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Ligand Exchange and Chelate Ring Closure Kinetics for Some *trans*-Bis(amino acid)(tetramine)cobalt(III) Complexes

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A detailed kinetic study of the reactions linking *trans*-bis(amino acid)(tetramine)cobalt(III) complexes with the corresponding chelated derivatives, for the flexible tetramine ligands 3,7-diaza-1,9-nonanediamine (2,3,2-tet), 4,7-diaza-1,10-decanediamine (3,2,3-tet), and 4,7-diaza-5-methyl-1,10-decanediamine (5-Me-3,2,3-tet), has shown that the overall reaction proceeds in two distinct steps. The first is the base hydrolysis of the complex to produce *trans*-(hydroxo)(amino acid)(tetramine)cobalt(III) species, with pseudo-first-order rate constants of about 5×10^{-2} min^{-1} at 40°. The second step is the chelate ring closure and topological shift which produce the chelated products, with rate constants ranging from 5×10^{-5} to 5×10^{-4} min^{-1} at 40°. Activation parameters have been interpreted in terms of an I_d mechanism for the base hydrolysis and an edge displacement for the chelate ring closure. The effects of substituents on the amino acids and on the flexible tetramine ligand are clearly shown by the activation parameters.

We have completed a detailed kinetic study which defines the course of the reaction linking the uniquely oxygen bonded *trans*-bis(amino acid)(tetramine)cobalt(III) complexes described earlier[2] with the corresponding cis-chelated (amino acid)(tetramine)cobalt(III) species[3]

$$trans\text{-}[Co(tetramine)(aa)_2]^+ \rightarrow uns\text{-}cis^2\text{-}[Co(tetramine)aa]^{2+} + aa^-$$ [4]

In this report, we will give the results of our kinetic study with an interpretation in terms of the steric demands of the chelate ring created as the new cobalt-nitrogen bond is formed constrained by a cobalt-oxygen bond which maintains its integrity throughout the process. In another report, we will describe an extension of this system which has evolved into a model for metal-assisted carboxy-terminal peptide hydrolysis.[5]

General Description of the Reaction

The reaction of the *trans*-bis(amino acid) complexes was studied spectrophotometrically at 48.5°, pH 9.12, and was found to proceed in two distinct first-order processes. The initial step, characterized by a color change from violet to red-violet, is the base hydrolysis of the reactant with the subsequent formation of the *trans*-hydroxyglycine intermediate [Co(tetramine)(OH)(gly)]$^+$

$$trans\text{-}[Co(tetramine)(gly)_2]^+ + OH^- \rightarrow trans\text{-}[Co(tetramine)(OH)(gly)]^+ + gly^-$$

Our observation of three isosbestic points clearly supports the presence of only two uniquely absorbing species. The base hydrolysis step was confirmed by the examination of the hydrolysis of the complexes *trans*-[Co(tetramine)(OAc)$_2$]$^+$ (for which under similar conditions no chelation step is possible). This reaction is identical with the consecutive base hydrolysis reactions reported by Illuminati, *et al.*, for *trans*-[Co(en)$_2$(OAc)$_2$]$^+$ [6] and other *trans*-bis(carboxylic acid) complexes.[7,8] The latter reaction was found to proceed in two steps

$$trans\text{-}[Co(en)_2(OAc)_2]^+ + OH^- \xrightarrow{k_1} trans\text{-}[Co(en)_2(OH)(OAc)]^+ + OAc^-$$

$$trans\text{-}[Co(en)_2(OH)(OAc)]^+ + OH^- \xrightarrow{k_2} trans\text{-}[Co(en)_2(OH)_2]^+ + OAc^-$$

with the reported rate constants $k_1 = 5.06 \times 10^{-2}$ and $k_2 = 0.125 \times 10^{-2}\ M^{-1}\ sec^{-1}$. The kinetic behavior of our *trans*-diacido(tetramine)cobalt(III) complexes is consistent with a correspondingly large difference in the rates of the first and second base hydrolysis. From these observations we have inferred that a similar sequence of reactions is operable in the bis(acetato) and bis(glycinato) complexes. The similarity of the reaction suggests that the base hydrolyses of *trans*-[Co(tetramine)(gly)$_2$]$^+$ and *trans*-[Co(tetramine)(OAc)$_2$]$^+$ proceed by similar processes with the formation of hydroxo intermediates

$$trans\text{-}[Co(tetramine)(OAc)_2]^+ + OH^- \rightarrow trans\text{-}[Co(tetramine)(OH)(OAc)]^+ + OAc^-$$

$$trans\text{-}[Co(tetramine)(gly)_2]^+ + OH^- \rightarrow trans\text{-}[Co(tetramine)(OH)(gly)]^+ + gly^-$$

Electronic spectral parameters obtained for the intermediates in solution, [Co(tetramine)(OH)(OAc)]$^+$ and [Co(tetramine)(OH)(gly)]$^+$, are listed in Table I, together with the corresponding λ_{max} and ϵ values for some related diacidobis(ethylenediamine) complexes. The isomeric *cis*- and *trans*-diacido complexes of bis(ethylenediamine) are easily distinguished by their electronic spectra. Thus *cis*-diacetato, -aquoacetato, and -diaquo species exhibit absorption maxima around 500 nm, whereas the *trans*-hydroxoacetato, and *trans*-bis(hydroxo) complexes exhibit maxima around 520 nm. The trans isomers have λ_{max} at longer wavelengths and with lower extinction coefficients. We have, therefore, assigned the trans configuration to [Co(tetramine)(OH)(OAc)]$^+$ and [Co(tetramine)(OH)(gly)]$^+$ from the similarity of their electronic spectra to those of the corresponding bis(ethylenediamine) complexes. All *trans*-diacido complexes studied undergo base hydrolysis in analogous manner with the formation of the hydroxo intermediate; each reaction exhibits three isosbestic points.

The second step in the reaction of *trans*-[Co(tetramine)-

(1) From the Ph.D. thesis of J. J. Fitzgerald, Illinois Institute of Technology, 1972. NDEA Predoctoral Trainee, 1969-1972.

(2) G. R. Brubaker and D. P. Schaefer, *Inorg. Chem.*, 10, 811 (1971).

(3) G. R. Brubaker and D. P. Schaefer, *Inorg. Chem.*, 10, 2170 (1971).

(4) Abbreviations used throughout this text: 2,3,2-tet, 3,7-diaza-1,9-nonanediamine; 3,2,3-tet, 4,7-diaza-1,10-decanediamine; aa, generalized amino acid; gly, glycine; ala, alanine; val, valine; sar, sarcosine; OAc, acetate; en, ethylenediamine; trien, triethylenetetramine.

(5) Submitted for publication in *J. Amer. Chem. Soc.*

(6) V. Carunchio, G. Illuminati, and G. Ortaggi, *Inorg. Chem.*, 6, 2168 (1967).

(7) F. Aprile, V. Caglioti, and G. Illuminati, *J. Inorg. Nucl. Chem.*, 21, 325 (1961).

(8) V. Carunchio, G. Illuminati, and F. Maspero, *J. Inorg. Nucl. Chem.*, 28, 2693 (1966).

Table I. Electronic Spectral Parameters for Some *trans*-Diacido(tetramine)cobalt(III) Complexes

Compd	λ_{max} (ϵ) Band I	Band II
cis-$[Co(en)_2(OAc)_2]^+$ [a]	505 (152)	360 (99)
cis-$[Co(en)_2(H_2O)(OAc)]^{2+}$ [a]	498 (100)	360 (95)
cis-$[Co(en)_2(H_2O)_2]^{3+}$ [b]	495 (93)	355 (91)
cis-$[Co(en)_2(OH)_2]^+$ [a]	517 (99)	370 (101)
cis-$[Co(en)_2(OH)(OAc)]^+$ [a]	512 (101)	365 (97)
trans-$[Co(en)_2(OAc)_2]^+$ [a]	540 (51)	360 (68)
trans-$[Co(en)_2(OH)(OAc)]^+$	527 (57)	365 (76)
trans-$[Co(en)_2(OH)_2]^+$ [a]	527 (86)	380 (86)
trans-$[Co(en)_2(H_2O)(OAc)]^{2+}$ [a]	543 (85)	355 (91)
trans-$[Co(en)_2(H_2O)_2]^{3+}$ [b]	545 (72)	349 (86)
trans-$[Co(2,3,2\text{-tet})(OH)(OAc)]^+$	532 (60)	370 (70)
trans-$[Co(2,3,2\text{-tet})(OH)(gly)]^+$	530 (58)	373 (78)
trans-$[Co(3,2,3\text{-tet})(OH)(OAc)]^+$	536 (60)	375 (77)
trans-$[Co(3,2,3\text{-tet})(OH)(gly)]^+$	527 (62)	370 (77)

[a] J. Bjerrum and S. E. Rasmussen, *Acta Chem. Scand.*, 6, 1265 (1952). [b] V. Carunchio, G. Illuminati, and G. Ortaggi, *Inorg. Chem.*, 6, 2168 (1967).

$(gly)_2]^+$ in alkaline solution is the closing of the glycinato chelate ring

$$trans\text{-}[Co(2,3,2\text{-tet})(OH)(OOCCH_2NH_2)]^+ \rightarrow uns\text{-}cis_2\text{-}[Co(2,3,2\text{-tet})gly]^{2+} + OH^-$$

The final product of this reaction step is spectrophotometrically identical with the chelated glycinato complex prepared by the reaction of *trans*-$[Co(2,3,2\text{-tet})Cl_2]Cl$ with glycine.[3] We found three isosbestic points in the electronic spectra taken during the course of this reaction indicating the presence of only two uniquely absorbing species. The chelation steps for the glycine (*S*)-alanine, (*S*)-valine, and sarcosine complexes are analogous with three isosbestic points in their electronic spectra.

Kinetic Results of the Base Hydrolysis Step

At pH 9.12, the base hydrolysis of the complexes *trans*-$[Co(tetramine)(aa)_2]^+$, where aa = acetate, glycine, (*S*)-alanine, (*S*)-valine, or sarcosine, was followed spectrophotometrically at the wavelengths 543, 539, 539, 553, and 553 nm for 2,3,2-tet complexes and at 550, 454, 475, 471, and 476 nm for 3,2,3-tet complexes, respectively. Under pseudo-first-order conditions, the optical density decreases from the *trans*-diacido(tetramine)cobalt(III) complexes to respective trans hydroxo acid intermediates.

Experimental rate constants were obtained over the temperture range 30.0–60.0°, under the conditions of Table II. All kinetic experiments were run in triplicate and the rate constants were determined by graph (Figure 1) and by the method of least squares. A linear plot of ln $(A_t - A_\infty)$ *vs.* time produced straight lines with correlation coefficients of at least 98.0%. Our k_{obsd} values correspond to pseudo-first-order conditions, following the first-order rate law[9]

$$d[complex]/dt = k_{obsd}(A_t - A_\infty)$$

where complex = *trans*-$[Co(tetramine)(aa)_2]^+$ ion. Activation parameters (Table II) were obtained from an Arrhenius plot; $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated at 40°.

Base hydrolysis of cobalt(III) complexes is expected to be first order in both hydroxide and complex. Accordingly, second-order rate constants were determined by conventional titrimetric methods in the concentration range $(2\text{–}8) \times 10^{-3}$

(9) One of the reviewers kindly pointed out that the concentration of the complex is not equal to $(A_t - A_\infty)$ but is related to the difference in absorbance through the Beer–Lambert law constants ϵ, molar absorptivity, and l, the cell path length. Kinetic parameters derived from the slope of a ln $(A_t - A_\infty)$ *vs.* time plot are independent of the Beer–Lambert constants.

Table II. Kinetic Parameters for the Base Hydrolysis of Some *trans*-Bis(amino acid)(tetramine)cobalt(III) Complexes[a,b]

2,3,2-tet System

aa	10^2k_1, min^{-1} 30.0°	40.0°	50.0°	60.0°	E_a, kcal/mol	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
OAc		2.13	8.28	26.0	26.6	20.0	8.8
gly	0.63	3.10	12.6	31.3	25.9	25.3	7.1
ala		2.60	12.9	21.5	22.5	21.9	−3.9
val		2.50	12.1	21.1	22.1	21.5	−5.1
sar		10.30	22.2	44.3	15.2	14.6	−24.4

3,2,3-tet System

aa	10^2k_1, min^{-1} 30.0°	35.0°	40.0°	50.0°	E_a, kcal/mol	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
OAc	1.37		6.59	24.4	28.0	27.4	15.5
gly	0.95		3.55	12.4	25.1	24.6	5.2
S-ala	3.08		9.52	28.4	21.7	21.1	−3.7
S-val	3.25		10.1	28.6	21.1	20.5	−5.5
sar	9.85	15.5	25.4		18.0	17.4	−13.6

[a] Kinetic experiments were run in triplicate. The tabulated data are derived from experiments run at complex concentrations in the range $(7.80\text{–}8.20) \times 10^{-3}$ *M*, pH 9.12 ($NaOH\text{–}H_3BO_3$ buffer), and $\mu = 0.08$. [b] The estimated errors in k_{obsd}, E_a, and $\Delta S^\ddagger$ are 3%, 0.6 kcal/mol, and 2 eu, respectively.

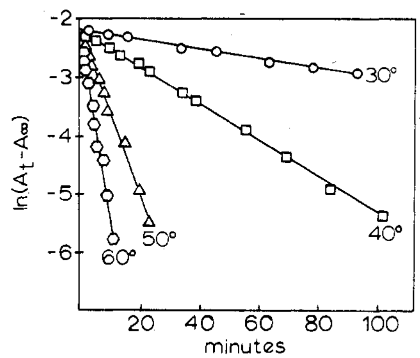


Figure 1. Typical plot of kinetic data, ln $(A_t - A_\infty)$ *vs.* t, for the base hydrolysis step. (Shown is the base hydrolysis of *trans*-$[Co(2,3,2\text{-tet})(gly)_2]^+$.)

M in both complex and hydroxide ion. Kinetic data for the first base hydrolysis of *trans*-$[Co(tetramine)(OAc)_2]^+$ were found to obey second-order kinetics and followed the rate law

$$-d[OH^-]/dt = k_{obsd}[complex][OH^-]$$

A plot of $(1/(a - b)(\ln[b(a - x)/(b - x)]))$ *vs.* time was found to be linear over at least 3–4 half-lives,[10] where k_{obsd} is 0.792 ± 0.028 and 2.1 ± 0.73 M^{-1} min^{-1} for *trans*-$[Co(2,3,2\text{-tet})(OAc)_2]^+$ and *trans*-$[Co(3,2,3\text{-tet})(OAc)_2]^+$, respectively, at 25°.

Kinetic Results of the Chelation of α-Amino Acids

At a pH of 9.12 in a H_3BO_3–NaOH buffer, the chelation of the hydroxo intermediates *trans*-$[Co(2,3,2\text{-tet})(OH)(aa)]^+$, where aa = glycine, (*S*)-alanine, (*S*)-valine, and sarcosine, was followed spectrophotometrically at the wavelengths 450, 451, 448, and 452 nm, respectively. The corresponding reactions of $[Co(3,2,3\text{-tet})(OH)(gly)]^+$ and $[Co(3,2,3\text{-tet})(OH)(ala)$ were followed at 541 and 555 nm, respectively.

(10) We attribute the discrepancy between the experimental pseudo-first-order rate constant and that calculated from the experimental second-order rate constant and the buffer pH to a combination of the effects of temperature, ionic strength, and the borate buffer.

The optical density increases in going from the trans hydroxo intermediates to the orange-red cis-chelated complexes. Linear plots of ln $(A_\infty - A_t)$ *vs.* time were obtained for these complexes over *ca.* 3–4 half-lives for the glycinato complex (Figure 2) over the temperature range 40.0–60.0°. First-order rate constants are summarized in Table III, together with calculated activation parameters. The k_{obsd} values correspond to the rate law[9]

$$d[\text{complex}]/dt = k_{obsd}[\text{complex}] = k_{obsd}(A_\infty - A_t)$$

All experiments were run in triplicate and the rate constants and activation parameters were determined by the methods described previously.

Discussion of the Base Hydrolysis

We have experienced insurmountable experimental difficulties in the measurement of second-order rate constants arising from the buffering action of the uncoordinated amine groups in the pH range of interest. We have, therefore, proceeded to analyze the pseudo-first-order kinetic data in terms of the steric demands of the amino acid residues.

At 40°, for example, the rate constants indicate the order of susceptibility to hydrolysis to be OAc $<$ Gly $\sim$ Ala $\sim$ Val $\ll$ Sar, for complexes with 2,3,2-tet, and Gly $<$ OAc $<$ Ala $\sim$ Val $\ll$ Sar, for complexes with 3,2,3-tet. From the data of Table II, it may be seen that the activation energy for base hydrolysis of the glycine and acetato complexes is *ca.* 25–28 kcal/mol, and the entropy of activation varies from about +5 to about +15 eu. For the Ala and Val complexes, however, the activation energies are some 4–7 kcal/mol lower, and the entropies of activation are negative. In general, the $\Delta H^\ddagger$ and E_a values vary exactly as expected, decreasing as the axial ligands increase in size, consistent with the ease with which a bulky group is expected to be displaced in a dissociative mechanism.

We note that the second-order rate constant for the base hydrolysis of *trans*-$[Co(2,3,2\text{-tet})(OAc)_2]^+$ is approximately 10 times that observed for the corresponding bis(ethylenediamine) complex[7] in agreement with other base hydrolysis reactions where the steric effects of additional chelate rings increase the rates of reaction. For example, the base hydrolysis of *trans*-$[Co(en)_2Cl_2]^+$ ($k_2 = 3000\ M^{-1}\ sec^{-1}$) and *trans*-$[Co(2,3,2\text{-tet})Cl_2]^+$ ($k_2 = 61{,}000\ M^{-1}\ sec^{-1}$) exhibits at least a 20-fold increase in rate. We note that the rate of base hydrolysis for 3,2,3-tet complexes is about 3 times faster than the rate for the corresponding 2,3,2-tet, in full agreement with the chelate ring interaction concept.

A characteristic feature of base hydrolysis reactions of diacidobis(ethylenediamine)cobalt(III) complexes is a large positive entropy change associated with a dissociative mechanism. The $\Delta S^\ddagger$ values seem to be inverted within this series, positive for those ligands with the least steric influence, yet negative for those ligands with large steric requirements as manifested in the $\Delta H^\ddagger$ and E_a values. We interpret these anomalous $\Delta S^\ddagger$ values to indicate a detailed mechanism closely related to the I_d mechanism proposed by Langford and Gray.[11] Association of the incoming OH^- group, either as an outer-sphere ligand or through an increase in coordination number of the central ion, results in increased crowding of the axial ligands early in the course of the reaction. This crowding would be observed as a negative $\Delta S^\ddagger$ contribution and would be increasingly negative as the bulk of the axial ligand increased in a common reaction species. This interpretation is in accord with the extremely slow rate of dissociation of our *trans*-bis(amino acid) complexes in neutral solution and with the results of the second-order base hydrolysis study of *trans*-bis(acetato) complexes. That the associative step generating the anomalous $\Delta S^\ddagger$ values precedes the dissociative step attributable to the $\Delta H^\ddagger$ terms is fully consistent with an I_d mechanism.

(11) C. H. Langford and H. B. Gray, "Ligand Substitution Processes," W. A. Benjamin, New York, N. Y., 1965, Chapter 1.

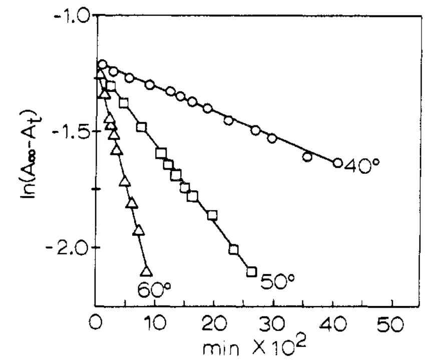


Figure 2. Typical plot of kinetic data, ln $(A_\infty - A_t)$ *vs.* *t*, for the isomerization and chelation step. (Shown is the 2,3,2-tet–gly system.)

Table III. Kinetic Parameters for Isomerization and Chelate Ring Closure of Some *trans*-(Hydroxo)(amino acid)(tetramine)cobalt(III) Complexes[a,b]

2,3,2-tet System

	$10^4 k_{obsd}$, min^{-1}				E_a, kcal/mol	$\Delta H^\ddagger$, kcal/mol	
aa	30.0°	40.0°	50.0°	60.0°			$\Delta S^\ddagger$, eu
gly	0.189	0.889	2.71	10.7	26.6	26.0	−2.1
ala		0.470	1.79	6.88	28.4	27.8	2.5
val		0.301	1.52	5.10	29.0	28.4	3.8
sar		0.118	0.485	1.48	26.4	26.8	−6.5

3,2,3-tet System

	$10^3 k_{obsd}$, min^{-1}			E_a, kcal/mol	$\Delta H^\ddagger$, kcal/mol	
aa	40.0°	50.0°	60.0°			$\Delta S^\ddagger$, eu
gly	0.52	1.35	7.88	28.0	27.6	5.8
S-ala	0.24	1.04	4.09	29.5	28.9	9.3

[a] Kinetic experiments were run in triplicate. The tabulated data are derived from experiments run at complex concentrations in the range $(7.80–8.20) \times 10^{-3}\ M$, pH 9.12 ($NaOH-H_3BO_3$ buffer), and $\mu = 0.08$. [b] The estimated errors in k_{obsd}, E_a, and $\Delta S^\ddagger$ are 3%, 0.6 kcal/mol, and 2 eu, respectively.

Discussion of the Chelate Ring Closure

To establish that the monodentate amino acid remains coordinated throughout the chelation process, (*S*)-alanine was added to the reaction solution of *trans*-$[Co(2,3,2\text{-tet})(gly)_2]^+$ following the base hydrolysis step

trans-$[Co(2,3,2\text{-tet})(OH)(gly)]^+$ + (*S*)-alanine

case I	case II
cis-$[Co(2,3,2\text{-tet})gly]^{2+}$	*cis*-$[Co(2,3,2\text{-tet})gly]^{2+}$
OH^-	*cis*-$[Co(2,3,2\text{-tet})(S\text{-ala})]^{2+}$
free (*S*)-alanine	OH^-
free glycine	free (*S*)-alanine
	free glycine

We expect the final reaction mixture to contain all free alanine (case I) if the cobalt(III)–oxygen bond remains intact or a mixture of coordinated and free alanine (case II) if the glycine–cobalt bond is ruptured. Case II is characterized by a complex pmr spectrum in the methyl proton region corresponding to the racemic complex. We found only a sharp doublet at 1.33 ppm in the pmr spectrum of the reaction

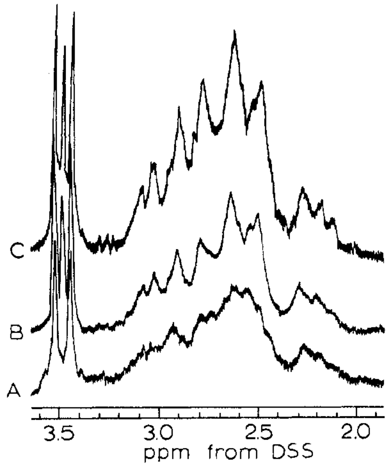


Figure 3.

mixture in pD 9 buffer and in the pmr spectrum of a simulated reaction mixture containing *cis*-[Co(2,3,2-tet)gly]$^{2+}$, free glycine, and free (*S*)-alanine. The excess (*S*)-alanine must, therefore, be present only as the free species, from which we infer that the cobalt–carboxyl oxygen bond remains intact throughout the reaction sequence.

It has been shown that *trans*-(acido)$_2$(3,2,3-tet)Co^{III} complexes are found exclusively in the *RR,SS* (racemic, about the secondary nitrogen atoms) configuration[12] and that this configuration is retained during the course of topological shifts of the kind we have studied. Our *trans*-(acido)$_2$(2,3,2-tet)Co^{III} species, on the other hand, are found in the *RS* (meso) configuration in alkaline media,[13] yet the chelated products adopt the *RR,SS* (racemic) configuration about the secondary donors. Isomerization about the secondary nitrogens may occur simultaneously with the base hydrolysis step, following the base hydrolysis step, or coincidentally with the chelation step.

Proton magnetic resonance spectra taken at intervals during the course of the reaction *trans*-[Co(2,3,2-tet)(gly)$_2$]$^+$ → *uns-cis*$_2$-[Co(2,3,2-tet)gly]$^{2+}$ at pD 9 in D_2O at 30° are shown in Figures 3 and 4. In the spectrum of the reactant *trans*-[Co(2,3,2-tet)(gly)$_2$]$^+$ (Figure 3A), we have assigned the multiplet at 2.25 ppm to the central methylene group of the 2,3,2-tet ligand, in accord with a previous assignment for the *trans*-dichloro complex.[13] The sharp singlets at 3.43 and 3.53 ppm are assigned to the methylene protons of the carboxyl-bonded glycine moieties, which are nonequivalent under the symmetry of the 2,3,2-tet complex in the *RS* (meso) configuration. As base hydrolysis proceeds, the multiplets appear to sharpen and a third signal which we have assigned to the methylene protons of free glycine liberated from the parent complex appears at 3.48 ppm.

Spectra taken during the second step are shown in Figure 4. Two broad signals at 3.50 and 3.54 ppm appear, which we have assigned to the methylene protons of the free and chelated glycine, respectively. The spectrum of the complex *uns-cis*$_2$-[Co(2,3,2-tet)gly]$^{2+}$ is given in Figure 4C. The broad signal at 3.55 ppm corresponds to the methylene protons of chelated glycine observed in spectra 4A and 4B. The distinguishing feature of these spectra is the multiplet at higher field (*ca.* 2.25–2.0 ppm), which is characteristic of the tetramine ligand in the cis topology. The corresponding signal in our trans complexes occurs at *ca.* 2.3 ppm.

(12) H. G. Hamilton and M. D. Alexander, *J. Amer. Chem. Soc.*, 89, 5065 (1967).
(13) H. G. Hamilton, Ph.D. Dissertation, New Mexico State University, 1968.

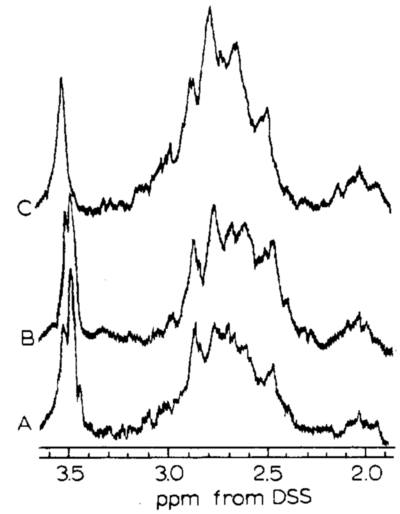
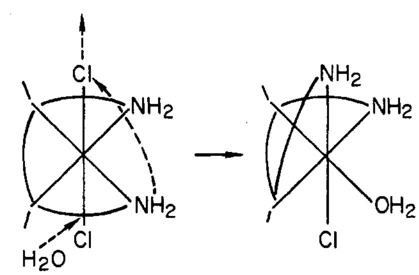


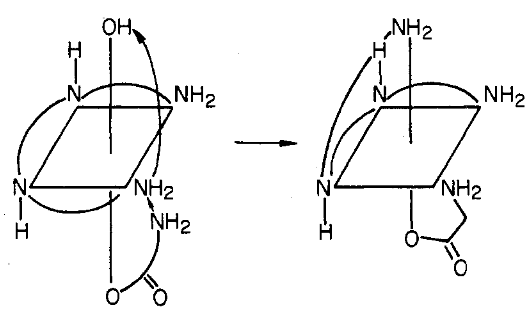
Figure 4.

Throughout the base hydrolysis step, the complex must be of the trans configuration, the trans–cis isomerization occurring after the base hydrolysis or occurring simultaneously with chelation, in agreement with the topological assignment of the long-lived intermediate from electronic spectral parameters. Further, Tobe[14] has shown that trans-*RS* (meso) complexes undergo both aquation and anation with retention of geometrical and asymmetric nitrogen configurations. Only a trans-*RS* (meso) hydroxo intermediate is consistent with all of the available data.

Sargeson and Searle[15] have suggested that the stereospecific aquation of *trans*-(*SS*)-[Co(trien)Cl$_2$]$^+$ may be explained in terms of a bimolecular attack by water, accompanied by an edge displacement of a terminal primary amine group



This mechanism is an attractive rationalization of the observation that each act of aquation leads to an uns-cis isomer in which the water is trans to the secondary amine nitrogen. In an edge displacement, a primary amine nitrogen of the tetramine ligand displaces the trans hydroxide ligand and the primary nitrogen atom of the coordinated amino acid competes with the solvent for the vacant coordination site



(14) R. Niththyananthan and M. L. Tobe, *Inorg. Chem.*, 8, 1589 (1969).
(15) A. M. Sargeson and G. H. Searle, *Inorg. Chem.*, 6, 2172 (1967).

Only the uns-cis$_2$- configuration is obtained for these chelated amino acid complexes.

The rate constants for the chelation step of the transformation

trans-[Co(tetramine)(OH)(aa)]$^+$ → *uns-cis*$_2$-[Co(tetramine)aa]$^{2+}$ + OH$^-$

are listed in Table IV. We have neglected isomerization about the tetramine secondary nitrogens, while analyzing the chelation step on the basis of the steric requirements of the substituents of the amino acid residues. In general, the addition of any substituent to the glycine moiety decreases the rate of reaction and increases the energy and enthalpy of activation (Table III).

Interpretation of the entropies of activation for the series is not readily apparent from a simple consideration of the changes in substituent bulk. We do, however, attribute the positive $\Delta S^{\ddagger}$ for both complexes in the 3,2,3-tet system to interaction with the tetramine chelate rings; the interaction of alanine is greater than that of glycine, as expected. Negative entropy values may be attributed, in part, to the chelate effect. Chelation of glycine and sarcosine leads to the formation of two products, of Δ and Λ or Δ-*S* and Λ-*R* absolute configuration, respectively, where *S* and *R* refer to the configuration about the nitrogen donor of sarcosine. That the sarcosine $\Delta S^{\ddagger}$ value is more negative than that for glycine may arise from stereospecific coordination of the asymmetric sarcosine nitrogen atom. Buckingham and Sargeson, *et al.*,[16] demonstrated this stereospecificity in the Δ-(*R*)- and Λ-(*S*)-[Co(en)$_2$sar]$^{2+}$ and -[Co(trien)sar]$^{2+}$ complexes. We have found evidence for this phenomenon in the *uns-cis*$_2$-[Co(2,3,2-tet)sar]$^{2+}$ complex; of the four possible isomers, Λ-*S*, Λ-*R*, Δ-*S*, and Δ-*R*, only a mixture of the Δ-*R* and Λ-*S* isomers is observed in the pmr spectrum.[1]

The $\Delta S^{\ddagger}$ values are positive for the chelation of (*S*)-valine and (*S*)-alanine. Both reaction mixtures are expected to produce Λ-*S* and Δ-*S* complexes, where *S* refers to the configuration about the α-carbon atom of the amino acid. The positive $\Delta S^{\ddagger}$ for the reaction with (*S*)-alanine or (*S*)-valine, compared with that of glycine, may be attributed to a more crowded complex which approximately neutralizes the negative $\Delta S^{\ddagger}$ contribution from the chelate effect. We expect a positive contribution to $\Delta S^{\ddagger}$ to result from rotation of the oxygen-bound amino acid into the coordination sphere during the chelation process. This rotation, while common to all amino acids, is more hindered for the substituted derivatives. The small differences in $\Delta S^{\ddagger}$ between the (*S*)-alanine and (*S*)-valine complexes may arise from the rotational isomerism of the isopropyl group at the α-carbon atom of valine.

The chelation steps for the 3,2,3-tet complexes are 6–8 times faster than the chelation steps of analogous 2,3,2-tet complexes. This significant difference may be attributed to the absence of an isomerization process about the secondary nitrogen atoms in the 3,2,3-tet system (*vide infra*). The reactants and products in the 3,2,3-tet complexes are both of the racemic *RR,SS* configuration. The activation parameters, higher E_a, and more positive $\Delta S^{\ddagger}$ values of the 3,2,3-tet complexes suggest that the chelated products are more sterically crowded than their 2,3,2-tet analogs.

The overall reaction mechanism proposed for the formation of chelated amino acid complexes from their *trans*-bis(amino acid) complexes is shown in Figure 5. The initial base hydrolysis step proceeds with retention of configuration to produce *trans*-(*RS*(meso))-[Co(2,3,2-tet)(OH)(gly)]$^+$. This complex then undergoes both isomerization about the secondary nitrogens and trans–cis topological change to produce complexes of the type *uns-cis*$_2$-[Co(2,3,2-tet)aa]$^{2+}$. Though meso–racemic isomerization does not occur for complexes in the 3,2,3-tet series, all other aspects of the process appear to parallel those of the 2,3,2-tet system. Chelation is envisioned to occur *via* edge displacement.

(16) D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, *Inorg. Chem.*, 5, 1649 (1966); J. F. Blount, H. C. Freeman, A. M. Sargeson, and K. R. Turnbull, *Chem. Commun.*, 324 (1967); L. G. Marzilli and D. A. Buckingham, *Inorg. Chem.*, 6, 1042 (1967).

Table IV. Kinetic Data for the (−)-5-Me-3,2,3-tet System[a,b]

Base Hydrolysis Step

aa	$10^2 k_{obsd}$, min^{-1} 30.0°	40.0°	50.0°	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
S-ala	2.9	9.0	24.0	20.4	19.8	−8.0
R-ala	2.7	11.0	26.0	22.1	21.5	−2.7

Isomerization and Chelation Step

aa	$10^3 k_{obsd}$, min^{-1} 40.0°	50.0°	60.0°	E_a, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
S-ala	0.40	2.0	6.96	29.7	29.1	+11.3
R-ala	0.05	0.37	1.77	36.9	36.3	+30.0

[a] Kinetic experiments were run in triplicate. The tabulated rate data were derived from experiments run under the following conditions: [complex] = (7.80–8.20) × 10^{-3} *M*, pH 9.12 (NaOH–H_3BO_3 buffer), μ = 0.08. [b] The estimated errors in k_{obsd}, E_a, and $\Delta S^{\ddagger}$ are 3%, 0.6 kcal/mol, and 2 eu, respectively.

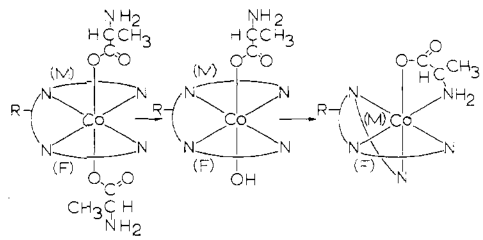


Figure 5.

We have extended this investigation to the ions *trans*-((*R*)-alanine)((−)-4,7-diaza-5-(*R*)-methyl-1,10-decanediamine)cobalt(III), *trans*-[Co(5-Me-3,2,3-tet)(*R*-ala)$_2$]$^+$, and the corresponding (*S*)-alanine derivative, *trans*-[Co(5-Me-3,2,3-tet)(*S*-ala)$_2$]$^+$. In earlier studies,[17,18] it was shown that (−)-5-Me-3,2,3-tet forms λ-trans and Λ-uns-cis complexes exclusively and that trans–cis isomerization in the 3,2,3-tet system is reversible with complete retention of configuration.[19] Stereospecific isomerization of the flexible tetramine ligand from the λ-trans to the Λ-uns-cis configuration implies that one of the terminal tetramine chelate rings may always be regarded as fixed (F) and the other as mobile (M). The configuration about carbon 5 of the tetramine completely determines not only which ring is mobile but also the only possible direction in which it can move. Our study of the kinetics of chelate ring formation, then, affords a unique probe of the interaction between the asymmetric centers of the tetramine and of the amino acid.

The (*S*)- and (*R*)-alanine complexes of (−)-5-Me-3,2,3-tet undergo base hydrolysis by the same pathway described for the 3,2,3-tet complexes. From a comparison of rates and

(17) G. Brubaker and J. Cragel, *Inorg. Chem.*, 11, 303 (1972).
(18) L. J. DeHayes, M. Parris, and D. H. Busch, *Chem. Commun.*, 1398 (1971).
(19) G. R. Brubaker and D. P. Schaefer, *Inorg. Chem.*, 9, 2373 (1970).

activation energies (Tables II and IV), it is apparent that the (*S*)-alanine complex undergoes base hydrolysis at a faster rate (with a lower E_a). The $\Delta S^{\ddagger}$ difference between these complexes is not significant.

The chelation rates of (*S*)- and (*R*)-alanine in the (−)-5-Me-3,2,3-tet complexes to produce Λ-*S*- or Λ-*R*-chelated complexes are summarized in Table IV. The (*S*)-alanine chelation step is *ca.* 8 times faster than the (*R*)-alanine rate, the activation energy *ca.* 7 kcal/mol lower, and $\Delta S^{\ddagger}$ *ca.* 19 eu more negative.[20] Clearly, the stereospecific (−)-5-Me-3,2,3-tet system exhibits kinetic stereoselectivity with respect to the enantiomeric (*R*)- and (*S*)-alanine molecules. In the chelated product, the (*S*)-alanine (δ conformer) is only slightly favored in the Λ absolute configuration. Conformational preferences have been found for other amino acid complexes, but Sargeson, *et al.*,[21] estimated no preference (Λ:Δ = 1) for the $[Co(en)_2(S\text{-ala})]^{2+}$ complex. The equilibrium ratio we calculate for the Λ isomer of chelated (*R*)- and (*S*)-alanine from our $\Delta G^{\ddagger}$ values is (*S*)-alanine:(*R*)-alanine = 1.13 at 40°.

In the 5-Me-3,2,3-tet system, the rate of chelation of (*R*)-alanine (λ conformer) is retarded and the rate of chelation of (*S*)-alanine (δ conformer) is enhanced relative to the rate of chelation of (*S*)-alanine in the 3,2,3-tet system. We attribute this observation to the ability of (*S*)-alanine, through nonbonded interactions involving its methyl substituent, to push the mobile tetramine chelate ring into the product configuration *via* an edge displacement. For (*R*)-alanine, the corresponding nonbonded interactions occur between the methyl substituent and the fixed tetramine chelate ring.

Experimental Section

Syntheses. All of the compounds employed in this study were synthesized and characterized as described previously.[2,3]

Physical Measurements. Infrared Spectra. Infrared spectra were recorded on a Beckman Model IR-8 double-grating spectrophotometer or a Perkin-Elmer 257 spectrophotometer. Spectra of the crystalline samples were recorded using the potassium bromide pellet technique. Aqueous D_2O spectra were recorded using silver chloride cells with a cell path length of 0.05 mm.

Proton Magnetic Resonance Spectra. The proton magnetic resonance spectra were recorded on Varian A-60 and Varian HA-60 spectrophotometers at the ambient probe temperatures (*ca.* 30°). The HA-60 spectrometer was operated using a TMS internal lock in the frequency sweep mode. A Varian C-1024 time-averaged computer (CAT) was used in connection with the DP-60, when necessary, to enhance signal response. The sample solutions were usually prepared by dissolving approximately 50 mg of sample in a minimum amount of 99.8% D_2O and filtering to remove any undissolved complex. In cases where the amine proton exchange rates were fast, these rates were decreased by preparing approximately 0.03 *M* H_2SO_4–D_2O solutions.

All chemical shifts were measured from the methyl resonance of tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), which served as the internal standard. A capillary TMS tube was used as the internal reference in many spectra, and the chemical shifts were adjusted to correspond to TMS as the reference

$$\delta(\text{TMS}) = \delta(\text{capillary TMS}) - 0.58 \text{ ppm}$$

$$\delta(\text{TMS}) = \delta(\text{DSS})$$

Electronic Spectra. Electronic spectra were measured with a Beckman Model DB-G spectrophotometer equipped with a Beckman Model 1005 10-in. potentiometric recorder and matched 10-mm silica cells.

Kinetic Measurements. Determination of Isosbestic Points. A 10.0-ml aliquot of the stock complex solutions (*ca.* 7×10^{-2} *M*) was added to 40.0 ml of pH 9.12 H_3BO_3–NaOH buffer solution which had been previously equilibrated in a constant-temperature bath (±0.2°). (Alternately for complexes of low solubility, 0.2 g of the complex was dissolved in 50.0 ml of the preequilibrated buffer). The resulting solutions were then maintained at a constant temperature, generally 41.5°, and at appropriate intervals, 5.0-ml aliquots were withdrawn, the reaction was quenched in a 10° ice bath, and a spectrum was recorded on the Beckman DB-G spectrophotometer.

Spectrophotometric Determination of Rate Constants. The changes in the absorbance during the course of each reaction were obtained using a Beckman Model DU spectrophotometer equipped with a Beckman DU power supply, a thermostated cell compartment (±0.02°), and 10-mm matched silica cells. The two reaction steps are essentially independent of one another: step 1 is virtually complete in 30 min at 60.0°, whereas step 2 requires 48 hr for completion. Isolation of the hydroxo intermediate was not required to obtain A_0 and A_∞ values for either reaction since the isosbestic points of the two reactions are well separated.

The method employed for determining absorbance changes during the course of the reaction was as follows. A 1.0-ml sample of complex stock solution (*ca.* 7×10^{-2} *M*) was quickly added to 9.0 ml of pH 9.12 H_3BO_3–NaOH buffer solution which had been previously equilibrated to the desired temperature in the circulator reservoir. The solutions were thoroughly mixed and transferred to the 10-mm thermostated cells, and absorbance values were recorded at appropriate time intervals. Approximately 30 sec elapsed between the start of the reaction and A_0 readings. The kinetic experiments were run in triplicate at all temperatures and for all complexes.

Potentiometric Determination of Rate Constants. A 100-ml volumetric flask was partially filled with a solution of the calculated amount of complex (*ca.* 0.9 g) in CO_2-free water and thermally equilibrated in a constant-temperature bath at 25 ± 0.1°. A calculated amount of 0.1005 *N* NaOH solution (usually 9.0 ml) was then added and the flask was filled to the mark with additional solvent. The final concentrations were *ca.* 2.0×10^{-3} *M* in the complex and 8.2×10^{-3} *M* in NaOH. At convenient time intervals, a number of 10.0-ml samples were withdrawn from the solution, transferred to a 25-ml beaker, and quenched by the addition of 4.0 ml of 0.02995 *M* $HClO_4$. The resulting solution (*ca.* 14.0 ml) was back-titrated with a carbonate-free 0.0100 *N* sodium hydroxide solution and pH measurements were recorded on successive 0.10-ml additions of the base using a Corning Model 10 pH meter equipped with a miniature combination electrode standardized at pH 4.01, 7.00, and 10.00. Blank experiments showed that repeated sampling and analysis of a 5-hr kinetic run according to this procedure was unaffected by atmospheric CO_2. All kinetic experiments were run in triplicate.

Registry No. *trans*-$[Co(2,3,2\text{-tet})(OAc)_2]^+$, 42198-38-9; *trans*-$[Co(2,3,2\text{-tet})(gly)_2]^+$, 42198-39-0; *trans*-$[Co(2,3,2\text{-tet})(S\text{-ala})_2]^+$, 42198-40-3; *trans*-$[Co(2,3,2\text{-tet})(S\text{-val})_2]^+$, 42198-41-4; *trans*-$[Co(2,3,2\text{-tet})(sar)_2]^+$, 42198-42-5; *trans*-$[Co(3,2,3\text{-tet})(OAc)_2]^+$, 42198-43-6; *trans*-$[Co(3,2,3\text{-tet})(gly)_2]^+$, 42198-44-7; *trans*-$[Co(3,2,3\text{-tet})(S\text{-ala})_2]^+$, 42198-45-8; *trans*-$[Co(3,2,3\text{-tet})(S\text{-val})_2]^+$, 42198-46-9; *trans*-$[Co(3,2,3\text{-tet})(sar)_2]^+$, 42198-47-0; *trans*-$[Co(en)_2(OH)(OAc)]^+$, 16986-91-7; *trans*-$[Co(2,3,2\text{-tet})(OH)(OAc)]^+$, 42198-49-2; *trans*-$[Co(2,3,2\text{-tet})(OH)(gly)]^+$, 42198-50-5; *trans*-$[Co(3,2,3\text{-tet})(OH)(OAc)]^+$, 42198-51-6; *trans*-$[Co(3,2,3\text{-tet})(OH)(gly)]^+$, 42198-52-7; *trans*-$[Co(2,3,2\text{-tet})(OH)(S\text{-ala})]^+$, 42198-53-8; *trans*-$[Co(2,3,2\text{-tet})(OH)(S\text{-val})]^+$, 42198-54-9; *trans*-$[Co(2,3,2\text{-tet})(OH)(sar)]^+$, 42198-59-4; *trans*-$[Co(3,2,3\text{-tet})(OH)(S\text{-ala})]^+$, 42198-60-7; *trans*-$[Co(5\text{-me-}3,2,3\text{-tet})(S\text{-ala})_2]^+$, 42198-55-0; *trans*-$[Co(5\text{-me-}3,2,3\text{-tet})(R\text{-ala})_2]^+$, 42198-56-1; *trans*-$[Co(5\text{-me-}3,2,3\text{-tet})(OH)(S\text{-ala})]^+$, 42198-57-2; *trans*-$[Co(5\text{-me-}3,2,3\text{-tet})(OH)(R\text{-ala})]^+$, 42198-58-3.

(20) We are unable, for the present, to explain fully the magnitude of the activation entropy difference between the *R*-ala and *S*-ala ring closure reactions. We believe that intramolecular interactions, similar to interactions which govern the solubility of diastereoisomeric salts, make a greater contribution than the effects of the isotropic solvent and buffer systems, etc.

(21) D. A. Buckingham and A. M. Sargeson, *Aust. J. Chem.*, 20, 257 (1969).