

Redox Properties of Metal Complexes with Internal Hydrogen Bonding

A Thesis Submitted for the Degree of
Doctor of Philosophy

by

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Abstract

Synthetic models represent powerful tools to study how important reactions such as the oxidations of substrates are catalyzed in Nature by metalloproteins. An important aspect in this chemistry is the redox behaviour of the metal and of the metal bound substrate(s). So far, most efforts have been focused on mimicking enzyme active sites in terms of the metal first coordination sphere. The second coordination sphere and hydrogen bonding however play a crucial role and facilitate these key reactions; but to what extent and how is not known.

In this thesis we incorporate hydrogen bonding features NH_2 (Am), NHCH_2^tBu (Np), and NHCO^tBu (Piv) in the pyridine 6th position of the tripodal ligand TPA (tris(2-pyridylmethyl)amine, L). Thus, ten ligands $\text{L}^{\text{X-n}}$ (X = Am, Np, Piv; n = 0, 1, 2, 3) derived from and including TPA have been made. Also, ligands with one and two amino groups in a similar position of the ligand *N,N*-bis(2-pyridylmethyl)-*N*-(glycine)amine (BPG), (APPG and BAPG, one and two amino groups, respectively) have been made. The structures of several $[\text{LMCl}]^0 \text{ or } +1$ complexes (M = Zn(II), Cu(I), Cu(II)) were determined by X-ray crystallography ($[(\text{L}^{\text{Am-3}})\text{ZnCl}]\text{BPh}_4$, $[(\text{L}^{\text{Piv-3}})\text{CuCl}]$, and $[(\text{BAPG})\text{CuCl}]\text{Cl}$). All these complexes exhibit intramolecular N-H...Cl hydrogen bonding.

For the Zn(II)Cl complexes of the $\text{L}^{\text{X-n}}$ ligands, the main structural changes caused by hydrogen bonds are the lengthening of the Zn-Cl and the Zn- N_{Py} bonds and shortening of the Zn- N_{Ax} bond. In general, these changes are more significant when the number of hydrogen bonds increases, and vary according to their strength. In related Cu(I) and Cu(II) complexes, an important factor affecting the strength of

the N-H...Cl hydrogen bonds is the oxidation state of the metal centre. Thus, the N-H...Cl interaction is stronger in the Cu(I) oxidation state.

The $[(L^{X-n})CuCl]^+$ complexes were used to investigate the effect of the N-H...Cl hydrogen bonding on the redox properties of the metal centre. Cyclic voltammetry studies showed that the reduced state of the metal centre is stabilised when stronger and more numerous hydrogen bonds are introduced. The half wave potential of the Cu(II)/Cu(I) redox couple shifted to more positive values by 58 mV in $[(L^{Am-1})CuCl]^+$ to 541 mV in $[(L^{Piv-3})CuCl]^+$ relative to the TPA complex. We estimated by means of infra-red spectroscopy that in these complexes, hydrogen bonds can contribute as much as 30% to the stabilisation of the Cu(I) over the Cu(II) oxidation state. Also, despite the overall magnitude of this effect being greater in multiply hydrogen bonded systems, the individual contribution of each hydrogen bond towards stabilising the Cu(I) state is greater the fewer interactions.

The effect of hydrogen bonding on the redox properties of zinc-bound DTBC (3,5-di-*tert*-butylcatechol) in $[L^{X-n}ZnDTBC]$ complexes was also investigated. The X-ray structure of $[L^{Am-1}ZnDTBC]$ was determined and showed internal N-H...O hydrogen bonding. Cyclic voltammetry and spectroelectrochemical studies showed that the reduction of DTBC complexes occurs at more positive potentials in the presence of hydrogen bonds. For $[L^{Piv-3}ZnDTBC]$, the reduction of DTBC was facilitated by as much as 470 mV relative to the TPA complex, and is accompanied in this case by a binding enhancement of 3.9×10^6 fold. These changes are compared with those obtained by changing the metal or its coordination sphere and with hydrogen bonds alone.

The results presented in this work provide important insights into the possible role(s) of the active site microenvironment in regulating the activity of redox active metalloproteins and may contribute to the development of better synthetic models and more efficient catalysts.

To Filipa

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained in this thesis is the original work of my own research since the registration of the PhD degree in January 2004, and any collaboration has been clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Laurent Metteau

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Abbreviations

AIBN	2,2'-azobis(2-methyl-propionitrile)
Am	amino
APPG	<i>N</i> -(6-amino-2-pyridylmethyl)- <i>N</i> -(2-pyridylmethyl)- <i>N</i> -(glycine)amine
BAPG	<i>N,N</i> -bis(6-amino-2-pyridylmethyl)- <i>N</i> -(glycine)amine
BPG	<i>N,N</i> -bis(2-pyridylmethyl)- <i>N</i> -(glycine)amine
CCDC	Cambridge Crystallographic Data Centre
CSD	Cambridge Structural Database
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DTBC	3,5-di- <i>tert</i> -butylcatechol
DTBQ	3,5-di- <i>tert</i> -butylquinone
DTBSQ	3,5-di- <i>tert</i> -butylsemiquinone
NHE	normal hydrogen electrode
ESI-MS	electrospray ionisation mass spectroscopy
FT	Fourier transform
IR	infrared
L	ligand
MeCN	acetonitrile
MPA	Mulliken population analysis
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
Np	neopentylamino
NPA	natural population analysis
Piv	pivaloylamido
SCE	saturated calomel electrode
TPA	tris(2-pyridylmethyl)amine

Courses and talks

1. *Weekly Inorganic Section Seminars* during terms 2004-2007. Prize for the best First Year Presentation, 2004.
2. *Weekly School of Chemistry Colloquia* during terms 2004-2007.
3. *Induction Course for Laboratory Demonstrators in Chemistry*, Centre for Teaching, Learning and assessment, University of Edinburgh, 2004.
4. *Postgraduate Course on NMR spectroscopy* by Dr. D. Uhrin, University of Edinburgh, 2005.
5. *Supramolecular Chemistry* by Pr. B. Chaudrey, University of Edinburgh and University of St Andrews, 2006.

Poster presentations

1. Coordination Chemistry Discussion Group, University of Leicester, 2004.
2. Macrocyclic and Supramolecular Chemistry Discussion Group Meeting, University of Leeds, 2006.

Publications

(1) LZnX complexes of tripodal ligands with intramolecular RN–H hydrogen bonding groups: structural implications of a hydrogen bonding cavity, and of X/R in the hydrogen bonding geometry/strength, J. C. Mareque-Rivas, R. Prabakaran, R. Torres Martin de Rosales, L. Metteau and S. Parsons, *Dalton Trans.*, 2004, 2800.

(2) The strength of hydrogen bonding to metal-bound ligands can contribute to changes in the redox behaviour of metal centres, J. C. Mareque-Rivas, S. L. Hinchley, L. Metteau and S. Parsons, *Dalton Trans.*, 2006, 2316.

(3) Hydrogen Bonding Cavities Regulating Redox Behavior and Binding of Metal-Bound Ligands, L. Metteau, S. Parsons, and J. C. Mareque-Rivas, *Inorg. Chem.*, 2006, **45**, 6601.

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Chapter 1:

Introduction

1.1. Introduction

This work is concerned with creating and studying synthetic model complexes to get insights into the role of the metal centre second coordination sphere and hydrogen bonding interactions on the redox properties of metalloenzymes involved in dioxygen activation chemistry. The second coordination sphere of the metal and hydrogen bonding interactions can exert an effect on both the metal centre and metal-bound substrates. Both aspects are investigated separately. For this we use the tripodal ligand tris(2-pyridylmethyl)amine (TPA). In this chapter a brief introduction about hydrogen bonding will be provided along with an overview of its main characteristics and relevant applications. Then the metal binding properties and uses of the ligand framework TPA will be presented followed by its use in mechanistic studies concerned with dioxygen activation. The aims of this thesis are also described in this Chapter. Chapters 2-4 contain my PhD work.

1.2. Hydrogen bonding

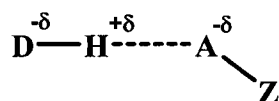
1.2.1. General features

The unusual behaviour of hydrogen bonded systems were observed long before the “hydrogen bond” obtained its name. Most of such observations date from the end of the 19th and the beginning of the 20th century. It was recognized that specific properties arise as a consequence of electrostatic interactions of a hydrogen

atom H, which is covalently bound to an electronegative atom D (denoted as proton donor), and another electronegative atom A (proton acceptor). Initially it was proposed that in these cases a “weak bond” had been formed. However, it was Linus Pauling who first used the term *hydrogen bond*:¹

“Under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms, instead of only one, so that it may be considered as acting as a bond between them. This is called the ‘hydrogen bond’”.

Scheme 1.1 illustrates a hydrogen bonding interaction between the electronegative donor atom (D) and an electronegative acceptor (A).



Scheme 1.1. Representation of a hydrogen bonding interaction (Z = any atom)

In the early investigations it was mainly strong hydrogen bonds that were studied, which involved the donor and acceptor being highly electronegative atoms, like halides, oxygen or nitrogen. A few decades later, the definition was broadened, allowing less electronegative atoms, like carbon, silicon, phosphorus, sulphur or even metals to be involved in hydrogen bonding.²⁻⁷

It should be noted that hydrogen bonds do not require the acceptor to bear a lone pair of electrons. Thus, regions of high electron density like aromatic rings or multiple bonds can act as hydrogen bond acceptors.⁸⁻¹³

The strength of this type of interactions is a consequence of hydrogen having solely one electron, which as the result of being attracted by the donor D leaves the

hydrogen nucleus available for the interaction with the electron cloud (lone pairs or π electrons) belonging to the acceptor A. The directionality of hydrogen bonds is governed by the electron density distribution around the hydrogen atom and the acceptor. Depletion of the electron density on the opposite side of the D-H bond favours a linear D-H $\cdots$ A hydrogen bonding arrangement. On the other hand, rich electron density around A in the direction of the lone pairs prefers a H $\cdots$ A-Z (Z = any atom) angle of around 110°. Such angular preferences have been revealed in hydrogen bonded systems both in the gas and solid phases.^{14,15} Even in crystals, where the angles can be distorted by other weak forces, linear D-H $\cdots$ A angles are statistically favoured over bent ones and the angular cut-off is usually set at >90°.¹⁶

Initially hydrogen bonds were thought to be purely electrostatic interactions in nature because electrostatic models often predict reasonable geometries for hydrogen bonded complexes. However, the nature of hydrogen bonds is now known to be much more complicated.¹⁷ Umeyama and co-workers estimated the contribution of various terms according to Equation 1.1:¹⁸

$$\Delta E = ES + PL + EX + CT + MIX \quad \text{Eq. (1.1)}$$

where ΔE is the stabilization energy gained in the dimer as compared to the monomer, ES is the electrostatic interaction, PL is the polarization interaction, EX is the exchange repulsion arising from the short distance between donor and acceptor atom, CT is the charge-transfer interaction and MIX a coupling term. In other words, hydrogen bonds are not a simple interaction but a complex conglomerate of at least four component interaction types: electrostatics (acid/base), polarization (hard/soft), van der Waals (dispersion/repulsion), and covalency (charge transfer). However of

these effects, electrostatic interactions are generally believed to play the largest role.¹⁹

1.2.2. Hydrogen bond strength

A common classification of hydrogen bonds is performed with respect to their energy, which distinguishes strong (15 - 40 kcal/mol), moderate (4 - 15 kcal/mol) and weak (1 - 4 kcal/mol) hydrogen bonds.²⁰

Strong hydrogen bonds are typically characterized by a small distance between the proton donor and the proton acceptor, which have ionic character.

Moderate bonds are the most common kind of hydrogen bonds. In this case the donor and acceptor atoms are typically neutral species. Medium to strong hydrogen bonds have been observed in the solid state, in solution and in the gas phase. In solution, if the solvent is polar, additional hydrogen bonds can be formed between the solvent and the solute molecules.

Weak hydrogen bonds are characteristic for complexes in the gas phase, but they have also been observed in crystal structures, for example in cases where the donor atom has only slightly higher electronegativity than the hydrogen atom (*e.g.* C or Si) and the acceptor possesses π electrons.

It should be mentioned that solvation plays an important, and sometimes major, role in determining the strengths of hydrogen bonds. Solvents with a strong attraction for either the hydrogen bond donor or acceptor will surround these components, preventing or affecting the interaction between them. Because of their

overwhelming stoichiometric excess, solvent molecules do not have to interact strongly to have drastic consequences in hydrogen bond formation.²¹

1.2.3. Identification of hydrogen bonds

Various techniques can be used to identify the presence of hydrogen bonds and also to evaluate their strength. In the solid phase, X-ray crystallography and neutron diffraction are the methods of choice. Locating the position of the hydrogen atom in a hydrogen bond gives unambiguous information on the existence and strength of the interaction, but this is generally difficult by X-ray diffraction studies. Thus, the sum of the van der Waals radii is commonly used as a convenient upper limit for a hydrogen bond distance.²² It is also accepted that protons within a 3 Å distance from a potential acceptor are involved in hydrogen bonding.

Infra-red spectroscopy can be used to prove the presence of hydrogen bonds in two ways. Since the interaction with a hydrogen atom decreases the electron density on the acceptor, it weakens the bond between the acceptor with other atoms.²³ Thus, in the presence of hydrogen bonds, the vibration frequency of this bond decreases. The shift of the D-H stretch in a molecule toward lower frequencies also gives evidence of its involvement in hydrogen bonding interactions.

NMR reveals the presence of hydrogen bonds through the strong deshielding of the hydrogen nucleus, which arises from the displacement of the centre of mass of the hydrogen atom. The signal corresponding to a hydrogen-bonded proton is shifted downfield relatively to a non hydrogen-bonded analogue.²⁴

Although the electrostatic character of hydrogen bonds dominates, the study of its charge-transfer component can be followed by UV-Vis spectroscopy.²⁵ Electronic transitions are affected by hydrogen bonding; for instance, hydrogen bonded carbonyl groups exhibit a blue shift in their $n\text{-}\pi^*$ transition and, usually, a red shift in the $\pi\text{-}\pi^*$ transition.

Finally, computational methods can also be applied to study hydrogen bonds.²⁶

1.2.4. Hydrogen bonding in Nature

Hydrogen bonds are ubiquitous in Nature. A consummate example is water. The water molecule can be seen as a molecule bearing a partial negative charge on the oxygen atom, and partial positive charges on the hydrogens. When two molecules of water are neighbouring, their regions of opposite charge attract each other. Thus, each hydrogen atom is linked to oxygen atoms through both an intramolecular covalent and an intermolecular hydrogen bond (Figure 1.1). The latter type of interaction gives water unusual properties such as an unexpectedly high heat of vaporization.

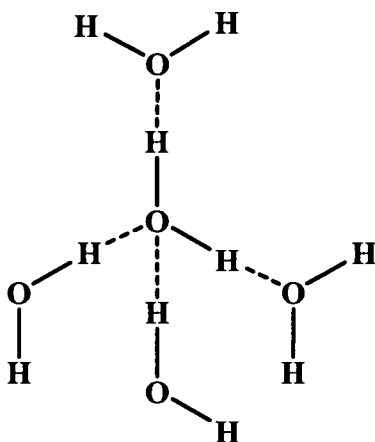


Figure 1.1. *Tetrahedral hydrogen bonding network in water.*

Although hydrogen bonds can be broken easily they play a very important role in determining the three-dimensional structure of chemical and biological systems as a consequence of their specificity and directionality. Macromolecules like DNA (Figure 1.2), proteins and cellulose owe their stable conformations to hydrogen bonding interactions.^{27,28}

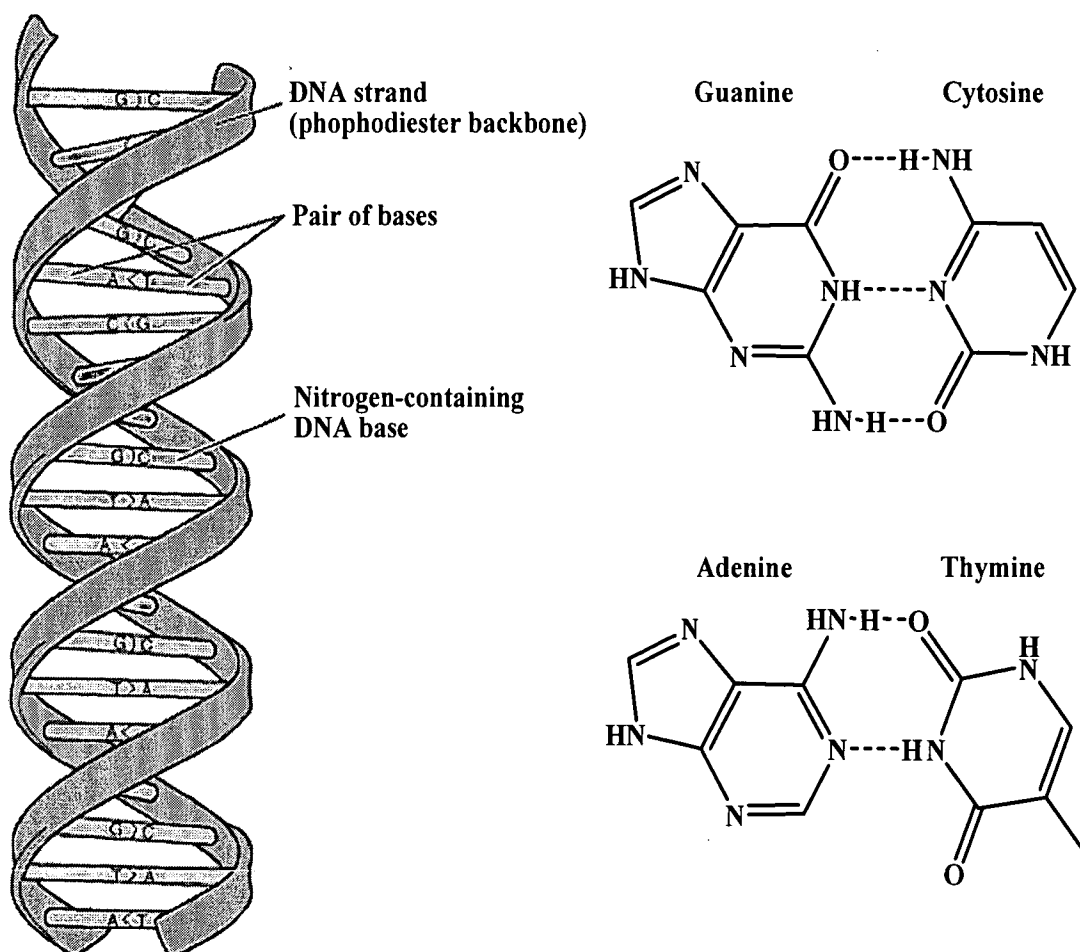


Figure 1.2. *Hydrogen bonding in DNA.*

Besides structural effects, hydrogen bonds influence certain biological processes by assisting enzymes to bind to substrates. Enzymes also need to bind strongly the transition state of the reaction to achieve effective catalysis.²⁸ Therefore bonding between the enzyme and the substrate/transition state must have two characteristics. It must be strong enough to recognise the substrate and stabilise the transition state, but at the same time weak enough to allow rapid release of the product. Natural enzymes achieve this difficult balance by providing functional groups for ionic, hydrogen bonding, and hydrophobic interactions. Unlike other

intermolecular forces, hydrogen bonds are directional, so multiple hydrogen bonds can be aligned in such a way to complement each other. This is often the case in enzyme active sites and results in the weaker binding of a 'less complementary' substrate than of the 'more complementary' transition state.

1.2.5 Hydrogen bonding in metal complexes

In metal complexes, hydrogen bonds can occur at different distances from the metal centre. Dance proposed the existence of three different domains of interaction.²⁹ At the metal site is the 'metal domain', where the metal acts as the hydrogen bond donor³⁰ or acceptor (Figure 1.3).³¹

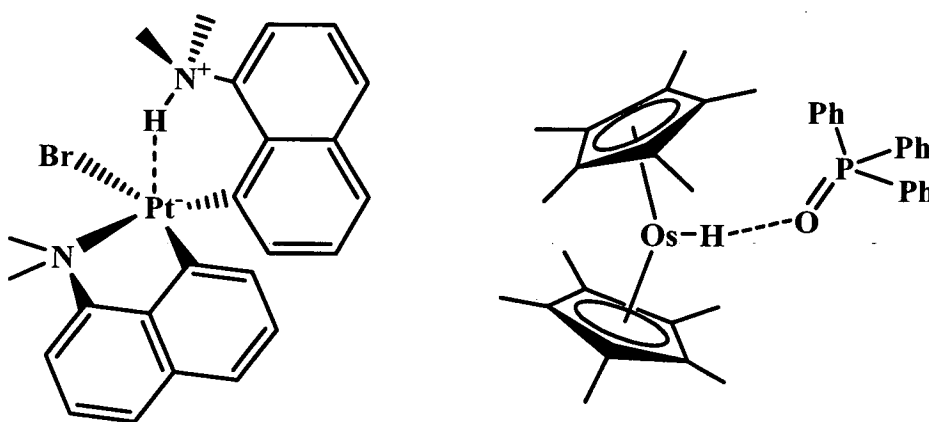


Figure 1.3. Metal centre as hydrogen bond acceptor (left) and donor (right).

In the 'ligand domain', hydrogen bonding occurs at a metal-bound ligand, or at a ligand that is strongly interacting with the metal (Figure 1.4). In this domain, the

metal centre alters the electronic properties of the hydrogen bond donor and/or acceptor.

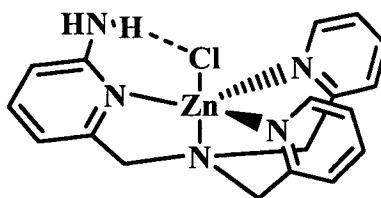


Figure 1.4. *Hydrogen bonding in the ligand domain.*

Thus, the hydrogen bond donating ability of the donor is increased by the electron withdrawing effect due to metal coordination. In contrast, the hydrogen bond acceptor can be rendered a better hydrogen bond acceptor by π back-donation from the metal centre. In both cases, the hydrogen bonds are strengthened.²² These types of interactions are of particular relevance to metalloprotein chemistry, where hydrogen bonding to metal-bound substrates and protein function have in some cases been correlated.

Finally, hydrogen bonding can also occur further away from the metal centre ('periphery domain', Figure 1.5). The role of the metal centre in this case is not so much to affect the electronic properties of the hydrogen bond donor and/or acceptor, but to preorganise the hydrogen bond donor and acceptors.³² Consequently, this type of system behaves mainly like organic compounds.

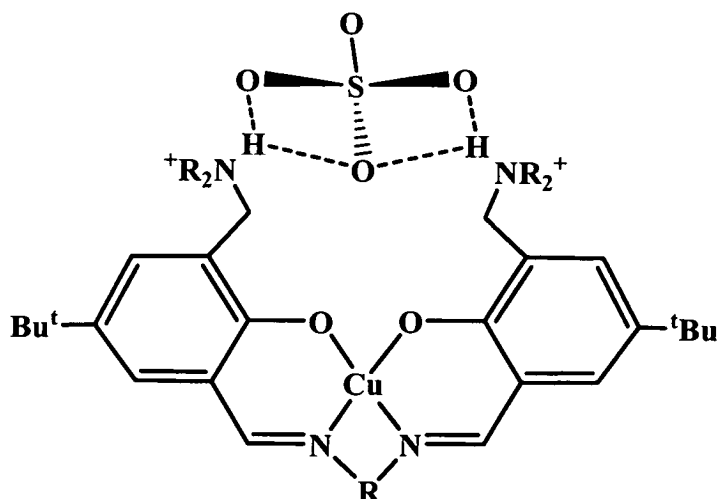


Figure 1.5. *Hydrogen bonding in the periphery domain.*³³

As mentioned above, it has been shown that metal-bound ligands can be made better acceptors by metal coordination. This is true, in particular for chloride anions.³⁴ Brammer and co-workers used the Cambridge Structural Database to examine the strength of hydrogen bonding to chlorine on a structural basis. They noted that in contrast to the C-Cl moieties, metal-chloride systems are good hydrogen bond acceptors. For instance, 60 % of the M-Cl complexes exhibit short H...Cl distances with a nitrogen hydrogen bond donor and 85 % with an oxygen hydrogen bond donor. Thus, it occurred to us that the use of chloride anions as hydrogen bond acceptors would be particularly suitable to study the effect of hydrogen bonds on the redox properties of metals.

1.2.6. Applications

1.2.6.1. Host-guest chemistry

The field of molecular recognition frequently utilizes hydrogen bonding to create host:guest systems. These exploit both the directionality and strength of hydrogen bonds to achieve strong and selective recognition.³⁵ An example of a synthetic receptor which utilizes hydrogen bonds as the basis for association is shown in Figure 1.6. This macrocyclic host from Hamilton *et al.* employs two diamido-pyridines to surround and capture a barbiturate with six hydrogen bonds.³⁶

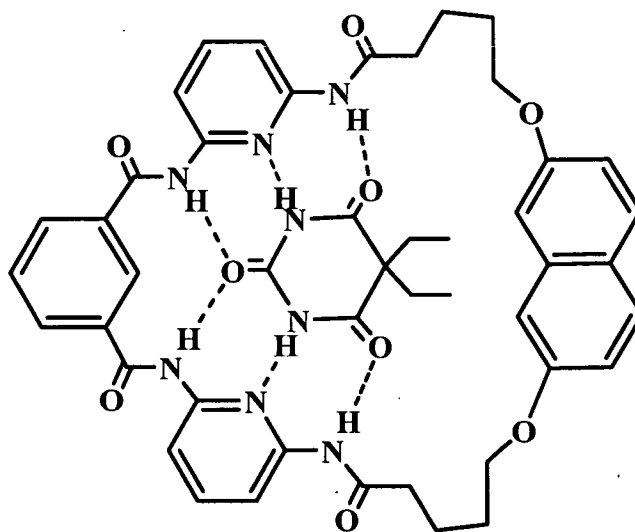


Figure 1.6. Hamilton's host:guest system.

This type of receptor has been used to evaluate the influence that the number of hydrogen bonding interactions has on the binding of the barbituric acid guest molecule represented in Figure 1.7.

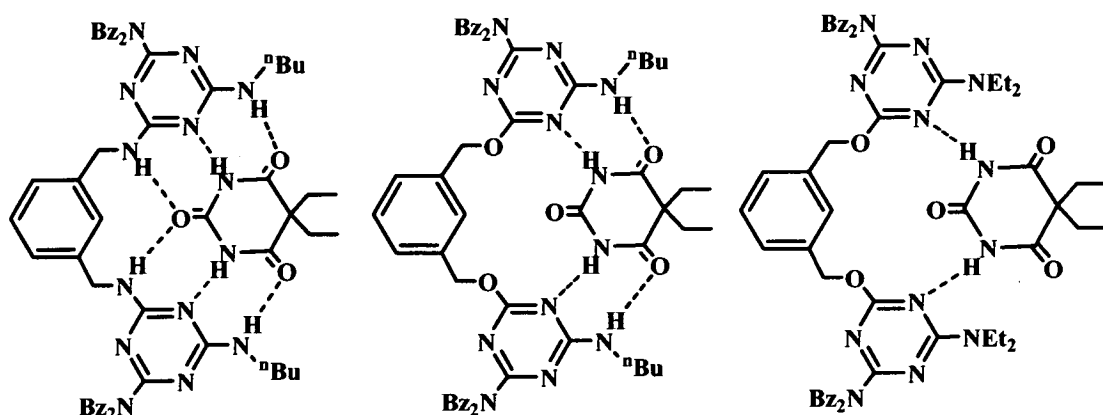


Figure 1.7. *Receptor:barbital host:guest systems with various hydrogen bonding number.*

In the system with six hydrogen bonding interactions (Figure 1.7, left), it was shown that the binding constant is $1.8 \times 10^5 \text{ M}^{-1}$. The binding constant decreases to 140 M^{-1} when only four interactions are present (Figure 1.7, middle), and could not be measured when only two interactions are possible (Figure 1.7, right). In this case, the formation of the host:guest adduct is weaker due to the fact that barbital self-assemble through two hydrogen bonding interactions with a binding constant of 14 M^{-1} .³⁷

The strength of hydrogen bonds not only depends on the number of interactions but also correlates with the acidity and basicity of the proton donors and acceptors, respectively.³⁸ More recently, it has been shown that the arrangement of donors and acceptors can also affect the overall stability of the hydrogen-bonded complex.³⁹ ‘Secondary interactions’ that occur between adjacent donors and acceptors on the opposite molecule can either augment or decrease the strength of the primary hydrogen bonds. The possible arrangements for a triply hydrogen bonded system are shown in Figure 1.8.

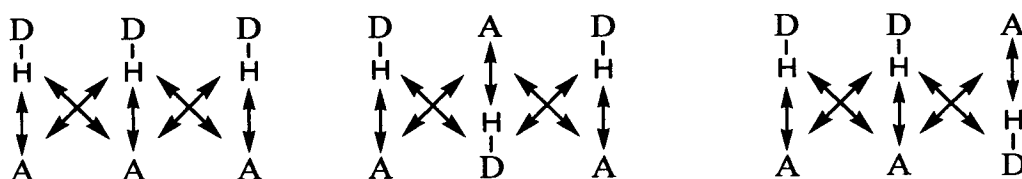


Figure 1.8. Schematic representation of a triply hydrogen bonded adduct with attractive interactions (black) and repulsive secondary interactions (red).

In organic host:guest systems, changes in the electrostatic and geometric properties of the host molecule have allowed tuning the selectivity of the interactions to generate systems that can reversibly associate, when affected by an external stimulus. Since hydrogen bonds are predominantly electrostatic in nature, they are greatly affected by changes of electron density in their vicinity. Thus, this stimulus can be for instance a change of redox state.^{40a,b} For instance, the reduction of the phenanthrenequinone moiety in Figure 1.9 (top) increases the binding of the guest molecule by at least 3000 fold. Another possible stimulus is irradiation with UV light (Figure 1.9, bottom), which by changing the conformation of the host molecule, can make the hydrogen bonds between host and guest more or less favourable.^{40c} For example, the *trans* isomer in Figure 1.9 (bottom) exhibits an affinity constant 3.5 times lower for a specific dicarboxylic acid guest molecule than the *cis* isomer. This has considerable potential for the synthesis of novel molecular shuttles, switches and logic gates, as well as biological sensors.

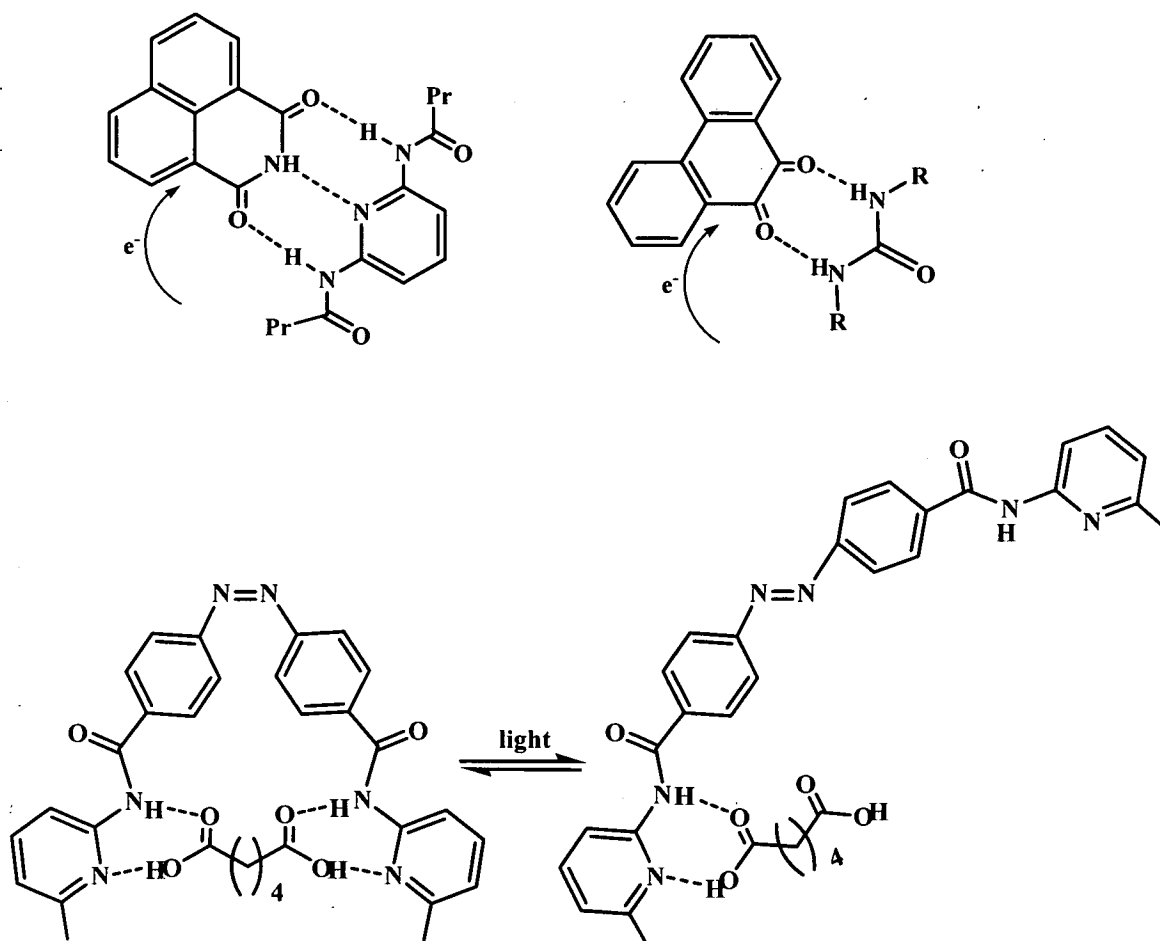


Figure 1.9. Examples of substrate binding modulated by redox chemistry (top) and UV irradiation (bottom).

Similarly in metal complexes the strength of hydrogen bonds can be affected by the oxidation state of the metal centre (Figure 1.10). The binding of phosphates by the two gold nanoparticles illustrated in Figure 1.11 was dramatically increased upon oxidation of the ferrocenyl moiety. Astruc *et al.* attributed the 6000 fold enhancement of $H_2PO_4^-$ binding in the Fe(III) complex to the increased positive charge on the iron cation, which in turns renders the amido proton more acidic.⁴¹

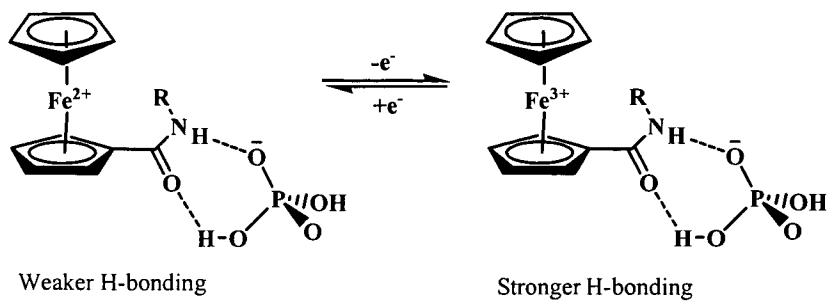


Figure 1.10. Increased phosphate binding by oxidation of the metal centre.

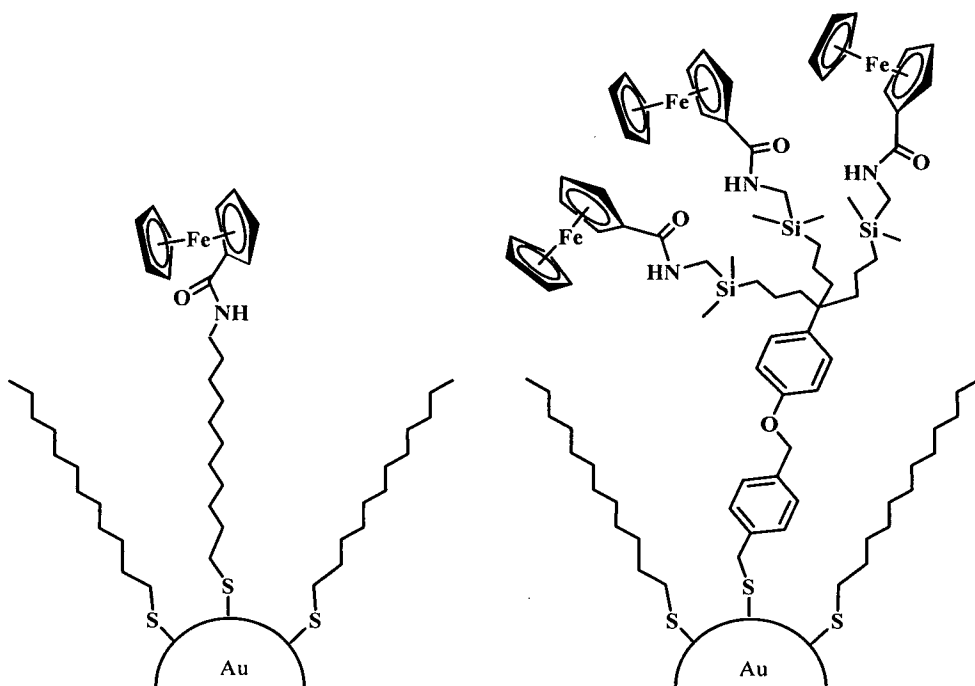


Figure 1.11. Gold nanoparticles where binding of anions through hydrogen bonding can be controlled by the oxidation state of the Fe centre.

1.2.6.2. Catalysis

Research fields such as catalysis are developing a growing interest in metal-free systems for economic and environmental reasons. The use of catalysts exploiting hydrogen bonding is seen as an attractive alternative to metal-based catalysts for reactions such as Friedel-Crafts substitutions and Diels-Alder cycloadditions.⁴² So far the catalytic acceleration achieved with these catalysts is smaller than with metal-based catalysts but they demonstrate that hydrogen bonds alone can be used in catalysis. For example, some systems can achieve metal-free Diels-Alder cycloadditions, where Lewis acid activation of a carbonyl group is important (Figure 1.12).

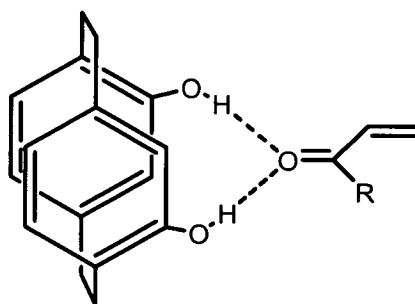


Figure 1.12. Carbonyl activation by hydrogen bonds.

Another example of metal-free catalysis mediated by hydrogen bonding is the Baeyer-Villiger reaction, as illustrated by Figure 1.13, where the addition of acetic acid to the reaction between peracetic acid and acetone leads to a hydrogen bonded network between these components.

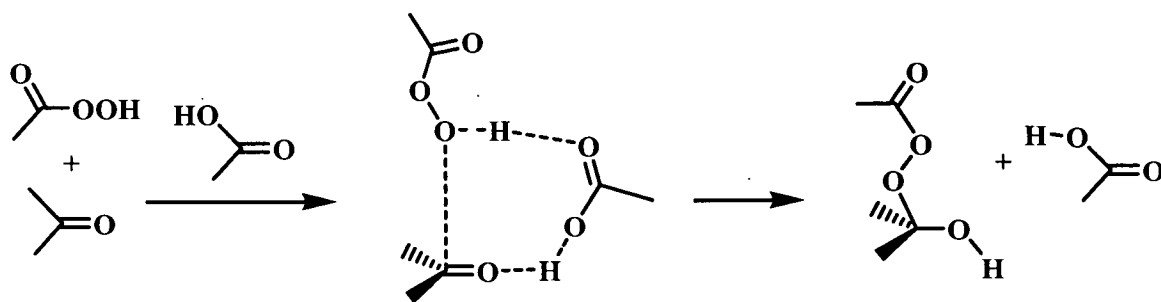


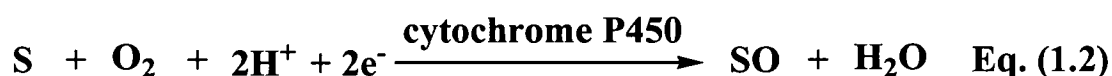
Figure 1.13. *Hydrogen bond catalyzed Baeyer-Villiger reaction.*

Since in Nature the combination of metal ions and hydrogen bonding interactions provides highly efficient catalysts, it is interesting to synthesize complexes which would benefit from both metal coordination and second sphere hydrogen bonding interactions as a way of getting even more efficient catalysts. In addition, these complexes can be used to improve our understanding of catalysis by metalloenzymes.

1.2.6.3. Hydrogen bonding in metalloenzymes and synthetic models for dioxygen activation

X-ray diffraction studies of the active site of cytochrome c peroxidase have revealed that hydrogen bonds exist between an arginine residue and the iron-oxo centre.⁴⁴ The activity of other enzymes such as horseradish peroxidase, bleomycin and methane monooxygenase has also been shown to present functionally important hydrogen bonding features.⁴⁵⁻⁵⁰ Among the enzymes involved in dioxygen activation, cytochrome P450s have been by far the most studied, and serve as a model for this chemistry.

Cytochrome P450s are capable of catalysing the hydroxylation of saturated carbon-hydrogen bonds, the epoxidation of double bonds and the oxidation of heteroatoms, to name only a few reactions. To catalyse these important and wide ranging transformations, cytochrome P450s insert one of the oxygen atoms of dioxygen into the substrate S, and reduce the second oxygen atom to a molecule of water (see Equation 1.2). In this process two electrons are provided by a reductase protein.⁵¹



Since only one of the oxygen atoms of dioxygen is transferred to the substrate, these enzymes are called monooxygenases.

The first step of the catalytic cycle is dioxygen binding to the metal centre. Triplet dioxygen reacts with ferrous cytochrome P450 to produce a η^1 -superoxide anion coordinated to a ferric centre. Groups in the second coordination sphere of the iron(III) centre donate hydrogen bonds to the distal oxygen atom of this dioxygen adduct. These hydrogen bonds are provided by the solvent medium and/or by the amino-acid residues present within the active site, and seem to stabilize the dioxygen adduct formed.

The next step involves proton and electron transfer processes. Proton coupled electron transfer events are involved in the structure and function of a broad range of natural systems, and hydrogen-bonding interactions appear to regulate the active site for this reactivity through the use of amino-acid chains and/or solvent water molecules as proton shuttles.^{52,53}

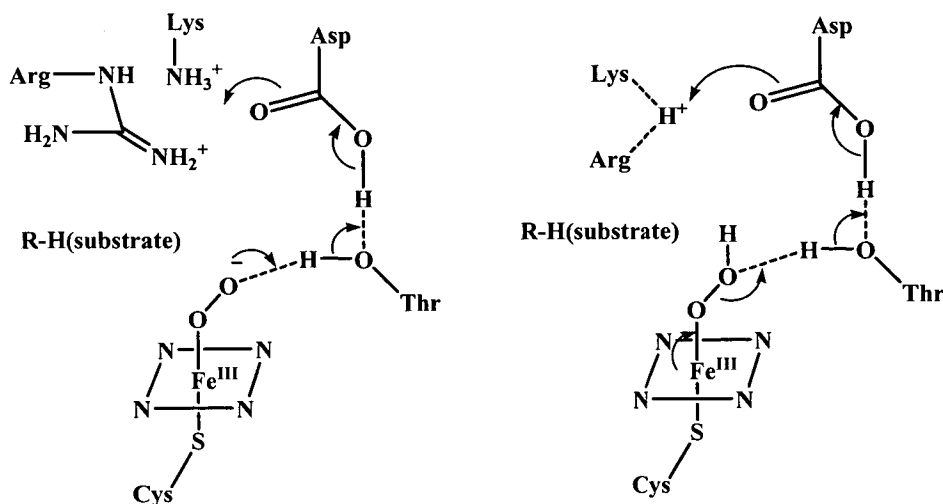


Figure 1.14. *Involvement of hydrogen-bonded networks in the protonation steps of cytochrome P450s catalytic cycle.*

In the active site of cytochrome P450s, the close interaction of a threonine with an aspartic residue creates a hydrogen bond network, which allows two fast proton transfers from the protonated forms of lysine and arginine. Breaking this network via the mutation of Asp or Thr changes the activity of the enzyme considerably,^{54,55} and sometimes even prevents any oxidation of the substrate. The second protonation step generates the postulated catalytically active high valent iron-oxo species. It should be noted that due to the protonation step being fast, the intermediates shown in Figure 1.14 are short-lived, and the nature of the oxidising species in cytochrome P450 is still a matter of debate.

For three decades, metalloporphyrin complexes have been made and used as cytochrome P450s models. Earlier work focused on elucidating the importance of the heme groups, and of thiolate ligation to the heme. This has allowed the isolation and full characterisation of some postulated intermediates.⁵¹ More recently attempts have been made to investigate the effect of the active site microenvironment, specifically

those arising from hydrogen bonding. In that respect, recent work has shown that hydrogen bonding groups around a synthetic porphyrin can stabilise metal-dioxygen adducts (Figure 1.15, left).⁵⁶ Moreover, hydrogen-bonding scaffolds have also been made to study the proton-coupled electron transfer events (Figure 1.15, right). These studies have shown that hydrogen bonding can participate in acid-base chemistry to provide kinetic control of proton transfer and bond polarisation for heterolytic O-O bond cleavage.⁵³

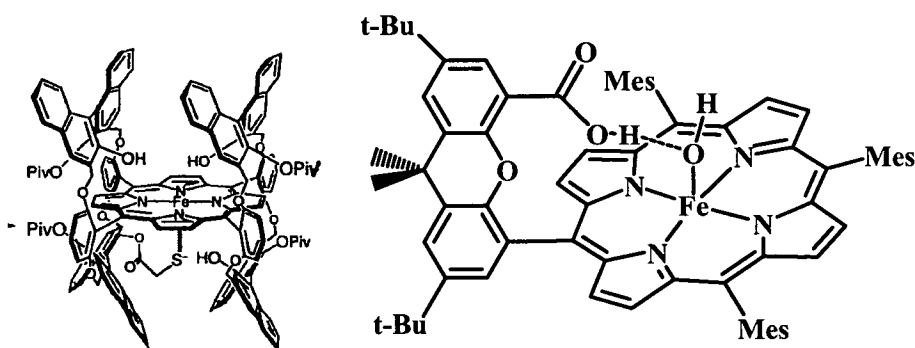


Figure 1.15. *Synthetic porphyrins with hydrogen bonding cavities*

Numerous non-heme monometallic synthetic metal complexes containing dioxygen derivatives have been synthesized and fully characterised; some of which successfully mimic structural, spectroscopic and/or functional properties of the active site of monometallic non-heme oxygenases. In that respect, tris[*(N'*-*tert*-butylureayl)-*N*-ethylene]amine (H_6buea , Figure 1.16) developed by Borovik *et al.*⁵⁷⁻⁶¹ has provided important results. This urea-functionalised tripodal ligand binds to a metal ion after deprotonation of the three αNH units. Upon metal ion binding, the ligand provides a rigid framework, which promotes intramolecular hydrogen bonds to external axially-bound ligands. The position of the α' nitrogen donors is of importance, since it forms thermodynamically favoured six-membered rings upon

hydrogen bond formation. Recently, the dioxygen activation chemistry of iron and manganese complexes of this ligand has been investigated. It was found that the α' NH and *tert*-butyl groups serve as functional elements for the steric and hydrogen bond stabilisation of metal-oxo and hydroxo units using dioxygen and/or water as O-source⁵⁷⁻⁶¹ (Figure 1.17). Importantly, prior to this work, the ferrate ion, FeO_4^- , was the only example of a stable mononuclear iron-oxo complex.

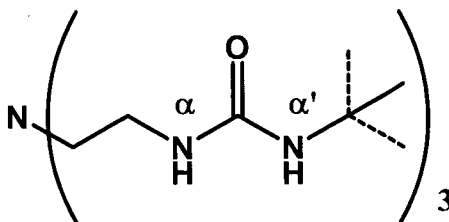


Figure 1.16. Urea-based tripodal ligand *H₆buea*.

The use of these ligands has led to isolating key intermediates in dioxygen activation, either from water or directly from dioxygen.

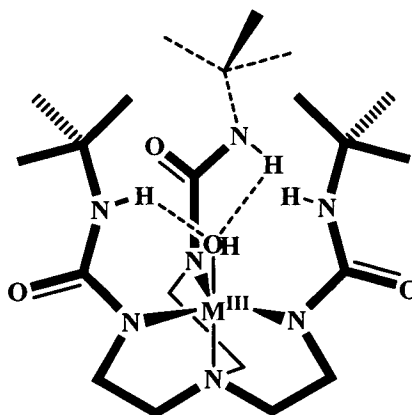


Figure 1.17. Structure of *M-O(H)* complexes stabilized by hydrogen bonding interactions (*M*=Mn, Fe).

Another ligand which has been widely used to investigate the effect of hydrogen bonding interactions in metal-dioxygen activation chemistry is tris(2-pyridylmethyl)amine-based (TPA), and ligands derived from it. The characteristics and applications of this ligand will be discussed later in this chapter

1.3. The ligand tris(2-pyridylmethyl)amine (TPA)

The coordination chemistry of tripodal ligands has considerable potential in many fields in chemistry. For example, they are essential constituents of many bioinorganic model compounds and catalysts.^{62,63} Among those, tris(2-pyridylmethyl)amine (TPA) and its derivatives are arguably one of the most extensively used. A search of the literature using Scifinder Scholar reveals that over 200 publications have used the unsubstituted TPA ligand, and over 3800 have involved TPA derivatives and their metal complexes.

The TPA ligand was introduced in 1967 by Anderegg and Wenk.⁶⁴ Since then, it has been widely used for many different purposes. A schematic representation of the ligand framework is shown in Figure 1.18.

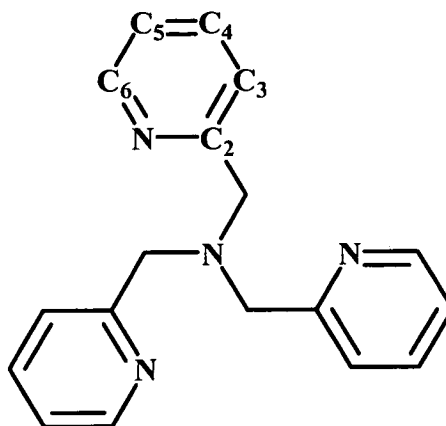


Figure 1.18. Representation of the TPA ligand and its numbering scheme.

1.3.1. TPA derivatives

Many modifications have been made to alter the properties of the TPA ligand. In particular, the nature of groups in the pyridine 6th position is crucial since the effect of several different R groups in these positions can be investigated relatively quickly. For instance, alkyl, aryl, halogen, hydroxy, and a range of NH hydrogen bond donor groups can be introduced in this position.⁶⁵⁻⁷⁵ The alkyl chains between the central nitrogen and the pyridyl groups can be longer, or can carry a chiral centre. Substitution of the pyridine 5th positions are less common, but recently, groups reported metal complexes of TPA with functionalities such as nitro, ester or methyl groups in that position. Some of these TPA derivatives are presented in Figure 1.19.

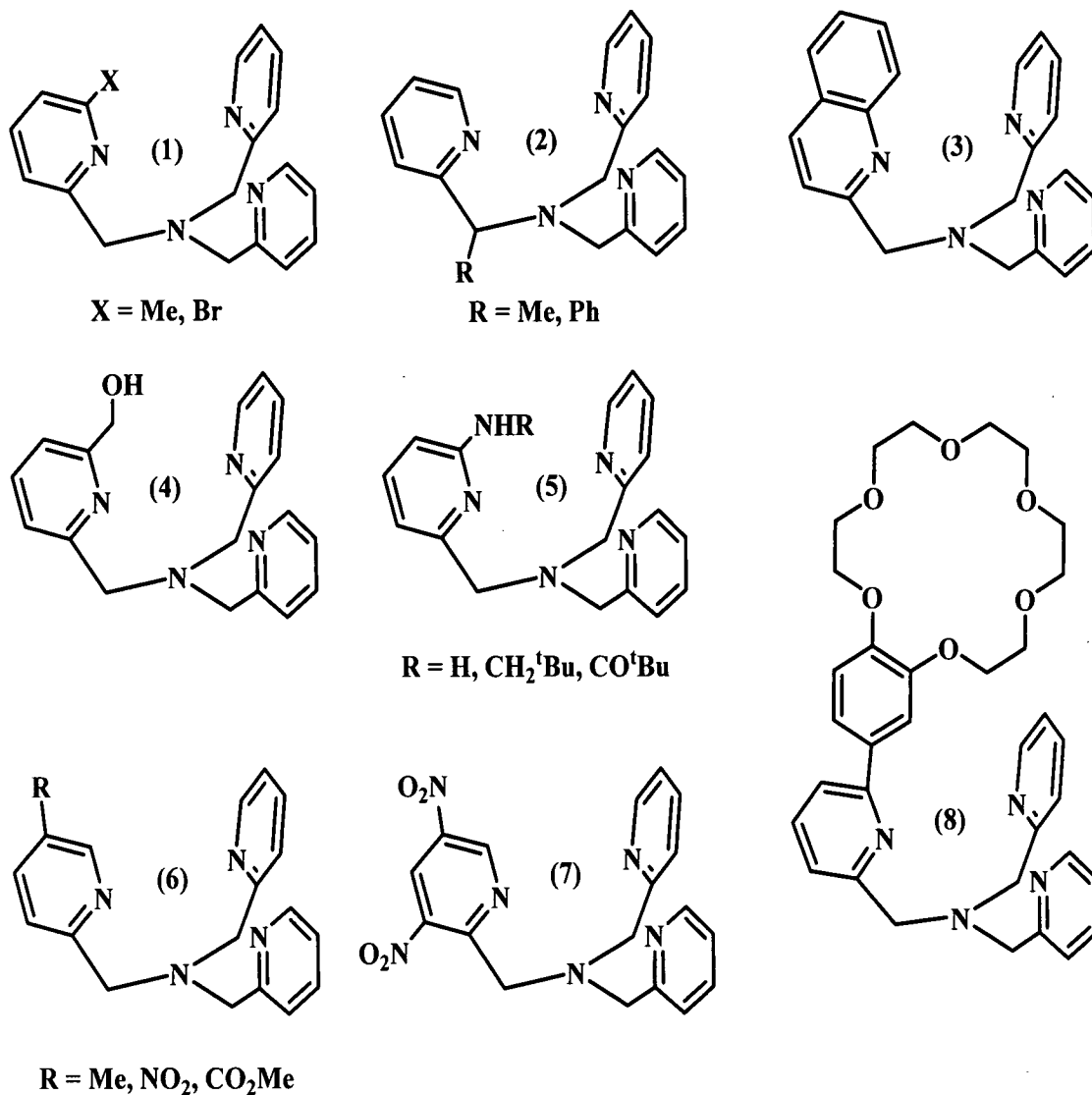


Figure 1.19. Representation of some TPA derivatives. References: (1) $X = \text{Me}^{65}$, $X = \text{Br}^{70}$; (2)⁷¹; (3)⁶⁸; (4)⁷²; (5)⁹; (6) $R = \text{Me}^{73}$, $R = \text{NO}_2^{74}$, $R = \text{CO}_2\text{Me}^{75}$; (7)⁷⁵; (8)⁷⁰.

These modifications allow changing features like the steric requirements, electronic properties, and geometry of the corresponding metal complexes. Important for biomimetic work is that the nitrogen atoms of the pyridine rings mimic histidine residues forming the primary coordination sphere of the metal in many oxygenases.

1.3.2. Complexes of TPA

The N₄ poly-dentate nature of the TPA ligand leads to stable metal complexes, while leaving empty coordination sites available for exogenous ligands. It allows binding to many metals, in various oxidation states.⁷⁶⁻⁸¹ Although most TPA complexes involve first row transition metals, second and third row transition metals have also been shown to bind to TPA and to its derivatives. A search of the Cambridge Structural Database reveals that structurally characterized complexes of TPA exist for as many metal centres as V, Cr, Mn, Re, Fe, Ru, Os, Co, Rh, Ir, Ni, Cu, Zn, Nd, Eu, Tb, Lu and U.

Most TPA complexes exhibit a pentacoordinate arrangement, in a trigonal bipyramidal or square pyramidal fashion. An additional exogenous ligand, typically a solvent molecule or an anion (Cl⁻, N₃⁻, etc...) lies in the remaining coordination site. Hexacoordinate complexes of TPA arise in general from the binding of a bidentate ligand, for instance a dioxolene unit, which chelates the metal centre to generate an octahedral complex.⁸²⁻⁸⁶ Alternatively, two other monodentate anions or solvent molecules can occupy an axial and an equatorial position.^{87,88} Tetracoordinate complexes of TPA or related ligands are also known, and they are encountered when exogenous ligands are absent⁸⁹ or when one of the pyridine rings is not bound to the metal centre.⁹⁰ Examples of different coordination modes found for TPA derivatives are illustrated in Figure 1.20.

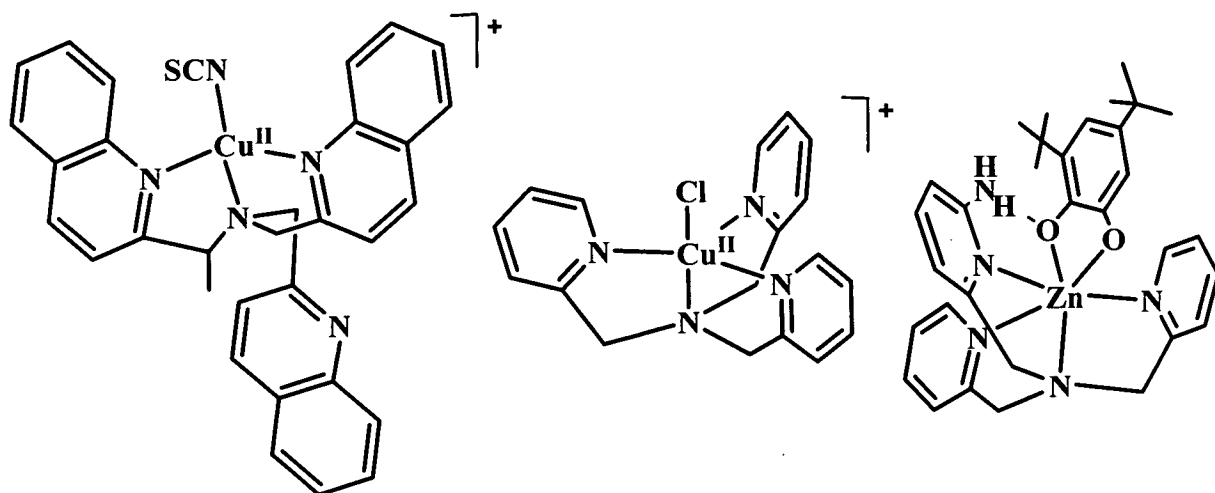


Figure 1.20. Representation of tetracoordinate (left),⁹⁰ pentacoordinate (middle)⁹¹ and hexacoordinate (right)⁹² TPA complexes.

Another interesting feature of TPA derivatives is that they lead not only to mononuclear but also polynuclear (typically dinuclear) complexes. This is important because in some cases the presence of two metal centres instead of one can increase the catalytic efficiency if the metals work cooperatively. However, it is useful to prevent dimerisation in order to obtain metal complexes which model the active site of monometallic enzymes. This is illustrated by the fact that TPAZnOH dimerises to form $[\text{TPAZn}(\mu\text{-OH})_2\text{ZnTPA}]^{2+}$, whereas the introduction of two or more neopentylamino groups in the pyridine 6th position affords a mononuclear LZnOH metal complex.^{93,94}

1.3.3. Biomimetic chemistry of TPA derivatives relevant to dioxygen activation

Studies of TPA-based metal complexes in relation with dioxygen activation have made significant contributions towards understanding how metalloenzymes achieve this chemistry. The use of structural and functional models for mono- and dinuclear active sites which contain iron, copper or manganese sites as dioxygen activation centres has been crucial in elucidating the role of parameters such as the spin state of the metal centre, the nature and structure of catalytically active intermediates, and more recently the second coordination sphere.⁹⁵⁻⁹⁸

The role of the spin state (e.g. low-spin or high-spin) of the metal centre was investigated through the use of 6-methyl-pyridine rings, which tends to favour the high-spin state of iron complexes.⁹⁹ This applies to the ferrous and ferric oxidation state. Comparison of the low-spin $[\text{Fe(III)(TPA)(OO}^t\text{Bu)}]^{2+}$ and the high-spin $[\text{Fe(III)(6-Me}_3\text{-TPA)(OO}^t\text{Bu)}]^{2+}$ analogue show a stronger Fe-O bond and a weaker O-O bond in the low-spin case. Importantly, the reactivity of high- and low-spin Fe(III)-OOR intermediates was shown to be different, highlighting the importance of the ligand environment in tuning the spin state of the metal centre and thereby its reactivity. In that respect, the TPA catalyst prefers to oxidise electron-rich olefins, whereas the 6-Me₃-TPA catalyst prefers to oxidise electron deficient olefins (Figure 1.21). These results have been interpreted in terms of the generation of an electrophilic oxidant for the former and a nucleophilic oxidant for the latter. It has also been shown that in the low spin state, Fe^{II} catalysts perform highly stereoselective alkane hydroxylation, olefin epoxidation and cis-dihydroxylation. In

contrast, high spin systems favour cis-dihydroxylation with lower selectivity.¹⁰⁰ The same type of alkane hydroxylation can be performed with other metals like Ru¹⁰¹ and Ni.¹⁰²

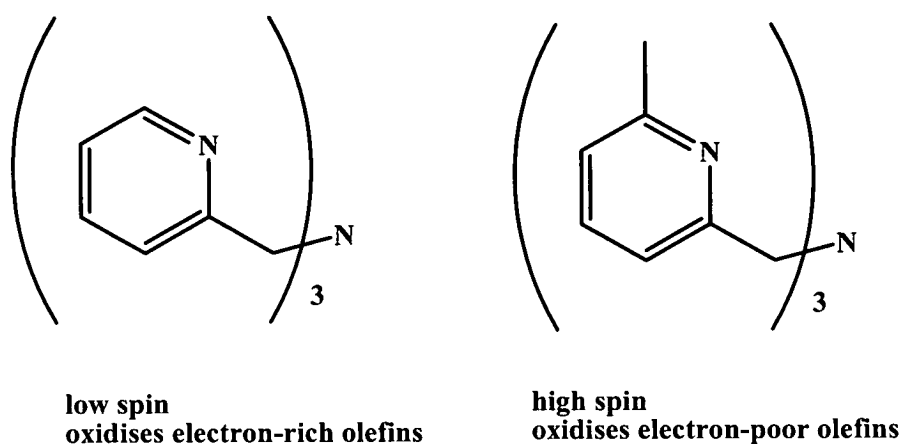


Figure 1.21. *Low-spin versus high spin reactivity.*

Approaches to modelling arene hydroxylases have involved the incorporation of the target arene in the pyridine 6th position of TPA.

Iron-catalysed arene hydroxylation reactions are important functional models of the pterin-dependant monometallic non-heme hydroxylases. These studies have established the nature of the metal-oxo oxidant. Thus, treatment of $[\text{Fe}(\text{6-Ph-TPA})(\text{NCCH}_3)_2]^{2+}$ with 1.5 equiv. of $t\text{BuOOH}$ in acetonitrile solution results in *ortho*-hydroxylation of the phenyl substituent in 87% yield (Figure 1.22).¹⁰³

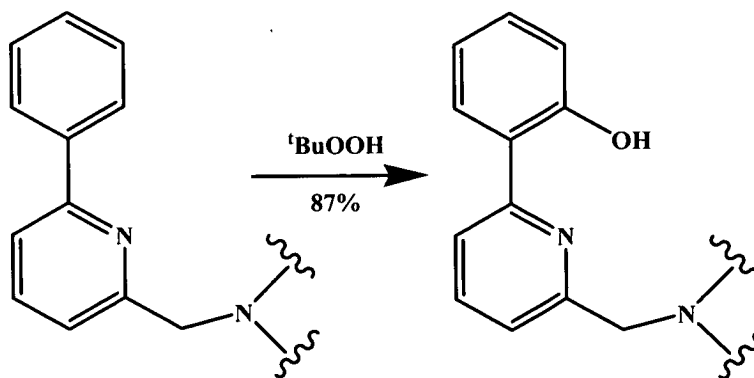


Figure 1.22. Conversion of the phenyl-TPA to the ortho-hydroxo derivative.

TPA-based systems have been found to mimic the function of catechol oxidases, that is, to oxidise a catechol moiety to its quinone form or to other oxygenated compounds, as shown by many publications by Que and others.¹⁰²⁻¹⁰⁷ Studies of the oxidation of ferric catecholate coordination complexes of Fe(III) have been useful in exploring mechanistic possibilities for catechol dioxygenases.¹⁰⁴ A series of ferric complexes of 3,5-di-*t*-butyl-catechol (DTBC) with different ligands *L* have been found to react with dioxygen to give oxidation of the catechol ligand. Modifications of the electronic properties of the ligand were found to affect the Lewis acidity of the metal centre, and this was correlated with the reactivity of the *L*Fe(III)DTBC complexes with dioxygen.¹⁰⁵⁻¹⁰⁷ Thus the more Lewis acidic the metal centre is, the more efficient the catalyst was found to be (in terms of both speed and yield). Among the various ligands used, TPA proved to generate one of the fastest and most efficient catalysts for the intradiol cleavage of DTBC, which was more than 10⁵ fold faster than the 6-Me₃TPA analogue.¹⁰⁸ In fact, the TPAFe(III)DTBC complex cleaves the otherwise unreactive chlorocatechol.¹⁰⁹

Recently, the effect of hydrogen bonding microenvironments was investigated through modifications of the pyridine 6th position, and provided important results. For example, the first structure of a mononuclear six-coordinate hydroxo-iron(III) complex was obtained using the ligand tris(6-neopentylamino-2-pyridylmethyl)amine (TNPA) (Figure 1.23).

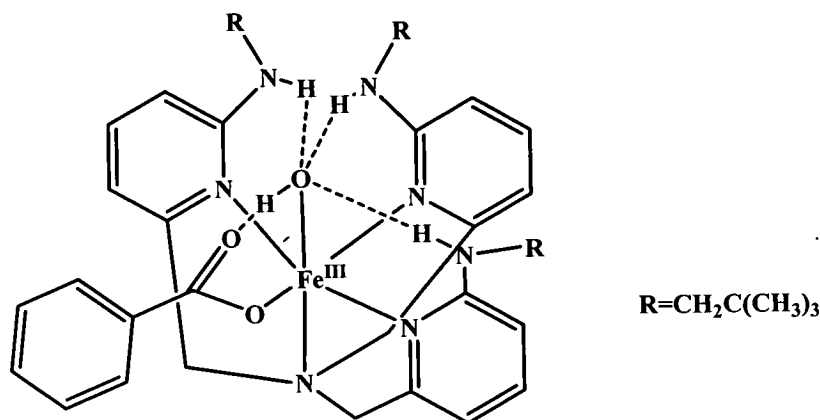


Figure 1.23. The six-coordinate iron(III)-hydroxo complex of TNPA.¹⁰³

Similarly, the first fully characterised (spectroscopically and structurally) hydroperoxo-copper(II) complex was that of $[\text{Cu}(\text{BPPA})(\text{OOH})]^+$ (BPPA = bis(6-pivalamide-2-pyridylmethyl)-(2-pyridylmethyl)amine) (Figure 1.24). In both cases it was claimed that intramolecular N-H $\cdots$ O hydrogen bonding exerts a stabilising effect.

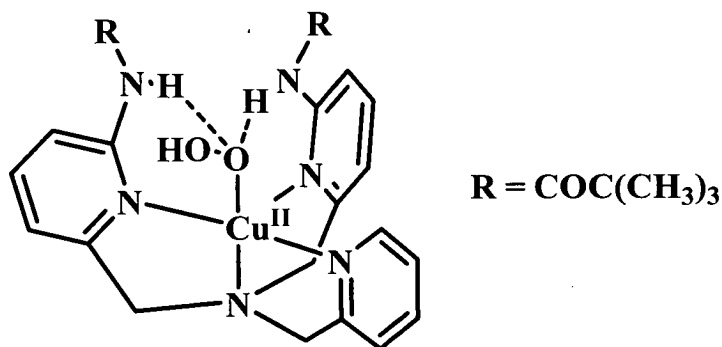


Figure 1.24. *The hydroperoxo-copper(II) complex.*¹¹⁰

1.4. Aims

The involvement of DH groups (D = N, O) of amino acid residues in hydrogen bonding interactions to metal-bound ligands is ubiquitous in redox metalloproteins. Many of these interactions are functionally important, but the mechanistic details regarding their precise roles remain unclear.

The main objective of this thesis is to use synthetic models to investigate how and to what extent hydrogen bonding interactions affect the redox properties of non-heme metalloproteins. In this context, the specific aims are the following.

1. To study the effect of hydrogen bonds on the redox properties of the metal centre itself.
2. To investigate and quantify the effect of hydrogen bonds on the redox properties of electroactive metal-bound substrates.

3. To elucidate the factors that influence the strength of hydrogen bonds in metal complexes with different oxidation states.

1.5. References

1. L. Pauling, "*The Nature of the Chemical Bond*", Cornell University Press, New York, 1939.
2. G. R. Desiraju and T. Steiner, '*The Weak Hydrogen Bond*', Oxford University Press, Oxford, 1999.
3. M. A. Adams, K. Folting, J. C. Huffman and K. G. Caulton, *Inorg. Chem.*, 1979, **18**, 3020.
4. L. M. Epstein, E. S. Shubina, A. N. Krylov, A. Z. Kreindlin and M. I. Ribinskaya, *J. Organomet. Chem.*, 1993, **447**, 277.
5. S. A. Fairhurst, R. A. Henderson, D. L. Hughes, S. K. Ibrahim and C. J. Pickett, *Chem. Commun.*, 1995, 1569.
6. E. Peris and R. H. Crabtree, *Chem. Commun.*, 1995, 2179.
7. D. Braga, F. Grepioni, E. Tedesco, K. Biradha and G. R. Desiraju, *Organometallics*, 1996, **15**, 2692.
8. S. Suzuki, P. G. Green, R. E. Bumgarner, S. Dasgupta, W. A. Goddard, III and G. A. Blake, *Science*, 1992, **257**, 942.
9. D. S. Trifan and R. Bacskai, *J. Am. Chem. Soc.*, 1960, **82**, 5010.
10. D. M. Roe, P. M. Bailey, K. Mosely and P. M. Maitlis, *Chem. Commun.*, 1972, 1273.
11. R. S. Drago, M. S. Norazi, R. J. Klinger and C. S. Chamberlain, *Inorg. Chem.*, 1979, **18**, 1254.
12. L. Brammer, J. M. Charnock, P. L. Goggin, R. J. Goodfellow, A. G. Orpen and T. F. Koetzle, *J. Chem. Soc., Dalton Trans.*, 1991, 1789.

13. L. Brammer, J. C. Mareque-Rivas and D. Zhao, *Inorg. Chem.*, 1998, **37**, 5512.
14. G. A. Jeffrey, "*An introduction to hydrogen bonding*", Oxford University Press, New York, 1997.
15. S. Schneider, "*Hydrogen bonding. A Theoretical Perspective*", Oxford University Press, Oxford, 1997.
16. T. Steiner and G. R. Desiraju, *Chem. Commun.*, 1998, 891.
17. P. A. Kollman and L. C. Allen, *Chem. Rev.*, 1972, **72**, 283.
18. H. Umeyama and K. Morokuma, *J. Am. Chem. Soc.*, 1977, **99**, 1316.
19. L. P. Stubbs and M. Weck, *Chem. Eur. J.*, 2003, **9**, 992.
20. G. Gilli and P. Gilli, *J. Mol. Struct.*, 2000, **552**, 1.
21. F. Diederich, *J. Chem. Ed.*, 1990, **67**, 813.
22. L. Brammer, *Dalton Trans.*, 2003, 3145.
23. E. A. Ebsworth, D. W. H. Rankin and S. Cradock, "*Structural methods in inorganic chemistry*", Second edition, Blackwell Scientific Publications, 1991.
24. P. J. Hore, "*Nuclear magnetic resonance*", Oxford University Press, 1995.
25. H. J. Neusser and K. Siglow, *Chem. Rev.*, 2000, **100**, 3921 and references therein.
26. A. A. Hasenein, M. W. Evans, "*Computational Methods in Quantum Chemistry*", World Scientific, 1996.
27. C. N. Pace, B. A. Shirley, M. McNutt and K. Gajiwala, *FASEB J.*, 1996, **10**, 75.

28. A. R. Fersht, *Trends Biochem. Sci.*, 1987, **12**, 301.
29. I. D. Dance, "Perspectives in supramolecular chemistry", Vol. 2, Ed. G. R. Desiraju, Wiley, 1996.
30. I. C. M. Wehman-Ooyevaar, D. M. Grove, H. Kooijman, P. van der Sluis, A. L. Spek and G. van Koten, *J. Am. Chem. Soc.*, 1992, **114**, 9916.
31. L. M. Epstein, E. S. Shubina, A. N. Krylov, A. Z. Kreindlin and M. I. Ribinskaya, *J. Organomet. Chem.*, 1993, **447**, 277.
32. D. Braga, F. Grepioni, P. Sabatino and G. R. Desiraju, *Organometallics*, 1994, **13**, 3532.
33. D. J. White, N. Laing, H. Miller, S. Parsons, S. Coles and P. A. Tasker, *Chem. Commun.*, 1999, 2077.
34. G. Aullon, D. Bellamy, L. Brammer, E. A. Bruton and G. Orpen, *Chem. Commun.*, 1998, 653.
35. G. Cooke and V. M. Rotello, *Chem. Soc. Rev.*, 2002, **31**, 275.
36. S.-K. Chang, D. Van Engen, E. Fan and A. D. Hamilton, *J. Am. Chem. Soc.*, 1991, **113**, 7640.
37. P. V. Mason, N. R. Champness, S. R. Collison, M. G. Fisher and G. Goretzki, *Eur. J. Org. Chem.*, 2006, **6**, 1444.
38. P. A. Kollman and L. C. Allen, *Chem. Rev.*, 1972, **72**, 284.
39. W. L. Jorgensen and J. Pranata, *J. Am. Chem. Soc.*, 1990, **112**, 2008.
40. (a) Y. Ge, R. R. Lilienthal and D. K. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 3976; (b) M. Gray, A. O. Cuello, G. Cooke and V. M. Rotello, *J. Am. Chem. Soc.*, 2003, **125**, 7882. (c) S. Goswami, K. Ghosh and M. Halder, *Tetrahedron Lett.*, 1999, **40**, 1735.

41. (a) A. Labande and D. Astruc, *Chem. Commun.*, 2000, 1007. (b) M.-C. Daniel, J. Ruiz, S. Nlate, J. Palumbo, J.-C. Blais and D. Astruc, *Chem. Commun.*, 2001, 2000.
42. (a) P. R. Schreiner, *Acc. Chem. Res.*, 2003, **32**, 289. (b) A. Wittkopp and P. R. Schreiner, *Chem. Eur. J.*, 2003, **9**, 407.
43. (a) S. Yamabe and S. Yamazaki, *J. Org. Chem.*, 2007, **72**, 3031; (b) Y. Okuno, *Chem. Eur. J.*, 1997, **3**, 212.
44. V. Fülöp, R. P. Phizackerley, S. M. Soltis, I. J. Clifton, S. Wakatuski, J. Erman, J. Hajdu and S. L. Edwards, *Structure*, 1994, **2**, 201.
45. M. F. Perutz, G. Fermi, B. Luisi, B. Shaanan and R. C. Liddington, *Acc. Chem. Res.*, 1987, **20**, 309.
46. B. A. Springer, S. G. Sligar, J. S. Olsen and G. N. Philips Jr., *Chem. Rev.*, 1994, **94**, 699.
47. N. C. Gerber, N. C and S. G. Sligar, *J. Am. Chem. Soc.*, 1992, **114**, 8742.
48. M. Sono, M. P. Roach, E. D. Coulter, and J. H. Dawson, *Chem. Rev.*, 1996, **96**, 2841.
49. M. Mukai, S. Nagano, M. Tanaka, K. Ishimori, I. Morishima, T. Ogura, Y. Watanabe, and T. Kitagawa, *J. Am. Chem. Soc.*, 1997, **119**, 1758.
50. S.-I. Ozaki, M. P. Roach, T. Matsui and Y. Watanabe, *Acc. Chem. Res.*, 2001, **34**, 818.
51. B. Meunier, S. P. de Visser and S. Shaik, *Chem. Rev.*, 2004, **104**, 3947.
52. V. Guallar, D. L. Harris, V. S. Batista and W. H. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 1430.

53. C. J. Chang, L. L. Cheng and D. G. Nocera, *J. Am. Chem. Soc.*, 2003, **125**, 1866.
54. J. Aikens and S. G. Sligar, *J. Am. Chem. Soc.*, 1994, **116**, 1143.
55. T. Deng, I. D. G. Macdonald, M. C. Simianu, M. Sykora, J. R. Kincaid and S. G. Sligar, *J. Am. Chem. Soc.*, 2001, **123**, 269.
56. M. Matsu-ura, M. Tani, S. Nakayama, N. Nakamura and Y. Naruta, *Angew. Chem. Int. Ed.*, 2000, **39**, 1989.
57. C. E. MacBeth, B. S. Hammes, V. G. Young Jr. and A. S. Borovik, *Inorg. Chem.*, 2001, **40**, 4733.
58. Z. Shirrin, B. S. Hammes, V. G. Young Jr. and A. S. Borovik, *J. Am. Chem. Soc.*, 2000, **122**, 1836.
59. R. Gupta, C. E. MacBeth, V. G. Young Jr. and A. S. Borovik, *J. Am. Chem. Soc.*, 2002, **124**, 1136.
60. Z. Shirrin, V. G. Young Jr. and A. S. Borovik, *Chem. Commun.*, 1997, 1967.
61. C. E. MacBeth, R. Gupta, K. R. Mitchell-Koch, V. G. Young Jr., G. H. Lushington, W. H. Thompson, M. P. Heindrich and A. S. Borovik, *J. Am. Chem. Soc.*, 2004, **126**, 2556.
62. N. Kitajima and Y. Moro-Oka, *Chem. Rev.*, 1994, **94**, 737.
63. M. Costas, M. P. Mehn, M. P. Jensen and L. Que, Jr, *Chem. Rev.*, 2004, **104**, 939.
64. G. Anderegg and F. Wenk, *Helv. Chim. Acta*, 1967, **50**, 2330.
65. H. Nagao, N. Komeda, M. Mukaida, M. Suzuki and K. Tanaka, *Inorg. Chem.*, 1996, **35**, 6809.

66. M. Merkel, D. Schnieders, S. M. Baldeau and B. Krebs, *Eur. J. Inorg. Chem.*, 2004, **4**, 783.
67. Z. He, J. Chaimungkalanont, D. C. Craig and S. B. Colbran, *Dalton Trans.*, 2000, 1419.
68. N. Wei, N. N. Murthy and K. D. Karlin, *Inorg. Chem.*, 1994, **33**, 6093.
69. K. Jitsukawa, M. Harata, H. Arai, H. Sakurai and H. Masuda, *Inorg. Chim. Acta*, 2001, **324**, 108.
70. C.-L. Chuang, O. Dos Santos, X. Xu and J. W. Canary, *Inorg. Chem.*, 1997, **36**, 1967.
71. J. W. Canary, C. S. Allen, J. M. Castagnetto and Y. Wang, *J. Am. Chem. Soc.*, 1995, **117**, 8484.
72. Z. He, P. J. Chaimungkalanont, D. C. Craig and S. B. Colbran, *J. Chem. Soc., Dalton Trans.*, 2000, 1419.
73. E. C. Wilkinson, Y. Dong, Y. Zang, H. Fujii, R. Fraczkiewicz, G. Fraczkiewicz, R. S. Czernuszewicz and L. Que, Jr, *J. Am. Chem. Soc.*, 1998, **120**, 955.
74. Y. Ma and P. B. Balbuena, *J. Phys. Chem. B*, 2007, **111**, 2711.
75. Z. Tyeklar, R. J. Jacobson, N. Wei, N. N. Murthy, J. Zubieta and K. D. Karlin, *J. Am. Chem. Soc.*, 1993, **115**, 2677.
76. T. Kojima, T. Amano, Y. Ishii, M. Ohba, Y. Okaue and Y. Matsuda, *Inorg. Chem.*, 1998, **37**, 4076.
77. H. Sugimoto, M. Kamei, K. Umakoshi, Y. Sasaki and M. Suzuki *Inorg. Chem.*, 1996, **35**, 7082.

78. R. M. Chin, R. H. Dubois, L. E. Helberg, M. Sabat, T. Y. Bartucz, A. J. Lough, R. H. Morris and W. D. Harman, *Inorg. Chem.*, 1997, **36**, 3553.
79. B. J. Brisdon, M. Cartwright, A. G. W. Hodson, M. F. Mahon and K. C. Molloy *J. Organomet. Chem.*, 1992, **435**, 319.
80. D. C. Bebout, D. E. Ehmann, J. C. Trinidad, K. K. Crahan, M. E. Kastner and D. Parrish *Inorg. Chem.*, 1997, **36**, 4257.
81. H. Sugimoto and Y. Sasaki, *Chem. Lett.*, 1998, **3**, 197.
82. T. Nagataki, K. Ishii, Y. Tachi and S. Itoh, *Dalton Trans.*, 2007, 1120.
83. M. Merkel, M. Pascaly, B. Krebs, J. Astner, S. P. Foxon and S. Schindler, *Inorg. Chem.*, 2005, **44**, 7582.
84. H. G. Jang, D. D. Cox and L. Que, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 9200.
85. D.-H. Jo, H.-M. Chiu and L. Que, Jr., *Inorg. Chem.*, 2001, **40**, 3181.
86. Y. Miyazato, T. Wada and K. Tanaka, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 745.
87. (a) G. J. P. Britovsek, J. England and A. J. P. White, *Inorg. Chem.*, 2005, **44**, 8125; (b) M. Yamaguchi, H. Kousaka, S. Izawa, Y. Ichii, T. Kumano, D. Masui and T. Yamagishi, *Inorg. Chem.*, 2006, **45**, 8342.
88. H. Nagao, N. Komeda, M. Mukaida, M. Suzuki and K. Tanaka, *Inorg. Chem.*, 1996, **35**, 6809.
89. D. Maiti, H. R. Lucas, A. A. Narducci Sarjeant and K. D. Karlin, *J. Am. Chem. Soc.*, 2007, **129**, 6998.
90. J. Zhang, K. Siu, C. H. Lin and J. W. Canary, *New J. Chem.*, 2005, **29**, 1147.

91. K. D. Karlin, J. C. Hayes, S. Juen, J. P. Hutchinson and J. Zubieta, *Inorg. Chem.*, 1982, **21**, 4106.
92. L. Metteau, S. Parsons and J. C. Mareque-Rivas, *Inorg. Chem.*, 2006, **45**, 6601.
93. N. N. Murthy and K. D. Karlin, *J. Chem. Soc., Chem. Commun.*, 1993, 1236.
94. J. C. Mareque-Rivas, R. Prabakaran and S. Parsons, *Dalton Trans.*, 2004, 1648.
95. A. Wada, S. Ogo, S. Wada, Y. Watanabe, M. Mukai, K. Jitsukawa, H. Masuda and H. Einaga, *Inorg. Chem.*, 1999, **38**, 3592.
96. M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *J. Am. Chem. Soc.*, 1994, **116**, 10817.
97. S. Ogo, S. Wada, Y. Watanabe, M. Iwase, A. Wada, M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Angew. Chem. Int. Ed.*, 1998, **37**, 2102.
98. M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Chem. Lett.*, 1996, **9**, 813.
99. Y. Zang, J. Kim, Y. Dong, E. C. Wilkinson, E. H. Appleman and Lawrence Que Jr., *J. Am. Chem. Soc.*, 1997, **119**, 4197.
100. K. Chen, M. Costas and L. Que Jr., *J. Chem. Soc., Dalton Trans.*, 2002, 672.
101. M. Yamaguchi, H. Kousaka, S. Izawa, Y. Ichii, T. Kumano, D. Masui and T. Yamagishi, *Inorg. Chem.*, 2006, **45**, 8342.
102. T. Nagataki, K. Ishii, Y. Tachi and S. Itoh, *Dalton Trans.*, 2007, 1020.

103. S. Ogo, R. Yamahara, M. Roach, T. Suenobu, M. Aki, T. Ogura, T. Kitagawa, H. Masuda, S. Fukuzumi and Y. Watanabe, *Inorg. Chem.*, 2002, **41**, 5513.
104. D. D. Cox and L. Que, Jr., *J. Am. Chem. Soc.*, 1988, **110**, 8085.
105. H. G. Jang, D. D. Cox and L. Que, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 9200.
106. L. Que, Jr., R. C. Kolanczyk and L. S. White, *J. Am. Chem. Soc.*, 1987, **109**, 5373.
107. L. S. White, P. V. Nilsson, L. H. Pignolet and L. Que, Jr., *J. Am. Chem. Soc.*, 1984, **106**, 8312.
108. D. -H. Jo, Y.-M. Chiou and L. Que, Jr., *Inorg. Chem.*, 2001, **40**, 3181.
109. T. Funabiki, T. Yamazaki, A. Fukui, T. Tanaka and S. Yoshida, *Angew. Chem. Int. Ed.*, 1998, **37**, 513.
110. A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa and H. Einaga, *Angew. Chem. Int. Ed.*, 1998, **37**, 798.

Chapter 2:

**Effects and strength of hydrogen bonds
in LMCl complexes (L = TPA derivative, M = Zn, Cu)**

2.1. Introduction

The importance of the ligand environment in determining chemistry at metal sites is well understood. As a result, the vast majority of ligand designs are aimed at tuning metal chemistry through rational selection of coordinating groups. In Nature, however, it is known that the microenvironment of the active site can also influence the function of metalloproteins through non-covalent interactions such as hydrogen bonding.¹ Thus, hydrogen bonding to metal-bound ligands is an ubiquitous feature of the active site of many metalloenzymes.^{1,2} As a consequence, the development of synthetic systems that resemble more faithfully the hydrogen bonding microenvironments of metalloproteins has become an area of intense research.³

In order to assess the real potential of exploiting or designing microenvironments around metal ion(s) as a novel approach in ligand design, it is important to investigate and contrast the magnitude of effects associated with non-coordinating and coordinating groups in structural and functional features of model coordination complexes. For instance, our group has shown that the presence of non-coordinating amino groups in the proximity of a zinc(II)-bound water molecule enhances its acidity by a similar magnitude to lowering the coordination number and/or increasing the positive charge of the zinc(II) centre, which increase its Lewis acidity.⁴ Our group has also shown that amino N–H hydrogen bond donors adjacent to a zinc(II) centre can increase the affinity of phosphates to a monometallic zinc(II) complex to an extent comparable to a second metal in bimetallic zinc(II) complexes.⁵

Important properties of metal-bound ligands, including nucleophilicity, electrophilicity and acidity depend on the interaction with the metal ion. In addition,

properties of the metal are modulated by the ligand environment. In all these aspects the metal–ligand distance(s) are an important parameter. Given the current intense interest in ligands that induce intramolecular hydrogen bonds to metal bound ligands,^{3–8} we considered it important to investigate the implications of the hydrogen bonding groups on metal–ligand distances. As a model, we investigate the extent to which ligands L that create a hydrogen bonding cavity in trigonal bipyramidal $[(L)Zn(Cl)]^+$ cations affect the L–Zn and Zn–Cl distances.

It is reasonable to expect that the magnitude of the effects exerted by the hydrogen bonding groups will depend on the geometry and strength of the hydrogen bonding interactions induced. Thus, it is also important to investigate factors affecting the geometry and strength of internal hydrogen bonds. Recently, our group has demonstrated that the metal geometry plays an important role in determining the geometry of internal N–H $\cdots$ Cl–Zn hydrogen bonds.⁶ Here we compare the geometries of hydrogen bonds as a function of the hydrogen bond donors involved, and of their number. Since many transition metals exist in different oxidation states, we investigated also the extent to which the oxidation state of the metal influences the strength of hydrogen bonding to metal-bound chlorides.

Clearly, to investigate the interactions between the second coordination sphere of metal complexes such as hydrogen bonds with exogenous ligands, it is necessary to induce and establish the formation of hydrogen bonding to metal-bound ligands. For this, we have chosen a series of ligands containing amino, neopentylamino and pivaloylamido groups, which were synthesized according to the literature.^{6–8}

To study the hydrogen bonding interactions formed, we used various techniques and procedures, such as infra-red and NMR spectroscopy, X-ray crystallography and theoretical calculations.

2.2. Ligand selection

The (6- R^1 -2-pyridylmethyl)amine ($R^1 = \text{NH}_2$ or NHCH_2^tBu) ligand unit has a suitable stereochemistry for the participation of the N-H group in internal hydrogen bonding to an adjacent metal-bound ligand.⁶⁻⁸ The ligand fragment 2-aminomethylpyridine has been incorporated into a very large number of polydentate ligands, thus allowing the examination of effects arising from different coordination environments in the chemistry of their metal complexes. Hence, ligands L, with either of these fragments, seemed suitable to investigate and contrast the relative importance of hydrogen bonding and coordinating groups in determining structural properties of their $[\text{LMCl}]^{+/0}$ complexes ($M = \text{Cu, Zn}$). As a series, $\text{N}(\text{CH}_2\text{Py})_3-n(\text{CH}_2\text{Py}-6-R)_n$ ligands ($R = \text{NH}_2$, $n = 1-3$ L^{Am1-3}; $R = \text{NHCH}_2^t\text{Bu}$, $n = 1-3$ L^{Np1-3}; $R = \text{NHCO}^t\text{Bu}$, $n = 1-3$ L^{Piv1-3}) offer a similar N_4 coordinating environment and a variable hydrogen bonding and hydrophobic microenvironment.

In all cases hydrogen bonding was only achieved to the metal-bound atom. Tripodal poly(2-pyridylmethyl)amine-based ligands (Figure 2.1) were chosen for the following reasons:

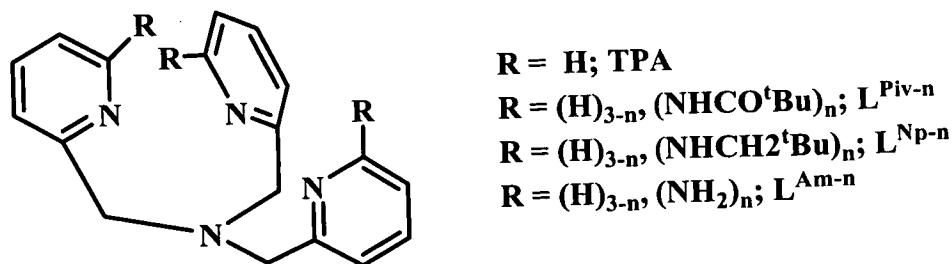


Figure 2.1. Schematic representation of the TPA-based ligands used.

- The poly-dentate nature of the ligand should stabilise the metal complexes formed.
- The nitrogen atoms of the pyridine rings should provide the bound metal with a primary coordination sphere resembling that of many oxygenases.
- The effect of several R groups (e.g. different numbers and types of hydrogen bonding groups) can be investigated relatively quickly.

Since TPA does not have the possibility of forming hydrogen bonds, it will be the “standard” to quantify the effect of the functional groups introduced.

2.3. Results and discussion

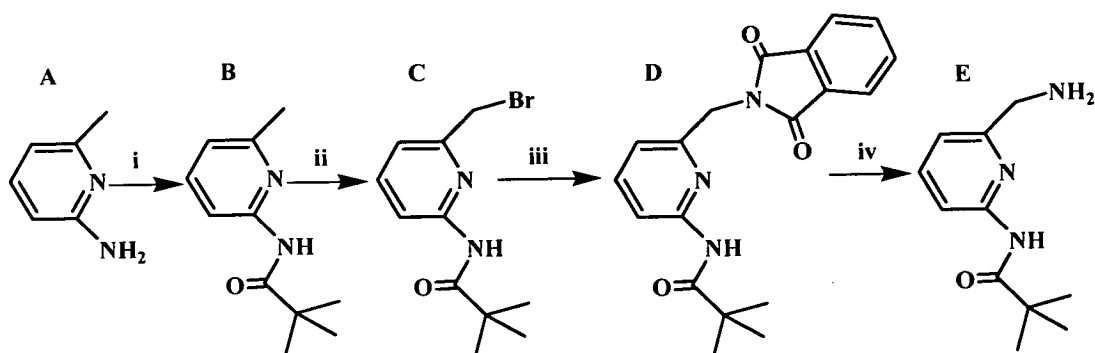
For this investigation, four ligands were prepared. L^{Am-3} was synthesized along with its $Zn(II)Cl$ complex, and L^{Piv1-3} along with its $Cu(I)Cl$ and $Cu(II)Cl$ complexes. This allows comparison with complexes previously reported in the literature⁶ and synthesized in our group by Dr. Rafael Torres Martin de Rosales, $[(L^{Am-2})Zn(Cl)](BPh_4)$, $[(L^{Np1-3})Zn(Cl)](BPh_4)$. All these complexes have BPh_4^- as

counter ion, the complex $[(L^{Am-3})Zn(Cl)](BPh_4) \cdot CH_3CN$, was synthesized according to the same procedure.⁹

2.3.1. Synthesis

2.3.1.1. Tripodal ligands

The synthetic steps for the tripodal ligands are as follows (Scheme 2.1).



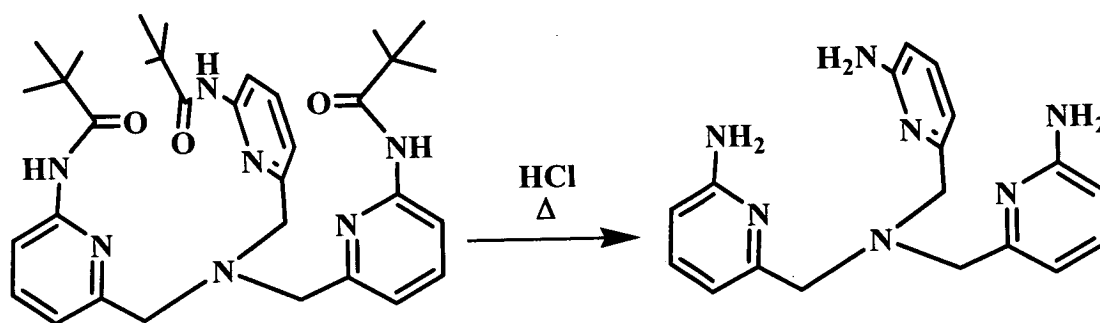
Scheme 2.1. Reagents and conditions used for the synthesis of the compounds; (i) $tBuCOCl$ (1.5 equiv.), CH_2Cl_2 , NEt_3 , 22 h; (ii) NBS (1.5 equiv.), AIBN (0.1 equiv.), CCl_4 , 80 °C, 3.5 h; (iii) potassium phthalimide (1 equiv.), DMF, 120 °C, 3 h; (iv) $N_2H_4 \cdot H_2O$ (1 equiv.), EtOH, 60 °C, 3 h.

The first step involves the protection of the amino group with trimethylacetylchloride, with triethylamine acting as an external base. The product is purified by flash chromatography and then reacted with *N*-bromosuccinimide (NBS) and a catalytic amount of 2,2'-azobis(2-methyl-propionitrile) (AIBN) to achieve the bromination of the picoline methyl group. The brominated compound **C** needs further purification by chromatography to ensure separation from the unreacted non-

brominated, and the bis-brominated species. The Gabriel synthesis of primary amines with mono-hydrated hydrazine finally yields quantitatively the final product **E**.

Coupling this amine **E** with 2 equivalents of the brominated compound **C** yields the symmetrical L^{Piv-3} . The reaction between 2 equivalents of this brominated compound with 2-aminomethylpyridine generates the bis-functionalised L^{Piv-2} , and the coupling between 2 equivalents of 2-picolylchloride and 1 equivalent of the amine **E** generates the monosubstituted L^{Piv-1} . The three coupling reactions were conducted in acetonitrile, using sodium carbonate in excess to facilitate the deprotonation of the amines. Purification in all cases is achieved by flash chromatography.

The ligand L^{Piv-3} can then be cleaved under acidic conditions as follows (Scheme 2.2).



Scheme 2.2. Generation of L^{Am-3} .

The complete hydrolysis of the three trimethylacetyl groups is achieved in several days, almost one day per protecting group to be removed. The pure target compound is extracted with dichloromethane after basification of the solution.

2.3.1.2. Metal complexes

The synthesis of the Zn(II) complexes of L^{Am-3} was achieved using $ZnCl_2$ as a precursor. Mixing equimolar amounts of L^{Am-3} and $ZnCl_2$ in acetonitrile yields $[L^{Am-3}Zn(Cl)](Cl)$, from which $[L^{Am-3}Zn(Cl)](BPh_4)$ was prepared by metathesis reaction with $NaBPh_4$. Upon addition of $NaBPh_4$, the complex precipitates, and is filtered over a Büchner filter and washed with methanol.

The synthesis of the Cu(I)Cl complexes of L^{Piv-n} were performed by mixing equimolar amounts of L^{Piv-n} and $CuCl$ in a glove box and in oxygen free acetonitrile. The $[L^{Piv-n}Cu(Cl)]$ complexes were isolated by simply removing the solvent under high vacuum. The synthesis of the Cu(II)Cl complexes of L^{Piv-n} were performed by mixing equimolar amounts of L^{Piv-n} and $CuCl_2$ in acetonitrile. The $[L^{Piv-n}Cu(Cl)](Cl)$ complexes were isolated by removing the solvent under high vacuum.

Crystals of $[L^{Am-3}Zn(Cl)](BPh_4)$ and $[L^{Piv-3}Cu(Cl)]$ suitable for X-ray diffraction were obtained by slow evaporation of MeCN solutions. The relevant crystallographic data and structure refinement details are given in Table 2.1 and Table 2.2.

Table 2.1 Crystallographic data and structure refinement details for [L^{Am-}₃Zn(Cl)](BPh₄)·CH₃CN

Empirical Formula	C ₄₄ H ₄₄ BClN ₈ Zn
<i>M</i> _r	796.5
<i>T</i> /K	150(2)
Crystal system	Triclinic
Space group	<i>P</i> $\bar{1}$
<i>a</i> /Å	11.8463(7)
<i>b</i> /Å	13.1403(8)
<i>c</i> /Å	13.5826(8)
α /°	95.634(3)
β /°	92.657(3)
γ /°	109.312(3)
<i>V</i> /Å ³	1978.7(2)
<i>Z</i>	2
<i>D</i> _c /g cm ⁻³	1.337
μ /mm ⁻¹	0.673
Reflexions measured, unique	15687, 6831
<i>R</i> _{int}	0.0557
<i>R</i> ₁ (<i>F</i>) ^a (all data)	0.1096
<i>wR</i> ₂ (<i>F</i> ²) ^a (all data)	0.1997
<i>S</i> (<i>F</i> ²) ^a (all data)	1.268
Largest difference peak, hole/e ⁻ Å ³	1.106, -0.734

$$^a R_1(F) = \sum(|F_o| - |F_c|) / \sum(|F_o|); wR_2(F^2) = [\sum w(F_o^2 - F_c^2)^2 / \sum wF_o^4]^{1/2}; S(F^2) = [\sum w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}.$$

Table 2.2. Crystallographic data and structure refinement details for [L^{Piv-}₃Cu(Cl)]

Empirical Formula	C ₃₃ H ₄₅ O ₃ ClN ₇ Cu
<i>M</i> _r	686.75
<i>T</i> /K	150(2)
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	10.1526(2)
<i>b</i> /Å	18.4259(3)
<i>c</i> /Å	18.6888(3)
α /°	95.634(3)
β /°	92.657(3)
γ /°	109.312(3)
<i>V</i> /Å ³	3496.13(11)
<i>Z</i>	4
<i>D</i> _c /g cm ⁻³	1.305
μ /mm ⁻¹	0.74
Reflexions measured, unique	61509, 10658
<i>R</i> _{int}	0.0579
<i>R</i> ₁ (<i>F</i>) ^a (all data)	0.0664
<i>wR</i> ₂ (<i>F</i> ²) ^a (all data)	0.1230
<i>S</i> (<i>F</i> ²) ^a (all data)	1.072
Largest difference peak, hole/e- Å ³	1.21, -1.267

$$^a R_1(F) = \Sigma(|F_o| - |F_c|) / \Sigma(|F_o|); wR_2(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma wF_o^4]^{1/2}; S(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}.$$

2.3.2. Geometrical features of LZnCl complexes (L = TPA derivative)

Recently several X-ray structures of [(L)Zn(Cl)]⁺ complexes, in which the zinc(II) centre was in a trigonal bipyramidal N₄Cl ligand environment with the Cl ligand occupying one of the axial positions have been reported. Some of these complexes contain internal hydrogen bonds between the axial chloride and a nitrogen donor (Figure 2.2).⁶

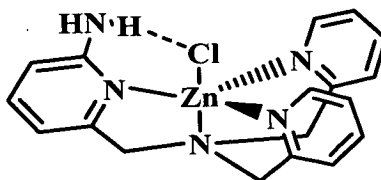


Figure 2.2. Schematic representation of a $[(L)Zn(Cl)]^+$ complex with internal hydrogen bonding.

It is interesting to compare the axial Zn–N and Zn–Cl distances in these complexes and in $[(TPA)Zn(Cl)](BPh_4)$,¹⁰ to see if hydrogen bonds exert a structural effect on these metal complexes. In principle, the introduction of substituents at the pyridine 6th position may also alter the steric requirements and electronic properties at the metal site, and thus affect the M–Cl and M–N distances.

2.3.2.1. Influence of the nature of hydrogen bonds on the M–N and M–Cl distances

It is reasonable to expect that the magnitude of the effects exerted by internal hydrogen bonding will depend on the geometry and strength of the interactions induced. Thus, it is also important to elucidate and investigate factors affecting the geometry/strength of internal hydrogen bonds. A suitable strategy is to change the nature of the hydrogen bonding groups involved.

The structures of $[(TPA)Zn(Cl)](BPh_4)$, $[(L^{Am1})Zn(Cl)](BPh_4)$, $[(L^{Np-1})Zn(Cl)](BPh_4)$ and $[(L^{Piv-1})Zn(Cl)](BPh_4)$ can be used to compare the influence of various hydrogen bonding groups on the metal–chloride and metal–nitrogen distances. These groups differ in terms of electronic, steric, and hydrogen bonding properties. Whereas amino and neopentylamino groups have comparable electronic

properties (they are electron donating), pivaloylamido groups are strongly electron-withdrawing. Also, neopentylamino and pivaloylamido groups have a comparable bulk, which is much greater than that of amino groups. These characteristics should allow us to determine if any of these factors is predominant, or if they all exert a similar effect on metal–ligand distances. Table 2.3 represents an attempt to predict the structural effect associated with steric, electronic and hydrogen bonding changes on the geometry of a trigonal bipyramidal complex.

Table 2.3. Plausible structural and electronic effect of substituents R in the pyridine 6th position on metal–ligand distances.

	M–Cl	M–N _{Py}	M–N _{ax}
Steric bulk	Decrease	Increase	Decrease
R being electron withdrawing	Decrease	Increase	Increase
R being electron donating	Increase	Decrease	Decrease
Hydrogen bonds	Increase	Decrease	

Bulky groups such as *tert*-butyl groups in the pyridine 6th position should lengthen the M–N_{Py} bond, especially the one carrying the hydrogen bonding group. This structural change could be compensated by a shorter M–N_{ax} distance. The presence of bulky groups near the M–Cl unit should also favour shorter M–Cl distances to reduce steric interaction between these groups and the chloride anion. Electron-withdrawing groups should render the N_{Py} nitrogen atoms less electron rich, and therefore reduce their ability to bind strongly the metal centre, potentially inducing shorter M–Cl bonds. The presence of hydrogen bonds between the R group

and the bound chloride anion should result in a longer M–Cl bond, as a result of making the chloride less electron rich. In contrast, the N_{Py} nitrogen atoms of the substituted pyridines could be shorter due to the formation of the hydrogen bond. Finally, one can expect two opposite effects of hydrogen bonds on the M–N_{ax} bond. On the one hand, the less electron-rich metal should prefer a shorter M–N_{ax} bond, but on the other hand, the shortening of the M–N_{Py} bonds should induce a longer M–N_{ax} due to geometrical constraints imposed by the tripodal ligand.

Table 2.4. Selected bond lengths (Å) and angles (°) for the cations in [TPAZn(Cl)] BPh₄,¹⁰ [L^{Am-1}Zn(Cl)]BPh₄,⁹ [L^{Np-1}Zn(Cl)] BPh₄,⁹ and [L^{Piv-1}Zn(Cl)] BPh₄⁹ complexes.

	[TPAZn(Cl)] ⁺	[(L ^{Am-1})Zn(Cl)] ⁺	[(L ^{Np-1})Zn(Cl)] ⁺	[(L ^{Piv-1})Zn(Cl)] ⁺
Zn–Cl	2.2754(14)	2.2959(7)	2.2806(9)	2.2812(7)
Zn–N _{ax}	2.271(3)	2.2247(18)	2.236(3)	2.1990(15)
Zn–N _{Py}	2.064(3)	2.0704(19)*	2.100(2)*	2.1351(15)*
Zn–N _{Py}	2.063(3)	2.1021(19)	2.072(3)	2.0885(16)
Zn–N _{Py}	2.080(3)	2.081(2)	2.093(2)	2.0651(17)
Average Zn–N _{Py}	2.069(5)	2.084(27)	2.088(4)	2.096(28)
Cl–Zn–N _{ax}	177.90(9)	170.00(5)	173.20(7)	174.09(4)
Cl–Zn–N _{Py}	102.26(10)	110.50(5)*	108.76(7)*	106.20(4)*
Cl–Zn–N _{Py}	103.90(11)	96.55(5)	102.55(8)	96.66(5)
Cl–Zn–N _{Py}	100.46(10)	104.24(5)	96.15(7)	104.24(5)
N _{ax} –Zn–N _{Py}	77.41(12)	79.11(7)*	77.46(9)*	78.02(5)*
N _{ax} –Zn–N _{Py}	78.10(13)	76.54(7)	77.72(11)	77.51(6)
N _{ax} –Zn–N _{Py}	78.14(12)	77.75(7)	77.72(9)	75.75(6)
τ	0.93	0.83	0.80	0.88

* indicates that the pyridine ring is carrying the hydrogen bonding group. τ = degree of trigonality (*vide infra*).

The first noticeable feature shown in Table 2.4 is the lengthening of the Zn–Cl bond from 2.275 Å in $[(\text{TPA})\text{Zn}(\text{Cl})]^+$ to 2.281 Å in $[(\text{L}^{\text{Np-1}})\text{Zn}(\text{Cl})]^+$ and $[(\text{L}^{\text{Piv-1}})\text{Zn}(\text{Cl})]^+$, and to 2.296 Å in $[(\text{L}^{\text{Am-1}})\text{Zn}(\text{Cl})]^+$. This can be explained from Table 2.3, since the latter benefits from electronic effects and hydrogen bonding, while the steric hindrance which could favour a shorter Zn–Cl is very small. Table 2.4 shows that the geometric features of the internal N–H $\cdots$ Cl–Zn hydrogen bond in $[(\text{L}^{\text{Np-1}})\text{Zn}(\text{Cl})]^+$ and $[(\text{L}^{\text{Piv-1}})\text{Zn}(\text{Cl})]^+$ cations are approximately the same despite amide N–H groups being presumably better hydrogen bond donors than amino groups.⁶ This is also reflected in the shorter H $\cdots$ Cl interaction (*vide infra*). One structural feature that may partly account for this result is the slightly longer Zn–N_{py*} distance of the pyridine carrying the pivaloylamido group presumably due to the electron withdrawing effect of these groups on the pyridine ring. The similarity between the Zn–Cl bond length with a neopentylamino and a pivaloylamido group can also be correlated to Table 2.3. The electron donating properties of the neopentylamino group ligand and hydrogen bonding favour a longer Zn–Cl bond than in the TPA complex, while only hydrogen bonding favours Zn–Cl bond lengthening in the case of the pivaloylamido group. For the pivaloylamido group, however, hydrogen bonds should be much stronger due to its presumably better hydrogen bond donating ability. Thus, the difference in hydrogen bonding strength seems to compensate for the change of electronic properties of the ligand. From this result, it appears reasonable to assume that hydrogen bonds exert the predominant effect on the Zn–Cl distance in these complexes. It should be noted, however, that the observed changes in Zn–Cl bond lengths are smaller (*ca.* 0.02 Å) than the changes on the substituted pyridyl nitrogen N_{py*}, and on the bridgehead nitrogen N_{ax} (*ca.* 0.07 Å). The Zn–N_{py*}

bond lengths are comparable for $[(\text{TPA})\text{Zn}(\text{Cl})]^+$ and $[(\text{L}^{\text{Am-1}})\text{Zn}(\text{Cl})]^+$, and increase by 0.035 Å and 0.070 Å in $[(\text{L}^{\text{Np-1}})\text{Zn}(\text{Cl})]^+$ and $[(\text{L}^{\text{Piv-1}})\text{Zn}(\text{Cl})]^+$, respectively. The lengthening of this bond can be attributed mainly to the steric hindrance due to the *tert*-butyl group in $[(\text{L}^{\text{Np-1}})\text{Zn}(\text{Cl})]^+$, and to both steric hindrance and electronic effects in $[(\text{L}^{\text{Piv-1}})\text{Zn}(\text{Cl})]^+$. The degree of trigonality was evaluated by means of the angular structural parameter $\tau = (\beta - \alpha)/60$ introduced by Addison *et al.*,¹¹ where α and β represent the two largest angles around the central atom with $\beta > \alpha$. A perfect trigonal bipyramidal geometry is associated with $\tau = 1$, while $\tau = 0$ is indicative of a perfect square pyramidal geometry. Here, all complexes exhibit a mainly trigonal bipyramidal arrangement.

From these results, it looks like the Zn–N bond lengths are mainly affected by steric and electronic effects, whereas the Zn–Cl bond length is governed by hydrogen bonds. In order to confirm this hypothesis, it is interesting to investigate how these distances change when the number of hydrogen bond changes.

2.3.2.2. Influence of the number of hydrogen bonds on the M–N and M–Cl distances

Since $[(\text{L}^{\text{Am1-3}})\text{Zn}(\text{Cl})](\text{BPh}_4)$ and $[(\text{L}^{\text{Np1-3}})\text{Zn}(\text{Cl})](\text{BPh}_4)$ exhibit internal N–H...Cl–Zn hydrogen bonds, we viewed it important to determine if there is a correlation between the number and geometries of N–H...Cl–Zn hydrogen bonding interactions and the length of the Zn–Cl bond. In order for this comparison to be made, it was necessary to determine the X-ray crystal structure of $[(\text{L}^{\text{Am-3}})\text{Zn}(\text{Cl})](\text{BPh}_4)$ (Figure 2.3 and Table 2.5).

All complexes verify the lengthening of the Zn–Cl bond by local N–H hydrogen bond donors (Table 2.5-2.6), and the concomitant shortening of the Zn–N bond to the axial bridgehead nitrogen N_{ax}. This effect increases with the number of hydrogen bond donors.

Table 2.5. Selected bond lengths (Å) and angles (°) for the cations in [TPAZn(Cl)]BPh₄⁹ and [(L^{Am-n})Zn(Cl)]BPh₄¹⁰ complexes.

	[TPAZn(Cl)] ⁺	[(L ^{Am-1})Zn(Cl)] ⁺	[(L ^{Am-2})Zn(Cl)] ⁺	[(L ^{Am-3})Zn(Cl)] ⁺
Zn–Cl	2.2754(14)	2.2959(7)	2.323(2)	2.3467(18)
Zn–N _{ax}	2.271(3)	2.2247(18)	2.181(3)	2.116(5)
Zn–N _{Py}	2.064(3)	2.0704(19)*	2.120(3)*	2.158(5)*
Zn–N _{Py}	2.063(3)	2.1021(19)	2.085(3)*	2.183(5)*
Zn–N _{Py}	2.080(3)	2.081(2)	2.093(3)	2.139(5)*
Average Zn–N _{Py}	2.069(5)	2.084(27)	2.099(5)	2.159(9)
Cl–Zn–N _{ax}	177.90(9)	170.00(5)	169.20(12)	177.39(15)
Cl–Zn–N _{Py} *	102.26(10)	110.50(5)*	101.62(10)*	102.24(15)*
Cl–Zn–N _{Py}	103.90(11)	96.55(5)	111.18(10)*	99.80(14)*
Cl–Zn–N _{Py}	100.46(10)	104.24(5)	93.81(13)	102.44(14)*
N _{ax} –Zn–N _{Py}	77.41(12)	79.11(7)*	76.85(10)*	79.0(2)*
N _{ax} –Zn–N _{Py}	78.10(13)	76.54(7)	79.01(10)*	77.59(19)*
N _{ax} –Zn–N _{Py}	78.14(12)	77.75(7)	78.23(11)	78.86(18)*
τ	0.86	0.83	0.80	0.94

* indicates that the pyridine ring is carrying the hydrogen bonding group.

The Zn–Cl distance follows the trend 2.275 Å in [(TPA)Zn(Cl)](BPh₄), 2.296 Å with one, 2.323 Å with two, and 2.347 Å with three amino groups, respectively (Table 2.5). It is interesting to note that the lengthening of the axial Zn–Cl bond is

accompanied by a progressive seemingly correlated shortening of the axial Zn–N_{ax} distance; 2.271 Å in [(TPA)Zn(Cl)](BPh₄), 2.225 Å with one, 2.181 Å with two, to 2.115 Å with three amino groups. As a result of the triply hydrogen bonding microenvironment the Zn–Cl distance of [(L^{Am-3})Zn(Cl)](BPh₄)·CH₃CN (Figure 2.3) is at the upper end of the range observed for Zn–Cl bonds (*vide infra*), whereas the axial Zn–N_{ax} distance is one of shortest among N₄ ligands that induce a trigonal bipyramidal geometry. Finally, the Zn–N_{py} bonds are lengthened when each amino group is introduced, despite their electron donating character, presumably due to steric reasons. Thus, the average Zn–N_{py} distance is progressively lengthened from 2.069 Å in [(TPA)Zn(Cl)](BPh₄) to 2.084 Å, 2.099 Å, and 2.159 Å on sequential addition of NH₂ groups.

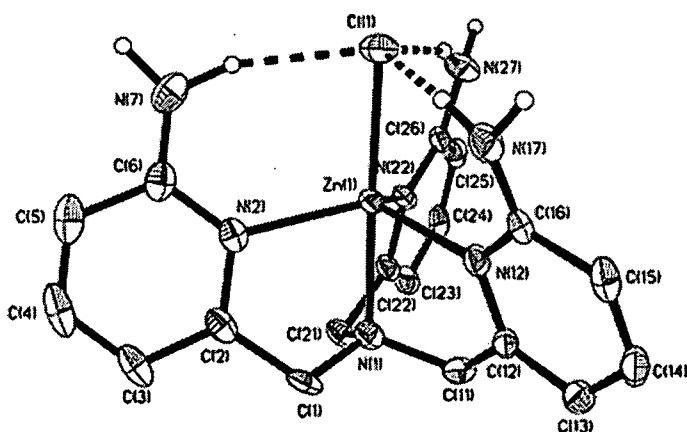


Figure. 2.3 Thermal ellipsoid plot drawn with 30% probability ellipsoids of the $[(L^{Am-3})Zn(Cl)]^+$ cation showing the triple internal N–H···Cl–Zn hydrogen bonding.

Only N–H hydrogens are shown for clarity.⁹

The Zn–Cl distances of the complexes with the neopentylamino groups are also longer than in [(TPA)Zn(Cl)](BPh₄), however, they are shorter than with the

amino groups and follow a different trend than those with the amino groups, 2.281 Å with one, 2.286 Å with three and 2.313 Å with two neopentylamino groups (Table 2.6). These structural differences could lead to functional differences between complexes with different internal hydrogen bonding groups. Conclusive structure–function relationships for these and related ligands have not been established yet. It is interesting to note, however, that differences arise between the extent to which the amino groups of the neopentylamino groups increase the zinc–water acidity of their zinc–aqua complexes.¹² Recently, it was also shown that the reactivity of ruthenium complexes of L^{Np1-3} is controlled by the nature of hydrogen bonding groups at the pyridine 6-position.¹³ Like in $[(L^{Am1-3})Zn(Cl)]^+$, as the number of hydrogen bonding groups increases in $[(L^{Np1-3})Zn(Cl)]^+$ complexes the axial Zn–N distance shortens progressively from 2.236 Å to 2.161 Å and 2.113 Å. Also noticeable are the changes induced by the neopentylamino groups on the equatorial Zn–N_{py} distances. Despite the electron donating character of these groups, the zinc(II) complexes have average Zn–N_{py} distances which increase from 2.088 Å to 2.121 Å and 2.183 Å, and hence are slightly longer than the corresponding amino analogues, presumably due to greater steric hindrance.

Table 2.6. Selected bond lengths (Å) and angles (°) for zinc(II) $[L^{Np-n}Zn(Cl)]BPh_4$ cations.^{9,10}

	$[TPAZn(Cl)]^+$	$[L^{Np-1}Zn(Cl)]^+$	$[L^{Np-2}Zn(Cl)]^+$	$[L^{Np-3}Zn(Cl)]^+$
Zn–Cl	2.2754(14)	2.2806(9)	2.3131(13)	2.2861(7)
Zn–N _{ax}	2.271(3)	2.236(3)	2.161(4)	2.113(2)
Zn–N _{Py}	2.064(3)	2.100(2)*	2.134(4)*	2.152(2)*
Zn–N _{Py}	2.063(3)	2.072(3)	2.120(4)*	2.186(2)*
Zn–N _{Py}	2.080(3)	2.093(2)	2.108(4)	2.211(2)*
Average Zn–N _{Py}	2.069(5)	2.088(4)	2.121(7)	2.183(4)
Cl–Zn–N _{ax}	177.90(9)	173.20(7)	170.18(12)	176.63(6)
Cl–Zn–N _{Py}	102.26(10)	108.76(7)*	103.07(12)*	103.76(6)*
Cl–Zn–N _{Py}	103.90(11)	102.55(8)	108.01(10)*	100.84(6)*
Cl–Zn–N _{Py}	100.46(10)	96.15(7)	93.54(16)	101.08(6)*
N _{ax} –Zn–N _{Py}	77.41(12)	77.46(9)*	78.95(16)*	79.45(8)*
N _{ax} –Zn–N _{Py}	78.10(13)	77.72(11)	79.88(15)*	76.98(8)*
N _{ax} –Zn–N _{Py}	78.14(12)	77.72(9)	77.36(15)	77.93(8)*
τ	0.86	0.80	0.83	0.94

* indicates that the pyridine ring is carrying the hydrogen bonding group.

Here, it should be noted that all these zinc(II) chloride complexes adopt a predominantly trigonal bipyramidal geometry, with τ ranging from 0.80 to almost unity. It is also greatest when three hydrogen bonding groups are present, which may reflect the greater symmetry of the ligand/metal complex.

In summary, the presence of internal N–H $\cdots$ Cl hydrogen bonds within the metal complexes contributes to the geometrical changes observed. They induce longer M–Cl bonds, and also maintain the structure in a predominantly trigonal bipyramidal arrangement.

2.3.3. H-Bond geometry/strength and nature of the H-bonding groups

Here, we report and compare geometric features of internal $RN-H\cdots Cl-Zn$ hydrogen bonds in a range of $[(L)Zn(Cl)]^+$ cations (Table 2.7). Based on steric considerations it may have been reasonable to expect the hydrogen bonds of the neopentylamino groups ($R = CH_2^tBu$) to be longer than those of the amino groups ($R = H$). It may have also been reasonable to expect the hydrogen bonds to be longer as the number of interactions increases, due to increasing steric hindrance and/or the $Zn-Cl$ unit becoming a poorer hydrogen bond acceptor. This structural study however, shows that amino and neopentylamino groups form hydrogen bonds with similar average hydrogen bond donor $\cdots$ acceptor distances. It shows also that increasing the number of local $RN-H$ groups does not result in longer hydrogen bonds. Thus, the average $N\cdots Cl$ distances are 3.213 Å in $[L^{Am-1}Zn(Cl)]^+$, 3.192 Å in $[L^{Am-2}Zn(Cl)]^+$ and 3.148 Å in $[L^{Am-3}Zn(Cl)]^+$, compared to 3.213 Å in $[L^{Np-1}Zn(Cl)]^+$, 3.219 Å in $[L^{Np-2}Zn(Cl)]^+$ and 3.169 Å in $[L^{Np-3}Zn(Cl)]^+$. It is, however, interesting to note that in the complexes bearing multiple hydrogen bonds, especially in the case of the $[L^{Np-3}Zn(Cl)]^+$ cation, the three hydrogen bonds are not equivalent; the $H\cdots Cl$ distance and the $N-H\cdots Cl$ angle are comparable for two of these interactions (2.26 Å and 2.23 Å / 155.1° and 156.1°) but the third interaction is dramatically different (2.12 Å / 167.1°). Finally, the presumably stronger hydrogen bond arising from the $N^{Piv}\cdots Cl$ interaction is not reflected in the $N\cdots Cl$ distance, 3.213 Å, which is identical to that observed for the amino and neopentylamino

complexes. Only the H $\cdots$ Cl distance appears to be slightly shorter (2.22 Å instead of 2.24 Å and 2.23 Å, respectively).

Table 2.7. Geometric features of internal hydrogen bonding interactions to the LZn–Cl units.⁹

Interaction	N–H ^a / Å	N $\cdots$ Cl/ Å	H $\cdots$ Cl/ Å	N–H $\cdots$ Cl/ ^o
<i>Amino group</i>				
[(L ^{Am-1})Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.213(3)	2.24	160.4
[(L ^{Am-2})Zn(Cl)] ⁺ N ^b –H ^b $\cdots$ Cl ^b	1.01	3.169(6)	2.45	127.2
N–H $\cdots$ Cl ^b	1.01	3.277(5)	2.31	160.1
N–H $\cdots$ Cl ^c	1.01	3.183(12)	2.22	157.8
N ^c –H ^c $\cdots$ Cl ^c	1.01	3.076(6)	2.15	150.9
[(L ^{Am-3})Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.157(8)	2.19	158.8
N–H $\cdots$ Cl	1.01	3.138(8)	2.18	158.7
N–H $\cdots$ Cl	1.01	3.149(8)	2.17	163.1
<i>Neopentylamino group</i>				
[L ^{Np-1} Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.213(3)	2.23	164.4
[L ^{Np-2} Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.211(4)	2.25	159.4
N–H $\cdots$ Cl	1.01	3.226(4)	2.27	157.2
[L ^{Np-3} Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.205(3)	2.26	155.1
N–H $\cdots$ Cl	1.01	3.187(3)	2.23	156.1
N–H $\cdots$ Cl	1.01	3.115(3)	2.12	167.1
<i>Pivaloylamido group</i>				
[L ^{Piv-1} Zn(Cl)] ⁺ N–H $\cdots$ Cl	1.01	3.213(4)	2.22	167.7

^a Extended distance: F. H. Allen, O. Kennard, D. G. Watson, L. Brammer and A. Guy Orpen, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1. ^b 67% Occupancy. ^c 33% Occupancy.

2.3.4. Comparison with changes occurring in the metal first coordination sphere

In order to evaluate the magnitude of the effects discussed above, it is interesting to compare them with the effects arising from changes in the first coordination sphere of the metal. For instance, are the changes in the geometry of the complex negligible or not when compared to changes induced by the change of axial ligand (Cl^- , $\text{NO}_3^- \dots$) or one (or more) of the pyridyl nitrogens? Changes which involve replacing one of the N_{py} donating arms of N_4 tripodal tris-pyridine ligands by another N-donating group lead to axial Zn–Cl distances that range from 2.264 Å in $[(\alpha\text{-PhTPA})\text{Zn}(\text{Cl})]^+$ to 2.289 Å in the mixed coordination/organometallic complex $[(\text{CpMn}(\text{CO})_2(\text{CH}_2\text{Pz}))\text{N}(\text{CH}_2\text{Py})_2]\text{Zn}(\text{Cl})$ in which an anionic pyrazole unit (Pz) is simultaneously coordinated to the zinc(II) and manganese(I) centres.^{14,15a}

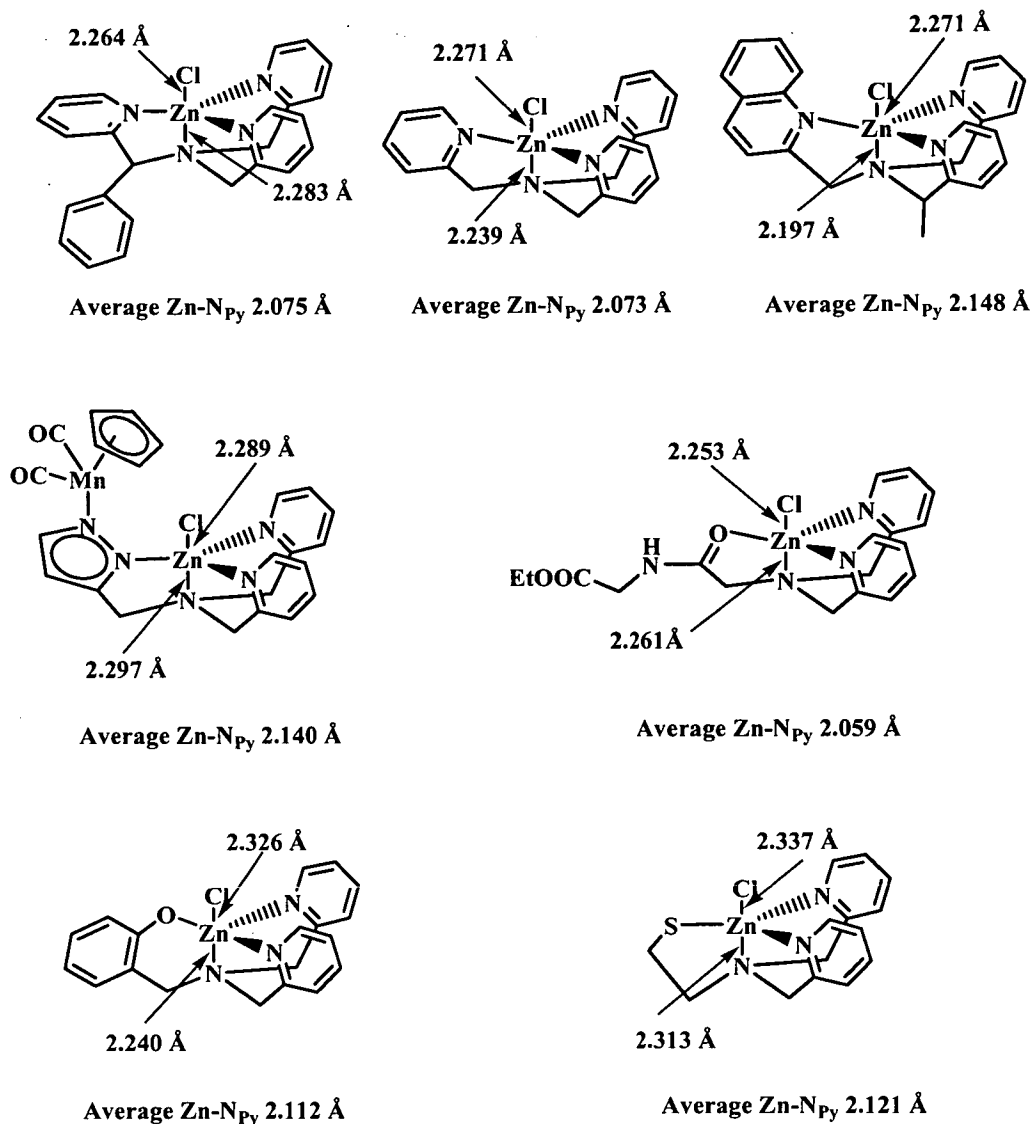


Figure 2.4. Zn-Cl and Zn-N bond lengths in some trigonal bipyramidal complexes.^{10,15}

Changes in the axial Zn-Cl distances are in this case accompanied by seemingly uncorrelated changes in the axial Zn-N distances of 2.271–2.297 Å.^{10,14-16} The average equatorial Zn-N_{py} distances are in the 2.070–2.140 Å range, with the longer distances corresponding to the more donating and/or sterically hindered ligand environments (Figure 2.4). It is interesting to compare the axial Zn-N and Zn-Cl

distances induced by a completely different tripodal N₄ ligand such as tris(2-aminoethyl)amine (tren); Zn–N 2.325 Å and Zn–Cl 2.308 Å to those shown in Figure 2.4.¹⁷ Thus, N₄ tripodal ligands induce axial Zn–Cl distances of 2.264–2.308 Å, and Zn–N_{ax} distances of 2.197–2.325 Å.

The replacement of one of the N_{py} donating arms by an O or S donating one, leading to N₃O or N₃S tripodal ligands, results in axial Zn–Cl distances of 2.253–2.371 Å and Zn–N distances of 2.240–2.398 Å, and equatorial Zn–N_{py} distances of 2.059–2.121 Å.¹⁸ The greater variability of distances found in this case probably reflects the greater differences in the ligand environment, with the poorer donating groups inducing shorter Zn–Cl and Zn–N_{py} distances.

It seems remarkable that the local non-coordinating N–H hydrogen bonding groups can induce changes in the Zn–Cl distances of comparable magnitude to those induced by major changes in the first coordination sphere of the zinc(II) centre. Moreover, it is remarkable that despite the electron donating nature of the hydrogen bonding groups the average equatorial Zn–N_{py} interaction is lengthened to a greater extent than by replacing a neutral by an anionic coordinating group. These changes induced by the hydrogen bonding groups may prove significant in determining the properties of these metal complexes. Also, from this structural analysis it appears that hydrogen bonding to the Zn–Cl causes a much greater influence in the *trans* Zn–N distance than changes in the first coordination sphere. The '*trans influence*' caused by the hydrogen bonding groups could, like conventional *trans influence*, be important in determining binding, properties and substitution mechanisms of metal-bound species.

Finally, the nature of the hydrogen bond acceptor can be proposed as a factor that influences the geometry of the hydrogen bond. Recently our group reported the X-ray structure of the $[L^{Np-2}Zn(OH)]^+$ cation showing two $N-H\cdots HO-Zn$ hydrogen bonds with an average $N\cdots O$ distance of 2.73 Å. The X-ray structure of $[L^{Np-2}Zn(X)]^+$ (X = Cl, NO_3) allows us to compare the geometries of internal hydrogen bonds to metal-bound hydrogen bond acceptor ligands as a function of the hydrogen bond acceptor. It is remarkable that despite the rigidity imposed by the $Zn-L$ binding, the average donor $\cdots$ acceptor distances are significantly different; 2.734 Å in $[L^{Np-2}Zn(OH)]^+$, 2.973 Å $[L^{Np-2}Zn(ONO_2)]^+$ and 3.219 Å $[L^{Np-2}Zn(Cl)]^+$.

It seems that hydrogen bonding to a metal bound ligand can dramatically affect the geometry of metal complexes. Since stronger hydrogen bonds could exert a greater effect than weaker ones, an important aspect would now be to investigate which factors can influence the strength of hydrogen bonds, so as to be able to modulate their impact to a desired extent.

2.3.5. Factors that influence the strength of hydrogen bonds

It is possible that the electron density on the acceptor atom could be one of the most, if not the most, important factors dictating the strength of $N-H\cdots Cl-M$ hydrogen bonds. To investigate this hypothesis, we decided to change the electron density on the acceptor atom by means of changing the metal oxidation state. Therefore, we synthesized and characterized the $[(L^{Piv-3})Cu(I)Cl]$ complex,¹⁹ and

compared it with its $[(L^{Piv-3})Cu(II)Cl]^+$ analogue, which was previously reported by Harata *et al.*²⁰

2.3.5.1. X-ray crystallography

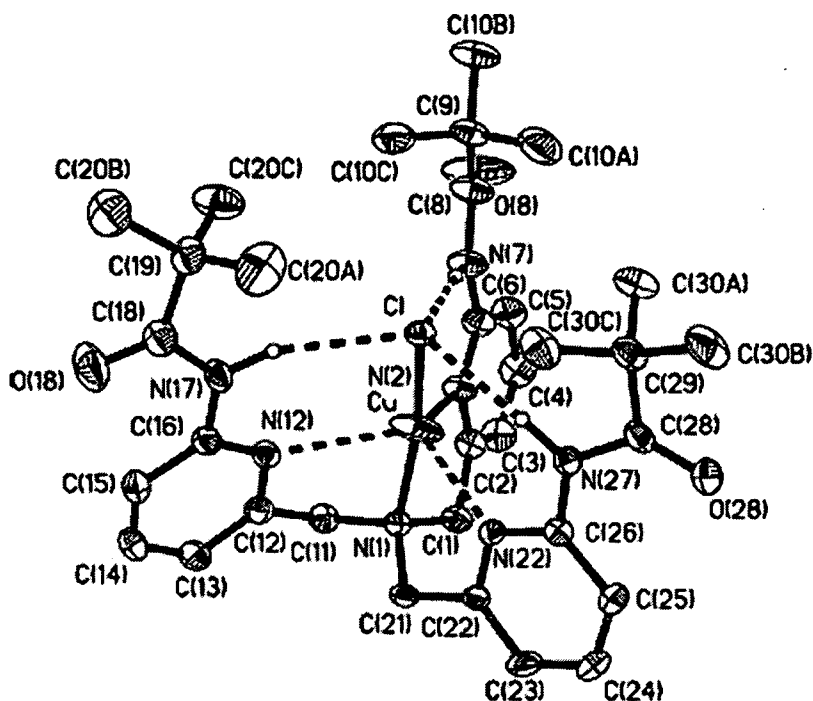


Figure 2.5. Thermal ellipsoid plot drawn with 50% probability ellipsoids of the $[(L^{Piv-3})Cu(I)Cl]$ showing the triple internal $N-H\cdots Cl-Cu$ hydrogen bonding. Only $N-H$ hydrogens are shown for clarity. Hydrogen bonds and weak interactions are highlighted with dashed lines.

The structure of $[(L^{Piv-3})Cu(I)Cl]$ (Figure 2.5) may be best described as pseudo-tricoordinate arising from the interaction of the Cu(I) centre with one pyridine nitrogen N(2), the alkylamine nitrogen N(1) and the chloride ion Cl(1). There appears to be two additional weak interactions between the Cu(I) centre and the two other pyridine N atoms, with $Cu-N(22) = 2.425 \text{ \AA}$ and $Cu-N(12) 2.635 \text{ \AA}$ outside the sum of their respective covalent radii (Table 2.8).

Interestingly, even though the lone pairs on the N atoms seem clearly directed toward the copper centre leading to a pseudo-trigonal bipyramidal structure, the Cu–N_{pyridine} distance is longer than those found in pentacoordinate Cu(II) complexes of these ligands. In general, Cu(II)–N_{py} distances range between 1.900 Å and 2.300 Å. Our findings reflect the weaker interaction between the pyridine rings and the Cu(I) centre as compared to Cu(II). This difference cannot be explained by the change of ionic radii alone, since Cu(II) is only 4 pm smaller than Cu(I). The degree of trigonality was evaluated by means of the angular structural parameter $\tau = (\beta - \alpha) / 60$. In the case of the [(L^{Piv-3})Cu(I)Cl], we found that $\tau = 0.85$.

Table 2.8. Selected bond lengths (Å) and angles (°) for [(L^{Piv-3})CuCl] and [(L^{Piv-3})CuCl]ClO₄²⁰.

	[(L ^{Piv-3})CuCl]	[(L ^{Piv-3})CuCl]ClO ₄
Cu–Cl	2.2244(6)	2.206(2)
Cu–N(1)	2.135(2)	1.955(5)
Cu–N(2)	2.192(2)	2.148(5)
Cu–N(12)	2.6354(21)	2.137(5)
Cu–N(22)	2.4247(20)	2.314(6)
Average Zn–N _{py}	2.3598	2.1997
Cl–Cu–N(1)	168.50(6)	174.88*
Cl–Cu–N(2)	110.86(6)	101.41*
Cl–Cu–N(12)	98.40(5)	100.96*
Cl–Cu–N(22)	101.44(5)	97.27*
N(1)–Cu–N(2)	79.91(8)	80.85*
N(1)–Cu–N(12)	72.72(7)	81.33*
N(1)–Cu–N(22)	75.98(7)	77.62*
τ	0.85	0.85

* indicates values for which the standard deviation was not calculated.

As expected the three amide N atoms are involved in N–H···Cl–Cu hydrogen bonding: N(7)···Cl(1) 3.342(2), N(17)···Cl(1) 3.418(2) and N(27)···Cl(1) 3.366(2) Å. The structure differs significantly from that of the $[(L^{\text{Piv-3}})\text{Cu(II)Cl}]^+$ complex (Cu–N_{pyridine} 2.148(5), 2.137(5) and 2.314(6) Å ; Cu–N_{amine} 1.955(5) Å ; Cu–Cl 2.206(2) Å; $\tau = 0.85$).²⁰ It is important to note that the three N–H···Cl–Cu hydrogen bonds in the $[(L^{\text{Piv-3}})\text{Cu(II)Cl}]^+$ complex are shorter by *ca.* 0.1–0.2 Å (N···Cl separation of 3.19, 3.15 and 3.24 Å) than in $[(L^{\text{Piv-3}})\text{Cu(I)Cl}]$, presumably due to the also shorter Cu–N_{pyridine} bonds.

2.3.5.2. Computational studies

In an attempt to correlate these experimental results with the electronic structure of the complexes in the Cu(I) and Cu(II) oxidation states, we performed *ab initio* MP2 calculations on both $[(L^{\text{Piv-3}})\text{Cu(I)Cl}]$ and $[(L^{\text{Piv-3}})\text{Cu(II)Cl}]^+$. The electronic structure was evaluated in terms of the Mulliken population analysis (MPA) and natural population analysis (NPA) to calculate the gross atomic charges for the atoms. The results are shown in Table 2.9.

Table 2.9. MPA and NPA calculations for the central copper and coordinating atoms in $[(L^{Piv-3})Cu(I)Cl]$ and $[(L^{Piv-3})Cu(II)Cl]^+$.

Atom	Cu(I) MPA	Cu(I) NPA	Cu(II) MPA	Cu(II) NPA
Cu	0.9277	0.9001	1.5759	1.7075
Cl	-1.0129	-0.9250	-0.7709	-0.6196
N _(ax)	-0.5999	-0.5998	-0.7349	-0.5590
N _(eq)	-0.6901	-0.6658	-0.8946	-0.7691
N _(eq)	-0.5600	-0.6167	-0.8004	-0.7487
N _(eq)	-0.6043	-0.6372	-0.8945	-0.7675

For the Cu(I) complex, both methods agree that there is an approximately equal positive and negative charge on the Cu and Cl, respectively. For the Cu(II) complex, both methods agree that there is a large positive charge on the Cu, and a reduced negative charge on the Cl, when compared to the Cu(I) complex. We used NMR and IR spectroscopy to investigate if the electron density of the metal-bound ligand acting as hydrogen bond acceptor is the major factor in determining the strength of the hydrogen bonds formed.

2.3.5.3. Infra-red studies

Infra-red spectroscopy can be used to study the strength of hydrogen bonds. Since the interaction of a hydrogen atom with an acceptor weakens the D–H bond, its stretching frequency decreases. The strength of the hydrogen bond can be approximately quantified, by using Iogansen's equation:²¹

$$-\Delta H = 1.3(\Delta\nu)^{1/2} \quad (\text{Eq. 2.1})$$

The IR spectra of $[(L^{Piv-1,2,3})Cu(I)Cl]$ and $[(L^{Piv-1,2,3})Cu(II)Cl]^+$ complexes in acetonitrile show the N–H stretching vibrations, ν_{N-H} , shifted to lower energy values

than in the corresponding ligand. The shifts, $\Delta \nu_{\text{N-H}}$, are shown in Table 2.10, as well as the strength of the N-H $\cdots$ Cl-Cu hydrogen bonding, approximately quantified from the positions of $\nu_{\text{N-H}}$ using Logansen's equation (Eq. 2.1). The magnitude of the shifts observed are bigger for the Cu(I) complexes and for the complexes with less H-bond donors, which indicates that the N-H $\cdots$ Cl-Cu hydrogen bond is stronger in the lower oxidation state, and when the Cl hydrogen bond acceptor is shared by less N-H donors (Figure 2.6).

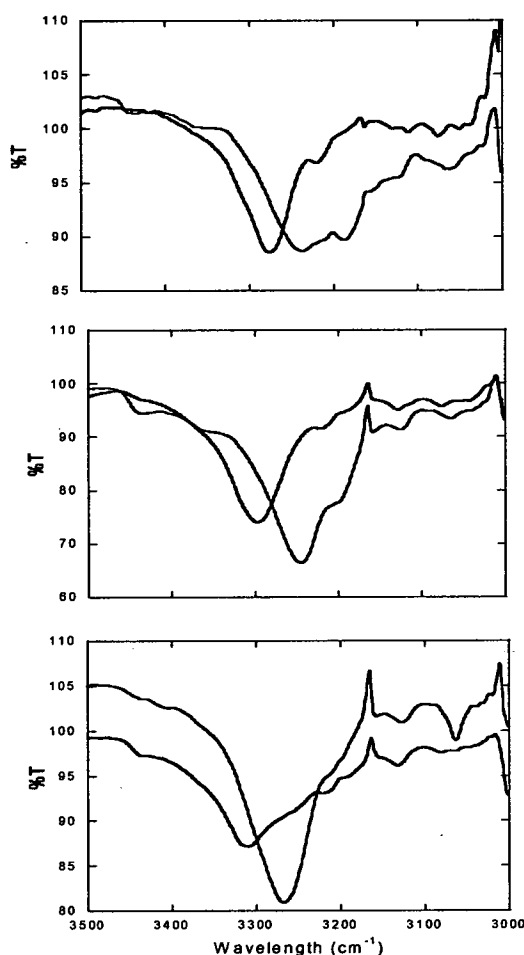


Figure 2.6. Partial IR spectra in acetonitrile solution showing $\nu_{\text{N-H}}$ of $[(L^{Piv-1})Cu(I)Cl]$ (top: red), $[(L^{Piv-1})Cu(II)Cl]^+$ (top: black), $[(L^{Piv-2})Cu(I)Cl]$ (middle: red), $[(L^{Piv-2})Cu(II)Cl]^+$ (middle: black), $[(L^{Piv-3})Cu(I)Cl]$ (bottom: red) and $[(L^{Piv-3})Cu(II)Cl]^+$ (bottom: black).

Table 2.10. Selected N-H vibration frequencies in the $[L^{Piv-n}Cu(I)Cl]$ and $[L^{Piv-n}Cu(II)Cl]^+$ complexes.

	$\nu_{(N-H)} (cm^{-1})$	$\Delta\nu (cm^{-1})$	H-bond energy (kJ.mol ⁻¹)
L^{Piv-1}	3439		
$[(L^{Piv-1})Cu(I)Cl]$	3237	202	18.5
$[(L^{Piv-1})Cu(II)Cl]^+$	3276	163	16.6
L^{Piv-2}	3440		
$[(L^{Piv-2})Cu(I)Cl]$	3244	196	18.2
$[(L^{Piv-2})Cu(II)Cl]^+$	3298	142	15.5
L^{Piv-3}	3442		
$[(L^{Piv-3})Cu(I)Cl]$	3267	175	17.2
$[(L^{Piv-3})Cu(II)Cl]^+$	3310	132	14.9

Another parameter which can be investigated in this way is the nature of the hydrogen bond acceptor. Different hydrogen bond acceptors have different electron density, and therefore a different ability to interact with hydrogen atoms in their vicinity.

IR spectroscopy was used to examine the strength of the hydrogen bonds due to the N-H groups in the $[L^{Np-2}Zn(OH)]^+$, $[L^{Np-2}Zn(ONO_2)]^+$ and $[L^{Np-2}Zn(Cl)]^+$ cations mentioned earlier on. They are characterized by ν_{N-H} of 3256, 3361 and 3305 cm^{-1} , respectively, compared to 3411 cm^{-1} in the 'free' L^{Np-2} ligand. Thus, as suggested by the X-ray crystallographic data the strength of N-H...X-Zn hydrogen bonds is strongly dependent on the nature of the hydrogen bond acceptor, and the strength order is $OH^- > Cl^- > NO_3^-$. This result is in accord with recent studies, which regard metal-bound chlorides as excellent hydrogen bond acceptors.²² An

interesting feature of this finding is that the strength of the interaction is much stronger in N–H $\cdots$ Cl–Zn than in N–H $\cdots$ ONO₂–Zn (13.4 kJ.mol⁻¹ and 9.2 kJ.mol⁻¹ respectively), despite the Zn $\cdots$ Cl distance (3.219 Å) being longer than the Zn $\cdots$ ONO₂ distance (2.973 Å).

2.3.5.4. NMR studies

We also used ¹H NMR spectroscopy to investigate if the oxidation state of the metal, and consequently the electron density on the chloride anion modulates the strength of the hydrogen bonds in the [(L^{Piv-n})CuCl]^{0/+} complexes. ¹H NMR studies (Figure 2.7) of the diamagnetic [(L^{Piv-n})Cu(I)Cl] complexes in acetonitrile reveal the characteristic downfield shift of the proton resonance of the hydrogen atom adjacent to the pivaloylamido group (H(5)) and the N–H, which is indicative of an orientation of the amide group suitable for C–H(5) $\cdots$ O=C and N–H $\cdots$ Cl–Cu hydrogen bonding. The position of the N–H resonance can be used to qualitatively evaluate the strength of N–H $\cdots$ Cl–Cu hydrogen bonding. The downfield shift of the N–H resonance relative to the free ligand follows the order L^{Piv-1} > L^{Piv-2} > L^{Piv-3} indicating the strength of the N–H $\cdots$ Cl–Cu hydrogen bonding interaction follows the same order.

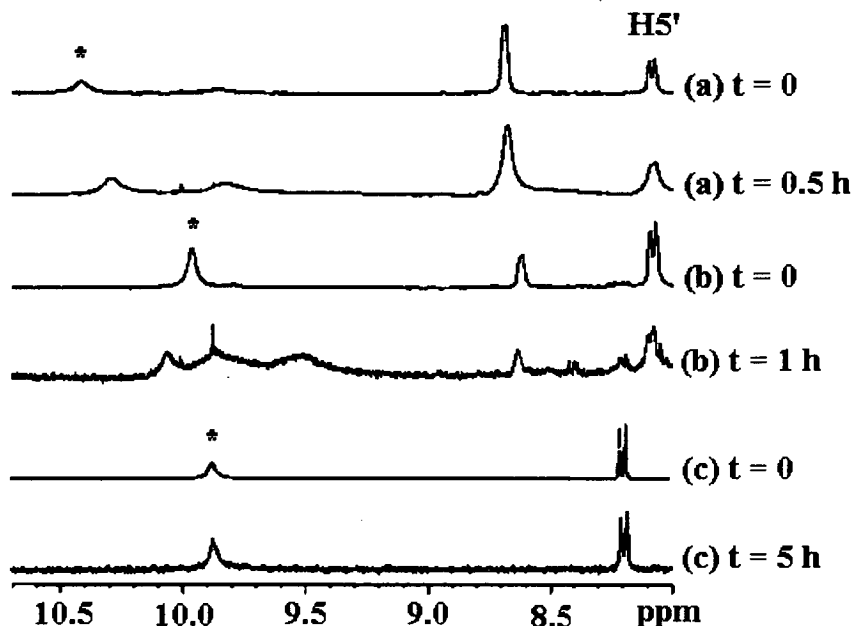


Figure 2.7. Selected region (NH and H5 proton resonances) of the ^1H NMR spectrum (360.1 MHz, CD_3CN , 293K) of $[(\text{L}^{\text{Piv-1}})\text{Cu}^{\text{I}}\text{Cl}]$ (a), $[(\text{L}^{\text{Piv-2}})\text{Cu}^{\text{I}}\text{Cl}]$ (b) and $[(\text{L}^{\text{Piv-3}})\text{Cu}^{\text{I}}\text{Cl}]$ (c), before (black spectra) and after exposure to air (red spectra). * indicates the position of the NH proton resonance.

On exposure to air additional peaks consistent with the oxidation product(s) appear over time. The rate of oxidation follows the order $\text{L}^{\text{Piv-1}} > \text{L}^{\text{Piv-2}} \gg \text{L}^{\text{Piv-3}}$, in excellent agreement with the increased steric hindrance and reduction potential (Chapter 3) of the copper centre in the same order. Surprisingly, the N–H resonances of the Cu(II) products are shifted upfield relative to that of the Cu(I) complexes. This is surprising because by inductive effects the N–H groups should be more acidic *i.e.* better hydrogen bond donors when the pyridine is bound to the Cu(II) centre. Moreover, copper ligand distances are generally shorter in the Cu(II) than Cu(I) oxidation state, which should bring the N–H and Cl hydrogen bonding groups in closer proximity in the former oxidation state. Clearly, the N–H $\cdots$ Cl–Cu hydrogen

bonds are stronger in the Cu(I) than in the Cu(II) complexes because the Cl is more electron rich and therefore a better hydrogen bond acceptor in the former case. Interestingly, the N–H resonances are progressively shifted upfield on going from $L^{\text{Piv-1}}$ (δ 10.41 ppm) to $L^{\text{Piv-3}}$ (δ 9.88 ppm), which suggests that the hydrogen bonding is weakened as the Cu–Cl hydrogen bond acceptor is shared between the N–H hydrogen bond donors. These results suggest that the electron density on a metal-bound substrate is a major factor determining the strength of internal hydrogen bonding to it. Thus, the agreement between the NMR and IR studies is excellent. Finally, the spectrum of the $[(L^{\text{Piv-3}})\text{Cu(I)Cl}]$ complex showed no noticeable change upon exposure to air. This indicates a remarkable stability, which allowed the isolation of crystals suitable for X-Ray crystallography, as discussed previously.

From this data it seems that even though the overall H-bond strength increases due to extra number of interactions, the magnitude of the effect of each H-bond is greater the fewer the interactions. Also, hydrogen bonds are stronger in Thus, chemistry at hydrogen bonding cavities may be most effectively pursued with fewer hydrogen bond donors and a more electron donating ligand environment.

2.4. Conclusion

This study has examined the effect that RN–H hydrogen bonding groups (R = H, CH_2^tBu) of $\text{N}(\text{CH}_2\text{Py})_{3-n}(\text{CH}_2\text{Py-6-NHR})_n$ ligands L (n = 1–3) have on L –Zn and Zn–Cl distances of trigonal bipyramidal $[(L)\text{Zn}(\text{Cl})]^+$ cations. The magnitude of the structural changes exerted by the hydrogen bonding groups is compared with those arising from a range of $\text{N}(\text{CH}_2\text{Py})_2(\text{CH}_2\text{Y})$ (Y = coordinating group) ligands. Among

the implications of introducing local RN–H hydrogen bonding groups is the shortening of the axial Zn–N, lengthening of the equatorial Zn–N_{py} and lengthening of the axial Zn–Cl bonds by as much as 0.16, 0.12 and 0.07 Å, respectively. In general, the magnitude of these changes increases as the number of the hydrogen bonding groups increases, and these changes are comparable or greater in magnitude than those arising from significant changes in the zinc(II) first coordination sphere. This result is consistent and contributes to recent studies showing the great potential of ligands with hydrogen bonding groups as a way to tune chemistry at metal sites.^{3–8} In some cases differences between the changes induced by R = H and CH₂^tBu were noted, which could lead to different chemistry. This structural study also provides the first comparison of geometries of internal N–H...X–Zn hydrogen bonds (X = Cl[–], OH[–], NO₃[–]) as a function of the hydrogen bond acceptor X. Despite the rigidity imposed by the Zn–L binding, the average N...X distances are significantly different as X is varied, and they follow the order OH[–] < NO₃[–] < Cl[–]. The strength of the N–H...X–Zn hydrogen bonds (X = Cl[–], OH[–], NO₃[–]), however, follows the order OH[–] > Cl[–] > NO₃[–], which suggests that metal-bound chloride ions are better hydrogen bond acceptors than metal-bound nitrate ions.

We have estimated the N–H...Cl hydrogen bond energy in the [L^{Piv-n}CuCl]⁺ complexes, and noticed that the individual contribution of each hydrogen bond introduced, to the destabilization of the Cu(II) system decreases when more numerous hydrogen bonds are present.

Importantly, NMR and infra-red studies reveal that the strength of the hydrogen bond depends on the oxidation state of the metal, and we propose that this

is due to a higher electron density on the chloride anion, as corroborated by *ab initio* MP2 calculations.

This study should facilitate the design of new models for modeling the active-site of redox-active metalloproteins.

2.5. Experimental section

2.5.1. Materials and Methods

Reagents were obtained from commercial sources and used as received unless otherwise noted. Solvents were dried and purified under N₂ by using standard methods²³ and were distilled immediately before use. All compounds were prepared under N₂ unless otherwise mentioned. The synthesis of TPA, L^{Am-3}, and L^{Piv-n} were adapted from the literature and their purity checked by both ¹H NMR spectroscopy and mass spectrometry. The NMR spectra were obtained using a Bruker DPX 360 at 20 °C in CD₃CN unless otherwise noted. ¹H chemical shifts are referenced with respect to the residual proton (δ_{H} 1.94 ppm) solvent peak. ¹³C and ¹H chemical shifts are referenced with respect to the carbon (δ_{C} 1.32 and 118.26 ppm) and residual proton (δ_{H} 1.94 ppm) solvent peaks. Mass spectra were performed on a Micromass Platform II system operating in Flow Injection Analysis mode with the electrospray method. Infrared spectra were recorded with a JASCO FTIR-410 spectrometer between 4000 and 250 cm⁻¹ as KBr pellets or as acetonitrile solutions in KBr cells. The strength of N-H...Cl-Zn hydrogen bonding was estimated using solution FTIR

studies applying Iogansen's equation.²¹ Intensity data for of $[(L^{Am-3})Zn(Cl)](BPh_4)$ and $[(L^{Piv-3})Cu(Cl)]$ were collected at 150 K using a Bruker-AXS SMART APEX area detector diffractometer with graphite-monochromated Mo-K α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined to convergence against F^2 data using the SHELXTL suite of programs.²⁴ Data were corrected for absorption applying empirical methods using the program SADABS,²⁵ and the structures were checked for higher symmetry using the program PLATON.²⁶ All non-hydrogen atoms were refined anisotropically unless otherwise noted. Hydrogen atoms were placed in idealised positions and refined using a riding model with fixed isotropic displacement parameters. The N-H hydrogens were located in the difference map and refined isotropically. All calculations were performed using the resources of the EPSRC National Service for Computational Chemistry Software (NSCCS) supercomputer Columbus.²⁷ Single-point energy calculations were performed for both $[(L^{Piv-3})Cu(I)Cl]$ and $[(L^{Piv-3})Cu(II)Cl]^+$ using the MP2(fc) method with a 6-311G* basis set.²⁸ Coordinates for $[(L^{Piv-3})Cu(I)Cl]$ were taken from the crystal structure described in this work, whilst coordinates for $[(L^{Piv-3})Cu(II)Cl]^+$ were obtained from the work of Harata *et al.*²⁰ using the resources of the Cambridge Crystallographic Data Centre.²⁹ Calculations were performed to analyse the charge distribution in the molecules. As atomic charge is not a quantum mechanical observable, two different methods to partition the electron density among the atoms in the molecular systems were explored, namely the Mulliken Population Analysis (MPA) and Natural Population Analysis (NPA).³⁰

2.5.2. Ligand synthesis

N,N-Bis(2-pyridylmethyl)-*N*-(6-pivaloylamido-2-pyridylmethyl)amine (**L^{Piv-1}**)

2-(Pivaloylamido)-6-(aminomethyl)pyridine (7 g, 34 mmol) and 2-picolyl chloride (11 g, 68 mmol) were dissolved in acetonitrile (100 mL) and stirred at room temperature for 5 minutes. Then, sodium carbonate (36.4 g, 0.34 mol) was added and the temperature was raised to 44 °C. After 48 h the solution was cooled to room temperature and poured into 200 mL of 1 M NaOH_(aq). The crude product was then extracted with dichloromethane (3 × 80 mL) and the organic fractions were dried over Na₂SO₄. The solvent was evaporated under vacuum to yield the crude product as a brown oil. The crude material was recrystallised from diethyl ether (100 mL) to yield the pure product as a dark red solid (7.6 g, 59 %).

Comparison of the ¹H NMR and mass spectra of the ligand with literature values confirmed its purity.³¹

¹H NMR (CD₃CN, 360.1 MHz) δ_H (ppm) 8.47 (dd, *J* = 4.9, 1.9 Hz, 2H, py-*H*6), 8.16 (s, 1H, *NH*), 7.98 (t, *J* = 8.2 Hz, 1H, py'-*H*5), 7.70 (td, *J* = 7.7 and 1.8 Hz, 2H, py-*H*5), 7.69 (t, *J* = 7.8 Hz, 1H, py'-*H*4), 7.60 (d, *J* = 7.7 Hz, 2H, py-*H*3), 7.32 (d, *J* = 7.3 Hz, 1H, py'-*H*3), 7.18 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 2H, py-*H*5), 3.79 (s, 4H, NCH₂-py), 3.71 (s, 2H, NCH₂-py'), 1.26 (s, 9H, C-(CH₃)₃). ESI-MS (+ion) Found 390.3, Calcd. 390.2.

N,N-bis-(6-pivaloylamido-2-pyridylmethyl)-*N*-(2-pyridylmethyl)amine (**L^{Piv-2}**)

2-(Aminomethyl)pyridine (0.37 g, 3.4 mmol) and 2-(pivaloylamido)-6-(bromomethyl)pyridine (2.0 g, 6.8 mmol) were dissolved in acetonitrile (80 mL) and stirred at room temperature for 5 minutes. Then, sodium carbonate (1.0 g, 9.43

mmol) and tetrabutylammonium bromide (10 mg, 0.03 mmol) were added and the temperature was raised to 44 °C. After 48 h the solution was cooled to room temperature and poured into 100 mL of 1M NaOH_(aq). The crude product was then extracted with dichloromethane (3 x 80 mL) and the organic fractions were dried over Na₂SO₄. The solvent was evaporated under vacuum to yield the product as a brown oil (2.2 g, 66%).

Comparison of the ¹H NMR and mass spectra of the ligand with literature values confirmed its purity.³²

¹H NMR (CD₃Cl, 360.1 MHz) δ_H (ppm) 8.53 (m, 1H py-*H6*), 8.11 (d, J = 8.3 Hz, 2H, py'-*H5*), 8.01 (s, 2H, NH), 7.67 (t, J = 7.9 Hz, 2H, py'-*H4*), 7.60 (d, J = 7.7 Hz, 2H, py-*H3*), 7.57 (m, 1H, py-*H4*), 7.29 (d, J = 7.3 Hz, 2H, py'-*H3*), 7.15 (m, 1H, py-*H5*), 6.88 (d, J = 7.2 Hz, 1H, py-*H3*), 3.87 (s, 2H, NCH₂-py), 3.76 (s, 4H, NCH₂-py'), 1.33 (s, 6H, C-(CH₃)₃). ESI-MS (+ion) Found 488.9, Calcd. 488.3.

***N,N,N*-Tris(6-pivaloylamido-2-pyridylmethyl)amine (L^{Piv-3})**

2-(pivaloylamido)-6-(bromomethyl)pyridine (7 g, 24.1 mmol) was dissolved in 100 mL of acetonitrile and 2-(pivaloylamido)-6-aminomethyl-pyridine (2.48 g, 12.0 mmol) was added. After 5 minutes of stirring, sodium carbonate was added (2.12 g, 20 mmol) and the mixture brought to reflux for 48 hours. The crude product is then purified by chromatography on neutral alumina. The final product is then dried under high vacuum.

Comparison of the ^1H NMR and mass spectra of the ligand with literature values confirmed its purity.²⁰

^1H NMR (CD_3CN , 360.1 MHz) δ_{H} (ppm) 8.18 (s, 3H, NH), 7.99 (d, $J = 7.8$ Hz, 3H, py'-H5), 7.70 (t, 3H, $J = 7.9$ Hz, py'-H4), 7.33 (d, $J = 7.7$ Hz, 3H, py'-H3), 3.74 (s, 6H, $\text{NCH}_2\text{-py}'$), 1.27 (s, 27H, C-(CH_3)₃). ESI-MS (+ion) Found 587.7, Calcd. 587.3.

***N,N,N*-Tris(6-amino-2-pyridylmethyl)amine ($\text{L}^{\text{Am-3}}$)**

$\text{L}^{\text{Piv-3}}$ (6 g, 10.2 mmol) was dissolved in 2M $\text{HCl}_{(\text{aq})}$ (100 mL) and the solution was refluxed for 48 h. The solution was then cooled to room temperature and poured into 1M $\text{NaOH}_{(\text{aq})}$. The product was extracted with dichloromethane (3 x 100 mL) and the organic fractions were dried over Na_2SO_4 . The solvent was evaporated under vacuum and washed with diethyl ether to yield the product as a brown solid (2.1 g, 61%).

Comparison of the ^1H NMR and mass spectra of the ligand with literature values confirmed its purity.⁴

^1H NMR ($\text{DMSO-}d_6$, 360.1 MHz) δ_{H} (ppm) 7.33 (t, $J = 7.5$ Hz, 3H, NH, py'-H4), 6.74 (d, $J = 7.5$ Hz, 3H, py'-H3), 6.28 (d, $J = 8.1$ Hz, 3H, py'-H5), 5.76 (s, 6H, NH), 3.48 (s, 6H, $\text{NCH}_2\text{-py}'$). ESI-MS (+ion) Found 336.1, Calcd. 335.2.

2.5.3. Metal complexes synthesis

Apart from $[\text{L}^{\text{Am-3}}\text{ZnCl}]\text{BPh}_4$ and $[\text{L}^{\text{Piv-3}}\text{CuCl}]$, the complexes synthesized were not isolated. However, the purity and identity was checked by mass spectrometry, and in several cases by X-ray crystallography and ^1H NMR.

Synthesis of [L^{Piv-1}CuCl]Cl

To a stirred solution (10 mL) of CuCl₂ (16.8 mg, 1.25 mmol) in dry MeCN was added L^{Piv-1} (48.6 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 487.3, Calcd. 487.1

Synthesis of [L^{Piv-2}CuCl]Cl

To a stirred solution (10 mL) of CuCl₂ (16.8 mg, 1.25 mmol) in dry MeCN was added L^{Piv-2} (61 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 586.1, Calcd. 586.2.

Synthesis of [L^{Piv-3}CuCl]Cl

To a stirred solution (10 mL) of CuCl₂ (16.8 mg, 1.25 mmol) in dry MeCN was added L^{Piv-3} (73.4 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 685.6, Calcd. 685.3.

Synthesis of [L^{Piv-1}CuCl]

Inside the glove box, L^{Piv-1} (48.6 mg, 1.25 mmol) was added to a stirred solution (10 mL) of CuCl (9.2 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 487.3, Calcd. 487.1.

Synthesis of [L^{Piv-2}CuCl]

Inside the glove box, L^{Piv-2} (61 mg, 1.25 mmol) was added to a stirred solution (10 mL) of CuCl (9.2 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 586.3, Calcd. 586.2.

Synthesis of [L^{Piv-3}CuCl]

Inside the glove box, L^{Piv-3} (73.4 mg, 1.25 mmol) was added to a stirred solution (10 mL) of CuCl (9.2 mg, 1.25 mmol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 685.3, Calcd. 685.3

Synthesis of [L^{Am-3}ZnCl]BPh₄

ZnCl₂ (20 mg, 0.146 mmol) and L^{Am-3} (49 mg, 0.146 mmol) were mixed in dry acetonitrile (20 mL) and the solution was stirred for 2 h at room temperature. The solvent was removed under vacuum. To the crude product in methanol (3 mL) was added sodium tetraphenylborate (51 mg, 0.146 mmol). The resulting solution was stirred at room temperature for 1 h and filtered. The precipitate was dried under vacuum to yield the compound as a pale grey solid (14 mg, 12%) (Found: C, 65.9; H, 5.6; N, 12.3. Calc. for C₄₂H₄₁ClN₇BZn·0.5H₂O: C, 65.99; H, 5.56; N, 12.83%).

¹H NMR (CD₃CN, 360.1 MHz): δH (ppm): 7.52 (dd, *J* = 7.2 and 8.3 Hz, 3H, py-*H*), 6.68 (br, 6H, NH₂-py), 6.59 (d, *J* = 8.6 Hz, 3H, py-*H*), 6.53 (d, *J* = 7.2 Hz, 2H, py-*H*), 3.76 (s, 6H, NCH₂-py); BPh₄ – 7.26 (m, 8H, Ar-*H*₂), 7.00 (t, *J* = 7.2 Hz, 8H, Ar-*H*₃) and 6.83 (t, *J* = 7.2 Hz, Ar-*H*₄). ¹³C NMR (CD₃CN, 90.5 MHz, 298 K): δC (ppm): 162.2 and 151.7 (py-*C*), 141.5, 112.9 and 112.5 (py-CH), 56.2 (NCH₂-py); BPh₄ 164.2 (B-*C*₁, *J*_{B-C} = 49 Hz), 136.6 (*C*₂), 126.5 (*C*₃), 122.7 (*C*₄).

ESI-MS (MH⁺) Found 433.9, Calcd. 434.1

2. 6. References

1. (a) R. H. Holm, P. Kennepohl and E. I. Solomon, *Chem. Rev.*, 1996, **96**, 2239; (b) Y. Lu and J. S. Valentine, *Curr. Opin. Struct. Biol.*, 1997, **7**, 495; (c) B. A. Springer, S. G. Sligar, J. S. Olsen and G. N. Philips, *Chem. Rev.*, 1996, **96**, 2239; (d) M. F. Perutz, G. Fermi, B. Luisi, B. Shaanan and R. C. Liddington, *Acc. Chem. Res.*, 1987, **20**, 309; (e) A. Ivancich, K. Artz, J. C. Williams, J. P. Allen and T. A. Mattioli, *Biochemistry*, 1998, **37**, 11812; (f) K. Rose, S. E. Shadle, M. K. Eidsness, D. K. Kurtz, Jr., E. A. Scott, B. Hedman, K. A. Hodgson and E. I. Solomon, *J. Am. Chem. Soc.*, 1998, **120**, 10743; (g) C. K. Vance and A.-F. Miller, *Biochemistry*, 2001, **40**, 13079.
2. (a) S. E. V. Phillips and B. P. Schoenborn, *Nature*, 1981, **292**, 81; (b) K. Nagai, B. Luisi, D. Shih, G. Miyazaki, K. Imai, C. Poyart, A. De Young, L. Kwiatkowsky, R. W. Noble, S.-H. Lin and N.-T. Yu, *Nature*, 1987, **329**, 858; (c) M. Mukai, S. Nagano, M. Tanaka, K. Ishmori, I. Morishima, T. Ogura, Y. Watanabe and T. Kitagawa, *J. Am. Chem. Soc.*, 1997, **119**, 1758; (d) D. E. Goldberg, *Chem. Rev.*, 1999, **99**, 3371; (e) M. S. Lah, M. M. Dixon, K. A. Patridge, W. C. Stallings, J. A. Fee and M. L. Ludwig, *Biochemistry*, 1995, **34**, 1646.
3. Representative examples: (a) C. E. MacBeth, A. P. Golombek, V. G. Young, Jr., C. Yang, K. Kuczera, M. P. Hendrich and A. S. Borovik, *Science*, 2000, **289**, 938; (b) A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa and H. Einaga, *Angew.*

- Chem., Int. Ed.*, 1998, **37**, 1703; (c) S. Ogo, S. Wada, Y. Watanabe, M. Iwase, A. Wada, M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Angew. Chem., Int. Ed.*, 1998, **37**, 2102; (d) M. Matsu-ura, F. Tani, S. Nakayama, N. Nakamura and Y. Naruta, *Angew. Chem., Int. Ed.*, 2000, **39**, 1989; (e) N. Suzuki, T. Higuchi, Y. Urano, K. Kikuchi, H. Uekusa, Y. Ohashi, T. Uchida, T. Kitagawa and T. Nagano, *J. Am. Chem. Soc.*, 1999, **121**, 11571; (f) N. Ueyama, N. Nishikawa, Y. Yamada, T. Okamura, S. Oka, H. Sakurai and A. Nakamura, *Inorg. Chem.*, 1998, **27**, 2415; (g) J. J. A. Cooney, M. D. Carducci, A. E. McElhaney, H. D. Selby and J. H. Enemark, *Inorg. Chem.*, 2002, **41**, 7086; (h) E. Kövári and R. Krämer, *J. Am. Chem. Soc.*, 1996, **118**, 12704; (i) L. Cronin and P. H. Walton, *Chem. Commun.*, 2003, 1572.
4. J. C. Mareque-Rivas, R. Prabakaran and R. Torres Martín de Rosales, *Chem. Commun.*, 2004, 76.
 5. J. C. Mareque-Rivas, R. Torres Martín de Rosales and S. Parsons, *Chem. Commun.*, 2004, 610.
 6. J. C. Mareque-Rivas, E. Salvagni, R. Torres Martín de Rosales and S. Parsons, *Dalton Trans.*, 2003, 3339.
 7. (a) M. M. Makowska-Grzyska, P. C. Jeppson, R. A. Allred, A. M. Arif and L. M. Berreau, *Inorg. Chem.*, 2002, **41**, 4872; (b) L. Berreau, M. M. Makowska-Grzyska and A. M. Arif, *Inorg. Chem.*, 2001, **40**, 2212; (c) C. Kimblin, X. Bu and A. Butler, *Inorg. Chem.*, 2002, **41**, 161; (d) K. Jitsukawa, M. Harata, H. Arai, H. Sakurai and H. Masuda, *Inorg. Chim. Acta*, 2001, **324**, 108.

8. (a) K. J. Tubbs, A. L. Fuller, B. Bennett, A. M. Arif, M. M. Makowska-Grzyska and L. M. Berreau, *Dalton Trans.*, 2003, 3111; (b) K. J. Tubbs, A. L. Fuller, B. Bennett, A. M. Arif and L. M. Berreau, *Inorg. Chem.*, 2003, **42**, 4790; (c) D. K. Garner, S. B. Fitch, L. H. McAlexander, L. M. Bezold, A. M. Arif and L. M. Berreau, *J. Am. Chem. Soc.*, 2002, **124**, 9970; (d) L. M. Berreau, R. R. Allred, M. M. Makowska-Grzyska and A. M. Arif, *Chem. Commun.*, 2000, 1423; (e) H. Arai, Y. Funahashi, K. Jitsukawa and H. Masuda, *Dalton Trans.*, 2003, 2115; (f) S. Ogo, R. Yamahara, M. Roach, T. Suenobu, M. Aki, T. Ogura, T. Kitagawa, H. Masuda, S. Fukuzumi and Y. Watanabe, *Inorg. Chem.*, 2002, **41**, 5513; (g) S. Yamauchi, I. Tokairin, Y. Funahashi, K. Jitsukawa and H. Masuda, *Chem. Lett.*, 2003, **32**, 406.
9. J. C. Mareque-Rivas, R. Prabakaran, R. Torres Martin de Rosales, L. Metteau and S. Parsons, *Dalton Trans.*, 2004, 2800.
10. H. Adams, N. A. Bailey, D. E. Fenton and Q.-Y. He, *J. Chem. Soc., Dalton Trans.*, 1997, 1533.
11. A. W. Addison, T. N. Rao, J. Reedijk, J. van Rijn and G. C. Werchoor, *J. Chem. Soc., Dalton Trans.*, 1984, 1349.
12. J. C. Mareque-Rivas, R. Prabakaran and S. Parson, *Dalton Trans.*, 2004, 1648.
13. K. Jitsukawa, Y. Oka, H. Einaga and H. Masuda, *Tetrahedron Lett.*, 2001, **42**, 3467.
14. (a) J. W. Canary, C. S. Allen, J. M. Castagnetto, Y.-H. Chiu, P. J. Toscano and Y. Wang, *Inorg. Chem.*, 1998, **37**, 6255; (b) J. W. Canary,

- C. S. Allen, J. M. Castagnetto and Y. Wang, *J. Am. Chem. Soc.*, 1995, **117**, 8484.
15. J. C. Roder, F. Meyer, R. F. Winter and E. Kaifer, *J. Organomet. Chem.*, 2002, **641**, 113.
16. C. S. Allen, C.-L. Chuan, M. Cornebise and J. W. Canary, *Inorg. Chim. Acta*, 1995, **239**, 29.
17. R. J. Sime, R. L. Dodge, A. Zalkin and D. H. Tempelton, *Inorg. Chem.*, 1971, **10**, 537.
18. (a) N. Niklas, S. Wolf, G. Liehr, C. E. Anson, A. K. Powell and R. Alsfasser, *Inorg. Chim. Acta*, 2001, **314**, 126; (b) N. Bag, S.-S. Chern, S.-M. Peng and C. K. Chang, *Inorg. Chem.*, 1995, **34**, 753; (c) A. Trosch and H. Vahrenkamp, *Eur. J. Inorg. Chem.*, 1998, 827; (d) H. Kurosaki, T. Tawada, S. Kawasoe, Y. Ohashi and M. Goto, *Biorg. Med. Chem. Lett.*, 2000, **10**, 1333; (e) R. Burth, A. Stange, M. Schafer and H. Vahrenkamp, *Eur. J. Inorg. Chem.*, 1998, 1759.
19. J. C. Mareque-Rivas, S. L. Hinchley, L. Metteau and S. Parsons, *Dalton Trans.*, 2006, 2316.
20. M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Chem. Lett.*, **1995**, 61.
21. (a) A. V. Iogansen, G. A. Kurkchi, V.M. Furman, V. P. Glazumov and S. E. Odinokov, *Zh. Prikl. Spektrosk.*, 1980, **33**, 460; (b) A. V. Iogansen, in *Vodorodnaya Svyaz (Hydrogen Bonding)*, ed. N. D. Solokov, Nauka, Moscow, 1981, p. 112 (in Russian); (c) A. V. Iogansen, *Spectrochim.*

- Acta, Part A*, 1999, **55**, 1585; (d) S. G. Kazarian, P. M. Hamley and M. Poliakoff, *J. Am. Chem. Soc.*, 1993, **115**, 9069.
22. G. Aullón, D. Bellamy, L. Brammer, E. A. Bruton and A. G. Orpen, *Chem. Commun.*, 1998, 653.
23. W. L. F. Armarego and D. D. Perrin, '*Purification of Laboratory Chemicals*', Butterworth-Heinemann, Oxford, 1997.
24. G. M. Sheldrick, '*SHELXTL 97*', University of Göttingen, 1997.
25. G. M. Sheldrick, '*SADABS, Empirical absorption correction program*', University of Göttingen, 1995, based upon the method of Blessing.
26. A. L. Spek, *Acta Crystallogr., Sect. A.*, 1990, **46**, C34.
27. EPSRC National Service for Computational Chemistry Software. URL: <http://www.nscs.ac.uk>.
28. (a) A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, 1980, **72**, 5639; (b) R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1980, **72**, 650.
29. Cambridge Crystallographic Data Centre. URL: <http://www.ccdc.cam.ac.uk>.
30. E. D. Glendening, A. E. Reed, J. E. Carpenter and F. Weinhold, *NBO Version 3.1*.
31. J. C. Mareque-Rivas, R. Torres Martín de Rosales and S. Parsons, *Dalton Trans.*, 2003, 2156.
32. M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, H. Einaga, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1031.

Chapter 3:

**Effect of internal H-bonding on redox properties
of $[\text{LCuCl}]^+$ complexes (L = TPA derivative)**

3.1. Introduction

The effects and roles of metals and their first coordination sphere in regulating chemical processes in biology have been extensively studied. The study of copper complexes is relevant to this type of chemistry since copper is a common cofactor to many biological processes, especially in dioxygen-related chemistry.^{1a} Copper proteins that bind and/or activate dioxygen perform a variety of critical biological functions, which include O₂ transport (hemocyanin^{1b}), aromatic ring oxidations (tyrosinase,^{1c} catechol oxidase,^{1d} and quercetin 2,3-dioxygenase^{1e}), the biogenesis of neurotransmitters and peptide hormones (dopamine β -monooxygenase,^{1f} and peptidylglycine R-amidating monooxygenase^{1g}), hydrogen peroxide generation (galactose and glyoxal oxidases)^{1h}, iron homeostasis (ceruloplasmin and Fet3p)¹ⁱ, and methane oxidation (particulate methane monooxygenase)^{1j}, among others.

A critical issue in these diverse chemistries is the redox properties of the metal. Owing to the fact that the Cu(III) oxidation state is generally considered to be inaccessible because of the highly positive Cu(III)/Cu(II) redox potentials that result from ligation of strongly basic and anionic ligands,² the most relevant oxidation states for copper are Cu(I) and Cu(II). Many factors are known to influence the redox potentials of copper complexes. These include the flexibility or constraints imposed by the ligand environment, which might favour a geometry preferred by one metal ion oxidation state, but not the other, the types of donor atoms (i.e., O vs N vs S), the geometry of coordinated complex, the second coordination sphere, etc.

3.2. Geometric preferences of Cu(I) and Cu(II) ions

Designing small-molecule models that mimic the active site of redox metalloenzymes is difficult since Nature uses exquisitely designed macromolecular engineering to achieve both remarkable levels of reactivity and substrate selectivity. Moreover, these active sites are able to survive many redox turnovers. Thus, their synthetic models may have to be able to accommodate metals in more than one oxidation state. Since copper is involved in many important redox metalloenzymes, it is important to examine the geometric preferences of Cu(I) and Cu(II) ions.

Cu(I) has a d^{10} electronic configuration and is relatively indifferent to the coordination geometry. This is dominated by steric factors and/or structural constraints in the case of polydentate ligands. The lability and geometric flexibility of Cu(I) complexes allow numerous geometries. Although tetrahedral or trigonal-pyramidal tetra-coordinate complexes are the most common ones,³ T- or Y-shaped tri-coordinate and linear di-coordinate complexes are frequently observed. Pentacoordinated Cu(I) complexes are also possible and in most cases they have at least one Cu-ligand bond that is significantly longer than the others.

On the other hand, complexes of the d^9 Cu(II) usually adopt a square-planar geometry. One or two ligands can be weakly associated in the axial position(s), thus leading to a 5-coordinate square-pyramidal or trigonal bipyramidal geometry, or a 6-coordinate tetragonal (distorted octahedral) geometry. Hence, reduction of an unconstrained Cu(II) system is often accompanied by the rupture of at least one of the coordinate bonds and the twisting of the remaining bonds.⁴

3.3. Effects of ligand sets on redox potential

The effect of ligands on the redox potential of metal complexes can arise from diverse features, among which the type of binding atoms, geometrical constraints and electronic effects are arguably the most obvious. Those effects are generally intertwined, and therefore hard to dissociate; this has led to some controversy about the causes of some electrochemical behaviours. As early as 1968, Vallee and Williams proposed that the geometry of the active site in all enzymes is constrained by the protein matrix in such way that the energy required for the reorganization upon change of oxidation state is minimized, and therefore the kinetics and reactivity maximized.⁵ They also noted that the coordination number and geometry often changes when Cu(II) is reduced to Cu(I). It was suggested that the intermediate geometries observed in blue copper proteins (trigonal pyramidal in plastocyanins or trigonal bipyramidal in azurins, as opposed to the expected tetragonal geometry) derived from this type of ligand environment constraints.⁶ However, more recent studies of these active sites indicated that it is the nature of the binding atoms and in particular of the Cu-S_(cys) covalent bond itself (Figure 3.1 in blue) which is responsible for these distortions.^{7, 8}

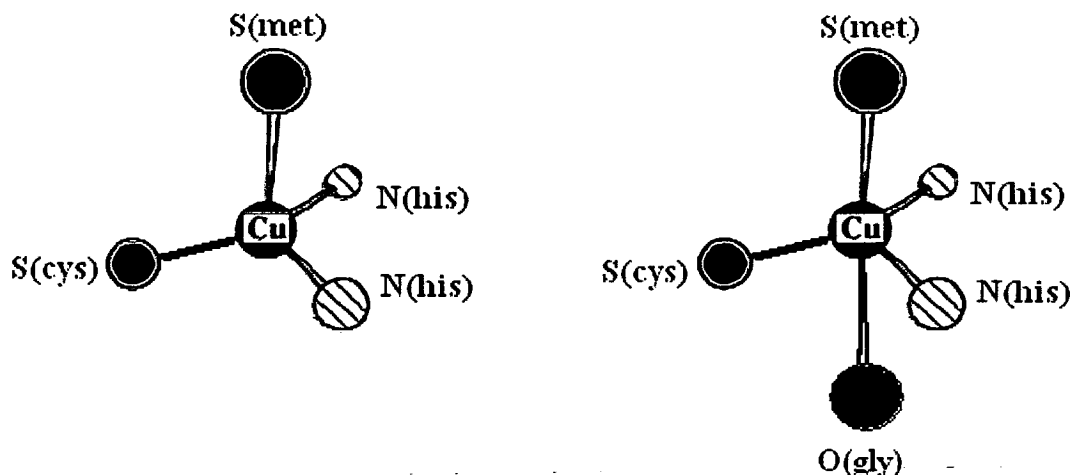


Figure 3.1. Schematic representation of the geometry of the copper site in both *plastocyanin* (left), and *azurin* (right) bearing an elongated Cu-O bond.

In the case of copper, attempts have been made to correlate directly the redox potential of Cu(II)/Cu(I) systems to the type and geometry of the ligand environment.^{9a} An empirical equation (Equation 3.1) has been derived from the systematic study of 45 copper complexes in various media, relating Cu(II)/Cu(I) potentials to a number of features of the complexed ligand: number of donor atoms of specific types (thioether sulphur, aromatic nitrogen, aliphatic nitrogen, carboxylic oxygen) and the morphology of the ligand (macrocyclic, tripodal, number of five-membered vs six-membered chelate rings). The resulting empirical relationship⁹ is of the form:

$$E_{1/2} = E_{(\text{solv})}^{\circ'} + (n\Delta E_L) \quad (\text{Eq. 3.1})$$

where $E^{\circ'}(\text{solv})$ represents the potential of the aqueous Cu(II)/Cu(I) redox couple (0.15 V vs SHE), ΔE_L represents the change in the Cu(II)/Cu(I) potential brought about by various ligand features (such as donor atom type, number of five-membered

chelate rings, etc.), and n represents the number of times that specific feature appears in a coordinated ligand Table 3.1).

Table 3.1. Empirical evaluation of the change of redox potential caused by various donor atoms and structural features:⁹

Variable feature	ΔE (mV)	Error (mV)
Thioether donor	+ 14	± 12
Aromatic N-donor	+ 52	± 13
Aliphatic N-donor	- 75	± 12
Carboxylate donor	- 26	± 23
Macrocyclic ligand	+ 24	± 44
5-membered rings chelates	- 46	± 10
Tripodal ligand	+ 29	± 52

This study led to the conclusion that, in addition to a linking atom donation effect, the geometrical constraints imposed by the ligand set are the main reason responsible for the changes of redox properties. Thus, the ability of the ligand set to accommodate the preferred coordination geometry of the two copper oxidation states is crucial.

3.3.1. Salen-type coordinating ligands

Salen-type ligands have proved useful in determining the effect of various parameters on the redox potential of Cu complexes.

In an study earlier to that of Addison *et al.*,^{9a} Patterson and Holm attempted to generate a correlation of Cu(II/I) redox potentials to the coordination geometry imposed by various ligands.¹⁰ They observed for instance that non planar bis-chelate complexes are reduced more easily than their planar analogues. The half wave

potential differs from 310 mV, to as much as 740 mV in the case shown in Figure 3.2.



Figure 3.2. Schematic representation of a non planar bis-chelate complex (left, $E_{1/2} = -1.52$ V) and the corresponding planar macrocycle complex (right, $E_{1/2} = -2.26$ V).¹⁰

Also, they noticed that planar tetradentate complexes showed a marked dependence on the nature of the donor atoms, with the potentials increasing in the order $N_4 < N_2O_2 < N_2S_2$. In these complexes, the replacement of two metal bound oxygen atoms by sulphur atoms produces an anodic shift of around 400 mV. This is in perfect agreement with the known preference of Cu(II) for nitrogen ligands than sulphur ones¹¹ and with the soft nature of Cu(I), which will accommodate soft thioether ligands more readily than Cu(II). They also showed that the introduction of electron-donating groups far away from the metal centre shifted the redox potential to more negative values (see Figure 3.3).

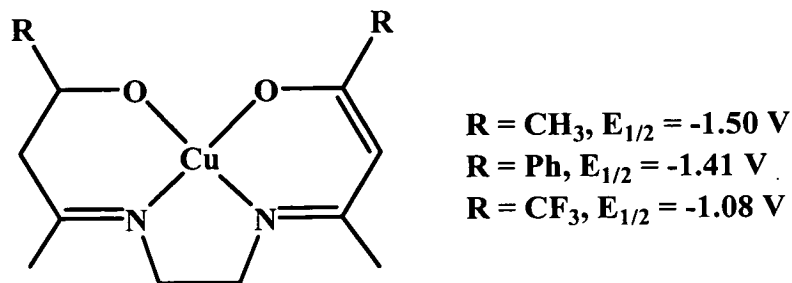
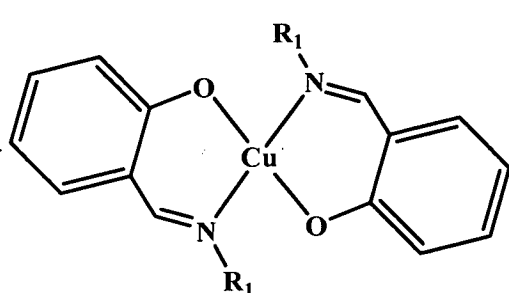
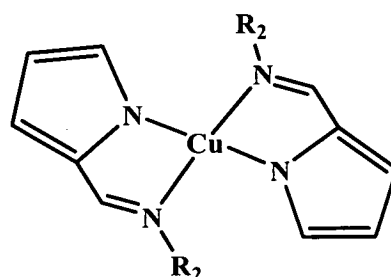


Figure 3.3. Ligand modifications which do not affect the geometry of the complex.¹⁰

Importantly, it was shown that in the systems shown in Figure 3.4, where the two chelating ligands are free to twist, the shift of redox potential occurs in the opposite direction.¹⁰



$R_1 = Me (-0.90 \text{ V}), Et (-0.86 \text{ V}),$
 $iPr (-0.74 \text{ V}), tBu (-0.66 \text{ V})$



$R_2 = H (-0.69 \text{ V}), Me (-0.61 \text{ V}), tBu (-0.46 \text{ V})$

Figure 3.4. Ligand modifications which induce a geometry change and the corresponding redox potential for their Cu^{III} complexes in DMF against SHE.¹⁰

The redox potential changes progressively to more positive values as the steric requirements of the substituent increases. This has been attributed to the fact that upon increase of steric bulk, the geometry around the metal centre changes from square planar to tetrahedral. The latter is more favourable to the $Cu(I)$ redox state and hence, the redox potential shifts to more positive potentials.

3.3.2. Tripodal ligands

Tripodal ligands have been widely used to investigate the Cu(II)/Cu(I) redox process. They can be easily modified to introduce functionality in the vicinity of the metal centre, to change the size of the chelate rings, to modify the hydrophilic/hydrophobic character of the complex etc.

The use of functionalised tripodal ligands to form Cu complexes generally leads to high potentials for the Cu(II)/Cu(I) redox couple, as noticed by Addison.⁹ A systematic study by Ambundo *et al.* with 12 tripodal tetradentate ligands (Figure 3.5) has correlated the redox potentials to the specific stability constants of the Cu(II) and Cu(I) complexes (Table 3.2).¹¹

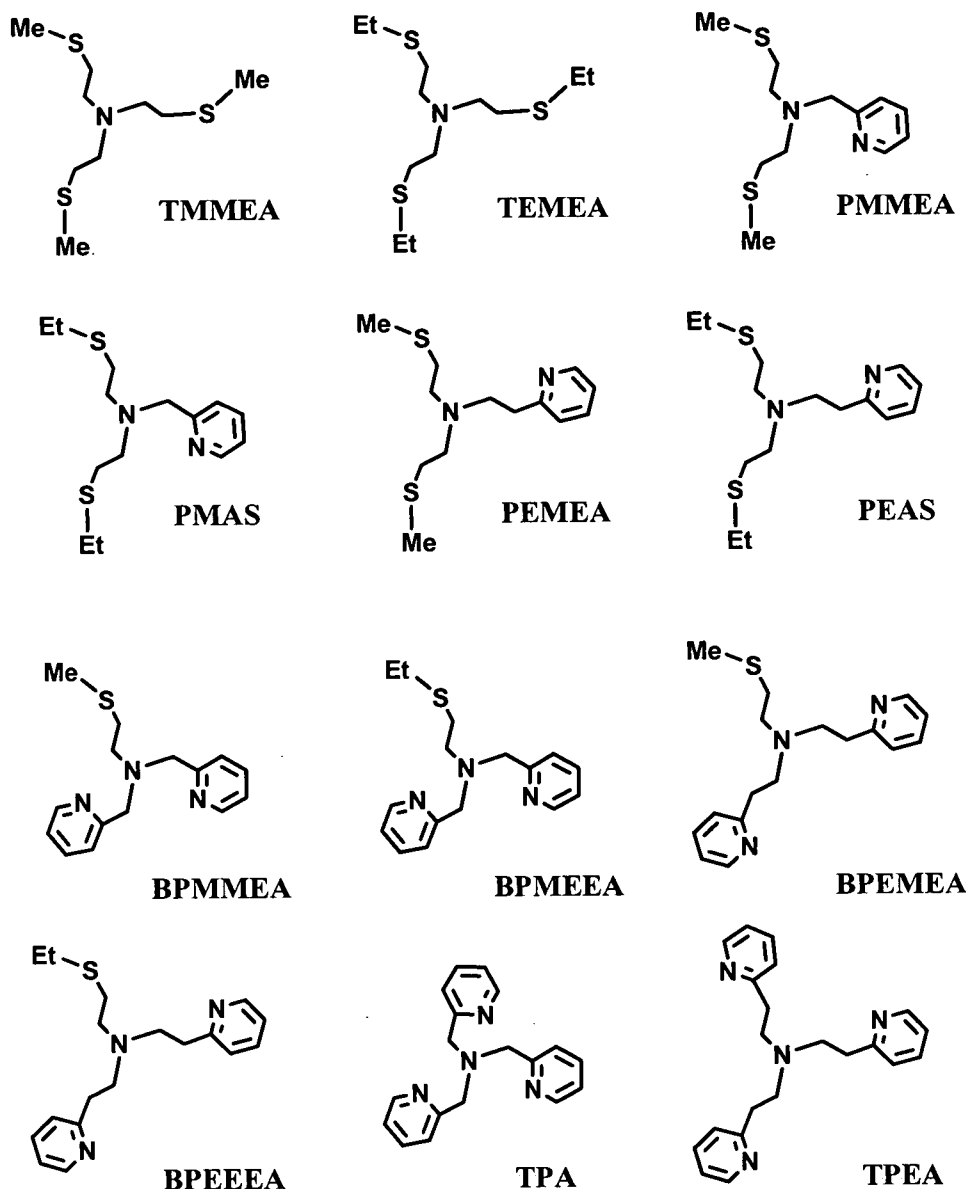


Figure 3.5. Structure of tripodal ligands used in Ambundo's study.

These authors examined how distortions on the Cu(II) or Cu(I) complexes affect their redox potential. First, the introduction of pyridines instead of alkylthioether groups enhances the stability of the Cu(II) complexes due to the higher affinity of Cu(II) for unsaturated nitrogens than for thioether sulphurs. Then, pyridylmethyl derivatives have a greater effect than the corresponding pyridylethyl analogues. This indicates that complexes of Cu(II) with 5-membered rings are thermodynamically more stable than their 6-membered ring analogues, and therefore

their redox potentials are less positive. Finally, the measurement of the half wave potential along with the determination of the stability constants of these complexes showed that the effects on the half-wave potential were essentially due to the destabilization of the Cu(II) complex, since the stability constants of the Cu(I) complexes remains virtually unchanged (Table 3.2).

Table 3.2. Redox potentials (vs SHE) of the Cu(II)/ Cu(I) redox couple of the LCu(II) complexes of the tripodal ligands shown in Figure 3.5.

Complex of the ligand	$E_{1/2}$ (V vs SHE)	Log $K_{Cu(II)L}$	Log $K_{Cu(I)L}$
TMMEA	0.69	6.29	15.80
TEMEA	0.67	6.35	15.53
PMMEA	0.38	11.06	15.36
PMAS	0.40	10.48	15.00
PEMEA	0.60	7.89	15.76
PEAS	0.61	7.87	15.94
BPMMEA	0.06	16.10	14.95
BPMEEA	0.08	15.82	14.99
BPEMEA	0.46	9.10	14.63
BPEEEEA	0.47	9.20	14.97
TPA	-0.15	17.59	12.90
TPEA	0.51	9.35	15.80

This is clearly shown by the correlation plot of the half wave potential of 35 copper complexes as a function of the logarithmic values of the Cu(II) species stability constant (Figure 3.6). It should be noted that the straight line shown in Figure 3.6 spans over 1.5 V, and that the stability constants differ by as much as 26 orders of magnitude.

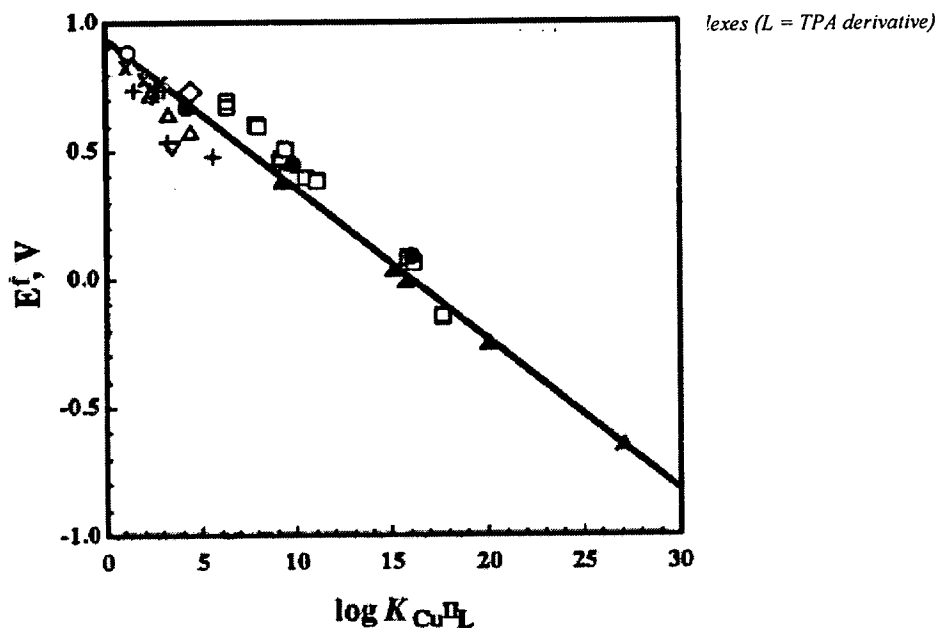
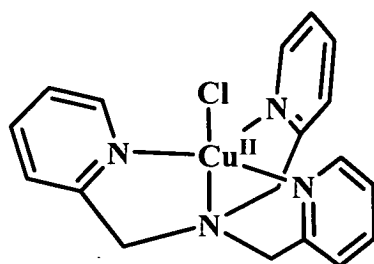


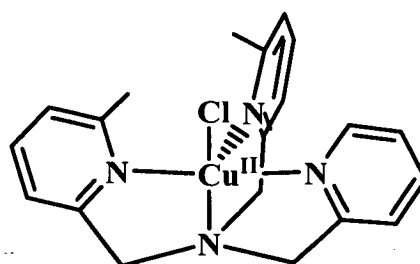
Figure 3.6. Plot of the formal potentials for 35 Cu(II)/Cu(I)L redox couples as a function of the logarithmic values of the Cu(II)L stability constants.¹¹

Nagao and co-workers have investigated the effect that the structure of Cu(II) complexes of methylated derivatives of the tetradentate tripodal ligand tris(2-pyridylmethyl)amine (TPA) has on their electrochemical behaviour.¹² The half wave potential is systematically shifted to more positive values when one (Me₁TPA), two (Me₂TPA) and three (Me₃TPA) methyl groups are introduced in the pyridine ring 6-positions. This has been interpreted in terms of structural changes in the metal complex, as measured by the structural index parameter τ introduced by Addison.¹³ Thus, the geometry changes from almost perfect trigonal bipyramidal ([TPACuCl]⁺, $\tau = 0.97$) to distorted square pyramidal in [Me₁TPACuCl]⁺, ($\tau = 0.20$), to almost perfect square pyramidal in [Me₂TPACuCl]⁺, ($\tau = 0.07$), and to intermediate between both in [Me₃TPACuCl]⁺ ($\tau = 0.43$). These structural changes (see Figure 3.7) are accompanied by the lengthening of the Cu-N bonds and angle deformations. It is interesting that the redox potential of the related [Me₁₋₃TPACu(H₂O)]²⁺/[Me₁₋

$_3TPACu(H_2O)]^+$ complexes shifts to less negative values with increasing Me substitution, approximately 10-20 mV per substitution.



Trigonal bipyramidal



Square pyramidal

Figure 3.7. Geometry change caused by methyl substitution of the pyridine rings.

The TPA ligand has also been used by other groups to investigate the influence of electronic and steric effects on the redox behaviour of copper complexes. Successive replacement of the pyridyl by quinolyl groups leads to a dramatic change in the structure of the complexes, which gradually goes from almost perfect trigonal bipyramidal ($\tau = 0.97$) to almost perfect square pyramidal ($\tau = 0.06$), with the chloride anion moving from an axial to an equatorial position (Figure 3.8).

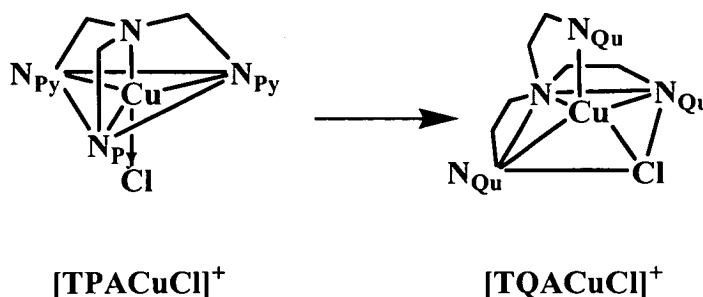


Figure 3.8. Change of metal geometry upon change of coordination.

The half wave potential increases with the number of quinolyl groups, mainly when one and two groups are incorporated.¹⁴ This trend can be explained in terms of an electronic effect, since the quinolyl group is less electron-donating than the pyridyl group, which makes the metal centre more difficult to oxidise. The hydrophobic character of the quinolyl derivatives may also account for this observation, since these groups increase the non-polar character of the metal microenvironment, and hence decrease the local dielectric constant. The same trend is observed in the corresponding series of [LCu(I)]⁺ complexes, however at lower potentials due to the absence of the strong electron-withdrawing chloride anion.

In the same way as in the study of Nagao and co-workers,¹³ other functionalities have been introduced in the pyridine 6-position, and exerted an effect on both the structure and redox behaviour of the corresponding copper complexes. He *et al.* introduced one, two and three hydroxymethyl groups in this position.¹⁵ They synthesized the corresponding series of [LCu(II)X]⁺ complexes (X = Cl, Br) and noted that the redox potential was shifted to higher values (> 100 mV) with each substitution. An interesting feature of these complexes is that although mono- and bis-substituted ligands form almost perfect square pyramidal structures upon complexation with the metal ($\tau = 0.14$ and 0.03 respectively), the tri-substituted ones yield a distorted octahedral structure, with one hydroxyl oxygen coordinated to the copper centre in an axial position (Figure 3.9).

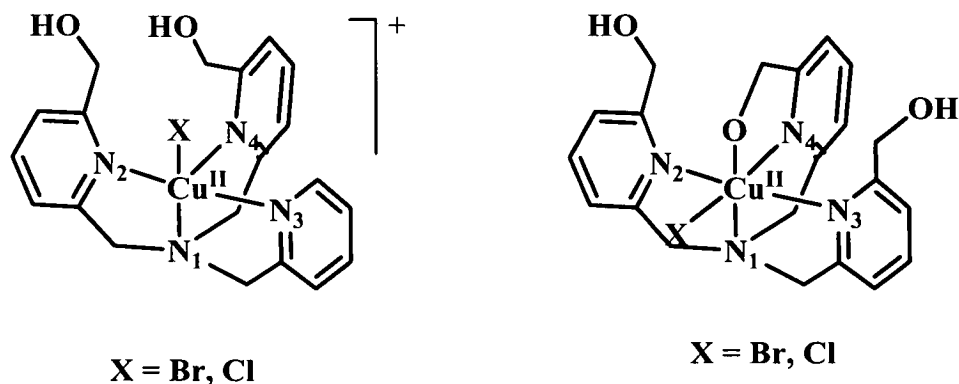


Figure 3.9. Schematic representation of the bis-hydroxylated square pyramidal complex (left) and the tris-hydroxylated distorted octahedral complex (right).

Another remarkable feature of the tris-hydroxylated complex is the unusual elongation of the Cu-N₂ and Cu-N₃ distances, 2.322 and 2.782 Å, respectively. When only two hydroxo groups are present and the complex is arranged in a square pyramidal manner, these distances are only 1.999 and 2.472 Å.

Chuang *et al.* used the relation between electronic interaction and redox potential to design electrochemical sensors.¹⁶ They synthesized metal complexes in which the ligand is capable of binding to a guest molecule, more precisely ammonium salts and alkali metals. Two types of these compounds were synthesized (Figure 3.10). Upon binding of the guest cation, the half wave potential was slightly shifted (the maximum shift observed was 14 mV) by the combination of steric and electronic interaction.

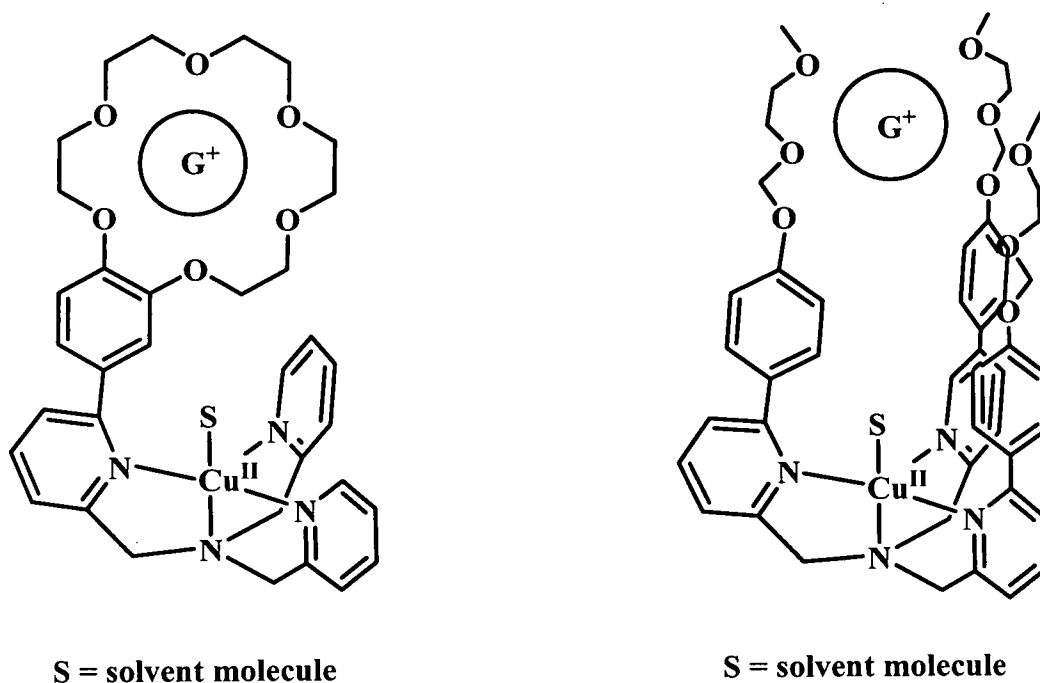


Figure 3.10. TPA-based host-guest electrochemical sensors for $G^+ = \text{alkali metal ions}$.

They also compared the half wave potential measured for the various halogenated $[LCu]^+$ complexes, and concluded that contrary to what would have been expected if inductive effects had dominated steric effects, the potential was shifted to more positive values when bromide was incorporated instead of chloride anions. Finally, they noticed that with phenyl-TPA, which cannot bind guest molecules, the half wave potential increased according to the same trend, but to a lesser extent.¹⁷

3.4. Microenvironment and hydrogen bonding

The microenvironment around a metal centre has also been shown to be responsible for changes in the redox potential of the metal. Solvent molecules and/or charged and polar residues in the vicinity of the metal centre can change the dielectric constant of the medium, and therefore affect the stability of the reduced or oxidised form of the metal. This is shown by equation 3.2, where IE is the ionization energy, 4.5 is the constant to convert from vacuum to the normal hydrogen electrode and U is a solvation term, which accounts for the reorganization and stabilization of the metal centre upon the change of oxidation.¹⁸

$$E^\circ(\text{eV}) = IE - 4.5 + U \quad (\text{Eq. 3.2})$$

The IE can be divided in four different components:

- The energy of the redox active molecular orbitals, which is strongly dependant on the ligand field. For instance, this energy is increased when anti-bonding interactions with the ligand occur.
- The effective nuclear charge of the metal centre, which depends on the donor ability of the ligands. The more donor ligands present, the easier it is to oxidise the metal centre.
- The geometric relaxation, which occurs after the change of oxidation state. It decreases E° upon oxidation of the metal centre.
- Finally electronic relaxation, which tends to limit the geometric relaxation and influences the redox potential in the same way.¹⁹

It is known, however, that the microenvironment of the metal can also influence its properties through non-covalent interactions such as hydrogen bonding. The

precise roles and magnitude of the effects associated with the second coordination sphere, however, are not well understood. Hydrogen bonds not only regulate dioxygen binding²⁰ or stabilize catalytically active species,²¹⁻²² they are also closely related to functionality and redox behaviour. Hydrogen bonds have been shown to affect the redox couple of metalloproteins. The presence of internal N-H...S hydrogen bonds in the active site of enzymes and their models, proved by crystallographic or spectroscopic means, leads to changes in Fe-S bonds lengths and higher Fe(III)/Fe(II) reduction potentials than those of the corresponding complexes without hydrogen bonds.²³ In synthetic iron-porphyrine complexes, it has been proposed that the stabilization of the reduced metal complex is due to the fact that hydrogen bonds decrease the electron density on the thiolate sulfur and therefore lower its electron-donating ability. The Fe-S bond length is affected in the opposite direction by alkanethiolate and arenethiolate ligation. This was proposed to be due to the position of the HOMO in the metal complex. In the case of a weak electron donor, the HOMO sits on the porphyrin ring, while with very basic ligands, the HOMO is located on the metal centre. The involvement of an anti-bonding metal-S interaction leads to shortened Fe-S distances as internal N-H...S hydrogen bonding are introduced.²³ For instance, the presence of a N-H...S hydrogen bond (N...S = 3.423 Å) caused the shortening of the Fe-S bond in the heme-arenethiolate complex by 0.02 Å.²⁴

Additional evidence for the influence of hydrogen bonds on the redox properties of metalloenzymes has been provided by Yikilmaz *et al.* who modified the hydrogen-bond network of iron superoxide dismutase (FeSOD) by mutation of a residue (Glu

instead of Gln, Figure 3.11). Without these hydrogen bonding interactions, the redox potential of the metal centre was raised by several hundreds of millivolts.²⁵

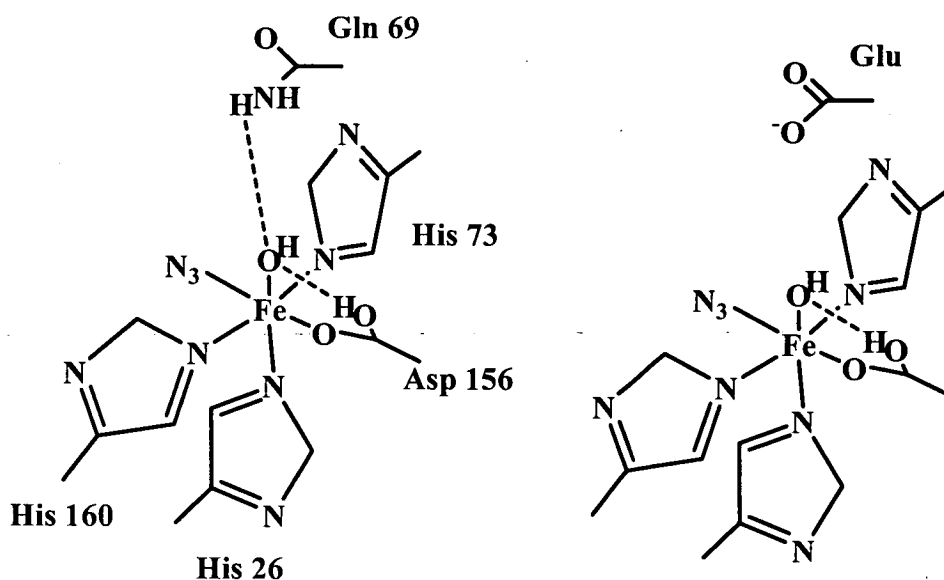


Figure 3.11. Modification of the hydrogen bonding donor Gln 69 by the isosteric and isoelectronic Glu in N_3 -FeSOD.

Also, Suzuki *et al.* showed that introducing a hydrogen bonding functionality in the alkanethiolate moiety leads to changes in the redox potential of the Fe(III)/Fe(II) couple (Table 3.3, Figure 3.12).²³

Table 3.3. Redox potentials (vs SCE) of some iron-porphyrin complexes. Conditions 0.1 M *n*-tetrabutylammonium perchlorate/ CH_2Cl_2 , with Pt electrode.

Complex	X	Y	Fe(III)/Fe(II) Redox potential (V)
Complex 1	NHCOCH ₃	H	-0.41
Complex 2	N(CH ₃)COCH ₃	H	-0.56
Complex 3	H	NHCOCH ₃	-0.53

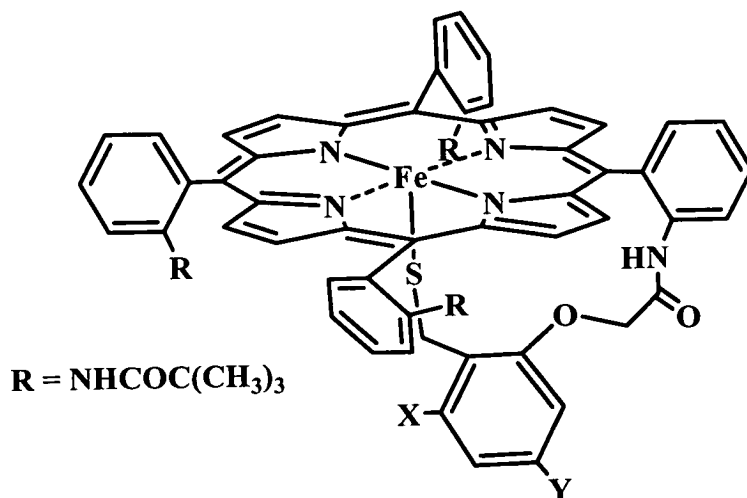


Figure 3.12. Structure of complexes 1-3.

These complexes were designed so they all have the same steric and electronic properties, but only complex 1 will have an internal hydrogen bond. As can be seen from Table 3.3, complex 1 exhibits a significant shift in the half wave potential. These complexes were used as models for cytochrome P450_{cam} where similar hydrogen bonding interactions occur.²³

The presence of hydrogen bonds in the vicinity of a metal has been shown to play a role in the redox properties of blue copper metalloproteins (Figure 3.13).

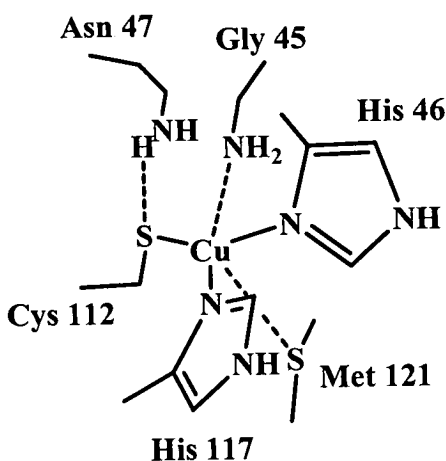


Figure 3.13. Schematic representation of the active site of azurin, showing the hydrogen bond between Asn 47 and Cys 112.²⁶

One of the effects exerted by hydrogen bonds in this case is to decrease the covalency of Cu-S_{cys} bonds.²⁴ This leads to a structure closer to a trigonal structure which is more favourable for a Cu(I) centre, and therefore destabilizes the oxidised form of the metalloprotein. A computational study by Dey *et al.* showed that there is a correlation between the change of redox potential and the covalency of M-S bonds.²⁷ As more hydrogen bonds are introduced the degree of covalency decreases and the redox potential increases. Moreover, they estimated that the introduction of the hydrogen bonding groups shown in Figure 3.14 induces an anodic shift of the Fe(III)/Fe(II) redox couple by 260 mV (1 hydrogen bonding group) and 330 mV (2 hydrogen bonding groups).

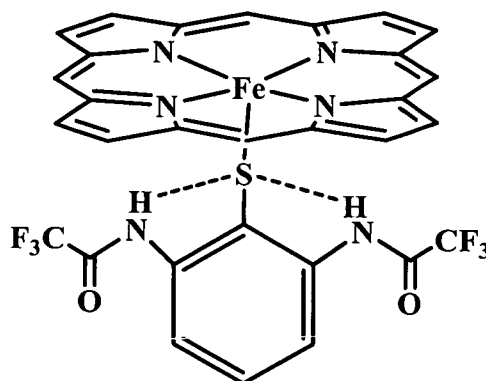


Figure 3.14. Schematic representation of Dey's complex with two hydrogen bonding groups.

Disruption of hydrogen bonds in the vicinity of the metal in blue copper proteins has also been shown to affect the protein fold.²⁸⁻³⁰ The structural changes induced favour one oxidation state better than the other, thus leading to changes in redox potential. Another study showing the implication of hydrogen bonds in the redox properties of metal complexes has been recently provided by Glaser *et al.*, who

synthesized two metal complexes of geometrically constrained salen-type ligands, where one of them contains two hydroxyl groups capable of hydrogen bonding to the oxygens bound to the metal centre (Figure 3.15).³¹

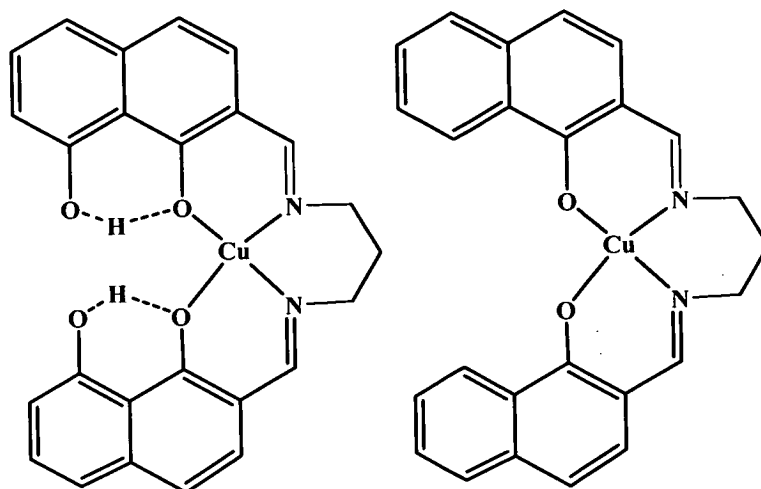


Figure 3.15. Structure of Glaser's salen-type system.

Electrochemical studies showed that the presence of the hydrogen bonding groups induced in this case a positive shift of the half wave potential of 270 mV without any noticeable change of geometry.

Finally, Masuda *et al.* introduced 1, 2 and 3 amino groups into the pyridine 6th position of TPA-based $Cu(II)N_3$ complexes, and observed a positive shift in the half-wave potential of + 20 mV and + 100 mV relative to the TPA complex when 2 and 3 functionalities are introduced, respectively. With one amino group the redox potential was 20 mV more negative. The presence of hydrogen bonds between the amino groups and the Cu-bound azide was noticed, but the progressive change of

geometry from trigonal bipyramidal (TPA complex, $\tau = 0.92$) to intermediate (3 amino groups, $\tau = 0.48$) was claimed to be the main reason for the observed changes of redox potential.³²

Overall, many factors contribute to the redox behaviour of copper complexes. In this chapter, the aim is set on obtaining a better understanding of the roles of the secondary coordination sphere, in particular hydrogen bonds, of Cu(II) complexes on their redox behaviour. The hydrogen bonds involve NH_2 (Am), $NHCO^tBu$ (Piv) and $NHCH_2^tBu$ (Np) groups. In all cases hydrogen bonding was only achieved to the metal-bound atom. As in chapter 2, the tripodal poly(2-pyridylmethyl)amine ligand (TPA, Figure 3.16) was chosen as the basic framework.

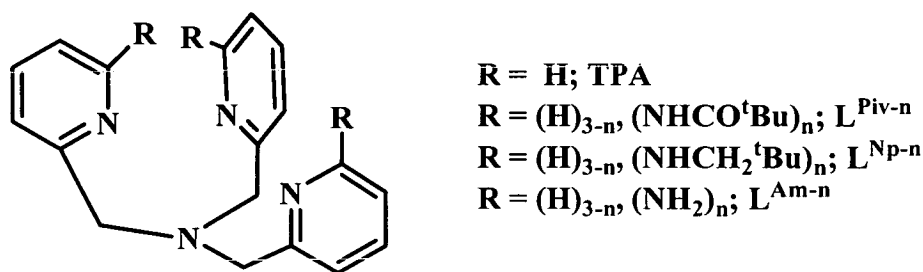


Figure 3.16. Schematic representation of the TPA-based ligands used.

Another ligand of the N_3O type has also been used. In this ligand one of the pyridine rings was replaced by a carboxylate function (Figure 3.17). The pyridine 6-position was be functionalised with zero (*N,N*-Bis(2-pyridylmethyl)glycine, BPG), one (*N*-(6-amino-2-pyridilmethyl)-*N*-(2-pyridylmethyl)glycine, APPG) and two amino groups (*N,N*-Bis(6-amino-2-pyridylmethyl)glycine, BAPG).

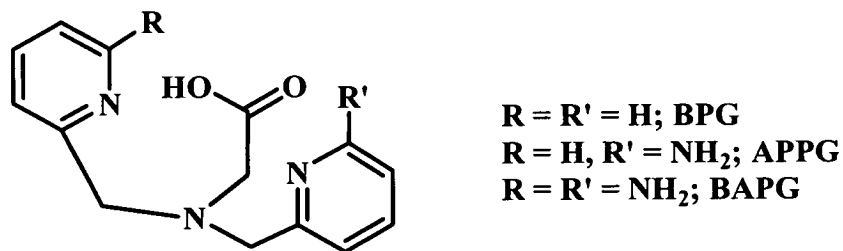
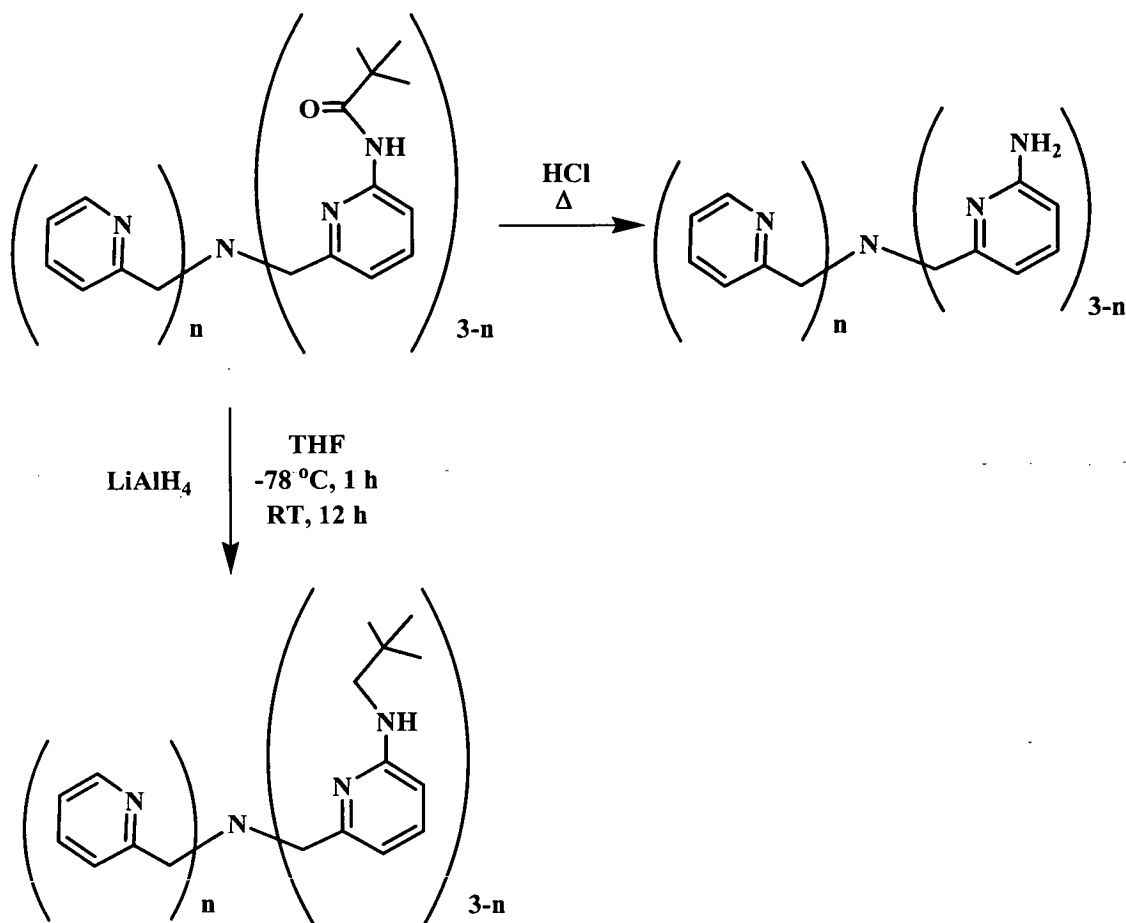


Figure 3.17. Schematic representation of the bis-pyridine-based ligands.

3.5. Results and discussion

3.5.1. Ligand synthesis

The synthesis of L^{Am-3} and L^{Piv1-3} were described in Chapter 2. The other ligands $L^{Am-1,2}$ and L^{Np1-3} were synthesized according to literature procedures,³⁶⁻³⁹ which are represented in Scheme 3.1.

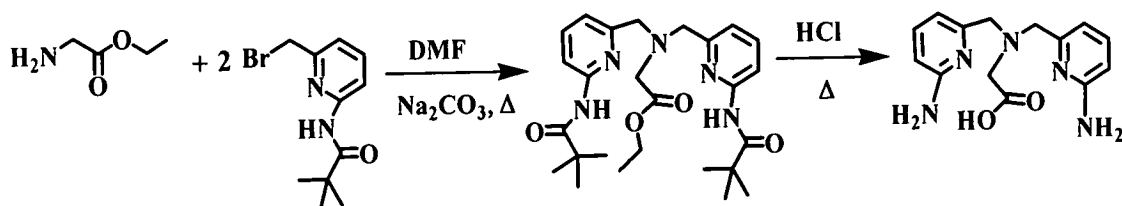


Scheme 3.1. Reagents and conditions used for the synthesis of L^{Am-n} and L^{Np-n} .

The synthesis of L^{Np-n} can be accomplished in one step (Scheme 3.1) starting from the corresponding tripodal ligand L^{Piv-n} . The 6-pivaloylamido-2-pyridylmethylamine fragment is reduced at low temperature by $LiAlH_4$ to generate the L^{Np-n} ligands. After quenching the reaction, filtration and extraction with dichloromethane, the crude product was purified by flash chromatography in neutral alumina using methanol:dichloromethane (2:98, v:v) as eluent.

The synthesis of L^{Am-n} was accomplished by cleaving of the amide function in acidic aqueous solutions under reflux. After basification of the resulting solution, the ligand can be extracted by dichloromethane.

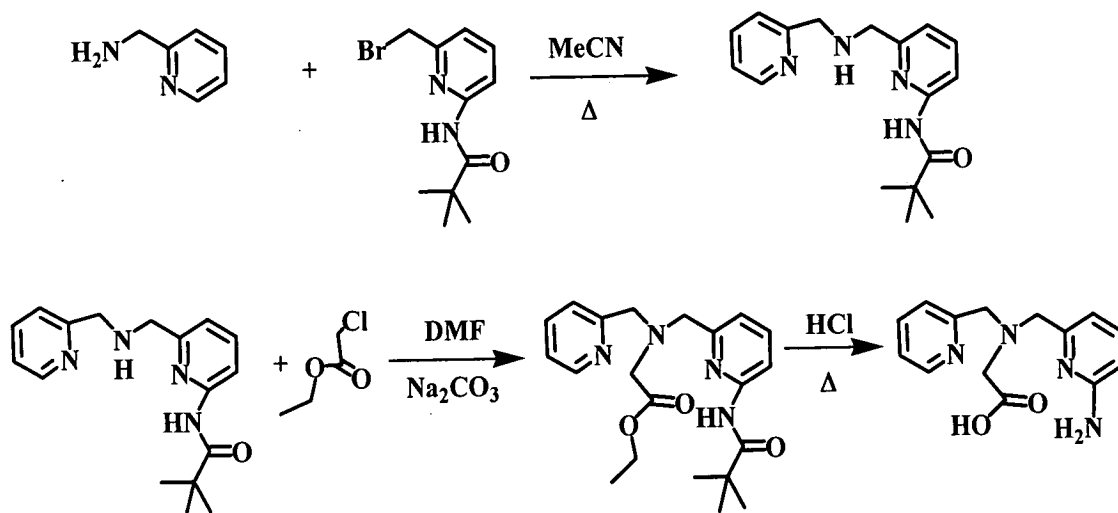
The synthesis of BAPG was accomplished according to scheme 3.2.



Scheme 3.2. Reagents and conditions used for the synthesis of BAPG.

The first step of this reaction is the coupling of one equivalent of 2-(pivaloylamido)-6-(bromomethyl)pyridine with one equivalent of protected glycine in DMF, in the presence of excess of sodium carbonate. Then, after filtration the crude product is directly deprotected by refluxing the solution under acidic conditions. The final product is then dried under high vacuum.

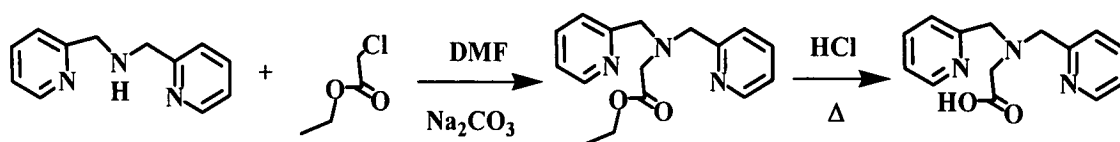
The synthesis of APPG was accomplished according to scheme 3.3.



Scheme 3.3. Reagents and conditions used for the synthesis of APPG.

The first step of this reaction is the coupling of one equivalent of 2-(pivaloylamido)-6-(bromomethyl)pyridine with one equivalent of 2-aminomethylpyridine. The crude product is then purified by chromatography on neutral alumina, and then reacted with protected glycine in DMF, with a large excess of sodium carbonate. Finally, the crude is directly deprotected in acidic conditions under reflux. The final product is then dried under high vacuum.

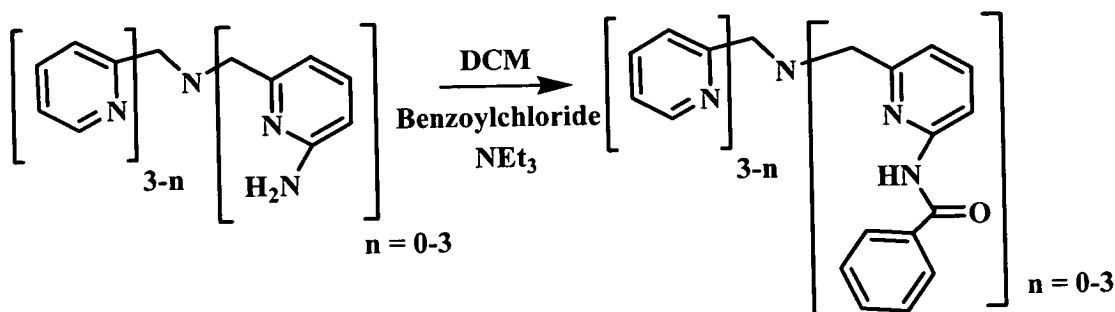
The synthesis of BPG was accomplished according to scheme 3.4.⁴⁰



Scheme 3.4. Reagents and conditions used for the synthesis of BPG.

The reaction occurs via direct coupling of the bis-pyridine with the protected glycine in DMF, with the presence of excess sodium carbonate. The glycine is then deprotected in acidic media under reflux, and the final product is then dried under high vacuum.

The synthesis of another series of TPA derivatives bearing one, two and three benzoylamino functionalities in the pyridine 6-position has also been attempted but was only partially successful. The aim was to extend the studies to more acidic NH hydrogen bonding groups, which may serve as functional groups for intramolecular proton transfer events to metal bound oxygenic ligands. A way of introducing more acidic NH groups is to replace the *tert*-butyl groups by phenyl rings, which was attempted by the direct coupling of the amino derivative with benzoylchloride BzCl (Scheme 3.5).



Scheme 3.5. Attempted synthesis of benzoylamino derivatives of TPA.

It was found that substitution of one of the amino hydrogen by a phenyl ring renders the remaining hydrogen so acidic that it is replaced by another phenyl ring, despite the steric hindrance of the phenyl group. This was demonstrated by mass spectroscopy with the appearance of two signals at $m/z = 432.1$ and 536.1 , corresponding to the first and second substitution on the amino nitrogen, respectively (Figure 3.18).

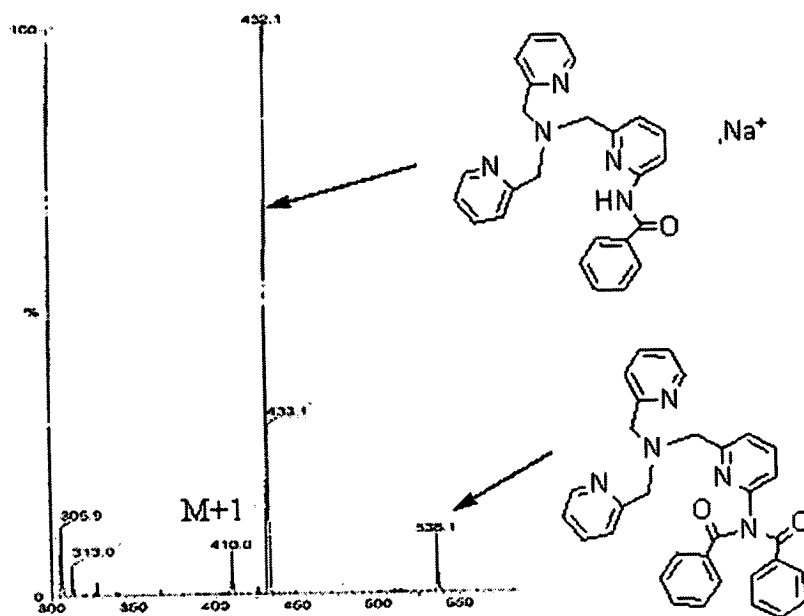


Figure 3.18. Mass spectrum of the reaction products of $L^{\text{Am-1}}$ with BzCl .

^1H NMR spectroscopy also shows different sets of CH_2 signals, with the intensity 8:3, consistent with the formation of mono- and bis-substituted products (Figure 3.19).

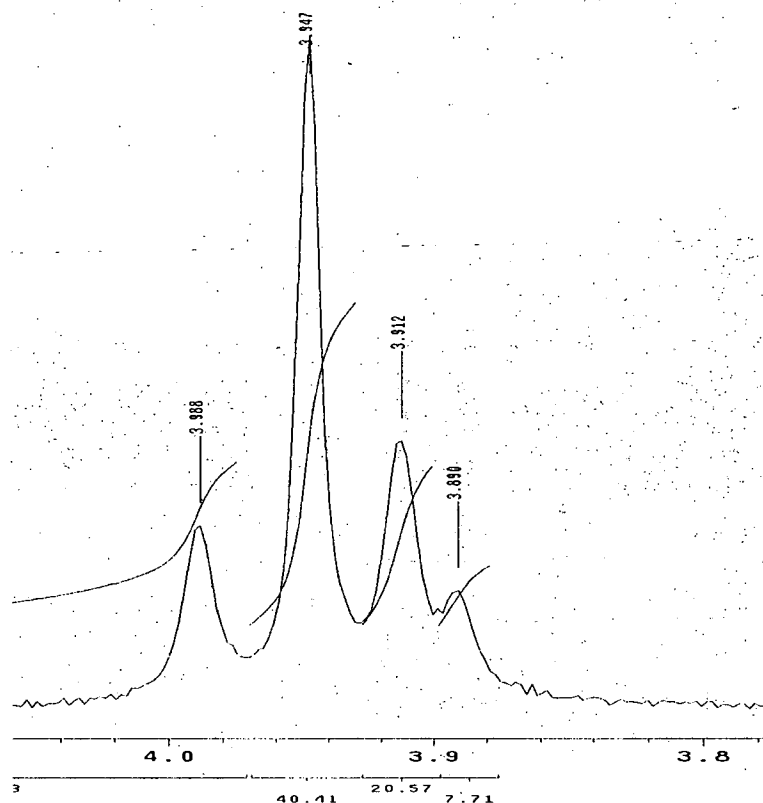
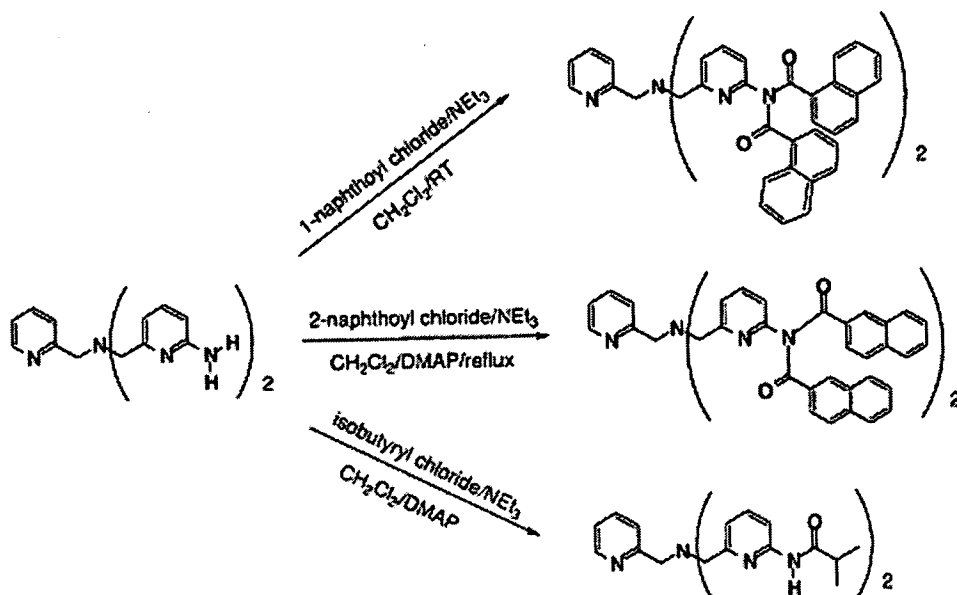


Figure 3.19. Selected region (CH_2 proton resonances) of the ^1H NMR spectrum (350 MHz, CD_3OD , 293K) for the reaction products of $L^{\text{Am-I}}$ with BzCl .

Purification could not be achieved by usual means, *i.e.* extractions, flash chromatography or crystallizations. It should be noted that this type of *bis* substitution has also been observed by Matsuda and co-workers (Scheme 3.6).³³



Scheme 3.6. Different substitution at the NH_2 amino groups for L^{Am-2} found by Matsuda et al.³³

Attempts were made to force the mono substitution on the nitrogen by using different conditions (lower number of equivalents of benzoyl chloride, presence or absence of base) but they all failed. We then tried to cleave one of the amide bonds, using zinc nitrate as a complexing agent. The reaction is immediate, and the NMR shows only two CH_2 signal at 4.40 and 4.21 ppm, respectively, with intensity 2:1. These signals are shifted downfield, which is indicative of complexation of the ligand to the zinc centre. The mass spectrum shows a major peak at $m/z = 472.2$, corresponding to the $TPANHCOPh-Zn$ complex. Removal of the Zn centre is then achieved by addition of cyanide and extraction in basic medium; the ligand remains in the organic layer which is then dried to yield the pure $TPANHCOPh$.

It was not possible to isolate the ligands $TPA(NHCOPh)_2$ and $TPA(NHCOPh)_3$, even by addition of $Zn(II)$ to promote amide cleavage of the bis-

substituted nitrogen. In both cases, ^1H NMR spectroscopy and/or mass spectrometry indicate the presence a mixture of compounds (Figure 3.20 and 3.21).

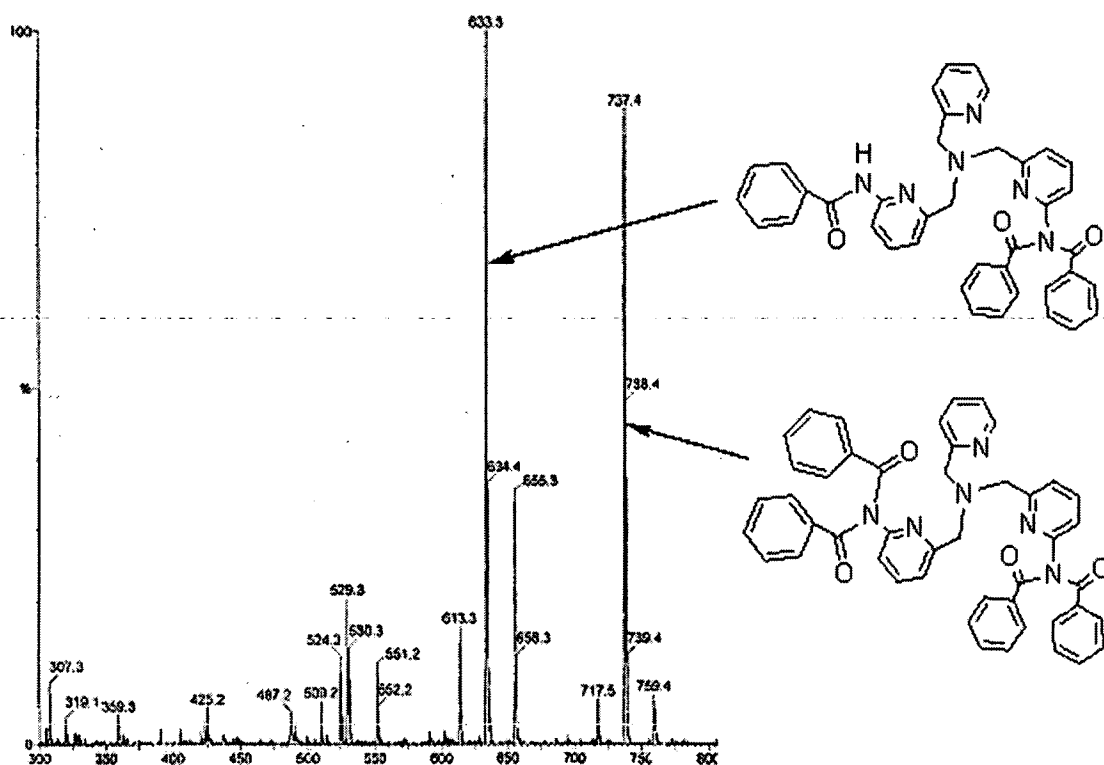


Figure 3.20. Mass spectrum for the reaction products of L^{Am-2} with $BzCl$.

For the reaction products of L^{Am-3} with $BzCl$, only NMR reveals the presence of a mixture. The mass spectrum shows only the expected peak at $m/z = 648$, but it can be accounted for by different compounds (Figure 3.21).

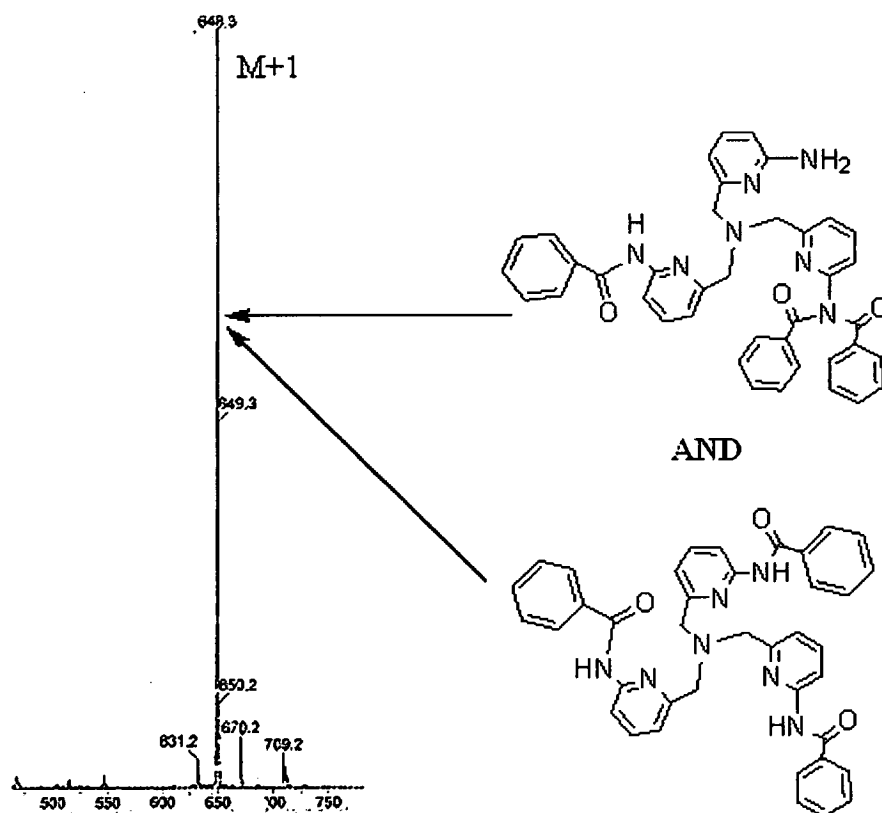


Figure 3.21. Mass spectrum for the reaction products of $L^{\text{Am-3}}$ with BzCl .

3.5.2. TPA-based Cu(II) complexes: electrochemical studies

First, it is interesting to examine how the nature of the hydrogen bonding groups incorporated into the TPA framework affects the redox behaviour of the copper centre.

Preparation of $[\text{LCu(II)Cl}]^+$ complexes was carried out *in situ* by reaction of the appropriate tripodal ligand L with equimolar amounts of CuCl_2 in dry acetonitrile. The cyclic voltammograms were carried out in acetonitrile in the presence of 0.1M tetrabutylammonium tetrafluoroborate (TBABF_4) as supporting

electrolyte, at room temperature. All the compounds produced a single quasi-reversible one-electron wave, where the difference between the anodic and cathodic waves of the Cu(II)/Cu(I) redox couple ranges between 0.07 and 0.1 V.

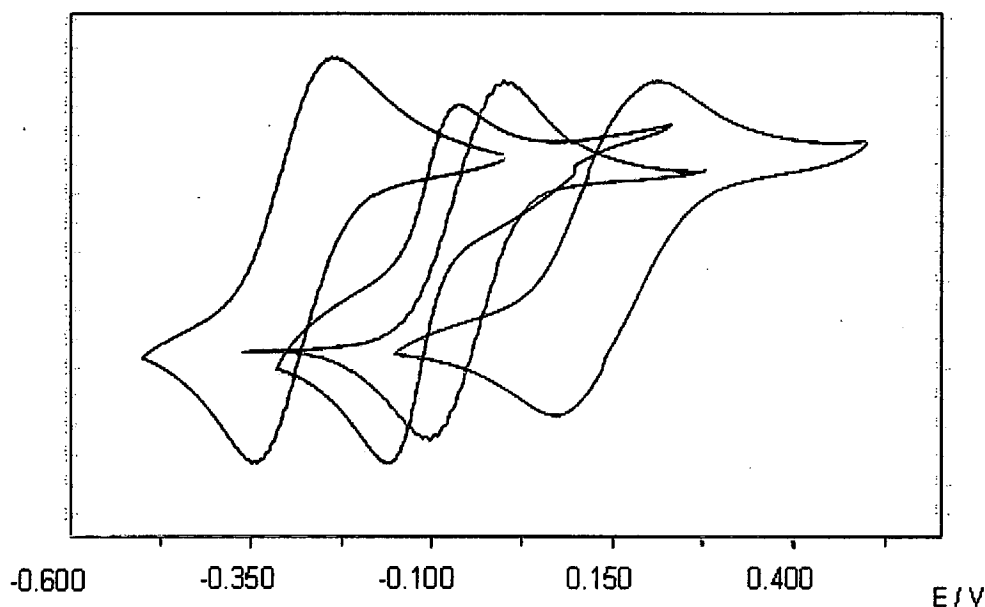


Figure 3.22. Cyclic voltammograms (against AgCl/Ag, scan rate 0.1 V.s^{-1}) in acetonitrile solution containing 0.1 M TBABF_4 of $[(\text{TPA})\text{Cu}^{\text{II}}\text{Cl}]^+$ (green), $[(\text{L}^{\text{Am-3}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (black), $[(\text{L}^{\text{Np-3}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (red) and $[(\text{L}^{\text{Piv-3}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (blue).

The half wave potential for the Cu(II)/Cu(I) redox couple of complexes with three hydrogen bonding groups is more positive than that of $[(\text{TPA})\text{CuCl}]^+$. This means that the reduced form of the metal complexes is stabilized with the introduction of hydrogen bonding groups (Figure 3.22 and Table 3.4). However, the change depends on the nature of the hydrogen bond donor. This difference is substantial, as shown by the separation between the voltammograms (Figure 3.22). It

is interesting that the redox potential of the complexes is more positive whether the hydrogen bonding group is electron withdrawing or electron donating. This suggests that changes are not due to electronic effects alone. Electronic effects would predict for the electron donating amino and neopentylamino groups a more electron rich metal, and therefore a shift in its redox potential to more negative values. The shifts induced by the neopentylamino groups are greater than those induced by the amino groups (Figure 3.22, Table 3.4). This indicates that steric effects also play a role. In chapter 2 we show that the introduction of bulky groups around the metal centre increases the Cu-N_{py} distances, and this presumably makes the copper centre less electron rich. Among the three hydrogen bond donors used, the biggest shifts to more positive redox potentials are induced by the pivaloylamido groups. In this case electronic and steric effects cooperate. Thus, the pivaloylamido groups are electron-withdrawing and bulky. The difference between the changes induced by the neopentylamino groups and pivaloylamido groups could be due not only to electronic effects but also hydrogen bond effects (*vide infra*).

In all cases the metal centre becomes harder to reduce as the number of hydrogen bonding groups increases (Figures 3.23-3.25 and Table 3.4).

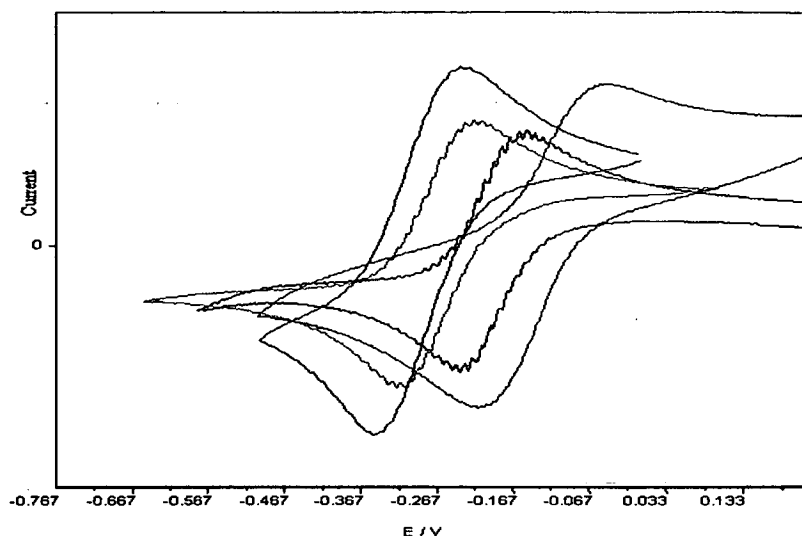


Figure 3.23. Cyclic voltammograms (against AgCl/Ag, scan rate $0.1.V s^{-1}$) in acetonitrile solution containing $0.1 M TBABF_4$ of $[(TPA)Cu^{II}Cl]^+$ (brown), $[(L^{Am-1})Cu^{II}Cl]^+$ (green), $[(L^{Am-2})Cu^{II}Cl]^+$ (blue) and $[(L^{Am-3})Cu^{II}Cl]^+$ (cyan).

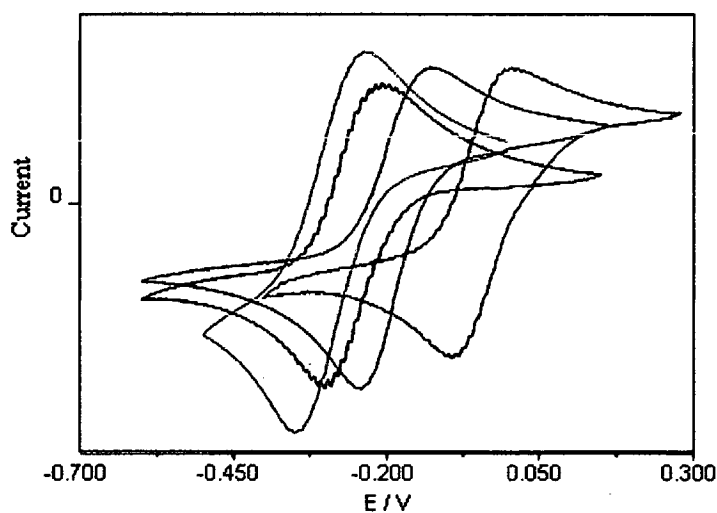


Figure 3.24. Cyclic voltammograms (against AgCl/Ag, scan rate $0.1.V s^{-1}$) in acetonitrile solution containing $0.1 M TBABF_4$ of $[(TPA)Cu^{II}Cl]^+$ (green), $[(L^{Np-1})Cu^{II}Cl]^+$ (blue), $[(L^{Np-2})Cu^{II}Cl]^+$ (brown) and $[(L^{Np-3})Cu^{II}Cl]^+$ (cyan).

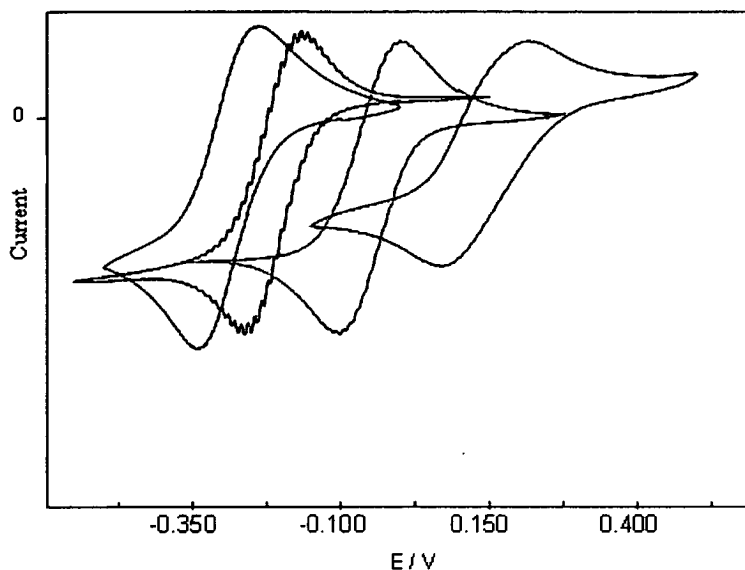


Figure 3.25. Cyclic voltammograms (against AgCl/Ag , scan rate 0.1 V s^{-1}) in acetonitrile solution containing 0.1 M TBABF_4 of $[(\text{TPA})\text{Cu}^{\text{II}}\text{Cl}]^+$ (blue), $[(L^{\text{Piv-1}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (green), $[(L^{\text{Piv-2}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (red) and $[(L^{\text{Piv-3}})\text{Cu}^{\text{II}}\text{Cl}]^+$ (black).

The replacement of the *tert*-butyl group of the pivaloylamido ligand by a phenyl ring makes the amide function even more electron withdrawing. It should be noted, however, that of the series only the TPA-(NHCOPh) ligand has been obtained as a pure compound. The cyclic voltammogram of the copper complex of this ligand is compared with that of TPA in Figure 3.26.

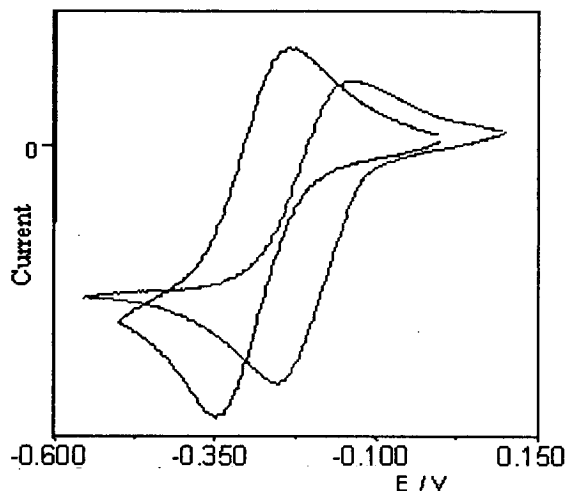


Figure 3.26. Cyclic voltammograms (against AgCl/Ag , scan rate 0.1 V s^{-1}) in acetonitrile solution containing 0.1 M TBABF_4 of $[(\text{TPA})\text{Cu}^{\text{II}}\text{Cl}]^+$ (cyan) and $[\text{TPA}(\text{NHCOPh})\text{Cu}^{\text{II}}\text{Cl}]^+$ (green).

Table 3.4. Corrected values of the half wave potential for $[\text{LCu}^{\text{II}}\text{Cl}]^+$ complexes against Fc^+/Fc ($E_{1/2}$ for the $[(\text{TPA})\text{Cu}^{\text{II}}\text{Cl}]^+ / [(\text{TPA})\text{Cu}^{\text{I}}\text{Cl}]$ couple is -0.77 against Fc^+/Fc , $E_{1/2}$ for the Fc^+/Fc couple is 0.5 V vs Ag/AgCl).

		Nature of the H-bond donor			
		NH_2	NHCH_2^tBu	NHCO^tBu	NHCOPh
	1	-0.74V	-0.73V	-0.70V	-0.66V
Number of functions	2	-0.67V	-0.67V	-0.52V	Not determined
	3	-0.60V	-0.52V	-0.26V	Not determined

Overall, the electrochemical studies for the TPA-based ligands show two general characteristics. One, the nature of the hydrogen bonding group affects the extent to which the reduced form of the metal complex is stabilized in the order: $\text{L}^{\text{Am-1}} < \text{L}^{\text{Np-1}} \ll \text{L}^{\text{Piv-1}} < \text{TPA-NHCOPh}$. Two, the impact of the hydrogen bonding increases with the number of hydrogen bond donors.

It is interesting to note that the introduction of only one hydrogen bonding group increases the half wave potential by at least 30 mV (one amino group) and up to 110 mV (one benzoylamino group), and that the highest redox potential measured is a remarkable 510 mV higher than that of the TPA complex (for three pivaloylamido functionalities).

So far we have only considered electronic and steric effects. However, the strength of the N-H...Cl-Cu hydrogen bond may affect the redox potential of the copper centre. This is analysed in the next section.

3.5.3. Contribution of hydrogen bonding to the redox behaviour.

An enhancement of the hydrogen bond acceptance ability of the axial chloride when the Cu(II) centre is reduced (i.e. electron richer) would make the hydrogen bond stronger in the Cu(I) redox state, and therefore could affect the Cu(II)/Cu(I) redox couple. Second, the nature of the tripodal ligand can enhance the hydrogen bonds strength. Attachment of an electron-withdrawing group increases the hydrogen bond donor capacity of the pendant N-H group. This could lead to more stabilisation of the reduced form of the copper centre for instance from the pivaloylamido group than from the amino group. Stronger hydrogen bonding could be a thermodynamical driving force for the stabilisation of the reduced complex.

In chapter 2, IR studies showed that hydrogen bonds are stronger in the Cu(I) than in the Cu(II) complexes, and that hydrogen bonds are individually stronger the fewer interactions. These studies together with X-ray crystallography and *ab-initio*

calculations revealed that the electron density on the axial-bound chloride is the main factor determining the strength of hydrogen bonds. To elucidate the extent to which changes in hydrogen bond strength between the oxidised and reduced states contributes to changes in the redox behaviour of the metal centre we need to calculate first the change in ΔG caused by incorporating one, two and three pivaloylamido groups. This can be done using Equation 3.3.

$$\Delta G = -nF(E_{1/2}[L^{piv-x}CuCl])^+ - E_{1/2}[tpaCuCl])^+ \quad (\text{Eq. 3.3})$$

The energies are 6.7, 24.1 and 49.2 kJ.mol⁻¹ for one, two and three pivaloylamido groups, respectively. From the IR data presented in Chapter 2, we can determine that the changes in the strength of N-H...Cl-Cu hydrogen bonding between the Cu(I) and Cu(II) complexes with one, two and three pivaloylamido groups are 1.9, 5.4 and 6.9 kJ.mol⁻¹. The results of this analysis are summarised in Table 3.5. Changes in hydrogen bonding strength contribute around 28% (one NHCOTBu), 22% (two NHCOTBu) and 14% (three NHCOTBu) to the observed changes in the Cu(II)/Cu(I) redox couple. From this data it seems that hydrogen bonding to a metal-bound ligand stabilises the more reduced form of that ligand (*i.e.* bound to Cu(I)).

Table 3.5 Contribution of H-bonds to the stabilisation of the $[(\text{L}^{\text{Piv-x}})\text{CuCl}]$ complexes.

Compound	X=1	x=2	x=3
H-bond energy ($\text{kJ}\cdot\text{mol}^{-1}$) in the $\text{LCu}^{\text{I}}\text{Cl}$ complex	18.5	18.2	17.2
H-bond energy ($\text{kJ}\cdot\text{mol}^{-1}$) in the $\text{LCu}^{\text{II}}\text{Cl}$ complex	16.6	15.5	14.9
Changes in H-bond strength ($\text{kJ}\cdot\text{mol}^{-1}$)	1.9	5.4	6.9
Overall contribution of each H-bond	28%	22%	14%

Also, the overall H-bond strength and induced stabilization of the Cu(I) form increases with an increased number of interactions, but the magnitude of the effect of each H-bond is greater the fewer the interactions. Presumably, this is because the hydrogen bonds get individually weaker as the number of hydrogen bond donors sharing the same acceptor increases. Thus, dioxygen reduction at hydrogen bonding cavities may be most effectively pursued with fewer hydrogen bond donors and a more electron donating ligand environment. A more electron donating ligand can be obtained by replacing one of the pyridine units with a carboxylate group.

3.5.4. Redox behaviour of complexes of ligands with one carboxylate group (BPG, APPG and BPPG).

Replacement of one pyridine arm by a carboxylate affords complexes with a Cu(II)/Cu(I) redox couple more negative than $[(\text{TPA})\text{CuCl}]^+$ (Figure 3.27, Table 3.6).

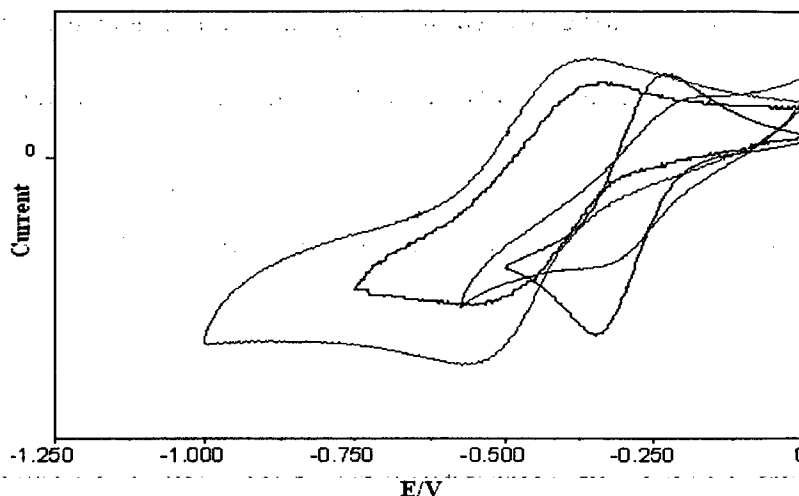


Figure 3.27. Cyclic voltammograms (against AgCl/Ag , scan rate 0.1 V s^{-1}) in acetonitrile solution containing 0.1 M TBABF_4 of $[(\text{BPG})\text{Cu}^{\text{II}}\text{Cl}]$ (green), $[(\text{APPG})\text{Cu}^{\text{II}}\text{Cl}]$ (blue), $[(\text{BAPG})\text{Cu}^{\text{II}}\text{Cl}]$ (purple) and $[(\text{TPA})\text{Cu}^{\text{II}}\text{Cl}]^+$ (brown).

The fact that the cyclic voltammograms exhibit such wide waves renders the half wave potential difficult to measure. This may be due to structural changes of the complex. In that case, we can assume that either the pyridine rings are not as strongly coordinating as before and can de-coordinate from the metal centre, or imagine an equilibrium between a complex where one of the oxygen coordinates, and a complex where it does not.

Table 3.6. Redox potentials for $[(L)\text{Cu}^{\text{II}}\text{Cl}]^+ / [(\text{TPA})\text{Cu}^{\text{I}}\text{Cl}]$ ($L = \text{TPA, BPG, APPG, BAPG}$) vs Fc^+/Fc .

Nature of the ligand	TPA	no amino group	1 amino group	2 amino groups
Half wave potential	-0.27V	-0.46V	-0.45V	$\sim -0.26\text{V}$

The presence of two amino groups causes a change of ca. 200 mV to more positive potentials. However, even in this case the reduction of Cu(II) to Cu(I) is more favourable than in $[(TPA)Cu^{II}Cl]^+$. The X-ray crystal structure of the $[(BAPG)CuCl]^+$ complex was determined (Figure 3.28).

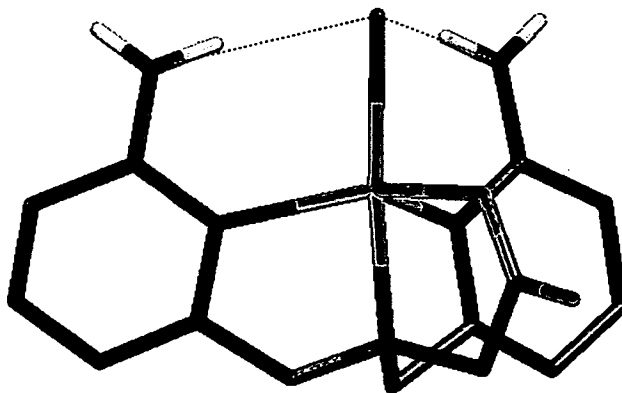


Figure 3.28. X-ray crystal structure of the $[(BAPG)CuCl]$ complex showing the Cu(II) coordination environment. C-bound H atoms and solvent molecules are omitted for clarity.

The main crystallographic data and refinement details are given in Table 3.7. Although it is of poor quality for publication purposes, it shows that the metal complex is mononuclear and has an intermediate structure between trigonal bipyramidal and square pyramidal ($\tau = 0.33$). The axial positions are occupied by the central amine N atom of the tripodal ligand and the chloride and the equatorial atoms are the two pyridine N atoms and an O atom from the carboxylate group. It shows also that the two amino groups are involved in internal hydrogen bonding with the axial chloride ($N\cdots Cl = 3.09 \text{ \AA}$ and $3.21 \text{ \AA}$). A noticeable feature is that these hydrogen bonds are not equivalent.

Table 3.7 Crystallographic data and structure refinement details for [(BAPG)CuCl]

Empirical Formula	C ₁₄ H ₁₆ ClCuN ₅ O ₂
<i>M_r</i>	385.31
<i>T</i> /K	150(2)
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁ /n
<i>a</i> /Å	9.8319(11)
<i>b</i> /Å	13.0269(14)
<i>c</i> /Å	12.2251(15)
α /°	90
β /°	94.086(7)
γ /°	90
<i>V</i> /Å ³	1561.8(3)
<i>Z</i>	4
<i>D_c</i> /g cm ⁻³	1.639
μ /mm ⁻¹	1.586
Reflexions measured, unique	3560,3402
<i>R</i> _{int}	0.059
<i>R</i> ₁ (<i>F</i>) ^a (all data)	0.1296
<i>wR</i> ₂ (<i>F</i> ²) ^a (all data)	0.1448
<i>S</i> (<i>F</i> ²) ^a (all data)	1.0373
Largest difference peak, hole/e ⁻ Å ³	5.44, -2.12

$$^a R_1(F) = \Sigma(|F_o| - |F_c|) / \Sigma(|F_o|); wR_2(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma wF_o^4]^{1/2}; S(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}.$$

3.6. Conclusion

The series of [LCu(II)Cl]⁺ complexes of TPA derivatives bearing hydrogen bonding groups in the pyridine 6-position has been made, and their redox behaviour have been investigated. In this study, we show that the Cu(I) system is favored compared to the Cu(II) whichever the nature of the functionality introduced. We also show that this effect can be counter-balanced by the replacement of a pyridine ring by a carboxylate.

Importantly, we showed that the changes of redox potential observed for the Cu(II)/Cu(I) centre cannot be explained only in terms of structural and electronic effects, and more precisely that hydrogen bonds play a role in determining which oxidation state of the metal will be favored. Moreover, we have quantified the extent to which hydrogen bonds contribute to the stabilization of the Cu(I) systems, and confirmed our electrochemical data by both infra-red and NMR spectroscopy.

These findings are important for the design of redox-active metalloprotein models, since hydrogen bonds are closely related not only to structure, but also to function.

3.7. Experimental section

3.7.1. General

Reagents were obtained from commercial sources and used as received unless otherwise noted. Solvents were dried and purified under N₂ by using standard methods³⁴ and were distilled immediately before use. All compounds were prepared under N₂ unless otherwise mentioned. The NMR spectra were obtained using a Bruker DPX 360 at 20°C. ¹H chemical shifts are referenced according to the residual proton solvent peak. Mass spectra were performed on a micromass Platform II system operating in Flow Injection Analysis mode with the electrospray method. Infra-red spectra were recorded with a JASCO FTIR-410 spectrometer between 4000 and 250 cm⁻¹ in acetonitrile using KBr cells. Electrochemical measurements were performed with an AUTOLAB PGSTAT-20 potentiostat. The cyclic voltammograms

were obtained by using a three-electrode configuration consisting of a 0.5 mm diameter Pt disk working electrode, a Pt rod counter electrode, and an Ag/AgCl (saturated KCl) reference electrode against which the ferrocenium/ferrocene couple was measured and used as internal reference.³⁵ All measurements were made under N_2 atmosphere in dry acetonitrile with 0.1 M tetrabutylammonium tetrafluoroborate (TBABF₄) as the supporting electrolyte at room temperature. The scan rate was set to 0.1V/s. No attempt was made to correct for internal resistances.

3.7.2. Ligand synthesis

***N*-(6-Neopentylamino-2-pyridylmethyl)-*N,N*-bis-(2-pyridylmethyl)amine, L^{Np-1}**

A solution of *N*-(6-pivaloylamido-2-pyridylmethyl)-*N,N*-bis(2-pyridylmethyl)amine L^{Piv-1} (3.0 g, 7.8 mmol) in 60 cm³ of dry THF was added for 15 min to a solution of LiAlH₄ (3.0 g, 78 mmol) in 60 cm³ of THF at -78 °C. The resulting solution was stirred for 1 h and then allowed to warm up to room temperature. After 12 h, the excess LiAlH₄ was quenched with dropwise addition of 10% aqueous THF. The precipitated inorganic salts were removed by filtration. Extraction of the filtrate with DCM (3 × 100 cm³), followed by drying the combined organic fractions over anhydrous sodium sulphate, filtration, and removal of the solvent under reduced pressure, yielded a brown oil. The crude material was purified by column chromatography on neutral alumina by eluting with MeOH–DCM (2 : 98) to afford the ligand as a brown solid (1.76 g, 54%).

Comparison of the ¹H NMR and mass spectra of the ligand with literature values confirmed its purity.³⁶

¹H NMR (CDCl₃, 250.1 MHz) δ_H (ppm) 8.50 (d, J = 6.2 Hz, 2H, py-H), 7.63 (m, 2H and 2H, py-H), 7.41 (t, J = 7.4 Hz, 1H, py'-H), 7.11 (m, 2H, py-H), 6.79 (d, J = 7.3 Hz, 1H, py'-H), 6.29 (d, J = 8.4 Hz, 1H, py'-H), 4.60 (t, J = 6.0 Hz, 1H, NHCH₂), 3.90 (s, 4H, NCH₂py), 3.74 (s, 2H, NCH₂py'), 3.02 (d, J = 6.0 Hz, 2H, NHCH₂C(CH₃)₃), 1.00 (s, 9H, CH₂(CH₃)₃). ESI-MS (+ion) Found 375.8, Calcd. 375.5.

N-N-Bis(6-Neopentylamino-2-pyridylmethyl)-N-(2-pyridylmethyl)amine, L^{Np-2}

A solution of *N*-(6-pivaloylamido-2-pyridylmethyl)-*N,N*-bis(2-pyridylmethyl)amine L^{Piv-1} (4.0 g, 8.2 mmol) in 60 cm³ of dry THF was added for 15 min to a solution of LiAlH₄ (3.15 g, 78 mmol) in 60 cm³ of THF at -78 °C. The resulting solution was stirred for 1 h and then allowed to warm up to room temperature. After 12 h, the excess LiAlH₄ was quenched with dropwise addition of 10% aqueous THF. The precipitated inorganic salts were removed by filtration. Extraction of the filtrate with DCM (3 × 100 cm³), followed by drying the combined organic fractions over anhydrous sodium sulphate, filtration, and removal of the solvent under reduced pressure, yielded a brown oil. The crude material was purified by column chromatography on neutral alumina by eluting with MeOH–DCM (2:98) to afford the ligand as a brown solid (1.93 g, 51%).

Comparison of the ¹H NMR and mass spectra of the ligand with literature values confirmed its purity.³⁶

¹H NMR (CD₃Cl, 360.1 MHz) δ_H (ppm). ¹H NMR (CD₃CN, 360.1 MHz) δ_H (ppm) 8.47 (m, 1H), 7.74-7.69 (m, 2H), 7.35 (t, J = 8.1 Hz, 2H), 7.19-7.17 (m, 1H, py-H), 6.76 (d, J = 7.1 Hz, 2H, py'-H), 6.34 (d, J = 8.2 Hz, 2H, py'-H), 5.01 (br, 2H, NH),

3.84 (s, 2H, NCH₂-py), 3.61 (s, 4H, NCH₂-py'), 3.17 (d, *J* = 6.3 Hz, 4H, CH₂-(CH₃)₃), 0.93 (s, 18H, C-(CH₃)₃). ESI-MS (+ion) Found 460.7, Calcd. 460.3.

Tris(6-Neopentylamino-2-pyridylmethyl)amine, L^{Np-3}

A solution of tris(6-pivaloylamido-2-pyridylmethyl) L^{Piv-3} (5 g, 8.5 mmol) in 60 cm³ of dry THF was added for 15 min to a solution of LiAlH₄ (3.3 g, 85 mmol) in 60 cm³ of THF at -78 °C. The resulting solution was stirred for 1 h and then allowed to warm up to room temperature. After 12 h, the excess LiAlH₄ was quenched with dropwise addition of 10% aqueous THF. The precipitated inorganic salts were removed by filtration. Extraction of the filtrate with DCM (3 × 100 cm³), followed by drying the combined organic fractions over anhydrous sodium sulphate, filtration, and removal of the solvent under reduced pressure, yielded a brown oil. The crude material was purified by column chromatography on neutral alumina by eluting with MeOH–DCM (2 : 98) to afford the ligand as a brown solid (2.92 g, 63%).

Comparison of the ¹H NMR and mass spectra of the ligand with literature values confirmed its purity.³⁷

¹H NMR (CD₃Cl, 360.1 MHz) δ_H (ppm) 7.39 (dd, *J* = 7.8 Hz, 3H, py-*H4*), 6.96 (d, *J* = 7.8 Hz, 3H, py'-*H3*), 6.23 (d, *J* = 7.8 Hz, 3H, py'-*H5*), 4.52 (t, *J* = 6.2 Hz, 3H, NH), 3.68 (s, 6H, NCH₂-py'), 3.01 (d, *J* = 6.2 Hz, 6H, CH₂-(CH₃)₃), 0.97 (s, 27H, C-(CH₃)₃). Found 546.1, Calcd. 545.8.

***N,N*-Bis(2-pyridylmethyl)-*N*-(6-amino-2-pyridylmethyl)amine, L^{Am-1}**

L^{Piv-1} (6 g, 15.4 mmol) was dissolved in 2 M HCl_(aq) (150 cm³) and the solution was refluxed for 24 h. The solution was then poured into 1 M NaOH_(aq). The product was

extracted with dichloromethane ($3 \times 100 \text{ cm}^3$) and the organic fractions were dried over Na_2SO_4 . The solvent was evaporated under vacuum and washed with diethyl ether to yield the product as a brown solid (1.61 g, 34.3 %). Comparison of the ^1H NMR and mass spectra of the ligand with literature values confirmed its purity.³⁸

^1H NMR (CD_3CN , 360.1 MHz): δ_{H} (ppm) 8.46 (m, 2H, py-*H*6), 7.68 (td, $J = 7.92$, 1.8 Hz, 2H py-*H*4), 7.58 (d, $J = 7.9$ Hz, 2H, py-*H*3), 7.37 (dd, $J = 8.2$, 7.5 Hz, 1H, py'-*H*4), 7.16 (m, 2H, py-*H*5), 6.82 (d, $J = 7.5$ Hz, 1H, py'-*H*3), 6.35 (d, $J = 8.2$ Hz, 1H, py'-*H*5), 4.8 (br, 2H, py'- NH_2) 3.8 (s, 4H, $\text{NCH}_2\text{-py}$), 3.6 (s, 2H, $\text{NCH}_2\text{-py}'$). ESI-MS (+ion) Found 306.1, Calcd. 306.0.

***N,N*-bis-(6-amino-2-pyridylmethyl)-*N*-(2-pyridylmethyl)amine, $\text{L}^{\text{Am-2}}$**

$\text{L}^{\text{Piv-2}}$ (2 g, 4.1 mmol) was dissolved in 2M $\text{HCl}_{(\text{aq})}$ (100 cm^3) and the solution was refluxed for 48 h. The solution was then cooled to room temperature and poured into 1M $\text{NaOH}_{(\text{aq})}$. The product was extracted with dichloromethane ($3 \times 100 \text{ cm}^3$) and the organic fractions were dried over Na_2SO_4 . The solvent was evaporated under vacuum and washed with diethyl ether to yield the product as a brown solid (0.92 g, 70%).

Comparison of the ^1H NMR and mass spectra of the ligand with literature values confirmed its purity.³⁹

^1H NMR ($\text{DMSO-}d_6$, 360.1 MHz) δ_{H} (ppm) 8.47 (m, 1H, py-*H*6), 7.78 (t, $J = 7.5$ Hz, 1H py-*H*4), 7.59 (d, $J = 7.6$ Hz, 1H, py-*H*3), 7.34 (t, $J = 7.6$ Hz, 2H, py'-*H*4), 7.24 (m, 2H, py-*H*5), 6.72 (d, $J = 7.2$ Hz, 1H, py'-*H*3), 6.28 (d, $J = 8.3$ Hz, 1H, py'-*H*5), 5.86 (br, 4H, py'- NH_2) 3.71 (s, 2H, $\text{NCH}_2\text{-py}$), 3.48 (s, 4H, $\text{NCH}_2\text{-py}'$). ESI-MS (+ion) Found 321.1, Calcd. 321.0.

***N,N*-Bis(2-pyridylmethyl)-*N*-(glycine)amine, BPG⁴⁰**

To a solution of 2-chloroethyl acetate (122 mg, 1 mmol) in 60 mL of anhydrous dimethylformamide was added *N,N*-Bis(2-pyridylmethyl)amine (199 mg, 1 mmol) in the presence of excess sodium carbonate (1.59 g, 15 mmol). The mixture was stirred at room temperature for 24 hours, and then the solvent was removed under high vacuum to yield the pure compound (200 mg, 87%).

NMR: ¹H (CD₃OD, 360.1MHz) δ_H (ppm): 8.86 (dd, J = 5.76 , 0.72 Hz, 1H, py-*H*6), 8.59 (td, J = 7.92 , 1.44 Hz, 1H, py-*H*4), 8.15 (d, J = 8.28 Hz, 1H, py-*H*3), 8.04 (t, J = 6.48 Hz, 1H, py-*H*5), 4.58 (s, 2H, CH₂-py), 3.69 (s, 1H, CH₂-COO). ¹³C NMR (CD₃OD, 90.5 MHz) δ_C (ppm): 173.2 (C=O), 154.2 (py-*C*2), 147.9 (py-*C*6), 142.3 (py-*C*3), 127.9 and 127.0 ((py-*C*5 and (py-*C*4), 56.3 (NCH₂-py), 54.9 (NCH₂-C=O). ESI-MS (MH⁺) Found 257.2, Calcd. 257.3.

***N*-(6-amino-2-pyridylmethyl)-*N*-(2-pyridylmethyl)-*N*-(glycine)amine, APPG**

To a solution of *N*-[6-(Bromomethyl)-2-pyridyl]pivalamide (280.2 mg, 10⁻³ mol) in dry acetonitrile (60 mL), was added *N*-[6-(Aminomethyl)-2-pyridyl]pivalamide (207 mg, 1 mmol) under stirring.. A large excess of sodium carbonate (1.59 g, 15 mmol) was added, and the mixture was left under stirring with the temperature raised to 80°C during 36 hours. After filtration, the solvents were removed and the yellow solid washed twice with 15 mL of distilled water before purification by column chromatography on neutral alumina by eluting with MeOH–DCM (3 : 97). The isolated product (166.9 mg, 57%) is then coupled to 2-chloroethyl acetate (68.2 mg, 0.57 mmol). The product is then dropped into a 2 M solution of chlorhydric acid, and left under stirring for 24 hours at 80°C. The solvents were then removed under high

vacuum, and the final product dissolved in the minimum cold methanol. The remaining salts were then filtered off. The methanol was removed under vacuum, the pure compound was finally obtained as a brown sticky solid (125.3 mg, 46%).

NMR: ¹H (CD₃OD, 360.1MHz) δ_H (ppm): 8.83 (dd, J = 5.76, 0.72 Hz, 1H, py-H6), 8.49 (td, J = 7.92, 1.44 Hz, 1H, py-H4), 8.03 (d, J = 7.92 Hz, 1H, py-H3), 7.93 (td, J = 6.8, 0.72 Hz, 1H, py-H5), 7.81 (t, J = 8.1 Hz, 1H, py'-H4), 6.91 (dd, J = 8.64, 0.36 Hz, 1H, py'-H3), 6.83 (dd, J = 7.2, 0.36 Hz, 1H, py'-H5), 4.46 (s, 2H, CH₂-py), 4.19 (s, 2H, CH₂-py'), 3.62 (s, 1H, CH₂-COO). ¹³C NMR (CD₃OD, 90.5 MHz) δ_C (ppm): 173.8 (C=O), 156.6 (py-C2), 155.4 (py'-C2), 147.2 and 146.9 (py-C6 and py'-C6), 145.4 (py'-C3), 143. (py-C3), 128.0 (py-C5), 127.1 (py-C4), 114.0 (py'-C5), 113.2 (py'-C4), 57.0 and 56.6 (NCH₂-py and NCH₂-py'), 55.3 (NCH₂-C=O).

ESI-MS (MH⁺) Found 273.2, Calcd. 272.1.

***N,N*-Bis(6-amino-2-pyridylmethyl)-*N*-(glycine)amine, BAPG**

To a solution of glycine ethyl ester hydrochloride (144 mg, 1 mmol) in 60 mL of anhydrous dimethylformamide was added *N*-[6-(bromomethyl)-2-pyridyl]pivalamide (560.4 mg, 2 mmol). A large excess of sodium carbonate (1.59 g, 15. mmol) was added, and the mixture was left under stirring with the temperature raised to 80°C during 36 hours. The mixture was then filtered, and the solvents were removed. The resulting yellow solid washed twice with 15 mL of distilled water, and dropped into a 2 M solution of hydrochloric acid to be deprotected. After removal of the solvents, the compound was dissolved in the minimum amount of cold methanol, and the remaining salt was filtered off. The pure compound (193.8 mg, 68%) was then dried under vacuum.

NMR: ^1H (CD_3OD , 360.1MHz) δ_H (ppm): 7.62 (t, J = 7.92 Hz, 1H, py' -H4), 6.73 (d, J = 6.64 Hz, 1H, py' -H3), 7.63 (d, J = 7.2 Hz, 1H, py' -H5), 4.02 (s, 2H, CH_2 - py'), 3.54 (s, 1H, CH_2 -COO). ^{13}C NMR (CD_3OD , 90.5 MHz) δ_C (ppm): 177.3 (C=O), 157.2 (py' -C6), 149.6 (py' -C2), 143.4 (py' -C3), 112.4 and 112.1 (py' -C5 and py' -C4), 59.3 (NCH_2 - py'), 57.8 (NCH_2 -C=O).

ESI-MS (MH+) Found 288.2, Calcd. 287.1.

3.7.3. Metal complexes synthesis

The $[LCu(II)Cl]^+$ complexes used in the electrochemical studies were prepared *in situ* by mixing equimolar amounts of L and $CuCl_2$ in acetonitrile or methanol. The purity and identity was confirmed by mass spectrometry.

Synthesis of $[L^{Am-1}CuCl]Cl$

To a stirred MeCN solution (10 mL) containing $CuCl_2$ (33.6 mg, $2.5 \cdot 10^{-4}$ mol) was added L^{Am-1} (76.2 mg, $2.5 \cdot 10^{-4}$ mol). The solution was then stirred for 1 h.

ESI-MS (MH+) Found 403.2, Calcd. 403.1

Synthesis of $[L^{Am-2}CuCl]Cl$

To a stirred MeCN solution (10 mL) containing $CuCl_2$ (33.6 mg, $2.5 \cdot 10^{-4}$ mol) was added L^{Am-2} (80 mg, $2.5 \cdot 10^{-4}$ mol). The solution was then stirred for 1 h.

ESI-MS (MH+) Found 418.2, Calcd. 418.1

Synthesis of [L^{Am-3}CuCl]Cl

To a stirred MeCN solution (10 mL) containing CuCl₂ (33.6 mg, 2.5.10⁻⁴ mol) was added L^{Am-3} (83.7 mg, 2.5.10⁻⁴ mol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 432.6, Calcd. 433.1

Synthesis of [L^{Np-1}CuCl]Cl

To a stirred MeCN solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added L^{Np-1} (70 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 473.3, Calcd. 473.1

Synthesis of [L^{Np-2}CuCl]Cl

To a stirred MeCN solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added L^{Np-2} (81 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 558.5, Calcd. 558.2

Synthesis of [L^{Np-3}CuCl]Cl

To a stirred MeCN solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added L^{Np-3} (92 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 643.6, Calcd. 643.3

Synthesis of [CuCl(TPA(NHCOPh))]Cl

To a stirred MeCN solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added TPA(NHCOPh) (63.6 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h.

ESI-MS (MH⁺) Found 507.2, Calcd. 507.1

Synthesis of [N,N-Bis(6-amino-2-pyridilmethyl)-N-(glycine)amineCuCl]

To a stirred MeOH solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added N,N-Bis(6-amino-2-pyridylmethyl)-N-(glycine)amine (32.1 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h, and the solvents removed under vacuum.

ESI-MS (MH⁺) Found 386.1, Calcd. 385.0.

Synthesis of [N-(6-amino-2-pyridilmethyl)-N-(2-pyridilmethyl)-N-(glycine)amineCuCl]

To a stirred MeOH solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added N-(6-amino-2-pyridylmethyl)-N-(2-pyridylmethyl)-N-(glycine)amine (35.9 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h, and the solvents removed under vacuum.

ESI-MS (MH⁺) Found 371.1, Calcd. 371.0.

Synthesis of [N,N-Bis(2-pyridilmethyl)-N-(glycine)amineCuCl]

To a stirred MeOH solution (10 mL) containing CuCl₂ (16.8 mg, 1.25.10⁻⁴ mol) was added N,N-Bis(2-pyridylmethyl)-N-(glycine)amine (32.1 mg, 1.25.10⁻⁴ mol). The solution was then stirred for 1 h, and the solvents removed under vacuum.

ESI-MS (MH⁺) Found 356.1, Calcd. 355.0.

3.8. References

1. Some representative examples (a) E. A. Lewis and W. B. Tolman, *Chem. Rev.*, 2004, **104**, 1047; (b) K. A. Magnus, H. Ton-That and J. E. Carpenter, *Chem. Rev.*, 1994, **94**, 727. (c) A. Sanchez-Ferrer, J. N. Rodriguez-Lopez, F. Garcia-Canovas and F. Garcia-Carmona, *Biochim. Biophys. Acta*, 1995, **1247**, 1. (d) C. Gerdemann, C. Eicken and B. Krebs, *Acc. Chem. Res.*, 2002, **35**, 183. (e) R. A. Steiner, I. M. Kooter and B. W. Dijkstra, B. W., *Biochemistry*, 2002, **41**, 7955. (f) L. C. Stewart and J. P. Klinman, *Annu. Rev. Biochem.*, 1988, **57**, 551. (g) N. J. Blackburn, F. C. Rhames, M. Ralle and S. Jaron, *J. Biol. Inorg. Chem.*, 2000, **5**, 341. (h) J. W. Whittaker, *Chem. Rev.*, 2003, **103**, 2347. (i) A. E. Palmer, L. Quintanar, S. Severancee, T.-P. Wang, D. J. Kosman and E. I. Solomon, *Biochemistry*, 2002, **41**, 6438. (j) R. L. Lieberman, D. B. Shrestha, P. E. Doan, B. M. Hoffman, T. L. Stemmler and A. C. Rosenzweig, *Proc. Natl. Acad. Sci. U.S.A.*, 2003, **100**, 3820.
2. W. Kaim and J. Rall, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 43.
3. B. J. Hathaway, *Coord. Chem. Rev.*, 1981, **35**, 211.
4. D. B. Rorabacher, *Chem. Rev.*, 2004, **104**, 651.
5. B. L. Vallee and R. J. P. Williams, *Proc. Natl. Acad. Sci. U.S.A.*, 1968, **59**, 498.
6. R. J. P. Williams, *Inorg. Chim. Acta Rev.*, 1971, **5**, 137.
7. E. I. Solomon, D. W. Randall, T. Glaser, *Coord. Chem. Rev.*, 2000, **200**, 595.
8. U. Ryde, M. H. M. Olsson, K. Pierloot, B. O. Roos, *J. Mol. Biol.*, 1996, **261**, 586.

9. (a) A. W. Addison, *Inorg. Chim. Acta*, 1989, **162**, 217; (b) M. M. Bernardo, M. J. Heeg, R. R. Schroeder, L. A. Ochrymowycz and D. B. Rorabacher, *Inorg. Chem.*, 1992, **31**, 191.
10. G. S. Patterson and R. H. Holm, *Bioinorg. Chem.*, 1975, **4**, 257.
11. E. A. Ambundo, M.-V. Deydier, A. J. Grall, N. Aguera-Vega, L. T. Dressel, T. H. Cooper, M. J. Heeg, L. A. Ochrymowycz and D. B. Rorabacher, *Inorg. Chem.*, 1999, **38**, 4233.
12. H. Nagao, N. Komeda, M. Mukaida, M. Suzuki and K. Tanaka, *Inorg. Chem.*, 1996, **35**, 6809.
13. A. W. Addison, T. N. Rao, J. Reedijk, J. van Rijn and G. C. Werschoor, *J. Chem. Soc., Dalton Trans.*, 1984, 1349.
14. N. Wei, N. N. Murthy and K. D. Karlin, *Inorg. Chem.*, 1994, **33**, 6093.
15. Z. He, J. Chaimungkalanont, D. C. Craig and S. B. Colbran, *J. Chem. Soc., Dalton Trans.*, 2000, 1419.
16. C.-L. Chuang, O. dos Santos, X. Xu and J. W. Canary, *Inorg. Chem.*, 1997, **36**, 1967.
17. C.-L. Chuang, K. Lim and J. W. Canary, *Supramol. Chem.*, 1995, **5**, 39.
18. E. I. Solomon, R. K. Szilagyi, S. DeBeer George, and L. Basumallick, *Chem. Rev.*, 2004, **104**, 419.
19. P. Kennepohl and E. I. Solomon, *Inorg. Chem.*, 2003, **42**, 689.
20. (a) C. J. Chang, L. L. Chang and D. G. Nocera, *J. Am. Chem. Soc.*, 2003, **125**, 1866; (b) C. J. Chang, M. C. Y. Chang, N. H. Damrauer and D. G. Nocera, *Biochim. Biophys. Acta*, 2004, **1655**, 13.

21. (a) K. Jitsukawa, M. Harata, H. Arai, H. Sakurai and H. Masuda, *Inorg. Chim. Acta*, 2001, **324**, 108; (b) S. Yamaguchi, A. Wada, Y. Funahashi, S. Nagatomo, T. Kitagawa, K. Jitsukawa and H. Masuda, *Eur. J. Inorg. Chem.*, 2003, 4378; (c) S. Ogo, R. Yamahara, M. Roach, T. Suenobu, M. Aki, T. Ogura, T. Kitagawa, H. Masuda, S. Fukuzumi and Y. Watanabe, *Inorg. Chem.*, 2002, **41**, 5513; (d) A. Wada, S. Ogo, S. Wada, Y. Watanabe, M. Mukai, K. Jitsukawa, H. Masuda and H. Einaga, *Inorg. Chem.*, 1999, **38**, 3592; (e) M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *J. Am. Chem. Soc.*, 1994, **116**, 10817; (f) S. Ogo, S. Wada, Y. Watanabe, M. Iwase, A. Wada, M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Angew. Chem. Int. Ed.*, 1998, **37**, 2102; (g) M. Harata, K. Jitsukawa, H. Masuda and H. Einaga, *Chem. Lett.*, 1996, 813; (h) A. Wada, M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, M. Mukai, T. Kitagawa and H. Einaga, *Angew. Chem. Int. Ed.*, 1998, **37**, 798.
22. (a) C. E. MacBeth, B. S. Hammes, V. G. Young Jr. and A. S. Borovik, *Inorg. Chem.*, 2001, **40**, 4733; (b) Z. Shirrin, B. S. Hammes, V. G. Young Jr. and A. S. Borovik, *J. Am. Chem. Soc.*, 2000, **122**, 1836; (c) R. Gupta, C. E. MacBeth, V. G. Young Jr. and A. S. Borovik, *J. Am. Chem. Soc.*, 2002, **124**, 1136; (d) Z. Shirrin, V. G. Young Jr. and A. S. Borovik, *Chem. Commun.*, 1997, 1967; (e) C. E. MacBeth, R. Gupta, K. R. Mitchell-Koch, V. G. Young Jr., G. H. Lushington, W. H. Thompson, M. P. Heindrich and A. S. Borovik, *J. Am. Chem. Soc.*, 2004, **126**, 2556; (f) R. Gupta and A. S. Borovik, *J. Am. Chem. Soc.*, 2003, **125**, 13234; (g) C. E. MacBeth, A. P. Golombek, V. G.

- Young Jr., C. Yang, K. Kuczera, M. P. Hendrich, and A. S. Borovik, *Science*, 2000, **289**, 938.
23. N. Suzuki, T. Higuchi, Y. Urano, K. Kikuchi, H. Uekusa, Y. Ohashi, T. Uchida, T. Kitagawa and T. Nagano, *J. Am. Chem. Soc.*, 1999, **121**, 11571.
24. E. I. Solomon, S. I. Gorelsky and A. Dei, *J. Comput. Chem.*, 2006, **27**, 1415.
25. E. Yikilmaz, J. Xie, T. C. Brunold and A.-F. Miller, *J. Am. Chem. Soc.*, 2004, **126**, 2556.
26. G. W. Canters, U. Kolczak, F. Armstrong, L. J. C. Jeuken, R. Camba and M. Sola, *Faraday Discuss.*, 2000, **116**, 205.
27. A. Dey, T.-a. Okamra, N. Ueyama, B. Hedman, K. O. Hodgson and E. I. Solomon, *J. Am. Chem. Soc.*, 2005, **127**, 12046.
28. P. Wittung-Stafshede, E. Gomez, A. Ohman, R. Aasa, R. M. Villahermosa, J. Leckner, G. Karlsson, D. Sanders, J. A. Fee, J. R. Winkler, B. G. Malmström, H. B. Gray and M. G. Hill, *Biochim. Biophys. Acta*, 1998, **1388**, 437.
29. D. K. Garner, M. K. Vaughan, H. J. Hwang, M. G. Savelieff, S. M. Berry, J. F. Honek and Y. Lu, *J. Am. Chem. Soc.*, 2006, **128**, 15608.
30. M. C. Machczynski, H. B. Gray and J. H. Richards, *J. Inorg. Biochem.*, 2002, **88**, 375.
31. T. Glaser, I. Liratzis, O. Kataeva, R. Fröhlich, M. Piacenza and S. Grimme, *Chem. Commun.*, 2006, 1024.
32. A. Wada, Y. Honda, S. Yamaguchi, S. Nagatomo, T. Kitagawa, K. Jitsukawa and H. Masuda, *Inorg. Chem.*, 2004, **43**, 5725.
33. T. Kojima, K.-I. Hayashi and Y. Matsuda, *Inorg. Chem.*, 2004, **43**, 6793.

34. W. L. F. Armarego and D. D. Perin, in 'Purification of Laboratory Chemicals', Oxford, Butterworth-Heinemann, 4th edn, 1997.
35. R. R. Gagné, C. A. Koval and G. C. Lisensky, *Inorg. Chem.*, 1980, **19**, 2854.
36. J. C. Mareque-Rivas, R. Prabakaran and S. Parsons, *Dalton Trans.*, 2004, 1648.
37. M. Harata, K. Hasegawa, K. Jitsukawa, H. Masuda, H. Einaga, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1031.
38. J. C. Mareque-Rivas, E. Salvagni, R. Torres Martín de Rosales and S. Parsons, *Dalton Trans.*, 2003, 3339.
39. J. C. Mareque-Rivas, R. Prabakaran and R. Torres Martín de Rosales, *Chem. Commun.*, 2004, 76.
40. D. D. Cox, J. C. Benkovic, L. M. Bloom, F. C. Bradley, M. J. Nelson, L. Que, Jr and D. E. Wallick, *J. Am. Chem. Soc.*, 1988, **110**, 2026.

Chapter 4:

Factors affecting the redox properties of metal-bound catechols

4.1. Introduction

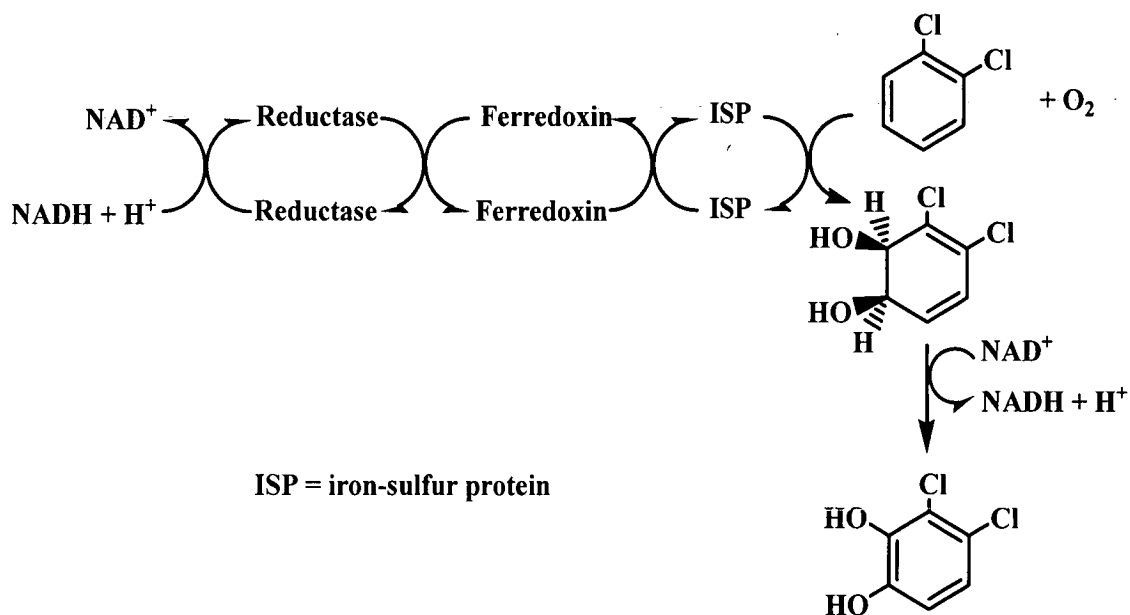
Many metalloproteins are involved in important redox processes such as respiration, activation of dioxygen or photosynthesis.^{1,2} A critical issue in these diverse chemistries is the ability of the protein to regulate the redox behaviour of the metal centre and dioxygen species. For these purposes, the active site of the metalloprotein is exquisitely defined in terms of structure, electronic environment and non-covalent interactions. How these proteins achieve the proper setting of the reduction potentials remains a fundamental question. Many groups have investigated how the redox properties of the metal centre are affected by various parameters in both enzymes and biomimetic models,³ however, fewer studies have been focused on the redox behaviour of the metal-bound substrate itself.⁴ Since the metals involved are typically redox active within the potential range for the ligand-based redox processes, the electrochemical results are complicated by intramolecular charge-transfer processes.

Catechols are examples of biologically important redox-active molecules, which can be used to learn about the factors affecting the redox properties of metal-bound substrates. More detail about these substrates will be provided below.

4.2. Catechols: introduction

Catechol (1,2-dihydroxybenzene) is used in a variety of applications. It is used as a reagent for photography, rubber and plastic production and in the dye and pharmaceutical industry.⁵ In humans and other mammals, catechols can arise from

the degradation of aromatic compounds such as benzene⁶ or estrogens⁷ or as endogenous compounds,⁸ such as neurotransmitters and their precursors (adrenaline, noradrenaline, dopamine and L-DOPA (L-3,4-dihydroxyphenylalanine) by microorganisms. The biological degradation mechanism of 1,2-dichlorobenzene is represented in Scheme 4.1.



Scheme 4.1. Degradation mechanism of 1,2-dichlorobenzene.

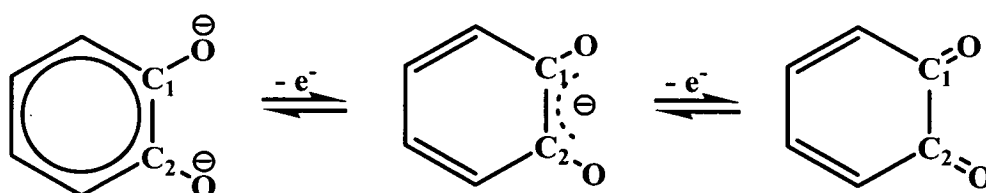
Additionally, catechols can be taken up in the form of tobacco smoke (as catechol, catechol semiquinones and polymerized catechols)⁹ or as food components (e.g. catechol, dopamine, caffeic acid, tea catechin).¹⁰

Catechols form stable complexes with di- and tri-valent metal ions like copper, zinc, iron, etc.¹¹⁻¹⁴ As a result, catechols can sequester metal ions from other complexes and prevent them from undergoing specific redox reactions.¹⁵ For example, catechol complexation to iron leading to dicoordinated iron (III) complexes

prevents the metal from being involved in electron transfer reactions, whereas the corresponding mono-coordinated complexes undergo those redox reactions.¹⁵

Several enzymes in plants, animals and bacteria such as the copper-containing fungal laccase and ascorbate oxidase,¹⁶ peroxidases¹⁷ and tyrosinase^{18,19} use metals to catalyse the oxidation of catechol to benzoquinone.

In terms of redox chemistry, 1,2-dioxolenes are redox active (or redox non-innocent) ligands able to undergo reversibly the one-electron reactions illustrated in Scheme 4.2.



Scheme 4.2. Redox transformations of catechols.

When catechol is oxidized enzymatically or in the presence of oxygen and heavy metals, one electron is transferred to molecular oxygen to form superoxide (O_2^-). In the presence of heavy metals (*e.g.* copper, iron), superoxide is further reduced to hydrogen peroxide (H_2O_2) and hydroxyl radicals ($\cdot\text{OH}$). All this redox activity can add to the redox processes of the central metal ion itself in the corresponding metal complexes, thus making it complicated to identify the charge distribution that takes place, or whether the redox process is ligand- or metal-centred in nature. In this context, it is important to note that in general, two bond lengths, the

intradiol C₁-C₂ and the C-O, are particularly diagnostic of the oxidation state of the quinoidal ligands of metal complexes, as shown in Table 4.1.

Table 4.1. *Important structural parameters for the determination of the redox state of quinoidal ligands.*

	C-O distance	Intradiol C ₁ -C ₂ distance
Quinone form	C-O $\approx$ 1.23 Å	C ₁ -C ₂ $\approx$ 1.53 Å
Semiquinone form	C-O $\approx$ 1.29 Å	C ₁ -C ₂ $\approx$ 1.44 Å
Catecholate form	C-O $\approx$ 1.35 Å	C ₁ -C ₂ $\approx$ 1.39 Å

These diagnostic distances have been obtained based upon the crystallographic data of the pertinent metal-free species (e.g. 1,2-dihydroxybenzene, 1,2-benzoquinone, 3,5-di-*tert*butyl- 1,2-benzoquinone, and tetrachloro-1,2-benzoquinone). The study of only the C-O distances, however, may not be sufficient to ascertain the redox state of the dioxolene unit. These values can be affected by the way the catechol binds to the metal (chelation, asymmetric binding, bridging) and Jahn-Teller distortions. A more precise analysis arises from a statistical approach, which takes into consideration both the C-O distances and all six intra-ring C-C distances. Therefore, this method takes into account the alternation of short and long bonds in the quinone form, while in the catechol form, the aromaticity of the ring makes all C-C bonds comparable.^{20,21} Finally, a diagnostic structural function based on a mathematical model could also be used to determine the form of the dioxolene species.²²

4.3. Redox properties of catechols

Several factors need to be taken into account when examining the influence of one particular feature (*i.e.* hydrogen bonding) on the redox properties of catechols in metal complexes, especially when trying to assess the extent to which this feature, among others, contributes to making the catechol easier (or more difficult) to oxidize. Hence, various issues need to be examined first: the nature of the catechol moiety, the presence or absence of protons, the nature of the metal centre (type of metal, oxidation state) and the nature of the ligand set (electron donating properties, steric requirements).

4.3.1. Effect of substituents on the catechol moiety

As early as 1986, Schultz and co-workers reported the redox properties of a series of $\text{Mo(VI)O}(\text{S}_2\text{CNEt}_2)_2$:catecholate adducts, using 9 different catechols,²³ shown in Figure 4.1.

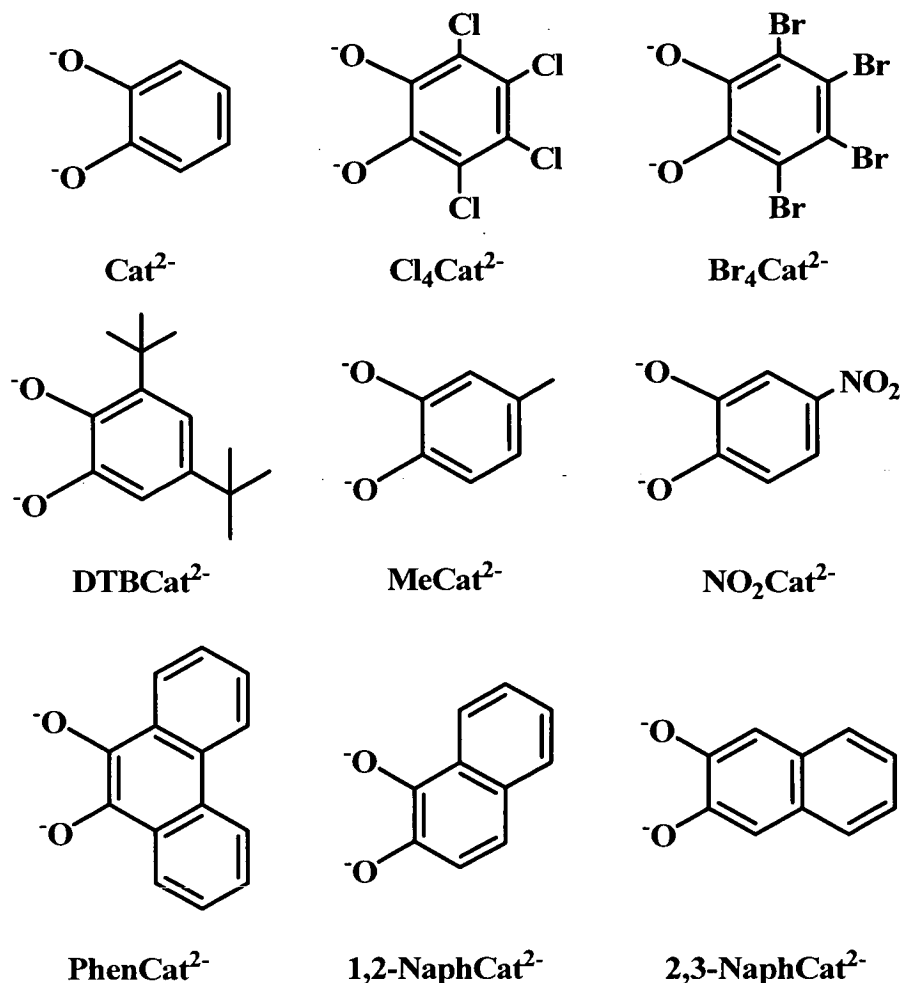


Figure 4.1. Schematic representation of the various catechols used by Schultz.²³

As can be seen from Figure 4.1, these catecholates have substituents which are either electron withdrawing (chlorides, bromides, nitro) or electron donating (methyl, *tert*-butyl, aromatics), and this is reflected in the redox potentials for the catechol-semiquinone (Cat/SQ) and semiquinone-quinone (SQ/Q) redox couples. The more electron donating the substituents are, the lower the redox potentials are, hence the easier it is to oxidize the catechol. For a wide range of catechols, the Cat/SQ and SQ/Q redox potential were found to increase by *c.a.* 1.7 V upon complexation to a Mo(VI) metal centre (see Table 4.2). Thus, it looks like the

substituents have the same effect on the free and the complexed catecholate. It is interesting that both oxidations seem to be affected to a similar extent.

Table 4.2. Redox potentials vs Fc^+/Fc for free catechols and $MoOCat(S_2CNEt_2)_2$ complexes in CH_2Cl_2 .²³

Type of catechol	Redox process	$E_{1/2}$ of the free ligand	$E_{1/2}$ of the metal complex	ΔE of the (complex-ligand) C/SQ couple
Cl_4Cat	Cat / SQ	-1.06 V	0.65 V	1.71 V
	SQ/Q	-0.31 V	1.20 V	1.51 V
Br_4Cat	Cat / SQ	-1.06 V	0.64 V	1.70 V
	SQ/Q	-0.31 V	1.19 V	1.50 V
NO_2Cat	Cat / SQ		0.67 V	
	SQ/Q	Not reported	1.20 V	
PhenCat	Cat / SQ	-1.71 V	-0.04 V	1.67 V
	SQ/Q	-1.11 V	0.64 V	1.74 V
1,2-NaphCat	Cat / SQ	-1.64 V	0.04 V	1.68 V
	SQ/Q	-1.03 V	0.88 V	1.91 V
2,3-NaphCat	Cat / SQ	Not reported	0.43 V	
	SQ/Q	-1.32 V	0.32 V	1.64 V
Cat	Cat / SQ		0.99 V	1.70 V
	SQ/Q	-0.71 V	0.22 V	
MeCat	Cat / SQ		0.88 V	
	SQ/Q	Not reported	0.88 V	
DTBCat	Cat / SQ	-1.68 V	0.15 V	1.83 V
	SQ/Q	-1.04 V	0.90 V	1.94 V

A similar study involving the same $MoO(VI)$ complexes of Cat, MeCat, NO_2Cat and DTBCat dioxolene ligands, but with two ONR_2 ($R = Me, Et, Bz$) ligands instead of two $S_2NCNEt_2^-$ to complete the coordination sphere around the metal centre gave similar trends.²⁴

4.3.2. Effect of coordination to a metal centre

From the point of view of the metal, the first parameter likely to influence the redox behaviour of the bound redox active ligand is the nature of the metal centre itself, both as a result of its size and Lewis acidity. Thus, it is interesting to examine the extent to which the redox potential of metal-bound catechols changes down a group and along a period, while keeping the same ligand set and oxidation state.

A strong Lewis acid should withdraw electron density away from the dioxolene ligand and render it more difficult to oxidize. However, considering that metal centres in general have different preferences in terms of coordination number and/or oxidation state, it is rather complicated to find extensive studies reporting the redox behaviour of metal-bound catecholates with a given ligand set. Nevertheless some studies provide interesting insights into the role of the metal in the redox potential of dioxolene ligands.

Owing to the considerable number of ligand frameworks involved in the study of metal/catecholate systems, it is convenient to examine first the effect of the metal centre on the dioxolene in complexes which do not contain any other ligand.

The case of *bis* and *tris* dioxolene transition metal complexes has been widely studied for many metals (see Table 4.3). However, the electron transfer possibilities between the metal centre and the various dioxolene moieties and solvents used make some electrochemical data difficult to interpret, even when this is available. Data exist for $[\text{Fe}(\text{Cl}_4\text{Cat})_3]^{3-}$ for which the three successive Cat/SQ oxidations were found at 0.37, 0.76 and 1.1 V (vs Ag/AgI) respectively.²⁵ The same type of data have been reported for $[\text{Fe}(3,6\text{-DTBCat})_3]^{3-}$, at -0.88, -0.66 and -0.34 V (vs Ag^+/Ag).²⁶

Comparison with the Ru (*resp.* Os) analogues is made difficult because the dioxolene C-O bond lengths are in between the values expected for catecholates and semiquinonates. As a result the electrochemical processes have not been clearly assessed and leads to some doubt concerning the oxidation state of the metal. In any case, it was postulated that a reduction at -0.52 V versus Fc/Fc⁺ for the Ru analogue (-0.47 V for Os) and two oxidations at 0.35 (0.52 V) and 0.960 V (1.11 V) are ligand centred.^{27,28} This suggest that the reduction potential for the dioxolene ligand is more positive going down the group.

Bis dioxolene complexes of group 10 metals have also been investigated. Thus, [Pd(3,5-DTBCat)₂]²⁻ and [Pt(3,5-DTBCat)₂]²⁻ exhibit the same electrochemical behaviour, which consists of two reversible redox process at -0.86 and -0.24 V followed by an irreversible oxidation at 0.56 V for the former, and at -0.80, -0.06 and 0.69 V for the latter. In the same conditions, the nickel analogue only exhibits the first two processes, at lower potentials, -1.07 and -0.38 V.^{29,30}

Table 4.3. Redox potentials metal dioxolene complexes vs Fc^+/Fc in MeCN and CH_2Cl_2 .

Metal oxidation state	Complex	Ligand based oxidations (V) First C/SQ couple	Solvent	ΔE (V) C/SQ couple	Ref
2	$[CuCat_2]^{2-}$	-0.70	CH_2Cl_2	0.62	25
	$[NiCat_2]^{2-}$	-0.83	CH_2Cl_2	0.49	25
	$[Ni(3,6-DTBCat)_2]^{2-}$	-1.07	CH_2Cl_2		29
	$[Pd(3,5-DTBCat)_2]^{2-}$	-0.86	CH_2Cl_2	0.82	30
	$[Pt(3,5-DTBCat)_2]^{2-}$	-0.80	CH_2Cl_2	0.88	30
3	$[Mn(3,5-DTBCat)_2]^-$	-0.77 ⁱ (E _{pc})	MeCN	1.07	32
	$[Fe(3,5-DTBCat)_2]^-$	-0.76 ⁱ	MeCN	1.08	33
	$[Fe(3,5-DTBCat)_3]^{3-}$ (tetrameric)	-1.35 ⁱ	MeCN	0.49	33
	$[Fe(3,6-DTBCat)_3]^{3-}$	-1.07	MeCN		26
	$[Ru(3,5-DTBCat)_3]^{3-}$	-0.52	CH_2Cl_2	1.16	27, 28
	$[Os(3,5-DTBCat)_3]^{3-}$	-0.47	CH_2Cl_2	1.21	27, 28
6	$[Tc(3,5-DTBCat)_3]$	0.45	CH_2Cl_2	2.13	34
	$[Re(3,5-DTBCat)_3]$	0.73	CH_2Cl_2	2.41	34

ΔE corresponds to the shift of $E_{1/2}$ of the metal complex relatively to the free ligand.ⁱ irreversible, E_{pa} . $E_{1/2(3,5-DTBCat/3,5-DTBSQ)} = -1.84$ V in MeCN.³¹ $E_{1/2(Cat/SQ)} = -1.32$ V, $E_{1/2(3,5-DTBCat/3,5-DTBSQ)} = -1.68$ V in CH_2Cl_2 .

Thus, it seems that the row to which the metal centre belongs to has significant effect on the redox potential of metal-bound ligands. Changing from Fe(III) to Os(III) and Ni(II) to Pt(II) induces a redox potential shift of up to 300 mV. A common trend indicates that the redox potentials of the dioxolene ligand increases down a group. The same trend has been observed for other groups, for instance the one electron oxidation of one dioxolene unit of $[Re(3,5-DTBCat)_3]$ and $[Tc(3,5-DTBCat)_3]$ have been reported, at 0.73 V and 0.45 V, respectively.³⁴

Bis dioxolene complexes of first row transition metals also give an interesting insight in the effect of the metal group on the redox potential of catechols. For instance, Röhrscheid and co-workers noticed a 130 mV shift in the redox potential between $[\text{Ni(II)Cat}_2]^{2-}$ and $[\text{Cu(II)Cat}_2]^{2-}$, the latter exhibiting the more negative redox potential.³⁵ This difference may be accounted for by the change of geometry around the metal centre, the Ni(II) complex being square planar,³⁶ and its Cu(II) analogue distorted towards tetrahedral with a dihedral angle between the catecholate planes being 22.48° .³⁷ The same shift in redox potential is observed for the corresponding Cl_4Cat complexes (120 mV). Other comparisons are more difficult to make, since studies were made in different solvents (CH_2Cl_2 , MeCN), with metals at different oxidation states (e.g. Fe(III) and Ru(III), Pd(II), Tc(VI), V(IV)) and with varying catechols. Nevertheless, no trend is observed when changing the metal group.

Thus, it seems that common to all these systems is that as the size of the metal increases, the more difficult it is to oxidize a bound dioxolene unit. This may be due to steric requirements and/or orbital overlap effects. Steric effects may be particularly important for the *bis* and *tris* quinoidal complexes. Elongated M-O bonds caused by steric hindrance presumably minimize the effect of metal binding on the redox properties of the dioxolene. In terms of orbital overlap, this can be expected to be greater when going down a group. The same behaviour occurs in metal complexes with a catecholate and another ligand.

Balch *et al.* showed that in $[\text{M}(\text{Cl}_4\text{Cat})(\text{PPh}_3)_2]$ complexes ($\text{M} = \text{Pd}, \text{Pt}$), the redox potential between them for the $\text{Cl}_4\text{Cat}/\text{Cl}_4\text{SQ}$ couple is shifted by 170 mV, the platinum complex being oxidized at higher potential.³⁸ Also, they showed that

$[M(Cl_4Cat)COCl((PPh)_3)_2]$, $M = Ir, Rh$ exhibit the same redox potential for the Cl_4Cat/Cl_4SQ couple.³⁹

Similar studies by Hartl and Vlcek investigated the differences between $Re(I)$ and $Mn(I)$ complexes of general formula $[M(CO)_xL_{(4-x)}(3,5-DTBSQ)]$ with $L = PPh_3$, Pyridine and $x = 2-4$ (see Table 4.4).^{35,40} They showed that the redox potential of the dioxolene unit is lower in the case of Mn centres by 50 mV, 90 mV and 190 mV, respectively, for the first $DTBC/DTBSQ$ redox couple. This shift increases to 200 mV, 240 mV and 250 mV for the second redox couple. An explanation for this shift is that $Re-CO$ bonds are in general stronger than $Mn-CO$ ones; this in turns favours π -backbonding from the Re centre to the carbonyl ligands, and decreases the electron density on the metal. This would lead to higher dioxolene redox potentials.

Table 4.4. Redox potentials metal dioxolene complexes vs Fc^+/Fc in CH_2Cl_2 .

Complex	Ligand based oxidations (V)		ΔE (V)	
	C/SQ couple	SQ/Q couple	C/SQ couple	SQ/Q couple
$[Mn(CO)_4(3,5-DTBSQ)]$	Not reported	0.29		1.33
$[Mn(CO)_3(PPh_3)(3,5-DTBSQ)]$	-0.92	0.04	0.76	1.08
$[Mn(CO)_3(Py)(3,5-DTBSQ)]$	-0.90*	0.11*	0.74*	1.15*
$[Mn(CO)_2(PPh_3)_2(3,5-DTBSQ)]$	-1.23	-0.46	0.45	0.58
$[Re(CO)_4(3,5-DTBSQ)]$	-0.51	0.43	1.17	1.47
$[Re(CO)_3(PPh_3)(3,5-DTBSQ)]$	-0.87	0.24	0.81	1.28
$[Re(CO)_3(Py)(3,5-DTBSQ)]$	-0.71	0.35	0.97	1.39
$[Re(CO)_2(PPh_3)_2(3,5-DTBSQ)]$	-1.14	-0.21	0.54	0.83

ΔE corresponds to the shift of $E_{1/2}$ of the metal complex relatively to the free ligand: $E_{1/2(3,5-DTBCat/DTBSQ)} = -1.68 V$, $E_{1/2(3,5-DTBSQ/DTBQ)} = -1.04 V$. * in pyridine.

Dei reported that the change of half-wave potential of $[M(CTH)(DTBCat)]^+/[M(CTH)(DTBSQ)]$ complexes, where $M = Ni(II), Zn(II), Fe(II)$ and CTH is a

tetraazamacrocyclic (see Figure 4.2), was never greater than 20 mV in CH_2Cl_2 (see Table 4.5).⁴¹ Thus, changes along a period seem to be less significant in these complexes.

Table 4.5. Redox potentials metal dioxolene complexes Vs Fc^+/Fc in CH_2Cl_2 . ΔE corresponds to the shift of $E_{1/2}$ of the metal complex relatively to the free ligand: $E_{1/2(3,5\text{-DTBCat}/3,5\text{-DTBSQ})} = -1.68 \text{ V}$.

Redox process	$E_{1/2} \text{ (V)}$	$\Delta E \text{ (V)}$
$[\text{Fe}(\text{CTH})(\text{DTBCat})] / [\text{Fe}(\text{CTH})(\text{DTBSQ})]^+$	-1.13	0.55
$[\text{Ni}(\text{CTH})(\text{DTBCat})] / [\text{Ni}(\text{CTH})(\text{DTBSQ})]^+$	-1.14	0.54
$[\text{Zn}(\text{CTH})(\text{DTBCat})] / [\text{Zn}(\text{CTH})(\text{DTBSQ})]^+$	-1.12	0.56

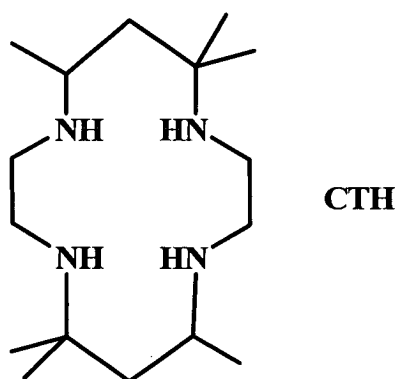


Figure 4.2. Schematic representation of the CTH ligand.

Finally, an interesting feature is that more drastic changes are observed when the degree of oxidation of the metal changes. If we consider that the effect of the metal group is negligible, the comparison of the Pt(II) and Pd(II) bis-quinolyl complexes with the Fe(III) and Mn(III) analogues indicates that an increase of oxidation number leads to a higher potential of *ca.* 0.1 V. Similarly, the redox

potential of the catechol in the Ru(III) and Os(III) tris-quinolyl complexes is *ca* 1 V less positive than in the Tc(VI) and Re(VI) analogues.

4.3.3. Effects of changes in the ligand set

Systematic changes in the nature of L in Table 4.6 allowed Hartl and Vlcek to investigate how the ligand set affects the redox potential of the catechol. They noticed that the redox potentials of the DTBC/DTBSQ and DTBSQ/DTBQ couples varied when the metal was coordinated to ligands with π -accepting capabilities such as PPh₃, pyridine and CO. Replacing a CO ligand by a PPh₃ leads to a dioxolene ligand that is easier to oxidize by *c.a.* 300 mV. This indicates that as the electron density of the metal centre increases due to less π -back donation to the CO ligand, the dioxolene becomes more electron rich. The strong interaction between a carbonyl and the dioxolene ligand has also been used to explain the dramatic change of half wave potential between [Ru(CO)(DTBSQ)(trpy)]⁺ (trpy = terpyridine) and [RuCl(DTBSQ)(trpy)]. It was observed that the first and second reversible redox processes at the dioxolene unit were increased by 540 mV and 700 mV, respectively, by replacing the Cl⁻ anion by a CO (Table 4.6).⁴⁰

Table 4.6. Redox potentials metal dioxolene complexes vs Fc^+/Fc in CH_2Cl_2 .

Complex	Ligand based oxidations (V)		ΔE (V)	
	C/SQ couple	SQ/Q couple	C/SQ couple	SQ/Q couple
$[Ru(CO)(trpy)(3,6-DTBSQ)]^+$	-0.72	0.33	0.96	1.37
$[RuCl(trpy)(3,5-DTBSQ)]^{36}$	-1.26	-0.37	0.42	0.67

ΔE corresponds to the shift of $E_{1/2}$ of the metal complex relatively to the free ligand: $E_{1/2}(3,5-DTBSQ/3,5-DTBQ) = -1.68$ V, $E_{1/2}(3,5-DTBQ/3,5-DTBSQ) = -1.04$ V.

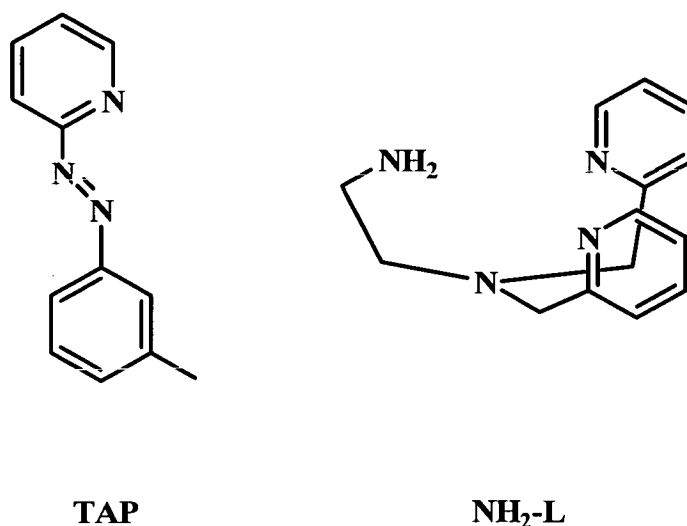
In this case, the increase can also be attributed to the change of electron density on the metal centre. Thus whereas the Cl^- is anionic, the CO is neutral and also drains electron density from the metal through π backbonding.⁴²

Finally, changes of the chelating ligand L in $[L_nMDTBCat]$ systems, ($n = 0$ or 1), can lead to considerable changes in the redox properties of the dioxolene ligand: changing L = bpy to L = tap, 2-(m-tolylazo)pyridine makes the $[L_2RuDTBSQ]/[L_2RuDTBCat]$ increase by as much as 710 mV,^{43,44} and the $[L_2RuDTBQ]/[L_2RuDTBSQ]$ by 730 mV. Meanwhile, these potentials are only decreased by *c.a.* 140 mV when the two bpy ligands are replaced by the tetradentate ligand NH_2 -L bis-(2-pyridylmethyl)-2-aminoethylamine as shown in Figure 4.3 (Table 4.7).⁴⁵ This result is consistent with the stronger π -accepting character of tap.

Table 4.7. Redox potentials of metal dioxolene complexes Vs Fc^+/Fc .

Complex	Solvent	Ligand based oxidations (V)		ΔE (V)	
		C/SQ couple	SQ/Q couple	C/SQ couple	SQ/Q couple
[Ru(tap) ₂ (3,5-DTBCat)]	CH ₃ CN	-0.23	0.53	1.61	1.73
[Ru(bpy) ₂ (3,5-DTBSQ)]	CH ₃ CN	-0.94	-0.20	0.90	1.00
[Ru(NH ₂ -L)(3,5-DTBCat)]	CH ₂ Cl ₂	-1.04		0.64	

ΔE corresponds to the shift of $E_{1/2}$ of the metal complex relatively to the free ligand: $E_{1/2}(3,5\text{-DTBSQ}/3,5\text{-DTBCat}) = -1.84\text{ V}$, $E_{1/2}(3,5\text{-DTBQ}/3,5\text{-DTBSQ}) = -1.20\text{ V}$ in CH_3CN ; ³¹ $E_{1/2}(3,5\text{-DTBSQ}/3,5\text{-DTBCat}) = -1.68\text{ V}$ in CH_2Cl_2 .

**Figure 4.3.** Schematic representation of TAP and NH₂-L ligands.

4.3.4. Effect of protons

The equilibrium potential for the second electron transfer between the semiquinone radical and the catechol dianion measured at pH 7, pH 11 and pH 13.5 revealed that the presence (or absence) of protons around the quinonyl moiety can

account for as much as 500 mV shift of the half wave potential.⁴⁶ In aprotic media, the addition of diverse hydrogen-bond donors (water,⁴⁷ or ethanol, 2-propanol, tert-butyl alcohol, trifluoroethanol⁴⁸) confirmed that the reduction of quinones occurs at higher potential in their presence. It was also noted that the second reduction is affected more (greater shift) than the first one, indicating that the increased negative charge on the oxygen atoms leads to a better quinone/hydrogen-bond donor interaction. Recently, Gupta *et al.* distinguished the role of protons in weak or strong hydrogen-bond donors systems.⁴⁸ In the case of weak acids, the positive shift of the equilibrium potential is due to the stabilization of the reduction products by hydrogen bonds. The same trend has been noticed for related molecules such as 4-benzoyl-*N*-methylpyridinium⁴⁹ and anthraquinone.⁵⁰ With strong acids, the reduction of quinones requires hydrogen bonding to occur prior to the electrochemical processes, and then it involves disproportionation of the hydrogen bonded semiquinone, and protonation of the dianion formed. Also, this study showed that the more basic the quinolyl residue is, the greater the number of hydrogen bonds it forms. Importantly, it revealed that in the case most favourable for strong hydrogen bonds (*i. e.* basic quinone and strong hydrogen-bond donor), an increase of acid concentration progressively replaces the hydrogen bonded system by the protonated one. This can be seen by cyclic voltammetry, where reduction peaks are shifted by 280 and 660 mV respectively, relatively to that of the quinone alone.

The effect of multiple hydrogen bonding on the redox behaviour of redox active molecules has also been investigated exploiting hydrogen bonded host:guest systems.

The effect of hydrogen bonds on the redox potential of electroactive substrates increases with their number and strength. For example, when two hydrogen bonds are present, it has been shown that the reduction potential of 1,2-quinones (G_{1-3}) bound to diphenylurea (H) as a host is increased by more than 100 mV, while anthraquinone (G_4), which is capable of hydrogen bonding to only one N-H proton exhibits a shift of only 49 mV (see Figure 4.4).⁵¹

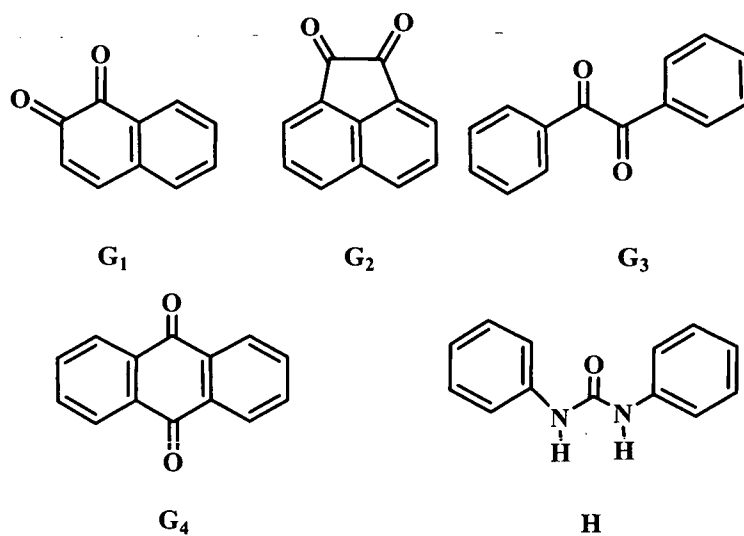


Figure 4.4. Schematic representation of various quinone guests and a urea-based host.

Triply hydrogen bonded systems are by far the most extensively studied, in part because they can mimic the redox behaviour of flavoproteins. Flavin containing enzymes are a family of several hundred proteins which are involved in diverse metabolic processes, electron transfer, detoxification of xenobiotics, and the regulation of neurotransmitters.⁵² The flavin moiety is another interesting electroactive molecule, which exhibits the same electrochemical pattern of two separate one-electron redox processes. It is clear that understanding the principles

which regulate the interplay between molecular recognition and redox processes is of crucial importance.

Thus, the effects of hydrogen bonds on the redox potential of electroactive ligands such as flavins has been widely investigated in the area of host:guest chemistry. Rotello *et al.* used different flavins and/or receptors to probe the influence of noncovalent interactions on biological systems. For instance, Figure 4.5 represents a flavin F_1 capable of forming three hydrogen bonds with the receptor, while for flavin F_2 , there is no such possibility.

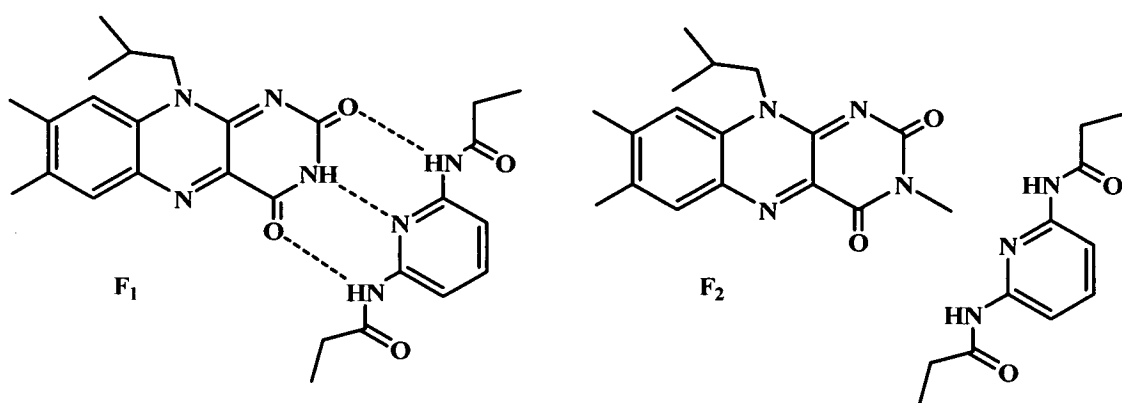


Figure 4.5. Schematic representation of a host:guest system with (left) and without (right) hydrogen bonds.

Examination of the half wave potential of the first flavin one-electron reduction shows that the system bearing the hydrogen bonds (F_1) is 155 mV less negative (easier to reduce) than the free flavin. The redox potential of the system F_2 :receptor, which does not exhibit hydrogen bonds, matches that of the free flavin.⁵³

Also, it was shown that different types of hydrogen bonds modulate these redox properties.⁵³

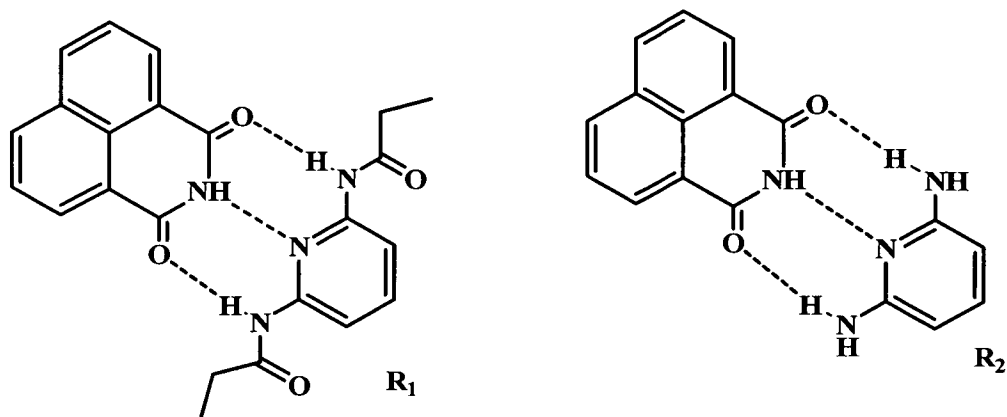


Figure 4.6. Schematic representation of a host:guest system with two different hydrogen bonded receptors.

In the system shown in Figure 4.6, the potential corresponding to the first flavin reduction is shifted positively by 44 mV relative to the free flavin when R₂ is present and by 145 mV when R₁ is present. This feature has been explained by means of calculations, which showed that the affinity of both receptors, although similar for the flavin in the oxidised state, differ when the flavin is reduced (the receptor R₁ shows higher affinity in this case).⁵⁴ Another possible reason is the higher acidic character of the amidopyridine N-H as compared to the aminopyridine N-H. This increase of acidity should induce stronger hydrogen bonds between the host and the guest, leading to greater interaction between them. It has also been noted that for similar substrates, the shift of redox potential increases with the number of hydrogen bonds, although not linearly, and that triple hydrogen bonding could induce a shift of as much as 207 mV.⁵⁵ The same type of findings, albeit to a lesser extent, have been noticed in related systems.⁵⁶⁻⁵⁹ Yano *et al.* also showed that increasing the number of hydrogen bonds in a flavin:melanine system increased the reduction potential of the former by 220 mV (5 hydrogen bonding groups) and 317 mV (7 hydrogen groups), see Figure 4.7.^{60,61}

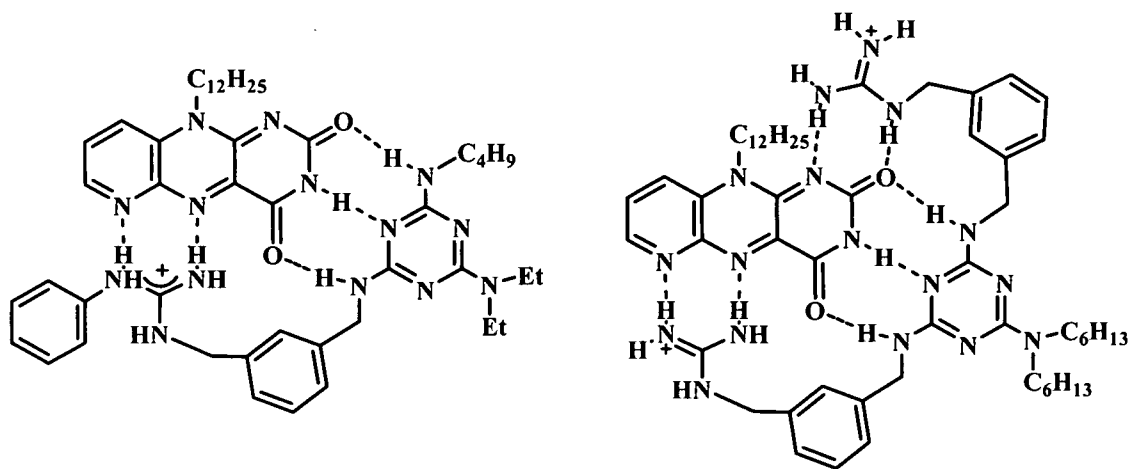


Figure 4.7. Penta and hepta hydrogen-bonded systems.

Other types of systems exploit intramolecular hydrogen bonding to affect the redox potential of quinones. For instance, a ferrocene-quinone dyad bearing only one hydrogen bond ($R = H$) showed a $Q^{\cdot-}/Q$ redox potential higher (by *c.a.* 240 mV) than its non hydrogen bonded counterpart (Figure 4.8, with Me replacing H).⁶² In contrast, the redox potential of the ferrocene unit is only slightly affected by the presence of this hydrogen bond (50 mV lower).

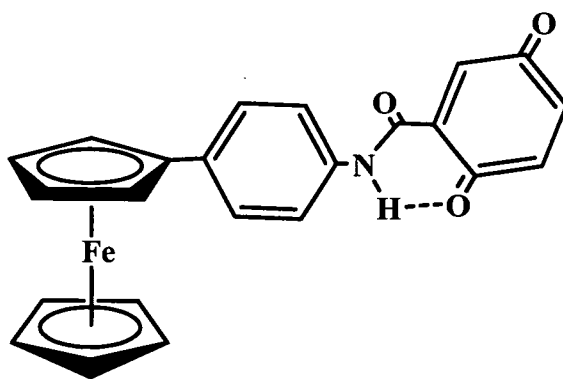


Figure 4.8. Schematic representation of host:guest systems with intramolecular hydrogen-bond.

4.4. Redox properties of metal-bound substrates in LZn(II)X complexes (L= TPA derivative, X = 3,5-di-*tert*-butylcatechol)

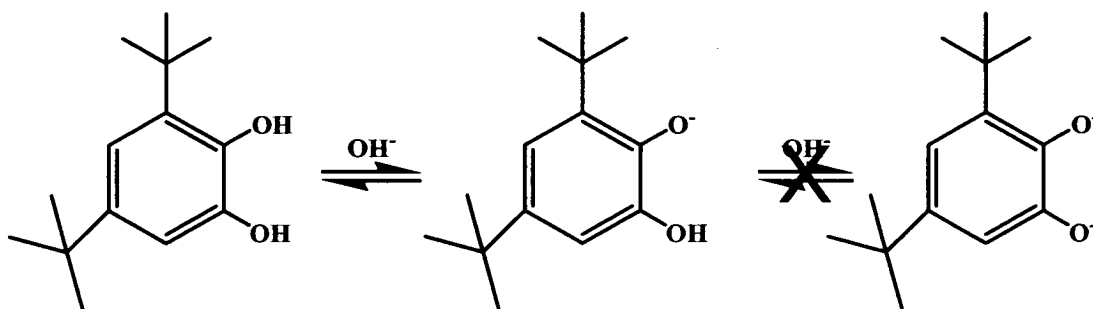
To investigate the extent to which hydrogen-bonds alone affect the redox properties of metal-bound ligands, complexes where 3,5-di-*tert*-butylcatechol is bound to the Zn(II) complexes of the tripodal ligands described in Chapter 3 have been synthesised. Zn(II) was selected because it is not redox-active within the range of potentials used, and also because its Lewis acidity should allow strong binding of 3,5-di-*tert*-butylcatechol. By examining the changes in half-wave potential corresponding to the oxidation/reduction of the electroactive ligand, we have determined the extent to which hydrogen-bonds modify the redox chemistry of redox-active substrates.

4.4.1. Synthesis and characterization

The Zn(II) complexes of the TPA derivatives [LZn(ClO₄)₂] were synthesized by mixing equimolar amounts of Zn(ClO₄)₂·6H₂O and the appropriate ligand in acetonitrile (L = TPA, L^{Am1}, L^{Np1-3}, L^{Piv1-3}). After stirring at room temperature for 1 h, the reaction was stopped. Owing to the low solubility of L^{Am2,3} in acetonitrile, [LZn(ClO₄)₂] (L = L^{Am2,3}) were prepared by mixing equimolar amounts of L and Zn(ClO₄)₂·6H₂O in methanol.

The catecholate 3,5-di-*tert*-butylcatecholate was generated in acetonitrile by mixing equimolar amounts of 3,5-di-*tert*-butylcatechol and tetramethylammonium hydroxide.⁶³ The solvent was then removed under high vacuum to generate a highly

hygroscopic blue/green solid. Addition of the base was used to give the dioxolene ligand an anionic character, and thereby enhance its binding to the Zn centre. This lead to monoanionic 3,5-di-*tert*-butylcatecholate as the second deprotonation cannot be achieved due to the very low acidity of the second phenol hydrogen (see Scheme 4.3).⁶³



Scheme 4.3. Deprotonation of the H_2DTBC .

The mono-deprotonated catecholate was then added as a solid to an acetonitrile solution of $LZn(ClO_4)_2 \cdot 6H_2O$ (1 equivalent) immediately prior to electrochemical and spectroelectrochemical measurements.

The formation of $LZn:DTBC$ adducts was studied by UV-vis in acetonitrile solutions containing the supporting electrolyte used in the electrochemical studies (0.1 M tetrabutylammonium tetrafluoroborate). The spectrum of H_2DTBC treated with $(Me_4N)OH \cdot 6H_2O$ to give $HDTBC^-$ changes in the presence of 1 equivalent of $[(L)Zn(CH_3CN)](ClO_4)_2$, with no further changes observed in the presence of more $LZn(II)$ indicating the formation of 1:1 adducts (Figure 4.9). This titration also indicates that the reaction is more complex than a simple coordination of one catechol moiety to the $LZn(II)$ complex, since the absorbance peaks do not follow a simple weighted addition.

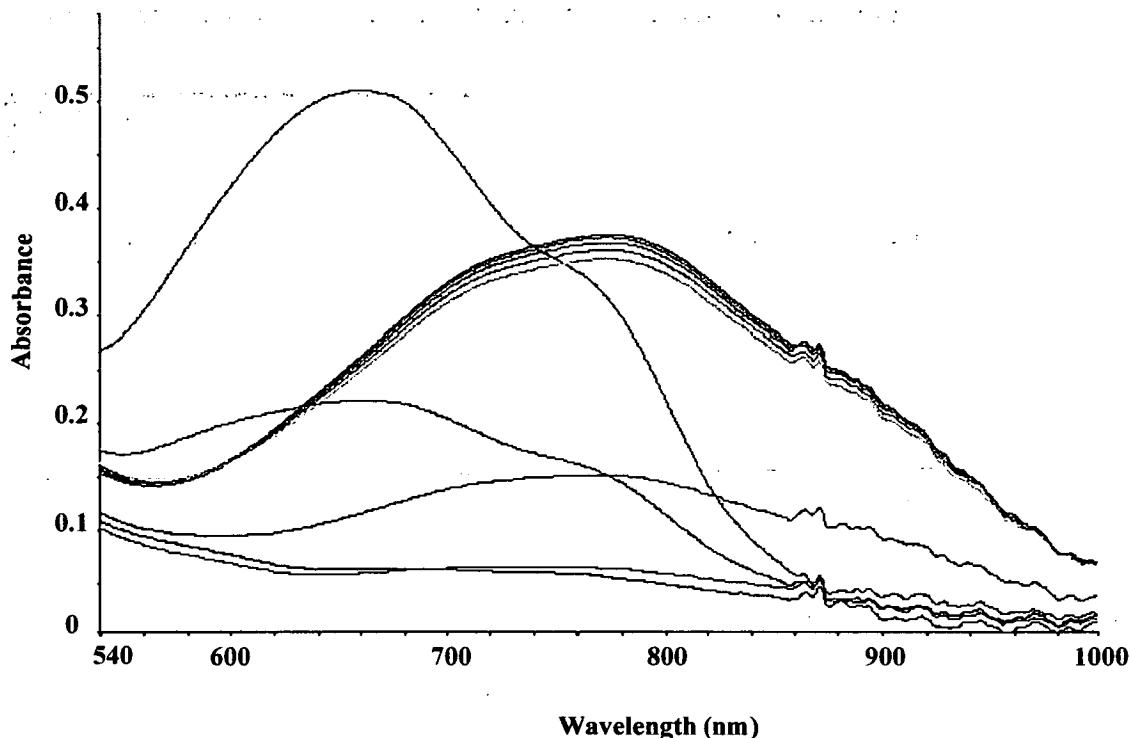


Figure 4.9. UV-visible titration of the NaHDTBC with $[L^{Am-1}Zn(ClO_4)_2]$.

Catecholate alone (blue); with 0.2 equivalent $L^{Am-1}Zn$ (red); 0.4 equivalent $L^{Am-1}Zn$ (green); 0.6 equivalent $L^{Am-1}Zn$ (pink); 0.8 equivalent $L^{Am-1}Zn$ (cyan); 1 equivalent $L^{Am-1}Zn$ (grey) and up to 2 equivalents.

Definitive proof for the formation of 1:1 LZn:DTBC adducts was obtained by X-ray crystallography. Crystals suitable for X-ray diffraction studies were obtained by slow evaporation of MeCN solutions of the 1:1 mixture of $[L^{Am-1}Zn(ClO_4)_2]$ and NaHDTBC. The main crystallographic data and refinement details are given in Table 4.8.

Table 4.8 Crystallographic data and structure refinement details for $[\text{L}^{\text{Am-}}\text{Zn}(\text{DTBC})]$

Empirical Formula	$\text{C}_{36}\text{H}_{45}\text{N}_6\text{O}_2\text{Zn}$
M_r	675.43
T/K	150(2)
Crystal system	Monoclinic
Space group	$P 2_1/c$
$a/\text{\AA}$	21.305(2)
$b/\text{\AA}$	11.4590(11)
$c/\text{\AA}$	32.481(3)
$\alpha/^\circ$	90
$\beta/^\circ$	115.455(6)
$\gamma/^\circ$	90
$V/\text{\AA}^3$	7159.92
Z	8
$D_c/\text{g cm}^{-3}$	1.253
μ/mm^{-1}	0.727
Reflexions measured, unique	11683, 11683
R_{int}	0.064
$R_1(F)^a$ (all data)	0.1000
$wR_2(F^2)^a$ (all data)	0.0782
$S(F^2)^a$ (all data)	1.0869
Largest difference peak, hole/ $e^- \text{\AA}^3$	0.90, -0.74

$$^a R_1(F) = \Sigma(|F_o| - |F_c|) / \Sigma(|F_o|); wR_2(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w F_o^4]^{1/2}; S(F^2) = [\Sigma w(F_o^2 - F_c^2)^2 / (n - p)]^{1/2}.$$

The structure of $[(\text{L}^{\text{Am1}})\text{Zn}(\text{DTBC})]$ shows two crystallographically independent molecules where the Zn(II) centre is in a distorted octahedral geometry and DTBC^{2-} acts as a bidentate ligand. The average C-O distance of 1.33 Å is characteristic of DTBC complexes,⁶⁴ in accordance with the typical C...O distances for catecholate complexes: Q, 1.23 Å; SQ, 1.29 Å; C, 1.34 Å.⁶⁵

Importantly, the structure shows the formation of intramolecular N-H...O hydrogen bonding (Figure 4.10) between the ligand aminopyridyl unit and the Zn(II)-bound DTBC (N...O distances of 3.059 Å for molecule 1 (not shown) and 3.002 Å for molecule 2). It is interesting to note that the O atom involved in

intramolecular hydrogen bonding is the O₁ oxygen, which is more basic than O₂. This is due to the closer proximity of the electron-donating *tert*-butyl group as compared with O₂. This in turns makes O₁ more electron rich than O₂, thus a better hydrogen bond acceptor.

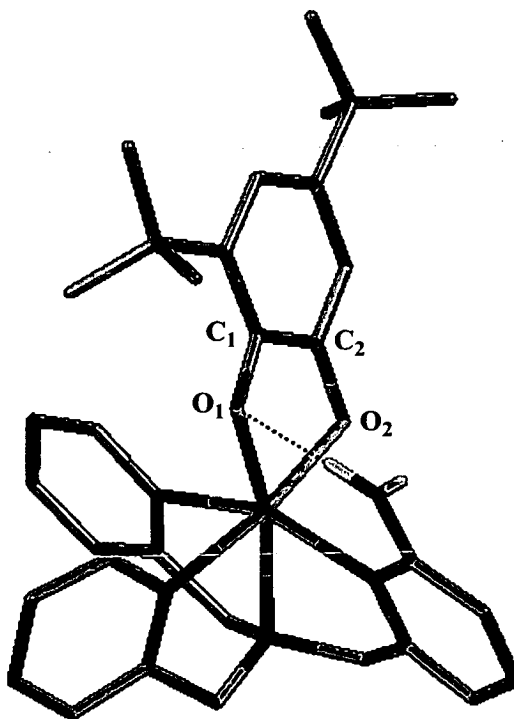


Figure 4.10. X-ray crystal structure of one of the $[(L^{AmI})Zn(DTBC)]^+$ cations showing the Zn(II) coordination environment. C-bound H atoms and solvent molecules are omitted for clarity.

This structure can be compared with the related $[(TPA)Fe(DTBC)]^+$,⁶⁶ $[(6-Me_3TPA)Mn(DTBCH)]^+$,⁶⁷ and $[(TPA)Mn(DTBSQ)]^+$.⁶⁸ The more important distances are summarized in Table 4.9.

Table 4.9. Selected bond lengths and angles for various metal-TPA-dioxolene complexes.

	$[(L^{Am1})Zn(DTBC)]$	$[(TPA)Fe(DTBC)]^+$	$[(6-Me_3TPA)Mn(DTBCH)]^+$	$[(TPA)Mn(DTBSQ)]^+$
Distances (Å)				
Zn-O ₁	1.966(4)	1.898(2)	2.020(3)	2.138(2)
Zn-O ₂	2.047(3)	1.917(3)	2.277(3)	2.121(2)
O ₁ -C ₁	1.336(5)	1.349(4)	1.342(5)	1.278(3)
O ₂ -C ₂	1.316(5)	1.347(4)	1.415(5)**	1.282(3)
C ₁ -C ₂	1.433(5)	1.418(5)	1.390(6)	1.428(4)
Zn-N _{Ax}	2.257(5)	2.221(3)	2.284(4)	2.334(2)
Average Zn-N _{Py}	2.217(5)	2.131(3)	N/A	2.244(2)
Zn-N _{Py*}	2.147(6)	N/A	2.318(4)	N/A
Angles(°)				
O ₁ -Zn-O ₂	83.70(16)	85.2(1)	75.76(10)	74.86(6)
Average N _{Ax} -Zn-N _{Py}	77.35(7)	77.63(1)	Not reported	72.13(7)

* indicates substituted pyridine rings; ** indicates that the oxygen atom is protonated.

As can be seen from Table 4.9, $[(L^{Am1})Zn(DTBC)]$ exhibits intermediate M-O distances within the catecholate complexes, with the shortest being the unsubstituted TPA complex. This could be explained in terms of steric hindrance. The shorter C-O distances in $[(L^{Am1})Zn(DTBC)]$ however indicate that the interaction between the Zn atom and the dioxolene unit is weaker in this case. Interestingly, the difference between C-O₁ and C-O₂ distances (C-O₁ being the longer) is greatest in $[(L^{Am1})Zn(DTBC)]$. This could be due to the N-H---O₁ hydrogen bond. The longer C-C distance is also to be noted, since it corresponds to a SQ intra-ring distance. In the same way as the other catechol complexes of TPA derivatives, the N_{pyridine}-Zn-N_{amine} is lower than 90°, due to the 5-membered chelate rings. Also, the M-N distances are in general shorter for the pyridine than for the aliphatic nitrogens. It is

also clear from the table that the catechol moiety is bound asymmetrically; the $M-O_1$ distance is shorter than the $M-O_2$ by 0.082 Å. This value is higher than in the $[(6-Me_3TPA)Mn(DTBCH)]^+$ and $[(TPA)Fe(DTBC)]^+$ complexes, but smaller than in the $[(TPA)Mn(DTBSQ)]^+$. This rules out the fact that the symmetry of the ligand could determine the symmetry of the bound catechol.

To the best of my knowledge, only two other examples of a catecholato complex bearing an internal hydrogen bond have been previously reported.⁶⁹ In these complexes the nitrogen and oxygen atoms involved in hydrogen bonding are distant by 2.638(7) (n = 4) and 2.675(6) Å (n = 5), respectively. Thus, they appear to be much closer than in the $[(L^{Am1})Zn(DTBC)]$ complex. In these terpyridine-based complexes, however, the N-H and dioxolene moieties are part of the same ligand framework, as opposed to the dioxolene being an exogenous ligand (see Figure 4.11).

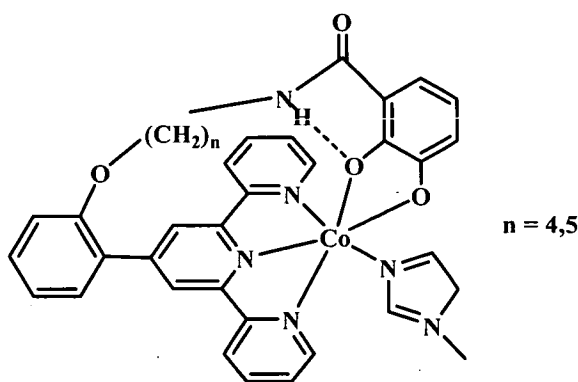


Figure 4.11. Representation of the Co(III)-catecholato complex cation with internal hydrogen bond.

4.4.2. Electrochemical studies

The cyclic voltammograms were carried out under nitrogen in acetonitrile in the presence of 0.1M tetrabutylammonium tetrafluoroborate (TBABF₄) as supporting electrolyte. The metal-complexes were generated in-situ just prior to the electrochemical studies. The concentration of the metal complexes in solution was 3.45 mM.

The voltammograms of the LZn:DTBC adducts exhibit a first quasi-reversible redox wave between -0.29 V and 0.1 V corresponding to the first oxidation of the bound catecholate to semiquinonate (LZn:DTBC to LZnDTBSQ, see Figure 4.12).

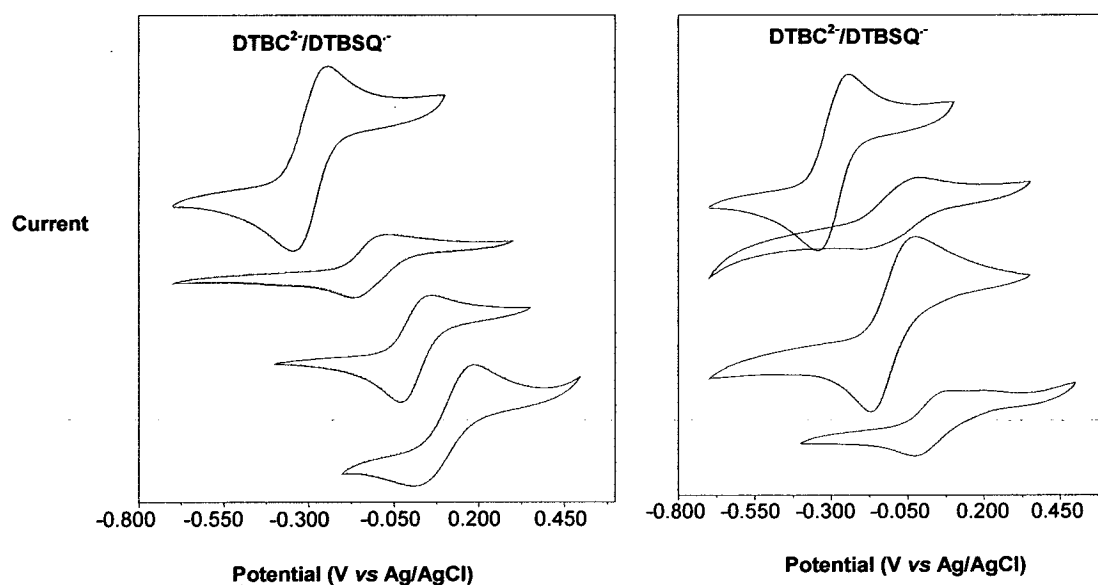


Figure 4.12. First electrochemical process for the $L^{(Piv)^n}ZnDTBC$ (left) and $L^{(Np)^n}ZnDTBC$ (right) complexes in acetonitrile at room temperature containing 0.1 M TBABF₄, scan rate 0.1 V.s⁻¹. $n=0$ (black); $n=1$ (blue); $n=2$ (green); $n=3$ (brown).

Another anodic wave, which is irreversible, is detected at higher potentials (0.64 V to 0.94 V, see Figure 4.13) and assigned to the oxidation of the LZn:DTBSQ

to LZnDTBQ.⁷⁰ The irreversible character of this phenomenon is attributed to the instability of the latter, as observed for similar dioxolene complexes.

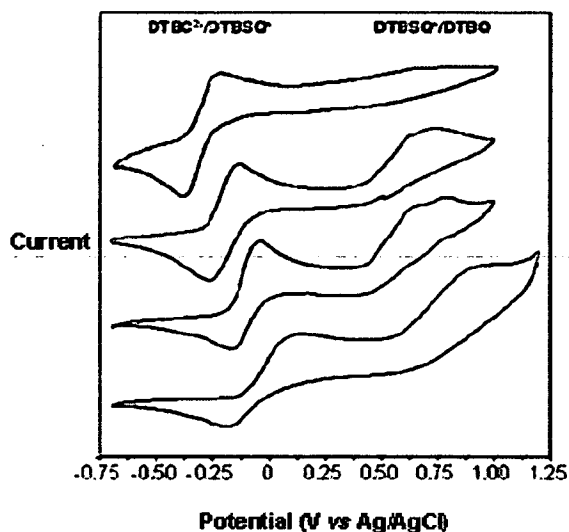


Figure 4.13. Both electrochemical processes for the $L^{(Am)n}ZnDTBC$ complexes. $n=0$ (black); $n=1$ (blue); $n=2$ (green); $n=3$ (brown) (against AgCl/Ag, scan rate 0.1 V s^{-1}) in acetonitrile solution containing 0.1 M TBABF_4 .

The ^1H NMR spectrum of 1:1 mixtures of $L^{Am-n}Zn$ and DTBQ in acetonitrile (see Figure 4.14), which perfectly fit the spectrum of the free DTBQ and $L^{Am-n}Zn$, indicate the absence of binding. Thus, it can be proposed that upon the second oxidation of bound DTBSQ to bound DTBQ, the quinone comes off the complex, introducing irreversibility to the electrochemical process.

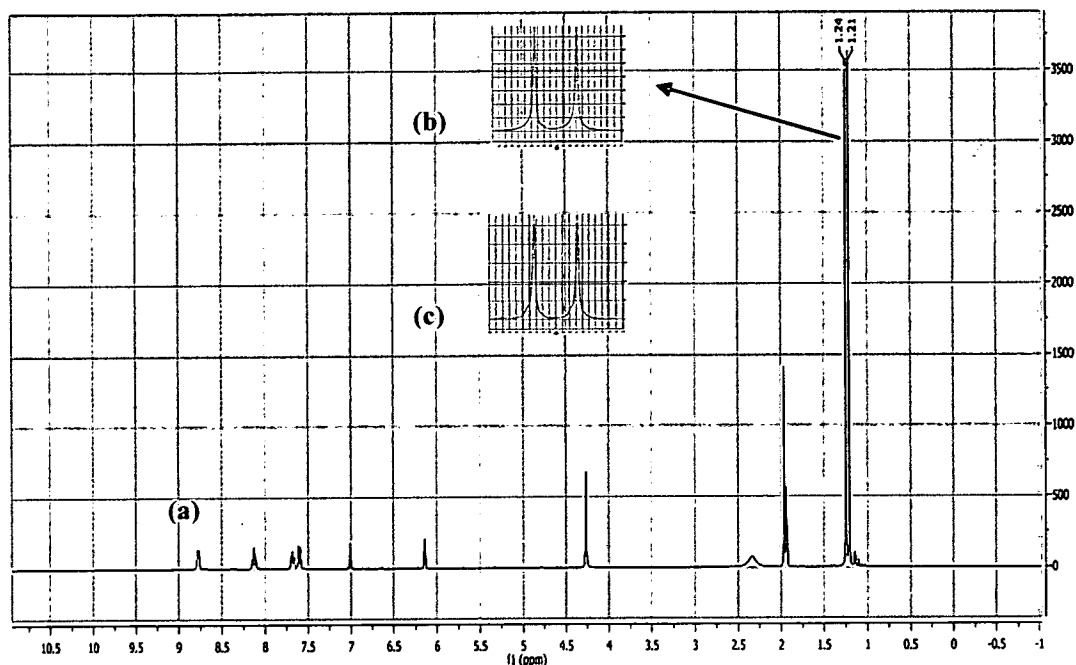


Figure 4.14. ^1H NMR spectrum of a 1:1 mixture of: (a) $[\text{TPAZnCH}_3\text{CN}]^{2+}$ and DTBQ, (b) expansion of the tert-butyl groups region, and (c) tert-butyl groups region of the free DTBQ.

It is also important to note that mixtures containing equimolar amounts of H_2DTBC and $[(\text{L}^{\text{Am}_{2,3}})\text{Zn}(\text{CH}_3\text{CN})]^{2+}$ afford a DTBSQ/DTBC redox couple close to that obtained using HDTBC^- . This is consistent with amino hydrogen bond donors progressively increasing the acidity of the protonated catechol, as found previously in our group.⁷¹

The measured redox values for the series of LZnDTBSQ/LZnDTBC and LZnDTBQ/LZnDTBSQ are given in Table 4.10.

Table 4.10. Measured potentials (in V) for the oxidation/reduction of the LZnDTBC complexes against Ag/AgCl.

Tripodal ligand L	Reduction1 (V)	Oxidation1(V)	$E_{1/2}$ (V)	Oxidation2 (V)
TPA	-0.35	-0.24	-0.29	0.64
L ^{Am1}	-0.27	-0.13	-0.20	0.73
L ^{Am2}	-0.17	-0.06	-0.11	0.78
L ^{Am3}	-0.19	0.14	-0.02	0.94
L ^{Np1}	-0.20	-0.01	-0.11	0.81
L ^{Np2}	-0.17	-0.02	-0.10	0.90
L ^{Np3}	-0.02	0.06	0.02	0.83
L ^{Piv1}	-0.17	-0.08	-0.12	0.66
L ^{Piv2}	-0.06	0.06	0	0.66
L ^{Piv3}	0.01	0.19	0.10	0.65

As can be seen from Table 4.10, the introduction of hydrogen bonds promotes in all cases the reduction of the dioxolene unit. This is easily explained by the decrease of electron density on the hydrogen bonded oxygen atom, which as a result accepts more readily an electron. Amino groups ($L^{(Am)n}$ derivatives) induce an almost linear increase of the half wave potential corresponding to the DTBSQ/DTBC couple, each function stabilizes the reduced species as much as 90 mV. The second oxidation potential also increases regularly to a first approximation. It is surprising to notice that with $L^{(Np)n}$ and $L^{(Piv)n}$ ligands, the second oxidation does not seem to follow any trend. Concerning the $L^{(Piv)n}$ complexes, only the first redox potential is changed, the second remains close to that of the TPA standard. Part of the explanation for such behaviour could arise from the fact that hydrogen bonds should be considerably weaker after the first oxidation has occurred, and therefore their influence on the second oxidation could be lessened. Since this behaviour takes place

only in the L^{Piv} complexes, it suggests that it is due to the peculiarities of this particular ligand.

It is quite probable that in such complexes, the steric bulk around the metal centre plays a crucial role. Rendering the metal centre more hindered could lengthen the $Zn \cdots N_{Py}$ distances, thus decreasing the electron density on the Zn centre and the catecholate, and raising the redox potential. Other structural changes affecting the redox behaviour of these complexes could implicate the decoordination of one of the pyridine rings. This should favor the reduction of the dioxolene ligand by decreasing the electron density on the metal. In the case of the L^{Piv} derivatives, coordination of one of the pendant pivaloylamido groups through the oxygen atom is a strong possibility as shown previously.⁷² This should favor the oxidation of the dioxolene unit by increasing the electron density of the metal.

Finally, it can be noted that the stabilization of the LZnDTBC compared to the LZnDTBSQ form follows the same order as the one found for the stabilization of the reduced form of the LCuCl complexes studied in chapter 3: $L^{Piv} > L^{Np} > L^{Am}$.

4.4.3. Binding strength of the catecholate to the metal

The difference of binding of the catecholate to the Zn(II) centre between the TPA complex and those bearing hydrogen bonding groups can be evaluated by measuring the stabilization of the reduced catecholate compared to its oxidized form according to Equation 4.1.

$$\Delta G = -nF(E_{\text{LZnDTBC}} - E_{\text{TPAZnDTBC}}) \quad \text{Eq. (4.1)}$$

The values given in Table 4.10 allow us to calculate the stabilization of the LZnDTBC with each type of ligand, which is reported in Table 4.11.

Table 4.11. *Stabilization energy and binding enhancement induced by the various hydrogen bonding groups.*

Tripodal ligand	$E_{1/2}$ (V)	Stabilization energy (kJ.mol ⁻¹)	Binding enhancement (folds)
TPA	-0.29	0	0
L ^{Am1}	-0.20	8.7	33
L ^{Am2}	-0.11	17.4	1.1×10^3
L ^{Am3}	-0.02	26	3.6×10^4
L ^{Np1}	-0.11	17.4	1.1×10^3
L ^{Np2}	-0.10	18.3	1.6×10^3
L ^{Np3}	0.02	29.9	1.8×10^5
L ^{Piv1}	-0.12	16.4	751
L ^{Piv2}	0	28	8.4×10^4
L ^{Piv3}	0.10	37.6	3.9×10^6

These calculations also allow the determination of how much each hydrogen bonding groups enhances the binding of the dioxolene, through the use of Equation 4.2:

$$K_a(\{(L)Zn\})/K_a(\{(TPA)Zn\}) = \exp[-(nF/RT)(E_{1/2}(\{(L)Zn\}) - E_{1/2}(\{(TPA)Zn\}))]$$

(Eq. 4.2)

Thus, the hydrogen bonding groups enhance binding of the DTBC to the Zn(II) complex by a minimum of 33 fold with L^{Am1} to a remarkable 3.9×10^6 fold with L^{Piv3} . Previous studies have shown that hydrogen bonding groups can enhance the binding of redox-inactive external ligands, but the magnitude of the effects found in this work for the redox-active DTBC are far greater.⁷³ These findings confirm that hydrogen bonds within the active site of metalloproteins⁷⁴ and their metal complex models can enhance the binding of redox-active substrates. The most relevant example has been reported recently by Masuda, and consists of a hydroperoxo Zn(II) complex stabilized by two neopentylamino hydrogen bonding groups, identified by NMR spectroscopy and mass spectrometry.⁷⁵

4.4.4. Spectroelectrochemical studies

This section represents a preliminary study aimed at determining the rate of electron transfer from the changes in the UV-vis spectra at given redox potentials. The LZnDTBC complexes were used in the same conditions as for the electrochemical studies, in acetonitrile containing 0.1 M TBABF₄, and at a concentration of 3.45×10^{-3} mol.L⁻¹. They were transferred to a UV cell fitted with the same set of electrodes as used for recording the cyclic voltammograms: Pt working and counter-electrodes and Ag/AgCl reference electrode. A UV beam was then passed through the cell and the UV/Vis spectra recorded over time. The

compounds were initially reduced at a negative potential (*i.e.* -0.7 V) until no change was observed in the UV spectrum, so as to make sure that the solution did not contain any oxidized species. Different potentials were then applied and the spectra compared to the initial spectrum at -0.7 V. The potentials were selected as follow: at the first oxidation potential, and at the potential 0 V. The reduction back to the reduced state was also investigated, in order to evaluate the reversibility of the process.

A typical set of spectra obtained is shown in Figure 4.15.

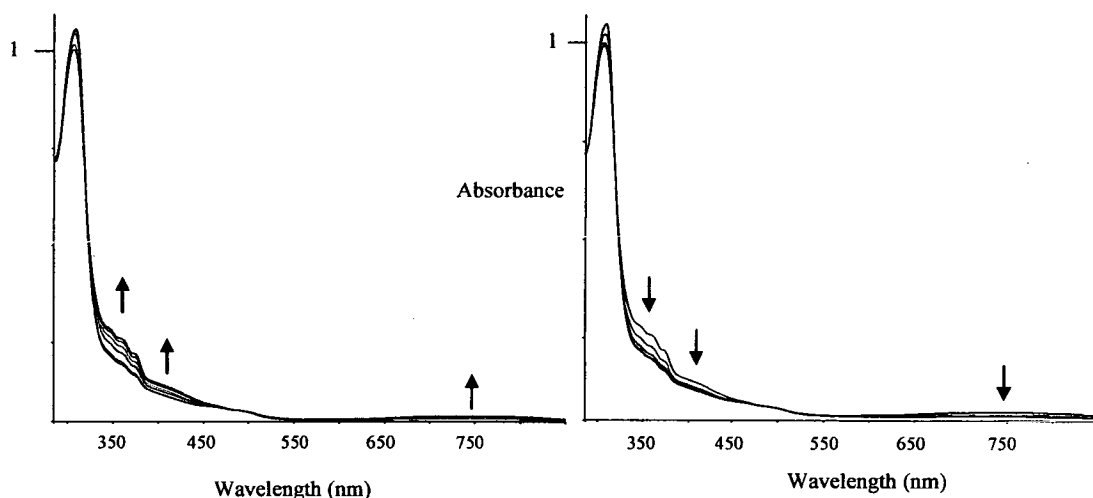


Figure 4.15. Evolution of the UV/Vis spectrum of TPAZnDTBC upon oxidation at 0.24 V (left) and reduction at -0.7 V (right).

The only transitions that can be observed correspond to the transition from the LZnDTBC to the LZnDTBSQ complexes. The maximum change in absorbance was found to be at 380 nm. Sawyer noted that the appearance of a peak at 382 nm was consistent with the formation of the semiquinonate form of the dioxolene unit.⁷⁶ The spectra were recorded every 2 min. For all metal complexes, we found that the

first electron transfer is reversible, as shown by the reversibility of the evolution of their absorption spectra at their first redox potential. Further oxidation leads to irreversible processes and to decomposition of the complexes, as shown by brown deposits at the bottom of the cell, and to results which are hardly reproducible.

At potential 0 V, the rate of oxidation of the zinc-bound DTBC seems to be affected by the presence of hydrogen bonding groups. In all cases, the tpa complexes seems to be oxidised more easily, followed by the complexes bearing fewer hydrogen bonding groups. Also, the complexes for which the half wave potential is more positive than 0 V (for instance $[L^{Np3}Zn(DTBC)]$, $E_{1/2} = 0.02$ V) do not exhibit significant changes in their absorption spectra (Figure 4.16).

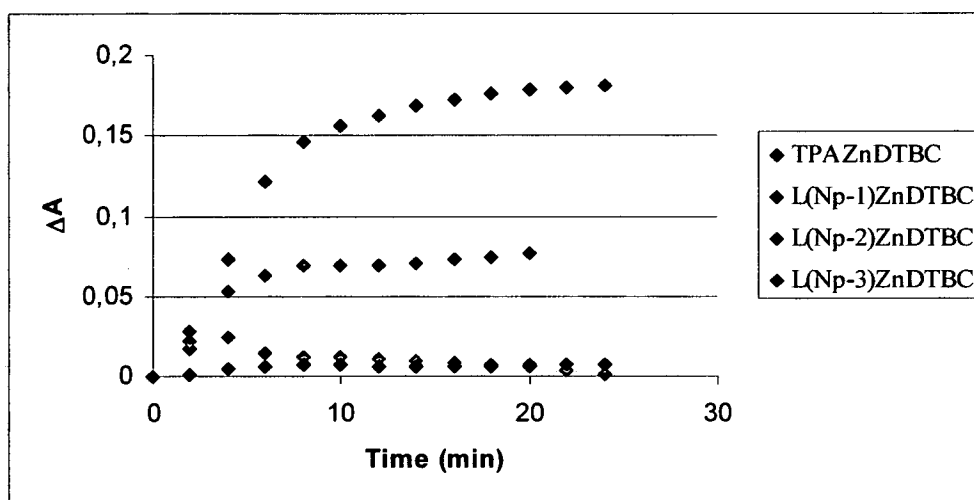


Figure 4.16. Evolution of the change of absorbance for the $L^{(Np-n)}ZnDTBC$ at 378 nm at potential 0 V.

At their respective oxidation potential, the TPAZnDTBC complex is oxidized much more easily than the $L^{Np(1-3)}ZnDTBC$ complexes. In fact, the $L^{Np(2,3)}ZnDTBC$

complexes exhibit little change, which can not be considered significant (Figure 4.17).

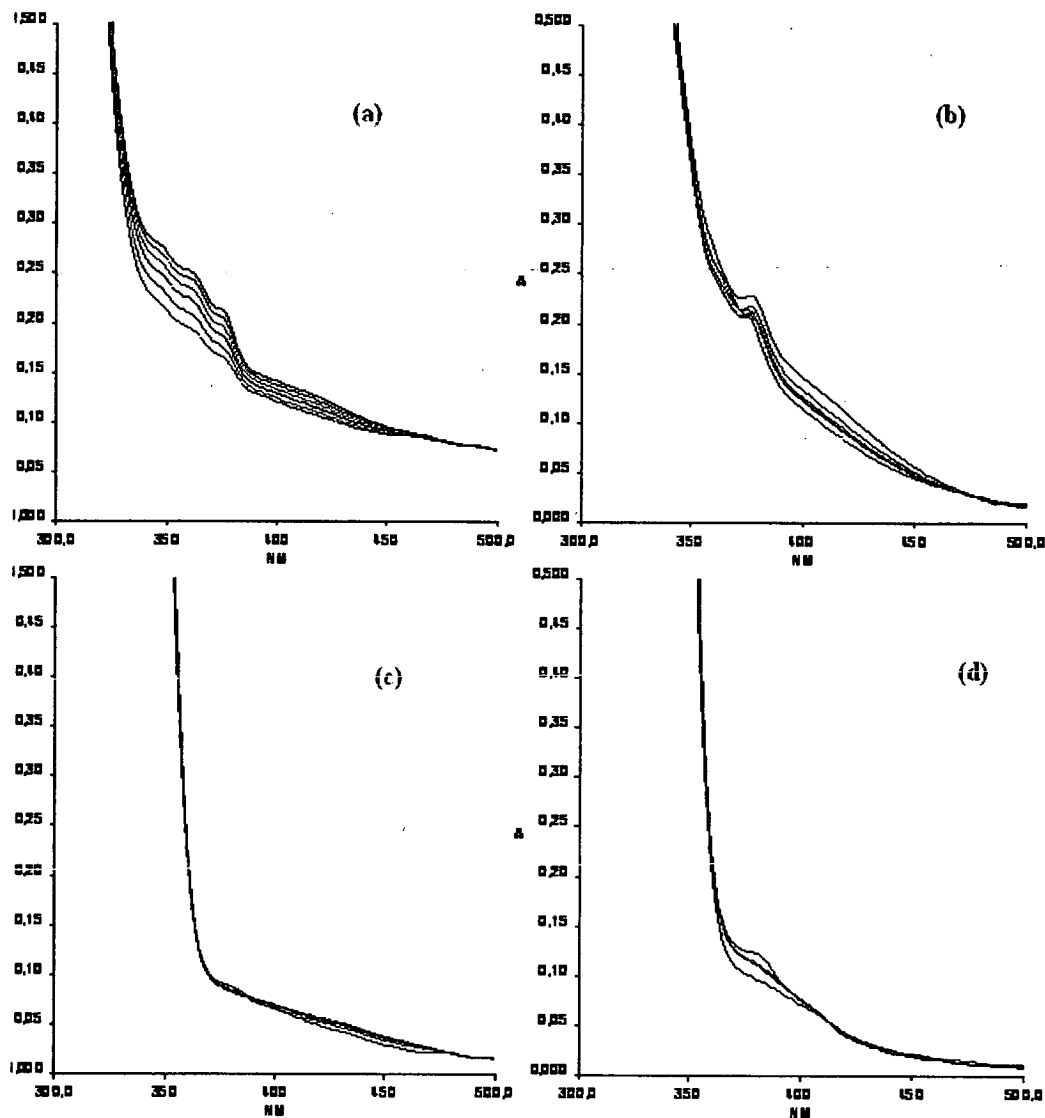


Figure 4.17. Selected region of the UV-Vis spectra of: (a) TPAZnDTBC at -0.24 V , (b) $L^{Np-1}\text{ZnDTBC}$ at -0.01 V , (c) $L^{Np-2}\text{ZnDTBC}$ at -0.02 V , and (d) $L^{Np-3}\text{ZnDTBC}$ at 0.06 V ; colour code: blue, $t = 0$; red, $t = 4\text{ min}$; green, $t = 8\text{ min}$; pink, $t = 12\text{ min}$; grey, $t = 16\text{ min}$; brown, $t = 20\text{ min}$.

With these experiments, we were hoping to find that the initial slope for the TPAZnDTBC complex would be greater than for the others, which would have been representative of this complex to get oxidised more quickly. Unfortunately, there seemed to be no correlation between the nature/number of hydrogen bonding groups and the ability of the LZnDTBC complexes to be oxidised, especially in the case of the $L^{\text{Piv1-3}}$ ligands (not shown). It should be noted, however, that these findings are preliminary results, and that they need further investigation. Hence, spectroelectrochemical studies of these complexes were complicated by a number of factors. Among those, the design of the electrochemical cell made it difficult to get reproducible results. These require the use of rigorously identical experimental conditions (alignment of the electrodes, position of the platinum gauze working electrode, etc) which were hardly obtained. However, the spectra seem to show that the TPA complex oxidises faster than the others; presumably due to the presence of hydrogen bonds. This corroborates perfectly our findings from the cyclic voltammetry studies.

4.5. Conclusion

In summary, this study has investigated the extent to which various hydrogen bonding groups influence the redox properties of electroactive ligands. It was found that their binding is dramatically enhanced by up to 3.9×10^6 fold for three pivaloylamido groups. Also, the presence of hydrogen bonds considerably facilitates their reduction. Thus, three pivaloylamido hydrogen bonding groups increase the redox potential by 430 mV. That corresponds to a shift greater than that found by

increasing the degree of oxidation of the metal, or changing a 1st row transition metal by another from the 2nd or 3rd row in the same group. It is also around 50 % of the change caused by protonation. Thus, it looks like the presence of hydrogen bonding groups in the second coordination sphere of metal complexes could have even greater influence on the redox properties of exogenous ligands than the nature and oxidation state of the metal itself.

The combination of both of these effects has to be considered when investigating the reactivity of redox metalloenzymes.

Finally, preliminary studies suggest that the rate of oxidation is slowed down by the presence of hydrogen bonding groups.

4.6. Experimental section

Reagents were obtained from commercial sources and used as received unless otherwise noted. Solvents were dried and purified under N₂ by using standard methods⁷⁷ and were distilled immediately before use. All compounds were prepared under N₂ unless otherwise mentioned. Electrochemical measurements were performed with an AUTOLAB PGSTAT-20 potentiostat. The cyclic voltammograms were obtained by using a three-electrode configuration consisting of a 0.5 mm diameter Pt disk working electrode, a Pt rod counter electrode, and an Ag/AgCl (saturated KCl) reference electrode against which the ferrocenium/ferrocene couple was measured and used as internal reference.⁷⁸ All measurements were made under N₂ atmosphere in dry acetonitrile with 0.1 M tetrabutylammonium tetrafluoroborate (TBABF₄) as the supporting electrolyte at room temperature. The scan rate was set to

0.1 V/s. UV/visible absorption spectra were obtained on a Perkin-Elmer $\lambda 9$ spectrometer. The NMR spectra were obtained using a Bruker DPX 360 at 20°C. ^1H chemical shifts are referenced according to the residual proton solvent peak. Intensity data for $[(\text{L}^{\text{Am-1}})\text{ZnDTBC}]$ were collected at 150 K using a Bruker-AXS SMART APEX area detector diffractometer with graphite-monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). The structures were solved by direct methods and refined to convergence against F^2 data using the SHELXTL suite of programs.⁷⁹ Data were corrected for absorption applying empirical methods using the program SADABS,⁸⁰ and the structures were checked for higher symmetry using the program PLATON.⁸¹ All non-hydrogen atoms were refined anisotropically unless otherwise noted. Hydrogen atoms were placed in idealised positions and refined using a riding model with fixed isotropic displacement parameters. Ligands were prepared according to procedures described in Chapter 2 and Chapter 3. Metal complexes were prepared under N_2 by mixing equimolar amounts of ligand and $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ in dry MeCN, immediately followed by one equivalent of mono-deprotonated catechol NaDTBCH. The solutions were used directly for electrochemical and spectroelectrochemical studies. Only $(\text{L}^{\text{Am1}})\text{Zn}(\text{DTBC})$ could be isolated by means of crystallisation from a MeCN solution.

4.7. References

1. P. Nordlund, I. Bertini, A. Sigel and H. Sigel, “*Handbook on Metalloproteins*”, Eds. Marcel Dekker, New York, 2001.
2. B. P. Rosen, S. M. Miller, E. D. Coulter, I. S. Isaac, J. H. Dawson, S. G. Sligar, D. M. Kurtz, Jr., A. G. Mauk, R. Hille, E. Neil, G. Marsh, J. W. Whittaker, J. B. Broderick, E. E. Trimmer, and J. M. Essigmann, “*Essays in Biochemistry, Vol. 34: Metalloproteins*”, Ed. D. P. Ballou, 2000.
3. M. Costas, M. P. Mehn, M. P. Jensen and L. Que, Jr, *Chem. Rev.*, 2004, **104**, 939 and references therein.
4. M. E. Bodini, G. Copia, R. Robinson and D. T. Sawyer, *Inorg. Chem.*, 1983, **22**, 126.
5. Merck (1989) The Merck Index, 11th edn. Rahway, NJ.
6. J. W. Porteous and R. T. Williams, *Biochem. J.*, 1949, **44**, 56.
7. L. Bolton, E. Pisha, F. Zhang and S. Qiu, *Chem. Res. Toxicol.*, 1998, **11**, 1113.
8. J.R. Van der Meer, W. M. de Vos, S. Harayama and A. J. B. Zehnder, *Microbiol Rev.*, 1992, **56**, 677.
9. W. A. Pryor, K. Stone, L.-Y. Zang and E. Bermudez, *Chem. Res. Toxicol.*, 1998, **11**, 441.
10. F. Hayakawa, T. Kimura, T. Maeda, M. Fujita, H. Sohmiya, M. Fujii and T. Ando, *Biochim Biophys Acta*, 1997, **1336**, 123.
11. J. S. Thompson and J. C. Calabrese, *J. Am. Chem. Soc.*, 2004, **108**, 1903.
12. M. J. Sever and J. J. Wilker, *Dalton Trans.*, 2004, 1061.

13. R. M. Buchanan, S. L. Kessel, H. H. Downs, C. G. Pierpont and D. N. Hendrickson, *J. Am. Chem. Soc.*, 1978, **100**, 7894.
14. S. W. Taylor, G. W. Luther III and J. H. Waite, *Inorg. Chem.*, 1994, **33**, 5819.
15. A. Avdeef, S. R. Sofen, T. L. Gregante and K. N. Raymond, *J. Am. Chem. Soc.*, 1978, **100**, 5362.
16. E. I. Solomon, U. M. Sundaram and T. E. Machokin, *Chem. Rev.*, 1996, **96**, 2563.
17. J. M. Harkin and J. R. Obst, *Science*, 1973, **180**, 296.
18. E. J. Land, C. A. Ramsden and P. A. Riley, *Acc. Chem. Res.*, 2003, **36**, 300.
19. P. E. M. Siegbahn, *J. Biol. Inorg. Chem.*, 2003, **8**, 567.
20. O. Carugo, C. Bisi Castellani, K. DjinoVIC and M. Rizzi, *J. Chem. Soc. Dalton Trans.*, 1992, 837.
21. O. Carugo, K. DjinoVIC, M. Rizzi and C. Bisi Castellani, *J. Chem. Soc. Dalton Trans.*, 1991, 1551.
22. R. Taylor and O. Kennard, *Acta Crystallogr., Sect. B.*, 1983, **39**, 517.
23. J. R. Bradbury and F. A. Schultz, *Inorg. Chem.*, 1986, **25**, 4411.
24. S. F. Gheller, W. E. Newton, L. Pabon de Majid, J. R. Bradbury and F. A. Schultz, *Inorg. Chem.*, 1988, **27**, 359.
25. F. Röhrscheid, A.L. Balch and R.H. Holm, *Inorg. Chem.*, 1966, **5**, 1542.
26. A.S. Attia, B.J. Conklin, C.W. Lange and C.G. Pierpont, *Inorg. Chem.*, 1996, **35**, 1033.
27. P. Zanello and M. Corsini, *Coord. Chem. Rev.*, 2006, **250**, 2000.

28. S. Bhattacharya, S.R. Boone, G.A. Fox and C.G. Pierpont, *J. Am. Chem. Soc.*, 1990, **112**, 1088.
29. C. W. Lange and C.G. Pierpont, *Inorg. Chim. Acta*, 1997, **263**, 219.
30. A. Fox and C.G. Pierpont, *Inorg. Chem.*, 1992, **31**, 3718.
31. Value calculated from the formula described in ref (25): $E_{1/2}(\text{quinone in CH}_2\text{Cl}_2)$
 $= E_{1/2}(\text{quinone in MeCN}) + 0.16$.
32. S. E. Jones, D.-H. Chin and D. T. Sawyer, *Inorg. Chem.*, 1981, **20**, 4257.
33. S. E. Jones, L. E. Leon and D. T. Sawyer, *Inorg. Chem.*, 1982, **21**, 3692.
34. L.A. deLearie, R.C. Haltiwanger and C.G. Pierpont, *J. Am. Chem. Soc.*, 1989, **111**, 4324.
35. F. Hartl and A. Vlcek Jr., *Inorg. Chem.*, 1992, **31**, 2869.
36. C. Brückner, D. L. Caulder and K. N. Raymond, *Inorg. Chem.*, 1998, **37**, 6759.
37. J. S. Thompson and J. C. Calabrese, *J. Am. Chem. Soc.*, 1986, **108**, 1903.
38. A. Y. Girgis, Y. S. Sohn and A. L. Balch, *Inorg. Chem.*, 1975, **14**, 2327.
39. L. Balch, *J. Am. Chem. Soc.*, 1973, **95**, 2723.
40. F. Hartl and A. Vlcek Jr., *Inorg. Chem.*, 1991, **30**, 3048.
41. A. Dei, *Inorg. Chem.*, 1993, **32**, 5730.
42. H. Sugimoto and K. Tanaka, *J. Org. Chem.*, 2001, **622**, 280.
43. P. F. H. Schwab, S. Diegoli, M. Biancardo and C. A. Bignozzi, *Inorg. Chem.*, 2003, **42**, 6613.
44. N. Bag, A. Pramanik, G. K. Lahiri and A. Chakravorty, *Inorg. Chem.*, 1992, **31**, 40.

45. Y. Miyazato, T. Wada and Koji Tanaka, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 745.
46. S. Steenken and P. Neta, *J. Phys. Chem.*, 1979, **83**, 1134.
47. S. Hayano and M. Fujihira, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2051.
48. N. Gupta and H. Linschitz, *J. Am. Chem. Soc.*, 1997, **119**, 6384.
49. N. Leventis, I. A. Elder, X. Gao, E. W. Bohannan, C. Sotiriou-Leventis, A. M. M. Rawashdeh, T. J. Overschmidt and K. R. Gaston, *J. Phys. Chem. B*, 2001, **105**, 3663.
50. J. Revenga, F. Rodriguez and J. Tijero, *J. Electrochem. Soc.*, 1994, **141**, 330.
51. Y. Ge, L. Miller, T. Ouimet, and D. K. Smith, *J. Org. Chem.*, 2000, **65**, 8832.
52. S. Ghisla and V. Massey, *Eur. J. Biochem.*, 1989, **181**, 1.
53. A. Niemz and V. M. Rotello, *Acc. Chem. Res.*, 1999, **32**, 44.
54. M. Gray, A. O. Cuello, G. Cooke and V. M. Rotello, *J. Am. Chem. Soc.*, 2003, **125**, 7882.
55. Y. Ge, R. R. Lilienthal and D. K. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 3976.
56. L. M. Goldenberg and O. Neilands, *J. Electroanal. Chem.*, 1999, **463**, 212.
57. A. S. F. Boyd, G. Cooke, F. M. A. Duclairoir and V. M. Rotello, *Tetrahedron Lett.*, 2003, **44**, 303.
58. G. Cooke, F. M. A. Duclairoir, P. John, N. Polwart and V. M. Rotello, *Chem. Commun.*, 2003, 2468.

59. G. Cooke and V. M. Rotello, *Chem. Soc. Rev.*, 2002, **31**, 275.
60. T. Kajiki, H. Moriya, S. Kondo, T. Nabeshima and Y. Yano, *Chem. Commun.*, 1998, 2727.
61. T. Kajiki, H. Moriya, K. Hoshino, T. Kuroi, S.-I. Kondo, T. Nabeshima and Y. Yano, *J. Org. Chem.*, 1999, **64**, 9679.
62. S. Fukuzumi, K. Okamoto, Y. Yoshida, H. Imahori, Y. Araki and O. Ito, *J. Am. Chem. Soc.*, 2003, **125**, 1007.
63. M. W. Lehmann and D.H. Evans, *J. Phys. Chem. B*, 2001, **105**, 8877.
64. S. Bhattacharya, S.R. Boone, G.A. Fox and C.G. Pierpont, *J. Am. Chem. Soc.*, 1990, **112**, 1088.
65. C. G. Pierpont and R. M. Buchanan, *Coord. Chem. Rev.*, 1981, **38**, 45.
66. H. G. Jang, D. D. Cox and L. Que Jr, *J. Am. Chem. Soc.*, 1991, **113**, 9200.
67. M. F. Reynolds, M. Costas, M. I. Du-Hwan Jo, A. A. Tipton, A. K. Whiting and L. Que, Jr, *J. Biol. Inorg. Chem.*, 2003, **8**, 263.
68. Y. Hitomi, A. Ando, H. Matsui, T. Ito, T. Tanaka, S. Ogo and T. Funabiki, *Inorg. Chem.*, 2005, **44**, 3473.
69. T. Nagata and K. Tanaka, *Inorg. Chem.*, 2000, **39**, 3515.
70. C. Benelli, A. Dei, D. Gatteschi and L. Pardi, *Inorg. Chem.*, 1990, **29**, 3409.
71. J. C. Mareque-Rivas, R. Prabakaran and R. Torres Martin de Rosales, *Chem. Commun.*, 2004, 76.
72. J. C. Mareque Rivas, E. Salvagni, R. Prabakaran, R. Torres Martin de Rosales and S. Parsons, *J. Chem. Soc., Dalton Trans.*, 2004, 172.

73. J. C. Mareque Rivas, R. Torres Martin de Rosales and S. Parsons, *Chem. Commun.*, 2004, 610.
74. D. E. Goldberg, *Chem. Rev.*, 1999, **99**, 3371.
75. A. Wada, S. Yamaguchi, S. K. Jitsikawa and H. Masuda, *Angew. Chem. Int. Ed.*, 2005, **44**, 5698.
76. M. D. Stallings, M. M. Morrison and D. T. Sawyer, *Inorg. Chem.*, 1981, **20**, 2655.
77. W. L. F. Armarego and D. D. Perrin, '*Purification of Laboratory Chemicals*', Butterworth-Heinemann, Oxford, 1997.
78. R. R. Gagne, C. A. Koval and G. C. Lisensky, *Inorg. Chem.*, 1980, **19**, 2854.
79. G. M. Sheldrick, '*SHELXTL 97*', University of Göttingen, 1997.
80. G. M. Sheldrick, '*SADABS, Empirical absorption correction program*', University of Göttingen, 1995, based upon the method of Blessing.
81. A. L. Spek, *Acta Crystallogr., Sect. A.*, 1990, **46**, C34.

Future Work

The redox properties of metals and metal-bound substrates are key parameters for the reactivity of many metalloproteins.

In this work, we showed that hydrogen bonding groups adjacent to metal-bound substrates affect dramatically the redox properties of the metal centre and of metal-bound electroactive ligands. The presence of hydrogen bonds in the vicinity of the metal centre favours not only the metal in a reduced oxidation state, but also the reduction of metal-bound substrates.

A natural continuation of this work could be the electrochemical study of metal complexes containing both a redox active ligand and a redox active metal centre. Indeed, knowing which of these effects is predominant would be significant to better understand how reactions catalyzed by redox active enzymes occur.

Also, it would be interesting to quantify the effect of hydrogen bonding on the rate of electron transfer of metal-bound redox-active ligands. Since the rate of electron transfer is also important, knowing how and to which extent hydrogen bonding affects it could help designing more efficient synthetic complexes and models for redox-active metalloprotein-catalyzed reactions.

Finally, an interesting extension of this work could be to investigate the reactivity of metal complexes of the TPA derivatives towards organic substrates, for example catechols or hydrocarbons. Hence, the presence of hydrogen bonding groups might enhance the activity of TPAFe(III) complexes, or favour different reaction mechanisms and/or oxygenated products. This would provide important additional insights into the functional significance of hydrogen bonding groups in

redox-active metalloproteins, and the functional elements required for the catalytic reactions that they perform. The suitability of such metal complexes to oxygenate other types of substrates could also be assessed. For instance, these metal complexes could be tested as bleaching agents for the removal of stains, using hydrogen peroxide or ideally dioxygen as the oxidant.