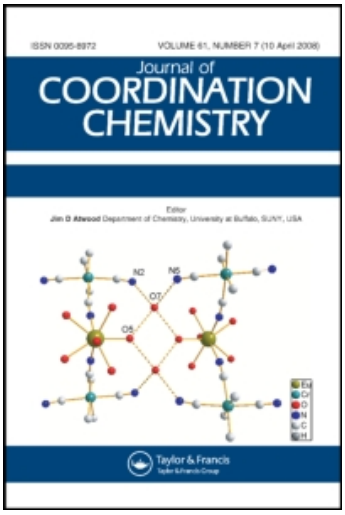

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CARBON-13 NMR: A TOOL FOR STUDYING DEUTERIUM EXCHANGE KINETICS IN COBALT(III) AMINOCARBOXYLATES

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CARBON-13 NMR: A TOOL FOR STUDYING DEUTERIUM EXCHANGE KINETICS IN COBALT(III) AMINOCARBOXYLATES

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Carbon-13 nmr spectral assignments of some Cobalt(III) Aminocarboxylates are presented. Natural abundance ^{13}C spectra were obtained with a Varian Associates XL-100/15 FT nmr spectrometer equipped with an integration subroutine and a broad band proton decoupler. The kinetics of deuterium substitution on glycinate rings of Co(III)EDTA, Co(III)CyDTA, and Co(III)PDTA were studied. Rate constants obtained here are in good agreement with those obtained in previous pmr studies. Rate constants for some glycinate proton exchanges that were previously unattainable by pmr are also presented. The advantages of using ^{13}C nmr over pmr in these studies are discussed. This study was done at 95°C and pD = 1.5. The rate of isotopic exchange was monitored by the decrease in the proton decoupled integral of the ^{13}C resonances.

INTRODUCTION

Proton magnetic resonance (pmr) has been widely used to study the structures and reactions of aminocarboxylate chelates of Cobalt(III).[1-7] To date, however, virtually no attempt has been made to study the chemistry of these rather complex systems by ^{13}C nmr spectroscopy. We report here the first example of the utility of ^{13}C nmr in studying the dueterium exchange kinetics of glycinate protons in cobalt(III)-aminocarboxylate compounds.

Previous (pmr) studies of these cobalt(III) chelates[3,4] have shown the acid-catalyzed and base-catalyzed deuterations of the glycinate protons to be stereospecific. Terrill and Reilley[3] have shown that acidic D_2O solutions of ethylenediaminetetraacetatocobaltate(III), $Co(EDTA)^-$, *trans*-1,2-cyclohexanediamine-N,N,N′,N′,-tetraacetatocobaltate(III), $Co(CyDTA)^-$, and *dl*-1,2-propylenediamine-N,N,N′,N′,-tetraacetatocobaltate(III), $CO(PDTA)^-$, when heated, undergo a decrease in intensity of the glycinate proton resonances indicating that isotopic substitution had indeed occurred. The symmetry (C_2) of the $Co(EDTA)^-$ and $Co(CyDTA)^-$ complexes render relatively simple pmr spectral patterns thus allowing the study of isotopic substitution to be accurately carried out. However, efforts to obtain reliable exchange rate data from the PDTA complex met with little success as a result of the extreme complexity of the glycinate portion of its pmr spectrum. The pmr spectra of cobalt(III) chelate complexes of aminopolycarboxylic acids frequently include a number of overlapping AB patterns due to various pairs of spin-coupled nonequivalent glycinate protons. A prime example of this is the $Co(PDTA)^-$ complex whose pmr spectrum consists of four overlapping AB patterns superimposed upon a rather complex set of proton resonances eminating from the propylenediamine backbone. These complicated mixtures of AB patterns have been extremely difficult to solve completely and unambigously (as summarized by Legg and coworkers[2d]) and have therefore rigorously defied precise kinetic exchange data. In this study we will illustrate the advantages that proton decoupled ^{13}C Fourier transform nmr spectroscopy offers in making deuterium exchange studies of these complexes.

One of the advantages that broad band (random noise) proton decoupled ^{13}C nmr spectroscopy offers is that the resonances are singlets (in the absence of ^2D exchange) and have little tendency to overlap. Since the peaks are singlets, one can monitor the deuteration of glycinate ring protons easily and ^{13}C spectral changes can accurately be measured.

Experimental

All ^{13}C spectra were recorded on a Varian Associates XL-100 nmr spectrometer equipped with a 15 in. magnet (operating at 25.2 MHz in the ^{13}C mode), a pulse unit, broad band random noise ^1H decoupler, and deuterium lock. In <24 min 3000 pulses of

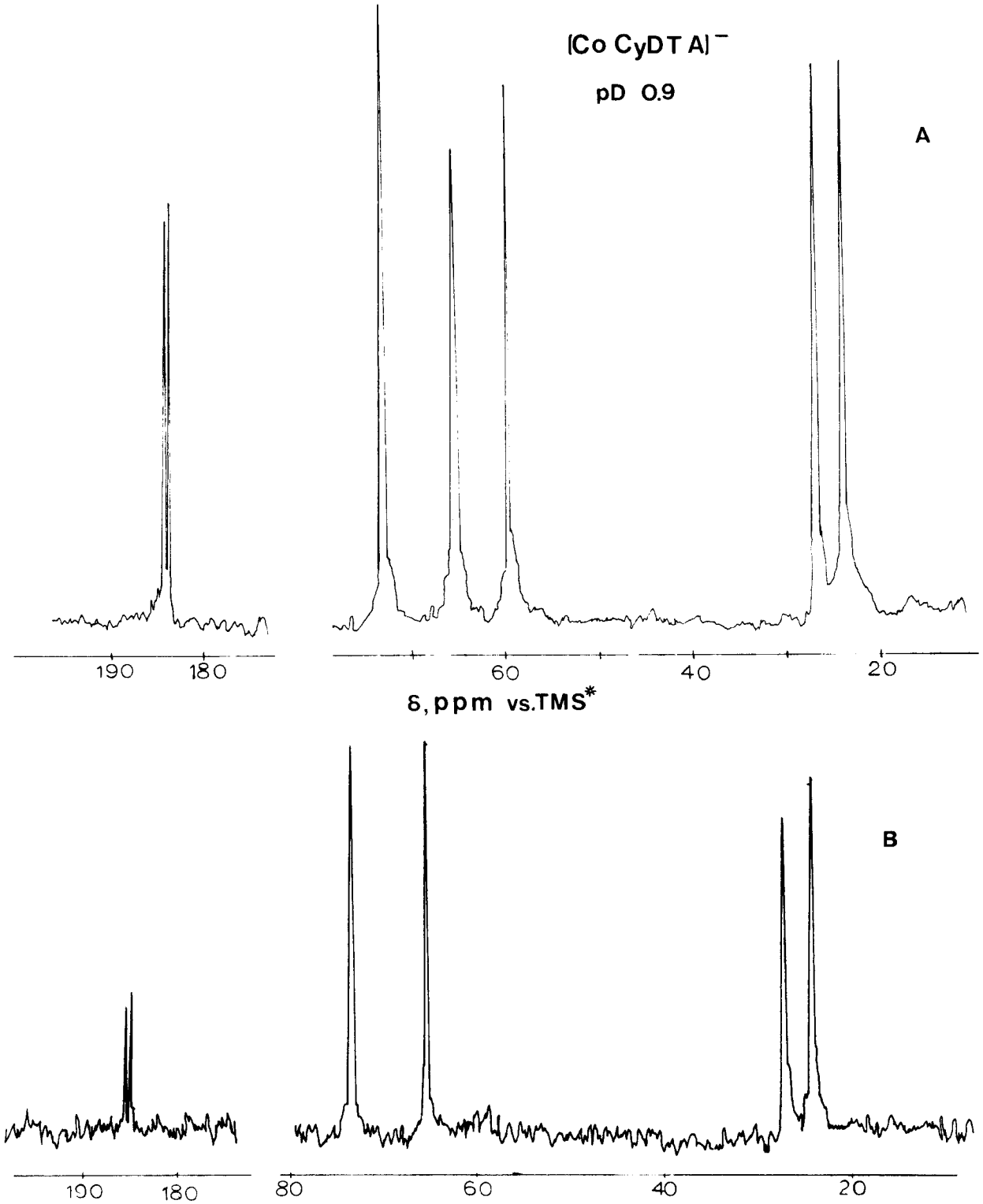


FIGURE 1 (A) Natural abundance ^{13}C FT nmr spectrum of $[Co^{III}CyDTA]^-$.
(B) ^{13}C spectrum recorded after several days of deuteration at 95°C. C_1 in I is completely deuterated.

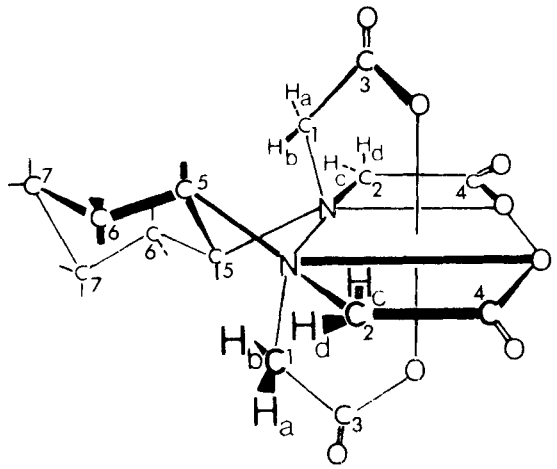
30 μ sec duration were applied with 0.4 sec acquisition time between pulses. The range of 5000 Hz was covered by 4096 addresses in the Fourier transform spectrum. All other variables in the system were held constant. pH measurements were done on a Sargent-Welch LS pH meter and pD was determined by the addition of 0.4 to the pH value. All chemicals used were of the highest purity available. The EDTA was obtained from the Baker Chemical Company and CyDTA was obtained from Geigy Chemical Company. The PDTA ligand was prepared by the method of Dwyer and Garvan.[14] DCl (38% in 99% D_2O) and D_2O (99.8% isotopic purity) were obtained from Stohler Isotope Chemical Company.

The chelates $K[Co^{III}CyDTA]\cdot 3H_2O$, $K[Co^{III}PDTA]\cdot H_2O$, and $K[Co^{III}EDTA]\cdot H_2O$ were prepared by existing methods[8,9] and found to be analytically pure. Solutions of the metal chelates (0.8 *M*) were adjusted to an appropriate pD value by addition of DCl and heated in a constant-temperature bath (95°) for the desired time. All spectra were recorded at probe temperature (~35°) thus effectively quenching the exchange reactions during the time of spectral accumulation.

RESULTS

$Co^{III}CyDTA$

The ^{13}C nmr spectrum of $Co(CyDTA)^-$ at pD = 0.9 is given in Figure 1A. The two low-field resonances occurring at 23.5 and 27.0 ppm *vs.* TMS* are assigned to the carbon atoms, C_6 and C_7, of the cyclohexane ring, in I, and are of no consequence in this study.



I

The extremely sharp and narrow high-field resonances at 183 and 184 ppm are assigned to the two types of carbonyl carbons C_3 and C_4 in I. The resonance at 73 ppm is assigned to the ring carbons between the two nitrogens of the backbone ring (C_5 in I). The in-plane carbon atoms, C_2, are found to resonate at 65 ppm downfield from TMS* and the out-of-plane glycinate carbon atoms, C_1, are found to resonate at 60 ppm. Assignments were made by single frequency irradiation at the observed pmr chemical shift of the out-of-plane protons (3.68 ppm *vs.* TMS*). Figure 1B shows the spectrum of $Co(CyDTA)^-$ after 31 hr at 95° in acidic D_2O (pD = 0.9). The decrease in intensity of the C_1 signal and the increase of its multiplicity is indicative of the fact that the spin-decoupled protons originally bound to the C_1 carbon have been replaced (at least in part) by deuterium atoms which resonate outside of the spin decoupling frequency range employed to decouple protons. Hence, the deuterium isotope (I = 1) spin-couples with the ^{13}C nucleus and imparts a marked multiplicity in the ^{13}C spectrum.

Of greater importance than the spin multiplicity imparted by the deuterium nucleus, however, is the loss of signal area (decreased integral) resulting from ^2D quadrupole broadening which yields a lower nuclear Overhauser enhancement.[10] The irradiation of protons in the original $Co(CyDTA)^-$ sample disturbs the Boltzmann distribution of the proton spin states and equalizes the ^1H upper and lower energy levels. Since ^{13}C nuclei depend primarily on the ^1H nuclei for spin-lattice relaxation mechanism, the ^{13}C nuclei must respond to this equalization of proton spin states by changing their own populations of spin states. The net result of this effect is that an excess of ^{13}C nuclei populate the lower energy level and more rf energy will be absorbed upon irradiation yielding an enhanced signal (the NOE effect). As the deuterium ions (possessing a quadrupole moment) replace the glycinate protons, a new mechanism will reestablish the Boltzmann distribution of the ^{13}C nuclei and impart a longer relaxation time (T_2), hence the signal is diminished in two ways; (1) the loss of the NOE and (2) the increased relaxation time and lack of spin equilibrium prior to each new pulse. Hence, a marked decrease in ^{13}C signal intensity accompanies the deuterium exchange process and the signal demise is a measure of the deuteration rate.

Plots of the logarithm of the intensities of the C_1 peaks *vs.* time were made over several half-lives under the same conditions used by Terrill and Reilley (95° and 0.31 *M* acid) and were completely linear. The ratio of the rate constant to the $[D_3O^+]$, $(k/[D_3O^+])$,

was found to be 3.8×10^{-5} l mol^{-1} sec^{-1} (in complete agreement with their pmr work). Having satisfactorily established the reliability of this technique a similar study was made using $Co(EDTA)^-$.

$Co^{III}EDTA$

Figure 2A shows the ^{13}C nmr proton decoupled spectrum of the $Co(EDTA)^-$ complex in the pD range 7.4 down to pD = 1.5.

The assignment of the spectrum is as follows: The peaks at 184.5 ppm and 183.5 ppm are assigned to the carboxylate carbons. The down-field resonance corresponds to the out-of-plane carboxylate group and the up-field resonance corresponds to the in-plane carboxylate carbon. This assignment was made by virtue of an observed decrease of the down-field resonance upon deuteration of the glycinate rings. Such a decrease in resonance intensity is a consequence of long range NOE. Further, the up-field carboxylate resonance decreases sharply as the in-plane rings become protonated at very low pD values (Fig. 2B). The resonance at 65.5 ppm is due to an overlap of the two equivalent out-of-plane glycinate carbons with the ethylenic backbone ring carbons. This is an unfortunate consequence of magnetic environment similarity, but good values for the deuteration rate may of course still be obtained. The resonance at 62.5 ppm is due to the two equivalent in-plane glycinate ring carbons and undergoes no change during deuteration.

At higher acid strengths ($pD < 1.5$) marked evidence of ligand protonation occurs. In the pD range used by Terrill and Reilley ($pD < 1.1$) the spectrum given in Figure 2B was obtained. The peak at 65.5 ppm is now visibly split as a consequence of differing environments of the two rings (C_1 *vs* C_5) resulting from the protonation of the in-plane rings.

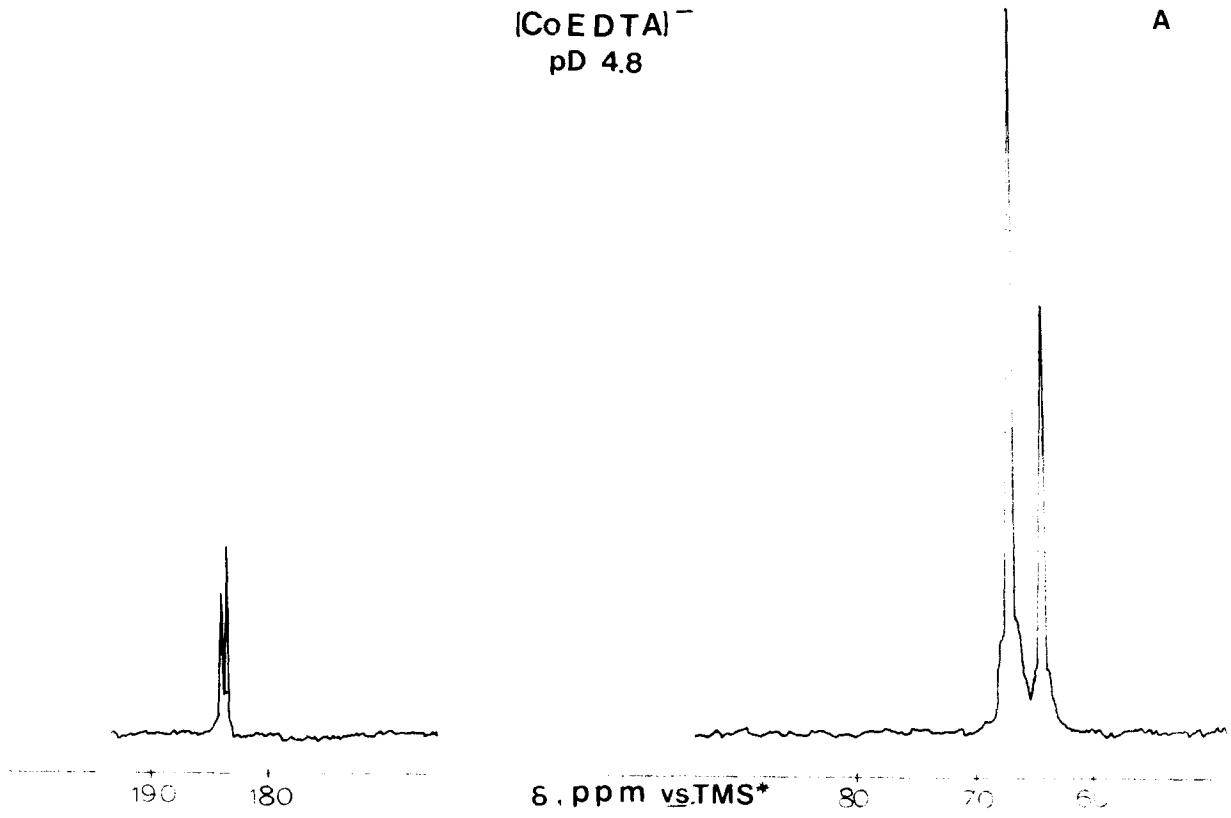


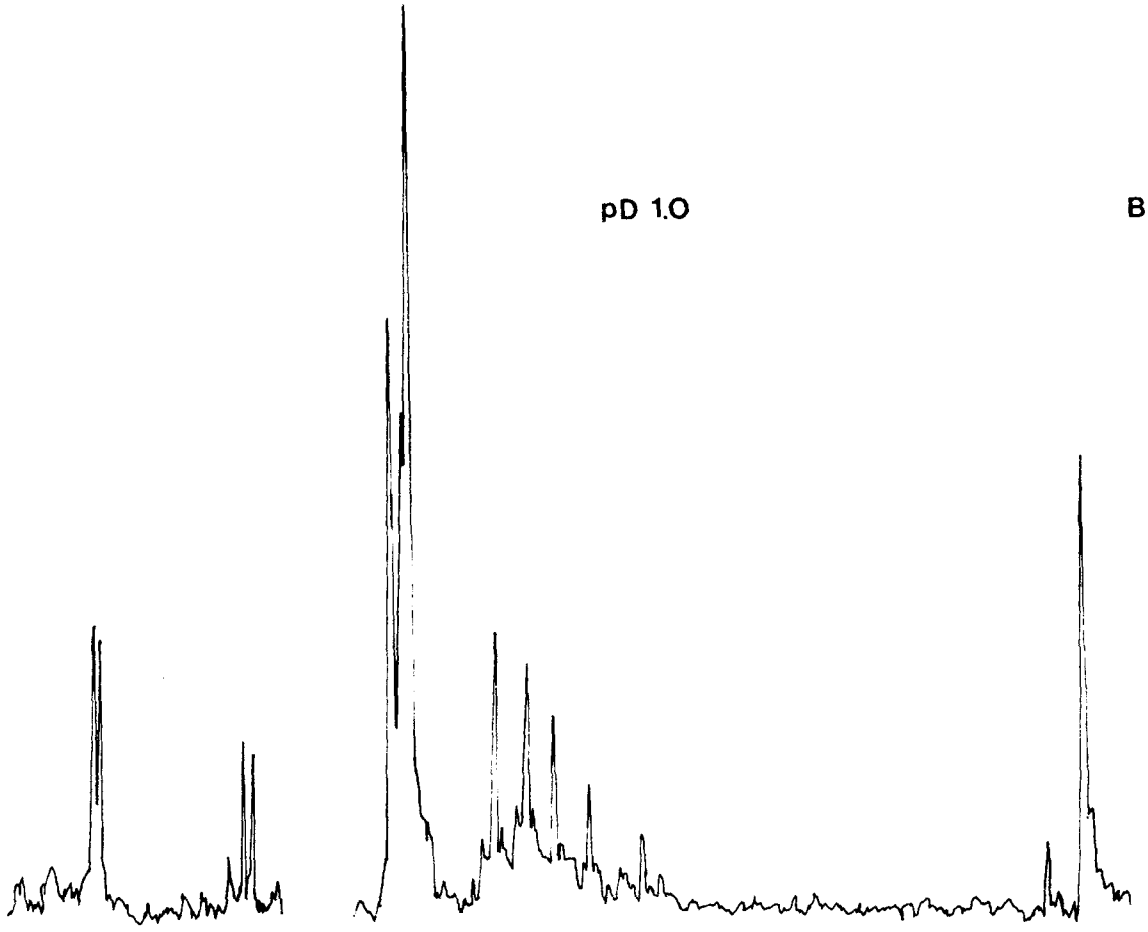
FIGURE 2 (A) Natural abundance ^{13}C FT nmr spectrum of [CoIIIEDTA] (ligand completely coordinated).

The addition of base to this sample regenerated spectrum 2A. The time of rechelation is ~10 min and the reaction is apparently quite reversible. Hence, we submit that if truly accurate kinetic data are to be obtained for the deuterium exchange of glycinate protons for the hexadentate complex, the acid concentration must be kept below 0.03 *M* in D_3O^+, (pD ≥ 1.5). Other deuterium exchange studies[11,12] have shown that the ease of glycinate proton exchange in pentadentate complexes of aminocarboxylate chelates vastly differs from that of the hexadentate species. Our studies under the conditions (pD = 1.5) and 95° gave $k/[D_3O^+] = 4.0 \times 10^{-5}$ l mol^{-1} sec^{-1}. This is at contrast somewhat to the value reported in the earlier pmr study.

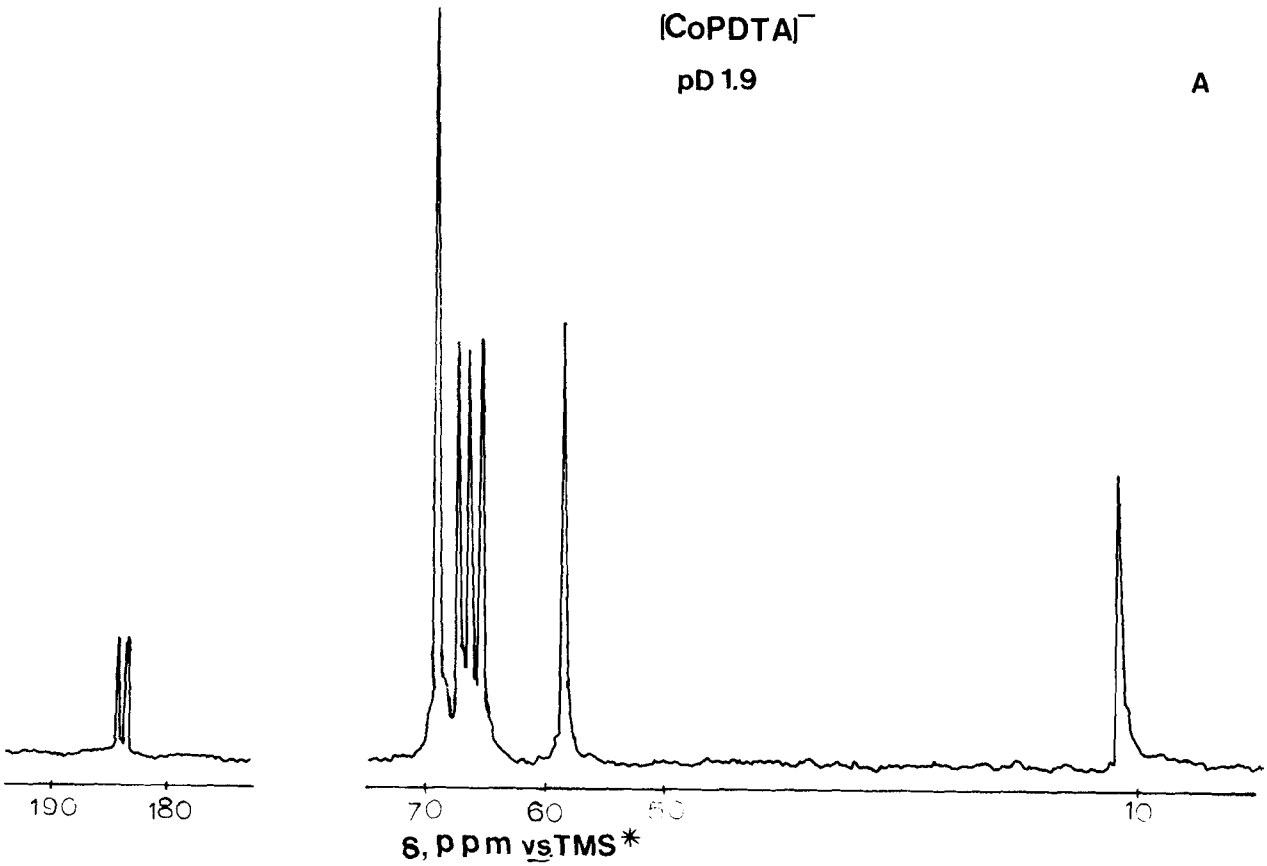
$Co^{III}(PDTA)^-$

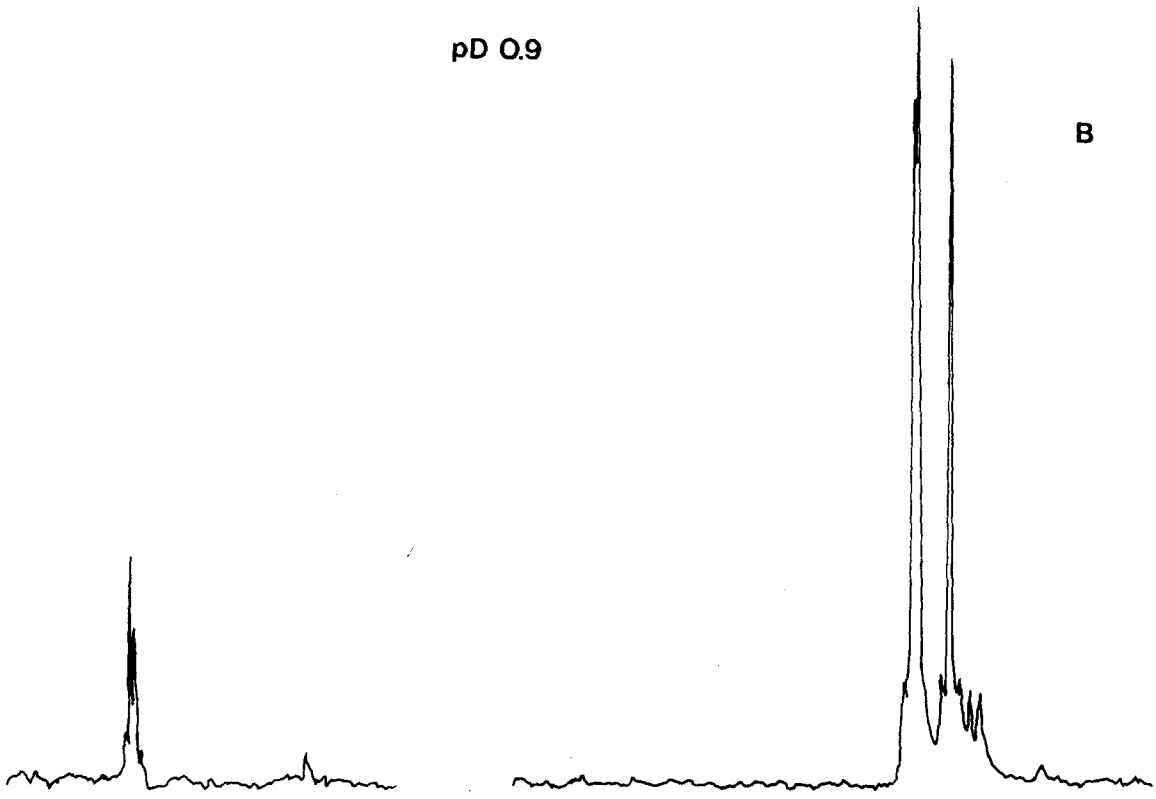
Similar evidence of ligand protonation was observed for the PDTA complex of cobalt(III) as shown in Figure 3. Spectrum 3A was obtained for the completely coordinated (hexadentate) species from pD = 7.4 to 1.9.

The assignment of peaks are as follows: The peaks at 183.7 ppm and 183.0 ppm correspond to the out-of-plane and in-plane carboxylate carbons respectively. There should be four carboxylate carbons due to the asymmetry of the backbone propylenediamine ring, but we were unable to resolve the carboxylate resonances any further at this sweep width. Narrower sweep widths could be used to obtain better resolution in this area of the spectrum when interest warrants. The peak at 69.7 ppm is assigned to the backbone carbon resonances (*E* ring). The resonances of these backbone carbons exhibit accidental overlap which is completely unexpected in view of their different local chemical environments. The peak at 68.0 ppm is assigned to the out-of-plane (*R'*) ring



(B) At pD = 0.9 evidence for the pentacoordinate species is observed. The up-field carboxylate resonance shows a marked decrease in intensity.





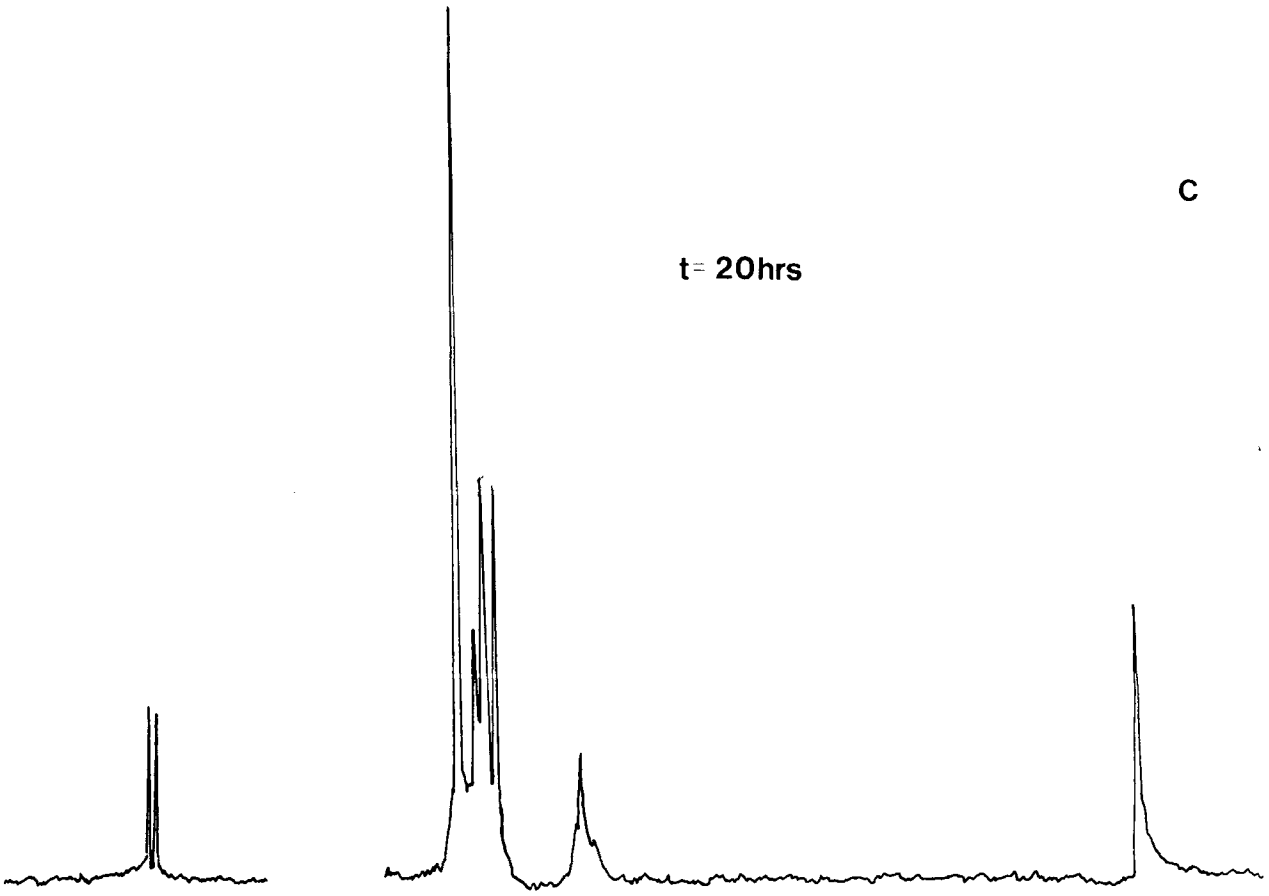
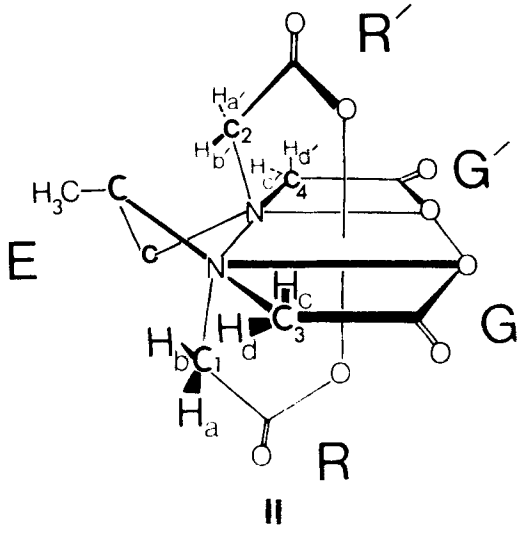


FIGURE 3 (A) Natural abundance ^{13}C FT nmr spectrum of $[Co^{III}PDTA]^-$ (ligand is completely coordinated).
(B) At pD ≤ 1.0 ligand protonation is dramatically observed. Spectrum indicates the presence of several species.
(C) Spectrum after 20 hrs of deuteration at 95°C and pD = 1.9. Deuterations of both C_1 and C_2 in **II** are observed.

carbon, C_2, in **II**. The $H_{a'}$ proton exchanges slower than the other out-of-plane arm resonating at 59.0 ppm (R ring proton H_a). The peaks at 66.0 and 67.0 ppm are the in-plane glycinate (G, G') carbons nearest and away from the methyl group respectively. This assignment was made on the basis of the rate of thermal racemization of the in-plane and out-of plane rings upon standing at 95° for several days. Racemization on the side of the methyl group occurs faster.[13] The peak at 12.0 ppm is assigned to the methyl group of the backbone E ring in **II**.

Spectrum 3B was obtained at a pD lower than 1.9. It is obvious that ligand protonation has occurred and several species now exist in solution, each of which may have vastly differing rates of deuteration. The mixtures of species present under these highly acidic conditions render any kinetic exchange data thus obtained of dubious value.



II

The obvious advantage of ^{13}C nmr spectroscopy over the pmr analog in studying the PDTA complex lies in the extreme and obvious simplicity of the spectra. Four discrete resonance lines are now observed for the glycinate carbon atoms (C_1 through C_4 in **II**) *vs.* a pmr spectral pattern consisting of sixteen overlapping AB patterns which are in turn superimposed upon a complex resonance pattern resulting from the backbone protons. When an asymmetric center (such as in PDTA) is present, the chelate ring carbons all have different environments which results in the resonant frequency of each of the glycinate arms being different. This enables one to study the deuteration rates of both of the out-of-plane glycinate arms as exchange occurs. In the proton exchange studies monitored by pmr spectroscopy[3] relative amounts of $C\begin{matrix}H\\H\end{matrix}$ *vs.* $C\begin{matrix}D\\H\end{matrix}$ (on C_2, in **II**) as exchange intermediates could not be ascertained because the AB pattern resulting from these two glycinate protons lies in the most complex portion of the resonance pattern.

The exact order of proton exchange in the PDTA complex has been established by a redox scrambling technique[13] and it is now known that 75% of the glycinate protons in the $H_{a'}$ position of C_1 undergo deuterium exchange before deuteration of the $H_{a'}$ proton on C_2 has progressed more than 33%. By the time the H_a; proton on C_2 has reached 50% completion, the C_1 proton exchange (H_a) is virtually complete. With this information in hand we are able, for the first time, to obtain accurate kinetic data for the deuterium exchange of one proton on each of the two out-of-plane glycinate rings in the completely chelated (hexadentate) PDTA complex of cobalt(III). The results of this study conducted at 95° and pD = 1.9 are:

(1) for C_1, $k/[D_3O^+] = 212 \times 10^{-5}$ l mol^{-1} sec^{-1}

(2) for C_2, $k/[D_3O^+] = 79 \times 10^{-5}$ l mol^{-1} sec^{-1}

CONCLUSIONS

Unlike the cobalt(III) complexes of PDTA and EDTA, the CyDTA complex was not observed to undergo protonation to form a pentadentate species (this study and Ref. 3). The relationship that exists between chelate ring strains and the ease with which the exchange phenomenon occurs is an important one. Based on an X-ray crystallographic study of $Co(EDTA)^-$ by Weakliem and Hoard[14] (which showed that the in-plane glycinate rings are bent and strained, while the out-of-plane rings are relatively strain-free) as well as their own pmr data, Terrill and Reilley postulated, "the difference in ability of the two nonequivalent acetate protons to undergo isotopic exchange is a function of ring strain." Thus, it becomes quite clear that if the ring strain changes, as it clearly does when a hexadentate complex becomes protonated (yielding a pentadentate species), so too then must the rate of deuteration change for these glycinate protons. It has been further shown that the two out-of-plane rings in "pentadentate" aminocarboxylate chelates of cobalt(III) show marked differences in their ability to undergo isotopic substitution with one of the out-of-plane rings resisting deuteration almost completely.[3,4,11-14]

The method of monitoring the degree of chelation and deuteration, reported here, can be applied to other forms of chelates involving various metal ions and such ligands as amino acids, polypeptides and various forms of biologically important compounds.

The relatively new field of bioinorganic chemistry will be most aided by ^{13}C nmr techniques of the type outlined here. As mentioned earlier, the more nonsymmetric the molecule, the more dissimilar are the local magnetic environments of the various carbon nuclei. The ^{13}C spectrum, in most cases, will have individual carbon sites in the molecule assigned to a specific resonance. This will enable inorganic chemists to observe slight changes in molecular conformations or configurations and be able to observe specific active sites as they undergo various reactions. The structural and kinetic study presented in this work is but a single example of the incorporation of a powerful analytical tool that inorganic chemists have, for the most part, failed to utilize.

ACKNOWLEDGEMENTS

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