The Evolution of Binucleating Ligands

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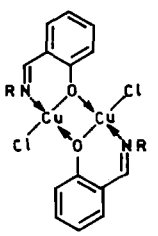
Introduction

This paper is composed of three linked sections as the function of the lecture from which it is taken was to provide first some insight into the nature and availability of binucleating ligands, and then to make observations of their application. For the latter purpose some examples are taken from our recent work and others from an area in which binucleating ligands have already made a substantial impact – bioinorganic chemistry. Here they have been used to provide speculative models for the active site in oxyhaemocyanin.

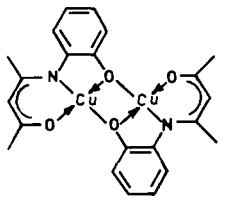
1. Binucleating Ligands

Many compounds have been found in which there are more than one metal present. These range from the salts of polyacids, *e.g.*, Na_2Ca edta, to organometallic species such as carbonyl derivatives, *e.g.*, $Mn_2(CO)_{10}$. Both homo- and hetero-polynuclear species are observed but the metals are not bound within a single ligand framework. Furthermore many binuclear complexes derived from Schiff base and β-triketonate precursors have been isolated but again there is no single encapsulating ligand present and it is through an associative process that the mononuclear components come together to produce the binuclear product, *e.g.*, (I–III) [1–3].

The early 1970's saw the first reports of metal complexes of binucleating ligands – although in certain cases the ligands themselves had been synthesised earlier and lain dormant in the literature as



(I)[1]



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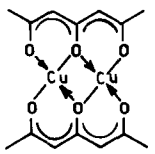
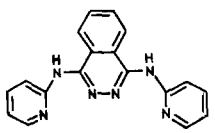
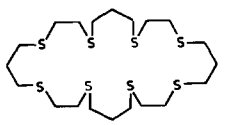


(III)[3]

they had been applied in other areas of chemistry. As is often the case several groups of research workers reached a similar conclusion through the employment of different techniques and three reports of what we know as binucleating ligands were published within a short period of time: Lever [4], using phthalhydrazones (IV), Busch [5] with a polythiaether (V), and Robson [6, 7] using acyclic and cyclic Schiff bases derived from diformylphenols (VI, VII).



(IV)



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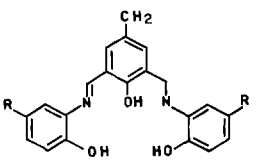
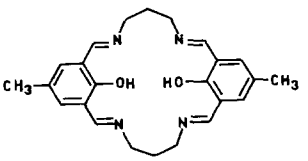


(VI)



(VII)

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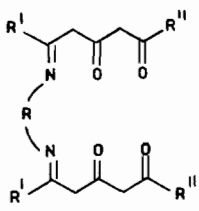
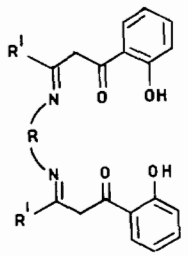
Robson introduced the term *binucleating ligand* and it is possible to define such a compound as a polydentate chelating ligand capable of simultaneously binding two metals in close proximity. Since 1970 there has been a steady increase in the number, and type, of binucleating ligands synthesised, and they are generally divided into two main classes [8]: (i) those in which metals share at least *one* donor atom in complexes containing adjacent sites in which the central donors provide a bridge, and (ii) those containing isolated donor sets.

Robson's compounds (VI, VII) serve as examples of the first class as do the numerous Schiff base compounds derived from β-triketones (VIII), β-ketophenols (IX) and 3-formylsalicyclic acid (X). The literature concerning these compounds has been well reviewed recently [9]. Collectively termed *compartmental ligands,* as they contain adjacent, dissimilar donor sets capable of metal complexation, this class has been used to prepare a wide range of both homo- and hetero-binuclear metal complexes.



(VIII)



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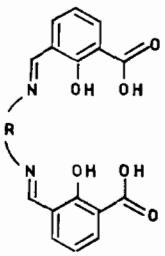
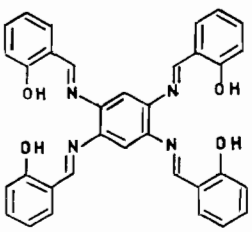


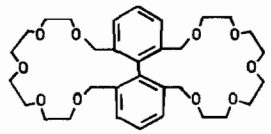
(X)

The category of isolated donor sets may be further subdivided [10]:

(a) Donor sets separated by aromatic, or other bridging groups, such as depicted by the ligand (XI) [11].

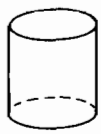


An interesting recent example of this type is found in the work of Rebek *et al.* [12]. The cyclic polyether species (XII) provides the first synthetic compound in which 'cooperativity' has been observed. On complexation of $Hg(CN)_2$ it is noted that the second metal is taken up at a rate ten times faster than that for the first metal. The ligand is symmetrically disposed and has a conformational mechanism available which allows enhanced receptivity at the second site after metal incorporation into the first.

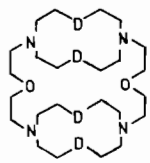


(XII)

(b) Isolated donor sets derived from planar macrocycles constrained by stacking one above each other. The example (XIV) shown here stems from the work of Lehn [13–15] and this class of compounds includes also the co-facial porphyrins [16], and related crown ether capped porphyrins [17]. (XIV) will complex different metals depending on the nature of the donor atoms.

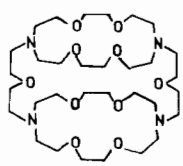


(XIII)



(XIV; D=O, or S)

When D = O it is possible to incorporate two silver cations and the X-ray structure of this complex has been determined [18]. This shows that the two silver cations are located within the central cavity at a distance of 3.88 Å apart. If the length of the ethyleneoxy- bridge in the terminal macrocycle is increased to include an additional oxygen donor, (XV), then it is possible to prepare a di-sodium complex. In this the distance between the metal ions is 6.4 Å, and results from partial penetration of the Na^+ cations into the macrocyclic cavities [19]. It is possible with (XV) to detect the presence of heterobinuclear species $[Ag^+Pb^{2+}(XV)]$ has been shown



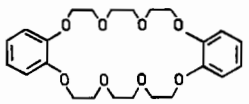
(XV)

to be in equilibrium with the corresponding two homobinuclear species [20].

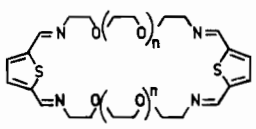
If D = S in (XIV) [21] the dicopper(II) and dicopper(I) complexes can be isolated. The crystal structure of the dicopper(II) complex gives a Cu–Cu distance of 5.62 Å [22]. The electronic absorption spectra, the e.p.r. properties and redox potentials of the dicopper(II) complex show features which present analogies with those of copper proteins.

(c) Isolated donor sets within extendable macrocycles. In these compounds the lengths of the macrocyclic chains may be altered to provide variable-sized cavities for metal inclusion. The first example of such a binuclear complex was (V), $Ni_2(BF_4)_4$ [5], and it was also from this class that the first X-ray structural confirmation of binucleating ligands came through the complex (XVI), $K_2(SCN)_2$ [23]. In this complex the K^+–K^+ distance is 3.4 Å. Recent additions to this class of macrocyclic ligand come from the work of Lippard (as discussed later), and from the Schiff base macrocycles of Nelson [24].

It is of interest to show here some recent results in which extendable Schiff base macrocycles have been synthesised without the necessity for the metal–template procedures which normally constitute the general synthetic route to such species [25]. The reaction of thiophen-2,5-dicarboxaldehyde with α,ω-amino ethers leads to the facile synthesis of the macrocycles (XVII), and it is possible to add, for example, two silver cations to this ligand. The binucleating function has been proved by X-ray structural determination of (XVIIb), $Ag_2(ClO_4)_2 \cdot (H_2O)_2$. In this complex the Ag–Ag distance is ~6 Å, and each silver atom is bound strongly to two imino nitrogen atoms and rather remotely to a water molecule. Other contacts between silver and the macrocyclic heteroatoms are rather too long to be interpreted as covalent bonds [25].

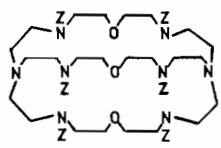


(XVI)

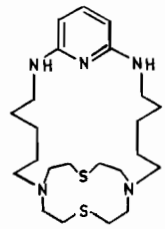


(XVIIa, n=0
XVIIb, n=1
XVIIc, n=2)

A necessary extension from the above 'two-dimensional' macrocycles is that to macrobicycles, and into the 'third dimension'. The examples selected are again from the work of Lehn and illustrate symmetrical (XVIII) [26] and non-symmetrical (XIX) ligands [27]. This gives rise to the opportunity for both homo- and hetero-binuclear complexes and also for mixed valence species as in the $Cu^{II}Cu^{I}$ derivative of (XIX) detected during electrochemical reduction.



(XVIII)

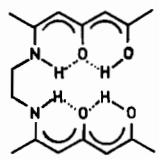


(XIX)

Compounds such as (XVIII) are of particular interest – as indeed are the majority of the extendable systems – as it is possible to incorporate a substrate between the two metal ions and so look at modified reactivity parameters caused by the presence of the bimetallic centre.

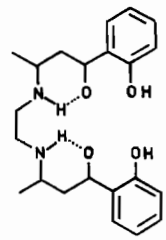
2. Some Aspects of the Chemistry of Compartmental Ligands

Our own work has centred on the development and utilisation of a series of compartmental ligands based on β-triketones and β-ketophenols. The ligands are derived from the reaction of these species with α,ω-alkanediamines and representative ligands are depicted below (XX, XXI) [9].



(H_4 daaen)

(XX)

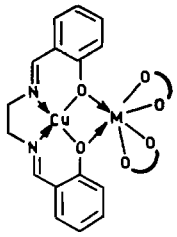


(H_4 aapen)

(XXI)

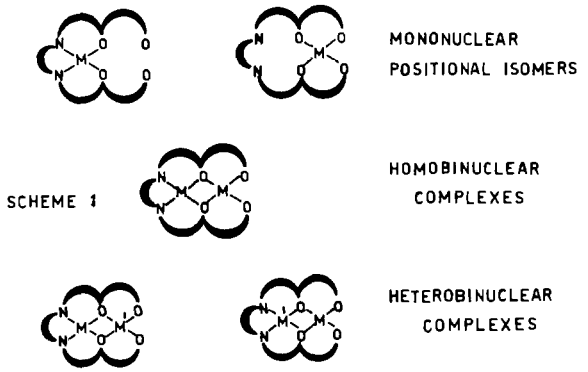
The ligand XXI provides an excellent example of a species which has been synthesised for one purpose [28] and has then lain dormant in the literature prior to its application in another. Ligands derived from β-triketones have also been extensively studied by Lintvedt and his co-workers [29].

The origin of this work stemmed from the use of metal complexes of Schiff bases as ligands for the strongly Lewis acidic metal in the bis(hexafluoroacetylacetonato)metal(II) series, (XXII) [30, 31]. It was postulated that if these two sites could be immediately juxtaposed then a binucleating ligand, having sites of different character and so capable of heterobinucleation, could be prepared. By using the



(XXII)

triketones and ketophenols this was found to be the case, and subsequent metal incorporation presents the opportunities shown in Scheme 1.



SCHEME 1

The ready availability of these possibilities is well illustrated by the reaction of copper(II) with (XX). (XX) reacts with copper(II) acetate in ethanol/chloroform mixtures to yield first (daaen)Cu_2 (50%, based on Cu), then a green, mononuclear species, and finally a purple, mononuclear species is recovered from the mother liquor [32]. The green species is identified as (H_2-daaen)$Cu_{O_2O_2}$, *i.e.* outer compartmental occupancy, by comparison of its spectral properties (i.r. and optical) with Cu(acac)$_2$. Similarly the purple species may be identified as (H_2-daaen)$Cu_{N_2O_2}$, *i.e.* inner compartmental occupancy, by comparison with the Schiff base analogue Cu(acen).

Using (H_2-daaen)$Cu_{N_2O_2}$ it is then possible to prepare heterobinuclear species, and reaction with VO(acetate)$_2$ yields (daaen)CuVO in which the copper is retained in the inner compartment [33]. This structure has been confirmed by an X-ray structural determination which shows the CuVO distance to be 2.9 Å [34]. However during recrystallisation of the bulk sample for crystal examination two types of crystal were obtained. One analysed as above and the other was shown to be (H_2-daaen)-$VO_{O_2O_2}$. In this species the VO^{++} is square pyramidal, with the normal parameters for such a VO^{++}, and the two ligand wings are essentially coplanar but with a torsion angle of 52.3° at the ethylenic bridge, On incorporation of the copper this angle was seen

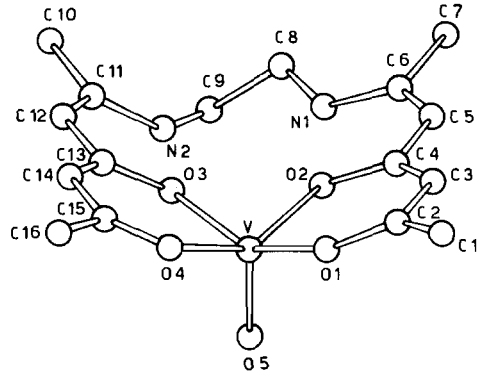


Fig. 1. The structure of (H_2-daaen)$VO_{O_2O_2}$. (Reproduced with permission from Ref. 34.)

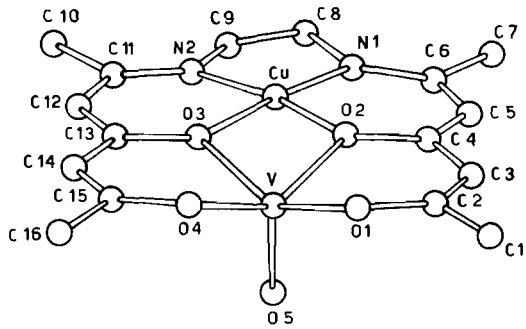
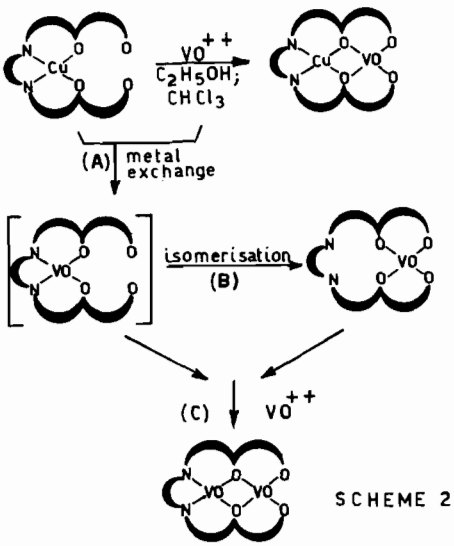


Fig. 2. The structure of (daaen)CuVO. (Reproduced with permission from Ref. 34.)

to drop to 13.6°, *i.e.* there is an opening of the molecule as a butterfly opens its wings.

On solution of the structure of (H_2-daaen)$VO_{O_2O_2}$ [34] extra electron density was found within the inner compartment, over and above that of the hydrogen atoms present. As indicated above there is a change of conformation on incorporation of copper, the obvious candidate for site occupancy, but the absence of any suggestion of the necessarily consequential ligand disorder and the observation that the inner compartment as ideally sited for VO^{++} occupancy without conformational change leads to the proposition that there is a co-crystallisation of a small percentage (~3%) of the homobinuclear complex (daaen)$(VO)_2$. That this is so is supported by the parallel observation that in the crystal structure of (H_2-daaen)$VO_{O_2O_2}$ [34], prepared solely from VO(acetate)$_2$, a similar site occupancy is detected.

The next problem is the route of formation of the homobinuclear species. It is possible that any HCl present in the $CHCl_3$:EtOH solvent mixture used for recrystallisation of (daaen)CuVO could have leached out both metals allowing for a reconstitution of a mixture of species including (daaen)$(VO)_2$ which then co-crystallises out. A further speculation is depicted in Scheme 2.



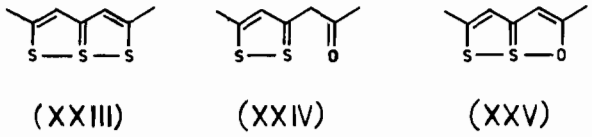
SCHEME 2

Replacement of Cu(II) by VO^{++}, step A, would represent an alternative pathway to heterobimetallic formation. Such exchange has been found in the reaction of nickel(II) with $(H_2\text{-daaen})Cu_{N_2O_2}$, where the isolated product is $(H_2\text{-daaen})Ni_{N_2O_2}$ [33]. Step B, isomerisation to give outer site occupancy would occur as it has been noted that VO^{++}has a strong preference for the $-O_2O_2$ environment [9]. Homobinuclear formation would then occur after either of these stages. Isomerisation has been detected in the synthesis of $(H_2\text{-daapn})Cu$ (pn = 1,2-propanediamine), where the $-N_2O_2$ species is recovered first as a purple oil which slowly crystallises to give the dark green $-O_2O_2$ compound [35]. The possibility of these processes occurring relatively easily leads to a necessary caution when considering the nature and reactivity of heterobinuclear complexes in solution.

(a) Ligand Modification: Change of Donor Atom

One recurrent question during the course of this study has been 'and have you put sulpur into your compounds?' We include here a brief account of some attempts to do this.

Attempts to incorporate sulphur into the precursor keto-derivatives led to organic derivatives from which we have been unable to proceed further in the synthesis of compartmental ligands. 2,4,6-Heptane-trione reacts readily, for example, with P_4S_{10} to give the trithiapentalene (XXIII) [36]. There are some reports that this compound forms simple metal complexes [37, 38], but in our hands we have only obtained obscure and unexplicable stoicheiometries on reaction with copper and nickel salts [39]. Bogdanovitch [40] has prepared a bis-(allylnickel) derivative of (XXIII) and this remains the sole example of a binuclear complex of this ligand.

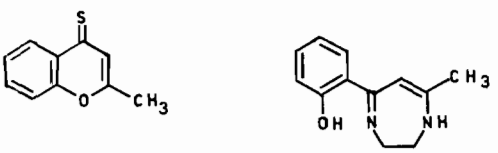


(XXIII) (XXIV) (XXV)

The reaction of (XXIII) with H_2SO_4/H_2O gives a monodesulphurised product (XXIV) [41], but we find that although it was designated as ketonic, on i.r. grounds, the ketone does not exhibit a typical ^{13}C n.m.r. spectrum nor does it react with amines and therefore is best formulated as (XXV) [39].

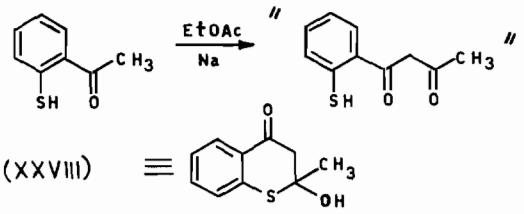
o-Acetoacetylphenol reacts with P_4S_{10} to give a 4H-chromonethione (XXVI) [39]. Related acetophenones had been shown to give also dithiolium derivatives [42] but in our work only (XXVI) was recovered. Previously we had found that with the analogous chromone and ethylenediamine a ring opening occurred to give the Schiff base (XXI), but with (XXVI) this reaction did not occur. The product of the reaction was the diazepin derivative (XXVII).

o-Acetothiophenone (XXVIII) was synthesised, as it was felt that the presence of sulphur in a precursor unit was desirable. This compound was then reacted



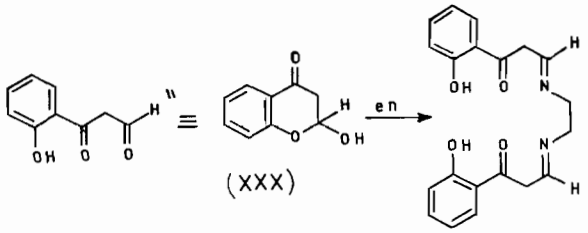
(XXVI) (XXVII)

with ethylacetate and sodium to prepare the diketone by the standard route. However the product found was (XXIX), a ring-chain tautomerism having occurred. This type of reaction had previously been

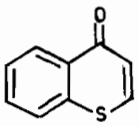


(XXVIII) ≡ (XXIX)

seen in the preparation of '*o*-formylacetophenone' (XXX) where subsequent reaction with ethylenediamine gave (XXXI) [43]. However (XXIX) merely dehydrated in the presence of ethylenediamine to give (XXXII).



(XXX) (XXXI)

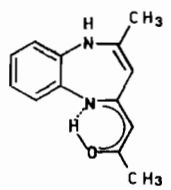


(XXXII)

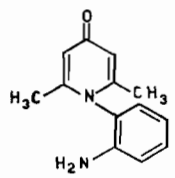
Attempts to utilise the elegant synthesis of Cummings [44] in order to introduce sulphur directly into the Schiff base have also, so far, met with no success. The reaction of (XXI) with NaSH and $Et_3O^+BF_4^-$ did not proceed in contrast to the reactions carried out by Cummings with *p*-substituted analogues. It is possible that the *ortho*-hydroxyl group in (XXXI) is sufficiently hydrogen bonded to the keto-function to inhibit the reaction. To date we have only succeeded in introducing sulphur into the bridge between the keto-moieties by using an α,ω-diaminothioether in the Schiff base reaction.

(b) Ligand Modification: Changing the Bridge

The reaction of 2,4,6-heptanetrione with 1,2-diaminobenzene did not give the desired Schiff base derivative, but gave instead a mixture of the diazepin (XXXIII) and the pyridone (XXXIV). The former has been characterised by i.r., m.s., and n.m.r., and the nature of the latter was confirmed with an X-ray crystal structure [45]. Pyridones similar to (XXXIV) have been prepared before by the reaction

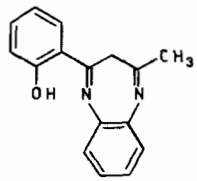


(XXXIII)



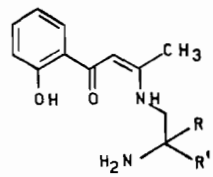
(XXXIV)

of triketones with amines but only under drastic reaction conditions [46]. The reaction of *o*-acetoacetylphenol with 1,2-diaminobenzene gave only the diazepin (XXXV) [47].



(XXXV)

It was thought that a possible steric effect was operating in these reactions, as a rigid phenyl bridge could lead to an interaction of the 3,6-hydrogens with the methyl groups of the keto-function on Schiff base formation. Reaction of the formyl derivative (XXX) with 1,2-diaminobenzene gave a small yield of the compartmental Schiff base, lending support to the above hypothesis and so it was felt that utilisation of this so-called steric effect would lead to open-chain 'half-units'. The reaction of *o*-acetoacetylphenol with 1,2-diaminopropane and 1,2-diamino-2-methylpropane in 1:1 ratio gave the 'half-units' (XXXVI) and (XXXVII) [48]. These compounds are identified using n.m.r., i.r. and m.s.

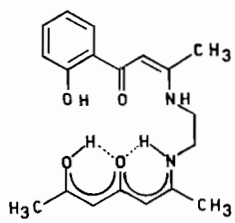


XXXVI : R=H, R'=CH_3
XXXVII : R=R'=CH_3
XXXVIII : R=R'=H

More recently it has been observed that the nature of the solvent and the dilution conditions of the experiment are also important, and the 'half-unit' containing ethylenediamine, (XXXVIII), has been synthesised [49]. A crystal structure of the copper-(II) acetate complex of (XXXVI) confirms the nature of the ligand, and shows that (XXXVI), Cu(OAc) exists as an acetate bridged dimer with a copper-copper distance of 3.5 Å [50].

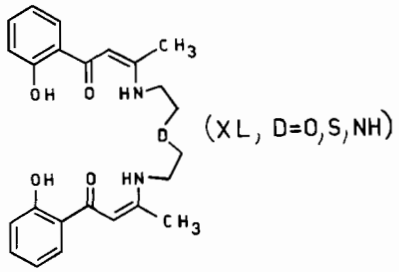
The 'half-units' may also be used in the synthesis of non-symmetric compartmental ligands, *e.g.* (XXXIX), and these compounds readily form mono-, homobi- and heterobinuclear complexes with transition metals, and also with actinides [48, 51].

A second area of modification has been to extend the length of the bridge, both using diamines having longer polymethylene chains, and with facultative diamines. In the case of the latter species this leads to



(XXXIX)

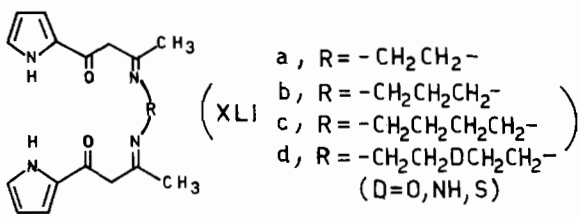
facile recovery of compartmental ligands of type, (XL) [52]. These ligands have been used for the synthesis of mono- and homobinuclear complexes of copper(II) and dioxouranium(VI) [52]. In the case of UO_2^{++} the metal has a choice of compartment



as both sites afford suitable equatorial coordination environments and allow achievement, by uranium, of a favoured 7-coordination. In the formation of inner occupied species the extra bridge donor atom can bind – as has been found in the precursor pentadentate Schiff base complexes [53] – and in the outer compartment a solvent molecule will fill the seventh site. Our results indicate outer site occupancy for the mononuclear species, and it is possible also to prepare homobinuclear dioxouranium(VI) species. This has potential application in metal recovery as one ligand recovering two metal ions has an increased efficiency over one ligand and one metal ion.

The copper complexes provide problems with site identity as in the mononuclear complexes the spectral data is ambiguous. The corresponding homobinuclear complexes are somewhat insoluble and it has not been possible to obtain suitable crystals for study from either species.

By moving from a ketophenol based system to a ketopyrrole based one it has been possible to obtain crystals of metal complexes, and also we have present in the system a useful i.r. probe for monitoring site occupancy in that one can detect the presence or absence of the pyrrole NH frequency. Acetoacetylpyrrole readily forms Schiff bases with α,ω-diamines to give compounds such as (XLI) [54].



Copper complexes have been prepared from these ligands, and, while there are no structures available for the complexes, the presence of ν_{NH} indicates

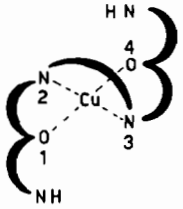
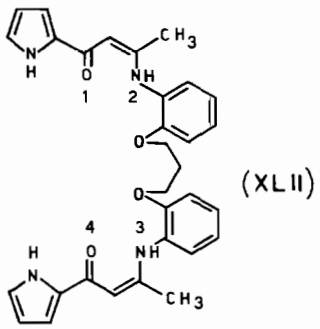


Fig. 3. Schematic view of Cu site in Cu (XLII).

an inner chamber occupancy. As the bridge length increases it is possible to lose the ν_{NH} suggesting an outer chamber occupancy. This is confirmed in the crystal structure of Cu (XLId) where D = O. The copper is bound in square planar fashion in the outer site leaving a 'macrocyclic' inner cavity [55]. As the bridge length is further increased the ν_{NH} frequency is again detected and the crystal structure of Cu (XLII) shows an inner site occupancy.



However the pyrroles have adopted a *'trans'*-like environment and the long chain provides a strap for the molecule (Fig. 3) [56].

It is therefore possible to consider that such effects are possible also in the phenolic complexes – even though the geometry of the outer site is necessarily modified by the pyrrole. This would suggest that proposals that with long chains only polymerisation is likely must be reconsidered [57]. However the nature of any bimetallic species with these ligands remains obscure.

3. An Application to Bioinorganic Chemistry

Impetus for the study of binucleating ligands and their complexes has come from, in the main, three areas – homogeneous catalysis, the opportunity to have useful model systems for the study of mechanisms of magnetic exchange, and a potential role as speculative models in bioinorganic chemistry.

There are many enzymes in which a bimetallic centre occurs. The role of the metals present may be an active, or a passive (structural) role, but as yet there is only limited X-ray structural information on these sites, and that present in superoxide dis-

TABLE I. Some Multi-metal Sites in Enzymes.

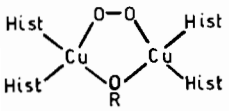
Site	*Enzyme*	*Function*
FeFe	haemerythrin	reversible O_2 carrier
CuCu	haemocyanin, oxidases	reversible O_2 carrier, oxidation
CuZn	superoxide dismutase	O_2^- disproportionation
CaCa	thermolysin	structural
MnCa	conconavalin A	formation of saccharide site

TABLE II. Properties of Oxyhaemocyanins.

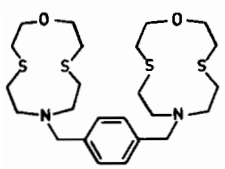
	Cu–Cu (A)	$-J$ (cm^{-1})	λ, nm
oxyhaemocyanin	3.55	~500	~330
$[(XLIV)Cu^{II}\cdot OH\cdot Cu^{II}]^{3+}$	3.38	~410	315, 375
$[(XLV\cdot Cu^{II}\cdot OH\cdot Cu^{II}\cdot ClO_4]^{2+}$	3.64	~500	330

mutase (CuZn) remains the only well-characterised site (Table I).

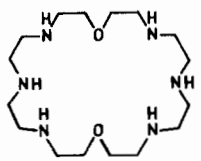
One area in which binucleating ligands have begun to play a role has been in the assisting of speculation concerning the metal site in haemocyanins. EXAFS studies [57] have suggested that the salient features of the copper site in oxyhaemocyanin are as shown (XLIII). Two elegant studies have provided very close physical models for this site and so are briefly described. Osborn [60] using a ligand having isolated donor sets, class a type, (XLIV), and Lippard [61], using an extendable macrocycle (XLV) have both synthesised dicopper complexes having an hydroxyl bridge present.



(XLIII)



(XLIV)



(XLV)

The structures of the complexes derived are shown schematically in Figs. 4 and 5.

The conformational flexibility of the ligands allows close juxtaposition of the metals, and both complexes show remarkable physico-chemical

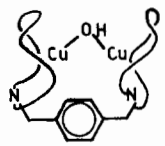


Fig. 4. $\{(XLIV)[Cu^{II}–OH–Cu^{II}]\}^{3+}$.

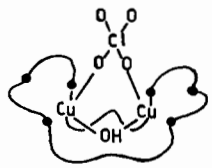


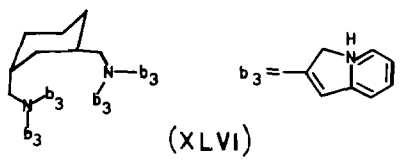
Fig. 5. $\{(XLV)[Cu^{II}–OH–Cu^{II}]ClO_4\}^{2+}$.

resemblance to the parameters measured for oxyhaemocyanin (Table II), and lead on to the proposition that the stability of the Cu_2OH^{3+} site suggests that the endogenous protein bridging group might simply be the hydroxide ion and not a tyrosine residue as peviously suggested. Certainly this view has received support from a study by Kino and coworkers [62] who through observation of the CD and optical spectra of haemocyanin from *S. lessonia* concluded that because no bonds are detected corresponding to the coordination of a phenolate to a tetragonal copper then it is likely that the bridge unit is oxide, O^{2-}, or hydroxide, OH^-.

Application of binucleating ligands has also been made to the activity of the oxyhaemocyanin site. Kida and his coworkers [63] have shown that the di-Cu^I complexes of ligands such as (XLVI) are

capable of effecting reversible dioxygen uptake. Furthermore the absorption spectra of the violet solution produced on passage of dioxygen through a solution of (XLVI) and copper(I) correspond to that recorded for the haemocyanin of *S. lessonia*.

Lever *et al.* [64] have shown that their binuclear copper complexes using 1,4-(di-2′-pyridyl)aminophthalazine, (IV), as the ligand represent unique mimics of catecholase binuclear copper enzymes,

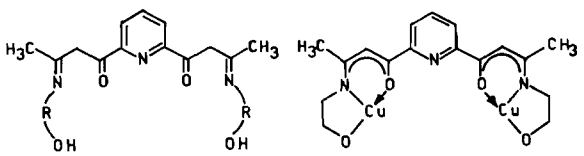


(XLVI)

and also exhibit phenolase activity. The complexes catalytically oxidise catechols to quinones.

4. Concluding Remarks

We have recently prepared some Schiff base derivatives (XLVII) from a pyridine tetraketone and synthesised also the dicopper complex (XLVIII) [65]. It is probable that association occurs to give a polymeric species – the compound is very insoluble

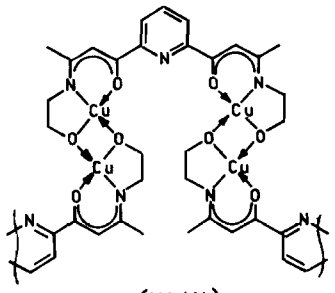


(XLVII) (XLVIII)

and also, as discussed at the outset, terdentate ligands can form binuclear complexes through association. In a sense a wheel has turned full circle as it is probable that we have binuclear complexes, as polymers, from binuclear complexes of binucleating ligands (XLIX).

That this area is in an expanding state may be seen from an appraisal of the immediate post-conference literature in which it was possible to find several papers and new ligand systems. The limit must simply be the ingenuity and creative ability of the chemist.

Such an account as this must necessarily be subjective and furthermore subjected to temporal constraint; several pertinent reviews of the area have appeared in the literature [8, 9, 24, 66, 67]. Necessarily some work has been omitted at the expense of the content (*e.g.*, the valuable contributions of Gagné and Kida over a wide spectrum of chemistry). Other aspects are covered in depth by the other speakers [68, 69].



(XLIX)

Acknowledgements

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