

# UREASE—A MUSE FOR THE COORDINATION CHEMIST

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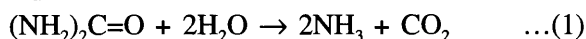
Coordination chemistry has been used to provide model compounds to simulate the first coordination sphere present at metallobiosites. There is also a synergistic relationship between coordination chemistry and bioinorganic chemistry in that knowledge retrieved from crystallographic studies on metallobiosites can be used to inspire the generation of new chemistry based on the coordination environments at these sites. It is in these aspects that urea has served as a muse for the coordination chemist and this review details this role detailing some of the resulting bio-inspired chemistry concerning the generation of dinuclear, trinuclear and tetranuclear nickel(II) complexes of unsymmetrical compartmental ligands. Of particular interest to the modelling of metallo-biosite has been the observation that cyanate can be readily produced by reaction of certain dinickel(II) complexes with urea. This has provided a new proposal for the mechanism of hydrolysis of urea by the metalloenzymes.

**Key Words :** Urease; Dinuclear Nickel(II) Complexes; Trinuclear Nickel(II) Complexes; Tetranuclear Nickel(II) Complexes; Unsymmetric Compartmental Ligands; Schiff Bases; Synthesis; Crystal Structures.

## 1 Introduction

If a METALLOPROTEIN, or a METALLOENZYME can be regarded as a highly elaborated coordination complex, the metal-containing site (METALLOBIOSITE) of which comprises one or more metal atoms and their ligands, then it is possible to contemplate simulating the immediate coordination environment of the metallobiosite by use of synthetic analogues derived from small molecule compounds. Just as it is possible to use coordination compounds to help gain insight into the nature of metallobiosites so it is also possible to use the knowledge acquired through crystallography concerning the nature of a metallobiosite to try and develop new chemistry – BIO-INSPIRED CHEMISTRY. The purpose of this article is to promote this philosophy and show that new coordination chemistry can be inspired by biology, in this case the metalloenzyme urea<sup>2</sup>.

The dinuclear metallohydrolase urease (urea amidohydrolase: E.C.3.5.1.5) is a nickel dependent metalloenzyme which is extremely efficient, in certain plants, fungi and microbes, at catalysing the hydrolysis of urea to ammonia and carbon dioxide (eq. (1)) with a rate enhancement over the non-catalysed reaction of the order of  $10^{14}$  <sup>2</sup>.



Urease is a beautiful molecule. It exemplifies the vitality of inorganic chemistry and provides insight into man's acquisition of knowledge by illustrating the time lapses and time spans that can occur in the process of scientific advance. The discovery, in 1926, that enzymes could be crystallised, thus showing that they are well-defined chemical compounds, led to James B Sumner being awarded a share in the 1946 Nobel Prize for Chemistry<sup>3</sup>. It has been remarked that "life has evolved from inorganic materials and in that evolution has incorporated every facet of inorganic chemistry that was profitable to it". In the case of the enzyme that Sumner had crystallised, urease from jack bean [*Canavalia ensiformis* ], this turned out to be true as in 1975 it was shown that the enzyme contained nickel. The discovery, by Dixon *et al.* of the presence of nickel(II) came from a critical analysis of the UV-visible spectrum that showed a distinct long wavelength absorption characteristic of octahedral nickel(II) in an oxygen- and nitrogen-donor environment<sup>5</sup>. Further studies, by the same group, using site inhibitors indicated that there were two nickel ions per active site and this led to the suggestion that the two nickel ions acted cooperatively<sup>6</sup>.

In 1995 Jabri *et al.* reported the crystal structure of microbial urease from *Klebsiella aerogenes* and this revealed that the active site did indeed consist of two nickel atoms sited *ca.* 3.5Å apart and bridged by a carbamate group that had been formed by reaction of carbon dioxide with the ε-amino acid of a lysine residue.<sup>7</sup>

In his essay "How should chemists think" Hoffman comments that modern chemistry faces the quandary that Raphael's fresco 'The School of Athens' epitomised<sup>1</sup>. Should it follow the hand of Aristotle, and look to Nature or that of Plato and search for the ideal?

Subsequently X-ray crystallographic studies on urease isolated from different sources [*Klebsiella aerogenes*]<sup>8</sup> and the native and inhibited metalloenzyme from *Bacillus pasteurii*<sup>9-11</sup> have enabled the development of a detailed description of the active site (Fig. 1).

Each nickel(II) ion is ligated by two histidine residues from the protein and a carbamylated lysine residue bridges the two nickel(II) ions. Ni(2) is further ligated by an aspartate residue. The coordination spheres at the metal ions are completed by two terminally coordinated water molecules and one bridging water molecule, or hydroxide ion. Consequently Ni(1) has a distorted square pyramidal environment and Ni(2) a pseudo-octahedral environment. A mechanism for urea hydrolysis has been proposed (Fig. 2)<sup>12, 13</sup>, based on the earlier suggestion by Zerner<sup>6</sup>, that one metal ion serves as a Lewis acid to polarise and stabilise the leaving group whereas the second metal deprotonates water and provides a local source of hydroxide for nucleophilic attack on the substrate. The nickel(1) atom is a good candidate to bind urea via its oxygen atom in a urea-binding pocket adjacent to the coordinated water molecule on nickel(2). Adjacent acidic and basic side chains are available to participate in the catalysis by helping to polarise the carbonyl group and to help deprotonate the water molecule to provide the nucleophile. Subsequent nucleophilic attack by the hydroxide at the carbonyl carbon atom of the bound substrate urea produces ammonia and carbamic acid which spontaneously decomposes to form carbon dioxide and a second molecule of ammonia. Subsequent analysis of structural information for both native and inhibited urease and molecular modelling of the purported catalytic mechanism led to the proposal that there might be a bridging coordination mode for urea

at the active site<sup>10, 11</sup>. Urea was envisaged to bind to Ni(2) through a nitrogen atom from one of its  $-NH_2$  groups and the Ni(1) via the oxygen atom of the carbonyl function. This would strongly activate the inert urea molecule towards nucleophilic attack by polarising the C-O and C-M bonds. It was also remarked that the pathway could be viewed also as an electrophilic attack of the activated urea carbon atom on a nickel-bridging hydroxide anion.

## 2 Small Molecule Modelling of the Active Site in Urease

Current awareness of the asymmetric nature of a number of homodinuclear, such as urea, or heterodinuclear transition metal-derived 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 which will give dinuclear complexes capable of acting as models for the metallobiosites<sup>14, 15</sup>.

The biosites in question have been classified in four distinct groupings as follows (Fig. 3)<sup>16</sup>: (a) symmetric — in which an identical number of donor atoms of the

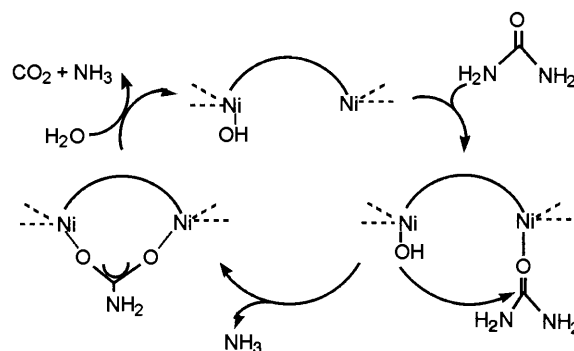


Fig. 2 A mechanism for urea hydrolysis

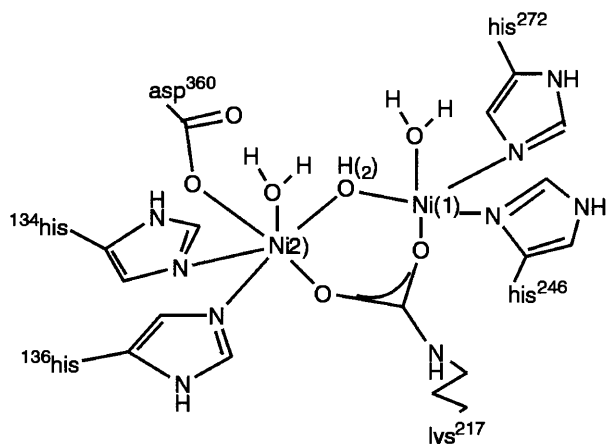


Fig. 1 Schematic depiction of the active site in urease

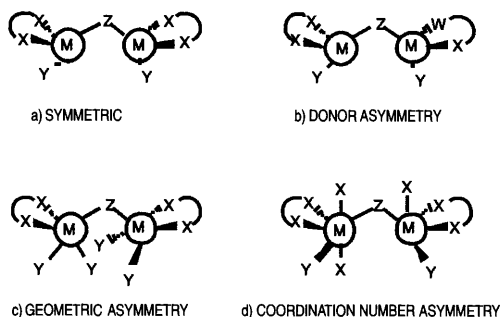


Fig. 3 A classification of metal coordination environments found at transition metal-derived dinuclear centres present in metallobiosites. (M is a transition metal and W, X, Y and Z are ligand donor atoms such as N, O, S etc.)

same type are bound to each metal atom in similar geometries; (b) donor asymmetry — where different types of donor atom coordinate to each metal atom; (c) geometric asymmetry — where there are inequivalent geometric arrangements of the donor atoms about each metal atom; and (d) coordination number asymmetry — where a different number of donor atoms are coordinated to each metal atom. To a first approximation the nature of the donor atom may be restricted to simply O, N, S *etc* but a more accurate definition would specify the functional grouping associated with the donor atom and so differentiate between an oxygen atom in water and carboxylate or a sulfur atom in a thiolate or a thioether. A combination of different types of asymmetry may also occur at a dinuclear centre — for example urea is coordination number asymmetric<sup>5, 6</sup>, donor asymmetric {N<sub>2</sub>O<sub>3</sub>; N<sub>2</sub>O<sub>4</sub>} and geometry asymmetric [distorted square pyramidal and pseudo-octahedral].

### 2.1 Unsymmetric Ligands

Since Richard Robson first developed dinucleating ligands in 1970<sup>17</sup> there has been a steady increase in the number and type of such ligands synthesised. The term *compartmental ligands* was later introduced to indicate when a dinucleating ligand contained adjacent but dissimilar coordination sites and then extended to cover two general classes of dinucleating ligands<sup>18</sup>. The first group consists of complexes in which the metals share at least one donor atom in species containing adjacent sites with the central donor atom(s) providing a bridge and the second group consists of those complexes in which central donor atoms are not shared, or not present, and so isolated donor sets exist<sup>19</sup>.

Compartmental ligands can be macrocyclic or acyclic in nature with acyclic compartmental ligands sub-divided into “*end-off*” and “*side-off*” ligands (Fig. 4). The former provide only one endogenous bridging donor and so have an exogenous bridging site available between the metal atoms, whereas the latter provide two endogenous bridges and present adjacent dissimilar coordination compartments. If the pendant arms in the ligand are constituted of different donor atoms then an unsymmetric ligand results. Several reviews have appeared concerning metal complexes of both acyclic and macrocyclic compartmental ligands<sup>20-24</sup>.

### 2.2 Nickel(II) Complexes of Dinucleating Ligands

The synthesis and investigation of dinickel(II) complexes having some relevance to the active site of

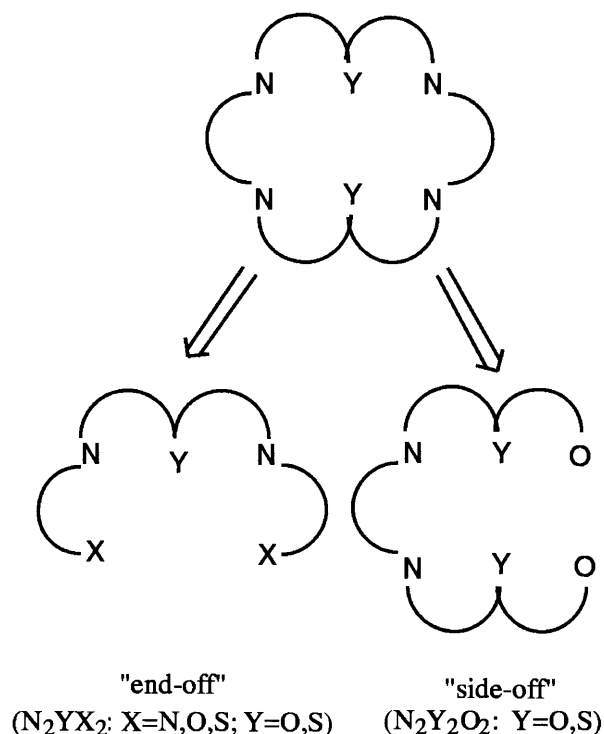
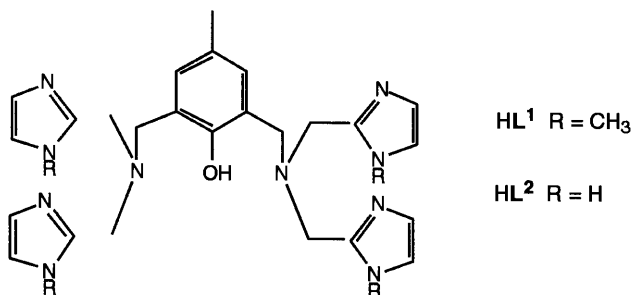


Fig. 4 Compartmental Ligands

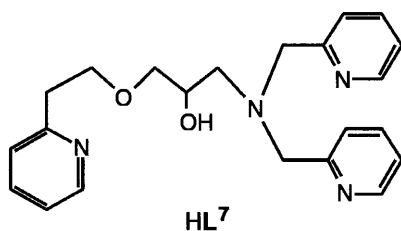
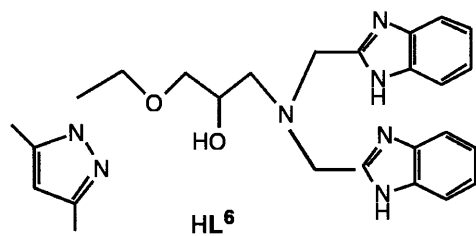
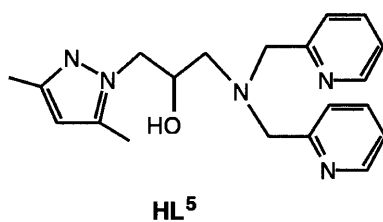
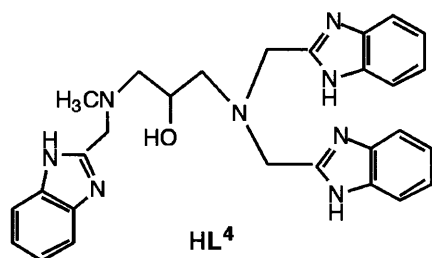
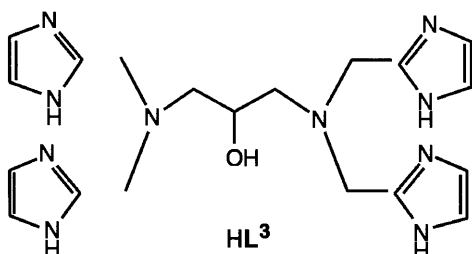
urea have been reported by a number of researchers and herein focus is on corroborative modelling carried out after the crystal structure was made available.

Prior to the availability of the crystal structure of urea speculative models, of which [Ni<sub>2</sub>L<sup>1</sup>(μ-CH<sub>3</sub>COO)<sub>2</sub>].ClO<sub>4</sub>.CH<sub>3</sub>OH (**1**) prepared from the symmetrical polypodal ligand HL<sup>1</sup><sup>25</sup> and [Ni<sub>2</sub>L<sup>2</sup>(ClO<sub>4</sub>)(H<sub>2</sub>O)(MeOH)](ClO<sub>4</sub>)<sub>2</sub>.Et<sub>2</sub>O (**2**)<sup>26</sup> serve as illustrations, were used to try to provide plausible information concerning the first coordination spheres at the dinuclear centre. The ligand donor sets containing imidazole N atoms, and the presence of bridging carboxylates in **1**, were deemed as relevant to simulation of the biosite. The crystal structures showed that each Ni(II) atom in the complex was six-coordinate and the electronic spectra and weak antiferromagnetic exchange were consistent with the corresponding properties of urease<sup>2</sup>.



### 2.2.1 Ligands bearing a 2-hydroxypropane Spacer

The symmetric proligand HL<sup>3</sup> and the unsymmetric proligands HL<sup>4</sup>- HL<sup>7</sup> have been used by Krebs and his co-workers to coordinate to nickel and so produce dinuclear complexes to serve as models for the dinickel(II) site in urease<sup>26-28</sup>



The complex  $[\text{Ni}_2\text{L}^4(\mu\text{-C}_6\text{H}_5\text{COO})(\text{EtOH})_2](\text{ClO}_4)_2\cdot\text{EtOH}$  (**3**) derived from proligand HL<sup>4</sup>, has the nickel atoms doubly bridged by the endogenous alkoxo-O atom and the benzoate anion<sup>26</sup>. One nickel is

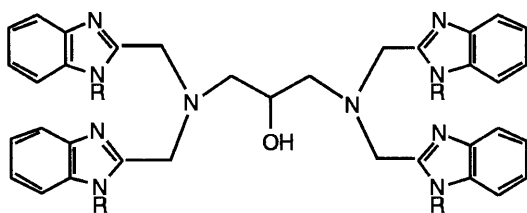
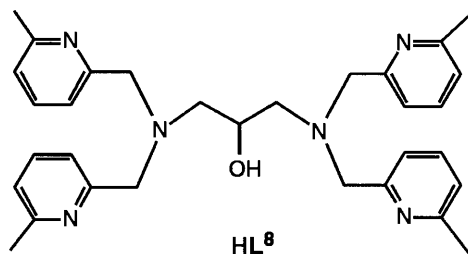
in a trigonal bipyramidal environment  $\{\text{N}_3\text{O}_2\}$  with the donor atoms from bis(benzimidazole) arm completing the donor array whilst the second nickel is six coordinate  $\{\text{N}_2\text{O}_4\}$  with the N-atoms of the second arm and the two solvent molecules completing the coordination sphere. The solvent molecules are in *cis*-positions. The coordination geometries at the metal ions in **3** are quite similar to those found in  $[\text{Ni}_2\text{L}^3(\mu\text{-CH}_3\text{COO})(\text{OH}_2)](\text{ClO}_4)_2\cdot\text{H}_2\text{O}\cdot\text{Et}_2\text{O}$  (**4**) in which an asymmetric complex with one nickel five coordinate  $\{\text{N}_3\text{O}_2\}$  and the second nickel six coordinate  $\{\text{N}_3\text{O}_3\}$  is prepared from the symmetric proligand HL<sup>1</sup><sup>26</sup>. The Ni...Ni separation in **3** is 3.514Å and in **4** is 3.521Å, both are close to the 3.5Å reported for urease from *Klebsiella aerogenes*<sup>7</sup>; this was related to the possible formation of a  $\mu$ -carboxylato- $\mu$ -hydroxo bridged dinuclear species in urease under physiological conditions.  $[\text{Ni}_2\text{L}^5(\mu\text{-CH}_3\text{COOH})(\text{ClO}_4)(\text{EtOH})]_2\cdot\text{Et}_2\text{O}$  (**5**), derived from proligand HL<sup>5</sup><sup>27</sup> has the metal atoms are separated by 3.531Å and are both six-coordinate  $\{\text{NO}_5\}$  and  $\{\text{N}_3\text{O}_3\}$ . The nickels are bridged by the endogenous alkoxo-O atom and a single acetate anion, a two benzoate anions.

A further model system  $[\text{Ni}_2\text{L}^6(\mu\text{-CH}_3\text{COO})(\mu\text{-H}_2\text{O})(\text{H}_2\text{O})](\text{ClO}_4)_2\cdot\text{H}_2\text{O}\cdot\text{Et}_2\text{O}\cdot 2\text{EtOH}$  (**6**) was derived from proligand HL<sup>6</sup><sup>26</sup>. In this complex 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  $\{\text{NO}_5\}$  is completed by interaction with the articular ether-O, a pyrazole-N and a water molecule. The Ni...Ni separation here is short at 3.171Å. Although neither **3** or **6** have shown hydrolytic activity towards urea.

$[\text{Ni}_2\text{L}^7(\mu\text{-C}_6\text{H}_5\text{COO})_2(\text{CH}_3\text{COOH})](\text{ClO}_4)_2\cdot\text{Et}_2\text{O}$  (**8**), derived from proligand HL<sup>7</sup> has the metal atoms separated by 3.387Å<sup>28</sup>. Both are six-coordinate and they are triply bridged by the the endogenous alkoxo-O atom, a two benzoate anions. One nickel atom  $\{\text{N}_3\text{O}_3\}$  is further bound by the nitrogen rich bis-pyridyl arm and the second  $\{\text{NO}_5\}$  by the articular ether-O, a pyridine-N and a monodentate of acetic acid molecule the coordination of which is stabilised 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.

Complexes **2** and **3** have one of the nickel atoms in a 5-coordinate trigonal bipyramidal geometry and thus show structural similarity to the active site of urease. Furthermore the UV-vis spectra of these compounds showed a better correspondence to the spectral properties of urease under physiological conditions, octahedral nickel(II) with an oxygen-rich donor environment<sup>29</sup>, than do regular octahedral nickel(II) complexes. Complexes **2**, **6** and **7** behaved antiferromagnetically but complexes **3** and **4** were ferromagnetically coupled. This sensitivity of magnetic behaviour with structural change was proposed to mirror the inconsistent results of magnetic studies on urease for which ferromagnetic<sup>30</sup> antiferromagnetic<sup>31</sup> and non-exchange behaviour<sup>32</sup> have all been reported.



The symmetric proligands **HL<sup>8</sup>** – **HL<sup>10</sup>** have also been used in the synthesis of dinuclear nickel(II) complexes. Yamaguchi *et al.*, prepared  $[\text{Ni}_2\text{L}^8(\mu\text{-CH}_3\text{COO})(\text{ClO}_4)(\text{MeOH})]\text{ClO}_4$  (**9**) the structure of which revealed that the two nickel(II) atoms were hexacoordinate, 3.622 Å apart and bridged by the endogenous alkoxide and an exogenous acetate anion<sup>33</sup>. A methanol of solvation is bound to one nickel and a monodentate perchlorate anion to the second such that the donor sets are both  $\{\text{N}_3\text{O}_3\}$ ; the coordination geometries are octahedral.

Hosokawa *et al.*, prepared several complexes of proligands **HL<sup>9</sup>** and **HL<sup>10</sup>**<sup>34</sup>. The structures of

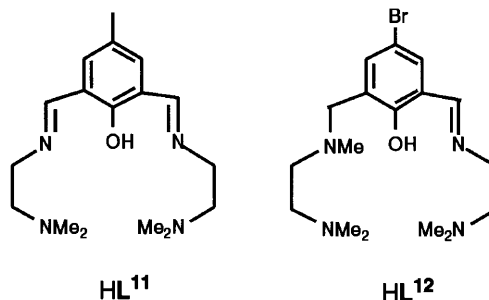
$[\text{Ni}_2\text{L}^{10}(\mu\text{-CH}_3\text{COO})(\text{MeOH})_2](\text{ClO}_4)_2\cdot\text{CH}_3\text{OH}\cdot\text{H}_2\text{O}$  (**10**) and  $[\text{Ni}_2\text{L}^{10}(\mu\text{-C}_3\text{H}_7\text{COO})(\text{MeOH})_2]\cdot(\text{ClO}_4)_2\cdot\text{CH}_3\text{OH}\cdot 2\text{H}_2\text{O}$  (**11**) showed that the nickel(II) bridged by the endogenous alkoxide and an exogenous carboxylate anion. Each was in an  $\{\text{N}_3\text{O}_3\}$  distorted octahedral environment and the metal separations were 3.521 and 3.507 Å respectively. The presence of imidazole N atoms and bridging carboxylato-O atoms in the in ligand donor sets was deemed appropriate to the simulation of the biosite and the complexes were found to couple antiferromagnetically as in jack bean urease<sup>30</sup>.

### 2.2.2 Unsymmetric Ligands Bearing a Phenolic Spacer

Phenol-based “end-off” compartmental ligands have been used to generate a range of nickel(II) complexes. As well as striving towards models for urease the compartmental ligands have provided a diverse range of oligonuclear nickel(II) complexes and have given routes to the systematic generation of dinuclear nickel(II) complexes bearing monodentate ethanoates and the generation of trinuclear nickel(II) cores supported by tridentate acetate bridges. This latter aspect of bio-inspired chemistry has been recently been the subject of a mini-review and so will receive brief comment here<sup>35</sup>.

#### 2.2.2.1 Dinuclear complexes

The symmetric proligand **HL<sup>11</sup>** and the asymmetric proligand **HL<sup>12</sup>** have been used by Koga *et al.* to synthesise the dinuclear nickel(II) complexes  $[\text{Ni}_2\text{L}^{11}(\mu\text{-CH}_3\text{COO})(\text{NCS})_2(\text{MeOH})]$  (**12**),  $[\text{Ni}_2\text{L}^{11}(\mu\text{-CH}_3\text{COO})(\text{NCS})_2(\text{MeOH})]\text{BPh}_4$  (**13**),  $[\text{Ni}_2\text{L}^{12}(\mu\text{-CH}_3\text{COO})(\mu\text{-NCS})(\text{NCS})(\text{MeOH})]$  (**14**),  $[\text{Ni}_2\text{L}^{12}(\mu\text{-CH}_3\text{COO})(\text{CH}_3\text{COO})]\text{BPh}_4$  (**15**) and  $[\text{Ni}_2\text{L}^{12}(\mu\text{-NCS})(\text{NCS})_2(\text{MeOH})]$  (**16**)<sup>36</sup>. In all of these complexes the phenolate serves as an endogenous bridge and the pendant arms act as chelates.



In **13** the phenolic bridge is augmented by two *syn-syn* acetates to provide a  $[(\mu\text{-phenoxo})\text{bis}(\mu\text{-$

acetato)dinickel(II) core with a Ni··Ni separation of 3.311Å. A methanol molecule coordinates to one of the nickel atoms leading to geometric asymmetry within a {5,6} coordination number set. The coordination geometries are square pyramidal and pseudo-octahedral.

The dinuclear core of **14** is triply bridged by the phenolato-O atom, a *syn-syn* acetate and an isothiocyanate anion. Each nickel(II) is six-coordinate with a methanol making up the donor set {N<sub>3</sub>O<sub>3</sub>} at the nickel in the iminic compartment (Ni<sub>iminic</sub>) and an isothiocyanate anion occupying the sixth position {N<sub>4</sub>O<sub>2</sub>} at the nickel in the aminic (N<sub>aminic</sub>) compartment the metals are separated by 2.99Å.

An unusual {4,6} coordination mode was found in **15** and the metals in the [(μ-phenoxo)(μ-acetato)dinickel(II)] are separated by 3.254Å. The coordination geometry {N<sub>2</sub>O<sub>2</sub>} of Ni<sub>iminic</sub> is slightly distorted towards a tetrahedron and that N<sub>aminic</sub> is pseudo-octahedral {N<sub>2</sub>O<sub>4</sub>} due to the presence of a chelating acetate anion.

Complex **16** has a [(μ-phenoxo)(μ-isothiocyanato)dinickel(II)] core and a {5,6} coordination number set. The geometry at Ni<sub>iminic</sub> is square pyramidal {N<sub>3</sub>O<sub>2</sub>} and that of N<sub>aminic</sub> is pseudo-octahedral {N<sub>4</sub>O<sub>2</sub>}. Each nickel has a coordinated isothiocyanate anion and Ni<sub>aminic</sub> is further coordinated by a methanol molecule. The Ni··Ni separation is 3.142Å.

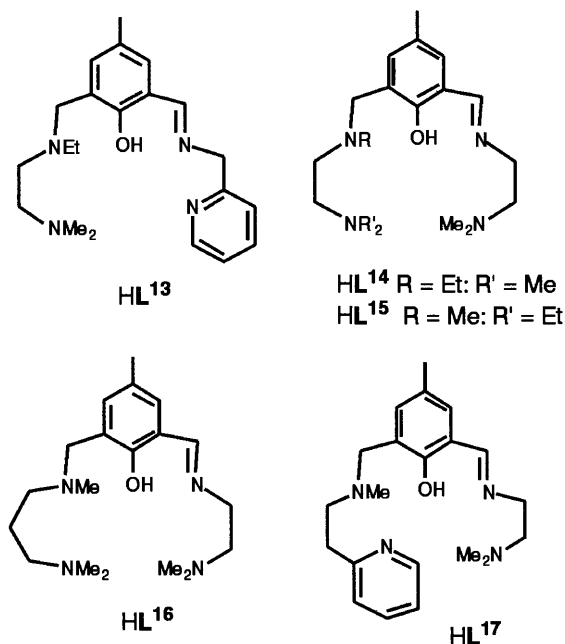


Fig. 5 Ligands used for the generation of bidentate bridging ethanoates

The magnetic moments of **12-14** gradually decrease with decreasing temperature suggesting the presence of an antiferromagnetic interaction between the nickel(II) atoms whereas that of **16** gradually increases with decreasing temperature suggesting a ferromagnetic interaction. The magnetic moment of **15** showed that it was a mixed-spin complex having present one low-spin ( $S = 0$ ) and one high-spin ( $S = 1$ ) nickel(II) atom. As with the complexes of Krebs and co-workers (**2-4**, **6** and **7**) a sensitivity of magnetic behaviour to structural change was indicated.

In our own work we have used asymmetric phenol-based compartmental ligands to generate a range of oligonuclear nickel (II) complexes<sup>36</sup>. In complexes bearing coordinating anions the presence of five-membered chelate rings at the iminic compartment in ligands such as HL<sup>13</sup>-HL<sup>17</sup> gave rise to complexes such as **17** with a *syn-syn* bidentate acetate bridge whereas under the same reaction conditions the presence of six-membered chelate rings at the iminic compartment in ligands such as HL<sup>18</sup>-HL<sup>22</sup> gave rise to complexes such as **18** with a *syn-syn* bidentate acetate bridge and a monodentate bridging acetate bridge<sup>37</sup>. In the presence of weakly or non-coordinating anions hydrolysis of the imine bond occurred to give dinuclear complexes of the precursor aldehyde<sup>38, 39</sup>.

The unsymmetrical **linear - dipodal** compartmental proligand HL<sup>26</sup> is capable of providing

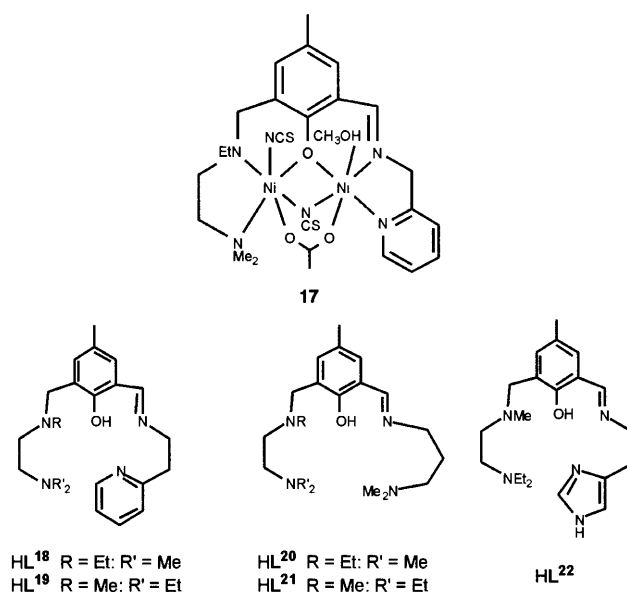


Fig. 6 Ligands used for the generation of monodentate bridging ethanoates

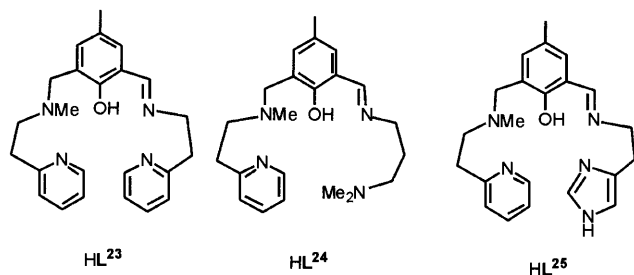
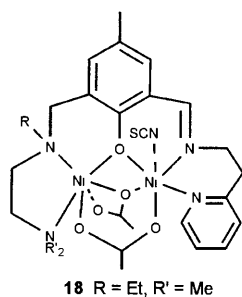
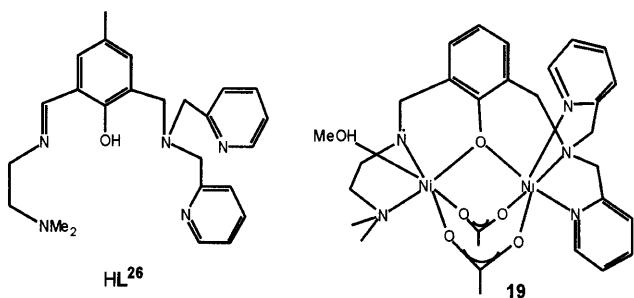


Fig. 7 Ligands used for the generation of monodentate bridging having [6,6] coordination sets, aminic (6-membered) and iminic (6-membered)

adjacent  $\{N_2O\}$  and  $\{N_3O\}$  donor compartments. The structure of  $[Ni_2L^{26}(\mu-CH_3COO)_2(MeOH)]PF_6$  (**19**) showed the presence of a donor asymmetric dinuclear core with a [5,5] coordination number set present<sup>40</sup>. In addition to coordination by the ligand donors the distorted octahedral nickel atoms were bridged by two *syn-syn* ethanoate groups with the nickel atom in the iminic compartment was further coordinated to a methanol of solvation.



This latter observation suggested that it would be of interest to incorporate the solvating atom into the pendant arm thus increasing the donor capacity of the arm whilst expanding the ligand framework. The resulting ligand would contain two potentially tetradentate binding sites, an iminic  $\{N_2OX\}$  site, based on a linear tridentate arm and an aminic  $\{N_3O\}$  site based on a dipodal tridentate arm (Fig. 8).

In order to achieve this objective two donor unsymmetric proligands were in each of which the

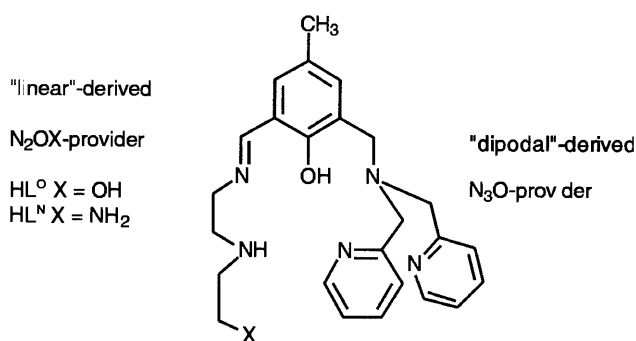
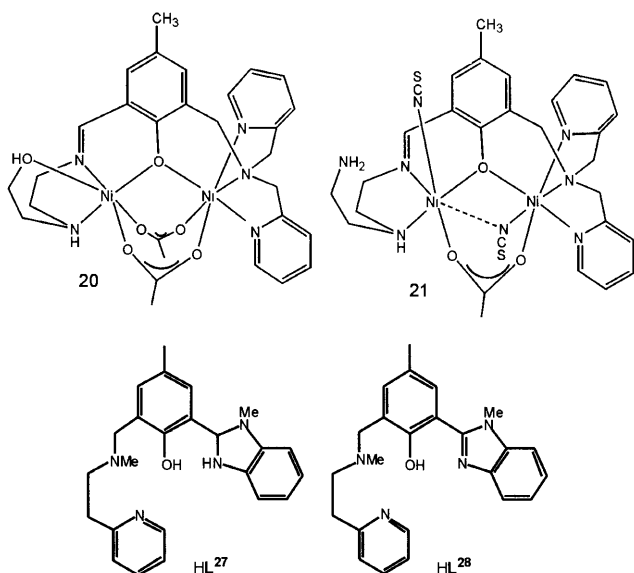


Fig. 8 Representation of unsymmetric linear-dipodal compartmental ligands

aminic site is derived from bis-pyridin-2-ylmethylamine, as in HL<sup>30</sup>. The iminic sites are derived from *N*<sup>1</sup>-(2-aminoethyl)ethane-1,2-diamine (diethylenetriamine), HL<sup>N</sup>, and 2-(2-aminoethylamino)-ethanol, HL<sup>O</sup><sup>41</sup>. In HL<sup>O</sup> the chelating ethylenediamine fragment remains with the appended hydroxyethyl group in HL<sup>O</sup> being used to simulate the solvent methanol present in **19**. The binding of the terminal donor atom of the terdentate linear arm appears to be dependent on the nature of the accompanying counter-anion. The reaction of  $Ni(CH_3COO)_2$  with HL<sup>O</sup> in the presence of the non-coordinating tetrafluoroborate anion gave  $[Ni_2L^O(\mu-CH_3COO)_2]BF_4$  (**20**). The structure of **20** resembles that of **19** with the terminal alcohol from HL<sup>O</sup> is coordinated. In the presence of added thiocyanate ion the terminal amine from HL<sup>N</sup>,  $[Ni_2L^N(\mu-CH_3COO)(\mu-SCN)(SCN)]$  (**21**), is not coordinated, but the anion is — this appears to reflect the comparative bond strengths of the putative donor groups. At first sight complex **21** is coordination number asymmetric. The nickel(II) atom in the aminic compartment is six coordinate and pseudo-octahedral whereas the nickel(II) in the iminic compartment appears to be close to square pyramidal, with an NCS<sup>-</sup> in an axial position. However the two isothiocyanate anions in the molecule are *trans* to each other and the NCS<sup>-</sup> coordinated at Ni<sub>am</sub> is disposed towards the open face of the square pyramid at Ni<sub>im</sub>. The Ni<sub>im</sub>-N<sub>br</sub> distance is 2.73 Å and so there is a weak interaction leading to an unsymmetrical isothiocyanato bridge the nickel atoms (Ni<sub>im</sub>-N<sub>br</sub> 2.73 Å; Ni<sub>am</sub>-N<sub>br</sub> 2.04 Å). The Ni...Ni separations are 3.332 Å in **20**, compared with 3.396 Å in **19**, and 3.203 Å in **21**.



#### 2.2.2.2 Trinuclear Complexes

The unsymmetric compartmental proligand HL<sup>27</sup> bearing a tridentate N<sub>2</sub>O donor set and a bidentate NO donor set has given the trinuclear nickel(II) complex, [Ni<sub>3</sub>(L<sup>28</sup>)<sub>2</sub>(μ-CH<sub>3</sub>COOAc)<sub>2</sub>(NCS)<sub>2</sub>], **22**, in which there are two unusual tridentate ethanoate bridges, each having a μ<sup>3</sup>,η<sup>2</sup>,η<sup>1</sup>-bridging mode, and the dihydrobenzimidazole ring system present in pro-ligand HL<sup>27</sup> has been oxidised to a benzimidazole ring system (HL<sup>28</sup>)<sup>42</sup>. The basis of the trinuclear structure is an isosceles triangle of Ni atoms, Ni(1)⋯Ni(2) = Ni(2)⋯Ni(1A) = 3.18 Å and Ni(1)⋯Ni(1A) = 4.91 Å (Fig. 9a). Each Ni atom has a distorted octahedral geometry. The three pairs of Ni atoms are each doubly

bridged (Fig. 9b). Ni(1)⋯Ni(2) and Ni(2)⋯Ni(3) are each bridged by a phenolic O and by a monodentate O atom from a coordinated acetate whereas Ni(1) and Ni(3) are bridged by the *syn-anti* bidentate O atoms from two μ<sup>3</sup>,η<sup>2</sup>,η<sup>1</sup>-acetates. Each acetate is acting as a tridentate ligand by using one O atom [O<sub>b</sub>] to bind in a monodentate fashion to one Ni atom with the second O atom [O<sub>d</sub>] acting as a monodentate bridge between the remaining two Ni atoms.

The denticity of the dinucleating ligand has been reduced from potentially pentadentate to potentially tetradentate. Vacant coordination sites then arise at the metal in the diminished compartment so providing the opportunity for the generation of a complex with enhanced nuclearity. This has been achieved by double μ<sup>3</sup>,η<sup>2</sup>,η<sup>1</sup>-acetate bridging. The wider application of this approach can be seen in the ready formation of the trinuclear Ni(II) complexes [Ni<sub>3</sub>(L<sup>29</sup>)<sub>2</sub>(μ-OAc)<sub>2</sub>(NCS)<sub>2</sub>] from unsymmetric compartmental ligands of the type HL<sup>29</sup>, prepared from the reaction of HL<sup>33</sup> and primary aliphatic amines.

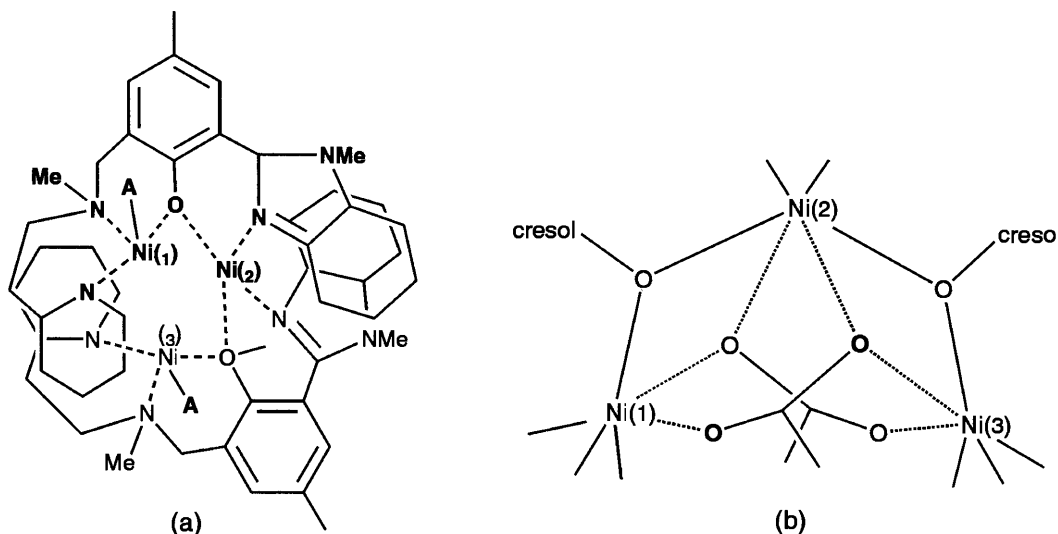
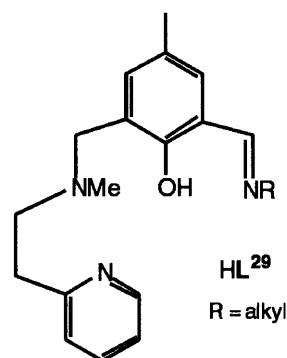
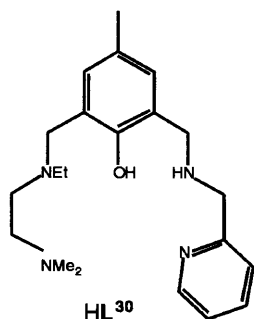


Fig. 9 Schematic representation of **19**, (a) with the *benzimidazole*-, *pyridinyl* and *acetate* groups removed for clarity and (b) depicting the μ<sup>3</sup>,η<sup>2</sup>,η<sup>1</sup>-bridging mode of the acetates

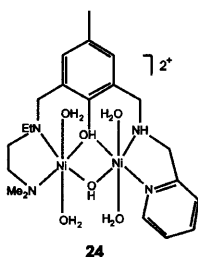


### 2.2.2.3 Tetranuclear Complexes

A tetranuclear species was prepared in attempts to prepare dinuclear nickel(II) complexes in the presence of weakly or non-coordinating anions and so encourage hydroxo-bridge formation<sup>43</sup>. The unsymmetric compartmental ligand HL<sup>13</sup> was reduced to the di-aminic analogue HL<sup>30</sup> which was then reacted with Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O in ethanol with addition of NaPF<sub>6</sub> to facilitate crystallisation. Crystal structural analysis revealed that complex formed was [Ni<sub>4</sub>(L<sup>30</sup>)<sub>2</sub>(OH)<sub>3</sub>(OH<sub>2</sub>ClO<sub>4</sub>)](PF<sub>6</sub>)<sub>2</sub>·C<sub>2</sub>H<sub>5</sub>OH·5H<sub>2</sub>O, so providing the first example of a tetranuclear nickel(II) complex assembled from an unsymmetric compartmental ligand.



The tetranuclear core, [Ni<sub>4</sub>(L<sup>30</sup>)<sub>2</sub>(μ-OH)<sub>2</sub>(μ-O<sub>2</sub>H<sub>3</sub>)(μ-ClO<sub>4</sub>)]<sup>2+</sup>, **23**, is assembled from two confacial bioctahedra with L<sup>30</sup> serving as a dinucleating and doubly face-capping anionic ligand. The shared faces of the bioctahedra are linked to each other by a bridging (μ<sup>4</sup>,η<sup>2</sup>,η<sup>2</sup>) tetradentate perchlorate and two μ-cresolato bridges link the pairs of open faces (Fig. 10). The intermetallic separation of the Ni atoms at the triply bridged faces (*ca.* 2.89Å) are considerably shorter than those of the Ni atoms in the single atom cresolato-bridges (*ca.* 3.72Å). The short central O...O contact distance of 2.46Å indicates the presence of a very strong hydrogen bond leading to the hydrated hydroxide anion [O(H)H·OH]<sup>-</sup> which provides an unusual (μ<sup>4</sup>,η<sup>2</sup>,η<sup>2</sup>)-bridge between the two dinuclear nickel centres with each O atom serving as a bridging atom to a pair of Ni(II) atoms (Fig. 4). It is possible that a μ-hydroxo bridged dinickel(II) species such as **24** provides the precursor for the tetranuclear assembly.



Okawa and co-workers have prepared tetranuclear complexes from the linear – dipodal ligand HL<sup>26</sup> 40. Reaction of the ligand, generated *in situ*, with Ni(ClO<sub>4</sub>)<sub>2</sub> and KPF<sub>6</sub> in MeOH gave [(Ni<sub>2</sub>L<sup>26</sup>(μ-OH)(MeOH))(μ-CO<sub>3</sub>)](PF<sub>6</sub>)<sub>2</sub> (**25**) (Fig. 11). The crystal structure revealed a carbonato-bridged dimer derived from an asymmetric dinuclear unit. In each unit a pair of nickel atoms [Ni(1)···Ni(2), 3.087Å] are bridged by the phenolic oxygen (O1) from the ligand and a hydroxo oxygen (O2). The nickel bound in the iminic compartment (Ni1) is in a distorted octahedral environment with the ligand nitrogen donor atoms (N1 and N2) and the carbonato oxygen atoms (O3 and O4) completing the ligation requirement. The second nickel is bound in the aminic compartment (Ni2) and also assumes a six-coordinate geometry with the ligand nitrogen donor atoms (N3, N4 and N5), a methanol O atom O5 and the carbonato oxygen atoms (O3 and O4) completing the ligation requirement. The dimeric

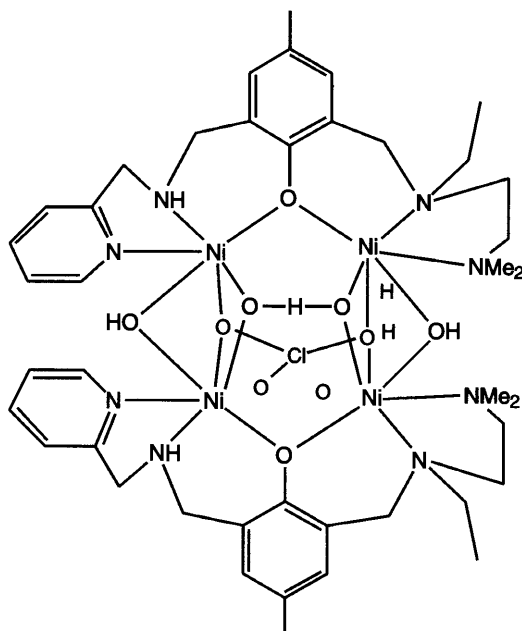


Fig. 10 Schematic representation of the tetranuclear core **15**

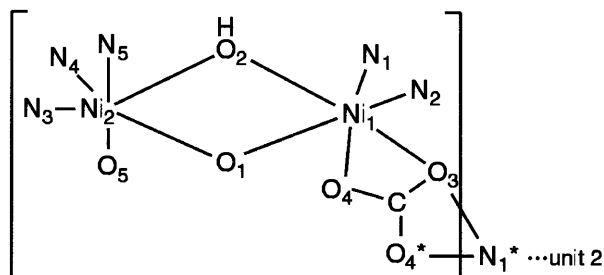


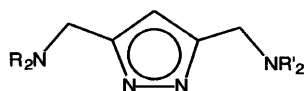
Fig. 11 Schematic representation of the asymmetric dinuclear units in **25**

structure is due to bridging by the carbonate group which binds to Ni1 through its oxygen atoms O3 and O4 and to Ni1\*, in the adjoining unit, via O3 and O4\*. The carbonate probably arises by adventitious fixation of carbon dioxide during formation or crystallisation.

### 2.2.3 Unsymmetric Ligands Bearing a Pyrazolate Spacer

Meyer and his co-workers have prepared both symmetric, HL<sup>31</sup><sup>44</sup>, HL<sup>32</sup><sup>44</sup>, HL<sup>33</sup><sup>45</sup>, HL<sup>34</sup><sup>46</sup>, and unsymmetric, HL<sup>35</sup><sup>45</sup>, pyrazolate-based dinucleating proligands.

Complex [NiL<sup>31</sup>(μ-Cl)Cl<sub>3</sub>] (**26**) was prepared from proligand HL<sup>31</sup>; the crystal structure revealed that the nickel atoms, 3.823 Å apart, were bridged by the endogenous pyrazolate group and by a chloride anion. Each nickel was further coordinated by a chloride anion and a sulfur from the pendant arm of the ligand and so was in a distorted octahedral environment provided by a {N<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>} donor set<sup>45</sup>.

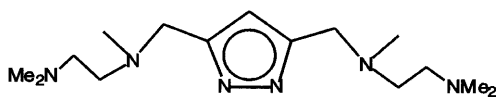


HL<sup>31</sup>: R = R' = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NMe<sub>2</sub>

HL<sup>32</sup>: R = R' = CH<sub>2</sub>CH<sub>2</sub>NEt<sub>2</sub>

HL<sup>33</sup>: R = R' = CH<sub>2</sub>CH<sub>2</sub>SEt

HL<sup>34</sup>: R = CH<sub>2</sub>CH<sub>2</sub>NEt<sub>2</sub> R' = CH<sub>2</sub>CH<sub>2</sub>SEt



HL<sup>35</sup>

With the unsymmetric proligand HL<sup>34</sup> the complex [NiL<sup>34</sup>(μ-Cl)Cl<sub>3</sub>] (**27**) was prepared<sup>45</sup>. In **27** the two nickel atoms are separated by 3.823 Å and again bridged by the endogenous pyrazolate group and by a chloride anion. However this complex exhibits geometric asymmetry; the nickel in the sulfur donor compartment is octahedral {N<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>} whereas the nickel in the nitrogen donor compartment is distorted square pyramidal {N<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>}. One diethylaminoethyl-arm of the ligand is non-coordinating. Reaction of **27** with NaBPh<sub>4</sub> gave [NiL<sup>34</sup>(μ-Cl)Cl][BPh<sub>4</sub>] (**28**) and induced interaction of the dangling arm such that the nickel atom was now in an {N<sub>4</sub>Cl} environment with distorted trigonal bipyramidal geometry. The

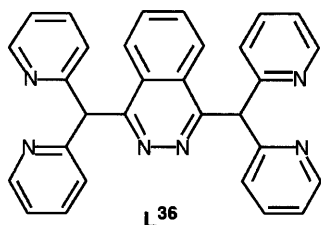
coordination at the sulfur compartment remained the same {N<sub>2</sub>S<sub>2</sub>Cl<sub>2</sub>} and the Ni...Ni separation is 3.903 Å. This was attributed to coordination of all of the side arms of the tren-type NN<sub>3</sub> coordination sub-unit of the ligand pulling the metal centres apart<sup>45</sup>. Complexes **26-28** showed antiferromagnetic behaviour with the decrease in  $-J$  for **28** due to the increased Ni...Ni separation.

The intriguing hydroxy-bridged complexes [NiL<sup>31</sup>(OH)][ClO<sub>4</sub>]<sub>2</sub> (**29**) and [NiL<sup>32</sup>(O<sub>2</sub>H<sub>3</sub>)]ClO<sub>4</sub> (**30**) were synthesised from the symmetric proligands HL<sup>31</sup> and HL<sup>32</sup><sup>47</sup>. Treatment with NaBPh<sub>4</sub> gave the corresponding complexes. The crystal structures complexes [NiL<sup>31</sup>(μ-OH)][BPh<sub>4</sub>]<sub>2</sub> (**29'**) and [NiL<sup>32</sup>(μ-O<sub>2</sub>H<sub>3</sub>)]BPh<sub>4</sub>·2 acetone (**30'**). In **29'** the hydroxide acts as a monoatomic bridge between the two pentacoordinate {N<sub>4</sub>O} nickel atoms. The coordination geometries of both metal atoms are square pyramidal and the Ni...Ni separation is 3.643 Å. In **30'** the shorter ligand side arms pull the metal atoms further apart ( $d(\text{Ni}\cdots\text{Ni})$ , 4.452 Å) inhibiting the bridging of a hydroxide but inducing the incorporation of a further water molecule which enables formation of [H<sub>3</sub>O<sub>2</sub>]<sup>-</sup> with a very strong intramolecular hydrogen bond [ $d(\text{O}\cdots\text{O})$ , 2.433 Å]. In this complex both nickel atoms are penta-coordinate but the geometries are now distorted trigonal bipyramidal. The magnetic data for **30'** indicated no significant coupling between the metals but that for **29'** corresponded to a strong antiferromagnetic coupling.

The proligand HL<sup>33</sup> has given [NiL<sup>33</sup>(μ-CH<sub>3</sub>COO)(acetone)<sub>2</sub>][ClO<sub>4</sub>]<sub>2</sub> (**31**) in which both nickel atoms are six-coordinate {N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>} and the Ni...Ni separation is 4.161 Å, elongated relative to the 3.823 Å found in **26** due the presence of the three atom acetate bridge<sup>48</sup>. Each nickel has a molecule of solvent coordinated as well as the ligand and bridging acetate. The UV-visible spectra indicate that the six-coordination is retained in solution and the complex is antiferromagnetic.

### 2.2.4 Ligands Bearing a Phthalazine Spacer

Barrios and Lippard have synthesised L<sup>36</sup> which although not strictly biomimetic is viewed as containing structural features analogous to those found at the active site of urease — the pyridine donor arms serve to imitate the histidine residues ligated to the nickels and the phthalazine moiety plays a role in bringing the metals close together<sup>49</sup>.

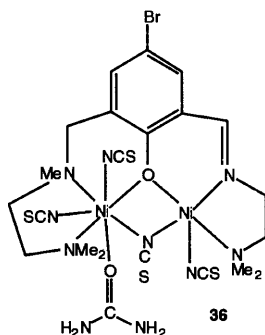


Treatment of  $L^{36}$  with  $[Ni(OH_2)_6](OTs)_2$  in acetonitrile gave water soluble  $[Ni_2L^{36}(\mu-OH_2)_2(OH_2)_2](OTs)_4$  (**32**). The crystal structure revealed that the phthalazine moiety bridged the two nickel atoms ( $dNi\cdots Ni, 3.0598\text{\AA}$ ) and the pyridinyl arms provided two nitrogen atoms to each metal. Each nickel is in pseudo-octahedral geometry  $\{N_3O_3\}$  with two water molecules bridging the nickel atoms which also have a terminally bound water present<sup>49</sup>. This tetraqua complex can be singly and doubly deprotonated to give  $[Ni_2L^{36}(\mu-OH)(\mu-OH_2)_3](OTs)_3$  (**33**) and  $[Ni_2L^{36}(OH)_2(OH_2)](OTs)_2$  (**34**). The structures of these reveal that (**33**) is monomeric but (**34**) is a dimer. Complex **33** has a core structure similar to that of **32** with ( $dNi\cdots Ni, 3.1398\text{\AA}$ ) and that one of the bridging water has been deprotonated is evidenced by a shortening of the Ni-O bond lengths from 2.148 to 2.048 $\text{\AA}$ .

### 2.3 Dinuclear Complexes with Bound Urea

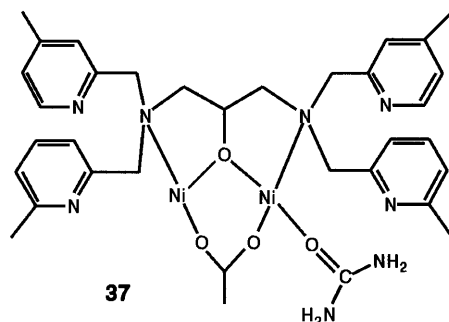
#### 2.3.1 Monodentate O-bound Urea

Several model complexes have been prepared with a urea bound to a nickel at the dinuclear through its carbonyl oxygen atom. Koga *et al.*, showed that complexes **15** and **16** reacted with urea to give  $[Ni_2L^{12}(\mu-CH_3COO)(CH_3COO)(urea)]BPh_4$  (**35**) and  $[Ni_2L^{12}(\mu-NCS)(NCS)_2(urea)]$  (**36**)<sup>36</sup>. The presence of O-bonded urea was inferred from the IR spectra and confirmed by the crystal structure of **36** which is similar to that of **16** with the geometry at  $Ni_{iminic}$  square pyramidal  $\{N_4O_1\}$  and that of  $Ni_{aminic}$  pseudo-octahedral  $\{N_4O_2\}$  but with the methanol at  $Ni_{aminic}$  replaced by O-bonded urea. The Ni $\cdots$ Ni separation is 3.155 $\text{\AA}$  and both complexes were found to exhibit ferromagnetic behaviour.



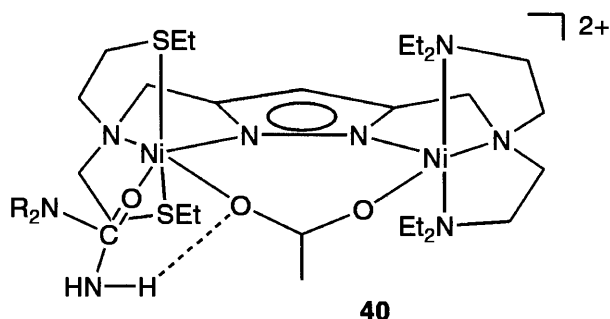
Urea adduct formation was not observed with complexes **12-14**. Complex **14** has a  $\{6,6\}$  coordination number set and **12** is likely to have a similar core. As both nickel atoms are coordinatively saturated this explains why urea is not bound. Complex **15** has a  $\{4,6\}$  coordination number set and so urea could bind at the four-coordinate nickel centre ( $Ni_{iminic}$ ). In **16**, which has a  $\{5,6\}$  coordination number set and is derived from an unsymmetric proligand, the methanol atom at  $Ni_{aminic}$  could be replaced by the urea whereas for **13** which also has a  $\{5,6\}$  coordination number set but is derived from a symmetric proligand and it was proposed that this core is effectively saturated towards weak donor molecules such as urea.

The reaction of **9** with urea gave  $[Ni_2L^8(\mu-CH_3COO)(ClO_4)(urea)](ClO_4)_2 \cdot urea$  (**37**) the crystal structure which revealed a  $\{6,5\}$  coordination number set. Only one nickel(II) atom  $\{N_3O_3\}$  binds to a urea through its oxygen atom while the second nickel atom is were five coordinate,  $\{N_3O_2\}$ . The Ni $\cdots$ Ni separation is 3.647 $\text{\AA}$ <sup>33</sup>.

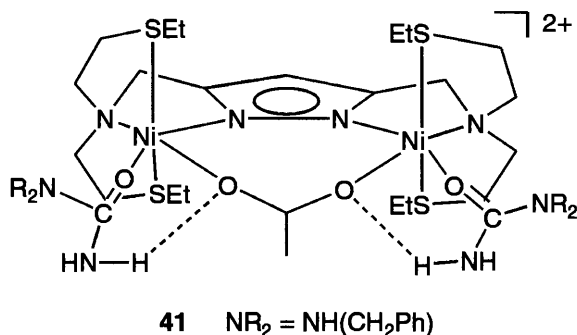


Yamane *et al.*, have synthesised a range of dinuclear complexes from  $HL^{10}$  of which  $[Ni_2L^{10}(\mu-CH_2ClCOO)(MeOH)_2](ClO_4)_2$  (**38**), for which the crystal structure was solved serves, as a representative compound<sup>50</sup>. Each nickel atom has an octahedral geometry with an  $\{N_3O_3\}$  donor set from a tertiary amino N atom and two imidazolyl N atoms from the ligand, a bridging chloroacetate O atom, an endogenous alkoxide O atom, and a methanol O atom. The Ni $\cdots$ Ni separation is 3.559 $\text{\AA}$ , similar to that in the related complexes **10** and **11**<sup>35</sup>. The nature of the bridging carboxylate anion was changed in the remaining complexes produced. The complexes were found to interact with urea. The IR spectra suggested coordination of urea through its carbonyl oxygen atom and the UV-visible spectra indicated the presence of octahedral nickel(II). The crystal structure of  $[Ni_2L^{10}(\mu-C_3H_7COO)(urea)(H_2O)](ClO_4)_2 \cdot 2(CH_3)_2CO$  (**39**) confirmed the presence of two octahedral

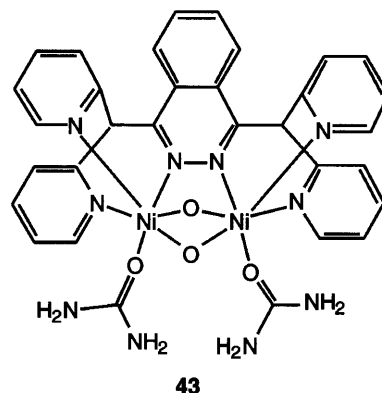
nickel (II) atoms with  $\{N_3O_3\}$  donor sets and a Ni...Ni separation of 3.522 Å. Relative to the closely related complex **10** a methanol bound at one nickel atom has been replaced by a water molecule and that at the second nickel (II) atom by a monodentate urea bound through its oxygen atom. There is an antiferromagnetic interaction between the nickel atoms in the urea adducts.



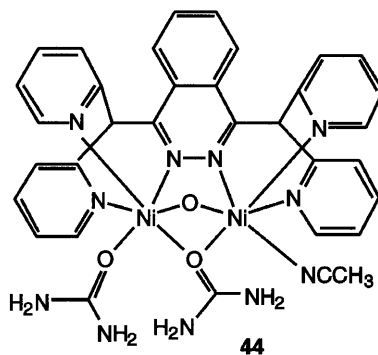
An *in situ* self assembly reaction has given  $[NiL^{33}(\mu-CH_3COO)(urea)][ClO_4]_2$  (**40**)<sup>48</sup>. The complex is geometrically asymmetric with a  $\{5,6\}$  coordination set as found previously for this ligand; the Ni...Ni separation is 4.221 Å<sup>46</sup>. The "nitrogen-only" side arm again supports the five coordinate nickel ion  $\{N_4O\}$  with a geometry intermediate between square pyramidal and trigonal bipyramidal. The urea molecule is O-bound at the second nickel ion which is pseudo-octahedral,  $\{N_2O_2S_2\}$  and is hydrogen bonded to an oxygen atom of the acetate bridge. Dinuclear nickel complexes bearing O-bonded substituted ureas,  $[NiL^{33}(\mu-CH_3COO)(benzylurea)_2][ClO_4]_2$  (**41**) and  $[NiL^{35}(\mu-CH_3COO)(N,N'-dimethylurea)_2(methanol)_2][ClO_4]_2$  (**42**) have also been studied<sup>48</sup>. In **41** the basic dinuclear framework of **31** has been retained with the acetone molecules being replaced by the O-bound benzylurea molecules and in **42** the nickel ions ( $dNi...Ni$  4.316 Å) are six-coordinate  $\{N_3O_3\}$  via a *fac*-tridentate interaction with a coordination compartment of  $L^{35}$  and the O-atoms from a bridging acetate, a methanol of solvation and an N,N'-dimethylurea molecule.



Reaction of nickel(II) perchlorate and  $L^{36}$  with an excess of urea in methanol has given  $[Ni_2L^{36}(\mu-OH)(\mu-OH_2)(urea)_2](ClO_4)_3$  (**43**)<sup>51</sup>. The crystal structure of **43** reveals a dinuclear nickel complex ( $dNi...Ni$  3.085 Å) bridged by the phthalazine moiety, a water molecule and a hydroxide anion. The pseudo-octahedral coordination geometry at each nickel  $\{N_3O_3\}$  is completed through ligation to two pyridine donor arms from the ligand and two O-bound urea molecules which are also hydrogen bonded to the bridging oxygen atoms.

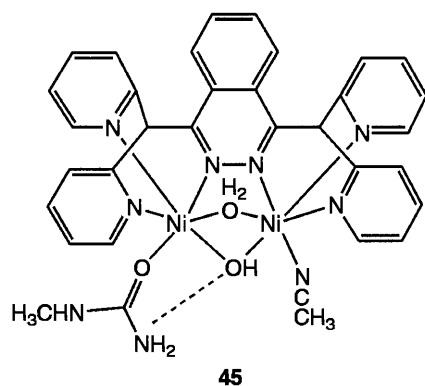


A second complex  $[Ni_2L^{36}(\mu-OH)(\mu-urea)(urea)(NCCH_3)](ClO_4)_3$  (**44**) bearing O-bound urea was recovered when the solvent in the above reaction was changed from methanol to acetonitrile<sup>51</sup>. The crystal structure shows that  $L^{36}$  is coordinated in the same manner as it is in **43**. The two remaining terminal coordination sites are each 50% occupied by an acetonitrile molecule and an O-bound urea molecule. The dinuclear(II) core, ( $dNi...Ni$  3.079 Å), is further bridged by a hydroxide anion and a urea molecule that forms a single atom bridge between the two metal ions via its carbonyl-O atom. Each nickel(II) ion is pseudo octahedral,  $\{N_3O_3\}$ :  $\{N_4O_3\}$  and that this is retained in solution is evidenced by the electronic spectrum.



N-Methyl urea has been found to bind to Ni through its carbonyl oxygen atom in  $[Ni_2L^{36}(\mu-OH)(\mu-OH_2)(N-methylurea)(NCCH_3)](ClO_4)_3$  (**45**)<sup>52</sup>. Again the

dinuclear nickel core ( $d\text{Ni}\cdots\text{Ni}$  3.069 Å) is bridged by the phthalazine moiety, a water molecule and a hydroxide anion. The pseudo-octahedral coordination geometry at one nickel  $\{\text{N}_3\text{O}_3\}$  is completed through ligation to two pyridine donor arms from  $\text{L}^{36}$  and an acetonitrile with completion at the second nickel  $\{\text{N}_4\text{O}_2\}$  arising from ligation to two pyridine donor arms and an O-bound urea molecule the  $\text{NH}_2$ -group of which is hydrogen bonded to the bridging hydroxide. The bridging water and hydroxide are distinguished through the average Ni-O distances of 2.206 Å and 2.030 Å respectively. In the same paper thiourea is shown to bind to nickel in complex  $[\text{Ni}_2\text{L}^{36}(\mu\text{-OH})(\mu\text{-OH}_2)(\text{thiourea})(\text{NCCH}_3)](\text{ClO}_4)_3$  (**46**)<sup>52</sup>. The complex is closely similar to **45** save that the thiourea is S-bound to the nickel atom previously bound by N-methylurea. A hydrogen-bond between one of the thiourea  $\text{NH}_2$  groups and the bridging hydroxide is again noted and this interaction has emerged as a consistent feature in all of the dinuclear complexes of  $\text{HL}^{39}$  and urea and urea derivatives so far studied.



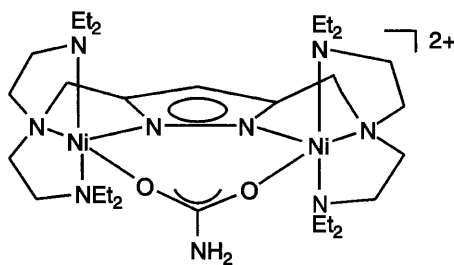
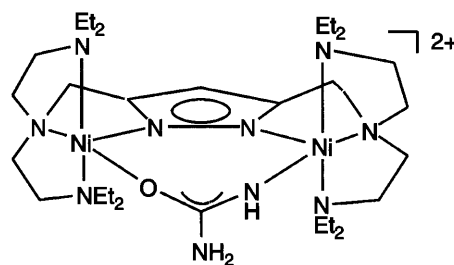
An early speculative model for urease was the dinuclear nickel(II) complex  $[\text{Ni}_2(\text{CH}_3\text{COO})_3(\text{urea})(\text{tmen})_2(\text{Otf})]$ , (**46**) where  $\text{tmen}$  is  $\text{N,N,N',N'}$ -tetramethyl ethylenediamine<sup>53</sup>. This complex provided the first example of a dinuclear nickel(II) complex with a monodentate carboxylate bridge as well as having an O-bonded urea molecule present. The nickel ions were pseudo-octahedral  $\{\text{N}_2\text{O}_4\}$  ( $d\text{Ni}\cdots\text{Ni}$  3.475 Å), and bridged by two syn-syn bidentate acetates as well as the monodentate carboxylate

### 2.3.2 Bridging Urea

In order to help elucidate possible binding modes of the substrate to the dinickel(II) centre complexes incorporating urea have been synthesised and used as models. As noted above the urea has generally been found to be  $\eta^1(\text{O})$ -coordinated but examples have also

been found in which bridging occurs. In complex  $[\text{Ni}_2\text{L}^{36}(\mu\text{-OH})(\mu\text{-urea})(\text{urea})(\text{NCCH}_3)](\text{ClO}_4)_3$  (**44**)<sup>52</sup> there is one O-bound urea molecule and the second urea molecule that forms a unique single atom bridge ( $\mu^2\text{-}\kappa\text{O}$ ) between the two metal ions via its carbonyl-O atom. This bridging mode had not been previously encountered and may be of relevance to the enzyme urease in that the urea molecule would be better activated by coordination to two nickel atoms rather than simply to one. At this point the bonding mode of urea which permits the catalytic reaction in urease is not known.

Double ( $\mu^2\text{-}\kappa\text{N}:\kappa\text{O}$ ) and triple ( $\mu^3\text{-}\kappa\text{N}:\kappa\text{N}':\kappa\text{O}$ ) bridging between Ni atoms, has been reported to occur with deprotonated urea. The reaction of complex **34** with urea in acetone gave complex  $[\text{Ni}_2\text{L}^{35}(\text{NH}(\text{O})\text{CNH}_2)](\text{ClO}_4)_2$  (**48**)<sup>47, 54</sup>. The crystal structure revealed the presence of an N,O-bridging deprotonated urea, and this was augmented by FAB mass spectrometry. To confirm that this reaction had occurred and that a carbamate had not been produced,  $[\text{Ni}_2\text{L}^{35}(\text{O}_2\text{CNH}_2)](\text{BPh}_4)_2$  (**49**) was synthesised by reaction of **34** with ammonium carbamate. The overall molecular geometry was similar to that of **48** but the  $\text{Ni}\cdots\text{Ni}$  separation was slightly shortened [**48**: 4.255 Å, **49**: 4.229 Å]<sup>54</sup>.



A tetranuclear nickel(II) complex derived from  $\text{HL}^{39}$   $\{[\text{Ni}_2\text{L}^{35}(\text{NH}(\text{O})\text{CNH}_2)(\text{urea})](\text{ClO}_4)_2\}_2$  (**50**) in which two urea molecules are in an unprecedented  $\mu^3\text{-}\kappa\text{N}:\kappa\text{N}':\kappa\text{O}$  bridging mode and two are  $\eta^1(\text{O})$ -

coordinated has been characterised<sup>55</sup>. There are two pyrazolate based dinuclear units linked by the  $\mu_3$ -ureate substrate. The central feature of the tetranuclear network (Fig. 12) is an eight-membered ring system derived from two nickel atoms spanned by two N,O-bound ureate molecules with the remaining ureate NH-groups coordinated to the additional outer nickel ions. The latter nickel ions are for-coordinated and square planar whereas the former (central) pair are in distorted octahedral environments. The two central high spin nickel(II) ions are ferromagnetically coupled.

#### 2.4 Ethanolysis Reactions

The ethanolysis of urea has been examined as a model reaction of urease. In the presence of **9** an ethanol solution of with urea gave rise to ethyl carbamate whereas no reaction occurred in the absence of the complex or in the presence of nickel(II) ions<sup>33</sup>.

The complex  $[\text{Ni}_2\text{L}^8(\mu\text{-OH})](\text{ClO}_4)_2 \cdot \text{acetone}$  (**51**) has been prepared by reaction of  $\text{HL}^8$  with triethylamine and  $\text{Ni}(\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$  in acetone and under a  $\text{N}_2$  atmosphere. This complex did not catalyse the ethanolysis of urea but on exposure of the acetone solution to the atmosphere carbon dioxide was absorbed to give a complex (**52**) chemical and spectroscopic analysis of which indicated a dinickel (II) complex bridged by a bidentate hydrogen carbonate anion ( $\text{HCO}_3^-$ ). This complex was found to catalyse the ethanolysis of urea. It was noted that the hydration of carbon dioxide by (**51**) resembled the activation of apourease in the presence of nickel (II) ions by carbon dioxide<sup>56</sup> and that  $\text{RCOO}^-$  bridging ligands such as acetate and hydrogen carbonate play an essential role for the ethanolysis of urea. This might be in the control of the acidity of the nickel ions for the activation of both urea and ethanol, and the stereochemical arrangement of the molecules for ethanolysis. In the reaction one nickel can bind urea with the second nickel activating ethanol by coordination. No conversion of urea to ethyl carbamate was found when the urea adduct **37** was interacted with ethanol at  $80^\circ$  for 2 days the reason for this is not yet clear<sup>33</sup>.

The pyrazolate-based complexes **31**, **40**, and **42** have been investigated as catalysts for the ethanolysis of urea<sup>48</sup>. The complexes were refluxed with urea for 6 days and analysed by  $^1\text{H}$  NMR spectroscopy. The degree of ethanolysis was found to depend on the number of and stereochemical arrangement of the accessible coordination sites in the complexes. In accord with the suggestion that both nucleophile and

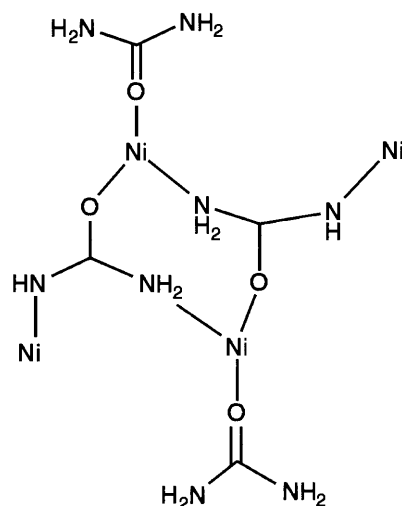


Fig. 12 Schematic representation of the tetranuclear nickel(II) core in  $\{[\text{Ni}_2\text{L}^{35}(\text{NH}(\text{O})\text{CNH}_2)(\text{urea})](\text{ClO}_4)_2\}_2$  (**50**)

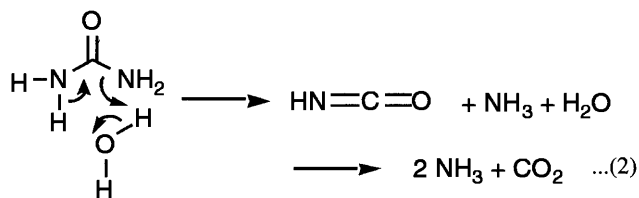
substrate are activated by coordination at the two nickel centres in urease<sup>12, 13</sup> it was proposed that the presence of only one accessible coordination site at the dinuclear core in **40** was insufficient to allow solvolysis to occur. In **31** which can meet the above requirement the unfavourable stereochemical orientation of the two remote *exo*-binding sites does not seem to allow effective intramolecular attack of the nucleophile on the bound substrate and so a low yield of ethyl carbamate results (0.8 equivalents w.r.t the catalyst used). Complex **42** in which there are several potentially available docking sites for the reactants was more active (2.2 equivalents ethyl carbamate w.r.t the catalyst used). However, it was suggested here that because of the many labile ligands in **42** a one-metal mechanism in which two adjacent sites on one nickel ion are involved in the ethanolysis reaction cannot be ruled out.

#### 2.5 Cyanate Complexes and An Alternative Mechanism for Hydrolysis

It is of interest to recall that in 1828 Wöhler synthesised urea, regarded as an organic compound, by reaction of silver isocyanate with ammonium chloride, both inorganic compounds; the ammonium isocyanate which is synthesised first undergoing a reversible molecular rearrangement. He wrote to his friend Berzelius saying "I can make urea without the necessity of a kidney, or even of an animal, whether man or dog. Ammonium cyanate is urea"<sup>57</sup>.

Urea hydrolyses very slowly to give isocyanic acid and ammonia eq. (2), the half life of the uncatalysed reaction is 3.6 years at room temperature<sup>58</sup>. The

decomposition is not hydrolytic but involves an elimination reaction.



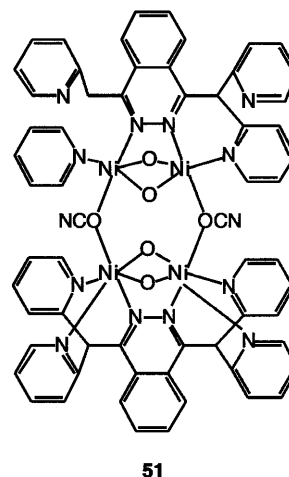
Uozomi *et al.*, reacted complexes of the linear – dipodal proligand  $\text{HL}^{26}$  with urea and obtained cyanate complexes, gaining the first recognition that urea can be converted into cyanate at a dinuclear core. Complexes **19**, **25** and  $[\text{Ni}_2\text{L}^{26}(\mu\text{-CH}_3\text{COO})(\mu\text{-NCS})(\text{NCS})]$  (**53**) gave as products  $[\text{Ni}_2\text{L}^{26}(\text{CH}_3\text{COO})(\text{NCS})(\text{NCO})]$ , (**54**),  $[\{\text{Ni}_2\text{L}^{26}(\mu\text{-NCO})(\text{EtOH})\}(\mu\text{-CO}_3)](\text{PF}_6)_2$ , (**55**), and  $[\text{Ni}_2\text{L}^{26}(\text{CH}_3\text{COO})(\text{NCO})(\text{EtOH})]\text{PF}_6$ , (**56**), respectively<sup>40</sup>. The low yields (10-15%) were ascribed to the poor solubility of urea in ethanol and were increased to 17-23% by prolonged heating (24 h). The presence of the cyanate group was supported by the recovery of the same products in >45% yield on direct reaction of potassium cyanate with the starting complexes and also by a vibration *ca.* 2180  $\text{cm}^{-1}$  in the IR spectrum. The crystal structure of **55** was similar to that of **25** except for the replacement of the bridging hydroxide by the N-bridging cyanate anion and methanol by ethanol.

Heating **48** or  $[\text{Ni}_2\text{L}^{35}(\text{NH}(\text{O})\text{CNH}_2)](\text{BPh}_4)_2$  (**57**) at 170° in vacuo led to the generation of complexes  $[\text{Ni}_2\text{L}^{35}(\text{NCO})](\text{ClO}_4)_2$  (**58**) and  $[\text{Ni}_2\text{L}^{35}(\text{NCO})](\text{BPh}_4)_2$  (**59**) respectively<sup>47</sup>. The presence of the  $\mu$ -1,3-cyanato bridge was inferred from the characteristic IR band at 2195  $\text{cm}^{-1}$  and confirmed by the crystal structure of **59**. The bridge spans the two nickel ions which are in different five coordinate environments.  $\text{Ni}_{\text{NCO}}$  has  $\tau = 0.32$  and  $\text{Ni}_{\text{OCN}}$  has  $\tau = 0.97$ , where  $\tau$  is the degree of trigonality ( $\tau = 0$  corresponds to a perfect trigonal bipyramid and  $\tau = 1$  corresponds to a perfect square pyramid)<sup>59</sup>. The Ni...Ni separation is 4.383 Å increased over that of 4.257 Å in **48**.

The thermal degradation of the tetranuclear complex **50** was investigated and caused conversion of urea to the cyanate anion<sup>55</sup>. This was evidenced by the appearance of the characteristic IR band at 2193  $\text{cm}^{-1}$  and a signal in the MS at  $m/z = 552$  assigned to  $[\text{L}^{35}\text{Ni}_2(\text{NCO})(\text{ClO}_4)]^+$ .

Complexes  $[\text{Ni}_2\text{L}^{36}(\mu\text{-OH})(\mu\text{-OH}_2)(\text{urea})_2](\text{ClO}_4)_3$  (**43**) and  $[\text{Ni}_2\text{L}^{36}(\mu\text{-OH})(\mu\text{-urea})(\text{urea})$

$(\text{NCCH}_3)](\text{ClO}_4)_3$  (**44**) have been found to effect the hydrolysis of urea upon heating via a two-step reaction<sup>52</sup>. In the first step a molecule of ammonia is eliminated from urea with concomitant formation of cyanate. When the cyanate bearing product is further heated in the presence of water the cyanate is hydrolysed. Attempts to obtain crystals of the cyanate-containing product were unsuccessful but the reaction of **33** with  $\text{NaNCO}$  in EtOH gave  $[\text{Ni}_2\text{L}^{36}(\mu\text{-OH})(\mu\text{-OH}_2)(\mu\text{-OCN})]_2(\text{OTs})_4$  (**51**) which serves as an analogue for the intermediate and has been shown to consist of two dinuclear nickel units each endogenously bridged by the phthalazine ligand, a water molecule and a hydroxide anion. The two units were then linked together by two O-bridging cyanate anions. Taken together these results established a precedence for the hydrolysis of urea via a cyanate intermediate as an alternative mechanism for the urease-catalysed hydrolysis of urea.



In the proposed mechanism (Fig. 13) the overall reaction at the dinickel (II) centre is hydrolysis of urea to ammonia and carbon dioxide via formation of a

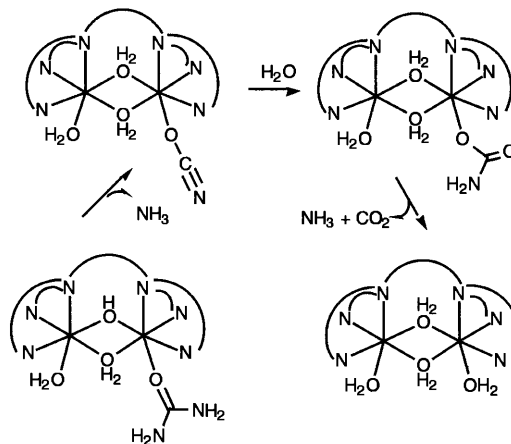


Fig. 13 An alternative mechanism for urea hydrolysis

cyanate intermediate and so contrasts with the route suggested in Fig. 2. Ammonia is first eliminated from the coordinated urea molecule, followed by hydrolysis of the resulting cyanate by an external water molecule. The coordination of urea to the dinuclear centre is critical and demonstrated by the rapid promotion of ammonia elimination by complexes **43** and **44** at a rate some 500 times as fast as the reaction between urea and a mononuclear centre or urea alone.

In a related series of experiments between **33** and N-methyl urea, N,N'-dimethyl urea, tetramethyl urea, and thiourea, N-methyl urea and N,N'-dimethyl urea reacted to form methylammonium cyanate and dimethylammonium cyanate respectively; thiourea gave ammonium thiocyanate after a longer reaction time<sup>52</sup>.

## 2.6 Concluding Remarks

The aim of this review was to illustrate the philosophy that it is possible to use the knowledge acquired from crystallographic studies on bimetallobiosites, in particular the dinickel(II) site in urease, for the generation of new coordination chemistry. To this end the site in urease is described together with the use of small molecule models for the site. In order to advance these studies novel unsymmetric dinucleating compartmental ligands have been derived and have provided a range of interesting coordination compounds. As well as the target dinuclear nickel(II) complexes, trinuclear and tetranuclear complexes have been found and open up an opportunity for studying the magnetic properties of oligomeric species, particularly as the synthetic route to the trinuclear species has proven to be generally applicable. Of significant interest to the modelling of the biosite has been the observation that cyanate can be readily produced by reaction of certain dinickel(II) complexes with urea. This has provided a new proposal for the mechanism of hydrolysis of urea by the metalloenzyme.

## 2.7 Addendum

Since this article was submitted further papers have been published concerning the subject area under review.

### (a) Unsymmetrical Ligands Bearing a Phenolic Spacer (section 2.2.2).

Tetranuclear nickel(II) complexes have been prepared from a new unsymmetric proligand having pendant arms bearing imidazole and carboxylic acid donor moieties leading to adjacent {N<sub>2</sub>O} and {N<sub>2</sub>O<sub>2</sub>} donor sets<sup>60</sup>. One of the complexes has been shown to coordinate urea via the carbonyl O atom. A dinuclear nickel(II) complex has been prepared from a new linear-dipodal proligand having adjacent {N<sub>2</sub>O} and {N<sub>3</sub>O} donor sets<sup>61</sup>. Fenton and co-workers have prepared new trinuclear nickel(II) complexes from proligands with adjacent {N<sub>2</sub>O} and {N, O, S} donor sets<sup>62</sup>. They have also extended the nuclearity range in oligonuclear nickel(II) clusters derived from unsymmetric compartmental ligands to include homopentanuclear nickel(II) complex bearing □<sub>3</sub>-OH bridges<sup>63</sup> and a heteropentanuclear (Ni<sub>4</sub>Na) complex<sup>64</sup>. Proligand HL<sup>N</sup> (Fig. 8) has been used to prepare a tetranuclear nickel(II) complex in which the iminic donor arm has been modified to give an amidic donor arm<sup>65</sup>; a mechanism invoking oxidation of the C-N bond of a carbinolamine has been proposed.

### (b) Unsymmetrical Ligands Bearing a Pyrazolate Spacer (section 2.2.3).

Mayer and co-workers have prepared new dinucleating pyrazole ligands with appended 1,4-diisopropyl-1,4,7-triazacyclononane pendant arms in the 3- and 5-positions<sup>66</sup>. These gave complex of formula {LNi<sub>2</sub>(H<sub>3</sub>O<sub>2</sub>)}(ClO<sub>4</sub>)<sub>2</sub> and [LNi<sub>2</sub>(OH)](BPh<sub>4</sub>)<sub>2</sub>. The former complex reacts with urea and N-substituted ureas to give products bearing N, O-bridging ureate anions. At high temperatures these lose NH<sub>3</sub> to give cyanate-bridged species. The first study of the equilibrium and kinetics of urea binding by a model dinickel(II) complex, [L<sup>32</sup>Ni<sub>2</sub>(OH)(H<sub>2</sub>O)]<sup>2+</sup>, has been reported<sup>67</sup>. The kinetic studies suggest that the binding of urea is a multi-step process and it is proposed that the OH<sup>-</sup> ligand in the complex acts as a base towards urea so forming the urea anion. In urease the OH<sup>-</sup> ligand acts as a nucleophile leading to the hydrolysis of urea.

\*Small molecule models have been classified as SPECULATIVE or CORROBORATIVE (HAO Hill *Chem Brit* **12** (1976) 119. A speculative model occurs when the structure of the microenvironment of the metal ion is unknown and the object is to reproduce some spectroscopic property of the metallobiomolecule using a simple complex. A corroborative model is used to try and directly imitate the coordination features of a structurally established site; the information recovered here can then be used to ascertain whether the properties of the site are dominated by interactions within the first coordination sphere of the metal.



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