

distance and angular parameters for any one proton with respect to all four iron centers. Further magnetic studies of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ complexes are in progress.

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Copper(II) Complex Catalysis of Amino Acid Ester Hydrolysis. A Correlation with Complex Stability

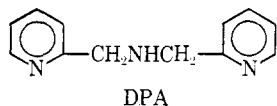
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Abstract: The hydrolysis of glycine methyl ester (MeGly) is catalyzed by the Cu(II) complex, $\text{Cu}(\text{DPA})^{2+}$, where DPA is bis(2-pyridylmethyl)amine. The kinetic and equilibrium results have been interpreted in terms of the mechanism $\text{Cu}(\text{L})^{2+} + \text{MeGly} \rightleftharpoons \text{Cu}(\text{L})(\text{MeGly})^{2+}$, K_x ; $\text{Cu}(\text{L})(\text{MeGly})^{2+} + \text{OH}^- \rightarrow \text{Cu}(\text{L})(\text{Gly})^+ + \text{MeOH}$, k_{OH} . Equilibrium constant determinations for the formation of $\text{Cu}(\text{DPA})^{2+}$ (K_L) and for its binding of MeGly (K_x) indicate that $\text{Cu}(\text{L})\text{MeGly}^{2+}$ is the predominant species in solution prior to rate-determining OH^- attack in the hydrolysis step. An examination of several $\text{Cu}(\text{L})^{2+}$ complexes, where L is DPA, $\text{HN}(\text{CH}_2\text{CH}_2\text{NH}_2)_2$, $\text{HN}(\text{CH}_2\text{CO}_2^-)_2$, or $\text{N}(\text{CH}_2\text{CO}_2^-)_3$, indicates that strongly coordinating L ligands (*i.e.*, those with high K_L values) reduce the ability of $\text{Cu}(\text{L})^{2+}$ to bind MeGly (low K_x values) and also reduce the rate (k_{OH}) of MeGly hydrolysis in $\text{Cu}(\text{L})(\text{MeGly})^{2+}$. These trends are understandable in terms of the reduced Lewis acidity of the metal ion in $\text{Cu}(\text{L})^{2+}$ complexes bearing strong donor L ligands. These results also suggest that the activity of metalloenzymes will be influenced by the nature of the donor groups which bind the metal ion to the apoenzyme.

Certain metalloenzymes are known² to catalyze the hydrolysis of amino acid esters. While the metal ion is known to be at the active site in some of these enzymes, the protein groups binding and neighboring the metal ion also play a major role in determining the overall catalytic properties of the enzyme. In order to provide some basis for understanding the effect of the protein on the catalytic activity of the metal ion, we have examined the catalytic effect of a series of Cu(II) complexes, $\text{Cu}(\text{L})^{2+}$, on the rates of methyl glycinate (MeGly) hydrolysis.³

In the present paper, we extend these studies to the Cu(II) complex, $\text{Cu}(\text{DPA})^{2+}$, of bis(2-pyridylmethyl)amine



and draw some general conclusions about the effect of the ligand L on the catalytic properties of $\text{Cu}(\text{L})^{2+}$ complexes in the hydrolysis of amino acid esters.

Experimental Section

Reagents. Glycine (Mann Research Laboratories), $\text{MeGly} \cdot \text{HCl}$ (Aldrich Chemical Co.), and the trihydrochloride salt of 2,2',2''-tris(aminoethyl)amine, $\text{tren} \cdot 3\text{HCl}$ (Strem Chemical Co.), were of the highest purity available and were used without further purification. Bis(2-pyridylmethyl)amine, DPA, was prepared by the slow addition of 12.3 g of freshly distilled 2-chloromethylpyridine to a

50 ml CH_3OH solution of 2-aminomethylpyridine (30.0 g) according to the general procedure of Romary, *et al.*⁴ Following reaction at 40–45° for 1 hr, the solution was evaporated under vacuum leaving an oil. This oil was dissolved in a minimum of H_2O ; the resulting solution was made strongly alkaline with KOH. The organic product layer was separated and the aqueous layer was extracted with CCl_4 . These organic phases were distilled giving DPA (bp 146–149° (0.5 mm), yield 56%). Anhydrous HCl was bubbled into an ethanol solution of DPA, whereupon $\text{DPA} \cdot 3\text{HCl}$ precipitated. It was recrystallized by dissolving in CH_3OH and adding acetone at 0°.

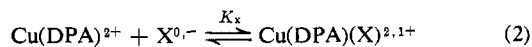
Glycine solutions were standardized by pH titration. Solutions of $\text{MeGly} \cdot \text{HCl}$, $\text{DPA} \cdot 3\text{HCl}$, and $\text{tren} \cdot 3\text{HCl}$ were standardized by passing them through a Dowex 50W-X8 strongly acidic cation-exchange resin and titrating the acidic effluent solutions with standardized NaOH.⁵ Metal ion solutions of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ were standardized similarly.

Potentiometric Measurements. A Corning Digital 112 Research pH meter was calibrated in terms of hydrogen ion concentration, pH_s , according to the procedure of Rajan and Martell⁶ using standard HCl, acetic acid, and NaOH solutions. Titrations were carried out in a doubled-walled titration cell of 50-ml capacity. The temperature of all solutions was maintained at $25.0 \pm 0.1^\circ$ by circulation of thermostated water through the outer jacket of the cell. The titration cell was fitted with Corning glass and calomel electrodes, a microburet delivery tube, and a nitrogen inlet tube. The solutions were stirred with a magnetic stirrer.

Protonation constants of DPA, Gly, and MeGly and the hydroxo formation constant of $\text{Cu}(\text{DPA})^{2+}$



were determined in this cell. Also the mixed ligand formation constants, K_x



(1) Fellow of the Alfred P. Sloan Foundation, 1970–1972.

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(3) R. J. Angelici and J. W. Allison, *Inorg. Chem.*, **10**, 2238 (1971), and references therein.

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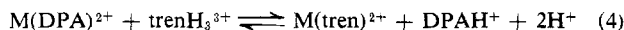
(6) K. S. Rajan and A. E. Martell, *J. Inorg. Nucl. Chem.*, **26**, 789 (1964).

where X = Gly⁻ or MeGly, were measured in this manner. All solutions were adjusted to an ionic strength of 0.05 M by addition of 0.10 M KNO₃ and all titrations were performed in triplicate.

Formation constants for the DPA chelates of Cu(II) and Ni(II)



were determined by the competing ligand method⁷ using trenH₃³⁺ in the reaction



in which trenH₃³⁺ and DPAH⁺ represent all possible protonated forms of those ligands. Equimolar M²⁺, DPA·3HCl, and tren·3HCl with enough 0.10 M KNO₃ added to give an 0.05 M ionic strength were entered into 25-ml bottles. After purging with N₂, enough base was added to reach the second buffer region where replacement of the DPA ligand by tren occurred. This region was ascertained by a preliminary titration. The bottles were sealed with Parafilm M (Marathon Products, Neenah, Wis.) and kept in a water bath at 25.0° for 2 hr, after which time equilibrium had been reached. A Corning semimicro combination pH electrode was used to determine the pH of these solutions.

Species included in the calculation of log K₁ were M(DPA)²⁺, M(tren)²⁺ and all of the protonated and unprotonated forms of DPA and tren. Schwarzenbach's stability constants⁷ for M(tren) and tren were used in the calculations. For the Cu(II) system, it was necessary also to include Cu(DPA)(OH)⁺ which is known (eq 1) to be present in the pH range used. All calculations were done on an IBM 360-65 digital computer.

Visible Spectra. Spectra of the solutions at various pH conditions were obtained by circulating the experimental solution from a titration cell with inlet and outlet tubes to a flow-through quartz cell (Precision Cells, Inc.) by means of a peristaltic pump. The cell compartment of the Beckman DB-G spectrophotometer was also maintained at 25.0°. Measurements were made at 25.0° and an ionic strength of 0.05 M on 4.5 × 10⁻³, 6.0 × 10⁻³, and 8.0 × 10⁻³ M metal ion concentrations containing equimolar DPA or a 2:1 ratio of DPA to metal ion.

Kinetic Measurements. Rates of MeGly hydrolysis in the presence of Cu(DPA)²⁺ were determined by pH-stat techniques described previously.⁸ Ten-milliliter solutions containing 8.0 × 10⁻³ M Cu(DPA)²⁺, 8.0 × 10⁻⁴ M MeGly, and enough KNO₃ to give a 0.05 M ionic strength were studied in the 7.50–8.75 pH range at 25.0 ± 0.1°. A 10% excess of DPA over Cu was used to ensure coordination of all Cu²⁺, which is itself an excellent catalyst.^{9,10} A 20% excess of DPA gave the same rates as with the 10% excess indicating that free Cu²⁺ was not involved in the observed catalysis.

After equilibrating Cu(DPA)²⁺ solutions at 25.0° under an N₂ flow, a solution of MeGly·HCl was added, and the pH was brought up to the desired value by addition of 0.02 M NaOH. The hydrolysis was then followed by automatic addition of 0.02 M NaOH. Pseudo-first-order rate constants, *k*_{obsd}, were obtained from slopes of plots of log (%_{end} - %_t) vs. time, where %_{end} is the per cent of the total syringe volume delivered at the end of the reaction and %_t is the per cent delivered at any time *t*.

Results

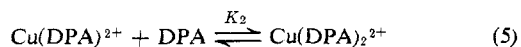
Equilibrium Constants. Protonation constants of DPA, Gly, and MeGly were calculated from titration data using Bjerrum's method.¹¹ The titration curve for DPA·3HCl consists of a low pH buffer zone terminated at *a* = 2 mol of base per mole of ligand, followed by a higher pH buffer region with an inflection at *a* = 3. Values of log K₂' and log K₃' protonation constants of the pyridine groups were calculated from data in the low buffer zone and were found to be 2.60 ±

0.01 and 1.13 ± 0.03, respectively. Data from the higher pH buffer zone were used to calculate 7.28 ± 0.01 for log K₁', the constant for the amino nitrogen. Protonation constants for the amino groups of Gly and MeGly were found to be 9.56 ± 0.01 and 7.73 ± 0.02, respectively. All of these data were obtained at 25.0° and 0.05 M ionic strength.

Titration curves of 1:1 DPA·3HCl with 3.5 × 10⁻³ M Cu(II) or Ni(II) consisted of a low pH buffer zone terminated by an inflection at *a* = 3. Visible spectra of these solutions did not change up to *a* = 3 indicating that M(DPA)²⁺ formation was complete even at the lowest pH; hence formation constants could not be determined by this method. The λ_{max} and ε_{max} values for Cu(DPA)²⁺ and Ni(DPA)²⁺ are 637 nm (114 M⁻¹ cm⁻¹) and 575 nm (9.6 M⁻¹ cm⁻¹), respectively. The Cu(DPA)²⁺ titration curve had a higher pH buffer zone terminated by an inflection at *a* = 4 indicating hydrolysis, as shown in eq 1. Visible spectra showed an isosbestic point in this region, and the product Cu(DPA)(OH)⁺ had λ_{max} and ε_{max} values of 625 nm and 105 M⁻¹ cm⁻¹, respectively. The value of log K_{OH} was calculated from titration data in this region to be 5.01 ± 0.01.

Values of log K₁ (eq 3) determined by Schwarzenbach's competing ligand method⁷ for Cu(DPA)²⁺ and Ni(DPA)²⁺ were 14.4 ± 0.1 and 8.8 ± 0.1, respectively. The value for Cu(DPA)²⁺ differs greatly from that (9.31) reported by Romary, *et al.*,⁴ who determined their value from pH titration data using Bjerrum's calculation method.¹¹ Our spectral results indicate that it is not possible to obtain accurate stability constants by the pH titration method in this system. Almost certainly the 9.31 value is in error. The log K₁ value of 8.8 for Ni(DPA)²⁺ is in reasonable agreement with two literature values^{4,12} (8.70 and 8.5) which were obtained by different methods under similar conditions.

Titration curves of 2:1 DPA·3HCl to Cu(II) exhibited a low pH buffer region terminated by an inflection after 5 mol of base per mole of Cu(II) were added. Visible spectra clearly indicated that only Cu(DPA)²⁺ was formed in this region. A higher pH buffer zone with an inflection after 1 more mol of base indicated the occurrence of the reaction



The log K₂ value calculated by Bjerrum's method from the titration data was 4.61 ± 0.02, in good agreement with 4.54 determined by Romary, *et al.*⁴ The λ_{max} and ε_{max} values of Cu(DPA)₂²⁺ are 645 nm and 98 M⁻¹ cm⁻¹, respectively.

In a titration of 2:1 DPA·3HCl to Ni(II), both Ni(DPA)²⁺ and Ni(DPA)₂²⁺ form throughout the titration and not in separate buffer regions as with Cu(II). The λ_{max} and ε_{max} values of Ni(DPA)₂²⁺ are 510 and 7.8 M⁻¹ cm⁻¹, respectively.

In titrations of 1:1:1 Cu(II) to DPA·3HCl to Gly (or MeGly), the Cu(DPA)²⁺ complex forms at low pH and this is followed by a higher pH buffer zone in which Gly (or MeGly) adds to the complex according to eq 2. Values of log K_x for Gly and MeGly at 25.0° and 0.05 M ionic strength were found to be 3.99 ± 0.02 and 2.81 ± 0.01, respectively.

Kinetics of MeGly Hydrolysis. Pseudo-first-order

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(9) H. L. Conley, Jr., and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).

(10) W. A. Connor, M. M. Jones, and D. L. Tuleen, *Inorg. Chem.*, **4**, 1129 (1965).

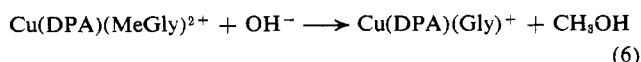
(11) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1957.

Table I. Rate Constants^a for the Hydrolysis of MeGly as Catalyzed by Cu(DPA)²⁺^b

pH ₀	10 ⁴ <i>k</i> _{obsd} , sec ⁻¹	10 ⁻² <i>k</i> _{OH} , M ⁻¹ sec ⁻¹
7.50	0.887	1.73
7.75	1.62	1.77
8.00	2.74	1.69
8.25	4.56	1.58
8.50	8.62	1.68
8.75	14.4	1.58

^a At 25.0° and 0.05 M (KNO₃) ionic strength. ^b [Cu(DPA)²⁺]_{total} = 8.00 × 10⁻³ M.

rate constants, *k*_{obsd}, for the hydrolysis of MeGly in the presence of Cu(DPA)²⁺ are given in Table I. Under the conditions of these studies, the equilibrium constants indicate that 85% or more of the MeGly is coordinated as Cu(DPA)(MeGly)²⁺, and after hydrolysis the Gly⁻ product remains coordinated as Cu(DPA)(Gly)⁺. Thus the predominant reaction occurring in the hydrolysis studies may be written as



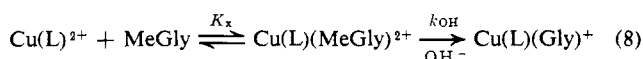
The total amount of NaOH consumed during the kinetic studies was always within 4% of the value expected from eq 6. The *k*_{obsd} values determined at different pH indicate that reaction 6 follows the rate law

$$\text{rate} = k_{\text{OH}}[\text{Cu(DPA)(MeGly)}^{2+}][\text{OH}^-] \quad (7)$$

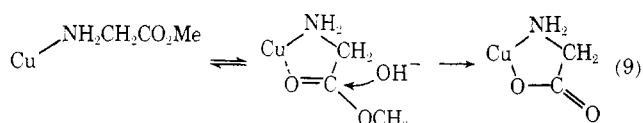
where *k*_{OH} = *k*_{obsd}/[OH⁻]. The average value of *k*_{OH} at 25.0° and 0.05 M ionic strength is 1.67 × 10² M⁻¹ sec⁻¹. In the pH range studied, the rate of hydrolysis of MeGly is negligible in the absence of Cu(DPA)²⁺.

Discussion

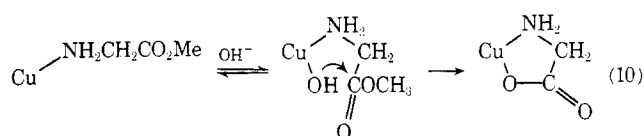
Cu(DPA)²⁺-Catalyzed Hydrolysis of MeGly. The overall Cu(DPA)²⁺-catalyzed hydrolysis of MeGly proceeds in the following two steps



Under the conditions of study here (where L = DPA), the MeGly ester is bound almost entirely as Cu(DPA)(MeGly)²⁺. Thus the observed rate law (eq 7) represents the second step (*k*_{OH}) only. The first-order dependence on OH⁻ concentration for this step may be accounted for by two general mechanisms. One involves an initial rapidly established equilibrium in which ester group coordination occurs, followed by rate-determining attack by OH⁻



The second involves rapid, equilibrium formation of the Cu-OH complex, followed by intramolecular OH⁻ attack



Elegant studies by Buckingham, Foster, and Sargeson¹³ showed that both pathways are important in the ester hydrolysis of the inert complex *cis*-Co(en)₂(Br)(NH₂-CH₂CO₂-*i*-Pr)²⁺. In the labile Cu²⁺-complex-catalyzed reactions of amino acid esters, it has not been possible to establish unequivocally whether one or the other or both of these mechanisms are involved in the observed hydrolysis. Studies of a related Cu²⁺-catalyzed ester hydrolysis¹⁴ using different nucleophiles suggested that external OH⁻ attack (eq 9) was the more likely mechanism. For simplicity in the following discussion, it will be assumed that the Cu(DPA)²⁺-catalyzed ester hydrolysis as well as all of the other Cu(II)-catalyzed ester hydrolyses proceeds by mechanism 9, although mechanism 10 also can account equally well for the observed correlations.

Correlation of Cu(II)-Complex Stability with Ester Hydrolysis Rates. In general, the overall rates of Cu(II)-complex-catalyzed hydrolyses of MeGly are determined by both the extent of ester coordination (*K*_x in eq 8) and the rate of hydrolysis (*k*_{OH}) of the coordinated ester. Considering first the magnitude of *K*_x, it is clear that high rates of ester hydrolysis will be favored by large *K*_x values. In Table II are listed *K*_x

Table II. Rate (*k*_{OH}) and Equilibrium Constants Associated with the Copper(II)-Catalyzed Hydrolysis of MeGly at 25°

Cu(L)(MeGly) ^m	<i>k</i> _{OH} , M ⁻¹ sec ⁻¹	Log <i>K</i> _L	Log <i>K</i> _x
Cu(EtGly) ²⁺	7.6 × 10 ⁴ ^a		4.04 ^b
Cu(IMDA)(MeGly)	3.2 × 10 ⁴ ^c	10.63 ^d	3.69 ^e
Cu(NTA)(MeGly) ⁻	4.6 × 10 ² ^f	13.10 ^g	3.06 ^{h,i}
Cu(DPA)(MeGly) ²⁺	1.7 × 10 ²	14.4	2.81
Cu(dien)(MeGly) ²⁺	1.4 × 10 ² ^j	15.91 ^k	2.52 ^j
MeGly	1.32 ^l		

^a Although not reported, the rate for Cu(MeGly)²⁺ would be somewhat faster (~2 times).^c ^b For EtGly: W. A. Connor, M. M. Jones, and D. L. Tuleen, *Inorg. Chem.*, **4**, 1129 (1965). ^c B. E. Leach and R. J. Angelici, *ibid.*, **8**, 907 (1969). ^d G. Anderegg, *Helv. Chim. Acta*, **47**, 1801 (1964). ^e For *n*-BuGly: R. J. Angelici and D. Hopgood, *J. Amer. Chem. Soc.*, **90**, 2514 (1968). ^f T. Moeller and R. Ferrus, *Inorg. Chem.*, **1**, 55 (1962). ^g D. Hopgood and R. J. Angelici, *J. Amer. Chem. Soc.*, **90**, 2508 (1968). ^h For MeGly. ⁱ R. J. Angelici and J. W. Allison, *Inorg. Chem.*, **10**, 2238 (1971). ^j J. W. Allison and R. J. Angelici, *ibid.*, **10**, 2233 (1971). ^k R. W. Hay, L. J. Porter, and P. J. Morris, *Aust. J. Chem.*, **19**, 1197 (1966). ^l Ligand L abbreviations: IMDA, HN(CH₂-CO₂)₂; NTA, N(CH₂CO₂)₃; dien, HN(CH₂CH₂NH₂)₂.

values for the coordination of glycine esters by a series of Cu(II) complexes. In Figure 1 these log *K*_x values are plotted vs. log *K*_L values for the formation of the Cu(L)²⁺ complexes



(where the charge on the complex will vary with the charge on L). From this plot it is evident that *K*_x decreases as *K*_L increases, i.e., the higher the stability constant for the formation of Cu(L)²⁺ the lower the tendency for Cu(L)²⁺ to bind MeGly. This trend may be explained by considering that the strongest binding (i.e., strongest donor) L ligands in Cu(L)²⁺ will be the most effective at reducing the Lewis acidity of the Cu-

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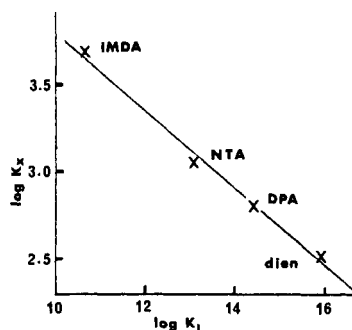


Figure 1. Correlation of $\log K_x$ with $\log K_L$ for a series of $\text{Cu(L)}\text{(MeGly)}^{2+}$ complexes. Ligand abbreviations are given in Table II (footnote *m*).

(II) toward MeGly. Thus $\text{Cu(L)}\text{(MeGly)}^{2+}$ complex formation is promoted by weakly donating L ligands. In the ligands given in Table II, the carboxylate group is much more weakly coordinating than any of the N-donor groups. Thus an increase in the number of N-donor groups in the L ligand will cause a decrease in the Lewis acidity (*i.e.*, K_x) of the Cu(L)^{2+} complex.

Assuming mechanism 9 for the hydrolysis of MeGly in the $\text{Cu(L)}\text{(MeGly)}^{2+}$ complexes, the OH^- attack step and possibly the rapid equilibrium coordination step would be favored for Cu(L)^{2+} complexes of high Lewis acidity. One measure of the Lewis acidity of these Cu(L)^{2+} complexes is their K_x values for the binding of MeGly. A plot (Figure 2) of the rate constant $\log k_{\text{OH}}$ vs. $\log K_x$ indeed shows a correlation in which complexes of highest Lewis acid character (high K_x) are the most effective promoters of the ester hydrolysis. Since it was shown in Figure 1 that Cu(L)^{2+} complexes with low formation constants (K_L) have the highest Lewis acidity, a correlation between low $\log K_L$ values and high rate constants ($\log k_{\text{OH}}$) for hydrolysis should be observed; this correlation is also shown in Figure 2. If mechanism 10 is assumed to be involved in the k_{OH} step of the reaction, these correlations could be explained by noting that complexes of highest Lewis acidity (lowest K_L and highest K_x) would promote the greatest amount of hydroxo-complex formation and thereby accelerate the rate of ester hydrolysis.

In summary, it is clear that weakly donating L ligands produce the most active Cu(L)^{2+} catalysts in the hydrolysis of MeGly. Such weak donors enhance the Lewis acidity of the Cu(II) which promotes Cu(L)^{2+} binding of the MeGly in the first step (K_x) of the hydro-

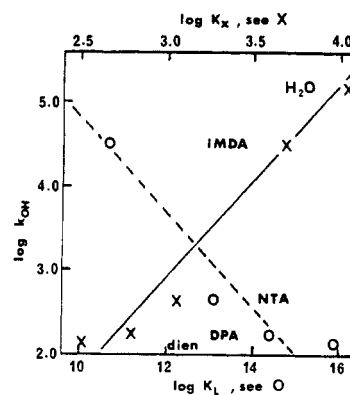


Figure 2. Cu(L)^{2+} -catalyzed hydrolyses of MeGly: solid line (X), plot of $\log k_{\text{OH}}$ vs. $\log K_x$; dashed line (O), plot of $\log k_{\text{OH}}$ vs. $\log K_L$. Straight lines are not meant to infer linear relationships. Ligand abbreviations are given in Table II (footnote *m*).

lysis mechanism (eq 8) and also facilitates OH^- attack (k_{OH}) in the second step (mechanism 9).

These conclusions can be extended to explain trends observed by Hay and Morris¹⁵ for the Cu(II) -complex-catalyzed hydrolyses of $\text{NH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{CH}_3$, E. In this case the values of k_{OH} decreased as follows ($\text{A}^- = \text{NH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{CO}_2^-$): $\text{CuE}^{2+} > \text{CuE}_2^{2+} > \text{CuE(OH)}^+ > \text{CuE(NH}_2\text{CH}_2\text{CH}_2\text{NH}_2)^{2+} > \text{CuEA}^+$. Again the decrease in k_{OH} follows an increase in $\log K_L$. The related Hg(II) -catalyzed reactions of this ester follow a similar trend. Finally, another study by Hay and Morris¹⁶ of the hydrolysis of histidine methyl ester as catalyzed by Cu(II) and Ni(II) complexes shows the same trend. Those authors interpreted their trend in rates in terms of the magnitude of the positive charge on the M(L)_n^+ complexes; those complexes with the higher positive charge yielded the highest k_{OH} . This explanation does not, however, account for their later data¹⁵ or for the trends reported herein. The correlation of hydrolysis rates with the Lewis acidity of the Cu(L)^{2+} complexes, as defined by values of K_L or K_x , however, provides a reasonable basis for understanding all of these reactions.

Acknowledgment. We are grateful to the U. S. Public Health Service for support of this research through Grant No. GM-12626 of the National Institute of General Medical Sciences.

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(16) R. W. Hay and P. J. Morris, *J. Chem. Soc. A*, 1524 (1971).