Synthesis and *X*-Ray Structure of L-Histidinyl-D-penicillaminatocobalt(III) and L-Histidinyl-D-penicillaminatochromium(III)

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Summary Reaction of $[M(L\text{-his})_2]$ (M=Co,Cr;his=histidyl) with D- or DL-penicillamine (pen) gives the octahedral complexes [M(L-his)(D-pen)], while reaction of [Co(L-his)-(D-his)] with DL-penicillamine gives [Co(L-his)(D-pen)] and [Co(D-his)(L-pen)], but under mild conditions [M(L-his)(L-pen)] and [M(D-his)(D-pen)] are not obtained.

THE binding of penicillamine and other cysteine derivatives to transition-metal ions is of great significance because of the use of these ligands in chelation therapy for metal poisoning.[1] Consequently, the crystal structures of a number of metal complexes of these ligands have been investigated,[2–5] and both bidentate and tridentate co-ordination has been observed. It is noteworthy that only D-penicillamine should be used in clinical treatment,[6] largely because the L-isomer is toxic for reasons which are totally unrelated to metal ions.[7] In the living system, the toxic metal ions bind to the peptide residues of the proteins, and so complexes which contain metal ions co-ordinated to both an amino-acid and D-penicillamine are probably better models for the biological activity of this ligand than are complexes of the free metal ions. We report here the syntheses and crystal structures of the first fully characterized complexes of this general type.

L-Histidinyl-D-penicillaminatocobalt(III) monohydrate (I) was prepared by the following method: to a solution of cobalt(II) chloride dihydrate (1 mmol) in water (5 ml) was added a solution of L-histidine (2 mmol) in water (15 ml) and to the resultant solution was added D-penicillamine (1 mmol). After a few hours, dark brown prismatic crystals of (I) formed. The formulation of the complex as containing cobalt(III) was confirmed by the diamagnetism of the sample. Replacement of D-penicillamine by DL-penicillamine in the above procedure also yielded (I), and did not produce any

of the diastereomeric material [Co(L-his)(L-pen)]. Similarly, the reaction of $CoCl_2 \cdot 2H_2O$ with DL-histidine followed by addition of D-penicillamine again yielded only complex (I). The reaction of $CoCl_2 \cdot 2H_2O$ with DL-histidine followed by addition of DL-penicillamine yields crystals of $[Co_2(D\text{-his})(L\text{-his})(D\text{-pen})(L\text{-pen})] \cdot 2H_2O$ (II) which contain the complexes [Co(L-his)(D-pen)] and [Co(D-his)(L-pen)], *i.e.* (I) and its enantiomer. Under no conditions have we been able to isolate complexes of the types [Co(L-his)(L-pen)] or [Co(D-his)(D-pen)]. The chromium(III) analogue of (I), L-histidinyl-D-penicillaminatochromium(III) monohydrate (III), was prepared in a similar manner, using chromium(III) chloride in place of cobalt(II) chloride. Brown rectangular crystals of (III) formed in a few hours.

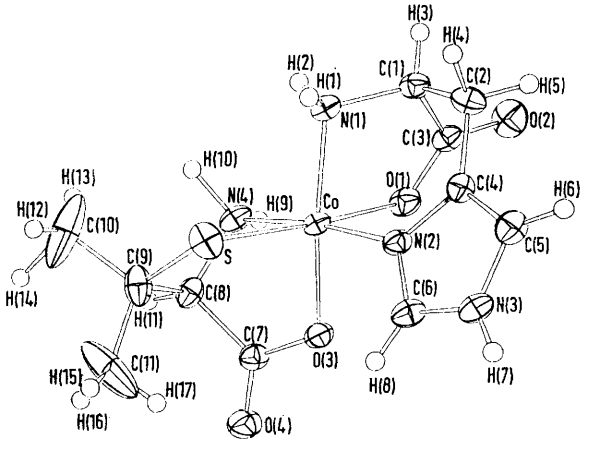

FIGURE. View of the co-ordination around cobalt(III) in $[Co(L\text{-his})(D\text{-pen})] \cdot H_2O$ (I). The structure of the analogous chromium(III) complex is very similar.

The complexes (I), (II), and (III) have been characterized by single-crystal *X*-ray diffraction methods. *Crystal data:* (I), $C_{11}H_{19}CoN_4O_5S$, $M = 378{\cdot}3$, monoclinic, $a = 7{\cdot}078(2)$, $b = 12{\cdot}263(4)$, $c = 8{\cdot}856(3)$ Å, $\beta = 96{\cdot}06(2)°$, $U = 764{\cdot}4$ Å^3, $D_m = 1{\cdot}60(2)$ g cm^{-3}, $Z = 2$, space group $P2_1$, $D_c = 1{\cdot}643$ g cm^{-3}, $F(000) = 392$, μ(Mo-K_α) = 13·3 cm^{-1}. Compound (II), $C_{11}H_{19}CoN_4O_5S$, $M = 378{\cdot}3$, orthorhombic, $a = 17{\cdot}537(6)$, $b = 7{\cdot}053(3)$, $c = 12{\cdot}314(7)$ Å, $U = 1523{\cdot}1$ Å^3, $D_m = 1{\cdot}62(2)$ g cm^{-3}, $Z = 4$, space group $Pca2_1$, $D_c = 1{\cdot}650$ g cm^{-3}, μ(Mo-K_α) = 13·4 cm^{-1}, $F(000) = 784$. Compound (III), $C_{11}H_{19}N_4O_5SCr$, $M = 371{\cdot}4$, monoclinic, $a = 7{\cdot}234(5)$, $b = 12{\cdot}148(9)$, $c = 8{\cdot}928(6)$ Å, $\beta = 95{\cdot}94(3)°$, $U = 780{\cdot}4$ Å^3, $D_m = 1{\cdot}60(2)$ g cm^{-3}, $Z = 2$, space group $P2_1$, $D_c = 1{\cdot}580$ g cm^{-3}, $F(000) = 386$, μ(Mo-K_α) = 8·69 cm^{-1}; crystals of (III) are isomorphous with those of (I). Intensity data for all three complexes were obtained using an automatic Picker four-circle diffractometer equipped with a graphite monochromator and using Mo-K_α radiation. The structures were solved by normal heavy-atoms methods and refined by least-squares techniques. At the present stage of refinement, the conventional *R*-factors for compounds (I), (II), and (III) are 0·032, 0·108, and 0·046, respectively. All atoms have been located in all three structures.

The structure of complex (I) is shown in the Figure. The co-ordination around the cobalt(III) centre is roughly octahedral, the ligating atoms being N(imidazole), N(terminal), and O of histidine and N, O, and S of penicillamine. The isomer isolated has S *trans* to O(histidinyl). The bond lengths to the histidinyl unit in the primary co-ordination sphere are Co–O, 1·989(3); Co–N(imidazole), 1·925(3); Co–N(terminal), 1·933(3) Å. Those involving penicillamine are Co–S, 2·281(1); Co–O, 1·921(3); Co–N, 1·973(4) Å. The bond angles between *cis*-atoms range from 82·6(1) to 98·3(2)°. The geometries of the other two complexes are quite similar to that of (I).

The penicillamine ligands in these complexes are all dianions, deprotonation occurring at the carboxy- and sulphhydryl groups; the same sites of deprotonation have been observed in dianionic penicillamine[3,4] and cysteine[8] complexes of other metals. As we have noted elsewhere,[2] tridentate co-ordination by cysteine derivatives to a single metal ion is relatively uncommon, and the only other metal complex which has been shown[4] to contain tridentate pen^{2-} in the solid state is $Pb(pen^{2-})$.

Thermodynamic stereoselectivity has been observed[9] in the binary pen^{2-} complex $[Ni(pen)_2]^{2-}$, where it was found that $[Ni(D\text{-pen})_2]^{2-}$ is more stable than $[Ni(D\text{-pen})(L\text{-pen})]^{2-}$. The stereochemical selectivity observed in these reactions may be of far-reaching biological significance. If, as may be expected, analogous results obtain in the living system in which toxic transition-metal ions are co-ordinated to L-amino-acid residues, these studies strongly suggest that D-penicillamine is a much more effective chelating agent than L-penicillamine. Hence, this study provides a compelling reason for choosing D-penicillamine over DL-penicillamine in laboratory tests and should also serve to warn clinical scientists that results obtained with DL-penicillamine may not apply to D-penicillamine and *vice versa*.

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