complex $[(Ph_3P)_2PdCO_3]$ tended to decompose in solution as it was formed, so with $[(Ph_3P)_2PdCl_2]$, the suspension was stirred only for about 15 min. However, the product obtained was always impure.

Adduct of Carbon Disulfide with $[(Ph_3P)_2PtO_2]$. Carbon disulfide was added dropwise to a solution or suspension of $[(Ph_3P)_2PtO_2]$ (0.75 g) in ice-cold benzene–ether (5 ml/5 ml) until no further reaction was observed (usually 3–4 drops). The orange crystals formed were filtered off rapidly, washed with ice-cold ether, and dried *in vacuo*. The compound tended to decompose to the dithiocarbonate analog in solution but was quite stable when dry; yield, 0.75 g (about 90%). A similar procedure with $[(Ph_3P)_2PdO_2]$ gave the dithiocarbonate directly, and oxygen was evolved on addition of CS_2.

Dithiocarbonatobis(triphenylphosphine)platinum(II). This adduct could be prepared by recrystallizing the above complex (0.5 g) from a methylene chloride–benzene solution containing triphenylphosphine (1.3–1.5 g) under nitrogen, as described above.

Aldehyde and Ketone Adducts. These were prepared by the following general method: about 1 g of $[(Ph_3P)_2PtO_2]$ was dissolved or suspended in benzene under nitrogen and an excess of ligand added with stirring. (The ligand was added in benzene solution if a solid.) With aldehydes, an immediate precipitate was noticed, and with ketones, a precipitate formed on stirring for a few minutes. The solid was then filtered off, washed with dry benzene, and dried *in vacuo;* yields, usually about 90%. Adducts with acetone oxime, thiourea, and thioacetamide were prepared in an exactly analogous manner. Ether was sometimes added to hasten precipitation.

Reduction of $[(Ph_3P)_2PtO_2 \cdot$ Acetone$]$. Bubbling a stream of nitrogen or hydrogen through a solution of $[(Ph_3P)_2PtO_2 \cdot$acetone$]$ ($\sim$1 g) in methylene chloride (25 ml) for several days gave the complex as a white solid. Solvent was added as necessary during this time to maintain a fairly constant level. The product was recovered by evaporation, washed with dry ether, and dried *in vacuo*. It was not ascertained whether or not the hydrogen or nitrogen was oxidized during this reaction. Attempts to reduce the aldehyde and ketone adducts with triphenylphosphine in the same manner as with peroxycarbonates resulted in the re-formation of tetrakis(triphenylphosphine)platinum(0).

Physical Measurements. Infrared spectra were recorded on a Beckman IR-4 prism instrument calibrated with a polystyrene film (4000–600 cm^{-1}) and atmospheric water vapor (600–300 cm^{-1}). Microanalyses were performed by Chemalytics Inc. and by Schwarzkopf Microanalytical Laboratories. Melting points were measured on a hot stage microscope in air and are uncorrected. Nmr spectra were obtained on a Varian A60 spectrometer using solutions in $CDCl_3$. Analyses of compounds are given in Table IV.

Reactions of Labile Metal Ions with Oligopeptides. V.[1] Copper(II) with Glycylglycine and Glycylsarcosine

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Abstract: The complexation reactions of glycylsarcosine and glycylglycine with copper(II) have been studied using the temperature-jump technique. At 25°, the rate constants for the reactions $Cu^{2+} + L^- \rightleftharpoons CuL^+$ (k_1, k_{-1}) are for glycylsarcosine, $k_1 = 4.0 \times 10^8\ M^{-1}\ sec^{-1}$, $k_{-1} = 170\ sec^{-1}$, and for glycylglycine, $k_1 = 3.5 \times 10^8\ M^{-1}\ sec^{-1}$, $k_{-1} = 960\ sec^{-1}$. In addition, for the latter ligand, a slower effect appears at pH $\sim$4, which has been ascribed to the reaction $Cu(HGG)^+ \rightleftharpoons CuGG + H^+$ (k_D, k_H). The rate constants at 25° are $k_D = 76\ sec^{-1}$ and $k_H = 8.7 \times 10^5\ M^{-1}\ sec^{-1}$. The bonding model for metal ion peptide complexes suggested by Rabin is consistent with these kinetic results. The reactions for glycylglycine were studied at other temperatures and the activation energies were determined. The activation energy for complexation is consistent with the suggestion that the rate-determining step is the removal of a water molecule from an axial position in tetragonally distorted $Cu(H_2O)_6^{2+}$. The activation energy for the protonation reaction is considerably larger than that usually obtained for reactions of this type and is consistent with structural rearrangement subsequent to proton attack.

Considerable interest has been shown recently in the structures of metal complexes of oligopeptides in solution. Special attention has been paid to the peptide complexes of nickel(II), cobalt(II), and especially copper(II). The emphasis on copper(II) is related quite likely to the important role this metal ion plays in certain biochemical processes and to the fact that it is unique in the extent to which it facilitates dissociation of peptide link hydrogen atoms. Most of the previous studies on the aqueous chemistry of copper–peptide complexes have involved potentiometric titration,[2-6] calorimetry,[3] optical rotary dispersion,[6] visible[6] and infrared spectroscopy,[4,5] nmr spectrometry,[7] and electron spin resonance.[8] Using the copper–glycyclglycine complex as a specific example, several workers suggest that the structure stable in the pH range in which the peptide nitrogen is protonated is one in which bonding occurs through the amine nitrogen and carbonyl oxygen[2] (*cf.* Figure 1a). However, other workers[4,5,7] have interpreted their results as indicating strong metal-to-carboxyl oxygen interaction which, in the absence of dimers,[8] leads them to suggest the structure shown in Figure 1b.

We are reporting on the kinetics of the reactions of copper(II) with glycylglycine and glycylsarcosine. The temperature-jump technique has been used to obtain

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(2) S. P. Datta and B. R. Rabin, *Trans. Faraday Soc.*, 52, 1123 (1956).

(3) A. P. Brunetti, M. C. Lim, and G. H. Nancollas, *J. Amer. Chem. Soc.*, 90, 5120 (1968).

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(7) M. K. Kim and A. E. Martell, *J. Amer. Chem. Soc.*, 91, 872 (1969).

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rate constants for the reaction

$$Cu^{2+} + L^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CuL^+ \quad (1)$$

for both dipeptides and over a temperature range for glycylglycine. Furthermore, for glycylglycine, the reaction

$$Cu(HGG)^+ \underset{k_H}{\overset{k_D}{\rightleftharpoons}} CuGG + H^+ \quad (2)$$

was also studied over a temperature range. The results of these studies are interpreted in terms of model a in Figure 1 with which they correlate very well.

Experimental Section

The temperature-jump apparatus has been described elsewhere.[9] The dipeptides used in these studies were obtained from Nutritional Biochemicals Corp. Baker reagent grade nitrate salts of potassium and copper were used. A stock solution of the copper ion was prepared and the concentration was determined *via* an EDTA titration using murexide as the indicator.[10] The indicator used to follow the course of the reactions was Allied Chemical methyl orange; all solutions were 4.7×10^{-5} *M*.

Solutions were freshly prepared from the solid dipeptide and stock solutions of KNO_3, $Cu(NO_3)_2$, and methyl orange. The solutions were degassed and the pH was adjusted by the dropwise addition of dilute NaOH and/or HNO_3 to ± 0.01 pH unit. The temperature for most of the studies was 25°. Blank experiments with solutions containing only the metal and indicator, or the ligand and the indicator (both solutions at ionic strength 0.1 *M*), did not show any relaxation effect in the time range of the instrument.

Thermodynamic data for the copper(II)–glycylglycine system were available in the literature[3] which permitted the analysis of relaxation data obtained at temperatures other than 25°. Therefore, the kinetics of this system were studied also at 10 and 15°. The lower limit results from our using a water bath for thermal control and the upper limit (25°) results from the coupling of the two effects (*vida infra*) at higher temperature. In other words, as the temperature is raised above 25°, the relaxation times for the two effects become nearly identical and cannot be determined independently with acceptable precision.

Results

(a) Glycylsarcosine. All of the data obtained for the glycylsarcosine system could be interpreted in terms of the reactions

$$Cu^{2+} + Glysar^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu(Glysar)^+$$
$$Cu(Glysar)^+ + Glysar^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu(Glysar)_2 \quad (3)$$

coupled to the much faster reactions

$$H_2Glysar^+ \rightleftharpoons H^+ + H\ Glysar$$
$$H\ Glysar \rightleftharpoons H^+ + Glysar^- \quad (4)$$
$$HIn \rightleftharpoons H^+ + In^-$$

The analysis of the data requires detailed knowledge of the equilibrium constants for the system; these are shown in Table I. The experimental conditions and a summary of the pertinent relaxation data are given in Table II. In treating these data, a reaction pathway involving the zwitterion form of the ligand was considered using a technique outlined in previous papers.[9,11] We concluded that the rate constant for zwitterion attack is within experimental error, and relaxation times were calculated (*cf.* Table II) without the inclusion of hydrogen-ion-dependent terms in the rate constants. We obtain values of $k_1 = 4.0 \times 10^8\ M^{-1}\ sec^{-1}$ and $k_2 \sim 2 \times 10^8\ M^{-1}\ sec^{-1}$, the relaxation times for all the solutions being considerably more dependent on k_1 than k_2.

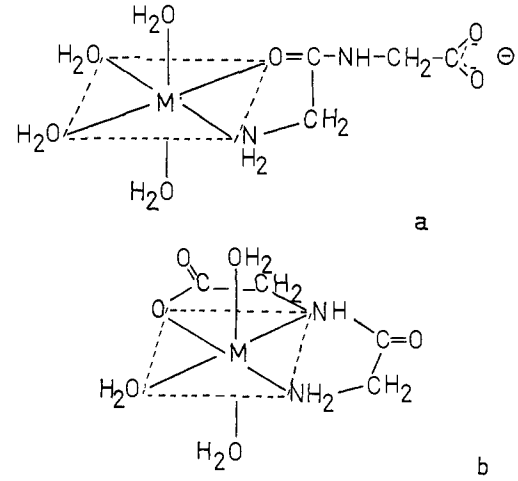

Figure 1. Two suggested structures for the metal ion–glycyclglycinate complex in a pH region in which the peptide nitrogen is protonated.

Table I. Thermodynamic Data for Copper(II)–Glycylsarcosine and Glycylglycine Systems, $\mu = 0.1\ M$

	At 25° Glysar[a,b]	Glygly[c]
$K_1^H = \frac{[H^+][HL]}{[H_2L^+]}$	6.76×10^{-4}	8.32×10^{-4}
$K_2^H = \frac{[H^+][L^-]}{[HL]}$	2.34×10^{-9}	8.13×10^{-9}
$K_1^{Cu} = \frac{[CuL^+]}{[Cu^{2+}][L^-]}$	2.29×10^6	3.63×10^5
$K_2^{Cu} = \frac{[CuL_2]}{[CuL^+][L^-]}$	1.38×10^5	
$K_1' = \frac{[CuL_{-H}][H^+]}{[CuL^+]}$		8.71×10^{-5}
$K_{In} = \frac{[H^+][In^-]}{[HIn]}$	$= 3.47 \times 10^{-4}$ for methyl orange[d]	

	At 10 and 15° for Glygly[c] 10°	15°
K_1^H	8.32×10^{-4}	8.32×10^{-4}
K_2^H	3.16×10^{-9}	4.36×10^{-9}
K_1^{Cu}	9.12×10^5	5.25×10^5
K_1'	4.68×10^{-5}	5.89×10^{-5}

[a] S. P. Datta and B. R. Rabin, *Trans. Faraday Soc.*, **52**, 1123 (1956). [b] Reference 1c. [c] Reference 3. [d] I. M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930).

(b) Glycylglycine. A single relaxation effect was obtained for each of the copper(II)–glycylglycine solutions in the pH range 3.2–3.9. This effect could be characterized as being due to complexation reactions. However, unlike the situation for the copper(II)–glycylsarcosine system, as the pH was raised to ~4, a second relaxation effect appeared which was slower than the first effect (*cf.* Figure 2). This second effect could be accounted for as being due to the loss of a peptide proton from the monosubstituted copper–diglycine complex—a reaction which had been reported and characterized in the previous thermodynamic work.[3] That this second effect does not appear in the glycylsarcosine

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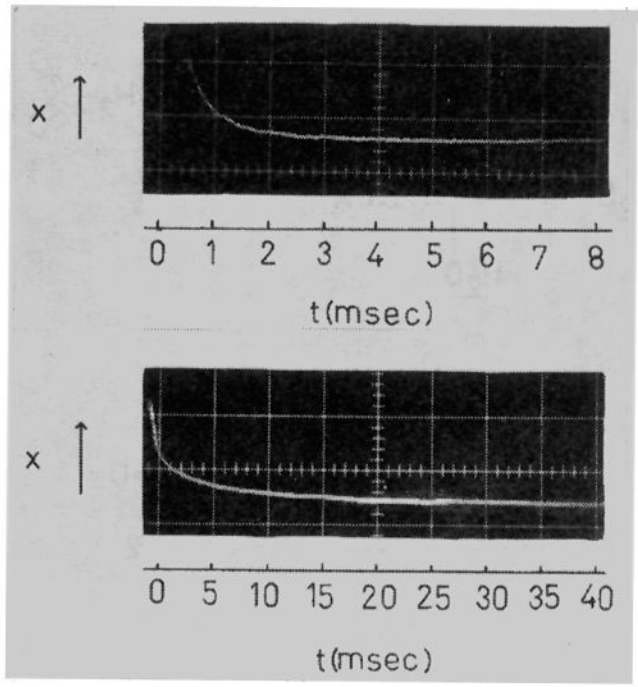

Figure 2. Top: relaxation effect obtained for a copper(II)–glycylsarcosine solution at a pH of 4.45. The initial conditions are $[Cu^{2+}]_0 = 1.40 \times 10^{-2}$ M, [glycylsarcosine]$_0 = 8.03 \times 10^{-2}$ M. The relaxation time obtained for this solution is 0.59 msec. Bottom: two relaxation effects obtained for a copper(II)–glycylglycine solution at a pH of 3.88. The initial conditions are $[Cu^{2+}]_0 = 1.68 \times 10^{-2}$ M, [glycylglycine]$_0 = 1.00 \times 10^{-2}$ M. The relaxation times obtained for this solution are 0.51 and 5.2 msec.

system is consistent with the kinetic assignment, since there is no peptide proton in this latter case.

In the analysis of the relaxation data, all thermodynamically stable species have to be considered. Therefore, the conservation equations for metal, ligand, and charge become, respectively

$$\begin{aligned} 0 &= \delta[Cu^{2+}] + \delta[Cu(HGG)^{+}] + \delta[Cu(HGG)_2] + \\ &\quad \delta[Cu(GG)] \\ 0 &= \delta[H_3GG^{+}] + \delta[H_2GG] + \delta[HGG^{-}] + \\ &\quad \delta[GG^{2-}] + \delta[Cu(HGG)^{+}] + \\ &\quad 2\delta[Cu(HGG)_2] + \delta[Cu(GG)] \\ 0 &= \delta[H_3GG^{+}] + \delta[Cu(HGG)^{+}] + 2\delta[Cu^{2+}] + \\ &\quad \delta[H^{+}] - \delta[HGG^{-}] - \delta[OH^{-}] - \\ &\quad \delta[In^{-}] - 2\delta[GG^{2-}] \end{aligned} \tag{5}$$

where HGG^- is the anionic form of the ligand and GG^{2-} is the symbol for the ligand after loss of a peptide proton. Certain simplifications are possible; the species GG^{2-} does not exist in solution at normal pH's, and $Cu(HGG)_2$ proves to be of no importance in fitting the kinetic data, which is again consistent with the thermodynamic studies.[3] Therefore, $\delta[GG^{2-}] = \delta[Cu(HGG)_2] = 0$. Also, since the reaction

$$Cu(HGG)^{+} \underset{k_H}{\overset{k_D}{\rightleftharpoons}} Cu(GG) + H^{+} \tag{6}$$

is slower than the complexation step, when considering complexation we may take $\delta[Cu(GG)] = 0$.

Then, the complexation step may be handled in the same manner as was done for glycylsarcosine. The equilibrium constants given in Table I were used to analyze the relaxation data. Once again, the rate constant for zwitterion attack fell within experimental error and relaxation times were calculated without the use of pH-dependent terms in the rate constants. A summary of the experimental conditions and observed and calculated relaxation times, τ_1^{obsd} and τ_1^{calcd}, respectively, are shown in Table III. We obtain for this system that $k_1 = 3.5 \times 10^8$ M^{-1} sec^{-1}.

The slower process leads to somewhat different simplifications in eq 5. It is still true that both $\delta[GG^{2-}]$ and $\delta[Cu(HGG)_2] = 0$, but now we treat the complexation step as if it is a preequilibrium. This leads to

$$\frac{1}{\tau_2} = \rho k_D + k_H([H^+] + \sigma[CuGG]) \tag{7}$$

where τ_2 is the relaxation time for the slower process

$$\begin{aligned} \sigma &= \frac{\gamma[H^+](\gamma + 1 - \rho)}{[HGG^-](1 + \alpha)} + \frac{\beta K_1^a K_2^a}{K_1^a K_2^a + 4\beta K_2^a[H_2GG] + \beta K_1^a[HGG^-]} \\ \rho &= \frac{(1 + \alpha)[HGG^-] + (1 + \gamma)[Cu^{2+}]}{(1 + \alpha)[HGG^-] + [Cu^{2+}] + (1 + \alpha)/K_1} \\ \gamma &= \frac{2\beta K_2^a[H_2GG] + \beta K_1^a[HGG^-]}{K_1^a K_2^a + 4\beta K_2^a[H_2GG] + \beta K_1^a[HGG^-]} \\ \alpha &= \frac{K_1^a[H^+] + \beta[H^+][H_2GG] + [H^+]^2 + \beta K_1^a[OH^-] + \beta[H^+][OH^-]}{K_1^a K_2^a + 4\beta K_2^a[H_2GG] + \beta K_1^a[HGG^-] + \beta K_1^a K_{2a}[OH^-]/[H^+]} \\ \beta &= \frac{K_{In} + [H^+]}{K_{In} + [H^+] + [In^-]} \end{aligned} \tag{8}$$

Table II. Relaxation Spectra of Copper(II)–Glycylsarcosine Solutions[a]

$[Cu]_0 \times 10^3$	$[Lig]_0 \times 10^3$	pH	τ_{obsd}, msec	τ_{calcd}, msec
5.35	9.99	3.95	2.5	2.3
2.68	2.84	4.03	3.7	3.0
2.68	8.93	4.01	3.1	2.8
2.68	15.0	3.86	2.9	3.2
10.7	20.1	3.53	3.2	3.1
7.02	15.0	3.57	3.7	3.5
13.3	14.9	3.27	2.6	3.9
13.3	14.9	3.62	2.6	2.6
14.0	40.2	4.48	1.6	1.7
14.0	80.3	3.65	2.6	2.1
14.0	80.3	4.01	0.76	1.2
14.0	80.3	4.45	0.59	0.70

$k_1 = 4.0 \times 10^8$ M^{-1} sec^{-1} $\quad k_2 \sim 2 \times 10^8$ M^{-1} sec^{-1}
$k_{-1} = 170$ sec^{-1} $\quad k_{-2} \sim 2 \times 10^3$ sec^{-1}

[a] All concentrations are molar. The subscript zero refers to the total stoichiometric concentration. $\mu = 0.1$ M, temperature = 25°.

Table III. Relaxation Spectra of Copper(II)–Glycylglycine Solutions[a]

$[Cu]_0 \times 10^3$	$[Lig]_0 \times 10^3$	pH	τ_1^{obsd}, msec	τ_1^{calcd}, msec	τ_2^{obsd}, msec	τ_2^{calcd}, msec
10.7	8.05	3.41	1.3	0.94		
11.2	8.67	4.12	0.57	0.53	5.8	6.5
11.2	8.67	4.48	0.26	0.26	5.2	4.5
11.2	8.19	3.19	1.0	1.0		
5.60	9.83	3.33	1.4	1.0		
5.60	9.83	4.05	0.63	0.73	6.2	6.9
11.2	15.0	3.35	1.2	0.94		
11.2	15.0	3.91	0.49	0.54	4.2	5.0
16.8	10.0	3.44	1.0	0.89		
16.8	10.0	3.88	0.51	0.64	5.2	4.2
16.8	10.0	4.24	0.25	0.34	4.8	4.1
22.4	10.0	3.41	0.86	0.87		
22.4	10.0	3.95	0.49	0.51	3.8	4.1
22.4	10.0	4.27	0.22	0.26	3.9	3.9
5.60	73.0	3.49	0.81	0.90		

$k_1 = 3.5 \times 10^8$ M^{-1} sec^{-1} $\quad k_H = 8.7 \times 10^5$ M^{-1} sec^{-1}
$k_{-1} = 960$ sec^{-1} $\quad k_D = 67$ sec^{-1}

[a] All concentrations are molar. The subscript zero refers to the total stoichiometric concentration. $\mu = 0.1$ M, temperature = 25°.

Table IV. Relaxation Spectra of Copper(II)–Glycylglycine Solutions at 10 and 15° [a]

Temp, °C	$[Cu]_0 \times 10^3$	$[Lig]_0 \times 10^3$	pH	τ_1^{obsd}, msec	τ_1^{calcd}, msec	τ_2^{obsd}, msec	τ_2^{calcd}, msec
10	11.1	5.06	3.46	2.7	2.9		
	11.1	5.06	3.97	1.5	1.4	15	14
	16.7	7.79	3.44	2.2	2.6		
	16.7	8.01	3.94	1.6	1.1	11	13
	16.7	8.01	4.24	0.67	0.52	12	14
	22.2	9.90	3.49	2.6	2.2		
	22.2	10.1	4.25	0.27	0.40	19	14
	$k_1 = 2.4 \times 10^8\ M^{-1}\ sec^{-1}$				$k_H = 3.0 \times 10^5\ M^{-1}\ sec^{-1}$		
15	11.2	5.08	3.41	2.3	2.0		
	11.2	5.08	3.93	1.3	1.1	12	7.6
	11.2	5.08	4.28	0.52	0.53	6.6	8.3
	16.8	8.41	3.52	1.6	1.6		
	16.8	7.71	3.95	0.88	0.85	5.3	7.0
	16.8	7.71	4.18	0.45	0.50	8.7	7.4
	22.4	10.0	3.21	1.6	2.0		
	22.4	10.0	3.95	0.87	0.70	5.9	6.2
	22.4	10.0	4.23	0.29	0.36	8.5	6.9
	$k_1 = 2.2 \times 10^8\ M^{-1}\ sec^{-1}$				$k_H = 5.3 \times 10^5\ M^{-1}\ sec^{-1}$		

[a] All concentrations are molar. The subscript zero refers to the total stoichiometric concentration. $\mu = 0.1\ M$.

The rate constants obtained at 25° are $k_H = 8.7 \times 10^5\ M^{-1}\ sec^{-1}$ and $k_D = 76\ sec^{-1}$. The experimental conditions and observed and calculated relaxation times are given in Table III.

In addition, experiments were conducted for the copper(II)–diglycine system at 10 and 15°. A summary of the experimental conditions and observed and calculated relaxation times is given in Table IV. Because of the limited temperature range available to us and the small value of the activation energy for complexation, this value could only be estimated as from 4 to 8 kcal/mol. However, for the protonation reaction, a standard approach to the determination of the activation energy proved feasible and we obtain an activation energy of 11 kcal/mol for the protonation step.

Discussion

A considerable number of complexation reactions involving labile transition metal ions have been studied in the last decade. A general two-step mechanism has been suggested which, when examined in detail, proves to be consistent with almost all of the kinetic results thus far obtained.[12] The mechanism begins with the diffusion-limited formation of an ion pair between the reactant species with the subsequent and rate-determining replacement of water molecules in the inner coordination sphere of the metal-containing species by the attacking ligand. The equations for the specific case of a bidentate ligand attacking the fully aquated metal ion are

$$M(aq) + A\text{–}B(aq) \underset{}{\overset{\text{very rapid}}{\rightleftharpoons}} W_2MW_1, A\text{–}B \qquad (9a)$$

$$W_2MW_1, A\text{–}B \underset{k_{-01}}{\overset{k_{01}}{\rightleftharpoons}} W_2M\text{–}A\text{–}B \qquad (9b)$$

$$W_2M\text{–}A\text{–}B \underset{k_{-01}'}{\overset{k_{01}'}{\rightleftharpoons}} M\begin{matrix}A\\B\end{matrix} \qquad (9c)$$

where W_1 and W_2 are the two water molecules in the inner coordination sphere of the metal ion, M, which are replaced by the ligand, A–B. By assuming that step 9a is very rapid and can be defined by an equilibrium constant K_{a1} and that $d[W_2M\text{–}A\text{–}B]/dt = 0$, an expression can be derived for the observed rate constant, k_1

$$k_1 = K_{a1}k_{01}\left(\frac{k_{01}'}{k_{01}' + k_{-01}}\right) \qquad (10)$$

An expression has been derived for the equilibrium constant[13] K_{a1}, which is difficult to measure, and although the value of this constant depends on distance of closest approach, ionic strength, etc., it depends, for simple ligand systems, most critically on the charge types of the reactant species.[14]

Equation 10 leads to two extreme cases. In case I, which is the most frequently encountered one, ring closure is considerably faster than is the rate of breaking a metal ligand bond; $k_{01}' > k_{-01}$. The observed rate constant is then $k_1 = K_{a1}k_{01}$. Since k_{01} is the rate constant for water loss from the inner coordination sphere of the metal ion and is relatively independent of ligand,[15] observed rate constants, k_1, should be invariant for ligands of a given charge type. Table V has a listing of rate constants for a number of metal–ligand systems. The first four ligands all have the same charge and, as may be seen from the table, the rate constants are in good agreement for a given metal. In the case of arginine, the attacking ligand is formally neutral and the rate constant is smaller by a factor of about 10 for cobalt(II) and nickel(II).

The second limiting case to be considered for eq 10 is that in which $k_{01}' < k_{-01}$. This case arises when the rate constant for ring closure is abnormally small due to the formation of a chelate ring containing more than five members and has been discussed previously.[16] An example of this situation is β-alanate⁻, as given in Table V. Here, once again, the rate constants obtained are approximately an order of magnitude smaller than for those anionic ligands for which case I is applicable.

The kinetic results for glycylglycinate⁻ and glycylsarcosinate⁻ are also included in Table V. It is im-

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(15) This need not be strictly true; *cf.* D. B. Rorabacher, *Inorg. Chem.*, 5, 1891 (1966).

(16) K. Kustin, R. F. Pasternack, and E. M. Weinstock, *J. Amer. Chem. Soc.*, 88, 4610 (1966).

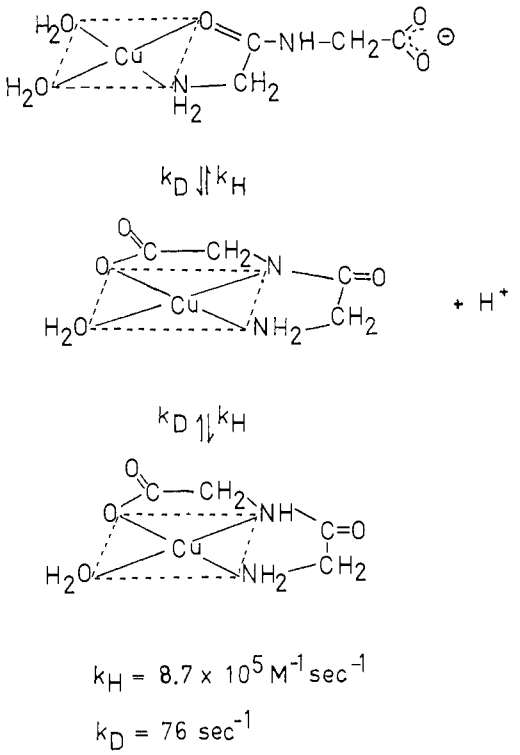

Figure 3. The protonation reaction for the copper(II)–glycylglycine system for each of the two bonding models for $Cu(HGG)^+$.

mediately apparent that the rate constants for these ligands are smaller than the normal rate constants for anions. However, the chelate rings are five-membered

Table V. Forward Rate Constants for Complexation (k_1, M^{-1} sec^{-1})

Ligand/metal	Ni^{2+}	Co^{2+}	Cu^{2+}	Ref
Glycinate$^-$	4×10^4	2×10^6	4×10^9	1d, *a*
α-Alanate$^-$	3×10^4	2×10^6	1×10^9	*b*, *c*
Leucinate$^-$	2×10^4	1×10^6	2×10^9	11, *d*
Serinate$^-$	3×10^4	2×10^6	3×10^9	*e*
Glycylglycinate$^-$	3×10^3	2×10^5	4×10^8	1d, *f*
Glycylsarcosinate$^-$	2×10^3	5×10^5	4×10^8	1c, *f*
β-Alanate$^-$	5×10^3	1×10^5	2×10^8	*b*, *c*
Arginine	2×10^3	2×10^5		*g*

[a] A. F. Pearlmutter and J. Stuehr, *J. Amer. Chem. Soc.*, **90**, 858 (1968). [b] R. F. Pasternack, K. Kustin, R. Reingold, and M. Angwin, in preparation. [c] W. B. Makinen, A. F. Pearlmutter, and J. E. Stuehr, *J. Amer. Chem. Soc.*, **91**, 4083 (1969). [d] J. C. Cassatt, Ph.D. Dissertation, State University of New York at Buffalo, 1969; J. C. Cassatt and R. G. Wilkins, *J. Amer. Chem. Soc.*, **90**, 6045 (1968). [e] R. L. Karpel, K. Kustin, and R. F. Pasternack, *Biochim. Biophys. Acta*, **177**, 434 (1969). [f] This work. [g] G. Davies, K. Kustin, and R. F. Pasternack, *Int. J. Chem. Kinet.*, **1**, 45 (1969).

regardless of the bonding model (*cf.* Figures 1a and 1b). Therefore, it seems very unlikely that case II of eq 10 is applicable. This leads us to conclude that the carboxylate portion of the ligand is quite far removed from the positive metal center in the "effective" ion pair, that is, in the ion pair which eventually yields the stable dipeptide complex. That the rate constants obtained for these dipeptides are similar to those obtained for neutral ligands may be seen in Table V and other tabulations of rate constants for labile metal ions.[12]

In aqueous solution the "effective range" of coulombic forces is 14 Å for a 2+, 1− interaction.[17] In the effective ion pair, the negative center is likely to be about this distance from the copper ion, and the electrostatic potential energy due to this coulombic interaction is therefore only of the order of kT. While these results do not preclude structure b of Figure 1, they are certainly consistent with structure a, in which the carboxylate portion of the molecule is not bound to the metal ion in the final complex.

The results for the proton attack reaction are also readily interpreted in terms of structure a of Figure 1. A considerable number of protonation reactions have been studied since the advent of the relaxation techniques. Generally the rates of these reactions are near diffusion controlled when the proton is bound more tightly at the acceptor than at the donor. Rate constants usually range[17] from 5×10^9 to 1×10^{11} M^{-1} sec^{-1}. However, there are a number of factors which can influence and greatly lower the rates of these acid–base reactions. One which seems applicable here is configurational changes accompanying proton attack. The structures involved in the proton attack of Cu(GG) are shown in Figure 3.

If the structure b of Figure 1 for the bonding of $Cu(HGG)^+$ is correct, the rate is determined by the proton attack itself. Clearly the mechanism is not as simple as it first appears in the figure. The lone electron pair is not localized on the peptide nitrogen in the Cu(GG) species; the hybridization type is probably sp^2 with appreciable resonance stabilization in the peptide link. Therefore, there could be a considerable potential barrier to the formation of $Cu(HGG)^+$, with concomitant loss of resonance stabilization. However, it should be noted that our results are consistent with those obtained by Pagenkopf and Margerum for the general acid catalysis of the formation of Cu(HGGG) from $Cu(GGG)^-$.[18] For the reaction with H^+, these workers obtained a rate constant of 5×10^6 M^{-1} sec^{-1} as compared to the value of 9×10^5 M^{-1} sec^{-1} obtained by us for the reaction of H^+ with the neutral Cu(GG). Furthermore, they obtained a value of unity for the Brønsted α factor even when there was no appreciable difference in pK between the donor and the acceptor, strongly suggesting that the proton exchange occurs prior to the rate-determining step. It seems quite reasonable to interpret our results in terms of structure a, the so-called Rabin model, where the slowness and large activation energy[19] may be accounted for by the structural rearrangement involving bond breaking which occurs with proton attack of Cu(GG). Whereas the kinetic results reported on here cannot be considered as unambiguous evidence for the Rabin model, we believe they do increase the level of confidence that one can feel in using this model.

Acknowledgment. The authors wish to acknowledge support from the Petroleum Research Fund for Grant No. 2982 B. We also wish to acknowledge most helpful conversations with Professor Kenneth Kustin of Brandeis University.

(17) M. Eigen, W. Kruse, G. Maass, and L. DeMaeyer, *Progr. React. Kinet.*, **2**, 286 (1964).

(18) G. K. Pagenkopf and D. W. Margerum, *J. Amer. Chem. Soc.*, **90**, 6963 (1968).

(19) We obtain a value of 11 kcal/mol, whereas protonation reactions normally have an activation energy of 2–3 kcal/mol: E. F. Caldin, "Fast Reactions in Solution," Wiley, New York, N. Y., 1964, p 267.