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Synthesis and Characterization of the Cobalt(III) Complexes with Tetraaza Macrocyclic Ligands Having Strategically Appended Functional Groups

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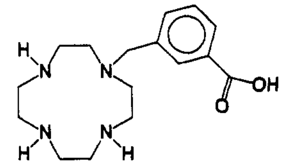
The ligands L^I and $L^{II}H$ are 1,4,7,10-tetraazacyclododecanes having single, strategically placed, appended functional groups attached to ring nitrogens, *m*-toluonitrile and *m*-toluic acid, respectively. The functional groups are positioned so that they cannot chelate to the metal ion so long as the macrocycle remains fully bound, but they can interact with adjacent atomic centers, such as the protons of coordinated water molecules or the carbonyl groups of chelated amino acid esters. Whereas previous studies yielded dinuclear complexes for $(L^{II})^-$, this work has produced mononuclear octahedral complexes for both ligands: $[CoL^ICl_2]Cl\cdot 2H_2O$, $[Co(L^{II}H)Cl_2]Cl\cdot H_2O$. The new compounds were characterized by elemental analyses, molar conductance, infrared spectra, and UV-vis spectra, and the acid dissociation constants were determined in water for the dangling carboxyl group and the coordinated water molecules in the aquation product $[Co(L^{II}H)(H_2O)_2]^{3+}$ ($pK_1 = 2.57 \pm 0.15$, $pK_2 = 7.25 \pm 0.16$, and $pK_3 = 10.13 \pm 0.12$). Rate studies, by spectrophotometry, on their aquation reactions revealed different behaviors (eqs 1 and 2); $L = L^I$ or L^{II}): (1) $[CoLCl_2]^+ + H_2O \rightarrow [CoL(H_2O)Cl]^{2+} + Cl^-$; (2) $[CoL(H_2O)Cl]^{2+} + H_2O \rightarrow [CoL(H_2O)_2]^{3+} + Cl^-$. The rate of the first aquation step for $[CoL^ICl_2]^+$ in aqueous solution at 25 °C is moderate, giving a value of $k_1 = 8.24 \times 10^{-3}\ s^{-1}$. In contrast, acid hydrolysis of $[Co(L^{II}H)Cl_2]^+$ is very rapid. In order to determine the first aquation rate for $[Co(L^{II}H)Cl_2]^+$, it was necessary to use a methanol–water medium and measure the rate by the stopped-flow technique; the observed rate constant at 25 °C is $1.8 \times 10^{-2}\ s^{-1}$. The second aquation process is also accelerated relative to comparable complexes, but its more moderate rate facilitated detailed studies. Increasing H_3O^+ concentration retards the rates of reaction of the complexes of $L^{II}H$, and the behavior is consistent with catalysis by the dangling carboxylate function. At 25 °C, the rate-derived value for the pK of the carboxylic acid group is 3.39 and the rate constants for aquation of the protonated and deprotonated forms of the complex are $k_2 = 2.1 \times 10^{-4}\ s^{-1}$ and $k_2' = 9.6_8 \times 10^{-3}\ s^{-1}$, respectively. These studies reveal a strong intramolecular catalysis due to the dangling carboxylate function of $(L^{II})^-$. Aquation reactions for both $[Co(L^{II}H)Cl_2]^+$ and $[Co(L^{II}H)(H_2O)Cl]^{2+}$ are inhibited by acid with limiting rates in both acid and neutral solutions. The maximum observed catalyzed rates were $0.36\ s^{-1}$ and $9.9 \times 10^{-3}\ s^{-1}$, respectively, and the total retardation observed was a factor of about 50 for the better-defined second aquation step, but much greater for the rapid first step.

Introduction

The role of metal ions in the catalysis of nucleophilic processes is a much-studied subject that remains a center of dynamic activity today.[1–3] Many of these studies have been justified on the basis of their fundamental relationships to the activity of those enzymes that promote nucleophilic reactions. Recently, research on the promoted hydrolysis of amino acid esters, amides, and peptides has used complexes with polydentate ligands that bind to the metal ion leaving *cis*-positions available for the catalytic reaction.[4–6]



$L^{II}H$

Whereas much has been learned about the manner in which metal ions may promote nucleophilic processes, modeling the multifunctionality of active sites in enzymes remains a less-developed area for research. Ligand $L^{II}H$ was designed to provide a functional group strategically positioned to act on the carbonyl carbon of a substrate while being stereochemically prevented from coordinating to the same metal ion.[7] Initial studies with $L^{II}H$ yielded a dinuclear complex in which the carboxylato groups of the two ligands each coordinated to the second metal ion, not the metal to which the macrocycle was chelated. That observation continued one of the major problems associated with the design of ligands for metal-based polyfunctional catalysis. The problem is that of producing free functional groups within the vicinity of a metal ion binding site in a polydentate chelate ligand. Unless the design is highly successful, the groups intended to be free will compete for binding sites at the metal ion. The problem is compounded when, as is common for catalysts, vacant metal ion binding sites are also necessary; still worse, the vacant coordination sites may need to be *cis* to one another. The design of $L^{II}H$ was aided by the fact that 1,4,7,10-tetraazacyclododecane must chelate to a transition metal octahedron in a folded fashion with the result that the two remaining octahedral sites are invariably adjacent to each other. The structure of $L^{II}H$ provides the remaining desirable feature; the carboxyl group in the ***meta*** position of the benzyl group cannot reach a binding site on the same metal ion. The problems we encountered with the formation of dinuclear species actually supported the view that the structure is appropriate for its intended purpose. Here we report the successful synthesis and characterization of mononuclear complexes with $L^{II}H$ in which the dangling carboxylic acid group remains free. Comparison of the cobalt(III) complex of $L^{II}H$ with the corresponding complex of its precursor L^I reveals the anticipated neighboring group effects of the strategically posi-

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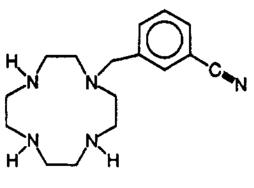

L^I

tioned carboxylic acid group. Thus, this is an example of the general family of ligands having strategically positioned functional groups, and for convenience we will refer to such species as SPF ligands.

Experimental Section

Synthesis of *N*-[(*m*-Cyanophenyl)methyl]-1,4,7,10-tetraazacyclododecane (VI). The chemicals used in these studies were of reagent grade. The ligand [12]aneN_4-*N*-*m*-toluonitrile (L^I) was prepared as previously described.[7] First the tosylate of diethanolamine (I) was prepared. To a stirred solution of 47.8 g of *p*-toluenesulfonyl chloride in 125 mL of pyridine at 0 °C was added dropwise 30 mL of a pyridine solution containing 6.55 g of diethanolamine; the period of addition was 40 min. After 4 h, 250 mL of water was added to the solution and the mixture was stirred vigorously for 1 h at room temperature. The pale yellow precipitate was collected by filtration, washed with water, and dried at 50–60 °C for 8 h. The crude product was recrystallized from about 300 mL of ethanol. Yield, 87%; mp 88–90 °C, and characterized by IR and NMR. ^{1}H NMR: δ 2.41, 2.46 (8.97 methyl protons), 3.45 (3 peaks, 4.19 methylene protons), 7.3, 7.6, 7.76 (11.8 aromatic protons, doublets); ^{13}C NMR: 21.96, 48.86, 68.73, 127.63, 128.36, 130.39, 130.46, 132.72, 135.58, 144.59, 145.66. Anal. Calcd (found): C, 52.98 (52.87); H, 2.47 (2.60); N, 5.15 (5.51).

The tosylate of diethylenetriamine (II) was prepared adding dropwise 57.2 g of toluenesulfonyl chloride solution in 400 mL of diethyl ether to a stirred solution of 10.32 g of diethylenetriamine and 12.0 g of sodium hydroxide in 100 mL of water, at room temperature. After stirring for 2–4 h, large amounts of white precipitate appeared, which was filtered, washed with water, and dried at 50 °C for 8 h. The yield is dependent on the extent of the stirring at this point in the synthesis. The crude product was recrystallized from ethanol. Yield, 88%; mp 179–181 °C, characterized by IR.

Tosylated 2,4,7,10-tetraazacyclododecane ([12]aneN_4, III) was prepared from I and II. A sodium ethoxide solution was prepared by reaction of 3.6 g of sodium in 70 mL of 100% ethanol. The NaOEt solution was added dropwise, at reflux, to a stirring solution of 40 g of the tosylate of diethylenetriamine (II), under a flow of nitrogen; period of addition was 30 min. After cooling, the ethanol was removed by rotary evaporation to yield the disodium salt of the tosylate of diethylenetriamine. A solution of the disodium salt in 690 mL of DMF was heated to 100 °C; a solution containing an equivalent amount of the tosylate of diethanolamine I (40 g) in 350 mL of DMF was added dropwise and the mixture was then heated for 2 h at 100 °C. After cooling, the volume of DMF was reduced to about $^1/_6$ the initial volume under reduced pressure. To the solution was slowly added 1200 mL of water to yield a yellowish white precipitate. The product was obtained by filtration, washed with water (about 600 mL), and dried at 50 °C for 8 h. The crude product was recrystallized from a mixed benzene/ethanol solvent. The crude product was sufficiently pure for the following procedure. Yield, 86%; mp >230 °C dec, characterized by IR and NMR. ^{1}H NMR: δ 2.45 (12 methyl protons), 3.44 (~16 methylene protons), 7.44, 7.7 (16 aromatic protons); ^{13}C NMR: δ 21.99, 52.79, 128.13, 130.30, 144.38.

The parent macrocycle [12]aneN_4 was prepared by hydrolysis of the tosyl groups from III. An amount of 49.2 g (0.062 mol) of tosylated III was dissolved by heating in 124 mL of concentrated sulfuric acid. The mixture was refluxed for 56–60 h, until all of the tosyl groups had been removed. The solution was cooled in ice–water, 240 mL of ethanol and 620 mL of ethyl ether were added, and the solution was vigorously stirred to facilitate separation of a pale yellow solid. The solid was collected by filtration and dried under vacuum for 6–8 h.

The sulfate salt of [12]aneN_4 from above was dissolved in a minimum amount of water and neutralized with excess sodium hydroxide. Several extractions with chloroform were then carried out; usually four extractions with 20–30 mL of chloroform each time. The chloroform was removed under reduced pressure leaving a pale yellow solution (about 4 mL), and this was allowed to stand until crystals formed. The product, pure [12]aneN_4 (IV), was recrystallized from ethyl ether. Yield of colorless crystals, 54%; mp 36–38 °C, characterized by IR and NMR. ^{1}H NMR: δ 1.08 (1.1 NH), 2.7 (4.4 CH); ^{13}C NMR δ 46.44.

α-Bromo-*m*-toluonitrile (V) was prepared as follows. An amount of 11.8 g (0.1 mol) of *m*-toluonitrile was dissolved in 100 mL of carbon tetrachloride. To this was added 17.8 g (0.1 mol) of *N*-bromosuccinimide and 1.0 g (0.04 mol) of benzoyl peroxide as the initiator, and the solution was maintained under reflux for 20 h. The solution slowly became blood red. After reflux, the suspended solid was separated and washed with water to remove starting material. The filtrate was cooled until the white crystalline product separated. The product was filtered, washed with water, and dried at room temperature. It was recrystallized from carbon tetrachloride. Yield, 31% as lustrous crystals; mp 87–89 °C, characterized by IR and NMR. ^{1}H NMR: δ 4.5 (1 CH), 7.25–7.72 (1.97 aromatic protons); ^{13}C NMR: δ 31.91, 130.42, 132.64, 133.18, 134.07.

The synthesis of *N*-[(*m*-cyanophenyl)methyl]-1,4,7,10-tetraazacyclododecane (VI) is completed by reaction of [12]aneN_4 (IV) and α-bromo-*m*-toluonitrile (V). An amount of 0.5 g (2.9 mmol) of [12]aneN_4 was dissolved in 50 mL of acetonitrile, and 1 mL of triethylamine was added to the solution. A solution of 0.54 g (2.8 mmol) of bromo-*m*-toluonitrile in 30 mL of acetonitrile was added dropwise to the above solution over a period of 45 min under reflux. The pale yellow solution was refluxed for 4 h. After cooling, the solvent was removed by rotary evaporation. The yellow oil was washed with ethyl ether and then the oil was dissolved in methylene chloride, leaving behind a white solid, the insoluble hydrobromide ($Et_3N\cdot HBr$). The insoluble material was removed by filtration. The filtrate was rotary evaporated until a pale glassy solid was obtained. The product was used without further purification. Yield, 88%; characterized by IR and NMR. ^{1}H NMR: δ 2.6–3.3 (CH_2 of ring), 3.4–3.7 (NH), 3.8–3.9 (CH_2), 7.38–7.78 (aromatic protons); ^{13}C NMR: δ 46.38, 47.39, 49.13, 52.32, (62), (113), 129.83, 131.43, 132.75, 133.61.

Synthesis of [CoL^ICl_2]Cl·2H_2). Equimolar amounts of cobalt(II) chloride 6-hydrate (2.6 mmol) and ligand were warmed in methanol for 20 min. Concentrated hydrochloric acid (1 mL) was added dropwise to the solution, followed by air oxidation for 2–3 h. The blue solution turned blue-purple, and the volume of the solution was reduced. The purple-blue complex separated and was isolated by filtration, washed with methanol, and dried in vacuo. Yield: ~31%. Anal. Calcd: C, 39.31; H, 5.93; N, 14.31. Found: C, 38.99; H, 5.78; N, 13.90. Mass spectra (*m*/*z*): 344 ($CoL^{I3+} - 2H^+$), 381 ($CoL^ICl^{2+} - H^+$), 416 ($CoL^ICl_2^+$). Electronic spectral bands, λ_{max}, nm (ϵ_{max}, dm^3 mol^{-1} cm^{-1}): CH_3OH solution, 578 (451), 396 (457); aqueous solution after 1 day, 544 (401), 376 (381); aqueous solution after 7 days, 536 (493), 370 (422).

Synthesis of [Co(L^{II}H)Cl_2]Cl·H_2O. This reaction proceeds by hydrolysis of the nitrile group of the bound ligand. [CoL^ICl_2]Cl·2H_2O (1.5 mmol) was dissolved in concentrated hydrochloric acid (55 mL) and refluxed for 30–35 h. Following hydrolysis of the nitrile function, the product separated from hot concentrated hydrochloric acid as blue microcrystals. [Co(L^{II}H)Cl_2]Cl·H_2O was collected by filtration, washed with water and acetonitrile, and dried in vacuo. Yield: ~72%. Anal. Calcd: C, 39.23; H, 5.72; N, 11.44. Found: C, 39.40; H, 6.01; N, 11.36. Mass spectra (*m*/*z*): 364 ($CoL^{II2+} - H^+$); 400 ($CoL^{II}HCl^{2+} - H^+$); 435 (CoL^{II}-$HCl_2^+ - H$). Electronic spectral bands, λ_{max}, nm (ϵ_{max}, dm^3 mol^{-1} cm^{-1}): CH_3OH solution, 570 (369), 392 (318); aqueous solution after 1 min, 570 (384), 398 (316); aqueous solution after 7 days, 524 (476), 360 (376).

Measurements. Elemental analyses were performed by the microanalysis laboration at The University of Kansas. Infrared spectra were obtained using a 1600 Series Perkin-Elmer FTIR spectrophotometer with the samples prepared in KBr disks. Conductivity measurements were made at 25 °C, using an YSI Model 35 conductance meter with aqueous and methanol solutions of the complexes (~1 mmol L^{-1}). Mass spectra were obtained with a VG Analytical Ltd. ZAB HS mass spectrometer (FAB), and electronic spectra were recorded using a Hewlett-Packard 8452A Diode Array spectrophotometer.

The acid dissociation constants (concentration constants)[8] for the complex *cis*-[Co(L^{II}H)(H_2O)$_2$]$^{3+}$ at 25 °C were estimated following the methods and conventions of Martell and Motekaitis.[8] The p[H] measurements were carried out using an Accumet Model 910 pH meter. The initial volume of ligand solution was 25.0 mL and the ligand concentrations were 0.913 and 0.906 mM. A definite volume of 0.01424

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Table I. Infrared Data for the New Complexes (cm^{-1})

$CoL^ICl_3 \cdot 2H_2O$	$Co(L^{II}H)Cl_3 \cdot H_2O$	
3447.8	3442.1	OH str
3198.3	3211.7	NH str
3131.5	3169.8	NH str
	3121.9	NH str
2233.2		C≡N str
	1715.2	C=O str
1623.7	1630.9	NH bending
870.0, 812.3	869.9, 815.2	CH rocking

M NaOH was added to a stirred aqueous solution of complex, and the p[H] was recorded in ~1 min after the addition of base. Rate measurements were conducted with the Diode Array spectrophotometer, using a thermostated cell compartment. Requisite volumes of $NaClO_4$ stock solution, as needed to bring the ionic strength to 0.1 M, were added to solutions prior to equilibrium or rate measurements. The addition was made quickly with vigorous swirling and then the solution was quickly transferred into a thermostated 1-cm cell. The kinetic measurements were made at wavelengths that were chosen because of substantial differences in the absorbances of reactants and products. The pseudo-first-order rate constants were calculated from the graph of $\log(A_t - A_\infty)$ vs time. The fit of the data to the rate law showed an average value of the standard deviation of ±0.7% of the measured value over all of the rates measured. Repeatability gave an average deviation of substantially less than 5% of the measured value. A stopped-flow technique was used in the measurement of the rate constants of the first aquation step (k_1) for $[Co(L^{II}H)Cl_2]^+$. A Durrum Dionex XD 110 stopped-flow spectrophotometer and Northstar Horizon computer were used for the measurement at 25 ± 0.1 °C (or 24.8 ± 0.1 °C), and a 1.98 mM (or 1.53 mM) methanol solution of the complex was mixed, in the stopped-flow instrument, with a 1:1 $MeOH/H_2O$ (or 1:2 $MeOH/H_2O$) solution to cause the aquation.

Results and Discussion

The dichloro(tetraamine)cobalt(III) complex of the SPF ligand [12]aneN_4-*N*-*m*-toluic acid, $[Co(L^{II}H)Cl_2]^+$, was prepared from the corresponding complex of its precursor ligand [12]aneN_4-*N*-*m*-toluonitrile (structure **2**), $[CoL^ICl_2]^+$, by hydrolysis of the nitrile group while the macrocyclic part of the ligand remained bound to cobalt(III).[7] The precursor complex, $[CoL^ICl_2]^+$, was synthesized by traditional air oxidation of the acid-buffered solution of cobalt(II) salt in the presence of the ligand and excess chloride ion.[7] The compositions of the complexes were verified by elemental analysis and FAB mass spectrometry (see Experimental Section). The mass spectrum of $[CoL^ICl_2]Cl \cdot 2H_2O$ features two strong peaks at 416 *m*/*e* and 381 *m*/*e*; these correspond to the parent cation $[CoL^ICl_2]^+$ and to the species that has lost 1 mol of HCl, $CoL^ICl^{2+} - H^+$. $[Co(L^{II}H)Cl_2]Cl \cdot H_2O$ showed strong peaks at 435 *m*/*e* and 400 *m*/*e*, corresponding to $Co(L^{II}H)Cl_2{}^+ - H$ and $Co(L^{II}H)Cl^{2+} - H^+$.

Characteristic infrared spectral bands nicely identify the appended functional groups[9] on the ligands in these complexes, and selected bands are listed in Table I. In the infrared spectrum of $[CoL^ICl_2]Cl \cdot 2H_2O$, a very sharp and intense band at 2233.2 cm^{-1}, assigned to the stretching mode of the nitrile group, signals the presence of that group. For $[Co(L^{II}H)Cl_2]Cl \cdot 2H_2O$, that band is absent and in its place a new band appears at 1715.2 cm^{-1}, which is identified as the carbonyl stretching vibration for the carboxylic acid function. Most significantly, the position of the carbonyl band requires that functional group to be free, rather than bound to the metal ion.[10]

In methanol solutions, the molar conductances (Table II) of the two complexes $[Co(L^{II}H)Cl_2]Cl \cdot H_2O$ and $[CoL^ICl_2]Cl \cdot 2H_2O$, fall in the range expected for 1:1 electrolytes,[11,12] a result that is consistent with their formulations. In keeping with the usual chemistry of dichloro(tetraamine)cobalt(III) complexes (eqs 1 and 2), the conductances of the aqueous solutions of the new complexes (Table II) increase with time, showing changes from 1:1, at very short times, eventually to 3:1 electrolytes. Semiquantitatively, the conductance data show that the changes from 1:1 to 2:1 electrolytes are much faster than the subsequent changes into 3:1 electrolytes. Also, a highly significant observation is that both aquation reactions in pure water for $[Co(L^{II}H)Cl_2]^+$ are much faster than those for $[CoL^ICl_2]^+$.

Table II. Molar Conductances of the Complexes (1.00 mM solutions at 25 °C)

complex	solvent	time, min	molar conductance, Ω^{-1} cm^{-1} mol^{-1}
$CoL^{II}Cl_3 \cdot 2H_2O$	H_2O	1	147 ± 12 (~1:1)
	H_2O	3	254 ± 9 (2:1)
	H_2O	20	290 ± 3 (2:1)
	H_2O	2880	327 ± 19 (2:1)
	H_2O	7 days	402 ± 11 (3:1)
	CH_3OH	–	91 ± 11 (1:1)
$Co(L^{II}H)Cl_3 \cdot H_2O$	H_2O	1	164 ± 5 (1:1)
	H_2O	3	233 ± 21 (2:1)
	H_2O	20	399 ± 3 (3:1)
	CH_3OH	–	91 ± 1 (1:1)

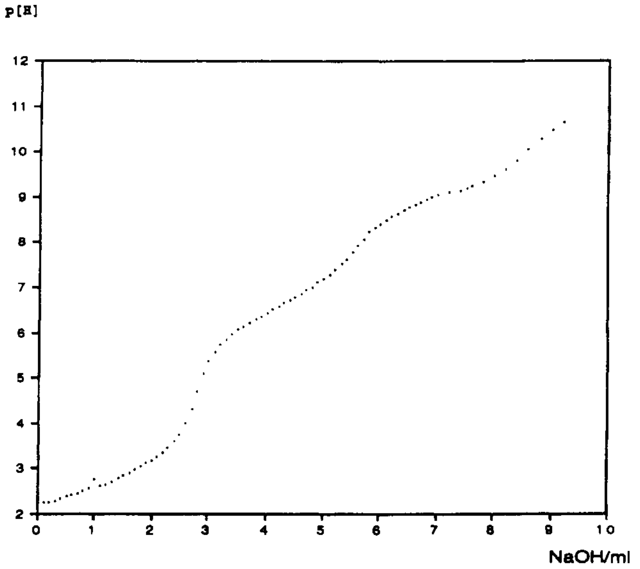

Figure 1. p[H] titration curve at 298 K for $[Co(L^{II}H)(H_2O)_2]^{3+}$; initial complex concentration, 7.48 mmol/L, μ = 0.1 M ($NaClO_4$).

$$[CoLCl_2]^+ + H_2O \rightarrow [CoL(H_2O)Cl]^{2+} + Cl^- \qquad (1)$$

$$[CoL(H_2O)Cl]^{2+} + H_2O \rightarrow [CoL(H_2O)_2]^{3+} + Cl^- \qquad (2)$$

The colors of the solutions also change, respectively, from blue to red-purple for $[CoL^ICl_2]^+$ and from blue to pink-purple for $[Co(L^{II}H)Cl_2]^+$, and these changes are evident in the electronic spectra. The electronic spectra of the dichloro complexes in methanol (see Experimental Section) and the spectra of their ultimate aquation products, $[CoL^I(H_2O)_2]^{3+}$ and $[Co(L^{II}H)(H_2O)_2]^{3+}$, show only two absorption bands in harmony with expectation for the *cis*-geometry of the chlorides or the water molecules.[13] Spectral bands for $[CoL^I(H_2O)_2]^{3+}$ and $[Co(L^{II}H)(H_2O)_2]^{3+}$: 536 nm ($\epsilon$ = 493 dm^3 mol^{-1} cm^{-1}), 370 nm (422), and at 524 nm (476), 360 nm (376), respectively.

A p[H] titration curve is shown in Figure 1 for the complex of the SPF ligand, $[Co(L^{II}H)(H_2O)_2]^{3+}$. The curve shows features associated with three acid dissociation steps, corresponding to

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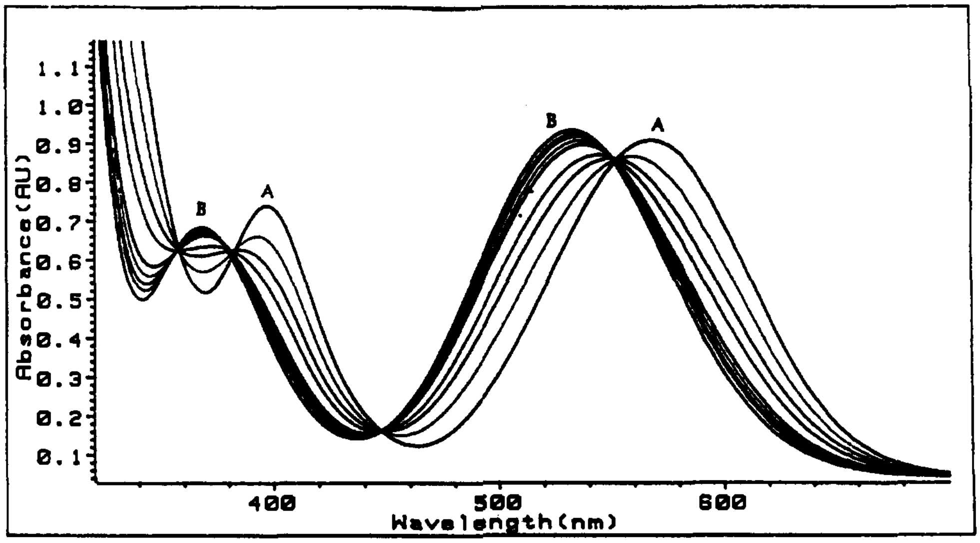

Figure 2. Spectral changes during hydrolysis of $[Co(L^{II}H)Cl_2]^+$: (A) initial trace; (B) final trace.

Table III. Values of Pseudo-First-Order Rate Constants for the Aquation of $[Co(L^{II}H)Cl(H_2O)]^{2+}$, Measured at Various $[H^+]$ and at Different Temperatures with $\mu = 0.1$ M

$[H^+]$, mM	$k_{obs} \times 10^3$, s^{-1} 20.0 °C	25.0 °C	29.2 °C	35.0 °C
0.00282		9.86 ± 0.37		
0.158		6.35 ± 0.26		
0.891	1.33 ± 0.09		4.42 ± 0.21	7.50 ± 0.13
1.41		2.66 ± 0.03		
2.00		1.87 ± 0.02		
2.24		1.69 ± 0.05		
3.16	0.484 ± 0.025	1.22 ± 0.03	1.92 ± 0.05	4.21 ± 0.21
5.62	0.300 ± 0.001	0.777 ± 0.022	1.39 ± 0.02	2.56 ± 0.24
6.31	0.288 ± 0.004	0.731 ± 0.012	1.30 ± 0.05	2.56 ± 0.02
11.22	0.214 ± 0.005	0.468 ± 0.015	0.893 ± 0.015	2.15 ± 0.01
19.95	0.188 ± 0.001	0.400 ± 0.021	0.703 ± 0.006	1.56 ± 0.03
k_2', s^{-1}	0.0070_8	0.0096_8	0.010_5	0.013_5
k_2, s^{-1}	0.00007_1	0.0002_1	0.0004_2	0.0009_8
K, M	0.00019_6	0.00040_6	0.00057_8	0.0010_0

the reactions of eqs 3–5. The pK_a values for the three processes

$$[Co(L^{II}H)(H_2O)_2]^{3+} + H_2O \leftrightarrow [Co(L^{II})(H_2O)_2]^{2+} + H_3O^+ \quad K_1 \quad (3)$$

$$[Co(L^{II})(H_2O)_2]^{2+} + H_2O \leftrightarrow [Co(L^{II})(H_2O)(OH)]^+ + H_3O^+ \quad K_2 \quad (4)$$

$$[Co(L^{II})(H_2O)(OH)]^+ + H_2O \leftrightarrow [Co(L^{II})(OH)_2] + H_3O^+ \quad K_3 \quad (5)$$

were calculated[8] and are 2.57 ± 0.15, 7.25 ± 0.16, and 10.13 ± 0.12. The correlation of the changes in spectra with p[H] and the pK_a values suggest that the absorption bands can be assigned to species as follows: $[Co(L^{II})(H_2O)_2]^{3+}$, 360, 526 nm; $[Co(L^{II})(H_2O)(OH)]^{2+}$, 362, 534 nm; and $[Co(L^{II}H)(OH)_2]^+$, 358, 542 nm.

Aquation Rates. The conductance data described above indicate that the rate of the first aquation step for $[CoL^ICl_2]^+$ is much more rapid than the second step; this simplifies determination of the primary aquation reaction. At 25 °C and in pure water, the rate constants at two wavelengths ($k_1 = 0.87 \times 10^{-3}$ s^{-1} (520 nm), $k_1 = 0.78 \times 10^{-3}$ s^{-1} (542 nm) agree within 10% of their values, giving an estimated half-life of 835 s. The spectral scans displayed four isosbestic points at 360, 382, 440 and 556 nm, and the final spectral trace gave λ_{max} at 380 and 542 nm, in agreement with the formation of the monoaqua species.

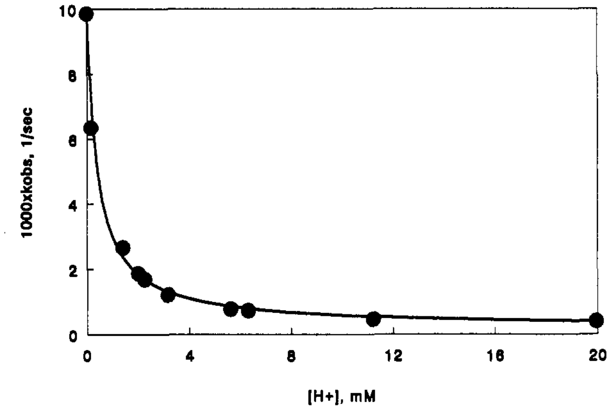

Figure 3. Variation of k_{obs} with $[H^+]$ for second aquation step at 298 K; reactant is $[Co(L^{II}H)Cl(H_2O)]^{2+}$.

Working at 25 °C, in aqueous media, with the slow speeds characteristic of ordinary spectrophotometers, spectral scans for solutions of $[Co(L^{II}H)Cl_2]^+$ display four well-defined isosbestic points at 358, 382, 448, and 552 nm, as shown in Figure 2. Further, the final spectrum is consistent with the well-characterized $[Co(L^{II}H)(H_2O)_2]^{3+}$ ion (λ_{max} = 360 and 524 nm). Clearly the second aquation step is being measured under these conditions. This second aquation reaction undergoes a most interesting acid inhibition, as shown in Table III and Figure 3. Because this inhibition falls in the range of pH values that might be associated with protonation of the appended carboxylic acid group, the phenomenon is attributed to a neighboring group effect associated with strong interaction between the dangling carboxylate group and a proton of the adjacent water molecule, or, possibly, a proton on a secondary amine group of the macrocyclic ligand. This is a distinctive conjugate base mechanism, and is presented in eqs 6–8.

$$[Co(L^{II}H)Cl(H_2O)]^{2+} + H_2O \leftrightarrow [Co(L^{II})Cl(H_2O)]^+ + H_3O^+ \quad K \quad (6)$$

$$[Co(L^{II}H)Cl(H_2O)]^{2+} + H_2O \rightarrow [Co(L^{II}H)(H_2O)_2]^{3+} + Cl^- \quad k_2 \quad (7)$$

$$[Co(L^{II})Cl(H_2O)]^+ + H_2O \rightarrow [Co(L^{II})(H_2O)_2]^+ + Cl^- \quad k_2' \quad (8)$$

Bringing in material balance and expressing the rate in terms of total unreacted cobalt(III) complex, gives eq 9 for the

$$k_{obs} = k_2'K/(K + [H^+]) + k_2[H^+]/(K + [H^+]) \quad (9)$$

mechanism of eqs 6–8. It is expected that $k_2' \gg k_2$ with the result that the second term will only be important at very high $[H^+]$ and under those conditions $[H^+] \gg K$ and the second term simplifies to just k_2. Over most of the pH range, the first term will dominate and a substantial retardation is predicted. The complete data set at each temperature has been fit to eq 9 using a least squares program, and the kinetic parameters k_2', k_2, and K appear in the last three rows of Table III. Our data is most extensive at 298 K and those derived parameters are most reliable. The parameters are generally well behaved, each increasing monotonically with increasing temperature. As indicated above, Figure 3 shows the fit of the data over the entire pH range from about 7 to 1.7 with a graph of k_{obs} versus $[H^+]$. The fit is excellent and the model is therefore deemed adquate. It is pleasing that the ionization constant determined from this kinetic data (pK = 3.39 at 25 °C) is in the range expected for this compound on the basis of the figures given above for the diaqua complex. The acid dissociation constants vary more greatly with temperature than might have been anticipated.

On the basis of the rate law and the structure of the complex and its ligand, we have proposed a conjugate base mechanism to account for the large acceleration observed for these aquation reactions. It is proposed that the conjugate base effect occurs because the carboxylate function is strategically well-positioned to interact with a proton of the coordinated water molecule (Scheme I). In the ground state for the system, the interaction might merely involve hydrogen bonding. However as the system moves to the transition state, the proton may be transferred to the carboxylate function, producing a coordinated conjugate base (OH^-), which could then release electron density to the oxygen atom that is bound to the cobalt(III). The water molecule in question is then able to promote the aquation of the chloride ion in analogy to the well-known S_N1cb mechanism for the base hydrolysis of cobalt amines. This highly distinctive behavior provides a clear confirmation that the appended carboxyl function is able to exert the neighboring group effects that provided the motivation for its design.

The first acid hydrolysis reaction for the cobalt(III) complex of the SPF ligand proceeds surprisingly rapidly for a dichloro tetraamine of this class. The rate constant for the first aquation step for $[Co([12]aneN_4)Cl_2]^+$ was reported[15] to be 4.2 × 10^{-3} s^{-1} in 0.1 mol aqueous HNO_3, but we have failed to measure the corresponding rate for $[Co(L^{II}H)Cl_2]^+$ under the same conditions. By dissolving the complex in methanol and mixing that solution with methanol/water mixtures in a stopped-flow spectrophotometer, we have been able to retard the first aquation reaction of $[Co(L^{II}H)Cl_2]^+$ sufficiently to facilitate its measurement. Even under these retarding conditions, the reaction proceeds quite rapidly, and a rate constant of 1.75 × 10^{-2} s^{-1} was determined in methanol/water at room temperature. The results of detailed studies in aqueous methanol (Table IV and Figure 4) show that the rate constants of the first aquation step are also retarded by increasing hydrogen ion concentration. The results are similar to those for the second aquation step, as described above.

Scheme I

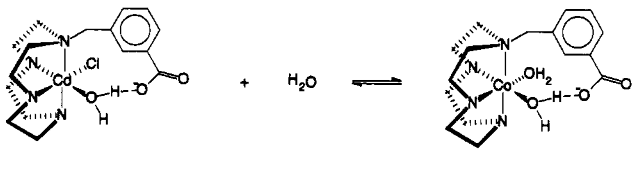

Table IV. Values of Pseudo-First-Order Rate Constants (k_{obs}) for the First Aquation Step of $[Co(L^{II}H)Cl_2]^+$ in 2:1 MeOH/H_2O Solution (0.1 mol L^{-1}) at 25 ± 0.1 °C

apparent $[H^+] \times 10^5$ [a]	$k_{obs} \times 10^3$	aqueous solution	$[H^+]_{H2O} \times 10^5$ [b]
0.020	357 ± 27	EHPES–NaOH	0.013
0.199	83.5 ± 1.0	HAC–NaOH	4.47
0.223	62.8 ± 8.6	EHPES–NaOH	0.141
1.12	31.9 ± 3.9	HAC–NaOH	14.1
14.1	13.9 ± 0.3	$NaClO_4$–H_2O	0.089
22.4	7.8 ± 0.2	$NaClO_4$–$HClO_4$	12.6
28.2	5.0 ± 0.2	$NaClO_4$–$HClO_4$	22.4
56.2	2.7 ± 0.1	CH_2ClCO_2H–NaOH	35.5
158.0	1.2 ± 0.1	$NaClO_4$–$HClO_4$	35.5

[a] The apparent $[H^+]$ was obtained by measurement in the mixed solvent with a glass electrode. [b] The p[H] values of buffer solutions as measured in water.

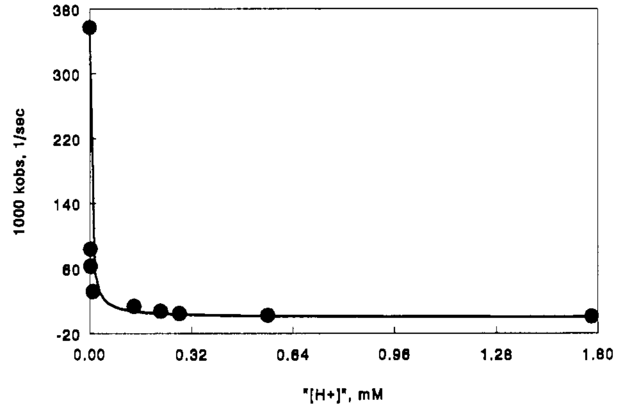

Figure 4. Graph of k_{obs} against apparent $[H^+]$ for first aquation step for $[Co(L^{II}H)Cl_2]^+$ at 298 K.

$$[Co(L^{II}H)Cl_2]^+ + H_2O \leftrightarrow [Co(L^{II})Cl_2] + H_3O^+ \; K \quad (11)$$

$$[Co(L^{II}H)Cl_2]^+ + H_2O \rightarrow [Co(L^{II}H)Cl(H_2O)]^{2+} + Cl^- \; k_1 \quad (12)$$

$$[Co(L^{II})Cl_2] + H_2O \rightarrow [Co(L^{II})Cl(H_2O)]^+ + Cl^- \; k_1' \quad (13)$$

We believe that the acceleration of the first aquation step for $[Co(L^{II}H)Cl_2]^+$ arises from a neighboring group effect geometrically related to that observed for $[Co(L^{II}H)Cl(H_2O)]^{2+}$. In the case of $[Co(L^{II}H)Cl_2]^+$, the critical intramolecular interaction would have to be between the free carboxylate group and the proton on an amine group of the macrocycle. The suggested mechanism of the first aquation process is presented in eqs 11–13. p[H] is not well defined in these systems, and for that reason rate parameters were not calculated. However, the conclusion that a corresponding catalytic mechanism is at work in this reaction remains qualitatively justified.

In conclusion, we have achieved the goal of producing and characterizing the monomeric complexes of cobalt(III) with a new ligand having a functional group strategically positioned so that it can promote certain reactions, but, also so that it cannot chelate to the metal ion. Further, the appended functional group has already revealed its capability by influencing the kinetics and mechanisms of the simple substitution reactions that are essential early steps in any catalytic or promoted reactions in which the new complex may participate. The acceleration of substitution reactions at the cobalt(III) center bodes well for the accessibility of the metal center to substrates. Work continues on the study of the catalytic capabilities of this addition to the arsenal of transition metal biomimics.

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