Kinetics of Formation of Mixed Ligand Complexes. I. The Copper(II)–2,2′-Bipyridyl–Glycine System in Aqueous Solution

Robert F. Pasternack[1a] **and Helmut Sigel**[1b]

Contribution from the Department of Chemistry, Ithaca College,
Ithaca, N. Y. 14850, and the Institute of Inorganic Chemistry,
University of Basel, CH-4000 Basel, Switzerland. *Received February 24, 1970*

Abstract: The temperature-jump technique has been used to determine the rate constants for the formation and dissociation of the mixed complex Cu(2,2′-bipyridyl)(glycinate)$^+$. Under the conditions of these experiments (temperature = 25°, μ = 0.1 M) it was shown that, within experimental error, the rate constant for attack by the glycine zwitterion is zero. For the reaction $\mathrm{Cu(bipy)^{2+} + gly^- \rightleftarrows Cu(bipy)(gly)^+}$ (k_{12}, forward; k_{21}, reverse), the rate constants are $k_{12} = 1.6 \times 10^9\ M^{-1}\ \mathrm{sec}^{-1}$ and $k_{21} = 19\ \mathrm{sec}^{-1}$. These rate constants are compared with literature values for the reactions $\mathrm{Cu^{2+} + gly^- \rightleftarrows Cu(gly)^+}$ and $\mathrm{Cu(gly)^+ + gly^- \rightleftarrows Cu(gly)_2}$. It is suggested that differences in forward and reverse rate constants can be accounted for in terms of statistical factors, charge effects, and an enhancement term due to the presence of 2,2′-bipyridyl in the inner coordination sphere of the copper ion.

The investigations of ternary Cu^{2+} complexes containing 2,2′-bipyridyl and another ligand demonstrate that these complexes are especially stable if the second ligand binds to the metal ion through oxygen atoms.[2-6] One way used for the characterization of the stability of a ternary complex is comparison of the stability constant, $K_{\mathrm{CuL}}{}^{\mathrm{Cu}}$, of the binary complex with the one, $K_{\mathrm{Cu(bipy)L}}{}^{\mathrm{Cu(bipy)}}$, of the mixed complex[7] according to

$$\mathrm{Cu + L \rightleftarrows CuL}$$

$$K_{\mathrm{CuL}}{}^{\mathrm{Cu}} = \frac{[\mathrm{CuL}]}{[\mathrm{Cu}][\mathrm{L}]} \tag{1}$$

$$\mathrm{Cu(bipy) + L \rightleftarrows Cu(bipy)L}$$

$$K_{\mathrm{Cu(bipy)L}}{}^{\mathrm{Cu(bipy)}} = \frac{[\mathrm{Cu(bipy)L}]}{[\mathrm{Cu(bipy)}][\mathrm{L}]} \tag{2}$$

$$\Delta \log K = \log K_{\mathrm{Cu(bipy)L}}{}^{\mathrm{Cu(bipy)}} - \log K_{\mathrm{CuL}}{}^{\mathrm{Cu}} \tag{3}$$

In Table I the Δ log K values for a few examples of ternary complexes are given. The most surprising fact is that the pyrocatechol dianion binds more strongly to the Cu^{2+}–2,2′-bipyridyl 1:1 complex than to the free hydrated Cu^{2+} ion. Similar results have been obtained for other ligands containing oxygen atoms at the binding site.[2-6] The Δ log K value observed for the 2,2′-bipyridyl–Cu^{2+}–ethylenediamine system is about of the order one would expect according to the general rule, $K_{\mathrm{CuL}}{}^{\mathrm{Cu}} > K_{\mathrm{CuL_2}}{}^{\mathrm{CuL}}$ (*cf.* ref 4 and 8). For the ligand glycine which binds to metal ions through an oxygen and a nitrogen atom, Δ log K has a value intermediate between those of the above-mentioned examples.[9] This Δ log K value is, therefore, considerably less negative than the difference usually observed for $\log K_{\mathrm{CuL_2}}{}^{\mathrm{CuL}} - \log K_{\mathrm{CuL}}{}^{\mathrm{Cu}}$.

Table I. Stability of Some Ternary Cu^{2+} Complexes

Complexes	Δ log K^a	Log X^b
2,2′-Bipyridyl–Cu^{2+}–ethylenediamine^c	−1.29	1.10
2,2′-Bipyridyl–Cu^{2+}–glycinate^c	−0.35	3.05
2,2′-Bipyridyl–Cu^{2+}–pyrocatecholate^c	0.43	6.15
Ethylenediamine–Cu^{2+}–pyrocatecholate^d	−0.76	2.65
Ethylenediamine–Cu^{2+}–oxalate^e	−1.1	1.3

^{a} *Cf.* eq 3. ^{b} *Cf.* eq 4. ^{c} See ref 2. ^{d} P. R. Huber, R. Griesser, B. Prijs, and H. Sigel, *Eur. J. Biochem.*, **10**, 238 (1969). ^{e} W. B. Schaap and D. L. McMasters, *J. Amer. Chem. Soc.*, **83**, 4699 (1961).

The described discriminating behavior of the Cu^{2+}–2,2′-bipyridyl 1:1 complex and the large stability of the ternary 2,2′-bipyridyl–Cu^{2+}–O-ligand complexes is strongly dependent on the presence of the aromatic ligand, 2,2′-bipyridyl.[2] The effect is far less pronounced when 2,2′-bipyridyl is replaced by the aliphatic ligand, ethylenediamine, as can be seen from the last two examples in Table I. In addition, these examples show that π system of the O ligand has a small influence too.[2]

Another way to characterize the stability of ternary complexes is according to

$$\mathrm{Cu(bipy)_2 + CuL_2 \rightleftarrows 2Cu(bipy)L}$$

$$X = \frac{[\mathrm{Cu(bipy)L}]^2}{[\mathrm{Cu(bipy)_2}][\mathrm{CuL_2}]} \tag{4}$$

The value expected for X on a purely statistical basis is 4, *i.e.*, log X = 0.6.[10] The log X values given in Table I for the ternary complexes are all larger than the statistical value. However, the most significant increase of stability is again observed in the 2,2′-bipyridyl–Cu^{2+} systems containing pyrocatechol or glycine.

We are now reporting kinetic results for the formation and dissociation of a ternary complex. Recently,

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[1] (a) To whom correspondence should be addressed at Ithaca College; (b) done in part at Ithaca College during a leave of absence from the University of Basel to Cornell University.

[2] R. Griesser and H. Sigel, *Inorg. Chem.*, **9**, 1238 (1970).

[3] G. A. L'Heureux and A. E. Martell, *J. Inorg. Nucl. Chem.*, **28**, 481 (1966).

[4] H. Sigel, *Chimia*, **21**, 489 (1967).

[5] H. Sigel, K. Becker, and D. B. McCormick, *Biochim. Biophys. Acta*, **148**, 655 (1967).

[6] R. Griesser, B. Prijs, and H. Sigel, *Inorg. Nucl. Chem. Lett.*, **4**, 443 (1968).

[7] Abbreviations used: 2,2′-bipyridyl, bipy; glycinate, gly; general bidentate ligand, L; total concentration of X, $[\mathrm{X}]_{\mathrm{tot}}$.

[8] L. G. Sillén and A. E. Martell, "Stability Constants of Metal Ion Complexes," Special Publication No. 17, The Chemical Society, London, 1964.

[9] Similar results were obtained with other ligands containing N and O as donors: H. Sigel and B. Prijs, *Helv. Chim. Acta*, **50**, 2357 (1967); H. Sigel, *Angew. Chem.*, **80**, 124 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 137 (1968).

[10] R. DeWitt and J. I. Watters, *J. Amer. Chem. Soc.*, **76**, 3810 (1954); S. Kida, *Bull. Chem. Soc. Jap.*, **29**, 805 (1956).

Table II. Results of the Relaxation Spectra for Cu^{2+}–2,2′-Bipyridyl–Glycine Solutions[a]

$[Cu^{2+}]_{tot}$ = $[bipy]_{tot} \times 10^3$	$[gly]_{tot} \times 10^3$	pH	$[Cu^{2+}]^b \times 10^6$	$[Hgly]^b \times 10^3$	$[gly]^b \times 10^8$	$[Cu(bipy)]^b \times 10^3$	$[Cu(bipy)(gly)]^b \times 10^3$	τ_{obsd}, msec
2.80	5.00	5.01	6.75	2.72	5.82	0.440	2.13	0.75
2.80	10.0	5.06	1.16	7.39	17.7	0.166	2.44	0.69
2.80	20.0	4.97	37.6	17.3	33.7	0.090	2.53	0.59
5.60	5.60	5.01	28.3	1.57	3.36	1.34	3.75	0.38
5.60	10.0	5.03	4.95	5.00	11.2	0.503	4.69	0.62
5.60	20.0	4.96	1.05	14.6	27.9	0.217	5.02	0.56
11.2	10.0	5.07	45.9	1.61	3.95	2.38	7.83	0.21
11.2	20.0	5.05	3.13	9.45	22.2	0.538	9.92	0.30
5.60	5.00	4.49	76.6	2.09	1.35	2.36	2.66	0.99
5.60	5.00	4.73	55.5	1.67	1.87	1.97	3.07	0.55
5.60	5.00	4.98	39.3	1.28	2.56	1.62	3.45	0.33
2.80	10.0	4.58	6.33	7.66	6.09	0.424	2.15	1.7
2.80	10.0	5.43	0.26	7.29	41.0	0.075	2.55	0.34
11.2	10.0	4.49	102.3	3.13	2.02	3.76	6.33	0.69
11.2	10.0	4.80	66.5	2.23	2.95	2.95	7.22	0.34
11.2	10.0	5.10	44.0	1.55	4.07	2.33	7.89	0.23
11.2	20.0	4.53	18.9	10.5	7.41	1.44	8.88	0.94
11.2	20.0	4.82	7.26	9.81	13.5	0.849	9.56	0.42

[a] All concentrations are molar. $\mu = 0.1\ M\ (KNO_3)$, temperature = 25°. [b] These concentrations were calculated taking into account all the thermodynamic constants given in Table III.

methods for studying the complexation reactions involving the highly labile Cu^{2+} by temperature jump have been developed.[11–14] We have applied these techniques to the 2,2′-bipyridyl–Cu^{2+}–glycine system in order to determine the factors responsible for the increased stability of this mixed complex.

Experimental Section

This kinetic study involved the use of the temperature-jump technique; the apparatus has been described elsewhere.[12] The nitrate salts of potassium and copper were obtained from Brothers Chemical Co. and from J. T. Baker Chemical Co., respectively. 2,2′-Bipyridyl was from Eastman Organic Chemicals and glycine from Sigma Chemical Co. The course of the relaxation process was followed through use of the indicator methyl red obtained from Allied Chemical Corp.

A 2,2′-bipyridyl stock solution was stored in the dark and never used for a period longer than two weeks. A copper stock solution was prepared and the concentration was determined *via* an EDTA titration using murexide as the indicator. Solutions, which were made within an hour of the time in which they were studied by T-jump, were prepared by the addition of solid glycine to aliquots of the copper and 2,2′-bipyridyl stock solutions. The aliquots were taken such that the stoichiometric concentration of the copper ion always equaled the stoichiometric concentration of 2,2′-bipyridyl. The ionic strength was adjusted to 0.1 *M* with KNO_3 and all solutions were 5.02×10^{-5} *M* in methyl red. The solutions were degassed and then the pH was adjusted with small amounts of NaOH and/or HNO_3 to ±0.01 pH unit. The temperature of this study was 25°.

Each relaxation time represents an average of at least three photographic determinations, with the relative error for these measurements at ±10%. Calculations were generally carried out at the Cornell Computer Center. The equilibrium concentrations of species in solution were calculated using a Newton–Raphson routine. The rate constants were obtained using a graphical technique involving a standard least-squares analysis (*vide infra*). The rate constants are reported to ± 25%.

Results

Under the conditions of these experiments, no relaxation effects were observed for solutions containing inert electrolyte, indicator, and equal concentrations of $Cu(NO_3)_2$ and 2,2′-bipyridyl. In the pH range 4.5–5.4 which was studied here, the concentration of the free hydrated Cu^{2+} ion represents only a small percentage of the total Cu^{2+} present:[15] $[Cu^{2+}] \simeq 0.05\ [Cu^{2+}]_{tot}$. Then, the absence of a relaxation effect in this pH range for the reaction

$$Cu^{2+} + bipy \rightleftharpoons Cu(bipy)^{2+} \qquad (5)$$

may be due to the equilibrium lying so far to the right that the 8° temperature jump does not appreciably perturb it; the reaction has effectively gone to completion.

For the solutions containing Cu^{2+}, 2,2′-bipyridyl, and glycine more than 90% of the total Cu^{2+} is present as Cu(bipy) and Cu(bipy)(gly) (*cf.* Table II). These solutions, containing also inert electrolyte and indicator, do show relaxation effects in the pH range 4.5–5.4 (*cf.* Figure 1 and Table II). Furthermore, relaxation

Table III. Thermodynamic Data for Cu^{2+}–2,2′-Bipyridyl–Glycine Solutions at 25° and μ = 0.1 *M*[a]

(a) 2,2′-Bipyridyl System[b]	
$Hbipy^+ \rightleftharpoons H^+ + bipy$	$pK_{HL}^{H} = 4.49$
$Cu^{2+} + bipy \rightleftharpoons Cu(bipy)^{2+}$	$\text{Log } K_{Cu(bipy)}^{Cu} = 8.00$
$Cu(bipy)^{2+} + bipy \rightleftharpoons Cu(bipy)_2^{2+}$	$\text{Log } K_{Cu(bipy)_2}^{Cu(bipy)} = 5.60$
(b) Glycine System[c]	
$H_2gly^+ \rightleftharpoons H^+ + Hgly$	$pK_{H_2L}^{H} = 2.33$
$Hgly \rightleftharpoons H^+ + gly^-$	$pK_{HL}^{H} = 9.68$
$Cu^{2+} + gly^- \rightleftharpoons Cu(gly)^+$	$\text{Log } K_{Cu(gly)}^{Cu} = 8.27$
$Cu(gly)^+ + gly^- \rightleftharpoons Cu(gly)_2$	$\text{Log } K_{Cu(gly)_2}^{Cu(gly)} = 6.92$
(c) Mixed System[c]	
$Cu(bipy)^{2+} + gly^- \rightleftharpoons Cu(bipy)(gly)^+$	$\log K_{Cu(bipy)(gly)}^{Cu(bipy)} = 7.92$

[a] Indicator, methyl red: $HIn \rightleftharpoons H^+ + In^-$; $K_{HIn}^{H} = 1.00 \times 10^{-5}$: I. M. Kolthoff, *J. Phys. Chem.*, **34**, 1466 (1930). [b] Values taken from ref 16. [c] Values taken from ref 2.

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(11) A. F. Pearlmutter and J. Stuehr, *J. Amer. Chem. Soc.*, **90**, 858 (1968).

(12) R. F. Pasternack, K. Kustin, L. A. Hughes, and E. Gibbs, *ibid.*, **91**, 4401 (1969).

(13) R. L. Karpel, K. Kustin, and R. F. Pasternack, *Biochim. Biophys. Acta*, **177**, 434 (1969).

(14) R. F. Pasternack, E. Gibbs, and J. C. Cassatt, *J. Phys. Chem.*, **73**, 3814 (1969).

(15) The concentrations of Hbipy, bipy, $Cu(bipy)_2$, and $Cu(bipy)_3$ are even smaller. These concentrations were calculated using the constants given in Table III and $\log K_{Cu(bipy)_3}^{Cu(bipy)_2} = 3.48$ (*cf.* ref 16). Hydrolysis of Cu(bipy) can be neglected in this pH range (*cf.* ref 17).

(16) G. Anderegg, *Helv. Chim. Acta*, **46**, 2397 (1963).

(17) D. D. Perrin and V. S. Sharma, *J. Inorg. Nucl. Chem.*, **28**, 1271 (1966).

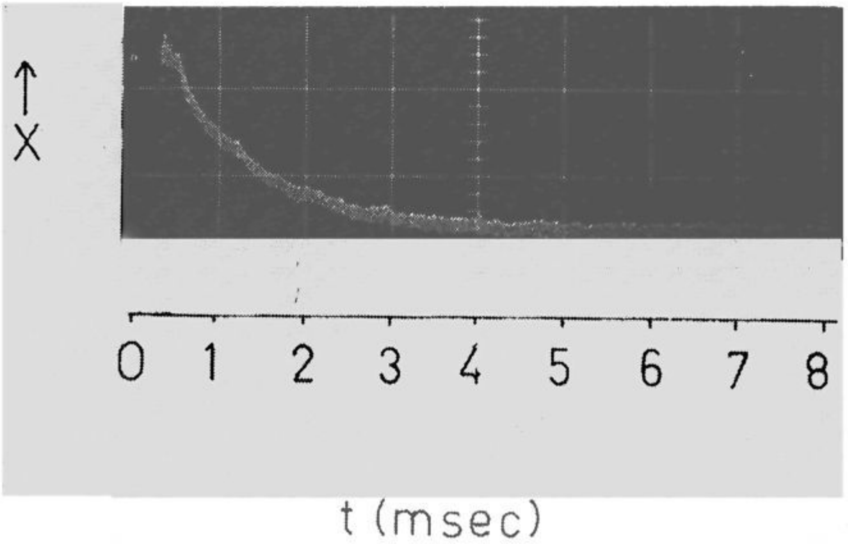


Figure 1. Relaxation effect obtained for a Cu^{2+}–2,2′-bipyridyl–glycine solution at pH 4.49. The initial conditions are $[Cu^{2+}]_{tot} = 5.60 \times 10^{-3}\ M$ and $[gly]_{tot} = 5.00 \times 10^{-3}\ M$. The relaxation time obtained for this solution is 0.99 msec.

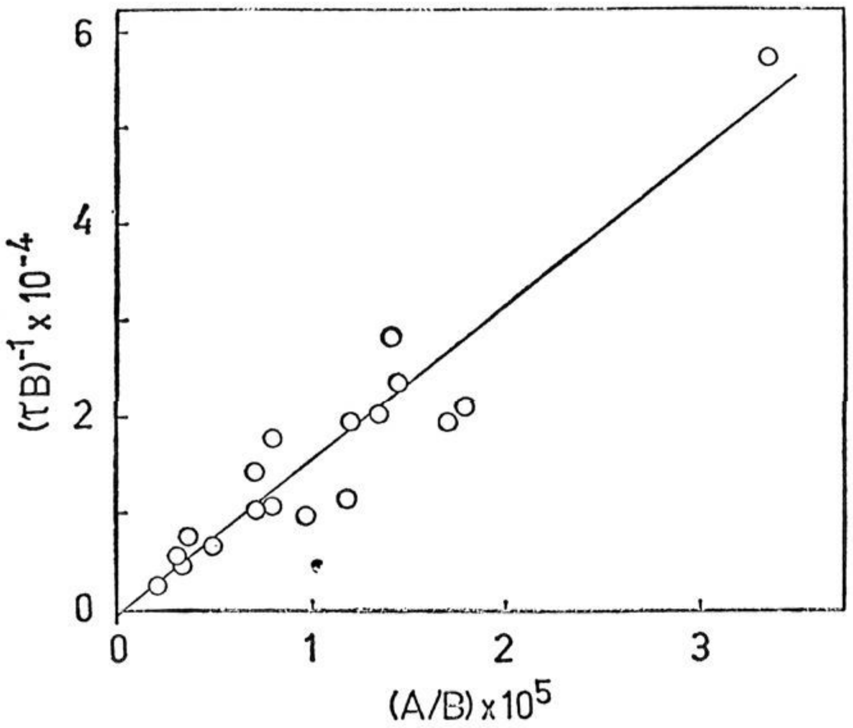


Figure 2. A plot of $(\tau B)^{-1}$ *vs.* A/B for the Cu^{2+}–2,2′-bipyridyl–glycine system. The rate constants obtained from this plot (ref 18) are $k_{12} = 1.6 \times 10^9\ M^{-1}\ sec^{-1}$ for attack by the anion (*cf.* eq 8) and $k_{12}' \leqq 0\ M^{-1}\ sec^{-1}$ for attack by the zwitterion (*cf.* eq 9).

times for eq 6 and 7 could be calculated from the known rate constants for this system,[11] but these calculated relaxation times are in poor agreement with the observed ones. Furthermore, the magnitude of the relaxation effect is too large to be interpreted as being due to reactions 6 and 7, for which the copper-containing reactants have concentrations <5% of $[Cu^{2+}]_{tot}$. However, it did prove possible to fit all of the experimental data with a single set of complexation reactions (eq 8 and 9) differing only in the number of acidic protons on the attacking glycine ligand

$$Cu^{2+} + gly^- \rightleftharpoons Cu(gly)^+ \qquad (6)$$

$$Cu(gly)^+ + gly^- \rightleftharpoons Cu(gly)_2 \qquad (7)$$

$$Cu(bipy)^{2+} + gly^- \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} Cu(bipy)(gly)^+ \qquad (8)$$

$$Cu(bipy)^{2+} + Hgly \underset{k_{21}'}{\overset{k_{12}'}{\rightleftharpoons}} Cu(bipy)(gly)^+ + H^+ \qquad (9)$$

These reactions are coupled to the more rapid processes 10–12, where HIn is the acidic form of the indicator, methyl red.

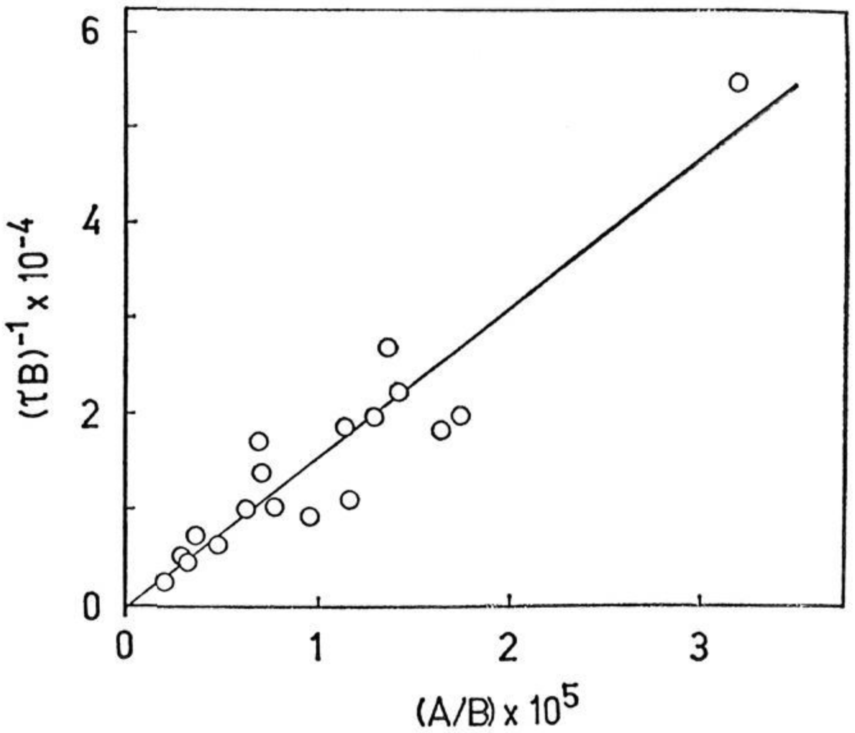


Figure 3. A plot of $(\tau B)^{-1}$ *vs.* A/B for the Cu^{2+}–2,2′-bipyridyl–glycine system. The assumption has been included that $[Cu^{2+}]_{tot} = [bipy]_{tot} = [Cu(bipy)^{2+}]$. The rate constants obtained from this plot (ref 18) are $k_{12} = 1.6 \times 10^9\ M^{-1}\ sec^{-1}$ and $k_{12}' \backsim 0\ M^{-1}\ sec^{-1}$.

$$H_2gly^+ \rightleftharpoons H^+ + Hgly \qquad (10)$$

$$Hgly \rightleftharpoons H^+ + gly^- \qquad (11)$$

$$HIn \rightleftharpoons H^+ + In^- \qquad (12)$$

The use of standard techniques for deriving expressions for relaxation times led to a variation of an equation (*cf.* eq 13) published earlier[12,14]

$$\frac{1}{\tau} = Ak_{12} + Bk_{12}' \qquad (13)$$

In eq 13

$$A = \frac{[Cu(bipy)]}{1 + \alpha} + [gly] + 1/K_{Cu(bipy)(gly)}{}^{Cu(bipy)} \qquad (14)$$

$$B = \alpha\frac{[Cu(bipy)]}{1 + \alpha} + [Hgly] + \frac{1}{K_{Cu(bipy)(gly)}{}^{Cu(bipy)}K_{HL}{}^{H}}\left([H^+] + \alpha\beta\frac{[Cu(bipy)(gly)]}{1 + \alpha}\right) \qquad (15)$$

In eq 14 and 15

$$\alpha = \frac{K_{H_2L}{}^{H}[H^+] + \beta[H^+][Hgly] + [H^+]^2 + \beta K_{H_2L}{}^{H}[OH^-] + \beta[H^+][OH^-]}{K_{H_2L}{}^{H}K_{HL}{}^{H} + 4\beta K_{HL}{}^{H}[Hgly] + \beta K_{H_2L}{}^{H}[gly] + \beta K_{H_2L}{}^{H}K_{HL}{}^{H}[OH^-]/[H^+]} \qquad (16)$$

$$\beta = \frac{K_{In} + [H^+]}{K_{In} + [H^+] + [In^-]} \qquad (17)$$

Equations 13–17 were applied to the data of Table II and $(\tau B)^{-1}$ was plotted *vs.* A/B as shown in Figure 2. From this plot,[18] we obtain that $k_{12} = 1.6 \times 10^9\ M^{-1}\ sec^{-1}$ and $k_{12}' \sim 0\ M^{-1}\ sec^{-1}$.

The data were also handled by including the assumption that

$$[Cu^{2+}]_{tot} = [bipy]_{tot} = [Cu(bipy)] \qquad (18)$$

Equations 13–18 were then applied and $(\tau B)^{-1}$ was plotted *vs.* A/B as shown in Figure 3. From this

[18] The best straight line in Figures 2 and 3 was drawn according to a simple regression method (least squares); the exact values obtained were: from Figure 2, $k_{12} = 1.58 \times 10^9\ M^{-1}\ sec^{-1}$ and $k_{12}' = -0.07 \times 10^4\ M^{-1}\ sec^{-1}$; from Figure 3, $k_{12} = 1.56 \times 10^9\ M^{-1}\ sec^{-1}$ and $k_{12}' = -0.06 \times 10^4\ M^{-1}\ sec^{-1}$.

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

Ligand	Ni^{2+} k_1	Ni^{2+} k_2	Co^{2+} k_1	Co^{2+} k_2	Cu^{2+} k_1	Cu^{2+} k_2	Ref
Glycinate$^-$	4×10^4	6×10^4	2×10^6	2×10^6	4×10^9	4×10^8	*b*, 11
α-Alanate$^-$	3×10^4	3×10^4	2×10^6	1×10^6	1×10^9	2×10^8	*c*, 22
Leucinate$^-$	2×10^4	4×10^4	1×10^6	2×10^6	2×10^9	8×10^8	14
Serinate$^-$	3×10^4	3×10^4	2×10^6	2×10^6	3×10^9	5×10^8	13
Picolinate$^-$	3×10^4	1×10^5	10^6–10^7	2×10^7			27
2,2′,2″-Terpyridyl[a]	1×10^3	2×10^5	3×10^4	$\sim 5 \times 10^6$	$\sim 2 \times 10^7$		*d*

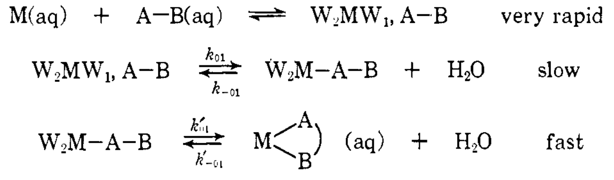
[a] The k_2 value for cobalt(II) and the k_1 value for copper(II) were determined at 5°. [b] G. Davies, K. Kustin, and R. F. Pasternack, *Inorg. Chem.*, **8**, 1535 (1969). [c] R. F. Pasternack, K. Kustin, R. Reingold, and M. Angwin, manuscript in preparation. [d] R. H. Holyer, C. D. Hubbard, S. F. A. Kettle, and R. G. Wilkins, *Inorg. Chem.*, **5**, 622 (1966).

plot,[18] we obtain that $k_{12} = 1.6 \times 10^9\ M^{-1}\ \text{sec}^{-1}$ and $k_{12}' \sim 0\ M^{-1}\ \text{sec}^{-1}$. That the assumption of complete formation of the Cu^{2+}–2,2′-bipyridyl 1:1 complex may be employed was also demonstrated during the determination of the thermodynamic constants for the 2,2′-bipyridyl–Cu^{2+}–glycine system.[2]

Therefore, we conclude that in solutions prepared as described above, we can assume that all the copper is in the forms $Cu(bipy)^{2+}$ or $Cu(bipy)(gly)^+$; that $k_{12} = 1.6 \times 10^9\ M^{-1}\ \text{sec}^{-1}$, $k_{21} = 19\ \text{sec}^{-1}$ (calculated from k_{12} and $K_{\mathrm{Cu(bipy)(gly)}}^{\mathrm{Cu(bipy)}}$; Table III); and that the glycine zwitterion attack of $Cu(bipy)^{2+}$ is negligible under the conditions of these experiments.

Discussion

Results for the complexation reactions of highly labile metal ions, and in particular cobalt(II) and nickel(II), are usually consistent with a mechanism in which the rate-determining step is the loss of a water molecule from the inner coordination sphere of a thermodynamically stable species.[19] In the particular case of the fully aquated metal ion and a bidentate ligand **A–B** this may be written as



where W_1 and W_2 represent the two water molecules in the inner coordination sphere replaced by A–B. The observed rate constant for the reaction is then

$$k_1 = K_{a1}k_{01} \qquad (19)$$

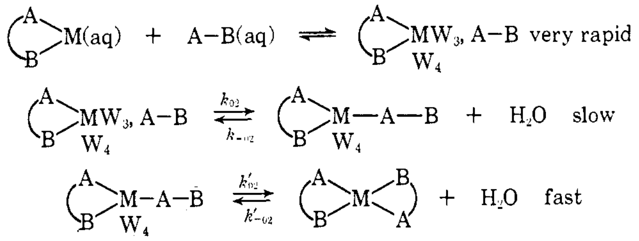
where K_{a1} is the equilibrium constant for ion pair formation

$$K_{a1} = \frac{[W_2MW_1,\ A\text{–}B]}{[M(aq)][A\text{–}B(aq)]}$$

Values of K_{a1} are usually calculated using an equation derived independently by Fuoss and Eigen.[20] The value of K_{a1} depends on a number of parameters of the system but, at fixed ionic strength and temperature, it depends primarily on the charge type of the interacting ions.[21] In the most frequently used conditions ($\mu = 0.1\ M$ and temperature = 25°), $K_{a1} \sim 1$ for $+1,-1$ interactions; ~ 2 for $+2,-1$ and $+1,-2$ interactions; ~ 15 for $+2,-2$ interactions; and ~ 0.3 when one of the reactants is uncharged.

Although several examples have now been reported in which a different rate-determining step is operative,[21–25] these examples are not frequent and depend on some readily identifiable property of the ligand. For simple ligands which form five-membered chelate rings, the above mechanism appears applicable.

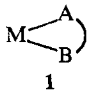
A similar mechanism has been proposed for the formation of higher order complexes. For example



The observed rate constant, k_2, is given by

$$k_2 = SK_{a2}k_{02} \qquad (20)$$

where S is a statistical factor and is approximately equal to the number of remaining water molecules in the complex ion



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divided by the total number of ligand positions[26] and K_{a2} is the equilibrium constant for ion pair formation for which the same formula is used as for K_{a1}.

Here again, the rate-determining step for most complexation reactions of the labile metal ions cobalt(II) and nickel(II) is the loss of a water molecule from the thermodynamically stable species, in this case **1**.[19] In these higher order complexes, the rate constant for the rate-determining step, k_{02}, shows some ligand dependence. The presence of a ligand other than water in the inner coordination sphere affects the lability of the remaining water molecules. For most ligands thus far studied, and in particular the amino acids, 2,2′,2″-terpyridyl, and picolinic acid, the remaining waters are labilized by the presence of a nonaquo ligand (*cf.* Table IV). The degree of en-

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(19) M. Eigen and R. G. Wilkins, *Advan. Chem. Ser.*, No. **49**, 55 (1965).

(20) (a) R. M. Fuoss, *J. Amer. Chem. Soc.*, **80**, 5059 (1958); (b) M. Eigen, *Z. Phys. Chem. (Frankfurt am Main)*, **1**, 176 (1954).

(21) A. Kowalak, K. Kustin, R. F. Pasternack, and S. Petrucci, *J. Amer. Chem. Soc.*, **89**, 3126 (1967).

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hancement of water loss is especially great for those ligands containing delocalized π orbitals, which interact with the d orbitals of the metal ion.[27]

For copper(II), the mechanism for complexation is necessarily more complicated. Unlike nickel(II) and cobalt(II), the inner coordination sphere for the fully aquated copper(II) ion is a highly distorted octahedron; the extreme lability of the copper(II) ion is interpreted in terms of this distortion. It has been suggested that the loss of a water molecule from the elongated axial position is the rate-determining process for complexation followed by a very rapid inversion with ligand attack bringing the ligand into the equatorial position.[28] Another possibility is that the water loss is more rapid than the subsequent inversion, making the latter the rate-determining process. For a bidentate ligand, two axial water molecules would have to be lost in turn with subsequent inversions so that both ligand to metal bonds are in the equatorial plane.

Should inversion be the rate-determining process in this complexation reaction, some ligand dependence might be expected in the forward rate constant, k_1. Unfortunately, thus far, not many copper complexation reactions have been studied, but from Table IV, it would appear that ligand dependence for the amino acids is negligible. Furthermore, the rate constants obtained for copper(II) with glycylglycine and glycylsarcosine may also be interpreted as consistent with water loss being rate determining.[29] However, some ligand dependence has been observed for the copper(II)–leucylglycine system.[30] Still for most ligands studied, it appears that similar mechanistic arguments may be applied for copper(II) as for cobalt(II) and nickel(II), and therefore $k_1 = K_{a1}k_{01}$. This would place the value of k_{01}, the rate constant for water loss from an axial position, at $1\text{–}2 \times 10^9\ \text{sec}^{-1}$.

The situation becomes even less clear-cut for the formation of higher order complexes. Unlike the results obtained for cobalt(II) and nickel(II), for copper(II), $k_2 < k_1$. However, the statistical factor S is more difficult to assess for copper complexes because of the distortions and square-coplanar–octahedron ambiguities.[31,32] Some workers believe that the statistical factor is large enough to completely account for these copper results.[32] However, other factors have to be involved too, as may be implied from the result that O ligands form more stable complexes with the Cu^{2+}–2,2′-bipyridyl 1:1 complex than with the (free) hydrated Cu^{2+} ion (*i.e.*, positive $\Delta \log K$ values are observed; *cf.* Table I).[2–6]

It has been suggested that the presence of the first nonaquo ligand in the inner coordination sphere may inhibit the inversion sufficiently that this becomes the rate-determining process.[12] It has also been shown that as the ligand field of the four closest ligands increases, the copper atom binds the axial positions less tightly and these positions become further removed from the positive center.[33] In fact, for a ligand like 2,2′-bipyridyl, which provides a very large ligand field, it is perhaps more nearly correct to consider the $Cu(bipy)^{2+}$ species as square coplanar rather than as a distorted octahedron. Then it is possible that the first ligand in the inner coordination sphere so thoroughly inhibits the inversion that the incoming ligand must replace equatorial waters, which are usually less labile, to form a stable complex. Therefore, kinetic results for copper complexation cannot, at present, be unambiguously interpreted on a molecular basis.

The reactions we are comparing here are

$$Cu^{2+} + gly^- \underset{22\ \text{sec}^{-1}}{\overset{4 \times 10^9\ M^{-1}\ \text{sec}^{-1}}{\rightleftharpoons}} Cu(gly)^+ \qquad (6)^{11,34}$$

$$Cu(gly)^+ + gly^- \underset{48\ \text{sec}^{-1}}{\overset{4 \times 10^8\ M^{-1}\ \text{sec}^{-1}}{\rightleftharpoons}} Cu(gly)_2 \qquad (7)^{11,34}$$

$$Cu(bipy)^{2+} + gly^- \underset{19\ \text{sec}^{-1}}{\overset{1.6 \times 10^9\ M^{-1}\ \text{sec}^{-1}}{\rightleftharpoons}} Cu(bipy)(gly)^+ \qquad (8)$$

A comparison of reactions 6 and 8 shows that the reverse rate constants therein are about the same. This is not surprising, as the charge of $Cu(gly)^+$ and $Cu(bipy)(gly)^+$ is the same; also, in both cases there is only one way to remove the glycine molecule. Considering the forward rate constants and taking into account the mentioned assumption that the $Cu(bipy)^{2+}$ species is rather square coplanar, the forward rate constant of eq 6 has to be "corrected" by a statistical factor, $S = 1/8$ (*cf.* ref 31), before being compared with the constant of eq 8. As the constants, K_a, for ion pair formation are the same in both cases, this leaves us with an unexplained additional factor of about 3 in the forward direction for the formation of the ternary complex.

Considering eq 7 and 8, and again first the reverse rate constants, the factor of about 2.5 can be accounted for in terms of statistical arguments and a small charge effect. There are two ways to remove a gly^- from $Cu(gly)_2$ but only one way from $Cu(bipy)(gly)^+$. Furthermore, in the former case, a negatively charged species is being removed from a neutral molecule, whereas in the latter, an anion is being removed from a cationic species. In the forward direction, regardless of the rate-limiting process, the mechanism must begin with an ion pair formation which can be characterized by an equilibrium constant, K_{a2}, discussed above. The value of K_{a2} for reaction 8 will be about twice the value for reaction 7 (a $+2,-1$ interaction as compared to a $+1,-1$ interaction). Therefore, left unexplained in this consideration is an additional factor of 2 in the forward direction.

An enhancement factor of 2–3 is a rather modest effect, at least when compared with Co^{2+} and Ni^{2+}

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[29] R. F. Pasternack, M. Angwin, and E. Gibbs, *J. Amer. Chem. Soc.*, in press.

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[31] A more satisfactory approach to the determination of the statistical factor, S, than that described in ref 26 is to compute the number of independent attacking sites available for the ligand. For a bidentate ligand substituting on a regular octahedron, there are 12 edges available for the first ligand but only 5 for the second; S is therefore 5/12. However, S is more difficult to obtain for the distorted octahedron. Considering inversion to be rapid, there are eight equivalent attacking positions for the first ligand. The value for the second ligand can vary from one to four depending on the relative rates of inversion and water loss from an equatorial position. Therefore S may be as large as 1/2 or as small as 1/8.

[32] D. L. Leussing, private correspondence.

[33] H. C. Freeman in "The Biochemistry of Copper," J. Peisach, P. Aisen, and W. E. Blumenberg, Ed., Academic Press, New York, N. Y., 1966, p 77 ff.

[34] The values for k_{21} were calculated using k_{12} of ref 11 and the thermodynamic constants of Table III.

complexes, where ligands containing delocalized π orbitals usually cause much larger rate enhancements (*cf.* Table IV). For copper(II), we cannot unequivocably state whether this factor is due to increased labilization of remaining water molecules in the complex (axial or equatorial) or a facilitation of inversion. It is quite possible, in fact, that Cu^{2+}, $Cu(gly)^+$, and $Cu(bipy)^{2+}$ undergo substitution reactions *via* different mechanisms; the two former perhaps by axial substitution and inversion and the latter by direct equatorial substitution.

In conclusion, we see that the stability of this mixed copper(II) complex may be explained in terms of relatively simple interactions and statistical arguments. Further studies on analogous systems are being undertaken in our laboratories to determine the relative importance of the structural and electronic features of the bound and attacking ligands. Clearly more work is necessary before we are able to account for the positive value of $\Delta \log K$ for the 2,2′-bipyridyl–Cu^{2+}–pyrocatechol system.

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Cobalt(III)-Promoted Hydrolysis of Glycine Amides. Intramolecular and Intermolecular Hydrolysis Following the Base Hydrolysis of the *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ Ions

D. A. Buckingham, D. M. Foster, and A. M. Sargeson

Contribution from the Research School of Chemistry,
Australian National University, Canberra 2600, Australia.
Received March 19, 1970

Abstract: Base hydrolysis of the *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ ions over the pH range 9–14 results in two paths for the production of $[Co(en)_2(gly)]^{2+}$. Following loss of Br^- ($k_{OH} = 260 \pm 20\ M^{-1}\ sec^{-1}$, $\mu = 1.0$, 25°), competition for the five-coordinate intermediate by solvent and amide carbonyl oxygen results in *cis*-$[Co(en)_2(OH)(glyNR_1R_2)]^{2+}$ and $[Co(en)_2(glyNR_1R_2)]^{3+}$ species in the ratios 54:46 ($R_1 = R_2 = H$), 34:66 ($R_1 = CH_3$; $R_2 = H$), and 18:82 ($R_1 = R_2 = CH_3$). The two paths have been isolated, and ^{18}O-tracer results support the product distribution ($R_1 = R_2 = H$) and demonstrate intra- and intermolecular hydrolysis in the hydroxoamide and chelated amide, respectively. Hydrolysis in the *cis*-$[Co(en)_2(OH)(glyNH_2)]^{2+}$ ion is faster by at least a factor of 10 than loss of Br^- at pH 9 and 13, requiring a rate at least 10^7, and possibly more than 10^{11}, times faster than hydrolysis for uncoordinated glycine amide. Stereochemical studies show 80% retention of configuration in the hydroxoamide path and 75% retention in the chelated amide path. The significance of the results is discussed in relation to the "carbonyl" and "hydroxide" mechanisms entertained for hydrolytic enzymes.

Previous studies have discussed the base hydrolysis of *cis*-$[Co(en)_2X(glyOR)]^{2+}$ (X = Cl, Br)[1,2] and β_2-$[Co(trien)Cl(glyOC_2H_5)]^{2+}$ [1,3] in terms of two competing processes: intermolecular hydrolysis of the chelated ester and intramolecular attack of coordinated OH^- at the carbonyl center of the monodentate ester. Both paths arose from competition for the five-coordinate deprotonated intermediate formed on loss of halide ion.[2,3] Evidence for these paths came entirely from ^{18}O-tracer results, and the interpretation remained partly equivocal in that both reactions were fast compared to hydrolysis of coordinated halide and could not be observed independently.

A recent study has demonstrated that N,O chelated glycine amides in $[CoN_4(glyNR_1R_2)]^{3+}$ [1] (R_1, R_2 = H, CH_3) base hydrolyze more slowly by a factor of $\sim 10^5$ than the corresponding chelated esters.[4] This rate difference allows hydrolysis in the chelated amide to be observed following loss of Br^- in *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$, and also allows that intramolecular hydrolysis by coordinated OH^- might be observed as a separate reaction. Such studies have direct relevance to the metal ion catalyzed hydrolysis of the amide bond in amino acid amides and peptides. In this paper the results of a kinetic, stereochemical, and ^{18}O-tracer study on the base hydrolysis of the *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ ions are reported.[4a]

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(1) Abbreviations used in this article are as follows: en = ethylenediamine; trien = triethylenetetramine; N_4 = trien or $(en)_2$; glyO = N-bound monodentate glycinate anion; glyOR = glycine alkyl esters; $glyNR_2$ = glycine amides; gly = chelated glycinate anion.

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(4a) NOTE ADDED IN PROOF. In a recent article [S. C. Chan and F. K. Chan, *Aust. J. Chem.*, **23**, 1175 (1970)], it is reported that base hydrolysis at 0° of *cis*-$[Co(en)_2Cl(glyNH_2)]^{2+}$ "definitely" results in a stable product $[Co(en)_2OH(glyNH_2)]^{2+}$, which only on acidification forms the N,O-chelated amide, $[Co(en)_2(glyNH_2)]^{3+}$. The present results do not substantiate their proposals.