Three Chromium(III) Complexes with Dipeptide Ligands

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The first chromium(III)–peptide complexes to be characterised by *X*-ray crystal structure analysis are reported.

The preparations and crystal structure analyses of three chromium(III)–dipeptide complexes are reported. At first sight it may seem remarkable that no crystal structure analysis of a peptide complex of chromium has been recorded previously, since there exists an extensive literature devoted to the chemical, spectroscopic, and structural characterisation of peptide complexes of cobalt, nickel, copper, and zinc. The absence of structural information concerning chromium–peptide complexation is all the more surprising in view of the intense interest which has been generated for almost thirty years by reports that chromium plays a role in the carbohydrate metabolism of animals including man, and that a chromium(III)-containing 'glucose tolerance factor' has a peptide component.[1,2] If chromium has a biological function (a hypothesis for which unequivocal evidence still has to be adduced), the analogy with other biologically active first-row transition metals suggests that chromium–protein interactions may be involved.

The reason why no chromium–peptide complex has hitherto been structurally characterised is no doubt connected with the well-known tendency of chromium(III) complexes to form hydroxo-bridged polymers in the presence of water. In the present work, the isolation of three chromium(III)–dipeptide complexes:† $NaCr(Gly\text{-}H_{-1}Gly)_2\cdot 4.5H_2O$ (**1**), $NaCr(L\text{-}Pro\text{-}H_{-1}Gly)_2\cdot H_2O$ (**2**), and $Cr_2(\beta\text{-}Ala\text{-}L\text{-}H_{-1}His)_2(OH)(OMe)\cdot 2.5H_2O$ (**3**), from mixtures of mono- and poly-nuclear species has been achieved partly by adjustment of the reaction conditions, and partly by the use of appropriate conditions for chromatography.

Table 1. Electronic spectra of chromium(III)–peptide complexes.

Complex	$\lambda_{max.}$/nm($\varepsilon_{max.}$/dm^3 mol^{-1} cm^{-1})	
$Cr_2(\beta\text{-}Ala\text{-}L\text{-}H_{-1}His)_2(OH)(OMe)$[a,b]	503 (64)	388 (56)
$Cr(Gly\text{-}H_{-1}Gly)_2^-$ [a]	552 (185)	420 (40)
$Cr(L\text{-}Pro\text{-}H_{-1}Gly)_2^-$ [a]	556 (254)	425 (89)

[a] In H_2O. [b] Dimer probably dissociates in solution. See text.

The structures of $Cr(Gly\text{-}H_{-1}Gly)_2^-$ in (**1**), $Cr(L\text{-}Pro\text{-}H_{-1}Gly)_2^-$ in (**2**), and $Cr_2(\beta\text{-}Ala\text{-}L\text{-}H_{-1}His)_2(OH)(OMe)$ in

† *Abbreviations:* $H_{-1}L^{2-}$ denotes the doubly anionic (peptide deprotonated) form of a dipeptide, $NH_2CHRCON^-CHR'COO^-$. Amino-acid residues are represented by standard 3-letter codes: Gly = glycine, Ala = alanine, His = histidine, Pro = proline.

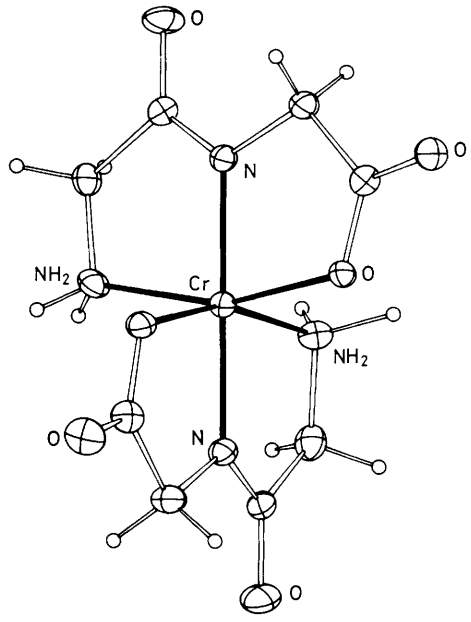

Figure 1. ORTEP view of $Cr(Gly\text{-}H_{-1}Gly)_2^-$ in (**1**). Selected average distances (Å) and angles (°): Cr–N(amino) 2.079(7), Cr–N(peptide) 1.956(7), Cr–O(carboxy) 1.991(7), N(amino)–Cr–N(peptide) 79.8(3), N(peptide)–Cr–O(carboxy) 81.0(3), N(amino)–Cr–O(carboxy) 160.5(2), N(peptide)–Cr–N′(peptide) 177.2(3).

(**3**) are shown in Figures 1—3.‡ In all three complexes the metal is co-ordinated by the dipeptide in a meridional fashion *via* the N(amino), N(peptide), and O(carboxy) atoms. In the dimeric β-alanyl-L-histidine complex each of the metal atoms is bonded, in addition, to an N(imidazole) atom. This hydroxo- and methoxo-bridged dimer belongs to a type common in Cr^{III} chemistry. The structure is stabilized by a pair of hydrogen bonds between the co-ordinated N(amino) atom in each half of the dimer and the co-ordinated O(carboxy) atom in the other.

The coplanarity of the bonds at the N(peptide) atoms in all three complexes indicates that the amide groups are deprotonated. The dimensions in (**1**) and (**2**) are more precisely determined than those in (**3**). The Cr–N(amino) and Cr–O(carboxy) bond lengths in (**1**) and (**2**) [2.079(7)—2.106(4) Å and 1.991(7)—2.004(4) Å, respectively] are at the tops of the ranges normally observed in Cr^{III} complexes of amino-acids.[3]

‡ *Crystal data:* (**1**) $C_8H_{21}CrN_4NaO_{10.5}$, M_r = 416.3, monoclinic, space group $P2_1/c$, a = 5.948(3), b = 23.416(4), c = 13.069(6) Å, β = 117.50(2)°, U = 1614 Å^3, D_c = 1.713 g cm^{-3}, Z = 4, μ(Mo-K_α) = 7.45 cm^{-1}, final R = 0.064, R_w = 0.055, 1623 unique reflections with $I \geq 2.5\sigma(I)$. (**2**) $C_{14}H_{27}CrN_4NaO_{9.5}$, M_r = 478.4, trigonal, space group $R32$, a = 12.303(2) Å, α = 73.74(1)°, U = 1675 Å^3, D_c = 1.423 g cm^{-3}, Z = 3, μ = 5.61 cm^{-1}, final R = 0.051, R_w = 0.055, 1590 unique reflections with $I \geq 2.5\sigma(I)$. (**3**) $C_{19}H_{33}Cr_2N_8O_{10.5}$, M_r = 645.5, orthorhombic, space group $P2_12_12_1$, a = 13.818(4), b = 13.970(4), c = 15.209(8) Å, U = 2935 Å^3, D_c = 1.461 g cm^{-3}, Z = 4, μ = 7.44 cm^{-1}, final R = 0.068, R_w = 0.074, 1990 unique reflections with $I \geq 2.5\sigma(I)$.

All reflections were measured on an Enraf–Nonius CAD4-F four-circle diffractometer using Mo-K_α radiation (λ = 0.710 69 Å). The structures were solved using MULTAN,[7] (**1**), and SHELX-76,[8] (**2**) and (**3**), and refined by blocked-, (**1**) and (**3**), or full-, (**2**), matrix least-squares techniques using SHELX-76. Hydrogen atoms were included in all structures at calculated positions (C–H 0.97, N–H 0.91 Å).

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1986.

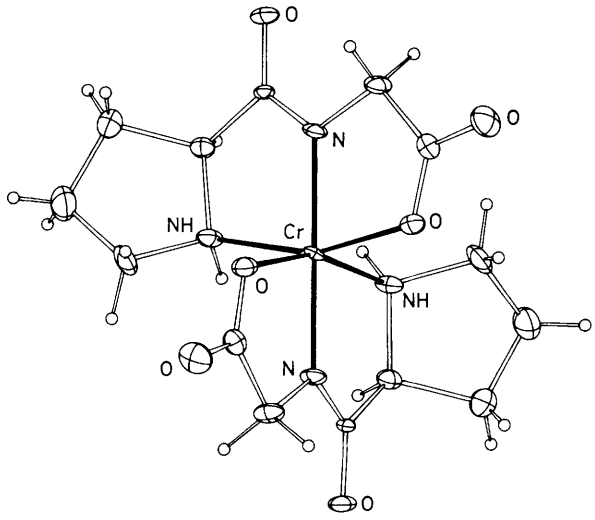

Figure 2. ORTEP view of $Cr(L\text{-}Pro\text{-}H_{-1}Gly)_2^-$ in (**2**). Selected distances (Å) and angles (°): Cr–N(amino) 2.106(4), Cr–N(peptide) 1.964(4), Cr–O(carboxy) 2.004(4), N(amino)–Cr–N(peptide) 80.2(2), N(peptide)–Cr–O(carboxy) 80.1(2), N(amino)–Cr–O(carboxy) 160.3(1), N(peptide)–Cr–N′(peptide) 178.9(1).

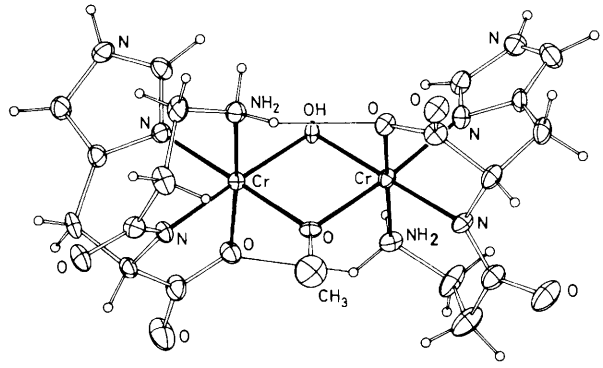

Figure 3. ORTEP view of $Cr_2(\beta\text{-}Ala\text{-}L\text{-}H_{-1}His)_2(OH)(OMe)$, (**3**). Selected average distances (Å) and angles (°): Cr–N(amino) 2.05(1), Cr–N(peptide) 1.98(2), Cr–O(carboxy) 1.98(2), Cr–N(imidazole) 2.05(1), Cr–OH 1.99(1), Cr–OMe 1.96(2), Cr ··· Cr 3.012(2), N(amino)–Cr–N(peptide) 93(1), N(peptide)–Cr–O(carboxy) 82.4(4), N(amino)–Cr–O(carboxy) 174.6(3), N(amino)–Cr–(imidazole) 92.8(8), N(peptide)–Cr–N(imidazole) 84.5(4), O(carboxy)–Cr–N(imidazole) 88.5(7), HO–Cr–OMe 80.5(4), Cr–OH–Cr′ 98.5(3), Cr–O(Me)–Cr 100.2(3).

The Cr–N(peptide) bonds are significantly shorter than the Cr–N(amino) bonds [1.956(7)—1.964(4) Å], reflecting the difference between sp^2 and sp^3 hybridisation.[4] The same relative order of metal–ligand bond lengths, M–N(amino) ≈ M–O(carboxy) > M–N(peptide), is found in the peptide complexes of Co^{III}, Ni^{II}, and Cu^{II}.[4] For all three types of bond, the values for Cr^{III} fit into the sequence $Ni^{II} > Cr^{III} > Cu^{II} > Co^{III}$ to be expected from the d-electron configurations and oxidation states of the metal atoms.

Among the three ligands, β-Ala-L-His appears to be the least strained and L-Pro-Gly the most strained. The N(amino)–Cr–N(peptide) angle is much closer to 90° in (**3**) than in (**1**) and (**2**), and the Cr–N(amino) bond lengths increase significantly in the order (**3**) < (**1**) < (**2**). These observations are consistent with the presence of a 6-membered chelate ring (characteristically less strained than a 5-membered chelate ring[4]) in (**3**),

and with the constraints imposed by the cyclic side-chain in (**2**). The $\lambda_{max.}$ and $\varepsilon_{max.}$ values of the electronic absorption bands of the complexes also increase in the order (**3**) < (**1**) < (**2**) (Table 1). A similar correlation between electronic spectra, metal–ligand bond lengths, and distortions from octahedral symmetry is found among $Co^{III}N_6$ complexes.[5]

The complexes were prepared by heating *trans*-tetraaquadichlorochromium(III) chloride with the ligand in methanol.§ After a short period of heating, sodium hydroxide was added. The colour of the mixture changed towards blue or purple, and no hydrated chromium(III) oxide was precipitated despite the fact that the solution was highly basic. Prolonged heating resulted in the formation of a number of products in each reaction. These included soluble anionic monomeric species with peptide and hydroxo- or methoxo- ligands, as well as intractable insoluble solids. The relative yields of these products depended on the proportions of metal, ligand, and base, and on the reaction conditions. The use of sodium methoxide as base gave essentially the same results as sodium hydroxide, whereas with triethylamine only insoluble solid products were obtained. The components of the reaction mixture could be separated by chromatography on silica-gel columns eluted with methanol. The required complex was the fastest-moving component in each case. Complex (**1**) crystallised from concentrated water solution, (**2**) from concentrated methanol solution diluted with acetone and cooled, and (**3**) from dilute methanol solution. When (**3**) was redissolved in water, dissociation of the dimers was suggested by the presence of neutral, anionic, and cationic species in solution. None of the three complexes showed 'glucose tolerance factor' activity in a biological assay system.[6]

§ (**1**): $CrCl_3 \cdot 6H_2O$ refluxed with peptide (2 equiv.), 2 h; NaOH (5 equiv.) and more peptide (1 equiv.) added; refluxed, 12 h. (**2**): $CrCl_3 \cdot 6H_2O$ and peptide (3 equiv.) refluxed, 2 h; NaOH (4 equiv.) added; refluxed, 26 h. (**3**): As for (**2**), but reactants in proportions 1:3:5.

The three chromium(III)–peptide complexes are water-soluble and persist in neutral aqueous solution for several weeks. Thus, chromium(III)–peptide complexes of this type are plausible as biological models, although it is not clear how they might be formed under biological conditions. The conditions required for the synthesis of these N- and O-co-ordinated complexes, together with the fact that the complexes are of limited solubility (in water and lower alcohols), suggest that it may be difficult to prepare the stable ternary chromium–peptide–nicotinate complexes which are among the currently favoured models for the biologically active form of chromium.[2,6]

This work was supported by the Australian Research Grants Scheme. The cited biological assays were performed at the Beltsville Human Nutrition Research Center, United States Department of Agriculture, by courtesy of Dr. Walter Mertz.

Received, 1st May 1986; Com. 582

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