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Nuclear Magnetic Resonance Studies of Rate and Mechanism of Stereospecific Acid- and Base-Catalyzed Deuterations of α-Hydrogen Atoms in Ethylenediamine-N,N'-diacetatocobalt(III) Chelates[1]

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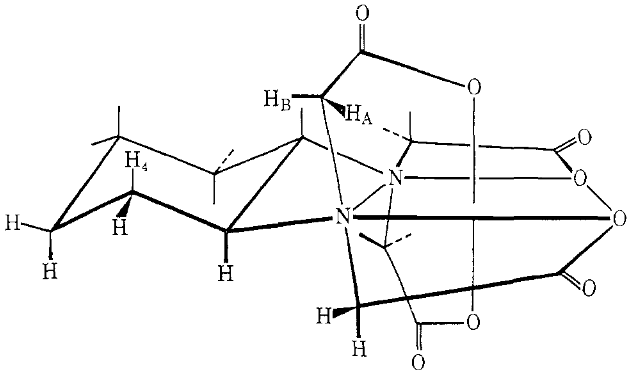
Received April 3, 1968

Certain α-hydrogen atoms in aminocarboxylate chelates of cobalt(III) undergo stereospecific deuteration in both acidic and alkaline D_2O. The reactions are stereospecific in that particular α-hydrogen atoms are deuterated more rapidly than their geminal α-hydrogen atoms. Base-catalyzed deuterations, often complete in minutes at room temperature, are more rapid than acid-catalyzed deuterations, and are approximately ten times more stereospecific. Enol and enolate species are proposed as intermediates in the deuteration reactions. The same reaction stereochemistry applies to all of the Co^{III}–EDTA analogs studied thus far (EDTA is ethylenediamine-N,N,N',N'-tetraacetate). This work makes possible a better understanding of nmr spectral assignments in these chelates and suggests better methods for the synthesis of deuterated chelating agents.

Williams and Busch[2] first showed that α-hydrogen atoms in Co(III) chelates of α-aminocarboxylate ligands, such as ethylenediamine-N,N,N',N'-tetraacetate (EDTA), undergo deuteration in alkaline D_2O, confirming earlier observations[3,4] on the tendency of the central metal ion to increase the acidity of ligand α-hydrogen atoms.

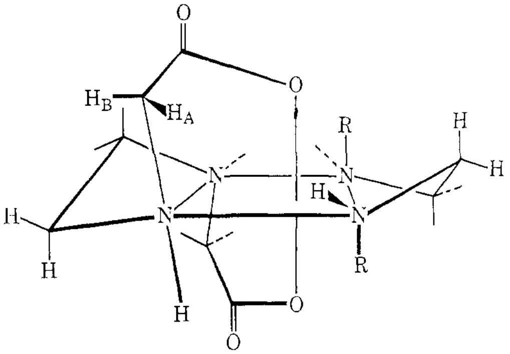
Terrill and Reilley[5] demonstrated the striking degree of stereospecificity in the acid-catalyzed deuteration of different kinds of out-of-plane α-hydrogen atoms in $Co^{III}CyDTA^-$ (I), where CyDTA = *trans*-1,2-cyclohexanediamine-N,N,N',N'-tetraacetate. The nmr spectrum of this chelate shows two AB patterns, representing four types of α-hydrogen atoms. When the sample is allowed to stand for days at 95° in acidified D_2O, only one of the AB patterns diminishes in intensity, indicating deuterium substitution. This AB pattern was assigned to the out-of-plane acetate group. The upfield portion, however, loses intensity approximately ten times faster than the downfield portion, showing the stereospecificity of the reaction.



I, $Co^{III}CyDTA^-$

Primarily on the basis of the assumed reaction stereochemistry, Terrill and Reilley assigned proton A in I to the upfield portion of the AB pattern and proton B to the downfield portion. This constitutes a crossover in the chemical shifts of out-of-plane A and B protons, as compared to those in similar Co(III) chelates,[6] and the magnitude of $\Delta\delta_{AB}$ (0.88 ppm) cannot be accounted for on the basis of previous explanations (*e.g.*, C–N anisotropic shielding[6]). Stereospecificity presumably occurs in the acid-catalyzed deuteration of the compound $Co^{III}EDTA^-$, but this tends to be obscured by small chemical shift differences and the interconversion of in-plane and out-of-plane acetate groups (*i.e.*, *dl* interconversion). Quantitative studies of the base-catalyzed deuteration of Co^{III}-CyDTA are hampered by decomposition of the chelate in alkaline solutions.

trans-$Co^{III}EDDA(en)^+$ (II), where EDDA = ethylenediamine-N,N'-diacetate and en = ethylenediamine, was first reported by Legg and Cooke.[6a] This chelate is octahedral and possesses only out-of-plane α-hydrogen atoms. Its $\Delta\delta_{AB}$ value is readily explained, not only from C–N anisotropic shielding[6b] but also from the magnitude of H–N–C–H coupling constants (this work), and thus its spectral assignments are quite certain. In addition, because Co^{III}-EDDA(en) is stable



II, *trans*-$Co^{III}EDDA(R_2en)^+$

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(1) This research was supported by U. S. Public Health Service Grant No. 1-R01-AM10889; presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) D. H. Williams and D. H. Busch, *J. Am. Chem. Soc.*, **87**, 4644 (1965).

(3) D. E. Metzler, J. D. Longnecker, and E. E. Snell, *ibid.*, **76**, 639 (1954).

(4) M. Murakami and K. Takahashi, *Bull. Chem. Soc. Japan*, **32**, 308 (1959).

(5) J. B. Terrill and C. N. Reilley, *Inorg. Chem.*, **5**, 1988 (1966).

(6) (a) J. I. Legg and D. W. Cooke, *ibid.*, **4**, 1576 (1965); (b) *ibid.*, **5**, 594 (1966).

toward base, both acid- and base-catalyzed deuterations can readily be studied. In order to determine the influence of steric and inductive effects upon the deuteration rates, two new compounds, *trans*-Co^{III}EDDA(dmen)$^+$ and *trans*-Co^{III}EDDA(deen)$^+$, where dmen = N,N′-dimethylethylenediamine and deen = N,N′-diethylethylenediamine, were synthesized.

The total rate of deuteration of proton A in the fully protonated complex (CoYH_A) as determined by monitoring the intensity of H_A is given by

$$\frac{-\text{d}[\text{CoYH}_\text{A}]}{\text{d}t} = k_{\text{D(acid)}}[\text{CoYH}_\text{A}]^m[\text{D}_3\text{O}^+]^n - k_{\text{H(acid)}}[\text{CoYD}_\text{A}]^m[\text{H}_3\text{O}^+]^n + k_{\text{D(base)}}[\text{CoYH}_\text{A}]^p[\text{OD}^-]^q - k_{\text{H(base)}}[\text{CoYD}_\text{A}]^p[\text{OH}^-]^q \quad (1)$$

An equation of similar form can be written for CoYH_B, where the intensity of proton B in II is monitored. In the present work, some of the above-mentioned rate constants are determined, and mechanisms for acid- and base-catalyzed deuterations are proposed.

Experimental Section

Chemicals.—Chemicals of the highest purity available were used without further purification in the preparation of the complexes. Ethylenediamine-N,N′-diacetic acid was obtained from K & K Laboratories, Inc.; en (98–100%) was obtained from Matheson Coleman and Bell; dmen and deen were obtained from Aldrich Chemical Co., Inc.; and *trans*-1,2-cyclohexanediamine-N,N,N′,N′-tetraacetic acid was obtained from Geigy Chemical Co.

Preparation of the Complexes.—The three Co^{III}–EDDA complexes were prepared by the method of Legg and Cooke.[6a] *Anal.* Calcd for *trans*-[Co^{III}EDDA(en)]$\text{NO}_3\cdot\text{H}_2\text{O}$ or $[\text{CoC}_8\text{H}_{18}\text{N}_4\text{O}_4]\text{NO}_3\cdot\text{H}_2\text{O}$: C, 25.74; H, 5.40; N, 18.77. Found: C, 25.72; H, 5.35; N, 19.31. Calcd for *trans*-[Co^{III}EDDA(dmen)]$\text{NO}_3\cdot\text{H}_2\text{O}$ or $[\text{CoC}_{10}\text{H}_{22}\text{N}_4\text{O}_4]\text{NO}_3\cdot\text{H}_2\text{O}$: C, 29.95; H, 5.99; N, 17.47. Found: C, 31.40; H, 5.77; N, 20.88. Calcd for *trans*-[Co^{III}EDDA(deen)]$\text{NO}_3\cdot\text{H}_2\text{O}$ or $[\text{CoC}_{12}\text{H}_{26}\text{N}_4\text{O}_4]\text{NO}_3\cdot\text{H}_2\text{O}$: C, 33.59; H, 6.59; N, 16.31. Found: C, 33.48; H, 6.63; N, 15.50. The yield was about 60% for all complexes. The chelate K[Co^{III}CyDTA] $\cdot 3\text{H}_2\text{O}$ was prepared by the method of Dwyer and Garvan.[7] *Anal.* Calcd for $\text{K}[\text{CoC}_{14}\text{H}_{18}\text{N}_2\text{O}_8]\cdot 3\text{H}_2\text{O}$: C, 34.00; H, 4.86; N, 5.67. Found: C, 33.74; H, 4.79; N, 6.45; yield, 80%. The C, H, and N analyses were done by Miss H. King of this department and by Elek Microanalytical Laboratories, Torrance, Calif. The nitrogen analyses are of doubtful value, as is often the case with nitrate compounds. Errors in the elemental analyses of Co^{III}EDDA(dmen) indicate that these crystals apparently contain a small amount of excess diamine. The nmr spectra of this and other chelate compounds are given below, however, and leave little doubt as to their identities.

Proton Magnetic Resonance Spectra.—All spectra were recorded on a Varian A-60 nmr spectrometer at 36 ± 1°, the internal temperature of the probe. Chemical shifts were conveniently measured relative to *t*-butyl alcohol internal standard, which is chemically shifted 1.233 ppm downfield of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). No attempt was made to remove dissolved oxygen from the solutions. A sweep width of 500 cps (1 cm = 10 cps) and a scan rate of 1 cycle/sec^2 were employed. For integration of peak areas, a sweep width of 100 cps (1 cm = 2 cps) and a scan rate of 2 cycles/sec^2 were used.

pD values of the alkaline solutions were maintained by the addition of boric acid–sodium borate buffers (0.1 *M* in total borate). The empirical formula pD = "pH" + 0.4[8] was employed to correct the values measured with a Radiometer pH meter, Model 26. These pD values were adjusted with a concentrated solution of NaOD in D_2O. In determining base-catalyzed rates, the solvent mixture was brought to probe temperature in a water bath before addition to a weighed amount of solid in the nmr tube at time zero. The concentration of the Co^{III}–EDDA complexes was 0.10 *M* in all studies and 0.40 *M* for Co^{III}–CyDTA. No attempt was made to keep ionic strength constant.

The acid-catalyzed isotopic exchange rates were determined in nitric acid solutions. The samples were placed in sealed nmr tubes and placed in a water bath at 95°. The nmr spectra, however, were recorded at 36°, with the exchange rate effectively quenched. In this case the peak areas of the nmr peaks were determined by weighing paper cutouts matching the peak areas. Least-squares analysis of kinetic data was carried out with the aid of the Olivetti–Underwood Programma 101 desk-top computer. J. T. Baker concentrated aqueous HNO_3 was used to prepare acidic D_2O solutions of the complexes. The maximum amount of H_2O thus introduced was ~4% by volume. For the determination of $k_{\text{H(acid)}}$, the monodeuterated complexes ($\text{CoYD}_\text{A}\text{H}_\text{B}$) were prepared as follows. Solutions of the chelates in alkaline D_2O (pD ≈11) were allowed to stand at room temperature for approximately 2 hr, and the solvent was removed in a rotary evaporator. The solid deuterated compounds were dissolved in aqueous 6 *M* HNO_3, the tubes were sealed, and the kinetic data were obtained as previously described.

Results

Acid-Catalyzed Deuteration. (1) ***trans*-Co^{III}EDDA(en)$^+$.**—The nmr spectrum of this complex in neutral solution has been reported previously by Legg and Cooke.[6a] Our spectra in acid solution (Figure 1a) reveal the presence of previously unreported N–H resonances and splitting of vicinal α-hydrogen atoms due to these N–H protons. The magnitude of coupling to the low-field protons (J = 8.0 cps) and high-field protons (J > 1 cps) confirms the previous assignment[6a] of H_A and H_B, provided that the Karplus equation is applicable to H–N–C–H vicinal couplings.

The AB pattern just upfield of the HOD peak is assigned to the α-hydrogen atoms. Spinning side bands are denoted by asterisks. Protons associated with the N-CH_2–CH_2–N rings of both EDDA and ethylenediamine are found between 2.6 and 3.5 ppm. The N–CH_2–CH_2–N rings of the EDDA molecule exhibit an AA′BB′ pattern owing to the different chemical shifts of axial and equatorial protons. The –CH_2– protons of ethylenediamine show a single resonance at 2.83 ppm, which has been interpreted[6a] as an indication of rapid twisting of the ring. In Figure 1a, the broad peaks centered at 5.46 and 7.30 ppm are assigned on the basis of their 2:1 areas relative to the N–H protons of ethylenediamine and EDDA, respectively.

Table I summarizes the assignment of the chemical shifts of Co^{III}-EDDA(en).

When Co^{III}-EDDA(en) is heated at 95° in 1 *M* HNO_3 for 17 hr (Figure 1b), the N–H resonances decrease to ~16% of their original area, and part of the splitting of α-hydrogen atoms disappears. Note that it is the *downfield* portion which decreases in intensity, rather than the *upfield* portion as in Co^{III}-CyDTA.[5] After heating for 40 hr (Figure 1c), deuteration of N–H protons is complete, and ~45% of the α-hydrogen atoms have undergone deuteration.

During the first 40 hr or so, the area of the peak at

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[7] F. P. Dwyer and F. O. Garvan, *J. Am. Chem. Soc.*, **83**, 2610 (1961).

[8] P. K. Glascoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

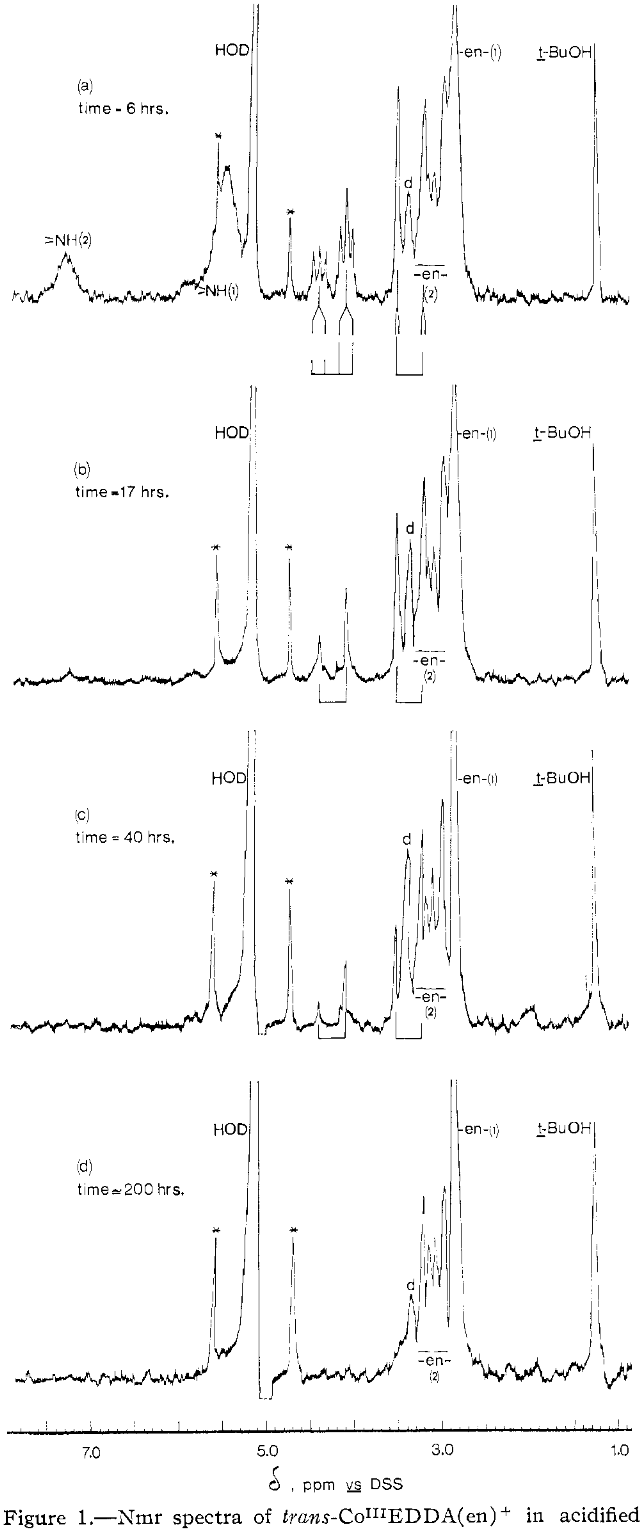


Figure 1.—Nmr spectra of *trans*-Co^{III}EDDA(en)$^+$ in acidified D_2O (1.0 *M* DNO_3).

3.38 ppm increases with time. This peak is assigned to the remaining α-hydrogen atoms which are, in effect, decoupling by deuteration of their geminal α-hydrogen atoms. This peak is broadened by unresolved coupling to the geminal deuterium atom. The acid-catalyzed deuteration rates were determined by monitoring the largest of the downfield peaks in the AB pattern as described in the Experimental Section.

The deuteration of proton A can be represented as

$$CoYH_A \longrightarrow CoYD_A \quad (2)$$

Table I

Spectral Assignments for *trans*-Co^{III}EDDA(diamine)$^+$ Chelates (δ, ppm *vs.* DSS)

Resonances	en	dmen	deen
$-H_A$ (EDDA)	4.23	4.21	3.94
$-H_B$ (EDDA)	3.39	3.39	3.34
$N-CH_2-CH_2-N$ (EDDA)	2.6–3.5	2.1–3.5	2.1–3.3
$N-CH_2-CH_2-N$ (diamine)	2.83	2.1–3.5	2.1–3.3
$-CH_3$ (diamine)	...	2.54	1.35
$-CH_2-$ (diamine)	...	...	2.1–3.5
>NH(1) (diamine)	5.46	6.08	5.73
>NH(2) (EDDA)	7.30	6.51	6.44

where $CoYH_A$ is the original complex and $CoYD_A$ is the monodeuterated chelate. In strongly acidic solution, the base-catalyzed terms in eq 1 are negligible, and when the reaction is far from equilibrium, the rate at constant pD can be expressed as

$$\frac{-d[CoYH_A]}{dt} = k'_{D(acid)}[CoYH_A]^m \quad (3)$$

where $k'_{D(acid)}$ is the apparent rate constant for acid-catalyzed deuteration at constant pD. If $m = 1$, eq 3 can be written in integrated form as

$$k'_{D(acid)}t = 2.3 \log \frac{[CoYH_A]_0}{[CoYH_A]} \quad (4)$$

where $[CoYH_A]_0$ is the initial concentration. Because a, the area of the monitored nmr peak, is directly proportional to $[CoYH_A]$ at any time, eq 3 can be expressed as

$$k'_{D(acid)}t = 2.3 \log \frac{a_0}{a} \quad (5)$$

A plot of log a *vs.* time at constant pD yielded straight lines, proving that $m = 1$. From the slopes of these lines, values of $k'_{D(acid)}$ were determined. The value of n, the reaction order with respect of $[D_3O^+]$, was determined by taking logarithms of the expression

$$k'_{D(acid)} = k_{D(acid)}[D_3O^+]^n \quad (6)$$

yielding

$$\log k'_{D(acid)} = \log k_{D(acid)} - n(pD) \quad (7)$$

pD values were calculated from the known concentrations of HNO_3, ignoring activity coefficients. Log $k'_{D(acid)}$ was plotted *vs.* pD, and least-squares analysis yielded a slope, n, of 0.93 ± 0.02, showing that the reaction is first order in $[D_3O^+]$. The pairs of experimental pD (±0.01) and $-\log k'_{D(acid)}$ (±0.1) values are: −0.78, 4.0; −0.48, 4.3; 0.00, 4.7; 0.60, 5.3.

Small deviations in n can be caused by changes in ionic strength at various pD values, and, in order to avoid emphasizing these small deviations, n is set equal to 1.00. The rate of deuteration in acidic D_2O is thus given by

$$\text{rate} = k_{D(acid)}[CoYH_A][D_3O^+] \quad (8)$$

where $k_{D(acid)} = 2.0 \pm 0.4 \times 10^{-5}\ M^{-1}\ sec^{-1}$ at 95°.

When solutions of Co^{III}-EDDA(en) in acidified D_2O are heated at 95° for longer times (~20–200 hr), the decoupled α-hydrogen atoms, H_B, finally undergo deuteration, as evidenced by the decrease in intensity of the peak at 3.38 ppm (Figure 1d). The rate constant for this process, k^d_D (where d means "decoupled"), was obtained by the method described above. The calculated value of $k_{D(acid)}$ is 2.0 ± 0.5 × 10^{-6} at 95°. The ratio of the rate constants, $k_{D(acid)}/k^d_{D(acid)}$, represents the degree of stereospecificity of the reaction. The observed ratio for Co^{III}-EDDA(en) (10 ± 3) agrees very well with the degree of stereospecificity (10) reported for Co^{III}-CyDTA.[5]

The value of $k_{H(acid)}$ is 4 ± 1 × 10^{-6} M^{-1} sec^{-1} at 95°, obtained by monitoring the area of the peak at 4.23 ppm as it increases for a single pD value, assuming a reaction order $n = 1.00$. The primary isotope effect, $k_{D(acid)}/k_{H(acid)}$, is 5 ± 2, as shown in Table II.

TABLE II

RATE CONSTANTS FOR ACID-CATALYZED EXCHANGE OF α-HYDROGEN ATOMS IN *trans*-Co^{III}EDDA(diamine)$^+$ CHELATES AT 95°

Diamine	$10^5k_{D(acid)}$, M^{-1} sec^{-1}	$10^6k^d_{D(acid)}$, M^{-1} sec^{-1}	$k_{D(acid)}/k^d_{D(acid)}$	$10^6k_{H(acid)}$, M^{-1} sec^{-k1}	$k_{D(acid)}/_{H(acid)}$
en	2.0 ± 0.4	2.0 ± 0.5	10 ± 3	4 ± 1	5 ± 2
dmen	3.4 ± 0.7	3.1 ± 0.7	11 ± 3	6 ± 1	6 ± 2
deen	6 ± 1	2.7 ± 0.5	22 ± 5	10 ± 3	6 ± 2

(2) ***trans*-$\mathbf{Co^{III}}$EDDA(dmen)$^+$.**—The nmr spectrum of this complex in acidified D_2O solution is shown in Figure 2. The resonances of protons associated with the N–CH_2–CH_2–N rings of EDDA and dmen are found at ~2.1–3.5 ppm. As in the case of Co^{III}-EDDA(en), the N–CH_2–CH_2–N protons of the EDDA molecule exhibit an AA′BB′ splitting pattern. The N–CH_2–CH_2–N protons of the dmen also exhibit an AA′BB′ pattern, unlike the corresponding protons in the en chelate, which exhibit a sharp singlet, probably because of rapid ring twisting, which is sterically forbidden in the dmen chelate. Because of the highly collapsed nature and the overlap of the AA′BB′ patterns, a complete analysis is impossible. The lone peak at 2.075 ppm is probably caused by an impurity. The N–H protons give rise to a pair of broad peaks of equal areas centered at 6.08 and 6.51 ppm, assigned to dmen and EDDA, respectively. The spectrum in Figure 2 reveals splitting by N–H protons of the vicinal protons on both dmen and EDDA.

The low-field α-hydrogen of EDDA (J_{AB} = 18.0 cps) is split by 8.0 cps, and the high-field proton, by <1 cps. In acid solution, the dmen methyl resonance, centered at 2.54 ppm, is split into a doublet (J = 5.5 cps) by vicinal N–H protons. The two types of N–H protons exchange at different rates, and the presence of the dmen methyl doublet after deuteration of the downfield N–H resonance allows unequivocal assignment of the N–H resonances.

The deuteration of α-hydrogen atoms in the dmen chelate is analogous to that described previously for the en chelate. That is, the downfield portion of the AB pattern is first to diminish in intensity, as H_A becomes deuterated, causing the collapse of the upfield portion into a broad singlet centered at 3.38 ppm. The rate data for dmen chelate were treated as described above for the en chelate, and the results are given in Table II. The pairs of experimental pD (±0.01) and $-\log k'_{D(acid)}$ (±0.1) values are: −0.78, 3.8; −0.48, 4.0; −0.18, 4.2; 0.30, 4.8. The orders of $[D_3O^+]$ in the reactions represented by $k_{D(acid)}$ and $k^d_{D(acid)}$ equal 0.96 ± 0.11 and 0.95 ± 0.01, respectively. These values were set equal to 1.00 in determining the rate constants, as in the case of the en chelate. The degree of stereospecificity for the dmen chelate is 11 ± 3, and the primary isotope effect is 6 ± 2.

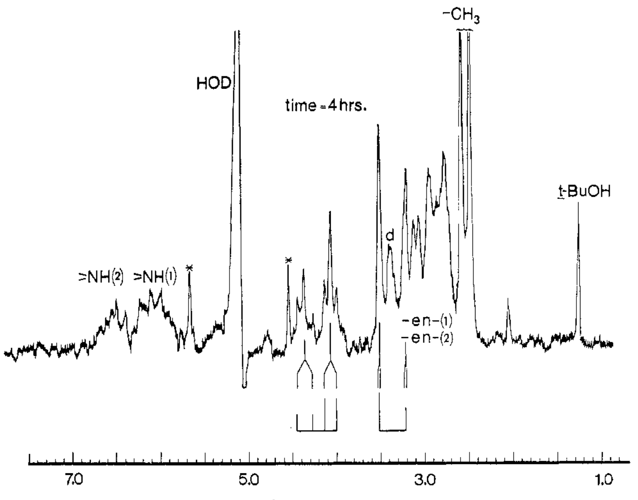


Figure 2.—Nmr spectrum of *trans*-Co^{III}EDDA(dmen)$^+$ in acidified D_2O (1.0 M DNO_3) after 4 hr at 95°.

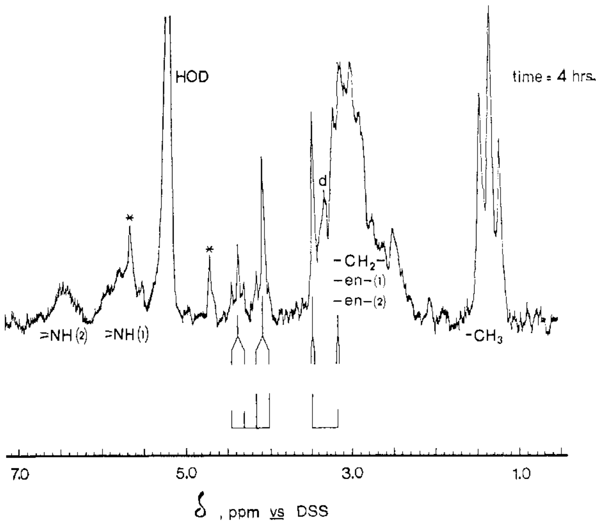


Figure 3.—Nmr spectrum of *trans*-Co^{III}EDDA(deen)$^+$ in acidified D_2O (1.0 M DNO_3) after 4 hr at 95°.

(3) ***trans*-$\mathbf{Co^{III}}$EDDA(deen)$^+$.**—The nmr spectrum of this complex in acidified D_2O is shown in Figure 3. The overlapping AA′BB′ patterns due to protons associated with the N–CH_2–CH_2–N rings of EDDA and deen are found at ~2.1–3.3 ppm. The deen methyl resonance is centered at 1.35 ppm and is split into a triplet (J = 7 cps) by the vicinal –CH_2– protons. The –CH_2– resonance of the deen ethyl group is complex (expected to be a quartet of doublets) and overlaps with AA′BB′ patterns. The N–H protons give rise to broad peaks of equal areas centered at 5.73 and 6.44

ppm, assigned to deen and EDDA, respectively, by analogy with the dmen chelate. The low-field α-hydrogen of EDDA (J_{AB} = 18.0 cps) is split by the vicinal N–H proton with a coupling constant of 8.0 cps, and the high-field α-hydrogen with a coupling constant <1 cps.

Rate data for the deen chelate were treated as described above, and the results are given in Table II. The pairs of experimental pD (±0.01) and $-\log k'_{D(\text{acid})}$ (±0.1) values are: −0.78, 3.5; −0.65, 3.6; −0.48, 3.9; −0.18, 4.1. The order of [D_3O^+] in the reactions represented by $k_{D(\text{acid})}$ and $k^d_{D(\text{acid})}$ equal 1.0 ± 0.2 and 0.9 ± 0.1. In determining the rate constants, the reaction orders were set equal to 1.00. The degree of stereospecificity for the deen chelate is 22 ± 5, and the primary isotope effect is 6 ± 2.

Base-Catalyzed Deuteration. (1) *trans*-Co^{III}EDDA(en)$^+$, *trans*-Co^{III}EDDA(dmen)$^+$, and *trans*-Co^{III}-EDDA(deen)$^+$.—Nmr spectra of these chelates in alkaline D_2O (pD ~9.3–10.2) were recorded for various times. The base-catalyzed deuterations were faster than the acid-catalyzed deuterations and were conveniently studied by electronic integration of areas as the reaction proceeded in the nmr probe at room temperature and lower. All three show AB patterns uncomplicated by the presence of N–H resonances or N–H splittings, due to the rapid exchange of the N–H protons in neutral and alkaline solution. In the spectrum of the dmen chelate (Figure 4), the entire low-field portion of the AB pattern and part of the high-field portion have disappeared after 4 hr.

In alkaline solution, the acid-catalyzed terms in eq 1 are negligible, and the rate at constant pOD can be expressed as

$$\frac{-d[\text{CoYH}_A]}{dt} = k'_{D(\text{base})}[\text{CoYH}_A]^p \qquad (9)$$

where $k'_{D(\text{base})}$ is the apparent rate constant for base-catalyzed deuteration at constant pOD. Values of $k'_{D(\text{base})}$ were obtained from the constant slopes resulting when log a was plotted *vs.* time, in a treatment exactly analogous to that described above for $k'_{H(\text{acid})}$. The linearity of these plots proves that p, the order of the base-catalyzed deuteration with respect to [CoYH$_A$], is equal to unity. The values of q, the reaction order with respect to [OD^-], determined by least-squares analysis of plots of $\log k'_{D(\text{base})}$ *vs.* pOD (analogous to eq 7), are 0.9 ± 0.1, 1.04 ± 0.08, and 0.91 ± 0.06 for the en, dmen, and deen chelates, respectively.

The pairs of experimental pOD (±0.01) and $-\log k'_{D(\text{base})}$ (±0.1) values at 36° are: for Co^{III}-EDDA(en), 2.30, 2.3; 3.03, 2.6; 3.42, 3.3; 3.78, 3.8; 4.58, 4.2; for Co^{III}-EDDA(dmen), 2.54, 2.2; 2.79, 2.5; 3.42, 2.9; 3.69, 3.4; 4.22, 3.9; for Co^{III}-EDDA(deen), 2.79, 2.3; 3.53, 3.0; 4.00; 3.2; 4.29, 3.5. Because the reaction is first order in [OD^-], q is set equal to 1.00. The values of $k_{D(\text{base})}$ obtained from the intercepts are given in Table III.

Determinations of $k_{D(\text{base})}$ at 14 and 55° were carried out at single pOD values and must therefore be accompanied by larger errors (estimated ±30%) than those of $k_{D(\text{base})}$ at 36° (average approximately ±20%). The pairs of experimental pOD (±0.01) and $-\log k'_{D(\text{base})}$ (±0.1) values at 14 and 55°, respectively, are: for Co^{III}-EDDA(en), 2.30, 3.6; 4.58, 3.0; for Co^{III}-EDDA(dmen), 2.54, 3.4; 4.22, 2.7; for Co^{III}-EDDA-(deen), 2.79, 3.7; 4.29, 2.7. The primary isotope

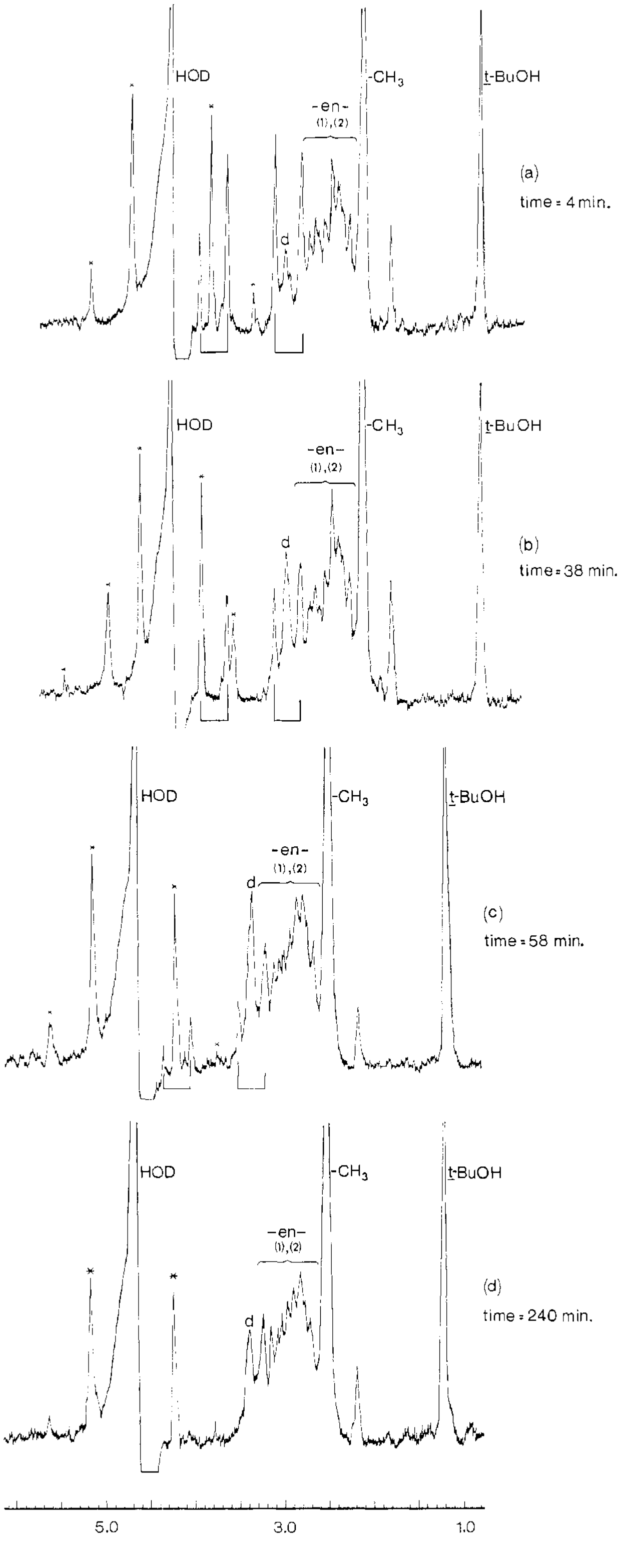


Figure 4.—Nmr spectra of *trans*-Co^{III}EDDA(dmen)$^+$ in alkaline D_2O (pD 9.9) at 36°.

TABLE III

RATE CONSTANTS FOR BASE-CATALYZED EXCHANGE OF α-HYDROGEN ATOMS IN *trans*-$Co^{III}EDDA(diamine)^+$ CHELATES AT VARIOUS TEMPERATURES

Diamine	Temp, °C	$k_{D(base)}$, M^{-1} sec^{-1}	$k^d_{D(base)}$, M^{-1} sec^{-1}	$k_{D(base)}/k^d_{D(base)}$
en	14	0.06 ± 0.01		
	36	2.0 ± 0.06	0.016 ± 0.003	$(1.3 \pm 0.3) \times 10^2$
	55	39 ± 8		
dmen	14	0.20 ± 0.04		
	36	3.0 ± 0.5	0.020 ± 0.004	$(1.5 \pm 0.4) \times 10^2$
	55	43 ± 9		
deen	14	0.20 ± 0.04		
	36	6.0 ± 0.8	0.027 ± 0.004	$(2.2 \pm 0.5) \times 10^2$
	55	46 ± 9		

effect cannot be determined for the base-catalyzed reaction by the techniques described herein, because the strong resonance of pure H_2O obscures the resonances of H_A and H_B.

According to transition-state theory, $K^{\ddagger}$, the formation constant of the activated complex, is given by

$$K^{\ddagger} = k_r h/\kappa k T \qquad (10)$$

where k_r is the specific rate constant. Assuming the transmission coefficient, κ, equals unity in all cases, we can calculate $K^{\ddagger}$ for $k_{D(base)}$ at various temperatures. When log $K^{\ddagger}$ is plotted *vs.* $1/T$, activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table IV) are obtained from slope and intercept.

TABLE IV

ACTIVATION PARAMETERS FOR BASE-CATALYZED DEUTERATION OF α-HYDROGEN ATOMS IN *trans*-$Co^{III}EDDA(diamine)^+$ CHELATES

Diamine	$\Delta G^{\ddagger}$, kcal/mol (25°)	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
en	18 ± 4	29 ± 3	36 ± 9
dmen	18 ± 4	24 ± 3	21 ± 9
deen	17 ± 3	24 ± 2	23 ± 8

(2) **$Co^{III}CyDTA^-$.**—Nmr spectra of an alkaline solution of this chelate were recorded for various times at 36° (Figure 5) and show that in the base-catalyzed exchange the highest field acetate proton is the most rapidly deuterated, as in the acid-catalyzed exchange.[5] A detailed study of the base-catalyzed exchange is difficult because of the broadening of spectral lines at pD >8, owing to the formation of mixed hydroxy complexes and paramagnetic Co(II) complexes. In spite of these difficulties, a value of $k_{D(base)}$ of $\sim 1.2\ M^{-1}$ was estimated for Co^{III}-CyDTA from the data presented in Figure 5.

Discussion

Mechanism of Base-Catalyzed Deuteration.—The mechanism of base-catalyzed deuteration, being simpler than that for acid-catalyzed deuteration, will be discussed first. The two-step mechanism

$$CoYH_A + OD^- \xrightarrow{k_D} CoY^- + HOD \quad \text{(slow)} \qquad (11)$$

$$CoY^- + D_2O \longrightarrow CoYD_A + OD^- \quad \text{(fast)} \qquad (12)$$

is proposed. Although determination of the kinetic isotope effect was impossible, the C–H bond rupture in the first step is without doubt rate determining. The intermediate CoY^- is stabilized by resonance with the enolate form, as shown in Scheme I.

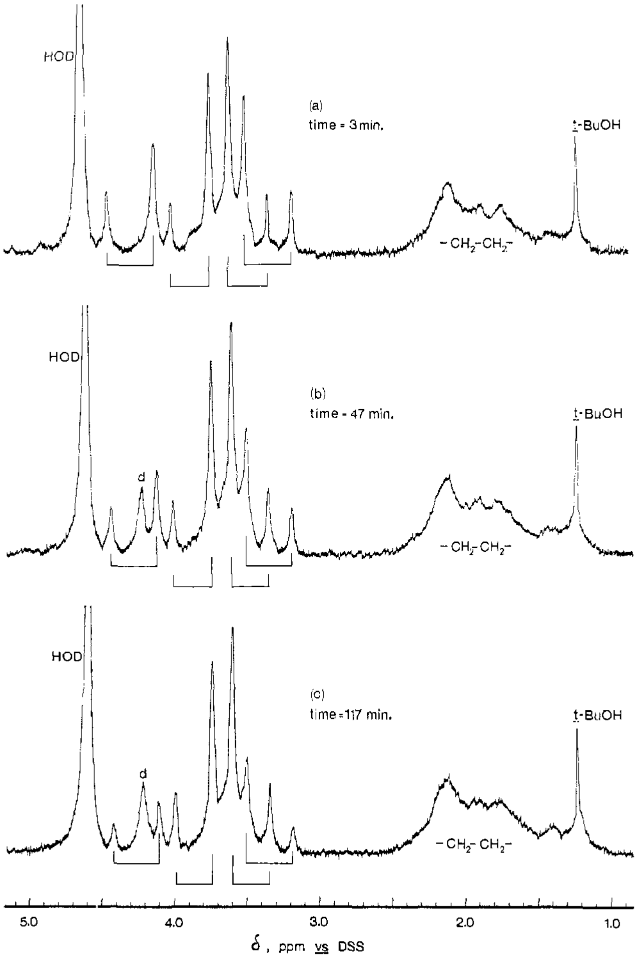
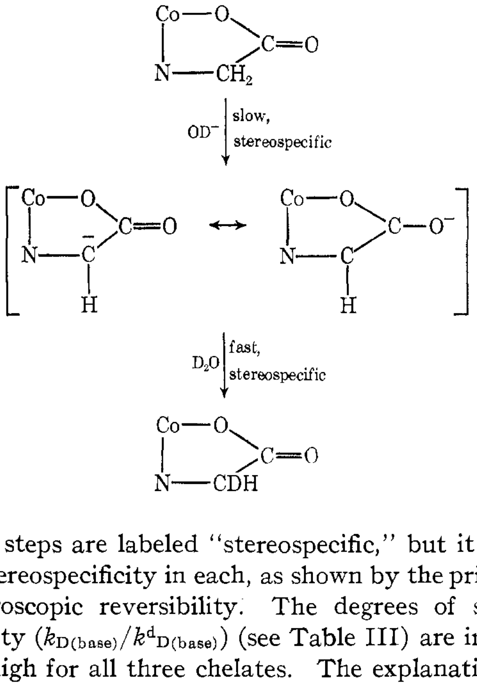


Figure 5.—Nmr spectra of $Co^{III}CyDTA^-$ in alkaline D_2O (pD 10) at 36°.

SCHEME I



Both steps are labeled "stereospecific," but it is the same stereospecificity in each, as shown by the principle of microscopic reversibility. The degrees of stereospecificity ($k_{D(base)}/k^d_{D(base)}$) (see Table III) are impressively high for all three chelates. The explanation for stereospecificity must lie in the protection of H_B in II from solvent molecules by the ethylenediamine "backbond" in EDDA. The large values of $\Delta S^{\ddagger}$ (Table IV) are characteristic of reactions of oppositely charged ions in aqueous solution[9] and are attributed to the release of water molecules of hydration in forming the transition state.

Mechanism of Acid-Catalyzed Deuteration.—The mechanism of stereospecific acid-catalyzed deuteration is represented by

$$\mathrm{CoYH_A} + \mathrm{D_3O^+} \rightleftharpoons \mathrm{CoYH_AD^+} + \mathrm{D_2O} \quad \text{(fast)} \qquad (13)$$

$$\mathrm{CoYH_AD^+} + \mathrm{D_2O} \xrightarrow{k_D} \mathrm{CoYD} + \mathrm{HD_2O^+} \quad \text{(slow)} \qquad (14)$$

$$\mathrm{CoYD} + \mathrm{D_2O} \longrightarrow \mathrm{CoYD_AD^+} + \mathrm{OD^-} \quad \text{(fast)} \qquad (15)$$

$$\mathrm{CoYD_AD^+} + \mathrm{D_2O} \rightleftharpoons \mathrm{CoYD_A} + \mathrm{D_3O^+} \quad \text{(fast)} \qquad (16)$$

The magnitude of the primary isotope effect, $k_{\mathrm{D(acid)}}/k_{\mathrm{H(acid)}}$ (Table II), indicates that the rate-controlling step is the rupture of a C–H bond.[10] The amount of stereospecificity is approximately one-tenth as large in acid-catalyzed deuterations as it is in base-catalyzed deuterations (Tables II and III).

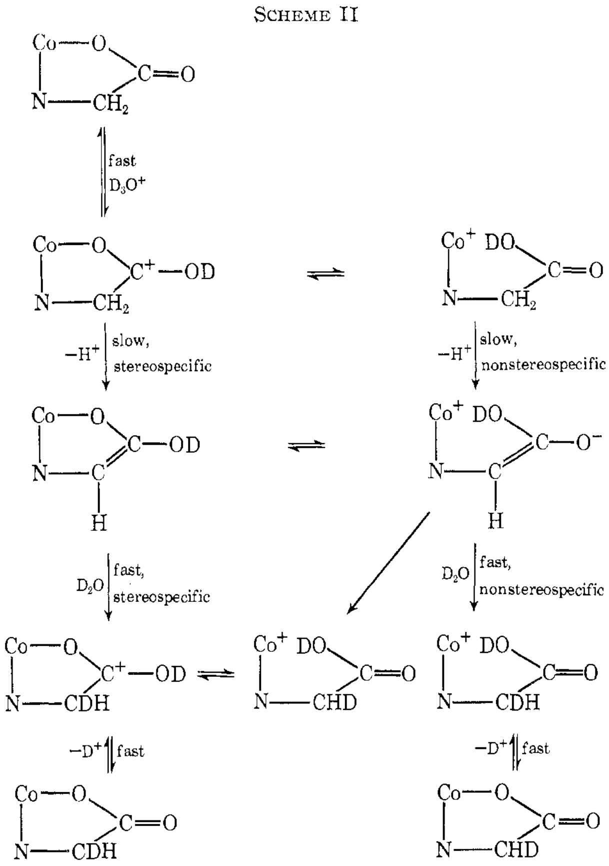
The degree of protection of H_B from solvent molecules by the ethylenediamine "backbone" should not depend strongly upon the method of catalysis in the present case, and thus we propose that an additional nonstereospecific deuteration pathway occurs in the acid-catalyzed mechanism shown in Scheme II.

The first step is the rapid deuteration of the carbonyl group followed by slow rupture of the C–H bond, yielding an enol. In the stereospecific pathway, first proposed by Terrill and Reilley,[5] the enol reacts consecutively with several solvent molecules, yielding the complex in which only H_A is deuterated. The strength of the cobalt-oxygen bond is presumably decreased by protonation, and an appreciable fraction of the protonated species may undergo rupture of the cobalt–oxygen bond. Such species would have free rotation about the α-carbon–nitrogen bond and could undergo deuteration of both α-hydrogens (H_A and H_B) with equal or almost equal facility in a nonstereospecific pathway.

The rate constants for acid-catalyzed deuteration reported herein are $^1/_{10}$ to $^1/_{30}$ as large as that reported for $\mathrm{Co^{III}}$-CyDTA.[5] This difference is due in part to the opposite ionic charges of $\mathrm{Co^{III}}$-CyDTA (−1) and the chelates reported herein (+1). That is, $\mathrm{Co^{III}}$-CyDTA should have greater affinity for protons (greater pK_a), which drives the first step (eq 13) to the right. This explanation is supported by the rate constants for base catalysis of $\mathrm{Co^{III}}$-CyDTA which are quite similar for the CyDTA and EDDA chelates.

Structures of *trans*-$\mathrm{Co^{III}}$EDDA(dmen)$^+$ and *trans*-$\mathrm{Co^{III}}$EDDA(deen).—The nmr spectra in Figures 2 and 3 show the presence of only one kind of methyl group in $\mathrm{Co^{III}}$-EDDA(dmen) and only one kind of ethyl group in $\mathrm{Co^{III}}$-EDDA(deen), indicating the preservation of the C_2 axes in both compounds. There are four conformational isomers of the *trans*-dmen or -deen chelates which preserve the C_2 axis. The alkyl groups can be either "axial" or "equatorial," and in each of these cases the ethylenediamine ring can be puckered in two different ways. Because of the kinetic inertness of Co–N bonds, the existence of at most two rapidly interconverting conformers is indicated.

SCHEME II



The fact that the diamine $\mathrm{N{-}CH_2{-}CH_2{-}N}$ protons exhibit a singlet in the spectrum of the en chelate and that the corresponding protons in the dmen and deen chelates exhibit AA′BB′ patterns supports the previous interpretation[6a] that the diamine molecule in the en chelate undergoes rapid interconversion between the two puckered forms. The two puckered forms of the diamine in the dmen and deen chelates are of different energies, and, according to molecular models, the conformation shown in II is the most favorable.

The rate constants also support a structure in which the alkyl groups are remote from α-hydrogens. Surprisingly, the rates of deuteration follow the order deen > dmen > en, indicating that, instead of hindering the reaction rates, the alkyl groups actually enhance them.

Chemical Shifts of α-Hydrogen Atoms.—In the reported acid-catalyzed deuteration of $\mathrm{Co^{III}}$-CyDTA,[5] the upfield out-of-plane α-hydrogen atom becomes deuterated most rapidly. Figure 5 shows that for base-catalyzed deuteration, it is also the upfield proton which undergoes deuteration most rapidly, in contrast to the $\mathrm{Co^{III}}$-EDDA(diamine) chelates, where the downfield α-hydrogens become deuterated most rapidly under both acid and base catalysis. It is evident from the present study that the ethylenediamine "backbone" alone is sufficient barrier to provide a high degree of stereo-

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[9] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley & Sons, Inc., New York, N. Y., 1958, p 132.

[10] L. Melander, "Isotopic Effects on Reaction Rates," Ronald Press Co., New York, N. Y., 1960, p 125.

specificity. The barrier in Co^{III}-CyDTA can only be larger, and thus we support the previously assigned stereochemistry for the deuteration of Co^{III}-CyDTA.[5] The downfield shift of H_A and the upfield shift of H_B in Co^{III}-CyDTA (as compared to, say, Co^{III}-EDTA) can be understood in terms of steric compression, as reported by Winstein, *et al.*, for half-cage compounds,[11] with the same result as the electron orbital interaction suggested by Terrill and Reilley.[5] The cyclohexane ring proton H_4 (see I) in Co^{III}-CyDTA must strongly compress H_B, producing a downfield shift in H_B and an upfield shift in H_A. The compressed hydrogens in half-cage compounds essentially attempt to occupy the same space, and it appears that H_B and H_4 in Co^{III}-CyDTA are likewise extremely close in space. Therefore, in addition to C–N anisotropic shielding, at least one additional factor, that of steric compression, may be necessary in order to account for chemical shifts of α-hydrogen atoms in aminocarboxylate chelates.

The present studies should prove useful in the assignment of metal chelate nmr spectra, in the synthesis of deuterated ligands, and in further studies of stereospecific substitutions in metal chelates.

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[11] S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

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The Solid-Phase Dehydration of *trans*-$[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$ and *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$

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Received May 14, 1968

The dehydration of *trans*-$[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$ and *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$ has been studied both in static air and *in vacuo*. The kinetics of the single-step loss of HCl and H_2O were investigated by measuring mass loss on a thermobalance and were correlated with changes in crystal structure and with microscopic observations of the solids. The ethylenediamine complex loses H_2O and HCl from all faces of the solid. The propylenediamine complex resists loss from the (100) faces, presumably because of the packing of the complex cations. The activation energy for dehydration of both compounds *in vacuo* was found to be 16 kcal mol^{-1} and independent of particle size. A suggestion is made as to the activation process.

Introduction

Many years ago Werner[1] reported that *trans*-$[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$[2] loses HCl and H_2O and isomerizes to *cis*-$[Co((\pm)pn)_2Cl_2]Cl$ when heated to about 100° in the solid phase. Recent preliminary studies[3] of this reaction have indicated that isomerization occurs only while HCl and H_2O are being evolved from the solid. As a first stage in an attempt to determine the mechanism of this *trans* to *cis* isomerization, a detailed study of the dehydration process was carried out.

It is of interest in this regard that the dehydration of *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$ proceeds without formation of the *cis* isomer. In solution, ethylenediamine complexes normally behave in very much the same fashion as their propylenediamine analogs. Furthermore, *trans*-$[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$ and *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$ have very similar crystal structures.[4-6] Therefore a study was also made of the dehydration of this ethylenediamine complex. Although several studies of complexes containing the $H_5O_2^+$ ion have been reported recently, no detailed studies of the dehydration of these compounds have appeared in the literature.

Experimental Section

Both *trans*-$[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$[7] and *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$[8] were prepared as described elsewhere except racemic propylenediamine was used in place of the resolved amine in the first preparation.[9] Both compounds were analyzed for chloride by titration with $AgNO_3$ and for total HCl and H_2O by weight loss accompanying heating to 110–120° on a thermobalance. *Anal.* Calcd for $[Co((\pm)pn)_2Cl_2](H_5O_2)Cl_2$: Cl, 36.76; HCl + H_2O, 18.80. Found: Cl, 36.9; HCl + H_2O, 18.56. Calcd for $[Co(en)_2Cl_2](H_5O_2)Cl_2$: Cl, 39.64; HCl + H_2O, 20.27. Found: Cl, 39.9; HCl + H_2O, 20.35.

Mass loss studies were conducted in static air and under reduced pressure (0.1–0.3 torr) using a Cahn Model RG recording electrobalance mounted in a Cahn vacuum bottle. Samples ranged from 15 to 20 mg in mass. Temperature control was maintained (to within ±0.5° during isothermal studies) by use of an F & M Scientific Model 240 power proportioning temperature programmer. The temperature immediately above the sample was measured with a calibrated iron–constantan thermocouple with a 0° cold junction. The rate of dehydration of both compounds studied appeared to be affected by the thickness of

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[1] A. Werner and A. Frohlich, *Chem. Ber.*, **40**, 2228 (1907).

[2] This compound is frequently formulated as *trans*-$[Co((\pm)pn)_2Cl_2]Cl\cdot HCl\cdot 2H_2O$. However, recent studies indicate that it contains $H_5O_2^+$ and Cl^- ions. The same is true of *trans*-$[Co(en)_2Cl_2](H_5O_2)Cl_2$.

[3] H. E. LeMay, Jr., unpublished results.

[4] A. Nakahara, Y. Saito, and H. Kuroya, *Bull. Chem. Soc. Japan*, **25**, 331 (1952).

[5] J. M. Williams, *Inorg. Nucl. Chem. Letters*, **3**, 297 (1967).

[6] Y. Saito and H. Iwasaki, *Bull. Chem. Soc. Japan*, **35**, 1131 (1962).

[7] J. C. Bailar, Jr., C. A. Stiegman, J. H. Balthis, Jr., and E. H. Huffman, *J. Am. Chem. Soc.*, **61**, 2402 (1939).

[8] J. C. Bailar, Jr., *Inorg. Syn.*, **2**, 222 (1946).

[9] A later preparation was carried out using *l*-propylenediamine. Preliminary dehydration studies on this compound have shown it to behave in the same fashion as the compound prepared from the racemic amine.