gerum and coworkers[19] have attributed the unusually high value for Cu(1,1,7,7-Et$_4$dien)(OH)$^+$ to the displacement of the axial water ligands by the bulky ethyl groups. This allows the copper to coordinate more strongly to the in-plane water ligand making it more acidic. This steric effect seems not to be of such major importance in the other Cu(Rdien)(OH)$^+$ complexes, even in Cu(1,1,4,7,7-Me$_5$dien)(OH)$^+$. The variations in K_{OH} are so small that it is difficult to cite factors which are responsible for them. However, two factors appear to contribute: first the steric effect, as in Cu(1,1-Et$_2$dien) and Cu(1,1-Me$_2$dien), which increases K_{OH}; second, alkyl substitution at the nitrogen trans to the OH group (*i.e.*, the 4 nitrogen). Such substitution appears to decrease K_{OH}, as in Cu(1,4-Me$_2$dien)(OH)$^+$, perhaps as a result of stronger electron donation by the 4 nitrogen thus making the trans H_2O ligand less acidic.[26] The values of K_{OH} for Cu(1,1,4,7,7-Me$_5$dien)(OH)$^+$ and Cu(1,4,7-Et$_3$dien)(OH)$^+$ may be explained by a combination of both effects.

(26) R. C. Beaumont, *Inorg. Chem.*, **8**, 1805 (1969).

Martell and coworkers[27] had previously determined K_{OH} values for a number of copper(II) complexes of bi- and tridentate ligands. For a variety of ethylenediamines, with widely varying substituents on the carbon and nitrogen atoms, the log K_{OH} values fell within the small range of 6.4–6.8. For tridentate ligands, log K_{OH} was generally smaller; for example, for the iminodiacetate complex, Cu(IMDA)(OH)$^-$, log K_{OH} was found[28] to be 5.7, similar to the values for the Cu(Rdien)(OH)$^-$ complexes. For the nitrilotriacetate complex, Cu(NTA)(OH)$^{2-}$, it was still smaller (4.4).[29] In general,[27] K_{OH} values seem to depend more upon the denticity than on other structural features of the ligand.

Acknowledgment.—We appreciate the support of this research by the U. S. Public Health Service through Grant No. GM-12626 of the National Institute of General Medical Sciences.

(27) A. E. Martell, S. Chaberek, Jr., R. C. Courtney, S. Westerback, and H. Hyytiainen, *J. Amer. Chem. Soc.*, **79**, 3036 (1957).
(28) B. E. Leach and R. J. Angelici, *Inorg. Chem.*, **8**, 907 (1969).
(29) D. Hopgood and R. J. Angelici, *J. Amer. Chem. Soc.*, **90**, 2508 (1968).

CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
IOWA STATE UNIVERSITY, AMES, IOWA 50010

Stability Constants for Amino Acid Coordination by Substituted Diethylenetriamine Complexes of Copper(II) and the Kinetics of Amino Acid Ester Hydrolysis

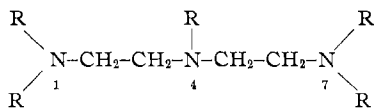
BY ROBERT J. ANGELICI*[1] AND JUANITA W. ALLISON

Received February 11, 1971

The amino acidates (A$^-$) of glycine, valine, sarcosine, and β-alanine coordinate to Cu(Rdien)$^{2+}$, where Rdien is a substituted diethylenetriamine bearing from one to five methyl or ethyl groups on the nitrogen atoms, to give the complexes Cu(Rdien)(A)$^+$. Stability constants, K_x, depend little on the structure of the Rdien ligand except for sarcosine where the *N*-methyl group of the amino acid significantly decreases K_x when Rdien contains two or more methyl or ethyl groups at the terminal nitrogens. When compared to other copper(II) complexes, Cu(dien)$^{2+}$ forms relatively unstable glycine complexes, as measured by K_x, which decreases as follows: Cu^{2+} > Cu(dipy)$^{2+}$ > Cu(NH$_3$)$_2^{2+}$ > Cu(Gly)$^+$ > Cu(IMDA) > Cu(NTA)$^-$ > Cu(dien)$^{2+}$. The hydrolysis of the amino acid ester methyl glycinate (MeGly) is catalyzed by Cu(dien)$^{2+}$. Kinetic and equilibrium studies suggest that the reaction proceeds by coordination of the ester to form Cu(dien)(MeGly)$^{2+}$ followed by either OH$^-$ or Cu(dien)(OH)$^+$ attack in the rate-determining step. As compared to other copper(II) complexes, Cu(dien)$^{2+}$ is a relatively poor catalyst. Rate constants for the OH$^-$ attack path decrease as follows: Cu^{2+} > Cu(IMDA) > Cu(NTA)$^-$ > Cu(dien)$^{2+}$. Stability constants for the coordination of methyl glycinate by these complexes decrease in the same order.

Introduction

In the preceding paper,[2] we reported proton stability constants, K_1, K_2, and K_3, for a series of *N*-methyl- and *N*-ethyl-substituted diethylenetriamines (Rdien)



as well as stability constants, K_f, for their coordination to Cu^{2+} to form Cu(Rdien)$^{2+}$. The hydroxo stability constants, K_{OH}, for the formation of the Cu(Rdien)(OH)$^+$ complexes were also detailed.

In the present communication, we report equilibrium constants, K_x, for the coordination of amino acids and amino acid esters with the Cu(Rdien)$^{2+}$ complexes

$$Cu(Rdien)^{2+} + A^{n-} \rightleftharpoons Cu(Rdien)(A)^{(2-n)+},\ K_x = \frac{[Cu(Rdien)(A)^{(2-n)+}]}{[Cu(Rdien)^{2+}][A^{n-}]} \quad (1)$$

where n is 1 if A is an amino acidate and n is 0 if A is an amino acid ester. These constants were used in interpreting kinetic studies of the hydrolysis of methyl glycinate, as catalyzed by Cu(dien)$^{2+}$.

(1) Fellow of the Alfred P. Sloan Foundation, 1970–1972.
(2) J. W. Allison and R. J. Angelici, *Inorg. Chem.*, **10**, 2233 (1971).

Experimental Section

Materials.—The amino acids were obtained from commercial sources and used without further purification. They were analyzed for total hydrogen ion content by titration with standard NaOH using a pH meter. To lower the pH at the end points, they were titrated in 10% aqueous formaldehyde solution ac-

cording to standard procedures.[3] All amino acids were found to analyze within 2% of the calculated hydrogen ion content. Glycine methyl ester hydrochloride (MeGly·HCl) was recrystallized from methanol and stored in a desiccator.

β-Alanine ethyl ester hydrochloride (Et-β-Ala·HCl) was prepared by treating 10 g of β-alanine in 100 ml of absolute ethanol with hydrogen chloride gas for 25 min. The solution was initially yellow, but it changed to green and darkened during 2 hr of refluxing. At the end of this time, the ethanol was removed by evaporation, leaving a pale yellow solid. The solid was recrystallized first from hot absolute ethanol and then from a room-temperature mixture of absolute ethanol and diethyl ether to yield white crystals of the product (mp 54–54.5°, lit.[4] mp 59°). Titration with NaOH confirmed the product as Et-β-Ala·HCl.

The purification, standardizations, and abbreviations of other chemicals are given in the preceding paper.[2] Abbreviations of amino acids are those in common use.[5]

Titrations.—The amino acids have two basic sites and pK_a values were determined for these sites by titrating 9×10^{-3} *M* H_2A^+ solutions of ionic strength 0.11 (KNO_3) with 0.2 *N* NaOH at 25.0°. The pH instrumentation and its calibration as well as the conversion of pH values to $-\log [H^+]$ (*i.e.*, pH_c) values were described previously.[2]

The determinations of the stability constants, K_x, for the mixed-ligand complexes, $Cu(Rdien)(A)^{(2-n)+}$, were carried out by titrating with 0.2 *N* NaOH a solution of 9×10^{-3} *M* $Cu(NO_3)_2$, 9×10^{-3} *M* Rdien, 9×10^{-3} *M* amino acid, 27×10^{-3} *M* HNO_3, and sufficient doubly distilled water and KNO_3 to bring the volume to 10 ml and the average ionic strength to 0.11. A typical titration curve of a solution containing Cu^{2+}, $dienH_3^{3+}$, and glycine is shown in Figure 1 together with that of a solution not containing the glycine. To minimize hydrolysis of the amino acid ester hydrochlorides during the titrations, solutions of the ester were the last to be added to the cell, and the titration was carried out as rapidly as possible. Based on kinetic studies, no significant hydrolysis should have occurred during the titrations.

Kinetic Measurements.—Rates of MeGly hydrolysis at 25.0° in the presence of $Cu(dien)^{2+}$ were determined by pH-Stat techniques described previously.[6] Ten-milliliter solutions containing approximately 9×10^{-3} *M* $Cu(NO_3)_2$, 10×10^{-3} *M* dien, 9×10^{-4} *M* MeGly, and sufficient KNO_3 to give an ionic strength of 0.11 were studied in the 7.7–8.9 pH range at 25.0. A 10% excess of dien as compared to Cu^{2+} was used to ensure that no uncomplexed Cu^{2+} was present, because it is known[7,8] to catalyze strongly the hydrolysis of glycine esters. Solutions containing equimolar Cu^{2+} and dien gave irreproducible results presumably due to variable and small amounts of free Cu^{2+}. Using from 10 to 50% excess dien gave reproducible rates which did not depend on the dien concentration.

The solutions were equilibrated at 25° while a stream of nitrogen was passed through the solution. An ester solution was then added and the hydrolysis at constant pH was followed by the automatic addition of 0.04 *N* carbonate-free NaOH. The pseudo-first-order rate constants, k_{obsd}, were obtained from first-order plots[9] of log ($\%_{end} - \%_t$) *versus* *t*, where $\%_{end}$ is the per cent of the total volume of NaOH delivered at infinite time and $\%_t$ is the per cent delivered after any time, *t*. At the higher pH values, the amount of NaOH consumed was always less than the theoretical amount calculated from the total ester present. This was due to the fact that at high pH appreciable amounts of $Cu(dien)(OH)^+$ were present which reacted with the product amino acidate to give $Cu(dien)(Gly^+)$ and OH^-; for this reaction there is no net consumption of OH^-. Hence all $\%_{end}$ values were determined experimentally. In the pH range studied, the amount of ester hydrolysis in the absence of $Cu(Rdien)^{2+}$ was negligible.

Results

Evaluation of K_a and K_f.—The two amino acid pK_a values, corresponding to proton dissociation from the carboxylate and amino groups, were calculated from titration data taken in the buffer regions preceding the addition of 1 and 2 equiv of NaOH. Since these two pK_a constants were so different, eq 9 from the preceding paper[2] was applied separately to the calculation of each of the constants. From pK_a values calculated at several points, an average value and a standard deviation were calculated by computer. The results, given in Table I, for the amino acids and esters are in good agreement with literature values.[10,11]

TABLE I
pK_a VALUES OF AMINO ACIDS AND THEIR ESTERS AT 25.0° AND 0.11 IONIC STRENGTH (KNO_3)

Amino acid	pK_a values	Amino acid ester	pK_a values
Gly	2.35 ± 0.02, 9.54 ± 0.01	MeGly	7.68 ± 0.01
Val	2.25 ± 0.02, 9.47 ± 0.02	Et-β-Ala	9.23 ± 0.02
Sar	2.17 ± 0.02, 9.98 ± 0.01		
β-Ala	3.55 ± 0.01, 10.08 ± 0.02		

The stability constants, K_x, for the formation of the mixed-ligand complexes, $Cu(Rdien)(A)^{(2-n)+}$, according to eq 1 were determined from titration data of the type shown for $Cu(dien)^{2+}$ and Gly in Figure 1. This figure shows an initial region in which 3 equiv of NaOH/mol of dien is being added. Since the curves without (A) and with (B) glycine are the same and the $Cu(dien)^{2+}$ complex is known[2] to form in this region, only $Cu(dien)^{2+}$ formation is assumed to occur in the solution containing glycine at pH values less than 4. Stability constants, K_f, for the formation of $Cu(Rdien)^{2+}$ in this region have been reported previously.[2]

In the region between the addition of 3 and 4 equiv of NaOH, there are several equilibria which must be considered: (1) proton dissociation (K_a) from the amino group of the amino acid or ester, $HA \rightleftharpoons H^+ + A^-$; (2) the formation of $Cu(Rdien)(A)^{(2-n)+}$ according to eq 1; and (3) the formation of $Cu(Rdien)(OH)^+$

$$Cu(Rdien)^{2+} + OH^- \rightleftharpoons Cu(Rdien)(OH)^+, \quad K_{OH} = \frac{[Cu(Rdien)(OH)^+]}{[Cu(Rdien)^{2+}][OH^-]} \quad (2)$$

Both K_a and K_{OH} have been evaluated independently,[2] and K_x is the only constant which remains to be determined.

To calculate K_x, expressions for total copper concentration, $[Cu_{TOT}]$, total amino acid (or ester) concentration, $[A_{TOT}]$, and added OH^- concentration, $[OH]_{add}$, are defined as

$$[Cu_{TOT}] = [Cu(Rdien)] + [Cu(Rdien)(OH)] + [Cu(Rdien)(A)] \quad (3a)$$

$$[A_{TOT}] = [A] + [Cu(Rdien)(A)] + [HA] \quad (3b)$$

$$[OH]_{add} = [OH] - [H] + [Cu(Rdien)(OH)] + [Cu(Rdien)(A)] + [A] \quad (3c)$$

After substituting expressions for K_a, K_{OH} (eq 2), and K_x (eq 1) into (3a), (3b), and (3c) and letting $[OH]_{add'} = [OH]_{add} + [H]$, these equations can be solved for $[Cu(Rdien)]$

$$[CuR(dien)] = \frac{[OH]_{add'} - [OH] - [A]}{K_{OH}[OH] + K_x[A]} \quad (4)$$

(3) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N. Y., 1961, p 515.
(4) G. Hilgetag, H. Paul, J. Günther, and M. Witt, *Chem. Ber.*, **97**, 704 (1964).
(5) Reference 3, Vol. 2, p 768.
(6) B. E. Leach and R. J. Angelici, *Inorg. Chem.*, **8**, 907 (1969).
(7) H. L. Conley, Jr., and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).
(8) W. A. Connor, M. M. Jones, and D. L. Tuleen, *Inorg. Chem.*, **4**, 1129 (1965).
(9) R. J. Angelici and B. E. Leach, *J. Amer. Chem. Soc.*, **89**, 4605 (1967).
(10) L. G. Sillén and A. E. Martell, *Chem. Soc., Spec. Publ.*, **No. 17** (1964).
(11) D. Hopgood and R. J. Angelici, *J. Amer. Chem. Soc.*, **90**, 2508 (1968).

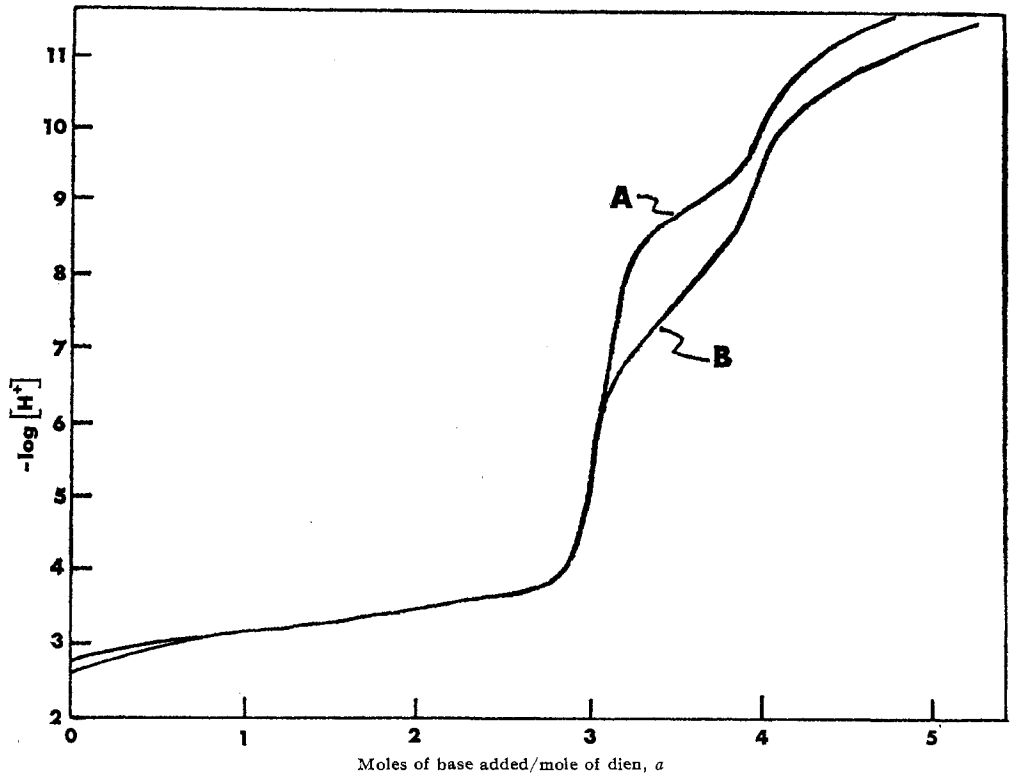


Figure 1.—Titration curves of equimolar (9×10^{-3} *M*) dienH_3^{3+} and Cu^{2+} at 25° and 0.11 ionic strength (KNO_3): A, no amino acid; B, with equimolar glycine.

TABLE II

LOG K_x VALUES FOR THE FORMATION OF Cu(Rdien)(A) AT 25.0° AND 0.11 IONIC STRENGTH (KNO_3)

Rdien	Gly	Val	Sar	β-Ala
dien[a]	4.42 ± 0.05	3.79 ± 0.09	3.98 ± 0.12	3.65 ± 0.19
1-(Me)dien	4.65 ± 0.07	3.99 ± 0.09	3.98 ± 0.12	3.15 ± 0.16
1,4-Me_2dien	4.68 ± 0.01	4.22 ± 0.04	3.79 ± 0.19	3.29 ± 0.08
1,1-Me_2dien	4.38 ± 0.04	3.96 ± 0.03	3.10 ± 0.30	2.89 ± 0.12
1,1,4,7,7-Me_5dien	5.04 ± 0.05[b]	4.79 ± 0.04[b]	3.23 ± 0.13	3.23 ± 0.06
1,1-Et_2dien	4.16 ± 0.04	3.46 ± 0.17	3.05 ± 0.18	3.43 ± 0.10
1,4,7-Et_3dien	4.25 ± 0.07	3.84 ± 0.02	NC[c]	NC[c]

[a] With MeGly, log K_x = 2.52 ± 0.08. [b] Undergoes color change during mixed-complex formation (see text). [c] No measurable mixed-complex formation.

Equation 4 is now substituted into eq 3a and 3b. The resulting expressions are solved for K_x and set equal to each other. The result, after considerable simplification, is a quadratic equation in [A]

$$[A]^2\{K_{OH}[OH] - K_w/K_b[OH]\} + [A]\{[Cu_{TOT}]K_{OH}[OH] + \frac{K_w([OH]_{add'} - [OH])}{[OH]K_b} - [OH]_{add'} + [OH] + [A_{TOT}] - 2K_{OH}[OH][OH]_{add'} + 2K_{OH}[OH]^2\} + \{[Cu_{TOT}]K_{OH}[OH]^2 - [Cu_{TOT}]K_{OH}[OH][OH]_{add'} + [OH]_{add'}([OH]_{add'} - [OH]) - [OH]([OH]_{add'} - [OH]) - [A_{TOT}]([OH]_{add'} - [OH]) - K_{OH}[OH]^2[OH]_{add'} + K_{OH}[OH][OH]_{add'}^2 - K_{OH}[OH]^2([OH]_{add'} - [OH])\} = 0 \quad (5)$$

Only one of the two roots of eq 5 is positive and less than $[A_{TOT}]$. This root is returned to either expression for K_x obtained from eq 3a and 3b to obtain a value for K_x. The calculations of K_x were carried out by computer using titration data between *a* values of 3.3 and 3.7 (Figure 1). The resulting constants and their standard deviations are given in Table II.

Some determinations of K_x were not completed because of complications. The titration curve of Cu^{2+}, 1,1,7,7-Et_4dienH^{3+}, and glycine is quite different from the others in the low-pH region. This is almost certainly due to the similar log K_f values (~8) for 1,1,7,7-Et_4dien and Gly toward Cu(II). The higher basicity of 1,1,7,7-Et_4dien means that it is more readily protonated, and Cu(Gly)$^+$ forms in this region. For this reason, no mixed complexes of Cu(1,1,7,7-Et_4dien)$^{2+}$ were investigated.

Attempts to measure K_x values for Cu(dien)(Et-β-Ala)$^{2+}$, Cu(1-(Me)dien)(Et-β-Ala)$^{2+}$, Cu(1,4,7-Et_3dien)-(β-Ala)$^+$, and Cu(1,4,7-Et_3dien)(Sar)$^+$ were unsuccessful because of the very low tendency of the amino acid or ester to coordinate in these complexes.

Kinetics of Ester Hydrolysis.—The hydrolysis of MeGly was carried out in the presence of at least 10-fold excesses of Cu(dien)$^{2+}$. In the 7.7–8.9 pH range of the studies, Cu(dien)(OH)$^+$ is present in significant concentrations (10–67%), and approximately 60 ± 10% of the MeGly is coordinated as Cu(dien)(MeGly)$^{2+}$. After hydrolysis virtually all of the product glycine is coordinated as Cu(dien)(Gly)$^+$.

Since Buckingham, *et al.*,[12,13] have shown that ethyl glycinate in $Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)^{3+}$ undergoes base-catalyzed intramolecular attack by a coordinated nitrogen atom to give $Co(NH_3)_4(NH_2CH_2CONH)^{2+}$ (glycinimide coordinated through both N atoms) and suggested that Cu^{2+} may catalyze the same type of amine–ester reaction, it was especially important to establish that the product was simply glycine[14,15] and not a glycinamide of dien. This was done by carrying out the reaction of Cu^{2+}, dien, and MeGly on a larger scale and identifying the products by nmr spectroscopy. A 450-ml solution of 0.04 *M* $Cu(NO_3)_2$, 0.05 *M* dien, and slightly less than 0.04 *M* methyl glycinate was allowed to react at room temperature for 2.5 hr with the pH maintained between 7.9 and 8.1 by the addition of sodium hydroxide. At the end of this time, slightly more than 1 equiv of sodium sulfide, $Na_2S \cdot 9H_2O$, was added to precipitate the Cu^{2+}. The solution was filtered and the volume of the filtrate reduced from 0.5 to 0.02 l., yielding a white precipitate. The precipitate and water were extracted twice with 40-ml portions of CH_2Cl_2. The nmr spectrum of this extract was identical with that of dien. A small amount of the precipitate dissolved in D_2O gave an nmr spectrum which was very similar to that of a known solution of dien and glycine, except the positions of the peaks differed by about 0.2 ppm. This difference may be due to slight variations in pH or the large amount of inert salt from the reaction mixture. From this analysis of the ligands, the products of the reaction can be formulated as Cu(dien)(Gly)$^+$ and methanol, and not the amide, $H_2NCH_2CH_2N(H)CH_2CH_2N(H)C(O)CH_2NH_2$. Pseudo-first-order rate constants, k_{obsd}, for MeGly hydrolysis were determined at constant $[Cu(dien)^{2+}]_{TOT}$ (same as $[Cu_{TOT}]$ of eq 3a and include $[Cu(dien)^{2+}]$, $[Cu(dien)(OH)^+]$, and $[Cu(dien)(MeGly)^{2+}]$) over a pH_c range of 7.7–8.9 (Table III(a)). Each k_{obsd} value in Table III is an average of three to six independent kinetic runs. A plot of log k_{obsd} *vs.* pH_c gives a straight line with slope 0.89. Since the rate constants are only known to ±10%, this slope indicates that the $[OH]^-$ dependence is within experimental error of 1.0. At constant pH_c 8.00, k_{obsd} was measured as a function of the $[Cu(dien)^{2+}]_{TOT}$ concentration. These data (Table III(b)) indicate that the rate is also first order in the $[Cu(dien)^{2+}]_{TOT}$ concentration and the overall experimental rate law becomes

$$\text{rate} = k[\text{MeGly}]_{TOT}[Cu(dien)^{2+}]_{TOT}[OH^-] \quad (6)$$

where $k_{obsd} = k[Cu(dien)^{2+}]_{TOT}[OH^-]$. As will be seen in the discussion of the mechanism, the simple first-order dependence on $[Cu(dien)^{2+}]_{TOT}$ and $[OH^-]$ is apparently fortuitous and results from a combination of experimental conditions and two different mechanisms.

TABLE III

PSEUDO-FIRST-ORDER RATE CONSTANTS, k_{obsd}, FOR THE HYDROLYSIS OF MeGly CATALYZED BY $Cu(dien)^{2+}$ AT 25.0° AND 0.11 IONIC STRENGTH (KNO_3)

(a) $[Cu(dien)^{2+}]_{TOT} = 9.54 \times 10^{-3}$ *M*

pH_c	$10^3 k_{obsd}$, sec^{-1}	pH_c	$10^3 k_{obsd}$, sec^{-1}
7.69	0.437	8.20	1.29
7.79	0.597	8.30	1.63
7.89	0.569	8.40	1.76
8.00	0.870	8.50	2.39
8.10	0.918	8.90	4.66

(b) Constant pH_c 8.00

$[Cu(dien)^{2+}]_{TOT}$, *M*	$10^3 k_{obsd}$, sec^{-1}
9.54×10^{-3}	0.870
14.3×10^{-3}	1.38
19.1×10^{-3}	1.95

Discussion

Stability Constants for Cu(Rdien)(A)$^+$, K_x.—Of the amino acidates (A^-) which were studied in the formation of Cu(Rdien)(A)$^+$ according to eq 1, glycine (Gly) formed the most stable complexes. The presumed structure of these complexes is one in which four nitrogens (three from Rdien and one from Gly) coordinate in a square plane and the carboxylate group of Gly binds at an apical position; this structure has been proposed[16] for the analogous alanine complex Cu(dien)(Ala)$^+$ on the basis of circular dichroism and infrared studies. The K_x values for the Cu(Rdien)(Gly)$^+$ complexes were surprisingly unaffected by the structure of Rdien since almost all of the values lay in the narrow range of 4.4 ± 0.2, although the bulky ethyl-substituted Rdien ligands tended to give the lower constants. The one ligand which falls significantly above this range is 1,1,4,7,7-Me_5dien. The unusual stability of both Cu(1,1,4,7,7-Me_5dien)(Gly)$^+$ and Cu(1,1,4,7,7-Me_5dien)(Val)$^+$ may be related to the unusual color changes occurring between *a* values of 3 and 4 which did not take place with any of the other dien complexes. Normally, the solution in this region is dark blue with some purple from Cu(Rdien)(OH)$^+$. In these two titrations the solutions were a much lighter blue color below $a = 4$ but darkened again above that point. It is not certain what causes this behavior, but five-coordinated Cu(1,1,4,7,7-Me_5dien)Cl_2 is known to be light blue,[17] and it presumably has a structure which is intermediate between that of a trigonal bipyramid and a square pyramid. This is based on its isomorphism[18] with Co(1,1,4,7,7-Me_5dien)Cl_2 which has been shown to have that structure.[19] The Cu(1,1,4,7,7-Me_5dien)(A)$^+$ complexes of Gly and Val may have analogous structures.

As found (Table IV) in the simple amino acid com-

TABLE IV

STABILITY CONSTANTS, LOG K_x, FOR THE REACTION $Cu(L) + A \rightleftharpoons Cu(L)(A)$ AT 25.0°

Cu(L)[a]	Gly	Val	Sar	β-Ala	MeGly	Et-β-Ala
Cu^{2+}	8.38[b]	7.92[c]	7.94[b]	7.34[d]	4.04[e]	...
Cu(IMDA)[f]	6.42	6.17	...	...	3.69[g]	...
Cu(NTA)$^-$[h]	5.44	5.10	...	4.56	3.06	3.65

[a] Ligand abbreviations: IMDA, $HN(CH_2CO_2^-)_2$; NTA, $N(CH_2CO_2^-)_3$. [b] Reference 14. [c] Reference 15. [d] Reference 10. [e] Reference 8. [f] Reference 6. [g] For BuGly. [h] Reference 11.

(12) D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *ibid.*, **91**, 3451 (1969).
(13) D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *ibid.*, **91**, 4102 (1969).
(14) F. Basolo and Y. T. Chen, *ibid.*, **76**, 953 (1954).
(15) L. E. Maley and D. P. Mellor, *Aust. J. Sci. Res., Ser. A*, **2**, 579 (1949).
(16) T. Murakami, T. Nozawa, and M. Hatano, *J. Amer. Chem. Soc.*, **92**, 5768 (1970).
(17) M. Ciampolini and G. P. Speroni, *Inorg. Chem.*, **5**, 45 (1966).
(18) M. Ciampolini, M. Nardi, and G. P. Speroni, *Coord. Chem. Rev.*, **1**, 222 (1966).
(19) M. Di Vaira and P. L. Orioli, *Inorg. Chem.*, **8**, 2729 (1969).

plexes, CuA^+, Val coordinates less strongly than does Gly. The values of K_x for Cu(Rdien)(Val)$^+$ fall in the range 3.8 ± 0.4, except for the 1,1,4,7,7-Me_5dien derivative which was noted above. There appear to be no reliable trends which suggest any steric repulsion between the isopropyl group in the valine and the methyl or ethyl groups in the Rdien ligands.

Toward Cu^{2+}, sarcosine (Sar) yields a complex which is less stable than Cu(Gly)$^+$. The same difference is observed with the Cu(Rdien)$^{2+}$ complexes. However there also appears to be a significant steric effect which gives log K_x values of 3.9 ± 0.1 for the top three Rdien ligands but 3.1 ± 0.1 for the four sterically more demanding ligands at the bottom of Table II. The *N*-methyl group causes sarcosine to form relatively unstable complexes with Cu(Rdien)$^{2+}$ derivatives which have two or more methyl or ethyl groups at the 1 and/or 7 nitrogen atoms.

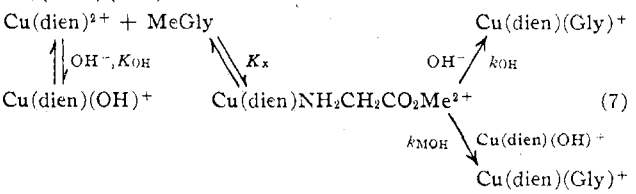
β-Alanine (β-Ala) gives still less stable derivatives than the already mentioned amino acids, as is expected and observed (Table IV) for a ligand which forms a six-membered chelate ring. The log K_x values cluster at 3.3 ± 0.4 with no trends being discernible.

The esters methyl glycinate (MeGly) and ethyl β-alaninate (Et-β-Ala) cannot chelate and thus give much lower K_x values (Tables II and IV). It is expected that the more basic ligand (Et-β-Ala) would form the more stable complex: this is observed for the complexes of Cu(NTA)$^-$. It is not clear why Et-β-Ala does not form a complex with Cu(dien)$^{2+}$ when MeGly does.

While methyl and ethyl substitution in Cu(Rdien)$^{2+}$ does not appear greatly to affect K_x values for coordination of Gly^-, other L ligands in the equilibrium, Cu(L) + $Gly^- \rightleftharpoons$ Cu(L)(Gly), make substantial changes in K_x. For this equilibrium, K_x decreases with Cu(L) as follows (log K_x in parentheses):[20] Cu^{2+} (8.38)[13] > Cu(dipy)$^{2+}$ (7.88)[21] > $Cu(NH_3)_2^{2+}$ (7.10)[22,23] > Cu(Gly)$^+$ (6.87)[13] > Cu(IMDA) (6.42)[6] > Cu(NTA)$^-$ (5.44)[11] > Cu(dien)$^{2+}$ (4.42). With the exception of Cu(dien)$^{2+}$, K_x decreases with decreasing charge on Cu(L), *i.e.* 2+ > 1+ > 0 > 1−. Even when compared with the other tridentate ligand complex, Cu(IMDA), the value of K_x for Cu(dien)$^{2+}$ is unexpectedly low. It should be noted that the trend with the charge on the complex is not general as seen in the analogous Ni^{2+} equilibrium, Ni(L) + $Gly^- \rightleftharpoons$ Ni(L)(Gly). Log K_x decreases with Ni(L) in the order:[24] Ni^{2+} (5.77) > Ni(dien)$^{2+}$ (5.13) > Ni(NTA)$^-$ (4.89) ≥ Ni(Gly)$^+$ (4.80). Jackobs and Margerum[24] have used seven parameters to account empirically for these mixed stability constants.

Cu(dien)$^{2+}$-Catalyzed Hydrolysis of MeGly.—Metal ion catalyzed hydrolyses of amino acid esters have been suggested to proceed by several mechanisms.[25] All require initial coordination of the ester NH_2 group by the metal ion. The ester may then undergo direct attack at the carbonyl carbon atom by OH^-, OH_2, or MOH (a metal hydroxo complex) or first form a chelate by coordinating one ester oxygen to the metal. The coordinated ester group may then undergo nucleophilic attack. A final mechanism is one in which the OH ligand of the mixed complex M(OH)(ester) intramolecularly attacks the coordinated ester.[13]

In the present study of methyl glycinate (MeGly) hydrolysis, the rate of hydrolysis is approximately first order each in OH^- and $[Cu(dien)^{2+}]_{TOT}$ concentrations (eq 6). To accommodate these results, three mechanisms must be considered. The two most probable paths are represented by rate-determining OH^- and Cu(dien)(OH)$^+$ attack as shown



The ester group is almost certainly not[25,26] coordinated to the metal in Cu(dien)(MeGly)$^{2+}$. Whether there is a small equilibrium amount of coordinated ester which is particularly reactive is unknown, but it has been postulated many times previously.[25] The third mechanism would involve intramolecular OH^- attack in the species Cu(dien)MeGly(OH)$^+$. Since Cu(II) is known to prefer four-coordination,[26] it is unlikely that an OH^- ligand would add to give a stable five-coordinated derivative. Together with the fact that no intramolecular attack by the dien ligand (to give a glycinamide) occurs, the evidence suggests that intramolecular OH^- attack is improbable and will not be considered further.

Under the concentration and pH conditions of the kinetic studies, approximately 60% of the MeGly is coordinated as Cu(dien)(MeGly)$^{2+}$, *i.e.*, the K_x equilibrium in eq 7 lies somewhat to the right. Thus for the k_{OH} mechanism, the order in $[Cu(dien)^{2+}]_{TOT}$ would be less than 1 and some other path with a higher order $[Cu(dien)^{2+}]_{TOT}$ dependence must be responsible for the observed approximate first-order dependence. Such a mechanism could be Cu(dien)(OH)$^+$ attack as indicated by k_{MOH} in eq 7. There is ample precedence for such an attack in the Cu(glygly)(OH)$^-$[27] and Hg(dien)(OH)$^+$-catalyzed[28] hydrolyses of *p*-nitrophenyl acetate, as well as the Mg(OH)$^+$- and Ca(OH)$^+$-catalyzed hydrolyses of acetyl phosphate.[29] In all cases the oxygen of the OH^- ligand in the complex is presumed to be the nucleophilic site.

If both the k_{OH} and k_{MOH} mechanisms are assumed to contribute to the MeGly hydrolysis, the rate law would be written as

$$\text{rate} = k_{OH}[\text{Cu(dien)(MeGly)}^{2+}][OH^-] + k_{MOH}[\text{Cu(dien)(MeGly)}^{2+}][\text{Cu(dien)(OH)}^+] \quad (8)$$

Substitution of expressions for $[Cu(dien)^{2+}]_{TOT}$ (eq 3a), $[MeGly]_{TOT}$ (eq 3b), K_{OH} (eq 2), K_x (eq 1), and $K_b = 1/K_a$ into eq 8 yields

$$k_{obsd} = \frac{K_x[\text{Cu(dien)}]_{TOT}}{K_x[\text{Cu(dien)}^{2+}]_{TOT} + (K_b[H^+] + 1)(1 + K_{OH}[OH^-])} \times \left\{k_{OH}[OH^-] + \frac{k_{MOH}K_{OH}[OH^-][\text{Cu(dien)}^{2+}]_{TOT}}{1 + K_{OH}[OH^-]}\right\} \quad (9)$$

(20) dipy = dipyridyl; other ligand abbreviations are given in Table IV.

(21) H. Sigel and R. Griesser, *Helv. Chim. Acta*, **50**, 1842 (1967); M. V. Chidambaram and P. K. Bhattacharya, *J. Inorg. Nucl. Chem.*, **32**, 3271 (1970).

(22) M. Bonnet and R. A. Paris, *Bull. Soc. Chim. Fr.*, 747 (1966).

(23) H. Sigel and D. B. McCormick, *Accounts Chem. Res.*, **3**, 17 (1970).

(24) N. E. Jackobs and D. W. Margerum, *Inorg. Chem.*, **6**, 2038 (1967).

(25) R. J. Angelici and B. E. Leach, *J. Amer. Chem. Soc.*, **90**, 2499 (1968), and references therein; J. Rodgers and R. A. Jacobson, *J. Chem. Soc. A*, in press.

(26) R. C. Courtney, R. L. Gystafson, S. Chaberek, Jr., and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 519 (1959).

(27) W. L. Koltun, M. Fried, and F. R. N. Gurd, *ibid.*, **82**, 233 (1960).

(28) M. Werber and Y. Shalitin, *Isr. J. Chem., Proc.*, **5**, 89p (1967).

(29) P. J. Briggs, D. P. N. Satchell, and G. F. White, *J. Chem. Soc. B*, 1008 (1970).

which can be rearranged to

$$k_{obsd}K_x + \frac{k_{obsd}(K_b[H^+] + 1)(1 + K_{OH}[OH^-])}{[Cu(dien)^{2+}]_{TOT}} = [Cu(dien)^{2+}]_{TOT}\left\{\frac{K_x k_{MOH} K_{OH}[OH^-]}{1 + K_{OH}[OH^-]}\right\} + k_{OH}K_x[OH^-] \quad (10)$$

Using data at pH 8.00 from Table III(b), the left side of eq 10 was plotted *vs.* $[Cu(dien)^{2+}]_{TOT}$. By introducing the experimental value of K_x (Table II), k_{OH} was determined to be 139 sec^{-1} M^{-1} from the intercept of the plot. Utilizing experimental values of K_x and K_{OH},[2] a k_{MOH} value of 0.614 sec^{-1} M^{-1} was obtained from the slope. The values of k_{OH} and k_{MOH} and the assumed mechanisms were supported by calculating the pseudo-first-order rate constant, k_{obsd}, from eq 9 at another pH, 8.2, which was found to be 1.26×10^{-3} sec^{-1}, the experimental value being 1.29×10^{-3} sec^{-1}. On the other hand, eq 9 was used to calculate log K_x from experimental values of k_{obsd}. At pH 8.4 and 7.7, these values are 2.54 and 2.76, respectively; both are within experimental error of the independently determined figure, 2.52. Hence the mechanisms in eq 7 are consistent with the experimental data.

As expected, the rate of attack of the OH^- in $Cu(dien)(OH)^+$ is much less than that of uncoordinated OH^-, 0.614 *vs.* 139 sec^{-1} M^{-1}. The OH^- attack mechanism has been postulated for a variety of other copper complex catalyzed hydrolyses of MeGly.[30,31] These data measured at 25° are summarized in Table V. The rate constants, k_{OH}, represent the rate of OH^- attack on the ester while coordinated to the copper(II). Since the rate for $Cu(MeGly)^{2+}$ has not been reported, it may be estimated by approximately doubling the value given for $Cu(EtGly)^{2+}$. By comparison with the non-metal-catalyzed base hydrolysis of MeGly (bottom entry in Table V), all copper(II) complexes exhibit significant catalytic effects which decrease in the order: Cu^{2+} > Cu(IMDA) > $Cu(NTA)^-$ > $Cu(dien)^{2+}$. This is the same order observed for K_x (Table V) in the complexation of the glycine esters by these copper(II) complexes. (Although K_x values of MeGly, EtGly, and *n*-BuGly are compared, they are known to have very similar K_x constants with $Cu(NTA)^-$.) Assuming that K_x is some measure of the donor–acceptor interaction between MeGly and copper(II), those complexes which bind MeGly most tightly should withdraw the most electron density from the ester making it most susceptible to OH^- attack. The electron-withdrawing ability of these complexes might also be measured toward other ligands, and the same trend is observed in K_x for complexation with glycine (Table IV). While one expects a correlation between k_{OH} and K_x to very general, this is the first series for which it has been observed. Similar correlations have not been observed when different metal ions are compared.[32,33]

TABLE V

RATE CONSTANTS, k_{OH}, FOR THE COPPER(II)-CATALYZED BASE HYDROLYSIS OF MeGly AND LOG K_x VALUES FOR GLYCINE ESTERS AT 25°

Cu(L)(MeGly)	k_{OH}, M^{-1} sec^{-1}	Log K_x (ester)
$Cu(EtGly)^{2+}$	7.6×10^{4} [a]	4.04[b]
Cu(IMDA)(MeGly)	3.2×10^{4} [c]	3.69[d]
$Cu(NTA)(MeGly)^-$	4.6×10^{2} [e]	3.06[f]
$Cu(dien)(MeGly)^{2+}$	1.4×10^{2}	2.52[g]
MeGly	1.32[h]	...

[a] Although not reported, the rate for $Cu(MeGly)^{2+}$ would be somewhat faster (perhaps 2 times)[6,30,31] than for $Cu(EtGly)^{2+}$ given above. Reference 7. [b] For EtGly. Reference 8. [c] Reference 6. [d] For *n*-BuGly. Reference 6. [e] Reference 30. [f] For MeGly. Reference 11. [g] For MeGly. [h] Reference 31.

Acknowledgment.—This research was supported by the U. S. Public Health Service through Grant No. GM-12626 of the National Institute of General Medical Sciences.

(30) R. J. Angelici and D. Hopgood, *J. Amer. Chem. Soc.*, **90**, 2514 (1968).
(31) R. W. Hay, L. J. Porter, and P. J. Morris, *Aust. J. Chem.*, **19**, 1197 (1966).
(32) J. E. Hix, Jr., and M. M. Jones, *Inorg. Chem.*, **5**, 1863 (1966).
(33) B. E. Leach and R. J. Angelici, *J. Amer. Chem. Soc.*, **90**, 2504 (1968).