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Examination of the Catalysis Afforded by a Copper-2,2'-Dipyridyl Complex (*Final Report*)

BY:

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EXAMINATION OF THE CATALYSIS AFFORDED BY A COPPER-2,2′-DIPYRIDYL COMPLEX

by

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Final Report

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Summary

The hydrolysis reactions of two organophosphorus esters (models for the agents GB, GD, and VX) has been shown to be dramatically increased by the addition of small concentrations (≤ 7 mM) of a copper (II) complex, [(2,2'-dipyridylamine)$Cu(OH_2)_2$]$^{++}$. These reactions have also been shown to be catalytic in the complex. This system has shown all the requirements needed for effective decontamination of the organophosphorus based agents.

The hydrolysis reaction of 2-chloroethyl ethylsulfide (a model for the agent sulfur mustard or HD) has been shown to be accelerated by up to 25 % by the addition of small concentrations (≤ 1 mM) of a copper (II) complex, [(2,2'-dipyridylamine)$Cu(OH_2)_2$]$^{++}$ in 80% v/v ethanol:water, this demonstrates binding of the model compound to the complex, however, in 50% v/v ethanol:water no rate acceleration was observed.

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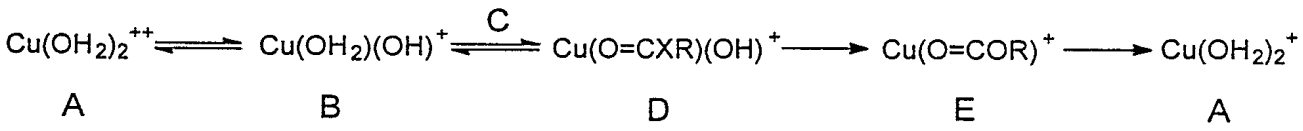
Background.

The recently reported catalytic acceleration ($2x10^6$) for the hydrolysis of methyl acetate at pH 7.0 and 25 °C by the *cis*-diaqua copper (II) complex, $[(2,2'\text{-dipyridylamine})Cu(OH_2)_2]^{2+}$ is a remarkable observation.[1] The same catalyst also catalyzes the hydrolysis of formamide, N-methylformamide and N,N-dimethylformamide in neutral solutions and at elevated temperatures (100.0 °C).[2] The proposed mechanism (scheme 1) for this reaction involves the coordination of the substrate (C, ester or amide) to the monoionised copper complex (B), to yield (D), this complex then undergoes intramolecular nucleophilic attack to give the hydrolyzed product complex (E), which regenerates the starting complex (A) by ligand exchange.



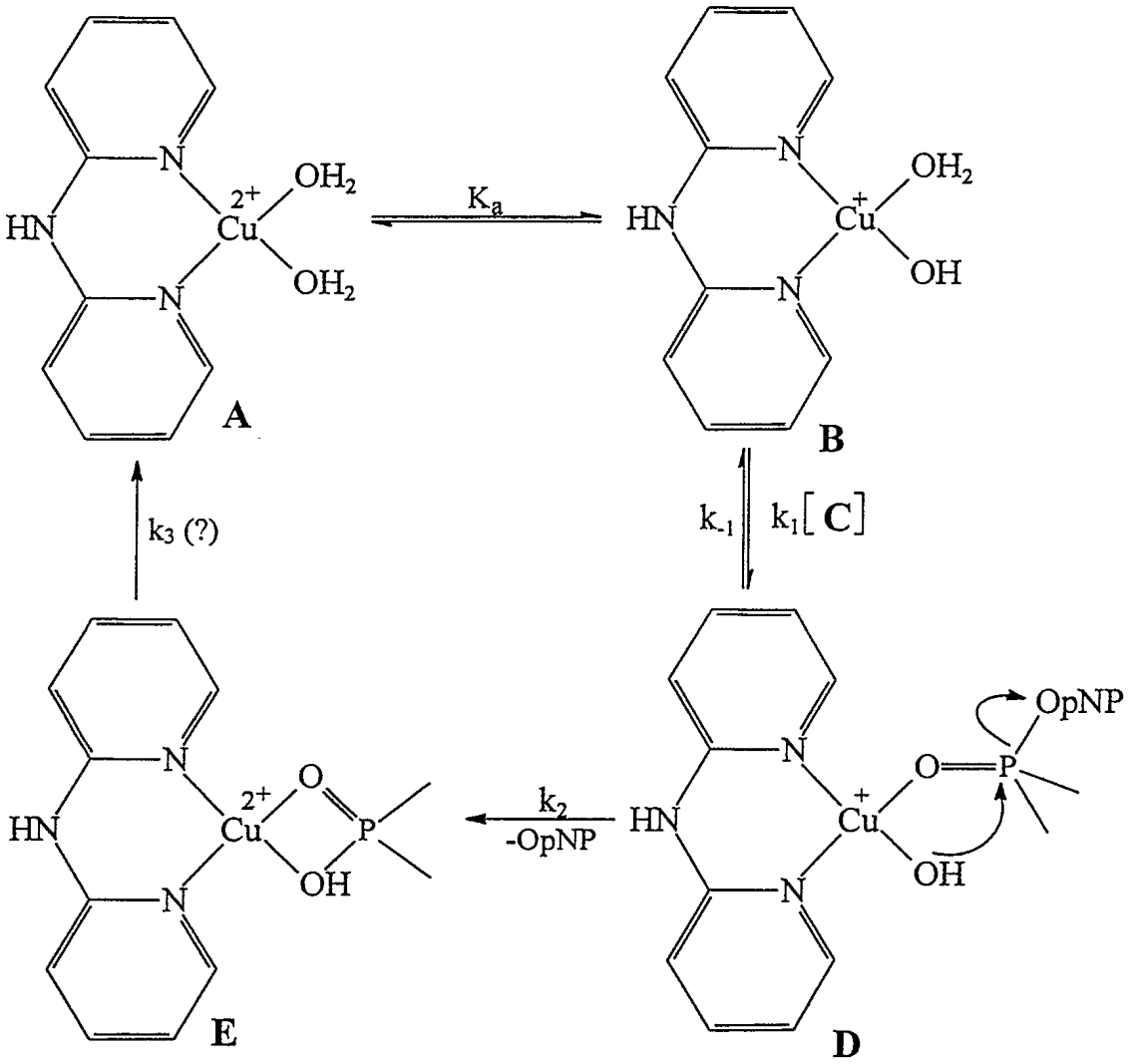
Scheme 1

Consequently, this project was undertaken to test the feasibility of this copper complex acting as a catalyst for the hydrolysis of phosphate ester linkages. Another aim of this project was to test the efficacy of the *cis*-diaqua copper (II) complex to hydrolyze 2-chloroethyl ethylsulfide as a model for the destruction of sulfur mustards.

Introduction (Phosphate Ester Hydrolysis).

The initial phase of this project involved studying the mechanism for the hydrolysis of two active phosphate esters, namely tris-(*p*-nitrophenyl) phosphate and diethyl (*p*-nitrophenyl) phosphate as models for the organophosphorus chemical agents. The minimum scheme for the mechanism of hydrolysis is shown in scheme 2, in which an initial coordination of the

organophosphate ester to an ionized copper complex is followed by an internal nucleophilic attack of a copper bound hydroxide. The expected kinetic behavior is outlined below.



Where C is tris(*p*-nitrophenyl)phosphate or
p-nitrophenyl diethylphosphate (paraoxon)

Scheme 2

Experimental (Phosphate Ester Hydrolysis).

Initial experiments showed that the more reactive substrate (tris-(*p*-nitrophenyl) phosphate) was insoluble in wholly aqueous solutions, and thus, the medium of the reaction was changed to 50% aqueous ethanol in which the substrate was more soluble. The conditions used in the hydrolysis experiments were, pH was varied between 6.20 and 7.85 using standard biological buffers (50mM: MES and MOPS) the ionic strength was maintained at 0.1M (KNO_3), temperature = 37 °C, the substrate concentration was 100μM, and the concentration of the copper complex was varied from 0 to 4mM (insoluble above 4mM, except at low pH).[3] The progress of the reaction was followed using a Cary-3E UV/Vis spectrophotometer at 400nm (pH ≥ 7), and at 360nm (pH < 7). These conditions were also used for the second substrate paraoxon.

Control experiments to show that the active species was the *cis*-diaqua copper species, showed that no hydrolysis was observed in the presence of 1mM dipyridylamine at pH 7.85. Copper nitrate (0.5mM) was insoluble in the reaction medium at pH 7.43. Catalytic turnover was followed at 460nm, using a catalyst concentration of 0.5mM and a paraoxon concentration of 1.0mM. When hydrolysis was complete a further addition of paraoxon (0.5mM) was added, after the hydrolysis was finished another portion of paraoxon (1mM) was added. After the reaction had finished five equivalents of *p*-nitrophenol had been released as shown by a standard calibration curve. The solvent isotope effect was measured at one pD in 50:50 v/v D_2O:CH_3CH_2OD.

Results (Phosphate Ester Hydrolysis).

The rate expression for the reaction depicted in scheme 1 is given in equation 1 (see appendix 1 for the derivation) where $k' = k_{obs} - k_o$, and k_o is the observed rate in the absence of catalyst.

$$k'_{obs} = \frac{k_2 K_{eq}[B]_T}{1+\left[\left[H_3O^+\right]/K_a\right]+K_{eq}[B]_T} \qquad (1)$$

This expression only holds for conditions in which the concentration of B remains constant throughout a kinetic run, i.e. the rate A is regenerated from E is greater than k_2, or the concentration of B is much greater than that of C (pseudo 1st order). Shown in figures 1a-g are the plots of k_{obs}-k_o (each point is the mean of either three or four separate determinations of the rate constant) vs. [copper complex], the solid lines are the calculated fits to equation 1 using a global analysis procedure (see below). All of the observed data can be used to characterize three constants namely k_2,K_{eq} and K_a. Shown in figures 2a-d are the plots of k_{obs} (k_o is negligibly small for this phosphate ester) vs. [copper complex], using paraoxon as the phosphate ester substrate, the solid lines are the calculated fits to equation 1. Shown in figure 3 is the data and the calculated fit for the hydrolysis of paraoxon in 50:50 v/v D_2O:CH_3CH_2OD at 37 °C and pD=8.6.

Global Analysis.

All data points (i.e., the mean value of three or four duplicate runs) were used in the non-linear least squares global minimization. For both tris-(*p*-nitrophenol) phosphate and paraoxon in 50:50 v/v ethanol:water at 37 °C all three variables k_2, K_{eq}, and K_a were unconstrained. The program used was "Systat" from SYSTAT, Inc. Evanston, Illinois. The algorithm used was either

a "Quasi-Newton" (numerical integration, on 1st and 2nd derivatives) or a "Simplex" (direct search) based procedure. The final solutions had corrected R-squared values of 0.991 and 0.996 for the hydrolysis of tris-(*p*-nitrophenol) phosphate and paraoxon respectively.

Discussion (Phosphate Ester Hydrolysis).

When *tris*-(*p*-nitrophenyl) phosphate was the substrate the following rate and equilibrium constants were calculated from the non-linear least squares analysis $pK_a = 6.71 \pm 0.04$, $K_{eq} = 380 \pm 35\ M^{-1}$, and $k_2 = 0.17 \pm 0.01\ s^{-1}$.

As can be seen in figure 1, the global fitting to the observed rate constants is qualitatively worse than the fit to the data for paraoxon (figure 2). Possible reasons include a small catalytic term for an non-ionized copper bound water, and a small term for the release of a second *p*-nitrophenol from the initially formed phosphate diester.

Clearly, the copper complex is an effective agent for the hydrolysis of this active phosphate ester. However, when using this system we cannot tell if the complex is catalytic (due to the poor solubility of the tris(*p*-nitrophenyl)phosphate. Therefore, a second substrate was chosen to probe whether catalytic turnover is occurring. The effect of deuteration of the solvent on the kinetic constants k_2 and K_{eq} has being investigated on this second phosphate ester. The selected substrate was diethyl-(*p*-nitrophenyl)phosphate which is also known as paraoxon. An additional advantage of using paraoxon as the model substrate is that all uncatalyzed reactions and attack by a copper bound water molecule are anticipated to be extremely slow. Also paraoxon only contains one active ester linkage, and thus, will not be prone to the hydrolysis of a second phosphorus-oxygen bond.

When paraoxon is used as the phosphate ester, the following rate and equilibrium constants are calculated from the non-linear least squares analysis $pK_a = 6.72 \pm 0.02$, $K_{eq} = 320 \pm 20\ M^{-1}$, and $k_2 = 5.1 \pm 0.2 \times 10^{-4}\ s^{-1}$. Analysis of the one set of data used in the solvent isotope effect study at pD 8.6, gave the following parameters $k_2 = 3.1 \pm 0.2_5 \times 10^{-4}\ s^{-1}$, and $K_{eq} = 525 \pm 82\ M^{-1}$. The solvent kinetic isotope effects can now be calculated as: $k_2\ (H_2O/D_2O) = 1.64 \pm 0.15$, and $K_{eq}\ (H_2O/D_2O) = 0.61 \pm 0.10$.

The fitted values for the ionization constant for both substrates are identical within experimental error. This lends further support to the analytical protocol used. The binding constants for the phosphate esters are also very similar, with the more electron deficient ester having a slightly higher affinity for the metal centre. The maximum rate for the catalytic hydrolysis of paraoxon is $3.1 \times 10^{-4}\ s^{-1}$ at 37 °C, which corresponds to a half time for hydrolysis of 37 minutes. The observation of catalytic turnover for the dipyridylamine copper complex, and that the absorbance verses time curve showed no evidence for biphasic behavior demonstrated that k_3 in scheme 1 is greater than k_2. The solvent kinetic isotope effect for the elimination of *p*-nitrophenol from the copper complex of 1.64 ± 0.15 can be explained in terms of fractionation factor analysis. Here as the metal bound hydroxide attacks the phosphate ester there is a corresponding weakening of the O-H bound. This bond weakening will generate a normal isotope effect. The equilibrium isotope effect on binding of the phosphate ester to the copper complex is consistent with a tightening of a O-H bond on binding, this effect arises from the copper bound water molecule that is replaced by the phosphate ester, the force constant of the O-H bonds increase as the charge on the oxygen atom decreases.

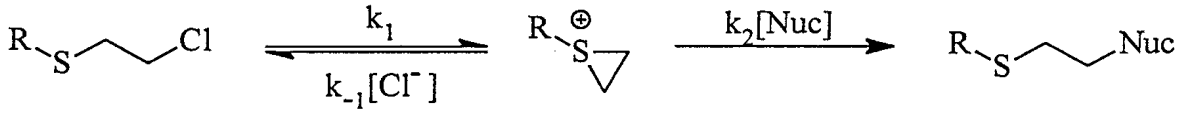
Conclusions (Phosphate Ester Hydrolysis).

The complexation of the phosphate ester to the copper complex has been demonstrated by the curvature shown in all the figures relating to the hydrolysis of tris(*p*-nitrophenyl)phosphate, and paraoxon. The maximum rate for the hydrolysis of these phosphate ester complexes to eject *p*-nitrophenol are 0.17 and 5.1 x 10^{-4} s^{-1}, which correspond to half times for hydrolysis of approximately 4 seconds and 37 minutes respectively at 37 °C.

The model systems used have shown all the requirements needed for effective decontamination. Although the hydrolysis of paraoxon is fairly sluggish at 37 °C (minimum half time for hydrolysis of approximately 37 minutes), the hydrolysis of phosphonate derivatives is anticipated to be much faster, e.g. k_{OH^-} ($(EtO)_2P(O)OpNP$; paraoxon) = 9.5 x 10^{-3} M^{-1} s^{-1},[4] while k_{OH^-} (Et(EtOP)(O)OpNP) = 0.15 M^{-1} s^{-1}.[4]

Introduction (Sulfur Mustard Hydrolysis).

The currently accepted mechanism for the hydrolysis of sulfur mustard (R=CH_2CH_2Cl, scheme 3) involves the intramolecular attack of the sulfur atom to produce an episulfonium (thiiranium) ion, this ion can either react with free chloride ion (via k_{-1}) to produce starting material or it can react with a nucleophile to yield product.[5] Because the transition state for solvolysis (nuc = R'OH) has a large degree of charge separation, the rate for this reaction is fairly sensitive to the polarity of the medium.[6] These two observations combine to explain the persistence of sulfur mustard. When the solvent is water the rate of solvolysis is high, however, sulfur mustard is extremely insoluble in water. In lower polarity solvents where sulfur mustard has an appreciable solubility, it's reactivity is very low, with a large degree of return to starting material in reasonably concentrated solutions of sulfur mustard.



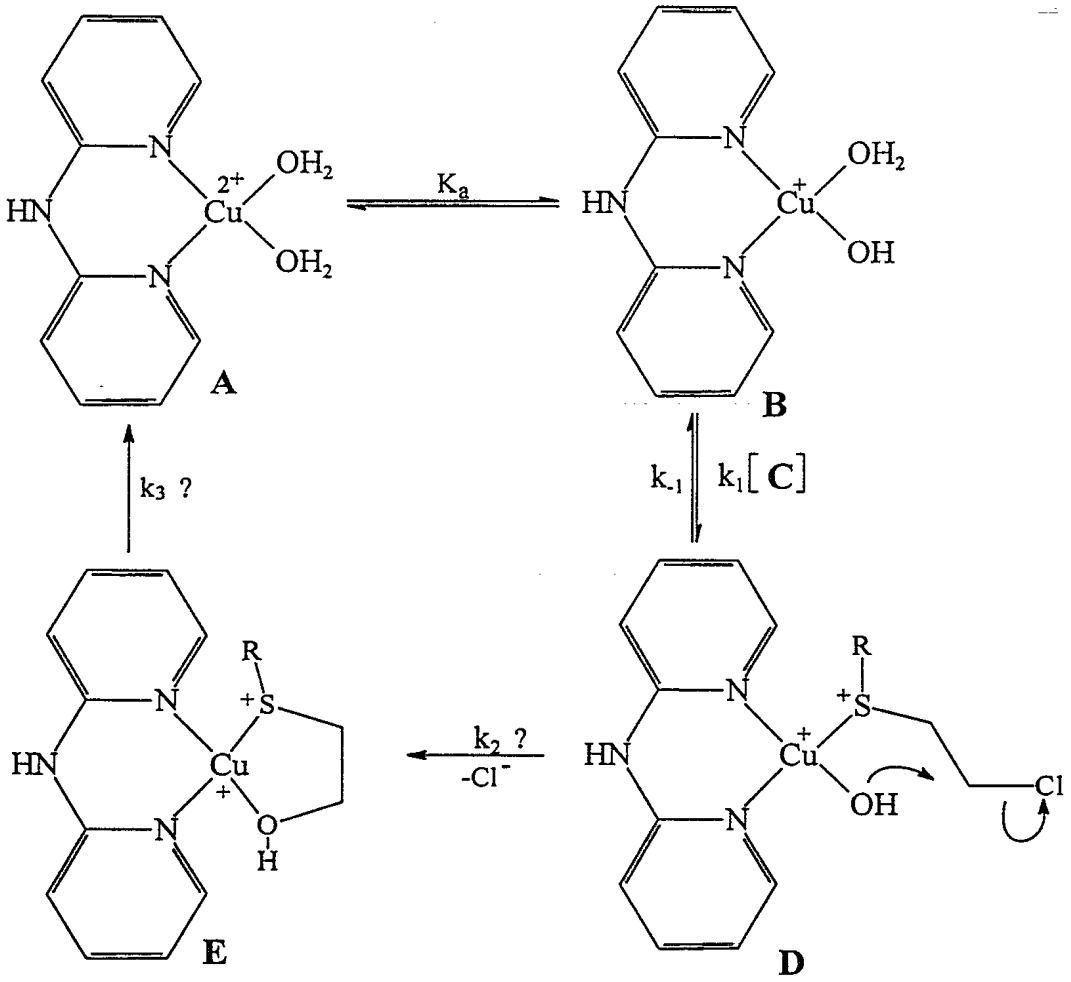
Scheme 3

Consequently, the aim was to see if the reaction of 2-chloroethyl ethylsulfide with the [(2,2'-dipyridylamine)$Cu(OH_2)_2$]$^{2+}$ complex could change the mechanism of solvolysis from an internal S_N2 reaction where the nucleophile is the sulfide sulfur atom, to a different internal S_N2 reaction where now the nucleophilic species is a copper bound hydroxide, which displaces the chloride ion from a sulfur bound ligand (scheme 4).

Experimental (2-Chloroethyl Ethylsulfide Hydrolysis).

The kinetics of solvolysis of 2-chloroethyl ethylsulfide were followed by a pH-stat technique. A solution which contained ethanol, "milli-Q pure" water (total volume 25 mL), and

the copper (II) complex at the required concentration. After the pH had been adjusted by addition of either dilute acid or base to give the required pH, the cell was allowed to equilibrate for 30 minutes before the reaction was initiated. The reaction was started when a solution of 2-chloroethyl ethylsulfide in dichloromethane (0.5 M; 0.2 mL, final concentration = 3.97mM)* was injected into the thermostatted titration cell The rate constant was calculated from the time vs. amount of base added to maintain a constant pH data, using a standard non-linear first-order equation (enzfitter), all fits to the kinetic data showed no systematic trends in the residuals.



Where R = Et, i.e., C = chloroethyl ethylsulfide

Scheme 4

* 20 µL was injected when no copper (II) complex was added to the reaction medium.

The titration system used consisted of a PHM82 pH meter, a TTT80 titrator, an ABU80 autoburette, and a TTA80 titration assembly. The complete system was interfaced to a 486-33 MHz based computer using a proprietary card supplied by Radiometer. The electrodes used in this study were a standard glass electrode (pHG281) and a silver chloride reference electrode (K8040), all of the above equipment was manufactured by Radiometer. The pH was maintained by the addition of 1.0M NaOH from the autoburette for the runs with the copper (II) complex present, and 0.1M when no complex was added. No inert salt was added to maintain a constant ionic strength. The measured pH in these aqueous ethanol solutions was corrected to give an accurate measure of the pH according to a published proceedure.[3,7]

Results (2-Chloroethyl Ethylsulfide Hydrolysis).

Shown in figures 4a-c are the plots of k_{obs} ± standard error (each point is the mean of three separate determinations of the rate constant) vs. [copper complex], in 50% v/v ethanol: water at 25 °C. The hydrolysis of the 2-chloroethyl sulfide is followed by the production of acid according to the following equation.

$$RSCH_2CH_2Cl + H_2O \rightarrow RSCH_2CH_2OH + HCl \quad (2)$$

The rate of production of HCl is monitored by the amount of alkali added that is required to maintain a constant pH (pH-stat). The rate of solvolysis of the 2-chloroethyl ethylsulfide in the absence of the copper (II) complex should be independent of the pH is which the reaction was run. Summarized below are the observed rate constant for the production of acid during the reactions of $EtSCH_2CH_2Cl$ at various pH's.

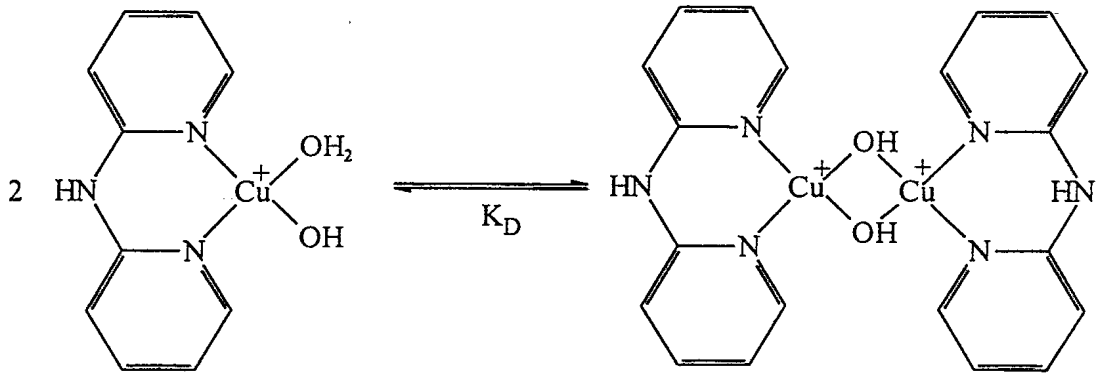
pH (corrected)	10^3 x k_{obsd} (s^{-1})
7.86	2.33 ± 0.02
6.86	2.53 ± 0.02
5.86	2.50 ± 0.10

Discussion (2-Chloroethyl Ethylsulfide Hydrolysis).

It is apparent that the observed rate constants for the solvolysis reactions in the absence of any copper complex are independent of the pH of the solution (within about 8%). This is consistent with all previous studies on the mechanism of hydrolysis of 2-chloroethyl sulfide derivatives, where the rate limiting step at low concentration of sulfide is the formation of the thiiranium ion (k_1 in scheme 3).[5,6] The measured data in 50% aqueous ethanol agrees well with the available data in the literature, where a value of approximately 2.0 x 10^{-3} s^{-1} can be extrapolated from a graph of log (k) vs. the mole fraction of ethanol in the solvent at 25 °C.[8] This number agrees satisfactorily with our values of 2.3-2.5 x 10^{-3} s^{-1} considering the extrapolation used a straight line and the plot of log (k) vs. the mole fraction of ethanol in the solvent is distinctly curved.[8] The value of 7.1 x 10^{-4} s^{-1} observed at 37 °C in 80% aqueous ethanol (figure 5) is similar to an interpolated value of 5.2 x 10^{-4} s^{-1} for the solvolysis of 2-chloroethyl methylsulfide.[9] The general agreement of the observed rate constants for the solvolysis of 2-chloroethyl ethylsulfide measured in this study with the extrapolated data in the literature gives confidence to the accuracy of the measured data in the presence of the copper (II) complex of dipyridylamine. On addition to the 50% aqueous ethanol solution of up to 3mM concentration of the *cis*-diaqua copper (II) complex, [(2,2'-dipyridylamine)Cu(OH_2)$_2$]$^{2+}$ the observed rate of solvolysis of the sulfur mustard analog decreases slightly (figures 4a-c). It is

also apparent that the decrease in rate of the solvolytic reaction is independent of the concentration of the complex. Because the concentration of the mustard analog in the reaction vessel was approximately 4mM not all of the sulfide present in the solution can be bound to the added copper complex. If the complex bound the sulfur and the complex was less reactive than the free 2-chloroethyl ethylsulfide then the observed rate should decrease with the addition of larger quantities of the complexing agent. Clearly, this is not observed, the question then remains as to the origin of the slight reduction in solvolytic rate. The decrease in rate is almost certainly due to a reduction in the ionizing power of the medium[5b] on the addition of 0.2 mL of dichloromethane (0.02 mL was added in the absence of the copper species) required to give an homogeneous solution. An interesting phenomenon is observed when the solvolytic reaction is carried out in 80% v/v ethanol:water solution (figure 5). Here the observed rate constant increases at low concentrations of the copper (II) species, however, on the addition of more complex a dramatic decrease in the measured production of acid occurs. The rate at the highest concentration of copper complex used (3 mM) is below the observed value with no catalyst present, and is probably due to the reduction in the ionizing power of the medium containing dichloromethane (0.8%). Therefore, the catalyst at lower concentrations increases the solvolytic rate, however, as the concentration of the copper complex is increased the rate decreases to eventually reach a point where there is no perturbation of the rate by the addition of more catalyst. The most reasonable explanation for these observations is that in the reduced polarity of 80% v/v ethanol:water solutions the binding and reactivity of copper increases with respect to the background reaction (which has slowed down considerably).[7,8] However, the complex becomes inactive as the concentration is increased, this is probably due to the dimerization of the copper

species in the poorly ionizing solvent as depicted in scheme 5. This type of dimerization of an active complex into a bridged dimer is expected to occur in solutions of lower polarity. Of note is that in the study of the solvolysis of the organophosphate esters in the more ionizing solvent 50% v/v ethanol:water no decrease in activity was observed.



Scheme 5

Conclusions (2-Chloroethyl Ethylsulfide Hydrolysis).

The complexation of the 2-chloroethyl ethylsulfide to the copper complex has been demonstrated only in the poorly ionizing solvent 80% aqueous ethanol at 37 °C, there is no evidence for binding of the mustard analog in more polar solvents. The maximum acceleration under these conditions for the decontamination of the sulfur mustard analog was an increase of approximately 22% over the spontaneous rate of solvolysis. No increase of observed solvolytic cleavage of the mustard analog was observed in the more ionizing solvent 50% aqueous ethanol. No information about the binding of the products of solvolysis (2-ethoxyethyl ethylsulfide and 2-hydroxyethyl ethylsulfide) was possible because of the intrinsic low affinity of the substrate for the copper (II) complex.

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7) The pH was calculated by subtracting 0.15 units from the reading of a standard pH glass electrode, according to reference 3.

9) Sunko, D.E.; Juršic, B.; Ladika, M., *J. Org. Chem.*, **1987**, *52*, 2299-301.

8) Yang, Y-C.; Ward, J.R.; Luteran, T., *J. Org. Chem.*, **1986**, *51*, 2756-9.

Appendix 1, Derivation of kinetic equations.

The rate of hydrolysis of the phosphate compound (i.e. D → E) is given as : $\frac{d[E]}{dt} = k_2[D]$

and because ligand exchange is rapid for copper (II) tetrahedral species, k_1 and $k_{-1} >> k_2$. So that species B + C are always in equilibrium with D. Hence, $K_{eq} = \frac{[D]}{[B][C]} = \frac{k_1}{k_{-1}}$, now if we define $[B]_T = [A]_0 + [B]_0$ as the amount of complex added at the start of the reaction. Clearly, the amount of active species $[B]_0$ varies as a function of pH, according to the following expression:

$[B]_0 = \left(\frac{K_a}{[H_3O^+] + K_a}\right) \times [B]_T$,. Now, if [B] >> [C] then, $[C]_0 - [C] - [D] = [E]$. So

$[D] = \left(\frac{K_{eq}[B]_0}{1 + K_{eq}[B]_0}\right) \times ([C]_0 - [E])$, however, when the hydrolysis is complete $[C]_0 = [E]_\infty$. Now,

$\frac{d[E]}{dt} = \frac{k_2 K_{eq}[B]_0}{1 + K_{eq}[B]_0}([E]_\infty - [E])$, i.e., the observed rate constant $k_{obs} = \frac{k_2 K_{eq}[B]_0}{1 + K_{eq}[B]_0}$, so

substituting for $[B]_0$ we get $k_{obs} = \frac{k_2 K_{eq}[B]_T}{1 + [[H_3O^+]/K_a] + K_{eq}[B]_T}$.

Appendix 2, Observed and calculated rate constants for the solvolysis of tris-(*p*-nitrophenyl) phosphate catalyzed by the copper-2,2'-dipyridylamine diaqua complex at 37 °C in 50% v/v aqueous ethanol.

pH = 7.88: figure 1a.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.17	11.3	9.6
0.33	21.0	17.7
0.50	28.5	25.4
1.00	44.2	44.2
2.00	67.6	69.9
3.00	83.6	86.8
4.00	98.5	98.7

pH = 7.58: figure 1b.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.17	9.8	9.1
0.33	19.0	16.8
0.50	27.1	24.1
1.00	44.9	42.2
2.00	67.9	67.4
3.00	83.6	84.2
4.00	101.6	96.2

pH = 7.31: figure 1c.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.17	7.6	8.3
0.33	16.2	15.3
0.50	22.9	22.2
1.00	37.0	39.2
2.00	63.9	63.5
3.00	78.9	80.1
4.00	90.9	92.1

pH = 7.08: figure 1d.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.17	5.8	7.3
0.33	12.0	13.6
0.50	18.3	19.8
1.00	34.9	35.4
2.00	58.8	58.4
3.00	77.1	74.6
4.00	90.1	86.6

pH = 6.93: figure 1e.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.17	5.0	6.5
0.33	9.8	12.2
0.50	14.3	17.8
1.00	29.2	32.2
2.00	52.2	54.0
3.00	67.2	69.8
4.00	72.2	81.7

pH = 6.55: figure 1f.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.17	4.0	4.3
0.33	6.4	8.2
0.50	9.3	12.1
1.00	22.2	22.6
2.00	41.5	39.8
3.00	59.2	53.4
4.00	71.4	64.3

pH = 6.20: figure 1g.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.17	1.5	2.5
0.33	3.3	4.8
0.50	4.8	7.2
1.00	11.2	13.8
2.00	25.0	25.5
3.00	34.3	35.6

Appendix 3, Observed and calculated rate constants for the solvolysis of paraoxon catalyzed by the copper-2,2'-dipyridylamine diaqua complex at 37 °C in 50% v/v aqueous ethanol.

pH = 7.90: figure 2a.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.25	0.024	0.036
0.50	0.062	0.067
0.75	0.092	0.094
1.00	0.114	0.119
1.50	0.163	0.159
2.00	0.200	0.193
2.50	0.235	0.220
3.00	0.239	0.243
3.50	0.258	0.263
4.00	0.270	0.280
4.50	0.292	0.295

pH = 7.39: figure 2b.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.25	0.030	0.032
0.50	0.058	0.060
0.75	0.083	0.085
1.00	0.107	0.107
1.50	0.152	0.146
2.00	0.173	0.177
2.50	0.204	0.204
3.00	0.225	0.227
3.50	0.248	0.246
4.00	0.274	0.263

pH = 6.92: figure 2c.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.25	0.019	0.024
0.50	0.048	0.046
0.75	0.067	0.066
1.00	0.094	0.085
1.50	0.121	0.117
2.00	0.145	0.145
2.50	0.169	0.169
3.00	0.183	0.191
3.50	0.208	0.209

pH = 6.26: figure 2d.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x k_{calc} (s^{-1})
0.25	0.008	0.010
0.50	0.016	0.020
0.75	0.024	0.030
1.00	0.033	0.039
1.50	0.056	0.057
2.00	0.074	0.073
2.50	0.088	0.088
3.00	0.105	0.102
3.50	0.110	0.116
4.00	0.123	0.128
4.50	0.144	0.140
5.00	0.152	0.151
6.00	0.169	0.171
7.00	0.195	0.189

Appendix 4, Observed and calculated rate constants for the solvolysis of paraoxon catalyzed by the copper-2,2'-dipyridylamine diaqua complex at 37 °C in 50% v/v D_2O:EtOD.

pD = 8.60: figure 3.

Catalyst mM	$10^3 \times k_{obs}$ (s^{-1})	$10^3 \times k_{calc}$ (s^{-1})
0.50	0.065	0.061
0.75	0.084	0.084
1.00	0.105	0.103
1.50	0.130	0.132
2.00	0.149	0.154
2.50	0.163	0.170
3.00	0.193	0.184

Appendix 5, Observed rate constants and the associated standard deviations for the solvolysis of 2-chloroethyl ethylsulfide in the presence of copper-2,2'-dipyridylamine diaqua complex at 25 °C in 50% v/v aqueous ethanol.

pH = 7.86: figure 4a.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x s.d. (s^{-1})
0.00	2.33	0.02
1.00	2.00	0.10
2.00	2.09	0.08
3.00	1.97	0.08

pH = 6.86: figure 4b.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x s.d. (s^{-1})
0.00	2.53	0.02
1.00	1.96	0.07
2.00	2.02	0.05
3.00	2.07	0.07

pH=5.86: figure 4c.

Catalyst mM	10^3 x k_{obs} (s^{-1})	10^3 x s.d. (s^{-1})
0.00	2.50	0.10
1.00	2.38	0.07
2.00	2.21	0.05
3.00	2.34	0.08

Appendix 8, Observed rate constants and the associated standard deviations for the solvolysis of 2-chloroethyl ethylsulfide in the presence of copper-2,2'-dipyridylamine diaqua complex at 37 °C in 80% aqueous ethanol.

pH = 7.85: figure 5.

Catalyst mM	10^4 x k_{obs} (s^{-1})	10^4 x s.d. (s^{-1})
0.00	7.1	0.2
0.05	8.3	0.2
1.00	8.9	0.2
2.00	6.5	0.3
3.00	5.7	0.2

Figure 1a

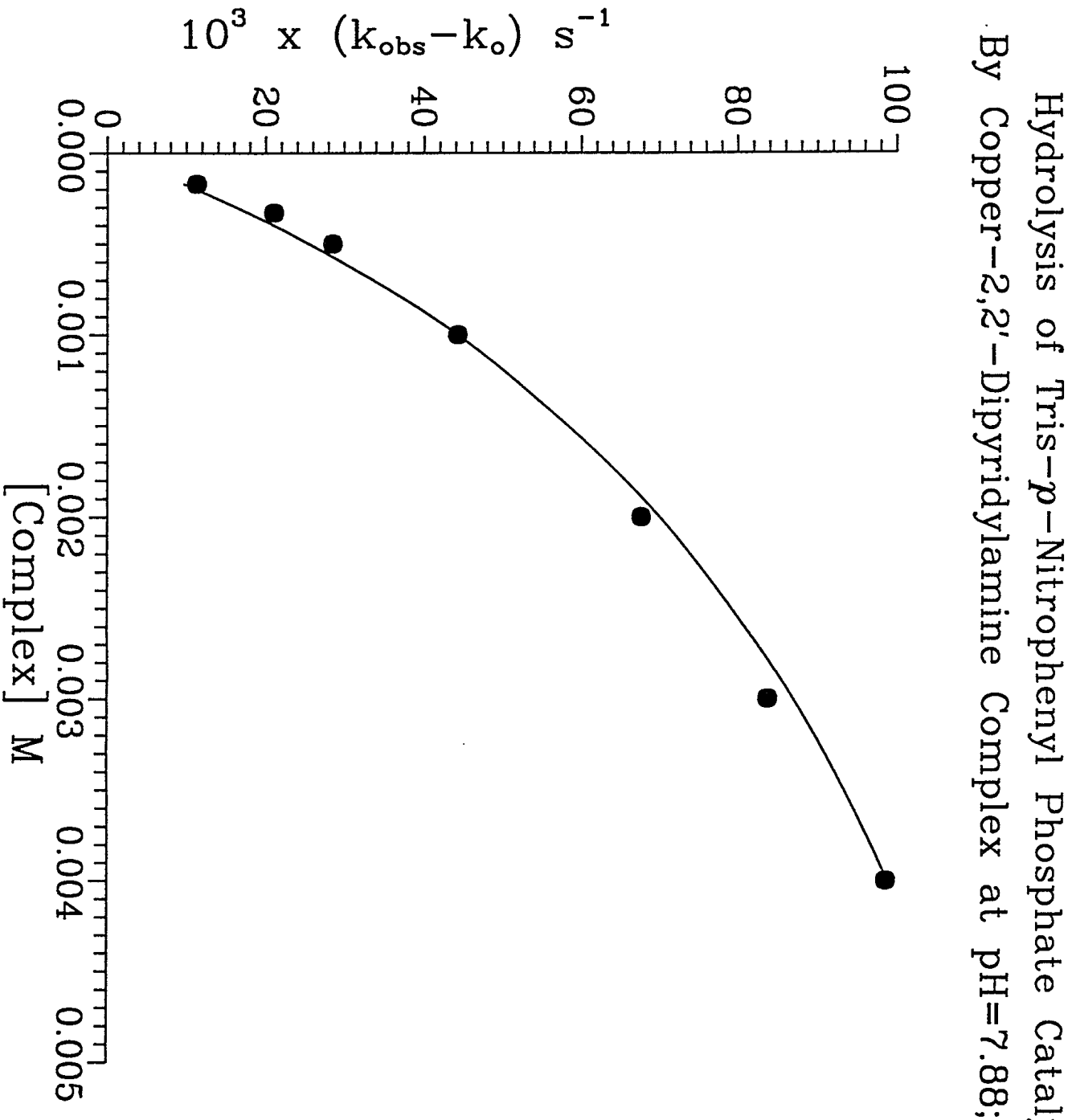
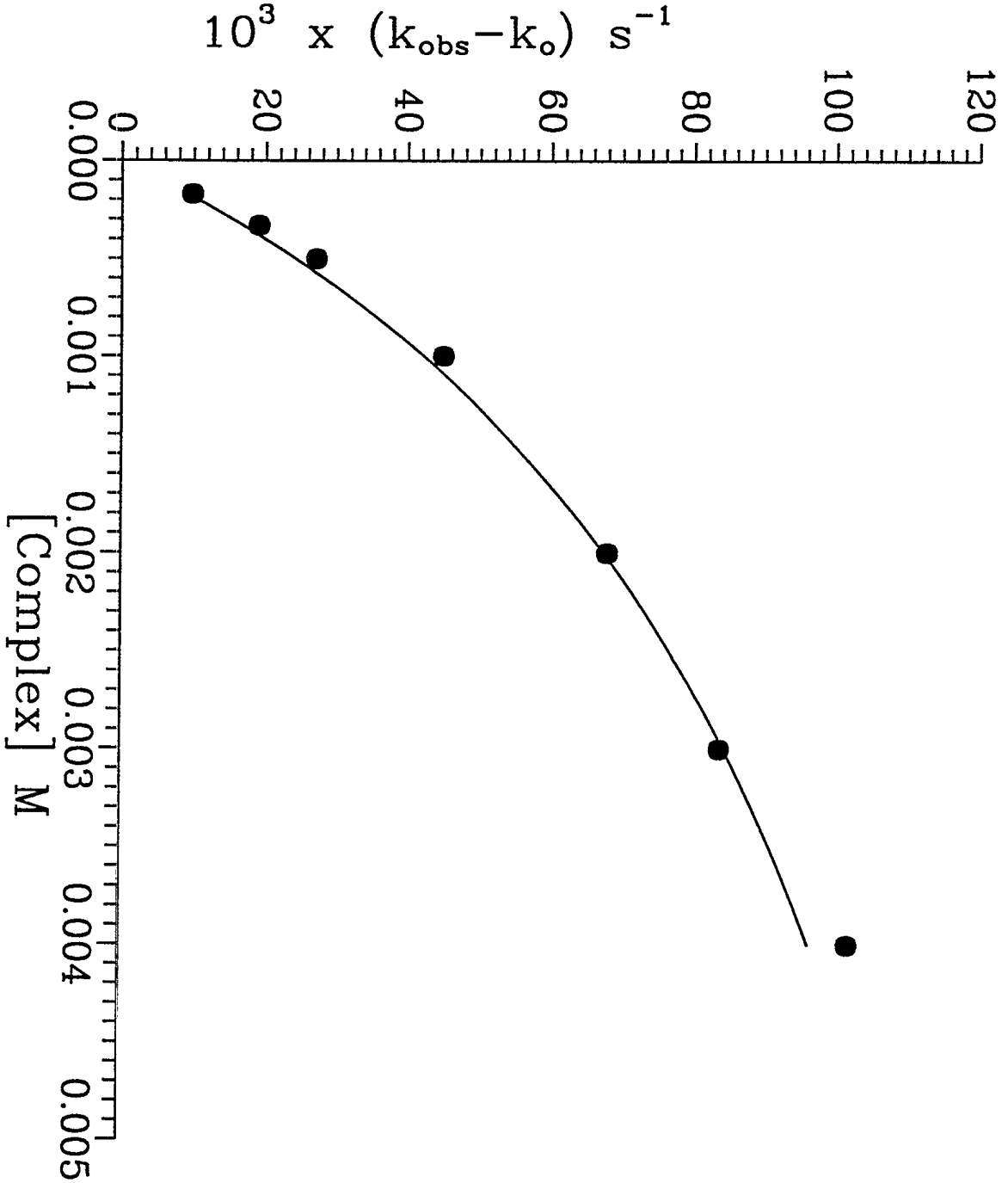

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=7.88; T=37°C.
10³ x (k_obs - k_o) s⁻¹
0
20
40
60
80
100
0.000
0.001
0.002
0.003
0.004
0.005
[Complex] M

Figure 1b



Hydrolysis of Tris-*p*-Nitrophenyl Phosphate Catalyzed By Copper-2,2'-Dipyridylamine Complex at pH=7.58; T=37°C.

Figure 1c

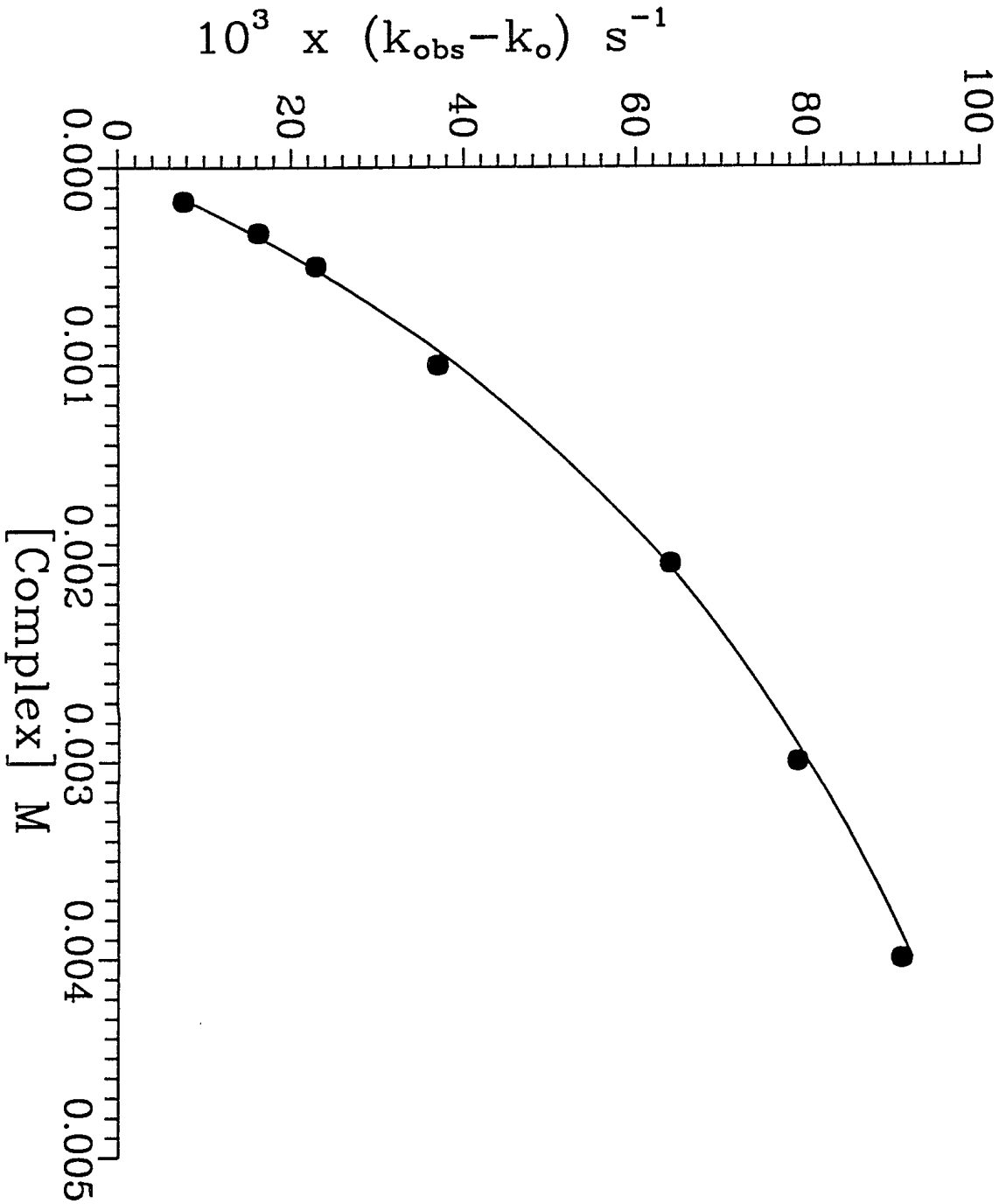

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=7.31; T=37°C.
10^3 x (k_obs-k_o) s^-1
0
20
40
60
80
100
0.000
0.001
0.002
0.003
0.004
0.005
[Complex] M

Figure 1d

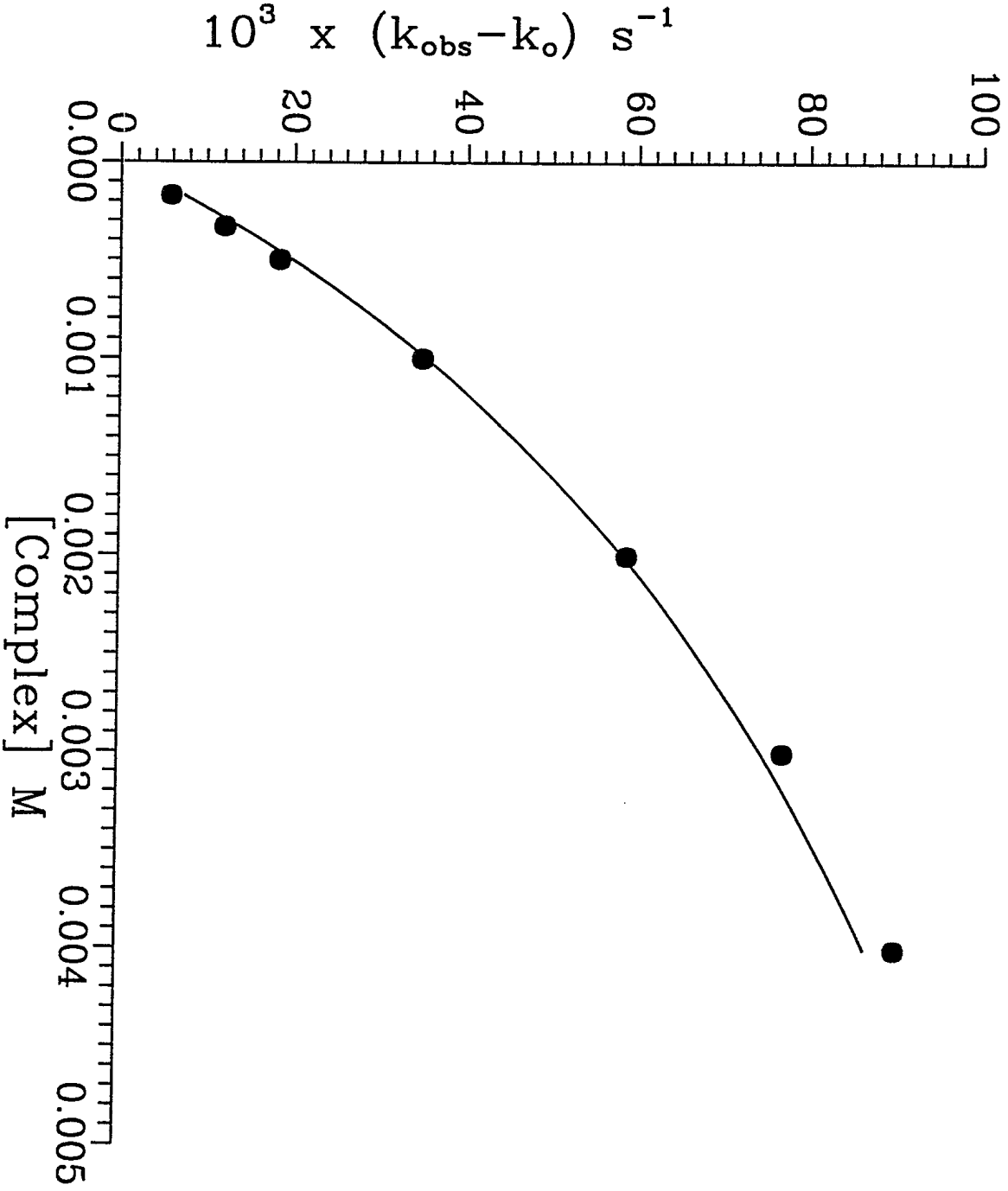

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=7.08; T=37°C.
10^3 x (k_obs - k_o) s^-1
0
20
40
60
80
100
0.000
0.001
0.002
0.003
0.004
0.005
[Complex] M

Figure 1e

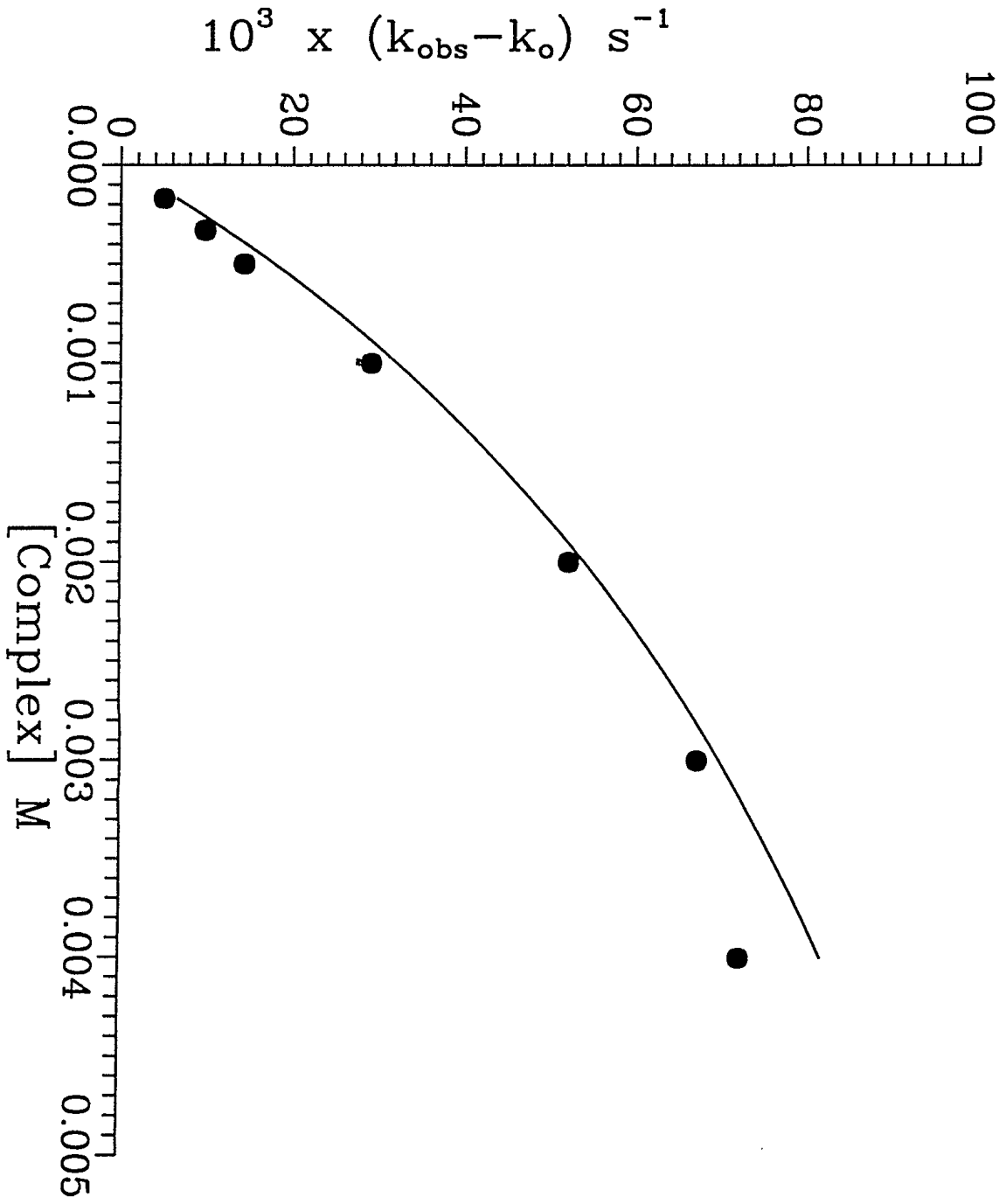

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=6.93; T=37°C.
10^3 x (k_obs - k_o) s^-1
0
20
40
60
80
100
0.000
0.001
0.002
0.003
0.004
0.005
[Complex] M

Figure 1f

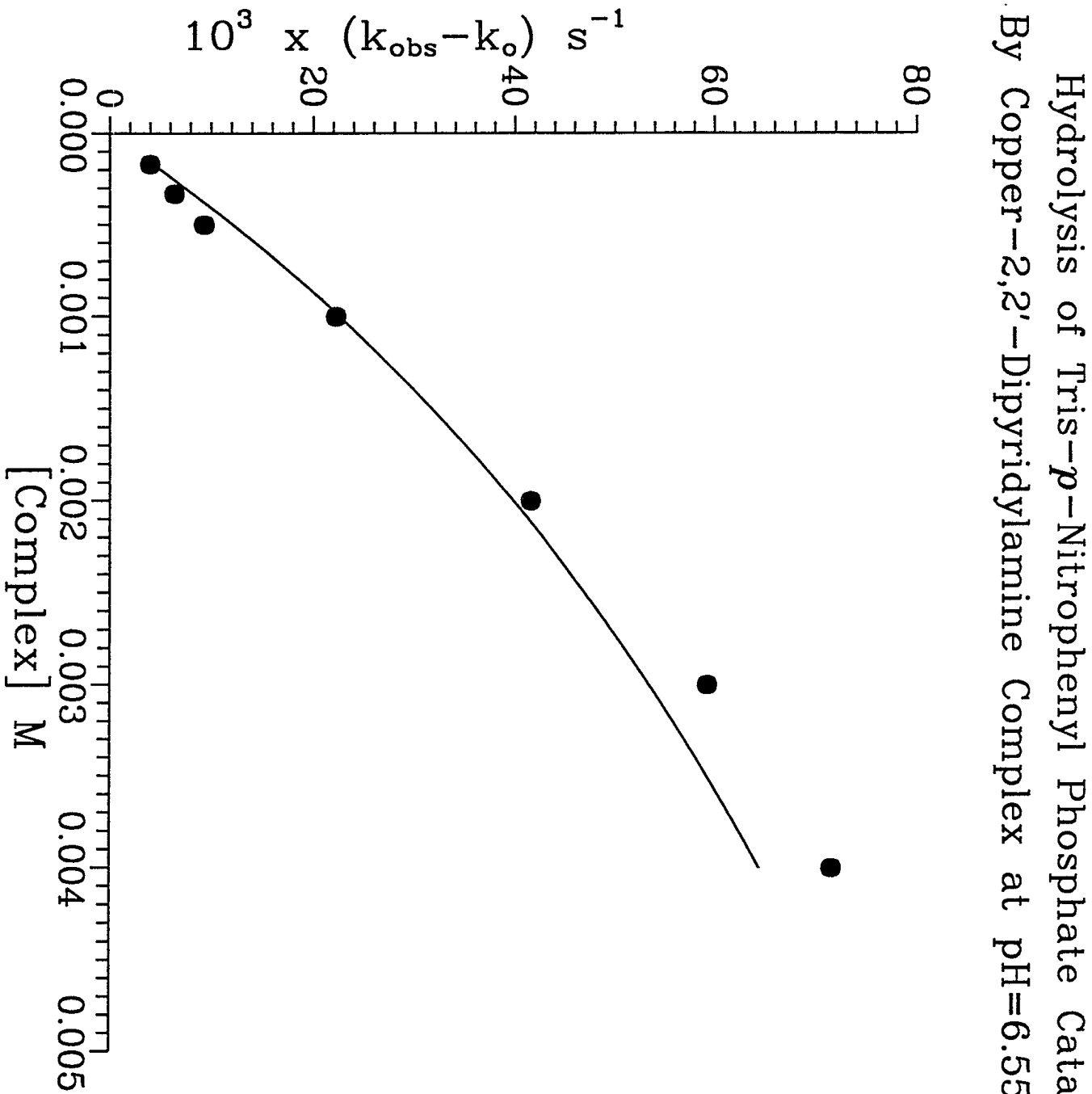

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=6.55; T=37°C.
10^3 x (k_obs - k_o) s^-1
0
20
40
60
80
0.000
0.001
0.002
0.003
0.004
0.005
[Complex] M

Figure 1g

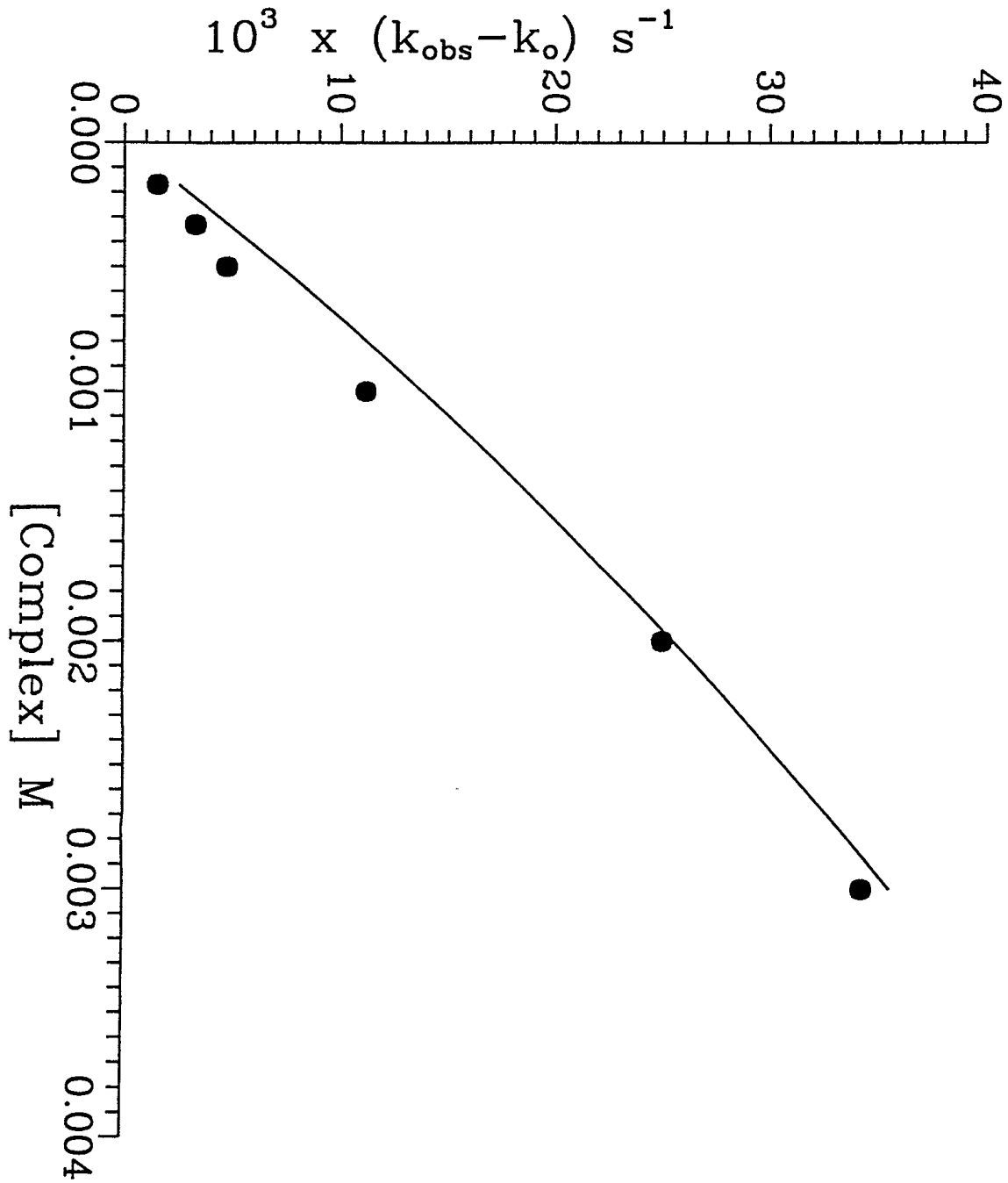

Hydrolysis of Tris-p-Nitrophenyl Phosphate Catalyzed
By Copper-2,2'-Dipyridylamine Complex at pH=6.20; T=37°C.
10^3 x (k_obs - k_o) s^-1
0
10
20
30
40
0.000
0.001
0.002
0.003
0.004
[Complex] M

Figure 2a

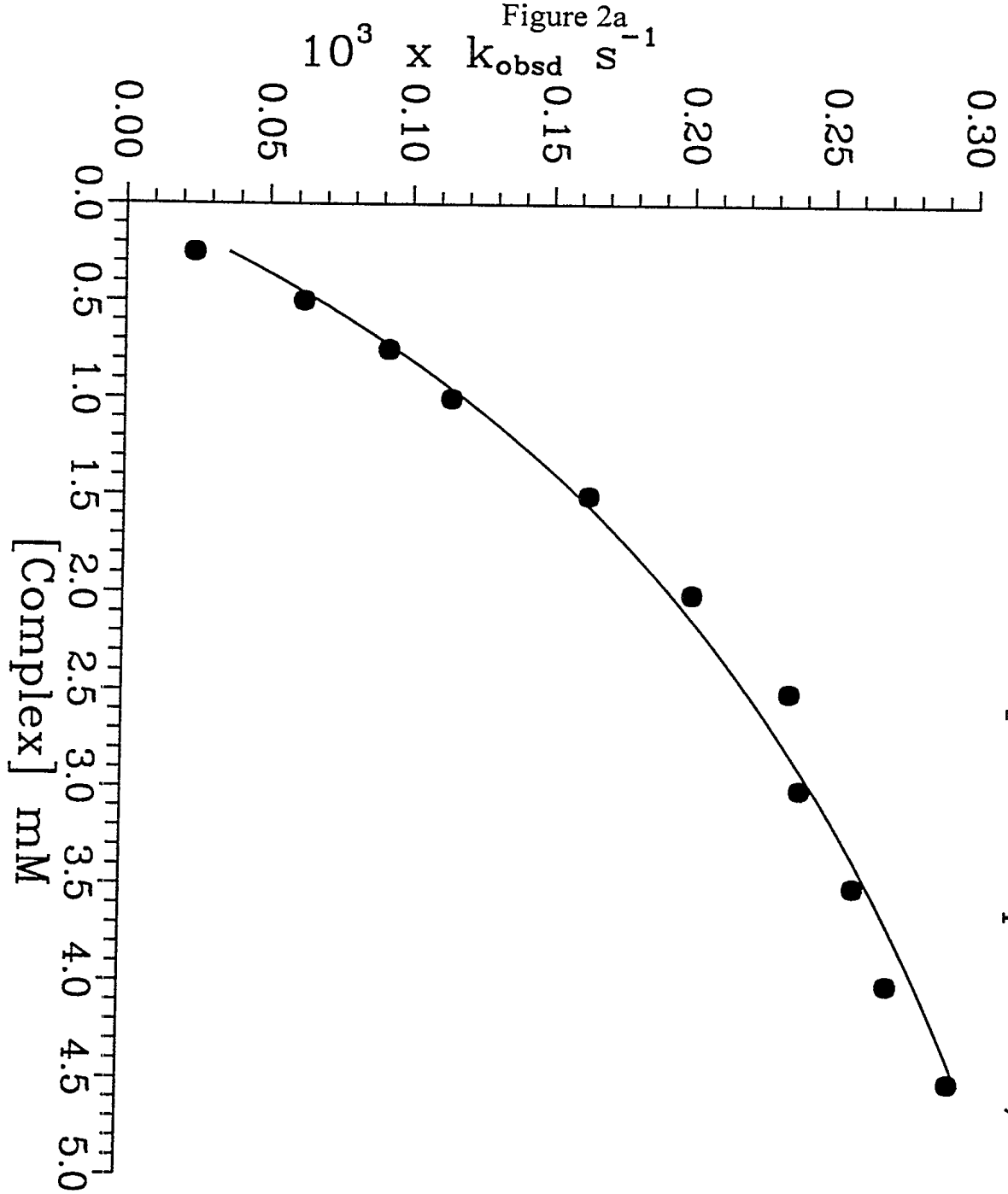

Paraoxon Hydrolysis Catalyzed by Copper-
2,2'-Dipyridylamine Complex at pH=7.90; T=37°C.
10^3 x k_{obsd} s^{-1}
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
[Complex] mM

Figure 2b

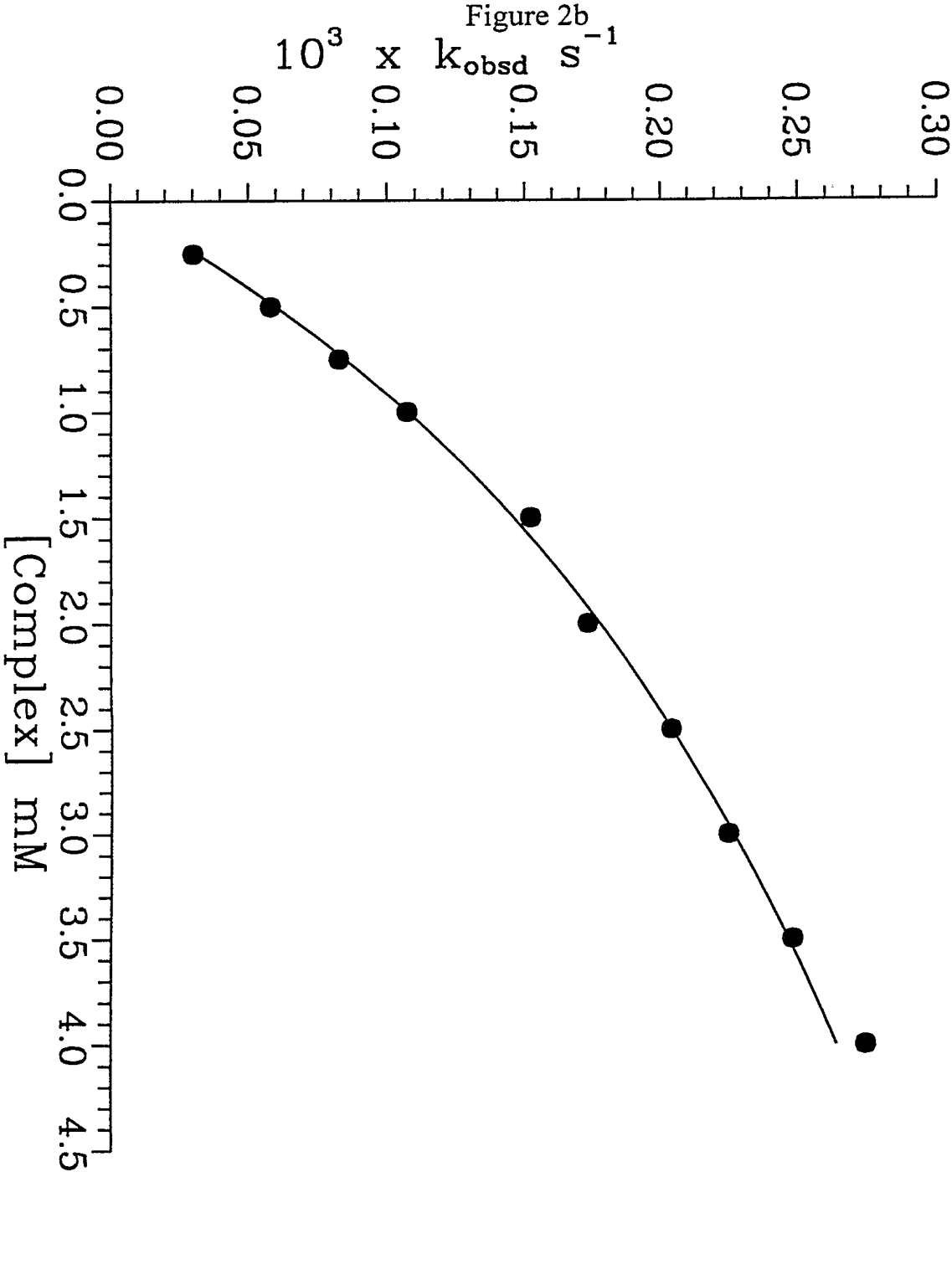

Paraoxon Hydrolysis Catalyzed by Copper-
2,2'-Dipyridylamine Complex at pH=7.39; T=37°C.
10^3 x k_{obsd} s^{-1}
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
[Complex] mM

Figure 2c

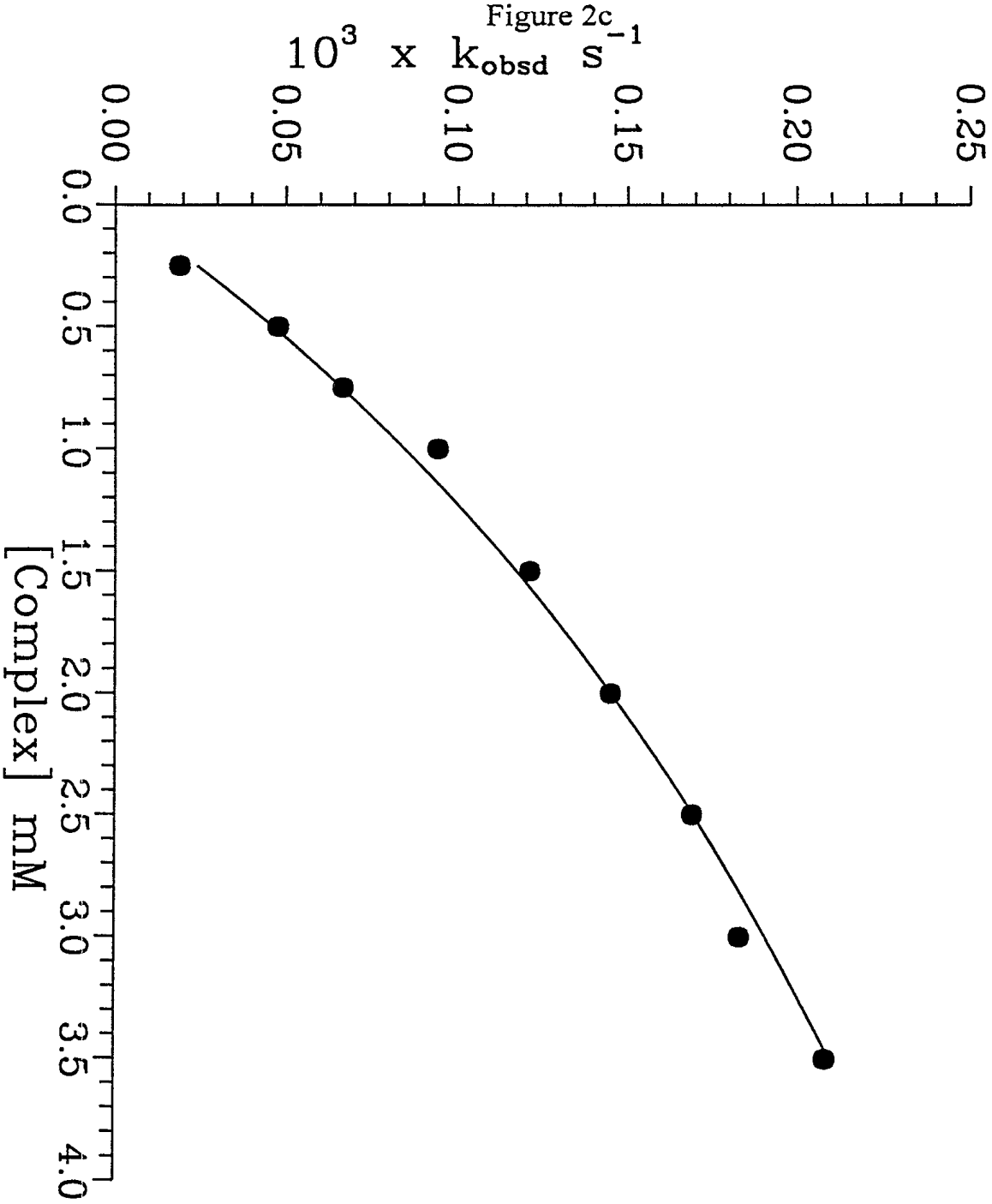

Paraoxon Hydrolysis Catalyzed by Copper-
2,2'-Dipyridylamine Complex at pH=6.92; T=37°C.
10^3 x k_{obsd} s^{-1}
0.00
0.05
0.10
0.15
0.20
0.25
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
[Complex] mM

Figure 2d

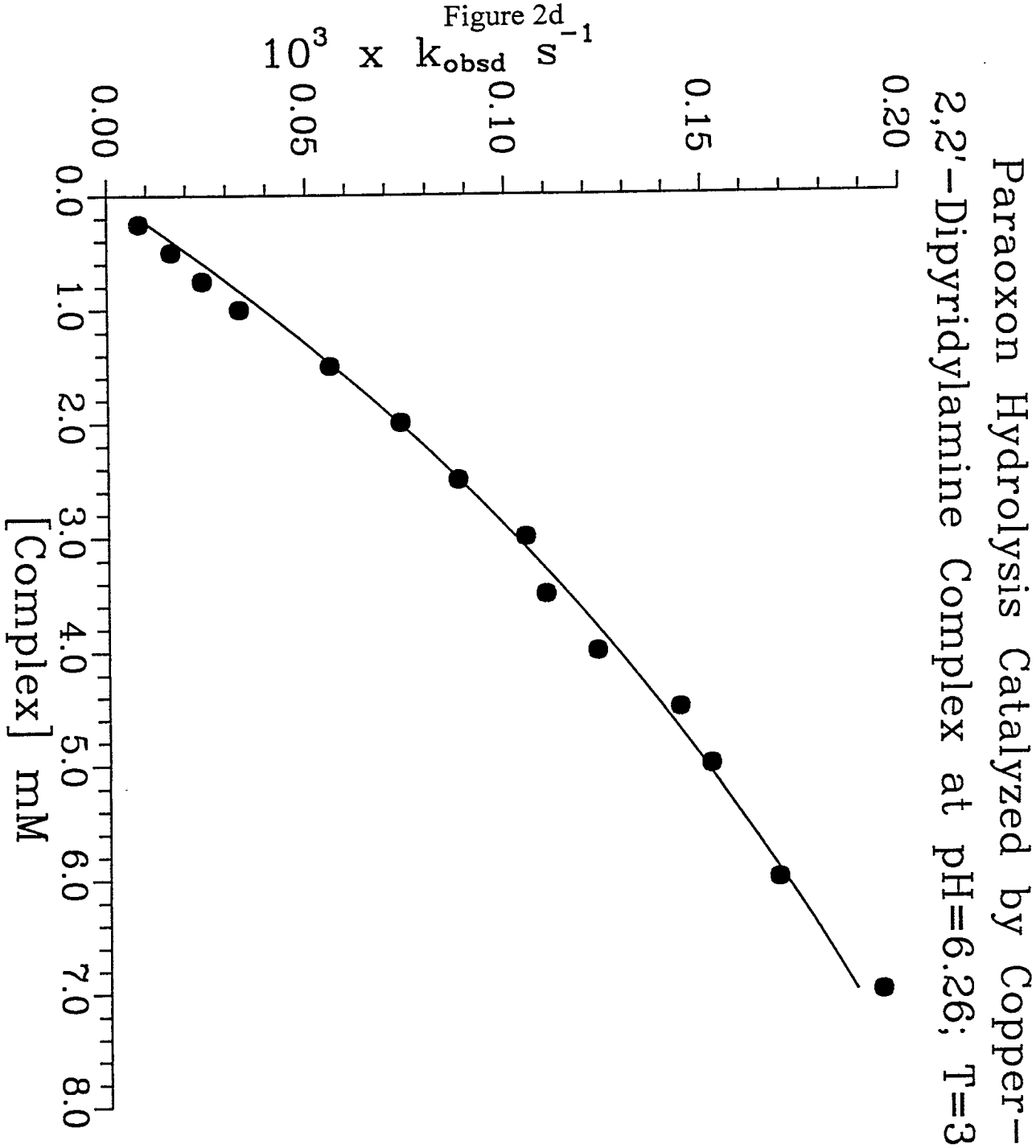

Paraoxon Hydrolysis Catalyzed by Copper-
2,2'-Dipyridylamine Complex at pH=6.26; T=37°C.
10^3 x k_{obsd} s^{-1}
0.00
0.05
0.10
0.15
0.20
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
[Complex] mM

Figure 3

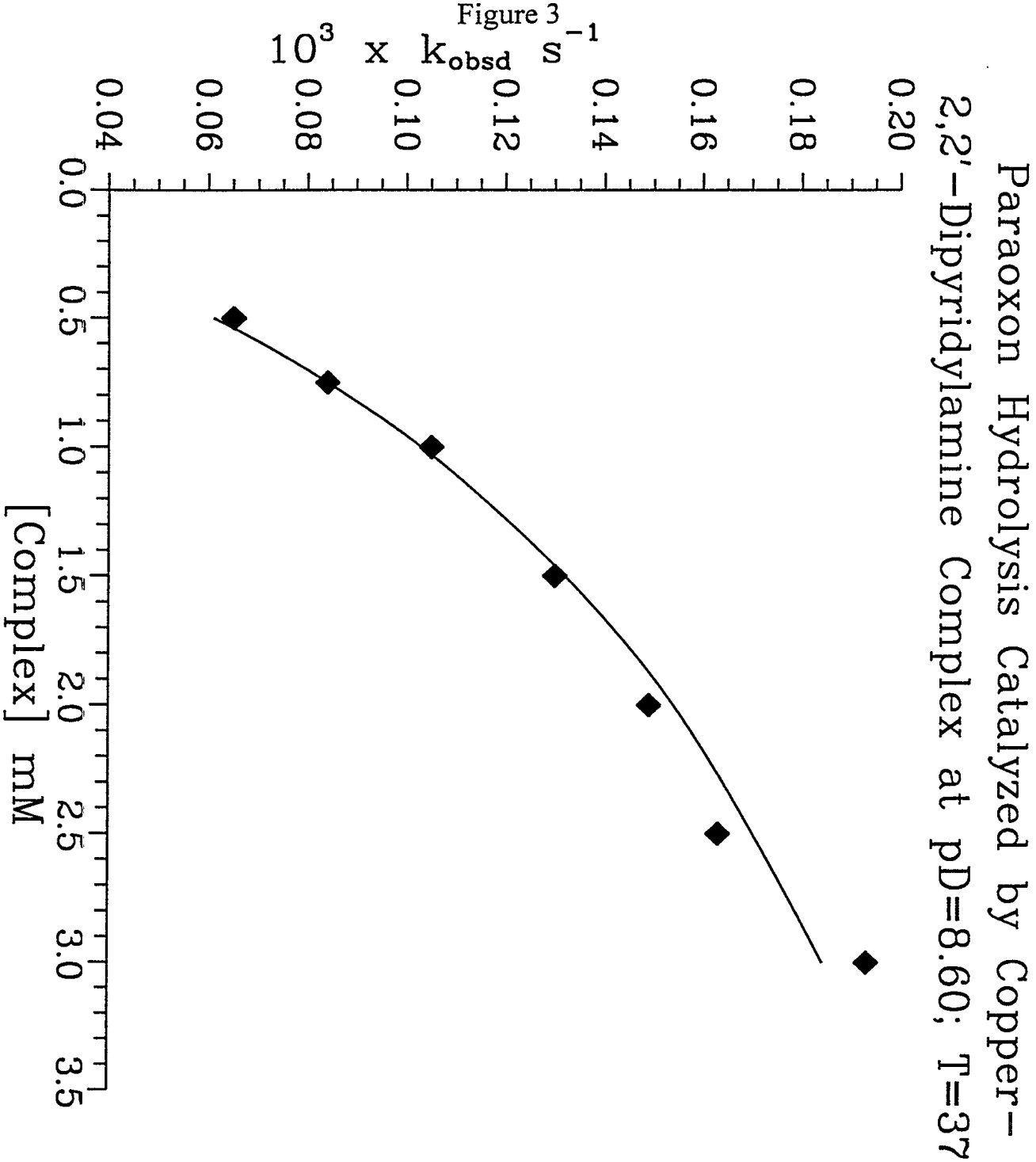

Paraoxon Hydrolysis Catalyzed by Copper-
2,2'-Dipyridylamine Complex at pD=8.60; T=37°C.
10^3 x k_{obsd} s^{-1}
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
[Complex] mM

Figure 4a

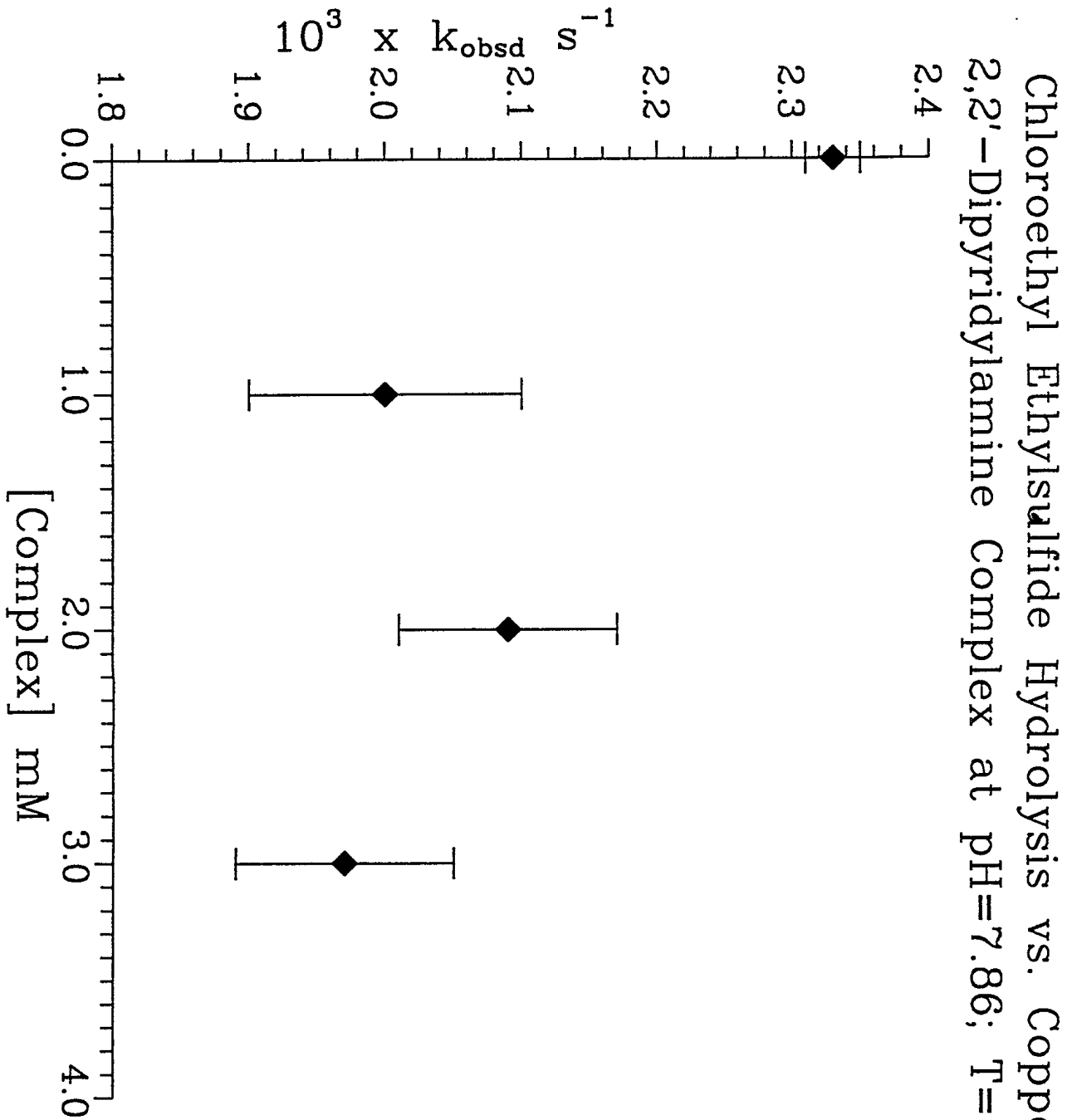

Chloroethyl Ethylsulfide Hydrolysis vs. Copper-2,2'-Dipyridylamine Complex at pH=7.86; T=25°C.
10^3 x k_obsd s^-1
1.8
1.9
2.0
2.1
2.2
2.3
2.4
[Complex] mM
0.0
1.0
2.0
3.0
4.0

Figure 4b

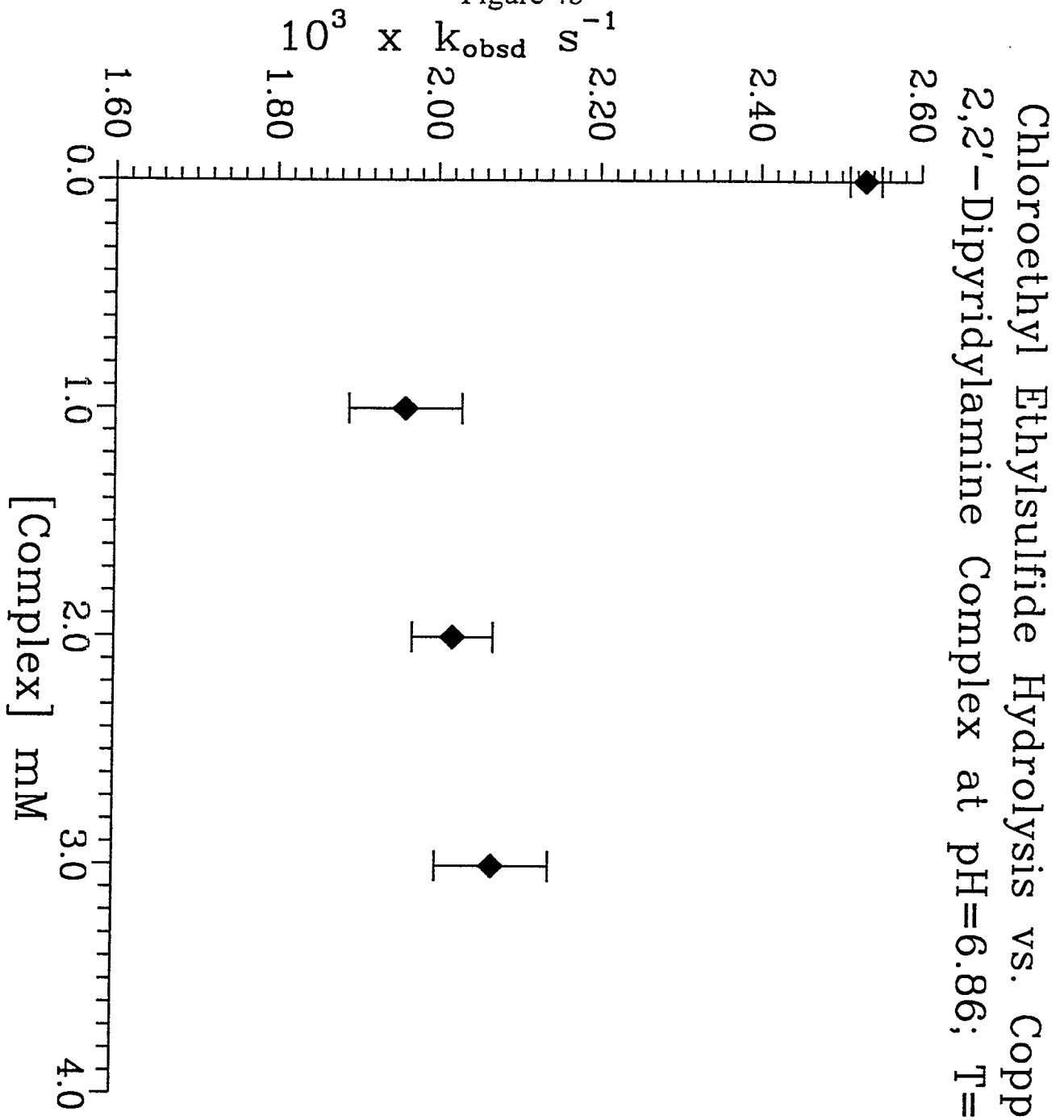

Chloroethyl Ethylsulfide Hydrolysis vs. Copper-2,2'-Dipyridylamine Complex at pH=6.86; T=25°C.
10^3 x k_{obsd} s^{-1}
1.60
1.80
2.00
2.20
2.40
2.60
0.0
1.0
2.0
3.0
4.0
[Complex] mM

Figure 4c

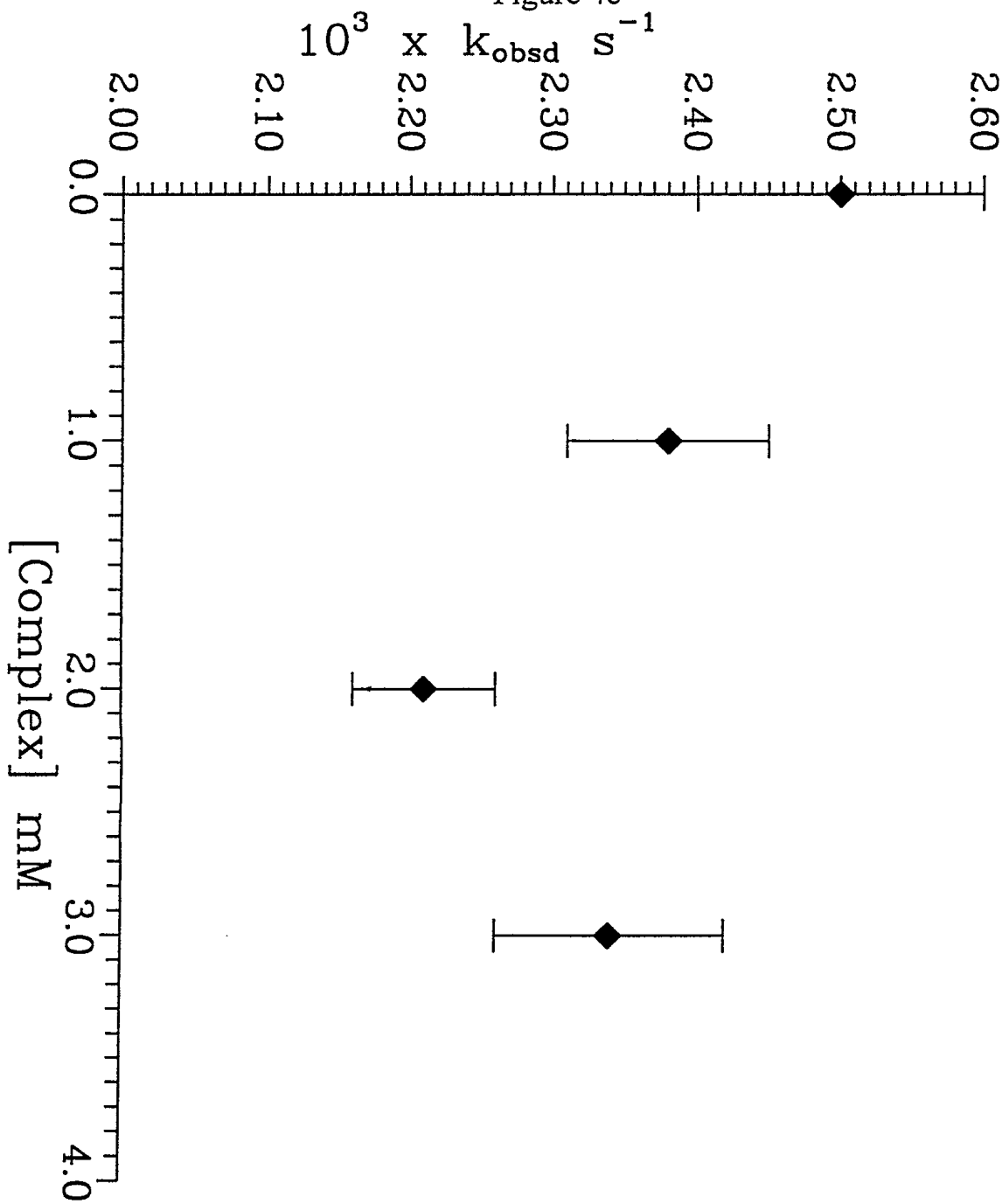
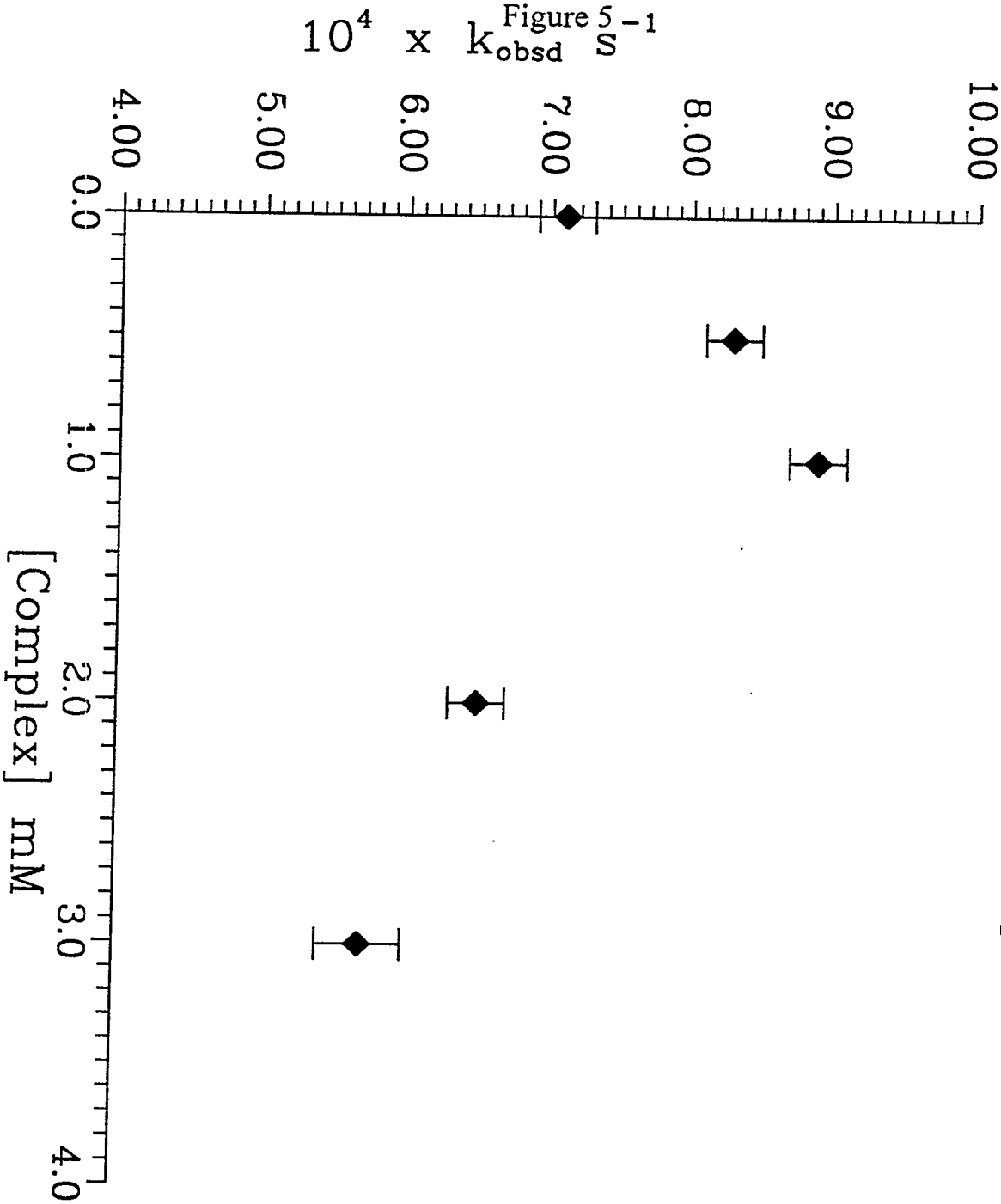

Chloroethyl Ethylsulfide Hydrolysis vs. Copper-2,2'-Dipyridylamine Complex at pH=5.86; T=25°C.
10^3 x k_{obsd} s^{-1}
2.00
2.10
2.20
2.30
2.40
2.50
2.60
0.0
1.0
2.0
3.0
4.0
[Complex] mM

Figure 5-1


Chloroethyl Ethylsulfide Hydrolysis vs. Copper-2,2'-Dipyridylamine Complex at pH=7.85; T=37°C.
10^4 x k_{obsd} s^{-1}
4.00
5.00
6.00
7.00
8.00
9.00
10.00
0.0
1.0
2.0
3.0
4.0
[Complex] mM

#507710