Inorg. Chem. **1999,** *38,* 6003−6007

Molecular Recognition of Activated and Unactivated Phosphate Diesters

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Received March 11, 1999

The molecular recognition of two simple phosphate diesters by a terpyridine−copper (TCu) complex was studied by X-ray crystallography and potentiometry. Molecular recognition of the substrate is the first step in a hydrolysis reaction. The two phosphate diesters bis(*p*-nitrophenyl) phosphate (BNP) and diphenyl phosphate (DPP) coordinate axially to an approximate square pyramidal copper complex where a chloride and three terpyridine nitrogens form the corners of the base. The coordination geometries are almost identical. The molecular recognition constants for the formation of TCu−BNP and TCu−DPP were measured potentiometrically and have log values of 1.2 and 2.5, respectively. By a significant margin, the TCu complex favors DPP over BNP in solution. A pH versus rate constant profile shows that TCu−OH can hydrolyze BNP but not DPP. Activated and unactivated phosphate diesters are typically hydrolyzed by similar mechanisms. In this study the difference in reactivity lies outside the process of molecular recognition. Activating (electron-withdrawing) effects of the *p*-nitro groups on the nature of the leaving groups must play an important role in the susceptibility of phosphate diesters to hydrolysis.

Introduction

There have been numerous model studies devoted to understanding how metalloenzymes hydrolyze phosphate diesters. The basic steps in the catalytic process involve (a) molecular recognition of the substrate, (b) generation of a hydroxide nucleophile, (c) preorganized attack on the phosphorus center by the nucleophile, and (d) stabilization and protonation of the negatively charged leaving group.[1] In most cases the substrate of choice is the “activated” phosphate diester bis(*p*-nitrophenyl) phosphate (BNP).[2] It is considered an activated phosphate diester because the *p*-nitro groups draw electron density away from the phosphorus center as well as help stabilize the negatively charged leaving group. Thus, activated phosphate diesters are more susceptible than unactivated phosphate diesters to a nucleophilic attack. BNP’s rate of spontaneous hydrolysis is ∼3 orders of magnitude larger than DPP’s (DPP = diphenyl phosphate) rate of spontaneous hydrolysis at pH 7.[3,4] Due to its relatively high rate constant, BNP is questioned as a viable substrate for model studies. Further credence was given to this argument by a report in the literature that showed a TCu complex could cleave RNA but not BNP.[5]

Our work studying TCu complexes has shown that the monohydroxo complex TCu−OH can indeed hydrolyze BNP. Although the rate enhancement over the uncatalyzed reaction is 230−500 (k_{obs}/k_{uncat}), it still takes 2−3 days to complete 1% of the reaction. The hydrolysis of the analogous, unactivated phosphate diester DPP is immeasurably slow under the same conditions. This makes TCu an ideal candidate for studying the first step in the catalytic hydrolysis of phosphate diesters, molecular recognition of the substrate. Crystal structures show BNP and DPP coordinate the TCu complex almost identically. Thermodynamically, molecular recognition by TCu favors DPP over BNP by 1.3 orders of magnitude.

Experimental Section

Caution. *Perchlorate salts are potentially explosive and should only be prepared in small quantities and handled with appropriate precautions.*

Materials. The following reagents were used: GR grade KCl from EM Chemical Co.; terpyridine, $Cu(ClO_4)_2$·$6H_2O$, $CuCl_2$·$2H_2O$, and bis(4-nitrophenyl) phosphate from Aldrich; CO_2-free Dilut-it ampules of KOH from J.T. Baker Inc.; diphenyl phosphate from TCI America; dehydrated 200-proof ethyl alcohol from McCormick Distilling Co., Inc. The Cu^{2+} solutions were standardized with primary standard EDTA in a NH_4OH/NH_4Cl buffer with 1% murexide in NaCl as an indicator. The KOH solution was standardized against potassium biphthalate with phenolphthalein as an indicator.

Potentiometry. Each system was isolated in a 100 mL thermostated cell and kept at 35 °C. Each system consisted of 37.5 mL of ethanol and 12.5 mL of aqueous solution. The initial volume for each 75% EtOH solution was determined volumetrically to be 49.02 mL. The pK_w under the described conditions was measured and calculated to be 14.65. The ionic strength was kept constant at 0.10 M with $NaClO_4$ or 0.10 M KCl for the determination of pK_a values and stability constants. Combinations of $NaClO_4$ and NaDPP, NaBNP, or NaCl were used to determine molecular recognition constants. For example, the molecular recognition constant of DPP by TCu was determined in a 75% EtOH solution of 0.1 mmol of terpyridine, 0.1 mmol of $Cu(ClO_4)_2$, 4.0 mmol of $NaClO_4$, and 1.0 mmol of NaDPP. Since the ionic strength was kept constant, p[H] is defined as $-\log [H^+]$. O_2-purified argon was bubbled through each solution to create an inert atmosphere. Direct millivolt measurements were taken on a Corning Model 150 pH meter as KOH was added to the system in small increments. The electrodes were calibrated by taking the average calculated $E°$ of 20 separate titration points of a titration of dilute standardized HCl. The program BEST was used to calculate all equilibrium constants.[6] Species distribution diagrams were computed and plotted from the equilibrium constants with the programs SPE and SPEPLOT, respectively.[6]

Kinetics. The hydrolysis of BNP occurs in the following manner:

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(1) Bashkin, J. K.; Jenkins, L. A. *Comments Inorg. Chem.* **1994**, *16*, 77.
(2) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145.
(3) Kaiser, E. T.; Kudo, K. *J. Am. Chem. Soc.* **1967**, *89*, 6725.
(4) Chin, J.; Banaszczyk, M.; Jubian, V.; Zou, X. *J. Am. Chem. Soc.* **1989**, *111*, 186.
(5) Bashkin, J. K.; Jenkins, L. A. *J. Chem. Soc., Dalton Trans.* **1993**, 3631.
(6) Martell, A. E.; Motekaitis, R. J. *Determination and Use of Stability Constants*, 2nd ed.; VCH Publishers: New York, 1992.

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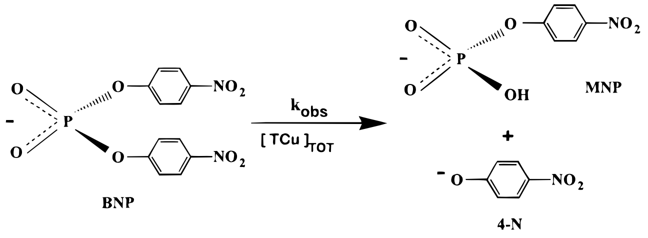

All kinetic studies were carried out in a 75% EtOH solution, with 0.10 M KCl present, and at 35 °C. The thermostated cell was connected to a pH-stat that delivers small amounts of base to keep the pH constant. It is important to note that the use of buffers to control pH in the kinetic experiments would have complicated the phosphate diester hydrolysis reaction by competing with the substrate for the TCu catalyst. The hydrolysis of BNP was followed by taking 20 μL aliquots from the thermostated cell at appropriate times, injecting the aliquots into an HPLC equipped with a UV−vis detector, and following the increase in absorption at 400 nm due to d[4-nitrophenolate (4-N)]/d*t*. A C18 Adsorbosphere column was employed, and the mobile phase consisted of a 50/50 methanol/phosphate buffer (25 mM total, pH 7). In each kinetic trial six to eight data points were recorded that defined a straight line, each of which had a Pearson's correlation coefficient of >0.99. The reactions were followed to ∼1% completion. Since only a small amount of BNP gets hydrolyzed, hydrolysis of mono(*p*-nitrophenyl) phosphate (MNP) is considered negligible. The kinetic data were analyzed by the method of initial rates, and the observed rate constants, k_{obs}, were calculated on the basis of the following derivation:

$$\mathrm{TCu} + \mathrm{BNP} \underset{K_d = 63\mathrm{mM}}{\overset{K_a = 16}{\rightleftharpoons}} \mathrm{TCu{-}BNP} \xrightarrow{k_{obs}} \mathrm{TCu} + \mathrm{MNP} + \text{4-N}$$

$$d[\text{4-N}]/dt = k_{obs}[\mathrm{TCu{-}BNP}]$$

$$d[\text{4-N}]/dt = k_{obs}[\mathrm{TCu}]_{TOT}[\mathrm{BNP}]_{INIT}$$ [16]

In each kinetic trial $[\mathrm{TCu}]_{TOT} = [\mathrm{BNP}]_{INIT} = \sim 0.002$ M. Spontaneous hydrolysis of BNP at pH 10.5 was measured at 35 °C in 75% EtOH. An observed rate constant, k_{uncat},was measured at 3×10^{-9} s^{-1}. This is significantly lower than the observed rate constants with TCu present, so no adjustments were made. Hydrolysis of DPP by TCu was not measurable due to the fact that TCu−Cl_2 precipitates from solution after prolonged time periods (∼1 week).

Synthesis. NaDPP was synthesized by mixing equimolar ethanolic solutions of NaOH and HDPP. The solvent was removed, and the solid was stirred in $CHCl_3$ and then filtered (90% yield). NaBNP was synthesized by mixing equimolar ethanolic solutions of NaOH and HBNP. The off-white precipitate that formed was filtered and dried (88% yield).

Aqua crystals of TCu−Cl−BNP, [chloro(bis(*p*-nitrophenyl)phosphato)(2,2′:6′,2″-terpyridyl)copper(II)], were obtained by allowing a solution of 0.002 M terpyridine, 0.002 M Cu^{2+}, 0.002 M BNP, and 0.10 M KCl to evaporate in air at pH ≈ 7. Aqua crystals of TCu−Cl−DPP, [chloro(diphenylphosphato)(2,2′:6′,2″-terpyridyl)copper(II)], were obtained by allowing a solution of 0.002 M terpyridine, 0.002 M Cu^{2+}, and 0.002 M DPP to evaporate in air at pH ≈ 7.

X-ray Crystallography. A crystal of TCu−Cl−DPP was mounted on a glass fiber with epoxy cement and then transferred to a Rigaku CCD X-ray diffractometer (Mo Kα, $\lambda = 0.710\,69$ Å radiation). Data are given in Table 1. Three standard reflections were taken every 150 measurements and showed no significant trends. Lorentz and polarization corrections were applied to 4251 unique reflections. A total of 334 parameters and 4048 intensity data with $|I| \geq 2.0\sigma(I)$ were used in the calculations. A crystal of TCu−Cl−BNP was mounted on a glass fiber and then transferred to a Siemens R3M X-ray diffractometer (Mo Kα, $\lambda = 0.710\,73$ Å). Three standard reflections were taken every 97 measurements and showed no significant trends. Lorentz and polarization corrections were applied to 4729 unique reflections. A total of 389 parameters and 3965 intensity data with $|I| \geq 2.0\sigma(I)$ were used in the calculations. The structures were solved by direct methods (SHELXS-97).[7] Full-matrix least-squares anisotropic refinement for all non-hydrogen atoms yielded $R = 0.0840$ and $R_w = 0.1443$ (TCu−Cl−DPP); R = 0.0638 and R_w = 0.1402 (TCu−Cl−BNP) (SHELXL-97).[7] Hydrogen atoms were placed at their geometrically calculated positions and refined riding on the heavy atoms to which they were connected.

Table 1. Crystallographic Data

	TCu−Cl−BNP	TCu−Cl−DPP
empirical formula	$C_{27}H_{19}ClCuN_5O_8P$	$C_{27}H_{21}ClCuN_3O_4P$
fw	671.43	581.43
temp/K	293	173
wavelength/Å	0.710 73	0.710 73
cryst syst	triclinic	monoclinic
space group	*P*-1	*P*2(1)/*C*
a/Å	8.067(5)	11.3146(18)
b/Å	10.199(7)	7.6932(12)
c/Å	16.806(11)	28.445(10)
α/deg	96.87(5)	90
β/deg	101.83(5)	99.322(3)
γ/deg	91.40(5)	90
V/Å^3	1341.9(15)	2443.4(10)
Z	2	4
d_{calcd}/(g/cm^3)	1.662	1.581
abs coeff/mm^{-1}	1.036	1.110
cryst size/mm	0.44 × 0.41 × 0.04	0.3 × 0.2 × 0.01
$R_f{}^a$	0.0509	0.0765
$R_{wf}{}^b$	0.1301	0.1411
θ range	2.01−25.00	1.85−25.00
total no. of reflns	5099	13 976
no. of unique reflns	4729	4251
GOF on F^2	1.034	1.354

[a] $R_f = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_{wr} = \{[\sum w(F_o{}^2 - F_c{}^2)^2]/[\sum wF_o{}^2]\}^{1/2}$. $w = 1/[\sigma^2 F_o{}^2 + (0.0500P)^2 + 3.000P]$ for TCu−Cl−DPP. $w = 1/[\sigma^2 F_o{}^2 + (0.0637P)^2 + 3.182P]$ for TCu−Cl−BNP. $P = [F_o{}^2 + 2F_c{}^2]/3$.

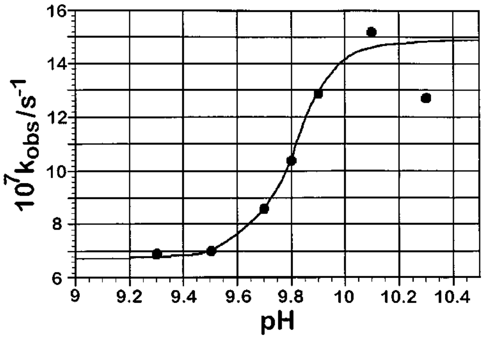

Figure 1. Rate constant versus pH profile for the hydrolysis of BNP by TCu (35 °C, 75% EtOH, ì = 0.10 M (KCl), [Terpy] = [Cu^{2+}] = [BNP] = $\sim 2 \times 10^{-3}$ M). Points are the average of two separate trials. Reactions were typically followed for 2−3 days or until ∼1% complete.

Results and Discussion

A pH versus rate constant profile is shown in Figure 1. The sigmoidal shape of the curve implies that the catalyst has a pK_a corresponding to the inflection point on the graph. The inflection point, at 9.8, is approximately the same as the pK_a of TCu−OH_2, so TCu−OH is believed to be the active catalyst for hydrolyzing BNP. The reason no hydrolysis was observed in previous work was that the reaction was too slow to measure at the pH that was used (7.0) and there was not enough active catalyst present at that pH.[5] With respect to spontaneous hydrolysis that was measured at pH 10.5, the observed rate constants of the catalytic system are 230−500 times faster. A turnover number was unobtainable since the half-life of BNP at pH 10.1 and with a saturated concentration of catalyst present (∼0.002 M) is 128 days.

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[7] Sheldrick, G. M. *SHELX-97: Program for Crystal Structure Determination*; Göttingen: Germany, 1997.

Table 2. Stability Constants for the Formation of Mononuclear Copper Complexes of Terpyridine[a] at 35 °C and 75% EtOH

equilibrium	$\mu = 0.10$ M $NaClO_4$	$\mu = 0.10$ M KCl	equilibrium	$\mu = 0.10$ M $NaClO_4$	$\mu = 0.10$ M KCl
[TCu]/[T][Cu]	12.59[b]	12.90[b]	$[TCu-(OH)_2][H]/[TCu-OH]$	11.48	11.19
[TCu−OH][H]/[TCu]	7.98	9.56	$[T_2Cu]/[TCu][T]$	5.88	4.12

[a] The pK_a values of terpyridine are 3.16 and 1.0 in 0.10 M $NaClO_4$ and 3.13 and 2.0 in 0.10 M KCl. [b] Since the TCu complex is 100% formed at pH 2, these values were determined in a competition experiment with the macrocycle bis(*m*-xylenediethylenetriamine).[23]

Table 3. Stability Constants for the Complexation of OH, Cl, DPP, and BNP by TCu ($T = 35$ °C, 75% EtOH, and 0.10 M Ionic Strength ($NaClO_4$))

equilibrium	log *K*	equilibrium	log *K*
[TCu−OH]/[TCu][OH]	6.67	[TCu−BNP]/[TCu][BNP]	1.2
[TCu−Cl]/[TCu][Cl]	2.8	$[TCu-ClO_4]/[TCu][ClO_4]$	assumed = 0
[TCu-DPP]/[TCu][DPP]	2.5		

Formation constants for mononuclear copper complexes of terpyridine are given in Table 2. The major difference from the literature values that were measured in 100% aqueous solution is that no dimerization occurs in the 75% EtOH systems that are described in this work.[8] This was demonstrated by the fact that the observed pK_a of $TCu-OH_2$ in both 0.10 M $NaClO_4$ and 0.10 M KCl does not change over a large concentration range (0.0004−0.01 M). The observed pK_a of $TCu-OH_2$ would be expected to decrease as the concentration of $[TCu]_{TOT}$ increases due to the formation of $TCu-OH_2-TCu$ dimers. Please see ref 9 for an in-depth look at determining a dimerization constant.

The TCu complex is 100% formed at pH 2 whether the ionic strength of the system under analysis is controlled by 0.10 M $NaClO_4$ or 0.10 M KCl. The major difference in stability constants is that the pK_a of $TCu-OH_2$ is 7.98 in 0.10 M $NaClO_4$ and 9.56 in 0.10 M KCl. The reason for this 1.58 log unit difference is that ClO_4^- is a weakly coordinating anion, whereas Cl^-, on the other hand, can coordinate to TCu to an appreciable extent. In our analysis we assume that ClO_4^- is noncoordinating and then use this assumption to determine the molecular recognition constants of DPP and BNP as well as the association constants of Cl^- and OH^-. The values are given in Table 3. A theoretical species distribution diagram involving TCu, Cl^-, DPP, and BNP was generated to demonstrate more clearly how TCu favors the coordination of $Cl^- >$ DPP > BNP (Figure 2).

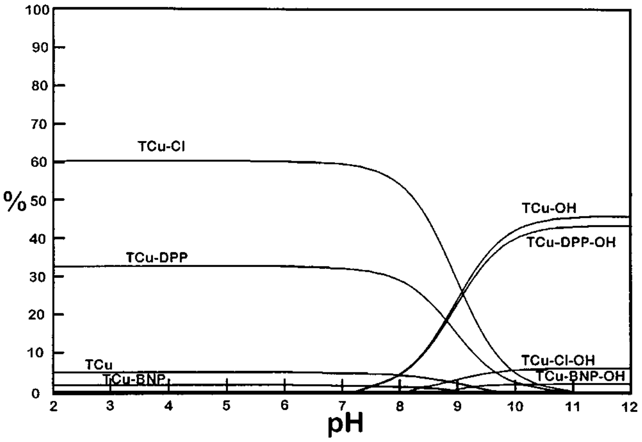

Figure 2. Theoretical species distribution diagram, based on the measured stability constants, containing $[TCu]_{TOT} = 0.1[Cl] = 0.1[DPP] = 0.1[BNP] = 0.002$ M.

The molecular recognition constants for DPP and BNP as well as the association constant for Cl^- are larger in 75% EtOH compared to those in 100% aqueous solution because the lower dielectric constant of the 75% EtOH system favors charge neutralization. That is, $[TCu-Cl]^+$ is favored over $[TCu]^{2+}$. This effect should be consistent with respect to Cl^-, DPP, and BNP. The overall values are quite small, and characteristic of phosphate diester coordination.[4,10,11] Clearly, TCu favors DPP over BNP by 1.3 log units. Thermodynamically, this tends to favor the hydrolysis of DPP over BNP because more TCu-DPP forms in solution than TCu−BNP at any given pH. Kinetically, BNP is hydrolyzed at a measurable rate and DPP is not; thus, the molecular recognition of the substrate in solution cannot account for a mechanism that favors the hydrolysis of BNP over DPP.

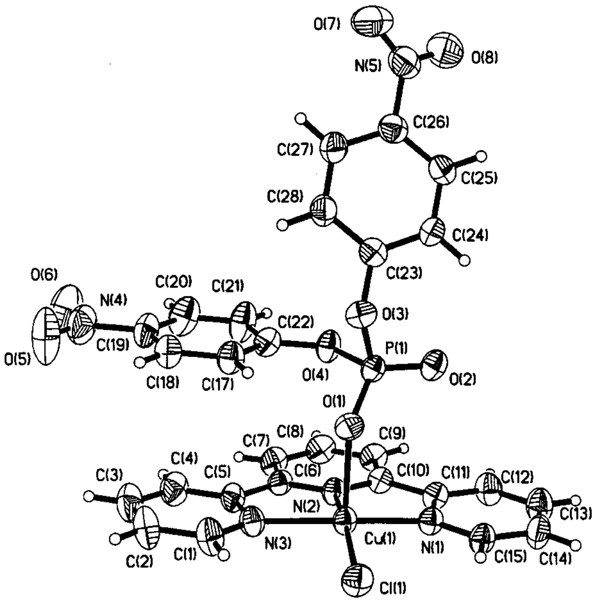

Figure 3. Thermal ellipsoid drawing of TCu−Cl−BNP with atomic numbering scheme.

The crystal structures of TCu−Cl−BNP and TCu−Cl−DPP, shown in Figures 3 and 4, show that the substrates coordinate to the catalyst in the same manner. In fact, the structures are almost identical. This means that any differences in the hydrolysis of DPP and BNP cannot be attributed to the substrate to catalyst binding mode. Selected bond lengths and angles are given in Table 4. Three nitrogens of terpyridine and a chloride ligand form the base of the square pyramid. Both phosphate diesters coordinate to the axial position of the square pyramid. Although both oxygens that are not involved in ester linkages are equivalent, only one is coordinated to the copper ion. Both structures conform to the trends observed in a number of other approximately square pyramidal terpyridine−copper complexes.[12−16] The Cu−N1 and Cu−N3 bonds are slightly longer

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(8) Smith, R. M.; Martell, A. E.; Motekaitis, R. J. Critical Stability Constants of Metal Complexes: Version 5.0, NIST-Database 46, Gaithersburg, MD, 1999.

(9) Gustafson, R. L.; Martell, A. E. *J. Phys. Chem.* **1963**, *67*, 576.

(10) Kim, J. H.; Chin, J. *J. Am. Chem. Soc.* **1992**, *114*, 9792.

(11) Takasaki, B. K.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 8582.

(12) Anderson, O. P.; Packard, A. B.; Wicholas, M. *Inorg. Chem.* **1976**, *15*, 1613.

(13) Henke, W.; Kremer, S.; Reinen, D. *Inorg. Chem.* **1983**, *22*, 2858.

Table 4. Selected Bond Lengths (Å) and Angles (deg)

	TCu−Cl−DPP	TCu−Cl−BNP		TCu−Cl−DPP	TCu−Cl−BNP
Cu(1)−N(1)	2.038(4)	2.020(4)	P(1)−O(1)	1.475(3)	1.465(3)
Cu(1)−N(2)	1.947(4)	1.949(3)	P(1)−O(2)	1.489(3)	1.459(3)
Cu(1)−N(3)	2.031(4)	2.029(4)	P(1)−O(3)	1.616(3)	1.615(3)
Cu(1)−Cl(1)	2.2252(14)	2.2140(18)	P(1)−O(4)	1.627(3)	1.623(3)
Cu(1)−O(2)[a]	2.250(3)	2.201(3)			
N(2)−Cu(1)−N(3)	79.46(15)	79.27(15)	O(1)−P(1)−O(2)	121.46(19)	121.87(19)
N(2)−Cu(1)−N(1)	79.33(16)	79.38(15)	O(1)−P(1)−O(4)	111.89(18)	110.73(18)
N(3)−Cu(1)−N(1)	157.21(16)	157.11(14)	O(2)−P(1)−O(4)	103.62(17)	105.17(17)
N(2)−Cu(1)−Cl(1)	167.17(12)	166.68(11)	O(1)−P(1)−O(3)	105.50(18)	104.14(17)
N(3)−Cu(1)−Cl(1)	99.36(12)	99.49(12)	O(2)−P(1)−O(3)	110.82(18)	111.76(18)
N(1)−Cu(1)−Cl(1)	99.45(12)	99.38(11)	O(4)−P(1)−O(3)	101.95(17)	101.40(17)
N(2)−Cu(1)−O(2)[a]	93.04(14)	96.89(14)	P(1)−O(2)−Cu(1)	124.90(18)	
N(3)−Cu(1)−O(2)[a]	97.44(13)	94.43(14)	P(1)−O(1)−Cu(1)		129.81(18)
N(1)−Cu(1)−O(2)[a]	91.93(14)	96.20(14)	C(16)−O(3)−P(1)	125.2(3)	
Cl(1)−Cu(1)−O(2)[a]	99.77(9)	96.43(10)	C(22)−O(4)−P(1)		125.5(3)
			C(22)−O(4)−P(1)	121.3(3)	
			C(23)−O(3)−P(1)		123.0(3)

[a] The oxygen bonded to the copper in TCu−Cl−BNP is labeled O(1).

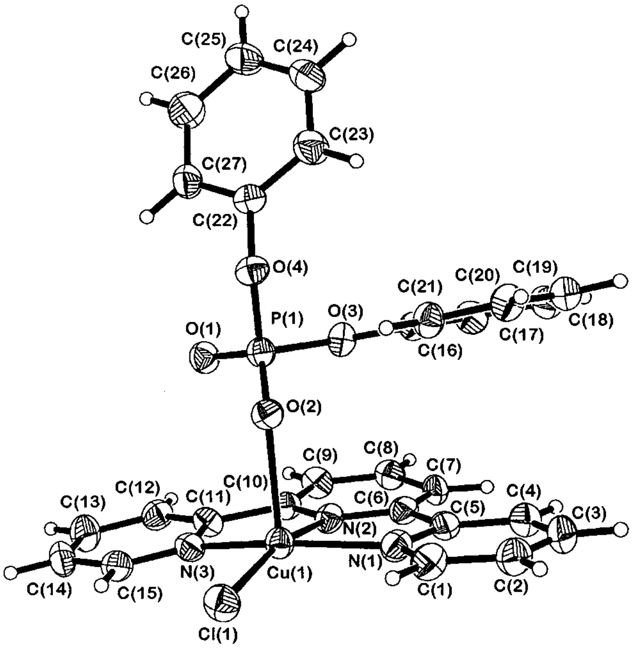

Figure 4. Thermal ellipsoid drawing of TCu−Cl−DPP with atomic numbering scheme.

than the Cu−N2 bond by 0.09 Å. The axial Cu−O bond is ~0.3 Å longer than a normal Cu−O bond, 2.25 Å versus 1.95 Å.

A proposed mechanism for the hydrolysis of BNP is shown in Figure 5. The chloride ion is displaced by a H_2O molecule in the equatorial position which then is deprotonated. The hydroxide nucleophile attacks the substrate which is in the axial position, forming MNP and 4-N. The product 4-N is stable in solution as an anion. BNP and Cl, which are in large concentration in solution, displace MNP, and the cycle starts again. The slow rate of hydrolysis is most reasonably attributed to poor preorganization. That is, a large amount of energy is required for the equatorial hydroxide to attack the axial substrate. Preorganization favors DPP hydrolysis over BNP hydrolysis on the basis of the molecular recognition constants. However, since BNP is hydrolyzed and DPP is not, the electron-withdrawing effect of the *p*-nitro groups plays a major role. Also, the leaving group, 4-N, is stable as an anion at pH > 9 (p$K_a = 7.75$, present conditions), so it does not need to be protonated to be stabilized. With respect to DPP hydrolysis, the leaving group of DPP is[XVII] phenol (p$K_a = 10.0$, present conditions). Phenol contains no electron-withdrawing groups and does need to be protonated to be stabilized. This stabilization of the leaving group of the phosphate diesters has been linked to their rates of hydrolysis.[4]

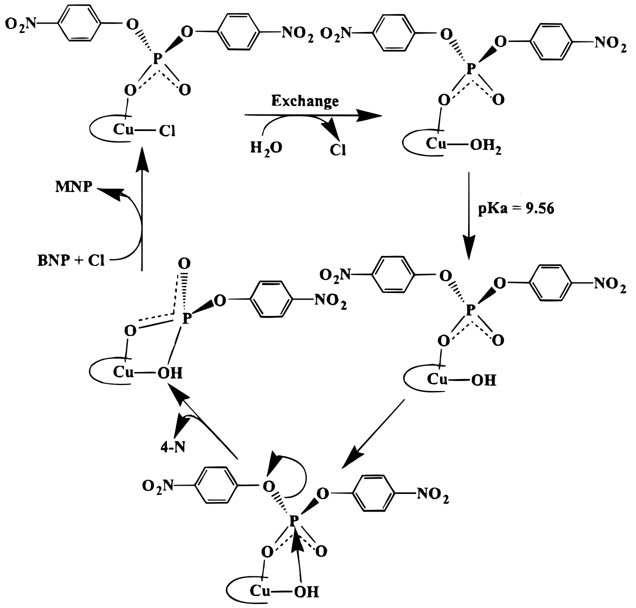

Figure 5. Proposed mechanism for the hydrolysis of BNP by TCu. The terpyridine ligand is represented by the curved line.

Conclusions

TCu hydrolyzes BNP to a measurable extent where TCu−OH is the active catalyst. Hydrolysis of DPP is immeasurably

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(14) Allmann, R.; Kremer, S.; Kucharczyk, D. *Inorg. Chim. Acta* **1984**, *85*, L19.
(15) Kwik, W. *J. Coord. Chem.* **1988**, *19*, 279.
(16) Emsley, J.; Arif, M.; Bates, P. A.; Hursthouse, M. B. *Inorg. Chim. Acta* **1988**, *143*, 25.
(17) Jurek, P. E.; Martell, A. E. Submitted for publication.
(18) Beese, L. S.; Steitz, T. A. *EMBO J.* **1991**, *10*, 25.
(19) Kostrewa, D.; Winkler, F. K. *Biochemistry* **1995**, *34*, 683.
(20) Hough, E.; Hansen, L. K.; Birknes, B.; Jynge, K.; Hansen, S.; Hordvik, A.; Little, C.; Dodson, E.; Derewends, Z. *Nature* **1989**, *338*, 357.
(21) Volbeda, A.; Lahm, A.; Sakiyama, F.; Suck, D. *EMBO J.* **1991**, *10*, 1607.
(22) Callahan, S. M.; Cornell, N. W.; Dunlap, P. V. *J. Biol. Chem.* **1995**, *270*, 17627.
(23) Menif, R.; Martell, A. E. *J. Chem. Soc., Chem. Commun.* **1989**, 1521.

slow under our conditions. If varying mechanisms exist for the hydrolysis of “activated” phosphate diesters versus unactivated phosphate diesters, no evidence exists with respect to the process of molecular recognition. Multinuclear model complexes clearly have an advantage over TCu in obtaining efficient phosphate diester hydrolysis:[17] The presence of ≥2 metal ions can neutralize more negative charge on the phosphorus nucleus, ≥2 metal ions have more coordination sites available to stabilize any leaving groups, and multinuclear complexes can preorganize a nucleophile so that it attacks the phosphorus away from the negatively charged oxygens. These strategies are most likely taken advantage of in the active sites of metal-dependent enzymes that hydrolyze phosphate diesters.[18−22]

Acknowledgment. The financial support of this research by the Robert A. Welch Foundation is greatly appreciated. We also thank Dr. J. H. Reibenspies for solving the crystal structures.

Supporting Information Available: X-ray crystallographic files, in CIF format, are availabe free of charge via the Internet at http://pubs.acs.org.

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