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Structural characterization of a dizinc(II) complex with bridging η^2-phosphate diesters and internal N–H · · · O–P hydrogen bonding †

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The first structurally characterized dizinc(II) complex with bridging η^2-phosphate diesters, in this case dibenzyl phosphate, and internal N–H···O–P H-bonding are reported.

The design of efficient host molecules for phosphate anion guests has been attracting much current attention because of the many important biological roles of phosphates and potential applications in biotechnology.[1] Organic receptors equipped with acidic hydrogens have been proved to be efficient hosts of phosphate anions due to strong complementary H-bonding in non-aqueous solutions.[2] H-bonding has also been used to activate phosphate esters toward nucleophilic attack.[3] These H-bonds, however, are typically disrupted in water and as a result it is generally difficult to achieve strong binding/activation of phosphates with organic hosts.[4] In Nature, many of the chemical transformations of phosphates, including hydrolysis, are performed by metalloenzymes and they are facilitated by the cooperative action of two or more metal ions, Zn^{2+} being one of the most frequently employed.[5] Typically, these metal ions are 3–5 Å apart. In addition to the metals, the involvement of XH groups (X = N, O) of arginine, lysine, histidine, tyrosine and/or serine residues in H-bonding interactions to phosphate groups is a ubiquitous feature of the active sites of these metalloenzymes.[5,6] Many of these interactions/amino acid residues are thought to be functionally important, but the mechanistic details regarding their precise roles remain unclear.

Recently, it has been shown that binding of a phosphate ester to two Cu^{2+} ions with simultaneous hydrogen bonding to one ammonium group can result in a remarkable acceleration (4×10^7-fold) of the hydrolysis of bis(*p*-nitrophenyl) phosphate (BNPP).[7] The excellent reactivity of this dicopper(II) complex was explained in terms of the additional electrostatic activation provided by the N–H · · · O–P H-bonding. Also very recently, metal co-ordination and internal N–H · · · O–P H-bonding have resulted in improved phosphate binding to a monometallic Co(III) complex.[8] Thus, the co-operation of metal ions and H-bonding groups appears to be a promising novel strategy to improve both the binding of phosphates and the efficacy of their chemical transformations by bio-inspired metallohosts in water. These metal complexes can also provide new insights into the enzyme chemistry.

Recent work has shown that the ligand unit (6-amino-2-pyridylmethyl)amine ideally positions an N–H for internal H-bonding to other metal-bound ligands.[9,10] Thus, the tripodal ligand *N*,*N*-bis-(2-pyridylmethyl)-*N*-(6-amino-2-pyridylmethyl)amine (bpapa) seemed suitable to pursue the biomimetic cooperation of zinc(II) ions and N–H groups as a way to improve binding and activation of phosphate anions at artificial receptor sites. In addition, zinc(II) complexes of the parent ligand without the H-bonding group, tris-(2-pyridylmethyl)amine (tpa), were known to bind phosphates.[11]

The dizinc(II) complex $[(bpapa)Zn(\mu\text{-}\eta^2\text{-}DBP)_2Zn(bpapa)](PF_6)_2$ **1** (DBP = dibenzyl phosphate) was assembled by reaction of equimolar amounts of $[Zn(NCCH_3)_4](PF_6)_2$, DBP and bpapa[9] in MeCN. Colourless crystals of $\mathbf{1}\cdot 0.3CH_3OH$ suitable for X-ray diffraction studies[12] were grown by slow evaporation of a CH_3OH solution. Each of the symmetry-related zinc(II) centres is six-coordinate, being ligated by the three pyridyl and single aliphatic nitrogens of bpapa and two oxygens of DBP^- (Fig. 1). The geometry about each of the zinc(II) centres is best described as distorted octahedral. The Zn · · · Zn distance of 4.91 Å is shorter than in flexible dizinc(II) complexes bridged by a single phosphate.[11,13] The Zn · · · Zn distance in **1** is also somewhat shorter than in dizinc(II) complexes bridged by two phosphates and a flexible dinucleating ligand framework such as $[30]aneN_6O_4$.[14] A key feature present in the structure of **1**, which is absent in any of the previously structurally characterized dinuclear metal complexes bridged by phosphate esters is the short intramolecular N–H · · · O–P H-bond (Fig. 1). Recently, it was suggested that H-bonding stabilizes metal-bound phosphates.[8] It may also orient the zinc(II)-bound phosphate diester. Thus, whereas the P(1)–O(4P)–Zn angle of 136.57(12)° is similar (±1°) to the corresponding angles in other crystallographically characterized dizinc(II) phosphate-bridged complexes,[11,13,14] the P(1)–O(3P)–Zn angle has expanded to 143.60(13)°, presumably to optimize the N(7)–H(7A) · · · O(3P) H-bond.

Binding of DBP^- to $\{(bpapa)Zn\}^{2+}$ and $\{(tpa)Zn\}^{2+}$ moieties was investigated by $^{31}P\{^1H\}$ NMR titration experiments of 5 mM DBP in D_2O at pD 7.4 with varying amounts of [(bpapa)-

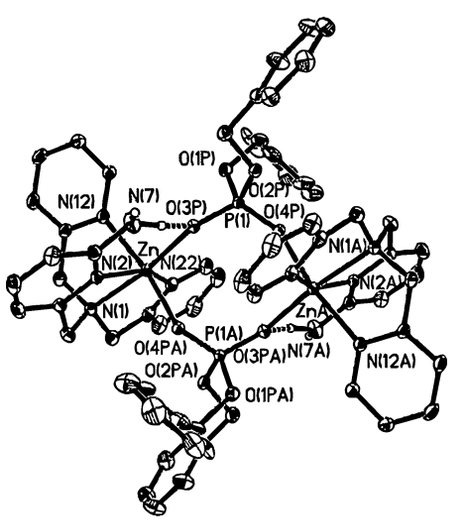

Fig. 1 A thermal ellipsoid plot of $[(bpapa)Zn(\mu\text{-}\eta^2\text{-}DBP)_2Zn(bpapa)]^{2+}$ drawn with 30% probability ellipsoids. Hydrogen atoms except those of N(7) are omitted for clarity. Selected bond lengths (Å): Zn–N(1) 2.225(2), Zn–N(2) 2.203(2), Zn–N(12) 2.176(2), Zn–N(22) 2.193(2), Zn–O(3P) 2.0255(19), Zn–O(4P) 2.0711(19). Selected hydrogen bonding interactions: N(7) · · · O(3P) 2.9321(3) Å, H(7A) · · · O(3P) 2.00 Å, N(7)–H(7A) · · · O(3P) 151° (for the N(7)–H(7A) extended to 1.01 Å).

† Electronic supplementary information (ESI) available: Experimental and X-ray crystallography details; Fig. S1–4: changes of the ^{31}P NMR chemical shift of DBP. See http://www.rsc.org/suppdata/dt/b3/b312281f/

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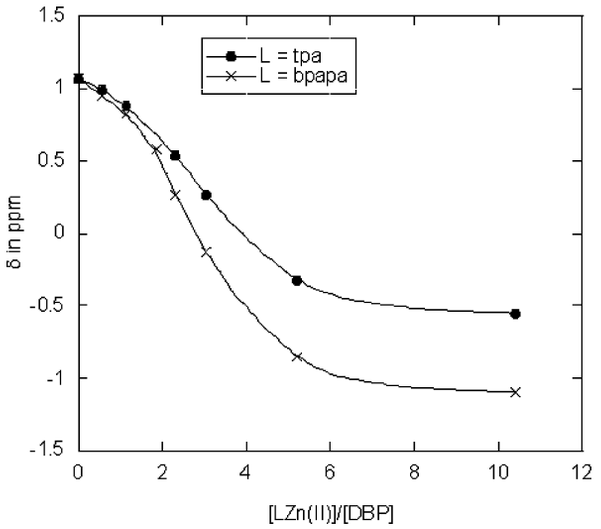

Fig. 2 Changes of the ^{31}P chemical shift of DBP at 20 °C (5 mM in D_2O, pD 7.4 upon addition of increasing amounts of $[(tpa)Zn(S)](PF_6)_2$ and $[(bpapa)Zn(S)](PF_6)_2$ (50 mM in S = CD_3CN).

$Zn(S)]^{2+}$ and $[(tpa)Zn(S)]^{2+}$ (50 mM in S = CD_3CN). The addition of increasing amounts of these zinc(II) complexes to solutions of DBP causes a progressive upfield shift of the ^{31}P signal relative to free DBP (Fig. 2). The upfield shift of the DBP signal for solutions containing less than 2 equiv. of Zn^{2+} relative to DBP^- is smaller than for solutions containing more than 2 equiv., and could be due to the formation of $DBP:(ZnL)_n$ complexes ($n > 1$). The rather large upfield shifts observed for the ^{31}P signal of the zinc-bound DBP, *ca.* 1.5–2.0 ppm, is also consistent with the occurrence of bridging coordination modes in solution. The fact that the upfield shifts can be more prominent by as much as 0.5 ppm, when $\{(bpapa)Zn\}^{2+}$ is added, indicates that this has higher binding affinity for DBP^- than $\{(tpa)Zn\}^{2+}$.[15,16] Recently, it was reported that the binding of dianionic phosphate ester NPP^{2-} to $[((2\text{-guanidyl})\text{ether-cyclen})Zn(OH_2)]^{2+}$ was *ca.* 10 times stronger than to $[(\text{cyclen})Zn(OH_2)]^{2+}$ due to phosphate-guanidium double H-bonding.[17] Interestingly, the maximum upfield shift observed for the ^{31}P signal of NPP^{2-} bound to $\{((2\text{-guanidyl})\text{ether-cyclen})Zn\}^{2+}$ relative to bound to $\{(\text{cyclen})Zn\}^{2+}$ was also 0.5 ppm.

There is much current interest in metal complexes with internal H-bonding. In particular, recent elegant studies have highlighted the importance of incorporating such interactions in synthetic models of metalloenzymes.[7,8,10,18] Here, we have reported the X-ray crystal structure of a dizinc(II) complex with the unique feature of internal N–H ··· O–P H-bonding to bridging η^2-dibenzyl phosphates. We expect the use of ligands with internal H-bond donors such as bpapa will provide synthetic hydrolases that resemble more faithfully the microenvironments and chemistry of phosphates in the active sites of nucleases, in which case they could allow the elucidation of the cooperative mechanisms between the metal(s) and the second co-ordination sphere. H-bonding features in synthetic hydrolases could also improve the catalytic properties of metal complexes by further activating ground state molecules and preferentially stabilizing the transition states of reactions.

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15 The same studies were carried out in the presence of I = 1 ($NaNO_3$) and I = 0.1 (NaCl). The titration data shows that in all cases DBP^- binds better to $\{(bpapa)Zn\}^{2+}$ than to $\{(tpa)Zn\}^{2+}$ (Fig. 2 and Figs. S1 and S2 (see ESI †)). It also shows that the affinity of DBP^- >> Cl^- >> NO_3^- to these zinc(II) complexes (Figs. S3 and S4 (see ESI †)), consistent with the zinc(II) co-ordinating abilities of these ligands.

16 The fact that the ^{31}P chemical shift of DBP^- changes up to large $[Zn^{2+}]/[DBP]$ ratios could indicate that DBP^- does not bind very strongly to these zinc(II) complexes. It is interesting, however, that binding of DBP^- to $\{(bpapa)Zn\}^{2+}$ is stronger than to $\{(tpa)Zn\}^{2+}$ given that electronically the amino group in bpapa is an electron-donating group and sterically it could hinder the approach of the external phosphate. The stronger binding of DBP^- to the $\{(bpapa)Zn\}^{2+}$ moiety could be explained if the amino group is acting as a hydrogen bond donor to the metal-bound DBP^- anion, as it does in the crystal structure of **1**·0.3CH_3OH.

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