According to the NMR spectra these complexes often exhibit a κ^1/κ^2 equilibrium (Fig. 14b).

Thiolates, carboxylates and hydroxamates are the most common zinc binding groups used in zinc peptidase inhibitors such as ACE inhibitors. Most of these models for carboxypeptidases have been characterised by X-ray structure determinations (Beck et al., 2001; Hegelmann et al., 2003; Smith et al., 2003; Smith et al., 2005), the model complexes helping to develop new zinc binding groups for potential peptidase inhibitors.

3.3 Other relevant biomimetic metal systems

In recent years complexes of scorpionate ligands were successfully used to mimic the activity of enzymes containing various metals such as vanadium, manganese, iron, cobalt, nickel, molybdenum and tungsten.

Vanadium. An important aim of the vanadium chemistry is to model vanadium histidine interactions thought to be present in the enzyme haloperoxidase (Butler, 1999). The

occurrence of vanadium in living systems and the relevant chemistry have been reviewed (Etienne, 1996). Recently, the vanadium complexes of general type $\{VO(O_2)[HB(pz)_3](Hpz)\}$ and $\{VO(O_2)[pzB(pz)_3](Hpz)\}$ were synthesized, characterized and indicated as model for haloperoxidase (VHPO) enzymes (Holmes & Carrano, 1991; Xing et al., 2007), that are able to catalyze the oxidation of halides to corresponding hypohalous acids, which readily undergo halogenation of organic substrates or conversion of hydrogen peroxide to singlet oxygen and generation of halides. The pseudooctahedral V(IV) complexes with tris(pyrazolyl)borate ligands, $\{[HB(pz)_3]V(O)Cl\}$ -DMF and $\{[HB(pz^{Me,Me})_3]V(O)Cl\}$ -DMF were found to exhibit potent biological activity (Ghosh et al., 1999).

Manganese. Mimicking the activity of manganese superoxide dismutase and of various binuclear manganese enzymes active in redox functions- was approached with $[HB(pz^{iPr,iPr})_3]Mn(OBz)$ and related binuclear complexes (Sheats et al., 1987; Kitajima et al., 1991; Kitajima et al., 1993) such as $[HB(pz^{iPr,iPr})_3]Mn_2(\mu-FOBz)_3(Hpz^{iPr,iPr})_2$ (Singh et al., 2006). Dehydrative condensation of the dinuclear Mn(III)-bis(μ -oxo) complex $\{[HB(pz^{iPr,iPr})_3]Mn(\mu-O)\}_2$ with H_2O_2 in the presence of 2-methylimidazole yielded the imidazole-containing peroxomanganese(III) complex $[HB(pz^{iPr,iPr})_3]Mn(\mu_2-O_2)(Him^{Me})$. This complex may mimic the essential role of the "distal" histidine residue in the hemoglobin/myoglobin (Singh et al., 2006).

Iron. In the area of iron-containing enzymes, the behavior of the oxo-bridged di-iron enzyme hemerythrin was approximated with complexes such as $\{[HB(pz)_3]Fe_2(\mu-O)(\mu-OOCR)\}$ and $\{[HB(pz)_3]Fe_2(\mu-OH)(\mu-OOCR)\}$ (Armstrong & Lippard, 1984; Armstrong et al., 1984; Czernuszewicz et al., 1987), while the complex $[HB(pz^{iPr,iPr})_3]Fe(OBz)(CH_3CN)$ was regarded as a synthetic model for the dioxygen binding site of nonheme iron proteins (Kitajima et al., 1990). The aliphatic α -keto carboxylate $[HB(pz^{Ph,Ph})_3]Fe^{II}(O_2CC(O)CH_3)$ and the carboxylate complexes $[HB(pz^{Ph,Ph})_3]Fe^{II}(OBz)$ and $[HB(pz^{Ph,Ph})_3]Fe^{II}(OAc)(Hpz^{Ph2})$ were synthesized and studied to clarify the key role that the α -keto functionality plays in oxygen activation by α -keto acid-dependent iron enzymes (Mehn et al., 2003). The complex $[HB(pz^{iPr,iPr})_3]Fe(OOPtn)$ (Ptn = Pterinperoxo) has been described as a relevant model for potential intermediates in pterin-dependent hydroxylases (Lehnert et al., 2003). Other related complexes were regarded as structural and functional models of catechol dehydrogenases (Ogihara et al., 1998) and as peroxo intermediate in the methane monooxygenase hydroxylase reaction cycle (Kim & Lippard, 1996). The complex $[HB(pz^{Me,Me})_3]Fe(catecholate)(Hpz^{Me,Me})$ has been prepared and its reactivity toward oxygen investigated as model for the catechol dioxygenases (Yat et al., 2003).

Cobalt. The cobalt complexes $[HB(pz^R)_3]Co(X)$ ($X = N_3, NCS; [HB(pz^R)_3] = [HB(pz^{Me,Me})_3]$ or $[HB(pz^{Ph})_3]$) have been used as catalysts in the bicarbonate dehydration reaction in the presence of inhibitors (Sun et al., 2004; Sun et al., 2004).

Nickel. Monomeric five-coordinate Ni-cysteine complexes of tris(3,5-disubstituted pyrazolyl)borates ($[HB(pz^{Me,Me})_3]^-$ and $[HB(pz^{Ph,Me})_3]^-$) and L-cysteine (diethyl ester and amino acid forms) were studied as being of relevance to the nickel component of the active site in several hydrogenase enzymes, which participate in the bio-generation of hydrogen and methane, as well as in nitrogen fixation (Desrochers et al., 1999). Hydrotris(3-phenyl-5-methylpyrazolyl)boratonickel(II) complexes with organoxanthate or dithiocarbamate coligands equilibrate between κ^2 - and κ^3 -chelation modes of the scorpionate ligand in solution, connecting N_2S_2 square-planar and N_3S_2 pyramidal ligand fields and a spin crossover. The complexes also exhibit quasi-reversible oxidations at low anodic potentials, thus modeling the structure, dynamics, and redox reactivity of the reduced nickel

superoxide dismutase (NiSOD) active site (Ma et al., 2008). The use of analogous sterically less demanding hydrotris(3,5-dimethylpyrazolyl)borate ligands allow to obtain paramagnetic pentacoordinate N_3S_2 structures for both xanthate and dithiocarbamate co-ligands in the solid state (Ma et al., 2009). However, these structures exhibit variable distortion towards a trigonal bipyramidal geometry due to enhanced rotation of the dithioacid chelates relative to the scorpionate face. Evidence was found nonetheless for retention of the spin equilibrium and one-electron redox couples in solution. These observations allow to consider steric effects arising from a pattern of 3-pyrazole ring substitution on the structure and dynamics of the biomimetic complexes.

Molybdenum and tungsten. The group 6 elements molybdenum and tungsten are the only second and third row transition metals essential to all forms of life on Earth. Molybdenum is found at the active sites of nitrogenase and all of the more than 50 known Mo-MPT enzymes (MPT = 'molybdopterin' or Metal-binding Pterin ene-1,2-diThiolate) that play vital roles in plant, animal, and human health, the carbon, sulfur, and nitrogen cycles, biofeedback systems, and the control of global climate (Hille, 1996; Tunney et al., 2004). The Mo-MPT enzymes feature active sites composed of a single (mononuclear) Mo atom coordinated by one or two MPT-based ligands; tungsten is also associated with MPT-based ligands in all its known biological manifestations. Chemical approaches to molybdenum enzyme sites have been directed toward mimicking a portion of the structural center in order to ascertain the role of that particular feature of the center on the chemical reactivity and the spectroscopic properties of the center. Existing sources (Holm, 1987; Holm, 1990; Enemark & Young, 1994; Stiefel, 1997; Young & Wedd, 1997; Young & Young, 1997; Hille et al., 1998; Fischer & Burgmayer, 2002; Enemark et al., 2004) provide background to earlier work in this area. The enzymology and other aspects of molybdenum biochemistry have been extensively considered elsewhere (Hille, 1996; Hille, 2002; Moura et al., 2004; Brondino et al., 2006; Schwarz & Mendel, 2006). The action of oxygen-atom transfer enzymes which contain tris(pyrazolyl)borate-based molybdenum and tungsten pterin enzyme models centres was discussed in a review of Young and Wedd (Young & Wedd, 1997). In a recent review we analyzed the overall progress on synthetic analogues of these enzyme centers and dissected the contributions of systems in which coordination spheres contain poly(pyrazolyl)borate ligands (Pellei et al., 2009).

3.3.1 Nitrogenase and related synthetic models having pyrazolylborate anions

The most extensively studied nitrogenase enzyme contains iron and molybdenum metals, and is called molybdenum nitrogenase (Burgess & Lowe, 1996; Smith, 1999; Christiansen et al., 2001; Igarashi & Seefeldt, 2003). In growth conditions where molybdenum concentration is low, a nitrogenase depending on iron and vanadium is expressed (Eady, 1996; Eady, 2003; Rehder, 2003; Crans et al., 2004). When both molybdenum and vanadium are unavailable, a third type of nitrogenase is expressed that contains iron as the only transition metal (Eady, 1996; Krahn et al., 2002; Siemann et al., 2002). Mo-nitrogenase is the only one for which both detailed structural and mechanistic data are available (Howard & Rees, 1996; Mayer et al., 1999; Einsle et al., 2002). The enzymatic complex comprises two proteins: the iron-protein (Fe-protein) and the molybdenum iron-protein (MoFe-protein). There are three catalytically necessary metal-sulfur clusters in iron-molybdenum nitrogenase: the Fe_4S_4 cluster in the Fe-protein, the FeMo-cofactor and the P-cluster. The iron-molybdenum cofactor (FeMo-co) of nitrogenase (Kim & Rees, 1992; Chan et al., 1993; Peters et al., 1997; Mayer et al., 1999; Einsle et al., 2002) is one of the most fascinating exhibits in bioinorganic chemistry, because it is

here that the enzyme somehow catalytically cleaves the strong triple bond of N_2 to give ammonia (Lowe et al., 1993). The FeMo-co has been observed in three redox states (Peters et al., 1997; Mayer et al., 1999; Schmid et al., 2002). Two different structures are known for the P-cluster and are assigned to different cluster core oxidation states. In the reduced or P^N (fully reduced) state, the Fe_8S_7 cluster can be described as two Fe_4S_4 cubes sharing one common hexacoordinate sulfur atom, the iron atoms being linked to the protein by cysteinate ligands, two of them bridging the subcubes (Fig. 15a). In the oxidized state P^{OX} state (P^{2+}), oxidized by two electrons relative to P^N , the central sulfur atom loses two bonds with two iron atoms in one of the subcubes, thus becoming more open. The tetrahedral coordination of these two iron atoms is then completed by extra ligations from neighboring cysteine or serine residues (Peters et al., 1997; Mayer et al., 1999; Einsle et al., 2002).

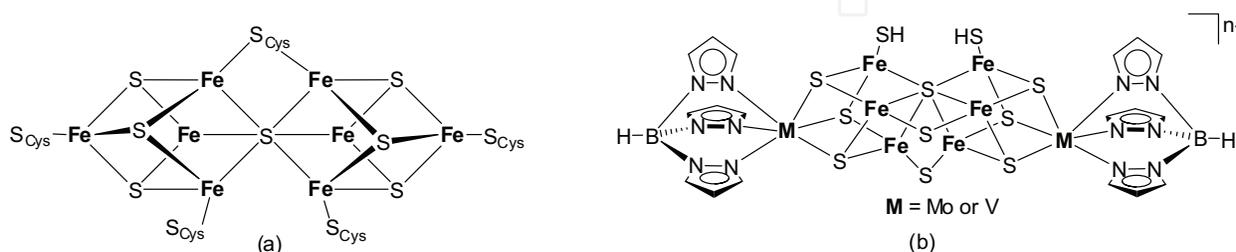


Fig. 15. a) Structure of the P-clusters of nitrogenase in the reduced state $[Fe_8(\mu_2-S_{Cys})_2(\mu_3-S)_6(\mu_6-S)]$ core, (P-Cluster, P^N state); b) molybdenum- or vanadium-containing P^N -cluster topological analogue of the P^N cluster of nitrogenase.

Synthetic chemists have created iron-sulfur clusters that mimic the unusual distribution of iron atoms in P^N (Huang et al., 1997; Osterloh et al., 1999; Osterloh et al., 2001; Zhang et al., 2002; Zhang & Holm, 2003; Zuo et al., 2003; Lee & Holm, 2004; Zhang & Holm, 2004). In particular monomeric clusters $\{[HB(pz)_3]_2M_2Fe_6S_9\}^{n-}$; ($M = Mo$, $n = 3$; $M = V$, $n = 4$) are stabilized by the tris(pyrazolyl)borate ligand, showing that the cluster topology found in P^N can exist as a free entity in solution (Zhang et al., 2002).

The species in Fig. 15b, is an example of a topological analog of the Fe_8S_7 P-cluster with the $[Mo_2Fe_6S_9]^{5-}$ core, isolated as the crystalline Et_4N^+ salt (Zhang et al., 2002; Zhang & Holm, 2003).

The P-cluster structure could be stabilized in other molecules, and in particular the vanadium-containing P^N -cluster topological analogue is reported (Hauser et al., 2002; Zhang et al., 2002; Zuo et al., 2003) (Fig. 15b). The clusters have a crystallographically imposed two-fold axis which contains atom μ_6-S and is perpendicular to the Fe_4 plane in the center of the molecule. The μ_6-S atom and its associated interactions constitute the most extraordinary part of the structures of the clusters reported in Fig. 15b. Sextuply-bridging sulfur atoms are not unprecedented in synthetic clusters, but they are rarely encountered. A best-fit superposition of the $V_2Fe_6S_9$ core of V-species in Fig. 15b with the core atoms of the P^N cluster of nitrogenase (*K. pneumoniae* MoFe protein) (Mayer et al., 1999) leads to an rms deviation of 0.33 Å in atom positions (Lee & Holm, 2004). The corresponding deviation for Mo-species is 0.38 Å. One source of the deviation between synthetic clusters and the P^N cluster is the significantly larger Fe-(μ_6-S)-Fe angle of 158° and its attendant effect on atom positions in the native cluster. The differences of a Mo_2Fe_6 or a V_2Fe_6 instead of an Fe_8 metal content and two μ_2-S atoms instead of two μ_2-S_{Cys} bridges notwithstanding. Therefore, clusters reported in Fig. 15b are the excellent examples of molecular topological analogues of the P^N cluster of nitrogenase.

High-nuclearity metal-sulfur clusters may function as precursors to other clusters related in structure to the P-cluster (Fe_8S_9) and FeMo-cofactor cluster (MoFe_7S_9) of nitrogenase (Zhou et al., 2002; Berlinguette et al., 2006). In particular, the double cubane $[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_8(\text{PEt}_3)_4$ system has been investigated as model for the reactivity of the nitrogenase P^{N} cluster (Zhang et al., 2002; Zhang & Holm, 2003; Zuo et al., 2003); the complex sustains terminal ligand substitution with retention of the $\text{Mo}_2\text{Fe}_6(\mu_3\text{-S})_6(\mu_4\text{-S})_2$ core structure and rearrangement to the $\text{Mo}_2\text{Fe}_6(\mu_2\text{-S})_2(\mu_3\text{-S})_6(\mu_6\text{-S})$ topology of the nitrogenase P^{N} cluster (Peters et al., 1997; Mayer et al., 1999) upon reaction with certain nucleophiles. Distinct processes for the conversion of double cubanes to P^{N} -type clusters are documented, affording the products $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_9(\text{SR})_2\}^{3-}$ (Zhang & Holm, 2004), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_9(\text{SH})_2\}^{3-}$ (Berlinguette & Holm, 2006), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_8(\text{OMe})_3\}^{3-}$ (Zhang & Holm, 2004), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_7(\text{OMe})_4\}^{2-}$ (Zhang & Holm, 2004), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_9(\text{OH})_2\}^{3-}$ (Hlavinka et al., 2007), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_9(\text{OMe})_2(\text{H}_2\text{O})\}^{3-}$ (Hlavinka et al., 2007), $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_9(\mu_2\text{-O})_2\}^{5-}$ and $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_8\text{Q}(\text{QH})_2\}^{3-}$ (Q = S, Se) in which HQ^- is a terminal ligand and Q^{2-} is a μ_2 -bridging atom in the core (Hlavinka et al., 2007). The reverse transformation of a P^{N} -type cluster to an edge-bridged double cubane has been demonstrated by the reaction of $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_8(\text{OMe})_3\}^{3-}$ with Me_3SiX to afford $\{[\text{HB}(\text{pz})_3]_2\text{Mo}_2\text{Fe}_6\text{S}_8\text{X}_4\}^{2-}$ (X = Cl⁻, Br⁻) (Zhang & Holm, 2004).

In biomimetic research, many fewer heterometal MFe_3S_4 cubane-type clusters have been synthesized with vanadium or tungsten than with molybdenum because of the well-established structural relationship of the latter to the molybdenum coordination unit in the nitrogenase MoFe-protein (Lee & Holm, 2003; Lee & Holm, 2004). A structural relationship appears to exist between VFe_3S_4 clusters and the vanadium site in VFe-proteins (Eady, 1996; Eady, 2003). Far fewer vanadium than molybdenum single cubanes (SC) clusters, containing the $[\text{VFe}_3(\mu_3\text{-S})_4]$ core of idealized trigonal symmetry, have been prepared since their inception in 1986-1987 (Kovacs & Holm, 1986; Kovacs & Holm, 1987; Kovacs & Holm, 1987), and the first and only examples of vanadium edge-bridged double cubanes (EBDC), with the core $[\text{V}_2\text{Fe}_6\text{S}(\mu_3\text{-S})_6(\mu_4\text{-S})_2]$ of idealized centrosymmetry, were obtained in 2002 (Zhang et al., 2002). The two cluster types may be generalized as $\{[\text{HB}(\text{pz}^{\text{R}})_3]\text{VFe}_3\text{S}_4\text{X}_3\}^z$ and $\{[\text{HB}(\text{pz}^{\text{R}})_3]_2\text{V}_2\text{Fe}_6\text{S}_8\text{X}_4\}^z$ of variable oxidation level z with diverse scorpionate ligands (hydrotris(pyrazolyl)borate or tris(pyrazolyl)methanesulfonate) bound to the octahedral heterometal site and ligands X (X = phosphine, thiolate, or halide) at the tetrahedral iron sites. These matters are best pursued with clusters in which $[\text{HB}(\text{pz}^{\text{R}})_3]^-$ is constant, facilitating the isolation of clusters of either heterometal with the same charge z . Infact, the tris(pyrazolyl)borate ligand conforms to the trigonal symmetry of the SC core and in synthesis generally affords SCs with $z = -2$ and EBDCs with $z = -3$ or -4 in species carrying monoanionic ligands X (Fomitchev et al., 2002; Hauser et al., 2002; Zhang & Holm, 2003; Zuo et al., 2003; Berlinguette et al., 2006; Pesavento et al., 2007).

Recently, a series of single cubane and edge-bridged double cubane clusters containing the cores $[\text{VFe}_3(\mu_3\text{-S})_4]^{2+}$ and $[\text{V}_2\text{Fe}_6(\mu_3\text{-S})_6(\mu_4\text{-S})_2]^{2+}$ have been prepared (Scott & Holm, 2008) by ligand substitution of the phosphine clusters $\{[\text{HB}(\text{pz})_3]\text{VFe}_3\text{S}_4(\text{PEt}_3)_3\}^+$ and $[\text{HB}(\text{pz})_3]_2\text{V}_2\text{Fe}_6\text{S}_8(\text{PEt}_3)_4$. The single cubanes $\{[\text{HB}(\text{pz})_3]\text{VFe}_3\text{S}_4\text{L}_3\}^{2-}$ and double cubanes $\{[\text{HB}(\text{pz})_3]_2\text{V}_2\text{Fe}_6\text{S}_8\text{X}_4\}^{4-}$ (X = F, N₃, CN, PhS) are shown by X-ray structures to have trigonal symmetry and centrosymmetry, respectively. Single cubanes form the three-member electron transfer series $\{[\text{HB}(\text{pz})_3]\text{VFe}_3\text{S}_4\text{X}_3\}^{3-,2-,1-}$. The ligand dependence of redox potentials and electron distribution in cluster cores as sensed by ^{57}Fe isomer shifts (δ) have been determined (Scott & Holm, 2008).

Examples of WFe_3S_4 clusters, nearly all in the form of tungsten-bridged double cubanes, were prepared nearly simultaneously with molybdenum containing clusters in the early development of M-Fe-S cluster chemistry (Wolff et al., 1980; Armstrong et al., 1982; Palermo et al., 1982). Few others have been prepared since that time (Coucouvanis et al., 1992; Raebiger et al., 1997). The structures of tungsten-iron-sulfur clusters have been explored using reactions based on $\{[HB(pz^{Me,Me})_3]WS_3\}^-$ as precursor, which reacts with $FeCl_2$, $NaSEt$ and S affording the cubane cluster $\{[HB(pz^{Me,Me})_3]WFe_3S_4Cl_3\}^-$, which with $NaSEt$ is converted to $\{[HB(pz^{Me,Me})_3]WFe_3S_4(SEt)_3\}^-$. Treatment of $\{[HB(pz^{Me,Me})_3]WFe_3S_4Cl_3\}^-$ with Et_3P yields the edge-bridged double $[HB(pz^{Me,Me})_3]_2W_2Fe_6S_8(PEt_3)_4$ with the $[W_2Fe_6(\mu_3-S)_6(\mu_4-S)_2]$ core. The cubane cluster $\{[HB(pz^{Me,Me})_3]WFe_3S_4Cl_3\}^-$ reacts also with an excess of Et_3P , BH_4^- and HS^- leading a mixture of products, from which $\{[HB(pz^{Me,Me})_3]_2W_2Fe_5S_9Na(SH)(MeCN)\}^{3-}$ was identified. This cluster, as closely related $\{[HB(pz)_3]_2Mo_2Fe_6S_9(SH)_2\}^{3-}$, exhibits a core topology $[W_2Fe_5Na(\mu_2-S)_2(\mu_3-S)_6(\mu_6-S)]$ very similar to the P^N cluster of nitrogenase (Hong et al., 2005).

3.3.2 Hydrogenase and related synthetic models

Hydrogenases comprise a fundamental group of bacterial enzymes that catalyze the reversible oxidation of dihydrogen to protons in aerobic and anaerobic microorganisms and, thus, play a key role in molecular bioenergetics (Fontecilla-Camps & Ragsdale, 1999; Adams & Stiefel, 2000; Matias et al., 2001; Carepo et al., 2002). Two classes of hydrogenases, [Fe]-only H_2 ases (Pandey et al., 2008) and [NiFe] H_2 ases (Higuchi et al., 1999), have been studied widely, each containing their metals in a high sulfur density environment. The X-ray crystallographic studies of the active-site structure of [NiFe] H_2 ases isolated from *Desulfovibrio gigas*, *Desulfovibrio Vulgaris*, *Desulfovibrio fructosovorans*, and *Desulfovibrio desulfuricans* ATCC27774 in combination with infrared spectroscopy have revealed an active site comprised of a heterobimetallic $(Scys)_2Ni(\mu-Scys)_2(\mu-X)Fe(CO)(CN)_2$ ($X = O^{2-}, HO_2^-, OH^-$) cluster (Volbeda et al., 1995; Rousset et al., 1998; Garcin et al., 1999; Ogata et al., 2002; Chiou & Liaw, 2008) (Fig. 16a). The bridging ligand X was proposed to be an oxide, hydroxide, or hydroperoxide in the oxidized state and was found to be absent in the reduced state.

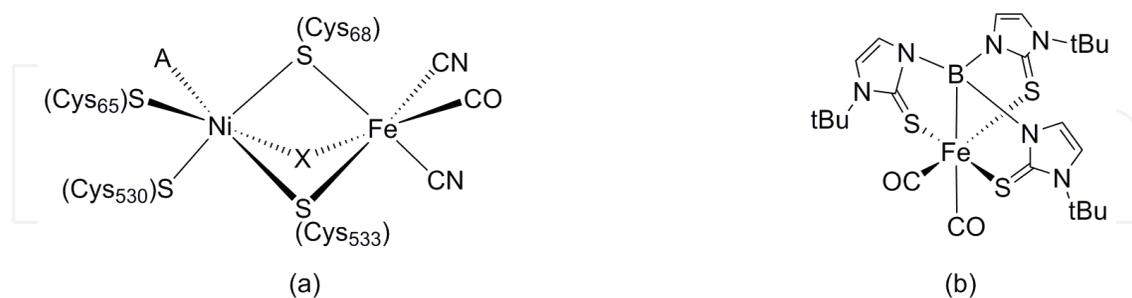


Fig. 16. a) Representation of the active site in the [NiFe] hydrogenase extracted from *Desulfovibrio gigas* showing the vacant coordination site (A) and the additional bridging oxo or hydroxo ligand (X) present only in the oxidized (inactive) form of the enzyme; b) structure of the boratrane $[B(tim^{tBu})_3]Fe(CO)_2$.

These enzymes have become excellent targets within biomimetic chemistry. Modelling of hydrogenase enzymes requires the efficient synthesis of half-sandwich complexes of the form $[HB(tim^R)_3]NiX$ or $[H_2B(tim^R)_2]NiX$. The chemistry of nickel is driven by the formation of bis-ligand complexes such as $[HB(tim^R)_3]_2Ni$ (Garner et al., 2003; Senda et al., 2006) and

$[\text{H}_2\text{B}(\text{tim}^{\text{R}})_2]_2\text{Ni}$ (Alvarez et al., 2001; Alvarez et al., 2004). The $[\text{H}_2\text{B}(\text{tim}^{\text{R}})_2]_2\text{Ni}$ complexes, having $[\text{NiS}_4\text{H}_2]$ cores and slightly distorted octahedral geometries resulting from the unexpected presence of two $\text{Ni}\cdots\text{H}-\text{B}$ interactions, constitute unprecedented structural mimics that resemble the nickel coordination environment in the active form of $[\text{NiFe}]$ hydrogenases. With $[\text{HB}(\text{tim}^{\text{Me}})_3]_2\text{Ni}$ it is possible to obtain the oxidised Ni(III) species $\{[\text{HB}(\text{tim}^{\text{Me}})_3]_2\text{Ni}\}^+$ albeit in very low yield. By contrast, a Ni(III) species has not been isolated from studies of the analogous $[\text{H}_2\text{B}(\text{tim}^{\text{R}})_2]_2\text{Ni}$ complex (Alvarez et al., 2001).

The use of a starting material containing a chelating diphosphine such as 1,2-bis(diphenylphosphino)ethane (dppe) may prevent the addition of a second $[\text{HB}(\text{tim}^{\text{R}})_3]$ -group to nickel and plausibly generate useful complexes such as $[\text{HB}(\text{tim}^{\text{R}})_3]\text{NiX}$ or $[\text{H}_2\text{B}(\text{tim}^{\text{R}})_2]\text{NiX}$, all while preserving the required soft donor ligand set around the metal center. Recently, using nickel phosphine complexes it was possible to obtain the species $[\kappa^3\text{-H,S,S-HB}(\text{tim}^{\text{Tot}})_3]\text{Ni}(\text{dppe})\text{Cl}$, $[\text{HB}(\text{tim}^{\text{Tot}})_3]\text{Ni}(\text{NO})$ and $[\kappa^3\text{-H,S,S-H}_2\text{B}(\text{tim}^{\text{Me}})_2]\text{Ni}(\text{PPh}_3)(\text{NO})$ (Alvarez et al., 2004; Maffett et al., 2007).

The simple chemistry of iron is also driven by the formation of bis-ligand species $[\text{HB}(\text{tim}^{\text{Me}})_3]_2\text{Fe}$ (Senda et al., 2006). Although $[\text{HB}(\text{tim}^{\text{Me}})_3]$ - produces an octahedral S_6Fe species $[\kappa^3\text{-S,S,S-HB}(\text{tim}^{\text{Me}})_3]_2\text{Fe}$ (Senda et al., 2006), the $[\text{HB}(\text{tim}^{\text{Ph}})_3]$ - ligand generated a different isomer namely $[\kappa^3\text{-H,S,S-HB}(\text{tim}^{\text{Ph}})_3]_2\text{Fe}$ (Kimblin et al., 2001). By altering the stoichiometry and reaction conditions it was possible to produce half sandwich $[\text{HB}(\text{tim}^{\text{Me}})_3]\text{FeCl}$ complexes and chloro bridged $\{[\text{HB}(\text{tim}^{\text{Me}})_3]\text{Fe}(\mu\text{-Cl})\}_2$ dimers of iron (Senda et al., 2006). The iron centres in hydrogenase are organometallic in nature, containing $\text{Fe}-\text{C}\equiv\text{O}$ moieties. Although carbonyl complexes of manganese can be produced (Bailey et al., 2003) as yet we have been unable to directly and simply produce the analogous iron complexes. Parkin *et al.* used a circuitous route to these species, which pass through a boratrane $[\{\kappa^4\text{B,S,S',S''-B}(\text{tim}^{\text{tBu}})_3\}]\text{Fe}(\text{CO})_2$ species (Fig. 16b). The molecular structure of $[\{\kappa^4\text{B,S,S',S''-B}(\text{tim}^{\text{tBu}})_3\}]\text{Fe}(\text{CO})_2$ has been determined by X-ray diffraction, which clearly reveals the presence of an $\text{Fe}\rightarrow\text{BX}_3$ σ -interaction. Significantly, $[\{\kappa^4\text{B,S,S',S''-B}(\text{tim}^{\text{tBu}})_3\}]\text{Fe}(\text{CO})_2$ exhibits novel reactivity towards a variety of reagents that results in eradication of the Fe-B bond via a formal 1,2-addition process and the formation of B-functionalized tris(mercaptoimidazolyl)borate derivatives, $[\text{XB}(\text{tim}^{\text{tBu}})_3]\text{FeY}$ (Figueroa et al., 2006).

It is noted that the reports generated which related to hydrogenase chemistry are thus far fragmented. However, if they can be linked a viable model of hydrogenase could potentially be generated. For example, species such as $[\kappa^3\text{-H,S,S-HB}(\text{tim}^{\text{Tot}})_3]\text{Ni}(\text{dppe})\text{Cl}$ contain a metal (boro)hydride interaction (Alvarez et al., 2001; Alvarez et al., 2004). Furthermore the hydride can be induced to leave the boron and a metal mediated hydride transfer can be initiated. As with much bio-mimetic chemistry, modelling reactions parallel the respective enzymes to a point (e.g. replacement of NAD^+ by benzylnicotinamide chloride in zinc alcohol dehydrogenase studies) and the manner in which the electrons are managed in the hydrogenase model reaction is unlikely to mimic that of the enzyme as there is no pathway for them to be sequestered. In this case it is likely that they will be stored in a bond such as the B-H bond (Reglinski & Spicer, 2009).

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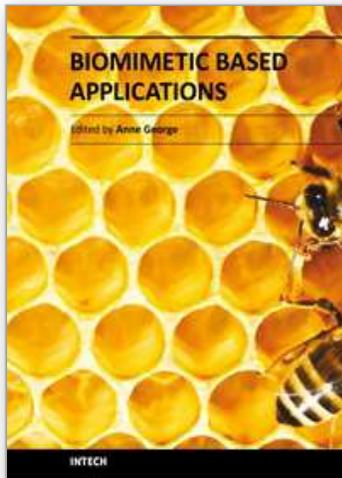
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