

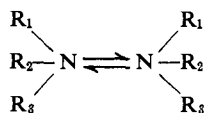
Racemization and Deuteration at an Asymmetric Nitrogen Center

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Abstract: The $(\text{Co}(\text{NH}_3)_4(\text{CH}_3\text{NHCH}_2\text{COO}))^{2+}$ ion has been resolved into its optical forms and the rates of racemization (k_r) and deuteration (k_D) at the asymmetric nitrogen center have been measured. The ratio k_D/k_r is ~ 4000 , which implies that the configuration about the N atom is retained most of the time the proton is off the quaternary N site. The result is analogous to some carbanion chemistry, and the possible reasons for retention are discussed. An analysis of the rates and equilibria involved suggests that the rate of inversion of the "tertiary amine" is $\sim 10^4 \text{ sec}^{-1}$.

The consistent failure of attempts to resolve tertiary amines of the type $\text{R}_1\text{R}_2\text{R}_3\text{N}$ has been attributed to the rapid inversion process. More recently the work



of Loewenstein, Meiboom, and Grunwald, *et al.*,¹⁻⁶ has shown the lability of the protons attached to nitrogen in NH_4^+ , CH_3NH_3^+ , $(\text{CH}_3)_2\text{NH}_2^+$, and $(\text{CH}_3)_3\text{NH}^+$ with respect to exchange with protons in the solvent water. In fact a combination of both factors may account for the apparent lack of optical stability of quaternary ammonium salts of the form $\text{R}_1\text{R}_2\text{R}_3\text{HN}^+$. However when one of the alkyl substituents on the quaternary ammonium ion is replaced by a metal ion such as Co(III), the rates of N-proton exchange with solvent water are enormously reduced. For example, the results of Anderson, *et al.*,⁷ indicate that $t_{1/2}$ for the deuteration of $(\text{Co}(\text{NH}_3)_6)^{3+}$ ion in 1 M D^+ is about 10^6 min. This large effect leads to the possibility of stabilizing a proton on an asymmetric nitrogen atom coordinated to a metal ion.

The possibility of resolving a quaternary ammonium salt where one of the substituents was a metal ion was already entertained by Meisenheimer, *et al.*,⁸ in 1924. These workers claimed to have resolved the $(\text{Co}(\text{en})_2\text{sarcosine})^{2+}$ ion (en = ethylenediamine) where the configurations about both the cobalt and the nitrogen are asymmetric (see Figure 1). Isomers were described in which the mutarotation of the activity due to the coordinated sarcosine was observed. However efforts^{9,10} to reproduce the mutarotation have failed and the reasons for this and their implications will be presented in a subsequent paper. One complicating issue

in the $(\text{Co}(\text{en})_2\text{sarcosine})^{2+}$ system is the presence of the two asymmetric centers. The present article is concerned with the resolution of the $(\text{Co}(\text{NH}_3)_4\text{sarcosine})^{2+}$ ion, Figure 2, in which the sole source of activity arises from the asymmetric N atom coordinated to Co(III), and with the rates and mechanism of deuteration and racemization of the "quaternary ammonium" ion.

Experimental Section

Racemic Sarcosinatotetraamminecobalt(III) Nitrate. Sarcosine (3.6 g) was dissolved in NaOH (35 ml, 1.0 N), $(\text{Co}(\text{NH}_3)_4\text{Cl} \cdot \text{H}_2\text{O})\text{SO}_4$ (11.1 g) was added, followed by ammonia (3 ml, 2.0 N), and the solution was stirred and heated to 70° . After 90 min, the solution was filtered, NH_4NO_3 (10 g) was added, and the solution was cooled overnight at 5° . The precipitate of $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ was filtered off and was washed with aqueous-methanol (1:1) and methanol (6.8 g, 50% yield). The complex was recrystallized from warm water with NH_4NO_3 and dried under vacuum. *Anal.* Calcd for $(\text{Co}(\text{NH}_3)_4\text{CH}_2\text{NHCH}_2\text{COO})(\text{NO}_3)_2$: C, 10.62; H, 5.35; N, 28.91. Found: C, 10.75; H, 5.7; N, 28.75.

Racemic Sarcosinatotetraamminecobalt(III) Chloride. $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ (5 g) was added to ice cold 5 N HCl (50 ml) and stirred for several minutes. The solution was filtered and methanol (100 ml) was added. After 15 min, the crude $(\text{Co}(\text{NH}_3)_4\text{sar})\text{Cl}_2$ was filtered off and washed with methanol (3.2 g, air-dried). The complex was recrystallized several times from warm 1 N HCl by adding NH_4Cl then methanol and dried under vacuum. *Anal.* Calcd for $(\text{Co}(\text{NH}_3)_4\text{CH}_2\text{NHCH}_2\text{COO})\text{Cl}_2 \cdot 0.5\text{H}_2\text{O}$: C, 12.21; H, 6.49; N, 23.74. Found: C, 12.25; H, 6.48; N, 23.44.

Resolution of $(\text{Co}(\text{NH}_3)_4\text{sar})\text{Cl}_2 \cdot 0.5\text{H}_2\text{O}$. (All rotations were measured in a 1-dm tube unless stated otherwise.) The complex (5.72 g) was dissolved in HClO_4 (40 ml, 0.001 M), $(+)\text{Na}(\text{Co}(\text{en})(\text{C}_2\text{O}_4)_2) \cdot \text{H}_2\text{O}$ (3.36 g) was added, and the solution was allowed to stand for 30 min. The diastereoisomer $(-)(\text{Co}(\text{NH}_3)_4\text{sar})(+)\text{Co}(\text{en})(\text{C}_2\text{O}_4)_2\text{Cl} \cdot \text{H}_2\text{O}$ was filtered off and washed with methanol and dried (4.0 g). *Anal.* Calcd for $(\text{Co}(\text{NH}_3)_4\text{CH}_2\text{NHCH}_2\text{COO})(\text{Co}(\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2)(\text{C}_2\text{O}_4)_2\text{Cl} \cdot \text{H}_2\text{O}$: C, 19.21; H, 5.02; N, 17.43. Found: C, 19.20; H, 5.40; N, 17.57.

l-Sarcosinatotetraamminecobalt(III) Nitrate. The diastereoisomer was ground in a mortar with NH_4NO_3 (6.0 g) in 0.001 M HClO_4 (10 ml) and the $(-)(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ was filtered off and fractionally crystallized from HClO_4 (0.001 M) with NH_4NO_3 into three fractions having $[\alpha]^{25\text{D}}$ values of -31 , -51 , and -51° (0.1% solution in 0.001 M HClO_4); $[\alpha]^{25\text{D}} = -220^\circ$ for the pure isomer. *Anal.* Calcd for $(\text{Co}(\text{NH}_3)_4\text{CH}_2\text{NHCH}_2\text{COO})(\text{NO}_3)_2$: C, 10.62; H, 5.35; N, 28.91. Found: C, 10.80; H, 5.63; N, 29.20.

D-Sarcosinatotetraamminecobalt(III) Nitrate. The filtrate from the diastereoisomer was treated with NH_4NO_3 and several fractions of the complex nitrate were collected of which the most soluble fraction was the most active $[\alpha]^{25\text{D}} + 48^\circ$, $[\alpha]^{25\text{D}} + 206^\circ$. *Anal.* Calcd for $(\text{Co}(\text{NH}_3)_4\text{CH}_2\text{NHCH}_2\text{COO})(\text{NO}_3)_2$: C, 10.62; H, 5.35; N, 28.91. Found: C, 10.61; H, 5.41; N, 29.31.

Racemization rates were followed at 436 m μ using a Perkin-Elmer 141 polarimeter. The initial rotations were of the order 0.250° , and the readings were accurate to $\pm 0.002^\circ$. All reactions were followed for at least two half-lives and some were taken to $10 \times t_{1/2}$ when the complex showed no rotation between 700 and 400

- (1) A. Loewenstein, *J. Phys. Chem.*, **67**, 1728 (1963).
- (2) A. Loewenstein and S. Meiboom, *J. Chem. Phys.*, **27**, 1067 (1957).
- (3) M. I. Emerson, E. Grunwald, and R. A. Kromhout, *ibid.*, **33**, 547 (1960).
- (4) E. Grunwald, P. J. Karabatsos, R. A. Kromhout, and E. L. Purlee, *ibid.*, **33**, 556 (1960).
- (5) E. Grunwald, *J. Phys. Chem.*, **67**, 2208 (1963).
- (6) M. I. Emerson, E. Grunwald, M. L. Kaplan, and R. A. Kromhout, *J. Am. Chem. Soc.*, **82**, 6307 (1960).
- (7) J. S. Anderson, H. V. A. Briscoe, and N. L. Spoor, *J. Chem. Soc.*, 361 (1943).
- (8) J. Meisenheimer, L. Angermann, H. Holsten, and E. Kiderlen, *Ann.*, **438**, 217 (1924).
- (9) F. Basolo, Ph.D. Thesis, University of Illinois.
- (10) D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, to be published.

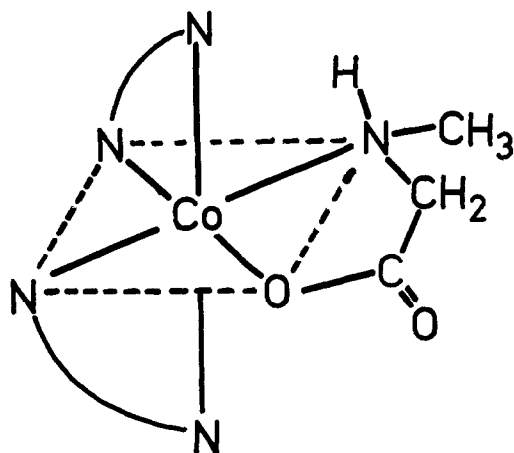


Figure 1. The structure of the $(\text{Co}(\text{en})_2\text{sar})^{2+}$ ion.

$m\mu$. The rotatory dispersion (RD) curves were obtained using the same instrument coupled to a Zeiss monochromator and a quartz-halogen lamp.

Deuteration rates were followed using a Perkin-Elmer R10 nmr spectrometer (see Results for discussion of pmr spectra), and a typical set of data is shown in Figure 5. Sodium trimethylsilylpropane sulfonate was used as a standard reference.

N-Deuterated $(-)(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$. $(-)(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ ($[\alpha]_{436}^{25} -221^\circ$, 0.22 g) was dissolved in 10.0 ml of D_2O containing 0.00315 g of HClO_4 (70%). The "pD" of this solution was 2.75. The solution was left at 33.3° for 17 hr when the complex was precipitated with ethanol and collected and dried under vacuum. The pmr spectrum showed a singlet at 2.4 ppm, and the infrared spectrum gave a strong absorption peak at 2400 cm^{-1} (ND stretch); $[\alpha]_{436}^{25} -211^\circ$ for an 0.1% solution in 0.01 M HClO_4 . The racemic complexes were deuterated in D_2O .

Protonation of Deuterated $(-)(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$. The deuterated complex (0.11 g) dissolved in dilute HClO_4 , pH 2.33 (for the solution) was left at 33.3° for 17 hr and then treated as above; $[\alpha]_{436}^{25} -221^\circ$ for an 0.1% solution in 0.01 M HClO_4 . The pmr spectrum gave a doublet at 2.4 ppm with no sign of the singlet peak, however the infrared spectrum still showed the ND stretching band at 2400 cm^{-1} but its intensity was much less than for the deuterated sample and this was attributed to residual deuteration in some of the ammonia groups.

Results

The rates of racemization of the $(\text{Co}(\text{NH}_3)_4\text{sarcosine})(\text{NO}_3)_2$ isomers were measured in buffer solutions at constant ionic strength over the pH range 4.44 to 8.02 at various temperatures (Table I). The isomers finally showed no rotation at any wavelength. In every kinetic run the plot of $\log \alpha_{436}$ against time gave a

Table I. Rate Constants for the Racemization of $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ at 30.3° in 0.1 M Acetate Buffers at an Ionic Strength $\mu = 0.1$

pH	$k_{r(\text{obsd})} \times 10^4 \text{ sec}^{-1}$	$k_r = k_{r(\text{obsd})}/\text{OH}^-$, $M^{-1} \text{ sec}^{-1} \times 10^{-4}$
4.80	0.134	2.12
5.31	0.407	2.00
5.83	1.28	1.89
6.62	7.75	1.86
5.80	1.17	1.85 ^b
5.83	0.215 (20.2°)	
	0.595 (26.0°)	
	3.12 (35.2°)	
	7.55 (40.2°)	

^a Complex concentration $3.3 \times 10^{-3} M$. ^b Measured in 0.01 M acetate buffer with NaCl added to $\mu = 0.1$.

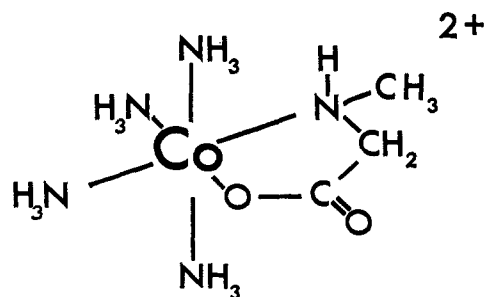


Figure 2. The structure of the $(\text{Co}(\text{NH}_3)_4\text{sar})^{2+}$ ion.

straight line for at least three half-lives, from which the pseudo-first-order rate constant $k_{r(\text{obsd})}$ (sec^{-1}) was obtained and thence the derived rate constant k_r ($M^{-1} \text{ sec}^{-1}$), taking into account the OH^- or OD^- concentration, respectively.

The rates of racemization measured at 30.30° in 0.1 M acetate buffers over a pH range of 1.8 units (Table I) gave a rate law

$$R = k_r(\text{complex})(\text{OH}^-)$$

and dilution of the buffer concentration at constant ionic strength did not affect the rate. The unimportance of the general base catalysis and catalysis by the solvent molecules is consistent with previous observations¹¹ in this type of system. The slight decrease in k_r as the acetate ion concentration increased might be attributed to ion pairing and this effect is discussed more fully in the section dealing with the phosphate buffer.

Table II. Rate Constants for the Racemization of $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ ($3.3 \times 10^{-3} M$) in Buffers (0.1 M) at 30.3° , $\mu = 0.2$

pH	$k_{r(\text{obsd})} \times 10^4 \text{ sec}^{-1}$	$k_r \times 10^{-4} M^{-1} \text{ sec}^{-1}$
HPO ₄ ²⁻ , H ₂ PO ₄ ⁻		
4.44	0.0377	1.37
5.15	0.168	1.19
5.42	0.315	1.20
5.93	0.872	1.02
6.43	2.07	0.770
6.96	5.37	0.589
6.96	5.37	0.589 ^a
7.16	8.55	0.590
7.61	19.3	0.474
6.38	3.40	1.45 ^b
7.03	14.1	1.32 ^b
Phthalate-NaOH		
6.06	0.452	0.393
β, β' -Dimethylglutaric acid-NaOH		
7.16	15.6	1.08
N-Ethylmorpholine		
7.15	22.0	1.56
sym-Collidine-HCl		
5.97	1.44	1.54
7.14	20.5	1.49
Imidazole-HCl		
6.23	2.20	1.29
6.23	2.20	1.29
6.71	6.95	1.35
7.15	20.7	1.47
7.15	21.3	1.51

^a Complex concentration $1.5 \times 10^{-3} M$. ^b Phosphate concentration 0.01 M. NaCl added to $\mu = 0.2$.

(11) H. Block and V. Gold, *J. Chem. Soc.*, 966 (1959).

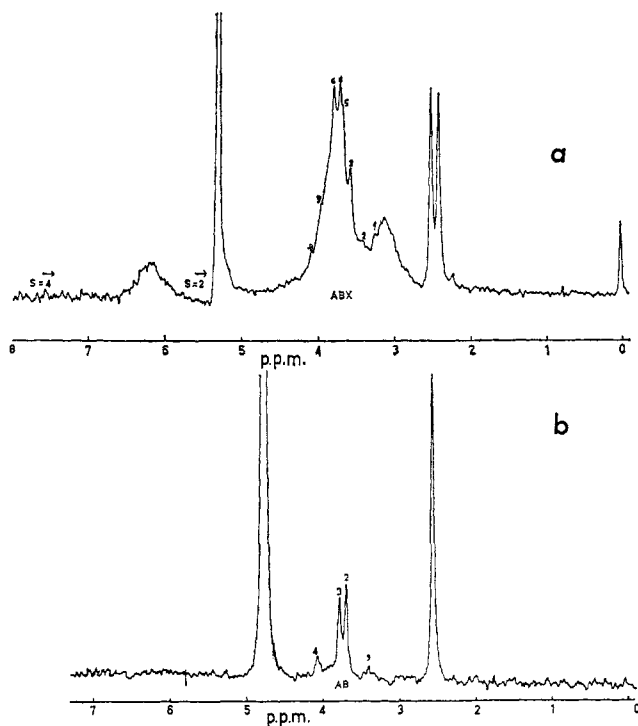
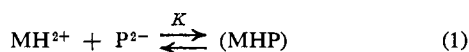


Figure 3. The 60-Mc pmr spectra of $(\text{Co}(\text{NH}_3)_4\text{CH}_3\text{NHCH}_2\text{COO})\text{Cl}_2$ (a) and $(\text{Co}(\text{ND}_3)_4\text{CH}_3\text{NDCH}_2\text{COO})\text{Cl}_2$ (b). TPSNa standard, Perkin-Elmer R10 spectrometer.

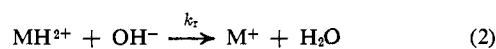
The rate of racemization was independent of the complex concentration.

The temperature parameters for the rate constants were determined in the range 20–40° at pH 5.83 (Table I) where $E_{a(\text{obsd})} = 32.5 \pm 0.5$ kcal/mole, $E_a = 19.2$ kcal/mole, and $\Delta S^\ddagger = 21$ eu. Acetate buffers show only very small changes in pH (<0.3%) with change in temperature in this region¹² and the pH was considered constant.

The racemization of the active complex was followed in a number of buffers other than acetate at an ionic strength $\mu = 0.2$ and the results are given in Table II. It can be seen that for all the buffers the value of k_r is less than that obtained for the acetate buffer, and in the phosphate buffers a substantial deviation from the "acetate" rate law is observed. The derived rate constant, k_r , decreases substantially in the higher pH region. Also k_r increases as the phosphate buffer is diluted at constant ionic strength. This anion-retardation effect is unusual and deserves some discussion. A possible explanation of the effect can be given if the complex reacts with the HPO_4^{2-} anion to give an ion pair which no longer reacts with OH^- at a rate comparable to that of the original complex. This possibility is consistent with our more recent observations¹³ that the rate of racemization decreases with decreasing charge on the complex. The data can be analyzed in terms of the reactions



and



(12) "pH Scale," British Standards Specification, 1647 (1950).

(13) D. A. Buckingham, L. Marzilli, and A. M. Sargeson, to be published.

where MH^{2+} is the sarcosine complex and (MHP) is the "inert" ion pair $(\text{Co}(\text{NH}_3)_4\text{sarcosine})^{2+} \cdot \text{HPO}_4^{2-}$. These reactions lead to a rate expression of the form

$$k_{\text{obsd}} = \frac{k_r(\text{OH}^-)}{k(\text{P}) + 1}$$

The values of $(\text{P}) = (\text{HPO}_4^{2-})$ were calculated from the pK 's of H_3PO_4 ,¹⁴ and the expression was solved using k_{obsd} at pH 5.93 and 7.16 (at 30.3°). This leads to $k_r = 1.1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ and $K = 19$, and the observed and calculated rate constants are compared in Table III for the pH range studied. The agreement is reasonable except perhaps for the 0.01 M buffer solutions.

Table III. Calculated and Observed Rate Constants for the Racemization of $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ in Phosphate Buffers at 30.3°, $\mu = 0.2$

	pH	$k_{r(\text{obsd})}$, sec ⁻¹	$k_{r(\text{calcd})}$, sec ⁻¹
0.1 M $\text{H}_2\text{PO}_4^- \cdot \text{HPO}_4^{2-}$	4.44	3.77×10^{-6}	3.07×10^{-6}
	5.15	1.68×10^{-5}	1.56×10^{-5}
	5.42	3.15×10^{-5}	2.85×10^{-5}
	5.93	8.72×10^{-5}	8.72×10^{-5}
	6.43	2.07×10^{-4}	2.37×10^{-4}
	6.96	5.37×10^{-4}	6.05×10^{-4}
	7.16	8.55×10^{-4}	8.55×10^{-4}
0.01 M $\text{H}_2\text{PO}_4^- \cdot \text{HPO}_4^{2-}$	7.61	1.93×10^{-3}	1.93×10^{-3}
	6.38	3.38×10^{-4}	2.57×10^{-4}
	7.03	1.41×10^{-3}	1.17×10^{-3}

The value of the derived rate constant ($k_r = 1.1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$), however, is only about half that obtained for the acetate system ($k_r = 1.9 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$), and this poor agreement casts some doubt on the validity of the ion-association mechanism. It is pertinent to add that no change in the visible spectrum of the complex was observed in 2 days in the phosphate buffer, pH 7.61, at 30°. This fact precludes the possibility that decomposition could account for the deviations observed in the rates for the phosphate buffers.

The ionic strength effect for the racemization was small. In 0.1 M phosphate buffer at pH 6.62 and 30.3°, k_r was 5.60×10^3 and $6.67 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ at $\mu = 1.14$ and 0.2, respectively.

The observed activation energies and entropies calculated from the data in Table IV at pH 5.93 and 6.96 were $E_a = 33.0$ kcal/mole and $\Delta S^\ddagger = 21$ eu and

Table IV. Temperature Dependence of the Racemization of $(\text{Co}(\text{NH}_3)_4\text{sar})(\text{NO}_3)_2$ in 0.1 M Phosphate Buffers, $\mu = 0.2$

pH	Temp, °C	$k_{r(\text{obsd})}$ $\times 10^4$ sec ⁻¹
5.93	20.2	0.131
	30.3	0.872
	35.7	2.22
	40.3	5.02
6.96	20.2	0.868
	25.5	2.35
	30.3	5.05

(14) R. G. Bates, *J. Res. Natl. Bur. Std.*, **30**, 129 (1943).

$E_a = 32.0$ kcal/mole and $\Delta S^\ddagger = 20$ eu, respectively, and they agree closely with the values obtained in the acetate buffers. The correspondence suggests that the same process was being observed in both media.

Pmr Spectra of $(\text{Co}(\text{NH}_3)_4\text{sarcosine})\text{Cl}_2$. Since pmr spectroscopy was used to follow the rate of deuteration of the N-H proton some discussion of the spectra is necessary. The spectra (Figure 3a,b) were obtained for 10% solutions of the salt in 1 M D_2SO_4 and in D_2O . The former figure shows the spectrum of the complex ion undeuterated while in the latter all the N centers are deuterated. In Figure 3a, the broad absorption at 6.2 ppm (one proton) is assigned to the sarcosine N-H and the broad absorption (14 protons) between 4.5 and 2.7 ppm is attributed to the four ammonia groups and the $>\text{CH}_2$ group of the coordinated sarcosine. The two protons of the latter moiety are not equivalent, and the resulting AB system is further coupled to the proton on the adjacent N atom to give an eight-line ABX spectrum superimposed on the broad NH_3 peaks. The coupling constant obtained from the separation of lines 1-3, 2-4, 5-7, and 6-8 in Figure 3a is 18 cps. The NH_3 region resolved approximately into one peak due to nine protons and another due to three protons, indicating that three NH_3 groups have the same chemical shift while the other is different. We suggest that the ammonia group which is *trans* to the coordinated oxygen atom is shielded more effectively than those adjacent, and the signal therefore appears at higher field.

The doublet at 2.4-2.5 ppm is assigned to the methyl group split by the sarcosine N-H proton. In the D_2O spectrum (Figure 3b) where the N-H is deuterated the doublet collapses to a singlet (two protons) and the ABX system reverts to a simple AB doublet pair (two protons) centered about 3.5 ppm ($J_{AB} = 18$ cps and $\delta_A - \delta_B = 16$ cps). The complex ion then has the constitution $(\text{Co}(\text{ND}_3)_4\text{CH}_2\text{NDCH}_2\text{COO})^{2+}$.

The above interpretation of the pmr spectra of $(\text{Co}(\text{NH}_3)_4\text{sarcosine})^{2+}$ ion is supported by the spectra of $(\text{Co}(\text{en})_2\text{sarcosine})\text{Cl}_2$ in 1 M D_2SO_4 and in D_2O (Figure 4a,b). Integration of the absorptions in Figure 4 allows the analysis shown in Table V.

Table V. Pmr Spectra in 1 M D_2SO_4 of $(\text{Co}(\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2)_2\text{CH}_3\text{NHCH}_2\text{COO})\text{Cl}_2$

Ppm	Integrated intens	Assignment
6.3-5.8 (broad band)	1	Sarcosine N-H
5.7-4.9 (broad band)	6	en NH_2
4.8-4.0 (broad band)	2	en NH_2
4.2-3.2 (ABX system)	2	Sarcosine CH_2 coupled with NH
3.0-2.7 (broad singlet)	8	en CH_2
2.6-2.5 (doublet)	2	CH_3 coupled with sarcosine NH

The eight-line ABX pattern in Figure 4a is better resolved than in the tetraammine complex and gives $J_{AB} = 18$ cps. It collapses to the doublet pair of the AB system when the complex is deuterated (Figure

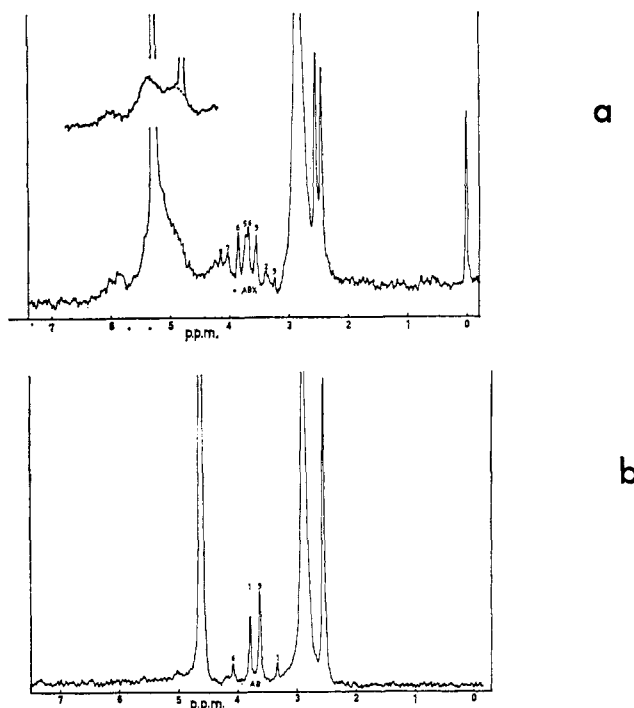


Figure 4. The 60-Mc pmr spectra of $(\text{Co}(\text{en})_2\text{CH}_2\text{NHCH}_2\text{COO})\text{Cl}_2$ (a) and $(\text{Co}(\text{N-D}_4\text{-en})_2\text{CH}_2\text{NDCH}_2\text{COO})\text{Cl}_2$ (b). TPNa standard, Perkin-Elmer R10 spectrometer.

4b), for which $J_{AB} = 18$ cps and $\delta_A - \delta_B = 21$ cps. In D_2O the broad N-H and NH_2 signals disappear but the broad singlet at 2.9 ppm due to the ethylenediamine CH_2 groups sharpened in the D_2O solution and the doublet formerly at 2.6-2.5 ppm was replaced by a singlet at 2.55 ppm. These changes are consistent with the assignments made from the spectrum in 1 M D^+ , if it is assumed that all the protons attached to N exchange with D^+ and the ion is in the form $(\text{Co}(\text{ND}_2\text{CH}_2\text{CH}_2\text{ND}_2)_2\text{CH}_3\text{NDCH}_2\text{COO})^{2+}$.

The rate of deuteration of the sarcosine N-H in the $(\text{Co}(\text{NH}_3)_4\text{sarcosine})^{2+}$ ion was measured by the rate of growth of the singlet up through the doublet at 2.45 ppm (Figure 5), and the pseudo-first-order rate constants were obtained from the plot of $\log(\text{peak height}_\infty - \text{peak height})$ against time. This procedure gave straight-line plots over at least two half-lives. The observed rate constants $k_{\text{D}(\text{obsd})}$ are given in Table VI.

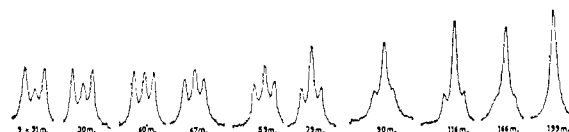


Figure 5. Deuteration at the sarcosine N atom in $(\text{Co}(\text{NH}_3)_4\text{-CH}_2\text{NHCOO})\text{Cl}_2$ (in 8.8×10^{-4} N D_2SO_4 for a 10% solution of the complex at 33.3°).

It would appear that the rate law for the deuteration of the N-H group

$$R = k_{\text{D}}(\text{complex})(\text{OD}^-)$$

is substantially obeyed and that $k_{\text{D}} = 1.2 (\pm 0.3) \times 10^8 \text{ M}^{-1} \text{ sec}^{-1}$ in D_2O at 33.3° . This is to be compared

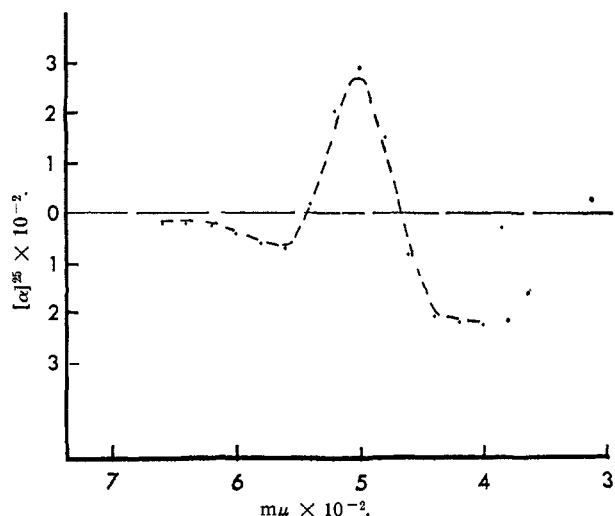


Figure 6. Rotatory dispersion curves for (—)(Co(NH₃)₄sar)(NO₃)₂ and for the deuterated complex - - - -.

with the rate constant for racemization at 33.3° and $\mu = 1$ in H₂O when $k_r = 3.3 \times 10^4 M^{-1} \text{sec}^{-1}$. The small racemization rate constant implies that racemization occurs during one exchange in ~ 4000 and that deuteration takes place substantially with retention of configuration. To confirm these results the optically active deuterated complex was isolated and then re-protonated with retention of configuration. The rotatory dispersion (RD) curves for the protonated and deuterated isomers are given in Figure 6. The infrared and pmr spectra of the optically pure starting material (A), the deuterated sample (B), and the re-protonated sample (C) were also measured (Table VII).

Table VI. Rate Constants for the Deuteration of the Sarcosine NH in (Co(NH₃)₄sar)Cl₂ at 33.3°, $\mu = 1$ in D₂O^a

	$k_{D(\text{obsd})}$, sec ⁻¹	k_D , M ⁻¹ sec ⁻¹
0.05 M KHP ^b	1.2×10^{-3}	12×10^7 ^c
$8.8 \times 10^{-4} N D_2SO_4$	2.2×10^{-4}	12×10^7
$3.40 \times 10^{-3} N D_2SO_4$	5.8×10^{-5}	11×10^7 ^d
$1.92 \times 10^{-2} N D_2SO_4$	1.2×10^{-5}	10×10^7 ^d
$1.00 \times 10^{-2} N DCl$	1.9×10^{-5}	12×10^7
$3.13 \times 10^{-2} N DCl$	5.7×10^{-6}	12×10^7
$6.00 \times 10^{-2} N DCl$	2.8×10^{-6}	11×10^7
$3.13 \times 10^{-2} N DCl$	1.3×10^{-5}	26×10^7 ^e
$3.13 \times 10^{-2} N DCl$	4.7×10^{-6}	96×10^7 ^f

^a $K_{D_2O} = 1.54 \times 10^{-15}$; see R. Kingerley and V. K. La Mer, *J. Am. Chem. Soc.*, **63**, 3260 (1941). ^b KHP = potassium hydrogen phthalate. ^c Calculated from the measured "pH" of the solution using the empirical method of P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960). ^d Calculated using $K_a(D_2SO_4) = 4.7 \times 10^{-3}$; see M. H. Lietzke and R. W. Stoughton, *ibid.*, **67**, 652 (1963). ^e Measured at 40.0°. ^f Measured at 50.0°.

Table VII. The Deuteration and Re-protonation of (—)₄₃₆(Co(NH₃)₄sar)(NO₃)₂ at 33.3°

	A	B	C
	$\xrightarrow[9 \times t_{1/2}]{D_2O^+}$		$\xrightarrow[20 \times t_{1/2}]{H_2O^+}$
[α] ²⁵ ₄₃₆	−221°	−211°	−221°
Pmr signal at 2.4 ppm	Doublet	Singlet	Doublet
Infrared absorption, cm ⁻¹	3250	3250	3250
KBr		2400	2400

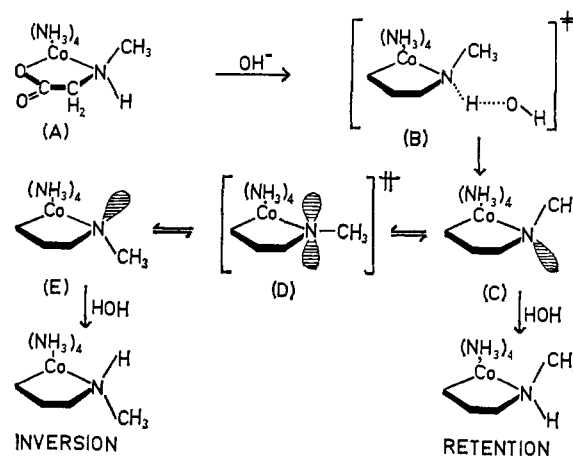


Figure 7. Mechanism for the deuteration and racemization of the (Co(NH₃)₄sar)²⁺ ion.

The sharp singlet in the pmr spectrum of the deuterated sample B showed that the sarcosine NH was fully deuterated and that it was re-protonated in the conversion to C. The infrared spectrum of C indicated however that some of the ammonia groups which had been partly deuterated in the conversion of A to B were not completely re-protonated in C. For each step, A → B and B → C, the recovery of the product was >90% and since the optically pure complex is more soluble than the racemic form, the specific rotation figures recorded indicate the complex retains its optical purity. The difference between the specific rotation of the protonated and deuterated forms is approximately consistent with the increase in molecular weight for the deuterated complex.

The observed activation energy for the deuteration was 28 ± 1 kcal/mole, whence $E_a = 14$ kcal/mole and $\Delta S^\ddagger = 21$ eu, and a comparison of the activation parameters and the rate constants for the deuteration of other cobalt(III) complexes is relevant. Palmer and Basolo¹⁵ have investigated the rates of proton exchange for D⁺ with complexes of the type (Co(NH₃)₅X)²⁺ (where X⁻ = F⁻, Cl⁻, Br⁻, NO₂⁻) and the rate constants were in the range $k = 0.11-0.38 \times 10^6 M^{-1} \text{sec}^{-1}$ at 25° with $E_{a(\text{obsd})} = 26-30$ kcal/mole. From these it might be expected that the NH₃ groups in (Co(NH₃)₄sarcosine)²⁺ would exchange with D⁺ at 33.3° with rate constants of the order $k = 1-4 \times 10^6 M^{-1} \text{sec}^{-1}$; that is the exchange would be slower than the observed sarcosine N-H exchange $k_D = 1.2 \pm 0.3 \times 10^8 M^{-1} \text{sec}^{-1}$ but faster than the racemization rate $k_r = 3.3 \times 10^4 M^{-1} \text{sec}^{-1}$. The infrared results (Table VII) qualitatively confirm this estimate.

Isotope Effects. The rate of deuteration of the (Co(NH₃)₄NHCH₃CH₂COO)²⁺ ion and the rate of protonation of (Co(ND₃)₄NDCH₃CH₂COO)²⁺ ion were approximately the same ($t_{1/2} = 15.5 \pm 1$ and 16 ± 1 hr, respectively, at 33.3° in $1.92 \times 10^{-2} M D_2SO_4$ and H₂SO₄). However, the OD⁻ concentration is approximately sevenfold less than the OH⁻ concentration, which means that the abstraction of the proton in the former instance by OD⁻ is considerably faster than the removal of the deuteron in the latter instance by OH⁻. While this result is consistent with the expected isotope effect a complete analysis is complicated by the fact that the

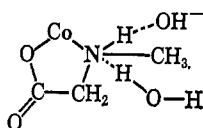
(15) J. W. Palmer and F. Basolo, *J. Phys. Chem.*, **64**, 778 (1960).

ammonia protons or deuterons also exchange and also give rise to a secondary isotope effect.

The isotope effect for racemization was small. At OH^- and OD^- concentrations of $4.17 \times 10^{-8} M$ at 30.3° $k_r(\text{H}_2\text{O}) = 1.87 \times 10^{-4} M^{-1} \text{sec}^{-1}$ and $k_r(\text{D}_2\text{O}) = 2.50 \times 10^{-4} M^{-1} \text{sec}^{-1}$. This is consistent with the fact that the racemization process does not involve the abstraction of a proton in the rate-determining step. Only solvent, secondary, and equilibrium isotope effects should appear and these would be expected to be small.

Discussion

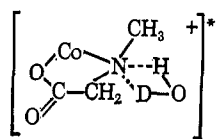
The same rate law holds substantially for both racemization and deuteration processes and is consistent with the proposal that the rate-determining step is the abstraction of the sarcosine N-H proton by OH^- or OD^- to give the intermediate C as shown in Figure 7. The large difference between the rate of racemization and the rate of deuteration under the same conditions (~ 4000) implies that the intermediate C preserves its original configuration most of the time before and after it reacts with the solvent molecule to revert to A. It is clear from the RD curves (Figure 6) that under suitable conditions deuteration takes place for all practical purposes with full retention of configuration and this excludes attack by OH^- at the sarcosine N atom on the side opposite to the proton and also a synchronous process such as



Both processes conform with the observed rate law but conflict with the rotatory dispersion evidence in that they lead to an inversion of the configuration about the N atom.

The racemization-rate law does not exclude the proposal that the abstraction of a proton from a coordinated ammonia group leads to rupture of the Co-sarcosine N bond and thus racemization. However, this means the racemization and sarcosine deuteration rates are unrelated. There is also no evidence for the proposal that the removal of a proton from one ammonia group leads to a more labile adjacent NH_2R group, nor is there any evidence that the complex changes its constitution during the deuteration or racemization. Moreover the general base hydrolysis results obtained with similar complexes indicate that the Co-O bond would sever in preference to the Co-N bond. For these reasons this process is excluded from further consideration.

The rate law is also consistent with the formation of an ion pair between $(\text{Co}(\text{NH}_3)_4\text{sar})^{2+}$ and OD^- leading to a transition state of the form

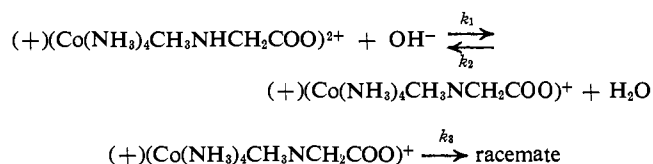


and also to retention of configuration. The dissociated ion-solvent pair then leads to racemization. It follows that this proposal may modify or replace the mechanism in Figure 7 since a contribution to retention by the

interchange of D for H in the ion pair cannot be excluded. The ion-association studies of Caton and Prue¹⁶ indicate that the association constant for $\text{Co}(\text{NH}_3)_6^{3+}$ and OH^- is 8.3 at 25° , $\mu = 0.2$, and therefore the value for the present system should be even less, and only a small part of the complex will be present as the ion pair. However, this does not lead to a distinction between the mechanisms. In the absence of other evidence, we prefer to assume that the "strongly dissociating" solvent does not allow the ion pair to persist and that the racemization and deuteration processes are related through a common intermediate.

It is apparent from the observed activation energies for deuteration (28 kcal/mole) and racemization (32.5 kcal/mole) that the rate difference resides substantially in this factor since ΔS^\ddagger is essentially the same for both processes. This implies that intermediate C requires additional energy to achieve the activated planar condition about the N atom (D) before racemization can be accomplished. The barrier to racemization is difficult to estimate since the dissociation constants for the removal of a proton from $\text{Co}(\text{III})$ amines probably are less than 10^{-14} in most instances and have not been measured. Certainly the $(\text{Co}(\text{NH}_3)_4\text{sarcosine})^{2+}$ ion has no measurable pK_a in aqueous solution. However the height of the barrier must exceed 5 kcal/mole, the difference between E_a for deuteration and racemization assuming a common intermediate C. The $E_{a(\text{obsd})}$ values are reduced by ΔH for the dissociation of D_2O and H_2O , respectively¹⁷ ($\Delta H_{\text{H}_2\text{O}} = 13.3$ kcal/mole, $\Delta H_{\text{D}_2\text{O}} = 14.3$ kcal/mole), to obtain E_a for the racemization and deuteration reactions. Under the conditions used here the exchange rate is fast at the sarcosine N atom when racemization is being measured.

The retention of configuration around an N atom having a "lone pair" of electrons is an unusual result. The frequency of inversion of the NH_3 molecule is enormously fast in the gas phase and although the inversion rate of a tertiary amine of the form $\text{RR}'\text{R}''\text{N}$ should be much slower in solution these compounds have never been resolved. Recent pmr studies of unsymmetrical amines¹⁸ and amides¹⁹ suggest that the inversion rate constant is of the order of 10^5sec^{-1} for the amines and 10^3sec^{-1} for the amides. If the data for the complex are analyzed according to the reaction scheme



Then for the steady-state condition $k_{\text{obsd}} = (k_1 k_3 / k_2) \cdot (\text{OH}^-)$, since $k_2 \gg k_3$ and K_a for the complex is about $10^{-14} - 10^{-15}$.²⁰ It follows that the derived rate constant $k_r = (K_a / K_w)(k_3)$ and if K_a and K_w are approximately equal then $k_3 \sim 10^4 \text{sec}^{-1}$, which is close to the inversion rates recorded for the organic amines.

(16) J. A. Caton and J. E. Prue, *J. Chem. Soc.*, 671 (1956).

(17) H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.*, **36**, 973 (1940); W. F. K. Wynne-Jones, *ibid.*, **32**, 1397 (1936).

(18) M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, **85**, 1882 (1963).

(19) T. H. Siddall and C. A. Prohaska, *Nature*, **208**, 582 (1965).

(20) R. G. Pearson and F. Basolo, *J. Am. Chem. Soc.*, **78**, 4878 (1956).

The retention of configuration may arise from the Co(III)-sarcosine ring system. If it is required that the configuration around the N atom in the transition state D (Figure 7) (CNCo bond angle $\sim 109^\circ$) must acquire the normal sp^2 (bond angles $\sim 120^\circ$) planar state before racemization can occur, the bond angles and atomic positions in the ring system must rearrange before D is reached. However, this type of factor does not appear to be grossly important in the inversion of N-ethylethylenimine where the ring C-N-C angle is 60° .²¹ Also it seems unlikely that the small conformational effects in the Co(III)-sarcosine ring could dominate the stereochemical course of the exchange since it can be expected that the ring system will be

close to planarity and the $\text{O}=\text{C}-\text{C}$ moiety should not be more than 6° out of the $\text{O}=\text{C}-\text{N}-\text{Co}$ plane.²²

Alternatively the lone pair of electrons in C may be stabilized in a particular configuration by hydrogen bonding to the nearest coordinated ammonia in the apical position. Space-filled Leybold models suggest that a proton on the ammonia group is sufficiently close for a tenuous attachment, enough to allow the incoming solvent molecules to react with retention. In addition, the lone pair (H bonded or not) is immediately exposed to the surrounding solvent while attack by water from the rear is hindered by both the methyl group and a coordinated ammonia molecule.

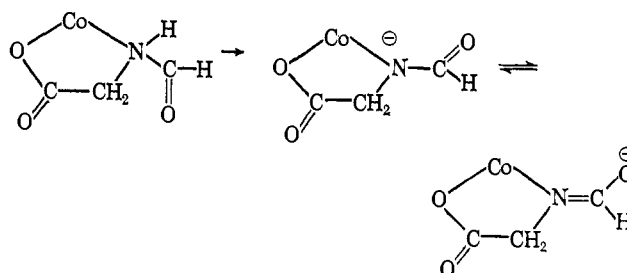
Experiments to check on the significance of these possibilities are at present being carried out. The effect of electronegative groups in the 1 and 6 positions and the effect of a total absence of groups in these positions is being examined along with other systems where the conformational effects are more pronounced. The instance where the asymmetric moiety arises from the coordination of a monodentate ligand is also being examined.

Some observations in the analogous field of carbanion chemistry suggest that racemization might be more favored if the planar sp^2 state can be stabilized. For

(21) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(22) H. C. Freeman, M. R. Snow, I. Nitta, and K. Tomita, *Acta Cryst.*, **17**, 1463 (1964).

example using coordinated N-formylglycine



the racemization and deuteration rates could be equal. In the present system while there is delocalization in the vicinity of the carbonyl group extending perhaps to the Co atom, there is no extensive delocalization in the region of the N atom.

It is suggested that the nonbonding electrons on the metal ion do not affect the degree of retention since they are essentially evenly distributed in "domains." However, the effect of variation in the metal ion is being examined since the metal has a substantial effect on the basicity of the protons. An intriguing factor in these studies is the large difference between Co(III) and an alkyl group as a substituent on the N atom. The rates of N-proton exchange are substantially lower for the former under equivalent conditions even though the Co(III) group frequently leads to a higher positive charge on the ion. The results suggest that the N atom is more basic with the Co(III) than with the alkyl substituent, and they agree with the analogy between $(\text{NH}_3)_5\text{CoOH}_2^{3+}$ ($K_a \sim 10^{-6}$) and HOH_2^+ ($K_a \sim 55$). Some contribution to this difference may arise from the difficulty in extracting H^+ from the "plasma" of the t_{2g} electrons of the metal ion. However, an alternative explanation for this lack of reactivity of N protons in coordination complexes has been offered in terms of the ligand field stabilization energies introduced by the metal ion.²³

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(23) J. W. Palmer and F. Basolo, *J. Inorg. Nucl. Chem.*, **15**, 279 (1960).