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 Δ 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

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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 ± 20 M^{-1} sec^{-1}, μ = 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]

(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.

(2) D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **91**, 4102 (1969).

(3) D. A. Buckingham, D. M. Foster, L. G. Marzilli, and A. M. Sargeson, *Inorg. Chem.*, **9**, 11 (1970).

(4) D. A. Buckingham, C. E. Davis, D. M. Foster, and A. M. Sargeson *J. Amer. Chem. Soc.*, **92**, 5571 (1970).

(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.

Experimental Section

Analar reagents were used throughout without further purification. Glycine N-methyl and N-dimethyl amides were prepared utilizing 5,5-dimethyl-2-cyclohexene-1,3-dione (dimedone) as an N-protecting group.[5,6] N-(5,5-Dimethyl-2-cyclohexen-1-on-3-yl)-glycine ethyl ester[6] was treated with either 40% aqueous methylamine or dimethylamine. The (N-dimedone)glycineamide product in each case was filtered from solution and recrystallized from ethanol at 70°; the dimedone protecting group was then removed with bromine[7] to form the glycine N-methyl and N-dimethyl amide hydrobromide salts, respectively. These salts were recrystallized from methanol at 30°, washed with ether, and dried in an evacuated desiccator. *Anal.* Calcd for $NH_2CH_2CONHCH_3 \cdot HBr$: C, 21.30; H, 5.37; N, 16.58. Found: C, 20.95; H, 5.39; N, 16.79. Calcd for $NH_2CH_2CON(CH_3)_2 \cdot HBr$: C, 26.22; H, 6.06; N, 15.31. Found: C, 25.97; H, 5.76; N, 15.51.

Pmr spectra were recorded on a Varian 100-mHz spectrometer, and visible spectra on a Cary 14 spectrophotometer. Spectrophotometric rates were obtained using a Cary 14 (1-cm cell) or a Durrum-Gibbs stopped-flow reactor (2-cm cell). Some cobalt estimations were made using a Techtron AA4 atomic absorption spectrophotometer. α_λ values for optically active complexes were measured at 25° with a Perkin-Elmer P22 spectropolarimeter, using a 1-dm cell. The following radiometer apparatus was used in the measurement of buffer pH and in pH-stat titrations: TTA_3 electrode assembly, ABU 1 autoburet, TTT 1 titrator, SBR_2 titrigraph, and pHA scale expander. In the pH-stat titrations, the titrant (NaOH) was added under a nitrogen atmosphere to the continuously stirred solution. Separation of reaction products was achieved using Bio-Rad Analytical Dowex 50W-X2 (200–400 mesh) cation-exchange resin. The ^{18}O content of CO_2 recovered from the labeled compounds was determined using an Atlas M-86 mass spectrometer.

Preparation of Complexes. *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$, *cis*-$[Co(en)_2(glyNHCH_3)]Br_2$, and *cis*-$[Co(en)_2Br(glyN(CH_3)_2)]Br_2$ were prepared from *trans*-$[Co(en)_2Br_2]Br \cdot HBr$ and the appropriate glycine amide hydrobromide using the method described by Alexander and Busch for the preparation of analogous glycine ester complexes.[8]

The product complexes were washed with acetone and air-dried. *Anal.* Calcd for $[Co(en)_2Br(glyNH_2)]Br_2$: C, 14.62; H, 4.50; N, 17.05. Found: C, 14.43; H, 4.71; N, 16.84. Calcd for $[Co(en)_2Br(glyNHCH_3)]Br_2$: C, 16.08; H, 4.63; N, 16.07. Found: C, 16.36; H, 4.48; N, 16.38. Calcd for $[Co(en)_2Br(glyN(CH_3)_2)]Br_2$: C, 17.88; H, 4.88; N, 15.65. Found: C, 17.90; H, 5.08; N, 15.25. The amide and N-methylamide complexes were converted to their perchlorate salts by dissolution in hot dilute $HClO_4$, followed by addition of excess $NaClO_4$ and cooling in an ice bath. They were washed with ethanol and air-dried. *Anal.* Calcd for $[Co(en)_2Br(glyNH_2)](ClO_4)_2$: C, 13.54; H, 4.17; N, 15.80. Found: C, 13.60; H, 4.49; N, 15.98. Calcd for $[Co(en)_2Br(glyNHCH_3)](ClO_4)_2$: C, 15.39; H, 4.43; N, 15.39. Found: C, 15.55; H, 4.53; N, 15.12. The following absorption maxima and absorptivities were obtained in dilute acetic acid (pH 5) at 25°: *cis*-$[Co(en)_2Br(glyNH_2)](ClO_4)_2$, 545 ± 2 nm (ε 84 ± 1); *cis*-$[(Co(en)_2Br(glyNHCH_3)](ClO_4)_2$, 545 ± 2 nm (ε 87 ± 1); *cis*-$[Co(en)_2Br(glyN(CH_3)_2)]Br_2$, 545 ± 2 nm (ε 86 ± 1). These values remained unchanged in 1 *M* $NaClO_4$ (pH 5).

Measurement of Oxygen Exchange in ^{18}O-Labeled $[Co(en)_2gly]^{2+}$ Produced *via* Base Hydrolysis of *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$ in Labeled Solvent. *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ (8 g) in enriched water (80 ml, 2.0 atom% ^{18}O) was hydrolyzed at pH 9.5 and 25° for 3 hr, by pH-stat titration against 30% NaOH. The solution was then taken to pH 7 with 12 *M* HCl and reduced to *ca.* 50 ml on a rotary evaporator at *ca.* 30°. Excess NaI and methanol were added, and $[Co(en)_2gly]I_2$ precipitated, after acidification to pH ~3, addition of $Na_2S_2O_4$, and warming to remove I_3^-. This material was collected, washed with cold NaI solution, methanol, and ether, and recrystallized by dissolution in hot water and addition of NaI. The final product (2 g) was washed as before and dried in an evacuated desiccator. The dried material was shaken with excess AgCl in water (20 ml) for 5 min and the precipitate of AgCl and AgI removed. The filtrate was made up to 50 ml, 0.1 *M* $HClO_4$, μ = 1.0 ($NaClO_4$). This solution was thermostated at 25° and 5-ml aliquots were withdrawn periodically. From these samples $[Co(en)_2gly](HgI_4)$ was recovered, and the ^{18}O content of the glycine determined as previously described.[9]

Measurement of Oxygen Exchange in ^{18}O-Labeled $[Co(en)_2gly]^{2+}$ Produced *via* Base Hydrolysis of $[Co(en)_2(glyNH)_2]^{3+}$ in Labeled Solvent. $[Co(en)_2(glyNH_2)](NO_3)_2ClO_4 \cdot H_2O$[4] (5 g) in enriched water (50 ml, 1.3 atom% $H_2{}^{18}O$) was hydrolyzed at pH 9.0 and 25° for 24 hr, by pH-stat titration against 30% NaOH. On addition of excess NaI, $[Co(en)_2gly]I_2$ precipitated. This product (4.5 g) was washed and dried as above, converted to the chloride salt by shaking with excess AgCl, made up to 50 ml with 0.1 *M* $HClO_4$, μ = 1.0 ($NaClO_4$), and thermostated at 25°; 10-ml aliquots were periodically withdrawn and treated as described above.

Resolution of *cis*-$[Co(en)_2Br(glyNH_2)](ClO_4)_2$ and Measurement of Optical Retention in the Product of the Hg^{2+}-Induced Hydrolysis in Acid Solution. *cis*-$[Co(en)_2Br(glyNH_2)](ClO_4)_2$ (11.3 g) was dissolved in hot, dilute acetic acid (20 ml, pH 3) and ammonium *d*-bromocamphorsulfonate (NH_4-(+)-BCS, 13.9 g) added. Ethanol (75 ml) and acetone (75 ml) were added, and on scratching and cooling in an ice bath, $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]$-(+)-$(BCS)_2$ slowly crystallized. On reduction of the solution volume, and further addition of acetone and ethanol, three further fractions of similar activity were obtained. The four fractions were combined and recrystallized from hot dilute acetic acid by cooling and adding ethanol (5.5 g). A 0.1% solution in 0.01 *M* $HClO_4$ gave α_{589} +0.001°, α_{546} +0.073°, whence $[\alpha]_{589}$ ~0 and $[\alpha]_{546}$ +73°. *Anal.* Calcd for $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]$-(+)-$(C_{10}H_{14}BrO_4S)_2$: C, 32.75; H, 5.29; N, 8.82. Found: C, 32.84; H, 5.60; N, 8.56. The diastereoisomer was converted to the bromide salt by trituration with excess NaBr in water (3 ml) and was recrystallized from hot dilute hydrobromic acid by addition of NaBr and cooling. The product (2.0 g) was washed with methanol and acetone and air-dried. A 0.1% solution in 0.01 *M* $HClO_4$ gave α_{589} −0.116° and α_{546} +0.018°, whence $[\alpha]_{589}$ −116° and $[\alpha]_{546}$ +18°. *Anal.* Calcd for $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$: C, 14.62; H, 4.50; N, 17.05. Found: C, 14.85; H, 4.64; N, 17.17.

The filtrate remaining after removal of the $(+)_{546}$ diastereoisomer was reduced to dryness and dissolved in methanol (30 ml). On addition of excess NaBr, $(+)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$ crystallized; it was recrystallized from hot dilute hydrobromic acid by addition of NaBr and cooling The product (1.6 g) was washed and dried as before. A 0.1% solution in 0.01 *M* $HClO_4$ gave α_{589} +0.118° and α_{546} −0.011°, whence $[\alpha]_{589}$ 118° and $[\alpha]_{546}$ −11°. *Anal.* Calcd for $(+)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$: C, 14.62; H, 4.50; N, 17.05. Found: C, 14.95; H, 4.50; N, 17.00.

A partial resolution of *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ was also achieved by chromatography on Biorad Cellex-P weakly acid cation-exchange resin.[10] The complex (0.05 g) in water (100 ml) was sorbed onto the H^+-form resin (70 × 2 cm) and eluted with 0.05 *M* HCl. Eluate aliquots (6 ml) were estimated for Co by atomic absorption spectroscopy, and the α_{589} values measured. Sixteen aliquots showed optical activity; the first samples were inactive, the next eight $(+)_{589}$, and the last eight $(-)_{589}$. Maximum specific rotations obtained were $[\alpha]_{589}$ +81° and −64°, representing 68% and 54% of the activity of the optically pure forms prepared above.

$(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$ (0.0519 g, $[M]_{589}$ −572°) was dissolved in a 0.305 *M* Hg^{2+}–1.0 *M* $HClO_4$ solution (25 ml) and allowed to stand at 25° for 90 min. A 5-ml aliquot, diluted to 10 ml, gave α_{589} −0.350°, whence $[M]_{589}$ −1662°. The solution was diluted with water and sorbed onto an H^+-form resin, from which it eluted as a homogeneous 3+ band ($[Co(en)_2(glyNH_2)]^{3+}$) using 2 *M* HCl. The eluate was taken to dryness and redissolved in 50 ml of water. The Co concentration was estimated spectrophotometrically (ϵ_{487} 98 for $[Co(en)_2(glyNH_2)]^{3+}$ [4]), [Co] = 1.84 × 10^{-3} *M*, and the optical activity measured spectropolarimetrically, α_{589} −0.309°, whence $[M]_{589}$ −1679°. The solution was then hydrolyzed at pH 9.0 for 8 hr at 25° by pH-stat titration against 0.2 *M* NaOH, quenched to pH 2 with 6 *M* HCl, and sorbed and eluted from an H^+-form resin, using 2 *M* HCl. The homogeneous 2+ eluate band ($[Co(en)_2gly]^{2+}$) was taken to dryness and redissolved in 50 ml of water. Using ϵ_{487} 98 for $[Co(en)_2gly]^{2+}$,[11] [Co] = 1.63 × 10^{-3} *M*. Also, α_{589} −0.253°; hence $[M]_{589}$ −1550°.

Product Analysis by Ion-Exchange Chromatography. (A) **Separation of the Products of Base Hydrolysis.** The *cis*-$[Co(en)_2Br$-

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Table I. Spectrophotometric Rate Constants for the Hydrolysis of Br^- in *cis*-$[Co(en)_2(glyNR_1R_2)Br]^{2+}$ Ions at 25°, μ = 1.0[a]

pH[b]	$k_{obsd} \times 10^4$, sec^{-1}	$k \times 10^{-2}$,[c] M^{-1} sec^{-1}
	(A) $R_1 = R_2 = H$	
7.84	1.80	2.6
8.16	3.73	2.6
9.00	25.66	2.6
	(B) $R_1 = H$, $R_2 = CH_3$	
7.83	1.80	2.7
8.15	4.13	2.9
9.00	28.17	2.8
	(C) $R_1 = R_2 = CH_3$	
7.78	1.60	2.6
8.14	3.40	2.4
9.00	23.57	2.4

[a] [Co] ~2 × 10^{-3} *M*, λ 490 nm, 0.2 *M* tris buffer, μ ($NaClO_4$). [b] Solution pH measured at the conclusion of the reaction. [c] $k = k_{obsd}/[OH^-]$, where $[OH^-]$ is calculated assuming $K_w = 10^{-14}$.

The isosbestic point for the bromoamide complex and the initial products of hydrolysis was determined by quickly scanning the spectrum after rapid mixing of an aqueous solution of the complex and 0.2 *M* glycine buffer using the Cary fitted with a stopped-flow mixing device.[12] Reactions occurring more slowly followng release of Br^- were then followed at this wavelength (*ca.* 522 nm) in the buffer or in standardized base. The rate in 1.0 *M* NaOH was also followed at 522 nm on the Durrum-Gibbs stopped flow reactor; a 2.0 *M* NaOH solution was mixed with a solution 2 m*M* in complex and 2 *M* in $NaClO_4$.

Results

(A) Kinetic Data. Table I gives spectrophotometric data (490 nm) for hydrolysis of Br^- in the *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ ions. At this wavelength large optical density changes (*ca.* 0.4 OD units) accompanied loss of Br^-; the subsequent slower hydrolysis of the chelated amide resulted in only small optical density changes (*ca.* 0.01 OD unit) and these were neglected in the following analysis. Plots of log ($D_\infty - D_t$) *vs.* time were linear for at least three half-lives and the rate data fit the rate law

$$v_{substrate} = k[Co(en)_2Br(glyNR_1R_2)^{2+}][OH^-]$$

The second-order rate constants, *k*, are similar for the three amide complexes (260 ± 20 M^{-1} sec^{-1}) and agree with that found for loss of Br^- in *cis*-$[Co(en)_2Br(glyOCH(CH_3)_2)](ClO_4)_2$ at μ = 1.0, 25° (270 ± 30 M^{-1} sec^{-1}).[2]

At pH 9.0, 9.6, and 10.8 reactions occurring after loss of Br^- in *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ were followed at the isosbestic point for Br^- release, 522 nm. The isosbestic points were determined by fast repetitive scans over the first ~2% of the reactions and were found to be almost pH independent (±2 nm). Using the 0.1-OD slide wire ([Co] = 5 m*M*) and the stopped-flow mixing device,[12] only one reaction was observed at this wavelength in the above buffer solutions. A similar result was found in 1.0 *M* NaOH using the Durrum-Gibbs stopped-flow reactor. For the reactions at pH 9.6 and in 1 *M* NaOH linear plots of log ($D_\infty - D_t$) *vs.* time were obtained for at least three half-lives, giving k_{obsd} values of 2.6 × 10^{-4} sec^{-1} and 5.0 × 10^{-2} sec^{-1}, respectively (Table II). No faster reaction was observed at 522 nm in 1 *M* NaOH with a rate constant $\leq$ 10 sec^{-1}.

(B) Product analysis was carried out by ion exchange of the acidified hydrolyzed solutions. Two orange bands, 2+ and 3+ species, were observed

Table II. Products of Hydrolysis of *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ Ions[a]

Complex R_1, R_2	k_1,[e] sec^{-1}	Recovered products (% of reactant complex) $[Co(en)_2(glyNR_1R_2)]^{3+}$	$[Co(en)_2gly]^{2+}$	$k_2 \times 10^4$, sec^{-1} (ref 4)[e,g]	Calcd[h] % $[Co(en)_2gly]^{2+}$	% (col 4 − col 6)
H, H	51 × 10^{-4}	34 (38)[f]	56 (62)[f]	2.6 (2.6)[d]	16 (8)[i]	46 (54)[i]
H, H[b]	52	36 (39)[f]	58 (61)[f]	636	6 (3)[i]	55 (58)[i]
H, CH_3	56 × 10^{-4}	66 (66)[f]	34 (34)[f]	0.15	0	34
CH_3, CH_3	57 × 10^{-4}	49 (82)[f]	11 (18)[f]	0.10	0	18
H, H[c]				508[c] (500)[e]		

[a] pH 9.0, 25°, quenched after 15 min (μ = 0.1). [b] Hydrolysis at pH 13.0 for *ca.* 1 sec. [c] pH 14.0, μ = 2.0. [d] pH 9.6 (0.2 *M* glycine buffer), μ = 1.0. [e] See ref 15. [f] Normalized to 100% recovery. [g] Values in parentheses are rates observed subsequent to Br^- hydrolysis in this work. [h] Using the expression $\% = 100A_0[1 + 1/(k_1 - k_2)\{k_2e^{-k_1t} - k_1e^{-k_2t}\}]$ (see text). [i] Values in parentheses corrected for $A_0 = {}^1/_2A_0$ in *h* (see text, Results section C).

$(glyNR_1R_2)]Br_2$ complexes (*ca.* 1 mmol) in water (20 ml), μ ~ 0.1, were hydrolyzed for 15 min at pH 9.0 and 25° by pH-stat titration against 0.2 *M* NaOH. The solutions were then neutralized to pH 5–6 with 3 *M* HCl, diluted to *ca.* 100 ml with water, sorbed on to an H^+-form resin, and eluted with 1 *M* NH_4Cl or 1 *M* HCl. The Co concentrations of the eluate fractions were determined by atomic absorption spectroscopy and/or visible spectrophotometry using known extinction coefficients.[4]

(B) Separation and Measurement of Optical Retention in the Products of Base Hydrolysis. $(-)_{589}$-*cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ (0.2983 g, $[\alpha]_{589}$ −116°) in water (20 ml) was hydrolyzed for 15 min at pH 9.0 by pH-stat titration. The solution was quenched to pH 3, diluted, sorbed on to an H^+-form resin, and eluted with 1 *M* and then 2 *M* HCl. The first eluted band (2+, orange, [Co] = 2.77 × 10^{-3} *M*, 100 ml of solution) gave α_{589} −0.240°, whence $[M]_{589}$ −866°. The second eluted band (3+, orange, [Co] = 3.35 × 10^{-3} *M*, 50 ml of solution) gave α_{589} −0.276°, whence $[M]_{589}$ −824°.

In a second experiment, $(-)_{589}$-*cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ (0.2994 g, $[\alpha]_{589}$ −116°) was dissolved in water (25 ml) and 0.2 *M* NaOH (25 ml) was rapidly added to the vigorously stirred solution. The reaction was immediately (*ca.* 1 sec) quenched by adding 5 ml of 12 *M* HCl. After dilution, the mixture was sorbed and eluted from an H^+-form resin, as described above. The first eluted band (2+, [Co] = 3.52 × 10^{-3} *M*, 100 ml) gave α_{589} −0.343°, whence $[M]_{589}$ −974°. The second eluted band (3+, orange, [Co] = 2.19 × 10^{-3} *M*, 100 ml) gave α_{589} −0.191°, whence $[M]_{589}$ −872°.

(C) Azide Competition. *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ (0.30 g) in water (20 ml, 0.9 *M* in NaN_3) was hydrolyzed for 15 min at pH 9.0, 25° by pH-stat titration against 0.2 *M* NaOH. The solution was then neutralized to pH 4 with 3 *M* HCl, diluted to *ca.* 100 ml, sorbed on to an H^+-form resin, and eluted with 1 *M* $NaClO_4$. Four bands separated, and their eluates were examined spectrophotometrically.

Kinetic Measurements. Base hydrolysis of bromide was followed spectrophotometrically at 490 nm and 25° after rapid dissolution of a weighed quantity of complex in 0.2 *M* tris(hydroxymethyl)aminomethane (tris) buffer, μ = 1.0 ($NaClO_4$) at 25°.

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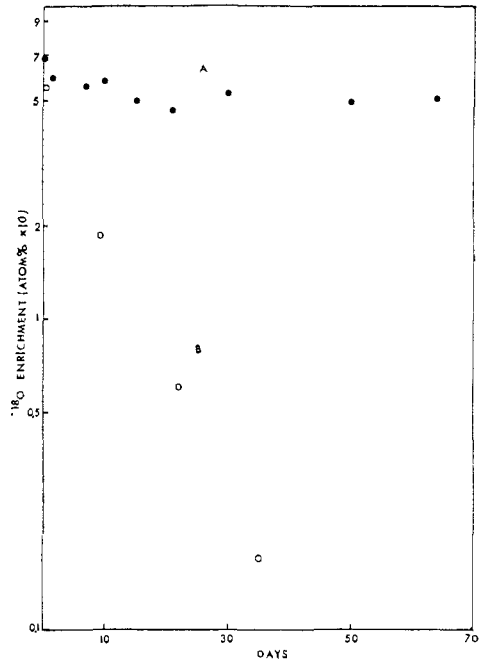


Figure 1. ^{18}O exchange in (A) $[Co(en)_2gly]^{2+}$ prepared by base hydrolysis of *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$ in ^{18}O-labeled water for 3 hr at pH 9.5, and in (B) $[Co(en)_2gly]^{2+}$ prepared by base hydrolysis of $[Co(en)_2(glyNH_2)]^{3+}$ in ^{18}O-labeled water for 24 hr at pH 9.0 (0.1 *M* H^+, $\mu = 1.0$, 25°).

using 1 *M* NH_4Cl or 1–2 *M* HCl eluents. For the reactions using *cis*-$[Co(en)_2Br(glyNHR)]Br_2$ complexes (R = H, CH_3) these species represented 90–100% of the reactant; for *cis*-$[Co(en)_2Br(glyN(CH_3)_2]Br_2$ they represented ~60%. For *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ a small amount of a brown material remained at the top of the ion-exchange columns (2–5%) and was not characterized; a similar material represented ~40% of the products from *cis*-$[Co(en)_2Br(glyN(CH_3)_2)]Br_2$. The isolated 2+ and 3+ products in base did not form any of this immobile material which must therefore result from reactions occurring before or during the course of bromide release. The same, or similar by-products, were observed for the hydrolysis of the related *cis*-$[Co(en)_2Cl(glyOR)]^{2+}$ ions.[2]

For *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$ quenched with acid after 15 min at pH 9.0 (pH-stat titration), 56% 2+ (λ_{max} 487 nm, ϵ 97) and 34% 3+ (λ_{max} 487 nm, ϵ 97) ions were recovered. The chromatographic behavior and visible spectrum of the 2+ ion were identical with those for authentic $[Co(en)_2gly]^{2+}$, and the correspondence was confirmed by the pmr spectrum of the product in dilute DCl. This pmr spectrum strongly suggested that the 2+ band did not contain the N,N-chelated imide species, $[Co(en)_2(NH_2CH_2CONH)]^{2+}$, since the analogous $[Co(NH_3)_4gly](ClO_4)_2$ and $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$[13] complexes were shown to be easily distinguished by their pmr spectra. The 3+ band had a visible spectrum and, additionally, chromatographic properties identical with those of the authentic N,O-chelated amide ion, $[Co(en)_2(glyNH_2)]^{3+}$.[4] Its rate of hydrolysis ($k_{obsd} = 2.6 \times 10^{-4}$ sec^{-1}, pH 9.0) at 25°, $\mu = 1.0$, also agreed with that of the authentic material, and the product of this reaction was identical with the 2+ species isolated from the ion-exchange column in the initial separation, *i.e.*, $[Co(en)_2gly]^{2+}$. In another experiment $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$ was hydrolyzed in 0.1 *M* NaOH for ~1 sec, and 58% $[Co(en)_2gly]^{2+}$ and 36% $[Co(en)_2(glyNH_2]^{3+}$ were recovered chromatographically.

Hydrolysis of *cis*-$[Co(en)_2Br(glyNHCH_3)]Br_2$ at pH 9.0 (pH-stat) for 15 min gave, following chromatography, 34% 2+ and 66% 3+ products. A similar experiment with *cis*-$[Co(en)_2Br(glyN(CH_3)_2)]Br_2$ gave 11% 2+ and 49% 3+ products. In both experiments the 2+ product was identified (visible spectra, chromatography) as $[Co(en)_2gly]^{2+}$ and the 3+ product as the chelated amide, $[Co(en)_2(glyNHCH_3)]^{3+}$ and $[Co(en)_2(glyN(CH_3)_2)]^{3+}$, respectively.

In the above experiments the reaction times were at least five half-lives for hydrolysis of coordinated Br^-, but were insufficient to result in substantial hydrolysis of the $[Co(en)_2(glyNR_1R_2)]^{3+}$ products. Assuming that the reaction proceeds entirely *via* the chelated amide through the two consecutive reactions

$$cis\text{-}[Co(en)_2Br(glyNH_2)]^{2+} + OH^- \xrightarrow{k_1} [Co(en)_2(glyNH_2)]^{3+} + Br^- + OH^-$$

$$[Co(en)_2(glyNH_2)]^{3+} + OH^- \xrightarrow{k_2} [Co(en)_2gly]^{2+} + NH_3$$

the amount of $[Co(en)_2gly]^{2+}$ produced after time t is given by $A_0[1 + 1/(k_1 - k_2)\{k_2e^{-k_1t} - k_1e^{-k_2t}\}]$, where A_0 is the initial concentration of *cis*-$[Co(en)_2Br(glyNH_2)]Br_2$.[14] Using the k_1, k_2, and t values given in Table II,[15] the amounts of $[Co(en)_2gly]^{2+}$ that would be formed by subsequent hydrolysis of the chelated amide were calculated (column 6). These values differ appreciably from the $[Co(en)_2gly]^{2+}$ actually observed, and for the experiment at pH 9 at least 54% $[Co(en)_2gly]^{2+}$ must be formed rapidly *via* a path not involving the chelated amide species (Table II, column 7). A similar analysis for the methyl- and dimethylamide compounds, Table II, requires all of the observed $[Co(en)_2gly]^{2+}$ to be formed by an alternative path.

(C) ^{18}O-Tracer Experiments. Table IIIA presents kinetic data for oxygen exchange in $[Co(en)_2gly]^{2+}$ isolated following complete base hydrolysis of $[Co(en)_2Br(glyNH_2)]^{2+}$. The hydrolysis was carried out in water of 2.0 atom% ^{18}O enrichment, and it is apparent that the isolated $[Co(en)_2gly]^{2+}$ ($t = 0$) contains at least 34% of the solvent enrichment. The discrepancy from 50% expected for incorporation of one solvent oxygen atom was also observed in the $[CoN_4gly]^{2+}$ products from the corresponding ester systems,[2,3,9] and is attributed to loss of label from the carbonyl position during recovery and recrystallization of the labeled $[Co(en)_2gly]I_2$.[2,3] Subsequent enrichments are given in Table IIIA and are plotted against time in Figure 1A. Extrapolation of the data at $t > 10$ days to zero time gives an intercept of ~0.5 atom%, or ~50% of the original complex enrichment, taken as one-half of the solvent value. Table IIIB gives data

(13) D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **91**, 3451 (1969).

(14) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 167.

(15) The k_1 values given in Table II are $2k_{obsd}$ for the same pH in Table I. The factor of 2 is used to adjust the rates of Table I to the lower ionic strength, $\mu = 0.1$, and is suggested by the twofold increase in the rate of base hydrolysis of Br^- in both *cis*-$[Co(en)_2Br(NH_3)]^{2+}$ and *cis*-$[Co(en)_2Br(glyOC_3H_7)]^{2+}$ on a similar reduction in ionic strength.[2] However, base hydrolysis in the $[Co(en)_2(glyNR_1R_2)]^{3+}$ ions has been shown to be independent of ionic strength in the range 1.0–0.1.[4]

Table III. Kinetic Data for Oxygen Exchange between Water and the Oxygen of $[Co(en)_2gly]^{2+}$ Recovered from Basic Solution[a]

Days	Atom % ^{18}O[b]
(A)[c] $H_2{}^{18}O$ + *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$	
0	0.685
0	0.684
7	0.557
10	0.574
15	0.494
21	0.467
30	0.527
50	0.497
64	0.509
(B)[d] $H_2{}^{18}O$ + $[Co(en)_2(glyNH_2)]^{3+}$	
0	0.559
9	0.185
22	0.060
34	0.017

[a] $[H^+]$ = 0.1, μ = 1.0 ($NaClO_4$), 25°, $[Co(en)_2gly]^{2+}$ ~0.1 *M*. [b] Represents the ^{18}O enrichment in atom %, less the atom % of ^{18}O in CO_2 of normal isotopic composition (0.201). Atom % of $^{18}O = 100R/(2 + R)$, where $R = [46/([45] + [44])$. [c] $H_2{}^{18}O$ solution enriched by 2.0 atom % ^{18}O. [d] $H_2{}^{18}O$ solution enriched by 1.3 atom % ^{18}O.

for the kinetics of oxygen exchange in $[Co(en)_2gly]^{2+}$ isolated from base hydrolysis of $[Co(en)_2(glyNH_2)]^{3+}$ in water of 1.3 atom % ^{18}O enrichment. The initial enrichment (t = 0) is 43% of the solvent value, indicating incorporation of close to one oxygen atom from the solvent; the discrepancy from 50% is again attributed to loss of label during recovery and recrystallization. Subsequent enrichments are given in Tabel IIIB and plotted against time in Figure 1B. It is apparent that the oxygen label is completely exchanging at a single rate, 1.3×10^{-6} sec^{-1}.

(D) Hydrolysis of $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$. When subjected to Hg^{2+}-induced bromide removal in acid solution, $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$ gave the 3+ species exclusively, $[M]_{589}$ −1662°; this value was virtually unchanged after sorption to and elution from an H^+-form resin, $[M]_{589}$ −1679°. Hydrolysis of this product at pH 9 produced a 2+ species exclusively, $[M]_{589}$ −1550°. This rotation, when compared with that for optically pure $(-)_{589}$-$[Co(en)_2gly]^{2+}$, $[M]_{589}$ −1546° in water,[11] gives an independent check on the optical purity of $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$, and also establishes that both the Hg^{2+}-induced removal of Br^- in acid solution and the alkaline hydrolysis of $(-)_{589}$-$[Co(en)_2(glyNH_2)]^{3+}$ proceed with full retention of configuration.

$$(-)_{589}\text{-}[Co(en)_2Br(glyNH_2)]^{2+} + Hg^{2+} \longrightarrow (-)_{589}\text{-}[Co(en)_2(glyNH_2)]^{3+} + HgBr^+ \quad ([M]_{589} -1662°)$$

$$(-)_{589}\text{-}[Co(en)_2(glyNH_2)]^{3+} + OH^- \longrightarrow (-)_{589}\text{-}[Co(en)_2gly]^{2+} + NH_3 \quad ([M]_{589} -1662°) \quad ([M]_{589} -1550°)$$

Using the above $[M]_{589}$ values for $(-)_{589}$-$[Co(en)_2(glyNH_2)]^{3+}$ and $(-)_{589}$-$[Co(en)_2gly]^{2+}$, and also the result that ion-exchange chromatography does not affect the optical purity, the retention of activity in the products of base hydrolysis of $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]Br_2$ was examined. Following hydrolysis at pH 9 for 15 min, the 2+ band ($[Co(en)_2gly]^{2+}$) gave $[M]_{589}$ −866°, 56% retention; the 3+ band ($[Co(en)_2(glyNH_2)]^{3+}$) gave $[M]_{589}$ −824°, 49% retention. During hydrolysis, some 8% of the product $[Co(en)_2gly]^{2+}$ results from hydrolysis of the chelated amide $[Co(en)_2(glyNH_2)]^{3+}$, Table II. Since this occurs with full retention of configuration, the corrected value for retention of activity in the $[Co(en)_2gly]^{2+}$ produced by the path not involving hydrolysis of $[Co(en)_2(glyNH_2)]^{3+}$ is 57%.

When $(-)_{589}$-$[Co(en)_2Br(glyNH_2)]^{2+}$ was hydrolyzed at pH 13.0 for 1 sec, the 2+ band ($[Co(en_2)gly]^{2+}$) gave $[M]_{589}$ −974°, 63% retention, and the 3+ band ($[Co(en)_2(glyNH_2)]^{3+}$) gave $[M]_{589}$ −872°, 52% retention.

(E) Azide Competition. The products from the base hydrolysis of *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$ at pH 9.0 in 0.9 *M* NaN_3, μ = 1.0, were, in order of elution from an H^+-form resin: *trans*-$[Co(en)_2(N_3)_2]^+$ (λ_{max} 560 nm, ~11%, using ϵ_{560} 335),[16] *cis*-$[Co(en)_2N_3(glyNH_2)]^{2+}$ (λ_{max} 505 nm, 16%), $[Co(en)_2gly]^{2+}$ (λ_{max} 487 nm, 43%), and $[Co(en)_2(glyNH_2)]^{3+}$ (λ_{max} 487 nm, 24%). The second eluate band was assigned to *cis*-$[Co(en)_2N_3(glyNH_2)]^{2+}$ on the basis of its absorption spectrum and from the observation that it formed $[Co(en)_2(glyNH_2)]^{3+}$ rapidly on treatment with HNO_2 in acid solution. The *cis*-$[Co(en)_2N_3(glyOC(CH_3)_3)]^{2+}$ ion gave $[Co(en)_2(gly)]^{2+}$ on similar treatment with HNO_2, whereas the *cis*-$[Co(en)_2N_3(glyO)]^+$ ion elutes as a 1+ ion under the same conditions.[2]

Discussion

The following discussion is confined to the paths leading to the formation of $[Co(en)_2gly]^{2+}$. The sections deal with loss of Br^- and order of events, the intervention of solvent during the course of the reaction, and the relative rates of the inter- and intramolecular hydrolysis reactions.

Loss of Br^- and Order of Events. All three *cis*-$[Co(en)_2Br(glyNR_1R_2)]^{2+}$ ions show similar rates for loss of Br^- (~260 M^{-1} sec^{-1}, Table I), and the rate law $v_{substrate} = k[Co][OH^-]$ is obeyed. The same rate law is found for a wide variety of related acidopentaaminecobalt(III) complexes,[17,18] and substantial evidence exists to support an SN1CB mechanism for the release of halide in these systems.[17,19-22] The incorporation of N_3^- during hydrolysis of *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$, to form $[Co(en)_2N_3(glyNH_2)]^{2+}$, supports the existence of an intermediate of reduced coordination number which competes for other species in solution.

$$cis\text{-}[Co(en)_2Br(glyNR_1R_2)]^{2+} + OH^- \overset{fast}{\rightleftharpoons} cis\text{-}[Co(en)(en\text{-}H)Br(glyNR_1R_2)]^+ + H_2O$$

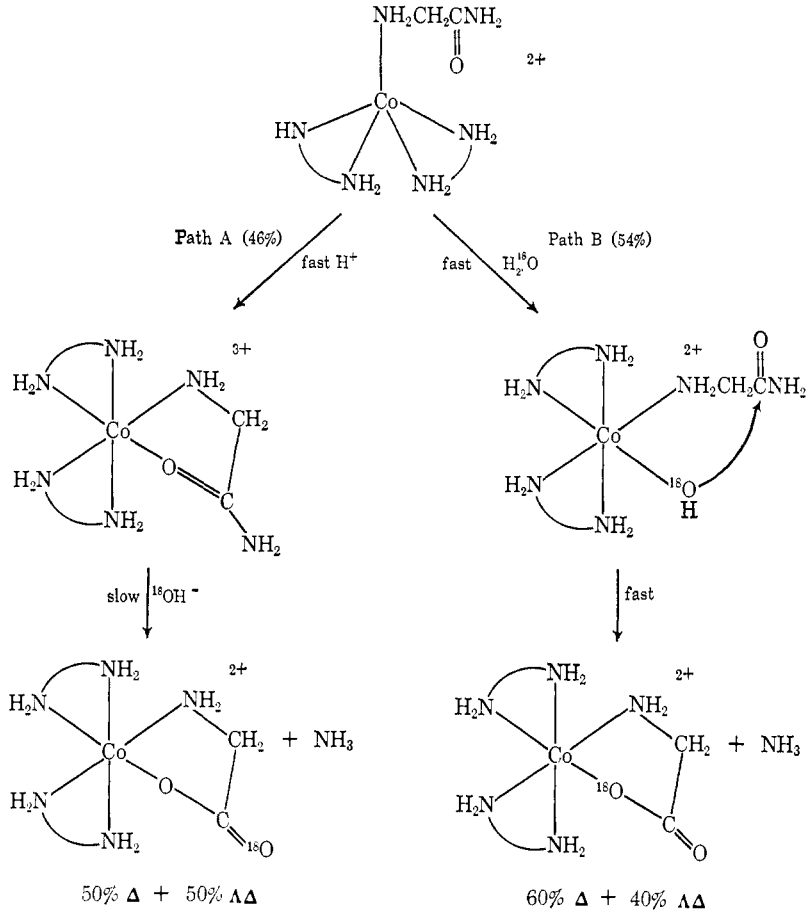
$$cis\text{-}[Co(en)(en\text{-}H)Br(glyNR_1R_2)]^+ \xrightarrow{k'\text{slow}\ (kK_b)} [Co(en)(en\text{-}H)(glyNR_1R_2)]^{2+} + Br^- \quad \text{(five-coordinate)}$$

$$[Co(en)(en\text{-}H)(glyNR_1R_2)]^{2+} \xrightarrow{fast} \text{products}$$

Also, the absence of *cis*-$[Co(en)_2N_3(glyO)]^+$ in this experiment implies that hydrolysis of the monodentate amide does not occur before or during loss of Br^-.

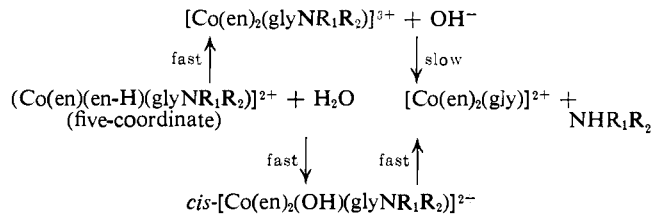
(16) P. J. Staples and M. L. Tobe, *J. Chem. Soc.*, 4803 (1960).
(17) F. Basolo and R. G. Pearson in "Mechanisms of Inorganic Reactions," 2nd ed, Wiley, New York, N. Y., 1967, p 124 ff.
(18) D. A. Buckingham, C. E. Davis, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **92**, 6159 (1970).
(19) M. Green and H. Taube, *Inorg. Chem.*, **2**, 948 (1963).
(20) D. A. Buckingham, I. I. Olsen, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **88**, 5443 (1966); **89**, 5129 (1967); **90**, 6654 (1968).
(21) C. K. Poon and M. L. Tobe, *Chem. Commun.*, 156 (1968).
(22) M. L. Tobe, *Accounts Chem. Res.*, in press.

Scheme I



The *cis*- and *trans*-$[Co(en)_2N_3(glyO)]^+$ ions have been prepared independently in a related study on the hydrolysis of $[Co(en)_2X(glyO)]^+$ species (X = Cl, Br),[23] and they are easily distinguished chromatographically from more highly charged $[Co(en)_2N_3(glyNH_2)]^{2+}$ ions. In the similar hydrolysis of *cis*-$[Co(en)_2Br(glyOCH)(CH_3)_2]^{2+}$, it was concluded that isopropyl alcohol was produced following loss of Br^-.[2] This result is consistent with the above analysis. The properties of the $[Co(en)_2N_3(glyNH_2)]^{2+}$ ions imply that hydrolysis of the monodentate amide in such complexes is a slow process.

Following loss of Br^- the five-coordinate intermediate competes for adjacent nucleophiles. Competition by water results in the hydroxoamide, while entry of the carbonyl oxygen of the monodentate amide forms the chelated N,O species $[Co(en)_2(glyNR_1R_2)]^{3+}$. The ^{18}O-tracer studies indicate that these two processes contribute about equally, and when the observed amounts of $[Co(en)_2(glyNH_2)]^{3+}$ and $[Co(en)_2(gly)]^{2+}$ from *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$ are corrected for the small amount of hydrolysis in the former ion during removal of Br^-, product analysis shows that the paths contribute 46% and 54% to the overall formation of $[Co(en)_2(glyNH_2)]^{3+}$ and $[Co(en)_2gly]^{2+}$, respectively (Table II). For the substituted-amide complexes, these proportions differ: 66% $[Co(en)_2(glyNH(CH_3))]^{3+}$, 34% $[Co(en)_2(gly)]^{2+}$, and 82% $[Co(en)_2(glyN(CH_3)_2)]^{3+}$, 18% $[Co(en)_2gly]^{2+}$. The pH independence of the product ratio is consistent with water and amide oxygen competition for the five-coordinate intermediate, and the $[Co(en)_2gly]^{2+}$ product is attributed to that path incorporating the hydroxoamide intermediate, *cis*-$[Co(en)_2(OH)(glyNR_1R_2)]^{2+}$.



It is of interest to note that methyl substitution results in an almost linear reduction in the hydroxoamide path; this is consistent with increased steric crowding by the amide group in the transition state, restricting *cis* entry of water.

^{18}O-Tracer Studies and Mechanism. Tracer studies following complete hydrolysis of *cis*-$[Co(en)_2Br(glyNH_2)]^{2+}$ in $H_2{}^{18}O$ demonstrate that approaching one solvent oxygen atom is incorporated in the $[Co(en)_2gly]^{2+}$ product, and that approximately half of this oxygen label is inert to exchange in 0.1 *M* $HClO_4$. By way of contrast, the N,O-chelated amide complex, $[Co(en)_2(glyNH_2)]^{3+}$, shows one rate of exchange in the $[Co(en)_2gly]^{2+}$ product formed on hydrolysis in $H_2{}^{18}O$, Figure 1B. Since the product analysis experiments demonstrate that some 46% $[Co(en)_2(glyNH_2)]^{3+}$ is formed during the former hydrolysis reaction, the firmly attached oxygen label must arise *via* the alternative hydroxo amide intermediate. The $[Co(en)_2gly]^{2+}$ ion has previously been shown to incur no scrambling of label under the present conditions of hydrolysis and recovery.[2]

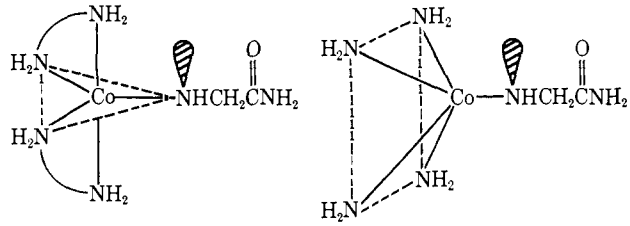
(23) D. A. Buckingham, D. M. Foster, A. M. Sargeson, and L. G. Warner, unpublished results.

The kinetically dissimilar oxygen atoms in $[Co(en)_2gly]^{2+}$ have previously been attributed[2] to the Co—O and >C=O moieties; that oxygen resistant to exchange in 0.1 *M* H^+ at 25° was attributed to the Co—O oxygen, and that with $k \sim 10^{-6}$ sec^{-1} at 25° to the carbonyl oxygen atom. The same analysis here requires *the path proceeding via the chelated amide intermediate to result in exclusive >C=O label and the path via the hydroxoamide intermediate to result in label exclusively in the Co—O position.* The former path therefore involves intermolecular attack of solvent OH^- at the cobalt(III) activated carbonyl carbon without opening of the chelate ring, and the latter path involves intramolecular attack of coordinated OH^- at the carbonyl carbon of the monodentate amide. This analysis is shown in the proposed mechanism (Scheme I) for decay of the five-coordinate deprotonated intermediate of Δ configuration.

It is of interest to note that the contribution of the two paths to hydrolysis is similar for glycine isopropyl ester[2] and glycine amide, ~50% each, implying similar competition between water and carbonyl oxygen in the intermediate. This correspondence may be extended to include the monodentate glycinate anion[23] and monodentate ethanolamine;[18] however, the correlation collapses when the amide nitrogen atom is substituted, Table II.

It is also pertinent that the amide nitrogen atom does not compete effectively with the carbonyl oxygen for the vacated site in the five-coordinate intermediate. Both products would involve five-membered chelate rings, and the N,N-bound isomer is certainly stable to subsequent reaction under the conditions, once formed.[13] Also, both the N- and O-bound isomers of monodentate formamide in $[Co(NH_3)_5(NH_2CHO)]^{3+}$ are known, although they are prepared from neutral nonaqueous solution.[24] The present result is not surprising when it is considered (1) that carbonyl oxygen is more basic than amide nitrogen in organic amides and (2) that the N,N product expected from amide nitrogen competition is deprotonated at this nitrogen, and the most basic center in this complex ion is the carbonyl oxygen.[13] These results, and other studies carried out in these laboratories,[25] suggest that amide nitrogen competition in aqueous solution occurs only under strongly basic conditions where some amide anion exists, and where the kinetically preferred O-bonded product is susceptible to base-catalyzed dissociation.[4]

The stereochemical results require that some racemization accompanies both paths, with 75 ± 2% retention of configuration *via* the chelated amide (path A), and 80 ± 2% retention *via* the hydroxoamide (path B). Similar values were obtained at pH 9 and 13, suggesting pH independence over this range. Other results on closely related ions[20] have been interpreted in terms of a single kinetically significant deprotonated reactant and five-coordinate intermediate, and the fact that in the present example only *cis* coordination by the amide carbonyl group can obtain the retention value implies that the five-coordinate intermediate cannot be of a symmetrical form involving deprotonated glycine amide.



A similar result is implied by the results for path B, and it is suggested that only the *cis*-hydroxoamide results in $[Co(en)_2gly]^{2+}$. This analysis is consistent with the slightly larger retention value found for the hydroxoamide path, and we tentatively propose that the small amounts (2–5%) of brown material found on the ion-exchange column may result from subsequent reactions of the *trans*-$[Co(en)_2(OH)(glyNH_2)]^{2+}$ ion. In support of this aspect of the mechanism it is found that the related *trans*-$[Co(en)_2(OH)(glyO)]^+$ ion does not rapidly[19] generate $[Co(en)_2gly]^{2+}$, and *trans–cis* isomerization in $[Co(en)_2(OH)NH_3]^{2+}$ is a very slow process.[26] The property of an inbuilt nucleophile to compete with the solvent or added anions for coordination is a sensitive method for investigating the stereochemical and electrophilic properties of reactive coordinately unsaturated intermediates. This aspect of the present study is being further investigated and results pertaining to these problems will be reported in a subsequent paper.

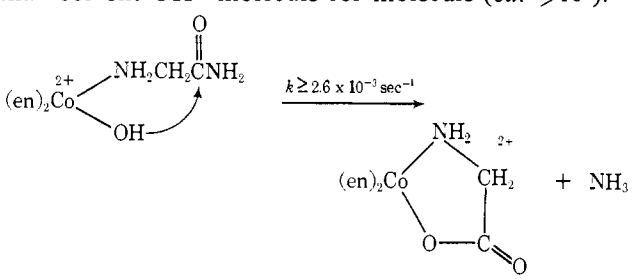
The proposed mechanism for hydrolysis is similar to that favored for hydrolysis of the $[Co(en)_2X(glyOR)]^{2+}$ ions, X = Cl, Br.[2] In the latter study possible mechanisms involving hydroxide attack on the monodentate ester either before or after Br^- removal could not be rigorously excluded, since it was not possible to isolate the two paths. In the present instance such possibilities are excluded. Similarly, the possibility of duality of mechanism, with synergic SN2 displacement of Br^- by carbonyl oxygen, accompanying SN1CB entry of water is unlikely, since this would imply either 100% retention or inversion of configuration in the $[Co(en)_2gly]^{2+}$ product formed *via* the former path.

Relative Rates of Inter- and Intramolecular Hydrolysis. The significance of the coordinated nucleophile in facilitating hydrolysis of monodentate glycine esters has previously been demonstrated for NH_2^- [13] and OH^-.[2,3] A similar large rate enhancement for NHR^- and OH^- lysis at a saturated carbon center has been observed.[18] The present study extends these results to neighboring-group effects in amide hydrolysis.

The bimolecular rate constant for base hydrolysis of monodentate Co(III)-bound glycine amide in $[(NH_3)_5Co(glyNH_2)]^{3+}$ is unknown. However, if the influence of the cobalt(III) center is similar to the 80-fold enhancement found for N-bound monodentate glycine ethyl ester,[13] then the former value may be estimated at ~0.2 M^{-1} sec^{-1}.[27] Direct activation of the carbonyl center in the chelated amide complex $[Co(en)_2(glyNH_2)]^{3+}$ results in significant additional activation. Hydrolysis presumably occurs by bimolecular attack of OH^- at the carbonyl carbon with a rate constant of 25 M^{-1} sec^{-1};[4] this represents a rate enhancement of 10^4 over the uncoordinated molecule.

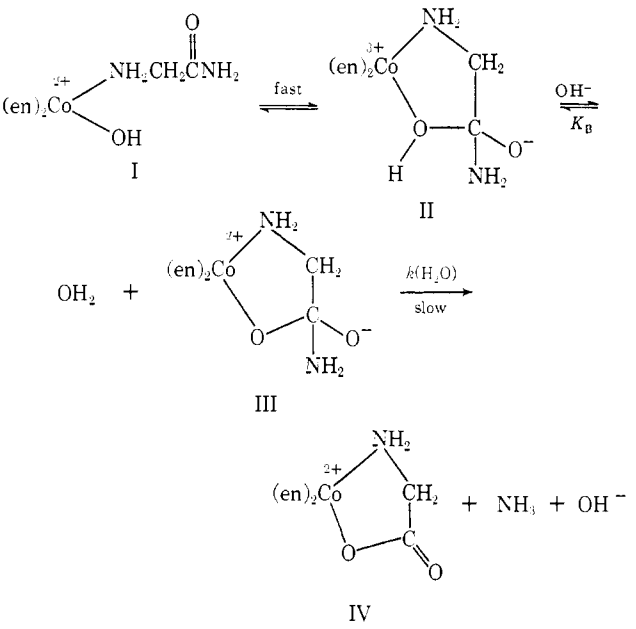
(24) R. J. Balahura and R. B. Jordan, *J. Amer. Chem. Soc.*, **92**, 1533 (1970).
(25) D. M. Foster, unpublished results.
(26) D. F. Martin and M. L. Tobe, *J. Chem. Soc.*, 1388 (1962).
(27) The bimolecular rate constant for glycinamide hydrolysis at 25°, μ = 0.1, is 2.2×10^{-3} M^{-1} sec^{-1}: H. L. Conley and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).

The present study demonstrates that amide hydrolysis *via* coordinated OH^- is rapid. The product analysis results demonstrate that this must be at least as fast as removal of Br^- at pH 9 (2.6×10^{-3} sec^{-1}) and pH 13 (26 sec^{-1}), and the failure to observe any $[Co(en)_2(OH)(glyNH_2)]^{2+}$ at the isosbestic point for Br^- removal suggests that internal hydrolysis is considerably faster than this. The similar $[Co(en)_2(OH)(glyO)]^+$ ion, formed in ~50% yield on hydrolysis of *cis*-$[Co(en)_2Br(glyO)]$,$^+$ is easily distinguished from $[Co(en)_2gly]^{2+}$ and $[Co(en)_2(glyNH_2)]^{3+}$ at the isosbestic point for bromide removal.[21] Also, the *cis*-$[Co(en)_2X(glyNH_2)]^{2+}$ and *cis*-$[Co(en)_2X(glyO)]^+$ ions (X = Cl, Br) have almost identical spectra between 350 and 650 nm, and this correspondence is likely to extend to the hydroxo ions, X = OH^-. On the basis of these similarities, we estimate that the inability to detect any hydroxoamide species implies that hydrolysis in this ion is faster by at least a factor of 10 than loss of Br^-. If hydrolysis were pH independent, as would be implied by rate-determining attack of bound hydroxide,[18] then the results in 1 *M* NaOH require the rate constant for intramolecular amide hydrolysis, *k*, to be at least 2.6×10^3 sec^{-1}, which at pH 9 corresponds to rate enhancements over the chelated and uncoordinated substrates of $\geq 10^7$ and $\geq 10^{11}$, respectively. Two factors are striking if this mechanism holds: (1) the rate of hydrolysis will be maintained at biological pH's, since the complex will still exist essentially in the hydroxo form ($pK_a \sim 6$); and (2) that despite the greatly reduced basic character of coordinated OH^- ($\sim 10^8$), it is apparently a much more efficient nucleophile than solvent OH^- molecule for molecule (*ca.* $\geq 10^9$).



Alternatively, if attack of coordinated OH^- were not rate controlling, a rate law first order in base is likely. This situation, which obtains for intramolecular lysis of glycine ethyl ester by coordinated NH_2^-,[13] would result from rate-determining loss of NH_3 from the deprotonated amino-diol intermediate (see I → IV). This mechanism would require an overall rate constant of at least 10^4 M^{-1} sec^{-1}, which is larger by a factor of $\sim 10^3$ than that for hydrolysis in the Co(III) chelated ion, and larger by a factor of 10^7 than the second-order rate constant for hydrolysis in the organic molecule.

Concluding Remarks. The remarkable facility of cobalt(III) in inducing hydrolysis of amino acid esters and amides is sufficiently dramatic to have relevance to metal-ion-catalyzed hydrolysis of these and similar substrates in biological systems. The present results demonstrate that the cobalt(III)-induced intramolecular hydrolysis reaction is at least 10^7, and possibly more than 10^{11}, times faster than the uncatalyzed reaction, and that this mechanism provides a pathway for hydrolysis which is decidedly more efficient than that provided by direct metal-ion polarization of the carbonyl function. Other discussion[28] suggests that divalent metal ions compare favorably with Co(III) in promoting hydrolysis in model systems, and we believe that there is no chemical reason to prevent many divalent metal ions behaving by mechanisms similar to those delineated here. Thus, provided amide nitrogen can be prevented from coordinating, and provided coordinated water is sufficiently acidic to exist in the hydroxo form, the present experiments suggest that divalent metal ions or aquo complexes containing one or more coordinated water molecules might well hydrolyze amide or ester linkages *via* an intramolecular process. This conclusion may have relevance to the action of divalent-metal-ion catalysis in the various hydrolytic enzymes. For instance in Zn^{2+}-activated bovine carboxypeptidase A, an enzyme of current topical interest, two mechanisms consistent with crystallographic studies[29,30] and the kinetic studies[31] are (1) the Zn–carbonyl mechanism,[32] in which a coordinated water molecule is displaced by the carbonyl oxygen of the peptide, resulting in activation of the carbonyl group toward nucleophilic attack; and (2) the Zn–hydroxide mechanism, in which Zn^{2+} increases the "availability" of bound OH^-. Davis[33] has proposed a similar Zn–hydroxide mechanism for the zinc metalloenzyme carbonic anhydrase. The present study offers a direct appraisal of the relative efficacies of the metal-ion promoted "carbonyl" and "hydroxide" mechanisms, and suggests that the latter path is far more efficient.



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