haps of a steric nature as suggested by the moderately large negative $\Delta S^{\ddagger}$ value for the water reaction as compared to essentially zero $\Delta S^{\ddagger}$ values for the other two species. A recent study of CO_2-catalyzed oxygen exchange of the $Cr(NH_3)_5OH^{2+}$ ion[29] has enabled an estimate of the rate constant for the reaction of this species with CO_2 at 25° and $I = 0.1$ M. The suggested lower limit of 11 M^{-1} sec^{-1} fits satisfactorily into the qualitative pattern with respect to relative basicity noted above, since the pK_a of the chromium(III) aquo complex ion is indeed somewhat smaller[30] than that of its cobalt(III) analog.

Turning now to the carbonic anhydrase catalyzed process, hydroxyl coordinated to zinc has long been believed to be the significant reactant,[7] a concept supported by a recent review of the metal ion function in this enzyme,[31] although a contrary opinion based on nmr data has also appeared.[32] The evidence is strong[31] that the pK of the presumed aquo–zinc(II) complex of the enzyme is probably about 7, very close to that of the cobalt(III) species of our study. It seems quite logical to expect that it is the metalloenzyme in its hydroxo form which does in fact react directly with CO_2 to yield the bicarbonate product as does the pentaamminecobalt(III) analog. However, there is no problem of the bicarbonate product being "trapped" on the metal ion of the metalloenzyme, due to the much greater lability of Zn(II) complexes as compared to Co(III),[33,34] so that rapid "turnover" of CO_2 to free HCO_3^- is possible. Furthermore, the data of Table IV indicate that the major factor facilitating rate acceleration by the metalloenzyme is the greatly decreased enthalpy of activation as compared to either $Co(NH_3)_5OH^{2+}$ or the free OH^- ion. Thus one need not invoke special stereochemical factors to explain the enzyme activity other than an ability to get the reacting species together effectively, which is of course the basic assumption of the Michaelis–Menten mechanism.[31] Nevertheless, a conclusion along these lines cannot be very definitive until more comprehensive data are available concerning the temperature parameters of the enzyme-catalyzed reaction.

Acknowledgments. We are grateful to F. Dwyer, Jr., and A. M. Sargeson for making their data (ref 26) available to us. Some of the earlier portions of our study received financial support through Grant No. GP-10641 from the National Science Foundation to the State University of New York at Buffalo.

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Aminolysis of Cobalt(III) Activated Esters. Stabilization of an Amine–Alcohol Intermediate

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Abstract: The reaction between isopropylglycinate bis(ethylenediamine)cobalt(III) perchlorate and glycine ethyl ester in dimethyl sulfoxide to form ethylglycylglycinate bis(ethylenediamine)cobalt(III) perchlorate and isopropyl alcohol occurs in two stages. The first reaction follows a rate law $k_{obsd} = k_1$[amine] with $k_1 = 14 \pm 1$ M^{-1} sec^{-1} at 25°, $\mu = 0.015$, and is attributed to addition of glycine ethyl ester to the carbonyl center. The second reaction follows the rate law $k_{obsd} = Kk$[amine]/(1 + K[amine]) with $K = 16$ M, $k = 1.4 \times 10^{-2}$ sec^{-1} at 25°, and $\mu = 0.015$. It is accounted for in terms of the general acid catalyzed removal of isopropyl alcohol from the conjugate base of the amine–alcohol intermediate. Infrared and quenching experiments have also been used to identify the intermediate and to investigate some of its properties.

The mechanism of aminolysis of organic esters still appears to be a viable issue. Whether the reaction is concerted or proceeds *via* an addition–elimination process remains uncertain in most instances.[1,2] Certainly amine–alcohol intermediates are required or implied in the addition of amines to some carbonyl centers[3–6] and their properties as a function of pH have been inferred by generating them from different sources and observing the breakdown products.[3,5] Even so in no single case of ester aminolysis has the amine–alcohol intermediate been directly observed and the rates and rate laws for its formation and decay established.

The possibility of observing such an intermediate arises by chelating to a metal an amino acid ester *via* the amino group and carbonyl oxygen atom, structure

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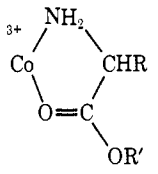

I

I. This arrangement provides a highly acyl-activated ester containing a poor leaving group. It was anticipated that addition of a nucleophile[7] would be facilitated by the positively charged metal substituent and that loss of alcohol would be retarded, compared to the uncoordinated ester. Provided the mechanism is not concerted and that the intermediate is stabilized with respect to the transition states for its formation and decay, the amine–alcohol might be directly observed. In this paper we report the realization of this prognosis.

Experimental Section

Reaction rates were followed using a Cary 16K spectrophotometer or a Durrum Gibson stopped-flow reactor. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. For the reactions followed with the Cary 16K spectrophotometer a small hand operated Teflon stopped-flow mixer was used to inject the solutions into a Helma QS flow-through cell (volume <2 ml). This apparatus consisted of two Teflon syringes (delivery volume 5 ml) and surrounded by a water thermostated metal case. The syringes could be filled independently of each other. The apparatus was suitable for reactions with $t_{1/2} > 1$ sec. A similar arrangement was adopted for the infrared experiment except that a NaCl cell (0.1-mm path) was substituted for the quartz cell.

Cobalt estimations were made with a Techtron AA4 atomic absorption spectrometer. Products from kinetic experiments were separated on Bio-Rad Analytical Dowex 50Wx2 (200–400 mesh, Na^+ or H^+ form) cation exchange resin, or on SE-Sephadex (C25 Na^+ form) resin. Absorption spectra of eluate fractions are recorded on a Cary 14 spectrophotometer.

Glassware used in the preparations of the chelated ester complex, kinetics, and product analysis experiments was washed carefully with water, then methanol, and dried in an oven at 200° for at least 1 day. It was then transferred to a drybox (N_2 atmosphere, desiccant P_2O_5) shortly before use.

Materials. Dimethyl sulfoxide (Mallinckrodt AR, 2 l.) was dried over Linde molecular sieves (type 4A) for 2 days. It was then shaken intermittently with calcium hydride (5 g) for 12 hr and fractionally distilled from fresh calcium hydride (5 g) under reduced pressure. The first fraction (100 ml) was discarded. The fraction used for kinetic experiments gave bp 48° at 3 mm, n_D 1.4785 at 25°, and was stored over Linde 4A molecular sieves previously preheated at 300° for 2 days. Tetraethylammonium perchlorate was prepared from the chloride salt (31 g) by dissolution in 50% ethanol (100 ml) and adding $LiClO_4 \cdot H_2O$ (22 g) in ethanol (20 ml). The perchlorate salt which immediately crystallized was collected and thoroughly washed with cold water and twice recrystallized from 80% ethanol. The final product was washed with ether and dried under vacuum over P_2O_5 at 60° for 2 days.

Ethyl glycinate was prepared from the hydrogen chloride salt (30 g) by adding it to a stirred saturated sodium hydroxide solution (50 ml). The separated ester layer was extracted with ether (100 ml) and this and two further ether extractions (100 ml) dried over anhydrous Na_2CO_3 for 2 hr. The ether extract was then filtered, the ether removed under reduced pressure, and the ester fractionally distilled. Three fractions (total 18 g) were collected (bp 40–42° at 7 mm) but only the middle fraction was used for kinetics (bp 41° at 7 mm, n_D 1.42365 at 25°). The dry ester was stored at −20° where it was stable over many months. *Anal.* Calcd for $NH_2CH_2COOC_2H_5$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.28; H, 8.85; N, 13.73. Solutions of the ester in dry dimethyl sulfoxide were prepared immediately prior to use.

$[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ was prepared in a drybox (N_2 atmosphere) by a modification of a previous method.[9] *cis*-$[Co(en)_2BrglyOCH(CH_3)_2](ClO_4)_2$[9] (18 g) was dissolved in methanol (Grignard dried, 50 ml) and treated with $AgClO_4$ (17 g) previously dried over P_2O_5 for 4 days. The mixture was shaken intermittently for 3 hr and filtered. Anhydrous ether was added to the orange-red filtrate, and the product was washed with two (100 ml) portions of methanol–ether (1:10) and then with ether to remove excess $AgClO_4$. The product was redissolved in anhydrous acetone (30 ml), filtered, and anhydrous ether (300 ml) added to give an oily product. The ether layer was removed by decantation, and the oily product was dissolved in acetone–methanol (150 ml, 1:4) and treated with ether. Crystallization was induced by scratching the beaker with a glass rod. The product was collected, the recrystallization from acetone–methanol (1:4) repeated, and adhering solvent removed under vacuum. The complex was stored in an evacuated desiccator over P_2O_5 (yield 12 g). *Anal.* Calcd for $[Co(C_4H_{16}N_4)(C_5H_{11}O_2N)](ClO_4)_3$: C, 18.17; H, 4.56; N, 11.79; Co, 9.91. Found: C, 18.08; H, 4.8; N, 12.1; Co, 9.9.

Kinetic Measurements. The aminolysis of $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ was followed spectrophotometrically (450 nm). Dimethyl sulfoxide solutions of the complex (5.0×10^{-3} *M*) and glycine ester were prepared and loaded into the stopped-flow reactor in a drybox. The reactor was transferred to the spectrophotometer and equilibrated at the reaction temperature (15 min). After each run the reactor was washed with dry methanol and redried for 6 hr in an evacuated desiccator over P_2O_5. For reactions with $t_{1/2}$ between 0.1 and 5 sec the Durrum-Gibson equipment was used and a similar procedure adopted for drying the syringe assembly and reservoirs. Rate data were not obtainable for $t_{1/2} < 0.1$ sec because of the high viscosity of the reactant solutions.

For the infrared experiments the reactor was charged with solutions of the complex (0.4 *M*) and ester (0.6 *M*) in the drybox, and the solutions were injected into the NaCl cell. Data were recorded at 1630 cm^{-1}.

Product Analyses. Products formed during the reactions were determined following quenching of mixtures of the chelated ester (25 ml, 5×10^{-3} *M*) and $NH_2CH_2COOC_2H_5$ (25 ml, 4×10^{-2} *M*) using 10.6 *M* HCl or H_2O. These solutions were diluted with water and the products sorbed on H^+ form Dowex 50Wx2 (200–400 mesh) or Sephadex SE C-25 cation-exchange resins. Elution from Sephadex using $KClO_4$ (0.05 *M*) separated $[Co(en)_2(glyglyOC_2H_5)]^{3+}$ from $[Co(en)_2gly]^{2+}$ and allowed concentration and isolation of the perchlorate salts. For most experiments, however, Dowex resin was used when elution with 2 *N* HCl resulted in the slow hydrolysis of the $[Co(en)_2(glyglyOC_2H_5)]^{3+}$ product to give $[Co(en)_2(glyglyOH)]^{3+}$. In all cases the recovered products represented more than 98% of the total cobalt. Cobalt analyses were carried out by both atomic absorption and visible spectroscopy.

Detection of Water in Dimethyl Sulfoxide. $[Co(en)_2glyOC_3H_7](ClO_4)_3$ (0.14 g) was dissolved in dimethyl sulfoxide (50 ml) and kept for 4 hr in the drybox. Fresh glycine ethyl ester (0.1 ml) was then added and the mixture quenched with 10.6 *M* HCl to pH 3–4 after 100 sec. The mixture was diluted with water, sorbed on the H^+ form Dowex resin, and eluted with 1.5 *M* HCl. When water was present in the dimethyl sulfoxide, both glycinato and dipeptide products were observed; when absent, only the dipeptide complex was formed. The solvent was periodically checked in this manner.

Results

Choice of Experimental Conditions. The condensation of $[Co(en)_2glyOCH(CH_3)_2]^{3+}$ with several amino

$$[Co(en)_2glyOCH(CH_3)_2]^{3+} + NH_2R \longrightarrow [Co(en)_2(glyNHR)]^{3+} + (CH_3)_2CHOH$$

acid esters and amines was followed in a number of nonaqueous solvents and shown to give quantitative amounts of the corresponding glycine–amide complex. However, the relatively basic methylamine, *n*-butylamine, diethylamine, and ammonia slowly gave a brown discoloration to the product, and this compli-

(7) It has been demonstrated that in aqueous solution amines and carboxylic acid anions act specifically as nucleophiles toward I irrespective of their proton basicity; that is, there is no detectable general base path for hydrolysis: D. A. Buckingham, J. Dekkers, A. M. Sargeson, and M. B. Wein, *J. Amer. Chem. Soc.*, **94**, 4032 (1972). Also, under the same conditions aminolysis is either not, or only very slightly, catalyzed by a second molecule of amine.

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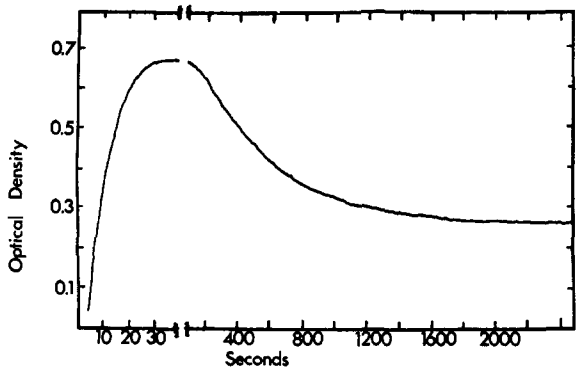


Figure 1. Change in optical density (×10 at 450 nm) *vs.* time on treating $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ (2.0×10^{-3} *M*) with $NH_2CH_2CO_2C_2H_5$ (1.0×10^{-2} *M*) in dimethyl sulfoxide at 25°.

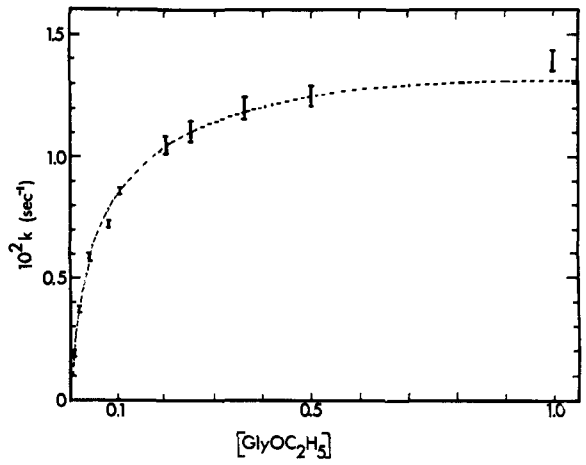


Figure 2. Comparison of experimental rate data for decay of the amine–alcohol intermediate (Co-IH) with the calculated curve (- - - - - - -) using the expression $k_{calcd} = k_2K[glyOC_2H_5]/(1 + K[glyOC_2H_5])$ with $K = 16\ M$ and $k_2 = 1.4 \times 10^{-2}$ sec^{-1}.

cated the kinetic analysis. The amine chosen for detailed study was ethyl glycinate primarily because it avoided this problem; also it was easy to prepare and purify, and dimerization to 1,4-diketopiperazine was effectively eliminated by storage at −20°. In dimethyl sulfoxide, ethyl glycinate produced the dipeptide more rapidly with $[Co(en)_2glyOCH_3](ClO_4)_3$ than with $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$, Table I. Since both reactions were relatively fast under normal amine concentrations (1–0.01 *M*), it was more convenient to use the isopropyl ester for the detailed study.

Table I. Kinetics of the Reaction between $[Co(en)_2glyOC_3H_7](ClO_4)_3$ and $glyOC_2H_5$ in DMSO at 25°[a]

	Rate I		Rate II	
$[glyOC_2H_5]$, *M*	$k(1)_{obsd}$, sec^{-1}	$k_1 = k_{obsd}/[glyOC_2H_5]$, M^{-1} sec^{-1}	$10^2k(2)_{obsd}$, sec^{-1}	$10^3 \times k_{calcd}$,[b] sec^{-1}
0.01	0.13 ± 0.05 (4)	13	1.87 ± 0.10 (3)	1.90
0.02	0.28 ± 0.10 (5)	14	3.65 ± 0.10 (3)	3.40
0.04	0.58 ± 0.05 (2)	14	5.78 ± 0.10 (3)	5.46
0.08	1.1 ± 0.05 (3)	14	7.20 ± 0.05 (3)	7.85
0.1	1.5 ± 0.05 (5)	15	8.50 ± 0.05 (4)	8.61
0.2	3.0 ± 0.03 (4)	15	10.5 ± 0.5 (4)	10.7
0.25	3.3 ± 0.03 (4)	13	11.0 ± 0.05 (2)	11.2
0.37			12.0 ± 0.5 (3)	12.0
0.5			12.5 ± 0.5 (2)	12.4
1.0			14.0 ± 0.5 (3)	13.2
0.02[c]	0.28		3.65	
0.02[d]	0.23		3.20	
0.02[e]	0.13		2.31	
0.02[f]	0.135		3.0	
0.02[g]	0.125		3.8	
0.025[h]	0.27	11	15.2	

[a] $[Co(en)_2glyOC_3H_7](ClO_4)_3$ is 2.5×10^{-3} *M* measured at 450 nm. Values in parentheses are the number of experiments performed. [b] Calculated from rate expression $k_{calcd} = k_2K[glyOC_2H_5]/(1 + K[glyOC_2H_5])$, $K = 16\ M$, and $k_2 = 1.4 \times 10^{-2}$ sec^{-1}. [c] μ = 0.015 (no added salt). [d] μ = 0.025. [e] μ = 0.05, adjusted with $[(C_2H_5)_4N]ClO_4$. [f] μ = 0.05 with $[(C_2H_5)_4N]ClO_4$ + $glyOC_2H_5 \cdot HClO_4$ (2.5×10^{-3} *M*). [g] μ = 0.05 with $[(C_2H_5)_4N]ClO_4$ + $glyOC_2H_5 \cdot HClO_4$ (2.0×10^{-2} *M*). [h] $[Co(en)_2glyOCH_3](ClO_4)_3$ 2.4×10^{-3} *M*, product >98% peptide.

The solvents examined were dimethylformamide, acetonitrile, *N*-dimethylacetamide, acetone, methanol, and dimethyl sulfoxide. Condensation occurred in each case, but some solvents showed more desirable characteristics than others. The complex was not sufficiently soluble in dimethylformamide, acetonitrile, and *N*-dimethylacetamide; all reacted with the amine under the reaction conditions slowly forming intense brown products or slowly decomposing the product dipeptide complex, and acetone condensed with the methylene group of the free ester in a Knoevenagel-type reaction. In methanol, addition of amine (5×10^{-2} *M*) to the orange chelated ester complex (5×10^{-3} *M*) immediately gave an intense red color which quickly faded (30 sec) to the orange color of the dipeptide complex, which could be quantitatively recovered. The red color may arise by deprotonation of the coordinated amine ligands or by formation of the tetrahedral intermediate. However this reaction has not been further examined. Dimethyl sulfoxide was chosen as the solvent for the detailed kinetic analysis since it did not generate any dubious or unwanted characteristics apart from a very slow decomposition of the peptide product at high amine concentrations (>1 *M*). This did not interfere with the rate measurements.

Kinetics. The aminolysis of $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ was measured spectrophotometrically at 450 nm; two rate processes were observed differing considerably in velocity, Figure 1. These processes were measured under pseudo-first-order conditions of amine, and the rate constants for various amine concentrations (separated graphically) are given in Table I. For the first process, plots of log $(D_\infty - D_t)$ against time were linear for at least four half-lives. The kinetics at each condition were at least duplicated and the same results were obtained with both types of stopped-flow reactor under the same conditions. The first process obeys the rate law $k(1)_{obsd} = k_1[glyOC_2H_5]$. For the second process plots of log $(D_\infty - D_t)$ against time were also linear for at least four half-lives. The observed data are given in Table I. This process fits the rate law $k(2)_{obsd} = k'[glyOC_2H_5]/(1 + K[glyOC_2H_5])$ and exhibits a limiting rate near 1 *M* amine, Figure 2. Table I shows a decrease in rate for both reactions as the ionic strength is increased using tetraethylammonium perchlorate as supporting electrolyte, and addition of protons in the form of $[NH_3^+CH_2COOC_2H_5]ClO_4$ increases the rate of the second reaction but does not

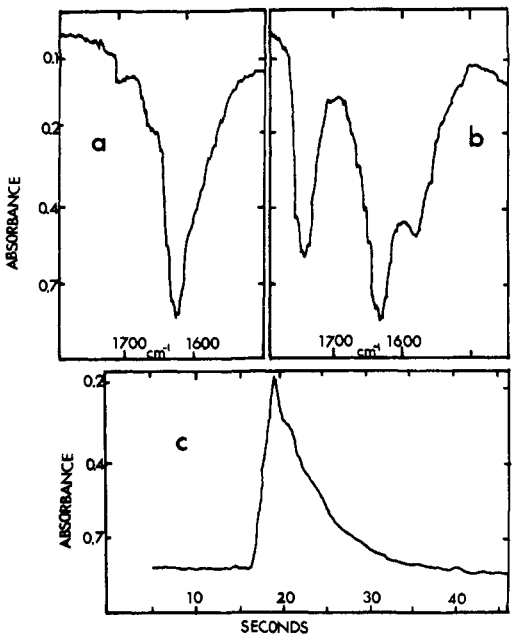


Figure 3. (a) Infrared spectrum (0.1-mm NaCl cell) of $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ (0.2 *M*) in dimethyl sulfoxide. (b) Infrared spectrum (0.1-mm NaCl cell) of products of the reaction between $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ (0.2 *M*) and $NH_2CH_2CO_2C_2H_5$ (0.3 *M*) in dimethyl sulfoxide. (c) Change in absorbance *vs.* time on treating $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ (0.2 *M*) with $NH_2CH_2CO_2C_2H_5$ (0.3 *M*) in dimethyl sulfoxide at 1630 cm^{-1} and *ca.* 25° (0.1-mm NaCl cell).

affect the first reaction. This latter effect is accommodated by the observed rate laws for the two processes.

Traces of water markedly increased the rate of the second reaction, and this factor made the kinetic experiments inordinately difficult to perform. Apart from rigorously drying the solvent and reagents, reproducible results were only obtained when the mixing apparatus was dismantled and rigorously dried between each run.

Product Analysis. The formation of chelated dipeptide complexes by the addition of a variety of amino acid esters to cobalt(III) chelated glycine esters in dimethyl sulfoxide, has been reported previously.[10] The peptide product from this study was identified after isolation from Sephadex SE-25 cation-exchange resin as $[Co(en)_2glyglyOC_2H_5]^{3+}$ by elemental analysis (perchlorate salt) and by visible, infrared, and proton magnetic resonance (100 MHz) spectral comparisons with the authentic material. Elution from Dowex 50WX2 resin using 2 *M* HCl resulted in hydrolysis of the ester moiety and recovery of the dipeptide acid complex as $[Co(en)_2glyglyOH]Cl_3$.

The reaction was also quenched with water or aqueous HCl at various times along the reaction path. The products (>98% of total Co), separated on ion exchange resins, are given in Table II. During the first reaction the products were identified as $[Co(en)_2gly]^{2+}$ and $[Co(en)_2glyglyOC_2H_5]^{3+}$ ions and similar amounts were formed regardless of whether the reaction was quenched with water (pH 10) or with HCl(aq) to pH 4. The product ratio is in fair agreement with that predicted from k_{obsd} for the first reaction, Table I, implying that

(10) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **89**, 4539 (1967).

Table II. Products of the Reaction of $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ with $glyOC_2H_5$ in DMSO at 25° [a]

	t, sec	$[Co(en)_2glyglyOC_2H_5]^{3+}$	$[Co(en)_2gly]^{2+}$	Quenching method
A		50	48	*d*
	5[b]	53 (47)[h]	47 (53)	*d*
		52	45	*d*
	10	70 (68)	26 (32)	*d*
	30	95 (97)	5 (3)	*d*
	32	95 (97)	4 (3)	*d*
	120	98 (100)		*d*
	500[c]	99 (100)		*d*
	1090[c]	98 (100)		*d*
B				
	5[b]	46	54 (53)	*e*
	40[c]	96	4 (1)	*e*
		71	29	*f*
		73	27	*g*
	300[c]	93	7	*e*
	1860[c]	97	3	*e*
	1860	96	4	*f*

[a] [Complex] = 2.5×10^{-3} *M*, [$glyOC_2H_5$] = 0.01 *M* 50 ml solution. [b] $t_{1/2}$ = 5.5 sec, rate I. [c] $t_{1/2}$ = 370 sec, rate II. [d] Solution added to calculated amount of 11 *N* HCl to neutralize base to pH ~4. [e] Water 50 ml added to reaction solution. [f] Solution added to 11 *N* HCl (1.5 ml). [g] HCl (50 ml, 0.2 *M*) added to solution. [h] Values in parentheses calculated product ratios from measured rate constants.

the unreacted ester rapidly forms $[Co(en)_2gly]^{2+}$ and that the intermediate product forms substantially $[Co(en)_2glyglyOC_2H_5]^{3+}$. After the first reaction was complete (~40 sec) quenching with water gave $[Co(en)_2glyglyOC_2H_5]^{3+}$ (>90%), but quenching with strong acid gave some 25% $[Co(en)_2gly]^{2+}$. The latter product was characterized by comparisons of its visible spectrum (ϵ_{487} 98), chromatographic behavior, and pmr spectrum (100 MHz) with those for authentic $[Co(en)_2gly]Cl_2$. The same result was obtained in acidic dimethyl sulfoxide and in 50% aqueous 0.1 *M* HCl. The two sets of results given in Table II were collected using different batches of chelated ester and the slight discrepancies in the second set reflect the presence of a 3–4% $[Co(en)_2gly]^{2+}$ impurity in the reactant.

Infrared Experiments. The spectra of $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ in anhydrous dimethyl sulfoxide and $[Co(en)_2glyOCH(CH_3)_2](ClO_4)_3$ treated with $glyOC_2H_5$ in anhydrous dimethyl sulfoxide at the same concentration (0.4 *M*) are given in Figures 3a and 3b. The strong absorptions at about 1630 cm^{-1} of approximately equal intensity in the chelated ester and the dipeptide product are consistent with the >C=O absorption of the coordinated carbonyl group.[9,11] The absorption at 1740 cm^{-1} in the peptide product is attributed to >C=O stretching of the uncoordinates ester group.

On mixing the ester complex with glycine ester a rapid and substantial decrease in the absorption at 1630 cm^{-1} was observed, Figure 3c. This was followed by a slower increase back to almost the same intensity. This experiment was reproduced several times but it did not give accurate kinetic data since the cell was not thermostated and the infrared beam caused substantial changes in the temperature of the sample during the course of the reaction. However the rate of re-forma-

(11) M. D. Alexander and D. H. Busch, *J. Amer. Chem. Soc.*, 88, 1130 (1966).

tion of the coordinated carbonyl group is roughly consistent with the rate data obtained in the visible region, Table I.

Discussion

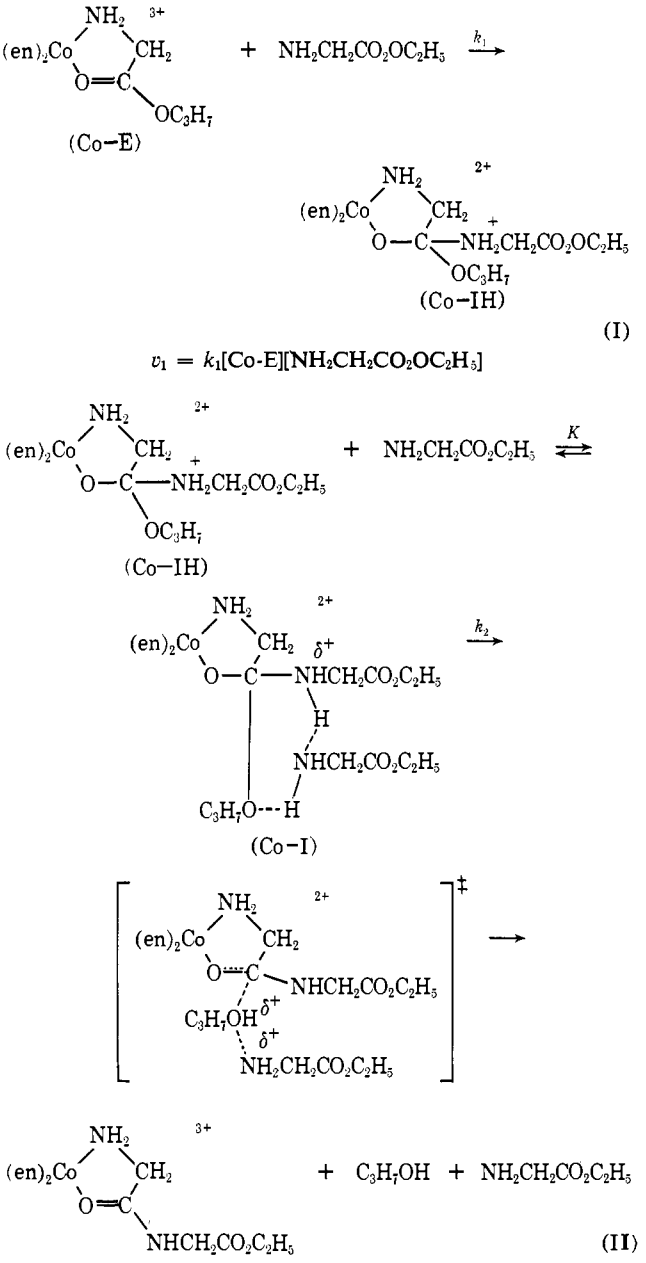
An obvious interpretation of the two rate processes is the formation and decomposition of an amine–alcohol complex. This is partly supported by the types of rate laws observed for similar systems with purely organic substrates. In those processes where addition is the rate-determining step a term first order in base is commonly observed; where the leaving group determines the rate, a more complicated rate law is frequently seen which is usually associated with some method of protonating the leaving group.[3,12]

This interpretation of the kinetics is supported by the products obtained from the quenching experiments. Quenching during the first reaction, Figure 1, produces $[Co(en)_2gly]^{2+}$ and $[Co(en)_2glyglyOC_2H_5]^{3+}$ (Table II). The former arises from the unreacted chelated ester which hydrolyzes rapidly in aqueous solution;[9,11] the latter arises rapidly from the amine–alcohol intermediate in the presence of a plentiful supply of proton donor and requires that 2-propanol is preferred as a leaving group over glycine ethyl ester. After completion of the first reaction, quenching with water (pH >5) rapidly produces the chelated dipeptide ester. Attempts to measure the rate of this reaction by rapidly mixing, in a stopped-flow reactor, water and a dimethyl sulfoxide solution of the intermediate showed that the reaction was complete in <0.1 sec at 25°.

A consequence of the formation of the tetrahedral carbon intermediate is that the >C=O stretching frequency of the chelated ester at 1630 cm^{-1} should vanish. The experiment where this frequency was monitored showed a sharp initial decrease, Figure 3, followed by a slow growth back to about the initial intensity. The result is also consistent with the rate data since the infrared spectrometer was not capable of following the formation of the intermediate species under the conditions used ($t_{1/2} \sim 0.1$ sec) but was capable of observing the spectrum of the tetrahedral intermediate and its relatively slower decay to give the >C=O absorption of the chelated dipeptide ester ($t_{1/2} \sim 7$ sec).

The three sets of experiments give unqualified support for the existence of the chelated tetrahedral intermediate, and it remains to discuss the mechanism in the light of previous studies on related organic substrates. Over the 0.01–0.25 M concentration range the first reaction follows a rate law first order in amine and we assert that the process is a simple bimolecular reaction, mechanism I, with $k_1 = 14 \pm 1\ M^{-1}\ sec^{-1}$ at 25°, $\mu = 0.015$.

The observed rate law for the decomposition of the amine–alcohol [Co-IH] intermediate requires an equilibrium process prior to the rate-determining step and is consistent with an amine-catalyzed transfer of a proton to the leaving group such that isopropyl alcohol rather than isopropoxide ion is lost. The argument that the former is a better leaving group than the latter may be especially strong in this instance where the substrate has an overall 3+ charge. Mechanism II accommodates all the observations, and gives a rate law $v_2 = k_2K[NH_2CH_2CO_2C_2H_5][Co]/(1 + K[NH_2CH_2CO_2C_2H_5])$ where [Co] = [Co-IH] + [Co-I] and $K = 16\ M$ and $k_2 = 1.4 \times 10^{-2}\ sec^{-1}$ at 25° and $\mu = 0.015\ M$.



The calculated rate constants are given in the last column of Table I and in Figure 2. A mechanism involving the amine-catalyzed stepwise transfer of a proton does not agree with the pseudo-first-order rate data obtained in the absence of added protonated amine, although added protonated amine appears to increase the rate slightly. This latter observation can be accommodated by an additional path involving protonated amine, *viz.* reaction III.

Attempts to carry out measurements at higher amine concentrations (0.1–0.5 M) in the presence of small quantities of added protonated amine gave progressively smaller optical density changes for the second reaction and were generally less reproducible. However they did demonstrate a slight increase in rate. A related mechanism involving the general acid catalyzed removal of alcohol has been preferred by Bunnett and

(12) W. P. Jencks in "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 526–533.

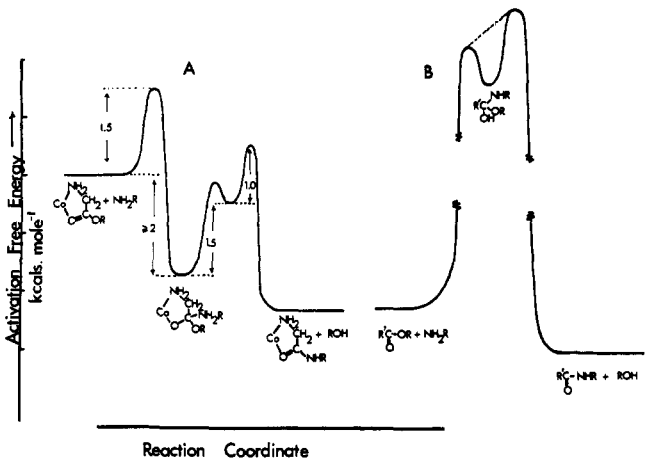
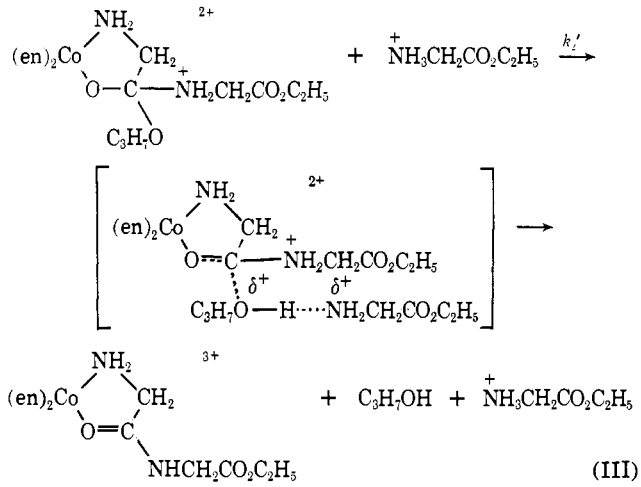


Figure 4. Comparison of reaction coordinate diagrams for metal ion assisted (A) and unassisted (B) aminolysis of an organic ester. Compared to B the tetrahedral intermediate in A is substantially stabilized with respect to the ester and this leads to more rapid addition of the amine. However, loss of alcohol in A is slow compared to B, the latter process being either subsequent to (full curve) or concurrent with (dotted curve) amine addition.



(III)

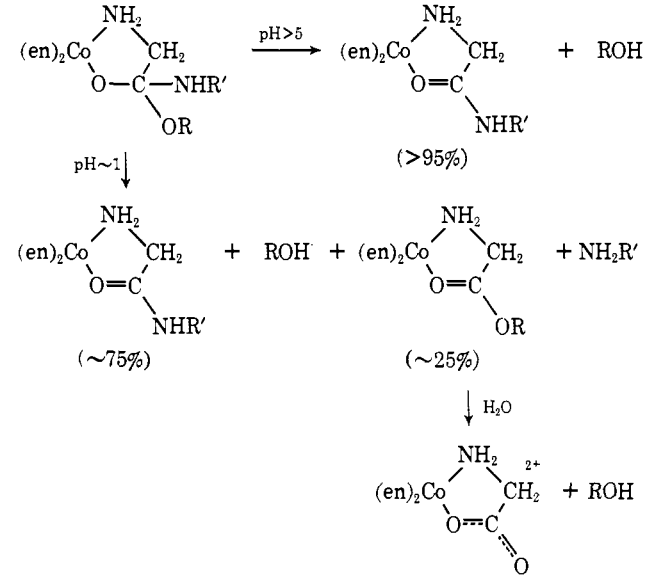
Davis for the aminolysis of ethyl formate in ethanol.[13] Removal of alcohol from the conjugate base of the amine–alcohol intermediate was accomplished by the solvent and protonated amine giving rise to terms $[\text{amine}]^{3/2}$ and $[\text{amine}]^2$, respectively.

Mechanism II appears to have two difficulties. The pK_a of glycine ethyl ester is likely to be greater than either $>CNH_2R^+$ or $>CO(H)C_3H_7^+$ and a concerted mechanism is therefore unlikely. Also, it is hard to believe that the intermediate [Co-I] is stable and remains undissociated when k_2 is quite slow. However another acceptable explanation of the rate law eludes us.

Finally, it is appropriate to discuss the points raised in the introduction, *viz.*, the exceptional reactivity of the metal activated ester and the factors which may account for stabilization of the amine–alcohol intermediate (IH). It is to be expected that the polarizing influence of a Co^{3+} ion on an acyl carbon center would promote nucleophilic attack, and data presented elsewhere demonstrate that this results in $\sim 10^6$ acceleration in rate for both O and N nucleophiles.[14,15] Axiomatically it should be harder for a group to leave with its electron pair. If these effects were important in determining an overall rate for addition and elimination, then the metal should have little influence. Such would be the case for a concerted addition–elimination process with the transition state representing largely bond breaking rather than bond making, but what is clear from this study is that relative to analogous organic reactions a pronounced stabilization of the addition intermediate has occurred, Figure 4. It is this effect which allows the addition and elimination processes to be observed as separate reactions and large amounts (>80%) of the amine–alcohol to be seen. Also it is this stabilization which lowers the overall $\Delta G^{\ddagger}$ for the two processes and accounts for the ability of metal ions to accelerate nucleophilic substitution reactions at unsaturated centers of coordinated groups. However, contrary to the polarization argument given above which might be expected to lower $\Delta H^{\ddagger}$, the limited data available show that the enhancements in rate arise from more positive $\Delta S^{\ddagger}$ values.[14,15] This entropy effect may be associated with a substantial increase in stability of the chelate ring in the transition from the rigid planar ring of the chelated ester to the pronounced gauche conformation of the amine–alcohol intermediate. Certainly saturated five-membered rings are known to be conformationally flexible, but it is difficult to see how such a large entropy change could be accommodated solely by this source.

The quenching experiments demonstrate that the amine–alcohol intermediate gives rise to amide product in neutral and alkaline solutions (Scheme I) but that

Scheme I



loss of amine competes with loss of alcohol (1:3) in acid solution. These results, while in agreement with the breakdown of organic amine–alcohol intermediates in alkaline solution vary from the products observed under acidic conditions. Thus, most imidates[1,3,16–18]

(13) J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, **82**, 665 (1960).

(14) D. A. Buckingham, D. M. Foster, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **92**, 5701 (1970).

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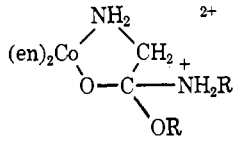
(16) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

(17) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

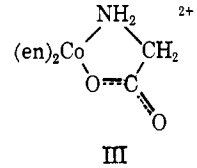
(18) K. D. Berlin and M. A. R. Khayat, *Tetrahedron*, **22**, 975 (1966).

yield esters in acid solution and this is regarded as resulting from the preferential loss of $-NH_2R^+$ from the tetrahedral intermediate. Certainly the amine moiety in II will be fully protonated in the acidic conditions

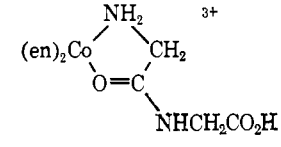


II

used ($pK_a \sim 7$)[19] and the products require that $-OC_3H_7$ and $-NH_2^+CH_2CO_2C_2H_5$ have similar leaving abilities from the tetrahedral carbon atoms. We do not understand the reason(s) for these differences but suggest that it may derive from effects similar to those giving rise to stabilization of the intermediate itself. Also the above is not an isolated example, as other studies in these laboratories demonstrate that approximately equal amounts of III and IV are formed in the intra-



III



IV

molecular condensation of $(en)_2Co(H_2O)^{3+}NH_2CH_2CONHCH_2CO_2H$ at pH 0–2, presumably *via* a similar tetrahedral intermediate.

Acknowledgment. The authors wish to thank the Microanalytical Unit for C, H, and N analyses and the referees for criticism and comments.

(19) Estimated from $K = 16\ M$ for mechanism II.

An ^{15}N–^1H Coupling Constant Study of the Bonding in Some N–P, N–As, N–S, and N–Si Compounds[1]

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Abstract: Fourteen ^{15}N-labeled aminophosphines, aminophosphoranes, aminoarsines, sulfenamides, and aminosilanes have been synthesized. The ^{15}N–^1H nmr coupling constants of these compounds have been determined in an attempt to test the validity of the N→P π-bonding hypothesis. It was found that it is unnecessary to employ the π-bonding model to explain the experimental data. The results are adequately dealt with by considering the redistribution of electrons within the σ frameworks of the molecules. The synthesis and characterization of the parent aminotetrafluorophosphorane, F_4PNH_2, are described.

Aminophosphines are of interest because they possess lone pair electrons on both the nitrogen and phosphorus atoms. Very early in the study of these compounds it became apparent that the phosphorus atom is more basic than the nitrogen atom. Thus, chemical and vibrational spectroscopic evidence indicate that it is the phosphorus atom which is quaternized in the $C_6H_5P[N(C_2H_5)_2]_2 \cdot CH_3I$[2] and $(CH_3)_2NP(CH_3)_2 \cdot CH_3I$[3] salts and that P–B bonding exists in the borane adducts $[(CH_3)_2N]_3PBH_3$,[4] $(H_2N)_3PBH_3$,[5] and $(CH_3)_2NPF_2 \cdot B_4H_8$.[6] Subsequent X-ray crystallographic studies[7,8] have confirmed that the phosphorus atom is the dative center in the last two compounds, and recent nmr and ir studies have established phosphorus donation when a variety of aminophosphines are treated with the Lewis acids CH_3^+,[9] alkylboranes,[10] PF_5,[11] and $(C_2H_5)_3Al$.[12] Similarly, the work of Sislers's group[13] indicates that chloramination always occurs at the phosphorus atom of aminophosphines. Furthermore, there is a substantial body of literature to the effect that the phosphorus atom is the donor atom when aminophosphines behave as ligands toward CuCl,[14] $RhCl_2$,[15] $CoBr_2$,[16] and a variety of metal carbonyl derivatives.[17] From the standpoint of the relative basicities of tertiary amines and the analogous tertiary phosphines, the

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