Monodentate-Bridged Phosphodiester and Sulfate Complexes: Structural Insights into the Biological Activation of Phosphodiesters, Sulfate, and Sulfate Esters

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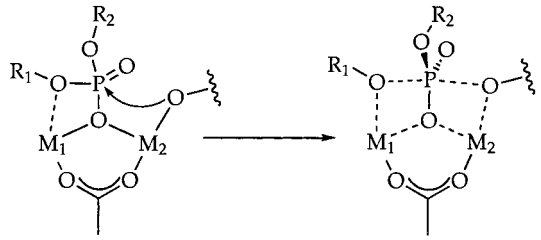
Phosphodiesters form the backbone of DNA and RNA, molecules that encode genetic information in cells. Nature has evolved many ways to activate the phosphodiester bond for phosphoryl group transfer reactions that are critical for life. One of these ways is to utilize two metal ions bridged by one carboxylate group to bind and activate phosphate diesters. Notable examples include 3′,5′-exonuclease that hydrolytically cleaves DNA and DNA polymerase that is responsible for forming the biopolymer. From crystallographic studies, a mechanism was proposed for these DNA-processing proteins in which one of the oxygen atoms of the phosphodiester group forms a monodentate bridge between two metal ions.[1,2] A well-positioned, terminally bound solvent water molecule or other nucleophile then attacks the bound phosphodiester group to form a pentavalent transition state as illustrated in Scheme 1. One metal with an open coordination site helps activate the nucleophile while the other stabilizes the leaving group. A similar mechanism has also been proposed for RNA hydrolysis.[3]

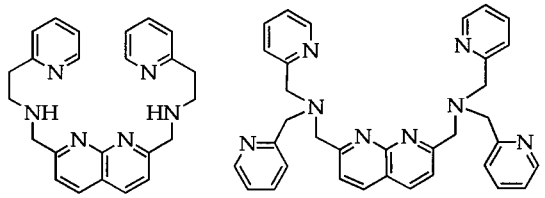
Sulfate ester groups have structures similar to those of phosphate esters. Like phosphorylation and phosphoryl group transfer, sulfurylation and sulfuryl group transfer are important for a variety of different biological processes. An increasing number of sulfotransferases and sulfurylases have been identified that perform vital biological functions,[4−6] several of which require manganese(II) ions for activity.[7−11] Although detailed structural and mechanistic information about these sulfotransferases remains largely unavailable, studies suggest that strategies for activating sulfate or sulfate ester groups are similar to those used for phosphate ester groups.[5,6] Considering the wide array of existing sulfotransferases and sulfurylases, a two-metal-activation mechanism similar to that indicated in Scheme 1 is conceivable.

The monodentate bridging mode of a phosphodiester bound to two metal ions depicted in Scheme 1 has not yet been established in any biological system. In fact, such a bridging mode had not been characterized in small molecule models until our recent description of a dicopper(II) complex, $[Cu_2(BPAN)(\mu\text{-}OH)(\mu\text{-}(PhO)_2PO_2)](ClO_4)_2$.[12] In this compound the diphenyl phosphate group bridges two five-coordinate copper(II) ions in a

Scheme 1



monodentate fashion. The multidentate ligand BPAN, 2,7-bis[2-(2-pyridylethyl)aminomethyl]-1,8-naphthyridine, having a bridging 1,8-naphthyridine unit, served as the dinucleating ligand. 1,8-Naphthyridine was employed not only to mimic a bridging carboxylate group but also to facilitate further functionalization to stabilize dimetallic centers. The most closely related previously characterized species is a dicopper complex having two monodentate bridging $H_2PO_4^-$ ligands.[13] In our continued study of the coordination chemistry of BPAN, we report here the synthesis and structure of the complex $[Ni_2(BPAN)(\mu\text{-}(PhO)_2PO_2)_2(MeCN)_2](ClO_4)_2$ (**1**), in which two nickel(II) ions are bridged by monodentate diphenyl phosphate groups with adjacent coordination sites occupied by solvent molecules. A dimanganese(II) complex $[Mn_2(BPMAN)(\mu\text{-}SO_4)_2]$ (**2**), prepared by using the related dinucleating ligand BPMAN, where BPMAN = 2,7-bis[bis(2-pyridylmethyl)-aminomethyl]-1,8-naphthyridine, is also reported.[14] In this complex a monodentate bridging sulfate group is coordinated between two manganese(II) ions, a structure that, to our knowledge, has never been reported in coordination chemistry.



BPAN **BPMAN**

The complex $[Ni_2(BPAN)(\mu\text{-}(PhO)_2PO_2)_2(MeCN)_2](ClO_4)_2$ (**1**) was prepared by allowing 2 equiv of $Ni(ClO_4)_2\cdot 6H_2O$ and 2 equiv of $Na(PhO_2)_2PO_2$ to react with 1 equiv of BPAN. The structure of **1**, depicted in Figure 1, reveals each nickel ion to have pseudooctahedral coordination geometry. The two nickel ions are 3.134(6) Å apart, bridged by two monodentate diphenyl phosphate groups and the 1,8-naphthyridine unit of the ligand BPAN. A dangling oxygen atom of each diphenyl phosphate molecule forms a hydrogen bond to one of the secondary amine groups of BPAN.

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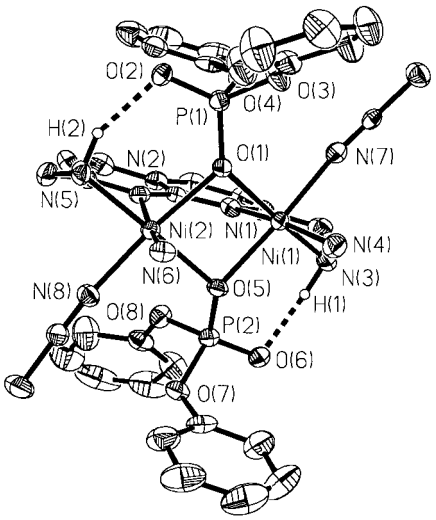

Figure 1. ORTEP diagram of $[Ni_2(\mu\text{-}(PhO)_2PO_2)_2(BPAN)(MeCN)_2](ClO_4)_2$ (**1**) showing the 40% probability thermal ellipsoids (part of the BPAN ligand and the anions are omitted for clarity).

Hydrogen atoms were found in the structure analysis, as shown in Figure 1. There is an available coordination site on each nickel ion for an acetonitrile solvent molecule, adjacent to the bridging phosphate ester group in a position similar to that occupied by the nucleophile proposed in Scheme 1. Compound **1** is the closest inorganic analogue of the monodentate bridged structure depicted in Scheme 1. Combined with the previously reported dicopper(II) structure,[12] these results clearly show that, with the right ligand environment, phosphodiester groups can form monodentate bridges between two five- or six-coordinate metal ions.

The compound $[Mn_2(BPMAN)(\mu\text{-}SO_4)_2]$ (**2**) was prepared from the reaction of 2 equiv of $MnSO_4 \cdot H_2O$ with 1 equiv of the ligand BPMAN. Yellow crystals of **2** were obtained from vapor diffusion of diethyl ether into a methanol/acetonitrile solution. The structure (Figure 2) reveals two manganese ions 3.760(3) Å apart, bridged by two sulfate groups and the 1,8-naphthyridine unit from BPMAN. One manganese ion has a pseudooctahedral geometry. The other manganese is best described as seven-coordinate with a long bond (2.885 Å) to one nitrogen atom of the 1,8-naphthyridine spacer. A sulfate group bridges the two metal ions in a normal *syn-syn* bidentate fashion. Another uses one of its oxygen atoms to bridge two manganese ions in a monodentate mode. A second oxygen atom of this sulfate group coordinates

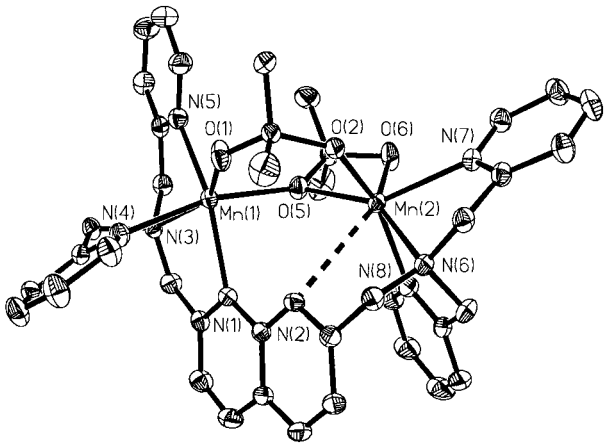

Figure 2. ORTEP diagram of $[Mn_2(\mu\text{-}SO_4)_2(BPMAN)]$ (**2**) showing the 40% probability thermal ellipsoids for all non-hydrogen atoms with two sulfate molecules in different bridging modes (crystal form 1).

to the seven-coordinate manganese ion. A different crystal form of **2** was obtained from vapor diffusion of diethyl ether into a solution of methanol/water. The structure of this form, shown in the Supporting Information, has two manganese ions 3.838(4) Å apart with the two sulfate groups both in a *syn-syn* bidentate bridging mode. The coordination geometry of each manganese ion is pseudooctahedral.

The monodentate bridging mode of the sulfate group resembles that adopted by many carboxylate groups. The different bridging modes of carboxylate groups are the result of structural variability, termed "carboxylate shifts",[15] that are important for a variety of enzymatic functions. The present findings suggest that sulfate and phosphate diester bridges can also have similar structural variations, which might be termed sulfate and phosphate shifts, respectively. The flexibility of these bridges may facilitate their activation at dimetallic centers in biology.

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Supporting Information Available: Details of the synthetic procedures for complexes **1** and **2**. Atom-labeling schemes for non-hydrogen atoms of **1** and **2**. X-ray crystallographic data for **1** and **2** and tables of atomic coordinates, thermal parameters, and bond lengths and angles.

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