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Studies of Hydroxy Acid Complexes. I. Complexes Containing Optically Active Lactic Acid and Pantoic Acid

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Complexes of the type $[Co(en)_2ha]Cl$, where ha is the diacid anion of lactic or pantoic (2,4-dihydroxy-3,3-dimethylbutyric) acid, were prepared by the reaction of optically active lactic acid with *rac*-$[Co(en)_2CO_3]^+$ and optically active pantoyl lactone with *trans*-$[Co(en)_2Cl_2]ClO_4$. Several optical isomers have been isolated from the reaction products by thin layer chromatography. These complexes have been characterized by nmr, electronic absorption, ORD, and CD spectra and their relative absolute configurations have been assigned. Data suggest that the hydroxy acid anions coordinate in a preferred conformation and configurational and vicinal contributions to the optical activity of these complexes are discussed.

Introduction

If a metal complex is formed using an optically active chelating ligand, one diastereoisomer is often favored over another. This stereoselective effect is not usually absolute but rather results in the predominance of one isomer over the other.

Many complexes of the type $[Co(en)_2aa]^{2+}$, where aa is an optically active amino acid, have been prepared[1-4] and extensive studies have been performed on them. Liu and Douglas[1] showed that for these complexes no dissymmetric synthesis occurred; *i.e.*, the proportions of the optical isomers were equal within experimental error. Recently, however, Hall and Douglas[2] have shown that only the $(-)_{589}$ isomer of $[Co(en)_2((S(-))\text{-proline})]I_2$ is formed and models show that this stereospecificity is due to the presence of steric interactions in that particular isomer. Other cases of marked stereoselectivity have been noted in the case of ligands such as glutamic acid, histidine, and peptides and this has been attributed to the interaction of polar sites on the ligand and the complex.[5]

Many of the complexes prepared with optically active amino acids as ligands have been found to be diastereomeric and possess different spectral properties.[1,2,6,7] It should be possible, therefore, to separate these dissymmetric isomers without the usual resolution process and this has been accomplished in several cases by repeated recrystallization. Matsuoka and coworkers[8] also have succeeded in separating isomers of $[Co(ox)((S)\text{-serine})_2]^-$ by ion-exchange chromatography.

Hydroxy acids are the oxygen analogs of the amino acids and information regarding the bonding of hydroxy acids in optically active molecules can be useful for comparison of the two systems. The amount of work reported on hydroxy acid complexes is not as great as for amino acids but several complexes have been isolated.[9,10] Further studies of reactions involving compounds of amino and α-hydroxy acids are worthwhile since they may serve as models for a variety of stereoselective effects observed in nature.

In this paper we wish to report some reactions involving coordination of optically active lactic acids and pantoic acids in complexes of the type $[Co(en)_2ha]^+$ where en is ethylenediamine and ha is the dianion of $(R(-))$- or $(S(+))$-lactic acid and $(R(+))$- or $(S(-))$-pantoic acid.

Experimental Section

All chemicals were used without further purification. $(R(-))$-lactic acid ($[\alpha]_{589}$ −1.76°) and $(S(+))$-lactic acid ($[\alpha]_{589}$ +2.58°) were obtained as 30% aqueous solutions from Miles Laboratories. $(R(-))$-pantoyl lactone (2,4-dihydroxy-3,3-dimethylbutyric acid γ-lactone) was obtained from Nutritional Biochemical Corp. ($[\alpha]_{589}$ −48.4°). The lactone was converted *in situ* to the sodium salt of the $R(+)$ acid ($[\alpha]_{589}$ +9.1°) by adding an equimolar quantity of sodium hydroxide. The $(S(+))$-pantoyl lactone ($[\alpha]_{589}$ +46.3°) was obtained from Eastern Chemical Corp. and the rotation of the $S(-)$ sodium salt was $[\alpha]_{589}$ −9.7°. Using the Fischer convention the R configurations of the acids are given in Figure 1.

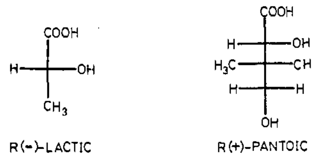

Figure 1.—The absolute configurations of $(R(-))$-lactic and $(R(+))$-pantoic acids.

Microanalyses were performed by Alfred Bernhardt, Elbach, West Germany. Absorption spectra were recorded on a Beckman DK-1 recording spectrophotometer. Nmr spectra were recorded on Varian T-60 or HA-100 spectrometers using deuterium oxide as solvent with sodium 2,2-dimethyl-2-silapentanesulfonate (NaDSS) as an internal reference. Optical rotation and circular dichroism spectra as well as some absorption spectra were recorded on a Durrum-Jasco ORD/UV-5/CD-1 spectropolarimeter. Solid-state CD spectra were obtained from approximately 2% mixtures of complex in KBr pressed pellets.

Reaction of Equimolar Quantities of Optically Active Lactic Acid with *rac*-Carbonatobis(ethylenediamine)cobalt(III) Chloride.—A mixture of 1.0 g of $[Co(en)_2CO_3]Cl$ and 1.10 g of either $(R(-))$- or $(S(+))$-lactic acid (30% solution) in 10–15 ml of water was refluxed on a steam bath for 4 hr. The mixture was then transferred to an evaporating dish and evaporated to dryness on the steam bath. The solid obtained was ground with absolute ethanol, filtered, washed with ether, and dried under a heat lamp.

Reaction of Equimolar Quantities of Optically Active Pantoyl Lactone with *trans*-Dichlorobis(ethylenediamine)cobalt(III) Perchlorate.—A mixture of 1.0 g of *trans*-$[Co(en)_2Cl_2]ClO_4$, 0.37 g of $(R(-))$- or $(S(+))$-pantoyl lactone and 0.23 g of sodium hydroxide in 15 ml of water was refluxed on a steam bath for 4 hr. The mixture was then evaporated to dryness on the steam bath in an evaporating dish. The solid obtained was ground with absolute ethanol, filtered, washed with ether, and dried under a heat lamp. The yield was 1.2 g.

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(1) C. T. Liu and B. E. Douglas, *Inorg. Chem.*, **3**, 1356 (1964).
(2) S. K. Hall and B. E. Douglas, *ibid.*, **8**, 372 (1969).
(3) J. H. Dunlop and R. D. Gillard, *J. Chem. Soc.*, 6531 (1965).
(4) R. D. Gillard and P. M. Harrison, *ibid.; A*, 1657 (1967).
(5) J. H. Dunlop, R. D. Gillard, and N. C. Payne, *ibid.*, *A*, 1469 (1967).
(6) J. Hidaka and Y. Shimura, *Bull. Chem. Soc. Jap.*, **40**, 2312 (1967).
(7) K. Yamosaki, J. Hidaka, and Y. Shimura, *ibid.*, **42**, 119 (1969).
(8) N. Matsuoka, J. Hidaka, and Y. Shimura, *Inorg. Chem.*, **9**, 719 (1970).
(9) R. D. Gillard and M. G. Price, *Chem. Commun.*, 67 (1969).
(10) R. D. Gillard and M. G. Price, *J. Chem. Soc. A*, 1813 (1969).

TABLE I

Sample[a]	Absorption		ORD		CD	
	λ, nm	ϵ_{max}, M^{-1} cm^{-1}	λ, nm	[α], deg	λ, nm	Δε, M^{-1} cm^{-1}
R-lact reaction product	516	146			565	−0.31
					505	+1.2
					400	−0.72
Λ-(+)$_{589}$-[Co(en)$_2$((*R*(−))-lactate)-δδλ]Cl·2H$_2$O (*R*-lact 3)	516	131	589	+752	521	+2.37
	360	139	557	+1050	405	−0.665
			546	+870	375	Shoulder
			481	−1957	333	+0.064
					275	−0.76
					212	−19.4
Fraction *R*-lact 4 (predominantly Δ-(−)$_{589}$-[Co(en)$_2$((*R*(−))-lactate)]Cl)	516	135	590	−375	553	−1.12
	360	145	546	+850	495	+0.958
			524	+1370	404	−0.847
			454	−541	259	+3.57
					211	+13.0
Δ-(−)$_{589}$-[Co(en)$_2$((*R*(−))-lactate)-λλλ]Cl·2H$_2$O[b]			590	−2020	550	−1.58
					488	+0.55
			520	+5030	404	−0.64
[Co(NH$_3$)$_4$((*R*(−))-lactate)]Cl	522	83	589	+13.7	570	−0.038
	360	81	546	+96.7	508	+0.093
			536	+105	390	−0.054
			463	−105		
R-pant reaction product	516	103			571	−0.30
					511	+0.93
					403	−0.70
Λ-(+)$_{589}$-[Co(en)$_2$((*R*(+))-pantoate)-δδλ]Cl·H$_2$O (*R*-pant 3)	520	142	589	+1065	525	+3.89
	364	161	563	+1428	408	−1.11
			546	+967	370	Shoulder
			490	−2710	312	+0.36
					270	+0.97
					216	−30.4
Δ-(−)$_{589}$-[Co(en)$_2$((*R*(+))-pantoate)-λλλ]Cl·H$_2$O (*R*-pant 4)	519	150	593	−802	551	−2.21
	367	180	589	−798	488	+0.213
			546	+851	404	−0.973
			522	+1563	265	+5.50
					210	+20.4

[a] The (*S*)-α-hydroxy acid complexes give virtually mirror-image CD curves. [b] ORD and CD curves obtained by subtracting 30% of the curves for the Λ isomer.

Chromatography of Reaction Products.—For the following section on chromatography a system of numbers was used for band identification. Numbers 1, 2, 3, etc., were used to indicate bands from the top to the bottom of the plates. The particular reaction product from which the sample was derived was designated as *R*- or *S*-lact or -pant.

A concentrated solution of the reaction product in water was spotted on 10 × 20 cm tlc plates of Camag DS-O silica gel 1 mm in thickness and developed with water. On developing, the plates contained five bands. In all cases band 1 was identified as *rac*-[Co(en)$_3$]$^{3+}$ and bands 2 and 5 were minor and not identified. Bands 3 and 4 were extracted with water and solid products were obtained by evaporating the filtered solutions to dryness at room temperature in an air stream. Bands 3 and 4 were rechromatographed three times to obtain better separations and for each fraction the optical activity was checked after each rechromatograph. The rechromatographed products were passed through an anionic exchange column of Dowex 1-X8, 200–400 mesh in the chloride form, and washed through with water. The eluent was evaporated to dryness at room temperature, washed with ether, and dried *in vacuo* at room temperature.

Anal. for isomers obtained from the (*R*(−))-lactic acid product. Calcd for [Co(en)$_2$(CH$_3$CHOCOO)]Cl: C, 27.28; H, 6.66; N, 18.51; Cl, 11.71; C/N, 1.50. Samples were dried before analysis and weight losses corresponded to approximately two water molecules. Found for band *R*-lact 3: C, 27.69; H, 6.87; N, 18.40; Cl, 11.59; C/N, 1.51. The molar conductivity was 100 mhos cm^2 mol^{-1}. Found for band *R*-lact 4: C, 27.81; H, 6.68; N, 18.33; Cl, 11.95; C/N, 1.52. The molar conductivity was 94 mhos cm^2 mol^{-1}.

Anal. for isomers obtained from the (*R*(+))-pantoic acid product. Calcd for [Co(en)$_2$(OOCCHOC(CH$_3$)$_2$CH$_2$OH)]Cl: C, 33.29; H, 7.27; N, 15.53; Cl, 9.83; C/N, 2.14. Samples were dried before analysis and weight losses corresponded approximately to one water molecule. Found for band *R*-pant 3: C, 33.19; H, 7.16; N, 15.35; Cl, 10.01; C/N, 2.16. Found for band *R*-pant 4: C, 33.42; H, 7.11; N, 15.41; Cl, 9.99; C/N, 2.17.

The complex [Co(NH$_3$)$_4$(*R*(−))-lactate)]Cl was prepared by a method analogous to that used by Bhatnagar and Kirschner[11] for some tartrate complexes.

Results and Discussion

At temperatures below 70° the reactions with hydroxy acids require several days to complete while at steam bath temperatures (95°), they proceeded to maximum optical activity after 4 hr of refluxing. Analytical results indicated that complexes of the type [Co(en)$_2$ha]$^+$ were prepared, where ha was coordinated as a bidentate ligand through the carboxylate group and the deprotonated α-hydroxyl oxygen. The hydroxy acid complexes can undergo disproportionation reactions similar to amino acid complexes of the type [Co(en)$_2$aa]$^+$,[12] but are less reactive.

The reaction products showed CD spectra with three peaks at 565, 505, and 400 nm, the pattern being −+− for the *R* acids and +−+ for the *S* acids (Table I). The intensity of the peaks was much greater than that for similar amino acid complexes[1] and it is interesting to note that the sign of the major CD peak of the reaction products correlates with the configuration at the α carbon of the optically active hydroxy acid, although this is possibly only fortuitous.

Circular Dichroism of the Resolved Isomers.—CD spectra for the complexes prepared from the *R* acids are shown in Figures 2 and 3 and characteristic absorption, ORD, and CD data are given in Table I.

[11] D. C. Bhatnagar and S. Kirschner, *Inorg. Chem.*, **3**, 1256 (1964).

[12] R. D. Gillard and P. M. Harrison, *J. Chem. Soc. A*, 1657 (1967).

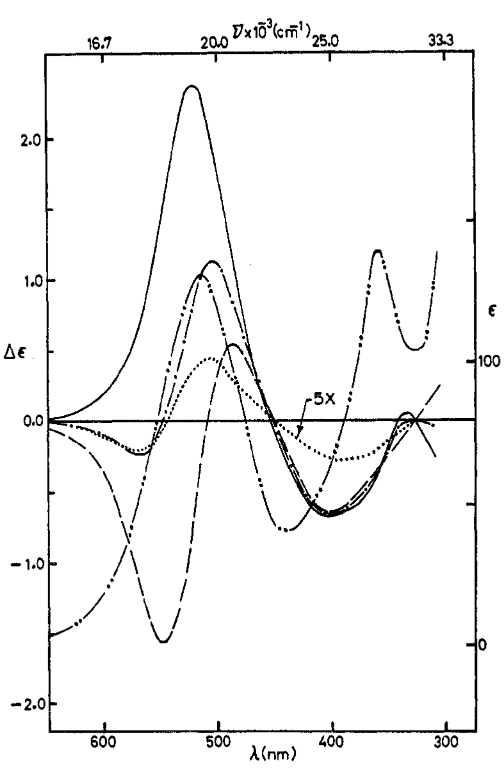

Figure 2—CD spectra for Λ-(+)$_{589}$-[Co(en)$_2$((R(−))-lactate)]-Cl·2H$_2$O (—), Δ-(−)$_{589}$-[Co(en)$_2$((R(−))-lactate)]Cl·2H$_2$O (— — —), and [Co(NH$_3$)$_4$((R(−))-lactate)]Cl (····) and the calculated vicinal-effect curve for [Co(en)$_2$((R(−))-lactate)]Cl·2H$_2$O (-·-·). The absorption curve (-··-) for [Co(en)$_2$((R(−))-lactate)]Cl·2H$_2$O is included.

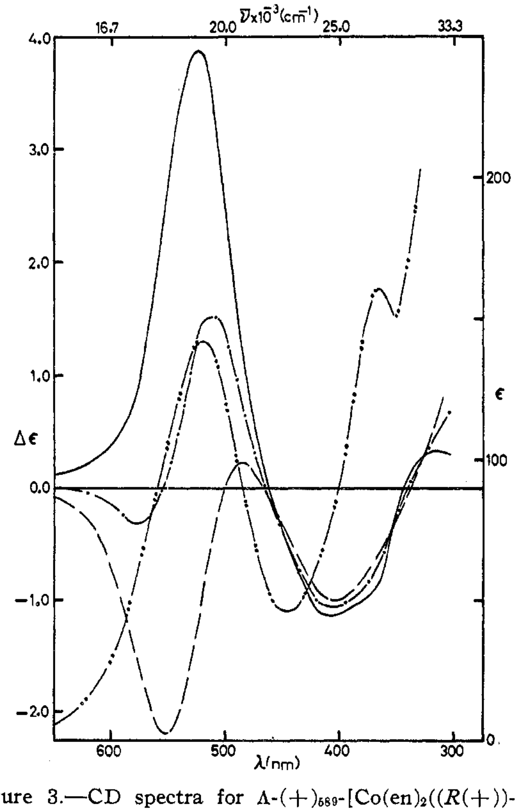

Figure 3.—CD spectra for Λ-(+)$_{589}$-[Co(en)$_2$((R(+))-pantoate)]Cl·H$_2$O (—) and Δ-(−)$_{589}$-[Co(en)$_2$((R(+))-pantoate)]Cl·H$_2$O (— — —) and the calculated vicinal-effect curve for [Co(en)$_2$((R(+))-pantoate)]Cl·H$_2$O (-·-·). The absorption curve (-··-) for [Co(en)$_2$((R(+))-pantoate)]Cl·H$_2$O is included.

Nmr data (*vide infra*) indicated that R-lact 4 which contained the (−)$_{589}$-[Co(en)$_2$((R(−))-lactate)]$^+$ isomer contained approximately 30% of the (+)$_{589}$-[Co(en)$_2$-((R(−))-lactate)]$^+$ isomer and accordingly a corrected curve was calculated for the (−)$_{589}$ isomer. Nmr data indicated that the pantoate isomers had been obtained optically pure. The ORD and CD curves for the two isomers obtained in each case are not mirror images indicating that the isomers are not enantiomers but are diastereomers. However, for each band a mirror-image spectrum was observed when the corresponding S acid was used. The solid state CD spectra have shapes similar to those obtained in solution indicating the species are the same. Only minor shifts in positions and relative intensities are observed.

Complexes of the type [Co(en)$_2$ha]$^+$ have C_1 molecular symmetry and the octahedral T levels are each broken down into three A levels, two of E (D_3) parentage and one of A$_2$ (D_3) parentage. The CD spectra of (−)$_{589}$-[Co(en)$_2$((R(−))-lactate)]$^+$ and (−)$_{589}$-[Co-(en)$_2$((R(+))-pantoate)]$^+$ show two bands of opposite sign in the first-band region. From comparison with similar complexes,[13] the dominant low-energy band may be considered to be of E parentage and the high-energy band of A$_2$ parentage. The CD spectra of the (+)$_{589}$ isomers show only one strong band in this region.

The relative absolute configurations of the hydroxy acid complexes can be obtained by comparison with similar complexes. The (−)$_{589}$-[Co(en)$_2$(sarcosinato)]I$_2$ complex has a dominant negative CD band[14] and an X-ray analysis[15] has shown that the absolute configuration is Δ.[16] For many other complexes[13] it has also been possible to relate the sign of the dominant CD band to the standard [Co(en)$_3$]$^{3+}$, and using these criteria, the assignments in Table I were made.

Assignment of absolute configuration may also be made from CD spectra obtained in the region of the ligand to metal $\sigma(t_{1u}) \rightarrow 3d(e_g)$ charge-transfer transition[17] in the ultraviolet region. The (+)$_{589}$ isomers with the (R)-hydroxy acids show a large negative CD band below 220 nm and the (−)$_{589}$ isomers show a positive band corresponding to the Λ and Δ configurations, respectively, and these assignments are consistent with those obtained from the CD spectrum of the low-energy ligand field band.

Optical Activity and Ring Conformation.—The generalized treatment of Corey and Bailar[18] has shown that for five-membered chelate rings, such as ethylenediamine, the Δλλλ and Λδδδ isomers are expected to be most stable. Here all C–C bond axes are parallel to the C_3 axis of the molecule and although many examples of such a situation have been found, recent nmr studies by Sudmeier[19] have indicated that in solution the Δ-δλλ and Λ-λδδ isomers of [Co(en)$_3$]$^{3+}$ are most stable. However, for complexes of the type [Co(en)$_2$-

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[13] A. J. McCaffery, S. F. Mason, and B. J. Norman, *J. Chem. Soc.*, 5094 (1965).

[14] D. A. Buckingham, S. F. Mason, A. M. Sargeson, and K. R. Turnbull, *Inorg. Chem.*, **5**, 1649 (1966).

[15] J. F. Blount, H. C. Freeman, A. M. Sargeson, and K. R. Turnbull, *Chem. Commun.*, 324 (1967).

[16] The nomenclature used in this paper is that proposed by IUPAC, *Inorg. Chem.*, **9**, 1 (1970).

[17] A. J. McCaffery, S. F. Mason, B. J. Norman, and A. M. Sargeson, *J. Chem. Soc. A*, 1304 (1968).

[18] E. J. Corey and J. C. Bailar Jr., *J. Amer. Chem. Soc.*, **81**, 2620 (1959).

[19] J. L. Sudmeier and G. L. Blackmer, *Inorg. Chem.* **10**, 2010 (1971).

ha]$^+$, both ethylenediamine rings would still be expected to have the same conformation with the C–C axis parallel to the C_3 axis of the molecule. The hydroxy acid chelate ring is almost planar and conformational properties associated with it should not be as pronounced. However, conformations of the analogous amino acid moieties have been found[15] and hence should also be exhibited in our complexes.

Several workers[16,20,21] have pointed out that the intensity of the CD band of A_2 parentage depends on the conformations of the chelate rings. This transition occurs parallel to the C_3 axis of the molecule and thus it is reasonable to assume that when the conformations of all of the chelate rings in the complex are such that the C–C bond axes are nearly parallel to the C_3 molecular axis, the transition will be more intense than when the conformation of one or more of the chelate rings is changed so that its C–C bond axis is oblique to the C_3 axis. For the hydroxy acid complexes the band of A_2 parentage is observed only for those cases where it is predicted that all the C–C bond axes are more nearly parallel to the C_3 molecular axis. The CD data are therefore consistent with the prediction of a preferred conformation of the hydroxy acid.

Configurational and Vicinal Effects.—Douglas and coworkers[1,2,20,21] have shown that the contributions to the optical activity from the configurational and vicinal effects are essentially additive. The vicinal effect includes any contributions from the asymmetric centers, the ring conformation, and differences in interligand interactions. The following relationships will then hold: $\Delta\epsilon(R) = {}^1/_2[\Delta\epsilon(\Lambda R) + \Delta\epsilon(\Delta R)]$ and $\Delta\epsilon(\Lambda) = {}^1/_2[\Delta\epsilon(\Lambda R) - \Delta\epsilon(\Delta R)]$. The vicinal CD due to the coordinated (R)-hydroxy acid $\Delta\epsilon(R)$ and the configurational CD $\Delta\epsilon(\Lambda)$ can be calculated by applying the relationship to the observed CD curves for the Λ and Δ configurations, $\Delta\epsilon(\Lambda R)$ and $\Delta\epsilon(\Delta R)$, respectively, for each R acid. The calculated vicinal effect curve is shown for each system in Figures 2 and 3 and is similar in shape and magnitude to the CD curve of the reaction products. The configurational effect curve consists of a single band, whose magnitude is in the range of 1.6–2.4 as for tris-chelated complexes.[22]

The vicinal effect curves for the hydroxy acid complexes are more intense than would be expected from comparisons with similar amino acid complexes.[1] This is unusual since the two systems to a first approximation would be expected to show similar effects. However, on examination of the energy separations of the two low-energy bands in the hydroxy acid and analogous amino acid complexes, it is found that the hydroxy acid complexes have a much larger separation. Thus the different intensities of the vicinal effect for the two systems may be due to a greater cancellation of the two components in the case of the amino acid complexes. Hence the vicinal effect should not always be regarded as a minor component of the net CD curve. It is strongly dependent on the energy separation of the component bands, and in cases such as the hydroxy acid complexes, it can contribute almost as strongly as the configurational effect to the net optical activity.

Consideration of the CD spectra of $[Co(en)_2aa]^{n+}$ for amino acids and hydroxy acids reveals that in both cases there is enhancement of the vicinal effect relative to that observed for the analogous tetraamine complexes. This would be consistent with the general observation that conformational effects contribute strongly to the net vicinal effect[23] and as pointed out above, arises from certain steric properties of the tris-chelated complexes.

Nuclear Magnetic Resonance.—Proton magnetic resonance has been well established as a method of studying the conformations of chelate rings and assigning the absolute configurations of cobalt(III) complexes.[23–29] The nmr data for the reaction products and optically active forms of the complexes are given in Table II and it can be seen that the diastereomers prepared containing optically active lactic and pantoic acids show significant differences in the chemical shifts of the methyl and methine protons. A discussion of the chemical shifts involving the magnetic anisotropy of the C–N single bonds of the ethylenediamine rings would require the postulation of a variable anisotropy, and the differences are better explained in terms of van der Waals interaction[29] or steric interactions between atoms.

TABLE II

100-MHZ NMR DATA FOR THE α-HYDROXY ACID COMPLEXES[a]

	Resonances, δ, ppm			
Sample	CH_3	CH_2[b]	CH_2	CH
R-lact reaction product	1.21	2.69		3.88
	1.25	2.72		3.95
	1.28			4.01
	1.32			4.09
				4.15
Λ-$(+)_{589}$-$[Co(en)_2((R(+))\text{-lactate})]^+$	1.21	2.69		3.97
	1.28	2.71		4.03
				4.10
				4.17
R-lact 4 (predominantly Δ-$(-)_{589}$-$[Co(en)_2((R(+))\text{-lactate})]^+$)	1.21[c]	2.69		3.90
	1.25	2.71		3.97
	1.28[c]			4.04
	1.32			4.10
R-pant reaction product	0.941	2.66	3.34	3.75
	0.972	2.67	3.45	3.87
	0.995	2.70	3.50	
		2.72	3.52	
			3.58	
			3.69	
Λ-$(+)_{589}$-$[Co(en)_2((R(+))\text{-pantoate})]^-$	0.941	2.65	3.34	3.87
		2.68	3.45	
		2.72	3.58	
		2.74	3.69	
Δ-$(-)_{539}$-$[Co(en)_2((R(+))\text{-pantoate})]^+$		2.65	3.50	3.75
	0.972	2.67	3.52	
	0.995	2.68		
		2.71		

[a] Spectra were run in D_2O and chemical shifts are relative to NaDSS. [b] Ethylenediamine resonance. [c] This doublet takes up approximately 30% of the integrated intensity of the methyl region.

For the (R)-lactate reaction product two pairs of methyl doublets are observed separated by 3–4 Hz

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(20) C.-Y. Lin and B. E. Douglas, *Inorg. Chim. Acta*, **4**, 3 (1970).

(21) B. E. Douglas, *Inorg. Chem.*, **4**, 1813 (1965).

(22) R. D. Gillard, *J. Inorg. Nucl. Chem.*, **26**, 657 (1964).

(23) J. I. Legg, D. W. Cooke, and B. E. Douglas, *Inorg. Chem.*, **6**, 700 (1967).

(24) D. A. Buckingham, L. Durham, and A. M. Sargeson, *Aust. J. Chem.*, **20**, 257 (1967).

(25) J. G. Brushmiller and L. G. Stadtherr, *Inorg. Nucl. Chem. Lett.*, **3**, 525 (1967).

(26) E. A. Berends and J. G. Brushmiller, *ibid.*, **6**, 847 (1970).

(27) L. G. Stadtherr and J. G. Brushmiller, *ibid.*, **6**, 907 (1970).

(28) L. N. Shoenberg, D. W. Cooke, and C. F. Liu, *Inorg. Chem.*, **7**, 2386 (1968).

(29) J. C. Dabrowiak and D. W. Cooke, *J. Amer. Chem. Soc.*, **92**, 1097 (1970).

with coupling constants of 7 Hz. The four methyl resonances are all of equal integrated intensities suggesting that the optically active hydroxy acid ligand has little or no preference for one or the other of the configurations of the ethylenediamine groups about the cobalt(III) atom. Hence the reaction is not a dissymmetric synthesis. The methyl resonances of the $(+)_{589}$-[Co(en)$_2$((*R*(−))-lactate)]$^+$ isomer are at higher field (1.21, 1.28 ppm) than the dominant doublet of the $(-)_{589}$-[Co(en)$_2$((*R*(−))-lactate)]$^+$ isomer (1.25, 1.32 ppm) suggesting that the methyl protons of the $(-)_{589}$ isomer are sterically compressed. Models of the Λ and Δ isomers of [Co(en)$_2$((*R*(−))-lactate)]$^+$, where (*R*)-lactate would adopt the λ conformation, indicate that there is a greater steric interaction of the methyl groups with the nitrogen protons in the Δ isomer than in the Λ isomer thus causing a shift of the methyl resonances to lower field in the Δ isomer (Figure 4). The $(+)_{589}$ isomer can thus be assigned the Λ configuration and the $(-)_{589}$ isomer the Δ configuration and these nmr assignments are in agreement with the CD assignments.

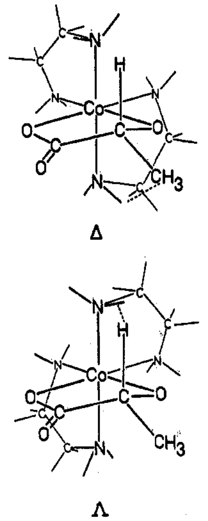

Figure 4.—The Λ and Δ diastereomers of bis(ethylenediamine)-((*R*(−))-lactato)cobalt(III).

Sargeson[14] reported the preparation of the analogous [Co(en)$_2$((*S*(+))-alanine)]$^{2+}$ isomers, but since actual nmr data were not reported, the (*R*(−))-alanine complexes were prepared by the method of Liu and Douglas.[1] The Λ-$(+)_{589}$-[Co(en)$_2$((*R*(−))-alanine)]$^{2+}$ isomer has its methyl resonances at higher field (1.41, 1.53 ppm) than the Δ-$(-)_{589}$-[Co(en)$_2$((*R*(−))-alanine)]$^{2+}$ isomer (1.43, 1.55 ppm) and these chemical shifts are consistent with those observed for the (*R*)-lactate complexes.

Similarly the coordinated (*S*(+))-lactate anion would prefer the δ conformation. The Δ-$(-)_{589}$ and Λ-$(+)_{589}$ isomers have nmr spectra identical with those of the Λ-$(+)_{589}$ and Δ-$(-)_{589}$ isomers, respectively, of the (*R*)-lactate compound. The chemical shifts appear to be independent of the isomeric form of the amino or hydroxy acid and depend only on the orientation of the C–C bond axis of the ligand which in turn depends on the preferred conformation of the ligand.

The nmr data for the methine region can also be used to distinguish the diastereomers. The reaction product gives a symmetrical five-line resonance pattern centered at 4.01 ppm, which is a superposition of two symmetrical quartets centered at 4.07 ppm for the Λ-$(+)_{589}$-[Co(en)$_2$((*R*(−))-lactate)]$^+$ isomer and 4.00 ppm for the Δ-$(-)_{589}$-[Co(en)$_2$((*R*(−))-lactate)]$^+$ isomer. The steric compression noted for the Λ-$(+)_{589}$ isomer is consistent with greater steric compression of the methine proton by the nitrogen protons in the Λ-$(+)_{589}$ isomer as compared to the Δ-$(-)_{589}$ isomer (Figure 4).

For the *R*-lact 4 fraction the methyl region consists of four resonances of which the doublet at 1.25, 1.32 ppm takes up approximately 70% of the integrated intensity. These data suggest that the *R*-lact 4 fraction contains approximately 70% of the Δ-$(-)_{589}$ isomer and 30% of the Λ-$(+)_{589}$ isomer. Repeated chromatographs failed to change this ratio which could be partly attributed to overlap of the chromatography bands; however, this equilibrium ratio of isomers may be kinetically controlled.

The discussion for the alanine and lactate complexes can be extended to include the pantoate and the corresponding valine complexes. The nmr spectra of these can be compared if account is taken of the CH$_2$OH tail on the pantoate ion. In valine where the grouping is replaced by a proton, splitting of the methyl group can occur but no such splitting of the methyl resonances is predicted for the pantoate anion and a simpler spectrum is predicted. The three methyl resonances of the (*R*)-pantoate reaction product may be separated into a singlet for the Λ-$(+)_{589}$-[Co(en)$_2$-((*R*(+))-pantoate)]$^+$ isomer and a doublet (separation 2.3 Hz) for the Δ-$(-)_{589}$ isomer. The integrated intensity of the singlet is approximately equal to that of the doublet. The data suggest that the methyl groups are equivalent in the Λ isomer and nonequivalent in the Δ isomer. Models of the Λ and Δ isomers with the (*R*)-pantoate ligand, which would adopt the λ conformation, indicate that there is greater steric interaction of one of the methyl groups with the nitrogen protons in the Δ than in the Λ isomer thus causing a shift of the methyl resonances to lower field in the Δ isomer. Thus in the Λ isomer, where there is no steric compression, the methyl groups are equivalent and in the Δ isomer, where the one methyl group is affected by steric interactions, they are nonequivalent and both shifted to lower field. On the basis of the lactate discussion, the C–C bond axis of the (*R*)-pantoate ligand in the Λ isomer should be slightly oblique to the pseudo-C_3 axis and in the Δ isomer parallel to the pseudo-C_3 axis.

Sargeson[24] has shown that the Λ-$(+)_{546}$-[Co(en)$_2$-((*S*(+))-valine)]$^{2+}$ complex has its methyl resonances at lower field (1.02, 1.15 ppm) than the Δ-$(-)_{546}$-[Co(en)$_2$((*S*(+))-valine)]$^{2+}$ complex (0.93, 1.13 ppm). If account is taken of the correlation between the Δ isomer with the *S* acid and the Λ isomer with the *R* acid, then the chemical shifts for the valine complexes are consistent with those observed for the (*R*)-pantoate complexes.

The asymmetric methine proton of the pantoate reaction product gives two resonances of equal integrated intensities. Along with the data obtained in the methyl region this suggests that the reaction was not a dissymmetric synthesis. The methine resonances may be separated into a singlet at 3.87 ppm for the

Λ-$(+)_{589}$-$[\mathrm{Co(en)_2}((R(+))\text{-pantoate})]^+$ isomer and a singlet at 3.74 ppm for the Δ-$(-)_{589}$-$[\mathrm{Co(en)_2}((R(+))\text{-pantoate})]^+$ isomer. Models indicate that in the Λ isomer the methine proton is forced into a position where it interacts strongly with the nitrogen proton. This causes a steric compression and a shift of the methine resonance to lower field as compared to the Δ isomer where the steric interaction is absent.

For the methylene region of the pantoate ligand, the reaction product gives a six-line resonance pattern. This can be separated into two doublets (separation 21 Hz with a coupling constant of 11 Hz) in the Λ-$(+)_{589}$-$[\mathrm{Co(en)_2}((R(+))\text{-pantoate})]^+$ isomer, typical of an AB pattern and a split resonance (separation 1 Hz) for the Δ-$(-)_{589}$-$[\mathrm{Co(en)_2}((R(+))\text{-pantoate})]^+$ isomer. Again the integrated intensities of the two sets of resonance lines are approximately equal. The $\mathrm{CH_2OH}$ tail of the pantoate ligand is possibly oriented so that the OH group could hydrogen bond to the uncoordinated oxygen of the carboxylate group. The methylene protons would then be oriented so they could be affected greatly by the methyl group and the observed spectra are consistent with the other resonances.

The data discussed for the hydroxy acid complexes and the analogous amino acid complexes suggest that the optically active ligand coordinates in a preferred conformation in the Λ and Δ configurations of the ethylenediamine rings about the cobalt atom. The chemical shift differences may be attributed to the steric interactions of the optically active ligand with the nitrogen protons of the ethylenediamine rings and can therefore be utilized to assign the absolute configurations of bis(ethylenediamine)cobalt(III) complexes of this type. Further studies of related complexes are now in progress.

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Kinetics of Formation of Mixed-Ligand Complexes. II. 2,2′-Bipyridylcopper(II) Reactions with Ethylenediamine, α-Alanine, and β-Alanine[1]

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The temperature-jump technique has been used to determine the rate constants ($\mu = 0.1$, 25°) for the formation and dissociation of the mixed complexes Cu(bipyridyl)(ethylenediamine)$^{2+}$, Cu(bipyridyl)(α-alaninate)$^+$, and Cu(bipyridyl)(β-alaninate)$^+$. The values found for the forward rate constants for the reaction Cu(bipy) + L $\rightleftarrows$ Cu(bipy)L are as follows: for ethylenediamine, $(2.0 \pm 0.4) \times 10^9\ M^{-1}\ \mathrm{sec}^{-1}$; for the protonated form of ethylenediamine, $(2.2 \pm 0.6) \times 10^4\ M^{-1}\ \mathrm{sec}^{-1}$; for α-alaninate, $(1.0 \pm 0.2) \times 10^9\ M^{-1}\ \mathrm{sec}^{-1}$; and for β-alaninate, $(3.4 \pm 0.7) \times 10^8\ M^{-1}\ \mathrm{sec}^{-1}$. The rate constants for attack by the zwitterion form of these amino acids are zero within experimental error. The reverse rate constants are as follows: for ethylenediamine, $1.4 \pm 0.3\ \mathrm{sec}^{-1}$; for the protonated form of ethylenediamine, $(1.2 \pm 0.4) \times 10^5\ M^{-1}\ \mathrm{sec}^{-1}$; for α-alaninate, $10 \pm 2\ \mathrm{sec}^{-1}$; for β-alaninate, $110 \pm 20\ \mathrm{sec}^{-1}$. These values are compared with the rate constants for the formation of the respective binary complexes Cu + L $\rightleftarrows$ CuL and CuL + L $\rightleftarrows$ $\mathrm{CuL_2}$. Mechanistic arguments are developed which lead to the conclusion that complexation reactions of copper(II) are likely S$_\mathrm{N}$2 and that sterically controlled substitution can occur for ternary systems as well as binary ones.

Introduction

It has been found[2-4] that ternary Cu(II) complexes often show an extraordinarily high thermodynamic stability compared with the corresponding binary complexes. This is especially true of mixed-ligand Cu(II) complexes containing 2,2′-bipyridyl or another aromatic ligand.[5] The size of this effect depends upon the kind of coordinating atoms of the second ligand as may be seen from the $\Delta \log K$ values given in Table I[2,4,6,7] for several mixed-ligand Cu(II) systems.

$$\Delta \log K = \log K^{\mathrm{Cu(bipy)}}{}_{\mathrm{Cu(bipy)L}} - \log K^{\mathrm{Cu}}{}_{\mathrm{CuL}} \tag{1}$$

In eq 1, $K^{\mathrm{Cu(bipy)}}{}_{\mathrm{Cu(bipy)L}}$ and $K^{\mathrm{Cu}}{}_{\mathrm{CuL}}$ are the equilibrium constants for the formation of the ternary and binary complexes, respectively.

Usually when the equilibrium constants are compared for complexes containing the same kind of ligand in varying numbers, one observes $K^{\mathrm{Cu}}{}_{\mathrm{CuL}_m} > K^{\mathrm{Cu}}{}_{\mathrm{CuL}_{m+n}}$. However, for the ternary complexes the $\Delta \log K$ values are frequently considerably less negative than expected from the difference $\log K^{\mathrm{Cu}}{}_{\mathrm{CuL_2}} - \log K^{\mathrm{Cu}}{}_{\mathrm{CuL}}$; in fact, in quite a number of cases these values are even positive.[2,3] These positive values for $\Delta \log K$ have been found for all systems which contain 2,2′-bipyridyl and a second ligand with oxygen atoms as donors.[8] By contrast, the 2,2′-bipyridyl–Cu^{2+}–ethylenediamine system has a "normal" $\Delta \log K$ of −1.3. Furthermore, when ethylenediamine is substituted for 2,2′-bipyridyl in the inner coordination sphere of copper(II),

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(1) Part I: R. F. Pasternack and H. Sigel, *J. Amer. Chem. Soc.*, **92**, 6146 (1970).

(2) R. Griesser and H. Sigel, *Inorg. Chem.*, **9**, 1238 (1970).

(3) H. Sigel, *Chimia*, **21**, 389 (1967).

(4) P. R. Huber, R. Griesser, B. Prijs, and H. Sigel, *Eur. J. Biochem.*, **10**, 238 (1969).

(5) P. R. Huber, R. Griesser, and H. Sigel, *Inorg. Chem.*, **10**, 945 (1971).

(6) R. Griesser, B. Prijs, H. Sigel, W. Fory, L. D. Wright, and D. B. McCormick, *Biochemistry*, **9**, 3285 (1970).

(7) H. Sigel, P. R. Huber, and R. F. Pasternack, *Inorg. Chem.*, **10**, 2226 (1971).

(8) H. Sigel and D. B. McCormick, *Accounts Chem. Res.*, **3**, 201 (1970), and references therein.