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Synergistic Effect between Metal Coordination and Hydrogen Bonding in Phosphate and Halide Recognition

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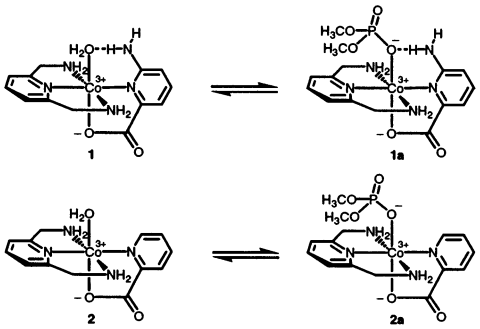
There has been much interest in developing receptors and catalysts that interact with phosphates because of the many important roles that they play in life (e.g., ATP, c-AMP, c-GMP, DNA, phosphatidyl choline, etc). Some of these receptors and catalysts have been used for sensing[1] or cleaving phosphates.[2] Organic receptors[3,4] have been shown to bind phosphates by H-bonding. Such H-bonding interactions can be used to activate and hydrolyze phosphate esters. Phosphate esters can also be activated by direct coordination to metal ions. Numerous mono-[5] and dinuclear[6] metal complexes have been developed as models for nucleases,[7] polymerases,[8] and phosphatases.[9] To sense phosphates efficiently, the receptor should bind tightly to the phosphates. However, it is generally difficult to achieve tight binding of phosphates in water.[10] One way to overcome this difficulty may be to combine H-bonding and metal coordination. Here we compare the binding of dimethyl phosphate to **1** and **2** to give **1a** and **2a**, respectively (Scheme 1).

Scheme 1



Complexes **1** and **2** were generated in water as their hydroxy forms (coordinated hydroxide instead of coordinated water) by adding 1 equiv each of sodium hydroxide and sodium picolinate or sodium 2-aminopicolinate[11] to $[(bamp)CoCl_3]$[12] (100 mM) and heating the mixture at 50 °C for 5 h. Picolinate or 2-aminopicolinate chelates regiospecifically to $[(bamp)CoCl_3]$ when 1 equiv of sodium hydroxide is added. The bound carboxylate anion of picolinate prefers to be trans to the bound hydroxide anion due presumably to charge repulsion.[13] Complexes **1** and **2** were formed by adding 1 equiv of $HClO_4$ to the corresponding hydroxy complexes. Complex **1a** was synthesized by adding sodium dimethyl phosphate (50 mM) to **1** (10 mM) and heating the mixture at 80 °C for 3 h. Figure 1 shows the crystal structure of **1a**.[14] As anticipated, the anionic phosphate diester is coordinated trans to the carboxlate anion. Furthermore, the bound phosphate is H-bonded to the amino group. The N−H···O distance is 2.77 Å with the N−H distance of 0.89 Å and H···O hydrogen bond distance of 1.96 Å. As shown below, this H-bond stabilizes the bound phosphate. It may also orient the coordinated phosphate and restrict the rotation of the Co−O bond.

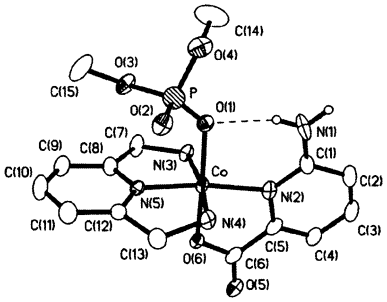


Figure 1. Crystal structure (ORTEP representation) of **1a**.

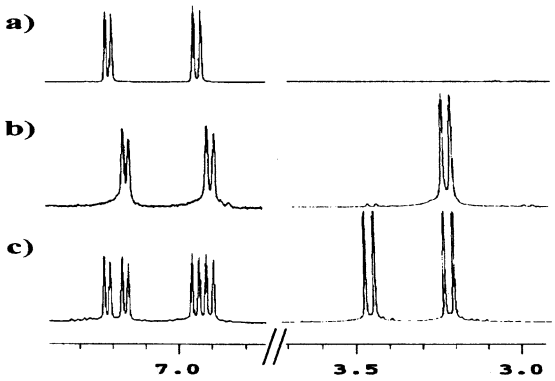


Figure 2. ^{1}H NMR of (a) complex **1**, (b) complex **1a**, and (c) complexes **1** and **1a** and dimethyl phosphate at equilibrium.

Co(III) complexes are ideal for studying the reversible binding of phosphates because the rate of equilibration is slow on the NMR time scale. Thus, the equilibrium constant can be obtained by comparing the intensities of the NMR signals due to the bound and the free species. Two of the ^{1}H NMR signals for **1** (Figure 2a) are clearly differentiated from those of **1a** (Figure 2b). The ^{1}H NMR signals for free dimethyl phosphate (δ 3.46) and the coordinated dimethyl phosphate (δ 3.22) in **1a** are also distinct (Figure 2c). Heating a solution of **1** and dimethyl phosphate (10 mM each) at 80 °C for 3 h gave equilibrium levels of **1**, **1a**, and dimethyl phosphate (Figure 2c). ^{31}P NMR (not shown) of the same mixture shows a singlet for the free phosphate and a second singlet at 5.6 ppm (relative to free phosphate) for the bound phosphate.

In contrast to the above results, **2a** does not form in any appreciable levels when dimethyl phosphate is added to **2** under

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Table 1. Equilibrium Constants ($K \times 10^{-1}$, M^{-1}) for Binding of Halides to **1** and **2** in Water at 80 °C

anions	1	2
F	25.0	2.3
Cl	2.5	1.6
Br	0.7	1.1

the same conditions used to produce Figure 2c. Greater concentrations of dimethyl phosphate (100 mM) can be used to detect the formation of **2a**. The equilibrium constants for binding of dimethyl phosphate to **1** and **2** are 210 and 6.2 M^{-1}, respectively, at 80 °C. We propose that the dramatic increase in the binding of dimethyl phosphate to **1** is due to the stronger H-bond between the amino group and the coordinated anionic phosphate in **1a** as compared to the H-bond between the amino group and the coordinated water molecule in **1**. In **1a**, the hydrogen bond acceptor is negatively charged, while the donor has partial positive charge (due to resonance stabilization of the amino group). In **1**, the charge on both the hydrogen bond donor and the hydrogen bond acceptor is partially positive. It has been shown that the hydrogen bond is strongest when the donor is positively charged and the acceptor is negatively charged.[15]

Interesting organic receptors that bind phosphates by H-bonding in nonaqueous solvents have been reported.[4,5] However, it is difficult to achieve tight binding of phosphates in water by H-bonds alone. Monodentate coordination of phosphate diesters to metal ions in water are also generally weak ($K < 10^1$ M^{-1}).[16] The binding constant can be increased to about 400 M^{-1} by coordinating both phosphoryl oxygens of the diester to dinuclear metal complexes.[17] It has been shown that there is considerable cooperativity between metal ions in dinuclear metal complexes not only for binding phosphate esters but also for hydrolyzing them.[18] It would be interesting to investigate the cooperativity effect of dinuclear metal complexes and H-bonding for phosphate recognition and hydrolysis.

Potentiometric titration reveals that the bound water molecule in **1** ($pK_a = 3.3$) is considerably more acidic than that in **2** ($pK_a = 5.4$). Thus, Lewis acidity of the metal complex can be increased considerably by the H-bonding. This also indicates that the equilibrium constant for hydroxide binding to **1** is about 100 times greater than that for binding of hydroxide to **2**. Here again, the stronger hydrogen bond (by about 3 kcal/mol) between the slightly positive H-bond donor and the anionic H-bond acceptor[15] appears to be the reason for the tighter binding of hydroxide to **1**. We investigated the binding of F, Cl, and Br to **1** and **2** by NMR methods. The equilibrium constants are shown in Table 1.[19] As expected, F binds more tightly to **1** than to **2**. However, Br binds more tightly to **2** than to **1**. Thus, **1** is much more selective than **2** for binding F over Br. We propose that the stronger binding of F to **1** than to **2** is due to the cooperativity between H-bonding and metal coordination. The slightly weaker binding of Br to **1** than to **2** is likely due to the unfavorable steric interactions between the coordinated bromide and the amino group. In addition, F is intrinsically a better H-bond acceptor than Br.

There is much current interest in metal coordinated anions that are H-bonded.[20] However, the functional role of such systems is not yet clear. Metal coordinated hydrides that are H-bonded intramolecularly may be highly reactive for reducing ketones and imines.[21] Active sites of some metalloenzymes also contain coordinated anionic ligands that are H-bonded,[22] but it is difficult to elucidate the cooperativity between metal coordination and H-bonding in enzymic systems. In our systems, cooperativity between H-bonding and metal coordination appears to be considerable not only for binding phosphates as shown in this work but also for hydrolyzing them as we showed previously.[23] Thus, this type of cooperativity may be important for recognition of ground state molecules as well as for stabilization of transition states of reactions. It has recently been shown that cooperativity between H-bonding and metal coordination also plays an important role in recognition of nucleobases.[24]

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Supporting Information Available: X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystal structure data for figure **1a**: orthorhombic, space group *Fdd*2, $a = 17.5069(6)$ Å, $b = 31.2182(11)$ Å, $c = 16.0615(6)$ Å, $Z = 16$; $R[I > 2\sigma(I)] = 0.0653$, w$R$ (all data) $= 0.1654$, GOF $= 1.107$.
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