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Cobalt(III)-Promoted Hydrolyses of O-Bound Amides: Hydrolysis of the $[Co(en)_2(S\text{-AlaenH})]^{3+/4+}$ and $\{[Co(en)_2(S\text{-Ala}-)]_2en\}^{6+}$ Ions

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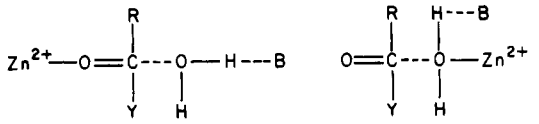
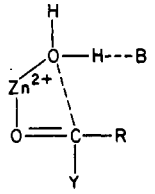
The synthesis, properties, and alkaline hydrolysis of Δ,Λ- and Δ-$[Co(en)_2(S\text{-AlaenH})](NO_3)_2(ClO_4)_2$ containing protonated ethylenediamine (pK_{a_1} = 8.44 ± 0.02, 25 °C, I = 1.0 ($NaClO_4$)) attached to the acyl function of chelated (*S*)-alanine are described. Hydrolysis (25 °C, I = 1.0 ($NaClO_4$)) proceeds via both the protonated (k_1 = 112 mol^{-1} dm^3 s^{-1}) and neutral (k_2 = 4.1 mol^{-1} dm^3 s^{-1}) ethylenediamine species, and deprotonation (pK_{a_2} = 11.8) of the amide center is observed. A crystal structure of Δ-$(-)_{546}$-$[Co(en\text{-}\delta)_2(S\text{-AlaenH})](NO_3)_2(ClO_4)_2$ [a = 9.448 (2), b = 15.858 (2), c = 8.232 (1) Å; β = 101.14 (1)°; monoclinic; $P2_1$; Z = 2; 2652 reflections; R = 0.0429, R_w = 0.0467] shows no interactions of the protonated ethylenediamine residue with other ligand atoms. The synthesis of the dimer Δ- and Δ,Λ-$[(Co(en)_2(S\text{-Ala}))_2en](ClO_4)_6\cdot 2H_2O$ is described; its alkaline hydrolysis conforms to k_1 and pK_{a_2} values of 18 mol^{-1} dm^3 s^{-1} and 11.3, respectively. The similar hydrolysis of the dipeptide complex ion $[Co(en)_2(S\text{-Ala-GlyOC}_3H_7)]^{3+}$ gives k_1 and pK_{a_2} values of 7 mol^{-1} dm^3 s^{-1} and 12, respectively. These data are interpreted in terms of rate-determining attack of OH^- at the acyl function.

Small-molecule studies continue to provide useful mechanistic alternatives for the carboxypeptidase (CPA)[1-3] (and related metalloenzymes, e.g. thermolysin[4]) catalyzed hydrolyses of esters and amides. Recent investigations have focused on the role played by proximal bases B (e.g., Glu-270 in CPA) in promoting attack by water. Three transition-state alternatives have been proposed[5-7] involving (I) only substrate coordination to Zn^{2+}, (II) activation

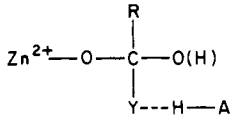


I II



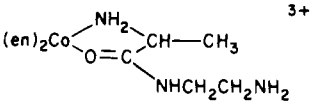
III

of coordinated water, and (III) a combination of I and II with both water and substrate coordination followed by intramolecular attack of water possibly assisted by B. In some instances, notably for peptide substrates, general-acid- (HA) catalyzed loss of amine from the addition intermediate appears to be significant (IV).[5]



IV

Our studies using Co(III) models and ^{18}O tracers have tested the relative merits of these possibilities.[8] For amides, hydrolysis via the Co(III) analogue of III was shown to involve general acid catalyzed loss of HY, and a transition state resembling IV was proposed.[9] This report extends this study to an investigation of the hydrolysis of $[Co(en)_2(S\text{-Alaen})]^{3+}$ (**1**) and its dimer $\{[Co(en)_2(S\text{-Ala}-)]_2en\}^{6+}$ (**2**). Only in **1** is there the possibility of an enhanced rate due to the intramolecular catalyzed loss of amine via a protonated $-NH_3^+$ function.



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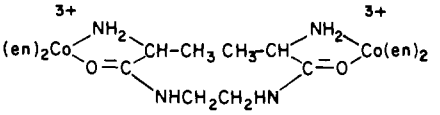

2

Experimental Section

Dimethyl sulfoxide (Me_2SO) and trimethyl phosphate (TMP) were redistilled under reduced pressure and stored over 3A molecular sieves. Methyl trifluoromethanesulfonate (methyl triflate) was prepared (*caution*, see below) by adding triflic acid (3M Co.) to excess dry dimethyl sulfate and fractionating the distillate. The initial fraction (bp 98 °C (atmospheric pressure)) was collected. Diethyl ether was dried over $CaCl_2$ (24 h), passed down an alumina column, and stored over 4A molecular sieves. Ethylenediamine was distilled under reduced pressure. Amino acids and other reagents were of Analar quality. (*Caution!* The preparation and subsequent handling of methyl trifluoromethanesulfonate should be carried out in an efficient fume hood, with avoidance of skin and respiratory contact. A fatality has been reported after a worker was exposed to the related alkylating agent methyl fluorosulfate (Magic methyl).[10]

Ion-exchange separations were carried out with Dowex 50W-X2 cation-exchange resin and large glass columns. ^1H NMR spectra were recorded on a Varian EM390 spectrometer and ^{13}C NMR spectra on a JEOL FX60 spectrometer (D_2O solvent, NaTPS reference).

Rate studies were carried out on a Cary 219 spectrophotometer. For the monomer, 35–60-μL aliquots of a ca. 0.2 mol dm^{-3} solution of $[Co(en)_2(AlaenH)](ClO_4)_2(NO_3)_2$ were injected into a cuvette containing 2.5 cm^3 of buffer. Initial repeat scans (650–300 nm) defined the wavelength of largest optical density change. At pH >11 this was 300 nm, but the OD decrease became smaller as the pK_a of the complex was approached, ultimately becoming an OD increase at pH <10.4. For kinetic runs in the range pH 11–10 the data at 300 nm were recollected at 400 nm where a small but consistent OD increase occurred. At pH <10 the OD increase at 300 nm was followed. For the initial reaction

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of the dimer $[(Co(en)_2Ala)_2en](ClO_4)_6 \cdot 2H_2O$ the OD decrease at 300 nm was larger than that for hydrolysis of the monomer at pH >10.4, and the subsequent slower reaction of the latter could be ignored. At pH <10 the initial OD change was now an increase, but only 2–3 times as great as that found for the monomer. Under these conditions biphasic kinetics were observed and $k_{(1)obsd}$ data were calculated by using a computer program[11] that fitted data to the expression $A_t = ae^{-k_{(1)obsd}t} + be^{-k_{(2)obsd}t}$. To initiate hydrolysis, 60 μL of a 0.04 mol dm^{-3} aqueous solution of the complex was injected into a cuvette containing 2.5 cm^3 of the buffer at 25.0 °C. Following hydrolysis, the solution pH was measured with a PHM62 pH meter calibrated with borate (1.0 mM, pH 9.18) and phthalate (2.5 mM, pH 4.01) buffers.

Triethylamine, morpholine, HEPES, and piperidine buffers (0.1–0.2 mol dm^{-3}) were made to I = 1.0 mol dm^{-3} ($NaClO_4$).

Preparations. **$[Co(en)_2CO_3]Cl$** was prepared as described by Springborg and Schaffer[12] and converted to the bromide salt by recrystallization from hot water with NaBr. *trans*-$[Co(en)_2Br_2]Br$ was prepared from $[Co(en)_2CO_3]Br$ with 47% HBr and washed with ethanol on a glass filter until free of acid. Δ,Λ-$[Co(en)_2(AlaO)]I_2$ was prepared as follows: *trans*-$[Co(en)_2Br_2]Br$ (12.6 g) was dissolved in 50% aqueous methanol (150 cm^3) at 50 °C. (*S*)-Alanine (2.76 g) was added followed by the slow addition of 1.23 g of $LiOH \cdot H_2O$ dissolved in 75 cm^3 of methanol. After heating for 2 h at 70 °C, the solution was diluted with water and the products adsorbed and separated on Dowex cation-exchange resin using 1–2 mol dm^{-3} hydrochloric acid. The orange 2+ band was collected and taken to dryness and $[Co(en)_2(AlaO)]I_2$ crystallized from neutral solution by adding NaI and cooling. It was recrystallized from hot water and was resolved into its Δ-*S* and Λ-*S* diastereoisomers with antimonyl *d*-tartrate as described by Liu and Douglas[13] ($[M]_{546}$ −3700°, Δ-*S* isomer).

Δ,Λ-$[Co(en)_2(AlaOCH_3)](CF_3SO_3)_3$ was prepared by dissolving Δ,Λ-$[Co(en)_2(AlaO)]I_2$ (12.0 g) in dry trimethyl phosphate (62 g) and carefully adding methyl triflate (18.8 g). After it was stirred for 1 h, the red solution was slowly poured into rapidly stirred dry ether (ca. 500 cm^3). The resulting red oil was dissolved in a small volume of dry methanol and the above precipitation process repeated until an orange powder was obtained. This was washed with ether and dried under vacuum. Good yields (>95%) of the chelated ester can be obtained if care is taken to exclude moisture. The complex is not hygroscopic and can be stored for many months in the dark.

Δ-$[Co(en)_2(AlaOCH_3)](CF_3SO_3)_3$ was prepared from optically pure Δ-$[Co(en)_2(AlaO)]I_2$ (6.0 g) by using the above procedure.

Δ,Λ- and Δ-$[Co(en)_2(AlaenH)](ClO_4)_2(NO_3)_2$. To Δ,Λ- or Δ-$[Co(en)_2(AlaOCH_3)](CF_3SO_3)_3$ (4.1 g) dissolved in dry dimethyl sulfoxide (80 cm^3) was added ethylenediamine (1.5 cm^3) and the solution stirred for 3 min before quenching with acetic acid (4 cm^3). The product was purified by ion-exchange chromatography on Dowex 50W-X2 cation-exchange resin using 3–4 mol dm^{-3} HCl as eluant. The orange 4+ band was collected, reduced to dryness, and crystallized from the minimum volume of H_2O by adding $LiNO_3$ and $LiClO_4$ (ca. 2 g of each). The complex was recrystallized several times from warm H_2O to obtain an analytical product. Anal. Calcd for $CoC_9H_{30}N_9O_{15}Cl_2$: C, 17.04; H, 4.76; N, 19.87. Found (for Δ,Λ racemate): C, 17.2; H, 4.9; N, 19.5. Found (for Δ isomer): C, 16.8; H, 4.9; N, 19.7.

Δ,Λ- and Δ-$[(Co(en)_2Ala)_2en](ClO_4)_6 \cdot 2H_2O$. This dimer could be obtained in small amounts as a 6+ band from the above preparation. It is best prepared, however, from the isolated monomer. $[Co(en)_2(AlaOCH_3)](CF_3SO_3)_3$ (5.7 g) was added to $[Co(en)_2(AlaenH)](NO_3)_2(ClO_4)_2$ (5 g) dissolved in dry dimethyl sulfoxide (75 cm^3) and triethylamine (1.5 g) added. After 1.5 h the stirred reaction mixture was quenched with HOAc (5 cm^3), diluted with water (200 cm^3), and loaded onto Dowex 50W-X2 cation-exchange resin. Elution with 2 mol dm^{-3} HCl removed $[Co(en)_2(AlaO)]^{2+}$ and unreacted $[Co(en)_2(AlaenH)]^{4+}$, and increasing the concentration to 4 mol dm^{-3} removed the desired 6+ product as a single orange band (ca. 90%). This eluate was reduced to dryness and the product crystallized from water by adding $NaClO_4$. Recrystallization from water and $NaClO_4$ gave an analytical sample. Anal. Calcd for $Co_2C_{16}H_{54}N_{12}O_{28}Cl_6$: C, 16.11; H, 4.56; N, 14.09. Found (for Δ,Λ isomer): C, 16.21; H, 4.77; N, 14.08. Found (for Δ isomer): C, 16.01; H, 4.42; N, 13.95.

$[Co(en)_2(Ala\text{-}GlyOC_3H_7)]Cl_3$. This dipeptide ester complex was prepared by adding freshly made glycine isopropyl ester (0.7 g) to $[Co(en)_2(AlaOCH_3)](CF_3SO_3)_3$ (2.6 g) dissolved in dry dimethyl sulfoxide (10 cm^3). The reaction was quenched after 5 min with HOAc (5 cm^3), the solution was diluted to 200 cm^3, the products were adsorbed on SP Sephadex cation-exchange resin, and the 3+ band was eluted with 0.5 mol dm^{-3} NaCl. The product was desalted following reduction to dryness by dissolution in the minimum volume of aqueous methanol and addition of ethanol.

Table I. Crystal Data and Data Collection and Refinement of Δ-$[Co(en)_2(AlaenH)](ClO_4)_2(NO_3)_2$

Crystal Data	
cryst system: monoclinic	formula: $C_9H_{30}N_9O_{15}Cl_2Co$
space group: $P2_1$	fw: 634.23
a = 9.448 (2) Å	D_{calcd} = 1.70 g cm^{-1}
b = 15.858 (2) Å	Z = 2
c = 8.232 (1) Å	$F(000)$ = 655.98
β = 101.14 (1)°	cryst size: 0.9 × 0.6 × 0.1 mm
V = 1210.0 Å^3	μ(Mo Kα) = 54.79 cm^{-1}

Data Collection and Refinement	
diffractometer: Nicolet P$\bar{3}$	
radiation: Mo Kα (λ = 0.710 69 Å)	
scan type: θ–2θ	
scan speed: 4.9–29.3° min^{-1}	
data limits: $1 < 2\theta < 54°$	
reflcns measd: $\pm h,k,l$	
cryst decay: <2%[b]	
total no. of obsd data: 2761	
no. of unique data: 2652 ($I > 2\sigma(I)$)	
abs cor: empirical[a]	
transmissn factors: 0.260–0.184	
no. of variables: 330	
R = 0.0429	
R_w = 0.0467	

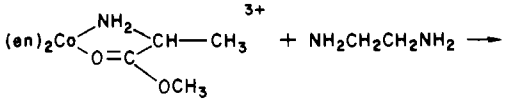
[a] See ref 16. [b] Standard reflections (080) (500) (043) measured after every 50 reflections.

pK_a of $[Co(en)_2(AlaenH)](ClO_4)_2(NO_3)_2$. A 25.5-mg sample of the complex dissolved in 30 cm^3 of 1.0 mol dm^{-3} $NaClO_4$ at 25.0 °C was titrated with 0.1 mol dm^{-3} NaOH with a Radiometer automatic titrator coupled to a PHM 62 pH meter. The solution pH was recorded as a function of NaOH added over the range 6.7–9.4, and the pK_a was calculated from the expression $pK_a = pH + \log([BH^+] + [OH^-])/([B] - [OH^-])$,[14] where pOH = 13.77 − pH.

X-ray Data Collection and Reduction. Crystals of Δ-$[Co(en)_2(S\text{-}AlaenH)](ClO_4)_2 \cdot (NO_3)_2$ were grown as described above, and an orange rhomb was selected and used for data collection. Precession photography using Cu Kα radiation indicated a monoclinic system. The systematic absences $0k0$ for $k = 2n + 1$ were consistent with the space group $P2_1$ (No. 4)[15] for the chiral molecule, and this was subsequently verified by the successful solution of the structure. Diffraction data were collected at 20 ± 1° on a Nicolet P$\bar{3}$, four-circle fully automated diffractometer. The unit cell dimensions and orientation matrices were calculated from 25 accurately centered reflections. Details of the crystal, data collection, and structure refinement are summarized in Table I. The data were processed and empirical absorption corrections applied by using programs from the SHELXTL package.[16]

Results and Discussion

1. Preparation and Properties of $[Co(en)_2(S\text{-}Alaen)]^{3+}$ (1) and $[Co(en)_2(S\text{-}Ala\text{-})]_2en^{6+}$ (2). Attachment of ethylenediamine to the activated ester function of $[Co(en)_2(S\text{-}AlaOCH_3)]^{3+}$ is easily achieved by mixing the two reactants at room temperature in a nonaqueous solvent such as dimethyl sulfoxide.



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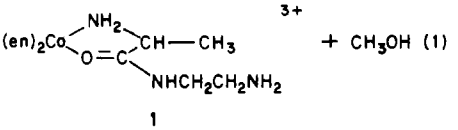

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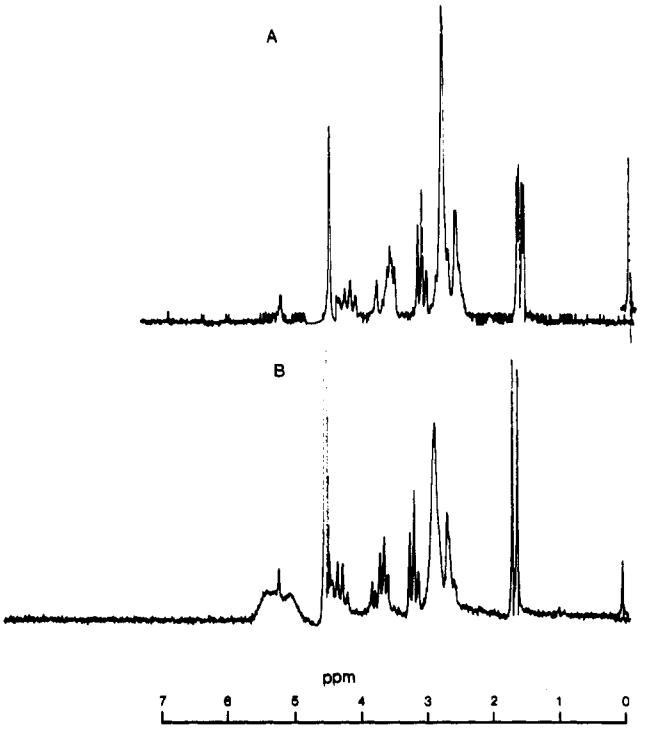
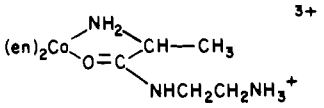


Figure 1. ^{1}H NMR spectra of Δ,Λ-$[Co(en)_2(AlaenH)]^{4+}$ (A) and Δ-$[Co(en)_2(AlaenH)]^{4+}$ (B) in D_2O.

Such condensations are fast, being complete in seconds or minutes; when an amino acid is used as the amine, the reaction is the basis of the Co(III) method of synthesizing small peptides.[17] In the present case the product 3+ ion was isolated as its protonated 4+ salt, $[Co(en)_2(S\text{-}AlaenH)](NO_3)_2(ClO_4)_2$ (**3**). Aqueous solutions



3

of **1** and **3** have visible spectra typical of the CoN_5O chromophore (λ_{max}, nm (ϵ, mol^{-1} dm^3 cm^{-1})): 488 (97), 343 (110); 488 (100), 344 (120); respectively. **3** is stable for long periods in neutral or acidic solutions; this contrasts with the chelated ester (**4**), which hydrolyzes within minutes under these conditions.

The acidity of the dangling amine function in **3** was determined by potentiometric titration in 1.0 mol dm^{-3} $NaClO_4$, pK_a = 8.44 ± 0.02, 25.0 °C (eq 2). This value is to be compared with 7.49

$$3 + H_2O \rightleftharpoons^{K_a} 1 + H_3O^+ \qquad (2)$$

for enH_2^{2+} and 10.17 for enH^+ in 1 mol dm^{-3} KNO_3. It suggests that Co(III) is somewhat less effective than H^+ in polarizing the amine function. Others[18] have found comparable effects; viz. pK_a = 6.70 (X = Cl) and 7.27 (X = Br) for monodentate ethylenediamine in *cis*-$[Co(en)_2(enH)X]^{2+}$ vs. 6.80 for enH_2^{2+} in 0.1 mol dm^{-3} $NaClO_4$. In these latter complexes, the amine function is directly coordinated to the metal but the overall charge has been reduced compared to that of **3**. Obviously several factors are important, but it is our contention that Co(III) is somewhat less effective than a proton in promoting such ionizations. It also appears to be less effective in promoting nucleophilic additions to acyl functions such as that given by reaction **1**.

Table II. ^{1}H NMR Assignments for the Δ,Λ- and Δ-$[Co(en)_2(AlaenH)]^{4+}$ and Δ,Λ- and Δ-$\{[Co(en)_2Ala]_2en\}^{6+}$ Ions

$[Co(en)_2(AlaenH)]^{4+}$			$\{[Co(en)_2Ala]_2en\}^{6+}$		
δ	J, Hz	assgnt[a]	δ	J, Hz	assgnt[a]
		Δ,Λ Mixture			
1.67 (d), 1.70 (d)	8	CH_3(a)	1.68 (d), 1.70 (d)	8	CH_3(a)
2.6-3.1		CH_2(e)	2.6-3.1		CH_2(e)
3.23 (t)	7	CH_2(d)	3.62 (s)		CH_2(c)
3.62-3.9		CH_2(c)			
4.32 (quint)	7	CH(b)	4.31 (quint)	7	CH(b)
		Δ Isomer			
1.67 (d)	8	CH_3(a)	1.68 (d)	8	CH_3(a)
2.6-3.1		CH_2(e)	2.6-3.1		CH_2(e)
3.23 (t)	7	CH_2(d)	3.62 (s)		CH_2(c)
3.70 (m)	6	CH_2(c)	4.40 (quart)		CH(b)
4.39 (quart)	7	CH(b)			

[a] Assignments a–e refer to diagram (for monomer) given in text.

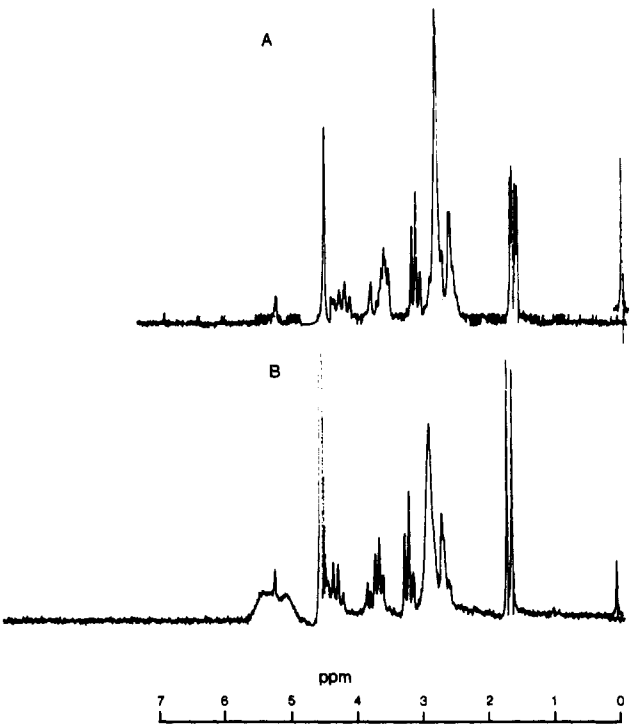


Figure 2. ^{1}H NMR spectra of the racemic dimer $[(Co(en)_2(Ala))_2en]^{6+}$ (A) and its Δ,Δ congener (B) in D_2O.

^{1}H NMR spectra show absorptions due to both the Δ-*S* and Λ-*S* diastereoisomers. Figure 1 compares the 90-MHz spectra of Δ,Λ-$[Co(en)_2(AlaenH)]^{4+}$ with that of optically pure Δ-$[Co(en)_2(AlaenH)]^{4+}$. Table II gives details. The two pairs of CH_3 doublets in the Δ,Λ-*S* complex occur as a single doublet in the Δ-*S* ion, and the apparent CH quintet is reduced to a single quartet in the optically active ion. The latter splitting (but not the former) was also found for chelated alaninate in the parent Δ,Λ-$[Co(en)_2(AlaO)]^{2+}$ ion.[19] Assignments for the ethylenediamine moiety (Table II)

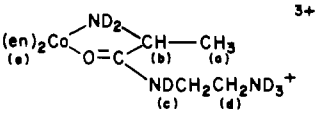


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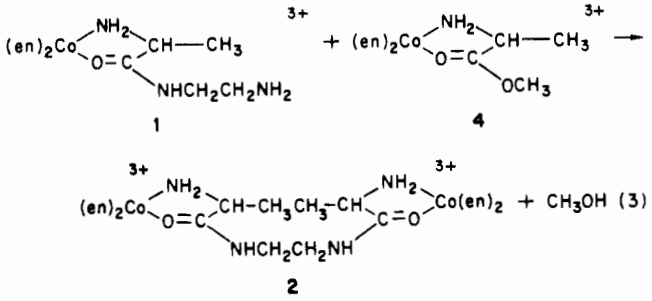
Table III. Final Positional Parameters for Δ-[Co(en)$_2$(*S*-AlaenH)](ClO$_4$)$_2$(NO$_3$)$_2$

atom	*x/a*	*y/b*	*z/c*	atom	*x/a*	*y/b*	*z/c*
Co	0.26000 (5)	0.4507 (0)	0.4381 (1)	Cl1	0.2223 (1)	0.1187 (1)	0.4639 (2)
N1	0.1840 (5)	0.5198 (3)	0.5997 (5)	O11	0.125 (1)	0.0764 (8)	0.544 (1)
C1	0.2164 (9)	0.6107 (5)	0.571 (1)	O12	0.3207 (8)	0.1636 (6)	0.5911 (7)
C2	0.354 (1)	0.6182 (5)	0.526 (1)	O13	0.165 (1)	0.1737 (5)	0.341 (1)
N2	0.3720 (4)	0.5517 (3)	0.4062 (5)	O14	0.3013 (9)	0.0560 (7)	0.401 (1)
N3	0.4121 (4)	0.4042 (3)	0.6083 (5)	Cl2	−0.3314 (2)	0.2377 (1)	−0.0296 (2)
C3	0.5264 (6)	0.3669 (4)	0.5292 (7)	O21	−0.433 (1)	0.2063 (8)	0.065 (2)
C4	0.4570 (6)	0.3258 (4)	0.3723 (7)	O22	−0.325 (1)	0.3274 (5)	−0.040 (1)
N4	0.3492 (4)	0.3867 (3)	0.2831 (5)	O23	−0.362 (4)	0.2078 (9)	−0.179 (1)
N5	0.1249 (4)	0.3589 (3)	0.4536 (5)	O24	−0.202 (1)	0.210 (1)	0.070 (2)
C5	−0.0089 (5)	0.3644 (3)	0.3227 (6)	N8	0.1335 (5)	0.3377 (3)	0.8737 (5)
C6	−0.1437 (6)	0.3606 (5)	0.3971 (8)	O81	0.0543 (6)	0.3932 (3)	0.7985 (6)
C7	0.0023 (4)	0.4442 (3)	0.2254 (5)	O82	0.2205 (6)	0.2997 (3)	0.8006 (6)
O1	0.1123 (3)	0.4905 (2)	0.2634 (4)	O83	0.1301 (5)	0.3182 (3)	1.0173 (4)
N6	−0.1001 (4)	0.4636 (3)	0.0994 (5)	N9	0.5155 (6)	−0.0030 (3)	0.0091 (6)
C8	−0.0821 (6)	0.5332 (4)	−0.0120 (6)	O91	0.4496 (5)	0.0141 (3)	0.1231 (5)
C9	−0.1049 (5)	0.6195 (4)	0.0571 (6)	O92	0.6445 (5)	−0.0251 (4)	0.0418 (6)
N7	−0.2594 (4)	0.6366 (3)	0.0609 (5)	O93	0.4526 (5)	0.0025 (3)	−0.1366 (5)

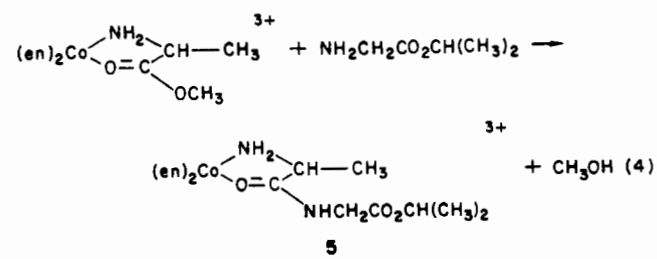
are made on the assumption that this asymmetry will be more apparent in the adjacent CH_2(c) protons than in the terminal CH_2(d) protons.

Dimer **2** was prepared by condensing the free amine function in **1** with **4** in dry dimethyl sulfoxide (eq 3). The product 6+



ion was crystallized as {[Co(en)$_2$(Ala−)]$_2$en}(ClO$_4$)$_6$·2H$_2$O. The visible spectrum [λ_{max} = 500 nm (ϵ = 243 mol^{-1} dm^3 cm^{-1}), λ_{max} = 346 (ϵ = 273)] is essentially the same as that of **1**, and the complex is again quite stable toward hydrolysis in neutral or acidic solutions. The ^{1}H NMR spectrum is also characterized by two sets of CH_3 doublets (J = 7.5 Hz; Table II) and two overlapping CH quartets (J = 7.5 Hz) for the Δ,Λ complex (Figure 2A). These are assigned to the Λ*S*-Λ*S*, Δ*S*-Δ*S* diastereoisomers. The optically pure Δ*S*-Δ*S* ion (Figure 2B) shows only one CH_3 doublet and one CH quartet. It is expected that the remaining Λ*S*-Δ*S* combination, which is presumably present in the racemic preparation, has chemical shifts identical with those of the Δ*S*-Δ*S*, Λ*S*-Λ*S* pair; no attempt was made to isolate this latter species.

The dipeptide ester complex [Co(en)$_2$(Ala-GlyOC$_3$H$_7$)]$^{3+}$ (**5**) was similarly prepared by coupling [Co(en)$_2$(AlaOCH$_3$)]$^{3+}$ and glycine isopropyl ester in dry dimethyl sulfoxide (eq 4). The ^{1}H NMR spectrum of this complex also shows two CH_3 doublets characteristic of the Δ-S, Λ-S diastereoisomers.



2. Crystal Structure of Δ-[Co(en)$_2$(*S*-AlaenH)](ClO$_4$)$_2$(NO$_3$)$_2$. The direct-methods program SOLV[16] unambiguously located the position of the cobalt atom in the Δ-[Co(en)$_2$(*S*-AlaenH)]$^{4+}$ cation; the remaining non-hydrogen atoms were found by successive difference Fourier syntheses and least-squares refinements.[20a]

Table IV. Selected Bond Lengths and Angles for Δ-[Co(en)$_2$(*S*-AlaenH)](ClO$_4$)$_2$(NO$_3$)$_2$

Bond Lengths (Å)

Co-N(1)	1.964 (4)	C(3)-C(4)	1.481 (8)
Co-N(2)	1.964 (4)	C(4)-N(4)	1.489 (7)
Co-N(3)	1.947 (4)	N(5)-C(5)	1.497 (6)
Co-N(4)	1.946 (4)	C(5)-C(6)	1.518 (7)
Co-N(5)	1.956 (4)	C(5)-C(7)	1.512 (7)
Co-O(1)	1.907 (3)	C(7)-O(1)	1.261 (6)
N(1)-C(1)	1.502 (9)	C(7)-N(6)	1.311 (6)
C(1)-C(2)	1.42 (1)	N(6)-C(8)	1.465 (7)
C(2)-N(2)	1.477 (8)	C(8)-C(9)	1.513 (8)
N(3)-C(3)	1.487 (7)	C(9)-N(7)	1.490 (6)

Bond Angles (deg)

N(1)-Co-N(2)	85.0 (2)	C(1)-C(2)-N(2)	110.0 (6)
N(1)-Co-N(3)	92.3 (2)	Co-N(2)-C(2)	111.0 (4)
N(1)-Co-N(4)	175.6 (2)	Co-N(3)-C(3)	109.5 (3)
N(1)-Co-N(5)	92.4 (2)	N(3)-C(3)-C(4)	108.7 (4)
N(1)-Co-O(1)	90.9 (2)	C(3)-C(4)-N(4)	106.9 (4)
N(2)-Co-N(3)	93.6 (2)	Co-N(4)-C(4)	110.9 (3)
N(2)-Co-N(4)	91.4 (2)	Co-N(5)-C(5)	112.4 (3)
N(2)-Co-N(5)	172.0 (2)	N(5)-C(5)-C(6)	111.4 (4)
N(2)-Co-O(1)	87.9 (2)	N(5)-C(5)-C(7)	107.1 (4)
N(3)-Co-N(4)	85.5 (2)	C(6)-C(5)-C(7)	113.4 (5)
N(3)-Co-N(5)	94.1 (2)	C(5)-C(7)-O(1)	119.6 (4)
N(3)-Co-O(1)	176.6 (2)	C(5)-C(7)-N(6)	119.9 (4)
N(4)-Co-N(5)	91.4 (2)	O(1)-C(7)-N(6)	120.4 (4)
N(4)-Co-O(1)	91.4 (2)	Co-O(1)-C(7)	116.3 (3)
N(5)-Co-O(1)	84.5 (1)	C(7)-N(6)-C(8)	121.0 (4)
Co-N(1)-C(1)	108.4 (4)	N(6)-C(8)-C(9)	113.8 (4)
N(1)-C(1)-C(2)	110.3 (6)	C(8)-C(9)-N(7)	112.6 (4)

Hydrogen atoms were introduced as members of rigid groups, constrained so that C–H = 0.99 and N–H = 0.95 Å, respectively. Each hydrogen atom was initially assigned an isotropic temperature factor equal to that of the atom to which it was bound. In subsequent refinement cycles the hydrogen atom temperature factors were held constant. All non-hydrogen atoms were assigned anisotropic temperature factors. Analysis of the weighting scheme revealed no serious dependence on either $|F_o|$ or $(\sin\theta)/\lambda$. Refinement of this model converged at R = 0.0429 and R_w = 0.0467 {$w = 1.9[\sigma^2(F) + 0.00119F^2]^{-1}$}, with no peaks in the final Fourier map higher than 0.64 e Å^{-3}. The perchlorate oxygen atoms were found to have characteristically high thermal parameters, and the areas of highest electron density in the final Fourier map were found in the vicinity of the perchlorate anions. However, the

(20) (a) Sheldrick, G. M. "SHELX-76, Program for Crystal Structure Determination"; University of Cambridge: Cambridge, 1976. (b) Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1968**, *A24*, 321. (c) Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **1970**, *53*, 1891.

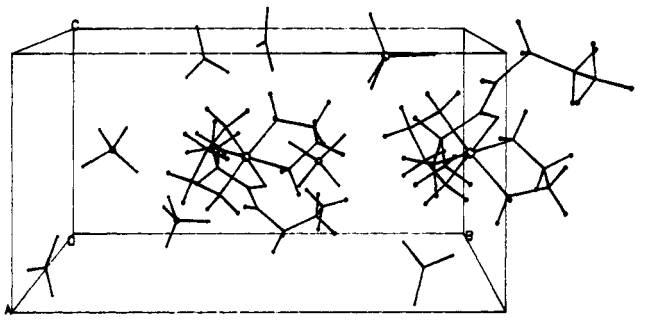


Figure 3. View of the unit cell of Δ-$[Co(en)_2(AlaenH)](ClO_4)_2(NO_3)_2$ along the *a* axis.

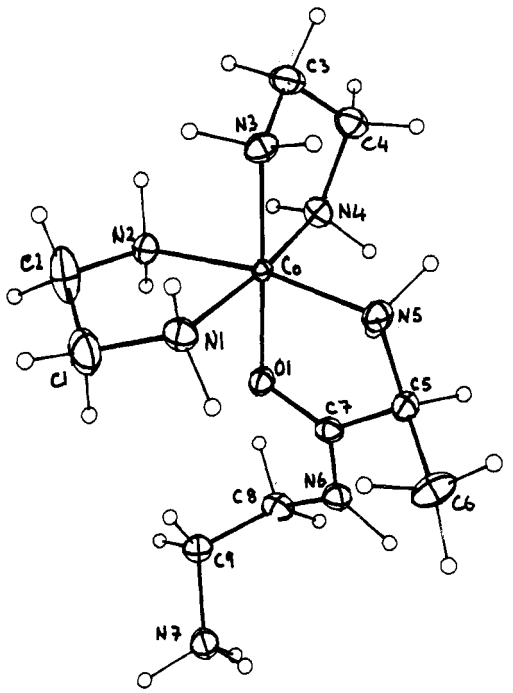


Figure 4. ORTEP diagram of the Δ-$[Co(en)_2(S\text{-}AlaenH)]^{4+}$ cation showing the atom-numbering scheme. The ellipsoids represent 50% probability.

possibility of disorder in the perchlorate anions was not investigated further. The structure was finally refined from the coordinates of the alternative enantiomer and gave $R = 0.0469$ and $R_w = 0.0512$, confirming that the absolute configuration of this crystal is indicated by the original model. The scattering factors for the cobalt atom were taken from Cromer and Mann,[20b] with corrections for anomalous dispersion from Cromer and Liberman.[20c]

Positional parameters for the non-hydrogen atoms are given in Table III and selected interatomic distances and angles in Table IV.

The structure consists of independent Δ-$[Co(en)_2(S\text{-}AlaenH)]^{4+}$ cations and nitrate and perchlorate anions held together by a network of hydrogen bonds. These link the nitrogen atoms of the cation to both the nitrate and perchlorate anions. The arrangement of cations and anions in the unit cell is shown in Figure 3.

The structure of the Δ-$[Co(en)_2(S\text{-}AlaenH)]^{4+}$ cation is shown in Figure 4. Anomalous dispersion of X-rays establishes the absolute configuration about Co as Δ and confirms the *S* configuration of the alanine moiety as anticipated from the known chirality of the materials employed in the synthesis (vide supra). Coordination about the cobalt atom is slightly distorted octahedral, with the two ethylenediamine ligands bound in the $\delta\delta$ conformation with C–C dihedral angles of 43.0 and 46.9°, respectively. The two remaining coordination positions are filled by the α-amino nitrogen, N(5), and carbonyl oxygen, O(1), of the alanine portion of the AlaenH ligand. This mode of substitution is generally found in amide complexes in which the amide nitrogen has not been deprotonated by the metal ion,[21] as in the copper tripeptide

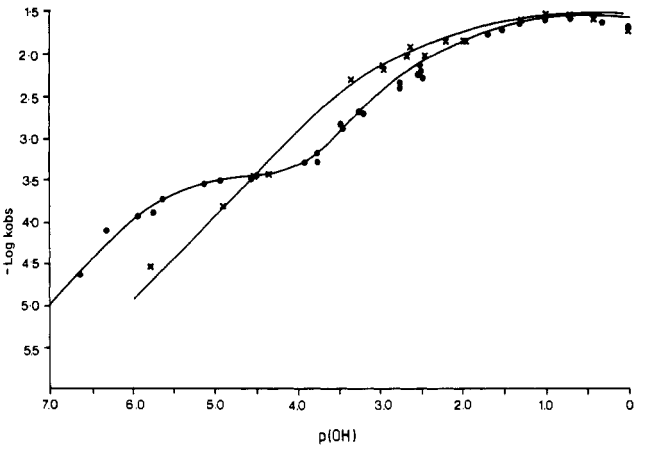


Figure 5. pH–rate profile for hydrolysis of $[Co(en)_2(AlaenH)]^{3+/4+}$ (●) and $[(Co(en)_2(Ala))_2en]^{6+}$ (×) at 25 °C and $I = 1.0$ ($NaClO_4$). Solid lines were calculated from eq 6 and 8 and the values of the constants given in the text.

complexes $Cu(Gly\text{-}Gly\text{-}Gly)^+$[22] and $Cu(Gly\text{-}Leu\text{-}Tyr)^+$,[23] or the Co(III) tetraamine complex of the glycylglycine O-ethyl ester.[24]

The Co–N(5), 1.956 (4) Å, and Co–O(1), 1.907 (3) Å, bond distances and N(5)–Co–O(1) bond angle, 84.5 (1)°, of the chelated alanine moiety are comparable to those found in similar amino acidate or dipeptide complexes.[25-28] The exo C(7)–N(6) distance, 1.311 (6) Å, is short and the angles subtended at C(7) and N(6) are close to 120°, suggesting that electron delocalization is important in the O(1)–C(7)–N(6) portion of the molecule. The amino acid atoms forming the chelate ring are reasonably coplanar, with a C(5)–C(7) dihedral angle of 0.3°.[29] The C(5) and C(7) atoms deviate from the Co, O(1), N(5) plane by +0.089 (5) and +0.072 (4) Å, respectively. The amide nitrogen N(6) of the pendant ethylenediamine residue lies 0.172 (6) Å from this plane, a further indication of the planarity of the amide function. The alanine methyl group is axial with an *S* conformation about the chiral C(5) center.[30] The C(9)–N(7) portion of the condensed ethylenediamine moiety is oriented in the same direction as the alanine methyl group with respect to the plane of the amino acid chelate ring. The molecular parameters for the dangling ethylenediamine fragment are not unusual, with C(8)–C(9) and C(9)–N(7) distances close to the single-bond values and approximately tetrahedral bond angles. The quaternary nitrogen atom, N(7), is well removed from the remaining amino acid portion of the cation so that the solid-state structure offers no support for the involvement of this terminal amine in protonation at the amide nitrogen (vide infra).

3. Hydrolysis Reactions. **1**, **2**, and the dipeptide ester complex **5** are stable to hydrolysis in neutral and acidic aqueous solutions; in 0.01 mol dm^{-3} $HClO_4$, **1** showed <10% hydrolysis over 5 weeks at 25 °C, giving $k_{H_2O} < 3 \times 10^{-8}$ s^{-1}. Under alkaline conditions, however, all three complexes hydrolyze at the amide bond to give

(21) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385.
(22) Freeman, H. C.; Robinson, G.; Schoone, J. C. *Acta Crystallogr.* **1964**, *17*, 719.
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(26) Anderson, B. F.; Buckingham, D. A.; Gainsford, G. J.; Robertson, G. B.; Sargeson, A. M. *Inorg. Chem.* **1975**, *14*, 1658.
(27) Voss, K. E.; Angelici, R. J.; Jacobson, R. A. *Inorg. Chem.* **1978**, *17*, 1922.
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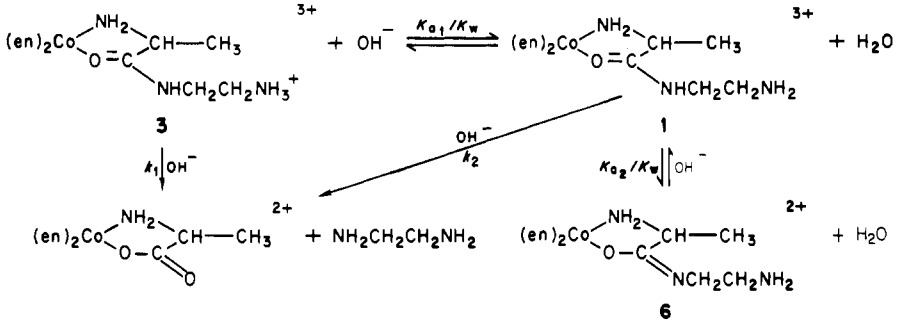
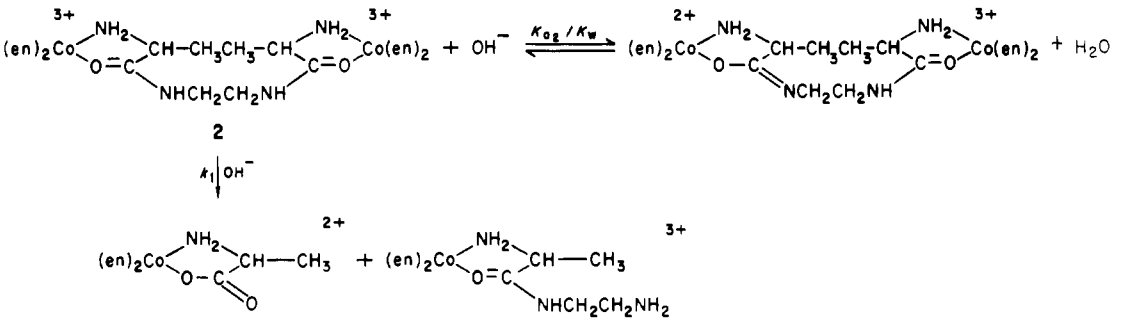
(30) Hawkins, C. J. "Absolute Configuration of Metal Complexes"; Wiley-Interscience: New York, 1971.

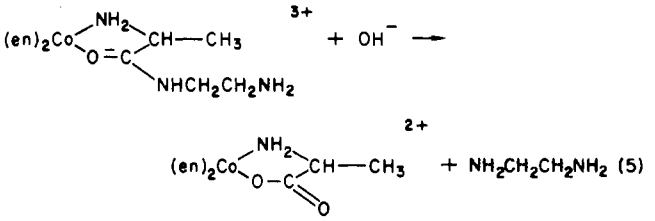
Scheme I



Scheme II



the chelated alaninate complex $[Co(en)_2(AlaO)]^{2+}$ and amine; e.g., for **1**



A 1 mol equiv portion of hydroxide is consumed (pH-stat titration), and the product ion was identified by its chromatographic behavior and its visible and ^1H NMR spectra.

Kinetic data for **1** over the range pH 7–14 (Table V) is given as a plot of log k_{obsd} vs. pOH by Figure 5. It is clear that a complex process is involved, with protonation of the dangling amine ($pK_a = 8.44$) significantly modifying the hydrolysis rate. Also, a leveling off in k_{obsd} occurs above pH 11. The data are consistent with Scheme I, which leads to the rate expression (6), where $[Co]_T$

$$-d[Co]_T/dt = k_{obsd}[CO]_T = \{[k_1[OH^-] + k_2K_{a_1}/K_w[OH^-]^2]/[1 + K_{a_1}/K_w[OH^-] + K_{a_1}K_{a_2}/K_w^2[OH^-]^2]\}[Co]_T \quad (6)$$

$= [\mathbf{1}] + [\mathbf{3}] + [\mathbf{6}]$. This expression reduces to $k_{obsd} = k_1[OH^-]$ at pH <8 when the reactant exists only as **3**, giving $k_1 = 112$ mol^{-1} dm^3 s^{-1} in 1.0 mol dm^{-3} $NaClO_4$ at 25.0 °C. When $[H^+]$ lies between K_{a_1} and K_{a_2} (i.e., between pH ~9 and 10), k_1 still dominates the rate but an increasing proportion of the reactant exists in the conjugate-base form (**1**) whence the rate approaches independence in $[OH^-]$ kinetics, $k_{obsd} \simeq k_1K_w/K_{a_1}$. At pH >10, the k_2 path begins to make its presence felt and again first-order kinetics in $[OH^-]$ are observed, $k_{obsd} = k_2[OH^-]$ whence $k_2 = 4.1$ mol^{-1} dm^3 s^{-1}. Above pH 12, additional deprotonation of the reactant occurs (to form **6**) and the rate again becomes independent of $[OH^-]$, $k_{obsd} = k_2K_w/K_{a_2}$. Using $k_2 = 4.1$ mol^{-1} dm^3 s^{-1} and $pK_w = 13.77$ (1.0 M $NaClO_4$) gives $pK_{a_2} = 11.8$. A similar deprotonation of the amide function was observed with chelated glycinamide in $[Co(en)_2(GlyNH_2)]^{3+}$ (but not with $[Co(en)_2(GlyN(CH_3)_2)]^{3+}$) and was shown to restrict hydrolysis.[18]

Data included in Table V for the optically active Δ-**1** complex agree with that for the racemate ion. Thus, there is no significant discrimination in hydrolysis rate between the Λ-*S* and Δ-*S* diastereoisomers.

Table V. Kinetic Data for the Alkaline Hydrolysis of Δ,Λ-$[Co(en)_2(AlaenH)]^{3+/4+}$ (25.0 °C, $I = 1.0$ ($NaClO_4$))

pH	$[OH^-]^b$	buffer[a]	k_{obsd}, s^{-1}
	1.0		2.04×10^{-2}
	0.5		2.40×10^{-2}
	0.2		2.70×10^{-2}
	0.1		2.48×10^{-2}
	5.0×10^{-2}		2.29×10^{-2}
	3.0×10^{-2}		1.91×10^{-2}
	2.0×10^{-2}		1.69×10^{-2}
	1.0×10^{-2}		7.45×10^{-3}
11.26[c]	3.09×10^{-3}	1:4[d]	6.18×10^{-3}
11.30	3.38×10^{-3}	1:3[d]	5.02×10^{-3}
11.23	2.88×10^{-3}	1:3[d]	6.02×10^{-3}
11.07	1.99×10^{-3}	1:2[d]	4.02×10^{-3}
11.00	1.69×10^{-3}	1:2[d]	4.53×10^{-3}
10.51	5.45×10^{-4}	1:1[d]	2.23×10^{-3}
10.55[c]	6.03×10^{-4}	1:1[d]	1.99×10^{-3}
10.31	3.47×10^{-4}	1:1[d]	1.41×10^{-3}
10.29	3.31×10^{-4}	1:1 (0.2 M)[d]	1.54×10^{-3}
10.00	1.69×10^{-4}	2.5:1[d]	6.76×10^{-4}
10.00[c]	1.69×10^{-4}	4:1[d]	5.37×10^{-4}
9.84	1.17×10^{-4}	4:1[d]	5.37×10^{-4}
9.25	3.02×10^{-5}	1:4[e]	3.22×10^{-4}
9.25	3.02×10^{-5}	1:1[e]	3.59×10^{-4}
8.82	7.12×10^{-5}	1:1[e]	3.19×10^{-4}
8.63[c]	7.24×10^{-6}	1:1[e]	2.78×10^{-4}
8.01	1.74×10^{-6}	4:1[e]	1.26×10^{-4}
7.82	1.12×10^{-6}	4:1[e]	1.18×10^{-4}
8.13	2.29×10^{-6}	1:3[f]	1.89×10^{-4}
7.43	4.57×10^{-7}	1:1[f]	7.58×10^{-5}
7.13	2.29×10^{-7}	3:1[f]	2.31×10^{-5}

[a] Buffer ratio, BH^+:B. [b] Calculated from solution pH using $pK_w = 13.77$. [c] Δ-$[Co(en)_2(AlaenH)]^{3+/4+}$. [d] 0.1 mol dm^{-3} NEt_3 buffers. [e] 0.1 mol dm^{-3} morpholine buffer. [f] 0.1 mol dm^{-3} HEPES buffers.

For the dimer (**2**) two consecutive reactions are possible: reaction 7 followed by reaction 5. Under most conditions, the OD

$$\mathbf{2} + OH^- \rightarrow \mathbf{1} + [Co(en)_2(AlaO)]^{2+} \quad (7)$$

change for reaction 7 was much larger than that for reaction 5 and good first-order kinetics were observed. However, this was not so when the solution pH was less than pK_{a_1}. Under these latter

Table VI. Kinetic Data for the Alkaline Hydrolysis of $\{[Co(en)_2(Ala)]_2en\}(ClO_4)_6 \cdot 2H_2O$ (25.0 °C, $I = 1.0$ ($NaClO_4$))

pH	$[OH^-]$, mol dm^{-3}	−log $[OH^-]^e$	$10^4 \times k_{obsd}$, s^{-1}
	1.0	0	209
	0.40	0.40	263
	0.20	0.70	282
	0.10	1.0	298
	0.05	1.3	247
	0.01	2.0	145
11.79[a]		1.98	137
11.56	0.01	2.21	148
11.30[b]		2.47	95
11.14[a]		2.63	119
11.09[a]		2.68	96
10.80[a]		2.97	67
10.80[a]		2.97	70
10.44[c]		3.33	21
10.40[a]		3.37	51
9.41[d]		4.36	3.8
9.22[d]		4.55	3.8
8.86[d]		4.91	1.6
7.98[d]		5.79	0.30

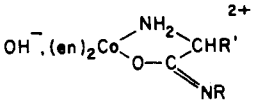
[a] 0.1 or 0.05 mol dm^{-3} NEt_3 buffer. [b] 0.1 mol dm^{-3} piperidine buffer. [c] 0.1 mol dm^{-3} piperidine buffer. [d] 0.1 mol dm^{-3} morpholine buffer. [e] Calculated from pH with $pK_w = 13.77$.

conditions, biphasic kinetics were observed and these were treated accordingly. Data for reaction 7 (Table VI) are given as a plot of log k_{obsd} vs. pOH in Figure 5. Again, a leveling off in rate is observed at pH >11, with a small decrease being observed in 1.0 mol dm^{-3} OH^-. These data were treated according to reaction Scheme II, which leads to the expression (8) with $k_1 = 18$ mol^{-1}

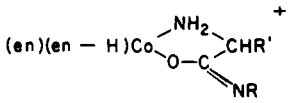
$$-d[Co]_T/dt = \{k_1[OH^-]/[1 + K_{a_2}/K_w[OH^-]]\}[Co]_T \quad (8)$$

dm^3 s^{-1} and $pK_{a_2} = 11.3$. The more acidic nature of the amide group in **2** compared to that in **1** ($pK_a = 11.8$) is expected since the former has the $Co(en)_2Ala$ moiety attached.

The decrease in rate in 1.0 mol dm^{-3} OH^- (compared to 0.1 mol dm^{-3} OH^-) has not been allowed for in this analysis. It could arise from deprotonation of the second amide residue; but, the data for the monomer (**1**) (Table V) show a similar effect, and it is also found in the hydrolysis of chelated glycinamides and dipeptides.[18] A possible explanation is ion-pair formation with OH^-, e.g.



or deprotonation of one of the coordinated primary amine functions, e.g.



The relative merits of these possibilities depend on the relative basicities of OH^- and the coordinated amide ion. Deprotonation has been observed previously with $[Co(tren)(NH_3)_2]^{3+}$ [31] and $[Ru(NH_3)_6]^{3+}$ [32] in strongly alkaline conditions, but for the present 2+ complex an ion pair is considered more likely with $K_{ip} \simeq 1$ mol^{-1} dm^3.

Limited data for the hydrolysis of the dipeptide ester, complex **5**, were obtained over the range pH 9.8–14 (Table VII). These data fit an expression similar to (8), with deprotonation of the amide function limiting the rate above pH 12, $k_1 \simeq 7$ mol^{-1} dm^3 s^{-1}, $pK_a \simeq 12$. This value for k_1 is to be compared with 3 mol^{-1} dm^3 s^{-1} fo β_2-[Co(trien)(GlyGlyOPr)]$^{3+}$ under the same conditions.[33]

Table VII. Kinetic Data for the Alkaline Hydrolysis of $[Co(en)_2(S\text{-Ala-Gly-}i\text{-Pr})]Cl_3$ (25.0 °C, $I = 1.0$ ($NaClO_4$))

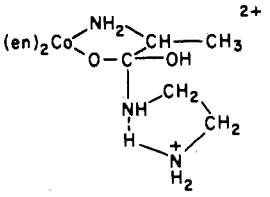
pH	$[OH^-]$, mol dm^{-3}	−log $[OH^-]^a$	$10^4 \times k_{obsd}$, s^{-1}
	0.68	0.17	157
11.30		2.47	83
10.15		3.62	17.7
9.88		3.89	7.3
9.81		3.96	7.7

[a] Calculated from pH data with pK_w 13.77.

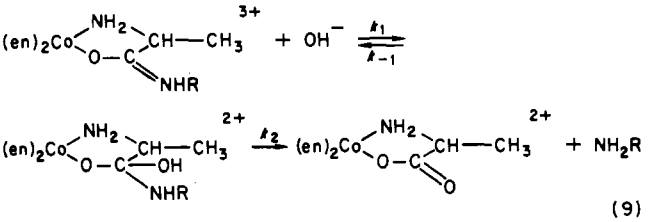
Table VIII. Comparison of k_1 Values for Alkaline Hydrolysis of Some Co(III)-Chelated Amides

compd	leaving gp	k_1, mol^{-1} dm^3 s^{-1}
1	$-NHCH_2CH_2NH_2$	4.1
2	$-NHCH_2CH_2NH(Ala)Co(en)_2^{3+}$	18
5	$-NHCH_2CO_2CH(CH_3)_2$	7
3	$-NHCH_2CH_2NH_3^+$	112

A comparison of k_1 values for the various amide complexes allows some comment on the effect of positive charge on the leaving group. A summary of the relevant data is given in Table VIII. Compared to **1** and **5** hydrolysis is enhanced by the presence of the second Co(III) moiety (in **2**) and by protonation of the terminal amine residue (in **3**). The former cannot assist protonation of the leaving group while the latter may via a transition state of the type



However, the magnitudes of the accelerations (ca. 4 and 30, respectively) are about what might be expected from simple inductive and polarization effects promoting addition of OH^- to the acyl center, i.e. k_1 in eq 9, with the proton being somewhat more



(9)

effective than the additional Co(III) center. A similar effect (ca. 4) was noted above for the acidity of the amide group in the presence of the additional Co(III) moiety. We therefore conclude that the cyclic transition state for the addition intermediate pictured above is unimportant in a rate sense, with k_1 being rate determining. This is in agreement with the absence of buffer catalysis found previously.[19]

Registry No. Δ,Λ-**2**, 93684-21-0; Δ-**2**, 93780-02-0; Δ,Λ-**3**, 93684-19-6; Δ-**3**, 93780-00-8; Δ,Λ-**4**, 80585-90-6; Δ-**4**, 93779-98-7; **5**, 93684-22-1; *trans*-$[Co(en)_2Br_2]Br$, 15005-14-8; Δ,Λ-$[Co(en)_2(alaO)]I_2$, 80586-00-1; Δ-$[Co(en)_2(alaO)]I_2$, 93684-23-2; Λ-$[Co(en)_2(alaO)]I_2$, 93684-25-4; en, 107-15-3; $alaOCH_3$, 10065-72-2; alaen, 93684-24-3.

Supplementary Material Available: Listings of thermal parameters of non-hydrogen atoms (Table S1), positional parameters for calculated hydrogen atoms (Table S2), F_o and F_c structure factors (Table S3), interatomic distances and angles for the perchlorate and nitrate anions (Table S4), least-squares planes for the complex cation (Table S5), inter- and intramolecular nonbonded contacts involving possible hydrogen bonds (Table S6), and selected dihedral angles (Table S7) (20 pages). Ordering information is given on any current masthead page.

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