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PAPER

The role of Zn–OR and Zn–OH nucleophiles and the influence of *para*-substituents in the reactions of binuclear phosphatase mimetics†

Lena J. Daumann,[a] Kristian E. Dalle,[a] Gerhard Schenk,[a] Ross P. McGeary,[a] Paul V. Bernhardt,[a] David L. Ollis[b] and Lawrence R. Gahan*[a]

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Analogues of the ligand 2,2′-(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene)bis((pyridin-2-ylmethyl)azanediyl)diethanol (CH_3H_3**L1**) are described. Complexation of these analogues, 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-methylphenol (CH_3H**L2**), 4-bromo-2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)phenol (BrH**L2**), 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-nitrophenol (NO_2H**L2**) and 4-methyl-2,6-bis(((2-phenoxyethyl)(pyridin-2-ylmethyl)amino)methyl)phenol (CH_3H**L3**) with zinc(II) acetate afforded $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$, in addition to $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$ and $[Zn_4(Br\mathbf{L2})_2(PO_3F)_2(H_2O)_2](PF_6)_2$. The complexes were characterized using ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, microanalysis, and X-ray crystallography. The complexes contain either a coordinated methyl- (**L2** ligands) or phenyl- (**L3** ligand) ether, replacing the potentially nucleophilic coordinated alcohol in the previously reported complex $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$. Functional studies of the zinc complexes with the substrate bis(2,4-dinitrophenyl) phosphate (BDNPP) showed them to be competent catalysts with, for example, $[Zn_2(CH_3\mathbf{L2})]^+$, $k_{cat} = 5.70 \pm 0.04 \times 10^{-3}$ s^{-1} ($K_m = 20.8 \pm 5.0$ mM) and $[Zn_2(CH_3\mathbf{L3})]^+$, $k_{cat} = 3.60 \pm 0.04 \times 10^{-3}$ s^{-1} ($K_m = 18.9 \pm 3.5$ mM). Catalytically relevant pK_as of 6.7 and 7.7 were observed for the zinc(II) complexes of $CH_3\mathbf{L2}^-$ and $CH_3\mathbf{L3}^-$, respectively. Electron donating *para*-substituents enhance the rate of hydrolysis of BDNPP such that k_{cat} *p*-CH_3 > *p*-Br > *p*-NO_2. Use of a solvent mixture containing H_2O^{18}/H_2O^{16} in the reaction with BDNPP showed that for $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$, as well as $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$, the ^{18}O label was incorporated in the product of the hydrolysis suggesting that the nucleophile involved in the hydrolysis reaction was a Zn–OH moiety. The results are discussed with respect to the potential nucleophilic species (coordinated deprotonated alcohol *versus* coordinated hydroxide).

Introduction

Organophosphorous compounds (OPs) are amongst the most commonly used pesticides.[1] They act by inhibiting acetylcholinesterase thus preventing proper functioning of nerve cells. This property has resulted in OPs such as sarin, soman and VX finding application as nerve agents.[1–3] OP-hydrolyzing enzymes are common[2–5] and were initially thought to natively contain a single Zn(II) in the active site,[6] but more recent analysis by atomic absorption spectroscopy and X-ray anomalous scattering suggested that the active form of these enzymes is binuclear with combinations such as Zn(II)/Fe(II) likely.[7] The enzymes are also catalytically active as Co(II), Cd(II), Mn(II) or Ni(II) substituted forms.[8,9] The active site is typically composed of a nitrogen/oxygen coordination environment for two divalent metal ions coordinated by nitrogen donors located on histidine ligands, oxygen donors typically from an aspartate, and often including a metal ion-bridging hydroxide ion.[10–14]

Model complexes capable of reproducing the electronic, structural and reactivity characteristics of OP-hydrolyzing metalloenzyme systems generally exhibit less substrate specificity and are often more robust than the metalloenzymes themselves.[15–18] The question of the nucleophilic agent in these models, and often with the enzymes themselves, requires examination. In most hydrolytic enzymes a metal-hydroxide is suggested as the nucleophile in the key hydrolysis step, although exogenous alcohol moieties are also implicated.[19,20] Examples of model systems with either or both a metal-OH and a metal-OR present, which are

[a]*School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, QLD 4072, Australia. E-mail: gahan@uq.edu.au*
[b]*Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia*

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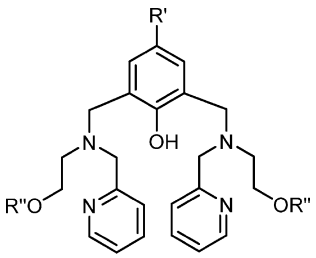
implicated in the mechanism, have been reported.[21–24] Interestingly, a coordinated alcohol is a stronger nucleophile than a coordinated hydroxide[21,23–28] and there is evidence that the coordinated alcohol is deprotonated at or below the same pH as a coordinated water molecule, particularly in the case of zinc(II) complexes.[22]

In this work we have explored the role of the coordinated alcohol and a coordinated water molecule using zinc(II) complexes of the previously described ligand 2,2′-(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene)bis((pyridin-2-ylmethyl)azanediyl)-diethanol (CH_3H_3**L1**),[24] and analogues of this ligand, 2,6-bis-(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-methyl-phenol (CH_3H**L2**) and 4-methyl-2,6-bis(((2-phenoxyethyl)-(pyridin-2-ylmethyl)amino)methyl)phenol (CH_3H**L3**). In addition, the chemistry of the substituted zinc(II) complexes of 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-nitrophenol (NO_2H**L2**) and 4-bromo-2,6-bis(((2-methoxyethyl)-(pyridin-2-ylmethyl)amino)methyl)phenol (Br**HL2**) has been studied (Chart 1). The catalytic potential of these complexes has been explored using the phosphodiester substrate bis(2,4-dinitrophenyl) phosphate (BDNPP).



R' = CH_3, R" = H **CH_3H_3L1**
R' = CH_3, R" = CH_3 **CH_3HL2**
R' = Br, R" = CH_3 **BrHL2**
R' = NO_2, R" = CH_3 **NO_2HL2**
R' = CH_3, R" = Ph **CH_3HL3**

Chart 1 Ligands discussed in this work.

Results and discussion

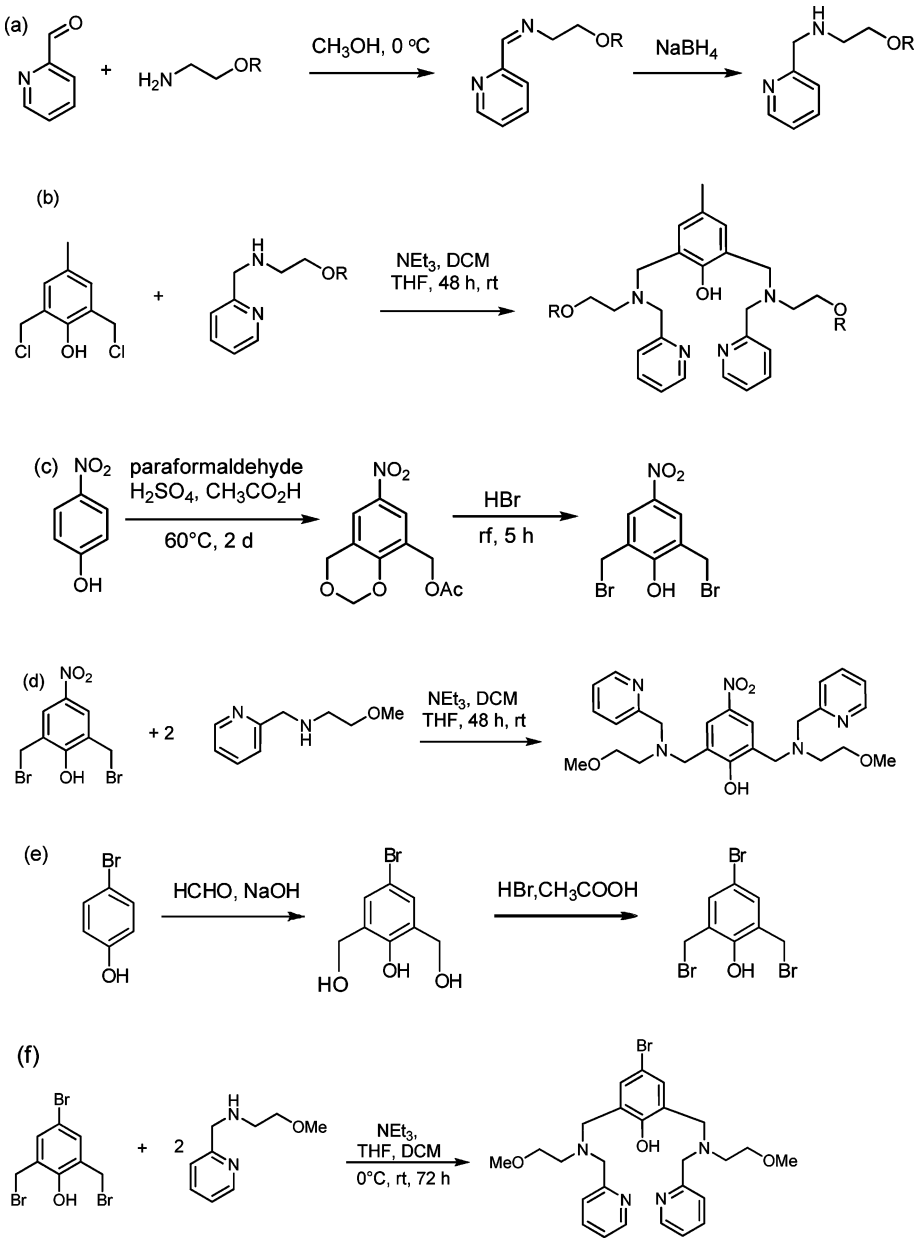
Syntheses and nomenclature of ligands and complexes

The previously reported ligand 2,2′-(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene)bis((pyridin-2-ylmethyl)azanediyl)diethanol (CH_3H_3**L1**),[24] in addition to 2,6-bis(((2-methoxyethyl)-(pyridin-2-ylmethyl)amino)methyl)-4-methylphenol (CH_3H**L2**) and 4-methyl-2,6-bis(((2-phenoxyethyl)(pyridin-2-ylmethyl)-amino)methyl)phenol (CH_3H**L3**) have been synthesized through a substitution reaction between 2,6-bis(chloromethyl)-4-methylphenol and 2-methoxy-*N*-(pyridin-2-ylmethyl)ethanamine and 2-phenoxy-*N*-(pyridin-2-ylmethyl)ethanamine, respectively. The 2-pyridylmethyl-2-hydroxyethylamine derivatives were prepared by condensation of 2-methoxyethanolamine and 2-phenoxyethanolamine with pyridine-2-carboxaldehyde at room temperature, followed by reduction with sodium borohydride. These ligands offer a direct comparison of methyl and phenyl ether donors with the alkoxide donor in the complex $[Zn_2(CH_3H$**L1**$)(CH_3COO)(H_2O)](PF_6)$.[24] The ligands, 4-bromo-2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)phenol (Br**HL2**) and 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-nitrophenol (NO_2H**L2**) are analogues of CH_3H**L2** with bromo- and nitro-substituents in the *para*-positions of the phenoxide, respectively. The syntheses are described in Scheme 1. The di-zinc(II) complexes of these ligands were prepared after reaction with zinc acetate and X-ray quality crystals were produced either on standing or by recrystallization.

The nomenclature employed for the ligands denotes the number of labile protons upon complexation and the substituent on the *para*-position of the phenoxide. Hence NO_2H**L2** and Br**HL2** are derivatives of the methyl ether parent (CH_3H**L2**) and have one potential site for deprotonation, the phenolic OH; complexation as NO_2**L2**$^-$ and Br**L2**$^-$ implies a single deprotonation. Thus, the previously reported complex with CH_3H_3**L1**, with a methyl substituent in the *para*- position and with potential sites for deprotonation being the phenol and the two pendant alcohol donors, was characterized as $[Zn_2(CH_3H$**L1**$)(CH_3COO)(H_2O)](PF_6)$ indicating complexation as CH_3H**L1**$^{2-}$ with deprotonation at the phenol and one alcohol.[24] The ligand CH_3H**L3** has a methyl substituent, one site for deprotonation and phenyl-ether pendants. Previous studies with the ligand CH_3H_3**L1** have employed different nomenclature (L);[24] the current nomenclature attempts to make more ready comparison between the various ligands reported herein. Ligands employed in this work are shown in Chart 1.

Solid state structures

The homologous series of binuclear complexes $[Zn_2(CH_3$**L2**$)(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3$**L3**$)(CH_3COO)_2](PF_6)\cdot CH_3OH$, $[Zn_2($Br**L2**$)(CH_3COO)_2](PF_6)$ and $[Zn_2(NO_2$**L2**$)(CH_3COO)_2](PF_6)$ were isolated and characterized structurally. In all cases the structures comprised the ligand monoanion, two zinc(II) ions and two bridging acetates with a hexafluorophosphate anion. The four complexes adopt the *anti*-configuration with respect to the plane of the phenoxide ring,[29] as does the complex $[Zn_2(CH_3H$**L1**$)(CH_3COO)(H_2O)](PF_6)$.[24] For the complex with CH_3**L3** a methanol solvate was present. In some instances the PF_6^- was resolved into two disordered octahedral anions sharing the same central atom. Selected crystallographic data are shown in Table 1 and selected bond lengths and angles are displayed in Table 2. ORTEP plots of the complex cations are shown in Fig. 1.[30] In all cases the complexes have the phenolate bridging the two zinc(II) centers which are six-coordinate. For $[Zn_2(CH_3$**L2**$)(CH_3COO)_2](PF_6)$, $[Zn_2($Br**L2**$)(CH_3COO)_2](PF_6)$, $[Zn_2(NO_2$**L2**$)(CH_3COO)_2](PF_6)$ and $[Zn_2(CH_3$**L3**$)(CH_3COO)_2](PF_6)$ the coordination environment of both metal ions is composed of the tertiary amine (Zn(1)–N(3): 2.184(3), 2.196(4), 2.193(3), 2.200(4) Å; Zn(2)–N(1): 2.188(3), 2.206(4), 2.197(3), 2.187(4) Å), the pyridine nitrogen (Zn(1)–N(4): 2.123(3), 2.114(4), 2.134(4), 2.108(4) Å; Zn(2)–N(2): 2.148(3), 2.127(4), 2.129(4), 2.123(4) Å), and the ether oxygens (Zn(1)–O(5): 2.397(3), 2.433(4), 2.380(4), 2.807 Å; Zn(2)–O(4): 2.467(3), 2.368(4), 2.323(3), 2.564 Å), respectively, in addition to the bridging acetates. The six-coordinate geometry is completed by the bridging oxygen from the phenolate (Zn(1)–O(1): 2.006(2), 2.007(3), 2.043(3), 2.003(3) Å; Zn(2)–O(1): 2.024(3), 2.020(3), 2.041(3), 2.024(3) Å) with Zn(1)–O(1)–Zn(2) 109.70(11)°, 110.21(14)°, 109.73(13)° and 107.49(16)° and Zn(1)–Zn(2) distances of 3.296, 3.304, 3.341 and 3.247 Å, respectively.



Scheme 1 Synthesis of (a) and (b) 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-methylphenol (CH_3H**L2**) and 4-methyl-2,6-bis(((2-phenoxyethyl)(pyridin-2-ylmethyl)amino)methyl)phenol (CH_3H**L3**); (c) bis(bromomethyl)-4-nitrophenol; (d) 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-nitrophenol (NO_2H**L2**); (e) 4-bromo-2,6-bis(bromomethyl)phenol; and, (f) 4-bromo-2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)-amino)methyl)phenol (BrH**L2**).

The Zn–O (phenolate) and Zn–N distances appear typical of those reported in this type of complex. The Zn–O (ether) distances are at the long end of the range seen previously for the Zn(II) complexes of 2,6-bis(bis(2-methoxyethyl)aminomethyl)-4-methylphenol (Hbomp; $[Zn_2(bomp)(CH_3COO)_2]BPh_4$; 2.214(5), 2.197(3), 2.362(4), 2.440(3) Å),[31] and 1,2-dimethoxyethane (glyme) ($[Zn_2Cl_2(glyme)]$, 2.1286(11), 2.1216(10) Å; $[Zn_2I_2(glyme)]$, 2.067(7) Å)[32,33] and are significantly longer than those observed for the deprotonated alkoxide ($Zn–O^-$) distances (1.906(3) Å) and coordinated water (2.074(3) Å) reported for $[Zn_2(CH_3HL1)(CH_3COO)(H_2O)](PF_6)$.[24] The analogous nickel(II) complex $[Ni_2(CH_3H_2L1)(CH_3COO)_2](PF_6)\cdot 0.5H_2O$ has been reported and in that case the two alkoxide arms are protonated, with the two nickel(II) sites bridged by two acetato ligands.[34]

X-ray structural data were obtained for two other complexes, bearing tetranuclear (dimer of dimers) structures, $[Zn_4(BrL2)_2(PO_3F)_2(H_2O)_2](PF_6)_2$ and $[Zn_4(CH_3L2)_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$. For $[Zn_4(BrL2)_2(PO_3F)_2(H_2O)_2](PF_6)_2$ each dimer is composed of a $[Zn_2(BrL2)]^+$ fragment, the metal ions in each fragment Zn(1)/Zn(2) and Zn(3)/Zn(4) separated by 3.724 Å and 3.572 Å, respectively. The two PO_3F^{2-} anions display a $\mu_3\eta^3$ coordination mode[35] and complete the coordination sphere for Zn(3) and Zn(4) such that two of the oxygen donors of

Table 1 Summary of crystallographic data for $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)\cdot CH_3OH$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_4(Br\mathbf{L2})_2(PO_3F)_2(H_2O)_2](PF_6)_2$ and $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2\ (H_2O)_2](PF_6)_2$

	$[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$	$[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)\cdot CH_3OH$	$[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$	$[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$	$[Zn_4(Br\mathbf{L2})_2(PO_3F)_2(H_2O)_2](PF_6)_2$	$[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$
Empirical formula	$C_{31}H_{41}F_6N_4O_7PZn_2$	$C_{41}H_{45}F_6N_4O_7PZn_2$	$C_{30}H_{38}F_6N_5O_9PZn_2$	$C_{30}H_{38}BrF_6N_4O_7PZn_2$	$C_{52}H_{68}Br_2F_{14}N_8O_{14}P_4Zn_4$	$C_{66}H_{80}F_{12}N_{10}O_{20}P_4Zn_4$
Formula weight	857.39	981.52	888.36	922.26	1840.32	1946.76
Temperature (K)	293(2)	293(2)	293(2)	293(2)	150(2)	293(2)
Wavelength (Å)	0.71073 (MoK_α)	0.71073 (MoK_α)	1.5418 (CuK_α)	1.5418 (CuK_α)	1.5418 (CuK_α)	1.5418 (CuK_α)
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
a (Å)	10.7745(5)	10.4535(7)	8.926(1)	8.9022(5)	13.3002(6)	26.602(5)
b (Å)	14.8184(8)	13.1726(8)	31.571(2)	13.1115(7)	15.8922(6)	14.3664(7)
c (Å)	23.1270(10)	16.4175(8)	13.3124(9)	16.6071(9)	19.6397(7)	23.0070(10)
α (°)		83.319(5)		99.071(5)	94.791(3)	
β (°)	102.967(5)	85.597(5)	103.264(9)	91.761(5)	109.511(4)	107.464(6)
γ (°)		84.177(5)		102.970(5)	112.586(4)	
Vol ($Å^3$)	3598.3(3)	2228.9(2)	3651.4(5)	1860.92(18)	3504.1(2)	8387.4(8)
Z	4	2	4	2	2	4
μ (mm^{-1})	1.459	1.188	2.823	3.954	4.658	2.883
$F(000)$	1760	1008	1816	932	1848	3976
ρ (Mg/m^3)	1.583	1.462	1.616	1.646	1.744	1.542
Reflns collected	15336	15104	20343	19461	36029	42499
Ind reflections (R_{int})	6333 (0.0456)	7839 (0.0565)	5800 (0.0621)	19461[a]	11083 (0.0402)	13255 (0.0592)
θ range for data collection (deg)	2.93–25	2.84–25	3.69–62.49	3.51–60.57	3.11–62.41	3.48–62.5
GOOF on F^2	0.79	0.704	0.93	1.042	1.037	0.816
final R indices	$R1 = 0.0399$,	$R1 = 0.0483$,	$R1 = 0.0476$	$R1 = 0.07$,	$R1 = 0.053$	$R1 = 0.05$,
$[I > 2\sigma(I)]$	$wR2 = 0.0735$	$wR2 = 0.0713$	$wR2 = 0.1149$	$wR2 = 0.1872$	$wR2 = 0.1522$	$wR2 = 0.1248$
R indices	$R1 = 0.0913$,	$R1 = 0.1673$,	$R1 = 0.0787$	$R1 = 0.0924$,	$R1 = 0.0778$	$R1 = 0.1089$,
(all data)	$wR2 = 0.0791$	$wR2 = 0.0855$	$wR2 = 0.1257$	$wR2 = 0.2067$	$wR2 = 0.1675$	$wR2 = 0.1415$
CCDC number	830841	830842	830843	830846	830845	830844

[a] Twinned refinement on all data ($R_{int} = 0$).

Table 2 Selected bond lengths (Å) and angles (°) for $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)\cdot CH_3OH$ and $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$

	$[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$	$[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)\cdot CH_3OH$	$[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$	$[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$
Zn(1)–O(1)	2.006(2)	2.003(3)	2.043(3)	2.007(3)
Zn(1)–O(2)	2.049(3)	1.979(3)	1.992(3)	2.000(4)
Zn(1)–O(5)	2.397(3)		2.380(4)	2.433(4)
Zn(1)–O(6)	1.997(3)	2.044(3)	2.055(3)	2.067(3)
Zn(1)–N(3)	2.184(3)	2.200(4)	2.193(3)	2.196(4)
Zn(1)–N(4)	2.123(3)	2.108(4)	2.134(4)	2.114(4)
Zn(2)–O(1)	2.024(3)	2.024(3)	2.041(3)	2.020(3)
Zn(2)–O(3)	1.992(2)	2.021(3)	2.076(3)	2.068(4)
Zn(2)–O(4)	2.467(3)		2.323(3)	2.368(4)
Zn(2)–O(7)	2.076(3)	1.982(4)	1.997(3)	1.991(3)
Zn(2)–N(1)	2.188(3)	2.187(4)	2.197(3)	2.206(4)
Zn(2)–N(2)	2.148(3)	2.123(4)	2.129(4)	2.127(4)
Zn(1) . . . Zn(2)	3.296	3.247	3.341	3.304
O(1)–Zn(1)–O(2)	91.69(11)	95.65(14)	98.64(13)	97.86(14)
O(1)–Zn(1)–O(5)	89.46(10)		91.72(13)	91.14(15)
O(1)–Zn(1)–O(6)	99.21(11)	95.01(13)	91.30(13)	92.35(14)
O(1)–Zn(1)–N(3)	91.24(11)	89.34(16)	89.11(11)	89.66(13)
O(1)–Zn(1)–N(4)	167.50(13)	167.69(17)	167.04(13)	167.80(16)
N(3)–Zn(1)–N(4)	77.71(13)	78.48(19)	78.24(13)	78.25(15)
O(1)–Zn(2)–O(3)	100.72(11)	93.12(12)	92.03(13)	91.79(14)
O(1)–Zn(2)–O(4)	88.43(10)		93.56(12)	95.33(14)
O(1)–Zn(2)–O(7)	92.69(11)	97.80(14)	98.56(12)	99.09(13)
O(1)–Zn(2)–N(1)	88.93(10)	89.24(15)	88.77(11)	89.33(13)
O(1)–Zn(2)–N(2)	167.01(11)	167.12(17)	166.63(13)	166.91(15)
N(1)–Zn(2)–N(2)	78.08(12)	78.02(18)	77.88(14)	77.66(16)
Zn(1)–O(1)–Zn(2)	109.70(11)	107.49(16)	109.73(13)	110.21(14)

the anion are bidentate (Zn(3)–O(3B) 2.099(4) Å, Zn(3)–O(6B) 1.962(4) Å, Zn(4)–O(2B) 1.999(4) Å and Zn(4)–O(7B) 2.078(5) Å), with the remaining oxygen donors coordinated monodentately to the other zinc(II) pair (Zn(1)–O(3A) 2.015(4) Å and Zn(2)–O(7A) 2.024(4) Å). The coordination spheres of Zn(1) and Zn(2) are completed by a terminal water molecule coordinated to each metal atom, Zn(2)–O(2A) 2.083(4) Å and Zn(1)–O(6A) 2.086(4) Å. The assignment of the PO_3F^{2-} is based on the overall charge of the molecule, the P–F bond *versus* P–O bond distances (P–O(av.) 1.506(4) Å; P–F(av.) 1.577(4) Å) and comparison with previous examples (P–F(av.) 1.568(2) Å).[36–38] The PO_3F^{2-} arose presumably from hydrolysis of the hexafluorophosphate on standing in aqueous solution. The presence of apparent hydrolysis products of $NaPF_6$ is not without precedent as in a previous study we characterized a zinc(II) complex with the PO_4^{3-} anion arising as an impurity in the $NaPF_6$ sample.[39]

The crystallization of the $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$ complex arose from a deliberate attempt to probe the structure of a substrate-bound complex using BPNPP as a slow substrate. The resulting complex contained PNPP, a hydrolysis product of the initial substrate. Each dimer is composed of a $[Zn_2(CH_3\mathbf{L2})]^+$ fragment, the metal ion separation Zn(1)/Zn(2) and Zn(3)/Zn(4) being 3.747 Å and 3.521 Å, respectively. Again, the $NO_2C_6H_5OPO_3^-$ moiety has a $\mu_3\eta^3$ coordination mode[35] and completes the coordination spheres with bidentate coordination to one pair of Zn(II) ions (Zn(3)–O(3B) 2.082(3) Å, Zn(4)–O(2B) 1.993(3) Å and Zn(3)–O(6B) 1.982(4) Å and Zn(4)–O(7B) 2.065(4) Å) and monodentate coordination to the other zinc(II) pair (Zn(1)–O(6A) 2.001(4) Å and Zn(2)–O(2A) 2.011(4) Å). The coordination spheres of Zn(1A) and Zn(2A) are completed by terminal aqua ligands, Zn(1)–O(3A), 2.080(3) Å and Zn(2)–O(7A) 2.128(3) Å. Other relevant bond distances and angles for $[Zn_4(Br\mathbf{L2})_2(PO_3F)_2(H_2O)_2](PF_6)_2$ and $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$ are reported in Table 3. The bridged structure of the phosphate esters is typical of other similar reported structures of di-zinc(II) complexes with bridging phosphate esters, dibenzyl phosphate,[40] diphenyl phosphate[41] and bis(4-nitrophenyl)phosphate.[42] In terms of the relevance to the catalytic studies (*vide infra*) the structure of $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$, in line with previous studies,[41] suggests that in these di-zinc(II) complexes bidentate coordination of substrate occurs.

Mass spectrometry

Mass spectral analysis, determined in both methanol and H_2O : MeCN (1 : 1), shows that the complexes exist as dinuclear zinc species with the isotopic patterns for $Zn(II)_2$ species being distinctly different from that observed for a mono-zinc species.[24] In methanol the complex with $CH_3H\mathbf{L2}$ shows acetate present ($[Zn(CH_3\mathbf{L2})(CH_3COO)_2]^+$, exp *m/z* 711.20; calc. *m/z* 711.15 (99.9%), 713.15 (100%)). Loss of acetate is considered a prerequisite for formation of the catalytically relevant species in solution.[43–46] Under the conditions employed for the catalytic studies (H_2O : MeCN, 1 : 1) and in the presence of the slow substrate PNPP (the latter a hydrolysis product of BPNPP) the mass spectrum showed the presence of a tetrameric species $[Zn_4(CH_3\mathbf{L2})_2(PNPP)_2(OH)(H_2O)]^+$ (exp *m/z* 1659.14; calc. *m/z* 1657.22 (100%), 1659.22 (87%)), a dimeric species $[Zn_2(CH_3\mathbf{L2})(PNPP)_2{+}2H]^+$ (exp *m/z* 1031.08; calc. *m/z* 1031.10 (100%)) as well as $[Zn_2(CH_3\mathbf{L2})(PNPP)]^+$ (exp *m/z* 811.4; calc. *m/z* 810.1 (97%), *m/z* 812.1 (100%)). Species such as

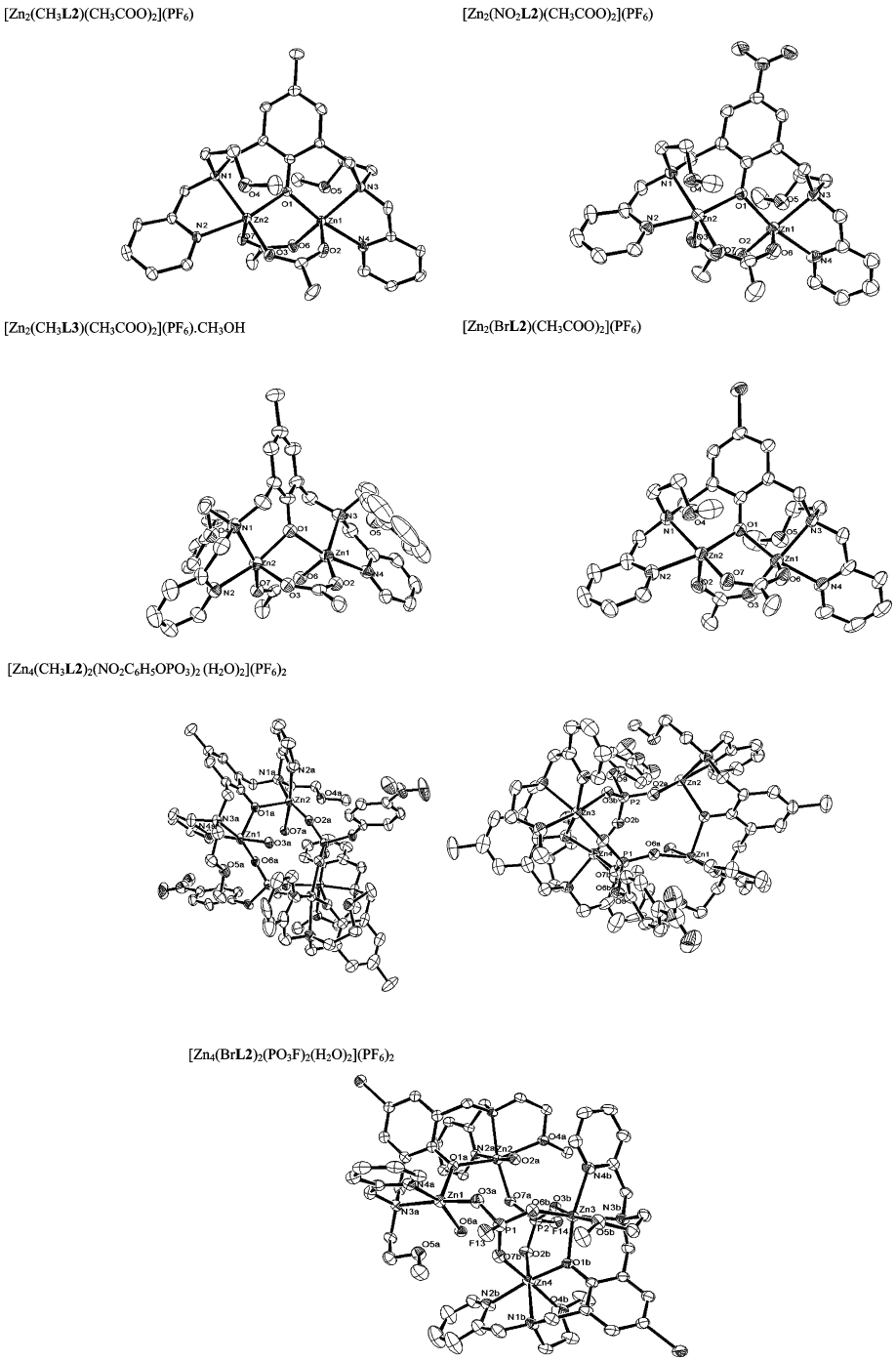


Fig. 1 ORTEP plots of $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)\cdot CH_3OH$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_4(CH_3\mathbf{L2})_2(NO_2C_6H_5OPO_3)_2\ (H_2O)_2](PF_6)_2$ and $[Zn_4(Br\mathbf{L2})_2(PO_3F)_2(H_2O)_2](PF_6)_2$ with 25% probability level of thermal ellipsoids. Hydrogen atoms, counter ions and non-coordinated solvent molecules have been omitted for clarity, as have carbon atom labels.

$[Zn_2(CH_3\mathbf{L2})(HCOO)–H]^+$ (exp m/z 639.4; calc. m/z 637.1 (98%), m/z 639.1 (100%)) and $[Zn_2(CH_3\mathbf{L2})(HCOO)_2]^+$ (exp m/z 684.4; calc. m/z 683.1 (98%), m/z 685.1 (100%)) are also present. The formate ion is commonly found in the mass spectra of these types of complexes[39,47] arising either from fragmentation of the acetate ion or adventitiously from the instrument. In the presence of BPNPP, again in a mixed H_2O : MeCN (1 : 1) solvent system, the mass spectrum shows the presence of $[Zn_2(CH_3\mathbf{L2})(BPNPP)(H_2O)(OCH_3)]^+$ (exp m/z 979.1; calc. m/z 981.1 (96%), m/z 983.1 (100%)) as well as evidence of BPNPP hydrolysis products $[Zn_2(CH_3\mathbf{L2})(PNPP)]^+$ (exp m/z 811.4; calc. m/z 810.1 (97%), m/z 812.1 (100%)) suggesting that under the conditions of the experiment the complex is able to hydrolyze BPNPP. In addition, in each case under the conditions of the mass spectral measurements, the predominant

Table 3 Selected bond lengths (Å) and angles (°) for $[Zn_4(BrL2)_2(PO_3F)_2(H_2O)_2](PF_6)_2$ and $[Zn_4(CH_3L2)_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$

	$[Zn_4(BrL2)_2(PO_3F)_2(H_2O)_2](PF_6)_2$	$[Zn_4(CH_3L2)_2(NO_2C_6H_5OPO_3)_2(H_2O)_2](PF_6)_2$
Zn(1)–O(6A)	2.086(4)	2.001(4)
Zn(1)–O(1A)	2.028(4)	2.065(4)
Zn(1)–O(3A)	2.015(4)	2.080(3)
Zn(1)–N(4A)	2.118(5)	2.111(4)
Zn(1)–N(3A)	2.164(5)	2.154(4)
Zn(2)–O(2A)	2.083(4)	2.011(4)
Zn(2)–O(1A)	2.159(4)	2.096(3)
Zn(2)–O(7A)	2.024(4)	2.128(3)
Zn(2)–N(2A)	2.114(4)	2.129(5)
Zn(2)–N(1A)	2.156(4)	2.164(5)
Zn(2)–O(4A)	2.296(4)	2.374(4)
Zn(3)–O(6B)	1.962(4)	1.982(4)
Zn(3)–O(1B)	2.057(4)	2.050(4)
Zn(3)–O(3B)	2.099(4)	2.082(3)
Zn(3)–N(3B)	2.165(6)	2.170(5)
Zn(3)–N(4B)	2.173(5)	2.184(6)
Zn(3)–O(5B)	2.269(4)	2.262(4)
Zn(4)–O(2B)	1.999(4)	1.993(3)
Zn(4)–O(1B)	2.054(4)	2.013(4)
Zn(4)–O(7B)	2.078(5)	2.065(4)
Zn(4)–N(2B)	2.159(6)	2.126(6)
Zn(4)–N(1B)	2.182(5)	2.202(5)
Zn(4)–O(4B)	2.285(5)	2.389(4)
O(1A)–Zn(1)–N(4A)	108.47(17)	93.61(16)
O(1A)–Zn(1)–N(3A)	93.55(17)	93.81(18)
N(4A)–Zn(1)–N(3A)	79.95(19)	80.01(18)
N(2A)–Zn(2)–N(1A)	80.38(17)	80.2(2)
N(2A)–Zn(2)–O(1A)	87.13(16)	90.71(16)
N(1A)–Zn(2)–O(1A)	92.02(17)	93.23(17)
O(1B)–Zn(3)–N(3B)	90.11(18)	89.64(19)
O(1B)–Zn(3)–N(4B)	164.7(2)	165.5(2)
N(3B)–Zn(3)–N(4B)	75.6(2)	77.3(2)
O(1B)–Zn(4)–N(2B)	166.47(18)	167.4(2)
O(1B)–Zn(4)–N(1B)	90.36(17)	89.8(2)
N(2B)–Zn(4)–N(1B)	76.8(2)	77.6(2)
Zn(1)–O(1A)–Zn(2)	125.56(19)	128.4(2)
Zn(4)–O(1B)–Zn(3)	120.67(19)	120.1(2)

species is the $[Zn_2(CH_3L2)]^{n+}$ complex and substrate, the acetate anions not being present.

NMR solution studies

When one equivalent of zinc(II) acetate was added to a CD_3CN solution of the ligand CH_3HL2 the resonances in the aromatic region of the ^1H NMR spectrum exhibited a downfield shift. The spectrum showed the presence of free ligand and signals identical to the spectrum when a second equivalent of zinc(II) acetate was added. Thus the spectrum with one equivalent zinc(II) added showed that only free ligand and ligand with two zinc ions coordinated are present, suggesting that the acetates support a cooperative binding of two zinc ions simultaneously to the ligand. In the NMR spectrum with two equivalents of zinc a second set of low intensity signals, but at higher field, was detected (also present in the spectrum with one equivalent but partially overlapping with free ligand signals) indicative of a minor, but different, isomeric form. To investigate possible temperature effects, the NMR spectrum of the complex was recorded at four different temperatures (298, 316, 333 and 343 K; Fig. 2)). The intensities of the resonances were temperature-dependent; at higher temperature the higher field less intense signals gained intensity. The process was reversible upon cooling of the sample. The same

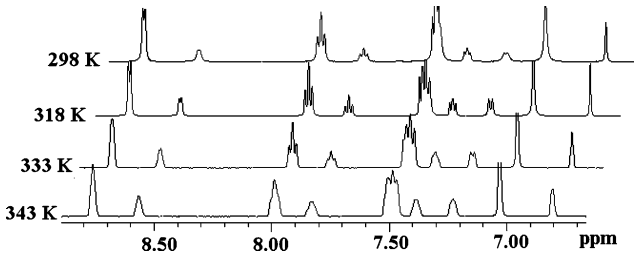


Fig. 2 ^1H NMR spectra of the aromatic region for $[Zn_2(CH_3L2)(CH_3COO)_2](PF_6)$ in CD_3CN at four different temperatures.

observation was made for the complex with the CH_3HL3 ligand although in this case the higher field signals were more intense at room temperature, again gaining intensity upon increasing the temperature of the sample. The second set of resonances for both complexes could thus be assigned to either (i) a reversible interchange of the two geometric forms, either *syn*- or *anti*- with respect to the plane of the aromatic ring, or (ii) to a species with only partially coordinated ether ($-OCH_3$ or –OPh) arms in solution. The interchange of *syn*- and *anti*-forms would involve a process necessitating inversion at the tertiary nitrogen donor. On replacing the CD_3CN solvent with $(CD_3)_2SO$ the apparent equilibrium position in solution was shifted, with the higher field resonances becoming relatively more intense. In terms of the donor number, DMSO would be expected to coordinate more strongly than acetonitrile.[48–51] Consideration of the effect of temperature and solvent coupled with the pronounced effect on the ^1H NMR spectrum of replacing methyl- with phenyl-ether donors suggests what is occurring in solution is more likely to be an effect of the loosely bound ether pendants, in line with the solid state structures of these complexes which display long zinc(II)–ether interactions. Interestingly, for $[Zn_2(CH_3HL1)(CH_3COO)(H_2O)](PF_6)$, with Zn–$O^-$ and Zn–OH donors, and crystallized as the *anti*-form, only one set of resonance is reported in the ^1H NMR spectrum.[24]

Phosphodiesterase-like activity

Phosphatase-like activities of the complexes were measured at various pH values ranging from 5 to 10.5 using the activated substrate BDNPP. The data were consistent with the presence of either one or two protonation equilibria and were thus fit to an equation derived for a monoprotic (eqn (1)) or diprotic (eqn (2)) system.[52]

$$V_0 = \frac{V_{max}}{1 + \frac{[H^+]}{K_{es}}} \quad (1)$$

$$V_0 = \frac{V_{max}}{1 + \frac{[H^+]}{K_{es_1}} + \frac{K_{es_2}}{[H^+]}} \quad (2)$$

Here, V_0 is the initial reaction rate, V_{max} is the maximum rate with BDNPP as substrate (5 mM), and K_{es} ($= K_a$) is the protonation equilibrium constant relevant to catalysis. The resulting fits and catalytic parameters are shown in Fig. 3 and Table 4, respectively. Most notable were the kinetically relevant pK_as for the complexes with CH_3HL1^{2-}, CH_3L2^- and CH_3L3^- (6.6; 6.7, 11.0; 7.7, 10.8; respectively). The substrate concentration dependence of catalysis

Table 4 Kinetic data for $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$

Complex	k_{cat} (s^{-1})	K_m (mM)	pK_a
$[Zn_2(CH_3H\mathbf{L1})(CH_3COO)_2](PF_6)$	$1.07 \pm 0.04 \times 10^{-3}$	12.5 ± 7.0	6.6
$[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$	$5.70 \pm 0.04 \times 10^{-3}$	20.8 ± 5.0	6.7 11.0
$[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$	$3.60 \pm 0.04 \times 10^{-3}$	18.9 ± 3.5	7.7 10.8
$[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$	$0.76 \pm 0.04 \times 10^{-3}$	6.5 ± 1.4	6.5
$[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$	$1.90 \pm 0.04 \times 10^{-3}$	7.1 ± 4.0	6.5 10.6

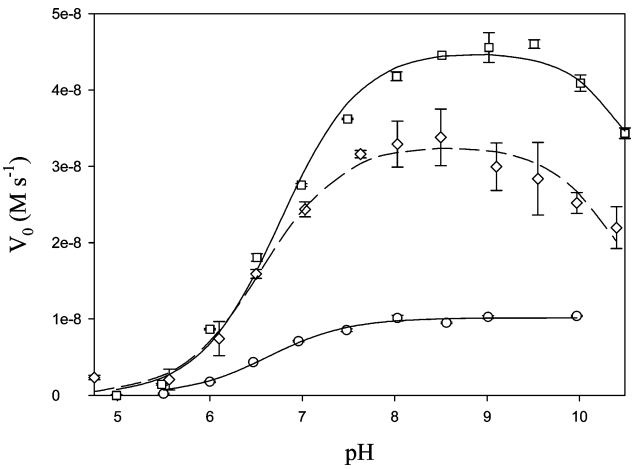


Fig. 3 pH dependence of rate of BDNPP cleavage by $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ (○) $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$ (□) and $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$ (◇); 25 °C; aqueous multi-component buffer (50 mM each of MES, HEPES and CHES), ionic strength controlled by 250 mM $LiClO_4$; 50 : 50 MeCN : buffer; 40 μM complex; 5 mM BDNPP.

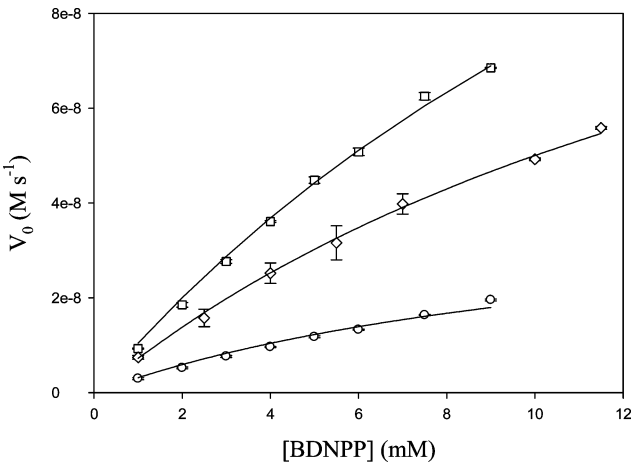


Fig. 4 Substrate concentration dependence for $[Zn_2(H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ (○) $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$ (□) and $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$ (◇); at 25 °C; aqueous multi-component buffer (50 mM each of MES, HEPES and CHES), ionic strength controlled by 250 mM $LiClO_4$; 50 : 50 MeCN : buffer; 40 μM complex.

was also measured at pH 10.5 for the $CH_3H\mathbf{L1}^{2-}$ and pH 8 for the $CH_3\mathbf{L1}^-$ and $CH_3\mathbf{L2}^-$ complexes. Michaelis–Menten type behaviour was observed in each case (Fig. 4) and the data were fit for each complex using non-linear least squares analysis (eqn (3)) to give the Michaelis constant, V_{max} and k_{cat} (V_{max}/[complex]) for each complex.[52]

$$V_0 = \frac{V_{max}[S]}{K_m + [S]} \quad (3)$$

Here, K_m is the Michaelis constant and [S] the substrate concentration. Relevant kinetic data (k_{cat}, K_m, pK_a) are reported in Table 4. For all complexes the rate of hydrolysis of BDNPP (5 mM) was linear for complex concentrations from 20–160 μM. The [substrate] and [complex] dependence studies for the di-Zn(II) complexes of $CH_3H\mathbf{L2}$ and $CH_3H\mathbf{L3}$ were carried out at pH 8.5, for $NO_2H\mathbf{L2}$ pH 9.5 and $BrH\mathbf{L2}$ pH 8.8.

Inductive effects

The linear plot of $\log_{10}(k_{cat})$ *versus* σ, the Hammett parameter,[53] for the three complexes $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)\cdot CH_3OH$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$ (Fig. 5) suggests that the substituent in the *para*-position influences the rate of the hydrolysis reaction with the substrate

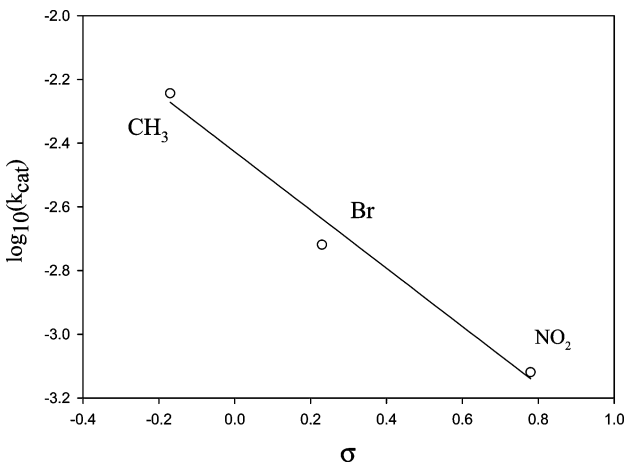


Fig. 5 Linear correlation for the Hammett parameter (σ) and $\log_{10}(k_{cat})$ for $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(Br\mathbf{L2})(CH_3COO)_2](PF_6)$.

BDNPP. The sequence k_{cat} *p*-CH_3 > *p*-Br > *p*-NO_2 is in accord with a previous example, $[Fe(III)Zn(II)(\mathbf{L1})(OAc)_2]^+$ ($H_2\mathbf{L1}$ = 2--(((3-((bis(pyridin-2-ylmethyl)amino)methyl)-2-hydroxy-5-methylbenzyl)(pyridin-2-ylmethyl)amino)-methyl)phenol), where the

same sequence of reactivity for the substrate BDNPP was observed.[54] The linear relationship between σ and pK_{a2}, the catalytically relevant dissociation constant, for $[Fe(III)Zn(II)(\mathbf{L1})(OAc)_2]^+$ suggested that the *para*-substituent influenced the acidity of the Fe(III)-OH_2 group.[54] The small range of pK_a values, and inherent errors, and the lower charge for di-Zn(II) complexes makes a similar analysis more problematic. What is clear is that in the complexes based on **L2** the hydrolase activity towards BDNPP is enhanced by the introduction of an electron donating substituent. There is no clear relationship for $[Fe(III)Zn(II)(\mathbf{L1})(OAc)_2]^+$ nor the di-Zn(II) complexes between the Hammett parameter, σ, and K_m suggesting that the effect of the substituent is primarily on the nucleophile and not on the binding of the substrate to the metal centre. For the di-Zn(II) complexes the influence of the *para*-substituent accounts for less than an order of magnitude change in k_{cat} but this effect in combination with previous studies which showed that second coordination sphere hydrogen bonding effects can also improve the efficiency of model systems[55,56] suggests that an approach combining both influences may be effective.

Interestingly, for the complex $[Zn_2(bomp)(CH_3COO)_2]BPh_4$ (bomp = 2,6-bis[bis(2-methoxyethyl)aminomethyl]-4-methylphenol), an aminopeptidase mimic, when the *para*-methyl group was replaced by *p*-Cl and *p*-NO_2 and the aminopeptidase activity studied using the substrate L-leucine-*p*-nitroanilide, the NO_2 complex was found to be the most active, the reactivity sequence being $NO_2 > Cl > CH_3$.[57] The difference between the two mechanisms is that the hydrolase mimics suggest a terminal hydroxide whereas the aminopeptidase mimic suggests a bridging hydroxide as the nucleophile.[54,57]

Mechanism of reaction

Comparison of the methyl and phenyl ether complexes $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$ and the analogue $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ towards the activated substrate BDNPP offers the opportunity to investigate the relative activities of potential nucleophilic zinc(II)-bound pendant alcohol (Zn–OR) or hydroxide (Zn–OH) groups. Previous potentiometric studies have shown that $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ displays two pK_as at 7.2 and 8.1.[24] Based on a comparison to other Zn(II) complexes[21–25,27,58,59] and theoretical studies,[28] pK_a = 7.2 was assigned to the alkoxide group and pK_a = 8.1 to the hydroxide. For monomeric Zn(II) systems it was shown that the metal-bound alcohol nucleophile is more reactive than the metal-bound hydroxide.[26–28] Thus, the mechanism proposed for $[Zn_2(CH_3H\mathbf{L1})]^{2+}$ involves a nucleophilic attack by the zinc-bound deprotonated alcohol group (pK_a = 7.2), which leads to the formation of a "transition complex".[24] Following breakage of the P–O bond of the substrate BPNPP and release of a nitrophenolate it remains unclear how the active site is regenerated. The nucleophilic attack by the alkoxide is expected to result in a complex with a covalently bound PNPP species, similar to that suggested for other copper(II) and zinc(II) complexes.[22,25,60,61] It has been proposed that PNPP is replaced by acetate groups to reform the catalytic site,[24] but the precise details for this process are currently unknown.

In contrast to $[Zn_2(CH_3H\mathbf{L1})]^{2+}$, $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(CH_3\mathbf{L3})(CH_3COO)_2](PF_6)$ have only one kinetically relevant pK_a (6.76 and 7.72, respectively), and the absence of the metal-bound alcohol allow the assignment of this pK_a to a zinc(II)-bound water molecule. Thus, this terminal hydroxide is the likely nucleophile in the reaction catalyzed by these two complexes. In order to explore the mechanism employed by these three systems further the incorporation of ^{18}O into the reaction product was monitored by NMR. Previous studies have shown that incorporation of ^{18}O (as Zn–^{18}OH) into a phosphate ester hydrolysis product results in a ~0.02 ppm shift in the ^{31}P NMR signal as a result of ^{18}O incorporation into the product.[62–64] 50% incorporation of the ^{18}O would be expected to result in a splitting of the original ^{31}P resonance attributed to the hydrolyzed substrate. Therefore a solvent mixture of H_2O^{16}/H_2O^{18} (50 vol%) in acetonitrile was employed in the reaction of $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$, $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ with BDNPP. In the absence of the label, no splitting in the ^{31}P NMR signal of the coordinated product of the reaction was observed in any sample. For $[Zn_2(CH_3\mathbf{L2})(CH_3COO)_2](PF_6)$ and $[Zn_2(NO_2\mathbf{L2})(CH_3COO)_2](PF_6)$ in the presence of the H_2O^{16}/H_2O^{18} mixture the ^{31}P NMR of the products showed a ~0.02 ppm splitting in resonances arising at −2.70 and −3.28 ppm, respectively. For $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ the ^{31}P NMR spectrum again showed a ~0.02 ppm splitting, the resonance arising at −10.9 ppm. The incorporation of the ^{18}O label in the product of the reaction suggests that for all three complexes the Zn–OH moiety has a significant nucleophilic role,[64] but the different chemical shifts observed for **L1** and the two **L2** systems suggest that the substrate in $[Zn_2(CH_3H\mathbf{L1})]^{2+}$ may be coordinated differently from the other systems.

The NMR results, however, do not entirely rule out a role for the alkoxide in reactions of $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$. Pathways involving both Zn–OH and Zn–OR nucleophiles have been suggested previously.[22,60,61] Thus, the di-zinc(II) complex of 4-(2-hydroxyethyl)-1,4,7,16,19,22-hexaaza-10,13,25,28-tetraoxacyclotriacontane, with both Zn–OR and Zn–OH moieties present as potential nucleophiles, has been employed to investigate the hydrolysis of carboxyester 4-nitrophenyl acetate (NA) and the phosphate ester BPNPP.[22] For NA hydrolysis it was suggested that the Zn-alkoxide acted as a nucleophile to give an acetyl derivative which was subsequently hydrolyzed to acetate by a Zn–OH nucleophile, with regeneration of the catalyst.[22] For BPNPP hydrolysis nucleophilic attack of the alkoxide led to a pendant alcohol phosphorylated intermediate which, after attack of the Zn–OH nucleophile, led to a phosphomonoester complex.[22] It may be that for $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ when both Zn(II)-alkoxide or Zn(II)–OH are present, similar sequential involvement of the nucleophiles occurs offering a pathway for incorporation of the ^{18}O label[22] and consequently a pathway for regeneration of the active form (Fig. 6).[19,22] In contrast, the mechanism employed by the **L2** and **L3** systems is similar to that proposed for related binuclear complexes such as the mimics of the enzyme purple acid phosphatase (PAP).[43,45,46,65,66] A nucleophilic attack by the terminally-bound hydroxide initiates hydrolysis and exchange of the metal-coordinated PNPP product by water molecules regenerates the active site for the next catalytic cycle.

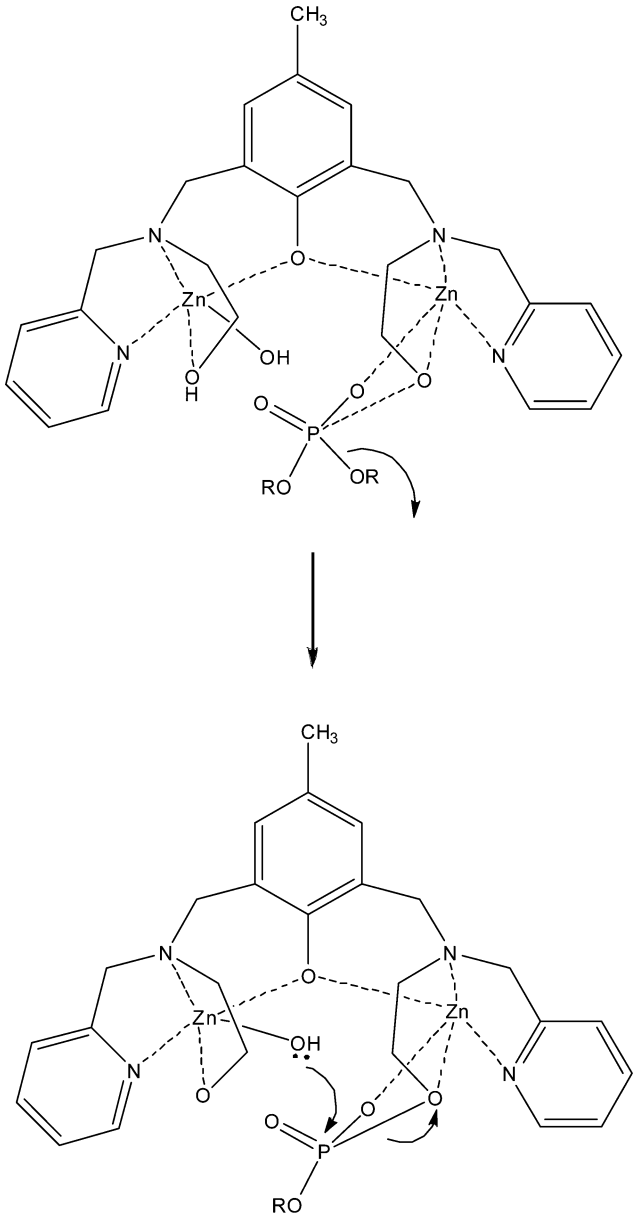


Fig. 6 Key steps in the mechanism, similar to that proposed for the alkoxide assisted hydrolysis mechanisms for the dinuclear zinc alkaline phosphatase enzyme where both the nucleophilic RO–Zn(II) and OH–Zn(II) are involved in the hydrolytic process.[19]

Conclusion

The di-zinc(II) complexes reported here possess properties analogous to binuclear metallohydrolases.[3,5,65] The results obtained for the hydrolysis of the activated substrate BDNPP suggest that complexes with CH_3**L2**$^-$ and CH_3**L3**$^-$ were more effective than with CH_3H**L1**, but electron-withdrawing *para*-substituents lower the rate of hydrolysis of BDNPP. Previous studies with the complex $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$[24] and related complexes with a coordinated alcohol moiety[22,60,61] suggested that the corresponding alkoxide was the nucleophilic agent in the reaction of these model systems with phosphate esters. The present study does not rule out this possibility but it indicates, based on an analysis of the incorporation of ^{18}O into the hydrolysis product, that the three systems investigated here may employ a similar mechanistic strategy with a metal-bound hydroxide as nucleophile. The previously proposed model for the mechanism of $[Zn_2(CH_3H\mathbf{L1})]^{2+}$ may still be applicable but would likely require the dual action of both the alkoxide and hydroxide nucleophiles, similar to the reaction scheme proposed for alkaline phosphatases.[19] In contrast, the remaining complexes in this study are good functional models for enzyme systems that do not have covalent reaction intermediates, such as PAPs or OP-degrading hydrolases.[2,3,46]

Experimental

Materials and methods

Nuclear Magnetic Resonance (NMR) spectra were measured with Bruker AV300, AV400 and AV500 instruments. The spectra were recorded in $CDCl_3$, CD_3OD, CD_3COCD_3, CD_3CN or $(CD_3)_2SO$. Chemical shifts were determined in ppm, relative to known residual solvent peak references. Coupling constants are given in Hz. Two-dimensional correlation spectroscopy (COSY), heterobinuclear single quantum correlation (HSQC) and heterobinuclear multiple bond connectivity (HMBC) experiments were used to assign each signal in the spectra of the final ligands. Low resolution mass spectral data were collected with a Bruker Esquire high capacity ion trap electrospray mass spectrometer (HCT ESI-MS), in methanol (MeOH) or acetonitrile (MeCN) or 50 : 50 MeCN : water, with a Bruker ES source. High resolution mass spectra were obtained using a Bruker microTOFQ ESI-MS in MeOH. The predicted isotopic splitting patterns of peaks were calculated using the program Molecular Weight Calculator.[67] Elemental analyses were performed using the microanalysis facilities at The University of Queensland.

Syntheses of ligands and complexes

2,6-Bis(chloromethyl)-4-methylphenol,[68] 2-(pyridyl-2-ylmethylamino)ethanol,[69] 2,6-bis(bromomethyl)-4-nitrophenol,[70] 2,2′-(2-hydroxy-5-methyl-1,3-phenylene)bis(methylene)bis((pyridin-2-ylmethyl)azanediyl)diethanol (CH_3H_3**L1**),[24] and $[Zn_2(CH_3H\mathbf{L1})(CH_3COO)(H_2O)](PF_6)$ were prepared as described previously.[24]

Synthesis of 2-methoxy-*N*-(pyridin-2-ylmethyl)ethanamine. Pyridine 2-carboxaldehyde (2.25 g, 0.02 mol) in methanol (5 mL) was added dropwise to 2-methoxyethanolamine (1.58 g, 0.02 mol) in methanol (10 mL) at 0 °C. The solution was brought to room temperature and stirred overnight. Sodium borohydride (0.83 g, 0.02 mol) was added in small portions at 0 °C and the solution was subsequently stirred for a further 2 h. Water (30 mL) was added and the reaction mixture was concentrated to 30 mL *in vacuo*. The solution was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed three times with brine, the solution was dried over Na_2SO_4 and the solvent was removed under vacuum. The desired product was obtained as a yellow oil in 90.6% yield (2.85 g). ^1H NMR ($CDCl_3$, 300.13 MHz); δ 2.26 (s, 1H, N*H*); 2.72 (t, 2H, HN–CH_2–, J = 5.4 Hz); 3.20 (s, 3H, OCH_3); 3.43 (t, 2H, CH_2–O, J = 5.4 Hz); 3.79 (s, 2H, HN–CH_2–ar); 7.02 (dq, 1H, pyC*H*, J = 7.5, 4.9 Hz); 7.19 (dt, 1H, pyC*H*, J = 7.7, 1.0 Hz); 7.48 (td, 1H, pyC*H*, J = 7.6, 1.8 Hz); 8.40 (dq, 1H, pyC*H*, J = 4.9, 1.73, 0.9 Hz). ^{13}C

NMR ($CDCl_3$, 100.62 MHz); δ 48.6 (HN–CH_2); 54.9 (OCH_3); 58.8 (HN–CH_2–ar); 71.8 (CH_2–O); 121.7 (*C*H); 121.9 (*C*H); 136.2 (*C*H); 149.1 (*C*H); 159.6 (*C*H). ESI mass spectrometry (methanol) *m*/*z* 167.10 $[C_9H_{14}N_2OH]^+$. FT-IR spectroscopy (*v*, cm^{-1}) 3318.5 (m, N–H str); 2889.1, 2830.3 (m, C–H str); 1592.2 (m, C=C str); 1434.7 (m, C–H def); 1356.5 (w, C–H sym. def); 1110.0 (s, C–O–C str); 757.1 (s, py–H).

Synthesis of 2-phenoxy-*N*-(pyridin-2-ylmethyl)ethanamine. Pyridine 2-carboxaldehyde (0.39 g, 0.004 mol) in methanol (2 mL) was added dropwise to 2-phenoxyethanolamine (0.5 g, 0.004 mol) in methanol (3 mL) at 0 °C. The solution was brought to room temperature and stirred overnight. Subsequently sodium borohydride (0.2 g, 0.005 mol) was added in small portions and the solution was stirred for a further 4 h. Water (6 mL) was added and the reaction mixture was concentrated to about 6 mL *in vacuo*. The remaining solution was extracted with dichloromethane (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum to yield 0.75 g of a yellow oil in 91.2% yield. ^{1}H NMR ($CDCl_3$, 500.13 MHz); δ 2.14 (s, 1H, N*H*); 3.04 (t, 2H, HN–CH_2, *J* = 5.3 Hz); 3.98 (s, 2H, HN–CH_2–ar); 4.09 (t, 2H, CH_2–O, *J* = 5.3 Hz); 6.89 (m, 2H, arC*H*); 6.91 (m, 1H, arC*H*); 7.13 (m, 1H, pyC*H*, *J* = 7.3, 4.9, 1.0 Hz); 7.24 (m, 2H, arC*H*, *J* = 7.4 Hz); 7.31 (d, 1H, pyC*H*, *J* = 7.8 Hz); 7.61 (td, 1H, pyC*H*, *J* = 7.7, 1.8 Hz); 8.54 (dq, 1H, pyC*H*, *J* = 4.9, 1.7, 0.9 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz); δ 48.4 (HN–*C*H$_2$); 55.1 (HN–*C*H$_2$–ar); 67.3 (*C*H$_2$–O); 114.5 (ar*C*H); 120.7 (ar*C*H); 121.9 (py*C*H); 122.1 (py*C*H); 129.3 (ar*C*H); 136.4 (py*C*H); 124.3 (py*C*H); 158.8 (O–*C*); 159.6 (CH$_2$–py*C*). ESI mass spectrometry (methanol) *m*/*z* 229.10 $[C_{14}H_{16}N_2OH]^+$. FT-IR spectroscopy (*v*, cm^{-1}) 3404.8 (m, N–H str); 2923.8 (m, C–H str); 1593.9 (m, C=C str); 1510.1 (s, N–H def); 1448.1 (m, C–H def); 1331.0 (w, C–H sym. def); 1212.3 (s, C–O–C str); 777.0 (w, Ar–H); 745.5 (s, py-H); 692.0 (w, Ar–H).

Synthesis of 2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)-amino)methyl)-4-methylphenol (CH_3HL2). To a solution of 2-methoxy-*N*-(pyridin-2-ylmethyl)aminoethanol (1.50 g, 0.009 mol) and triethylamine (0.91 g, 0.009 mol) in tetrahydrofuran (4.5 mL) was added dropwise a solution of 2,6-bis(chloromethyl)-4-methylphenol (0.94 g, 5 mmol) in dichloromethane (4 mL) at 0 °C. A white precipitate formed immediately. The reaction mixture was stirred for 48 h and then filtered to remove precipitated triethylamine hydrochloride. Removal of the solvents left a yellow oil (2.17 g) which was further purified by flash column chromatography (EtOAc/MeOH 8 : 2 (900 mL), EtOAc/MeOH 1 : 1 (400 mL), I_2 stain, R_f = 0.66 in EtOAc/MeOH 8 : 2). The ligand was obtained as yellow oil in 65.4% yield (1.35 g). ^{1}H NMR ($CDCl_3$, 500.13 MHz); δ 2.21 (s, 3H, CH_3); 2.75 (t, 2H, N–CH_2, *J* = 5.8 Hz); 3.25 (s, 6H, OCH_3); 3.50 (t, 4H, CH_2OCH$_3$, *J* = 5.8 Hz); 3.77 (s, 4H, arCH_2N); 3.84 (s, 4H, NCH_2ar); 6.92 (s, 2H, arC*H*); 7.10 (ddd, 2H, pyC*H*, *J* = 7.4, 4.9, 1.1 Hz); 7.46 (d, 2H, pyC*H*, *J* = 7.8 Hz); 7.60 (td, 2H, pyC*H*, *J* = 7.6, 1.8 Hz); 8.47 (dq, 2H, pyC*H*, *J* = 4.9, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz); δ 20.6 (*C*H$_3$); 53.8 (N*C*H$_2$), 55.6 (ar*C*H$_2$N); 58.7 (O*C*H$_3$); 60.9 (N*C*H$_2$py); 71.0 (*C*H$_2$OCH$_3$); 123.0 (py*C*H); 124.0 (py*C*H); 124.7 (ar*C*); 128.2 (ar*C*CH$_3$); 130.3 (ar*C*H); 137.4 (py*C*H); 149.8 (py*C*H); 154.6 (ar*C*–OH); 159.8 (py*C*). FT-IR spectroscopy (*v*, cm^{-1}) 2921.8, 2875.2, 2817.0 (m, C–H str); 1590.6 (m, C=C str); 1434.1 (m, O–H def); 1365.0 (m, C–O–C str): 1109.1 (m, C–O str): 843.8 (m, Ar–H); 755.9 (s, py–H). ESI mass spectrometry (methanol) *m*/*z* 487.18 $[C_{27}H_{36}N_4O_3Na]^+$, 465.22 $[C_{27}H_{36}N_4O_3H]^+$.

4-Methyl-2,6-bis(((2-phenoxyethyl)(pyridin-2-ylmethyl)amino)-methyl)phenol (CH_3HL3). 2,6-bis(chloromethyl)-4-methylphenol (0.16 g, 0.55 mmol) in dichloromethane (2 mL) was added dropwise to a mixture of 2-phenoxy-*N*-(pyridin-2-ylmethyl)ethanamine (0.25 g, 1.09 mmol) and triethylamine (0.30 g) in tetrahydrofuran (2 mL) at 0 °C. The resulting yellow solution was stirred for 48 h at room temperature then filtered to remove the white precipitate of triethylamine hydrochloride and the solvent was removed under vacuum. The yellow oil was purified by flash column chromatography (EtOAc/MeOH, 9 : 1, $FeCl_3$ stain, R_f = 0.75 in EtOAc/MeOH 9 : 1) (0.17 g, 52%). ^{1}H NMR ($CDCl_3$, 500.13 MHz); δ 2.26 (s, 3H, CH_3); 3.03 (t, 4H, CH_2O, *J* = 5.8 Hz); 3.88 (s, 4H, arCH_2N); 3.98 (s, 4H, NCH_2py); 4.10 (t, 4H, NCH_2, *J* = 5.8 Hz); 6.85 (m, 4H, arC*H*, *J* = 8.7, 1.0 Hz); 6.92 (tt, 2H, arC*H*, *J* = 7.4, 1.0 Hz); 6.99 (s, 2H, arC*H*); 7.13 (ddd, 2H, pyC*H*, *J* = 7.4, 4.9, 1.1 Hz); 7.24 (m, 4H, C*H*, *J* = 7.4 Hz); 7.49 (d, 2H, pyC*H*, *J* = 7.8 Hz); 7.60 (td, 2H, pyC*H*, *J* = 7.6, 1.8 Hz); 8.53 (dq, 2H, pyC*H*, *J* = 4.8, 1.7, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz); δ 20.5 (*C*H$_3$); 52.3 (*C*H$_2$O), 55.2 (ar*C*H$_2$N); 60.4 (N*C*H$_2$py); 65.5 (N*C*H$_2$); 114.4 (ar*C*H); 120.6 (ar*C*H); 122.0 (py*C*H); 123.2 (py*C*H); 123.3 (ar*C*); 127.6 (CH$_3$*C*); 129.3 (ar*C*H); 136.5 (py*C*H); 148.8 (py*C*H); 153.6 (*C*OH); 158.6 (py*C*). FT-IR spectroscopy (*v*, cm^{-1}) 2921.7, 2831.4 (m, C–H str); 1596.8 (m, C=C str); 1475.4 (m, C–H def); 1241.6 (m, C–O–Ph str); 752.2 (s, py- H); 729.9, 690.9 (s, Ar–H). ESI mass spectrometry (methanol) *m*/*z* 611.23 $[C_{37}H_{40}N_4O_3Na]^+$; 589.25 $[C_{37}H_{40}N_4O_3H]^+$.

2,6-(((2-Methoxyethyl)(pyridin-2-ylmethyl)amino)methyl)-4-nitrophenol (NO_2HL2). 2-Methoxy-*N*-(pyridin-2-ylmethyl)-aminoethanol (0.51 g, 31 mmol) was dissolved with triethylamine (0.7 g) in THF (5 mL) and cooled to 0 °C. Upon dropwise addition of 2,6-bis(bromomethyl)-4-nitrophenol (0.5 g, 15 mmol) in dichloromethane (7 mL) the solution turned bright yellow and a precipitate formed immediately. The mixture was stirred for 3 days at room temperature, filtered and concentrated *in vacuo*. After purification by column chromatography (EtOAc/MeOH, 8 : 1, $FeCl_3$ stain, R_f = 0.76) a yellow oil (0.5 g) was obtained in 68% yield. ^{1}H NMR ($CDCl_3$, 500.13 MHz); δ 2.80 (t, 3H, NCH_2, *J* = 5.6 Hz); 3.29 (s, 6H, OCH_3); 3.52 (t, 4H, CH_2OCH$_3$, *J* = 5.6 Hz); 3.85 (s, 4H, arCH_2N); 3.91 (s, 4H, NCH_2py); 7.16 (dd, 2H, pyC*H*, *J* = 6.9 Hz); 7.42 (d, 2H, pyC*H*, *J* = 7.8 Hz); 7.65 (td, 2H, pyC*H*, *J* = 7.8, 1.7 Hz); 8.14 (s, 2H, arC*H*); 8.52 (d, 2H, pyC*H*, *J* = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz); δ 53.2 (N*C*H$_2$); 54.6 (ar*C*H$_2$N); 58.8 (O*C*H$_3$); 60.3 (N*C*H$_2$py); 70.6 (*C*H$_2$OCH$_3$); 122.2 (py*C*H), 123.0 (py*C*H); 124.5 (py*C*H); 125.0 (ar*C*H); 136.7 (py*C*H); 139.7 (*C*NO$_2$); 148.9 (py*C*H); 158.5 (py*C*); 162.5 (*C*OH). FT-IR spectroscopy (*v*, cm^{-1}) 3372.3 (m, O–H str); 2927.1, 2877.8, 2820.8 (m, C–H str); 1591.6 (m, C=C str); 1513.7 (m, N=O asym. str); 1471.4 (m, C–H def); 1329.8 (s, N=O sym. str); 1094.5 (m, C–O str); 845.3 (w, Ar-H); 752.3 (s, py-H). ESI mass spectrometry (methanol) *m*/*z* 496.25 $[C_{26}H_{33}N_5O_5+H]^+$.

4-Bromo-2,6-bis(hydroxymethyl)phenol. 4-Bromo-2,6-bis(hydroxymethyl)phenol was prepared by a modification of a previously published procedure.[71] 4-Bromophenol (17.3 g, 0.1 mol) in methanol (25 mL), aqueous sodium hydroxide solution (25%, 50 mL) and formaldehyde were combined and left at room

temperature for 12 days. Subsequently water (50 mL) and glacial acetic acid (15 mL) were added and after 2 h the solution was concentrated to 50 mL *in vacuo* and then cooled on ice. The solution was decanted from the orange oil/precipitate obtained on standing and the remaining oil was dissolved in aqueous sodium hydroxide solution (10%, 50 mL). Activated charcoal was added and the suspension stirred overnight. After filtration the solution was acidified with 2 M HCl to pH 5. The resulting yellow precipitate was collected on a sintered glass funnel, recrystallized from water, dried in air and washed with cold chloroform (~20 mL) to yield 7 g of the desired product as a white powder in 23% yield. ^{1}H NMR (CD_3COCD_3, 300.13 MHz); δ 4.73 (s, 4H, CH_2); 7.28 (s, 2H, arCH) ^{13}C NMR (CD_3COCD_3, 100.62 MHz); δ 61.4 (CH_2); 111.6 (ar$C$Br); 129.5 (ar$C$H); 130.5 (ar$C$CH2); 153.4 (ar$C$OH). FT-IR spectroscopy (ν, cm^{-1}) 3400.8, 3300.3 (s, O–H str); 2965.6, 2911.5, 2886.2 (w, CH_2 str); 1649.0, 1610.3, 1586.9 (w, C═C str); 1453.5 (s, CH_2 def); 1331.3 (s, O–H def); 1064.7 (s, C–OH def); 870.0 (m, Ar–H def).

4 - Bromo - 2, 6 - bis(bromomethyl)phenol. 4-Bromo-2,6-bis(hydroxymethyl)phenol (3 g, 13 mmol) was added to hydrogen bromide in acetic acid (30%, 15 mL) and stirred for 10 min until all the starting material had dissolved. Upon addition of water the clear orange solution formed a precipitate which was collected and dried on a filter and then washed thoroughly with cold petroleum spirit. The desired product was obtained as yellow powder, 3.3 g, in 70.5% yield. ^{1}H NMR ($CDCl_3$, 300.13 MHz); δ 4.49 (s, 4H, CH_2); 5.66 (bs, 1H, OH); 7.39 (s, 2H, arCH) ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 27.9 (CH_2); 112.7 (ar$C$Br); 127.2 (ar$C$CH$_2$); 133.7 (ar$C$H); 152.3 (ar$C$OH).FT-IR spectroscopy (ν, cm^{-1}) 3537.1 (s, O–H str); 3050.3, 2979.8 (w, CH_2 str); 1647.9, 1603.6 (w, C═C str); 1467.1 (s, CH_2 def); 868.8 (m, Ar–H def).

4-Bromo-2,6-bis(((2-methoxyethyl)(pyridin-2-ylmethyl)amino)-methyl)phenol (BrHL2). To a solution of 2-methoxy-*N*-(pyridin-2-ylmethyl)aminoethanol (0.925 g, 5.6 mmol) and triethylamine (1.25 g) in tetrahydrofuran (10 mL) was added dropwise a solution of 4-bromo-2,6-bis(bromomethyl)phenol (1 g, 2.7 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 72 h and then filtered to remove the precipitate of triethylamine hydrobromide. Removal of the solvent resulted in a yellow oil which was further purified by flash column chromatography (1 g crude ligand, l = 30 cm, $\varnothing$ = 1.5 cm, EtOAc (until first band is eluted) then MeOH/EtOAc 1 : 5, $FeCl_3$ stain, R_f = 0.55 in EtOAc). The ligand was obtained as a yellow oil in 63% yield (930 mg). ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 2.79 (t, 4H, NCH_2CH$_2$); 3.26 (s, 6H, OCH_3); 3.52 (t, 4H, CH_2OCH$_3$); 3.79 (s, 4H, CH_2N); 3.96 (s, 4H, NCH_2py); 5.17 (s, 1H, OH); 7.08 (m, 2H, pyCH); 7.19 (s, 2H, arCH); 7.44 (m, 2H, pyCH), 7.64 (m, 2H, pyCH); 8.50 (m, 2H, pyCH). ^{13}C NMR ($CDCl_3$, 100.62 MHz); δ 52.8 (CH_2); 54.6 (CH_2); 58.7 (CH_3); 59.8 (CH_2); 69.9 (CH_2); 110.7 (ar$C$H); 122.45 (py$C$H); 123.6 (py$C$H); 123.8 (ar$C$H); 131.9 (ar$C$H); 136.8 (py$C$H); 148.9 (py$C$H); 156.0 (ar$C$H); 156.8 (py$C$H). FT-IR spectroscopy (ν, cm^{-1}) 3230.6 (m, O–H str); 2927.3, 2879.1 (m, CH_2 str); 1591.8, 1572.1 (m, C═C str); 1435.2 (s, CH_2 def); 1111.8 (s, C–O str); 831.5, 755.7 (s, Ar–H). ESI mass spectrometry (methanol) m/z 529.10, 531.07 [$C_{26}H_{33}BrN_4O_3$+H]$^+$; 551.16, 553.16 [$C_{26}H_{33}BrN_4O_3$+Na]$^+$.

[Zn_2(CH_3L2)($CH_3COO)_2$](PF_6). CH_3H**L2** (0.250 g, 0.5 mmol) was dissolved in MeOH (20 mL), and a solution of zinc acetate dihydrate (0.240 g, 0.9 mmol) in MeOH (10 mL) was added dropwise. The resulting pale yellow solution was then heated under reflux for 0.5 h. The solution was permitted to cool to room temperature and $NaPF_6$ (0.140 g, 0.8 mmol) was added. Upon standing colourless crystals were deposited and these were collected by filtration (0.31 g, 71%). Anal. calc. for $C_{31}H_{41}Zn_2N_4O_7PF_6$: C 43.42, H 4.82, N 6.53% Found: C 43.25, H 4.79, N 6.53%. ESI mass spec (methanol) m/z: 711.2 [$C_{31}H_{41}N_4O_7Zn_2$]$^+$. FT-IR spectroscopy (ν, cm^{-1}): 2924.0, 2850.5 (w, C–H str), 1593.8 (m, C═O asym str, acetate); 1476.2 (m, C═O sym str, acetate); 1427.7 (m, C–H def); 1092.5 (w, C–O str), 830.8 (s P–F str), 555.4 (s, P–F str). ^{1}H NMR (CD_3CN, 500.13 MHz); δ 1.90 (s, 6H, acetateCH_3); 2.22 (s, 3H, CH_3); 2.52 (m, 4H, NCH_2, J = 5.7 Hz); 2.71 (bm, 4H, CH_2CH_2O); 2.98 (s, 6H, OCH_3); 3.63 (d, 2H, arCH_2N, J = 11.9 Hz); 3.85 (d, 2H, NCH_2py, J = 14.7 Hz); 4.39 (d, 2H, NCH_2py, J = 13.8 Hz); 4.48 (d, 2H, arCH_2N, J = 9.3 Hz); 7.03 (s, 2H. arCH); 7.49–7.51 (m, 4H, pyCH); 7.99 (t, 2H, pyCH, J = 7.4 Hz); 8.74 (d, 2H, pyCH, J = 4.6 Hz). ^{13}C NMR (CD_3CN, 100.62 MHz); δ 20.4 (CH_3); 24.6 (acetateCH_3); 55.1 (NCH_2); 59.0 (OCH_3); 61.3 (arCH_2N); 61.6 (NCH_2py); 69.7 (CH_2O); 125.2 (py$C$H); 125.8 (ar$C$); 126.8 (CCH_3); 132.8 (ar$C$H); 140.8 (py$C$H); 148.6 (py$C$H); 155.8 (py$C$); 161.1 (COH); 177.7 (CO_2^-). Second set of low intensity (25%) signals: ^{1}H NMR (CD_3CN, 500.13 MHz) H,H-COSY; δ 2.07 (s, 6H); 3.12 (s, 6H); 3.27 (d, 2H, J = 5.4 Hz); 3.74 (m, 4H); 3.74 (s, 2H); 3.86 (d, 2H, J = 15.8 Hz); 4.01 (s, 2H); 6.77 (s, 2H); 7.21 (d, 2H, J = 6.1 Hz); 7.37 (t, 2H, J = 5.8 Hz); 7.81 (t, 2H, J = 7.3 Hz); 8.51 (bs, 2H).

[Zn_2(CH_3L3)($CH_3COO)_2$](PF_6)·CH_3OH. This complex was prepared in a similar manner to that described for [Zn_2(CH_3**L2**)($CH_3COO)_2$](PF_6); (0.31 g, 71%). Anal. calc. for $C_{41}H_{45}Zn_2N_4O_7PF_6CH_3OH$: C 49.77, H 4.87, N 5.53% Found: C 49.50, H 4.60, N 5.55%. ^{1}H NMR (CD_3CN, 400.13 MHz); δ 1.72 (s, 6H, acetateCH_3); 2.24 (s, 3H, CH_3); 2.77 (m, 3H); 3.04 (m, 3H); 3.37 (d, 4H); 3.54 (m, 3H); 3.65 (d, 2H, J = 12.3 Hz); 3.77 (d, 2H, J = 11.8 Hz); 3.94 (m, 5H); 4.18 (m, 5H); 7.21 (m, 4H, arCH); 6.94 (m, 2H, arCH); 6.62 (d, 4H, J = 8.1 Hz, arCH); 7.41–7.50 (m, 4H, pyCH); 7.97 (td, 2H, J = 7.7, 1.4, pyCH); 8.71 (d, 2H, J = 5.1, pyCH). Second set of low intensity aromatic proton signals: 7.21 (m, 4H); 6.94 (m, 2H); 6.73 (d, 4H, J = 8.6 Hz); 7.41–7.50 (m, 4H); 7.93 (td, 2H, J = 7.7, 1.6 Hz); 8.75 (d, 2H, J = 5.3 Hz). ESI mass spectrometry (methanol) m/z: 855.7 [$C_{41}H_{47}N_4O_8Zn_2$]$^+$; 825.7 [$C_{40}H_{47}N_4O_7Zn_2$]$^+$. FT-IR spectroscopy (ν, cm^{-1}): 2927.4 (w, C–H str), 1593.9 (m, C═O asym str, acetate); 1482.6 (m, C═O sym str, acetate); 1433.7 (m, C–H def); 1224.6 (w, C–O str), 832.5 (s P–F str), 760.3 (s, Ph–H); 694.1 (s, Ph–H); 555.4 (s, P–F str).

[Zn_2(NO_2L2)($CH_3COO)_2$](PF_6). This complex was prepared in a similar manner to that described for [Zn_2(CH_3**L2**)($CH_3COO)_2$](PF_6); (0.31 g, 71%). Anal. calc. for $C_{30}H_{38}Zn_2N_5O_9PF_6$·$CH_3OH$: C 40.45, H 4.60, N 7.61% Found: C 39.36, H 4.27, N 7.67%. ESI mass spectrometry (methanol) m/z: 744.0 [$C_{30}H_{38}N_5O_9Zn_2$]$^+$. FT-IR spectroscopy (ν, cm^{-1}) 2931.1 (w, C–H str); 1596.3 (m, C═O asym str, acetate); 1505.9 (w, NO_2 asym str); 1426.3 (m, C═O sym str, acetate); 1320.4 (m, NO_2 sym str); 1091.8 (m, C–O str); 832.8 (s P-F str); 755.2 (m, py C–H def); 659.3 (w, Ar–H def); 556.1 (s, P-F). ^{1}H NMR (CD_3CN, 500.13 MHz); δ 1.91 (s, 6H, acetateCH_3); 2.57

(m, 4H, NCH_2); 2.74 (bm, 4H, CH_2CH_2O); 2.99 (s, 6H, OCH_3); 3.82 (d, 2H, arCH_2N, J = 12.3 Hz); 3.90 (d, 2H, NCH_2py, J = 14.8 Hz); 4.42 (d, 2H, NCH_2py, J = 15.1 Hz); 4.48 (d, 2H, arCH_2N, J = 12.7 Hz); 7.52 (m, 4H, pyCH); 8.01 (t, 2H, pyCH, J = 6.9 Hz); 8.2 (s, 2H. arCH); 8.72 (m, 2H, pyCH).

[Zn_2(BrL2**)($CH_3COO)_2$](PF_6).** Br**HL2** (100 mg) was dissolved in methanol (8 mL) with zinc acetate dihydrate (82 mg). The mixture was heated under reflux for 30 min, permitted to cool to room temperature and dry sodium hexafluorophosphate (95 mg) was added. After filtration the solution was left to stand at room temperature. Colourless crystals, suitable for X-ray crystallography, emerged after 2 h (62 mg). Anal calc. for $C_{30}H_{38}BrN_4O_7Zn_2PF_6$ C: 39.07, H: 4.15, N: 6.07% Found: C 39.33, H 4.13, N 6.14% ESI mass spectrometry (methanol) m/z: 749.0 $[C_{29}H_{38}BrN_4O_6Zn_2]^+$, 707.3 $[C_{27}H_{36}BrN_4O_5Zn]^+$, 593.1 $[C_{26}H_{32}BrN_4O_3Zn]^+$. FT-IR spectroscopy ($\nu$, cm^{-1}) 2930.0 (w, CH_2 str); 1596.9 (s, bridging acetate antisym. str); 1424.4 (s, bridging acetate sym. str); 829.4 (s, P–F str); 760.0, 657.6 (m, Ar–H def); 555.1 (m, P–F). ^{1}H NMR (CD_3CN, 500.13 MHz); δ 1.99 (s, 6H, acetateCH_3); 2.54 (m, 4H, NCH_2); 2.72 (bm, 4H, CH_2CH_2O); 2.99 (s, 6H, OCH_3); 3.64 (d, 2H, arCH_2N, J = 12.1 Hz); 3.84 (d, 2H, NCH_2py, J = 14.7 Hz); 4.38 (d, 2H, NCH_2py, J = 14.4 Hz); 4.44 (d, 2H, arCH_2N, J = 11.3 Hz); 7.38 (s, 2H. arCH); 7.48–7.50 (m, 4H, pyCH, J = 5.4 Hz); 7.99 (t, 2H, pyCH, J = 7.1 Hz); 8.72 (m, 2H, pyCH).

[Zn_4(BrL2**)$_2$($PO_3F)_2$($H_2O)_2$]($PF_6)_2$.** This complex was prepared in a similar manner to [Zn_2(Br**L2**)($OAc)_2$](PF_6) complex but the sodium hexafluorophosphate employed for the crystallization was wet. Colourless crystals, suitable for X-ray crystallography, were obtained upon standing (40 mg). Anal calc. for $C_{52}H_{68}Br_2N_8O_{14}Zn_4P_4F_{14}$: C: 33.94, H: 3.72, N: 6.09% Found: C 33.35, H 3.61, N 5.99%. ESI mass spectrometry (methanol) m/z: 754.9 $[C_{26}H_{32}BrN_4O_3Zn_2PFO_3]^+$, 593.1 $[C_{26}H_{32}BrN_4O_3Zn]^+$. FT-IR spectroscopy ($\nu$, cm^{-1}) 2854.3, 2928.9, 2892.97 (w, CH_2 str); 1460.1, 1445.2 (m, CH_2 def); 1182.6 (m, P═O, str); 1121.0 (s, C–O–C str); 830.7 (s, P–F str); 774.4 (m, Py–H def); 555.1 (m, P–F).

X-ray crystallography

X-ray diffraction data for crystals of [Zn_2(CH_3**L2**)($CH_3COO)_2$](PF_6), [Zn_2(CH_3**L3**)($CH_3COO)_2$](PF_6)·CH_3OH, [Zn_2(NO_2**L2**)($CH_3COO)_2$](PF_6), [Zn_2(Br**L2**)($OAc)_2$](PF_6) and [Zn_4(CH_3**L2**)$_2$($NO_2C_6H_5OPO_3)_2$($H_2O)_2$]($PF_6)_2$ were collected at 293(2) K whilst data for [Zn_4(Br**L2**)$_2$($PO_3F)_2$($H_2O)_2$]($PF_6)_2$ were collected at 150(2) K. An Oxford Diffraction Gemini Ultra dual source (Mo and Cu) CCD diffractometer with Mo ($\lambda_{K\alpha}$ = 0.71073 Å) or Cu ($\lambda_{K\alpha}$ = 1.5418 Å) radiation was used. The structures were solved by direct methods (SIR-92) and refined (SHELXL 97)[72] by full matrix least squares methods based on F^2. These programs were accessed through the WINGX 1.70.01 crystallographic collective package.[73] All non-hydrogen atoms were refined anisotropically unless they were disordered. Hydrogen atoms were fixed geometrically and were not refined. Drawings of molecules were produced with ORTEP.[30] Selected crystal data and some details of refinements are given in Table 1. Selected bond distances and angles are presented in Tables 2 and 3. X-ray data were deposited with the Cambridge Crystallographic Data Centre CCDC 830841–830846. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Catalytic studies

The phosphoesterase-like activity of each complex was determined by measuring hydrolysis of the substrate BDNPP. A Varian Cary50 Bio UV/Visible spectrophotometer with a Peltier temperature controller was used to measure changes in absorbance values in 10 mm quartz cuvettes. The initial rate method was employed and assays were measured such that the initial linear portion of the data was used for analysis. Product formation was determined at 25 °C by monitoring the formation of 2,4-dinitrophenol. Throughout the pH range studied the extinction coefficient of this product at 400 nm is 12 100 M^{-1} cm^{-1}.[45,74] For each assay corrections for the rate of autohydrolysis were applied. An aqueous multi-component buffer (50 mM in each of 2-(*N*-morpholino)ethanesulfonic acid (MES), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) and 2-(*N*-cyclohexylamino)ethane sulfonic acid (CHES), with the ionic strength controlled by 250 mM $LiClO_4$) was used. Assays were carried out in 50 : 50 MeCN : buffer, with substrate and complex initially dissolved in MeCN. Assays conducted to investigate pH dependence were 40 μM in complex and 5 mM in BDNPP and showed no significant buffer effects. Substrate dependence assays were 40 μM in complex and 1–11.5 mM in BDNPP, and complex dependence assays were 20–120 μM in complex and 5 mM in BDNPP. Background assays of autohydrolysis were subtracted from the data. The change in absorbance produced by hydrolysis of BDNPP by free Zn(II) (from $Zn(ClO_4)_2$), in the same concentration as the complex did not differ significantly from autohydrolysis values. All data were fitted by non-linear least squares regression analysis. Mass spectral studies of the hydrolysis reaction were conducted by mixing one equivalent of [Zn_2(CH_3**L1**)($CH_3COO)_2$]$^+$ with twenty-five equivalents of either bis(4-nitrophenyl)phosphate (BPNPP) or 4-nitrophenylphosphate (PNPP), the latter a hydrolysis product of the former, in 1 : 1 MeCN : H_2O, and recording the spectrum of the resulting mixture after 1 h. BPNPP and its hydrolysis product PNPP were used as they are slower substrates and permitted more ready analysis than the substrate used for the kinetic studies (BDNPP).

^{18}O labelling Studies

^{31}P NMR spectra were recorded with a 400 MHz Bruker AV400 spectrometer at room temperature in the digital acquisition mode (operating frequency 161.9 MHz). Chemical shifts are reported in δ units relative to 85% H_3PO_4 in D_2O as external reference (δ_P = 0.00). For the ^{18}O-labeled sample (50% ^{18}O; 97% purity) (Novachem, Victoria, Australia) the solution was made up from a solution of complex (0.01 mmol) in acetonitrile (0.3 mL), 100 mM HEPES buffer pH 8 (0.15 mL) and ^{18}O-water (97%, 0.15 mL) (50 : 50 mixture of acetonitrile : buffer). To this, one equivalent BDNPP (5.1 mg) was added and the mixture left for one week at room temperature prior to recording the ^{31}P spectra. For experiments with ^{16}O-water the solution was composed of complex (0.01 mmol) in acetonitrile (0.3 mL), 100mM HEPES buffer pH 8 (0.15 mL) and distilled water (0.15 mL). To this, one equivalent BDNPP (5.1 mg) was added and the mixture left for one week at room temperature prior to recording the ^{31}P NMR spectra.

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