In summary, we have developed a new family of 1,4-diphosphanes **1** with an imidazolidin-2-one backbone as chiral ligands and showed their utility in the hydrogenation of α-enamides. The modular construction of this ligand class allows for wide structural diversity. Studies of this kind and mechanistic investigations are underway.

Experimental Section

For details on the synthesis of **1a**–**1k** and their precursors, see Supporting Information.

General procedure for the asymmetric hydrogenation of enamide **4**: **1** (0.0074 mmol) was added to a solution of $[Rh(cod)_2]BF_4$ (2.5 mg, 0.0062 mmol; cod = 1,5-cyclooctadiene) in CH_2Cl_2 (2 mL). After the reaction mixture had been stirred at 20 °C for 20 min, enamide **4** (0.62 mmol) was added. The hydrogenation was performed at 20 °C under 1 atm of hydrogen for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excess and the reaction conversion were measured by chiral GC or HPLC without any further purification.

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Mimicking Metallophosphatases: Revealing a Role for an OH Group with No Libido[**]

Marcello Forconi and Nicholas H. Williams[*]

Typically, descriptions of enzyme catalysis use multiple simultaneous interactions between the substrate and the active site to explain the remarkable efficiency which is normally observed.[1] This poses the intriguing question—do the different interactions operate cooperatively? That is, can a catalytic interaction have a bigger impact when it acts in concert with other complementary interactions than when it is used alone. This is difficult to mimic with simple compounds; usually when multiple interactions are introduced into a model system, it is found that they act independently rather than simultaneously, and such models generally do not rival enzyme efficiency.[2] Here we report how catalysis of phosphate monoester hydrolysis by an intramolecular OH group becomes much more effective when combined with catalysis by a dinuclear metal ion complex.

We have incorporated phosphate monoesters **1a**–**c** into dinuclear Co^{III} complexes **2a**–**c**. We have previously studied this type of complex as a structural and functional model for dinuclear metallophosphatases.[3] We wanted to investigate the effect of combining intramolecular general acid catalysis with this highly reactive core, as X-ray crystallography has revealed that as well as the metal ions in the active sites of metallophosphatase such as protein phosphatase-1 (PP-1) and kidney bean purple acid phosphatase (KBPAP), potential

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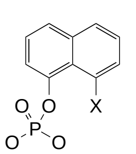
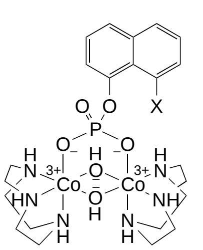


1a, X = H
1b, X = OH
1c, X = OMe



2a, X = H
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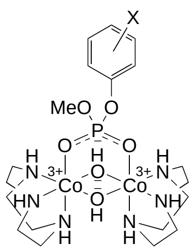
2c, X = OMe



3, X = 3 and/or 4 substituents

general acids are poised to protonate the leaving group.[4] It has previously been reported that amide hydrolysis promoted by a mononuclear Co^{III} complex can be accelerated an additional 60 fold by an intramolecular phenol in DMSO–water.[5] Similarly, ammonium groups acting in concert with a Cu^{II} complex provide an additional 1000-fold rate acceleration for phosphate diester hydrolysis in ethanol–water; however, this decreases to <100 fold if the water content is increased to 15%, and would presumably be even less in purely aqueous solution.[6]

Detailed studies on these complexes with bridging aryl phosphate monoesters[3, 7] and with bridging methyl aryl diesters (**3**)[8] show that hydrolysis of the phosphate ester occurs by intramolecular attack of a deprotonated μ-OH group which displaces the aryloxy group. With relatively poor leaving groups, base-catalyzed dissociation of the phosphate group from the complex is also observed in parallel with (or instead of) hydrolysis. Complexes **2a** and **2c** behave just as expected from these closely related studies. Complex **2a**, whose leaving group has a pK_a of 9.4,[9] undergoes both base-catalyzed hydrolysis ($k_{HO} = 0.24 \pm 0.01\,\text{M}^{-1}\,\text{s}^{-1}$) and dissociation ($k_{HO} = 0.17 \pm 0.01\,\text{M}^{-1}\,\text{s}^{-1}$) in a ratio of 59:41. Complex **2c** has a leaving group whose pK_a is 11.4[10] and thus the ester dissociates from the complex with $k_{HO} = 0.11 \pm 0.01\,\text{M}^{-1}\,\text{s}^{-1}$ and without any observable hydrolysis.

^{31}P and ^{1}H NMR spectroscopy show that **2b** predominantly hydrolyzes in wholly aqueous solution to give **4** (Scheme 1) and leave inorganic phosphate bridging the Co^{III} ions in the complex **5**. Interestingly, we also observe that about 5% of the product is cyclic diester **6**. This arises because once deprotonated, the OH group can act as an efficient intramolecular nucleophile, displacing CoO^{2-} from the phosphate (Scheme 1). Once the monodentate diester is formed, this can partition between starting complex and dissociation; we do not observe this species accumulating.

The pH-rate profile (Figure 1) shows that the rate of reaction of **2b** increases with pH until it reaches a plateau

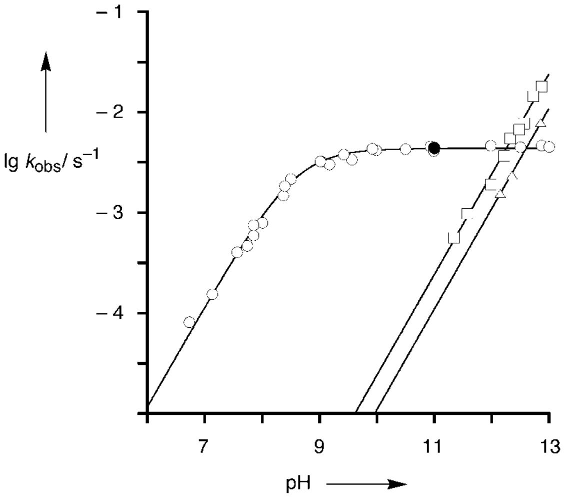
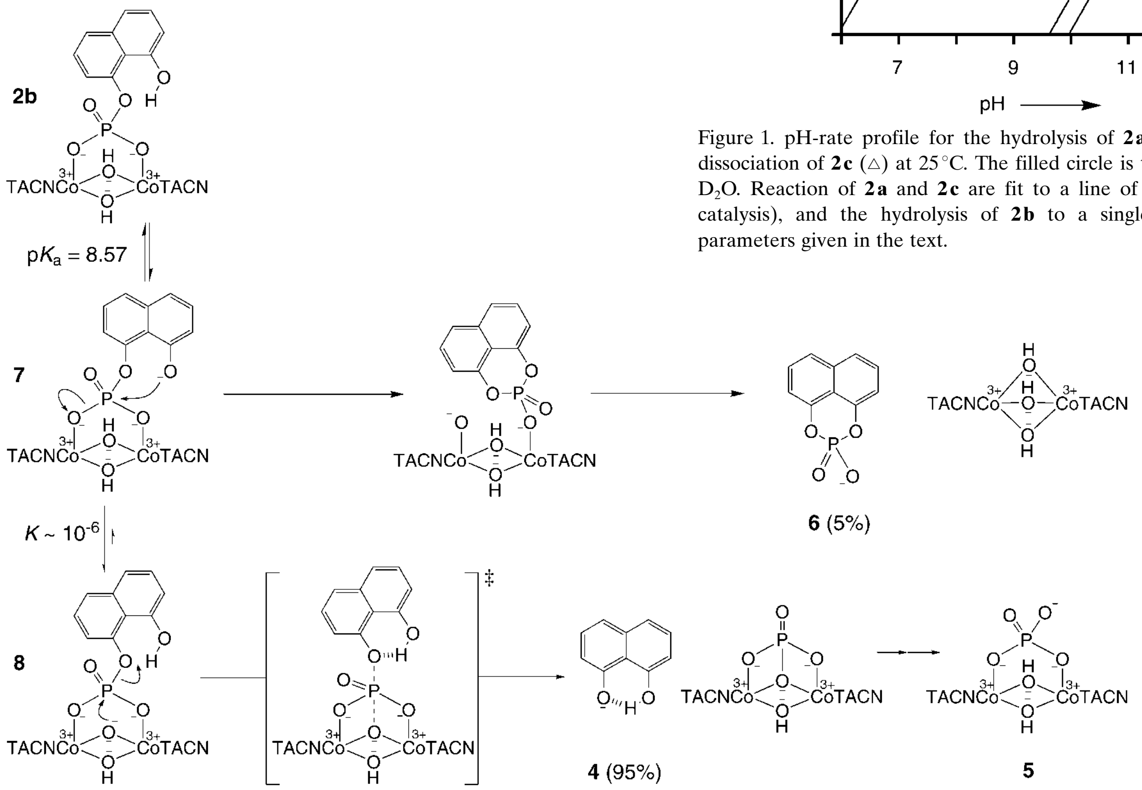


Figure 1. pH-rate profile for the hydrolysis of **2a** (□) and **2b** (○), and dissociation of **2c** (△) at 25 °C. The filled circle is the hydrolysis of **2b** in D$_2$O. Reaction of **2a** and **2c** are fit to a line of slope 1 (specific base catalysis), and the hydrolysis of **2b** to a single ionization with the parameters given in the text.



Scheme 1. Proposed mechanism for the reaction of **2b**. TACN = 1,4,7-triazacyclononane.

around pH 9. We assign this pH dependence to the ionization of the ArOH group which means that the observed rate is proportional to the concentration of **7**. Nonlinear least-squares regression gives the pK_a value as 8.57 ± 0.02, and the plateau rate constant as $0.0044 \pm 0.0001\ s^{-1}$. Spectroscopic titration of **2b** confirms that the ArOH group has a pK_a of 8.55 ± 0.03, in excellent agreement with the kinetically determined pK_a value. Based on the mechanism of the closely related aryl phosphate monoester complexes, we propose that hydrolysis proceeds through the (kinetically equivalent) minor tautomer **8** as shown in Scheme 1. Consistent with this interpretation, the solvent isotope effect (at pD = 11) is 1.0. Displacement of the naphthalenediol dianion in this pH range is not observed because this is a much poorer leaving group (the pK_a of **4** is > 13[9]).

As the dianion of a phenyl phosphate with a leaving group pK_a value of 9.4 has an estimated rate constant for hydrolysis of $3 \times 10^{-12}\ s^{-1}$ at 39 °C,[11] the rate on the plateau represents a $> 10^9$-fold rate acceleration. However, as the pK_a value of the bridging OH group is at least six units higher than the ArOH,[3] only about 0.0001 % of the substrate is in the reactive tautomer in the pH-independent region. This means that the first-order rate constant for the reaction of **8** is about $4000\ s^{-1}$ at 25 °C which corresponds to a rate acceleration of approximately 10^{15} fold.

Proton transfer is an essential part of most transformations, and although it is assumed to be efficiently carried out by enzymes it has proved to be a difficult process to model effectively in aqueous solution.[12] Jencks has suggested that a requirement for general acid catalysis to play a significant catalytic role in solution is the "libido" rule. If the leaving group is less basic than the general acid in the starting material, but becomes more basic in the product, then there is a thermodynamic benefit to catalyzing the reaction by transferring the proton from acid to leaving group in the course of the reaction.[13] This contributes to effective catalysis without any requirement for special properties of hydrogen bonds in the transition state, as has been the subject of recent debate.[14] In our complex, the pK_a value of the general acid and the leaving group are identical in the product, so the rule is not obeyed and the intramolecular OH group can only contribute to catalysis by hydrogen-bond formation.

However, within the complex, the OH group accelerates specific base-catalyzed hydrolysis of the monoester very effectively (below pH 8, the reaction is specific base-catalyzed with $k_{HO} = 1160 \pm 50\ M^{-1}s^{-1}$). Compared to the H analogue **2a**, hydrolysis is accelerated 5000 fold, and compared to the OMe analogue **2c**, more than 50000 fold.

It is possible that the OH group could accelerate attack at the phosphate group by protonating the P=O unit to catalyze the formation of a pentacoordinate intermediate similarly to the suggested "triester-like" mechanism for RNA transesterification.[15] However, we note that in the diester complex **3** which models the reactivity of a fully protonated P=O unit, k_{HO} is approximately $20\ M^{-1}s^{-1}$[8] for a leaving group with a pK_a value of 9.4 which is about 60 fold slower than **2b**. Hence, the OH group is not accelerating the reaction by protonating the P=O unit of the ester. Increasing the steric hindrance near the labile bond also needs to be considered in case this makes a partial contribution to the overall acceleration. However, we note that in fact **2a** hydrolyzes about fourfold slower than an aryl phosphate complex with a leaving group with the same pK_a value but without substituents in the 2-position,[3] showing that increasing steric hindrance destabilizes the transition state slightly more than the ground state. Hence, substituents in the 8-position of the 1-naphthol leaving group will inhibit rather than accelerate the rate of reaction.

When the monoester **1b** is not bound to the complex, it is only hydrolyzed tenfold faster than **1c**.[16] This is consistent with other data which also show that an adjacent OH group of similar pK_a value to the leaving group provides only approximately tenfold rate acceleration (in carboxylic ester hydrolysis[17] and phosphate triester hydrolysis[18]). In phosphate monoester dianion hydrolysis in solution, the bond to the leaving group is largely broken, with an estimated charge of -0.88 on the leaving group O atom in the transition state,[3] and so the scope for the OH group to play a role might be expected to be greatest. Thus, it is particularly striking that the effect of the adjacent hydroxy group is so much greater in this complex. Within complex **2**, the extent of bond cleavage in the transition state is considerably less, giving an estimated charge of -0.36 on the leaving group O atom in the transition state,[3] but the catalytic effect is much greater.

In conclusion, combining several functional groups to promote phosphate monoester hydrolysis has revealed a large catalytic role for a carefully positioned OH group, even though it doesn't obey the libido rule. In energetic terms, the effect of the adjacent OH group on the transition state (5000-fold rate acceleration $\sim 21\ kJ\,mol^{-1}$) is actually greater than in the product anion (the first pK_a of 1,8-naphthalenediol is 6.6,[9] 2.8 units lower than 1-naphthol $\sim 16\ kJ\,mol^{-1}$)[19] despite only partial charge development at the leaving group.

Experimental Section

The hydrolysis of complexes **2a**, **2b**, and **2c** (0.05 mM) at 25 °C in aqueous buffers (50 mM HEPES, EPPS, CHES, or CAPS, $I = 0.1$ M (NaClO$_4$); or dilute NaOH, $I = 0.1$ M (NaClO$_4$)) were monitored by following the changes in UV/Vis absorbance using a Cary 1Bio spectrometer with a thermostatted cell holder. Reactions were initiated by the addition of 0.05 mL of a stock solution of the substrate to 3 mL of the buffer which had been equilibrated in the cell compartment for at least 20 min. pH values were measured after each reaction and did not change from the previously measured pH value of each buffer. Isosbestic points and good first-order kinetics for at least three half lives were observed in each case. Pseudo-first-order rate constants were obtained by fitting the change in absorbance (at 317, 341, and 286 nm for **2a**, **2b**, and **2c**, respectively) with time to an exponential function by nonlinear least-squares regression. The products were identified by comparison of the ^{1}H and ^{31}P NMR spectra with those of authentic samples, and ratios were determined by integration of the ^{1}H NMR spectra. The pK_a values of 1-naphthol (9.43 ± 0.02) and 1,8-dihydroxynaphthol (6.59 ± 0.04; second p$K_a > 13$) were determined by spectroscopic titration at 341 nm under our conditions ($I = 0.1$ M (NaClO$_4$), 25 °C) and correspond with literature values.[9] The pK_a value of **2b** (8.55 ± 0.03) was determined similarly; in this case, due to the rate of hydrolysis, it was necessary to extrapolate the observed absorbance back to the time of mixing to evaluate the absorbance of **2b** at various pH values. These extrapolations were for ≤ 20 s and were obtained by using the same first-order exponential curve fitting as for the kinetic measurements over ≥ 5 half lives (≥ 770 s). Complex **1a** was obtained from Aldrich and used as received. Complexes **1b**, **1c** and **2** were synthesized according to previously reported methods.[3, 16]

2a: ^{1}H NMR (250 MHz, D_2O): $\delta = 2.5-2.75$ (12H, m; CH_2), 3.05–3.35 (12H, m; CH_2), 6.05 (2H, bs; NH), 6.30 (2H, bs; NH), 6.70 (2H, bs; NH), 7.40 (1H, d, $J = 7.82$ Hz; ArH), 7.50 (1H, t, $J = 7.82$ Hz; ArH), 7.58–7.67 (2H, m; ArH), 7.75 (1H, d, $J = 7.82$ Hz; ArH), 7.95–8.03 (1H, m; ArH), 8.22–8.30 (1H, m; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 14.1$, ESMS: 831 [MH^+], 731 [$M - ClO_4^-$], 631 [$M - ClO_4^- - HClO_4$].

2b: ^{1}H NMR (400 MHz, D_2O): $\delta = 2.40-2.65$ (12H, m; CH_2), 2.95–3.15 (12H, m; CH_2), 6.20 (2H, bs; NH), 6.27 (2H, bs; NH), 6.53 (2H, bs; NH), 6.90 (1H, d, $J = 7.70$ Hz; ArH), 7.28 (1H, d, $J = 7.70$ Hz; ArH), 7.30–7.38 (2H, m; ArH), 7.44 (1H, d, $J = 9.30$ Hz; ArH), 7.58 (1H, d, $J = 9.30$ Hz; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 13.0$, ESMS: 847 [MH^+], 747 [$M - ClO_4^-$], 647 [$M - ClO_4^- - HClO_4$].

2c: ^{1}H NMR (250 MHz, D_2O): $\delta = 2.5-2.75$ (12H, m; CH_2), 3.05–3.35 (12H, m; CH_2), 3.95 (3H, s; OMe), 6.20 (2H, bs; NH), 6.60 (2H, bs; NH), 6.85 (2H, bs; NH), 7.08 (1H, d, $J = 7.70$ Hz; ArH), 7.33 (1H, d, $J = 7.70$ Hz; ArH), 7.42–7.60 (3H, m; ArH), 7.75 (1H, d, $J = 9.30$ Hz; ArH); ^{31}P NMR (160 MHz, D_2O): $\delta = 11.9$.

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