Cobalt(III)–Promoted Amidolysis of Glycine Ethyl Ester. An Example of Internal Nucleophilic Displacement

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

Contribution from the Research School of Chemistry, Australian National University, Canberra, Australia. *Received December 2, 1968*

Abstract: Treatment of $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$ with OH^- in the pH range 9–14 results in the formation of both $[Co(NH_3)_5(NH_2CH_2CO_2)]^{2+}$ (containing the monodentate glycinate anion) and $[Co(NH_3)_4(NH_2CH_2CONH)]^{2+}$ (containing glycine imide chelated through both N atoms). Rate data fit the rate law $d/dt\{[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]^{3+}\} = \{k_1[OH^-] + k_2[OH^-]^2\}\{[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]^{3+}\}$ with $k_1 = 50\ M^{-1}\ sec^{-1}$ and $k_2 = 6.6 \times 10^6\ M^{-2}\ sec^{-1}$ at 25° and $\mu = 0.1$ (KNO_3). The k_1 path is shown to result in the monodentate glycinate product, and the k_2 path in the formation of the chelated imide. Acid hydrolysis of $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$ results exclusively in the formation of $[Co(NH_3)_5(NH_2CH_2CO_2H)]^{3+}$. The complexes $[Co(NH_3)_5(NH_2CH_2CO_2)]Br_2 \cdot H_2O$, $[Co(NH_3)_5(NH_2CH_2CO_2H)]Cl_3 \cdot H_2O$, $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$, $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$, and $[Co(NH_3)_4(NH_2CH_2C(OH)NH)](ClO_4)_3$ are also described. Pmr spectra establish that protonation of the chelated imide occurs at O rather than at N, to form the chelated iminol tautomer of glycineamide.

On numerous occasions in the literature concerned with reactions at coordinated ligands, it has been proposed that the nucleophile which initiates the reaction is also attached to the metal ion. Authentic examples of this behavior are few, if any, and this publication describes a reaction where it is unequivocally shown that the substituent which enters the coordinated reactant is also attached to the metal ion.

Experimental Section

Analar reagents were used throughout without further purification. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer, pmr spectra on a Varian HA-100 spectrometer (using tetramethylsilane or *t*-butyl alcohol as internal reference), and uv and visible spectra on a Cary 14 spectrophotometer. Spectrophotometric rates were measured either with the Cary or a Durrum-Gibson stopped-flow reactor. Some cobalt estimations were made using a Techtron AA4 Atomic absorption spectrophotometer. The following Radiometer pH equipment was used in measuring the buffer pH's, dissociation constants, and base consumption at constant pH: TTA_3 electrode assembly, ABU 1 autoburet, TTT 1 titrator, SBR_2 titrigraph, and pHA scale expander. The thermostated reaction vessel was continuously stirred as the titrant (NaOH of appropriate concentration) was added under a nitrogen atmosphere. Separation of the reaction products was achieved using Bio-Rad Analytical Dowex 50W × 2 (200–400 mesh) cation-exchange resin.

$[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$. The preparation of this complex uses a method already described[1] for the preparation of complexes of the pentaamminecobalt(III) class. $[Co(NH_3)_5N_3]Cl_2$[2] was converted to the perchlorate salt using silver acetate and then sodium perchlorate to crystallize the complex perchlorate. $[Co(NH_3)_5N_3](ClO_4)_2$ (10 g) was suspended in tri(*n*-butyl) phosphate (80 ml) containing molecular sieves. Dry $NOClO_4$[3] was added slowly to the stirred solution until all evolution of NO and N_2O had ceased. The resulting deep red-violet solution of $[Co(NH_3)_5(n\text{-}BuO)_3PO]^{3+}$ was allowed to stir overnight and then freshly prepared dry glycine ethyl ester (12 g) was added. The solution was stirred continuously and kept at 50° for 10 min until a deep orange color had formed. Upon addition of ethanol (~0.4 l.) and ether (~1 l.), a flocculent precipitate formed, which was washed with ether, dried in an evacuated desiccator, and recrystallized twice from hot, dilute HBr by addition of NaBr and cooling. The final product was washed with methanol and dried in an evacuated desiccator (6 g).

Anal. Calcd for $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$: C, 9.51; H, 5.19; N, 16.65. Found: C, 9.56; H, 5.16; N, 17.15. The absorption maxima occurred at 480 mμ (ε 63) and 340 mμ (ε 57) in H_2O at 25°. These values were unaltered in 1 *M* $NaClO_4$.

$[Co(NH_3)_5(NH_2CH_2CO_2)]Br_2$. $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$ (0.34 g) in water (40 ml) was hydrolyzed by pH-stat titration at pH 9.0 and 25° for 100 min. The solution volume was reduced by rotary evaporation to about 5 ml, whereupon yellow crystals began to form. These were collected, recrystallized from hot water by the addition of NaBr, and dried in an evacuated desiccator. *Anal.* Calcd for $[Co(NH_3)_5(NH_2CH_2CO_2)]Br_2 \cdot H_2O$: C, 6.05; H, 5.33; N, 21.20. Found: C, 6.06; H, 5.34; N, 21.28. Absorption maxima occurred at 480 mμ (ε 66) and 342 mμ (ε 59) in H_2O at pH 5.0 ($HClO_4$) and 25°. These values were unaltered in 1 *M* $NaClO_4$ at the same pH.

$[Co(NH_3)_5(NH_2CH_2CO_2H)]Cl_3$. $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$ (1.3 g) was dissolved in HCl (20 ml, 3 *M*) and allowed to stand for 12 hr at room temperature. The product was collected and twice recrystallized from hot water by dropwise addition of HCl. The crystals were washed with ethanol and ether and dried in an evacuated desiccator. Absorption maxima appeared at 480 mμ (ε 64) and 342 mμ (ε 54) in 1 *M* $HClO_4$ at 25° for the bromide salt (see later). *Anal.* Calcd for $[Co(NH_3)_5(NH_2CH_2CO_2H)]Cl_3 \cdot H_2O$: C, 6.99; H, 6.45; N, 24.46. Found: C, 6.72; H, 6.76; N, 24.13. The deprotonated complex $[Co(NH_3)_5NH_2CH_2COO]Br_2 \cdot H_2O$ was also prepared by this route.

$[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$. $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$ (1.5 g) was dissolved in warm water (10 ml) and NaOH (10 ml, 1 M) was added. After 10 min, the solution was brought near to neutrality by dropwise addition of $HClO_4$, and then excess $NaClO_4$ was added. On cooling, orange needles precipitated, which were collected, washed with ethanol, air-dried, and recrystallized from warm water by cooling, yield 1.4 g. Absorption maxima appeared at 484 mμ (ε 87) and 335 mμ (ε 69) in H_2O at 25°, and these values were unchanged in 1 *M* $NaClO_4$.

$[Co(NH_3)_4(NH_2CH_2C(OH)NH)](ClO_4)_3$. $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$ (0.5 g) was dissolved in hot water (7 ml) and concentrated $HClO_4$ (0.5 ml) was added. On cooling, yellow plates of the product separated. These were collected, washed with ethanol and ether, and dried in an evacuated desiccator. *Anal.* Calcd for $[Co(NH_3)_4(NH_2CH_2C(OH)NH)](ClO_4)_3$: C, 4.81; H, 3.63; N, 16.83. Found: C, 5.19; H, 3.87; N, 17.64.

This complex was prepared and analyzed several times and the C, N analyses were always slightly high. This was attributed to the loss of $HClO_4$ from the complex in the evacuated desiccator.

$[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3 \cdot H_2O$ (0.34 g in water, 40 ml) was hydrolyzed at pH 9.0 and 25° by pH-stat titration and the resulting solution eluted from an ion-exchange column with 1 *M* $NaClO_4$. The orange (imide) and yellow (acid) eluate fractions were collected and taken to dryness by rotary evaporation. The residues were dissolved in methanol and the products crystallized on cooling. The acid was recrystallized from hot water by addition of NaBr and cooling and the imide was recrystallized from water with $NaClO_4$. Both were dried in an evacuated desiccator. *Anal.*

(1) R. B. Jordan, A. M. Sargeson, and H. Taube, *Inorg. Chem.*, **5**, 1091 (1966).
(2) M. Linhard and H. Flygare, *Z. Anorg. Allgem. Chem.*, **262**, 328 (1950).
(3) G. Brauer, "Handbuch der Preparativen Chemie," F. Enke Vertag, Stuttgart, 1954, p 253.

Calcd for $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$: C, 6.02; H, 4.29; N, 21.06. Found: C, 5.82; H, 4.27; N, 21.12. Calcd for $[Co(NH_3)_5(NH_2CH_2CO_2)]Br_2 \cdot H_2O$: C, 6.05; H, 5.33; N, 21.20. Found: C, 5.82; H, 5.55; N, 21.39.

Kinetic Measurements. The hydrolysis of $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$ was followed both spectrophotometrically and by base uptake at constant pH. A weighed quantity of complex was dissolved in water and allowed to equilibrate to 25° in one premixing chamber of a stopper-flow reactor.[4] In the other premixing chamber was 0.1 *M* carbonate buffer, 2 *M* in $NaClO_4$ and of known pH. After mixing the two solutions the absorbance change was followed at 2475 Å. The pH of the final solution was measured. Some fast rates were measured with a Durrum stopped-flow reactor. Solutions of standard base (0.1 *M* in KNO_3) were mixed with complex (10^{-3} and 0.1 *M* in KNO_3) and the reaction rate followed at 4800 Å. The pH of the final solution was measured.

Base hydrolysis was also followed by pH-stat titration. A weighed quantity of complex (~0.1 g) in 0.1 *M* KNO_3 was transferred to the thermostated reaction vessel and titrated with standardized NaOH.

Product Identification. After hydrolysis at known pH and ionic strength, the reaction mixture was sorbed on an ion-exchange resin (*ca.* 1.5 × 25 mm), washed, and eluted with 1 *M* $NaClO_4$ (pH 6). The orange imide was displaced first followed by the yellow acid complex. The complex concentrations were determined spectrophotometrically using the molar absorptivities given previously. A fine black precipitate formed during the hydrolysis, some of which adsorbed on the reaction vessel and electrodes. The remainder collected at the top of the ion-exchange column and was finally eluted with 3 *M* HCl to give an eluate containing Co^{2+}. We assumed, therefore, that the sorbed material was cobalt(III) oxide. The concentration of Co^{2+} measured in one instance (pH 10.34) was 4% of the initial reactant (0.072 g). In this experiment 90% of the cobalt was accounted for. Also, after hydrolysis at pH 9 for 100 min and ion-exchange removal of the Co(III) products, ammonia was detected with Nessler's reagent in the eluate.

$[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$ (0.5 g) was dissolved in 0.1 *M* NaOH (5 ml) and allowed to stand for 10 min. H_2S, followed by air, was bubbled through the solution, which was then filtered. The filtrate was made acid with $HClO_4$ and reduced almost to dryness, whereupon white needles crystallized from solution. These were collected, washed with acetone, and dried in an evacuated desiccator.

Authentic $NH_2CH_2CONH_2 \cdot HClO_4$ was prepared by dissolving $NH_2CH_2CONH_2 \cdot HCl$ in a minimum volume of water, adding excess 3 *M* $HClO_4$, and cooling. The hydroperchlorate crystallized and was collected and dried in an evacuated desiccator.

Dissociation Constants. The pK_a of $[Co(NH_3)_4(NH_2CH_2CONH)]Br_3 \cdot H_2O$ (0.12 g/100 ml of stock solution) was measured spectrophotometrically at 400 mμ, in the H^0 range of perchloric acid, −2.2 to 7.0. The pK_a of $[Co(NH_3)_5(NH_2CH_2CO_2H)]Cl_3 \cdot H_2O$ (0.018 g/10 ml of water) was measured by potentiometric titration with 0.5-ml aliquot volumes of 0.1 *M* NaOH at 25°.

Results

The hydrolysis of $[Co(NH_3)_5NH_2CH_2COOC_2H_5](ClO_4)_3$ in NaOH (0.1 *M*) gave an almost quantitative yield of the chelated imide ion $[Co(NH_3)_4(NHCOCH_2NH_2)]^{2+}$ which was isolated as the perchlorate (orange). The complex was characterized by elemental analysis, by the pK of protonation of the chelated imide (~0.4), and by visible, ir, and pmr spectra. The protonated chelated imide was also isolated as the perchlorate (yellow) and characterized in a similar manner. Moreover, glycineamide hydroperchlorate was recovered from the complex following treatment with H_2S, and its decomposition temperature or sublimation temperature agreed with that of an authentic sample (≃360°). Similarly, the infrared spectra of the isolated and authentic samples were identical.

When the hydrolysis was carried out at lower pH values, some of the yellow monodentate glycinato complex $[Co(NH_3)_5(NH_2CH_2COO)]^{2+}$ was produced, and both acid and imide complexes were isolated. The acid complex was isolated as the perchlorate and characterized by elemental analysis, by the $pK_{25°}$ of protonation of the monodentate acid anion, 2.43 ± 0.03, and by the visible, ir, and pmr spectra. In addition it was prepared by acid hydrolysis of the parent ester complex.

The 100-Mc pmr spectra of these species are given in Figures 1 and 2, relative to internal standards of tetramethylsilane or *t*-butyl alcohol. Figure 1A shows the spectrum of $[Co(NH_3)_4(NHCOCH_2NH_2)](ClO_4)_2$ in DMSO-d_6, and the broad signals at 1.6 and 2.1 ppm (12 protons) are assigned to the four ammonia groups. The triplet at 1.9 ppm (two protons) is attributed to the protons on the CH_2 group split by the protons on the adjacent NH_2 moiety. The broad signal (one proton) at 2.6 ppm is ascribed to the imide proton, and the broader signal at lowest field (two protons at 3.4 ppm) is ascribed to the NH_2 moiety of the imide. In neutral D_2O all the protons of the nitrogen centers exchange and the spectrum collapses to a singlet which corresponds to the collapse of the CH_2 triplet. In acidic D_2O a similar spectrum was observed to that in DMSO except that the ammine signals broadened and the imide signal was not seen. The complex ion was stable in 3 *M* HCl and 1 *M* NaOH over at least 2 days at 25°.

The pmr spectrum of the chelated imide complex in DMSO-d_6 containing H_2SO_4 is given in Figure 1D. The addition of acid altered the spectrum sharply so that the CH_2 triplet moved downfield beyond the signals due to the coordinated ammonia groups (Figure 1D). Also the signal (one proton) due to the imide center originally at 2.6 ppm moved downfield to 6.1 ppm (one proton) (Figure 1D). This shift was established by adding successively small amounts of H_2SO_4 and following the gradual change in chemical shift with increase in acidity (Figure 1A–D). The spectrum for the isolated protonated species is also given in Figure 2C along with the spectrum for the protonated complex plus additional H_2SO_4 (Figure 2D). Clearly the last instance does not differ from the unprotonated form plus H_2SO_4 (Figure 1D). No sign of an OH signal was found down to 15 ppm.

The methylene signal in acidic DMSO (Figures 1D and 2D) appears to have lost resolution, but it is clear from the DMSO signal that this is not due to the instrument. There may be some long-range coupling between the proton on the oxygen and the CH_2 protons which broadens the original triplet. The large change in chemical shift for the imide complex in the unprotonated and protonated forms may be explained by the change from the shielding due to i to that of ii. The

i ii

broad signal (2.6 ppm) (Figure 1D) arises from the CH_2 protons since a sharp singlet appeared at this position when the N-deuterated complex was measured under the same conditions.

The pmr spectrum of the pentaammine monodentate glycinate complex is given in Figure 2B, and this spectrum can be reproduced with different samples under the same conditions. The broad signal at 4.6 ppm (two protons) is assigned to the glycinato NH_2 moiety, and

(4) Y. Inoue and D. D. Perrin, *J. Phys. Chem.*, **66**, 1689 (1962).

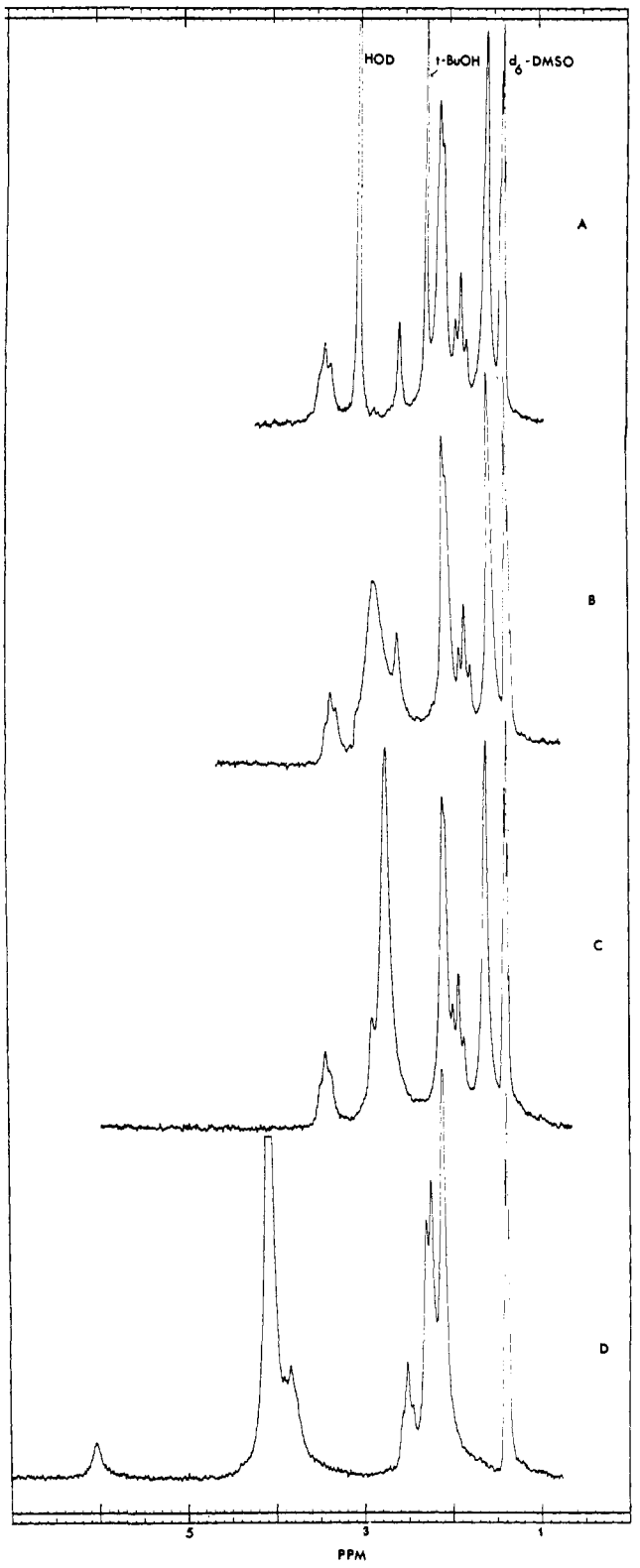


Figure 1. Pmr spectra in dimethyl-d_6 sulfoxide of (A) $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$ and (B–D) $[Co(NH_3)_4(NH_2CH_2CONH)](ClO_4)_2$ with increasing concentrations of H_2SO_4 (internal reference, *t*-butyl alcohol).

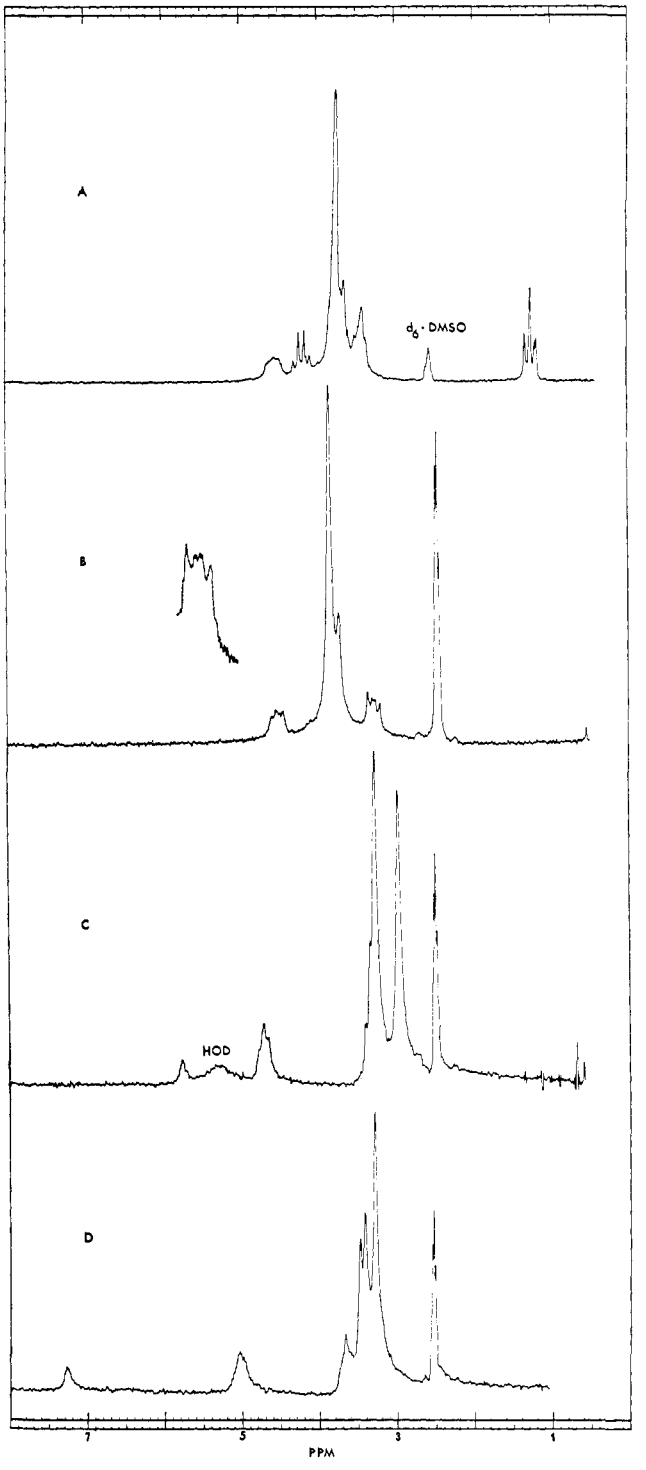


Figure 2. Pmr spectra in dimethyl-d_6 sulfoxide of (A) $[Co(NH_3)_5(NH_2CH_2CO_2CH_2CH_3)]Br_3$, (B) $[Co(NH_3)_5(NH_2CH_2CO_2H)]Cl_3$ (inset 3.5 ppm), (C) $[Co(NH_3)_4(NH_2CH_2C(OH)NH)](ClO_4)_3$, and (D) $[Co(NH_3)_4(NH_2CH_2C(OH)NH)](ClO_4)_3$, with 1 drop of H_2SO_4 (internal reference, tetramethylsilane).

that at 3.8 ppm (15 protons) is assigned to the five NH_3 groups. The broad signal at 3.5 ppm is due to the methylene protons, and this is usually observed as a triplet arising from a coupling with the glycinato NH_2 protons. The increased structure (inset) may be due to restricted rotation of the glycinato moiety which makes the NH_2 protons nonequivalent and possibly the CH_2 protons also.

The pmr spectrum of the parent $[Co(NH_3)_5(NH_2CH_2COOC_2H_5)](ClO_4)_3$ salt is given in Figure 2A, and the signals due to the ethyl group are readily identified at 1.3 and 4.2 ppm. The signal due to the ammonia groups is centered about 4.75 ppm and the broad signal showing signs of some structure at ~4.5 ppm is due to the glycine ester NH_2 group. The triplet expected for

the methylene center (3.4 ppm) shows indications of more structure like the glycinato complex which may arise from long-range coupling or restricted rotation of the ester moiety. Clearly the products which arise from this reactant show no sign of the original ester group.

The infrared spectrum of the parent ester complex was characterized by a sharp absorption band at 1750 cm^{-1} attributed to the C=O stretching mode. This signal vanishes in both the imido and glycinato products, to be replaced by a broad absorption at 1600 cm^{-1} for the latter complex and an even broader band around 1610–1620 cm^{-1} for the former. The spectra of the protonated species were also broad and unrevealing in this region.

The rates of hydrolysis of the $[Co(NH_3)_5(NH_2CH_2COOC_2H_5)](ClO_4)_3$ salt were followed titrimetrically with NaOH (0.1 *N*) using a Radiometer pH stat at 25° and an ionic strength μ = 0.1 (KNO_3). Plots of log (NaOH) against time were resolved into two rates. The faster rate corresponded to the production of the chelated imide plus monodentate glycinato, and the second rate led finally to the production of cobalt(III) oxide which precipitated. The two products due to the first rate were separated on an ion-exchange column and their concentrations measured spectrophotometrically and in some instances by atomic absorption spectroscopy. The reaction leading to decomposition was only significant at the lowest pH values used and accounted at most for 22% of the consumption of the reactant complex (pH 9.02). The results listed in Table I show that the base consumed correlates with the total glycinato and imido complex recovered. The exact nature of the side reaction is not yet understood, but it released ammonia which accounts for the cobalt(III) oxide and the failure of this portion of the reaction to consume NaOH. Despite our incomplete understanding, the side reaction can be separated completely from the first reaction, and since it is irrelevant to the main issue it is not considered further.

Table I. Products of Base Hydrolysis of $[Co(NH_3)_5(NH_2CH_2COOC_2H_5)]Br_3$ at 25° and μ = 0.1 (KNO_3)

pH	$[Co(NH_3)_4NH_2CH_2CONH]^{2-}$ [a]	$[Co(NH_3)_5NH_2CH_2COO]^{2+}$ [a]	NaOH consumed[a]
9.02	0.43	0.35	0.71
	0.41	0.37	
9.26	0.49	0.29	0.83
9.45	0.63	0.26	0.89
9.60	0.67	0.24	
9.75	0.79	0.17	0.97
14.0	0.95	<0.02	

[a] Concentration in moles/mole of initial complex.

Tables II and III show the rate constants for the principal reaction under the pH conditions used, and Table III gives the relative percentages of imido and glycinato complexes produced under these conditions. It is apparent that at the high pH values the reaction occurs primarily through the imide path and little decomposition occurs. In 0.1 *M* NaOH the rate was too fast to measure with our existing equipment, but the production of imide was at least 95%. The rates of hydrolysis were also followed spectrophotometrically using a stopped-flow reactor and carbonate buffers (0.1 *M*) at 25° and an ionic strength μ = 1.0 ($NaClO_4$).

Plots of log ($D - D_\infty$) against time were linear for at least three half-lives, except at the lowest pH value where a little curvature was obtained presumably from the competing decomposition observed during the titrimetric measurements. The rate constants obtained are given in Table II for the pH conditions used. These values differed considerably from those obtained with the radiometer, but the ionic strength in the two instances also varied. The rate at pH 9.75 was slower by a factor of ~4 in the higher ionic strength.

Table II. Base Hydrolysis of $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)](ClO_4)_3$ in Carbonate Buffer (0.1 *M*)[a]

pH	10^2k, sec^{-1}	$10^{-2}k/[OH^-]$, M^{-1} sec^{-1} Obsd	Calcd[b]
9.74	0.60	1.08	1.08
10.00	1.85	1.85	1.71
10.08	2.48	2.04	2.00
10.33	7.14	3.32	3.32

[a] Spectrophotometric rate data at 2475 Å and μ = 1.0 ($NaClO_4$); [complex] = 3×10^{-4} *M*, 25°. [b] Calculated using $k_{Ac} = 0.3 \times 10^2\ M^{-1}\ sec^{-1}$; $k_{Im} = 1.4 \times 10^6\ M^{-2}\ sec^{-1}$.

Table III. Base Hydrolysis of $[Co(NH_3)_5(NH_2CH_2CO_2C_2H_5)]Br_3$[a]

pH	$10^3 \times k_{obsd}$, sec^{-1}	$10^{-2}k/[OH^-]$, M^{-1} sec^{-1} Obsd	Calcd[b]	$[(NH_3)_5Co\text{-}NH_2CH_2\text{-}COO]^{2+}$ Obsd[c]	Calcd[d]	$[(NH_3)_4Co\text{-}NH_2CH_2\text{-}CO_2NH]^{2+}$ Obsd[c]	Calcd[d]
9.02	1.29	1.22	1.19	45	42	55	58
9.26	3.04	1.67	1.70	37	29	63	71
9.45	6.4	2.27	2.36	29	21	71	79
9.60	12.8	3.20	3.14	27	16	73	84
9.65	15.4	3.42	3.47	16	14	84	86
9.75	27.2	4.83	4.22	17	12	83	88
10.94	5330	60.5[e]	58.6				
11.41	35000	136[e]	172				

[a] Radiometer data, μ = 0.1 (KNO_3), 25°; [complex] = 0.01 *M*. [b] Calculated using $k_{Ac} = 0.5 \times 10^2\ M^{-1}\ sec^{-1}$; $k_{Im} = 6.6 \times 10^6\ M^{-2}\ sec^{-1}$. [c] Values in Table I normalized to 100%. [d] Calculated assuming k_{Ac} path leads to pentaammine acid, and k_{Im} to tetraammine imide. [e] Rates measured with Durrum stopped-flow reactor at μ = 0.1 (KNO_3), 25°, [complex] = 5×10^{-4} *M*.

The rate data presented in Tables II and III show both sets of results are consistent with a rate law of the form

$$k_{obsd} = k_{Ac}[OH^-] + k_{Im}[OH^-]^2$$

where k_{Ac} and k_{Im} are the constants for production of acid and imide, respectively. The derived rate constants for the carbonate system are k_{Ac} = 30 M^{-1} sec^{-1} and $k_{Im} = 1.4 \times 10^6\ M^{-2}\ sec^{-1}$ and for the titrimetric conditions k_{Ac} = 50 M^{-1} sec^{-1} and $k_{Im} = 6.6 \times 10^6\ M^{-2}\ sec^{-1}$.

Two hydrolyses were carried out in carbonate buffer, pH 9.75 at 34 and 25°, and the imide and glycinato products were separated to give 49% imide and 21% glycinato at 34° and 44% imide and 25% acid at 25°. This result implies a somewhat greater activation energy for the production of imide than for acid which is increased if the temperature dependence of the buffer is corrected for.

Discussion

The two paths of the rate law can be equated to the production of coordinated monodentate acid anion and to chelated imide, respectively. For an understanding of the mechanisms involved the analogy can be drawn in part from experience in the hydrolysis of simple organic esters. The term which is first order in $[OH^-]$ is consistent with a bimolecular attack of OH^- at the carbonyl carbon leading to the complexed acid anion

$$(NH_3)_5CoNH_2CH_2\underset{\underset{O}{\|}}{C}OC_2H_5 + OH^- \longrightarrow (NH_3)_5CoNH_2CH_2\underset{\underset{O}{\|}}{C}O^- + C_2H_5OH$$

The rate constant for this process, 50 M^{-1} sec^{-1}, μ = 0.1, is to be compared with that attributed to the path first order in $[OH^-]$ for the hydrolysis of $NH_3^+CH_2COOC_2H_5$, 24 M^{-1} sec^{-1} (μ = 0.16).[5] By contrast for the deprotonated ester $NH_2CH_2COOC_2H_5$ the path first order in $[OH^-]$ has a rate constant of 0.58 M^{-1} sec^{-1}.[5] These results for the ester hydrolysis imply that the $Co(NH_3)_5^{3+}$ moiety plays a similar role to H^+. This similarity is also reflected in the identical acid dissociation constant for $NH_3^+CH_2COOH$[6] and $[(NH_3)_5CoNH_2CH_2COOH]^{3+}$ (pK_1 = 2.43, μ = 0.1, 25°) and probably arises from the distance between the protonated or coordinated center and the reactive site. The pK_a of a proton attached to a metal–oxygen center ($[Co(NH_3)_5OH_2]^{3+}$, $pK_a \sim 6$) is vastly different from that of the protonated species (H_3O^+, $pK_a \sim 0$).

The term second order in $[OH^-]$ which leads to chelated imide can be accounted for by the mechanism in Scheme I where the over-all charges on the complex ions do not include the localized charges at specific sites which we consider contribute to an understanding of the reaction.

Provided steady-state conditions hold and proton exchange is established rapidly under the conditions used, the derived rate law takes the form

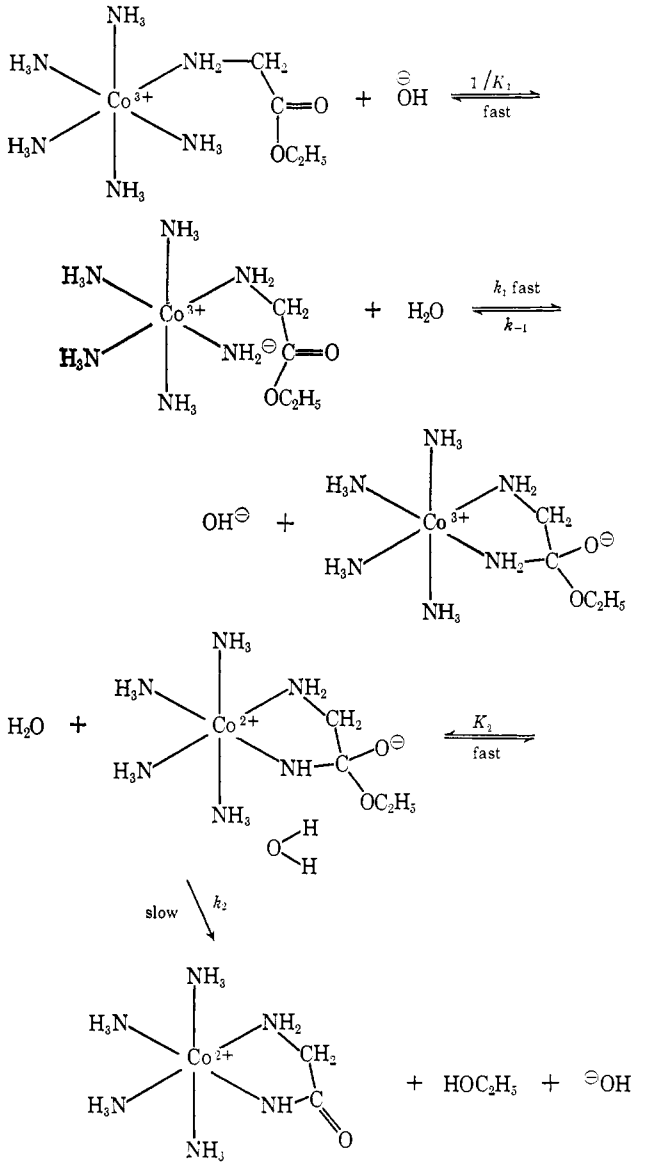
$$-\frac{d}{dt}\{[Co(NH_3)_5NH_2CH_2COOC_2H_5]^{3+}\} = \frac{k_2}{K_1K_2}\frac{k_1}{k_{-1}}[Co(NH_3)_5NH_2CH_2COOC_2H_5][OH^-]^2$$

and

$$k_{Im} = \frac{k_2}{K_1K_2}\frac{k_1}{k_{-1}}$$

Generally cobalt(III) ammine complexes of this type exchange their N–H protons rapidly with rate constants in the vicinity of 10^5 M^{-1} sec^{-1}, and this behavior would ensure that the equilibria are established rapidly relative to imide formation. It is also anticipated that pK_1 will be >2 from studies of related complexes.[7,8] The paths k_1, k_{-1} are required to be fast relative to k_2 from the observed rate law. They are also analogous to the formation and decomposition of intermediates in the frequently observed shifts of acyl groups from O to N

Scheme I



centers in organic chemistry.[9] Finally, pK_2 should be >2 since O^- and OC_2H_5 in the intermediate will donate electrons to the N center, and in addition the charge is now reduced relative to the parent ester complex. This analysis is consistent with the rate law observed.

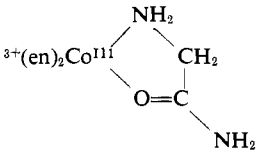
The mechanism proposed is analogous to that suggested for the aminolysis of formate esters by amines[10] which comprises a series of prior equilibrium steps followed by a slow process in which the alkoxy group is lost. It implies the formation of a tetrahedral intermediate prior to the loss of the ester moiety and allows a water molecule to assist the latter process. Alternatively, two protons could be removed from one coordinated ammonia directly. However, since the pK_a for the first deprotonation is greater than 14, the concentration of the doubly deprotonated species must be exceedingly small and the previous mechanism is therefore preferred. Also, in the K_2 step for the mechanism proposed, one of the ammonia molecules

(5) H. L. Conley and R. B. Martin, *J. Phys. Chem.*, **69**, 2914 (1965).
(6) F. Basolo and Y. T. Chen, *J. Am. Chem. Soc.*, **76**, 953 (1954).
(7) R. G. Pearson and F. Basolo, *ibid.*, **78**, 4878 (1956).
(8) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *ibid.*, **89**, 3428 (1967).
(9) F. Bell, *J. Chem. Soc.*, 2962 (1931); R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Am. Chem. Soc.*, **86**, 2406 (1964); M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
(10) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

could be deprotonated instead of the amide center. However, we see no reason why this process should labilize the ester moiety, whereas in the mechanism proposed the imide formation could contribute to the lability of the ester group. In fact, we cannot discriminate at present between the mechanism proposed and concerted amide deprotonation and loss of ethoxide or alcohol. However, if a better leaving group than ethoxide were used the initial deprotonation or chelation may become rate determining, and a first-order dependence on [OH^-] should be observed for imide formation.

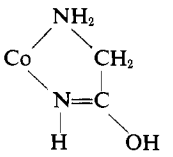
The metal ion presumably contributes to the ease of the reaction by holding the two reactants in juxtaposition. Also the reaction can be called metal ion promoted since the formation of amino acid amide in the form of the self-condensation of glycine ethyl ester to 2,5-diketopiperazine is rather slow (92% complete in 5.7 days at 37°).[11] Moreover, under similar conditions to those used for the aminolysis of the complex ester, glycylglycine ethyl ester (1 g/25 ml of 0.2*M* Tris buffer, pH 8, 25°) failed to yield any observable 2,5-diketopiperazine after 10 days.

Presumably part of the driving force for the process is the formation of the chelate ring which is exceptionally stable. The stability can be gauged from the failure of the N,N-chelated imide to hydrolyze relative to the species

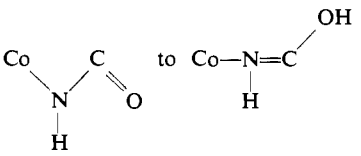


which hydrolyzes at pH 12 to the chelated glycinato complex with a rate constant ~0.03 sec^{-1}.[12] Clearly if these forms were interconverting, then both species would hydrolyze. Both results are consistent with a general observation that if the moiety to be hydrolyzed forms part of the chelate skeleton, then the reaction is inhibited by the presence of the metal ion.[13]

A factor which is related to the chelation of peptides is the propensity of a chelated amide to lose a proton from the bound amido NHR group. It seems likely that this is a function of the combined electron-withdrawing capacity of the metal ion and the C–O group. The dual effect leads to the oxygen becoming more basic than the N center, and the evidence requires protonation at O rather than N to form



In acidic DMSO another proton is not added to the imide center since the integrated pmr spectrum clearly shows one proton in the region. Also the large shift downfield on protonation is consistent with the change from



if we assume that diamagnetic and paramagnetic shielding occurs similar to that in the analogous aldehydes. The fact that the protonated complex is a strong acid is also consistent with rapid proton exchange between HOD and the proton on the imide oxygen in DMSO. The protonated complex OH signal would then coincide with the HOD signal.

The results have some bearing on previous proposals which have been made from stability constant and structural studies where it has been argued that peptides chelate by losing the amide proton.[14] In those instances where the N–H is retained, chelation takes place through the carbonyl group. It would appear from this simple system that protonation at the amide site is resisted, and this factor coupled with the stability of the system in acid and base solutions suggests that the chelate ring in complexes of this type is extremely stable. Finally, it is conceivable that rapid amide formation from amino acid esters might be achieved by mixing amine and ester in the presence of a transition metal ion such as Cu^{2+} or Ni^{2+}.

(11) E. Abderhalden and S. Suzuki, *Z. Physiol. Chem.*, **176**, 101 (1928).
(12) D. A. Buckingham, unpublished work.
(13) F. P. Dwyer, "Metal Chelates and Chelating Agents," F. P. Dwyer and D. P. Mellor, Ed., Academic Press, New York, N. Y., 1964.
(14) H. C. Freeman, *Advan. Protein Chem.*, 22, 257 (1967).