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COMMUNICATION

Synthesis of a series of M(II) (M = Mn, Fe, Co) chloride complexes with both inter- and intra-ligand hydrogen bonding interactions

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Hydrogen bonding networks are vital for metallo-enzymes to function; however, modeling these systems is non-trivial. We report the synthesis of metal chloride (M = Mn, Fe, Co) complexes with intra- and inter-ligand hydrogen bonding interactions. The intra-ligand hydrogen bonds are shown to have a profound effect on the geometry of the metal center.

Hydrogen bonding networks found within metalloproteins play an essential role in the structure and function of enzymes. Intermolecular hydrogen bonds are responsible for positioning and stabilizing substrate at the active site while intramolecular hydrogen bonds between amino acids can function to change the metal's ligand field, reduction potential, and geometry within the metalloprotein (**Figure 1A**).[1–4] While these interactions are ubiquitous throughout enzymatic systems, modelling both intra- and intermolecular hydrogen bonding interactions in synthetic systems is difficult.[5]

Many reported examples of hydrogen bonding in synthetic complexes use C_3-symmetric ligands with three ligand arms capable of providing or receiving hydrogen bonds from a ligand bound to a metal. Examples by Borovik,[6–12] Szymczak,[13,14] Scarborough,[15] and Fout[16–19] have all used ligands which incorporate hydrogen bond donors or acceptors in the secondary coordination sphere of a metal to model biological systems.

Less developed are synthetic complexes that do not feature C_3-symmetric ligands but also incorporate hydrogen bonding motifs.[20–23] Most of these complexes are designed to interact with a metal-bound extrinsic ligand via inter-ligand hydrogen bonds, such as hydrogen bond donation to O_2 or oxyanions prior to (or during) reaction with those species.[23–30] Synthetic heme systems have focused on trying to incorporate hydrogen bonds to ligands that are meant to act as amino acid mimics to demonstrate how protein scaffolds can also use intramolecular hydrogen bonds to tune metal reactivity patterns.[31,32]

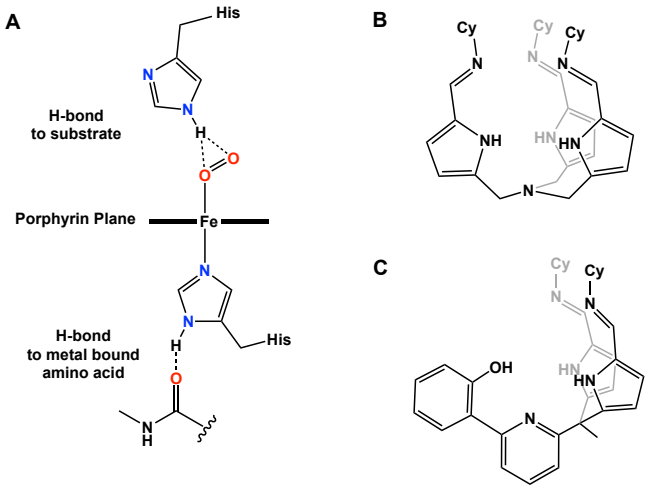

Figure 1 A. Hydrogen bonding to bound substrate and amino acid residues characterized in heme proteins. **B.** Ligand used in previous studies with C_3 symmetry. **C.** Ligand used in this study with approximate C_S symmetry.

Herein we report the synthesis of metal (M = Mn, Fe, Co) chloride complexes that exhibit both intra- and inter-ligand hydrogen bonds with a new biomimetic ligand scaffold. The intra-ligand hydrogen bonds are shown to have a profound effect on the coordination geometry of the metal centre, while maintaining a separate inter-ligand hydrogen bond with an axially bound chloride ligand.

Our group has previously reported the use of a C_3-symmetric tripodal ligand, ($N(pi^{Cy})_3$) (**Figure 1B**), and its complexation with late first row metals (M = Mn, Fe, Co, Zn).[16–18] One of the unique features of this ligand system is the ability of the pyrrole-imine (pi) functionalities to tautomerize to an azafulvene-amine (afa) tautomer upon binding of a metal. The tautomerization allows for the ligand arms to present as either a hydrogen bond donor

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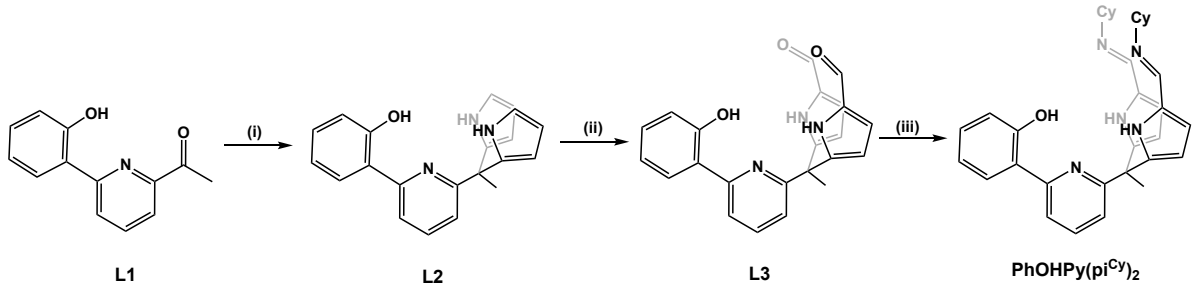

Figure 2. (i) Pyrrole, cat. trifluoroacetic acid (TFA), 18 h, room temperature (r.t.) (ii) 2.1 equiv. $POCl_3$, dimethylformamide (DMF) /dichloromethane (DCM), r.t. to 40 °C, 2 h; sat. sodium acetate (aq), 45 °C, 1 h (iii) 2.2 cyclohexylamine (H_2N-Cy), 18 h, r.t. DCM.

or acceptor for axially bound ligands, as well as alternating between anionic or dative coordination of the metal center.

Many metalloproteins have a non-symmetric ligand field around the metal centre, and so we sought to desymmetrize the chelating ligand field through the replacement of an axial pyrrole-imine ligand arm with a tyrosine-like ligand in the form of a phenoxide. The incorporation of the phenoxide arm with the pyrrole-imine arms was accomplished in the synthesis of the new ligand 2-(6-(1,1-bis(5-(cyclohexylimino)methyl)-pyrrol-2-yl)ethyl)pyridin-2-yl)phenol, PhOHPy(pi^{Cy})$_2$ (**Figure 1C,** see Supplemental Information, SI, **Figures S1-S6, S9-S11**). The ligand was prepared from a previously reported precursor,[33] 2-hydroxyphenol-6-actylpyridine (L1), over three steps (**Figure 2**), and its complexation with metal salts was investigated.

The synthesis of the metal complexes PhOPy(afa^{Cy})$_2$MCl (Mn = **1**, Fe = **2**, Co = **3**) was accomplished by treating PhOHPy(pi^{Cy})$_2$ with potassium hydride (KH) in tetrahydrofuran, followed by addition of the corresponding metal dichloride salts (MCl_2 = Mn, Fe, Co, **Figure 3**). The resulting solutions were stirred overnight and volatiles removed thereafter. Metal complexes were subsequently dissolved in dichloromethane and filtered through dichotomous earth to remove insoluble salts. Analytically pure samples were recrystallized from concentrated solutions of metal complex in dichloromethane with vapor diffusion of diethyl ether.

Examination of **1-3** using IR spectroscopy (**Table 1**, **Figures S12-S14**) revealed that ligand arms with hydrogen bonding functionality had tautomerized to the azafulvene-amine tautomer, based on the C=N stretching energies compared with previously characterized complexes (1635-1655 cm^{-1}).[16-17] Each complex also displayed what were assigned as N-H stretches above 3200 cm^{-1}, with **3** displaying multiple N-H stretching

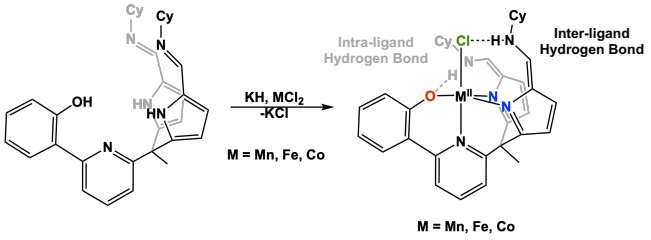

Figure 3. General procedure for the synthesis of complexes **1-**

Table 1. Spectroscopic Characterization of 1-3

Complex	$\nu_{C=N}$ (cm^{-1})	ν_{N-H} (cm^{-1})	μ_{eff} (μ_B)
1	1640	3284	6.10(22)
2	1638	3250	5.26(12)
3	1654	3183	4.62(16)

modes (*vide infra*). Compounds **1-3** were found to adopt high-spin states at ambient temperature based on paramagnetic ^{1}H NMR spectra (**Figures S7-S8**) and characterization of the complexes using Evans' method (**Table 1**).

Crystals appropriate for single crystal X-ray diffraction studies were grown using the same solvent system as for bulk purification and the solid-state structures of **1-3** were characterized. The manganese analogue, **1**, refined as a pseudo-square pyramidal complex (**Table 2**, **Figure 4**) with an equatorial plane consisting of anionic coordination from the deprotonated phenoxy arm, and tautomerization of the ligand arms from the initial pyrrole-imine motif to the azafulvene-amine motif, as suggested by IR spectroscopy. Interestingly, hydrogen bonding interactions are observed from the ligand arms to both the bound chloride (inter-ligand), and the coordinated phenoxy arm (intra-ligand), in analogy to hydrogen bonding interactions observed in metalloprotein scaffolds. The corresponding iron complex, **2**, displayed a similar coordination geometry and hydrogen bonding interactions (**Table 2**, **Figure 4**).

As a contrast to **1** and **2**, the cobalt derivative, **3**, presented an asymmetric unit cell with two unique molecules that are differentiated by their hydrogen bonding interactions. One complex (**3a**) was isostructural to **1** and **2** with both intra- and inter-ligand hydrogen bonding interactions, whereas the other cobalt complex (**3b**) presented with only one inter-ligand hydrogen bond to the chloride atom (**Table 2**, **Figure 4**) with the other ligand arm not engaging in hydrogen bonding.

The inter-ligand hydrogen bonds observed in complexes **1-3** have N-H---Cl distances of 3.0938(16)- 3.1786(15) Å and H---Cl bond lengths of 2.26-2.31 Å, while the intra-ligand hydrogen bonds had N-H---O distances of 2.804(14)- 3.155(3) Å and H---O bond lengths of 2.01-2.15 Å. These values are consistent for expected hydrogen bonding interactions, though the inter-ligand hydrogen bond distances are slightly weaker in comparison to similar characterized complexes with the N(pi^{Cy})$_3$

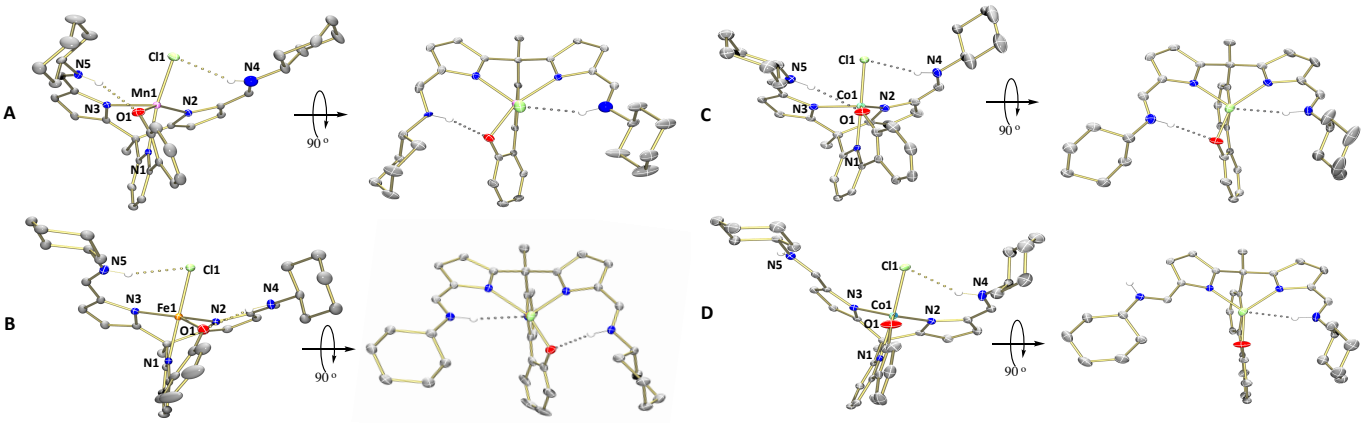

Figure 4. Structural characterization of complexes **1-3**. The solid-state structures of **1** (Mn, A) and **2** (Fe, B) displayed both inter- and intra-ligand hydrogen bonds, whereas the cobalt analogue displayed one isostructural complex **3a** (C), and **3b** with only an inter-ligand hydrogen bond (D). Corresponding bond lengths, angles, and τ_5 values can be found in Table 2.

ligand framework.[17] Interestingly, upon the loss of the inter-ligand hydrogen bond from **3a** to **3b**, there is a slight contraction of the Co-O bond length and elongation of the Co-Cl bond length (**Table 4**). This suggests that the inter-ligand hydrogen bond tunes the donor ability of the phenolic oxygen.

To further understand how the hydrogen bonding interactions effected the geometry of **1-3**, each complex was analysed using the structural parameter τ_5 (**Equation 1**).[34] The analysis identifies whether the geometry of a five-coordinate species is closer to being trigonal bipyramidal (τ_5 = 1) or square pyramidal (τ_5 = 0), where β and α (β > α) are the two greatest valence angles of the metal centre.

$$\tau_5 = \frac{\beta - \alpha}{60^\circ} \qquad (Eq.\,1)$$

Complex **1** has the lowest τ_5 value (τ_5 = 0.27), indicating its structure is best described as distorted square pyramidal, whereas complexes **2** and **3** have τ_5 values of τ_5 = 0.40 and τ_5 = 0.47, respectively, showing an intermediate geometry (Calculations available in SI). Interestingly, **3b** has a τ_5 value of 0.71, indicating it is best described as distorted trigonal bipyramidal. While the metal(II) ion size contributes to the ligand conformation, the comparison of **3a** and **3b** highlights how the presence or absence of a hydrogen bond to a bound ligand can greatly affect the geometry of the metal centre. The increased τ_5 value of **3b** upon the loss of the inter-ligand hydrogen bond from **3a** to the phenol oxygen reflects a more trigonal pyramidal structure. Geometry changes, such as this, could be used to control substrate coordination to the metal centre by favouring (or disfavouring) an open face *cis* to the axial ligand.

Complexes **1-3** demonstrate a break from the trend of 5-coordinate complexes with a secondary coordination sphere being best describes as trigonal bipyramidal. The introduction of the intramolecular hydrogen bond to the phenoxy ligand arm causes a change in geometry of the metal centre and creates a potential binding site on the more square pyramidal complexes. It is possible this change in geometry could lead to better synthetic models for enzymes, such as non-heme iron halogenases that activate dioxygen and go through a number of 5-coordinate intermediates during catalytic turnover.[35,36] Furthermore, the tuning of the oxygen donor ability by the inter-ligand hydrogen bond as evidenced in **3a** and **3b** may be used to influence reactivity at the axial position. This system showcases the ability of hydrogen bonds from the secondary coordination sphere as a way to not only bond to axial ligands but also as a new design principle for future complexes that seek to tune a metal centre's geometry and reactivity through hydrogen bonding to the ligand framework.

Table 2. Selected bond lengths and angles of complexes 1-3.

Bond length (Å)	1 (Mn)	2 (Fe)	3a (Co, arm in)	3b (Co, arm out)
M1-O1	2.0304(1)	1.9378(1)	1.9203(16)	1.8751(17)
M1-Cl1	2.4355(5)	2.4518(5)	2.4357(6)	2.4712(6)
M1-N1	2.3083(1)	2.2358(2)	2.2238(18)	2.2249(18)
M1-N2	2.1240(1)	2.0549(2)	2.0275(18)	2.0244(18)
M1-N3	2.1337(1)	2.0766(2)	2.0142(18)	2.0047(18)
N#-H---Cl (# = 4 or 5)	3.1786(15)	3.0938(16)	3.116(2)	3.129(2)
N#-H---O (# = 4 or 5)	2.804(14)	2.922(2)	3.155(3)	--
Bond Angles (degrees)				
O1-M1-N2 or –N3 (α)	154.62(5)	154.10(6)	148.33(8)	132.73(8)
N1-M1-Cl1 (β)	171.04(3)	178.32(5)	176.54(5)	175.44(5)
N2-M1-N3	95.17(7)	96.26(7)	97.05(7)	96.46(7)
N2-M1-O1	154.62(6)	105.74(7)	148.33(7)	132.73(7)
N3-M1-O1	100.38(7)	154.10(7)	111.98(7)	129.12(7)
τ_5	0.27	0.40	0.47	0.71

Conclusions

We have reported the synthesis of a new ligand platform that upon complexation with metal chloride salts demonstrates both intra- and inter-ligand hydrogen bonding interactions. The intra-ligand hydrogen bonding interactions with the phenoxy ligand arm are shown to have a profound effect on the geometry of the metal centre, and this study provides the foundation of a new design principle for future biomimetic complexes that incorporate hydrogen bonding motifs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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