A Polymeric Amine–Copper(II) Complex as Catalyst for the Hydrolysis of 1,2,2-Trimethylpropyl Methylphosphonofluoridate (Soman) and Bis(1-methylethyl)phosphorofluoridate (DFP)*

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SYNOPSIS

The Cu(II) complex of poly-4-vinylpyridine, quaternized with 19 mol % ethyl bromide and 36 mol % 4-chloromethyl-4'-methyl-2,2'-bipyridine, was examined as a catalyst for the hydrolysis of the toxic organophosphorous compounds bis(1-methylethyl) phosphorofluoridate (**1**,[‡] DFP) and 1,2,2-trimethylpropyl methylphosphonofluoridate (**2**,[‡] soman). Studies were carried out at 25.0 and 37.0°C for both substrates in MOPS buffer at pH 7.0. In the presence of $7.31 \times 10^{-3} M$ catalyst at 25.0°C, soman is hydrolyzed with a first-order rate constant of 0.019 min^{-1} ($t_{1/2} = 37.5$ min), whereas DFP hydrolyzes with a rate constant of 0.011 min^{-1} ($t_{1/2} = 63.8$ min). For soman, this represents a 14-fold increase over the uncatalyzed rate in the same buffer. Other studies examined the effect of a strongly sorptive polymeric resin on catalysis by this copper-containing polymer and found a dramatic decrease in the hydrolysis rate of soman in the presence of the polymeric sorbent.

INTRODUCTION

The hydrolysis of toxic organophosphorous compounds is of both theoretical and practical interest since these compounds present considerable hazards as potent acetylcholinesterase inhibitors. A number of studies have examined the catalytic hydrolysis of organophosphorous esters, in efforts to develop a general method for detoxification of this class of compounds.[1a-j]

Metal ions and their chelated complexes have been extensively evaluated, over a number of years, as catalysts for the hydrolysis of organophosphorous esters. The hydrolysis of bis(1-methylethyl) phosphorofluoridate (**1**, DFP) is catalyzed by a number of these metal complexes.[2] For example, a CuSO$_4$-dipyridyl (1 : 1) complex ($2.28 \times 10^{-2} M$ in pH 7.6 buffer, 38°C) reduced the half-life for DFP to 4.5 min from the uncatalyzed half-life of > 2500 min.[2]

$$\begin{array}{c} O \\ \| \\ R_1 - P - F \\ | \\ R_2 \end{array}$$
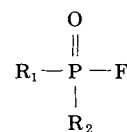
1 (DFP), $R_1 = R_2 = i - C_3H_7O$

2 (Soman), $R_1 = (CH_3)_3CCH(CH_3)O$; $R_2 = CH_3$

The Cu(II)-metal complex-catalyzed hydrolysis of the chemical warfare agent ethyl N,N-dimethylphosphoramidocyanidate (tabun) has also been examined.[3] Courtney et al.[4] examined a series of chelation compounds and various metal complexes as

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catalysts for the hydrolysis of DFP and the chemical warfare agent 1-methylethyl methylphosphono-fluoridate (sarin). Those studies demonstrated that the Cu(II) catalysts were, as a group, more active than other metal-based catalysts for promoting the hydrolysis of both DFP and sarin. More recently, it has been shown that in the presence of the CuCl₂ complex of N,N,N'-trimethyl-N'-tetradecylethylenediamine, at 25°C and pH 7.0, the half-life of 1,2,2-trimethylpropyl methylphosphonofluoridate (soman) could be reduced to under 1 min from 60 h at pH 10.[5a] In addition, the kinetic activity of a very interesting group of polymer-bound copper complexes has been examined for their ability to catalyze the hydrolysis of two organophosphorous ester "simulants" for toxic nerve agents such as soman.[5b]

The Cu(II) complex of poly(4-vinylpyridine), quaternized with 19 mol % ethyl bromide and 36 mol % 4-chloromethyl-4'-methyl-2,2'bipyridine (**3**), was provided to our laboratory by workers at the Research Triangle Institute and has been reported to have significant catalytic activity against DFP.[6]
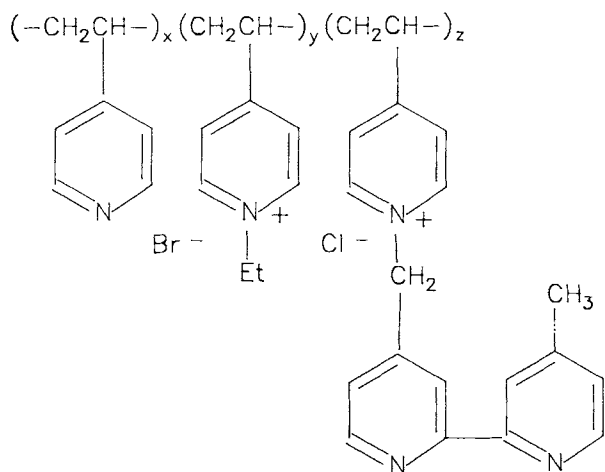
3, $y = 0.19$ $z = 0.36$

In an ongoing effort to identify catalytic decontaminants with the potential for cutaneous applications against organophosphorous chemical warfare agents, we have examined the ability of **3** to catalyze the hydrolysis of both DFP and soman. These studies were initiated for several reasons. Kinetic studies with DFP had already been conducted, thus providing data for validation of the activity of this catalyst. The techniques needed to work with the more toxic organophosphonate soman were available in our laboratory. We believed that studies examining the

activity of **3** against the actual chemical agent were needed to provide a more complete understanding of the chemistry of these types of catalysts.

Studies were carried out at 25.0 and 37.0°C for both soman and DFP, at pH 7.0. Reaction kinetics were followed through use of an ion-specific electrode for measurement of fluoride released during the hydrolysis reaction. Other studies examined the effect of a strongly sorptive polymeric resin on catalysis by the copper-containing polymer, **3**.

EXPERIMENTAL

Materials

MOPS, 4-morpholinepropane sulfonic acid and DFP were available from Sigma Chemical Company. TISAB III was obtained from Orion Research and contains ammonium acetate, ammonium chloride, 1,2-cyclohexylene dinitrilo tetraacetic acid (CDTA), and acetic acid. Other buffer components were of reagent grade and were used as received. Soman was obtained from the Chemical Research, Development and Engineering Center's Research Laboratory, Aberdeen Proving Ground, Maryland, and was analyzed (gas chromatography and ³¹P NMR) for content and found to be > 95% pure. Stock solutions of this compound were prepared as dilute solutions in water (glass-distilled) and were stored frozen prior to use. DFP was prepared as stock solutions in ethanol and made up as dilute aqueous solutions prior to use. Final concentrations of ethanol in the reaction mixtures were typically 1% (v/v), except as noted. Stock solutions of DFP were prepared at a minimum of once a week and stored in a refrigerator between uses. Samples of Ambersorb XE348F (a carbonaceous sorbent resin) were obtained from the Rohm and Haas Co., Spring House, PA, and were used as received.

Buffer Solutions

MOPS buffer was prepared as follows: 4-Morpholinepropanesulfonic acid $0.1 M$; MgCl₂, $0.01 M$; 0.002% (w/v) NaN₃; 0.01% (w/v) bovine serum albumin (BSA), with pH adjusted to 7.0 with aqueous NaOH. (This specific MOPS buffer was used so that parallel determinations of the substrate concentration might be made by following inhibition of acetylcholinesterase. Although this technique was not used in these studies, it was used in later studies.) Ten percent TISAB (pH 5.5) was prepared from

reagent-grade TISAB III by dilution of the stock buffer 1 : 10 with glass-distilled water.

Kinetic Studies

Hydrolysis reactions for **1** and **2** were followed through measurement of fluoride release over time. Fluoride analyses were carried out using an Orion Model EA940 Ion Analyzer with a combination fluoride electrode. Prior to a series of kinetic runs, a standard curve was established using solutions of catalyst, buffer, and a sodium fluoride standard solution. Concentrations of buffer and catalyst were equivalent to those in the actual reaction solutions. Concentrations of NaF used for the standard solutions typically covered the range of 1.0×10^{-4} to $1.0 \times 10^{-3} M$, with a minimum of five concentrations used for each standard curve. Each day, a minimum of three standards were reanalyzed and compared to the standard curve to detect any deviation.

For a standard curve, as well as for the samples containing substrate, aliquots of the solution to be analyzed were added to either $0.1N$ aqueous NaOH or to 10% TISAB buffer. Following a waiting period of not less than 15 min (to allow for hydrolysis of substrate), the NaOH-treated samples were then diluted with 10% TISAB buffer. All samples were then analyzed for fluoride concentrations. Aliquots added to buffer provided a measure of fluoride released through hydrolysis of substrate, whereas samples added to $0.1N$ NaOH gave a measure of total available fluoride, e.g., fluoride and remaining substrate. The difference in fluoride concentrations between these two samples provided a measure of unhydrolyzed substrate. For kinetic runs, between six and 12 samples were taken at various time points during the reaction period, with two aliquots removed at each time point.

A typical kinetic run for the hydrolysis of **1** or **2** was carried out as follows: An appropriate amount of catalyst (**3**) was added to 11.1 mL of MOPS (pH 7.0) buffer in a reaction flask. The reaction flask was placed in a fume hood and was equipped with a syringe fitted with Teflon tubing. The tubing was placed into the reaction mixture to allow for periodic sampling during the reaction period. To initiate a reaction, a 0.9 mL aliquot of substrate (5.3–$7.0 \times 10^{-3} M$ for DFP and approximately $1.1 \times 10^{-2} M$ for soman) in aqueous solution was added to the catalyst mixture with rapid stirring. Final concentrations of substrate were typically in the range of 4–$11 \times 10^{-4} M$. Reaction temperatures were maintained at 25.0 or $37.0 \pm 0.1°C$ through use of a constant temperature water bath. Reactions were car-

ried out with constant stirring. First-order rate constants, k_{obs}, were calculated using either an exponential fitting routine[7] or through linear regression analysis of ln ([fluoride]$_{inf}$ − [fluoride]$_t$) vs. time.

To determine the kinetics of the hydrolysis of soman in the presence of the sorbent resin XE348F, reactions were carried out in an ultrafiltration cell equipped with a 0.45 μm pore-size filter and modified so that stirring was carried out at a constant speed with a mechanical stirrer. Buffer, catalyst **3**, and samples of the solid sorbent resin were added to the cell, and the cell was placed in a constant temperature bath. This was then equipped with a three-way stopcock attached via Teflon tubing to the sampling port and, with a tube extending down into the slurry of catalyst, to the resin and buffer. Blank samples (100 μL) were removed from both the sampling port (filtered samples) and from the slurry and were added to aliquots of 10% TISAB or $0.1N$ NaOH. Samples added to aqueous NaOH were allowed to stand for approximately 1 h and were then further diluted with 10% TISAB prior to measurement of fluoride concentration. Buffer samples were measured as soon as practical following sampling to minimize further hydrolysis. These samples were used to provide background readings for fluoride prior to addition of substrate. Reactions were initiated through addition of a 4.5 mL aliquot of approximately $1.1 \times 10^{-2} M$ soman in aqueous solution to a slurry containing 55.5 mL MOPS buffer and catalyst or 55.5 mL buffer, catalyst, and sorptive resin. Note that the total amount of filtrate removed during the course of any kinetic run remained less than 10%, to avoid concentration of soman in the slurry and thus minimize the potential for deviation from first-order kinetics. As with the background blanks, aliquots of filtrate and slurry were removed periodically through the course of the reaction and added either to buffer or to $0.1N$ NaOH. Filtrate samples added to buffer provide a measure of fluoride that results from the hydrolysis of substrate during the reaction. Filtrate samples added to base provide a measure of both free fluoride and fluoride liberated from remaining substrate in the solution. Similarly, samples of slurry added to either buffer or $0.1N$ NaOH provided measures of bound (to the polymeric sorbent resin) and free fluoride and measures of total fluoride liberated on hydrolysis of bound and free substrate. Through manipulation of the data, bound and free fluoride concentrations and bound and free substrate concentrations may be derived for each time point sampled during the reaction. Typically, plots of ln [soman] vs. time, cal-

culated from these data, were well fit by linear regressions and appear to obey first-order kinetics.

RESULTS AND DISCUSSION

At constant pH in aqueous buffer solutions, the observed rate of hydrolysis for organophosphorous esters, such as **1** and **2**, may be represented as the sum of a number of different terms in the kinetic equation. These include, but are not limited to, the terms for water- and hydroxide-mediated hydrolysis, terms for catalysis by various buffer components, and, in the present case, a term for that portion of the overall rate catalyzed by the Cu(II) complex, **3**:

$$-d[OP]/dt = k_{OH}\text{-}[OP][^-OH] + k_{HOH}[OP]$$
$$+ \sum (k_B[OP][\text{Buffer}]) + k_{cat}[OP][\textbf{3}]$$

Under the conditions examined for catalysis by compound **3**, at pH 7.0, the terms for the contribution by water and hydroxide hydrolysis are small and may be ignored. Further, as will be shown later, buffer catalysis contributes relatively little to the hydrolysis of **2** and may also be ignored. Thus, for true catalysts or where a catalyst is present in large excess, hydrolysis of substrates like **1** and **2** follows first-order kinetics with the rate of hydrolysis approximately equal to the first-order rate constant times the concentration of substrate:

$$-d[OP]/dt = k_{obs}[OP]$$

where $k_{obs} = k_{cat}[\textbf{3}]$.

For our studies, ratios of catalyst to substrate were in the range of 3 : 1 to 34 : 1 and all reactions appeared to obey first-order kinetics. Because of a relatively small supply of available catalyst, only a limited number of kinetic studies were carried out for the hydrolysis of **1** and **2** by compound **3**.

For hydrolysis of DFP by **3** at $7.31 \times 10^{-3}M$ catalyst concentration and 25°C, the observed first-order rate constant was 0.011 min^{-1}, with k_{cat} = $1.49M^{-1}$ min^{-1} (Table I). Raising the reaction temperature to 37.0°C increased the second-order rate constant to $3.38M^{-1}$ min^{-1}, a 2.3-fold increase in the rate of hydrolysis. Addition of a second aliquot of DFP to this same reaction mixture gave k_{cat} = $3.00M^{-1}$ min^{-1}. The half-life for hydrolysis of DFP at pH 7.0 and 37.0°C, catalyzed by $6.8 \times 10^{-3}M$ **3**, was found to be 30.1 min. This value is in relative agreement with that found by Bao et al.[6] for this same catalyst at $5.63 \times 10^{-3}M$, 38°C and pH 7.0, where the half-life was found to be 27 min.

The Cu(II) catalyst also showed substantial activity against the chemical warfare agent soman. At 25.0°C, soman was hydrolyzed with a second-order rate constant of $2.55 \pm 0.3M^{-1}$ min^{-1} ([**3**] = 7.31 $\times 10^{-3}M$, Table I). This represents a 1.7-fold increase over the k_{cat} found when DFP is the substrate at this same temperature. At 37.0°C, the second-order rate constant for soman hydrolysis increased to $5.1M^{-1}$ min^{-1}, an increase of approximately twofold over k_{cat} determined at 25.0°C. At 25.0°C, a catalyst concentration of $7.31 \times 10^{-3}M$ provides a 14-fold enhancement in the observed first-order rate constant for soman hydrolysis over that found in the absence of catalyst. Compound **3** is a somewhat less effective catalyst for soman hydrolysis than was o-iodosobenzoic acid or its derivatives, with those examined at pH 7.5 and 25.0°C in micellar solutions. In that case, the ratio of k_{obs}/k_{uncat} was found to be 26.3 for o-iodosobenzoic acid even at much lower catalyst concentrations, i.e., $1 \times 10^{-4}M$.[1j] Compound **3** is also catalytically less effective for soman hydrolysis than is a series of copper(II)/O-alkylpyridine-2-carboximidate complexes recently reported by Katritzky et al.[8] These complexes, examined under comparable conditions, gave k_{obs} values for soman hydrolysis approximately tenfold greater than those found for **3**.

Over the past several years, other work in our laboratory has focused on examining the effect of polymeric decontaminants against chemical warfare agents in both aqueous and nonaqueous solvents.[§] Our ultimate goal in these studies has been to identify materials that might be of use for cutaneous decontamination applications. Based on this work, and the knowledge that the carbonaceous polymeric sorbent resin Ambersorb XE348F rapidly sorbs the organophosphorous compounds DFP and soman from aqueous solutions, we decided to examine the effect of this sorptive polymer on the catalytic activity of **3** against soman. Our aim in this work was to assess the decontamination potential for a mixture of resins that should rapidly sorb and then hydrolyze these toxic compounds.

As noted previously, in the absence of catalyst **3**, the $t_{1/2}$ for hydrolysis of soman in MOPS, pH 7.0,

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[§] Our laboratory has extensively examined a variety of polymeric cationic and anionic resins (Amberlite resins and others), as potential decontaminants for toxic chemicals. These materials, available from the Rohm and Haas Co., Philadelphia, PA, have been shown to act as effective decontaminants of soman and DFP (unpublished results). In addition, carbonaceous sorbent resins such as Ambersorb XE348F have been shown to be effective at the rapid sorption of these same hydrophobic organophosphorous materials from aqueous mixtures.

Table I Hydrolysis of 1 (DFP) and 2 (Soman) in the Presence of the Cu(II) Catalyst 3, in MOPS Buffer, pH 7.0, at 25.0 and 37.0°C[a]

Subst	10^4 [Sub] (M)	Temp (°C)	10^3 [3] (M)	$\dfrac{[3]}{[\text{Subst}]}$	$10^2\,k_{\text{obs}}$ (min^{-1})	k_{cat} $(M^{-1}\,\text{min}^{-1})$	$t_{1/2}$ (min)
1	8.65	25.0	29.30	33.9	3.96	1.36	10
1	5.25	25.0	7.31	14.1	1.09	1.49	63.8
1	4.00	37.0	6.80	17.0	2.30	3.38	30.1
1[b]	3.90	37.0	6.30	16.2	1.89	3.00	36.5
2	11.80	25.0	0.00	0.0	0.13	—	545.7
2	9.95	25.0	7.31	7.3	1.86 (.2)[c]	2.55 (0.3)	37.5
2[b]	9.05	25.0	6.73	7.44	1.97 (.6)	2.93 (0.9)	37.0
2	8.78	25.0	3.66	4.17	1.04	2.86	66.3
2[b]	8.72	25.0	3.36	3.85	0.78	2.32	88.9
2	9.43	37.0	3.66	3.88	1.88	5.14	36.9
2[b]	11.17	37.0	3.35	3.00	2.23	6.66	31.1

[a] Conditions: MOPS buffer—$0.1M$ MOPS; $0.01M$ $MgCl_2$; 0.002% (w/v) NaN_3; 0.01% (w/v) BSA; pH = 7.0.

[b] Rate determined for reaction when a second aliquot of substrate was added to the reaction mixture remaining at the end of the run summarized in the previous line.

[c] (Standard deviations.)

buffer at 25.0°C was found to be 545.7 min (Table II). Addition of $7.31 \times 10^{-3}M$ **3** gave a first-order rate constant of $1.86 \times 10^{-2}\,\text{min}^{-1}$ ($t_{1/2} = 37.5$ min). Addition of the sorbent resin at 0.56% (w/v) dramatically reduced the effectiveness of catalyst **3**, with the first-order rate constant dropping to approximately $0.1 \times 10^{-2}\,\text{min}^{-1}$ either in the presence or absence of catalyst ($t_{1/2} = 580$–780 min). Increasing the amount of sorbent resin available for sorption of the agent from the aqueous solution further reduces the first-order rate constant. Thus, at 0.83% (w/v) of XE348F, k_{obs} drops to $0.074 \times 10^{-2}\,\text{min}^{-1}$ ($t_{1/2} = 932$ min). Even though less than 5%

of the soman is free in solution at any time for either of the levels of XE348F used, these results appear to indicate that the average residence time on the sorptive resin has increased for the experiment in which a greater amount of agent was used.

In an effort to displace the soman from the hydrophobic sorbent resin, and thus allow the agent access to catalyst **3**, 7.5% (v/v) of ethanol as a cosolvent was added to the reaction mixture in one experiment. Under this reaction condition, we observed an apparent increase in the rate of hydrolysis, with $k_{\text{obs}} = 0.16 \times 10^{-2}\,\text{min}^{-1}$ ($t_{1/2} = 441$ min, Table II). Thus, although not conclusive, the catalyst may

Table II Hydrolysis of 1 (Soman) in the Presence of 3 and the Sorbent Resin XE348F in MOPS Buffer at pH 7.0, 25.0°C[a]

XE348 % (w/v)	10^3 [3] (M)	10^4 [Soman] (M)[b]	$\dfrac{[\text{Catalyst}]}{[\text{Soman}]}$	$10^2\,k_{\text{obs}}$ (min^{-1})	$t_{1/2}$ (min)
0.0	0.0	11.8	0.0	0.13	545.7
0.0	7.31	9.95	7.3	1.86 (.2)[c]	37.5
0.56	0.0	9.6	0.0	0.12	582.4
0.56	7.31	7.8	9.4	0.09	779.5
0.83	7.31	5.8	12.6	0.07	931.5
0.83[d]	7.31	8.4	8.7	0.16	441.4

[a] Conditions: All reactions carried out in $0.1M$ MOPS buffer, pH 7.0, and 25.0°C except as noted.

[b] In cases were XE348F was present, this value is the concentration of soman calculated from samples of resin placed in buffer or 0.1 N NaOH (See Experimental section for details). In cases where the sorptive resin was present, < 4% of the actual available soman was in solution. The remainder was sorbed onto the resin after the first 10 min of reaction, or less.

[c] Standard deviation for first-order rate constant.

[d] Reaction carried out in MOPS with 7.5% (v/v) ethanol as cosolvent.

remain active in the presence of the sorbent resin, but simply is unable to compete effectively for the substrate.

There is an observed shift to greater hydrolysis rates for substrate **2** compared to **1** when catalyzed by **3** (Table I). This shift to more rapid hydrolysis is similar to changes found in the activity of similar Cu(II) catalysts with other substrates. In general, when comparisons are made between the rate constants for hydrolysis of phosph*oro*fluoridates (such as DFP) and phosph*ono*fluoridates, hydrolysis of the phosphonate esters proceeds with larger k_{cat} values. Hydrolysis of 1-methylethyl methylphosphono-fluoridate (sarin), catalyzed at 25.3°C, pH 7.40, by the 1 : 1 complex of Cu(II)-dipyridine ($2.24 \times 10^{-3} M$), proceeds with a half-life of 3.0 min ($k_{obs} = 2.3 \times 10^{-1}$ min^{-1}).[4] Under similar conditions, i.e., at pH 7.0 and $2.07 \times 10^{-3} M$ in the same catalyst, DFP hydrolyzed with a $t_{1/2}$ of 23 min. Thus, the conclusions that simulants are generally less reactive than the actual chemical agent and that catalysts with substantial activity against these will likely be effective against the actual agents appear to be supported.[5b]

Studies with the 1 : 1 Cu(II)/2,2'-bipyridine complex, cited previously, have shown this metal complex to be an effective catalyst against both DFP and the chemical agent sarin.[4] More recently, this same catalyst has been closely examined for its activity in the hydrolysis of both phosphate diesters and triesters.[9] Based on these earlier results, it appeared that the 2,2'-bipyridine-Cu(II) portion of **3** was likely to be the major contributor affecting the hydrolysis of DFP and soman. Therefore, it is of interest to compare the results found for DFP hydrolysis at 25.3°C by Courtney et al.[4] with those found by Bao et al.[6] for catalyst **3** in the hydrolysis of DFP at 38°C with our results. For compound **3** at $5.63 \times 10^{-3} M$ and pH 7.0, Bao et al. found the $t_{1/2}$ for hydrolysis of DFP to be 27 min. Since **3** contains 36 mol % of the 2,2'-bipyridine functionality, this corresponds to an effective concentration of the Cu(II)-bipyridine complex of $(5.63 \times 10^{-3} M) \times (0.36)$ or $2.03 \times 10^{-3} M$. For roughly equimolar concentrations of the Cu(II)-dipyridine complex, Courtney et al.[4] found the rate of hydrolysis of DFP to be essentially the same, but with those experiments carried out at 25.3°C rather than at 38°C. Based on these and our results at 25.0 and 37.0°C, we conclude that catalyst **3** is approximately 2.3-fold less active against DFP than against the monomeric Cu(II)-dipyridine complex. [The reason for this decrease in activity for the Cu(II)-2,2'-bipyridyl

moiety when located in **3** rather than in the free dipyridyl-Cu(II) complex is not clear. In part, it may result from a solubility limit for catalyst **3** in aqueous buffers, it could also arise through distribution of the copper atoms to other than (and catalytically less active than) bipyridyl sites in catalyst **3**, or it may result from effects determined by the means of attachment to the polymer matrix. These latter effects have recently been examined by Menger and Tsuno.[5b]]

In summary, it has been shown that **3** is an effective catalyst for the hydrolysis of both DFP and the toxic chemical warfare agent soman, under mild conditions of temperature and pH. Catalysis appears to obey first-order kinetics under the conditions examined. Further, a mixture of this polymer-bound catalyst and a sorptive carbonaceous polymeric resin rapidly sorb the organophosphorous agent from solution and may maintain some catalytic activity against this extremely toxic chemical warfare agent.

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