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Coordination Isomers of Biological Iron Transport Compounds. IV.[1-3] Geometrical Isomers of Chromic Desferriferrioxamine B

John Leong and Kenneth N. Raymond*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received August 8, 1974*

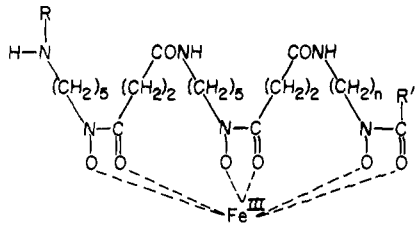
Abstract: A number of microbial iron sequestering and transport agents (the siderochromes) are polyhydroxamic acids. In several of these agents, ferric ion has been replaced by chromic ion to induce kinetic inertness and thereby allow the possibility of isomer separation. The preparation and characterization of the chromic complex of desferriferrioxamine B are reported. Five enantiomeric pairs of geometrical coordination isomers are possible: one cis and four trans. The separation of the cis geometrical isomer from one or more trans isomers and their characterization are described. This is the first preparation and characterization of coordination isomers for metal complexes of ligands involved in microbial iron transport. The cis isomer has visible absorption maxima at 419 (68) and 583 (71) nm (ϵ), while the trans isomers have the same bands at 411 (51) and 589 (72) nm. Both the cis and trans isomers of chromic desferriferrioxamine B isomerize with half-lives of several days in solution at room temperature. The structurally similar chromic complex of desferriferrioxamine D_1 also has been prepared and characterized. The corresponding cobaltic complexes appear to be unstable because of gradual oxidation of the ligands by cobaltic ion.

The linear ferrioxamines (Figure 1), an important class of microbial iron transport agents,[4] are produced by several species of *Streptomyces* and *Nocardia*.[5-11] A characteristic structural feature of the ferrioxamines is repeating units of 1-amino-5-hydroxyaminopentane and succinic acid, such that a stable octahedral ferric complex is formed from three hydroxamate groups. The pathogenicity of certain infections apparently is associated with microbial iron transport, and several ferrioxamines are potent and broad spectrum antibiotics, while others are growth factors.[4,10-13] For example, ferrioxamine B is a growth factor for *Microbacterium lacticum*[10,14] and is capable of reversing ferrimycin antibiotic activity[10,13,15-19] against Gram-positive organisms such as *Bacillus subtilis*.[12,16,20] Ferrimycin A_1 is a derivative of ferrioxamine B in which the free amino group of the latter is substituted.[10,19] The substituent thus converts a growth factor, ferrioxamine B, into a powerful antibiotic.

The sequestering agent desferriferrioxamine B (Desferal) is used in the treatment of acute, accidental iron poisoning.[13,21,22] Schwarzenbach and coworkers demonstrated that desferriferrioxamine B exhibits remarkable affinity for ferric ion, little affinity for other ions which differ in charge or size, and, in particular, little or no affinity for ferrous ion.[23] Emery concluded from proton exchange rates that desferriferrioxamine B undergoes a dramatic conformational change upon complexation with ferric ion,[24] and Bock and Lang interpreted the Mössbauer spectrum of ferrioxamine B.[25] Ferrioxamine E, a cyclic ferrioxamine, crystallizes as a racemic mixture of Λ-cis and Δ-cis isomers.[26,27] All of these considerations raise the question of the possible role specific coordination isomers of siderochromes might play in microbial iron transport.

Many of the questions regarding the structure-function relationships of the siderochromes cannot be answered because of the kinetic lability of these high-spin ferric complexes. The coordination chemistry of hydroxamic acids with metal ions other than ferric is largely unknown.[28] In a previous paper[1] we described the preparation of a simple model diastereoisomeric chromic complex, tris(*N*-methyl-*l*-menthoxyacethydroxamato)chromium(III), and the resolution and characterization of its four geometrical and optical isomers: Λ-cis, Δ-cis, Λ-trans, and Δ-trans.[27] We also prepared and characterized the Λ-cis coordination isomer of two metal-substituted desferrisiderochrome complexes, chromic desferriferrichrome and chromic desferriferrichrysin,[2] and found that Λ-cis chromic desferriferrichrome transports at comparable rates to the native ferric complex in *Ustilago sphaerogena*.[3]

Five enantiomeric pairs of geometrical isomers of ferrioxamine B are possible from an examination of molecular models: one cis and four trans[5] (Figure 2). These five geometrical isomers are named as follows.[27] (i) The absolute configuration about the metal ion defines a rotation direc-



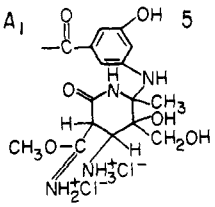
	R	n	R′
Ferrioxamine B	H	5	CH_3-
Ferrioxomine D_1	$CH_3\overset{O}{\overset{\|}{C}}-$	5	CH_3-
Ferrioxomine G	H	5	$HO_2C(CH_2)_2-$
Ferrioxomine A_1	H	4	$HO_2C(CH_2)_2-$
Ferrimycin A_1		5	CH_3-

Figure 1. Structure of the linear ferrioxamines. The basic structural feature of the ferrioxamines is repeating units of 1-amino-5-hydroxyaminopentane and succinic acid.

tion about the C_3 axis, which, when viewed down that axis, is clockwise for Λ and counterclockwise for Δ. The molecule is positioned such that the ring sequence 1, 2, 3 corresponds to the rotation direction. This choice corresponds to whichever of the two possible "up" directions for the C_3 axis is chosen. The ring nearest the free amine terminus is designated as ring 1. (ii) If ring 1 has the carbon atom of the hydroxamate group below the nitrogen, it is denoted "C". If the reverse is true it is called "N." (iii) For rings 2 and 3, each is called "cis" or "trans," depending upon whether it has the same or opposite relative orientation with respect to the coordination C_3 axis as does ring 1. The five geometrical isomers with Λ absolute configuration are shown in Figure 2. The Δ-C-cis,cis isomer is the mirror image of Λ-C-cis,cis; Δ-N-cis,trans is the mirror image of Λ-N-cis,trans, etc.

Replacement of ferric ion by chromic ion should induce kinetic inertness in these complexes and allow the separation of coordination isomers that exist in an equilibrium mixture. We describe here the preparation of the chromic complex of desferriferrioxamine B, the separation of the cis geometrical isomer from one or more trans isomers, and their characterization. *These are the first coordination isomers to be separated and characterized for complexes of ligands involved in microbial iron transport.* The structurally related chromic desferriferrioxamine D_1 complex consists of a similar distribution of isomers. The corresponding cobaltic complexes appear to be unstable because of gradual oxidation of the ligands by cobaltic ion.

Experimental Section

Ultraviolet-visible spectra were measured with a Cary Model 118 spectrophotometer. Chemical analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

Materials. Reagent grade chemicals were used throughout. Desferriferrioxamine B (Desferal) was obtained as a generous gift from Ciba-Geigy Corporation, Summit, N.J. Cobaltic hydroxide was purchased from K and K Chemical Co. The $CrCl_3 \cdot 3THF$ was prepared and stored under a purified nitrogen atmosphere.[29] Absolute ethanol and *N,N*-dimethylformamide were dried over Linde 3A molecular sieve, pyridine was distilled from barium oxide and stored over molecular sieve, and acetic anhydride was dried over

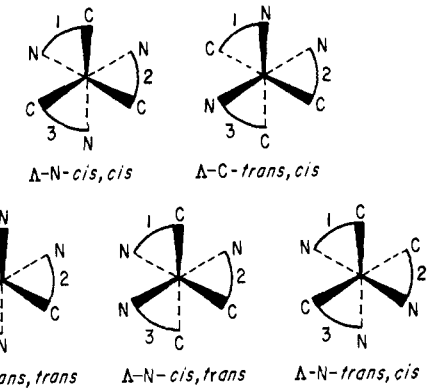


Figure 2. The five enantiomeric geometrical isomers of ferrioxamine B. The oxygen donor atoms of each hydroxamate group have been omitted for clarity. The Λ optical isomer is shown in each case. See text for nomenclature of these geometrical isomers.

molecular sieve, then distilled. Gel filtration was performed on Bio-Gel P-2 (200–400 mesh, Bio-Rad Laboratories). Ion-exchange chromatography was performed on the cation exchange resins, AG 50W-X2 (200–400 mesh, sodium form, Bio-Rad Laboratories) or AG 50W-X4 (minus 400 mesh, sodium form).

Thin-Layer Chromatography. Camag Kieselgel D-O silica gel and Macherey Nagel cellulose powder MN 300 were used for thin-layer and column chromatography. Thin-layer chromatography was performed on all of the metal complexes, and spots were detected visually or stained with iodine vapor.

Ferrioxamine B. In one portion 61.7 mg (0.228 mmol) of $FeCl_3 \cdot 6H_2O$ was added to a rapidly stirred solution of 100 mg (0.152 mmol) of Desferal in 10 ml of H_2O. The reddish brown solution was stirred for 3 hr at room temperature, then adjusted to pH 5.5 with dilute sodium hydroxide solution. After the solution was concentrated to dryness *in vacuo*, the reddish brown residue was dissolved in a minimal amount of water and chromatographed on 12 g of Bio-Gel P-2 with water as the eluent on a glass column with o.d. of 14 mm. The major reddish brown fraction was concentrated to dryness *in vacuo* and the residue was chromatographed on 10 ml of AG 50W-X2 sodium cation exchange resin on a glass column (o.d. of 11 mm) with 0.3 *M* NaCl as the eluent. Gel filtration on Bio-Gel P-2 then was performed on the reddish brown solid as described above. The complex is hygroscopic.

Anal. Calcd for $C_{25}H_{46}N_6O_8ClFe \cdot 3H_2O$: C, 42.65; H, 7.44; N, 11.94; Fe, 7.93. Found: C, 42.6; H, 7.5; N, 11.8; Fe, 8.09.

Cobaltic Desferriferrioxamine B. A slurry of 334.6 mg (3.05 mmol) of cobaltic hydroxide and 250 mg (0.381 mmol) of Desferal in 50 ml of water was stirred rapidly at room temperature for 2 days. The slurry was suction filtered, and the green filtrate was concentrated to dryness *in vacuo*. Gel filtration on Bio-Gel P-2 was performed as described above. Unreacted Desferal was separated from the cobaltic complex by cellulose powder column chromatography as follows. Cellulose powder (23 g) in a solvent mixture of *n*-butyl alcohol:*n*-propyl alcohol:water (9:6:5) was packed under nitrogen pressure in a glass column with o.d. of 25 mm. After topping the column with washed Monterey sand, a solution of 150 mg of complex dissolved in a minimal amount of eluent was applied to the column and eluted under nitrogen pressure. A yellow band containing unreacted Desferal eluted first, followed by a green band containing the desired cobaltic complex. The green residue was chromatographed on a sodium cation exchange column then on a Bio-Gel P-2 column as described above. Both the cobaltic complex and ferrioxamine B elute as single bands with identical R_f's on tlc with cellulose powder with various solvent systems.[30]

Chromic Desferriferrioxamine B. A solution of 142.6 mg (0.381 mmol) of $CrCl_3 \cdot 3THF$, 300.0 mg (0.457 mmol) of Desferal, and 449.7 mg (5.48 mmol) of anhydrous sodium acetate in 150 ml of ethanol was refluxed under dry air ($CaCl_2$ drying tube) for 12 hr, and then concentrated to dryness *in vacuo*. The blue-green residue was chromatographed first on a sodium cation exchange column then on a Bio-Gel P-2 column as described above. Finally the blue-green solid was chromatographed on a cellulose powder column as described above. Both the chromic complex and ferrioxamine B

elute as single bands with identical R_f's on tlc with cellulose powder with various solvent systems.

Separation of Geometrical Isomers. The cis geometrical isomer was separated from one or more trans isomers by sodium cation exchange column chromatography as follows. AG 50W-X4 sodium cation exchange resin (84 ml) in 0.3 *M* NaCl was packed under nitrogen pressure in a glass column with o.d. of 18 mm. After topping the column with washed Monterey sand, a solution of the chromic complex in 10 ml of water was applied to the column and eluted with 0.3 *M* NaCl under nitrogen pressure. Two blue-green fractions were collected within 3.5 hr at 0° and stored in solution at −20° until spectra and analyses were obtained. Both blue-green fractions were concentrated to dryness *in vacuo* between 0 and 10°. A minimal amount of cold anhydrous methanol was added to the residue to dissolve the chromic complex. The methanolic slurry was filtered to remove sodium chloride, and the cold filtrate was concentrated to dryness *in vacuo*. The residue was resuspended then in cold methanol, and sodium chloride was filtered off. This procedure was repeated once more. Finally gel filtration on Bio-Gel P-2 was performed on both blue-green fractions as described above. Both blue-green fractions were ascertained to be greater than 99% pure by chromatographing again the two blue-green bands on somewhat less of the sodium cation exchange resin (60 ml).[31] Both chromic complexes are hygroscopic.

Anal. Calcd for $C_{25}H_{46}N_6O_8ClCr\cdot 5H_2O$: C, 40.78; H, 7.67; N, 11.42; Cr, 7.06. Found for faster eluting band: C, 40.6; H, 7.0; N, 11.6; Cr, 6.45. Calcd for $C_{25}H_{46}N_6O_8ClCr\cdot 2.5H_2O$: C, 43.45; H, 7.44; N, 12.16; Cr, 7.52. Found for slower eluting band: C, 43.5; H, 7.4; N, 12.0; Cr, 7.07.

Chromic Desferriferrioxamine D_1. A solution of 210 mg (0.325 mmol) of chromic desferriferrioxamine B hydrochloride, 15 ml of pyridine, 15 ml of acetic anhydride, and 20 ml of DMF was stirred rapidly at 5° for 10 hr, and then concentrated to dryness *in vacuo*. The blue-green residue was chromatographed first on a sodium cation exchange column then on a Bio-Gel P-2 column as described above. The chromic complex elutes as two blue-green bands with R_f differences of less than a tenth on tlc with silica gel with aqueous methanolic solvent systems, typically 10% H_2O–CH_3OH. The slower eluting band is approximately twice as abundant as the faster eluting band. Silica gel column chromatography was performed on the chromic complex in an attempt to separate the two blue-green bands as follows. Kieselgel (9 g) in absolute methanol was packed under nitrogen pressure in a glass column with o.d. of 16 mm. After topping the column with washed Monterey sand, a solution of 88 mg of complex in 0.4 ml of eluent was applied to the column and eluted under nitrogen pressure. One unresolved blue-green band eluted within 2.5 hr.[32] Finally, gel filtration on Bio-Gel P-2 was performed as described above. The complex is hygroscopic.

Anal. Calcd for $C_{27}H_{47}N_6O_9Cr\cdot 2H_2O$: C, 47.15; H, 7.47; N, 12.22. Found: C, 47.1; H, 7.0; N, 12.4.

Physical Measurements. Visible spectra of all chromic complexes were determined in water solution at room temperature. The solution concentrations of chromium(III) were determined spectrophotometrically as $[CrO_4]^{2-}$ (ϵ_{372}^{max} 4815 *l.* mol^{-1} cm^{-1})[33] after oxidation of an aliquot of the chromium-containing solution with alkaline hydrogen peroxide. Excess hydrogen peroxide was removed by boiling the solution for 0.5 hr. Both the cis geometrical isomer and one or more trans isomers of chromic desferriferrioxamine B were ascertained to be greater than 99% pure by chromatographing these isomers on a sodium cation exchange column as described above.[31]

Results and Discussion

Cation exchange chromatography of the chromic desferriferrioxamine B cation results in two blue-green bands whose properties are summarized in Table I and Figure 3. The more abundant blue-green band with the smaller R_f value has visible absorption maxima very similar to those of the cis optical isomers of tris(*N*-methyl-*l*-menthoxyacethydroxamato)chromium(III), which have spin-allowed d–d transitions $^4A_{2g} \rightarrow {}^4T_{1g}$ and $^4A_{2g} \rightarrow {}^4T_{2g}$ at 425 (66) and 592 (70) nm (ϵ), respectively.[1] We therefore assign the cis geometrical isomer (shown in Figure 2) to this particular blue-green band with the smaller R_f value on the basis of their similar extinction coefficient maxima. The less abundant blue-green band with the greater R_f value has visible absorption maxima very similar to those of the trans optical isomers of tris(*N*-methyl-*l*-menthoxyacethydroxamato)-chromium(III), which have bands at 416 (50) and 596 (70) nm (ϵ).[1] We conclude that the blue-green band with the greater R_f value must consist of one or more trans geometrical isomers (shown in Figure 2) whose visible spectra are indistinguishable from one another. In addition, the visible absorption maxima of the present resolved cis and trans isomers exhibit trends similar to those of the model chromic complexes;[1] *i.e.*, the λ_{max}'s of the cis isomers are bracketed by those of the trans isomers.

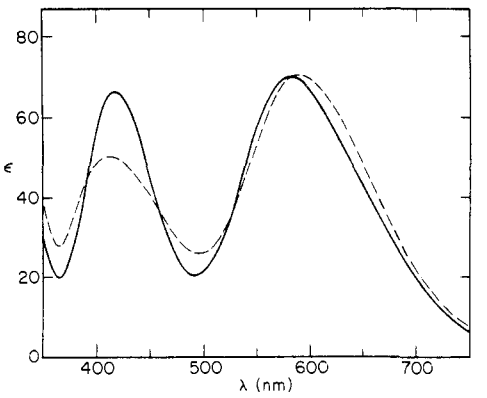


Figure 3. Absorption spectra of the cis isomer and trans isomers of chromic desferriferrioxamine B in aqueous solution: cis (—), trans (- - -).

Table I. Characterization of Chromic Desferriferrioxamine B

Assigned isomer[a]	Abundance, % of total	Absorption, max, nm (ϵ)[b]
Cis chromic desferriferrioxamine B	65	419(67.9), 583(70.7)
Trans chromic desferriferrioxamine B	35	411(50.7), 589(71.5)

[a] See text for discussion of these assignments. [b] Data refer to the visible region only. Units are l. mol^{-1} cm^{-1}.

The structurally similar chromic complex of desferriferrioxamine D_1 also elutes as two blue-green bands with very similar R_f values on silica gel tlc with various solvent systems.[32] If the slower eluting band is assigned as the cis geometrical isomer from direct analogy with the chromatographic properties of model chromic complexes,[1] the observed cis to trans ratio of approximately two, from thin-layer chromatograms, is identical with that found for chromic desferriferrioxamine B. The chromatographic data of chromic desferriferrioxamine B and D_1 suggest that these chromic complexes may consist of only two geometrical isomers and that two geometrical isomers of chromic desferriferrioxamine B have been resolved: cis and trans. Which trans isomer is produced will have to await an X-ray crystallographic investigation.

Both the cis and trans geometrical isomers of chromic desferriferrioxamine B isomerize with half-lives of several days in solution at room temperature.[31] The observed rate of isomerization is considerably slower than that reported for the model chromic complexes,[1] since considerable rearrangement of atoms and/or multiple bond breakage must occur before isomerization can take place.

In conclusion, this is the first preparation and resolution of coordination isomers for metal complexes of ligands involved in microbial iron transport. Visible absorption data

for the cis and trans geometrical isomers of chromic desferriferrioxamine B are very similar to the corresponding data for the previously reported model chromic complexes.[1] Further studies of the preparation and biological activities of these and related compounds are in progress.

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Structures of Metallocarboranes. V. Synthesis and Crystal and Molecular Structure of the Closo 20-Electron Bimetallocarborane 1,6-Bis(η-cyclopentadienyl)-1,6-diferra-2,3-dicarba-*closo*-decaborane(8), 1,6-(η-C_5H_5)$_2$-1,6,2,3-$Fe_2C_2B_6H_8$[1]

Kenneth P. Callahan, William J. Evans, Frederick Y. Lo, Charles E. Strouse, and M. Frederick Hawthorne*

Contribution No. 3353 from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received July 3, 1974*

Abstract: The polyhedral expansion of 4,5-$C_2B_7H_9$ with ferrous chloride and sodium cyclopentadienide produced a new ferracarborane formulated as $(C_5H_5)_2Fe_2C_2B_6H_8$, which exists in paramagnetic and diamagnetic forms. The crystal and molecular structure of the diamagnetic form has been determined by a three-dimensional X-ray diffraction study at −160°. The compound crystallized in the monoclinic centrosymmetric space group $P2_1/n$ with a = 8.999 (7) Å, b = 12.860 (10) Å, c = 11.989 (4) Å, β = 92.00 (5)°, and Z = 4. Observed (25°) and calculated (−160°) densities are 1.58 (3) and 1.623 g cm^{-3}, respectively. Diffraction data to 2θ(max) = 50° (Mo Kα radiation) were collected on a Syntex P1 automated diffractometer, and the structure was solved by conventional Patterson, Fourier, and full-matrix least-squares techniques. The final discrepancy index is R = 3.6% for the 1642 independent nonzero reflections. All atoms were located. The polyhedral geometry observed in this compound is a new ten-vertex species which is derived from a bicapped square antiprism. Structures of the title compound and its cobalt analog are discussed in terms of the bonding theory of metallocarboranes.

The polyhedral expansion reaction,[2] *i.e.*, the addition of NaC_5H_5 and a transition metal chloride to a solution of a reduced carborane or metallocarborane, has been used to synthesize numerous bimetallocarboranes of the general formula $(C_5H_5)_2Co_2C_2B_nH_{n+2}$ (n = 4–10)[2-4] and $(C_5H_5)_2CoNiCB_7H_8$.[5] Recently, paramagnetic bimetallocarboranes containing formally one Co(III) vertex and one Fe(III) vertex have also been prepared in this manner.[6]