Metal Complexes of Amino Acids. XV. Racemization and Deuteration of Bis(biguanide)sarcosinatocobalt(III) Complex

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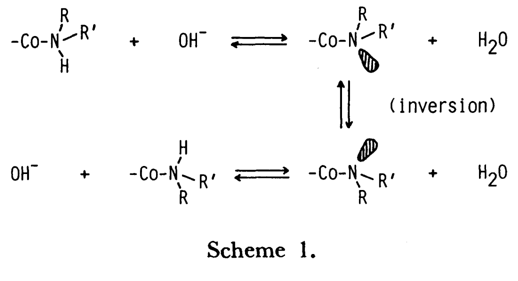
All four possible optical isomers ($\Delta(S)$, $\Delta(R)$, $\Lambda(S)$, and $\Lambda(R)$) of the bis(biguanide)sarcosinatocobalt(III) ion, $[Co(sar)(Hbg)_2]^{2+}$, were isolated and characterized by their absorption, CD, and ^1H NMR spectra. The optically active $[Co(sar)(Hbg)_2]^{2+}$ ion in a basic aqueous solution showed a loss of CD intensity due to racemizations at both the chiral cobalt center ($\Delta\rightleftarrows\Lambda$) and the asymmetric nitrogen center ($R\rightleftarrows S$). The rate of an $R\rightleftarrows S$ change was ca. 50 times slower than that of a $\Delta\rightleftarrows\Lambda$ change. The rate of deuteration (H→D) at the asymmetric nitrogen atom was slower than those of other sarcosinato complexes. The ratio k_{H-D}/k_{inv} was about 10^2—10^3. The rates of racemization ($\Delta\rightleftarrows\Lambda$) for the $[Co(amino acidato)(Hbg)_2]^{2+}$ ion series increased in the order L-valine<L-alanine<glycine<sarcosine.

The tris(biguanide)cobalt(III) ion, $[Co(Hbg)_3]^{3+}$ [where biguanide (imidodicarbonimidic diamide) has the chemical formula $NH_2C(=NH)NH-C(=NH)NH_2$], is more reactive compared with $[Co(N)_6]$ type complexes containing amino and/or imino nitrogens as donor atoms, such as $[Co(en)_3]^{3+}$.[1] The racemization of an optically active $[Co(Hbg)_3]^{3+}$ complex was investigated in an aqueous solution and a twist mechanism has been proposed on the basis of the fact that the value of the probability factor was very small from the point of view of a unimolecular type change.[2] However, another type study was conducted for *fac*-$[Co(Ph-Hbg)_3]^{3+}$, where Ph-Hbg is $C_6H_5-NHC(=NH)NH-C(=NH)NH_2$, in which a bond-rupture mechanism was proposed regarding the intramolecular racemization process.[3] Previously, we found that optically active $[Co(am)(Hbg)_2]^{2+}$ complexes (am denotes amino acidate anion) racemize more rapidly compared to $[Co(Hbg)_3]^{3+}$ and $[Co(am)_3]$ complexes.[4,5] $[Co(am)(Hbg)_2]^{2+}$ complexes are of interest from the point of view of the reaction mechanism.

On the other hand, the kinetics of racemization and deuteration at an asymmetric nitrogen in an aqueous solution have been studied for several cobalt(III) complexes containing sarcosine (Hsar)[6,7] or *N*-methylethylenediamine (Me-en).[8] For these complexes, deuteration rates were several orders of magnitude faster than racemization rates, and both reaction processes could be described by a similar rate law, $R=k[OH^-][complex]$. A mechanism which has been proposed by Buckingham and Sargeson to account for these results is shown in Scheme 1.[8] The reactivities (proton exchange and inversion) at secondary nitrogen centers in *mer*-$[Co(dien)_2]^{3+}$[9] and $[CoX(trenen)]^{n+}$[10] complexes were also studied and are discussed in connection with racemization and deuteration at the nitrogen centers of the complexes described above.



Scheme 1.

$[Co(sar)(Hbg)_2]^{2+}$ ion provides four possible optically active isomers ($\Delta(R)$, $\Lambda(R)$, $\Delta(S)$, and $\Lambda(S)$) arising from two chiral centers (cobalt and sarcosinate nitrogen). In this paper we describe the isolation of the four isomers, the kinetics of racemization at these two chiral centers, and the kinetics of deuteration at the nitrogen centers of coordinated sarcosinates. In addition, we also report on rate data regarding racemization for $[Co(am)(Hbg)_2]^{2+}$ complexes, where am is glycinate, L-alaninate, and L-valinate anions.

Experimental

Preparation, Separation, and Optical Resolution. Bis(biguanide)sarcosinatocobalt(III) Chloride: An isomeric mixture of bis(biguanide)sarcosinatocobalt(III) perchlorate was prepared according to the method described in a previous paper.[4]

About six grams of $[Co(sar)(Hbg)_2](ClO_4)_2$ was dissolved in warm water (ca. 50 cm^3). The solution was poured into a SP-Sephadex C-25 column (4.7 cm×90 cm, Ba^{2+} form) and the adsorbed band was developed with a 0.2 M (M=mol dm^{-3}) $BaCl_2$ solution. Developing was repeated on the same column using a micropump until the adsorbed band completely separated into two bands (E-1 and E-2 in the order of effluence). Each eluting solution from the two bands was concentrated to a small volume under reduced pressure at 35—40 °C. Then, methanol was added to the concentrated solution and deposited barium chloride was filtered off. The filtrate was again evaporated and the remaining $BaCl_2$ was eliminated by the addition of methanol to the concentrated solution by the same procedure as described above. Finally, the methanolic solution was evaporated almost to dryness and the complex was extracted with hot methanol. A crude complex, obtained by evaporating the extracted solution to dryness, was recrystallized from a small amount of water after adding a mixture of methanol–ethanol (1:3). The deposited crystals were filtered and washed with a mixture of methanol–ethanol (1:3) containing a little water and then with ethanol. The crystals were dried in air.

$(-)^{\mathrm{CD}}_{480}$-$\Delta(S)$- and $(+)^{\mathrm{CD}}_{480}$-$\Delta(R)$-[Co(sar)(Hbg)$_2$]Br$_2\cdot$C$_2$H$_5$OH$\cdot$H$_2$O: A solution containing 5.0 g (0.0075 mol) of K_2Sb_2(d-tart)$_2\cdot 3H_2O$ in ca. 150 cm^3 of warm water was slowly added to an aqueous solution containing 6.3 g (0.015 mol) of the E-1 racemate, $\Delta(S)\Delta(R)$-[Co(sar)(Hbg)$_2$]Cl$_2$, in ca. 150 cm^3 of water without scratching the side of the vessel. The mixed solution was kept in a refrigerator for 1—2 h. The diastereomer (sparingly soluble in water) became deposited in red needle-like crystals and was filtered and washed with ice-water until the color of the filtrate turned almost colorless. They were then dried in air. The yield was 6.1 g.

The diastereomer (powdered in a mortar) was suspended in ca. 150 cm^3 of warm water together with a Dowex 1-X8 resin (Br$^-$ form, 150 cm^3 in wet). The mixture was stirred vigorously until the color of the solution changed to red, and then filtered. The same procedure was repeated several times until the diastereomer completely disappeared. All of the red solutions were combined and concentrated using a rotary evaporator. Methanol, ethanol, and a few drops of concentrated NaBr solution were added to this concentrated solution. Red needle-like crystals were filtered, washed with 80% ethanol, and dried under reduced pressure. The crystals were recrystallized from a little warm water upon adding a few drops of concentrated NaBr solution, methanol, and ethanol (in this order). The yield was 2.7 g. Found: C, 18.52; H, 4.91; N, 27.02%. Calcd for CoC$_9$H$_{28}$N$_{11}$O$_4$Br$_2$=$(-)^{\mathrm{CD}}_{480}$-$\Delta(S)$-[Co(sar)(Hbg)$_2$]Br$_2\cdot$C$_2$H$_5$OH$\cdot$H$_2$O: C, 18.86; H, 4.92; N, 26.88%. $\Delta\varepsilon_{560}$=+3.275, $\Delta\varepsilon_{480}$=−5.349.

The $(+)^{\mathrm{CD}}_{480}$-$\Delta(R)$ isomer was obtained as follows. The filtrate obtained upon a separation of the above diastereomer was evaporated under reduced pressure at 35—40 °C. A large amount of methanol was added to the concentrated solution. Deposited potassium chloride was filtered off and the filtrate was again evaporated to dryness. The obtained crude complex was dissolved in water, and then the chloride salt was converted to a bromide salt using a short column containing a Dowex 1-X8 resin (Br$^-$ form). After a concentration of the bromide solution, a crude complex was obtained upon the addition of methanol and ethanol to the concentrated solution. Recrystallization was carried out by the same method as that for the $(-)^{\mathrm{CD}}_{480}$-$\Delta(S)$ isomer. The yield was 1.6 g. $(+)^{\mathrm{CD}}_{480}$-$\Delta(R)$-[Co(sar)(Hbg)$_2$]Br$_2\cdot$C$_2$H$_5$OH$\cdot$H$_2$O. $\Delta\varepsilon_{560}$=−3.350, $\Delta\varepsilon_{480}$=+5.405.

$(-)^{\mathrm{CD}}_{485}$-$\Delta(R)$- and $(+)^{\mathrm{CD}}_{485}$-$\Delta(S)$-[Co(sar)(Hbg)$_2$]Br$_2\cdot$H$_2$O: The optical resolution of the E-2 racemate ($\Delta(R)\Delta(S)$-[Co(sar)(Hbg)$_2$]Cl$_2$) was made by the same method used for the E-1 isomer. The $(-)^{\mathrm{CD}}_{485}$-$\Delta(R)$ isomer was obtained from the less soluble diastereomer. Found: C, 15.97; H, 4.32; N, 29.27%. Calcd for CoC$_7$H$_{22}$N$_{11}$O$_3$Br$_2$=[Co(sar)(Hbg)$_2$]Br$_2\cdot$H$_2$O: C, 15.95; H, 4.21; N, 29.23%. $\Delta\varepsilon_{563}$=+2.851, $\Delta\varepsilon_{485}$=−5.754. For the $(+)^{\mathrm{CD}}_{485}$-$\Delta(S)$ isomer, $\Delta\varepsilon_{563}$=−2.932, $\Delta\varepsilon_{485}$=+5.814.

Other complexes examined here were prepared and resolved according to a method described in the literature[4] and were found to be analytically pure. $(-)^{\mathrm{CD}}_{478}$-[Co(gly)(Hbg)$_2$]Br$_2\cdot$1.5H$_2$O ($\Delta\varepsilon_{478}$=−4.79), $(-)^{\mathrm{CD}}_{473}$-[Co(L-ala)(Hbg)$_2$]I$_2\cdot$H$_2$O ($\Delta\varepsilon_{473}$=−4.81), $(+)^{\mathrm{CD}}_{475}$-[Co(L-ala)(Hbg)$_2$]Br$_2$ ($\Delta\varepsilon_{475}$=+5.19), $(-)^{\mathrm{CD}}_{473}$-[Co(L-val)(Hbg)$_2$]Cl$_2\cdot$1.5H$_2$O ($\Delta\varepsilon_{473}$=−5.67), $(+)^{\mathrm{CD}}_{475}$-[Co(L-val)(Hbg)$_2$]Br$_2\cdot$3.5H$_2$O ($\Delta\varepsilon_{475}$=+5.28).

Racemization. All the chemicals used were of a reagent grade, and deionized water was degassed before use. The racemization reactions (at the chiral cobalt center and at the asymmetric nitrogen center) were followed spectrophotometrically with the use of a JASCO J-22 spectropolarimeter. A reaction vessel with a jacket and a water-jacketed cell mounted in a cell holder of the spectropolarimeter were thermostated at a constant temperature (±0.1 °C) with circulating water from a constant-temperature bath. During the experiments, the temperatures of the reaction vessel and the cell were checked with a thermistor thermometer (Takara D-221), and the pH of the reaction solution in the vessel with a Toa TSC-10A pH meter. The reaction was started by adding a buffer solution (5.0 cm^3) with stirring to the complex solution (20.0 cm^3) in the reaction vessel. About 3 cm^3 of this solution was quickly transfered to the cell in order to record the loss of the CD intensity at a suitable wave-length (485 nm for the sarcosinato complex and 475 nm for the glycinato, L-alaninato, and L-valinato complexes). The following conditions were set. For the racemization at the chiral cobalt center; pH 7.5—9.0 (Na$_2$HPO$_4$–KH$_2$PO$_4$, H$_3$BO$_3$–NaCl–Na$_2$B$_4$O$_7$, and NaHCO$_3$–Na$_2$CO$_3$ buffers), complex concentration (1.2—3.6)$\times 10^{-3}$ M, ionic strength 0.15—1.0 (NaClO$_4$), temperature 25—35 °C. For the racemization at the asymmetric nitrogen center of the [Co(sar)(Hbg)$_2$]$^{+2}$ complex; pH 9.0—10.1 (NaHCO$_3$–Na$_2$CO$_3$ buffer), complex concentration (2.0—3.0)$\times 10^{-3}$ M, ionic strength 0.15 (NaClO$_4$), temperature 30—40 °C.

For both of the racemization processes, plots of $\ln[(L_0-L_{eq})/(L_t-L_{eq})]$ vs. time, where L represents CD intensity at the subscripted time, gave straight lines over three half-lives, from which the pseudo-first-order rate constant k' (s^{-1}) were obtained. Analyses of the kinetic data were carried out on an NEC-9801F computer using the least-squares methods. In each of the rate analyses, the value of the standard error was within ±2% of the rate constant.

Deuteration. The deuteration reactions were carried out for both the $\Delta(S)$- and $\Delta(R)$-[Co(sar)(Hbg)$_2$]$^{2+}$ complexes in D$_2$O solutions buffered with D$_3$BO$_3$–NaCl–Na$_2$B$_4$O$_7$, and were followed with a ^{1}H-NMR spectrometer (JEOL MH-100). All the solutions were 0.104 M in complex concentration. The reaction was started by an addition of 1.0 cm^3 of Na$_2$B$_4$O$_7$–D$_2$O(0.0015 M) to the complex solution in 1.0 cm^3 of D$_3$BO$_3$(0.2 M)–NaCl(0.045 M)–D$_2$O in a thermostat at a constant temperature (40, 45, or 50 °C). About 0.5 cm^3 aliquot of the reaction solution was quickly transfered to a NMR tube which was kept in the probe of the spectrometer throughout the run at a constant temperature (40, 45, or 50 °C). The pD of the reaction solution in the vessel was checked using a Toa TSC-10A pH meter. The formulae, pD=pH+0.4[11] and $K_{\mathrm{D_2O}}$=0.195K_{w}[12], were used to evaluate [OD$^-$].

pH Titration. In order to obtain the pK_a value for the [Co(am)(Hbg)$_2$]$^{2+}$ complex, the complex solution (1.00$\times 10^{-2}$ M) was titrated with carbonate-free sodium hydroxide in an atmosphere of nitrogen at 30.0 °C using a

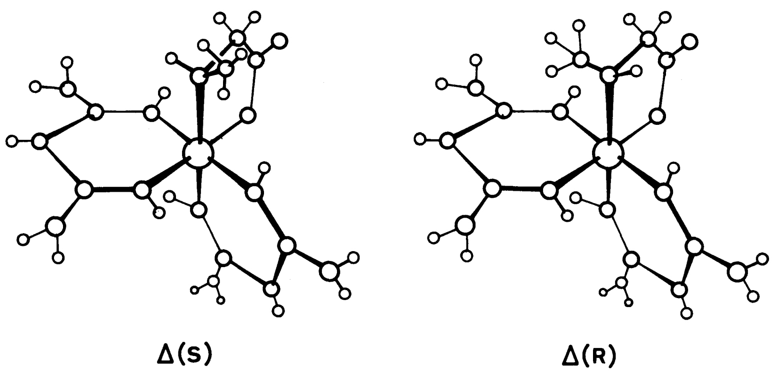


Fig. 1. Structures of $\Delta(S)$- and $\Delta(R)$-$[Co(sar)(Hbg)_2]^{2+}$.

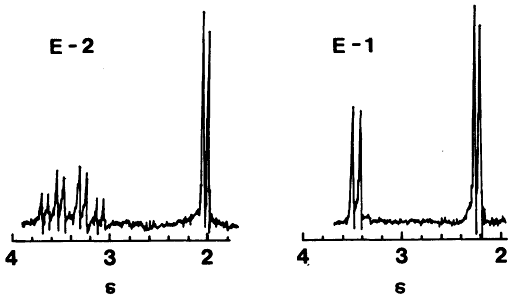


Fig. 2. ¹H NMR spectra of the E-1 ($\Delta(S)\Lambda(R)$) and E-2 ($\Delta(R)\Lambda(S)$) racemates of $[Co(sar)(Hbg)_2]^{2+}$ in D_2O.

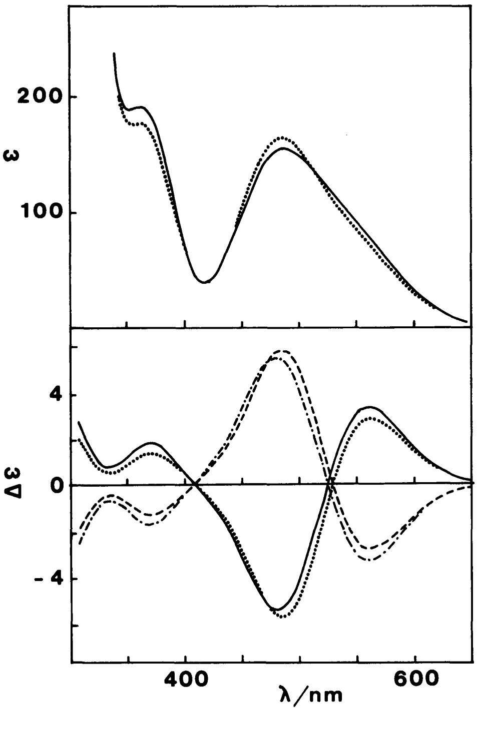


Fig. 3. Absorption and CD spectra of $[Co(sar)(Hbg)_2]^{2+}$ in water: $(-)^{CD}_{480}$-E-1 (——), $(+)^{CD}_{480}$-E-1 (—·—), $(-)^{CD}_{485}$-E-2 (······), $(+)^{CD}_{485}$-E-2 (----).

Toa TSC-10A pH meter. The obtained titration data were analyzed using the method of Noyes.[13)]

Results and Discussion

Four Isomers of the Bis(biguanide)sarcosinatocobalt(III) Ion. The $[Co(sar)(Hbg)_2]^{2+}$ ion, which contains a chiral cobalt and an asymmetric nitrogen, gives four possible optical isomers ($\Delta(S)$, $\Delta(R)$, $\Lambda(S)$, and $\Lambda(R)$). Figure 1 shows two of the isomers, $\Delta(S)$ and $\Delta(R)$, that are different from each other only with respect to their configurations about the nitrogen atom. The cobalt-biguanide ring is a six-membered plane with π-electrons[14–16)] and the cobalt-sarcosine ring is almost planar (within 6°).[17)] The N-CH_3 group of the sarcosinato ligand is different in a chemical environment regarding the $\Delta(S)$ and $\Delta(R)$ configurations. The N-CH_3 group is perpendicular to one of the biguanide planes in the $\Delta(R)$ configuration, but is coplanar to that plane in the $\Delta(S)$ configuration. A similar situation is found for the $\Lambda(R)$ and $\Lambda(S)$ isomers which are antipodes of the $\Delta(S)$ and $\Delta(R)$, respectively.

The ¹H NMR spectra of the E-1 and E-2 racemates (measured in D_2O) are given in Fig. 2. As the deuteration of the NH proton of the sarcosinato ring is slow, even in neutral D_2O, N-CH_3 proton resonance is observed as a doublet signal due to coupling with the NH proton at 2.25 ppm (J=6 Hz) for E-1 and at 2.02 ppm (J=6 Hz) for E-2. The methyl signal of E-2 lies in a higher field than that of E-1. Hence, in E-2 the methyl group should be in a shielding position with respect to one of the biguanide rings with π-electrons; it occupies a position perpendicular to the biguanide plane. This indicates that the E-1 and E-2 racemates can be assigned to $\Delta(S)\Lambda(R)$ and $\Delta(R)\Lambda(S)$, respectively.

The -CH_2- moiety of the sarcosinato ring in E-1 gives a doublet signal centered at 3.48 ppm (J=8 Hz) while coupling with an NH proton. After a deuteration of the NH proton, the doublet signal changes to a singlet one, indicating that the two protons of -CH_2- are in same magnetic environment. However, the two protons of the -CH_2- moiety in E-2 are in a different environment, and the resulting AB system is further coupled to the proton on the adjacent nitrogen atom to give an eight-line ABX spectrum: H_A=3.61, H_B=3.21 ppm ($J_{H_A\text{-}H_B}$=17, $J_{NH\text{-}H_A}$=7, and $J_{NH\text{-}H_B}$=8 Hz).

The absorption and CD spectra for isomers of the $[Co(sar)(Hbg)_2]^{2+}$ complex are shown in Fig. 3 and their numerical data are listed in Table 1. The E-1 and E-2 racemates, which are diastereomeric to each other, show a slightly different absorption spectra in the first d-d band region. A similar behavior was observed for the diastereomers of the $[Co(sar)(en)_2]^{2+}$ complex.[7] In the first absorption band region, each of the four isomers of $[Co(sar)(Hbg)_2]^{2+}$ shows two CD bands of opposite signs with higher intensity in the higher energy side (Fig. 3). The CD curves of the $(-)^{CD}_{480}$-E-1 and $(+)^{CD}_{480}$-E-1 isomers are exactly symmetrical to each other, indicating that these isomers are in an enantiomeric relationship. The same relationship is found between the $(-)^{CD}_{485}$-E-2 and $(+)^{CD}_{485}$-E-2 isomers. Previously, the Λ configuration was assigned to $[Co(am)(Hbg)_2]^{2+}$ complexes which exhibited the same CD sign patterns as shown for the $(+)^{CD}_{480}$-E-1 and $(+)^{CD}_{485}$-E-2 isomers in Fig. 3.[4] From the CD and ^1H NMR data, the structures of four isomers of the isolated $[Co(sar)(Hbg)_2]^{2+}$ complex were assigned as follows: $(-)^{CD}_{480}$-E-1, $\Delta(S)$; $(+)^{CD}_{480}$-E-1, $\Lambda(R)$; $(-)^{CD}_{485}$-E-2, $\Delta(R)$; $(+)^{CD}_{485}$-E-2, $\Lambda(S)$.

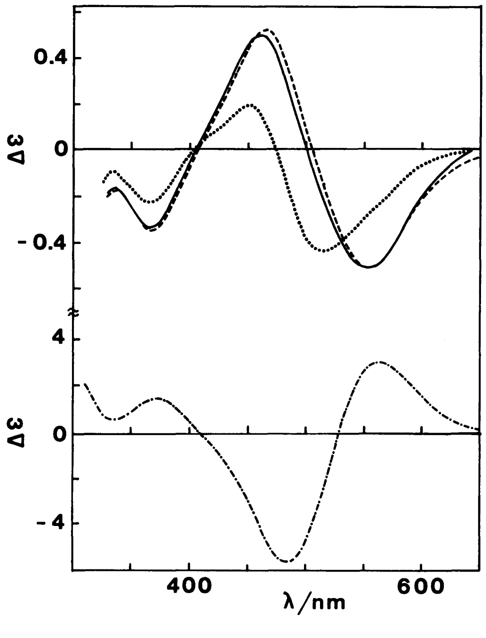


Fig. 4. Configurational and vicinal CD curves of $[Co(sar)(Hbg)_2]^{2+}$: $[\Delta(R)+\Delta(S)]/2$ (—·—), $[\Delta(R)-\Delta(S)]/2$ (······). The CD curve of the reaction solution at the pseudo-equilibrium state (——), and the CD curve calculated for the mixture of the $\Lambda(R)$ and $\Delta(R)$ isomers with the $\Lambda(R)/\Delta(R)$ value of 1.22 (----).

The $(-)^{CD}_{436}$-$[Co(R\text{-}sar)(NH_3)_4]^{2+}$ ion shows three CD peaks of alternating sign (−, +, −) in the first absorption band region.[6] It is known that the "vicinal" CD curve of the $[Co(sar)(en)_2]^{2+}$ ion is quite similar to the CD curve of the $[Co(sar)(NH_3)_4]^{2+}$ ion.[7] As shown in Fig. 4, the halved difference of the CD curves of the $(-)^{CD}_{485}$-E-2 and $(-)^{CD}_{480}$-E-1 isomers of $[Co(sar)(Hbg)_2]^{2+}$, showing an *R*-vicinal contribution of asymmetric nitrogen, is similar to the CD spectrum of $[Co(R\text{-}sar)(NH_3)_4]^{2+}$ except for relative peak intensities. This similarity can be taken as additional evidence for our assignment of the absolute configuration of the isomers.

Racemization at the Cobalt Center of $[Co(sar)(Hbg)_2]^{2+}$ Ion. The optically active isomers of the $[Co(am)(Hbg)_2]^{2+}$ ions gradually lost their CD intensities in a weak basic aqueous solution without any change in their absorption spectra.[5] Figure 5 shows the time-course change of the CD intensities at 485 nm when $\Delta(R)$- and $\Lambda(R)$-$[Co(sar)(Hbg)_2]^{2+}$ ions were used as starting materials at pH 8.15 and 35.0 °C. After ca. 80 min, both of the isomers gave a weak residual CD with a positive sign. The loss of the residual CD was very slow under these conditions. However, a CD loss in the second step occurred at a considerable rate in the higher pH region.

A portion of the reaction solution mentioned above was neutralized with 0.1 M HCl at the pseudo-equilibrium state. The neutralized solution gave a CD curve that was slightly different from the vicinal CD (Fig. 4). If the neutralized solution contains only the $\Lambda(R)$ and $\Delta(R)$ isomers, the ratio $\Lambda(R)/\Delta(R)$ at the pseudo-equilibrium state can be calculated from the CD intensities at 485 nm in Figs. 3 and 5. The value

Table 1. Absorption (AB) and CD Data of the $[Co(sar)(Hbg)_2]^{2+}$ Complex in an Aqueous Solution

Complex	Config.		AB (ε)	CD (Δε)	
			nm	nm	
$(-)^{CD}_{480}$-E-1	$\Delta(S)$	1st band	486(155)	560(+3.32)	480(−5.45)
		2nd band	361(191)	372(+1.78)	
$(-)^{CD}_{485}$-E-2	$\Delta(R)$	1st band	485(163)	563(+2.85)	485(−5.76)
		2nd band	361(177)	372(+1.78)	

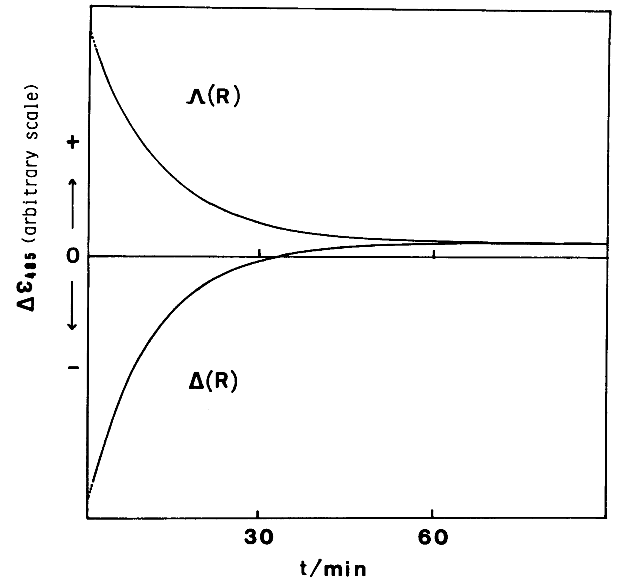


Fig. 5. The time-course change of the CD intensities of the $\Lambda(R)$- and $\Delta(R)$-$[\mathrm{Co(sar)(Hbg)_2}]^{2+}$ ions measured at 485 nm (35.0 °C, pH=8.15, $\mu=0.15$).

Table 2. The Rate Constants and the Activation Parameters for the $\Delta(R)\rightarrow\Lambda(R)$ Change of the $[\mathrm{Co(sar)(Hbg)_2}]^{2+}$ Ion

Run	T / °C	pH[a)]	$k'_{\Delta(R)-\Lambda(R)}$[b)] / $10^{-4}\,\mathrm{s^{-1}}$	$k_{\Delta(R)-\Lambda(R)}$ / $10^{2}\,\mathrm{M^{-1}\,s^{-1}}$	$\Delta H^{\ddagger}$[c)] / kJ mol^{-1}	$\Delta S^{\ddagger}$[c)] / JK^{-1} mol^{-1}
1	30.0	7.43	0.618	1.57	83.9±2.9	73.6±9.9
2	30.0	7.78	1.34	1.53		
3	30.0	8.14	3.13	1.55		
4	30.0	8.07	2.63	1.51	(μ=0.5)	
5	30.0	8.00	1.87	1.26	(μ=1.0)	
6	30.0	8.62	11.99	1.95	(higher pH)	
7	25.0	8.12	1.16	0.823		
8	26.3	8.12	1.46	1.01		
9	32.5	8.12	4.72	2.06		
10	35.0	8.15	7.57	2.56		

a) Phosphate buffer. b) Calculated from the values of both the pseudo-first-order rate constants (k') and the equilibrium constants ($\Lambda(R)/\Delta(R)$). The values of $\Lambda(R)/\Delta(R)$: 1.18 (run 4), 1.20 (run 5), 1.14 (run 6), 1.22 (other runs). c) Calculated from the data of $k_{\Delta(R)-\Lambda(R)}$ (at 30 °C). μ=0.15 except for the run of 4 and 5.

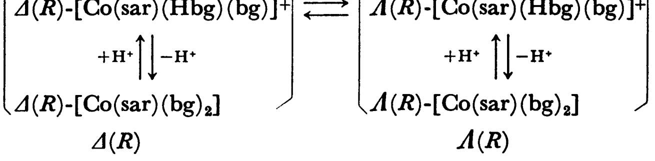
is estimated to be 1.22. The CD curve calculated for a mixture of the $\Lambda(R)$ and $\Delta(R)$ isomers with a $\Lambda(R)/\Delta(R)$ value of 1.22 coincides exactly with the spectrum of the neutralized reaction solution (Fig. 4). Moreover, in the present sarcosinato complex, both the "configurational effect" (Δ or Λ) and the "vicinal effect" (R or S) contribute to the observed CD spectrum in the d-d band region. Also, the "vicinal effect" makes a relatively small contribution to the observed CD. These considerations show that the large CD loss in the first step can be attributed to a racemization of $\Delta(R)\rightleftarrows\Lambda(R)$ and that the small CD loss in the second step can be attributed to a racemization of $R\rightleftarrows S$.

The progress of the $\Delta(R)\rightleftarrows\Lambda(R)$ change was followed by a loss of the CD intensity at 485 nm. Each of the $\Delta(R)$ and $\Lambda(R)$ isomers was used as a starting material under the same conditions, and the average value of the $[\mathrm{CD}]_{\mathrm{eq}}$ (CD intensity at the pseudo-equilibrium state) was used for a kinetic analysis. The values of the equilibrium constant ($\Lambda(R)/\Delta(R)$) are invariable within experimental error under conditions of pH 7.5—8.5 and 25—35 °C. The mean value is 1.22±0.03, indicating that the $\Lambda(R)$ isomer is favored. The value of $\Lambda(R)/\Delta(R)$ is reported to be 5.58 for the $[\mathrm{Co(sar)(en)_2}]^{2+}$ complex. The stereoselectivity is smaller in the bis(biguanide)-cobalt(III) complex, since a smaller steric interaction might be expected because of the nearly planar biguanide chelate rings.

In Table 2, the rate constants, $k'_{\Delta(R)-\Lambda(R)}$, of the $\Delta(R)\rightarrow\Lambda(R)$ change, which are calculated from values of both the pseudo-first-order rate constants (k') and the equilibrium constants ($\Lambda(R)/\Delta(R)$), are summarized. The values of $k_{\Delta(R)-\Lambda(R)}(=k'_{\Delta(R)-\Lambda(R)}/[\mathrm{OH^-}])$ are regarded as essentially constant in the lower pH region (<8.0); however, the values increase with a pH above ca. 8.5. Namely, the rate deviates from a first-order-relationship with $[\mathrm{OH^-}]$ in a higher pH region. As the biguanide which is coordinated to a cobalt(III) ion dissociates its proton in a basic aqueous solution,[18] the following equilibrium is established for the $[\mathrm{Co(sar)(Hbg)_2}]^{2+}$ ion:

$$[\mathrm{Co(sar)(Hbg)_2}]^{2+} \xrightleftharpoons{k_{a1}} [\mathrm{Co(sar)(Hbg)(bg)}]^{+} + \mathrm{H^+} \xrightleftharpoons{k_{a2}} [\mathrm{Co(sar)(bg)_2}] + 2\mathrm{H^+} \qquad (1)$$

(The pK_a values are listed in Table 3.) Deprotonation equilibrium was established much faster than the racemization equilibria of $\Delta\rightleftarrows\Lambda$ and $R\rightleftarrows S$. Therefore, the "$\Delta(R)\rightleftarrows\Lambda(R)$" change is described by Eq. 2.



$$\left(\begin{array}{c}\Delta(R)\text{-}[\mathrm{Co(sar)(Hbg)_2}]^{2+}\\ +\mathrm{H^+}\uparrow\downarrow-\mathrm{H^+}\\ \Delta(R)\text{-}[\mathrm{Co(sar)(Hbg)(bg)}]^{+}\\ +\mathrm{H^+}\uparrow\downarrow-\mathrm{H^+}\\ \Delta(R)\text{-}[\mathrm{Co(sar)(bg)_2}]\end{array}\right) \rightleftarrows \left(\begin{array}{c}\Lambda(R)\text{-}[\mathrm{Co(sar)(Hbg)_2}]^{2+}\\ +\mathrm{H^+}\uparrow\downarrow-\mathrm{H^+}\\ \Lambda(R)\text{-}[\mathrm{Co(sar)(Hbg)(bg)}]^{+}\\ +\mathrm{H^+}\uparrow\downarrow-\mathrm{H^+}\\ \Lambda(R)\text{-}[\mathrm{Co(sar)(bg)_2}]\end{array}\right)$$

$\Delta(R)$ $\Lambda(R)$

(2)

The deviation of the data from a first-order-relationship with $[\mathrm{OH^-}]$ may be explained by a

Table 3. Acid Dissociation Constants of the $[Co(am)(Hbg)_2]^{2+}$ Complexes (30.0 °C)

Complex	pK_{a1}	pK_{a2}
$[Co(sar)(Hbg)_2]^{2+}$	8.84±0.04	10.32±0.05
$[Co(gly)(Hbg)_2]^{2+}$	9.06±0.06	10.36±0.08
$[Co(\text{L-ala})(Hbg)_2]^{2+}$	9.07±0.05	10.41±0.04
$[Co(\text{L-val})(Hbg)_2]^{2+}$	9.04±0.02	10.37±0.03

Table 4. The Rate Constants and the Activation Parameters for the $\Lambda\to\Delta$ Change of the $[Co(am)(Hbg)_2]^{2+}$ Ions

am	T °C	pH[a]	$k'_{\Lambda-\Delta}$[b] 10^{-4} s^{-1}	$k_{\Lambda-\Delta}$ 10^2 M^{-1} s^{-1}	$\Delta H^{\neq}$[c] kJ mol^{-1}	$\Delta S^{\neq}$[c] JK^{-1} mol^{-1}
gly	25.0	8.02	0.494	0.423		
	30.0	8.01	1.19	0.788	94.0±1.0	102±3
	35.0	7.73	1.58	1.48		
	30.0	8.76	9.60	1.16		
	30.0	8.80	15.3	1.61	(carbonate buffer)	
	30.0	8.89	30.4	2.67	(borate buffer)	
L-ala	25.0	8.02	0.192	0.183		
	30.0	8.01	0.510	0.338	96.3±1.7	102±6
	35.0	7.73	0.686	0.641		
L-val	25.0	8.02	0.094	0.0894		
	30.0	8.02	0.304	0.196	101 ±9	112±30
	35.0	8.02	0.721	0.345		

a) Phosphate buffer. μ=0.15 for all the runs. b) Calculated from the values of both the pseudo-first-order rate constants (k') and the equilibrium constants. c) Calculated from the data of $k_{\Lambda-\Delta}$ (at 30 °C).

Table 5. The Rate Constants and the Activation Parameters for the $R\rightleftarrows S$ Change of the $[Co(sar)(Hbg)_2]^{2+}$ Ion

Run	T °C	pH[a]	k' 10^{-4} s^{-1}	k_{rac}[b] 10 M^{-1} s^{-1}	$\Delta H^{\neq}$[c] kJ mol^{-1}	$\Delta S^{\neq}$[c] JK^{-1} mol^{-1}
1	30.0	9.29	2.08	0.730	89.2±4.4	91.2±14.3
2	32.6	9.30	3.70	1.05		
3	35.0	9.29	5.60	1.38		
4	35.2	9.74	16.7	1.45		
5	35.2	9.82	19.7	1.42		
6	35.1	9.97	28.0	1.44		
7	35.2	10.04	32.0	1.39		
8	37.0	9.31	9.26	1.85		
9	39.8	9.31	12.7	2.15		

a) Carbonate buffer. μ=0.15. b) $k_{rac}=(k_{R-S}+k_{S-R})=2k_{inv}$. c) Calculated from the data of k_{rac}(at 30 °C).

higher reactivity of the higher order conjugate-base species which are expected to be present in considerable concentration in a higher pH region (>9.0). Similar deviations have been found regarding racemization rates for other (amino acidato)bis-(biguanide) complexes and for $[Co(Hbg)_3]^{3+}$ [19] and $[Co(Ph\text{-}Hbg)_3]^{3+}$ [3] complexes. Hereafter, we only discuss experimental data obtained in a lower pH region where the rate law is described as $R=k_{\Delta(R)-\Lambda(R)}[OH^-][\text{complex}]$.

The rate constants of the $\Lambda\to\Delta$ change for other (amino acidato)bis(biguanide)cobalt(III) complexes are summarized in Table 4. These data were obtained in a pH region where the rates show a first order dependence on $[OH^-]$. The diastereomeric equilibrium constants, $K=\Delta(\text{L})/\Lambda(\text{L})$, of $[Co(\text{L-amino acidato})(Hbg)_2]^{2+}$, which were calculated from CD data in the d-d band region, were essentially constant under the present experimental conditions (25—35 °C, pH <8.5). The constants are 0.803±0.010 and 0.504±0.005 for the L-alaninato and L-valinato complexes, respectively. In Table 2, an increase in ionic strength from 0.15 to 1.0 caused a decrease in the rates of the $\Delta(R)\to\Lambda(R)$ change (about 20%). Further, as shown for the case of the $[Co(gly)(Hbg)_2]^{2+}$ complex (Table 4), the rates of the $\Lambda\to\Delta$ change depend on the type of buffer and the rate decreases in the phosphate buffer. This result may be due to a difference in the formation constant of the ion pair between the complex and each of the buffer anions. It is supposed that the ion pair no longer reacts with OH^- at a rate comparable to that of the original complex. The same results were also obtained for the other complexes studied here.

Ray and Dutt proposed a twist mechanism for the racemization of the $[Co(Hbg)_3]^{3+}$ ion in a neutral aqueous solution on the basis of an abnormally lower probability factor; a large value of $\Delta S^{\neq}$ with a negative sign.[2] However, in the $[Co(am)(Hbg)_2]^{2+}$ series the activation entropies, $\Delta S^{\neq}$, are positive. The racemization rates for a series of the $[Co(am)(Hbg)_2]^{2+}$ ion increase in the order L-valine<L-alanine<glycine<sarcosine; an alkyl-substitution on the nitrogen atom of glycine increases the rate and an alkyl-substitution on the α-carbon atom decreases the rate. A higher reactivity of the sarcosinato complex is not favorable to the twist mechanism because the transition state of the twist mechanism for the sarcosinato complex is expected to be higher in energy than that for the glycinato complex due to the intramolecular repulsion. One of the possible mechanisms may be a bond-rupture mechanism through the conjugate-base species. However, it is not clear which bond severs, Co–O(sarcosine) or Co–N(biguanide).

Racemization and Deuteration at the Asymmetric Nitrogen Center. The racemization rates at the asymmetric nitrogen center ($R\rightleftarrows S$) in the $[Co(sar)(Hbg)_2]^{2+}$ ion were obtained from the CD loss of the second step at 485 nm. Kinetic data are summarized in Table 5. The constancy of $k_{rac}=k'/[OH^-]$

Table 6. The Rate Constants and the Activation Parameters for the Deuteration at the the Sarcosinato-N in the $[Co(sar)(Hbg)_2]^{2+}$ Ion

Isomer	T / °C	pH a)	k' / $10^{-4}\,s^{-1}$	k_{H-D} / $10^3\,M^{-1}\,s^{-1}$	$\Delta H^{\ddagger}$ b) / kJ mol^{-1}	$\Delta S^{\ddagger}$ b) / JK^{-1} mol^{-1}
$\Delta(S)$	39.6	7.11	2.54	3.57	45.0±4.5	−0.48±14.7
	45.2	7.02	4.34	5.17		
	50.7	7.05	8.30	6.62		
$\Delta(R)$	39.6	6.98	5.48	10.4	48.4±2.3	−0.20± 7.7
	45.2	7.02	12.0	14.3		
	50.7	7.00	22.8	20.4		

a) Borate buffer. b) Calculated from the values of k_{H-D} (at 30 °C).

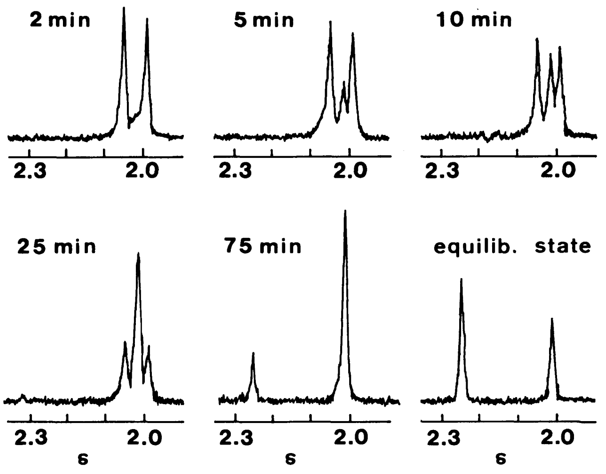


Fig. 6. Deuteration at the sarcosinato-N atom in the $\Delta(R)$-$[Co(sar)(Hbg)_2]^{2+}$ ion as followed by the collapse of the methyl doublet to a singlet (pD=6.98, 39.6 °C). An appearance of the singlet peak at 2.25 ppm is ascribed to the formation of the $\Lambda(R)$ isomer.

in a pH region of 9.0—10.0 (35 °C) indicates that the rate law is given by $R=k_{rac}[OH^-][complex]$. As the values of pK_{a1} and pK_{a2} (deprotonation equilibrium constants) are 8.84 and 10.32, respectively, this result shows that the rate of the $R\rightleftarrows S$ change for each of the species in deprotonation equation (1) is not greatly different. In Table 6, the rate constants for deuteration on the sarcosinato NH proton of $\Delta(S)$- and $\Delta(R)$-$[Co(sar)(Hbg)_2]^{2+}$ are listed. The kinetic data were obtained by following the collapse of the methyl doublet signal to a singlet as the NH proton exchanged with D^+. Part of a typical set of data for the $\Delta(R)$ isomer is shown in Fig. 6. Plots of ln[(doublet peak height)$_t$/(total peak height)] vs. time were linear for two half-lives. As the deuteration rates of NH protons observed in other complexes6—10,20) show a first-order dependence on $[OD^-]$ concentration, the deuteration runs studied here were also analyzed according to the rate law $R=k_{H-D}[OD^-]\times[complex]$. In Table 6, the deuteration rate for the $\Delta(S)$ isomer is about 3 times slower than that for the $\Delta(R)$ isomer. The NH proton of the sarcosinato in the $\Delta(S)$ isomer, which lies in a position perpendicular to one of the biguanide rings, is more effectively hindered with the biguanide ring than in the $\Delta(R)$ isomer. Thus, the kinetic results described above can be interpreted if the rate-determining step is the nucleophilic attack of OD^- on the NH proton. (The rate of deuteration is faster enough than that of the $\Delta\rightleftarrows\Lambda$ change. See Tables 2 and 6.) The small rate constant of the $R\rightleftarrows S$ change compared with that of the deuteration implies that deuteration takes place with a substantial retention of the configuration.

The $[Co(sar)(en)_2]^{2+}$ complex shows no racemization at the cobalt center even in a basic aqueous solution.7) In the $[Co(sar)(Hbg)_2]^{2+}$ ion, the rate of the $\Delta\rightleftarrows\Lambda$ change is faster than that of the $R\rightleftarrows S$ change. The rates of the $R\rightleftarrows S$ change and deuteration at the nitrogen center are ca. 10^4 and ca. 10^4—10^5 times slower than those for the $[Co(sar)(NH_3)_4]^{2+}$ ion, respectively. However, the ratio of k_{H-D}/k_{inv}, where the k_{H-D} and $k_{inv}(=k_{rac}/2)$ denote the rate constants of the deuteration and inversion at the asymmetric nitrogen center, is ca. 10^2—10^3 for the $[Co(sar)(Hbg)_2]^{2+}$ ion. Although both the rates of the inversion and the H→D change at the nitrogen center for $[Co(sar)(Hbg)_2]^{2+}$ are much slower than those of other sarcosinato complexes, the present kinetic results regarding the asymmetric nitrogen center can be interpreted by a mechanism proposed by Buckingham and Sargeson (Scheme 1).6—10) Recently, the racemization at the asymmetric nitrogen center of $[Co(Me\text{-}en)(acac)_2]^+$, where the acac ring is also planar structure with π-electrons such as the biguanide ring, has been studied. It was found that the second rate constant is $1.2\times10^{-2}\,M^{-1}\,s^{-1}$ for the $\Lambda(R\rightleftarrows S)$ change at 25.1 °C.21) This value is about 10^4 times smaller than that of $[Co(Me\text{-}en)(NH_3)_4]^{3+}$. These results indicate that the racemization rate at the coordinated asymmetric nitrogen center is extremely affected by the natures of coexisting ligands such as Hbg or $acac^-$, both of which produce a planar chelate ring with π-electrons.

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