Unsymmetric Dinucleating Ligands for Metallobiosite Modelling

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Received October 22, 1996

Keywords: Metallobiosites / Metalloproteins / Metalloenzymes / Dinucleating ligands / Transition metals

Awareness of the asymmetric nature of numerous dinuclear metallobiosites and of the ability of the individual metal ions to have quite distinct roles in the functioning of the metalloenzyme concerned has led to a search for carefully designed unsymmetric dinucleating ligands that will give dinuclear complexes capable of acting as models for the metallobiosites. This review surveys progress made in the design and synthesis of complexes capable of serving as models for donor atom, coordination number and geometric asymmetries found at dinuclear metal centres.

There is now an abundance of information available in the literature concerning the structures and roles of the transition-metal-derived dinuclear centres present in certain metalloproteins and metalloenzymes. Such centres may be homodinuclear or heterodinuclear in nature and may also contain metals in different oxidation states. The metals may have different roles to play in the overall functioning of the site and numerous sites have been found to be asymmetric in character. The search for designed unsymmetric dinucleating ligands which would provide model complexes for donor atom, coordination number and geometric asymmetries at dinuclear metal centres is well under way and this microreview draws attention to recent progress made in the area.

Site Asymmetry at Metallobiosites

Homodinuclear sites may be exemplified by those structurally characterized in non-heme manganese catalase [Mn,Mn][1]; deoxyhemerythrin[2]; the hydrolase protein of methane monooxygenase[3] and ribonucleotide reductase B2 [Fe,Fe][4]; methionine aminopeptidase [Co,Co][5]; urease

David Fenton was born in Tidworth, England. He gained his B.Sc in 1963 and his Ph.D. in 1966, both at Queen Mary College, London. In 1986 he was awarded a D.Sc. by the University of London. He was a Senior, then Principal Scientific Officer with the Agricultural Research Council from 1969–1972. In 1972 he moved to the University of Sheffield as a Lecturer, where he has subsequently been a Senior Lecturer and Reader before being appointed to a Personal Chair in 1990. He is currently Professor of Inorganic Chemistry in Sheffield. His research interests lie in the general areas of macrocyclic coordination chemistry, and the use of coordination compounds in metallobiosite mimicry.

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In 1996 Okawa and Fenton were awarded a Daiwa Award by the Daiwa Anglo-Japanese Foundation for their collaborative research on metallobiosite modelling.

MICROREVIEWS: This feature introduces Berichte's readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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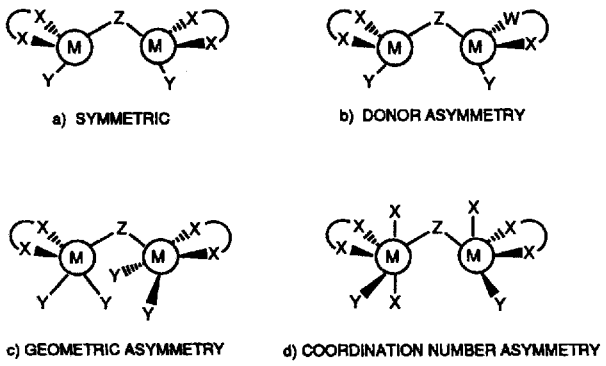
[Ni,Ni][6]; leucine aminopeptidase[7], alkaline phosphatase[8] and phospholipase C [Zn,Zn][*][9].

Representative *heterodinuclear* sites are those structurally characterized in bovine erythrocyte superoxide dismutase [Cu,Zn][10], purple acid phosphatase[11], human calcineurin [Fe,Zn][12] and human protein phosphatase 1 [Mn,Fe][13].

The roles of the individual metal ions present at a biosite may be quite distinct in character. For example one metal may play a *structural* role by helping to maintain the structural integrity of the protein, whilst the second metal has a *functional* role through binding to a substrate[14]. The role of the metals may also be defined as *cocatalytic*, whereby the two metal atoms in close proximity operate together as a catalytic site[15].

In order to facilitate these modes of behaviour the metal ions can be present in chemically distinct environments. Recently a classification of the potential coordination environments available to dinuclear sites has been made; four distinct groupings have emerged (Figure 1)[16] and representative examples are shown in Figure 2.

Figure 1. A classification of metal coordination environments found at transition-metal-derived dinuclear centres present in metallobiosites (M is a transition metal and W, X, Y and Z are ligand donor atoms such as N, O, S etc.)



The classification is as follows:

(a) *Symmetric* – An identical number of donor atoms of the same type are bound to each metal atom in similar geometries. The dinuclear iron site in bacterioferritin has been shown to contain a symmetric site in which each iron atom is coordinated by a histidine-N atom, and three glutamate-O atoms (two glutamate residues serve as bridging groups between the iron atoms)[17].

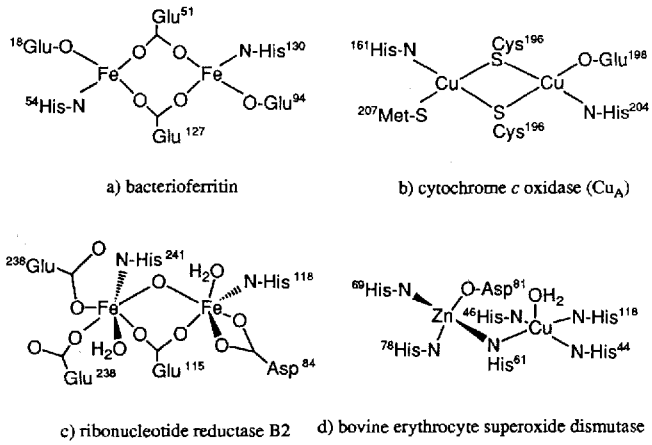
(b) *Donor Asymmetry* – Different types of donor atom coordinate to each metal atom. This can be found in methionine aminopeptidase [N_3O and O_4][5], in D-xylose isomerase [O_6 and O_5N][18] and in the Cu_A site of cytochrome *c* oxidase [N_2S_2 and N_2SO][19]. In the hydrolase protein of methane monooxygenase[3] both sites have an O_5N donor array but there is an asymmetry induced as one metal has a water molecule present and the second has a glutamate-O atom in addition to otherwise equivalent donor sets.

[*] The last two sites are actually trinuclear constellations, $[Zn_2Mg]$ and $[Zn_3]$ respectively; it is the homodinuclear fragment that is pertinent to this discussion.

(c) *Geometric Asymmetry* – There are inequivalent geometric arrangements of the donor atoms about each metal atom. This occurs in ribonucleotide reductase B2 where one iron atom has a regular octahedral geometry whereas the geometry at the second iron atom has both octahedral and trigonal bipyramidal features because a chelating aspartate may be viewed as occupying two donor sites to give a severely distorted octahedron, or as utilizing one equatorial site of a trigonal bipyramid[4]. A further example is found in purple acid phosphatase where the iron atom has an almost perfectly octahedral coordination environment whilst the zinc atom is in a distorted octahedral environment[11]. A modification of this asymmetry is available when the donor atom distribution within a given coordination geometry differs; for example in an N_4O square-pyramidal complex the O donor could be either axially or equatorially coordinated, giving rise to spatial asymmetry.

(d) *Coordination Number Asymmetry* – An unequal number of donor atoms are coordinated to each metal atom. Examples of this asymmetry are found with deoxyhemerythrin with five- and six-coordinate iron atoms[2], leucine aminopeptidase with three- and four-coordinate zinc atoms[7], urease with three- and five-coordinate nickel atoms[6], and bovine erythrocyte superoxide dismutase where the zinc atom is four-coordinate and the copper atom is five-coordinate[10].

Figure 2. Schematic representations of dinuclear metallobiosites serving as examples of the four symmetry classes: site (a) is symmetric; (b) exhibits donor asymmetry: N_2S_2 and N_2SO; (c) shows geometric asymmetry: Oh and Oh/tbp; (d) has coordination number asymmetry: 4 and 5



To a first approximation the nature of the donor atom may be restricted to simply O, N, or S atoms, but a more accurate definition would specify the functional grouping associated with the donor atom and so differentiate between O in water and carboxylate or S in a thiolate or thioether. Combination of different types of asymmetry may also occur at a dinuclear centre.

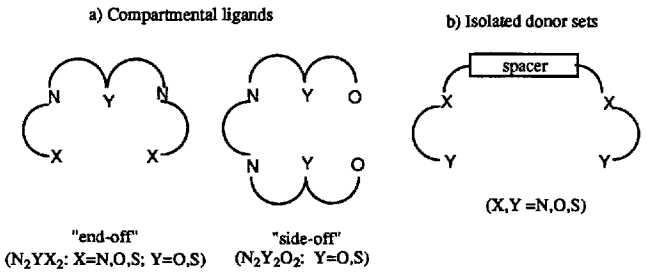
Although many examples of coordination complexes derived from symmetric acyclic dinucleating ligands have been prepared and investigated as potential model complexes for metallobiosites, polydenate ligand systems that would give necessarily asymmetric dinuclear complexes remained rare;

site asymmetry was often only accessed through good fortune. This, and the awareness of the asymmetric nature of many metallobiosites, led to the suggestion that for modelling studies unsymmetrical dinucleating ligands should be viewed as desirable targets[20]. This article presents an overview of the progress that has been made in this area of research.

Unsymmetric Dinucleating Ligands: The Background

Since Robson introduced the concept of dinucleating ligands in 1970 there has been a steady increase in the number and type of such ligands synthesized[21]. The IR complexes have been divided into two general classes (Figure 3)[22]. The first group consists of those complexes where the metals share at least one donor atom from ligands containing adjacent sites, the central donor atom(s) of which provide a bridge; the ligands giving these bridging donor sets have been collectively termed *compartmental ligands*. The second group consists of those complexes in which donor atoms are not shared and so *isolated donor sets* exist. Acyclic compartmental ligands are further divided into *"end-off"* and *"side-off"* ligands; the former provide only one endogeneous bridging donor and so have an exogeneous bridging site available between the metal atoms, whereas the latter provide two endogeneous bridges and present adjacent dissimilar coordination compartments.

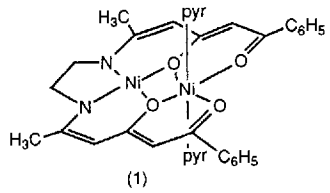
Figure 3. Schematic representations of dinucleating ligands: mono- or bibracchial pendant arms may be attached to the N atoms in the "end-off" compartmental ligands and to the X atoms in the isolated donor sets; the spacers in the isolated donor sets do not provide bridging atoms



"Side-Off" Acyclic Compartmental Ligands

These ligands, generally derived from the "2 + 1" condensation of a 1,3,5-triketone, β-ketophenol or 3-formylsalicylic acid with an α,ω-alkanediamine, have been the subject of review[23]. They provide homo- and heterodinuclear complexes which as well as being donor-asymmetric can also be geometry- and coordination-number-asymmetric. For example the dinuclear nickel(II) complex $[Ni_2L^1] \cdot$ 2-pyridine (**1**) derived from 1-phenyl-1,3,5-hexanetrione and 1,2-diaminoethane has nickel present in a four-coordinate $[N_2O_2]$ square-planar environment and a six-coordinate $[N_4O_2]$ octahedral environment[24]. Unfortunately these ligands are relatively rigid with an invariant intermetallic separation which is usually close to 3.0 Å; these properties have not facilitated their use as biomimetic molecules.

Scheme 1. The synthesis of unsymmetric phenoxo-bridge ligands

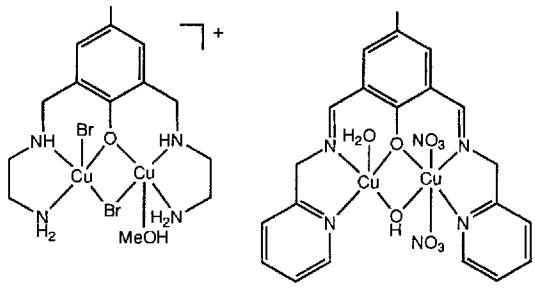


(1)

"End-Off" Acyclic Compartmental Ligands

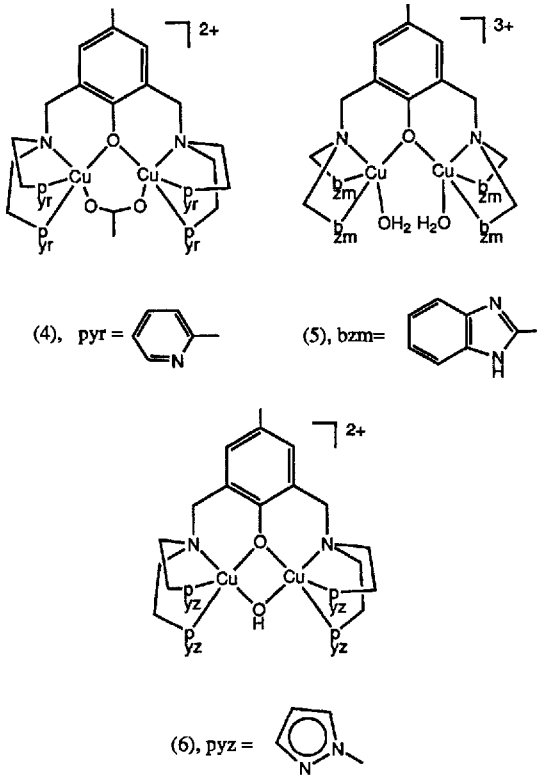
Much of the early work concerning this group of ligands focused on the synthesis of homodinuclear copper(II) complexes of ligands, derived from the condensation of 3-formyl-5-methylsalicylaldehyde with a wide range of amines, and was stimulated by the need to provide speculative models for the type-III dinuclear site in cuproproteins. The complexes formed were usually symmetric, and where asymmetry existed it had arisen fortuitously as in the complex $[Cu_2L^2Br]BrClO_4 \cdot MeOH$ (**2**) in which both copper atoms are five-coordinate[25]. One copper atom utilizes a bromide anion as its fifth ligand to achieve a square-pyramidal geometry utilizing an N_2OBr_2 set, whilst the second copper achieves a trigonal-bipyramidal geometry with an N_2O_2Br donor set by coordinating to a methanol molecule. There is an exogeneous bridging bromide anion and the molecule exhibits both geometric and donor asymmetry. Coordination number asymmetry was evidenced in $[Cu_2L^3 OH(NO_3)_2] \cdot H_2O$ (**3**) where one copper was five-coordinate, having a water molecule present in addition to a ligand donor set, and the second copper atom was six-coordinate, with both nitrate anions acting as monodentate ligands[26].

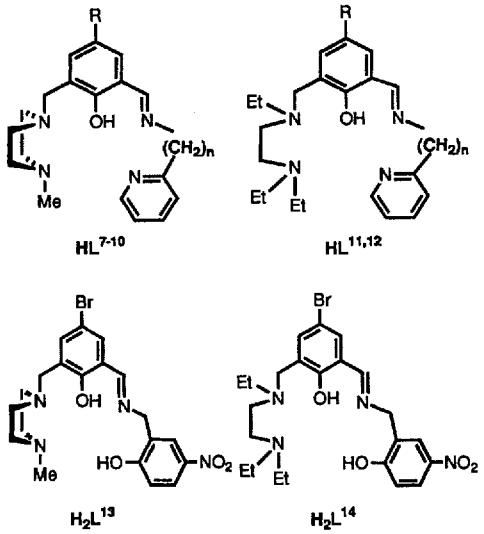
Scheme 2. Proposed structures for the semimet forms of hemerythrin; glu = L-glutamic acid; asp = L-aspartic acid; his = histidine



(2) (3)

Inequivalent copper atoms have also been found in complexes having two sets of bibracchial pendant arms. In both $[Cu_2L^4(CH_3COO)](PF_6)_2$ (**4**)[27] and $[Cu_2L^5(H_2O)_2])ClO_4)_3 \cdot 3\ H_2O$ (**5**)[28] the copper atoms were found to be square pyramidal with equivalent donor sets, but a spatial asymmetry had been introduced because one copper atom had the bridging phenoxide oxygen atom occupying an axial position whereas it was equatorially bound to the second copper atom. Geometric asymmetry was also noted in $[Cu_2L^6(OH)](BF_4)_2$ (**6**) where the equivalent donor sets give rise to square-pyramidal and trigonal-bipyramidal coordination geometries at the metals[29].





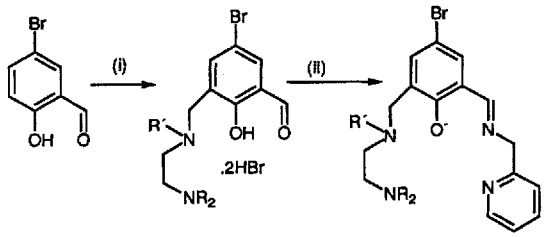
R	n	
Br	1	HL^7
Br	2	HL^8
H	1	HL^9
CH_3	1	HL^{10}
Br	1	HL^{11}
Br	2	HL^{12}

Unsymmetric Dinucleating Ligands: Recent Progress

Since 1990 much progress has been made in the synthesis of dinucleating ligands with built-in asymmetric features. The ligands fall into two classes: (i) those capable of producing a phenoxo-bridge to link the two metals and (ii) those which would provide an alkoxo-bridge.

(i) Endogenous Phenoxo-Bridge Ligands

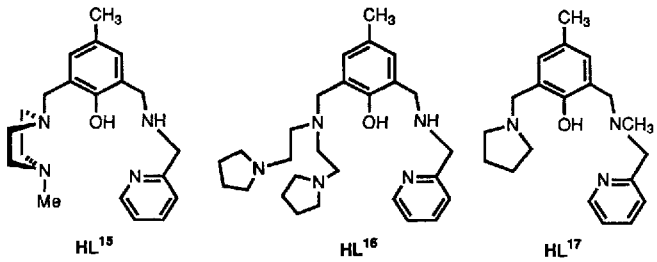
The introduction of a single pendant arm into 5-bromosalicylaldehyde by the Mannich reaction followed by condensation of the resulting aminomethyl salicylaldehyde with a primary amine (Scheme 1) afforded the unsymmetric dinucleating Schiff base proligands HL^7, HL^8, HL^{11}, $HL^{12}H_2L^{13}$ and H_2L^{14}[30,31].



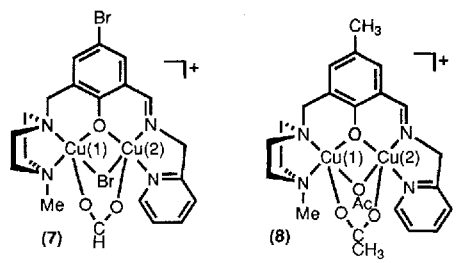
(i) $R_2NCH_2CH_2NHR'$, $CH_2O_{aq.}$; (ii)2-aminomethylpyridine, $HC(OEt)_3$

The first four of these "side-off" compartmental ligands are donor atom symmetric with N_2O donor sets; one donor set however incorporates two sp^3 N atoms and the second has present two sp^2 N atoms. The remaining pair of proligands have one N_2O and one NO_2 donor set.

Feringa[32,33] later applied this synthetic procedure to the generation of unsymmetric proligands such as HL^9 and HL^{10} derived from salicylaldehyde and 5-methylsalicylaldehyde, and showed that reduction of the Schiff base ligand gave the corresponding diamino compound e.g. HL^{15}. Such compounds were also prepared by reductive amination of the monoaminomethylated salicylaldehyde with a secondary amine (HL^{16}) or by starting from *p*-cresol and employing sequential Mannich reactions using two different amines (HL^{17})[33].



The reaction of these asymmetric proligands with copper(II) salts gave homodinuclear copper(II) complexes; the crystal structures of $[Cu_2Br(HCO_2)L^7]ClO_4 \cdot H_2O$ (**7**)[30,31] and $[Cu_2(CH_3CO_2)L^{10}]ClO_4$] (**8**)[32] have been reported.



The copper atoms present in **7** are both five-coordinate and in distorted square-pyramidal environments. Each copper is coordinated by the oxygen atom of the non-symmetrically bridging phenoxide, and by atoms from two exogenous bridging groups: a bromide and a formate. Coordination at each metal is completed by interaction with two nitrogen atoms from the appropriate pendant arm. Cu(1) is more distorted towards a trigonal bipyramid than is Cu(2); the indices of trigonality (τ)[**] are 0.4 and 0.29 respectively[34]. The Cu···Cu separation is 3.24 Å.

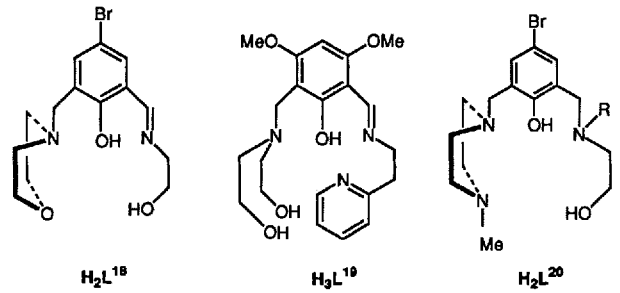
Complex **8** has a related structure in which there is a more symmetric phenoxide bridge and two non-symmetric acetate bridges, one of which is *syn-syn* bidentate the other being monodentate. Each copper is five coordinate, which the remaining donor atoms being the articular nitrogen atoms. In **8**, Cu(1) is less distorted towards a trigonal bipyramid than is Cu(2), the τ values being 0.07 and 0.25 respectively. The Cu···Cu separation is 3.029 Å.

In addition to geometric asymmetry, spatial asymmetry is also noted in both molecules. In **7** the square-pyramidal environment at Cu(1) has a formate oxygen atom at its apex whilst that at Cu(2) has the bromide anion at its apex; in **8** Cu(1) has an oxygen atom from the bidentate acetate at an apex whilst Cu(2) has the oxygen atom of the monodentate acetate at its apex.

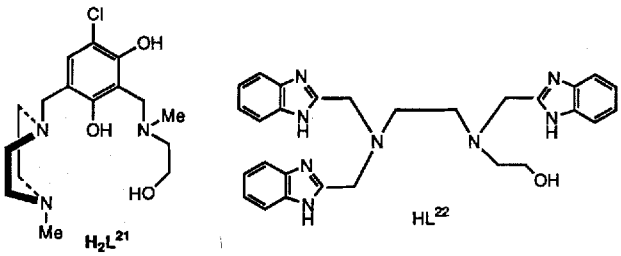
The molecules exhibit small antiferromagnetic couplings [$J = -42$ cm^{-1} (**7**) and -15 cm^{-1} (**8**)]. Although these values do not model accurately the strongly antiferromagnetically coupled type-3 copper centres found in haemocyanin and tyrosinase, it has been remarked that the presence of different environments for the two copper atoms may be related to the different modes of bonding proposed for the two copper atoms in tyrosinase[33,35,36].

In order to introduce a wider range of oxygen and nitrogen donor atoms into the proligands and so extend the range of this type of "side-off" ligand, the necessary Mannich bases have been prepared under non-aqueous aprotic conditions prior to condensation, leading to proligands such as H_2L^{18} and H_3L^{19}[37,38]. Related compounds such as H_2L^{20} were synthesized by condensation of the functionalized salicylaldehydes with secondary amines followed by in situ reduction of the iminium species with sodium borohydride[38]. It was also shown that the tandem Mannich reactions starting from 4-chlororesorcinol would give saturated unsymmetric dinucleating proligands as exemplified by H_2L^{21}[38].

One of the problems associated with the design of unsymmetric dinucleating ligands is that it is not always certain that the ligand will react to give a dinuclear complex and this is shown by the reaction of H_2L^{18} with copper



perchlorate to give the mononuclear complex $[Cu(H_2L^{18})](ClO_4) \cdot 2\ H_2O \cdot MeOH$. The crystal structure showed that the phenolic hydroxyl function had been deprotonated with consequent protonation of the morpholino nitrogen atom; the ligand behaves as a tridentate [O_2N] ligand and binds to the copper atom through the alcoholic and phenolate oxygen atoms as well as the imino nitrogen atom[39].

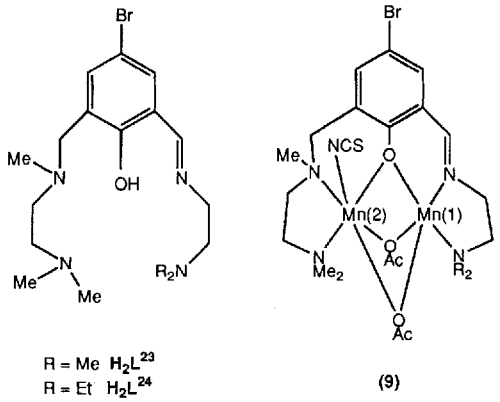


It is also noteworthy that the first unsymmetrical non-biological μ-oxo diiron(II) complexes $[(HL^{22})FeOFeX_3]X$ (X = Cl, Br) were constructed from a potentially dinucleating unsymmetric proligand HL^{22} that binds to only one of the iron atoms. This iron atom is six-coordinated by the five nitrogen atoms of the ligand and to the oxo-bridge, with the second iron atom tetrahedrally coordinated to the oxo-bridge and three halide anions[40].

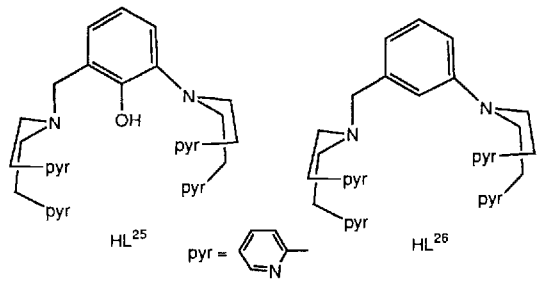
Homodinuclear manganese(II) complexes of unsymmetric phenol-based dinucleating proligands bearing amino- and imino-pendant arms have been studied in pursuit of complexes which can give catalase-like behaviour[41]; manganese catalases facilitate the disproportionation of hydrogen peroxide into dioxygen and water. The proligands HL^{23} and HL^{24} were synthesized by the Mannich route and provide donor asymmetric ligands in which one compartment includes one sp^2 and one sp^3 nitrogen and the second compartment includes two sp^3 nitrogen atoms.

The structure of the dimanganese(II) complex $[Mn_2L^{24}(MeCOO)_2NCS]$ (**9**) shows that the manganese atoms are separated by 3.376 Å and that the geometries at the two metal sites are different. Mn(1) is in a distorted square-pyramidal geometry ($\tau = 0.34$) provided by the imino-N, two acetato-O, the phenoxo-O and an amino-N atom, whereas Mn(2) is in a distorted octahedral environment provided by the thiocyanate anion, two acetato-O, the phenoxo-O and two amino-N atoms. Three types of asymmetry are involved: donor atom, coordination number and geometrical.

[**] τ is the index of the degree of trigonality within the structural continuum between square-pyramidal and trigonal-bipyramidal geometries. If A is the apical donor atom of a square-based pyramid then it should not be any of the atoms which define the largest two angles (α, β) at the metal centre. Donor atoms B and C are associated with the greater basal angle (β) and atoms D and E with the smaller basal atom (α). $\tau = (\beta - \alpha)/60$ and is therefore 0 for a square pyramid and 1 for a trigonal bipyramid[34].



In reactions of these dinuclear manganese complexes with hydrogen peroxide a catalase-like activity is found; a dinuclear *cis*-[Mn(IV)(=O)]$_2$ species has been detected as an active intermediate in the disproportionation reaction together with a less reactive [Mn(II)Mn(IV)=O] species[42,43]. There is a significant difference between the behaviour of **9** and that of the symmetric Schiff base and amino analogues, in that for the symmetric species the theoretical yield (100%) of dioxygen is evolved whereas for the unsymmetric species only 60–70% of the expected dioxygen is evolved. It appears that a side reaction occurs to consume H_2O_2 when the manganese atoms are not in electronically equivalent environments, suggesting that a symmetric environment would be required in the metalloenzyme.

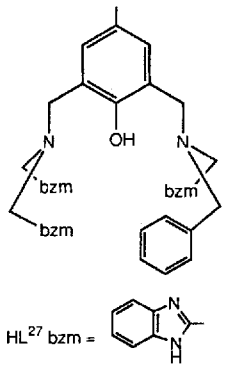


In the course of his seminal studies on the interaction of dioxygen with copper(I) complexes and its application to our understanding of the interaction of dioxygen with haemocyanin and tyrosinase, Karlin has made direct observation of reversible dioxygen binding by using a dicopper complex of an unsymmetric ligand as a copper monooxygenase model[44]. The complex [$Cu_2L^{25}OH$][PF_6]$_2$ (**10**) is derived from the proligand HL^{25}, which is itself synthesized from the reaction of dicopper(I) complex [Cu_2L^{26}][PF_6]$_2$ (**11**) with dioxygen.

The ligands provide unsymmetric environments due to the difference in bond connectivity between the aromatic ring and the pendant arms: one arm is directly connected to the ring whilst the second arm is connected via a methylene group. The structure of **10** shows each copper to be in a square-pyramidal geometry with an equivalent [N_3O_2] donor set comprised of the ligand donor atoms and a bridging hydroxo group. The sites are slightly distorted (τ = 0.14 for the copper in the $-CH_2-$-linked site and 0.05 for the copper in the directly linked site. The Cu···Cu separation is 3.037 Å and there is a less efficient antiferromagnetic coupling in **10** than in the symmetric complex with two methylene connectors. The reaction of **10** with dioxygen is reversible – four oxygenation/deoxygenation cycles being carried out without severe decomposition – whereas with the symmetric complex the reaction with dioxygen is rapid and irreversible.

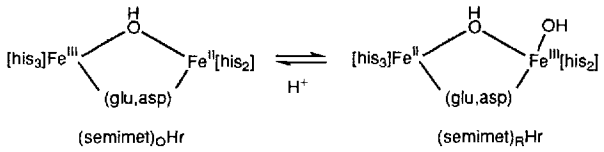
Studies of the phenoxo-bridged dicopper(I) complex of HL^{25}, [Cu_2L^{25}]PF_6 (**12**), have produced, using the ferricinium ion as an oxidant, a mixed valence complex [Cu(I)Cu(II)L^{25}][PF_6]$_2$ which reversibly reacts with dioxygen to give a superoxide complex [$Cu_2L^{25}(O_2)$][PF_6]$_2$[45]. The thermally stable hydroperoxo and peroxo complexes [Cu_2L^{25}(OOH)][PF_6]$_2$ and [Cu_2L^{25}(OO)][PF_6]$_2$ have been isolated by low-temperature precipitation at −85 °C following the reaction of copper(I) complexes of HL^{25} with dioxygen. The reaction of **12** gave the peroxide and that of [Cu_2HL^{25}][PF_6]$_2$ gave the superoxide[46]. These studies have added considerably to the knowledge base involving the interaction of copper with dioxygen. The structure of **12**[45] showed the copper(I) atoms to be present in trigonal pyramidal environments and it was speculated that the subtle differences in the relationship of the two copper atoms in the unsymmetric coordination environment may be important in the stabilization of the above copper-peroxo complexes.

The proligand HL^{27} was designed to offer two different suites of donor atoms to a pair of metal atoms[47]. The structure of [$CuL^{27}Cl$(HOEt)](ClO_4)$_2$ · 4 H_2O · EtOH (**10**) revealed that the chloride and phenoxo-O atoms asymmetrically bridge the copper atoms. Coordination of one copper is completed by an amino-N and two imino-N atoms of the N_3 arm in a distorted square-pyramidal array, and at the second copper atom it is completed by an amino-N and one imino-N atom of the N_2-benzyl arm together with an ethanol-O atom to give a very distorted five-coordinate geometry. In the former the phenoxo-O is axial and in the latter the chloride is axial. The Cu···Cu separation is 3.348 Å and the copper atoms are not significantly magnetically coupled.

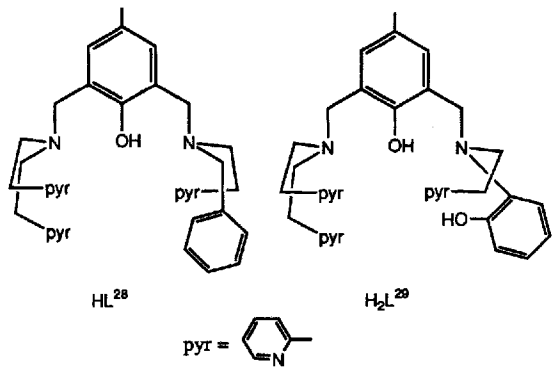


Latour and co-workers have used the related proligand HL^{28} in a study designed to provide a model for semimethemerythrin by having a free coordination site on one iron atom of the dinuclear pair[48]. The semimet forms (Scheme 2)[49,50] have present a mixed-valence iron pair [Fe(II)-

Fe(III)]; NMR studies in solution have suggested that there is a localization of the valence[51].



The complex $[Fe(II)Fe(III)L^{28}(H_2O)(Mpdp)](BPh_4)_2 \cdot 2\ H_2O$ (mpdp = 1,3-benzenedipropionate) was synthesized from proligand HL^{28}. The structure of the cation reveals two iron atoms bridged by the phenolate-O atom and two carboxylate groups from the mpdp anion[48]. The coordination sphere of the iron atom in the N_3 arm $[N_3O_3]$ is completed by binding to all three nitrogen donors and that of the iron in the N_2-benzyl arm $[N_2O_4]$ includes a water molecule as well as the two articular nitrogen atoms. The intermetallic separation of 3.409 Å is close to that of 3.357 Å determined by EXAFS for the azide derivative of semimet hemerythrin[52]. The strong asymmetry of the Fe–O–Fe unit suggests that the valences of the iron atoms are delocalized, with the Fe(III) in the N_3O_3 site and Fe(II) in the N_2O_4 site. The latter is therefore in a site which is accessible to an exogenous ligand, in this case water. The site occupancy proposal was supported by Mössbauer and NMR studies.

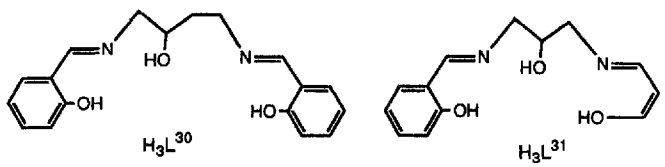


Valence localization was also found in the diiron complex of proligand H_2L^{29}, $[Fe(II)Fe(III)L^{29}(mpdp)](BPh_4)$ (mpdp = 1,3-benzenedipropionate) (**13**)[53]. The two iron atoms are again in very different coordination environments and are bridged by the cresolate-O atom and by the two carboxylate bridges of mpdp. The iron atom in the N_3 arm $[N_3O_3]$ is further coordinated by all three articular nitrogen donors and that of the iron in the N_2O arm $[N_2O_4]$ is bonded to the articular phenolate atom as well as to the two nitrogen atoms of the arm. The intermetallic separation of 3.417 Å is comparable to that of 3.52 Å determined by EXAFS for reduced uteroferrin[54]. The asymmetry of the Fe–O–Fe unit, supported by Mössbauer studies, suggests that there is charge localization, with Fe(III) in the N_2O_4 site and Fe(II) in the N_3O_3 site.

The complex **13** has been described as a model for the diiron purple acid phosphatases. Two forms of diiron unit have been characterized in these enzymes – Fe(II)Fe(III) (active) and Fe(II)Fe(III) (inactive) – and an oxygen-rich coordination environment similar to that in ribonucleotide reductase has been proposed as likely. Electrochemical studies of **13** showed that there are stable Fe(III)Fe(III) and Fe(III)Fe(II) forms as in the purple acid phosphatases and that the terminal phenolato ligand destabilizes the Fe(II)-Fe(II) in terms of chemical reactivity, thus rationalizing the observation that reduction of porcine purple acid phosphatase is accompanied by release of iron[55].

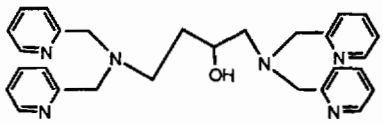
(ii) Endogenous Alkoxo-Bridge Ligands

Unsymmetric pentadentate Schiff base ligands derived from aminoalcohols were first used in studies investigating the magnetic properties of dinuclear metal complexes. The dinuclear copper(II) complexes $[Cu_2L^{30}X]$ (X = μ-Cl, μ-pyrazolate) have been synthesized from the proligand H_3L^{30}, itself prepared from the condensation of salicylaldehyde with 1,4-diaminobutan-2-ol[56,57]. In these molecules the asymmetry arises from the availability of five- and six-membered chelate rings in the bridging ligand skeleton. Donor set asymmetry was introduced into a related proligand, H_3L^{31}, by the introduction of salicylideneimine and acetylacetoneimine terminal groups. The dicopper(II) and dinickel(II) complexes $[M_2L^{31}pz]$ (M = Cu, Ni; pz = μ-pyrazolate) were prepared and their physicochemical properties studied[58]. The above dicopper(II) complexes showed moderate antiferromagnetic coupling.

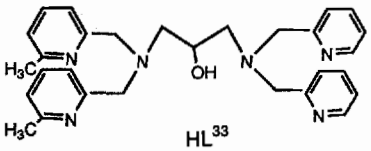


Asymmetry in dinuclear complexes involving proligand HL^{32} arises from the formation of five- and six-membered chelate rings in the bridging skeleton[59]. The dicobalt(II) complexes $[CO_2L^{32}(RCOO)](ClO_4)_2 \cdot nH_2O$ (R = CH_3, C_6H_5) have been synthesized and found to react reversibly with dioxygen in acetonitrile. The structure of a resulting dicobalt(II) peroxo complex, $[Co_2L^{32}(CH_3COO)(O_2)](PF_6)_2 \cdot CH_3CN \cdot H_2O$ (**14**), has been determined and shows two crystallographically independent dinuclear complex cations. Although each cation is unsymmetric, disorder involving the five- and six-membered chelate rings in the bridging skeleton results in the presence of a mirror plane. Each cobalt(II) is in a distorted octahedral environment provided by a *cis,cis*-$[N_3O_3]$ donor set and the metals are triply bridged by the alkoxo-O, an acetate anion and the peroxo-group. Dioxygen affinity for symmetric dinuclear complexes, and its reversibility, has been shown to be highly ligand dependent[60]; that the dioxygen affinity of **14** is intermediate to that of the appropriate symmetric parent complexes further illustrates this point.

A second unsymmetric proligand with potential for alkoxo-bridging, HL^{33}, readily forms the diiron(II) complex $[Fe_2L^{33}(CF_3COO)](BF_4)_2 \cdot nH_2O$[61]. No structural information is available for this complex, which reacts rapidly



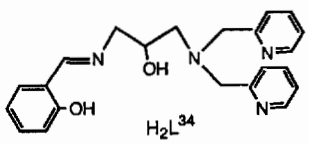
HL^{32}



HL^{33}

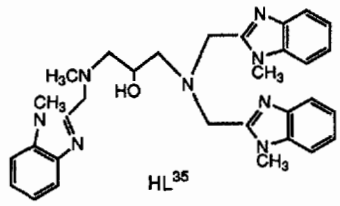
with dioxygen in solution at −60 °C to give a μ-peroxo compound. No reversibility is found and the μ-peroxo compound gradually decomposes within a few hours, even at −100 °C.

The proligand H_2L^{34} has present two adjacent, dissimilar donor sets, NO_2 and N_3O[62]. The structure of the dicopper complex $[Cu_2L^{34}(CH_3COO)]ClO_4 \cdot H_2O \cdot 0.5\ NaClO_4$ shows that two geometrical isomers result from asymmetry of the skeletal bridge carbon atom. In each isomer the copper atoms are doubly bridged by the endogenous alkoxo-O and the acetate anion; one copper is in a square-planar site based on the NO_2 donor set and the second in a distorted square-pyramidal site ($\tau \approx 0.5$) derived from the N_3O donor set. The two isomers exhibit very weak antiferromagnetic coupling and the Cu···Cu separations are ca. 3.43 Å.

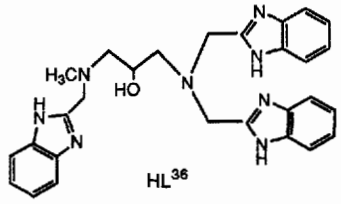


H_2L^{34}

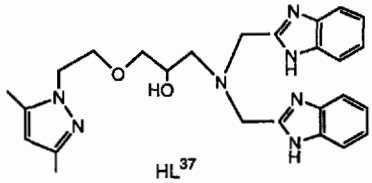
Proligand HL^{35} was designed in order to introduce coordinative unsaturation at one metal centre within a dinuclear complex[16]. Reaction of HL^{35} with copper(II) perchlorate gave only a mononuclear product $[CuHL^{35}](ClO_4)_2 \cdot CH_3CN$ but reaction with copper(II) acetate gave $[Cu_2L^{35}(CH_3COO)](ClO_4)_2 \cdot 2\ H_2O$ (**15**). In this complex the metal atoms are doubly bridged by endogenous alkoxo-O and the exogenous acetate anion, and as a result of the inherent asymmetry in the ligand one copper is in a distorted trigonal-bipyramidal environment provided by an N_3O_2 donor set and the second is in a distorted square planar environment provided by an N_3O_2 donor set. In the solid state one of the perchlorate anions is weakly bound to the four-coordinate copper atom (Cu−O = 2.57 Å), suggesting that a vacant coordination site could exist at this copper atom. The potential for site-directed reactivity at the unsaturated copper atom was demonstrated by adding azide ion to **15**, whereby the azide-bridged complex $\{[Cu_2L^{35}(CH_3COO)]_2N_3\}(ClO_4)_3 \cdot 8.5\ H_2O$ was isolated and structurally characterized. Complex **15** is regarded as the first example of a dinuclear copper complex to be both coordination-number asymmetric and to have directed reactivity at one metal centre due to a constraint imposed by ligand design.



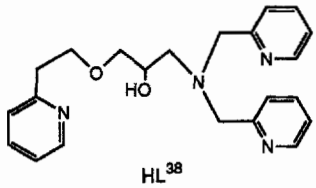
HL^{35}



HL^{36}

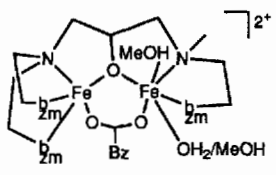


HL^{37}

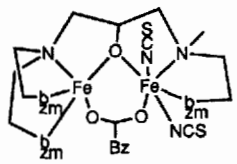


HL^{38}

The same authors have used HL^{35} to prepare $[Fe_2L^{35}(C_6H_5COO)(CH_3OH)_{1.5}(H_2O)_{0.5}](BF_4)_2$ (**16**), the structure of which contains one five-coordinate and one six-coordinate iron atom doubly bridged by the endogenous alkoxo-O and a benzoate anion[63]. The former site has a distorted trigonal-bipyramidal geometry with an N_3O_2 donor set, the residual donors being two benzimidazole-N atoms and an amine-N atom from one ligand arm; the latter site has an octahedral geometry and an N_2O_4 donor set, with the residual donors being one benzimidazole-N atom and an amine-N atom from the second ligand arm together with a methanol and a site which models as a shared methanol and water molecule. Solvation occurs at the site with the lower coordination from the ligand. Treatment of **16** with thiocyanate anion introduces tow N-bonded thiocyanate anions at the sites previously occupied by solvent molecules to give $[Fe_2L^{35}(C_6H_5COO)(NCS)_2]_2$ (**17**). The potential to introduce accessible sites for reaction at one metal of a dinuclear pair is an important aspect in the development of dinuclear complexes with coordination number asymmetry.



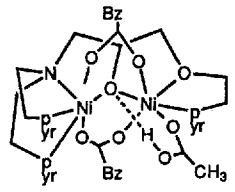
(16)



(17)

bzm =  Bz = C_6H_5-

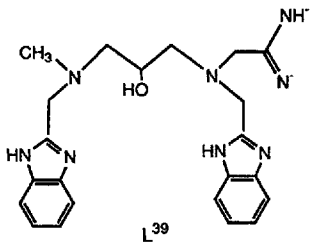
The related proligand HL^{36} has been used by Krebs and his co-workers to coordinate to nickel and so produce a dinuclear complex to serve as a model for the dinickel(II) site in urease[64]. The complex $[Ni_2L^{36}(C_6H_5COO)(EtOH)_2](ClO_4)_2 \cdot EtOH$ (**18**) has the nickel atoms doubly bridged by the endogenous alkoxo-O atom and the benzoate anion. One nickel is in a trigonal-bipyramidal environment $[N_3O_2]$ with the donor atoms from the bis(benzimidazole) arm completing the donor array, whilst the second nickel is six-coordinate $[N_2O_6]$ with the N atoms of the second arm and the two solvent molecules completing the coordination sphere. The solvent molecules are in *cis* positions and the spatial arrangement is similar to that found in **16** and **17**. The Ni···Ni separation is 3.514 Å and thus is close to the 3.5 Å reported for urease from *Klebsiella aerogenes*[6]; this can be related to the possible formation of a μ-carboxylato-μ-hydroxo-bridged dinuclear species in urease under physiological conditions. A second model system was derived from proligand HL^{37}, $[Ni_2L^{37}(CH_3COO)(H_2O)_2](ClO_4)_2 \cdot H_2O \cdot Et_2O \cdot 2\ EtOH$ (**19**)[64]. Both metals are six-coordinate and triply bridged by the endogenous alkoxo-O atom, the acetate anion and a water molecule. The water molecule is asymmetrically bound, with the longer interaction (2.394 Å) being with the more sterically encumbered nickel atom. This nickel is that bound to the three N atoms of the bis(benzimidazole) arm, and the coordination geometry may be regarded as either distorted octahedral or square pyramidal if the elongated binding to the water molecule is not considered. The coordination sphere of the second nickel atom $[NO_5]$ is completed by interaction with the articular ether-O, a pyrazole-N and a water molecule. The Ni···Ni separation here is shorter at 3.171 Å. Although neither **18** nor **19** has shown hydrolytic activity towards urea, complex **19** has shown an accelerated hydrolysis of the substrate 4-nitrophenyl phosphate. A further model for urease, $[Ni_2L^{38}(C_6H_5COO)_2(CH_3COOH)](ClO_4)_2 \cdot Et_2O$ (**20**), is derived from proligand HL^{38}[65]. The metal atoms are separated by 3.387 Å and are both six-coordinate; they are triply bridged by the endogenous alkoxo-O atom, and two benzoate anions. One nickel atom $[N_3O_3]$ is further bound by the nitrogen-rich bispyridyl arm and the second $[NO_5]$ by the articular ether-O, a pyridine-N and a monodentate acetic acid molecule, the coordination of which is stabilized by a strong intramolecular hydrogen bond from the acidic proton to the endogenous alkoxo-O atom. The acid is present at the site with the lower coordination from the ligand, which may therefore be viewed as the likely site for substrate interactions.



(20)

pyr =  Bz = C_6H_5-

The heptadentate proligand ligand HL^{36} has been used to prepare $\{Fe_2(L^{36})[O_2As(CH_3)_2]Cl_2(CH_3OH)\}(ClO_4)_2 \cdot 4\ CH_3OH$ (**21**), the first unsymmetrical μ-alkoxo-bridged dinuclear iron complex[66]. The coordination environments of the two iron atoms are different: Fe(1) is surrounded by an N_3O_2Cl donor set and Fe(2) by an N_2O_3Cl donor set, and the Fe···Fe separation is 3.535 Å. The former set is comprised of two benzimidazole-N atoms and a tertiary amine-N atom coordinated facially, and a chloride atom, a bridging alkoxo atom from the ligand and an O atom from the bridging dimethylarsenito-group; the latter set is comprised of a benzimidazole-N atom and a tertiary amine-$N(CH_3)$ atom together with a chloride atom, a methanol group, the bridging alkoxo atom from the ligand and an O atom from the bridging dimethylarsenito group. The chloro and methanol ligands are labile and complex **21** reacts with hydrogen peroxide to give a peroxide adduct which is stable over several hours. Complex **21** exhibits very limited catalase properties but in the presence of hydrogen peroxide oxidizes the diammonium salt of 2,2′-azinobis(3-ethylbenxothiazoline-6-sulfonic acid), which has been used to quantify the enzymatic activity of peroxidases[67], to its radical cation so behaving as a functional model for peroxidase.



L^{39}

Conclusion

This is a burgeoning area of coordination chemistry not only with respect to ligand design and synthesis but also in the application of the formed dinuclear complexes, as speculative, and to an extent corroborative, models for bimetallobiosites. Given that asymmetric coordination of metal ions seems to be a prerequisite for the catalytic activity of a dinuclear metallobiosite it is interesting to see the evolution of complexes which mimic, in a predictable manner, the differential functions of the metal ions at such a metallobiosite. Additionally comparison of the physico-chemical properties of the asymmetric complexes with those of their symmetric parent complexes can give insight into the fine-tuning available from subtle changes in ligation at dinuclear metal centres.

We would like to thank the *Daiwa Anglo-Japanese Foundation* and the *British Council* for their support.

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