Synthesis and Structural Characterization of L-Histidinato-D-penicillaminatochromium(III) Monohydrate

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The novel chromium(III) amino-acid complex L-histidinato-D-penicillaminatochromium(III) monohydrate, [Cr(L-his)(D-pen)]·H_2O (his = histidine, pen = penicillamine), has been prepared by the reaction of D-penicillamine with an aqueous solution containing chromium(III) chloride (or nitrate) and L-histidine. The crystal structure of the complex has been determined from three-dimensional *X*-ray counter data. The complex crystallizes in the monoclinic space group $P2_1$, $Z = 2$, in a cell of dimensions $a = 7.235(4)$, $b = 12.150(8)$, $c = 8.929(6)$ Å, $\beta = 96.00(3)$°. Full-matrix least-squares refinement of the structure, using 1 635 intensities, yielded a final *R* of 0.035. The complex is monomeric, the distorted octahedral geometry at the chromium giving rise to *cis* bond angles in the range 79.8(2)—102.2(2)°. The tridentate D-penicillamine moiety co-ordinates as the dianion, being deprotonated at S and O, with Cr–S, Cr–N, and Cr–O bond lengths of 2.332(2), 2.094(5), and 1.989(4) Å, respectively. The histidine monoanion is also tridentate, co-ordinating through N(amino), N(imidazole), and O, with associated chromium–ligand bond lengths of 2.063(4), 2.057(5), and 2.013(4) Å, respectively. The geometry of this complex is, therefore, quite similar to that found for the corresponding cobalt(III) complex; in both cases, the isomer isolated has S *trans* to O(his) and N(pen) *trans* to N(imidazole).

THE interactions of toxic metal ions with sulphur-containing chelating agents, notably cysteine, penicillamine, *S*-methyl-L-cysteine, and methionine, have been the subjects of intense research activity.[1-12] This work has been stimulated by the therapeutic use of D-penicillamine (D-pen) and its derivatives, and also other sulphur containing chelates such as 2,3-dimercaptopropanol (BAL, British Anti-Lewisite), in the treatment of various forms of metal poisoning in humans.[13-16]

The toxic effects of chromium are well established. While contact with chromium is fortunately less widespread than with some other toxic metals, the metal is found in the dust near cement factories as well as in the chromium-plating industry. Chromium compounds are carcinogens and are corrosive to human tissue; insoluble chromium compounds are retained in the lungs, and are implicated in the occurrence of lung cancer. Chromium has also been shown to cause cancer in the respiratory system and the antrum.[17]

The principal toxic effect of most metals, at the molecular level, is their ability to bind to peptide residues of proteins, notably to histidine (his) and cysteine residues. Hence, complexes in which the metal ion is

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co-ordinated to an L-amino acid (especially L-histidine) may be better models for the therapeutic action of D-pen and its analogues than are complexes of the free metal ion. We have, therefore, initiated a thorough study of such complexes, and report here the characterization of a chromium(III) complex of this type, namely L-histidinato-D-penicillaminatochromium(III) monohydrate, [Cr-(L-his)(D-pen)]·H_2O.

EXPERIMENTAL

The complex was synthesized in a manner entirely analogous to that used for the corresponding cobalt complex.[9] L-Histidine (2×10^{-3} mol in 15 ml water) was added to a solution of chromium(III) chloride (1×10^{-3} mol in 5 ml water), and D-penicillamine (1×10^{-3} mol) was added to the resulting mixture. After several hours, red-brown prismatic crystals of the title complex formed. Substitution of DL-penicillamine for D-penicillamine also yielded the title complex only; we were unable to isolate any of the diastereoisomeric material, [Cr(L-his)(L-pen)], or its enantiomer, by this procedure or by substituting D-his for L-his. This apparent specificity may merely be the result of the greater solubility of [Cr(L-his)(L-pen)] than that of either the title complex or of [Cr(L-his)$_2$]Cl (Found: C, 35.0; H, 5.25; N, 14.85; S, 8.45. Calc. for $C_{11}H_{19}CrN_4O_5S$: C, 35.57; H, 5.16; N, 15.09; S, 8.63%).

The crystals were examined by Weissenberg and precession photography, and were assigned to the monoclinic system. Accurate cell constants were obtained by least-squares procedures.

Crystal Data.—$C_{11}H_{19}CrN_4O_5S$, $M = 371.4$, Monoclinic, $a = 7.235(4)$, $b = 12.150(8)$, $c = 8.929(6)$ Å, $\beta = 96.00(3)°$, $U = 780.4$ Å^3, $D_m = 1.60(2)$ g cm^{-3}, $Z = 2$, $D_c = 1.580$ g cm^{-3}, space group $P2_1$, $F(000) = 386$, μ(Mo-K_α) = 8.69 cm^{-1}.

Data Collection.—Data were collected from a prismatic crystal bounded by faces (010), (0$\bar{1}$0), (100), ($\bar{1}$00), (001), (00$\bar{1}$), (012), and (01$\bar{2}$). The specimen used had approximate dimensions $0.19 \times 0.31 \times 0.09$ mm, and was mounted roughly parallel to the crystallographic b axis. Data were collected on a Picker four-circle automatic diffractometer equipped with a graphite monochromator and a molybdenum tube (Mo-K_α radiation). The data were collected at a tube take-off angle of 1.6° by the θ—2θ scan technique at a scan rate of 0.5° min^{-1}. Peaks were scanned from $-0.80°$ below the calculated K_{α_1} peak position to $+0.80°$ above the calculated K_{α_2} peak position; stationary counter, stationary crystal background counts were measured for 20 s at each end of the scan.

A data set having 2θ(Mo) $< 55°$ was gathered, a total of 2 224 intensities being recorded; for $2\theta > 55°$, there were extremely few data above background. The intensities of three standard reflections were measured periodically throughout the data-collection process, and showed no statistical decline.

Data processing was carried out as described by Corfield *et al.*[18] After correction for background, the intensities were assigned standard deviations according to the formula[19] $\sigma(I) = [C + 0.25(ts/tb)^2(BH + BL) + (pI)^2]^{1/2}$ and the value of p was selected as 0.04. The values of I and $\sigma(I)$ were corrected for Lorentz-polarization effects and for absorption factors. The absorption coefficient for this compound for Mo-K_α radiation is 8.69 cm^{-1}, and for the crystal chosen the transmission coefficients[20] evaluated by numerical integration ranged from 0.854 to 0.930. Of the 2 224 data collected, 1 635 had $I > 2.6\sigma(I)$; only these data were used in the subsequent structure analysis and refinement.

Solution and Refinement of the Structure.—An initial model, in which the co-ordinates of all non-hydrogen atoms of the cobalt analogue[9] (with Cr replacing Co) were used in an isotropic least-squares refinement, gave values of $R\{= [(\Sigma||F_o| - |F_c||)/(\Sigma|F_o|)]\}$ and $R'\{= [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{1/2}\}$ of 0.076 and 0.097, respectively; the weights w were taken as $4F_o^2/\sigma^2(F_o)^2$. Anisotropic refinement of this model led to $R = 0.046$ and $R' = 0.064$. All hydrogen atoms were located in a subsequent difference-Fourier map, and were included in subsequent refinements; because of the relatively small number of data available, the positions of the hydrogen atoms were not varied, and they were assigned isotropic thermal parameters of 4.0 Å^2. This refinement gave the final values of $R = 0.035$ and $R' = 0.048$. The final values of F_o and F_c suggested that no correction for secondary extinction was necessary. In the final cycle of least-squares refinement no parameter underwent a shift in excess of 0.83σ, which is taken as evidence that the refinement had converged. A final difference-Fourier synthesis was featureless, with no peak higher than 0.41 eÅ^{-3} except for one of height 0.59 eÅ^{-3} in the vicinity of the Cr atom. The value of R' showed no unusual dependence on $\sin\theta$ or on $|F_c|$.

The positional and thermal parameters derived from the final least-squares cycle are given in Tables 1 and 2. Observed and calculated structure amplitudes and thermal parameters are deposited as Supplementary Publication No. SUP 22046 (13 pp.).* The scattering factors used throughout this analysis were taken from ref. 21 for Cr,

TABLE 1

Fractional atomic co-ordinates for [Cr(L-his)(D-pen)]·H_2O with estimated standard deviations in parentheses

Atom	x	y	z
Cr	0.141 1(1)	1/4	0.199 20(8)
S	0.073 3(2)	0.360 8(1)	−0.012 7(2)
N(1)	0.422 8(6)	0.281 4(4)	0.224 2(4)
C(1)	0.484 4(6)	0.264 8(5)	0.386 4(5)
C(2)	0.453 4(7)	0.370 2(5)	0.475 0(6)
C(3)	0.375 0(7)	0.171 2(5)	0.447 9(6)
C(4)	0.258 3(7)	0.411 1(5)	0.460 7(5)
C(5)	0.182 1(9)	0.485 3(5)	0.548 3(6)
C(6)	−0.032 1(7)	0.429 8(5)	0.373 0(6)
N(2)	0.124 0(6)	0.375 1(4)	0.352 3(4)
N(3)	−0.001 0(9)	0.495 5(5)	0.491 1(7)
O(1)	0.224 7(5)	0.143 2(3)	0.364 9(4)
O(2)	0.428 3(6)	0.127 6(4)	0.567 8(5)
O(3)	−0.122 6(5)	0.205 8(3)	0.206 6(4)
O(4)	−0.358 7(5)	0.125 4(4)	0.072 0(4)
N(4)	0.119 4(7)	0.124 8(4)	0.037 2(5)
C(7)	−0.195 0(7)	0.159 4(5)	0.087 9(6)
C(8)	−0.072 3(7)	0.150 6(4)	−0.038 8(5)
C(9)	−0.066 2(8)	0.258 5(5)	−0.127 7(5)
C(10)	0.019 7(15)	0.238 0(8)	−0.275 1(8)
C(11)	−0.265 8(11)	0.305 2(6)	−0.163 1(9)
O(W) *	0.435 9(7)	0.014 2(4)	−0.157 2(5)

* O(W) refers to the oxygen atom of the water molecule.

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* For details, see Notices to Authors No. 7 in *J.C.S. Dalton*, 1976, Index issue.

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S, O, N, and C and from ref. 22 for H. The effects of the anomalous dispersion of Cr and S were included in calculations of F_c, the values of $\Delta f'$ and $\Delta f''$ being from ref. 23.

TABLE 2

Fractional co-ordinates of the hydrogen atoms in [Cr(L-his)(D-pen)]·H_2O

Atom	Attached to	*x*	*y*	*z*
H(1)	N(1)	0.456	0.344	0.191
H(2)	N(1)	0.489	0.243	0.170
H(3)	C(1)	0.615	0.247	0.408
H(4)	C(2)	0.530	0.425	0.461
H(5)	C(2)	0.475	0.361	0.586
H(6)	C(5)	0.229	0.533	0.625
H(7)	N(3)	−0.038	0.543	0.508
H(8)	C(6)	−0.146	0.422	0.318
H(9)	N(4)	0.134	0.049	0.070
H(10)	N(4)	0.215	0.133	−0.031
H(11)	C(8)	−0.111	0.096	−0.114
H(12)	C(10)	0.053	0.309	−0.322
H(13)	C(10)	0.132	0.221	−0.239
H(14)	C(10)	−0.034	0.190	−0.350
H(15)	C(11)	−0.256	0.364	−0.221
H(16)	C(11)	−0.334	0.245	−0.255
H(17)	C(11)	−0.309	0.354	−0.060
H(18)	O(W)	0.523	0.055	−0.086
H(19)	O(W)	0.458	0.050	−0.233

RESULTS

The crystal contains monomeric [Cr(L-his)(D-pen)] units which are hydrogen-bonded to water molecules of solvation. A view of the co-ordination around the chromium(III) centers is given in Figure 1. The co-ordination around chromium is approximately octahedral, the six co-ordination sites being occupied by the two tridentate amino-acid anions. The histidine ligand is deprotonated at the carboxyl group, co-ordinating to the metal as the monoanion through both amine [N(1)] and imidazole [N(2)] nitrogen atoms and a carboxyl oxygen atom [O(1)] with metal–ligand bond lengths of 2.063(4), 2.057(5), and 2.013(4) Å, respectively. The corresponding values in the cobalt(III) analogue are[9] 1.933(3), 1.925(3), and 1.989(3) Å, respectively, which suggests that the Cr–O bond in the present complex is relatively stronger than that in the cobalt complex. The terdentate co-ordination observed here for L-his is similar to that observed in a number of complexes of cobalt, nickel, molybdenum, and copper;[9,24-29] it is noteworthy, however, that both unidentate and bidentate his co-ordin-

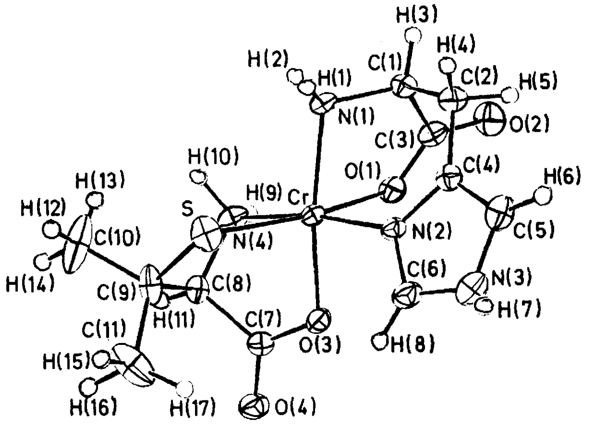

FIGURE 1 View of the co-ordination around chromium in [Cr(L-his)(D-pen)]·H_2O. Hydrogen atoms are represented as spheres of arbitrary size

TABLE 3

Bond distances (Å) and bond angles (°), with estimated standard deviations in parentheses, for [Cr(L-his)(D-pen)]·H_2O

(*a*) Bond distances

Cr–S	2.332(2)	Cr–N(1)	2.063(4)
Cr–O(1)	2.013(4)	Cr–N(2)	2.057(5)
Cr–O(3)	1.989(4)	Cr–N(4)	2.094(5)
N(1)–C(1)	1.484(6)	C(4)–C(5)	1.349(8)
C(1)–C(2)	1.534(8)	C(4)–N(2)	1.369(7)
C(1)–C(3)	1.521(7)	C(5)–N(3)	1.375(9)
C(3)–O(1)	1.296(7)	N(3)–C(6)	1.322(8)
C(3)–O(2)	1.220(7)	C(6)–N(2)	1.340(7)
C(2)–C(4)	1.490(7)		
N(4)–C(8)	1.511(7)	C(9)–S	1.845(6)
C(8)–C(9)	1.536(8)	C(8)–C(7)	1.513(7)
C(9)–C(10)	1.533(8)	C(7)–O(3)	1.265(6)
C(9)–C(11)	1.533(10)	C(7)–O(4)	1.248(6)

(*b*) Bond angles

S–Cr–N(1)	95.9(1)	N(1)–Cr–N(4)	102.2(2)
S–Cr–N(2)	95.2(1)	N(2)–Cr–O(1)	91.3(2)
S–Cr–O(1)	171.9(1)	N(2)–Cr–O(3)	93.0(2)
S–Cr–O(3)	93.5(1)	N(2)–Cr–N(4)	172.2(2)
S–Cr–N(4)	82.2(1)	O(1)–Cr–O(3)	91.0(2)
N(1)–Cr–N(2)	85.3(2)	O(1)–Cr–N(4)	92.0(2)
N(1)–Cr–O(1)	79.8(2)	O(3)–Cr–N(4)	79.9(2)
N(1)–Cr–O(3)	170.5(2)		
Cr–N(1)–C(1)	105.9(3)	C(2)–C(4)–C(5)	127.9(5)
C(2)–C(1)–C(3)	109.2(4)	N(2)–C(4)–C(5)	108.7(5)
N(1)–C(1)–C(2)	110.2(4)	C(4)–C(5)–N(3)	106.3(5)
N(1)–C(1)–C(3)	109.8(4)	C(5)–N(3)–C(6)	108.6(5)
C(1)–C(2)–C(4)	115.0(4)	N(3)–C(6)–N(2)	109.5(5)
C(1)–C(3)–O(1)	115.3(5)	C(6)–N(2)–C(4)	106.9(5)
C(1)–C(3)–O(2)	120.8(5)	C(6)–N(2)–Cr	124.6(4)
O(1)–C(3)–O(2)	123.9(5)	C(4)–N(2)–Cr	128.2(4)
C(2)–C(4)–N(2)	123.4(5)		
Cr–N(4)–C(8)	99.1(3)	S–C(9)–C(11)	108.0(5)
N(4)–C(8)–C(9)	109.6(4)	C(8)–C(9)–C(10)	110.0(6)
N(4)–C(8)–C(7)	105.2(4)	C(8)–C(9)–C(11)	110.0(5)
C(7)–C(8)–C(9)	112.1(4)	C(9)–S–Cr	96.8(2)
C(10)–C(9)–C(11)	109.7(6)	C(8)–C(7)–O(3)	115.7(4)
S–C(9)–C(8)	109.3(3)	C(8)–C(7)–O(4)	121.0(4)
S–C(9)–C(10)	109.8(5)	O(3)–C(7)–O(4)	123.2(5)

(*c*) Hydrogen bonding

X–H · · · Z	X · · · Z	H · · · Z	X–H–Z
N(1)–H(1) · · · O(W$^{\text{I}}$)	3.087(7)	2.24	168
N(1)–H(2) · · · O(4$^{\text{II}}$)	2.896(6)	2.06	168
N(3)–H(7) · · · O(1$^{\text{III}}$)	2.815(7)	2.22	152
O(W)–H(18) · · · O(4$^{\text{II}}$)	2.754(6)	1.79	167
O(W)–H(19) · · · O(2$^{\text{IV}}$)	2.812(6)	2.01	162

Roman superscripts refer to atoms in the following positions: I: $1 - x, \frac{1}{2} + y, -z$; II $1 + x, y, z$; III $-x, \frac{1}{2} + y, 1 - z$; IV $x, y, -1 + z$

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ation have also been documented.[30-35] The bond angles subtended at chromium by the three chelating rings of the his ligand are N(1)–Cr–O(1) = 79.8(2), N(1)–Cr–N(2) = 85.3(2), and O(1)–Cr–N(2) = 91.3(2)°; as anticipated, the angles increase with increasing ring size (from five- to seven-membered ring).

The D-pen ligand, which is deprotonated at both the sulphur and carboxyl groups, co-ordinates to the metal as the dianion through S, N, and O with associated metal–ligand bond lengths of 2.332(2), 2.094(5), and 1.989(4) Å, respectively. These distances can be compared to values of 2.4164(8), 2.062(2), and 1.981(1) Å in [3] Na[Cr(L-cys)$_2$] (cys = cysteinato) and to average values of 2.337(2), 2.096(4), and 1.966(3) Å in [36] mercaptoacetatobis(ethylenediamine)chromium(III), and appear to be normal. The [pen]$^{2-}$ ligand subtends angles at the chromium of S–Cr–N(4) = 82.2(1), S–Cr–O(3) = 93.5(1), and N(4)–Cr–O(3) = 79.9(2)°; here, therefore, we again note that the six-membered ring has a larger associated angle than do the five-membered rings. The terdentate co-ordination by [D-pen]$^{2-}$ is reminiscent of that found [37] in Pb(D-pen) and that [10] in K[Co(D-pen)(L-pen)]·2H$_2$O, but is different from its co-ordination in a variety of other complexes in which it is unidentate or bidentate.[4-6,38] The bond lengths in the D-pen dianion are similar to those contained in a recent compilation [3] of metal complexes of cysteine and penicillamine, and are apparently normal. The bond lengths and angles found in the complex are listed in Table 3. The dihedral angles associated with the ligands in this complex are tabulated in Table 4.

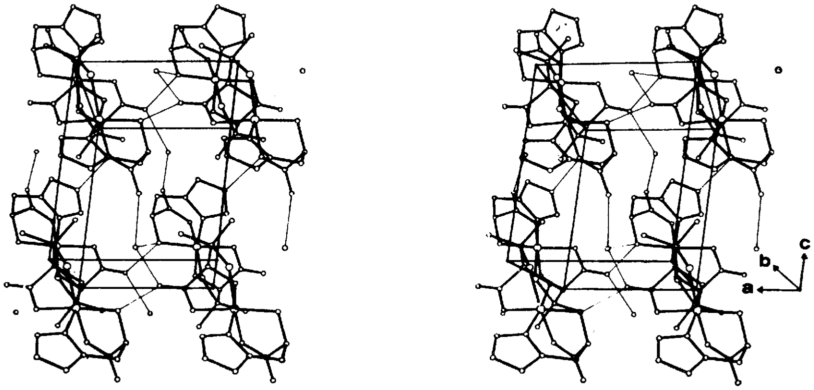

FIGURE 2 The packing in the crystals of [Cr(L-his)(D-pen)]·H$_2$O. Hydrogen bonds are shown as thin lines

The packing in the crystals is depicted in Figure 2, which is a stereoscopic view of the cell contents. As can be seen in this figure, there is extensive hydrogen bonding in the crystals.

TABLE 4

Dihedral angles of interest for [Cr(L-his)(D-pen)]·H$_2$O

(a) L-Histidine

O(1)–C(3)–C(1)$^{\alpha}$–C(2)	104.6 *	Cr–N(1)–C(1)$^{\alpha}$–C(2)	−84.9
O(1)–C(3)–C(1)$^{\alpha}$–N(1)	−16.4	Cr–O(1)–C(3)–C(1)$^{\alpha}$	−12.8
N(1)–C(1)$^{\alpha}$–C(2)–C(4)	57.3	Cr–N(2)–C(4)–C(2)	6.6
C(3)–C(1)$^{\alpha}$–C(2)–C(4)	−6.5	C(1)$^{\alpha}$–C(2)–C(4)–N(2)	−14.6
Cr–N(1)–C(1)$^{\alpha}$–C(3)	35.4		

(b) D-Penicillamine

O(3)–C(7)–C(8)$^{\alpha}$–C(9)	−80.1	Cr–N(4)–C(8)$^{\alpha}$–C(7)	−50.8
O(3)–C(7)–C(8)$^{\alpha}$–N(4)	38.8	Cr–O(3)–C(7)–C(8)$^{\alpha}$	−2.6
N(4)–C(8)$^{\alpha}$–C(9)–S	−43.6	Cr–S–C(9)–C(8)	−1.1
Cr–N(4)–C(8)$^{\alpha}$–C(9)	68.9		

* Values are taken as positive when far atom rotates anticlockwise relative to near atom to be eclipsed. The α-carbon atoms are denoted by C$^{\alpha}$.

The amino-group of the L-his residue participates in hydrogen bonds of lengths 2.896(6) and 3.087(7) Å with the free carboxyl oxygen atom [O(4)] of the D-pen ligand and with the water molecule, respectively. The protonated, unco-ordinated imidazole nitrogen atom [N(3)] forms a hydrogen bond of length 2.815(7) Å to the co-ordinated histidine oxygen atom [O(1)]. The water molecule, in addition to the acceptor hydrogen bond above, forms hydrogen bonds to the two free carboxyl oxygen atoms [O(2) and O(4)], with lengths of 2.812(6) and 2.754(6) Å, respectively. Other details concerning these hydrogen bonds are given in Table 3.

This research was supported by the National Institute of Environmental Health Sciences.

[6/1901 *Received*, 11*th October*, 1976]

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