Inorganic Chemistry
Article
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Comparison of Cu(II)-Promoted Leaving Group Stabilization of the Cleavage of a Homologous Set of Phosphate Mono-, Di-, and Triesters in Water, Methanol, and Ethanol

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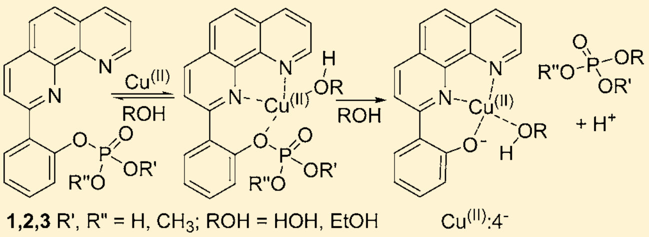


1,**2**,**3** R', R'' = H, CH$_3$; ROH = HOH, EtOH

Cu$^{(II)}$:4$^-$

ABSTRACT: The cleavage of a set of phosphate mono-, di-, and triesters having a Cu(II)-complexed 2-phenanthrolyl group at the *ortho*-position of a departing phenoxide was studied in water and ethanol. Experimentally observed pH/rate profiles, solvent deuterium kinetic isotope effects, and activation parameters are compared with those obtained in methanol. The pH/rate profile in each solvent exhibits an extended plateau due to solvent attack on forms designated as [Cu(II):**1b**/**c**]^0 for the monoester, [Cu(II):**2b**]$^+$, for the diester, and [Cu(II):**3a**]$^{2+}$ for the triester. The solvent dkie values (k_H/k_D) for the three complexes are 0.91, 0.95, and 0.83 for decomposition of [Cu(II):**1b**/**c**]^0 in water (W), methanol (M), and ethanol (E), 1.22, 1.09, and 1.29 for [Cu(II):**2b**]$^+$ in W, M, and E, and 1.94, 2.2, and 1.96 for [Cu(II):**3a**]$^{2+}$ in W, M, and E. Near unit, or slightly inverse values for the monoester are taken as evidence for little involvement of solvent in a highly dissociative TS for P−OAr cleavage, with slightly higher solvent dkie values for the diester signifying the onset of some solvent participation in assisting the nucleophilic displacement. The larger primary dkie for the triester gives evidence for a solvent-assisted delivery of ROH in the cleavage through a more associative mechanism. Activation parameters for each substrate in the solvents are compared, indicating that the transition from methanol to ethanol for each substrate involves a near cancellation of the $\Delta\Delta H^{\ddagger}$ and $-T\Delta\Delta S^{\ddagger}$ values (25 °C) so that the respective rates in both solvents are very similar. The transition from alcohol to water produces variable effects, with $\Delta\Delta H^{\ddagger}$ and $-T\Delta\Delta S^{\ddagger}$ values canceling for cleavage of the triester and being additive for the mono and diester, explaining their 100−500 rate reduction in passing from methanol to water. The rate enhancing effects of the Cu(II)-promoted leaving group assistance in all three solvents are substantial and estimated at 10^{12}−10^{15} for the monoester, 10^{12}−10^{14} for the diester, and 10^5 for the triester relative to their background reactions.

1. INTRODUCTION

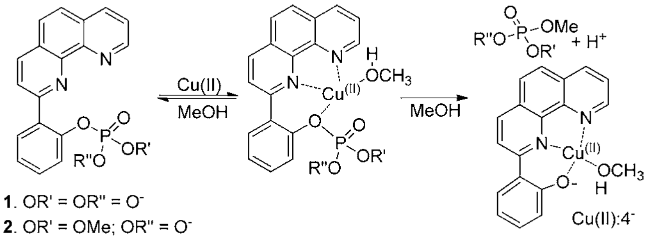
The monoesters and diesters of phosphoric acid participate in a variety of biologically important phosphoryl transfer and hydrolysis reactions involving proteins, DNA, and RNA. The ionization of mono- and diester derivatives of these under physiological conditions is central to their suitability as biomolecules since it serves to prevent them from crossing biological membranes as well as to resist hydrolytic cleavage by simple nucleophilic means.[1] Triesters have no natural biological function, but man-made versions are used commercially as acetylcholinesterase inhibitors.[2] Phosphatase enzymes, some containing dinuclear active sites, have evolved to catalyze the cleavage of both naturally-occurring and man-made phosphate esters with very large rate enhancements over the uncatalyzed solvolysis reactions.[3] Various modes of metallo-catalysis[4] have been discussed, such as: (1) Lewis acid activation of the substrate via M^{x+}—O═P binding; (2) delivery of a metal-bound hydroxide or alkoxide that serves as a nucleophile or a base; (3) electrostatic stabilization of the anionic substrate and nucleophile/base through binding to the (+)-charged active site and subsequent lowering of the transition state energy of the reaction;[5] and (4) stabilization of the leaving group through metal ion coordination. As important as the latter effect is believed to be, studies of systems incorporating metal ions that provide leaving group assistance (LGA) in the reactions of small molecules is documented in only a few cases.[6−14]

In the absence of catalysts, the mechanisms by which phosphate esters react depend on their state of *O*-alkylation (R) or arylation (Ar).[15] Monoesters react either by a dissociative mechanism ($D_N + A_N$) or a concerted mechanism (A_ND_N) with a loose transition state. Diesters and triesters tend to react through concerted A_ND_N mechanisms (when containing an activated LG) with progressively tighter transition states to the limit of an associative mechanism involving a phosphorane intermediate when substituted with a poor LG. We have compared the rates and properties of the methanolysis reactions of molecules **1**−**3** in the presence of Cu(II) (Scheme 1) showing there is strong assistance of the LG departure by a closely situated *ortho*-phenanthroline-bound Cu(II).[16] The methanolyses are greatly accelerated (10^{14}−10^{15} for monoester, 10^{14} for diester, and 10^5 for triester) over the background reactions in methanol. In all these cases, the Cu(II)-promoted LGA changes the reaction mechanism relative to the non-LGA process, with

Received: January 10, 2012
Published: March 7, 2012

dx.doi.org/10.1021/ic300059e | *Inorg. Chem.* 2012, 51, 3846−3854

Scheme 1. Cu(II)-Promoted Methanolysis of Phosphate Esters 1−3



1. OR' = OR'' = O⁻
2. OR' = OMe; OR'' = O⁻
3. OR' = OR'' = OMe

solvent methanol, rather than methoxide, as the active nucleophile in transition states that are more dissociative than are found for related processes in the absence of catalysts.

Herein we report on an expanded study where the reaction medium changes from methanol to both ethanol and water, how these solvents affect the reaction mechanisms, and the acceleration provided by LGA.

2. EXPERIMENTAL SECTION

2.1. Materials. Ethanol-OD (99 atom % D), trifluoromethanesulfonic acid (≥99%), $Cu(CF_3SO_3)_2$ (98%), 2-picoline (98%), 2,6-lutidine (99+%), 2,4,6-collidine (99%), 4-ethylmorpholine (99%), 1-methylpiperidine (≥98%), 1-ethylpiperidine (99%), triethylamine (99%), and 2,2,6,6-tetramethylpiperidine (99+%), were used as supplied from Aldrich. Tetrabutylammonium ethoxide (40% in ethanol, titrated against N/2 certified standard aqueous HCl solution and found to be 1.13 M) was purchased from Fluka. Absolute ethanol (anhydrous, degassed, and stored under argon, freshly dispensed between kinetic experiments) and deuterium oxide (D, 99.9%) were purchase from Fisher and CIL, respectively. Reverse-osmosis (RO) purified water was further deionized to 18.2 MΩ·cm using a Millipore filtration apparatus. The following phosphate esters *O*-(2-[2′-phenanthrolyl]phenyl) phosphate (**1**), *O*-(2-[2′-phenanthrolyl]phenyl) *O*-methyl phosphate (**2**), and *O*-(2-[2′-phenanthrolyl]phenyl) *O*,*O*-dimethyl phosphate (**3**) were synthesized and characterized as previously reported.[16]

2.2. General Methods. Concentration of H_3O^+ and $CH_3CH_2OH_2^+$ were determined potentiometrically using a combination glass Fisher Scientific Accumet electrode calibrated with certified standard aqueous buffers (pH 4.00 and 10.00) as described previously.[17a] The pH was determined as $-\log[ROH_2^+]$. The autoprotolysis constant for ethanol was taken to be $10^{-19.1}$ M^2 and the ${}^{s}_{s}$pH values[17b] in ethanol were determined by subtracting a correction constant of −2.54[17a] from the electrode readings. The ${}^{s}_{w}$pH values for the kinetic experiments were measured at the end of the reactions in order to avoid any effects associated with KCl leaching from the electrode.

2.3. General UV−vis Kinetics. The Cu(II)-catalyzed hydrolyses and ethanolyses of **1**, **2**, and **3** were followed at 390 and 415 nm, respectively, to determine the rate of appearance of Cu(II)-bound phenoxide **4** using a UV−vis spectrophotometer with the cell thermostatted at 25.0 ± 0.1 °C. Reactions were conducted in the presence of buffers composed of various ratios of amines (2-picoline, 2,6-lutidine, 2,4,6-collidine, *N*-isopropylmorpholine, 1-methylpiperidine, 1-ethylpiperidine, triethylamine, 2,2,6,6-tetramethylpiperidine) and HOTf. For reactions at pH 3 or lower, an appropriate amount of HOTf was added to achieve the required $[ROH_2^+]$ in solution. Typical kinetic experiments involved preparing a buffer solution (0.4−1.2 mM) followed by addition of the phosphate substrate (0.02 mM) in a 1 cm path length UV cuvette. To this was added an aliquot of Cu(II) stock solution to obtain a final concentration of 0.02 M to initiate the reaction. Under these conditions, it was found that the substrates existed entirely as 1:1 complexes with the Cu(II). In the case of reasonably fast reactions (but still slower than stopped-flow timescale), duplicate kinetic experiments were carried out and the resulting abs vs time traces were fit to a standard first-order exponential equation to obtain the observed first-order rate constants (k_{obs}). For very slow reactions, such as the Cu(II)-promoted hydrolysis or ethanolysis of **2**, initial rates of the reactions were obtained by fitting the first 5−10% of the abs vs time traces to a linear regression. To obtain the k_{obs} values, the initial rates were then divided by the expected absorbance change (ΔAbs) if the reaction were to reach 100% completion. Separate pH/rate profiles were constructed for the Cu(II)-catalyzed cleavages of **1**−**3** in the presence of 20-fold excess buffer in water and ethanol. A typical solvent kinetic isotope experiment involved the addition of 1 mM $Cu(OTf)_2$ and 5 mM HOTf stock solutions in ROD to UV cells containing either ROH or ROD so that the final concentrations of $Cu(OTf)_2$, phosphate ester, and buffer were 0.02, 0.02, and 0.4 mM. The kinetic competition experiments were carried out in duplicate and the pH and pD values were measured after the reactions were complete. (The pD values measured at the end of the reactions were recorded as the pH meter readings (+2.54 in the case of the ethanolysis reactions) and are not corrected for the effect of the deuterated solvent on the reading or on the pK_a of the buffer. The actual pD value is less important since the experiments are carried out in the extensive plateau regions of the pH/rate profiles.)

2.4. Stopped-Flow Kinetics. The Cu(II)-promoted cleavage of **1** was monitored at 390 nm in water and 415 nm in ethanol, obtaining the rate of appearance of product using a stopped-flow apparatus thermostatted at 25.0 ± 0.1 °C. One syringe of the stopped-flow instrument was loaded with a 0.8 mM solution of the desired buffer in water or ethanol containing 0.04 mM **1**. The second syringe was loaded with 0.04 mM $Cu(OTf)_2$ in water or ethanol. When mixed, the final concentrations of $Cu(OTf)_2$, **1**, and buffer were 0.02, 0.02, and 0.4 mM. At least five kinetic experiments were conducted at each pH and the obtained Abs vs time traces were fitted to a standard first-order exponential equation to give the k_{obs} constants: these were averaged to give the reported values in the tables. Solvent kinetic isotope experiments were performed in same way as those previously described and the pH and pD values were measured after the reaction.

2.5. Activation Parameters. Kinetic experiments with Cu(II):**1** were performed at different temperatures using a thermostatable stopped-flow analyzer, while those for substrates Cu(II):**2** and Cu(II):**3** were determined using a UV−vis spectrophotometer. The solution temperatures were determined with a thermometer inserted into the cell at the end of the reaction. First-order rate constants were measured in at least duplicate at a minimum of six different temperatures ranging from 15 to 40 °C for the Cu(II)-promoted hydrolysis or ethanolysis of **1** (both at 0.02 mM) in the presence of 0.4 mM 2,6-lutidine buffer, pH 6.9 ± 0.2, or 2,2,6,6-tetramethylpiperidine buffer, ${}^{s}_{s}$pH 11.4 ± 0.2. Eyring plots of $\ln(k/T)$ vs $1/T$ provided the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values given in Table 1. The activation parameters given in Table 2 for substrate **2** were determined using solutions containing 0.02 mM $Cu(OTf)_2$, 0.02 mM **2**, and 1.0 mM HOTf in water (pH 3.0 ± 0.2) and ethanol (${}^{s}_{s}$pH 3.0 ± 0.2) at seven temperatures ranging

Table 1. Activation parameters, Rate Constants, and SKIE for Cleavage of Cu(II):1 in Water, Methanol,[16] and Ethanol (ε_r = 78, 31.5, 24.3, respectively) at their pH Optima in the Plateau Region Where the Reactive Form Is the Formally Neutral Complex $[Cu(II):\mathbf{1b}]^0$ and/or $[Cu(II):\mathbf{1c}]^0$ [a]

phosphate complex	solvent	k_{cat}^{max} (s^{-1})	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·mol^{-1}·K^{-1})	$\Delta G^{\ddagger}$ (25 °C) (kcal·mol^{-1})	k_H/k_D
[Cu(II):**1b**/**c**]	H_2O	0.11	22.9 ± 0.2	13.6 ± 0.7	18.8	0.91 ± 0.01
[Cu(II):**1b**/**c**]	MeOH	14.7	21.4 ± 0.7	18 ± 2	16.0	0.95 ± 0.05
[Cu(II):**1b**/**c**]	EtOH	4.4	18.4 ± 0.1	5.8 ± 0.5	16.7	0.83 ± 0.06

[a] Data in methanol from ref 16.

Table 2. Activation Parameters, Rate Constants, and SKIE Values for Cleavage of Cu(II):2 in Water, Methanol,[16] and Ethanol (ε_r = 78, 31.5, 24.3, respectively) at Their pH Optima in the Plateau Region Where the Reactive Form Is the Formally Positively Charged Complex [Cu(II):2b]$^{+}$ [a]

phosphate complex	solvent	k_{cat}^{max} (s^{-1})	$\Delta H^‡$ ($kcal \cdot mol^{-1}$)	$\Delta S^‡$ ($cal \cdot mol^{-1} \cdot K^{-1}$)	$\Delta G^‡$ (25 °C) ($kcal \cdot mol^{-1}$)	k_H/k_D
[Cu(II):**2b**]$^+$	H_2O	5.6×10^{-6}	23.0 ± 0.2	−5.8 ± 0.5	24.7	1.22 ± 0.01
[Cu(II):**2b**]$^+$	MeOH	2.5×10^{-3}	21.6 ± 0.4	2.3 ± 1.1	20.9	1.01 ± 0.04
[Cu(II):**2b**]$^+$	EtOH	3.5×10^{-3}	18.3 ± 0.2	−8.5 ± 0.6	20.8	1.29 ± 0.03

[a] Data in methanol from ref 16.

Table 3. Activation Parameters, Rate Constants, and SKIE Values for Cleavage of Cu(II):3 in Water, Methanol,[16] Ethanol (ε_r = 78, 31.5, 24.3, respectively) at their pH Optima in the Plateau Region Where the Reactive Form Is the Formally Doubly Positive Charged Complex [Cu(II):3a]$^{2+}$ [a]

phosphate complex	solvent	k_{cat}^{max} (s^{-1})	$\Delta H^‡$ ($kcal \cdot mol^{-1}$)	$\Delta S^‡$ ($cal \cdot mol^{-1} \cdot K^{-1}$)	$\Delta G^‡$ (25 °C) ($kcal \cdot mol^{-1}$)	k_H/k_D
[Cu(II):**3a**]$^{2+}$	H_2O	1.7×10^{-5}	19.1 ± 0.1	−16.4 ± 0.3	24.0	1.94 ± 0.01
[Cu(II):**3a**]$^{2+}$	MeOH	2.0×10^{-5}	21.6 ± 0.5	−7.4 ± 1.7	23.8	2.2 ± 0.1
[Cu(II):**3a**]$^{2+}$	EtOH	7.3×10^{-5}	18.4 ± 0.3	−16.0 ± 0.9	23.2	1.96 ± 0.05

[a] Data in methanol from ref 16.

from 15.0 to 45 °C. The activation parameters given in Table 3 for substrate **3** were determined with solutions containing 0.02 mM $Cu(OTf)_2$, 0.02 mM **3**, and 1.0 mM HOTf in water (pH 3.0 ± 0.2) and ethanol (${}^s_s$pH 3.0 ± 0.2) at six temperatures ranging from 15.0 to 68.0 °C.

3. RESULTS

3.1. Cu(II)-Promoted Hydrolysis and Ethanolysis of 1.

The pH/rate profile for hydrolysis of Cu(II):**1** in Figure 1 can be fit by nonlinear least-squares methods to eq 1, derived for the model given in Scheme 2 having two ionizable groups with pK_a values of 4.33 and 9.17. Based on the ${}^s_s$pH/rate profile of Cu(II):**1** observed earlier in methanol,[16] in the lower pH regions [Cu(II):**1a**]$^+$ (or a kinetically equivalent form where the nonbridging phosphate O^- binds to Cu(II) displacing solvent) undergoes possible microscopic ionizations in water to form two formally neutral forms, [Cu(II):**1b**]^0 and [Cu(II):**1c**]^0 which differ by coordination of a nonbridging O^- to Cu(II) with displacement of solvent. The relative proportion of these may be influenced by solvent polarity and thus different in the three media. However, due to the availability of both nonbridging oxyanions to assist in the departure of the LG in [Cu(II):**1b**]^0, this is likely the more active of the two species. Further ionization leads to a less active (or possibly inactive) species, [Cu(II):**1d**]$^-$.

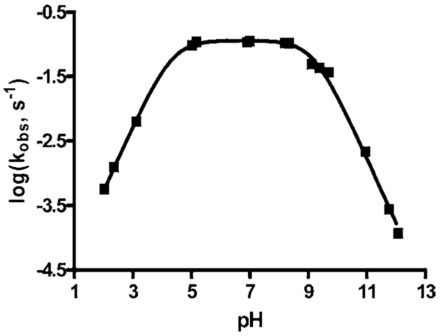
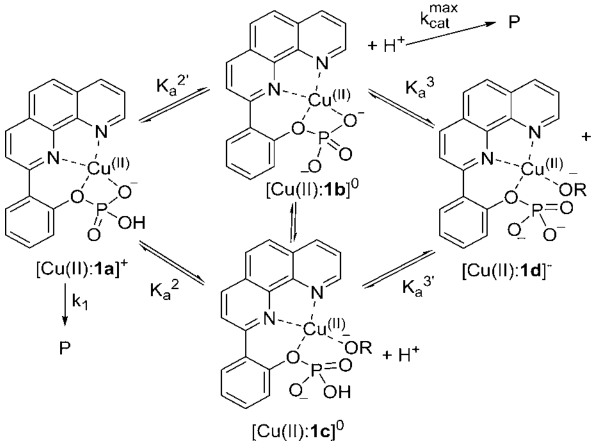


Figure 1. pH/rate profile for hydrolysis of Cu(II):**1** (0.02 mM each of Cu(II) and **1**) under aqueous buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data are fitted by NLLSQ methods to eq 1 to give two macroscopic pK_a^2 and pK_a^3 values of 4.33 ± 0.05 and 9.17 ± 0.04 and a maximum rate constant (k_{cat}^{max}) of 0.115 ± 0.007 s^{-1}; r^2 = 0.9972. The solvent dkie was determined to be 0.91 ± 0.01 in the center of the pH 5−8 plateau region, at a measured pD = 6.8 ± 0.2 (0.4 mM 2,6-lutidine buffer).

Scheme 2. Microscopic Ionizations for Hydrolysis of [Cu(II):1]



$$k_{obs} = \left(\frac{k_{cat}^{max} K_a^2}{K_a^2 + [H^+]}\right)\left(\frac{[H^+]}{K_a^3 + [H^+]}\right) \qquad (1)$$

The ${}^s_s$pH/rate profile data in Figure 2 for ethanolysis of Cu(II):**1** can be fit to eq 2 derived for the model represented schematically in Scheme 3 where [Cu(II):**1**]$^{2+}$ undergoes two sequential acid dissociations having macroscopic ${}^s_s$pK_a^1 and ${}^s_s$pK_a^2 values of 2.1 and 7.7. The [Cu(II):**1a**]$^+$ formed at lower ${}^s_s$pH may undergo two possible microscopic ionizations to produce [Cu(II):**1b**]^0 and [Cu(II):**1c**]^0. For similar reasoning as was described above for water, [Cu(II):**1b**]^0 probably represents the more active species. In the less polar ethanol, further ionization of this to form [Cu(II):**1d**]$^-$ (see Scheme 2) is not observed up to at least ${}^s_s$pH 12.

$$k_{obs} = \left(\frac{k_{1s} {}^s_sK_a^1}{{}^s_sK_a^1 + [H^+]}\right) + \left(\frac{k_{cat}^{max} {}^s_sK_a^2}{{}^s_sK_a^2 + [H^+]}\right) \qquad (2)$$

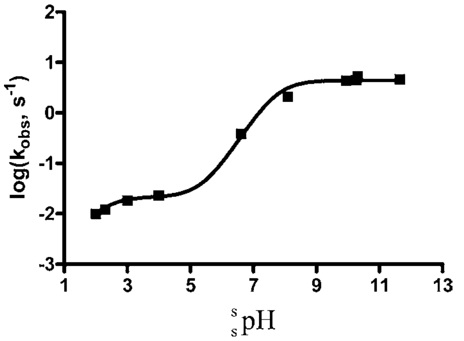
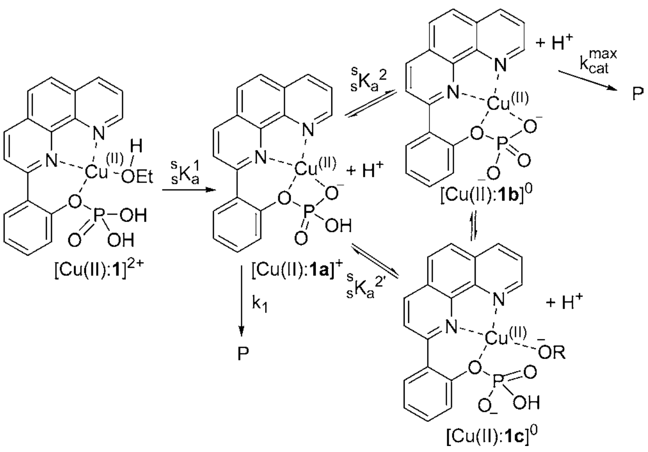


Figure 2. $^{s}_{s}\mathrm{pH}$/rate profile for cleavage of Cu(II):**1** (0.02 mM each of Cu(II) and **1**) in anhydrous ethanol under buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data are fitted by NLLSQ methods to eq 2 to give two macroscopic $^{s}_{s}\mathrm{p}K_a$ values: 2.1 ± 0.2 producing $[\mathrm{Cu(II)}:\mathbf{1a}]^+$ decomposing with a $k_1 = (2.1 \pm 0.2) \times 10^{-2}\ \mathrm{s}^{-1}$ and 7.7 ± 0.2 associated with formation of $[\mathrm{Cu(II)}:\mathbf{1b}]^0$ and $[\mathrm{Cu(II)}:\mathbf{1c}]^0$, jointly decomposing with a maximum rate constant ($k_{\mathrm{cat}}^{\mathrm{max}}$) of 4.4 ± 0.6 s^{-1}; $r^2 = 0.9971$.

Scheme 3. Microscopic Ionizations for Ethanolysis of [Cu(II):1]



The solvent dkie of $k_H/k_D = 0.83 \pm 0.06$ was determined in the plateau region at an estimated $^{s}_{s}\mathrm{pD}$ value of 11.4 ± 0.2, uncorrected for D in the solvent (0.4 mM 2,2,6,6-tetramethylpiperidine buffer).

3.2. Cu(II)-Promoted Hydrolysis and Ethanolysis of 2.

$$\log(k_{\mathrm{obs}}) = \log(k_{\mathrm{cat}}^{\mathrm{max}}) + \log\left(\frac{[\mathrm{H}^+]^2}{K_a^2/K_{\mathrm{dim}} + [\mathrm{H}^+]^2}\right) \qquad (3)$$

In Figure 3, the pH/rate profile for hydrolysis of Cu(II):**2** is shown. At low pH, $[\mathrm{Cu(II)}:\mathbf{2a}]^{2+}$ (Scheme 4) ionizes (not observed) to form the reactive species $[\mathrm{Cu(II)}:\mathbf{2b}]^+$ (or a chemically equivalent species where the nonbridging O^- is displaced from the Cu(II) by solvent) with an extended pH independent region followed by its ionization (pK_a 7.94) to some inactive form, suggested to be the dimer of $[\mathrm{Cu(II)}:\mathbf{2c}]^0$. That the descending portion of the profile at higher pH has a gradient of −2 may indicate involvement of two lyoxide molecules leading to a dimeric species with lower activity such as was proposed previously.[16] The solvent dkie in the plateau region is 1.22 ± 0.01 at a measured pD value of 3.0 ± 0.2 (1 mM DOTf).

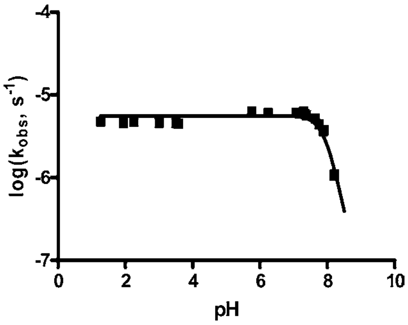
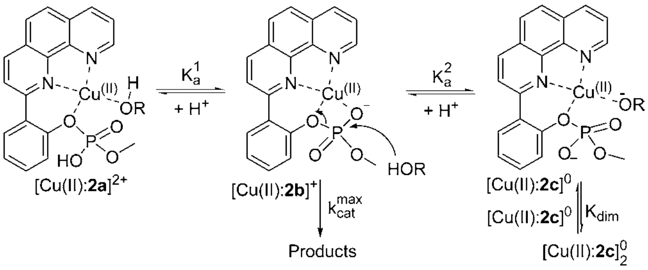


Figure 3. pH/rate profile for cleavage of Cu(II):**2** (0.02 mM of Cu(II) and **2**) under aqueous buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data are fitted by NLLSQ methods to eq 3 to give one macroscopic pK_a value of 7.94 ± 0.03 and a maximum rate constant ($k_{\mathrm{cat}}^{\mathrm{max}}$) of $(5.6 \pm 0.2) \times 10^{-6}\ \mathrm{s}^{-1}$; $r^2 = 0.9009$.

Scheme 4. Microscopic Ionizations for Hydrolysis and Ethanolysis of [Cu(II):2]



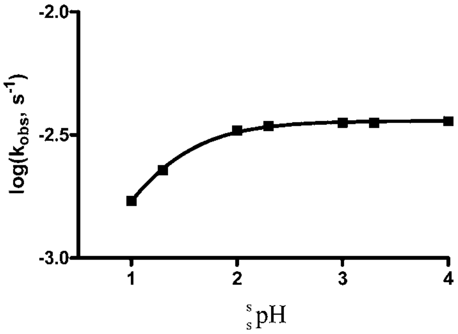


Figure 4. $^{s}_{s}\mathrm{pH}$/rate profile for cleavage of Cu(II):**2** (0.02 mM of Cu(II) and **2**) in anhydrous ethanol under buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data are fitted by NLLSQ methods to eq 4 to give one macroscopic $^{s}_{s}\mathrm{p}K_a^1$ value of 1.05 ± 0.01 and a maximum rate constant ($k_{\mathrm{cat}}^{\mathrm{max}}$) of $(3.60 \pm 0.02) \times 10^{-3}\ \mathrm{s}^{-1}$; $r^2 = 0.9984$.

The ionization process and plateau region indicated by the $^{s}_{s}\mathrm{pH}$/rate profile for ethanolysis of Cu(II):**2** (Figure 4) are represented mechanistically in Scheme 4. At low $^{s}_{s}\mathrm{pH}$, $[\mathrm{Cu(II)}:\mathbf{2a}]^{2+}$ ionizes to produce $[\mathrm{Cu(II)}:\mathbf{2b}]^+$ (or its similarly charged chemical equivalent with a solvent incorporated on the Cu(II)) which then reacts over a pH-independent region. The solvent dkie in the plateau region is $k_H/k_D = 1.29 \pm 0.03$ at a measured $^{s}_{s}\mathrm{pD}$ value of 3.0, uncorrected for effect of D in solvent (1 mM DOTf).

$$\log(k_{\mathrm{obs}}) = \log(k_{\mathrm{cat}}^{\mathrm{max}}) + \log\left(\frac{^{s}_{s}K_a^1}{^{s}_{s}K_a^1 + [\mathrm{H}^+]}\right) \qquad (4)$$

3.3. Cu(II)-Promoted Hydrolysis and Ethanolysis of 3.

The important species in the pH/rate profile for hydrolysis of Cu(II):**3** (Figure 5) are presented in Scheme 5. A broad

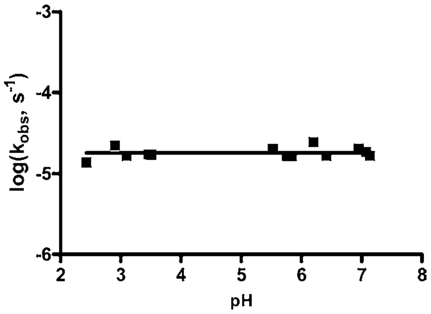
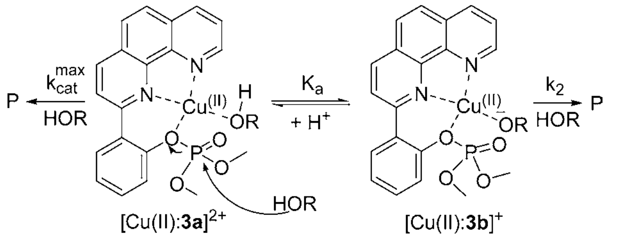


Figure 5. pH/rate profile for hydrolysis of Cu(II):**3** (0.02 mM each of Cu(II) and **3**) under aqueous[18] buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data in the pH range 2.4−7.1 are averaged to give a rate constant of $k_{obs} = 1.7 \times 10^{-5}$ s^{-1}.

Scheme 5. Microscopic Ionizations for Hydrolysis and Ethanolysis of [Cu(II):3]



pH-insensitive region exists between pH 2.5 and 7 where $[\text{Cu(II)}:\mathbf{3a}]^{2+}$ is likely the most active species. The solvent dkie is $k_H/k_D = 1.94 \pm 0.01$ at an estimated pD value of 3.0 ± 0.2 in the plateau region (1 mM DOTf).

Figure 6 shows the ${}^s_s$pH/rate profile for the ethanolysis of Cu(II):**3** where a broad ${}^s_s$pH-insensitive region exists between ${}^s_s$pH 2.5 and 9.5 followed by an ionization to produce $[\text{Cu(II)}:\mathbf{3b}]^{+}$ (Scheme 5) which reacts with lower activity in the ${}^s_s$pH-insensitive region. The solvent dkie was determined in the plateau region to be 1.96 ± 0.05 at an estimated ${}^s_s$pD value of 3.0, uncorrected for the effect of D (1 mM DOTf).

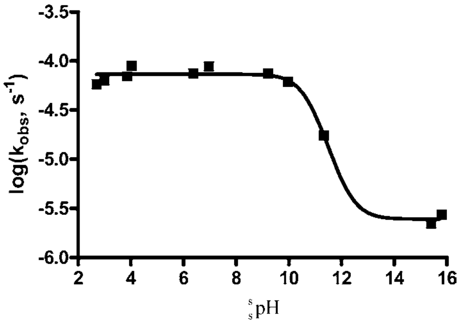


Figure 6. ${}^s_s$pH/rate profile for the cleavage of Cu(II):**3** (0.02 mM of Cu(II) and **3**) in anhydrous ethanol under buffered conditions (0.4 mM amine, 0.2 mM HOTf) at 25 °C. The data are fit by NLLSQ methods to eq 5 to give one macroscopic ${}^s_s$pK_a value of 10.8 ± 0.1 and a maximum rate constant (k_{cat}^{max}) of (7.3 ± 0.4) × 10^{-5} s^{-1} and k_2 = (2.5 ± 0.3) × 10^{-6} s^{-1}; r^2 = 0.9907.

$$\log(k_{obs}) = \log\left(k_{cat}^{max}\frac{[H^+]}{{}^s_sK_a + [H^+]} + k_2\frac{{}^s_sK_a}{{}^s_sK_a + [H^+]}\right) \qquad (5)$$

3.4. Activation Parameters.

Temperature dependent studies at the pH optima for the Cu(II)-promoted solvolyses of **1**−**3** in water, methanol,[16] and ethanol afforded the activation parameters that appear in Tables 1−3.

4. DISCUSSION

There are postulates that the effective dielectric constants inside the enzyme active site resemble those of organic solvents rather than water.[19] Organic solvents like methanol and ethanol, with dielectric constants of 31.5 and 24.3[20] and properties and structures closest to water, might be considered appropriate models for the media extant in the active sites of some enzymes,[19] although this ignores specific solvation effects such as the solvent's H-bond and electron accepting and donating properties. The large rate accelerations that we see for the transesterifications of phosphate di- and triesters in methanol[12,13,21] and ethanol,[16] are anomalous when compared with what is generally seen in water[22] but, as will be seen, there are very large accelerations for the cleavages of [Cu(II):**1**,**2**,**3**] in water as well.

According to X-ray diffraction studies of a close model for the metal-bound leaving group ($[\text{Cu(II)}:\mathbf{4}^-]$, Scheme 1), namely $[(\text{Cu(II)}_2:\mathbf{4}^-)_2:(\mu\text{-MeCO}_2^-)][\text{PF}_6^-]$,[23] the departing phenoxy oxygen is positioned within ∼1.9 Å of the Cu(II) ion. This is expected to be the situation in all solvents investigated. The proposed driving force for the cleavage of the phosphates in methanol[16] stems from progressively enhancing the metal cation's and departing phenoxy anion's interactions during the transformation of [Cu(II):**1**,**2**,**3**] into Cu(II):$\mathbf{4}^-$. Thus, the endothermicity of the P−O(LG) bond cleavage process is offset by an exothermic binding of the transition state attributable to the progressively enhanced Cu(II):$^-$O(LG) electrostatic interaction. The activation parameters and rate constants in Tables 1−3 refer to the reactions in the plateau regions of the pH/rate profiles where the effective nucleophile is solvent, (either external, or metal ion−coordinated in the case of attack on $[\text{Cu(II)}:\mathbf{1b}]^0$, $[\text{Cu(II)}:\mathbf{2b}]^+$, and $[\text{Cu(II)}:\mathbf{3a}]^{2+}$) and the charges of the active forms of the three Cu(II) complexes vary by one unit each in passing from $[\text{Cu(II)}:\mathbf{1b}]^0$ to $[\text{Cu(II)}:\mathbf{2b}]^+$ and $[\text{Cu(II)}:\mathbf{3a}]^{2+}$.

4.1. pH and ${}^s_s$pH/Rate Profiles for the Cleavage of [Cu(II):1,2,3] in Water, Methanol, and Ethanol.

General: The rate constants for the solvolysis of the three complexes were determined under conditions similar to what was used previously for the study in methanol.[16] The kinetics were determined using 1:1 mixtures of Cu(II)(triflate)$_2$ and substrate under the assumption that the Cu(II):substrate binding is essentially complete. This assumption is warranted since the rate constants obtained for this study are independent of increasing total concentration of Cu(II) + substrate, when these are introduced to the solution in a 1:1 mixture. In addition, Cu(II) binding to phenanthroline systems is known to be very strong. For example, the binding constant of phenanthroline and Cu(II) in water[24] is 1.6 × 10^9 M^{-1}, and we have previously determined that the dissociation constant of Cu(II):**3** in methanol is 2.8 × 10^{-7} M[16]. While we have not determined the binding constants for the mono- and diesters, these are also expected to be stronger than that for Cu(II):**3** due to electrostatic interactions, particularly in ethanol. In all cases, the product of the solvolyses is the corresponding 2[2′-phenanthrolyl]-phenoxide:Cu(II) complex which is verified by the characteristic UV/vis spectrum as derived from authentic material. Finally, as is the case in methanol, there is no effect of buffer as can be judged from the pH/rate profiles which show no evidence of breaks between different buffers.

4.1.1. [Cu(II):1]. The general pH-dependent species of [Cu(II):**1,2,3**] and processes for the decomposition of each ester are expected to be similar in the three solvents, although the pH range over which each of their microscopic states of ionization exist is expected to be different. The pH/rate profile from 2 to 12 for the hydrolysis of Cu(II):**1** shown in Figure 1 is bell-shaped with a $k_{\mathrm{cat}}^{\mathrm{max}}$ of 0.12 s^{-1} and two acid dissociation constants of ${}_{s}^{s}\mathrm{p}K_a^2$ = 4.33 and ${}_{s}^{s}\mathrm{p}K_a^3$ = 9.17 corresponding to the transition from [Cu(II):**1a**]$^+$ to two possible neutral forms [Cu(II):**1b/c**]^0 and transformation of [Cu(II):**1b/c**]^0 into [Cu(II):**1d**]$^-$ as in Scheme 2. In methanol, from ${}_{s}^{s}$pH 2.5−12.5, the profile is also bell-shaped with two ${}_{s}^{s}\mathrm{p}K_a^2$ and ${}_{s}^{s}\mathrm{p}K_a^3$ values of 7.83 and 11.8, with plateaus from ${}_{s}^{s}$pH 2.4−4, $k_1 = 6.3 \times 10^{-4}\ \mathrm{s}^{-1}$, and from ${}_{s}^{s}$pH 8−11, $k_{\mathrm{cat}}^{\mathrm{max}} = 14.7\ \mathrm{s}^{-1}$.[16] However, in the lowest polarity solvent ethanol, the ${}_{s}^{s}$pH/rate profile (Figure 2) is sigmoidal with the hint of a ${}_{s}^{s}\mathrm{p}K_a^1$ at 2.4, a plateau from ${}_{s}^{s}$pH 3−5 ($k_1 = 2.1 \times 10^{-2}\ \mathrm{s}^{-1}$), a ${}_{s}^{s}\mathrm{p}K_a^2$ of 7.70 followed by a long plateau with $k_{\mathrm{cat}}^{\mathrm{max}} = 4.4\ \mathrm{s}^{-1}$. There is no evidence of a ${}_{s}^{s}\mathrm{p}K_a^3$ value for ionization of [Cu(II):**1**] in ethanol up to ${}_{s}^{s}$pH 12. The difference in observed ${}_{s}^{s}\mathrm{p}K_a^3$ and ${}_{s}^{s}\mathrm{p}K_a^2$ values from water to methanol and ethanol media might be a consequence of the poorer ability of the alcohol to stabilize anion formation (as in [Cu(II):**1d**]$^-$) and/or a change in the relative amounts of [Cu(II):**1b/c**]^0 in the three solvents. The autoprotolysis constants of the three solvents increase ($\mathrm{p}K_{\mathrm{auto}}$ = 14, 16.77, and 19.1, respectively[17]) so that neutrality is at pH 7 and ${}_{s}^{s}$pH 8.4 and 9.55 respectively. Thus, in passing from methanol to ethanol, ${}_{s}^{s}\mathrm{p}K_a^2$ ionization occurs at substantially less than neutrality which is consistent with the lower polarity solvent favoring the formation of the charge neutral species [Cu(II):**1b/c**]^0.

The rate constants for decomposition of [Cu(II):**1a**]$^+$ can be compared only in methanol and ethanol, since the ${}_{s}^{s}$pH/rate profiles in these solvents exhibit plateaus in the low ${}_{s}^{s}$pH domain. The k_1 value in ethanol is about 30 times greater than in methanol ($2.1 \times 10^{-2}\ \mathrm{s}^{-1}/6.4 \times 10^{-4}\ \mathrm{s}^{-1}$), suggesting that ethanol favors a transition state where charge is being dispersed relative to the monocationic ground state of the complex. The $k_{\mathrm{cat}}^{\mathrm{max}}$ rate constants for the decomposition of the formally neutral complex [Cu(II):**1b/c**]^0 varies by a factor of about 100 in the three solvents from 0.12 s^{-1} in water to 14.7 and 4.4 s^{-1} in methanol and ethanol. There is not a simple rationalization for this apparently inverted order as a function of solvent polarity; perhaps this is consistent with the proportions of [Cu(II):**1b/c**]^0 being different in the two alcohol solvents and/or greater stability of the ground state of the neutral species in water than in either alcohol since $\mathrm{p}K_a{}^2$ in water is less than ${}_{s}^{s}\mathrm{p}K_a^2$ in either methanol or ethanol, even accounting for the differences in the autoprotolysis constants. Nevertheless, considerable ambiguity exists due to trade-offs in dielectric constant effects and specific solvent interactions with the ground and transition states making any rationale highly speculative.

4.1.2. [Cu(II):2,3]. With [Cu(II):**2**] in water, no $\mathrm{p}K_a{}^1$ value is observed down to pH 1 but there is a second apparent $\mathrm{p}K_a{}^2$ value for ionization of [Cu(II):**2b**]$^+$ of 7.94 which is tied to a following dimerization of [Cu(II):**2**]^0. The latter value shifts to a ${}_{s}^{s}\mathrm{p}K_a^2$ value of 10.25 in methanol. The only observed ionization of [Cu(II):**2**] in ethanol is ${}_{s}^{s}\mathrm{p}K_a^1$ = 1.05 forming [Cu(II):**2b**]$^+$. The rate constants for decomposition of [Cu(II):**2b**]$^+$ vary by about 2000 in the three solvents, with the lowest in water being $5.6 \times 10^{-6}\ \mathrm{s}^{-1}$, while those in methanol and ethanol are 2.5×10^{-3} and $3.5 \times 10^{-3}\ \mathrm{s}^{-1}$.

With [Cu(II):**3**] there is no possible acid dissociation of the phosphate, so the only pH dependent change in charge on the complex results from the formation of Cu(II) hydroxides or alkoxides. No process corresponding to the conversion of [Cu(II):**3a**]$^{2+}$ to the Cu(II):hydroxide form [Cu(II):**3b**]$^+$ is observed from pH 1−7 in water. In methanol, the ${}_{s}^{s}\mathrm{p}K_a^1$ value is 6.05 and shifts to a value of 10.75 in ethanol. The observed rate constants for decomposition of [Cu(II):**3a**]$^{2+}$ in the three solvents are very similar, being $1.7 \times 10^{-5}\ \mathrm{s}^{-1}$ in water, $2.0 \times 10^{-5}\ \mathrm{s}^{-1}$ in methanol, and $7.3 \times 10^{-5}\ \mathrm{s}^{-1}$ in ethanol. As will be shown, this stems from a compensation of change in both the activation enthalpies and entropies in the three solvents.

4.2. Trends in Enthalpies and Entropies of Activation for Decomposition of Cu(II)-Bound Phosphate Esters.

The rates of solvolytic cleavage of complex molecules depend on the relative energy levels of the ground- and rate-limiting transition states. Thus, a change in reaction rate brought on by a change in solvent relate to how the medium alters these relative energies.[25] The relevant free energies for the processes and their transfer from one solvent to another are shown in Scheme 6, where S1 and S2 are the two solvents in question and $\Delta G^{\circ}_{(\mathrm{S1}\rightarrow\mathrm{S2})}$ and $\Delta G^{\ddagger}_{(\mathrm{S1}\rightarrow\mathrm{S2})}$ represent the free energies of transfer of the ground and transition states between the two solvents. The latter values are determined[26] by interactions of the solvent molecules with (1) the ground state, (2) the transition state, and (3) other solvent molecules.

Equation 6 gives an expression for the $\Delta\Delta G^{\ddagger}$ resulting from a solvent change on the free energies of the transition and ground states, which is further broken into the effects on $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ as in eqs 7 and 8. For the three complexes in question, the changes in free energies computed on

$$\Delta\Delta G^{\ddagger} = \Delta\Delta G^{\ddagger}_{(\mathrm{S1}\rightarrow\mathrm{S2})} - \Delta\Delta G^{\circ}_{(\mathrm{S1}\rightarrow\mathrm{S2})} \qquad (6)$$

Scheme 6. Free Energies for Dissolution and Reaction Transition State of [Cu(II):1,2,3] and the Change in Free Energies Induced by Changing the Solvent

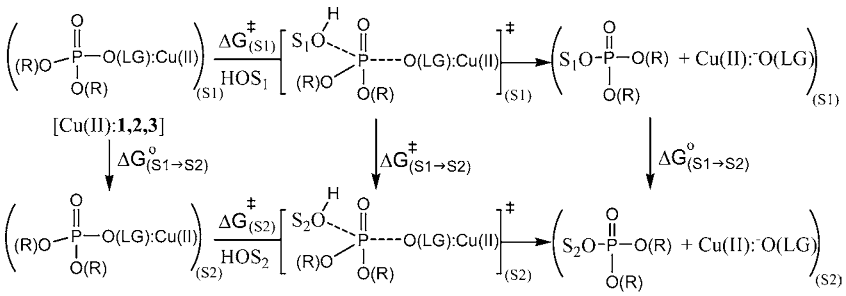


Table 4. Listing of Changes in Activation Parameters for the Decomposition of [Cu(II):**1**,**2**,**3**] Accompanying Changes in Solvent from Methanol to Water and Methanol to Ethanol

	$CH_3OH \rightarrow H_2O$				$CH_3OH \rightarrow CH_3CH_2OH$			
complex	$\Delta\Delta H^{\ddagger a}$	$\Delta\Delta S^{\ddagger}$ (e.u.)^{b}	$-T\Delta\Delta S^{\ddagger a}$ (25 °C)	$\Delta\Delta G^{\ddagger a}$ (25 °C)	$\Delta\Delta H^{\ddagger a}$	$\Delta\Delta S^{\ddagger}$ (e.u.)^{b}	$-T\Delta\Delta S^{\ddagger a}$ (25 °C)	$\Delta\Delta G^{\ddagger a}$ (25 °C)
[Cu(II):**1b**/**c**]^{0}	1.5	−4.4	1.3	2.8	−3.0	−12.2	3.6	0.6
[Cu(II):**2b**]$^{+}$	1.4	−8.1	2.4	3.8	−3.3	−10.8	3.2	−0.1
[Cu(II):**3a**]$^{2+}$	−2.5	−9	2.7	0.2	−3.2	−8.6	2.6	−0.6

^{a}In kilocalories per mole. ^{b}In calories per kelvin mole.

$$\Delta\Delta H^{\ddagger} = \Delta\Delta H^{\ddagger}_{(S1\rightarrow S2)} - \Delta\Delta H^{\circ}_{(S1\rightarrow S2)} \tag{7}$$

$$\Delta\Delta S^{\ddagger} = \Delta\Delta S^{\ddagger}_{(S1\rightarrow S2)} - \Delta\Delta S^{\circ}_{(S1\rightarrow S2)} \tag{8}$$

the basis of the changes in the activation parameters for the decomposition of [Cu(II):**1b**/**c**]^{0}, [Cu(II):**2b**]$^{+}$, and [Cu(II):**3a**]$^{2+}$ in passing from water to methanol and methanol to ethanol at 25 °C are given in Table 4. This can be more clearly seen in Figure 7 where $-T\Delta S^{\ddagger}$ is plotted vs $\Delta H^{\ddagger}$ for the decomposition of [Cu(II):**1**,**2**,**3**] in water, methanol, and ethanol. The figure can be referred to using a compass, where moving along the diagonal southeast (SE) in Figure 7 increases the activation $\Delta H^{\ddagger}$ but reduces the $T\Delta S^{\ddagger}$ contribution to $\Delta G^{\ddagger}$, resulting in little effect on the reaction rate. Moving NE increases both the enthalpy and entropy contribution, slowing the reaction considerably. In the case of cleavage of [Cu(II):**3a**]$^{2+}$, moving NW from MeOH to water leads to a decrease in $\Delta H^{\ddagger}$ and more positive $T\Delta S^{\ddagger}$, compensating each other to an extent that the reaction rate does not change appreciably.

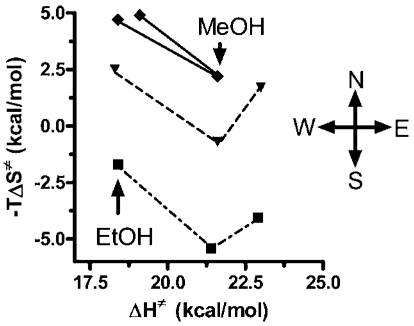


Figure 7. Plot of $-T\Delta S^{\ddagger}$ vs $\Delta H^{\ddagger}$ for the decomposition of [Cu(II):**1**,**2**,**3**] (■, ▼, ♦, respectively) in ethanol (leftmost vertical points), methanol (center vertical points), and water (unmarked points) at 25 °C in the plateau regions where the active forms are [Cu(II):**1b**/**c**]^{0}, [Cu(II):**2b**]$^{+}$, and [Cu(II):**3a**]$^{2+}$. The various lines connecting the three species are not fits, but aids for visualization.

Pertinent to Figure 7 are Leffler's and Lumry and Rajender's treatises discussing the enthalpy−entropy relationship for various solvolytic and other reactions where emphasis was put on the possible linear relationships between the two activation parameters.[27,28] These refer to related reactions or equilibria involving modest changes in substrate or solvent, where it is often found that the ΔH and ΔS parameters vary in a dependent way. The Figure 7 data indicate that, for the decomposition of [Cu(II):**1b**/**c**]^{0}, [Cu(II):**2b**]$^{+}$, and [Cu(II):**3a**]$^{2+}$, moving from methanol (center vertical points) to ethanol (leftmost vertical points), there is a decrease in the $\Delta H^{\ddagger}$ of each reaction of roughly 3.0−3.3 kcal/mol, which is offset by a net increase in the $-T\Delta S^{\ddagger}$ term of 2.6−3.6 kcal/mol; thus the change in the overall free energy of reaction for all three substrates does not vary appreciably at 25 °C. However, passing from methanol to water causes wider variations of the activation parameters in the series, increasing both $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ by moving NE in Figure 7 for [Cu(II):**1b**/**c**]^{0} and [Cu(II):**2b**]$^{+}$ such that the $\Delta G^{\ddagger}$ for these two reactions is raised by 2.8 and 3.8 kcal·mol^{-1}. This accounts for the 10^{2}−10^{3} drop in the rates of these reactions in passing from methanol to water. By contrast there is an approximate cancelation of these two terms for cleavage of [Cu(II):**3a**]$^{2+}$ in passing from methanol to water moving NW, leading to a reduction of 2.5 kcal/mol in $\Delta H^{\ddagger}$ and an increase in the $-T\Delta S^{\ddagger}$ of 2.7 kcal/mol such that the net change in $\Delta G^{\ddagger}$ is only −0.2 kcal/mol.

Moving from alcohol to water induces irregular perturbations on $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ in the series for reasons that are not obvious. Winstein and Fainberg[25] have pointed out how exceedingly difficult it is to evaluate the effect of solvent changes such as MeOH → water and EtOH → water even on an apparently simple process like the solvolysis of *tert*-butyl chloride. While not strictly comparable to the more complex situation of spontaneous solvolysis of the Cu(II) complexes here with their varying formal charges, it is clear that changes in the free energy of solvation of the ground state ($\Delta\Delta G^{\circ}_{s}$) are just as, or more, important as those on the transition state, $\Delta\Delta G^{\ddagger}_{s}$.[29] Given the difficulties in separating the effect of solvent changes on $\Delta\Delta G^{\circ}_{s}$ into the individual $\Delta\Delta H^{\circ}_{s}$ and $\Delta\Delta S^{\circ}_{s}$ terms, it is inappropriate to attempt further interpretations as to the origins of the solvent effect on the activation parameters other than to say that water seems to be the outlier.

4.3.1. Mechanistic Picture. *Cleavage of Phosphate Esters in Solution without Catalysts.* In water, the decomposition of phosphate monoester dianions containing aryloxy leaving groups proceeds by an apparent unimolecular route involving a significant positive entropy and unit solvent isotope effect that is consistent with a dissociative mechanism with little involvement of a nucleophilic role for solvent.[30] There is a significantly more positive entropy of activation for the solvolysis of *p*-nitrophenyl phosphate dianion in *tert*-butyl alcohol which supports a dissociative ($D_N + A_N$) mechanism confirming that racemization at phosphorus in this reaction is attributed to the direct formation of meta-phosphate anion, with no nucleophilic role for the solvent in the P−OAr cleavage.[31]

Kirby and Younas[32] reported that the aqueous cleavage of phosphate diesters is exceedingly slow and highly dependent on the LG basicity. The reaction is bimolecular with hydroxide being the active nucleophile down to pH 5 where a water-promoted reaction was observable with leaving groups as good as, or better than, 4-nitrophenoxy but not with poorer ones like phenoxy or 4-methoxyphenoxy. Methanolysis of aryl methyl phosphates involves methoxide attack on the monoanion, probably with a concerted departure of leaving group via an A_ND_N mechanism.[33]

Hydrolyses of dialkyl aryl phosphate triesters[34] with good leaving groups in water are subject to HO^-, H_3O^+, and solvent promoted reactions. For the least reactive of the tested esters (such as the 4-nitrophenyl derivative), the base and acid wings account for the hydrolysis over almost all the investigated pH range except for a small deviation at ~pH 4 that may result from a water reaction. The methanolysis of dimethyl aryl phosphates is methoxide promoted.[35] Recent computational studies indicate that both the hydroxide[36] and methoxide[37] reactions are enforced concerted with good aryloxy leaving groups having pK_a ($^{s}_{s}pK_a$) values <8 (*m*-nitrophenol in water) or <12.3 (3,5-dichlorophenol in methanol), but stepwise with rate-limiting formation of an anionic 5-coordinate phosphorane intermediate when the phosphate has poorer leaving groups.

4.3.2. Decompositions of Cu(II):1,2,3 Promoted by Leaving Group Assistance. Rate data presented here and earlier[16] support the idea that positioning the Cu(II) ion close to the leaving group's developing oxyanion results in a loosening of the transition state for P−O(LG) cleavage for [Cu(II):**1**,**2**,**3**] by reducing the requirement for nucleophilic participation in expelling the leaving group. Using More O'Ferrall-Jencks diagrams, the effect of Cu(II) on the cleavage relative to the uncatalyzed methanolysis of mono-, di-, and triesters has been rationalized as moving the transition state earlier with respect to P−nucleophile interaction with little change in the extent of P−O(LG) cleavage,[16] and the same is likely true in ethanol and water. The leaving group acceleration provided by Cu(II) coordination comes from converting the poor leaving group, uncomplexed 2(2′-phenathrolyl)phenoxide, into a far better leaving group.[38] Extant data indicate that the β_{Nuc} for the attack of oxyanion nucleophiles on phosphate triesters becomes smaller as the leaving group gets better,[34] and also that the k_{H2O} for water attack on both phosphate diester anions[32] and monoester dianions[30] increases as the leaving group gets better. It follows that, in the limit when the leaving group is very good, the effective nucleophile will be the one having the highest concentration in solution, namely solvent. For all three phosphate complexes in this study, this is the case since the reactions in ethanol, methanol or water involve only solvent attack on $[\mathrm{Cu(II)}:\mathbf{1b/c}]^0$, $[\mathrm{Cu(II)}:\mathbf{2b}]^+$, or $[\mathrm{Cu(II)}:\mathbf{3a}]^{2+}$.

The data herein also indicate that there is a very large acceleration of P−O(LG) cleavage attributable to LGA relative to the background reactions in each solvent. While this is quantified in only methanol[16] as being 10^{14}−10^{15} for the monoester, 10^{14} for the diester, and 10^5 for the triester, the fact that similar rate constants are observed in all solvents (changes from little effect to no more than 500-fold rate reduction in the case of $[\mathrm{Cu(II)}:\mathbf{2b}]^+$ in moving from methanol to water) suggests that the high degree of acceleration obtained from LGA is attainable in all three media.

The synthetic difficulties in making appropriate small molecule systems that position the metal ion optimally to assist in the departure of the leaving group impose serious limitations in achieving significant LGA. Nevertheless, the present results seem to suggest that in optimized cases, such as enzymes where the tertiary structure controls the placement of the metal ion relative to the departing leaving group, this mode of catalysis could provide a significant source of acceleration.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial assistance of the Natural Sciences and Engineering Research Council of Canada (NSERC), Queen's University, and the Canada Foundation for Innovation (CFI). In addition they acknowledge helpful discussions with, and the technical assistance of, Dr. Alexei A. Neverov.

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(17) (a) Gibson, G. T. T.; Mohamed, M. F.; Neverov, A. A.; Brown, R. S. *Inorg. Chem.* **2006**, *45*, 7891. (b) For the designation of pH in non-aqueous solvents, we use the nomenclature recommended by *IUPAC: Compendium of Analytical Nomenclature. Definitive Rules 1997*, 3rd ed.; Blackwell: Oxford, U.K., 1998. The pH meter reading for an aqueous solution determined with an electrode calibrated with aqueous buffers is designated as $^{w}_{w}pH$; if the electrode is calibrated in water and the "pH" of the neat buffered methanol solution is then measured, the term $^{s}_{w}pH$ is used; and if the electrode is calibrated in the same solvent in which the pH reading is made, then the term $^{s}_{s}pH$ is used. In ethanol, $^{s}_{w}pH - (-2.54) = {}^{s}_{s}pH$, and since the autoprotolysis constant of ethanol is $10^{-19.1}$, the neutral $^{s}_{s}pH$ is 9.6.

(18) Solvent composition = water − methanol (95−5 mol %).

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