IH to form I is preferred as the rate-determining step for the decomposition of IH under alkaline conditions, but this aspect remains uncertain.

Acknowledgment. We thank Dr. F. Bergersen and G. Turner of the Division of Plant Industry, CSIRO, Canberra, Australia, and Dr. J. Hulston of the Institute of Nuclear Sciences, DSIR, Lower Hutt, New Zealand, for carrying out the ^{18}O tracer measurements.

Registry No. $[Co(en)_2(\beta\text{-alaOMe})](ClO_4)_3$, 103477-77-6; $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$, 103477-73-2; *cis*-$[Co(en)_2(OH_2)(\beta\text{-alaO-}i\text{-Pr})](NO_3)_2(ClO_4)$, 103498-63-1; *cis*-$[Co(en)_2(OCO_2)(\beta\text{-alaO-}i\text{-Pr})]ClO_4$, 103477-79-8; *cis*-$[Co(en)_2Br(\beta\text{-alaOMe})]Br_2$, 101695-41-4; *cis*-$[Co(en)_2Br(\beta\text{-alaO-}i\text{-Pr})]Br_2$, 101695-40-3; *cis*-$[Co(en)_2(OH_2)(\beta\text{-alaO-}i\text{-Pr})](NO_3)_3$, 103477-81-2; *trans*-$[Co(en)_2(OH)(\beta\text{-alaO})]^+$, 103477-82-3; *cis*-$[Co(en)_2(OH)(\beta\text{-alaO})]^+$, 103531-54-0; $[Co(en)_2(\beta\text{-alaO})]^{2+}$, 63771-19-7; *trans*-$[Co(en)_2(OH_2)(\beta\text{-alaOH})]^{3+}$, 103477-83-4; *cis*-$[Co(en)_2(OH_2)(\beta\text{-alaOH})]^{3+}$, 103531-55-1; β-alaO-*i*-Pr, 39825-36-0; β-alaOMe, 4138-35-6; OH^-, 14280-30-9; PO_4^{3-}, 14265-44-2; Et_3N, 121-44-8; CO_3^{2-}, 3812-32-6; H_2O, 7732-18-5; HCO_3^-, 71-52-3; ethanolamine, 141-43-5; diethanolamine, 111-42-2; morpholine, 110-91-8; triethanolamine, 102-71-6; *N*-methylmorpholine, 109-02-4; Hepes, 7365-45-9; piperidine, 110-89-4.

Supplementary Material Available: Listings of rate data for the hydrolysis of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ in alkaline solution (Table II), for buffer-catalyzed hydrolysis (Table III), for alkaline hydrolysis of *cis*-$[Co(en)_2(OH)(\beta\text{-alaO-}i\text{-Pr})]^{2+}$ (Table VII), and for buffer-catalyzed hydrolysis (Table XII) (12 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry, University of Otago, Dunedin, New Zealand

Metal Ion Activated Aminolysis of Esters. Reaction of Glycine Ethyl Ester with $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ and General-Base-Catalyzed Decomposition of Metal Alcohol–Amine Intermediates

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The aminolysis of the Co(III)-chelated, acyl-activated, β-alanine isopropyl ester in $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ by glycine ethyl ester in aqueous solution follows the rate expression $k_{obsd} = k'[B] + k''[GlyOEt][B]$ with only the k'' terms resulting in the aminolysis product $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$; k' terms result in hydrolysis of the ester to give $[Co(en)_2(\beta\text{-alaO})]^{2+}$. k'' takes values 3.9×10^3 (B = HO^-), 3.5×10^{-2} (B = GlyOEt), and 2.9×10^{-2} (B = Im) mol^{-2} dm^6 s^{-1}, and k', 5.0×10^3 (B = HO^-), 3×10^{-3} (B = GlyOEt) and 4.5×10^{-3} (B = Im) mol^{-1} dm^3 s^{-1}, all at I = 1.0 (NaCl) mol dm^{-3} and 25.0 °C. The requirement for another catalyzing base to be present in the aminolysis reaction is interpreted as rate-determining deprotonation of an amine–alcohol intermediate. The properties of such metal addition intermediates are discussed.

Several years ago in a study of the O and N lysis of cobalt(III)-chelated glycine esters in aqueous solution we left unresolved mechanistic details of the aminolysis reaction.[1] It was shown that $[Co(en)_2(glyNHR)]^{3+}$ was formed from $[Co(en)_2(glyO\text{-}i\text{-}Pr)]^{3+}$ by first and second order in $[NH_2R]$ pathways, but the rates of reaction were too fast to establish a rate law from kinetic measurements. The possible rapid formation of an alcohol–amine intermediate that slowly lost RO^- or ROH via general-base- or general-acid-catalyzed processes was suggested but not proven. In another study using Me_2SO media, an addition intermediate was clearly identified and amine-catalyzed loss of ROH was established.[2]

By using the less reactive ester isopropyl β-alaninate chelated to Co(III), it has now been possible to examine the aminolysis reaction in aqueous solution in some detail. This paper reports its reaction with glycine ethyl ester to form the chelated dipeptide $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$. The form of the rate law and the characterization of the rate-determining step are expected to be general features in the aminolysis of all metal-activated esters. Hydrolysis of the same chelated ester is considered in an accompanying paper.[3]

Experimental Section

The preparation of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$ has been described previously.[3] Imidazole was recrystallized from toluene and dried under vacuum, and glycine ethyl ester hydrochloride was twice recrystallized from methanol–ether. $[Co(en)_2(\beta\text{-ala-glyOEt})](ClO_4)_2(NO_3)\cdot H_2O$ was prepared as follows. To a solution of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$ (1.217 g) and GlyOEtHCl (0.70 g) in dry Me_2SO (20 cm^3) was added Et_3N (0.303 g) and the mixture allowed to stand at room temperature for 10 min before dilution with water (200 cm^3). IE chromatography (Sephadex SP-C25) using NaCl eluent (0.2–0.5 mol dm^{-3}) resulted in the recovery of an orange 3+ band. This was reduced to dryness (rotary evaporator) and the product complex desalted by extracting into MeOH (20 cm^3), filtering, and evaporating to dryness. This procedure was repeated a further two times with MeOH–EtOH (1:1) being used in the final extraction. The orange product was dissolved in water (4 cm^3, 70 °C) and $LiNO_3$ (0.3 g) and $NaClO_4$ (0.4 g) added. On cooling, $[Co(en)_2(\beta\text{-ala-glyOEt})](ClO_4)_2(NO_3)\cdot H_2O$ crystallized. This was washed with EtOH and then Et_2O and air-dried. Anal. Calcd for $[CoC_{11}H_{30}N_6O_3](ClO_4)_2(NO_3)\cdot H_2O$: C, 20.90; H, 5.10; N, 15.51.

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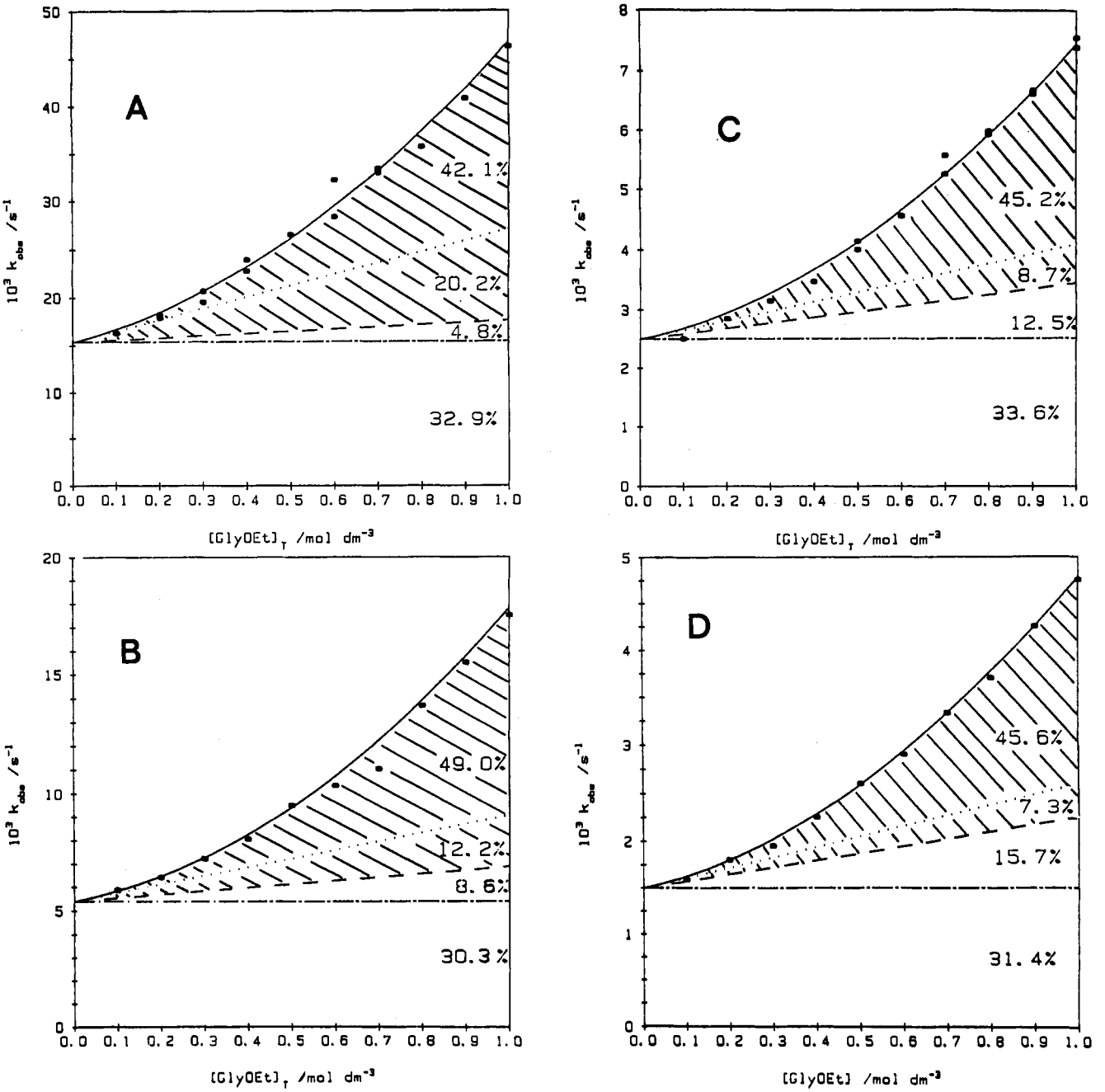

Figure 1. k_{obsd} vs. $[GlyOEt]_T$ rate profiles for the reactions of GlyOEt with $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ in aqueous solution (25.0 °C, I = 1.0 mol dm^{-3} (NaCl)): (A) pH 8.28, [GlyOEt] = 0.75 $[GlyOEt]_T$; (B) pH 7.82, [GlyOEt] = 0.5 $[GlyOEt]_T$; (C) pH 7.50, [GlyOEt] = 0.31 $[GlyOEt]_T$; (D) pH 7.32, [GlyOEt] = 0.25 $[GlyOEt]_T$. Percentage contributions of the different paths at $[GlyOEt]_T$ = 1.0 mol dm^{-3} (eq 2) are given against right-hand ordinate, and shaded areas represent contributions to $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$. The curves or lines are calculated from rate constants given in Table III.

Found: C, 20.9; H, 5.4; N, 15.9. ϵ_{max} = 118 (494 nm) and 84 (340 nm) in 0.25 mol dm^{-3} NaCl.

pK_a (25.0 °C) values for imidazole and glycine ethyl ester hydrochloride were measured in 1.0 mol dm^{-3} NaCl by titrating 20 cm^3 of a 0.1 mol dm^{-3} solution with 1.00 mol dm^{-3} hydrochloric acid or sodium hydroxide respectively, with use of a Radiometer titrator assembly. The observed pK_a's of 7.20 ± 0.02 and 7.82 ± 0.02, respectively, compare well with literature values for these constants.[13]

Kinetic data were collected at 495 nm (OD increase) on a Cary 219 spectrophotometer. Buffered solutions (1.0 mol dm^{-3}) of glycine ethyl ester ($GlyOEtH^+$/GlyOEt) were freshly prepared for each set of runs and kept cold in an ice bucket during the runs. Appropriate mixtures (total volume 10 cm^3) of glycine ester, NaCl (1.0 mol dm^{-3}) and imidazole buffer (1.0 mol dm^{-3}, same pH) were made up, a sample thermostated in a 1-cm cuvette, and 10 μL of a concentrated solution of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$ in Me_2SO injected and rapidly mixed. Plots of log $(A_\infty - A_t)$ vs. time were linear over $3t_{1/2}$.

Reaction products were analyzed in two ways. (1) Conventional IE separation was carried out on SP-C25 cation-exchange resin (0.25, 0.50 mol dm^{-3} NaCl eluent) following reaction (10 half-lives) of 40–50 mg of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$ dissolved in 10 cm^3 of reactant solution. Spectrophotometric analysis was at 496 nm (ϵ = 118, $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$; ϵ = 128, $[Co(en)_2(\beta\text{-alaO})]^{2+}$). (2) RP–HPIPC analysis[14] of the kinetic solutions using a Radial-Pak C_{18} cartridge (10 μm, 100 × 2.5 mm) and Waters Associates Z module, Varian 5000 pump and Waters U6K injector assembly, thermostated Varian UV-50 detector (492 or 250 nm), and HP 3390A integrator in conjunction with a Varian 9176 recorder was carried out. A two-solvent elution program consisting of aqueous (A) and 67% methanol–aqueous (B) mixtures 25 mM in hexanesulfonic acid (pH 3.5), with % B (time in min) 20 (0), 20 (5), 70 (30), 20 (40) allowed both the 2+ $[Co(en)_2(\beta\text{-alaO})]^{2+}$ and 3+ [Co-

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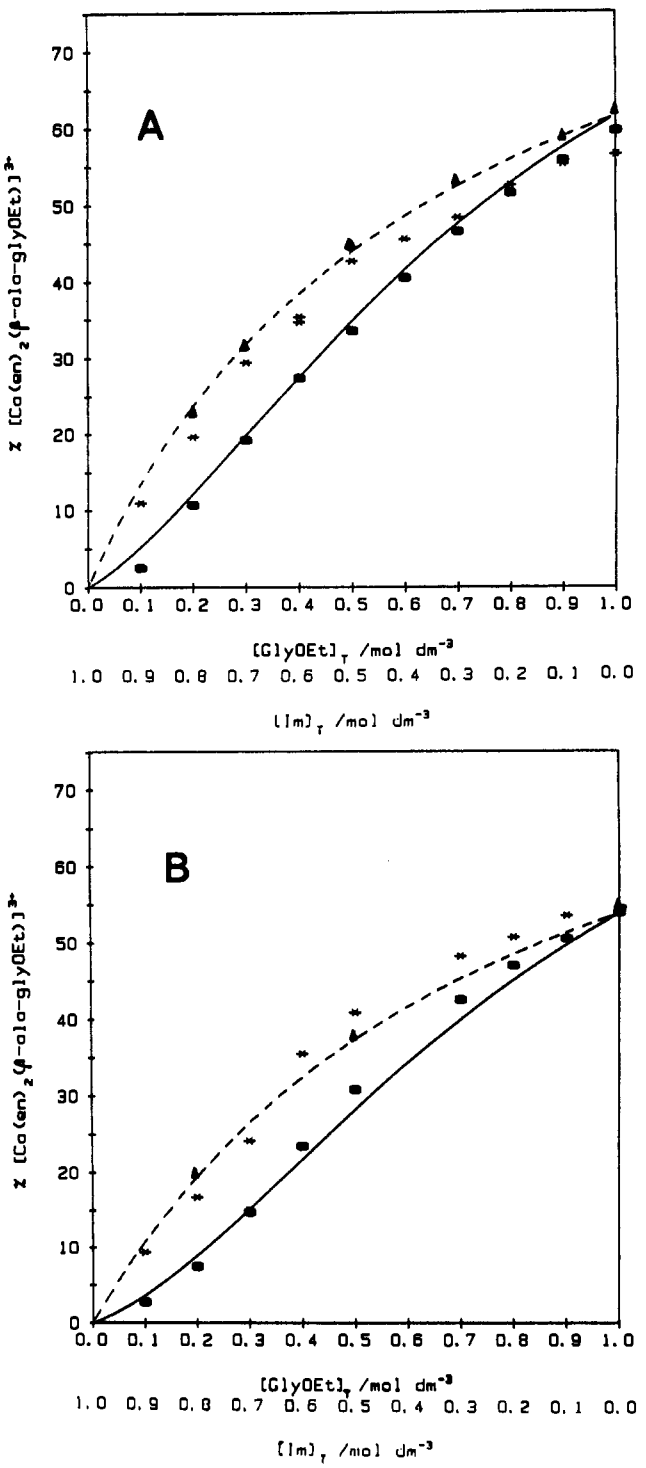


Figure 2. % $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ formed in the reactions of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ with GlyOEt in the absence (—) and presence (---) of Im (25.0 °C, I = 1.0 mol dm^{-3}): (A) pH 7.82, [GlyOEt] = 0.5 $[GlyOEt]_T$; (B) pH 7.50, [GlyOEt] = 0.31 $[GlyOEt]_T$. ■ and * represent RP–HPIPC data and ▲ IE data. The curves are calculated from data in Table III assuming k_0, k^I, and k^{IV} result in hydrolysis and k^{II}, k^{III}, and k^V in aminolysis.

$(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ products to be separated and analyzed (10-μL injections, 492 nm, AUFS = 0.05; 3-μL injections, 250 nm, AUFS = 0.5). Very sharp (~30 s width-half-height) absorptions at 19.0 and 29.9 min, respectively, were obtained, and analysis was by using standard sample mixtures.

Results and Discussion

Glycine Ethyl Ester. Spectrophotometric rate data collected at 495 nm (maximum OD change in visible spectrum) for the reaction of glycine ethyl ester self-buffered at pH 8.28, 7.82, 7.50, and 7.32 with $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ in an aqueous environment

Table II. Products[a] for the Aminolysis of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ at pH 8.28 and 7.32 (I = 1.0 mol dm^{-3} (NaCl), 25.0 °C)

pH	$[GlyOEt]_T$	% $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$
8.28	1.0	61.5, 59.2
	0.5	36.0, 35.6
7.32	1.0	54.0, 52.2
	0.5	30.8, 29.8

[a] IE chromatography (SP-C25 cation-exchange resin).

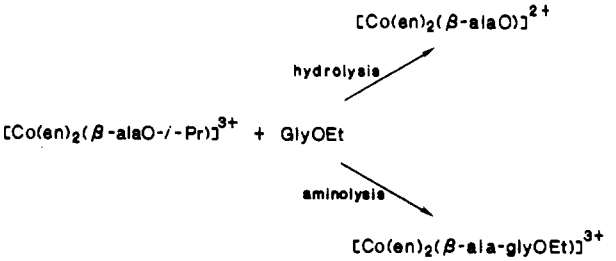
Table III. Rate Constants for the Aminolysis and Hydrolysis of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ (I = 1.0 mol dm^{-3} (NaCl), 25.0 °C)

term in rate law	rate const (pH)	reacn, product
k_0	15.4×10^{-3} [a] (8.28)	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
	5.4×10^{-3} [a] (7.82)	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
	2.5×10^{-3} [a] (7.50)	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
	1.50×10^{-3} [a] (7.32)	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
k^I[GlyOEt]	3×10^{-3} [b]	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
k^{II}[GlyOEt][OH]	3.9×10^{3} [c]	aminolysis, $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$
k^{III}[GlyOEt]^2	3.5×10^{-2} [c]	aminolysis, $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$
k^{IV}[Im]	4.5×10^{-3} [b]	hydrolysis, $[Co(en)_2(\beta\text{-alaO})]^{2+}$
k^V[GlyOEt][Im]	2.9×10^{-2} [c]	aminolysis, $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$

[a] Units in s^{-1}. [b] Units in mol^{-1} dm^3 s^{-1}. [c] Units in mol^{-2} dm^6 s^{-1}.

(I = 1.0 mol dm^{-3} (NaCl), 25.0 °C) are listed in Table I (supplementary data) and are given as plots of k_{obsd} vs. $[GlyOEt]_T$ (=$[GlyOEtH^+]$ + [GlyOEt]) in Figure 1. A separately measured pK_a under the conditions (7.82 ± 0.02, 1.0 mol dm^{-3} NaCl, 25.0 °C) gives free amine fractions of 0.75, 0.50, 0.31, and 0.25, respectively. Extrapolation of the rates to $[GlyOEt]_T$ = 0 gives hydrolytic rates at these pHs, k_0 = 15.4, 5.4, 2.50, and 1.50 × 10^{-3} s^{-1}, respectively. These latter values agree well with those obtained from the expression $k_0 = k_{OH}[OH^-]$ with k_{OH} = 5.0 × 10^3 mol^{-1} dm^3 s^{-1} established from extensive data with other buffer systems.[3] Curvature in the plots of Figure 1 clearly require the presence of a term of order higher than 1 in [GlyOEt], and careful examination shows that each set of data can be divided into contributions first and second order in [GlyOEt] (see below).

Reaction products at pH 7.78 and 7.50 are given as plots of % $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ vs. $[GlyOEt]_T$ in Figure 2, and less extensive data at pH 8.28 and 7.32 are listed in Table II. These data were obtained by IE and RP–HPIP chromatography and involved the separate analysis of the 2+ hydrolysis product and 3+ chelated dipeptide (eq 1). The latter method provides a very



(1)

fast and reliable analysis with excellent peak shape and high sensitivity.[14]

A combination of the rate and product data at the four pHs leads to the rate law

$$k_{obsd} = k_0 + k^I[GlyOEt] + k^{II}[GlyOEt][OH^-] + k^{III}[GlyOEt]^2 \quad (2)$$

with the first two terms (k_0, k^I) resulting in hydrolysis of the

chelated ester ($[Co(en)_2(\beta\text{-alaO})]^{2+}$ product) and the k^{II} and k^{III} terms in aminolysis ($[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ product). Rate constants are listed in Table III, and computed fits for the rate and product data are given as full curves in Figures 1 and 2. Contributions to the rate resulting in aminolysis are shaded in Figure 1, and the individual contributions of expression 2 are given as dotted or dashed lines. Percentage contributions at [GlyOEt] = 1.0 mol dm^{-3} are given against the right-hand ordinate. Of some significance is the division of the first order in [GlyOEt] contribution for each set into k^{I} and k^{II} parts. Their combined contribution to the rate does not change much (from a minimum of 20.7% at pH 7.82 to a maximum of 25.0% at pH 8.28), but they give rise to different products. The k^{II} aminolysis contribution steadily decreases from 20.3% at pH 8.28 to 7.3% at pH 7.32 for $[GlyOEt]_T$ = 1.0 mol dm^{-3}. It is also apparent that under the pH conditions used here the total percentage of aminolysis product changes little in the aqueous environment (62.3% at pH 8.28 to 52.9% at pH 7.32 for 1.0 mol dm^{-3} GlyOEt).

Imidazole. Rate data at pH 7.82 and 7.50 are listed in Table IV (supplementary data) and are given as plots of k_{obsd} vs. $[Im]_T$ (=$[ImH^+]$ + [Im]) in Figure 3. A separately determined pK_a under the conditions (7.20 in 1.0 mol dm^{-3} NaCl, 25.0 °C) gives free amine fractions of 0.81 and 0.67, respectively. The data fit expression 3 with k^{IV} = 4.5 × 10^{-3} mol^{-1} dm^3 s^{-1}. This value is

$$k_{obsd} = k_0 + k^{IV}[Im] \quad (3)$$

to be compared with a less precise value of 8 × 10^{-3} mol^{-1} dm^3 s^{-1} obtained previously in 1.0 mol dm^{-3} $NaClO_4$.[3] Imidazole catalysis results only in hydrolysis product $[Co(en)_2(\beta\text{-alaO})]^{2+}$, as demonstrated by the absence of 3+ amide product on IE and RP-HPIP chromatography. Also, stopped-flow studies at 300 nm did not detect the accumulation of any intermediate species during this reaction.

Glycine Ethyl Ester and Imidazole. Rate data at pH 7.82 and 7.30 for $[GlyOEt]_T$ + $[Im]_T$ = 1.0 mol dm^{-3} mixtures are listed in Table V (supplementary data) and are given as plots of k_{obsd} vs. ($[GlyOEt]_T$ + $[Im]_T$) in Figure 3. Reaction products are given in Figure 2 along with the data for glycine ethyl ester by itself. The increased $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ production, especially at low $[GlyOEt]_T$, arises from imidazole catalysis and can be accommodated by including a term in [GlyOEt][Im] in the overall rate (eq 4).

$$k_{obsd} = k_0 + k^{I}[GlyOEt] + k^{II}[GlyOEt][OH^-] + k^{III}[GlyOEt]^2 + k^{IV}[Im] + k^{V}[GlyOEt][Im] \quad (4)$$

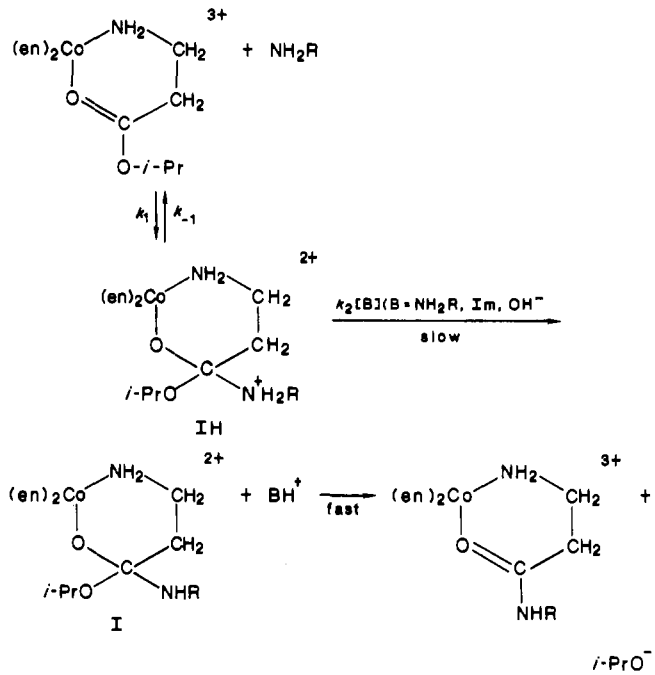
The correspondence between the rate and products arising from this term shows that none of it results in hydrolysis. Its contribution to aminolysis is substantial, as can be seen by comparing the shaded areas in Figure 3. Imidazole catalysis is thus similar to that resulting from the second molecule of glycine ethyl ester, and this can be seen by comparing k^{III} and k^{V} values (Table III).

Mechanism of the Aminolysis Reaction. The appearance of two base components in the rate law for aminolysis in addition to the substrate is compelling evidence for stepwise, bimolecular, addition–elimination processes. A termolecular collision such as would be required by a concerted addition–elimination reaction is considered unlikely. We suggest that initial rapid addition of amine to form a stable amine–alcohol intermediate is followed by rate-determining, base-catalyzed, loss of RO^-. Scheme I outlines this proposal with IH representing the intermediate separating the two bimolecular reactions. It is possible that the loss of RO^- also occurs as a subsequent reaction with the deprotonated intermediate I also being reasonably stable although this aspect is not certain (see below). Steady-state treatment leads to (5), which agrees with the observed rate law, eq 4, when $k_{-1} \gg k_2[B]$, whence $k_{obsd} = k_1k_2/k_{-1}[GlyOEt][B] = k_B[GlyOEt][B]$.

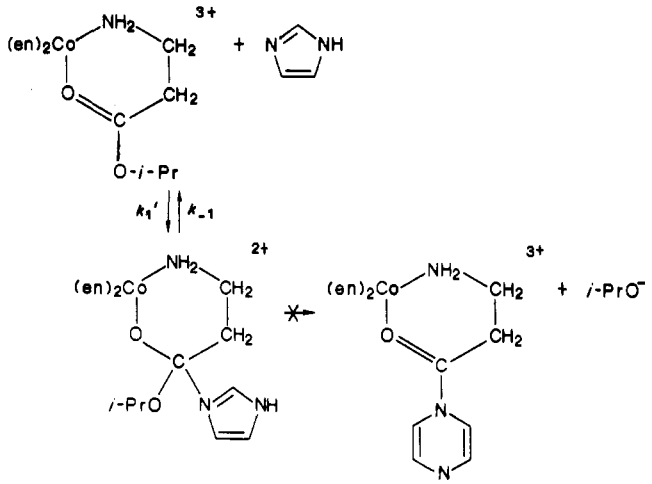
$$\frac{-d[Co(ester)]}{dt} = \frac{k_1k_2[GlyOEt][B]}{k_{-1} + k_2[B]}[Co(ester)] \quad (5)$$

It is significant that the terms $k^{I}[GlyOEt]$ and $k^{IV}[Im]$ do not contribute to amide formation; they only contribute to hydrolysis.

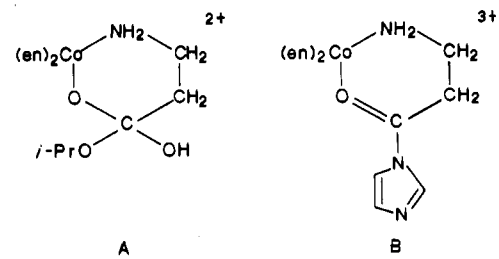
Scheme I



Scheme II



The absence of a term first order in [GlyOEt] leading to aminolysis products implies that addition of amine is not rate-determining and that there is no uncatalyzed route to amide from IH; deprotonation is a requirement. This is consistent with protonated amine being a better leaving group (k_{-1}) than RO^- or ROH,[4] and non-rate-determining addition of amine is in agreement with activation by metals moving the rate-determining process to removal of the alcohol function from the acyl carbon atom. Another example of this is in the hydrolysis reaction[3] when at pHs <9 hydrolysis by OH^- also involves rate-determining loss of RO^- from the similar neutral intermediate (A). Only when A is deprotonated is addition of OH^- to the parent ester rate controlling. Also, the absence of terms in [Im] or [Im][OH^-] leading to amide product is consistent with the absence of aminolysis by imidazole



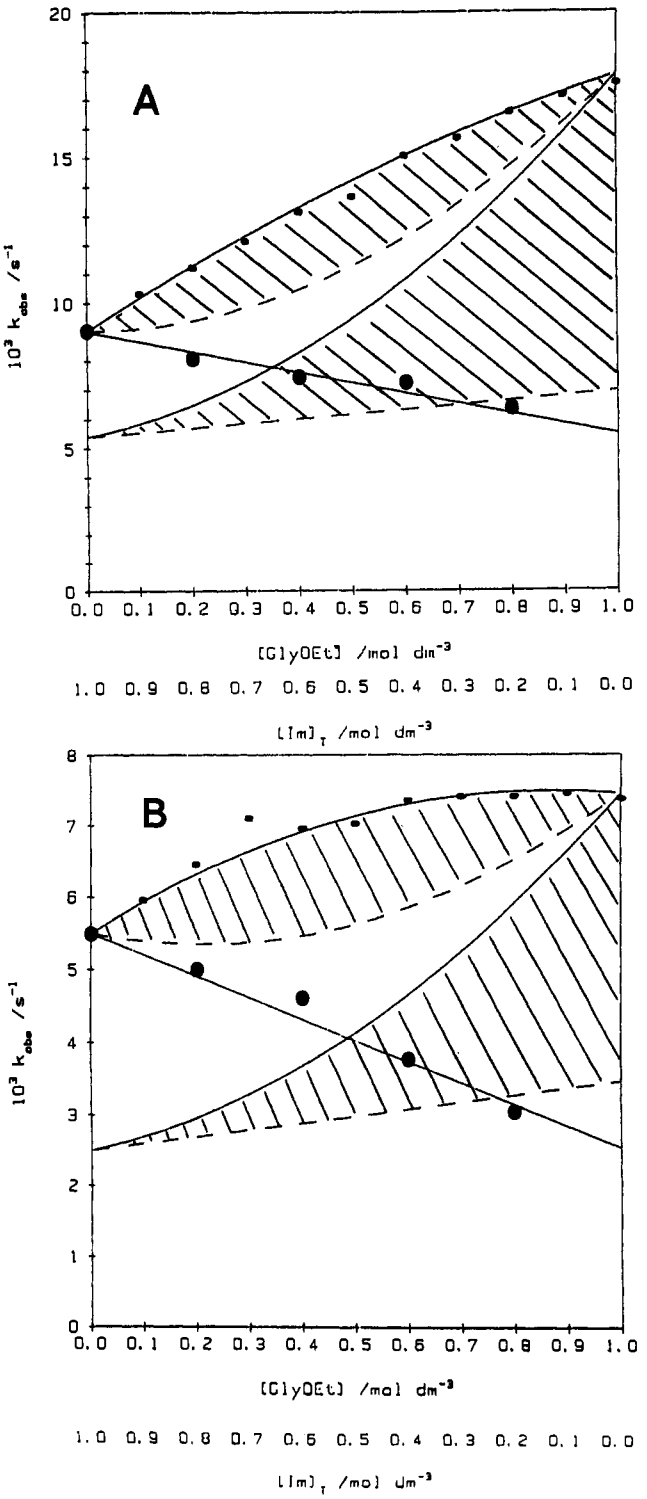


Figure 3. Rate profiles for the reactions of $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ with Im in the absence (● data) and presence (■ data) of GlyOEt (25.0 °C, I = 1.0 mol dm^{-3} (NaCl)): (A) pH 7.82, [GlyOEt] = 0.75 $[GlyOEt]_T$; [Im] = 0.81 $[Im]_T$; (B) pH 7.50, [GlyOEt] = 0.31 $[GlyOEt]_T$, [Im] = 0.67 $[Im]_T$. Shaded areas represent contributions to $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$. The curves shown are calculated from rate constants given in Table III.

and formation of the acyl-imidazole species (B). This would be expected to undergo fast subsequent aminolysis by GlyOEt (and hydrolysis) under the conditions. Addition of imidazole almost certainly occurs, but in the resulting intermediate (or in its deprotonated form) imidazole is the better leaving group[5] (Scheme II), so that this process is a dead end as far as aminolysis by GlyOEt is concerned.

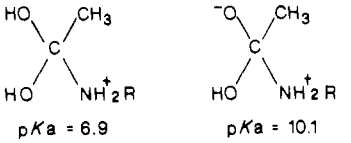
Relating the observed rate constants of Table III to the shortened form of expression 5 leads to k^{II}, k^{III}, and $k^V = k_1k_2/k_{-1}$ = k_B, with differences in k_B residing in the deprotonation rate constant k_2. Table VI lists these factors and compares $\Delta \log k_B$ values with ΔpK_B where K_B is the conventional acidity constant for the acid conjugate of B. There is an obvious parallel and approaching correspondence (Brønsted $\beta \sim 0.6$), suggesting significant proton removal in the transition state for this elimination step. k_2 then relates largely to deprotonation of IH rather than to loss of PrO^-, and these two processes could also be distinct rather than concerted. Stabilization of addition intermediates appears to be a fairly general feature of metal ion activation (see below) with IH being a clearly identifiable species in Me_2SO.[2] However, in the latter solvent, proton abstraction from IH does not appear to be rate-determining since the elimination rate approaches a constant value at high [GlyOEt] and protonated amine also appears to catalyze the loss of RO^- under these conditions. The change from rate-determining proton abstraction in aqueous solution to the slower loss of ROH in nonaqueous environments is possibly due to the easier solvation of the leaving group in the aqueous environment.

Table VI. Comparisons of Rate and Equilibrium Constants for Proton Abstraction

B	pK_B	log k_B	ΔpK_B	Δpk_B
OH^-	15.7	3.6	7.9	5.0
$NH_2CH_2CO_2Et$	7.8	−1.4	0.6	0.1
	7.2	−1.5		

Factors other than basicity of B are also important. When triethanolamine (pK_a = 7.76) was used in the presence of glycine ethyl ester ($[N(CH_2CH_2OH)_3]_T$ + $[GlyOEt]_T$ = 1.0 mol dm^{-3}, pH 7.85), no acceleration in rate (Table I) or increase in $[Co(en)_2(\beta\text{-ala-glyOEt})]^{3+}$ production (33% for $[N(CH_2CH_2OH)_3]_T$ = $[GlyOEt]_T$ = 0.5 mol dm^{-3}) occurred. Steric constraints would seem to prevent such bases from contributing to proton abstraction.

An estimate of the acidity of IH can be made by considering the polarizing power of $(en)_2Co^{3+}$ to be somewhat less than that of a proton and the *i*-PrO substituent to be somewhat less electron deficient than HO. DeTar[6] has listed conventional pK_a values for a number of intermediates of the type involved here, and estimated values for the species



would suggest a pK_a value of about 7 for IH (Scheme I). This would imply nearly diffusion-controlled deprotonation by OH^- ($k_2 \cong 10^{10}$ mol^{-1} dm^3 s^{-1}), whence $k_1/k_{-1} \cong 10^{-6}$ for the equilibrium addition of GlyOEt. Such an estimate would be in agreement with our inability to detect IH in aqueous solution by stopped-flow experiments.[7]

General Comments. The amine used here is representative of other primary and secondary amines. All appear to form stable amide products $[Co(en)_2(\beta\text{-ala-NHR})]^{3+}$ in aqueous or nonaqueous solutions. NH_3, $NHMe_2$, NH_2CH_2CN, amino acids, and their carboxyl-protected derivatives have been used in this laboratory, and the 3+ product can be easily recovered from the 2+ hydrolyzed species by IE chromatography on Sephadex or Dowex cation-exchange resins. Nonaqueous solvents eliminate hydrolysis, and Me_2SO has been the solvent of choice for the synthesis of small peptides.[8]

The six-membered chelate used here, $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$, behaves in a fashion identical with that of five-membered amino acid chelates $[Co(en)_2(AAOMe)]^{3+}$, and the conclusions reached here regarding mechanism are considered to apply to all ester substrates coordinated to the metal via the carbonyl function. Chelation appears to play only a minor role. The five-membered glycinate system reacts somewhat faster than the six-membered β-alaninate system when compared to the case of the uncoordinated ester; Table VII contains some comparative hydrolysis and aminolysis data. An examination of available structural data

Table VII. Comparison of Rate Constants for Hydrolysis and Aminolysis of Chelated and Free Glycine and β-Alanine Esters (25.0 °C)

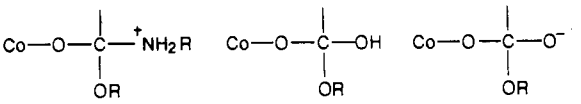
	n = 1, mol^{-1} dm^3 s^{-1}	n = 2, mol^{-1} dm^3 s^{-1}	ref
$H_3N^+(CH_2)_nCO_2Et + H_2O$	1×10^{-10}	1×10^{-11}	*a,b*
$H_2N(CH_2)_nCO_2i\text{-}Pr + OH^-$	0.2	2×10^{-2}	*c,d*
$[Co(en)_2(H_2N(CH_2)_nCO_2i\text{-}Pr)]^{3+} + H_2O$	2.0×10^{-5}	8.3×10^{-7}	*e,f*
$[Co(en)_2(H_2N(CH_2)_nCO_2i\text{-}Pr)]^{3+} + OH^-$	1.5×10^{6}	4×10^{4}	*g,f*
$[Co(en)_2(H_2N(CH_2)_nCO_2i\text{-}Pr)]^{3+} + NH_2CH_2CO_2Et + OH^-$	4.7×10^{5}	3.9×10^{3}	*g,d*
$[Co(en)_2(H_2N(CH_2)_nCO_2i\text{-}Pr)]^{3+} + 2H_2NCH_2CO_2Et$	0.39	3.5×10^{-2}	*g,d*

[a] Conley, H. L.; Martin, R. B. *J. Chem. Phys.* **1965**, *69*, 2914. [b] Based on a factor of 10 slower for the β-alanine ester. [c] Hay, R. W.; Porter, L. J.; Morris, P. J. *Aust. J. Chem.* **1960**, *19*, 1197. A factor of 5 slower for R = *i*-Pr vs. Et. [d] This study. [e] Alexander, M. D.; Busch, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 1130. [f] Reference 3. [g] Reference 1.

suggests that this may be due in part to greater relief of chelate ring strain on forming the addition intermediate in the five-membered system, facilitating addition, and in this regard the rate accelerations found for the β-alanine system are more likely to be applicable in the general case to monodentate esters.

It is now clear from this study and from the companion study on hydrolysis[3] that direct activation by the metal facilitates the addition of nucleophiles and retards elimination sufficient to require the formation of stable addition intermediates. Although this simple principle is the basis of all metal ion activation and has been recognized for many years,[9] previously only the addition part has been examined experimentally. A good example of this is in the metal-ion-catalyzed hydrolysis of nitriles[1] where only addition is involved. It is now clear that for esters (and the data for the hydrolysis of amides[11] can be similarly interpreted) that elimination is rate-controlling with good nucleophiles. Of more fundamental significance is the observation that the metal appears to stabilize the addition intermediate between transition states for addition and elimination. That is, a stepwise process is favored as opposed to a concerted reaction.[12] The reason for this is not entirely clear at the present time, but stabilization of such intermediates may well be largely entropic in nature.[3] For Co(III) overall rate accelerations vary from 10^4 to 10^6 depending on whether aminolysis or hydrolysis is involved. A further 10-fold increase is found for Ru(III) and Pt(IV), and first-row divalent transition metals are some 10^2 less effective.

Amine addition is not rate-determining because loss of $^+NH_2R$ from the intermediate is always favored over loss of RO^-. For the corresponding hydrolysis intermediate competitive loss of HO^- and RO^-



occurs with the order being $HO^- > MeO^- > EtO^- > i\text{-}PrO^-$.[3] Deprotonation of this intermediate accelerates loss of RO^- by $\sim 10^5$. General acids will affect in a similar way the departure of both leaving groups, and no general-acid catalysis has been observed in the reactions of these activated esters. For the amine–alcohol intermediate general-acid-catalyzed loss of ROH has not been observed in aqueous solution probably because the solvent provides this factor, but it has been observed in Me_2SO.[2]

Registry No. $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})](ClO_4)_3$, 103477-73-2; $[Co(en)_2(\beta\text{-ala-glyOEt})](ClO_4)_2(NO_3)$, 103477-75-4; β-alanine isopropyl ester, 39825-36-0; glycine ethyl ester, 459-73-4.

Supplementary Material Available: Rate data for the reactions of glycine ethyl ester (Table I), imidazole (Table IV), and glycine ethyl ester and imidazole (Table V) with $[Co(en)_2(\beta\text{-alaO-}i\text{-Pr})]^{3+}$ (4 pages). Ordering information is given on any current masthead page.

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Equilibria for Phosphine Ligation to Ferrous Protoporphyrin IX Dimethyl Ester and Related Systems in Toluene[1]

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Spectrophotometrically derived equilibrium constants for tributylphosphine (PBu_3) and tributyl phosphite ($P(OBu)_3$) binding to methylimidazole (MeIm) complexes of iron protoporphyrin IX dimethyl ester (Hm) are reported and compared with new and literature-derived values for ferrous phthalocyanine (FePc) and ferrous dimethylglyoxime ($Fe(DMGH)_2$) analogues. Affinities increase for all three systems in the order MeIm < $P(OBu)_3$ < PBu_3. Carbon monoxide binding and mutual trans destabilization of $P(OBu)_3$ increases in the order FePc < $Fe(DMGH)_2$ < Hm, consistent with axial π-donor ability of iron being greatest in hemes and least in FePc. New carbonyl derivatives of hemes with trans PR_3 have Soret bands at 440 nm. Trans to CO, MeIm is preferred to phosphine ligands. Rate constants for the heme systems estimated from equilibrium data and measured at low temperature are compared with those for FePc and $Fe(DMGH)_2$ analogues. Trends in K_{eq} are most easily understood in terms of rate constants for ligand dissociation, which provide a reliable indicator of coordinate bond energies. Trans effects in hemes and phthalocyanine complexes are similar but differ somewhat from previously established trends in bis(dioxime) complexes of iron.

Introduction

Axial ligand substitution reactions of low-spin six-coordinate hemes proceed via a dissociative mechanism with rates at 25 °C in the range 10^4–10^{-2} s^{-1}.[2-5] Equilibrium constants for ligation of imidazoles, carbon monoxide, etc. to a variety of hemes have also been obtained by spectrophotometric methods.[6-10] Extensive rate and equilibrium data are also available for non-heme FeN_4XY

(1) Abbreviations: Equilibrium constants $K^T_{X,Y}$ are for replacement of X by Y trans to T. Rate constants k^T_{-X} are for dissociation of X trans to T; k^T_{+X} is for addition of X trans to T. The shortened forms N (MeIm), P (PBu_3), and PO ($P(OBu)_3$) are used as subscripts and superscripts.
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