910; ^{1}H NMR (CCl_4) δ 1.40 (3 H, s), 2.30 (2 H, d, J = 7 Hz), 4.80–5.20 and 5.56–6.04 (4 H and 2 H, allyl H); m/e (M^+) 112. 1-Phenyl-1,5-hexadien-3-ol:[72] bp 70 °C (1mmHg); IR (cm^{-1}, CCl_4) 3300, 1640, 1600, 995, 960, 910; ^{1}H NMR (CCl_4) δ 2.35 (2 H, t, J = 7 Hz), 2.40 (1 H, b s, OH), 4.95–5.20 and 5.60–6.00 (2 H and 1 H, allyl H), 6.20 (1 H, dd, J = 7 and 16 Hz), 6.35 (1 H, d, J = 16 Hz), 4.25–4.50 (1 H, m), 7.10–7.40 (5 H, m); m/e (M^+) 174. An authentic sample was prepared from the reaction of **18** with cinnamaldehyde.[7c,72]

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Intramolecular Lactonization at a Metal Center. The Rapid Reactions of Coordinated H_2O and OH^- with an Adjacent Carboxylic Acid Residue

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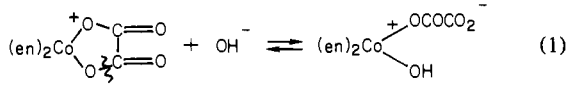
Abstract: ^{18}O-tracer studies show that cyclization of *cis*-$[Co(en)_2(OH_2)(glyOH)]^{3+}$ and *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ (glyOH = N-bound glycine; glyO = N-bound glycinate) to give $[Co(en)_2(glyO)]^{2+}$ containing chelated glycinate occur intramolecularly without displacement of coordinated water. The rates of these reactions are relatively fast with $t_{1/2} \simeq 40$ s at pH 0–1 and $t_{1/2} \simeq 400$ s at pH 4; the overall rate law takes the form $k_{obsd} = (k_H[H^+]^2 + k_H'K_1[H^+] + k_{OH}K_1K_2)/(K_1K_2 + k_1[H^+] + [H^+]^2)$ with $k_H = 1.9 \times 10^{-2}$ s^{-1}, $k_H' = 1.05 \times 10^{-3}$ s^{-1}, $k_{OH} = 1.74 \times 10^{-5}$ s^{-1}, $pK_1 = 2.3$, $pK_2 = 6.3$ at 25.0 °C, and μ = 1.0 ($NaClO_4$). The reaction of the *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ ion is catalyzed by general acids (including H_3O^+), and this is interpreted in terms of rate-determining protonation of an intermediate cyclic species. Cyclization in the *cis*-$[Co(en)_2(OH)(glyO)]^+$ ion is considerably slower ($t_{1/2} \simeq 10$ h) and is not catalyzed by monofunctional buffers. Comparisons with O exchange in glycine show large accelerations for the metal-based system (10^7–10^{12} M), and the rates compare favorably with those found for intramolecular lactone formation in purely organic molecules.

Esterification of carboxylic acids R–COO(H) by alcoholic species R′–OH is normally slow in the absence of additional activation or specific coupling reagents.[1] However, by employing the entropic advantages of the intramolecular situation[2] and by using substituents which produce ground state strain,[3,4] ester formation (or lactone formation in the intramolecular case) can be enhanced by factors of up to 10^{15}.[5]

When the alcoholic function involves a metal hydroxide M–OH, the simple bimolecular esterification of carboxylic acids is unknown. Metal hydroxides only add to activated carbonyl functions (e.g., CO_2[6]) or displace "good" leaving groups such as in their reactions with anhydrides,[7] acetylacetone,[8] and the reactive esters 2,4-DNPA and 4-NPA.[9] However, when the process is made intramolecular by incorporating the metal hydroxide and substrate in the same molecule, large increases in rate are again realized. Normal alkyl esters, nitriles, amides, and even peptide fragments can now be readily hydrolyzed.[9]

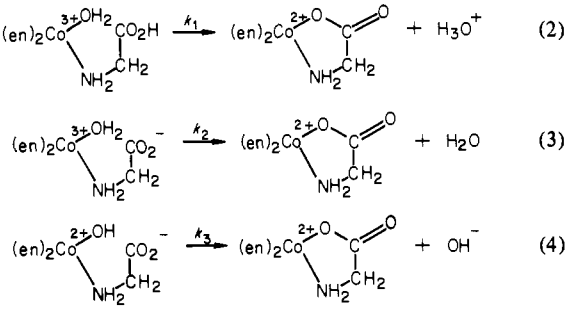
This leads to the possibility of metal esterification of carboxylic acids via the intramolecular process. Although unknown, there are good precedents for this; the reverse of the base-catalyzed ring opening of oxalate in $[Co(en)_2C_2O_4]^+$[10] is a required example (eq 1) and other likely candidates include cyclization in [Co-



(1)

$(EDTA)(OH/H_2O)]^{2-/1-}$[11,12] and $[Co(en)_2(OH_2)(C_2O_4)]^{1+}$[13] without cleavage of the metal–oxygen bond.

In this paper we describe the first clear examples of this type of process; the cyclization of N-bound glycine in the *cis*-$[Co(en)_2(OH_2/OH)(glyO/H)]^{3+/2+/1+}$ species. Depending on pH this occurs via the addition of coordinated water or coordinated hydroxide to the carboxylic acid function (reactions 2–4) with the



(2)

(3)

(4)

coordination sphere about the metal remaining intact. These processes can be considered as adjuncts to the H^+- and OH^--catalyzed exchange of oxygen atoms in the $[Co(en)_2(glyO)]^{2+}$

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(1) The estimated rate constant for attack of phenol on acetic acid in a mol dm^{-3} H^+ is 10^{-10} mol^{-1} dm^3 s^{-1} at 25 °C: Milstein, S.; Cohen, L. A. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1143.
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product of reactions 2–4, as described previously,[14] and the two studies allow the entire process of chelation, ring opening, and O exchange to be described in some detail.

Perhaps the most remarkable feature of this work is the discovery that coordinated water (eq 2 and 3) can add very rapidly and that its reaction with the carboxylate function (eq 3) can be catalyzed by general acids. Thus the addition of Co–OH_2 is more efficient than addition of the more nucleophilic Co–OH species, and this leads to an entirely new concept in the esterification of carboxylic acids. For biological substrates (carboxylates, phosphates) it introduces new routes for metal-promoted reactions and from this point alone warrants further exploration.

Experimental Section

Preparation of Complexes. *cis*-$[Co(en)_2X(glyOCH_3)]X_2$ (X = Cl, Br) was prepared as described by Alexander and Busch.[15] For X = Br the complex was resolved into its optical enantiomers as described previously.[16] *cis*-$[Co(en)_2Br(glyOH)]Br_2$ (or $(ClO_4)_2$) was prepared from the ester as detailed recently.[17] The optically pure forms Δ- and Λ-$[Co(en)_2Br(glyOH)]Br_2$ were similarly prepared.

$[Co(en)_2(glyO)]^{2+}$ was prepared from *trans*-$[Co(en)_2Cl_2]Cl$, glycine, and KOH[15] and purified by using Dowex 50W-X2 cation exchange using 1–3 mol dm^{-3} HCl as eluant. The recovered complex was recrystallized from warm water by slow addition of methanol and cooling to 0 °C. $[Co(en)_2(glyO)]Cl_2 \cdot H_2O$ was washed with methanol and air-dried.

Anal. Calcd: C, 21.1; H, 6.5; N, 20.5. Found: C, 21.4; H, 6.5; N, 20.2. The optically pure forms Δ- and Λ-$[Co(en)_2(glyO)]I_2$ were obtained as described previously:[18] $[M]_{589} = \mp 1580°$, $[M]_{546} = \mp 3300°$, $[M]_{473} = \pm 5900°$.

cis- and *trans*-$[Co(en)_2OH(glyO)]^+$ was obtained by alkaline hydrolysis of *cis*-$[Co(en)_2Br(glyOH)]Br_2$ (pH 9–10) and removing unwanted $[Co(en)_2(glyO)]^{2+}$ (~46%) by chromatography on SP-Sephadex C25 resin at 0 °C (0.2 mol dm^{-3} $NaClO_4$, pH 10).[17] The 1+ band was adjusted to $\mu = 1.0$ ($NaClO_4$), flushed with N_2, and kept at ca. 0 °C. Aliquots were withdrawn for kinetic runs as required.

Rate Data. Kinetic data were obtained spectrophotometrically by using a Cary 16K spectrophotometer fitted with a thermostated cell (3.2-cm path length) which allowed for pH-stat control (±0.02) and for N_2 flushing.[19] pH was controlled by using a PHM62 pH meter together with a Radiometer ABU 12 autoburette, REA titragraph, and TTT 60 titrator. The calomel electrode was protected with a $NaNO_3$ (0.2 mol dm^{-3})/NH_4NO_3 (1.6 mol dm^{-3}) salt bridge. Freshly prepared buffer solutions, or HCl or NaOH (1.0 mol dm^{-3}), were added by injection. For runs at pHs >10 the rate was followed by withdrawing aliquots at various times and determining the products by ion-exchange chromatography (Dowex 50W-X2, 1.0 mol dm^{-3} $NaClO_4$, pH 8). Co concentrations were measured by AA spectroscopy. In the presence of buffers the reactions were followed at 485 nm and otherwise at 315, 350, and 485 nm.

Some rates were measured polarimetrically at 480 nm by using a Perkin-Elmer P22 polarimeter and a thermostated 1-dm cell.

Reaction Products. $[Co(en)_2(glyO)]^{2+}$ was recovered by ion-exchange chromatography (Dowex 50W-X2, Na^+ form, NaCl then HCl eluant, 1–3 mol dm^{-3}) and crystallized as $[Co(en)_2(glyO)]I_2$ for identification purposes. The existence of *trans*-$[Co(en)_2(OH)(glyO)]^+$ in the reactant solution was established by following reactions at pHs <6 by its separation as a 1+ ion from $[Co(en)_2(glyO)]^{2+}$ using ion-exchange chromatography (Dowex 50W-X2, Na^+ form, pH ~11, 0.5–1.0 mol dm^{-3} $NaClO_4$). Details of this are given in ref 17. The optical purity of the product was compared with that of optically pure Λ-$[Co(en)_2(glyO)]I_2$ (see above), at 589 and 473 nm.

Acidity Constants. pK_1 for *cis*-$[Co(en)_2Br(glyOH)]^{2+}$ was measured by pH titration of a solution of *cis*-$[Co(en)_2Br(glyOH)]Br_2$ (1×10^{-2} mol dm^{-3}) in 1.0 mol dm^{-3} $NaClO_4$, 25.0 °C, using 0.5 mol dm^{-3} NaOH according to the method of Serjeant and Albert.[20] pK_2 for *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ was measured spectrophotometrically (490 nm) by titration of ca. 10^{-3} mol dm^{-3} solutions of *cis*-$[Co(en)_2(OH)(glyO)]^+$, 1.0 mol dm^{-3} in $NaClO_4$, with 1.0 mol dm^{-3} $HClO_4$. This titration was done quickly at pHs <6 to avoid complications arising from aqua products.

^{18}O-Tracer Experiments. A 5-g sample of *cis*-$[Co(en)_2Br(glyOH)]Br_2$ was suspended in 50 cm^3 $H_2{}^{18}O$ (Biorad 1.562 atom %) and hydrolyzed by pH-stat methods, pH 10.5–11.0 (30% wt/v NaOH solution); complete hydrolysis required 15 min. A sample (~1 cm^3) of the solution was taken for solvent enrichment analysis. The solution was diluted and adsorbed on, and then eluted from, Sephadex C25 exchange resin (Na^+ form) using 0.1 M $NaClO_4$, pH ~11. Excellent separation of *cis*- and *trans*-$[Co(en)_2OH(glyO)]^+$ from $[Co(en)_2(glyO)]^{2+}$ was achieved, and the band was recovered within 30 min (500 cm^3). This product was divided into four equal parts which were treated as follows: (1) added to 125 cm^3 of 0.1 mol dm^{-3} $HClO_4$, left for 10 min, diluted, and readsorbed on C25-exchange resin, and *trans*-$[Co(en)_2OH(glyO)]^+$ removed as before (the $[Co(en)_2(glyO)]^{2+}$ band was eluted with 0.5 mol dm^{-3} $NaClO_4$ (pH ~6) and recovered as the insoluble HgI_4^{2-} salt as described previously);[21] (2) added to 100 cm^3 of citrate (0.2 mol dm^{-3})/phosphate (0.1 mol dm^{-3}) buffer (pH 3.7), left for 10 min, and then treated as in 1; (3) pH-stated against 1.0 mol dm^{-3} $HClO_4$ at pH 4.0 for 10 min and then treated as in 1; (4) added to 100 cm^3 of phosphate (0.2 mol dm^{-3})/citrate (0.1 mol dm^{-3}) buffer (pH 8.82), left for 30 min, and then treated as in 1.

All $[Co(en)_2(glyO)]HgI_4$ samples were pyrolyzed to recover glycine, and this converted to CO_2, as described previously.[22]

To determine the position of the ^{18}O label, we converted a sample of the $[Co(en)_2(glyO)]HgI_4$ (0.2 g) to the chloride salt, made up to 0.1 mol dm^{-3} $HClO_4$ and 0.9 mol dm^{-3} $NaClO_4$, and thermostated at 25.0 °C for 30 days. The complex was then recovered and analyzed as before.

The ^{18}O content of the solution used for incorporation of the aqua label was determined by equilibration at 80 °C with normal CO_2. The enrichment in $[Co(en)_2(glyO)]^{2+}$ produced in the initial-base hydrolysis of the bromo complex was also analyzed.

Results

(1) Reactant and Product Identification. The *cis*-$[Co(en)_2(OH_2/OH)(glyO/H)]^{3+/2+/1+}$ reactants were prepared by the base hydrolysis of *cis*-$[Co(en)_2Br(glyOH)]Br_2$ at pH 9–11 as described earlier.[17]

$$cis\text{-}[Co(en)_2Br(glyO)]^+ + OH^- \rightarrow \underset{\text{cis + trans}}{[Co(en)_2(OH)(glyO)]^+ + [Co(en)_2(glyO)]^{2+}} + Br^- \quad (5)$$

The cis (45%) and trans (9%) 1+ ions were easily separated from the directly formed $[Co(en)_2(glyO)]^{2+}$ product (46%) by using ion-exchange chromatography. The presence of the trans isomer together with the cis did not interfere with the subsequent cyclization reactions except in alkaline solution (pH >8), and even then it did not distort the kinetic results at the wavelengths used. The chemistry of the trans isomer is described separately.[23]

Spectral data for *cis*-$[Co(en)_2(OH)(glyO)]^+$ and the cyclized product $[Co(en)_2(glyO)]^{2+}$ are given in Figure 1, and it is obvious that substantial OD differences occur at 350 and 485 nm, the two wavelengths used to follow the cyclization reactions. A similar result holds for the *cis*-$[Co(en)_2(OH_2)(glyO/H)]^{2+/3+}$ ions in neutral and acid solution, respectively (315, 350, 485 nm), although these ions reacted too rapidly for accurate spectra to be recorded.

pH-stat titration of *cis*-$[Co(en)_2Br(glyOH)]^{2+}$ and *cis*-$[Co(en)_2OH(glyO)]^+$ gave pK_1 and pK_2 values for the ionization processes

$$[Co(en)_2Br(glyOH)]^{2+} + H_2O \rightarrow [Co(en)_2Br(glyO)]^+ + H_3O^+ \quad (6)$$

$$[Co(en)_2(OH_2)(glyO)]^{2+} + H_2O \rightarrow [Co(en)_2(OH)(glyO)]^+ + H_3O^+ \quad (7)$$

of 2.3 ± 0.05 and 6.3 ± 0.1, respectively, at 25.0 °C, $\mu = 1.0$ ($NaClO_4$).

The product of the cyclization reactions was shown to be $[Co(en)_2(glyO)]^{2+}$ containing the chelated glycinate moiety by

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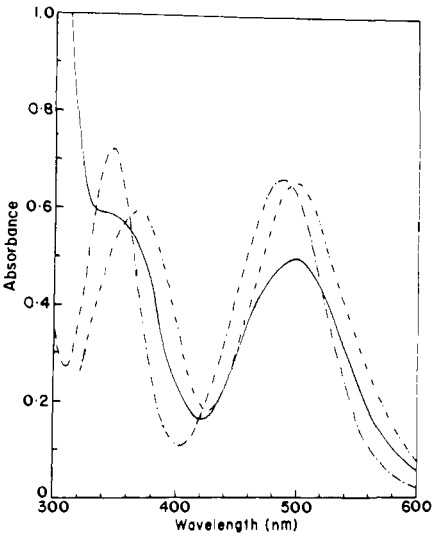


Figure 1. Visible absorption spectra for *cis*-$[Co(en)_2(OH)(glyO)]^+$, pH 10.0 (-··), *trans*-$[Co(en)_2(OH)(glyO)]^+$, pH 8.0 (—), and $[Co(en)_2(glyO)]^{2+}$ produced from *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ at pH 4.5 (-·-): [Co] = 3.47×10^{-3} mol dm^{-3}.

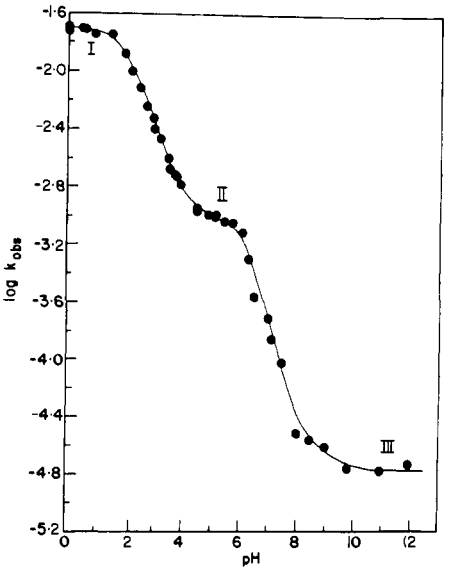


Figure 2. Plot of log k_{obsd} vs. pH for the reaction of *cis*-$[Co(en)_2(OH/OH_2)(glyO/H)]^{+/2+/3+}$ ions to give $[Co(en)_2(glyO)]^{2+}$ in the absence of buffer species (eq 8). Regions I, II, and III are described in the text (T = 25 °C, μ = 1.0 ($NaClO_4$)).

its ion-exchange properties (2+ ion at all pHs), by its ^1H NMR (CH_2 triplet at 3.7 ppm) and visible spectra (Figure 1), and by its isolation and characterization as $[Co(en)_2(glyO)]I_2$.

It has previously been shown by using optically pure $(+)_{589}$-$[Co(en)_2Br(glyO)]^{2+}$ that full retention of configuration about the metal center obtains in the reactions in acidic and neutral solutions[17] reactions 2 and 3.

(2) Rates in the Absence of Buffers. Spectrophotometric rate data obtained under pH-stat control and some spectropolarimetric rate data are given in Table I (supplementary material), μ = 1.0 ($NaClO_4$), 25.0 °C. Figure 2 gives a plot of k_{obsd} (s^{-1}) vs. pH with k_{obsd} being obtained from linear log ($D_\infty - D_t$) or log ($\alpha_\infty - \alpha_t$) vs. time plots (at least $3t_{1/2}$) and from linear log (100–% reacted) vs. time plots in the pH range 9.7–12.0. Above pH 12 an induced decomposition ensues which involves the removal of the glycine moiety, and in 1.0 mol dm^{-3} NaOH only $[Co(en)_2(OH)_2]^+$ results. This alternative reaction curtails useful data to pHs <12.0.

Figure 2 depicts five clearly defined regions of reactivity; (1) pH 0–1, where the rate ($t_{1/2}$ = 40 s) is independent of $[H^+]$; (2) pH 1–4, where the rate decreases as the carboxylate residue becomes ionized; (3) pH 4–5, where $t_{1/2} \simeq 400$ s is independent of pH; (4) pH 5–8, where k_{obsd} decreases as coordinated water is converted to coordinated OH^-; and (5) pH >9 where k_{obsd} again becomes independent of pH ($t_{1/2} \simeq 10$ h). The data fit the expression

$$k_{obsd} = \frac{k_H[H^+]^2 + k_H'K_1[H^+] + k_{OH}K_1K_2}{K_1K_2 + K_1[H^+] + [H^+]^2} \quad (8)$$

and a computer simulated least-squares analysis using $k_H = 1.9 \times 10^{-2}$ (s^{-1}), $k_H' = 1.05 \times 10^{-3}$ (s^{-1}), $k_{OH} = 1.74 \times 10^{-5}$ (s^{-1}), $K_1 = 5.01 \times 10^{-3}$ (mol dm^{-3}), and $K_2 = 5.01 \times 10^{-7}$ (mol dm^{-3}) gives the solid curve in Figure 2. These kinetically determined K_1 and K_2 values agree with those found by titration for dissociation of the acid function in *cis*-$[Co(en)_2Br(glyOH)]^{2+}$[24] (eq 6) and dissociation of the water molecule in *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ (eq 7), so that the rate of reaction may also be expressed.

$$\text{rate} = k_{obsd}[Co]_T = k_H\{[Co(en)_2(OH_2)(glyOH)]^{3+}\} + k_H'\{[Co(en)_2(OH_2)(glyO)]^{2+}\} + k_{OH}\{[Co(en)_2(OH)(glyO)]^+\} \quad (9)$$

(3) Rates in the Presence of Buffers. Buffers accelerate the cyclization, particularly in the pH region 2–6 where the $[Co(en)_2(OH_2)(glyO)]^{2+}$ ion predominates. At pH 1 where the reactant is $[Co(en)_2(OH_2)(glyOH)]^{3+}$, little catalysis occurs while at pHs >6 only HPO_4^{2-} has any effect. The kinetic data (Table II, supplementary material) are summarized by the second-order rate constants k_{HA} listed in Table III. For monofunctional buffers (one dissociable proton) the rate law takes the form

$$\text{rate} = k_H'\{[Co(en)_2(OH_2)(glyO)]^{2+}\} + k_{HA}\{[Co(en)_2(OH_2)(glyO)]^{2+}\}[HA] \quad (10)$$

with

$$k_{obsd} - k_{hyd} = \frac{k_{HA}[\text{buffer}]_T}{K_3 + [H^+]} \frac{K_1[H^+]^2}{K_1K_2 + K_1[H^+] + [H^+]^2} \quad (11)$$

where K_1 and K_2 are as before, K_3 is the acid dissociation constant for HA, and k_{hyd} is k_{obsd} in the absence of the buffer (eq 8). Figure 3 shows the magnitude of the effect and the degree of agreement for one such buffer (HA = formic acid) over the useful pH range

Table III. Second-Order Rate Constants (k_{HA}) for the General-Acid-Catalyzed Reaction of the *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ Ion (μ = 1.0 ($NaClO_4$), 25.0 °C)

buffer	pK_a[a]	k_{HA}, mol^{-1} dm^3 s^{-1}
tris(hydroxymethyl)aminomethane	8.3	2×10^{-4}
imidazole	7.21	$(7.8 \pm 0.2) \times 10^{-3}$
phosphoric acid ($H_2PO_4^-$)	6.53	0.68 ± 0.03
hydroxylamine	6.17	0.068 ± 0.004
maleic acid ($HMal^-$)	5.53	0.16 ± 0.04
pyridine	5.52	0.064 ± 0.005
succinic acid ($HSucc^-$)	5.14	0.105 ± 0.01
acetic acid	4.44	0.46 ± 0.1
succinic acid (H_2Succ)	3.87	1.63 ± 0.04
semicarbazide	3.71	0.30 ± 0.01
formic acid	3.40	0.56 ± 0.05
chloroacetic acid	2.45	1.09 ± 0.02
phosphoric acid (H_3PO_4)	1.72	3.1 ± 0.6
maleic acid (H_2Mal)	1.70	1.53 ± 0.1
dichloroacetic acid	1.13	1.17 ± 0.2
selenic acid	1.00	1.6 ± 0.3
hydronium ion (H_3O^+)	−1.7	3.83

[a] Either measured in 1.0 mol dm^{-3} $NaClO_4$[26] or taken from the literature.

(24) It is expected that K_1 for the glycinate function in $[Co(en)_2Br(glyOH)]^{2+}$ and $[Co(en)_2(OH_2)(glyOH)]^{3+}$ will be similar; the higher overall charge on the latter complex will have little effect on an acidic group two atoms removed from the metal center: Cf. Bennett, L. E.; Lane, R. H.; Gilroy, M.; Sedor, F. A.; Bennett, J. P. *Inorg. Chem.* **1973**, *12*, 1200.

Table IV. ^{18}O-Tracer Results for Cyclization under Various Conditions (25.0 °C)

expt	reaction	R values[a] complex	R values[a] blank[b]	atom enrichment[c]	% retention[d]
1	H_2O (solvent)	0.028 52 (H_2O)	0.004 449	1.185	100
2	0.05 M $HClO_4$	0.015 210	0.004 480	0.534	45.1
3	citrate/phosphate buffer, pH 3.7	0.015 820	0.004 420	0.564	47.6
4	pH-stat, 4.0	0.015 910	0.004 421	0.568	47.9
5	citrate/phosphate buffer, pH 8.82	0.015 650	0.004 480	0.555	46.8
6	30 days, 0.1 M $HClO_4$, μ = 1.0 ($NaClO_4$)	0.014 301	0.004 441	0.445	37.6
7	unenriched complex[e]	0.006 20	0.004 477	0.088	7.4

[a] Observed R values, $R = [46]/([44] + [46])$ (for CO_2). [b] Normal CO_2 for comparison purposes. [c] Atom enrichment = $R/(2 + R) - R'/(2 + R')$ where R is for CO_2 recovered from $[Co(en)_2(glyO)]HgI_4$ and R' that for normal CO_2 blank. [d] % retention of solvent ^{18}O in complex (per O atom). [e] $[Co(en)_2(glyO)]^{2+}$ produced immediately on base hydrolysis of *cis*-$[Co(en)_2Br(glyO)]Br_2$.

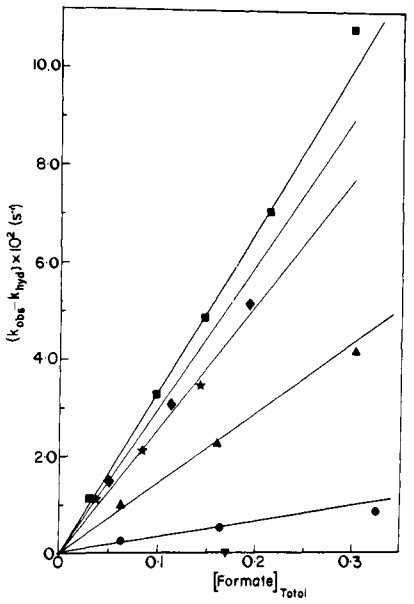


Figure 3. Plot of $k_{obsd} - k_{hyd}$ vs. [formate]$_T$ for the cyclization of *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ as a function of pH (T = 25 °C, μ = 1.0 ($NaClO_4$)): pH 0.53 (▼); pH 2.3 (*); pH 2.72 (■); pH 3.22 (♦); pH 3.84 (▲); pH 4.60 (●). The solid lines are least squares fitted to eq 11 by using $k_{HA} = 0.56$, $K_1 = 5.01 \times 10^{-3}$, $K_2 = 5.01 \times 10^{-7}$, and $K_3 = 3.98 \times 10^{-4}$.

0.53–4.6. It will be noted that the k_H term for cyclization of $[Co(en)_2(OH_2)(glyOH)]^{3+}$ (eq 9), has been included with the $k_{HA}[Co(en)_2(OH_2)(glyO)]^{2+}[HA]$ term of eq 10 with HA = H_3O^+. Also, eq 10 equates the effect of buffers in terms of HA catalysis of $[Co(en)_2(OH_2)(glyO)]^{2+}$ rather than the alternate A^- catalysis of the conjugate acid $[Co(en)_2(OH_2)(glyOH)]^{3+}$.

For bifunctional buffers, phosphoric, maleic, and succinic acids, the rate expression takes the extended form

$$k_{obsd} - k_{hyd} = \frac{(k_{H2A}[H^+] + K_3k_{HA})[buffer]_T}{K_3K_4 + K_3[H^+] + [H^+]^2} \frac{K_1[H^+]^2}{K_1K_2 + K_1[H^+] + [H^+]^2} \quad (12)$$

where K_3 and K_4 represent the dissociation constants for H_2A and HA^-, respectively.

No curvature was observed in any of the plots of $(k_{obsd} - k_{hyd})$ vs. [buffer]$_T$ at high buffer concentrations (0.3–0.4 mol dm^{-3}) nor of any retardation in rate, and extrapolation to [buffer]$_T$ = 0 gives the same k_{obsd} value as that obtained from the pH-stat measurements (eq 8).

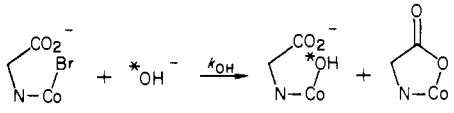
(4) ^{18}O-Tracer Results. Table IV refers to retention in the product $[Co(en)_2(glyO)]^{2+}$ of ^{18}O-enriched (*O) bound water or hydroxide

$$[Co(en)_2(*OH_2/*OH)(glyO/H)]^{3+/2+/+} \rightarrow [Co(en)_2(gly*O)]^{2+} + H_2O/OH^- \quad (13)$$

Since two oxygens are involved in the carboxylate moiety, 100% retention corresponds to 50% incorporation per oxygen atom. Experiments 2 and 4 correspond to the uncatalyzed reactions of $[Co(en)_2(OH_2)(glyOH)]^{3+}$ and $[Co(en)_2(OH_2)(glyO)]^{2+}$, respectively, and experiments 3 and 5 to the phosphate-catalyzed reactions of $[Co(en)_2(OH_2)(glyO)]^{2+}$ and $[Co(en)_2(OH)(glyO)]^+$. Clearly close to complete retention (>90%) of the bound label occurs in these instances. Experiment 6 shows that some 25% of the label in the $[Co(en)_2(glyO)]^{2+}$ product is lost to the solvent in 30 days in 0.1 mol dm^{-3} H^+; this allows the position of the label to be determined. Experiment 7 relates to $[Co(en)_2(glyO)]^{2+}$ produced directly in the alkaline hydrolysis of *cis*-$[Co(en)_2Br(glyO)]^+$ (eq 5). The small amount of solvent incorporation (~15%) almost certainly arises from subsequent cyclization of the $[Co(en)_2(OH/OH_2)(glyO)]^{+/2+}$ ions under the experimental conditions so that the directly produced $[Co(en)_2(glyO)]^{2+}$ must result from direct entry of the intact carboxylate moiety.

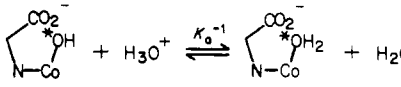
Discussion[25]

Intramolecular Nature of the Reaction. At the outset it was important to establish the intramolecular nature of the lactonization reactions since most substitutions at metal centers occur via displacement of coordinated water or hydroxide. Labeled hydroxide, introduced via the removal of coordinated bromide (eq 14, $k_{OH} = 64$ mol^{-1} dm^3 s^{-1}),[26] is firmly retained in the resulting



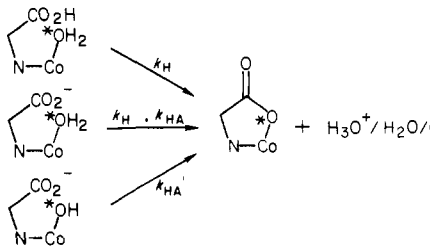
(14)

cis-hydroxo and aqua complexes (pK_a = 6.3) (eq 15). This is



(15)

a property of cobalt(III) complexes not in general shared by other transition-metal ions, particularly those of biological interest, but it is essential to the study here. The ^{18}O label is completely incorporated in the subsequent unbuffered reactions in acidic (pH 1) and neutral (pH 4) solutions (eq 16) and also in the



(16)

$H_2PO_4^-/HPO_4^{2-}$-catalyzed reactions of $[Co(en)_2(OH_2)(glyO)]^{2+}$

(25) The complexes are drawn to emphasize the intramolecular nature of the reactions with the formation of a five-membered ring. This description was used earlier in the related intramolecular hydrolysis of glycinamide species.[19]

(26) Boreham, C. J. Ph.D. Thesis, The Australian National University, July 1978.

and $[Co(en)_2(OH)(glyO)]^+$. There is no direct experimental proof for the unbuffered reaction of $[Co(en)_2(OH)(glyO)]^+$ although the continuity of the rate data and other comparisons[27] suggest that this will be the case.

Differences from 100% incorporation (Table IV) result in part from the method of recovery and analysis[22] and in part from contamination of the cis reactant with ~18% of the trans isomer. This trans species also ultimately results in $[Co(en)_2(glyO)]^{2+}$, but at a slower rate, and via a mechanism which involves the displacement of coordinated water or hydroxide.[23] Thus the reactions of the cis isomer are quantitatively intramolecular.

The position of the label in the five-membered ring of the product is confirmed by the 25% loss of enrichment over 30 days in 0.1 mol dm^{-3} $HClO_4$. This corresponds almost exactly with the previously determined[14] exchange rate for this oxygen atom, $k_{ex} = 7 \times 10^{-8}$ s^{-1}; if the exocyclic oxygen atom were involved, a considerably faster exchange rate would occur ($k_{ex} = 1 \times 10^{-6}$ s^{-1} in 0.1 mol dm^{-3} H^+).[14]

Unassisted and Buffer Catalysis. The remaining results demonstrate the following general properties. (1) The unassisted cyclizations via Co–OH_2 are faster than that of Co–OH. (2) Addition of Co–OH_2 to protonated carboxylate (–CO_2H) is faster than addition to the carboxylate anion (–CO_2^-); however a different mechanistic interpretation is possible (vide infra). (3) There is no evidence for specific OH^- catalysis of the reaction of Co–OH, unlike that found for the similar intramolecular glycinamide reaction.[19] (4) Buffer species appear to act as general acids in catalyzing the reaction of Co–OH_2 with the carboxylate anion (–CO_2^-). These observations, of which the last is the most unusual, are now briefly considered.

The particular rates for the different reactants $[Co(en)_2(OH_2)(glyOH)]^{3+}$, $[Co(en)_2(OH_2)(glyO)]^{2+}$, and $[Co(en)_2(OH)(glyO)]^+$ are characterized in Figure 2 by the three plateau regions. The close agreement between the directly determined and kinetic pK_a values (eq 6–8) demonstrate that the rates are fully accountable in terms of these three reactants. Thus there is no kinetic evidence for changes in rate-determining step and hence of intermediates on the various pathways to the cyclized product.

However, the demonstration of marked general-buffer catalysis in the neutral to acid pH range gives indirect evidence that at least one intermediate is involved before the rate-determining step. A plot of log k_{HA} (k_{HA}, Table III) vs. pK_{HA} is given in Figure 4,[28] and two limiting regions corresponding to slopes of $\alpha = 0$ and $\alpha = -1.0$ are apparent. This suggests a simple proton-transfer process which changes from being thermodynamically favorable at low pH ($\alpha = 0$) to being unfavorable ($\alpha = -1.0$) at high pH.[29] The pK_a of the transition, obtained as the point where the extrapolated lines of $\alpha = 0$ and $\alpha = -1.0$ intersect, is ~4.8. It will be seen that the buffers in this transition region fall below the intersecting value, and this is again consistent with limiting acid–base proton exchanges of this type.[30,31] Also the value for HA = H_3O^+ fits the low pH region, suggesting an alternative description for the uncatalyzed reaction of $[Co(en)_2(OH_2)(glyOH)]^{3+}$ as H_3O^+ catalysis of $[Co(en)_2(OH_2)(glyO)]^{2+}$. Although proton transfer to the anionic carboxylate group will be diffusion controlled for H_3O^+ (and for other HA of $pK_a < 4.8$), this agreement suggests that the direct pathway via the 3+ reactant is energetically less feasible than that via the "zwitterionic conjugate" $[Co(en)_2(OH_2)(glyO)]^{2+}$. Since the two sites for protonation in the reactants have pK_a's sufficiently distinct from the transition point for HA catalysis, protonation of a subsequent

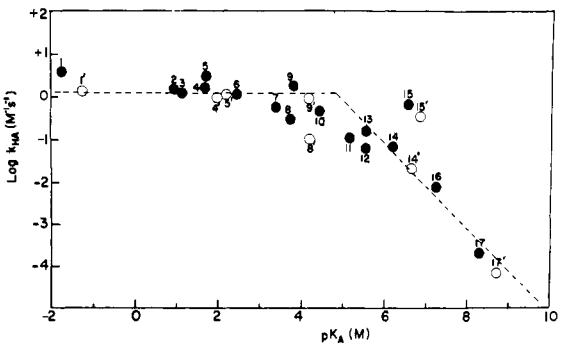
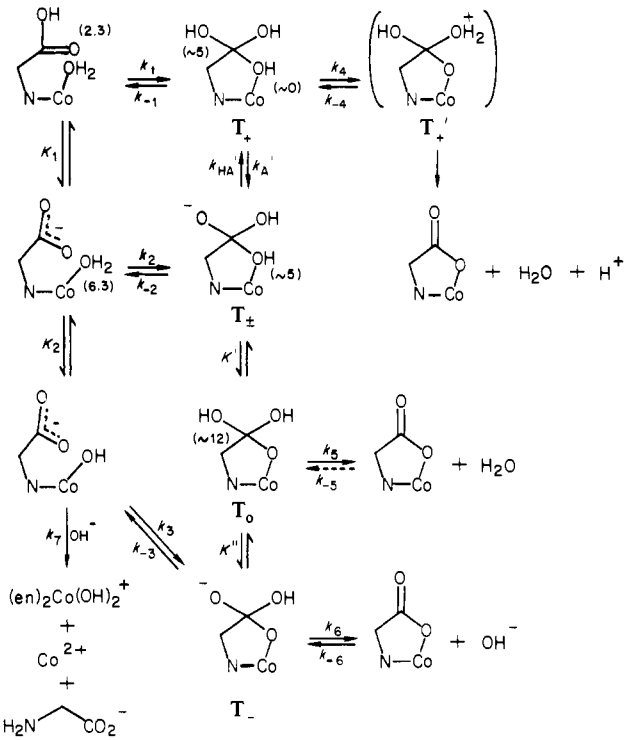


Figure 4. Brønsted plot of log k_{HA} (Table III) vs. pK_{HA} for the general-acid-catalyzed reaction of *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$ at $T = 25$ °C ($\mu = 1.0$ ($NaClO_4$)): (1) H_3O^+, (2) selenic acid ($HSeO_4^-$), (3) dichloroacetic acid, (4) maleic acid (H_2Mal), (5) H_3PO_4, (6) chloroacetic acid, (7) formic acid, (8) semicarbazide, (9) succinic acid (H_2Succ), (10) acetic acid, (11) succinic acid ($HSucc^-$), (12) pyridine, (13) maleic acid ($HMal^-$), (14) hydroxylamine, (15) $H_2PO_4^-$, (16) imidazole, (17) tris(hydroxymethyl)aminomethane. The buffers 1, 4, 5, 8, 9, 14, 15, and 17 have been corrected for statistical factors in both log k_{HA} and log K_{HA} whence ● becomes ○.

Scheme I



intermediate appears to be rate determining in the neutral to acid pH region.

Mechanism. The mechanism given by Scheme I follows that adopted for lactonizations of purely organic hydroxyacids[5] although the reversal in the acidities of the phenolic and carboxylate sites due to the presence of the metal adds a new feature. The present cyclization study together with the previous results[14] on the H^+- and OH^--induced O exchange in the cyclic product allows the various pathways to be depicted in some detail.

The absence of any kinetic evidence for a change in rate-determining step leaves four situations for ring closure, viz., (a) the rate-determining steps at all pHs (i.e., the three plateaus of Figure 2) are the initial cyclizations (i.e., k_1, k_2, and k_3); any subsequent intermediates rapidly decay to the lactone, and general-buffer catalysis in neutral to mildly acid solutions involves k_1 (A^- catalysis) or k_2 (HA catalysis); (b) the lactone derives from the rate-determining decay of only one intermediate throughout the pH region 0–12 (i.e., T_+ or $T_\pm$) and this intermediate has pK_a values similar to those of the reactant; (c) a change from rate-

(27) Coordinated hydroxide is usually slow to exchange with the solvent, $t_{1/2}$ for *trans*-$[Co(en)_2(NH_3)OH]^{2+}$ = 200 h: Martin, D. F.; Tobe, M. L. *J. Chem. Soc.* **1962**, 1388. Similar rates are likely for *cis*-$[Co(en)_2(RNH_2)(OH)]^{2+}$ ions.

(28) Figure 4 gives two points for buffers containing more than one proton (H_3O^+, maleic acid, semicarbazide, succinic acid, hydroxylamine, $H_2PO_4^-$, Tris), the log k_{HA} value of Table III, and the statistical value per proton.

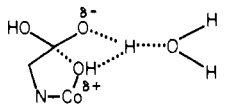
(29) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(30) Jencks, W. P.; Sayer, J. M. *Symp. Faraday Soc.* **1975**, *No. 10*, 41.

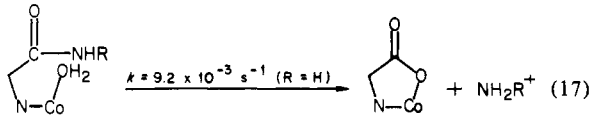
(31) Fox, J. P.; Page, M. I.; Satterthwait, A.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4729.

determining decay to rate-determining formation of an intermediate (i.e., $T_{\pm}$ or T_-) occurs at a pH similar to pK_2; (d) if more than one intermediate is involved in rate-determining decay to the lactone, then the division between the two intermediates fortuitously coincides with the pK_a values of the reactants, i.e., a 50:50 division occurs at pK_1 or pK_2.

The results are best interpreted in terms of c with rate-determining general-acid-catalyzed decay of $T_{\pm}$ occurring at acid to neutral pHs while in basic solution the rate-determining step is cyclization to form T_-. In acid conditions (plateau region I, Figure 2) addition of water to the protonated acid function may be concerted (k_1, Scheme I) with proton redistribution to form T_+ occurring via a cyclic transition state such as



with or without the help of the solvent. The weak acidity of the coordinated water molecule (ca. $pK_a = 5$–6) and the poor basicity of the $-CO_2H$ group (ca. $pK_a \ll 0$) will prevent proton transfer before bond formation, but the acidities will change rapidly in the early stages of reaction allowing an early transfer. Alternatively T_+ may be avoided entirely, with concerted removal of H_2O via a proton-tunneling mechanism and a transition state such as T_+'. Either possibility is preferred by previous studies on organic hydroxyacids,[5] and a similar mechanism was postulated for the analogous rapid intramolecular amide hydrolysis (eq 17) reported recently.[19]



$$+ NH_2R^+ \quad (17)$$

However, as mentioned above, the acid-independent reaction can perhaps better be interpreted in terms of H_3O^+ catalysis of the conjugate base form of the reactant $[Co(en)_2(OH_2)(glyO)]^{2+}$, and the good agreement obtained between $k_{H_3O^+}$ ($k_{H_3O^+} = 3.8$ mol^{-1} dm^3 s^{-1}) and k_{HA} for the other general acids (Brønsted curve, Figure 4) supports this description. This would require the preequilibrium (nonrate determining) k_2 step to be followed by rate-determining protonation, and the step $T_{\pm} \rightarrow T_+$ seems to have the required prerequisite of a pK_a for the hydroxyl function of T_+ of about 5.[32] This fits the change in Brønsted slope at about the same pK_a value. Other possibilities such as the HA-catalyzed stepwise formation of T_+', from T_0 or concerted proton donation and bond cleavage would not give the observed Brønsted relationship. Formation of T_+ from $T_{\pm}$ will be diffusion controlled for all HA of $pK_a < 5$ ($k_{HA}' = 10^{10}$ mol^{-1} dm^3 s^{-1}) and from the average k_{HA} value of 1 mol^{-1} dm^3 s^{-1} ($k_2/k_{-2} \simeq 10^{-10}$). Certainly the reverse O exchange in the lactone product under acid conditions[14] occurs via an intermediate such as T_+ or T_0, but although slower than cyclization ($k_{ex} = 1 \times 10^{-5}$ mol^{-1} dm^3 s^{-1}), this does not require the transition state for ring opening to occur prior to T_+ (or T_0). Indeed the present study and the inability to find any ring opened product in the exchange study[14] concur that the transition state for ring opening occurs between T_+ and $T_{\pm}$. This is depicted schematically by the reaction coordinate–energy profile of Figure 5a.

For the uncatalyzed reaction of $[Co(en)_2(OH_2)(glyO)]^{2+}$ (plateau region 2, Figure 2) trapping of the intermediate $T_{\pm}$ by H_2O[33] is unfavorable due to a large difference in pK_a (~11) and

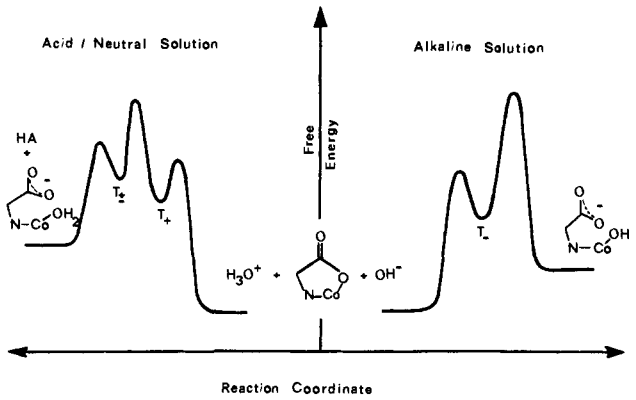
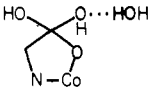


Figure 5. Reaction coordinate profile for ring closure and ring opening in acid/neutral solutions and in alkaline solution.

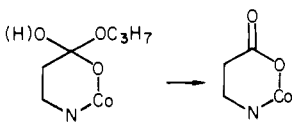
the reaction is more likely to proceed via T_0 where ΔpK_a is smaller (~4).



With use of the fact that this pathway becomes important at pH 2.3, $K'k_5 = k_{H_3O^+}'[H_3O^+] \simeq (3.8 \times 10^{10})(5 \times 10^{-3}) = 10^8$ s^{-1}. Alternatively, if a change in rate-determining step to formation of $T_{\pm}$ occurs, $k_2 = 1.05 \times 10^{-3}$ s^{-1}, whence (since $k_2/k_{-2} \simeq 10^{-10}$) $k_{-2} = 10^7$ s^{-1}.

In alkaline solution where ionization of the coordinated water molecule is complete and the rate becomes independent of pH (plateau region 3, Figure 2), addition (k_3 in Scheme I) is rate determining. This is required by a combination of the ^{18}O-tracer results and the absence of any $[Co(en)_2(OH)(glyO)]^+$ in the reaction of OH^- with $[Co(en)_2(glyO)]^{2+}$.[14] The absence of ring-opened product during complete exchange of the exo-oxygen atom under conditions where exchange is faster ($k_{ex} = 3.0 \times 10^{-4}$ s^{-1} in 0.1 mol dm^{-3} OH^-) than ring closure requires $k_{-6} > k_3$. Also, since the OH^- catalyzed complete removal of glycine from the chelated product (to give $[Co(en)_2(OH)_2]^+$ and Co(II) products, k_{dec})[14] is considerably slower than the analogous reaction of $[Co(en)_2OH(glyO)]^+$ even though the latter is on the same pathway[14] ($k_7[OH^-]$ in Scheme I), the overall rate-determining step for decomposition is the opening of the chelate ring. Thus $k_{dec} = k_{-6}k_{-3}/k_6$, and with $k_{-6} = 6.1 \times 10^{-3}$ mol^{-1} dm^3 s^{-1} [14] and $k_{dec} = 1.8 \times 10^{-5}$ mol^{-1} dm^3 s^{-1},[14] $k_6/k_{-3} \simeq 340$. Thus loss of OH^- from T_- is favored over ring opening by a significant factor. This is probably in part a reflection of the fact that protonation of T_- is required in the ring-opening process and this is unfavorable under the alkaline conditions and in part a result of the inherent stability of metal ring systems. Figure 5b summarizes these conclusions in terms of an energy profile.

It is likely that protonation of T_- to form T_0 (K'', Scheme I) is diffusion controlled in mildly alkaline solutions (pH <12) so that T_0 will normally predominate. However, since it has already been shown for the related intramolecular hydrolysis of $[Co(en)_2OH(\beta\text{-alaOC}_3H_7)]^{2+}$ [35] that k_6/k_5 is about 10^5 and since a similar preference for k_6 is likely here, T_- will be the important intermediate leading to the lactone under alkaline conditions.



$$+ C_3H_7OH \quad (18)$$

It is also interesting that in the present system the alkaline cyclization reaction is not catalyzed by OH^- or general bases;

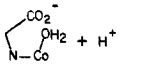
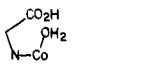
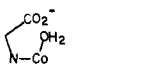
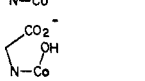
(32) pK_a values which have been estimated are given by (~) in Scheme I. These values were obtained by the method first put forward by: Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436. Aldersley, M. F.; Kirby, A. J.; Lancaster, P. W.; McDonald, R. S.; Smith, C. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1498. They were used by us previously in the glycinamide investigation.[19,26]

(33) $T_{\pm}$ will break down preferentially to form the reactant $[Co(en)_2(OH_2)(glyO)]^{2+}$ in the absence of further protonation (to form T_+) or proton redistribution (to form T_0) since Co–OH is a much better leaving group than OH^-.

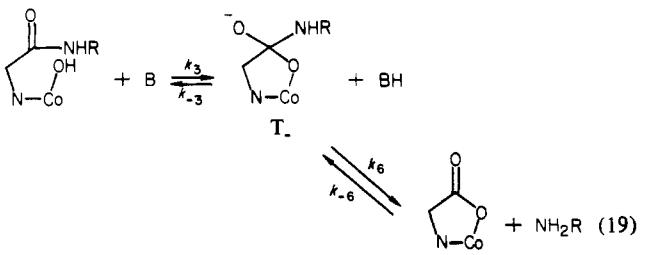
(34) Data was taken from: O'Connor, C.; Llewwllyn, D. R. *J. Chem. Soc.* **1965**, 2669. In some cases extrapolation to 25 °C from about 100 °C was necessary.

(35) Baraniak, E. Ph.D. Thesis, The Australian National University, March 1973.

Table V. Comparison of the Metal-Induced Cyclic Addition of H_2O and OH^- to Glycine and the Related Solvent Paths for O Exchange (at 25 °C)

reaction	rate const (k_{intra})	reaction	rate const[34] (k_{gly})	k_{intra}/k_{gly}, M
	3.83	$NH_3^+CH_2CO_2^- + H^+ + H_2O$	1.3×10^{-12}	3×10^{12}
	1.7×10^{-2}	$NH_3^+CH_2CO_2H + H_2O$	2×10^{-10}	9×10^{7}
	1.05×10^{-3}	$NH_3^+CH_2CO_2^- + H_2O$	1.1×10^{-13}	1×10^{10}
	1.7×10^{-5}	$NH_3^+CH_2CO_2^- + OH^-$	4.4×10^{-13}	4×10^{7}

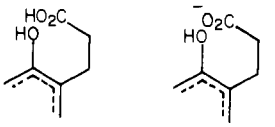
clearly the formation of T_- does not require it. However in the similar cyclization of the hydroxoamide (reaction 19) where k_3



(19)

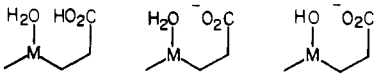
is also rate determining, appreciable catalysis by OH^- and other bases is observed.[19] Here the formation of T_- requires proton abstraction, and this is best achieved in a concerted manner.

Comparison with Organic Lactonizations and Rate Enhancement. Undoubtedly the major difference between the metal system and lactone formation by organic hydroxyacids is in the nature of the reactant. Whereas the latter takes the forms



a b

the metal system has an additional proton on the hydroxyl function even when the carboxyl group is ionized (as in **d**). For the organic



c d e

systems **a** is the reactant in acid media, and a change from rate-determining formation of an intermediate analogous to T_0 (which subsequently undergoes rapid acid-catalyzed decomposition) to decay of T_0 has been observed kinetically. In neutral solutions either **b** or OH^--catalyzed reaction of **a** is involved, and for some substrates an intermediate analogous to T_- is required.[5b] For the metal systems where the hydroxyl group is protonated (i.e. in acidic solution) either **c** or more likely **d** is involved, and rate-controlling formation of T_+ via $T_\pm$ is involved. In neutral and alkaline solution addition of the hydroxyl function of **e** is rate determining, and an intermediate such as T_- is required. Thus the nature of the hydroxyl (or aqua) function in the reactant does not appear to be very important, presumably because proton redistribution can rapidly take place in the addition intermediate. It is the leaving group abilities of the various functions in the intermediates which decide both the overall course of the reaction and the rate-determining step. It is also pertinent to point out that unlike organic lactones the metal species are stable toward acid and alkaline hydrolysis, and this allows lactone formation to be studied over a wide range of pHs.

The rates of cyclization of the courmarinic acids[5] and the *cis*-$[Co(en)_2(OH_2)(glyO/H)]^{2+/3+}$ ions are also similar with large accelerations over the acyclic systems. Both have k_{obsd} values about 10^{-2} s^{-1} at pH 1 and 10^{-3} s^{-1} at pH 4–5. For the metal system an appreciation of the rate enhancement can be obtained by comparisons with the various paths for O exchange in glycine.[34] Table V summarizes these. Clearly the metal-based intramolecular processes are very effective with $k_{intra}/k_{gly} = 10^7$–10^{12} mol dm^{-3}, and in concord with the results of Winans and Wilcom[4] we expect this to arise from overall energy consideration rather than from conformational locking of reactant sites.

Supplementary Material Available: Rate data for the unbuffered (Table I) and buffered (Table II) reactions of the *cis*-$[Co(en)_2(OH_2)(glyOH)]^{3+}$, *cis*-$[Co(en)_2(OH_2)(glyO)]^{2+}$, and *cis*-$[Co(en)_2(OH)(glyO)]^+$ ions (6 pages). Ordering information is given on any current masthead page.