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Metal complexes of bibracchial Schiff base macrocycles[1]

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Contents

Abstract

This article discusses polynuclear metal complexes of Schiff base macrocycles and their potential application to the modelling of metallobiosites, in particular di- and tri-nuclear copper(II)-containing sites. A brief perspective of the area is presented and then the article addresses the development of pyridinyl-derived bibracchial (doubly pendant-armed) Schiff base macrocycles and their metal complexes. The cleft-like configurations of the complexes bear resemblance to the metal-containing pockets present in metalloproteins. A 'first generation' model for the trinuclear copper site in ascorbate oxidase, and a dinuclear manganese(II) complex bearing a single acetato-bridge, and which may have relevance to the modelling of dinuclear manganese biosites, are discussed. An extension of the work to thiophene-derived macrocycles and their dicopper(I) complexes is also presented.

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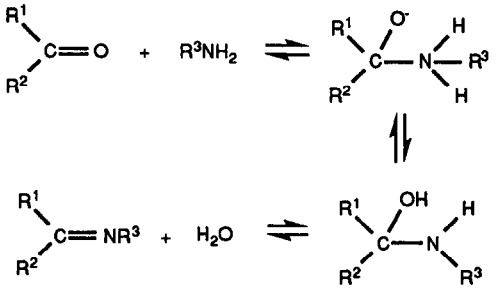
1. Introduction

The purpose of this lecture was to introduce the audience to the application of Schiff base macrocyles to the modelling of metallobiosites. It therefore began with brief comment on Schiff bases, Schiff base macrocycles, and the modelling of metallobiosites before describing the modelling of di- and tri-nuclear copper containing sites. The development of bibracchial, or doubly pendant-armed, tetraimine Schiff base macrocycles and their application in the provision of molecular clefts relating to the metal-binding pockets provided in metalloproteins was then discussed.

2. Schiff bases

Schiff bases, compounds containing an imine or azomethine group (-RC=N-), are usually formed by the condensation of a primary amine with an active carbonyl; they are named after Hugo Schiff who first reported them in 1864 [1]. The reaction to prepare Schiff bases is reversible, progressing through a carbinolamine intermediate, and requires the removal of water, often by azeotropic distillation with benzene,



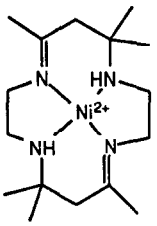
to achieve high yields. The reaction is acid-catalysed but catalysts are not generally required when aliphatic amines are involved. Schiff also discovered the experimental technique of preparing metal–imine complexes by reacting a preformed metal salicylaldehyde compound with a primary amine [2]. This technique may be viewed as an ancestor of the 'metal-template' approach that has evolved as an efficient route for the synthesis of macrocyclic ligands and complexes.

Schiff bases have played an important role in the development of coordination chemistry as they readily form stable complexes with most of the transition metals. In the area of bioinorganic chemistry interest in Schiff base complexes has centred on the role such complexes may have in providing synthetic models for the metal-containing sites in metallo-proteins and -enzymes.

3. Synthesis of Schiff base macrocycles

For the purposes of coordination chemistry a macrocycle is a ligand which contains three or more potential donor atoms in a nine-membered heteroatom ring. Nature

has used macrocycles — porphyrins and corrins — for millenia but man has only recently exploited this area of chemistry. Before the 1960s there were only the phthalocyanins and isolated species such as van Alphen's cyclam and the Luttringhaus polyethers available, and often only in very small yields. The 1960s saw the advent of a range of polyaza-, polythia- and azathia- macrocycles, generally prepared by 'template' procedures, and of Pedersen's crown polyethers. These discoveries led to an upsurge of interest in the area which in turn has generated supramolecular chemistry and its enormous diversity of topics [3,4].



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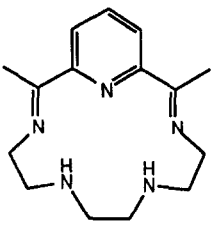

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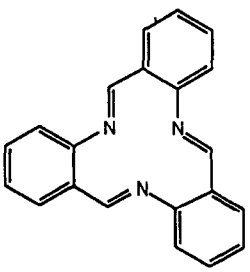

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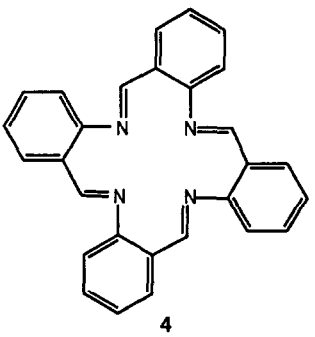

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The earliest example (**1**) of a synthetic macrocyclic ligand containing an imine linkage was derived from the mixed Schiff base–aldol condensation of acetone with nickel(II) ethylenediamine complexes [5]. In 1964 Curry and Busch reported the iron(II)-templated condensation of 2,6-diacetylpyridine with triethylenetetramine to give iron(III) complexes of the macrocycle (**2**) [6]. This was followed by the observation that the self-condensation of *o*-aminobenzaldehyde gave, in the presence of nickel(II) ions, complexes of the macrocyclic ligands (**3,4**) [7]. In all of these examples no macrocycle was obtained in the absence of a metal ion.

Schiff bases have therefore provided a foundation stone for the building of contemporary macrocyclic chemistry. A wide range of Schiff base macrocycles has evolved from the early studies. many of which involve the use of 2,6-diacetylpyridine (PDA) or 2,6-diformylpyridine (PDF) as building blocks. It is possible to find an oligomeric series of macrocycles based on the condensation of these pyridine dicarbonyls with 1,*n*-diaminoalkanes [8] and routes to the formation of [1+1] and [2+2] Schiff base macrocycles (i.e. macrocycles based on the condensation of one dicarbonyl with one diamine, and two dicarbonyls with two diamines, respectively) are shown in

Fig. 1 using the reaction of PDA with α,ω-diaminoethers as an example [9]. It is important to draw attention to the seminal contribution that Nelson et al. made during the foundation of this area of study [10].

The role of the metal ion in these metal-ion templated cyclisations is to control the supramolecular assembly of pre-cyclisation fragments, most likely through the formation of metal complexes derived from the precursors. The desired cyclisation product then results from an intramolecular interaction in the transition state. In the syntheses shown alkali metal cations and transition metal ions are ineffective as templates but alkaline earth cations and lead(II) promote cyclisation. The size and ionic potential of the template appear to be important factors in the reaction. In the formation of [1+1] macrocycles the larger Ca^{2+}, Sr^{2+}, and Ba^{2+} cations give the hexadentate macrocycle derived from 1,11-diamino-3,6,9-trioxaundecane whereas the smaller Mg^{2+} cation gives only the pentadentate macrocycle derived from 1,8-diamino-3,6-dioxaoctane. Rather interestingly when Pb^{2+} is used, under conditions which could have given the [1+1] product derived from 1,8-diamino-3,6-dioxaoctane, it promotes formation of a homodinuclear complex of the [2+2] macrocycle which is therefore acting as a dinucleating ligand.

By varying the nature of the heterocyclic dicarbonyl ('head unit') and the 1,*n*-diamine ('lateral unit'), a wide range of dinucleating tetraimine Schiff base macro-

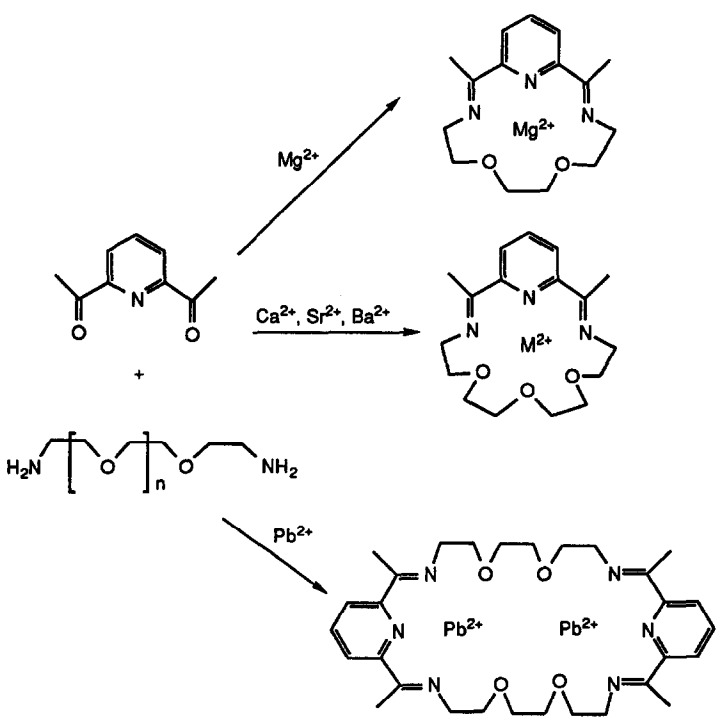
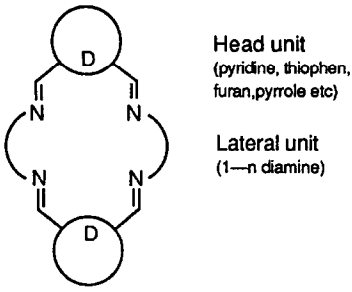


Fig. 1. Routes to macrocyclic Schiff bases.

cycles can be synthesised. The range of template has also been extended and includes lanthanides, actinides, silver(I) and manganese(II).



4. The modelling of metallobiosites

The final arbiter for biological structure determination has for many years been single crystal X-ray diffraction. However, it is often difficult to obtain good crystals and the resolution of the structure determination is often limited. The structure, when solved, will only give detailed information about the crystallised form of the metalloprotein, and it may not be easy to infer from this the nature of any structural changes which might occur on conversion to another form by processes such as the binding of substrates. As a consequence many inorganic chemists become involved in inorganic biochemistry by attempting to devise small molecule models the properties of which can be compared with those of the metalloprotein and hence provide a model compound.

The properties of a metal in a metalloprotein are dependent upon its chemical environment — the coordination geometry at the metal, the number of coordinated ligands and the nature of their donor groups. These structural parameters affect the electrochemical, spectroscopic, and, in multinuclear systems, the magnetic characteristics of the metallobiosite. It is possible, by comparing a range of model compounds having slightly different metal environments, to build up an understanding of the effects of these parameters on the physico-chemical properties of the models and this can then be used in the deduction of structural features of the metalloprotein under study.

Two useful definitions for model compounds of metalloproteins, speculative models and corroborative models, were introduced by Hill [11]. Speculative models are prepared when the structure of the microenvironment of the metallobiosite is unknown and the objective is to reproduce some physico-chemical property of the system in a small molecule complex. When the structure of the metallobiosite is known a corroborative model can be prepared. This is usually a small molecule complex in which the environment of the metal is reproduced as accurately as possible. It then becomes possible to determine whether the observed properties of the metal in the protein are dominated by the first coordination sphere and can give

insights into the relationship between structural features of the metallobiosite and its physical properties.

5. Modelling dinuclear copper-containing proteins

The copper(II) atoms present in copper metalloproteins have been classified according to their spectroscopic properties [12]. Type-1, as found in 'blue' copper proteins such as plastocyanin, azurin and stellacyanin, contains a mononuclear copper biosite with a distorted tetrahedral N_2S_2-donor set and has high absorption in the visible region ($\varepsilon > 3000\ M^{-1}\,cm^{-1}$ at 600 nm) and an EPR spectrum with $A_{II} < 95 \times 10^{-4}\,cm^{-1}$. Type-2, or normal, is present in all multicopper 'blue' oxidases and displays spectroscopic properties similar to those found for typical mononuclear Cu(II) complexes, i.e. a broad unresolved band near to 700 nm in the UV–vis spectrum and an EPR spectrum typical of small molecule copper(II) complexes ($A_{II} > 140 \times 10^{-4}\,cm^{-1}$). Type-3, which has a strong absorption in the near UV region ($\lambda_{max} = 330$ nm) and no EPR signal, consists of a pair of antiferromagnetically coupled copper(II) ions.

The nature of the type-3 sites has provided a challenge to the synthetic chemist and made them prime targets for modelling studies. To date research in this area has concentrated on modelling the type-3 sites present in the oxygen transport protein haemocyanin, which is found in the two phyla *Mollusca* and *Arthropoda* and the polyfunctional oxidase tyrosinase [13,14]. Our early work concerning the use of dinucleating Schiff base macrocyclic ligands in the modelling of copper biosites was based on the premise, derived from cumulative spectroscopic studies and EXAFS data, that there was a protein-based endogenous bridge, derived from tyrosine, serine, threonine, or even the hydroxide anion, present in oxy-haemocyanin (Fig. 2) [15]. This proposal generated many model studies the thrust of which was to provide an endogenous bridge, as this was held responsible for the observed strong antiferromagnetic coupling between the two copper(II) ions and to replicate this together with the intercopper distance of ca. 3.5 Å, and the charge transfer band at 330 nm. Much of the work concerning the role of dinuclear copper complexes in the activation of dioxygen came from the laboratory of Karlin [16], on dinuclear copper complexes derived from pendant armed phenolic ligands such as (5), and represents a considerable contribution to our understanding of this area of chemistry. The xylyl model has permitted reversible dioxygen uptake, and provided a functional mimic for

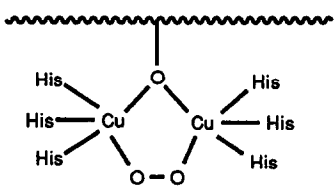
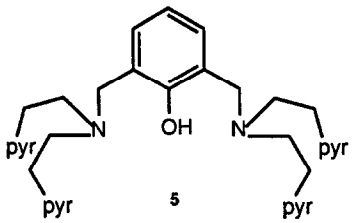


Fig. 2. The spectroscopically derived dicopper(II) site in oxy-haemocyanin.

copper hydroxylases such as tyrosinase by showing how dioxygen can be activated by copper for electrophilic attack and oxygenation of an aromatic substrate [17].



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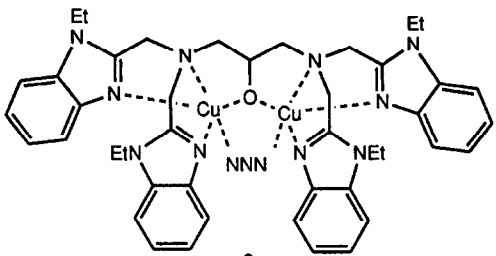
A further model was derived from a polypodal ligand reported by Reed et al. [18], which gave the dinuclear Cu^{II}-azido complex schematically depicted as (**6**). The physico-chemical properties of this complex [Cu···Cu separation (from the X-ray crystal structure), 3.62 Å; diamagnetic; charge transfer band, 364 nm] compare closely with those found for *met*-azidohaemocyanin and it was concluded that as 'the popularity of phenoxide may be at odds with the absence of enhanced tyrosine vibrational modes in resonance Raman studies of oxyhaemocyanin···alkoxide from serine or threonine now becomes a particularly viable candidate' for the EXAFS-predicted endogenous bridge.



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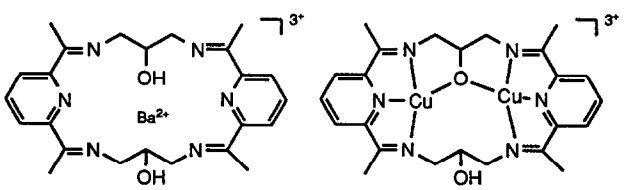
Our own system was derived from the barium-templated cyclocondensation of 2,6-diacetylpyridine and 1,3-diamino-2-propanol to give the barium complex (**7**) followed by transmetallation with copper to give the dinuclear complex (**8**), the crystal structure of which was obtained [15]. The two copper atoms were separated by 3.64 Å and antiferromagnetically coupled. The complex also provided the first example of a structurally-characterised copper dimer with a single alkoxo-bridge, and so could be considered as modelling a possible serine or threonine interaction.

The eventual solution of the crystal structure of deoxy-haemocyanin from *Panulirus*



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interruptus (the spiny lobster) by Hol and his group (Fig. 3) [19] confirmed the dinuclear nature of the site and the presence of three histidine ligands per copper atom but eliminated the concept of an endogenous bridge as there was no conserved candidate suitable for such bridging within 12 Å of the site. The two Cu(I) ions were each coordinated by three histidine residues and separated by 3.6 Å. More recently the X-ray crystal structure of the deoxy-form of haemocyanin from *Limulus polyphemus* (horseshoe crab) has revealed that the copper(I) ions are again trigonally coordinated by three histidines but that the inter-copper distance is 4.6 Å [20]. This suggested that it is necessary to look for small molecule models which do not contain endogenous bridges, a premise that was reinforced when structural information became available concerning the nature of the oxygenated form of haemocyanin.

An intriguing model complex, derived from tris-(3,5-di-isopropylpyrazolyl)borate, $[Cu\{HB\text{-}(3,5\text{-}iPr_2pz)_3\}]_2[O_2]$, emerged from the laboratory of Kitajima and Morooka [21], the X-ray crystal structure of which showed that dioxygen had inserted between the two Cu(II) ions which were then linked solely by an $\eta^2{:}\eta^2$ peroxide. The spectroscopic properties were remarkably similar to those found for oxyhaemocyanin and the subsequent solution of the X-ray crystal structure of oxy-form of haemocyanin from *Limulus polyphemus* by Magnus [22] confirmed that there is no endogenous bridge present at the dinuclear site in oxyhaemocyanin.The structure is as that shown schematically in Fig. 2 in which the $\eta^2{:}\eta^2$ peroxide moiety is present. Interestingly this mode of binding had been proposed much earlier by Mason et al. who, in a study which established the diamagnetism of oxy-, deoxy- and apohaemocyanin from *Cancer magister*, suggested that dioxygen could insert between two copper(II) atoms in order to mediate the magnetic property [23]. The Cu(II)···Cu(II) separation in the model complex is 3.56 Å as compared with 3.6 Å in the oxyhaemocyanin from *Limulus polyphemus*.

During the course of studies on ligands capable of providing endogenous bridges it became apparent from the structures of several mononuclear barium complexes of functionalised tetraimine Schiff base macrocycles that the macrocyclic ligands had folded to present molecular clefts into which the metal ions coordinated particularly if the lateral unit of the macrocycle contained an odd number of carbon atoms the

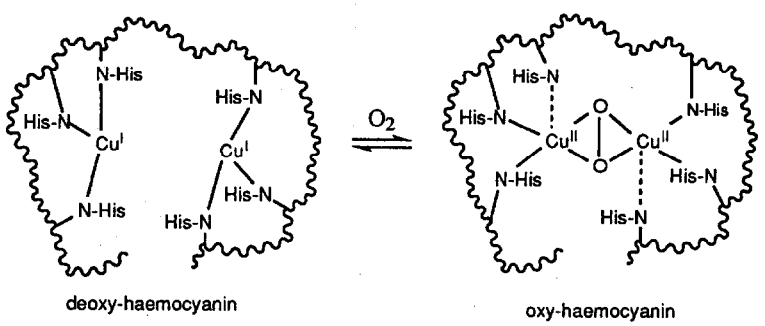


Fig. 3. Schematic representations of the dicopper(I) site in deoxy-haemocyanin and the dicopper(II) site of oxy-haemocyanin.

central one of which was functionalised [24]. This mode of metal incorporation is not dissimilar to that of metalloproteins in which the requisite metal is bound in a pocket or cleft produced by the conformational arrangement of the protein. The objective then became the synthesis of flexible macrocycles capable of generating clefts for metal coordination without the presence of a ligand-based endogenous bridge. In order to do this a series of bibracchial, or doubly pendant armed, macrocycles were synthesised from 2,6-diacetylpyridine and a range of *N,N*-bis(3-aminopropyl)- and *N,N*-bis(2-aminoethyl)-alkylamines using barium or silver(I) templates [25]. The resulting mononuclear barium complexes and dinuclear silver(I) complexes were found to have the required conformation and in the latter cases the metals were separated by distances ranging from 2.9 to 6.0 Å depending on the nature of the donor groups in the pendant arms and on the length of the carbon atom chains present in the lateral diamine derived spacers (Fig. 4).

The transmetallation of the barium complex of the corresponding macrocycle derived from *N,N*-bis(2-aminoethyl)-2-methoxyethylamine (**9**) readily gave a dinuclear copper(II) complex (**10**). However, the X-ray crystal structure of (**10**) showed that the cleft conformation had been destroyed (Figs. 5 and 6) [26]. As the primary objective at that time was to recover a dicopper complex in which the cleft conformation was retained thus providing a complex which could be used as an endogenous bridge-less haemocyanin model it was obviously necessary to rethink. It was first decided that reduction of the imine bonds in the ligands would produce a more flexible and more stable ligand system. This was achieved by reductive demetallation of the disilver complexes using sodium borohydride. Unexpectedly the reaction of the reduced metal-free macrocycles with copper(II) gave complexes of stoichiometry $Cu_3L(OR)_2(ClO_4)_4 \cdot nH_2O$ [27]. This immediately suggested that

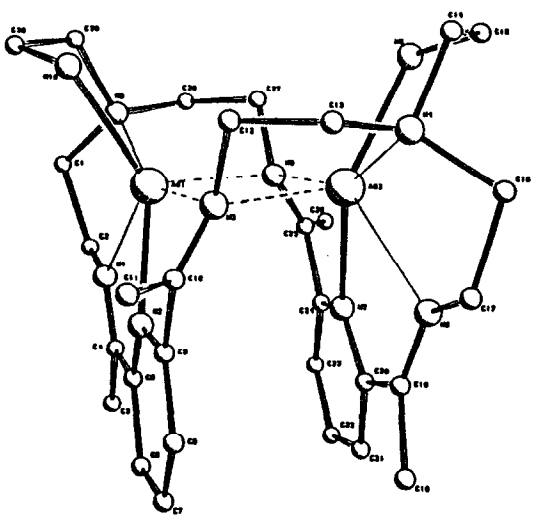


Fig. 4. The structure of a disilver(I) complex of a molecular cleft derived from 2,6-diacetylpyridine and tris(2-aminoethyl)amine.

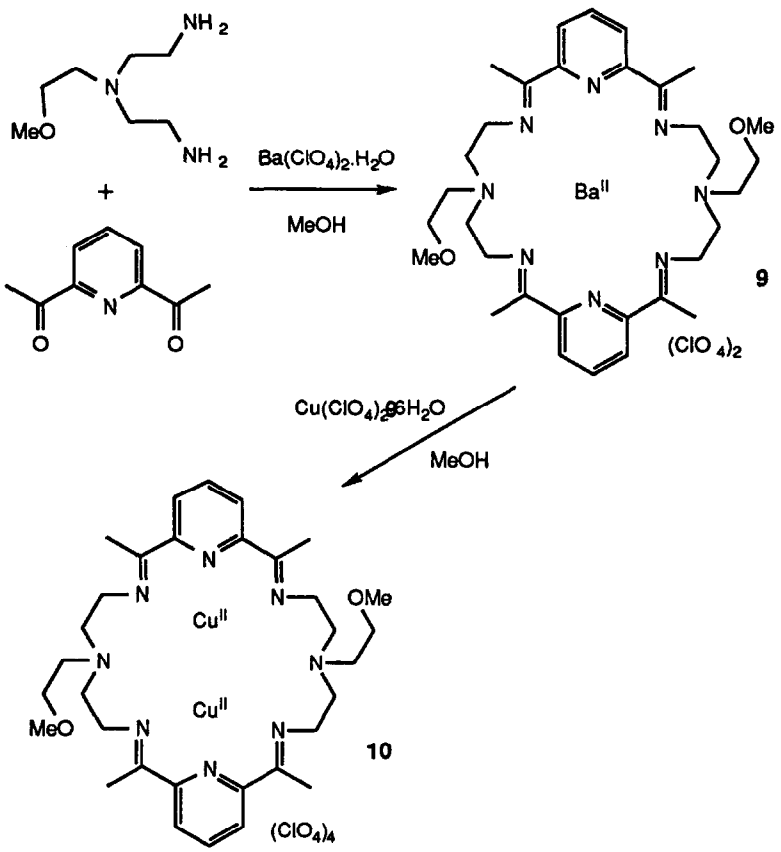


Fig. 5. The transmetallation of a mononuclear barium complex (**9**) to a dinuclear copper(II) complex (**10**).

appropriate modification of the macrocyclic Schiff bases, which have present both a dinucleating centre and pendant-arms which could entrap a further metal, macrocycles could be obtained which would yield trinuclear copper complexes and therefore lead to a model for the trinuclear copper site in ascorbate oxidase.

6. A 'first generation' model for the trinuclear copper site in ascorbate oxidase

Laccase ($M \approx 65\,000$) is the simplest member of a family of multi-copper enzymes, including ascorbate oxidase and ceruloplasmin, which are known as 'blue' oxidases. They catalyse the one-electron oxidation of the substrate with concomitant four electron reduction of dioxygen to water [28]. Laccase contains four copper(II) atoms (one type-1, one type-2 and two type-3) [12]; dimeric ascorbate oxidase contains eight copper atoms [29]. Cumulative spectroscopic and azide bonding

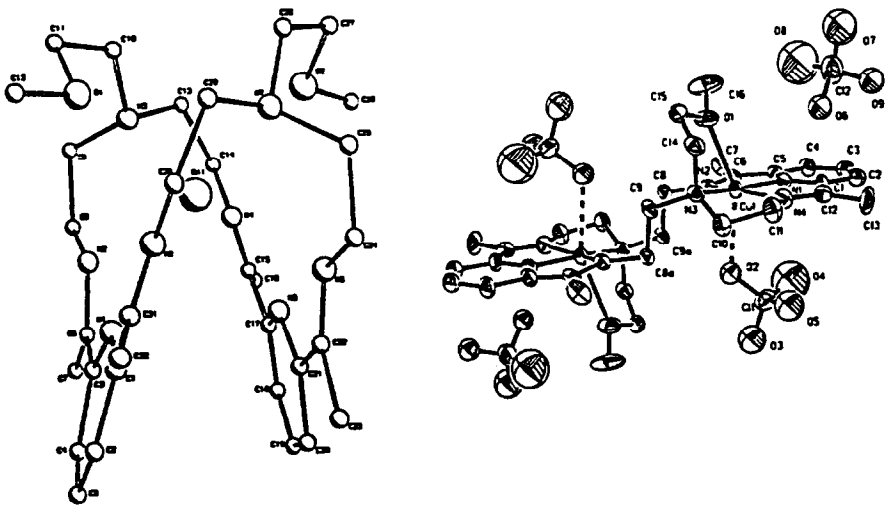
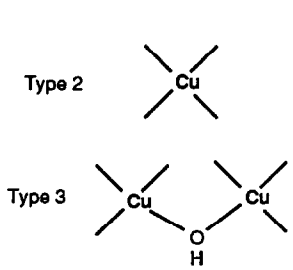


Fig. 6. The structures of the cations from the mononuclear barium (**9**) and dinuclear copper(II) (**10**) complex showing the opening up of the cleft.

studies on *Rhus vernicifera* laccase led to the proposal that the type-2 and type-3 centres defined a trinuclear copper cluster site (**11**) [30].



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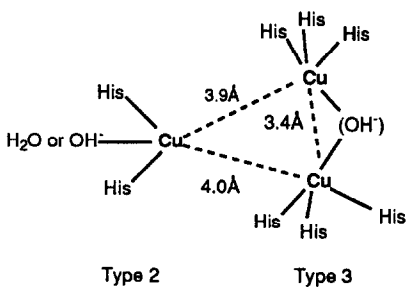

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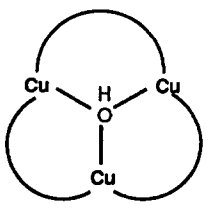
The crystal structure of oxidised ascorbate oxidase from green zucchini has shown that each sub-unit of the dimeric metalloenzyme has four copper atoms present bound as mononuclear and trinuclear species [31]. The mononuclear copper is of type-1, and being bound to two histidines, one cysteine and one methionine ligand resembles plastocyanin; it is isolated from the trinuclear site by ca. 15 Å. The trinuclear site (**12**) is comprised of a type-2 copper and a pair of type-3 copper atoms held in an approximately isosceles triangular array. The type-2 copper, 3.9 Å from one type-3 copper and 4.0 Å from the second, is coordinated to two histidine ligands and an oxygen atom from water or hydroxide. The type-3 copper atoms are each coordinated by three histidine ligands and the intermetallic separation is 3.4 Å. In contrast to the structure of the type-3 site in oxy-haemocyanin, the X-ray data indicate the existence of an oxo- or hydroxo- bridging ligand. Further refinement of

the structure [32] has given metal separations of 3.66, 3.78 and 3.68 Å in subunit A and 3.69, 3.90 and 3.73 Å in subunit B; the data from the original report have been adhered to here as they provided the crystallographic information on which the first generation model, described below, was based.

Although numerous examples of hydroxo-bridged triangulo-copper(II) complexes have been reported they are mostly based on equilateral triangles of copper atoms, with intermetallic distances close to 3.0 Å, and a μ_3-hydroxo bridge (**13**) [33]. There is a single complex derived from a polytopic macrocyclic ligand which has a double μ_3-hydroxo bridge [34]. In contrast synthetic analogues for the trinuclear site in ascorbate oxidase and the related 'blue' oxidases are scarce; for example, one hexanuclear copper(II) complex, derived from a polypodal ligand (**14**, X = N_3^-), has been reported [35] in which there are two approximately isosceles triangular arrays of copper(II) atoms present, each having type-3-like pairs of copper atoms having 3.11 Å separation and supported by an endogenous phenoxo-bridge derived from the ligand; the third copper is distant from the pair by 7.78 and 7.46 Å, respectively.



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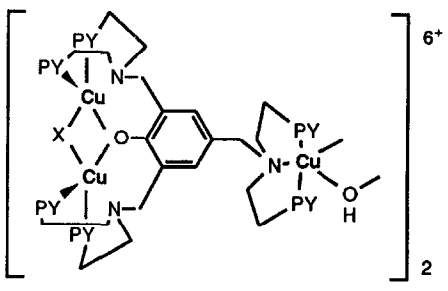

14 X = OH, N_3 ; PY = 2-pyridyl

The synthetic route used to prepare a synthetic analogue for the trinuclear site in ascorbate oxidase is shown in Fig. 7. The disilver complex (**15**) was prepared according to Fig. 7. Synthesis of the trinuclear model complex (15) silver(I) templated [2+2] cyclocondensation of tris-(2-aminoethyl)amine (tren) and 2,6-diacetylpyridine [36]. The structure of the dication shows the ligand to have the cleft conformation with the silver ions bound in the diimino pyridyl head units of the macrocycle and separated by 3.17 Å. In order to introduce a strong exo-macrocyclic type-2 copper binding site functionalisation of (**15**) was achieved by reaction with salicylaldehyde to yield the dinuclear silver(I) complex (**16**). Transmetallation was effected using copper(II) salts and addition of an excess of sodium perchlorate led, on cooling, to the isolation of dark green crystals of the tricopper(II) hydroxo species $Cu_3(OH)(L)(ClO_4)_3 \cdot H_2O$ (**17**).

The presence of a discrete trinuclear copper species bound within the macrocyclic framework was confirmed by X-ray crystallography (Fig. 8) [36] A μ_2-hydroxo-bridged pair, Cu(1) and Cu(2), and a nonbridged copper atom Cu(3) comprise the metallocluster and the two metal ions of the dinuclear moiety are separated by 3.6 Å with a Cu(1)–OH(1)–Cu(2) angle of 137.8°. A scalene triangular array is completed

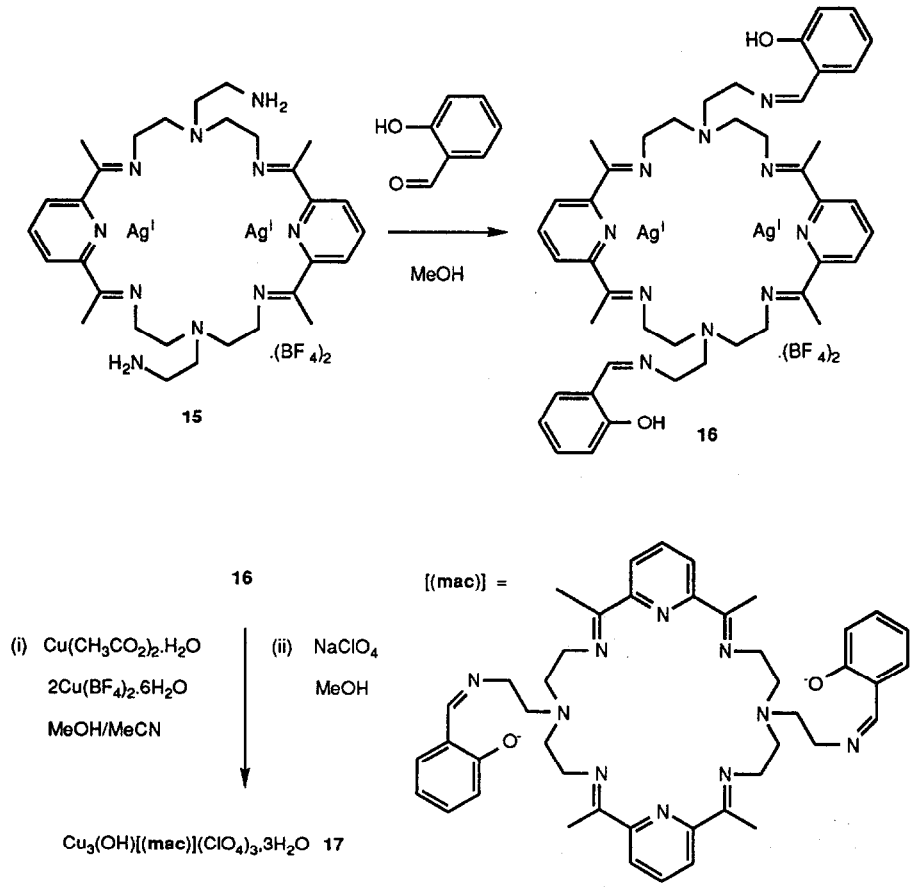

Fig. 7. Synthesis of the trinuclear model complex (**15**).

by the third copper atom Cu(3); the Cu(1)–Cu(3) and Cu(2)–Cu(3) distances are 5.9 and 4.9 Å, respectively.

The coordination geometries around the copper atoms of the hydroxo-bridged pair, Cu(1) and Cu(2), may be described as distorted square based pyramidal. The basal donors for Cu(1) are provided by the nitrogen atoms, N(1), N(2) and N(8), of one pyridine-diimine unit and the bridging hydroxide OH(1). The axial site is filled by the oxygen atom Os(1) of a water molecule. Cu(2) is coordinated by the donor atoms, O(1) and N(10), of a salicylaldimine pendant arm, a tertiary amino nitrogen N(7) of the macrocyclic ring, the bridging hydroxide OH(1) and one of the imine nitrogen atoms N(6) of the second pyridine-diimine unit. The source of the hydroxide ion is most likely to be water present in the reaction medium which originates either from the hydration sphere of the copper(II) salts employed in the transmetallation or from the solvent itself, with the two copper(II) atoms acting in concert as a super acid pair to promote the generation of a nucleophile. The third

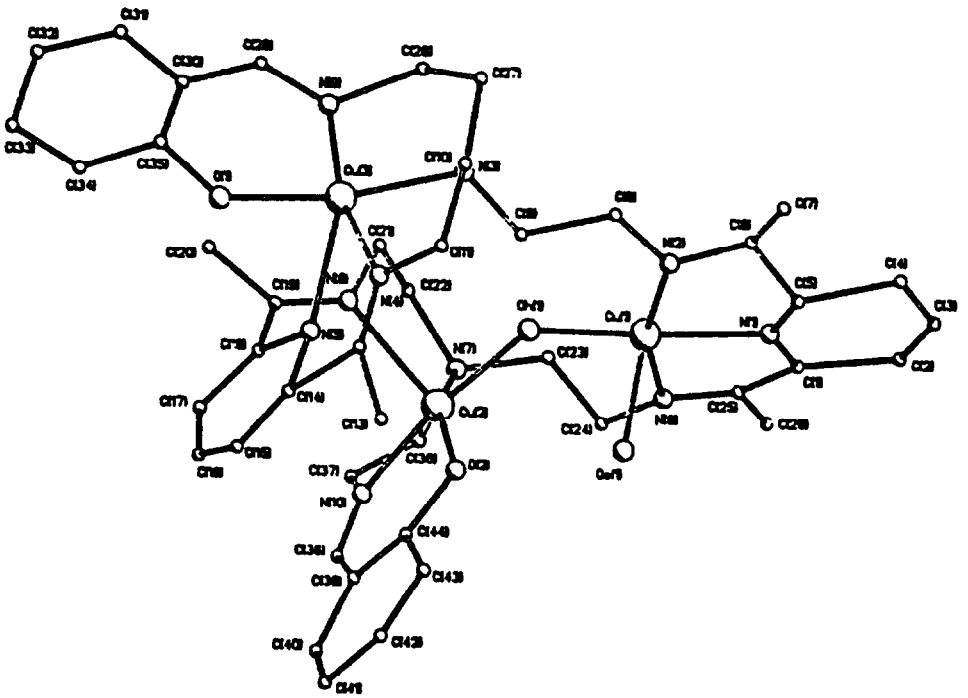

Fig. 8. The structure of the cation in the first generation model complex (17).

copper atom Cu(3) also has a distorted square pyramidal coordination environment which is derived from the donors, O(1) and N(9), of the second pendant arm, a tertiary amino nitrogen N(3), the remaining imine nitrogen N(4) from the second macrocyclic head unit and a pyridyl nitrogen N(5).

The trinuclear site in ascorbate oxidase may be subdivided into a type-3 pair of copper atoms and a type-2 copper. Each type-3 copper atom is coordinated by three histidine residues; the metals are separated by ca 3.4 Å and bridged by an oxo- or hydroxo- ligand [31]. The type-2 copper is coordinated by two histidines, and an oxygen derived ligand, possibly OH^- or H_2O. There are therefore significant differences between the coordination geometries found in (17) and the metallobiosite and these are illustrated schematically in Fig. 9; the detection of a hydroxo-bridge in (17) gives credence to the proposal that the bridge in ascorbate oxidase is of the same type. Magnetic susceptibility measurements carried out on (17) in the temperature range 5 to 300 K are consistent with a system composed of an antiferromagnetically coupled copper(II) pair ($2J = -192\ cm^{-1}$) and a third, magnetically independent, copper(II) ion.

Because of the differences in the nature and geometric arrangement of the donor atoms in the coordination spheres of the metal ions and in the bond distances involved the trinuclear copper(II) complex does not provide a precise replication of the ascorbate oxidase cluster. There is a greater degree of conformational freedom

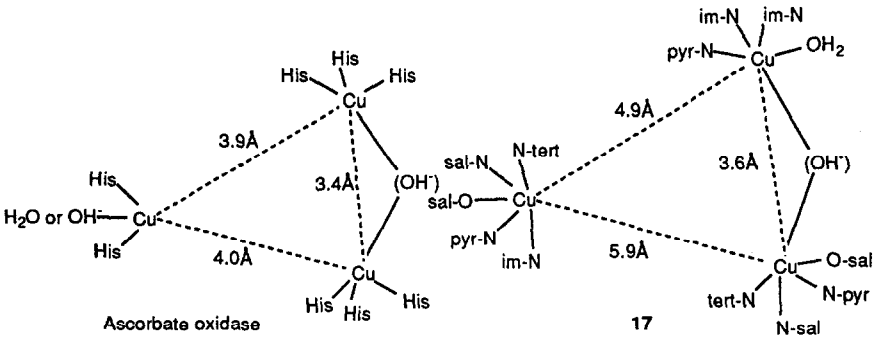

Fig. 9. A comparison of the trinuclear sites in ascorbate oxidase and the model complex (**17**).

in the cleft provided by the small molecule model than in the more highly defined proteinaceous clefts and so the need to build in features which will constrain this mobility is apparent. The trinuclear copper(II) complex does however serve as a 'first generation' model for a type-3 oxidase site in that it reproduces structural features of the biosite to a greater extent than in any synthetic complex previously reported.

7. Dinuclear copper(I) centres

The reaction of the diprotonated cryptand (**18**), prepared by [2+3] cyclocondensation of 2,6-diacetylpyridine and tris(2-aminoethyl)amine in the presence of hydrochloric acid followed by filtration into a solution of sodium tetrafluoroborate in methanol [37], with $Cu(CH_3CN)_4BF_4$ in methanol gave a dinuclear copper(I) complex (**19**) of the neutral cryptand. The X-ray crystal structure of this complex (Fig. 10(b)) shows that both the integrity of the cryptand and the unusual *trans–trans* conformations of the dicarbimine functions found in the protonated cryptand (Figure 10(a)) are retained in the structure of the complex. The Cu(I)···Cu(I) separation is 6.25 Å. This copper separation is well in excess of that reported, 3.04 Å, for the dicopper(I) complex, $[L^3Cu_2](ClO_4)_2$, in which L^3 is the [3+2] Schiff base cryptand derived from 2,6-pyridinedicarbaldehyde and tris(2-aminoethyl)amine [38]. Each copper is coordinated to three imino N atoms and there are further weak interactions to the bridgehead N atom and to a pyridine N atom. The dicarbimine functions in this complex are in *cis–cis* conformations.

In contrast, the reaction of $Cu(BF_4)_2$ with the diprotonated cryptand (**18**) in methanol (Fig. 11) gave a dinuclear complex of $[L^2Cu_2](BF_4)_4 \cdot H_2O$ (**20**). The crystal structure (Fig. 10(c)) confirms that a single ring-opening of the Schiff base cryptand, caused by scission of one pyridinyl-diimine unit, has occurred such that the dicopper(II) moiety is held inside a cleft with a Cu(II)···Cu(II) separation of 4.53 Å. Although this separation is comparable with the dicopper(I) sparation of 4.6 Å found in deoxygenated haemocyanin from *Limulus polyphemus*; [20] we have not yet been

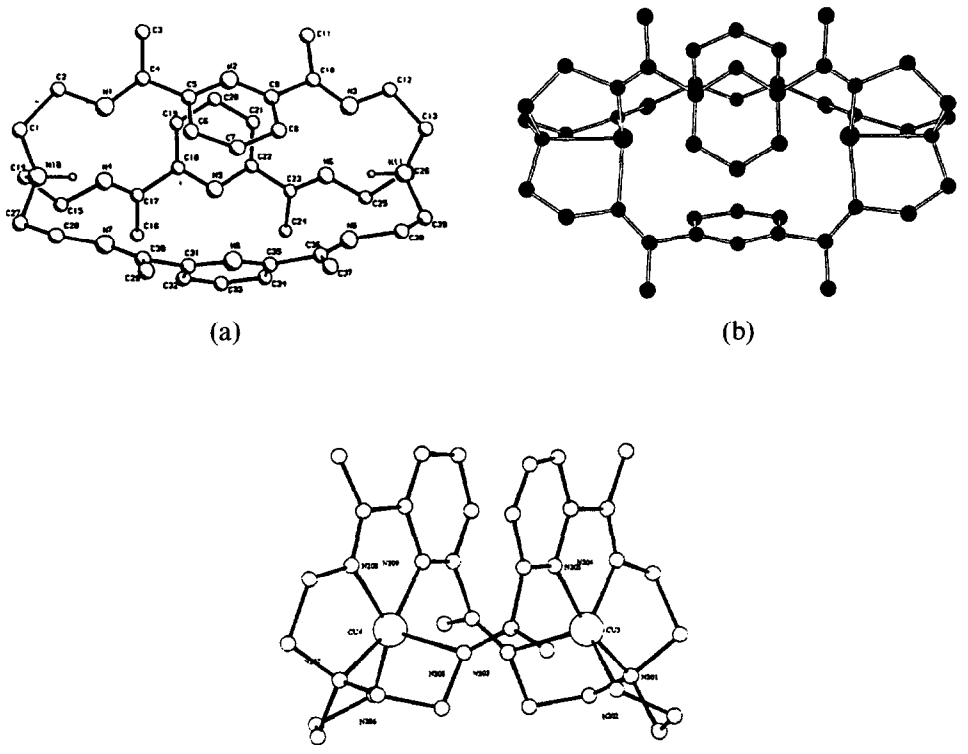

Fig. 10. The structures of the cations in (a) the diprotonated cryptand (**18**), (b) the di-Cu(I) complex (**19**), and (c) the di-Cu(II) complex $[L^2Cu_2](BF_4)_4 \cdot H_2O$ (**20**).

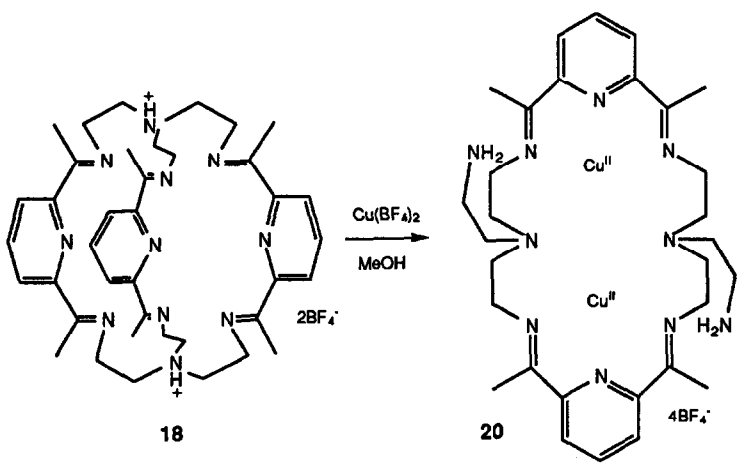

Fig. 11. Synthesis of the dicopper(II) complex (**20**).

able to prepare a dicopper(I) complex of L^2. The N-donor atoms of the pendant arms in (**20**) approach the metal atoms from the same side of the macrocyclic ring ('*cis*') consistent with the clipping out of one bridge from the cryptate precursor. This may be contrasted with the approach of the pendant arms from opposing side ('*trans*') found when the dicopper(II) complex of the directly related tetraimine macrocycle bearing methoxyethyl pendant arms is prepared by transmetallation of the mononuclear barium precursor complex [26].

Although we have not yet been able to prepare a dicopper(I) complex of L^2 it has been possible to prepare such complexes of bibracchial tetraimine Schiff base macrocycles in which the head units are derived from thiophen-2,5-dicarbaldehyde (TDA) and the arms are simply aliphatic chains. It has been noted that there is an interesting coincidence concerning conformer distribution in heterocyclic dicarbonyls and the need for a metal template in condensation reactions to produce tetraimine macrocycles [39]. The dicarbonyls may exist as *cis,cis* (*c,c*), *cis,trans* (*c,t*) and *trans,trans* (*t,t*) conformers. N.m.r studies, usually in nematic phases, have shown that whereas for 2,6-diformylpyridine (PDF) the only important conformer is *t,t* [40], for TDA there is a distribution of 80:20 of *c,c:c,t* [41]. Furthermore the dipole moments, in benzene, of PDF and 2,6-diacetylpyridine (PDA) have been interpreted as arising from a very high percentage of *t,t* with *ca.* 5% *c,t* and negligible *c,c* [42]. The structures of metal complexes of macrocycles bearing these 'head units' show the macrocycles to have *c,c* conformations and so if it is the *c,c* conformer that leads most readily to cyclisation then only with TDA is that conformer present in excess to allow metal-free cyclocondensation to occur. For PDF the metal template procedure is required with the metal redirecting the conformer distribution through complexation with the PDA prior to cyclocondensation. We have previously confirmed that for thiophen-derived tetraimine Schiff bases macrocycles nontemplate methodology may be used [43]. In this work we have applied this strategy to the synthesis of (**21**); the synthetic route to (**21**) and its dicopper(I) complex (**22**) are shown in Fig. 12.

The macrocycle is prepared by cyclocondensation of TDA with the t-butyl centrally functionalised triamine in methanol and reacted with $Cu(CH_3CN)_4PF_6$ in acetonitrile to give the crystalline product (**22**). The X-ray crystal structure (Fig. 13) shows that the two metal ions are 5.2 Å apart and that each copper(I) is four coordinated by the lateral nitrogen-atoms and an acetonitrile of solvation [44]. The complex is relatively air-stable, probably because coordinative saturation of the copper has been achieved through solvation. The sulphur atoms of the thiophen are nonbonding, as has previously been observed for related silver(I) complexes [41], and so this unit may be regarded as simply acting as a spacer. We are currently extending our study of these complexes in order to modify the intermetallic separation and also to induce reaction with dioxygen.

8. Dinuclear manganese centres

The dinuclear manganese centres which have been found in *Lactobacillus plantarum* catalase (LPC) [45] and *Thermus thermophilus* catalase (TTC) [46] have attracted

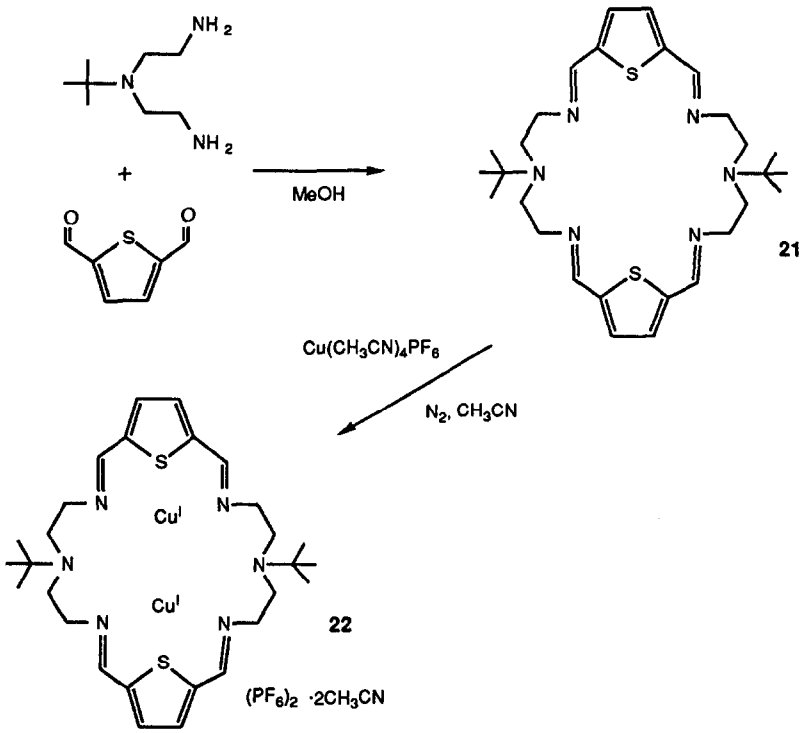

Fig. 12. The synthesis of the dicopper(I) complex (**22**).

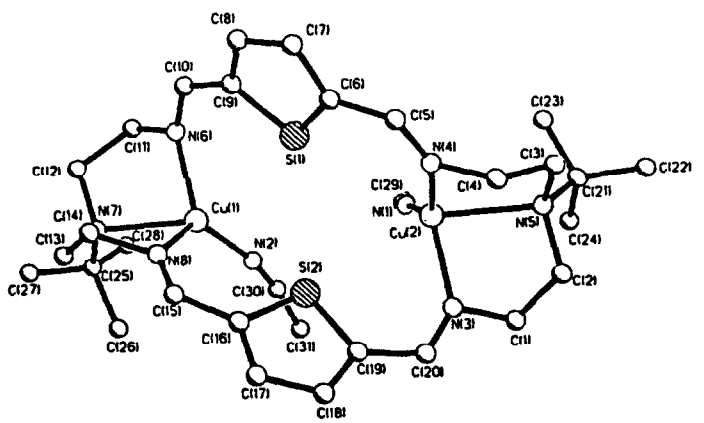

Fig. 13. The structure of the dicopper(I) cation in (**22**).

attention as targets for synthetic modelling with small molecules. The catalases have at least four accessible oxidation states [$Mn^{II}Mn^{II}$, $Mn^{II}Mn^{III}$, $Mn^{III}Mn^{III}$, and $Mn^{III}Mn^{IV}$] and it is believed that the $Mn^{II}Mn^{II}$ / $Mn^{II}Mn^{III}$ redox couple is effective

in catalysing the disproportionation of water. Preliminary crystallographic studies on TTC (oxidation state not defined) suggest a Mn···Mn separation of ca. 3.6 Å [46] and ESR studies on the reduced $Mn^{II}Mn^{II}$ form show that the metal ions are weakly coupled with a metal separation of 3.8 Å [47]. EXAFS studies on the reduced $Mn^{II}Mn^{II}$ form of LPC did not permit an unambiguous assignment of the Mn···Mn separation but did lead to the proposal that bridging structures containing (μ-carboxylato)n, [$n=1$–3], were consistent with the experimental data [45].

The crystal structure of the Mn^{II}-reconstituted Ribonucleotide reductase B2 subunit from *Escherischia coli* has established the presence of two Mn^{II} ions separated by 3.6 Å and connected by two carboxylato bridges [48]. To our knowledge no report has yet been made of a dinuclear manganese(II) complex containing only a single carboxylato bridge. Such a complex has now been prepared using a tetraimine Schiff base and can be viewed, through its provision of structural and spectroscopic parameters, as providing a speculative model for such a species at a metallobiosite.

Reaction of the diprotonated Schiff base cryptate $[L^1H_2][BF_4]_2$ (**18**), with manganese(II) acetate in methanol-acetonitrile (1:1) to which sodium tetrafluoroborate and triethylamine have been added leads to recovery of the product as orange crystals (yield, 20%) (Fig. 14). Recrystallisation from acetonitrile-ethanol gives orange crystals of $[L^2Mn_2(OCCH_3)](BF_4)_3 \cdot CH_3CN \cdot 0.5CH_3CH_2OH$, (21). The Fast Atom Bombardment mass spectrum has a peak of highest mass at m/e = 889 which corresponds to $[L^2Mn_2(OCCH_3)(BF_4)_2]^+$, indicating that a ring-opening has occurred. No peaks are observed which can be assigned to a species retaining the intact Schiff base cryptand.

The crystal structure structure (Fig. 15) confirms that a single ring-opening of the Schiff base cryptand, caused by scission of one pyridinyl-diimine unit, has occurred to yield a carboxylato-bridged dinuclear manganese(II) complex of the bibracchial tetraimine Schiff base macrocycle (**23**). The Mn(II) atoms are separated by 4.83 Å

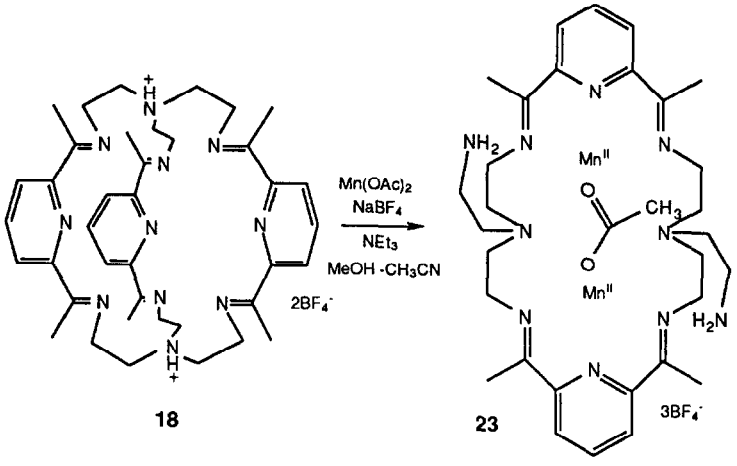

Fig. 14. Synthesis of the dimanganese(II) complex (**23**).

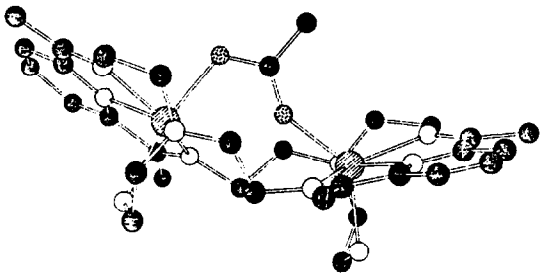

Fig. 15. The crystal structure structure of the dimanganese(II) complex.

and are in severely distorted six-coordinate environments provided by five N atoms from the macrocycle and one O atom from a *syn–anti* bridging carboxylate anion. This is a relatively rare bridging bonding mode for the anion which, as evidenced in two recent structures containing dinuclear Mn(II) centres — $[Mn_2(OAc)_2(bipy)_4](ClO_4)_2$ and $[Mn_2(OAc)_2(bpen)_2](ClO_4)_2$ {bpen = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-ethane-1,2-diamine}, in which the metals are bridged by two *syn–anti* carboxylates, leads to an expanded dimetallic centre relative to other carboxylate bridging modes [49,50]. The metal separations in these two complexes are 4.58 and 4.29 Å respectively. More generally dinuclear acetate bridged species have been synthesised in which a single μ_2-O bridge is also present. This leads to a *syn–syn* bridging mode for the acetate and a metal separation of ca. 3.5 Å. The absence of the singly bridging atom appears to lift any steric constraints imposing a *syn–syn* bridge and allow the facile achievement of the sterically less demanding *syn–anti* configuration. The N-donor atoms of the pendant arms approach the metal atoms from the same side of the macrocyclic ring ('*cis*') consistent with the clipping out of one bridge from the cryptate precursor. This may be contrasted with the approach of the pendant arms from opposing side ('*trans*') found when the dicopper(II) complex of the directly related tetraimine macrocycle bearing methoxyethyl pendant arms is prepared by transmetallation of the mononuclear barium precursor complex [26].

There is a very weak antiferromagnetic exchange interaction ($J = -0.37\ cm^{-1}$) in (**23**), mediated by the single bridging acetate group. This is reminiscent of the situation found in manganese substituted ribonucleotide reductase in which the two manganese(II) ions are bridged by two glutamate residues and saturated magnetization data point to a very small exchange interaction [51].

9. Summary

Metal complexes of tetraimine Schiff base macrocycles have been prepared by the metal-templated cyclocondensation of the appropriate heterocyclic dicarbonyl with a functionalised diamine. When the 'lateral unit' of the macrocycle contains an odd number of atoms the ligand folds about the central atom to provide a molecular

cleft reminiscent of the clefts found in metalloproteins and enzymes. This has been capitalised on by the preparation of bibracchial macrocycles which act as hosts for di- and tri-nuclear metal arrays. Such complexes have the potential to serve as models for polymetallobiosites and we have prepared systems which can be related to the dinuclear copper sites in haemocyanin and tyrosinase, a 'first generation' model for ascorbate oxidase and a novel mono-acetato bridged dinuclear manganese(II) complex which may be viewed as a speculative model for dinuclear manganese biosites.

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