Iron(III), cobalt(II) and zinc(II) coordination compounds with a carboximidamide ligand: synthesis, structures and properties

Francois Eya'ane Meva[1,2*], Timothy John Prior[2], David John Evans[2#], Sachin Shah[2#] and Oscar Cespedes[3]

1 Department of Pharmaceutical Sciences, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, PO Box 2701, Cameroon.
2 Department of Chemistry and Biochemistry, University of Hull, HU6 7RX, England
3 School of Physics & Astronomy, University of Leeds, LS2 9JT, England

Francois Eya'ane Meva
*Correspondence e-mail:
mevae@daad-alumni.de

Current address: John Innes Centre, Norwich Research Park, Norwich, NR4 7UH, UK

Abstract

Coordination complexes of iron(III), cobalt(II) and zinc(II) with the ligand N′-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide (pmhpa) have been synthesised and were structurally characterized by elemental analysis, mass spectrometry, X-ray diffraction and infrared spectroscopy. The mononuclear iron(III) complex, $[Fe(pmhap)_2][FeCl_4]$, (1), adopts the orthorhombic non-centric space group $P2_12_12_1$. The iron is present in an octahedral environment in the ion $[Fe(pmhap)_2]^+$. The crystallographically-determined formula of the cobalt(II) complex (2) is $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$. The compound crystallizes in the non-centrosymmetric space group $P2_1c$ with a single cobalt ion in the asymmetric unit. The complex is dinuclear, with two cobalt ions bridged by chloride and the two nitrogen atoms of N=N of the pmhap ligand. The zinc(II) complex;

$[Zn_2(pmhpa)_3](NO_3)_4$.2.75MeOH (3) crystallizes in the cubic space group Pa with disordered methanol molecules present. This is dinuclear with the two zinc atoms being bridged by three N=N links from the ligand to form a threefold symmetric rotor. Infrared spectroscopy confirms that coordination occurs through the azide bridge. Measurements of magnetic susceptibility for the iron(III) and cobalt(II) complexes show that they are paramagnetic between 5 and 300 K. Mössbauer spectroscopic data supports the structure of the iron(III) complex being composed of an octahedral and a tetrahedral iron atom.

Keywords: Coordination complexes, Carboxamidrazine, X-ray structure, Magnetism

Introduction

Thiosemicarbazone molecules, known to coordinate various metal ions, have aroused considerable interest in chemistry and biology [1, 2]. They show pharmacological activity as antiparasitic, antimalarial, antiproliferative, or antitubercular molecules and have structural resemblance to carboxamidrazone [1]. There is recently a strong demand for novel metal-based compounds for therapeutics or detection.

The use of coordination complexes in therapeutics is attractive due to intrinsic properties of the metal ions such as redox activity, variable coordination modes, reactivity toward various substrates, magnetism or fluorescence. [3] Ligand substitution and modification of chemical structures has led to the synthesis of a wide range of metal-based compounds which have demonstrated enhanced properties [4]. Studies by Billington *et al*. have established N-pyridine-2-carboxamidrazone as a lead molecule of a N-benzylidene-pyridine carboxamidrazone derivatives series with a minimum inhibitory concentration (MIC) value less than 50 mg/mL against *Mycobacterium forutitum* [5]. The azido-bridged complexes have attracted intense interest, due to their coordination versatility and the magnetic diversity of the complexes [6]. Gokhale *et al*. have examined the structure of the ligand-based distorted square planar copper(II) complex, cis-[dichloro(N1-(2-benzyloxybenzylidene)pyridine-2-carboxamidrazone)copper(II)], and its analogue with N′-(2-acetylpyridine)pyridine-2-carboxamidrazone. The activity against the human breast cancer cell line MCF-7 and the mouse melanoma cell line

B16F10 has been evaluated [7, 8]. They have also presented the crystal structure and antimalarial activity of cis-[dichloro(N1-2-acetylthiophene-pyridine-2-carboxamidrazone)copper(II)] with a highly distorted square planar geometry (see Figure 1A) [9]. The ligand, N′-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide, presents an unusual arrangement of potential donor sites, with the possibility of monodentate coordination modes to the pentadentate limit. Free rotation about the N-N single bond would lead to both folded *trans* and *cis* conformations due to the flexibility of the ligand around the N–N single bond [10, 11].

In previous work, we have described the crystal structure of the N-H···N bounded networks of the N′-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide molecule and its precursor N'-amino-pyridine-2-carboximidamide [12]. As part of the continuing investigation, we here complete the library of carboxamidrazone complexes through the synthesis and structural investigation of new iron(III) [13], cobalt(II) [14], and zinc(II) [15] complexes (Figure 1B), in which the metal-ion centres are bridged by single bonds to the polydentate ligand N′-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide (pmhap).

Results and discussion

The pmhap ligand readily forms complexes with first row transition metals. Here we present the structure and properties of complexes of iron, cobalt and zinc. Crystal structure data for these compounds are summarized in the Supplement 1.

The iron(III) complex, $[Fe(pmhap)_2][FeCl_4]$ (1), crystallises as well-formed very dark brown needles. It adopts the orthorhombic non-centric space group $P2_12_12_1$. The asymmetric unit (Figure 2A) contains two independent $[Fe(pmhap)_2]^+$ and two $[FeCl_4]^-$ ions. The two $[Fe(pmhap)_2]^+$ ions contain iron(III) in approximately octahedral coordination with each iron surrounded by six nitrogen ligands. The two $[Fe(pmhap)_2]^+$ ions are held together in a dimer by two hydrogen bonds: N14-H14A···N8 (0.89(3) Å N14 - H14A, 3.298(8) Å N14 - N8, 160(9)° N14 - H14A - N8) and N4-H4A···N18 (0.89(3) Å N4 - H4A, 3.493(9) Å N4 - N18, 145(9)° N4 - H4A - N18). Between the $Fe(pmhap)_2 \cdots Fe(pmhap)_2'$ dimers (Figure 2B), the $[FeCl_4]^-$ ions are arranged in sheets that extend in the xy plane. Similarly, the dimers are also arranged in sheets such that there is ABAB stacking of these two types of sheets parallel to the c-axis (Figure 2C). There are a large number of C-H···Cl and C-H···N interactions that enforce this arrangement. The mass spectrum of the $[Fe(pmhap)_2][FeCl_4]$ molecule shows only one ion peak signal at m/z 532.1 corresponding to the $[Fe(pmhap)_2]^+$ molecular fragment.

The crystallographically-determined formula of the cobalt(II) complex (2) is $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ where half of the solvent is crystallographically resolved. The compound crystallises in the non-centrosymmetric space group $P2_1c$ with two different cobalt ions in the asymmetric unit as shown in Figure 3A. The $[Co_2(pmhap)_2Cl_3]^+$ unit is derived from two cobalt ions bridged by a single chloride and held together by two ligands through the N=N bond. Each cobalt ion then lies in a distorted octahedral environment (Figure 3B). The two halves of the cluster are related by the symmetry operation $1-x$, $2-y$, z (2-fold rotation about z). Cobalt is also found within a second ion, $[CoCl_4]^{2-}$. A single molecule of methanol was identified within the structure. This methanol acts as a hydrogen bond donor to the cluster and a hydrogen bond acceptor to N-H of a different cluster. Analysis using PLATON suggests there are other solvent molecules present that are not crystallographically ordered. The solvent resides in two pockets within the unit cell at locations ½, ½, 0 and 0, 0, ½. Each of these pockets comprises about 11.38 % of the unit cell volume. The SQUEEZE routine was used to model the solvent in these regions; a total of 141 electrons were located in these regions. This corresponds to a little more than four molecules of methanol and gives an approximate formula $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ for the crystal. In the solid the metal clusters are packed to form pockets that are filled with methanol. The packing facilitates N-H···Cl hydrogen bonds between $[Co_2(pmhap)_2Cl_3]_2^+$ and $[CoCl_4]^{2-}$ ions. There are also C-H···Cl interactions between the clusters. Two views of the packing arrangement are shown in Figure 3C. The zinc(II) complex (3) contains two metals and is best formulated as $[Zn_2(pmhap)_3]^{4+}$. It crystallizes in the cubic space group Pawith nitrate and poorly-ordered methanol. The crystallographically determined composition is thus $[Zn_2(pmhpa)_3](NO_3)_4.2.75MeOH$. Figure 4A shows an asymmetric unit for (3). The $[Zn_2(pmhpa)_3]^{4+}$ is sited within the unit cell so that the two independent zinc ions lie on the threefold axis (.3. site symmetry) and hence the overall complex has threefold symmetry and can be described as a symmetric rotor (Figure 4B). Each zinc is octahedrally coordinated by six nitrogen atoms; each ligand binds through pyridine and the two nitrogen atoms of the diazine unit. The Zn−N bond lengths are of typical length for zinc to nitrogen (2.101(4) Å - 2.172(4) Å). The complexes and nitrate anions are arranged within the cell to leave small voids. There is evidence that these hold methanol but this solvent is not crystallographically resolved. The SQUEEZE routine was used for the modelling. Each of the four voids, located at 1/2, 1/2, 1/2 and symmetry-related positions contains approximately 5.5 molecules of methanol. The $[Co_2(pmhap)_2Cl_3]_2[CoCl_4]$.4MeOH complex and the $[Zn_2(pmhpa)_3](NO_3)_4$.2.75MeOH showed molecular ion peak at m/z 709.7 and 846.2 corresponding to the cation $[Co_2(pmhap)_2Cl_3]^+$ and $[Zn_2(pmhpa)_3]^{4+}$ respectively together with different molecular fragment parts (see Supplement 2). The infrared spectrum of the ligand showed two characteristic stretching absorption peaks at 3464 and 3317 cm^{-1} due to an intramolecularly hydrogen bonded $-NH_2$ group. The imino (C=N) grouping showed sharp peaks around 1613 and 1584 cm^{-1}. The amine-protons peaks of ligand pmhap are masked in the complexes by the broad stretching vibration of O-H from methanol solvent molecules. In related copper complexes the peaks due to $-NH_2$ are generally shifted to lower frequencies due to the loss of intramolecular hydrogen bonding [9]. The imino C=N frequencies are shifted to higher frequencies in all complexes: 1649, 1635 cm^{-1} in the iron complex, 1649, 1620 cm^{-1} in the cobalt complex and 1651, 1623 cm^{-1} in the zinc complex, due to back bonding. Thus, ligand in the complex is bound through nitrogen of the imine [9]. Pyridine ring breathing bands are found at 988 cm^{-1} for the ligand and 1018 cm^{-1} in the three complexes, consistent with the pyridine ring coordination [16]. Moreover, the zinc complex exhibits a very strong vibration at 1380 cm^{-1} characteristic of a nitrate salt (see supplement 3) [17]. Mössbauer spectra of $[Fe(pmhap)_2][FeCl_4]$ were recorded between 80 and 298 K to confirm the spin states of the complex and their change with temperature. Mössbauer parameters and spectra are presented in Supplement 4. The spectra are consistent with the presence of an octahedral low spin (S = 1/2) iron(III) and a tetrahedral high-spin (S = 5/2) iron (III) (Figure 5). The 1:1 contribution is confirmed at 80K whereas a discrepancy is found at higher temperature [18]. The magnetic moment vs temperature graph at 5 kOe for $[Fe(pmhap)_2][FeCl_4]$ (1), 5 kOe and 0.5 kOe for $[Co_2(pmhap)_2Cl_3]_2[CoCl_4]$.4MeOH (2) is predominantly paramagnetic. The curves deviates from a purely paramagnetic signal below ~20-30 K (see Figure 6). At low temperatures, the shape of the loop is not a straight line, but has an “S-shape” indicative of superparamagnetism. This superparamagnetism could emerge from an intrinsic magnetic behaviour of the compound or perhaps from the presence of magnetic nanoparticles and/or magnetic aggregates.

Three coordination complexes based on N′-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide (pmhap): $[Fe(pmhap)_2][FeCl_4]$ (1), $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ (2) and $[Zn_2(pmhpa)_3](NO_3)_4.2.75MeOH$ (3), have been synthesized and characterized. Complexes 1 and 2 exhibit a superparamagnetic interaction and the octahedral and tetrahedral components of complex 1 have been confirmed by Mössbauer spectroscopy. The synthesized materials may find application for both human health and industry related processes.

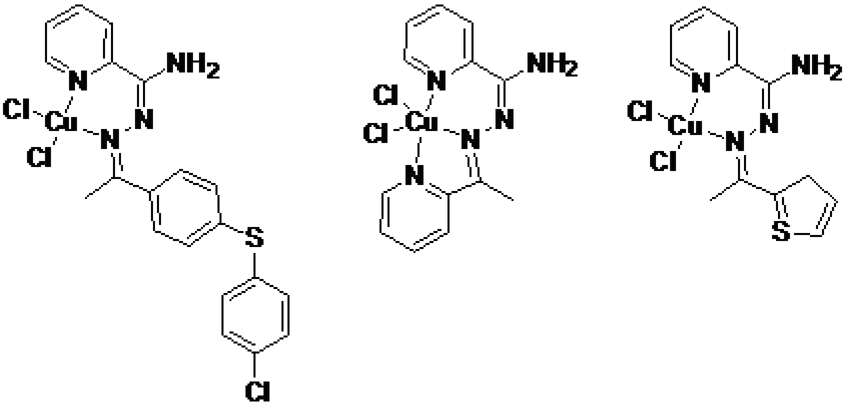

Figure 1A. Structurally characterized carboxamidrazine-copper(II) complexes [7-9]

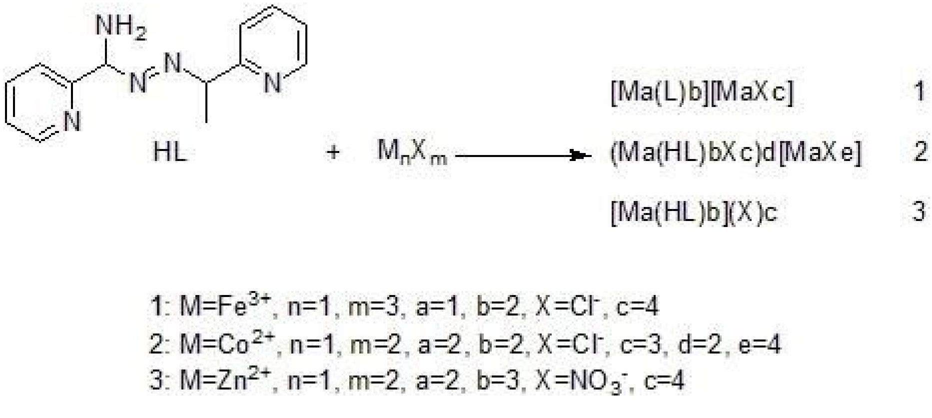

Figure 1B. Synthetic scheme for the complexes 1-3

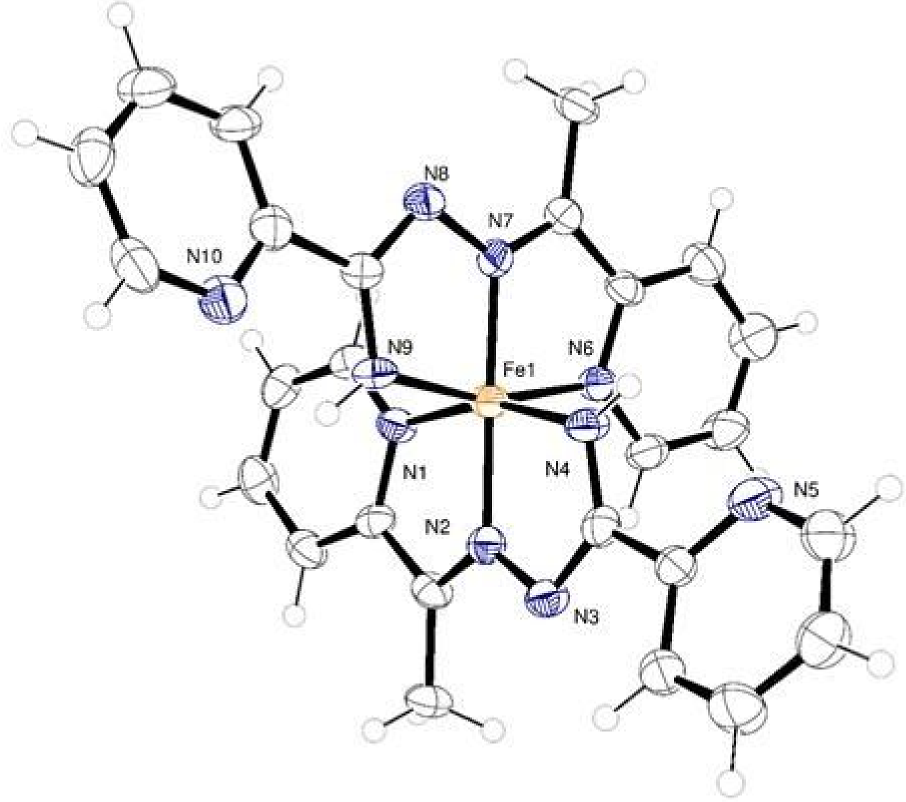

Figure 2A: ORTEP representation of complex $[Fe(pmhap)_2][FeCl_4]$ (1) showing the coordination of Fe^{3+} ion in one of the symmetry-unique iron complexes with displacement ellipsoids drawn at the 50% probability level

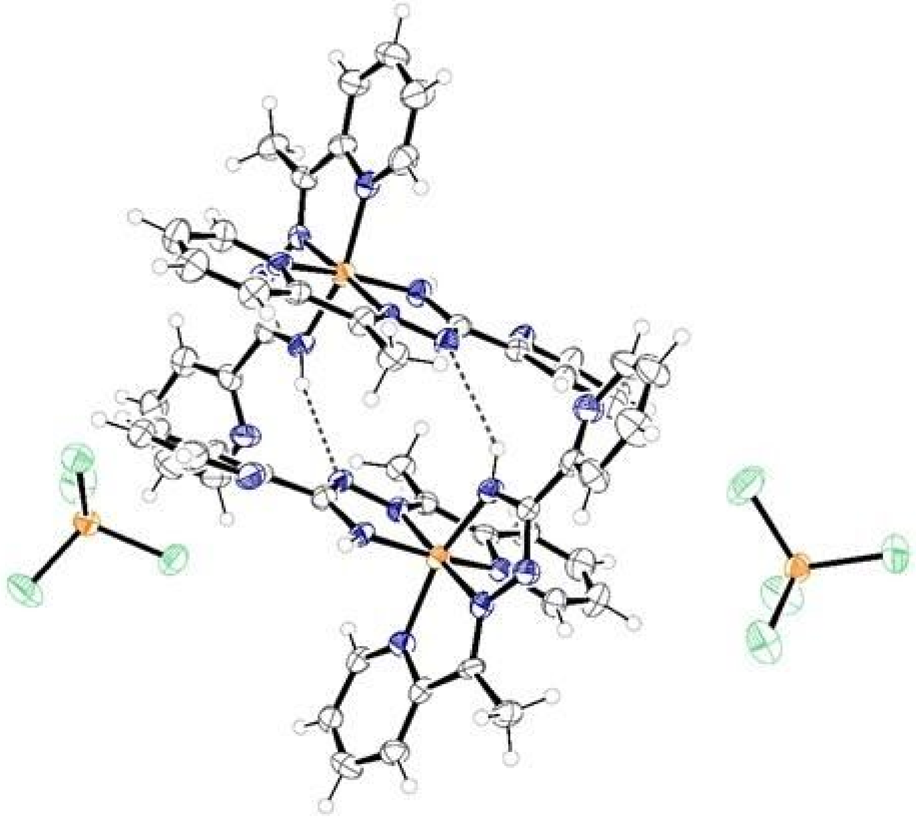

Figure 2B: Complex $[Fe(pmhap)_2][FeCl_4]$ (1) ORTEP representation of the Hydrogen-bonded dimer; $Fe(pmhap)_2 \cdots Fe(pmhap)_2$ with displacement ellipsoids drawn at the 50% probability level

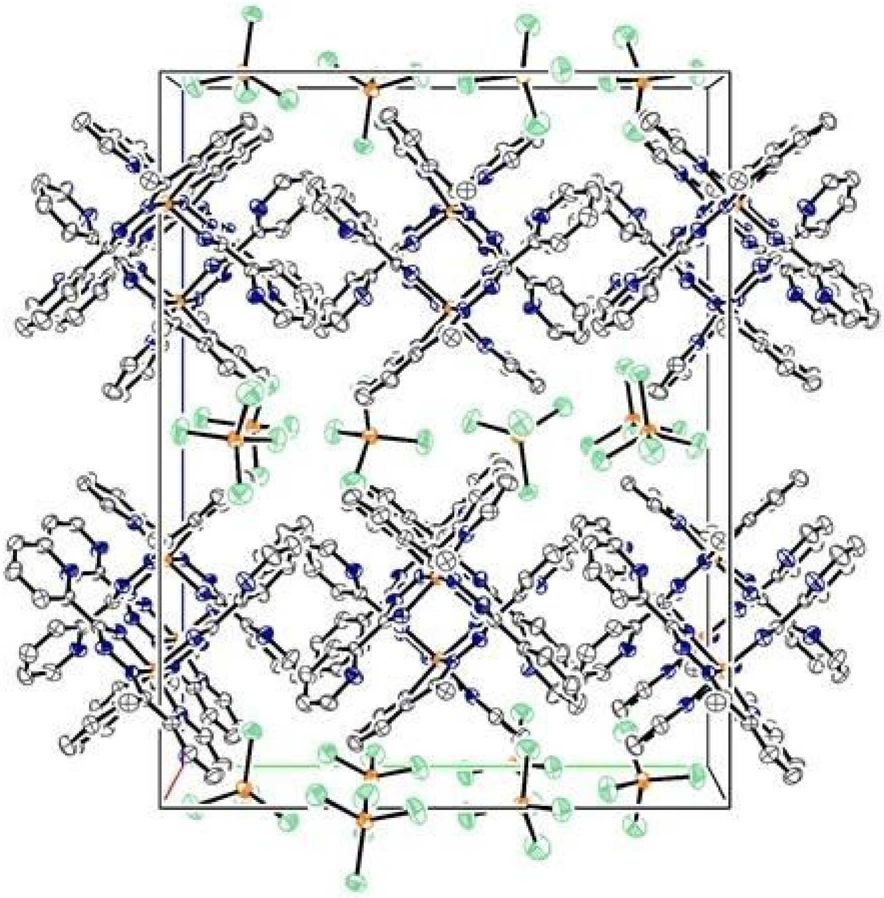

Figure 2C: ORTEP representation of the Packing of complex $[Fe(pmhap)_2][FeCl_4]$ (1) viewed down the a-axis with displacement ellipsoids drawn at the 50% probability level

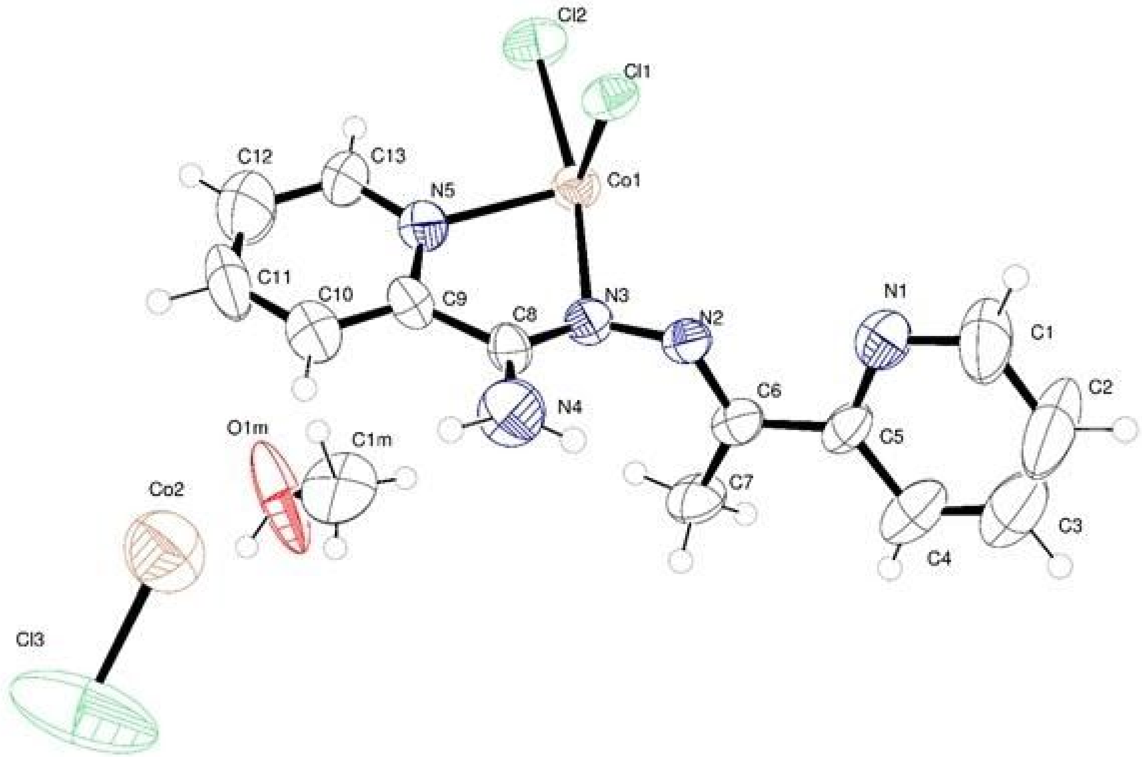

Figure 3A. ORTEP representation of the asymmetric unit of complex $[Co_2(pmhap)_2Cl_3]_2[CoCl_4]$.4MeOH (2) with displacement ellipsoids drawn at the 50% probability level

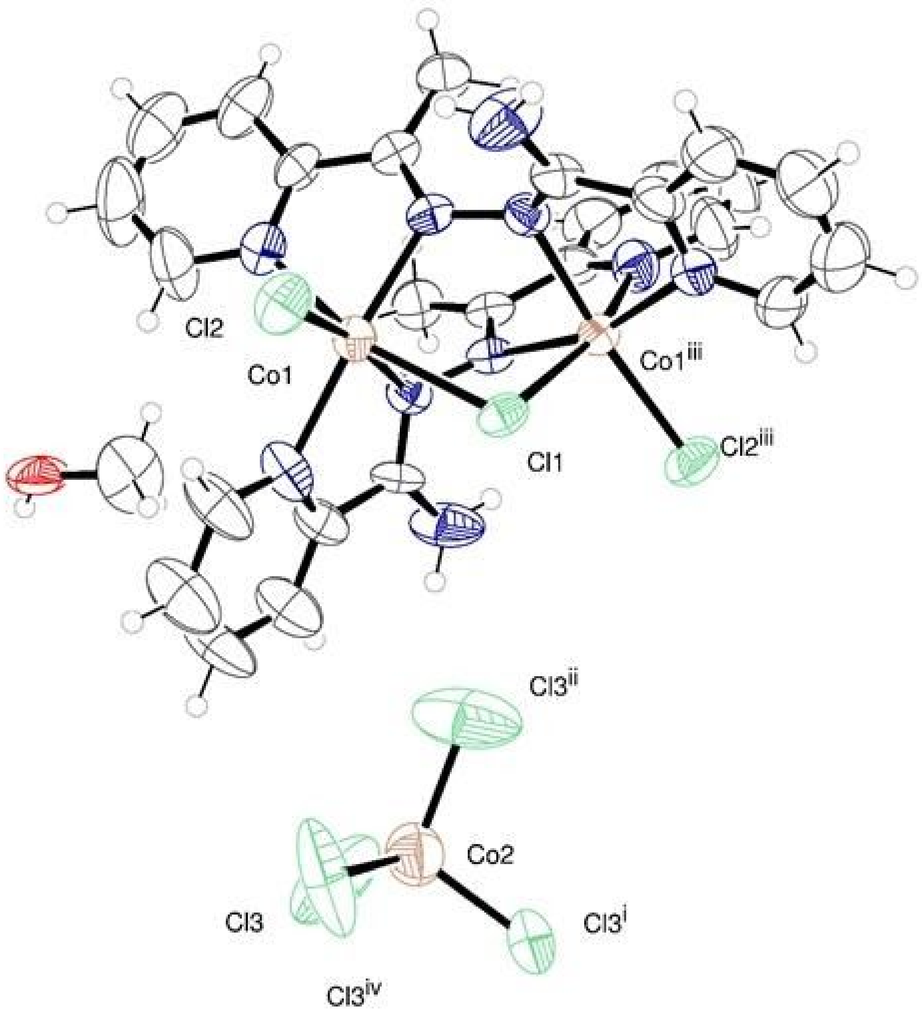

Figure 3B. Molecular structure of complex $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ (2) with atoms drawn as 50% probability ellipsoids

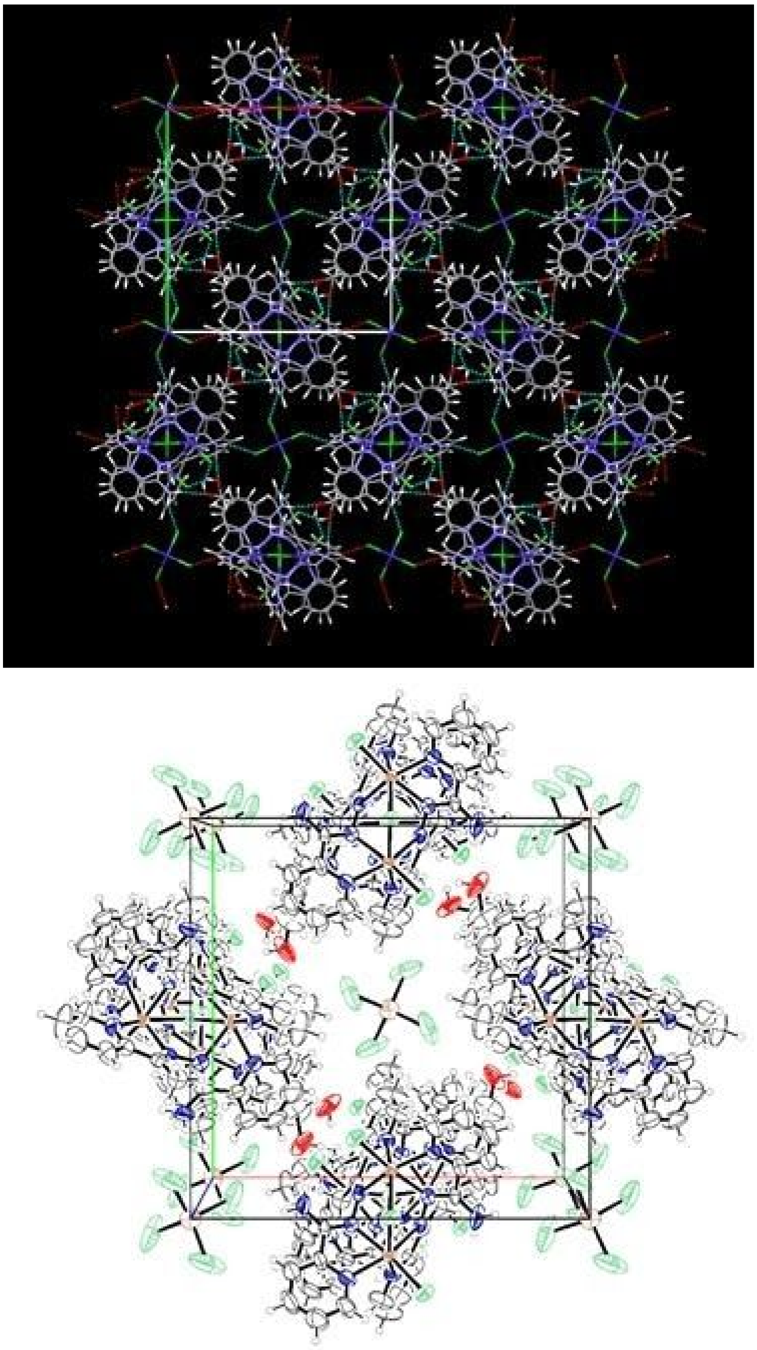

Figure 3C. Two views of complex $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ (2) down the c-axis. In the upper figure hydrogen bonds are shown as dashed lines.

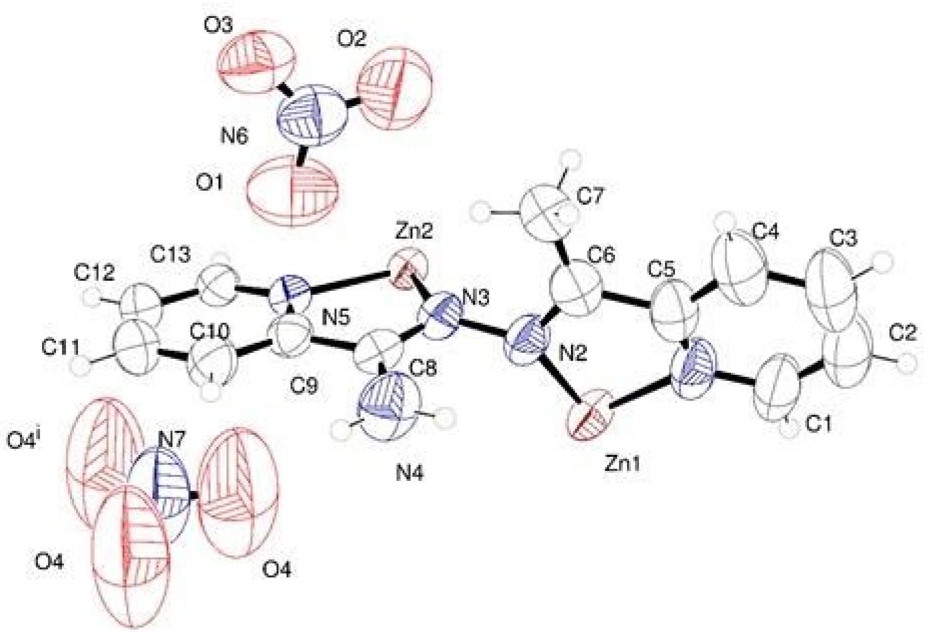

Figure 4A. ORTEP representation of the asymmetric unit of complex $[Zn_2(pmhpa)_3](NO_3)_4.2.75MeOH$ (3) with displacement ellipsoids drawn at the 50% probability level (minor disorder in the nitrate anions is not shown).

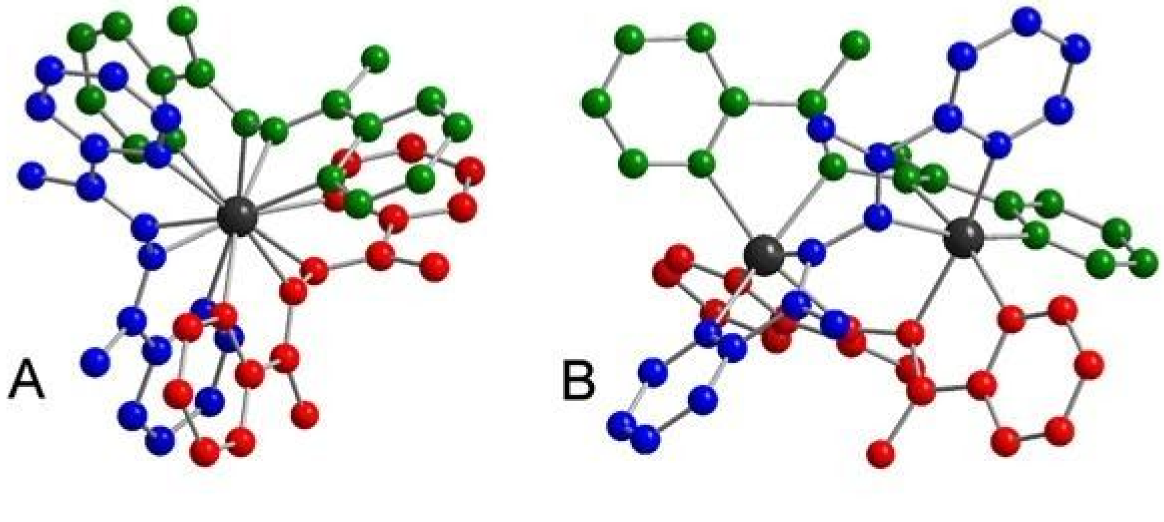

Figure 4B: (A) view of complex $[Zn_2(pmhpa)_3](NO_3)_4.2.75MeOH$ (3) down the threefold axis; each separate ligand is coloured differently. (B) side view of the complex. rounded by six nitrogen ligands. (For bond lengths see the crystal data file)

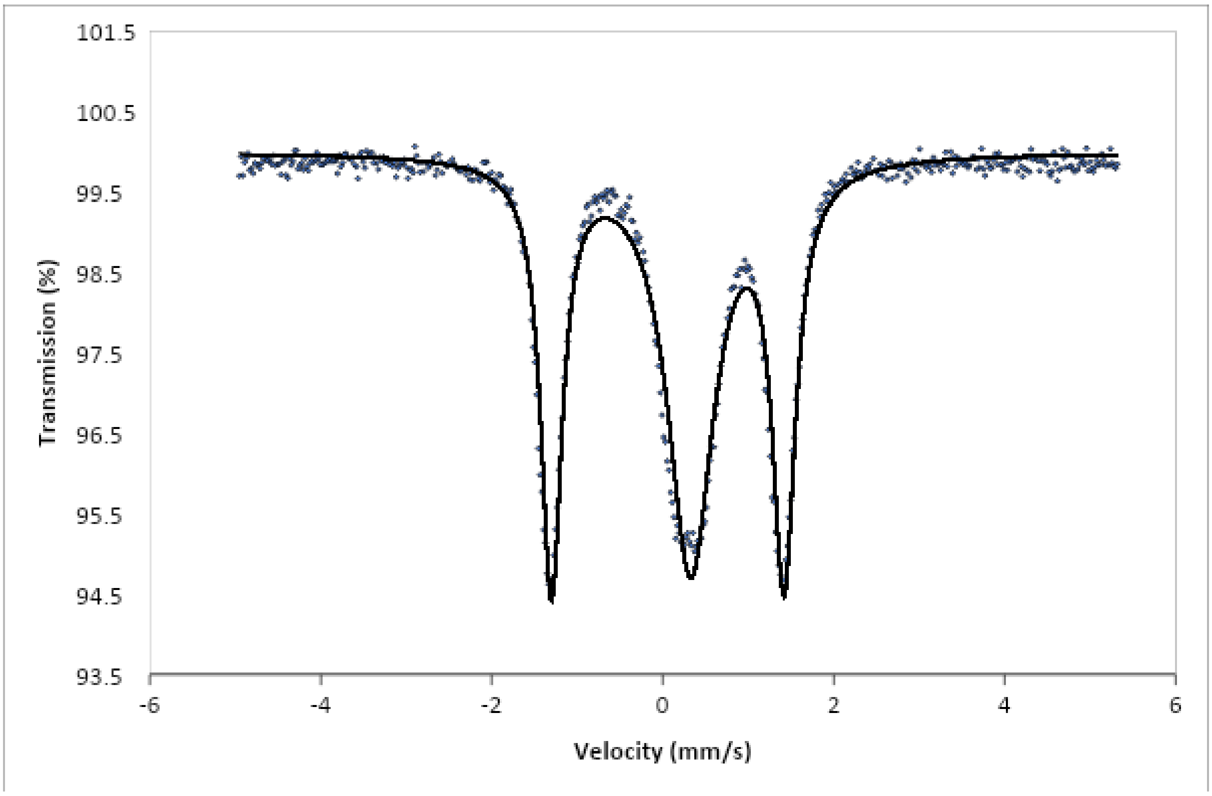

Figure 5. 80K Mossbauer spectrum of complex $[Fe(pmhap)_2][FeCl_4]$ (1)

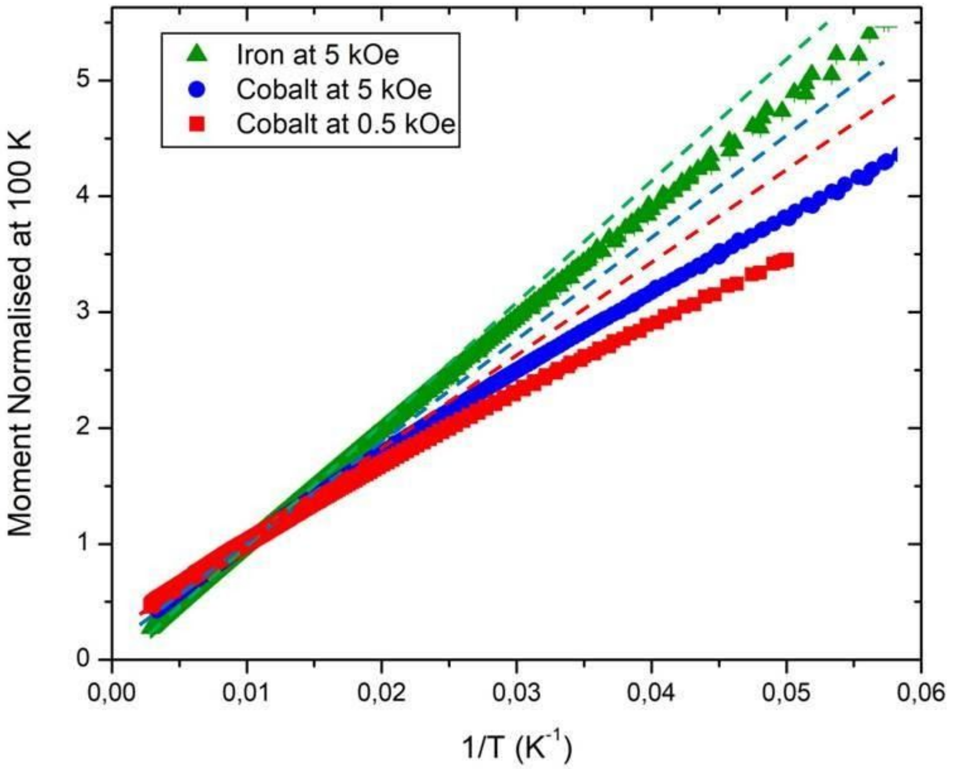

Figure 6. Magnetic moment vs temperature graph at 5 kOe for $[Fe(pmhap)_2][FeCl_4]$ (1), 5 kOe and 0.5 kOe for $[Co_2(pmhap)_2Cl_3]_2[CoCl_4].4MeOH$ (2).

References

[1] N.P. Prajapati, H.D. Patel, Novel thiosemicarbazone derivatives and their metal complexes: Recent development, Synth. Commun. 49 (2019) 2767–2804.

[2] W. Hernandeza, J. Paz, A. Vaisberg, E. Spodine, R. Richter, L. Beyer, Synthesis, characterization, and in vitro cytotoxic activities of benzaldehyde thiosemicarbazone derivatives and their palladium(II) and platinum(II) complexes against various human tumor cell lines, Bioinorg. Chem. Appl. ID 690952 (2008) doi:10.1155/2008/690952

[3] M. Frezza, S. Hindo, D. Chen, A. Davenport, S. Schmitt, D. Tomco, Q.P. Dou, Novel metals and metal complexes as platforms for cancer therapy, Curr. Pharm. Des. 16(16) (2010) 1813–1825.

[4] U. Ndagi, N. Mhlongo, M.E. Soliman, Metal complexes in cancer therapy – an update from drug design perspective, Drug. Des. Dev. Ther. 11 (2017) 599–616.

[5] D. Billington, M. Coleman, J. Ibiabuo, P. Lambert, D. Rathbone, K. Tims, Synthesis and antimycobacterial activity of some heteroarylcarboxamidrazone derivatives, Drug Des. Discov. 15 (1995) 269–275.

[6] Y.-F. Yue, E.-Q. Gao, C.-J. Fang, T. Zheng, J. Lianga, C.-H. Yan, The crystal structures of four azido-bridged Zn(II) complexes based on open-chain diazine Schiff-base ligands. CrystEngComm. 10 (2008) 614–622.

[7] N.H. Gokhale, S.S. Padhye, S.B. Padhye, C.E. Anson, A.K. Powell, Copper complexes of carboxamidrazone derivatives as anticancer agents. 3. Synthesis, characterization and crystal structure of [Cu(appc)Cl_2], (appc=N1-(2-acetylpyridine)pyridine-2-carboxamidrazone), Inorg. Chim. Acta 319(1-2) (2001) 90–94

[8] N.H. Gokhale, S.B. Padhye, D.L. Rathbone, D.C. Billington, P. Lowe, C. Schwalbe, C. Newton, The crystal structure of first copper(II) complex of a pyridine-2-carboxamidrazone–a potential antitumor agent, Inorg. Chem. Commun. 4 (2001) 26–29 (2001).

[9] N.H. Gokhale, S.B. Padhye, D.C. Billington, D.L. Rathbone, S.L. Croft, H.D. Kendrick, C.E. Anson, A.K. Powell, Synthesis and characterization of copper(II) complexes of pyridine-2-carboxamidrazones as potent antimalarial agents. Inorg Chim Acta 349 (2003) 23–29.

[10] Z. Xu, L.K. Thompson, D.O. Miller, Dicopper(II) Complexes Bridged by Single N-N Bonds. Magnetic exchange dependence on the rotation angle between the magnetic planes, Inorg. Chem. 36 (1997) 3985–3995.

[11] Z. Xu, L.K. Thompson, C.J. Matthews, D.O. Miller, A.E. Goeta, C. Wilson, J.A.K. Howard, M. Ohbac, H. Okawa, Dinuclear and tetranuclear copper(II) complexes with

bridging (N–N) diazine ligands: variable magnetic exchange topologies, J. Chem. Soc., Dalton Trans. (2000) 69–77

[12] F. Eya'ane Meva, T.J. Prior, D.J. Evans, E.R. Mang, Crystal structures of N'-aminopyridine-2-carboximidamide and N'-{[1-(pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide, Acta Cryst. E73 (2017) 1021–1025.

[13] Crystals of N'-{[1-(Pyridin-2-yl)ethylidene]amino}pyridine-2-carboximidamide (pmhpa) were obtained according to our previous report [12]. Complex $[Fe(pmhap)_2][FeCl_4]$ (1) was prepared by mixing equimolar amounts of pmhap ligand (0.5 g, 2.2 mmol) and $FeCl_3{\cdot}6H_2O$ (0.44 g, 2.2 mmol) in acetonitrile (20 mL). The title complex was crystallized by allowing the solution to concentrate in the air. Dark-brown crystals suitable for single crystal diffraction studies were obtained in three days. Yield: 0.70 g (86%). Anal. Calc. for $[Fe(pmhap)_2][FeCl_4]$ C, 42.78; H, 3.31; N, 19.19. Found: C, 41.99; H, 4.04; N, 19.44%. IR vC=N 1649, 1635. m/z $[Fe(pmhap)_2]^+$ 532.1

[14] $[Co_2(pmhap)_2Cl_3]_2[CoCl_4]$.4MeOH (2) was prepared by mixing equimolar amounts of pmhap ligand (0.31 g, 1.4 mmol) and $CoCl_2{\cdot}6H_2O$ (0.34 g, 1.4 mmol) in acetonitrile (20 mL). A green precipitate formed which was filtered and air dried. The title complex was crystallized by allowing diethyl ether to diffuse in to a methanolic solution of the powder. Violet-red crystals suitable for single crystal diffraction studies were obtained in one week. Yield: 0.20 g (35%). Anal. Calc. for $[Co_2(pmhap)_2Cl_3]_2[CoCl_4]$.4MeOH C, 38.78; H, 3.95; N, 16.15. Found: C, 38.39; H, 4.14; N, 16.44%. IR vC=N 1649, 1620, m/z $[Co_2(pmhap)_2Cl_3]^+$H 709.7.

[15] $[Zn_2(pmhpa)_3](NO_3)_4$.2.75MeOH (3) was prepared by mixing equimolar amounts of pmhap ligand (0.55 g, 2.4 mmol) and $Zn(NO_3)_2{\cdot}6H_2O$ (0.72 g, 2.4 mmol) in acetonitrile (20 mL). During the first hour of agitation a yellow-white precipitate formed which dissolved on continuous agitation and reprecipitated on standing. The mixture was left 24h under continuous agitation. A white precipitate was then filtered off and air dried. The title complex was crystallized by allowing diethyl ether to diffuse in to a methanolic solution of the powder. Colourless crystals suitable for single

crystal diffraction studies were obtained in three weeks. Yield: 0.40 g (42%). Anal. Calc. for $[Zn_2(pmhpa)_3](NO_3)_4.2.75MeOH$ C, 42.18; H, 3.63; N, 22.61. Found: C, 41.69; H, 4.14; N, 21.74%. IR vC=N 1651, 1623. m/z $[Zn_2(pmhpa)_3]^{4+}$ 846.2

[16] Z. Xu, L.K. Thompson, D.A. Black, C. Ralph, D.O. Miller, M.A. Leech, J.A.K. Howard, N–N Bridged dinuclear complexes with Mn(II), Ni(II), Cu(II), Zn(II) and Cd(II); examples with antiferromagnetic and ferromagnetic coupling. J. Chem. Soc., Dalton Trans. (2001) 2042–2048.

[17] F.A. Miller, C.H. Wilkins, Infrared spectra and characteristic frequencies of inorganic ions and their use in qualitative analysis, Anal. Chem. 24(8) (1952) 1253–1294

[18] T.K. Jana, D.P. Kumar, R. Pradhan, S. Dinda, P.N. Ghosh, C. Simonnet, J. Marrot, I. Imaz, A. Wattiaux, L. Fournès, J.-P. Sutter, F. Sécheresse, R. Bhattacharyya, Synthesis and structure of iron (III) and iron (II) complexes in S4P2 environment created by diethyldithiocarbamate and 1,2-bis(diphenylphosphino)ethane chelation: Investigation of the electronic structure of the complexes by Mössbauer and magnetic studies, Inorg. Chim. Acta 362 (2009) 3583–3594.