4 for complexes **1** and **5** and for only one pyridine ligand. The difference between the former total electronic energy and two times the energy for a single pyridine gave an estimate of the interaction energy. This is the interaction between two *undistorted* Fe$_3$O complexes as a result of their two pyridine ligands overlapping. The values for the interaction energies are as follows: 0.44 Kcal/mol for C$_6$H$_6$ solvate **4**; 0.88 kcal/mol for pyridine solvate **6**; 1.11 kcal/mol for CHCl$_3$ solvate **5**; and 1.22 kcal/mol for the CHCl$_3$ solvate **1**. This is a variation of 0.78 kcal/mol (= 270 cm^{-1}), a quantity which is comparable to the quantum of the e$_g$ Fe$_3$O stretching mode which is coupled to the electronic coordinates in these complexes.

Concluding Comments

For the series of *R*32-symmetry complexes [Fe$_3$O(O$_2$CCH$_3$)$_6$(L)$_3$]S onset of intramolecular electron transfer occurs cooperatively in a phase transition. It seems likely that changing the solvate molecule leads to changes in the intermolecular interactions via the pyridine–pyridine overlaps.

It is also generally found that the onset of dynamics of the solvate molecule occurs in the same phase transition which involves an increase in the rate of electron transfer. Since the phase transition is a cooperative process, it is not perhaps appropriate to ask whether the onset of solvate molecule motion causes an increase in the rate of electron transfer or vice versa. However, it is fascinating that even a solvate molecule such as the C_3 symmetry CHCl$_3$ molecule moves seemingly synchronously with the vibronic coordinate changes occurring in neighboring Fe$_3$O molecules in complex **5**.

The van der Waals interaction between a solvate molecule S which is positioned asymmetrically relative to the C_3 axis of a nearby Fe$_3$O complex may lead to an interaction energy of only 10–100 cm^{-1} per solvate molecule. However, this amount of Fe$_3$O···S interaction may be large enough to modify the ground-state potential energy surface for a Fe$_3$O complex to appreciably affect the rate at which such a complex can tunnel from one vibronic minimum to another. It would be very instructive if one could employ laser flash photolysis on an asymmetric complex such as [Co^{II}Fe$_2$^{III}O(O$_2$CCH$_3$)$_6$(py)$_3$](py) to measure the rate of electron transfer (Co^{II} → Fe^{III}) as a function of whether the pyridine solvate molecules are or are not rapidly jumping between the three positions on the C_3 axis. We have already established[31] with heat capacity measurements on this Co^{II}Fe$_2$^{III}O complex that it does have a phase transition which involves the onset of pyridine solvate dynamics.

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Supplementary Material Available: Tables of bond lengths and angles, anisotropic thermal parameters, and hydrogen atom coordinates and thermal parameters for [Fe$_3$O(O$_2$CCH$_3$)$_6$(4-Me-py)$_3$(CHCl$_3$) (**1**) and [Fe$_3$O(O$_2$CCH$_3$)$_6$(py)$_3$](CHCl$_3$) (**5**) (3 pages); listings of structure factor amplitudes for **1** and **3** (15 pages). Ordering information is given on any current masthead page.

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[31] Sorai, M.; Kaji, K.; Jang, H. G.; Hendrickson, D. N. Manuscript in preparation.

Co(III) Complex Promoted Hydrolysis of Phosphate Diesters: Comparison in Reactivity of Rigid *cis*-Diaquotetraazacobalt(III) Complexes

Jik Chin,* Mariusz Banaszczyk, Vrej Jubian, and Xiang Zou

Contribution from the Department of Chemistry, McGill University, Montreal, Canada H3A 2K6.

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Abstract: The efficiencies of three rigidly held *cis*-aquohydroxotetraazacobalt(III) complexes [(cyclen)Co(OH)(OH$_2$)]$^{2+}$, [(tren)Co(OH)(OH$_2$)]$^{2+}$, [(trpn)Co(OH)(OH$_2$)]$^{2+}$ in promoting the hydrolysis of bis(*p*-nitrophenyl)phosphate (BNPP) have been compared. In neutral water at 50 °C, the rate constant for hydrolysis of the phosphate diester bond in [(cyclen)Co(OH)(BNPP)]$^+$, [(tren)Co(OH)(BNPP)]$^+$, [(trpn)Co(OH)(BNPP)]$^+$ are 4.6×10^{-1}, 8.1×10^{-3}, and 2.5 s^{-1}, respectively. [(trpn)Co(OH)(BNPP)]$^+$ is hydrolyzed at about the same rate as BNPP bound to a real enzyme from *Enterobacter aerogenes* and about 10^{10} times more rapidly than free BNPP. The dramatic increase in the activity of the Co(III) complex with change in the tetraamine ligand structure can be explained in terms of a detailed mechanism of the reaction.

Currently there is considerable interest in developing catalysts that can cleave DNA sequence specifically. Due to the stability of the DNA phosphate diester backbone toward hydrolytic cleavage, emphasis to date has been mainly focused on oxidative cleavage of DNA.[1] A major challenge remains in developing catalysts that can cleave DNA hydrolytically.[2] We recently showed that Co(III) complexes can be by far the most efficient in promoting the hydrolysis of phosphate diesters with good[3] or poor leaving groups.[4] Interestingly, the activity of the cobalt complexes is sensitive to the tetraamine ligand structure. For

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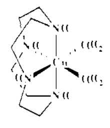
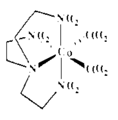
example, $[(trien)Co(OH)(OH_2)]^{2+}$ is more reactive than $[(en)_2Co(OH)(OH_2)]^{2+}$. However, it is difficult to evaluate the structure-reactivity relationship in this system because both cobalt complexes undergo rapid cis–trans equilibration with the trans forms being inactive. We now compare the reactivities of **1**, **2**, and **3** in promoting the hydrolysis of bis(*p*-nitrophenyl) phosphate (BNPP). **1**, **2**, and **3** are ideal for evaluating the structure-reactivity relationship since they are held rigidly in the cis form[5] and cannot undergo cis–trans or other similar isomerization processes.



1



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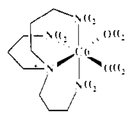

3

Experimental Section

Instruments. ^1H NMR and ^{31}P NMR were taken on a Varian XL-300 and XL-200 spectrometers.

Kinetic studies were carried out by a UV–vis method with a Hewlett-Packard 8451 diode array spectrophotometer equipped with a Lauda RM6 thermostat.

Titrations of the Co(III) complexes were carried out with a Radiometer PHM63 pH meter equipped with a Radiometer RTS822 automatic titrator.

Materials. Bis(*p*-nitrophenyl)phosphate (BNPP) was purchased from Sigma. Tris(2-aminoethyl)amine (tren) was purchased from Aldrich. $[Co(cyclen)Cl_2)]Cl$[6] and $[Co(tren)Cl_2]Cl$[7] were prepared according to well-known procedures (cyclen:1,4,7,10-tetraazacyclododecane). Bis(2,4-dinitrophenyl)phosphate (BDNPP) was synthesized by the method of Milburn et al.[8]

Tris(3-aminopropyl)amine (trpn). This compound had been synthesized previously in 40% yield.[9] The following procedure gave quantitative yield of tris(3-aminopropyl)amine. Tris(2-cyanoethyl)amine (6.13 g) and 3.3 g of Raney nickel slurry were added to a 250-mL glass hydrogenation vessel containing a solution of 2.33 g of NaOH in 83 mL of 95% ethanol. The mixture was placed under hydrogen (40 psi) in a Parr hydrogenation apparatus and shaken until hydrogen uptake was complete (approximately 7 h). The catalyst was vacuum filtered and rinsed with 95% ethanol. Ethanol was evaporated, and the residue was extracted with methylene chloride. The organic layer was dried over NaOH, filtered through anhydrous aluminum oxide, and evaporated. The crude product was distilled (bp 118 °C, 0.1 mm): ^1H NMR (200 MHz, $CDCl_3$, (TMS)) 1.15 (6 H, s), 1.59 (6 H, q), 2.45 (6 H, t), 2.72 (6 H, t).

$[Co(trpn)Cl_2]Cl$. To a methanolic solution of $CoCl_26H_2O$ (0.47 g), a solution of tris(3-aminopropyl)amine (0.37 g) in methanol (20 mL) was added dropwise. The solution mixture was aerated with CO_2 free, dry air for 2 h followed by slow addition of HCl gas until some green precipitate formed. After cooling the mixture in a refrigerator overnight, the precipitate was filtered and rinsed with absolute ethanol and ether and vacuum dried over P_2O_5 (yield 35%).

Anal. Calcd for $C_9H_{24}N_4CoCl_3$: C, 30.06; H, 6.84; N, 15.84; Co, 16.67; Cl, 30.08. Found: C, 29.71; H, 6.55; N, 15.88; Co, 16.83; Cl, 30.25.

Kinetics. The hydrolysis of BNPP was monitored by following the visible absorbance change at 400 nm. The reactions were carried out under pseudo-first-order conditions with a large excess of the cobalt complex over the phosphate ester. *p*-Nitrophenol (2 equiv) is released with no observable accumulation of the phosphate monoester intermediate. The rate constants were obtained by fitting the first 3 half-lives of the reaction according to a first-order kinetics equation (correlation coefficient >0.995). Each kinetic run was reproducible to within 3% error. In a typical kinetics experiment, 0.01 M $[(trpn)Co(OH)(OH_2)]^{2+}/[(trpn)Co(OH_2)_2]^{3+}$ solution in water was prepared by adding 1.5 equiv of NaOH to $[Co(trpn)Cl_2]Cl$. After 5 min (1 h for $[Co(tren)Cl_2]Cl$) the solution pH was adjusted to 7.0. The rate of aquation of $[(N_4)CoCl_2]Cl$ is sensitive to the tetraamine ligand structure.[10] Completion of aquation was confirmed by visible absorption spectra. The hydrolysis of BNPP was initiated by addition of 5 μL of a 0.01 M BNPP stock solution in water to 3 mL of the freshly prepared 0.01 M cobalt complex solution at 50 °C. The pH of the reaction solution did not change appreciably (pH 7.0 ± 0.2) during the course of the hydrolysis reaction due to the buffering effect of the cobalt complex solution. Addition of $NaClO_4$ (0.1 M) had no appreciable effect on the rate of the hydrolysis reaction. The rate constants for anation of $[(trpn)Co(OH)(OH_2)]^{2+}$, $[(tren)Co(OH)(OH_2)]^{2+}$, and $[(cyclen)Co(OH)(OH_2)]^{2+}$ with inorganic phosphate was obtained by monitoring the increase in the absorbance at 540 nm. The experimental condition for anation of the cobalt complexes and the experimental condition for the cobalt complex promoted hydrolysis of BDNPP was the same as that for the cobalt complex promoted hydrolysis of BNPP.

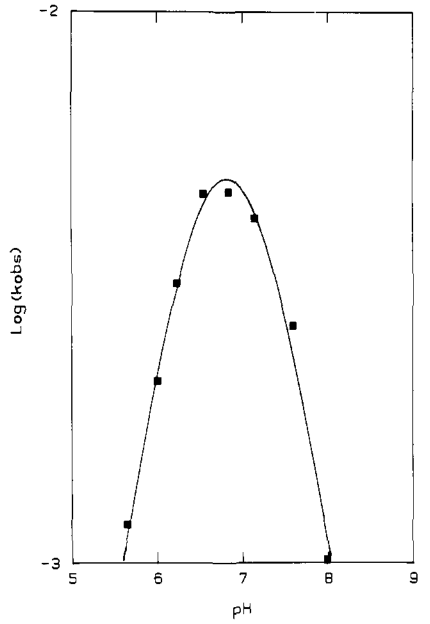

Figure 1. pH-rate profile for **1** (0.01 M) promoted hydrolysis of BNPP (10^{-5} M) at 50 °C.

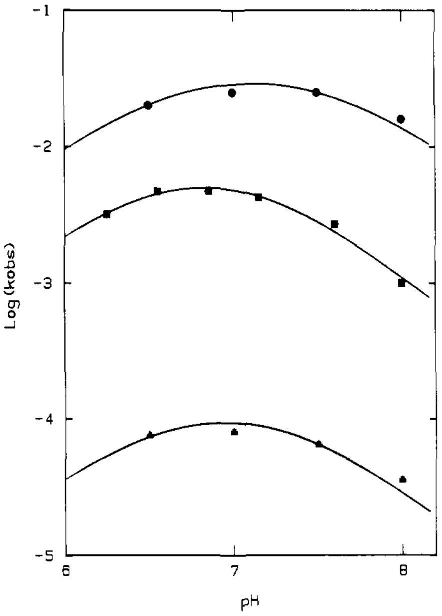

Figure 2. pH-rate profile for **1** (■), **2** (▲), and **3** (●) (0.01 M) promoted hydrolysis of BNPP (10^{-5} M) at 50 °C.

Equilibrium. The equilibrium constant for anation of $[(N_4)Co(OH_2)_2](ClO_4)_3$ with dimethyl phosphate was measured by ^{31}P NMR (Figure 4). Best results were obtained when 1:1 ratio (0.1 M) of $[(N_4)Co(OH_2)_2](ClO_4)_3$ and sodium dimethyl phosphate were allowed to react in D_2O. Equilibrium was established within half an hour for **1** and **3** and within a day for **2** at 20 °C.

Titration. A 10-mL, (10^{-3} M) solution of $[(N_4)Co(OH_2)_2]^{3+}$ in water (25 °C) was titrated with a 0.01 M NaOH solution. The ionic strength was maintained at 0.1 M with $NaClO_4$.

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Table I. Observed First-Order Rate Constants for Reactions of **1**, **2**, and **3** (10^{-2} M) with BNPP, BDNPP, and Inorganic Phosphate (10^{-5} M) at pH 7.0, 50 °C[b]

	BNPP	BDNPP	PHOS	k_2
1	4.6×10^{-3}	1.1×10^{-2}	8.7×10^{-2} [a]	4.6×10^{-1}
2	8.1×10^{-5}	1.6×10^{-3}	2.5×10^{-2}	8.1×10^{-3}
3	2.5×10^{-2}	1.1×10^{-1} [a]	1.2[a]	2.5

[a] At 25 °C. [b] k_2 is as defined in Scheme **II**.

Table II. First and Second Acid Dissociation Constants of **1**, **2**, and **3**

	1	**2**	**3**
pK_{a1}	5.6	5.5	4.8
pK_{a2}	8.0	8.0	7.6

Results

The pH rate profiles for **1**, **2**, and **3** promoted hydrolysis of BNPP is shown in Figures 1 and 2. The data were fit according to eq 1 (see Discussion) with a curve-fitting program based on the Newton–Raphson algorithm (**1**: $k = 5.4 \times 10^{-1}$ M^{-1} s^{-1}, $K_{a1} = 3.0 \times 10^{-6}$, $K_{a2} = 3.4 \times 10^{-8}$; **2**: $k = 9.2 \times 10^{-3}$ M^{-1} s^{-1}, $K_{a1} = 3.0 \times 10^{-6}$, $K_{a2} = 1.5 \times 10^{-8}$; **3**: $k = 2.6$ M^{-1} s^{-1}, $K_{a1} = 3.0 \times 10^{-6}$, $K_{a2} = 5.3 \times 10^{-9}$). The rate of hydrolysis of BNPP increases linearly with increase in concentration of the cobalt complexes (Figure 3). The slopes for **1**, **2**, and **3** promoted hydrolysis of BNPP are, respectively, 4.38×10^{-1} M^{-1} s^{-1}, 8.14×10^{-3} M^{-1} s^{-1}, and 3.00 M^{-1} s^{-1} (correlation coefficient >0.999). Table I shows the observed first-order rate constants for the reactions of **1**, **2**, and **3** with BNPP, BDNPP, and with inorganic phosphate.

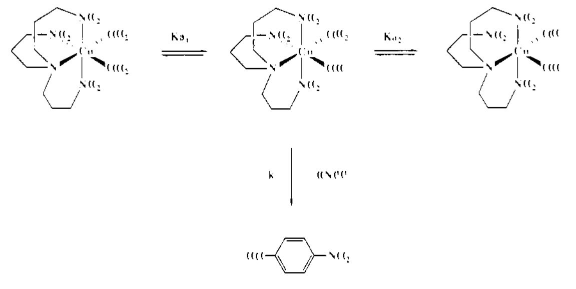
The equilibrium constants for anation of **1**, **2**, and **3** with dimethyl phosphate, as measured by ^{31}P NMR, are 4 ± 1 M^{-1} for all three complexes. Figure 4 shows a typical NMR experimental result for binding of dimethyl phosphate to $[(trpn)Co(OH_2)_2]^{3+}$. Two isomers are possible for the cobalt bound phosphate diester $[(trpn)Co(OH_2)(OP(O)(OCH_3)_2)]^{2+}$ (^{31}P NMR (200 MHz, D_2O, trimethyl phosphate) δ 6.4, 6.7): one isomer with the phosphate ester adjacent to the tertiary nitrogen and the other isomers with the phosphate ester adjacent to the primary amine. Upon addition of excess dimethyl phosphate, two more NMR signals appear at 4.9 and 5.2 corresponding to the diadduct $[(trpn)Co(OP(O)(OCH_3)_2)_2]^+$. ^{31}P NMR of dimethyl phosphate with the cobalt complexes is very simple compared to ^{31}P NMR of ATP or triphosphate with cobalt complexes.[11] ATP and triphosphate being polyanionic have multiple interaction sites for the metal complexes, whereas dimethyl phosphate has only one interaction site.

The acid dissociation constants for the two water molecules bound to **1**, **2**, and **3** are listed on Table II. The pK_a values were reproducible to within 0.05 pH units.

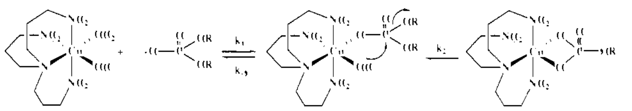
Discussion

About 20 years ago, Spiro et al.[12] showed that $[(trien)Co(OH)(OH_2)]^{2+}$ promotes the hydrolysis of phosphate monoesters (trien:triethylenetetraamine). Since then numerous articles have been written on various Co(III) complex promoted hydrolysis of phosphate monoesters.[13] For example, Cornelius and Norman[14] studied **1** promoted hydrolysis of triphosphate. Milburn's group[15] studied **2** promoted hydrolysis of diphosphate as well as **3** promoted hydrolysis of ATP. We[3,4] recently showed that Co(III) complexes give a much greater rate acceleration for the hydrolysis of phosphate diesters than for the hydrolysis of phosphate monoesters. Further, Co(III) complexes are much more reactive than any other types of man-made catalysts[16] in promoting the hydrolysis of phosphate diesters. Limited studies on the effect of the tetraamine ligand structure on the efficiency of the Co(III) complex promoted hydrolysis of ATP when anation is the rate-determining step had been reported.[17] It is well known that the rate of anation of Co(III) complexes is highly sensitive to the tetraamine ligand structure.[10] Systematic studies on the effect of the tetraamine ligand structure on the efficiency of the Co(III) complex when anation is not the rate-determining step had not been done previous to this work. **1**, **2**, and **3** are ideal for studying such structure-reactivity relationship since they exist only in the active, cis form. **1** exists only in the cis form because of the small ring size of cyclen.[5] **2** and **3** exist only in the cis form for obvious structural requirements. BNPP is a suitable model for DNA since Co(III) complexes give comparable rate enhancements for the hydrolysis of phosphate diesters with good and poor leaving groups.[3,4]

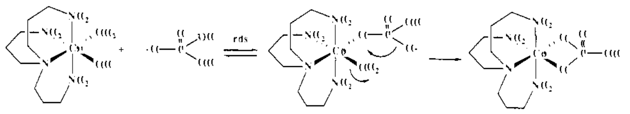
Scheme I



Scheme II



Scheme III



In solution, each of the cobalt complexes **1**, **2**, and **3** exists in three different protonation states (Scheme I). The first and second acid dissociation constants (K_{a1},K_{a2}) of the cobalt complexes are listed on Table II. It is apparent from the bell-shaped pH-rate profile (Figure 1) that the cobalt aquo–hydroxo form is the active species that promotes the hydrolysis of bis(*p*-nitrophenyl)phosphate (BNPP). The observed rate constant (k_{obsd}) for *p*-nitrophenol production in Scheme I is given by eq 1 where $[Co]_T$ is the total cobalt complex concentration. The pH-rate profiles (Figures 1 and 2) were fit according to eq 1 with a curve-fitting program

$$k_{obsd} = k[Co]_T/(1 + [H]/K_{a1} + K_{a2}/[H]) \qquad (1)$$

based on the Newton–Raphson algorithm. The acid dissociation constants obtained from the pH-rate profiles (Results) are only approximately equal to those obtained by direct titration (Table II) since the two experimental conditions are quite different.

The mechanism for the cobalt aquo–hydroxo complex promoted hydrolysis of BNPP is shown in Scheme II.[4] Under our experimental conditions the phosphate monodentate intermediate must be a steady intermediate since the rate of production of *p*-nitro-

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phenol increases linearly with increase in the concentration of the cobalt complex (Figure 3). Since the hydrolysis reaction is first order with respect to the cobalt complex, only one cobalt complex should be involved in the mechanism. The rate constant k in Scheme I can be expressed in terms of the rate constants in Scheme II (eq 2). If $k_{-1} \gg k_2$, then k_2 is the rate-determining step and $k = K_1k_2$ where $K_1 = k_1/k_{-1}$. If $k_{-1} \ll k_2$, anation (k_1 step) is the rate-determining step and $k = k_1$.

$$k = K_1k_2/(k_{-1} + k_2) \qquad (2)$$

It can be shown that the anation step (k_1, Scheme II) is too fast to be the rate-determining step. k_1 cannot be measured directly. However, it is well known that the rate of anation of Co(III) complexes is independent of the basicity of the anionic nucleophile.[18] The rate of anation of **1**, **2**, and **3** with inorganic phosphate can be measured readily following published procedures.[19] The reaction of *cis*-$[(N_4)Co(OH)(OH_2)]^{2+}$ with inorganic phosphate involves rate-determining anation followed by rapid ring closure via the Co–O bond cleavage (Scheme III). The four-membered ring product has a characteristic absorbance at 540 nm. The Co(III) complexes **1**, **2**, and **3** react with inorganic phosphate much more rapidly than with BNPP (Table I). Therefore k_1 step (Scheme II) cannot be the rate determining for **1**, **2**, or **3** promoted hydrolysis of BNPP and eq 2 is reduced to eq 3. Another evidence that k_1 is not the rate-determining step

$$k = k_1k_2 \qquad (3)$$

is that the cobalt complexes hydrolyze BDNPP (bis(2,4-dinitrophenyl)phosphate) much more rapidly than BNPP (Table I). The mechanism for cobalt complex promoted hydrolysis of BDNPP is analogous to that for the cobalt complex promoted hydrolysis of BNPP. If k_1 is the rate-determining step, the rates of cobalt complex promoted hydrolysis of BDNPP and BNPP should be comparable. Since the cobalt complexes react considerably more rapidly with BDNPP than with BNPP, k_1 cannot be the rate-determining step (Table I).

In neutral water, the rate of hydrolysis of BNPP at 50 °C is too slow to be measured directly. However the rates could be measured directly at 80 °C, 90 °C, and 100 °C following known procedures[20] ($k = 1.0 \times 10^{-8}$ s^{-1}, 2.5×10^{-8} s^{-1}, and 6.5×10^{-8} s^{-1}, respectively). The activation enthalpy and entropy for the hydrolysis reaction are 24.8 Kcal and −25.4 eu. The rate constant at 50 °C calculated from the activation parameters is 3×10^{-10} s^{-1}. With added cobalt complex (10 mM **1**, **2**, or **3**) the observed rate constant for hydrolysis of BNPP is increased 10^5–10^8-fold depending on the cobalt complex used (Table I). The difference in the reactivity of the cobalt complexes may be due to the difference in the equilibrium constants for binding of BNPP to the cobalt complexes (K_1) or to the difference in the reactivity of BNPP bound to the cobalt complexes (k_2). It is clear from the titration studies that the equilibrium constants for binding of hydroxide, an anionic nucleophile, to the three cobalt complexes are comparable (Table I). Furthermore, we find that the equilibrium constants for binding of dimethyl phosphate to the cobalt diaquo complexes (**1**, **2**, or **3**) as measured by ^{31}P NMR (Figure 4) are comparable (4 ± 1 M^{-1}). This value is also close to the equilibrium constant for binding of $-OP(O)(OH)_2$ to $[(NH_3)_5Co(OH_2)]^{3+}$ (8 M^{-1}).[21] The equilibrium constant for binding of dimethyl phosphate to the cobalt aquo–hydroxo complexes of **1**, **2**, and **3** should be somewhat less than that for binding of dimethyl phosphate to the corresponding cobalt diaquo complexes. Binding of dimethyl phosphate to the cobalt aquo–hydroxo complexes could not be measured directly due to significant dimerization of the aquo–hydroxo complexes at 0.1 M concentration.[22] We have previously estimated the equilibrium constant for binding of phosphate diesters to cobalt aquo–hydroxo complexes (1 M^{-1}).[4] Under our experimental conditions (10 mM **1**, **2**, or **3**), about 99% of BNPP is in the free form and 1% in the cobalt-bound form. It is also clear from Figure 3 that saturation of BNPP has not been reached at 0.01 M cobalt complex. BNPP bound to **3** is hydrolyzed an amazing 10^{10} times more rapidly than free BNPP and about 300 times more rapidly than BNPP bound to **2**, a close structural analogue of **3** (k_2, Table I).

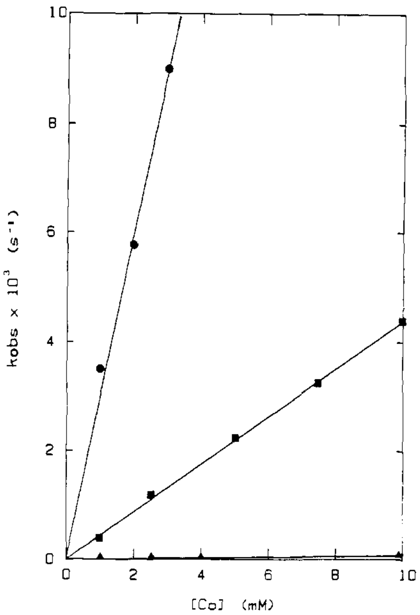

Figure 3. Effect of increasing the concentration of **1** (■), **2** (▲), and **3** (●) on the rate of the cobalt complex promoted hydrolysis of BNPP at pH 7.0, 50 °C.

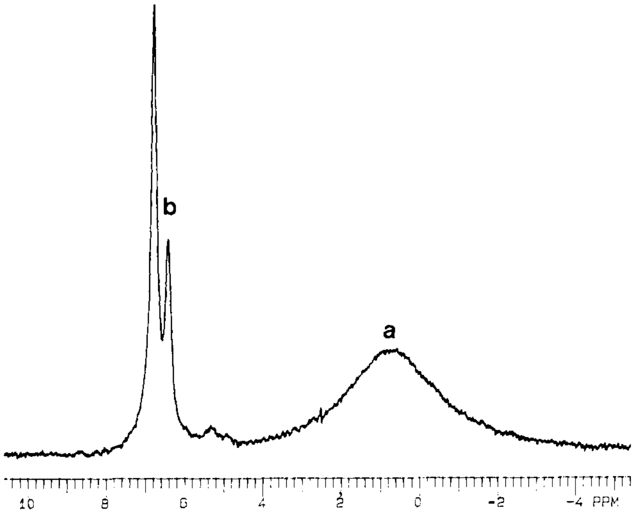

Figure 4. ^{31}P NMR for binding of dimethyl phosphate (0.1 M) to **3** (0.1 M) at 20 °C: (a) dimethyl phosphate and (b) $[(trpn)Co(OH_2)(OP(O)(OCH_3)_2]^+$.

It is surprising and interesting that the k_2 step is so sensitive to the tetraamine ligand structure. This striking dependence of the reactivity on the structure is indicative of an intramolecular nucleophilic mechanism.[23] Intramolecular general base mechanism would not result in such a structure-reactivity relationship.[23] Why should the k_2 step be so sensitive to the tetraamine ligand structure? The k_2 step involves formation of a four-membered ring. In general four-membered rings are unstable. However, four-membered rings involving Co(III) are relatively stable. For example, X-ray structures of four-membered Co(III) carbonato[24]

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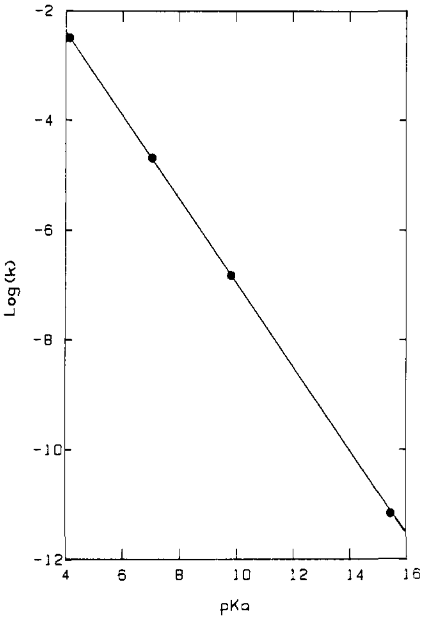

Figure 5. Linear free-energy relationship between the second-order rate constant for hydroxide-catalyzed hydrolysis of phosphate diesters at 25 °C and the pK_a of the conjugate acid of the leaving group. Data from ref 29.

and Co(III) phosphato[25] complexes are known. The O–Co–O bond angles of $[(\text{tren})\text{CoCO}_3]^+$ (68.5°)[26] and $[(\text{cyclen})\text{CoCO}_3]^+$ (68.4°)[27] are significantly reduced from the acyclic, NO_2–Co–NO_2 bond angles of $[(\text{tren})\text{Co}(\text{NO}_2)_2]^+$ (85.7°)[28] and $[(\text{cyclen})\text{Co}(\text{NO}_2)_2]^+$ (84.5°).[5] It is interesting to note that the angle opposite the O–Co–O bond angle in $[(\text{cyclen})\text{CoCO}_3]^+$ (103.1°) is about 8° larger than the corresponding angle in $[(\text{cyclen})\text{Co}(\text{NO}_2)_2]^+$ (95.4°). On the other hand, in a more rigid system, the angle opposite the O–Co–O bond angle in $[(\text{tren})\text{CoCO}_3]^+$ (87.9°) is about the same as the corresponding angle in $[(\text{tren})\text{Co}(\text{NO}_2)_2]^+$ (87.3°). It appears that a major factor in stabilizing the four-membered Co(III) complexes is increasing the bond angle opposite the four-membered ring.

Although BNPP bound to **3** is hydrolyzed an unprecedented 10^{10} times more rapidly than free BNPP, further rate enhancement is required to hydrolyze unactivated phosphate diesters within hours at 25 °C. The required rate enhancement factor can be estimated as follows. There is a linear free energy relationship between the rate of hydroxide-catalyzed hydrolysis of phosphate diesters at 25 °C and the basicity of the leaving group (Figure 5).[29] The fit is remarkably good (correlation coefficient = 0.9997)

$$\log k = 0.69 - 0.76\ \text{p}K_a \qquad (4)$$

considering that the plot spans about 12 orders of magnitude in the basicity of the leaving group and includes both alkyl and aryl leaving groups. It is also worth noting that the four data points on Figure 5 are from four different sources. Assuming that the pK_a of the 5′OH or 3′OH groups in 2′deoxynucleosides is about 13,[30] the observed rate constant for hydroxide-catalyzed hydrolysis of DNA at pH 7 should be about 10^{-16} s^{-1} (half life = 200 million years). In order to hydrolyze DNA in hours at 25 °C, a catalyst must increase this rate by a factor of 10^{12}.

In conclusion we have shown that rigid *cis*-diaquotetraazacobalt(III) complexes are highly reactive in promoting the hydrolysis of phosphate diesters. BNPP bound to $[(\text{trpn})\text{Co}(\text{OH})(\text{OH}_2)]^{2+}$ is hydrolyzed about 10^{10} times more rapidly than free BNPP under neutral pH conditions. By comparison, typical rate enhancement brought about by nonenzymic catalytic systems for hydrolysis of phosphate diesters is in the order of 10^3. Indeed, the reactivity of $[(\text{trpn})\text{Co}(\text{OH})(\text{BNPP})]^+$ is comparable to that of BNPP bound to a real enzyme from *Enterobacter aerogenes*.[31] Interestingly, the activity of the cobalt complexes changes dramatically with change in the tetraamine ligand structure even when anation is not the rate-determining step. Such ligand effect has not been observed previously. Two valuable pieces of information are obtained from the sharp structure-reactivity relationship. First, it shows that the reaction involves an intramolecular nucleophilic addition process. Second, it gives insight into the rational design of highly reactive Co(III) complexes.

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Registry No. 1, 117559-16-7; **2**, 75363-51-8; **3**, 117559-17-8; trpn, 4963-47-7; tren, 7528-78-1; BNPP, 645-15-8; $[\text{Co}(\text{trpn})\text{Cl}_2]\text{Cl}$, 117559-15-6; $CoCl_2$, 7646-79-9.

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