Model Compounds for Metal–Protein Interaction: Crystal Structure of Three Platinum(II) Complexes of L- and DL-Methionine and Glycyl-L-methionine

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Summary The structures of dichloro-DL- and dichloro-L-methioninеplatinum(II) have been determined by *X*-ray diffraction, and the structure of chloroglycyl-L-methioninatoplatinum(II) monohydrate by *X*-ray and neutron diffraction.

THREE complexes, dichloro-DL-methioninеplatinum(II) [Pt(DL-MetH)Cl_2 (A)], dichloro-L-methioninеplatinum(II) [Pt(L-MetH)Cl_2 (B)], and chloroglycyl-L-methioninatoplatinum(II) monohydrate [Pt(Gly-L-Met)Cl,H_2O (C)] have been prepared by the interaction of $PtCl_4^{2-}$ with the free ligands in aqueous solution. All three structures have been determined by *X*-ray diffraction and the last by neutron diffraction.

The methionine molecules in (A) and (B) co-ordinate through the N(amino) and S(thioether) atoms. In (C) the peptide is tridentate, co-ordinating through the N(amino), N(peptide), and S(thioether) atoms to form adjacent five- and six-membered chelate rings. The square-planar co-ordination in all three complexes is completed by chlorine atoms (see Figure).

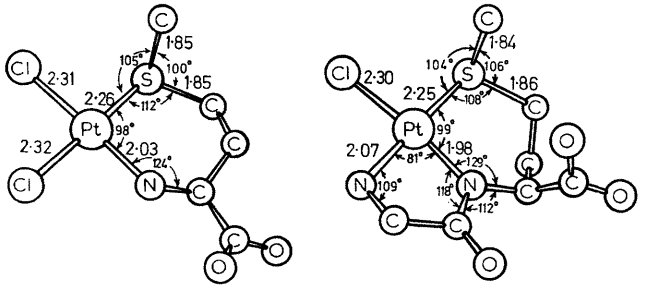
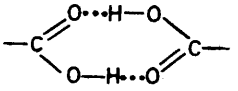


FIGURE. *Left*: *One molecule of* Pt(L-MetH)Cl_2 *in* (A) *and* (B), *showing average dimensions taken from the two* X-*ray structure analyses at the present level of refinement. Right*: *Molecule of* Pt(Gly-L-Met)Cl *in* (C). *The dimensions are from the* X-*ray structure analysis.*

The configurations of the bonds about all the S(thioether) atoms are trigonal pyramidal. It follows that co-ordination creates chiral centres at the sulphur atoms. In (A) the sulphur atoms in centrosymmetrically related complexes obviously have opposite chiralities. In (B) there are two independent Pt(L-MetH)Cl_2 molecules in the crystallographic asymmetric unit, and the sulphur atoms in these again have opposite chiralities (only one of which is illustrated in the Figure). There are significant conformational differences between (A), (B), and (C). In (A) and (B) the chelate rings are in the "chair" conformation, and the carboxyl and methyl groups are quasi-equatorial and quasi-axial, respectively. The complex (C) has its six-membered ring in the "boat" form, and the carboxyl and methyl groups are both quasi-axial (*i.e.* almost perpendicular to the co-ordination square). The "chair" conformation with a quasi-equatorial carboxyl group is unfavourable in this structure due to steric hindrance between the O(carboxyl) and O(peptide) atoms. Similar steric hindrance occurs in the structure of (glycyl-L-histidinato)copper(II) sesquihydrate.[1]

Intermolecular contact distances show that the only hydrogen bonds in (A) and (B) are between protonated carboxyl groups,  They link the complexes in pairs. Co-ordination of methionine to platinum(II) through nitrogen and sulphur in these complexes was predicted on the basis of chemical[2] and i.r.[3] evidence. The same type of co-ordination has been found in the crystal structure of an analogous palladium(II) complex,[4] and has been suggested for the complexes of platinum(II) with DL-ethionine and *S*-methyl-L-cysteine.[5] At higher pH, platinum(II) forms a complex in which methionine is reported to act as a tridentate chelate through the amino, thioether, and carboxyl groups.[6] Models based on the dimensions of the present structures show that considerable strain would be involved in tridentate chelation of square-planar platinum(II) by methionine. The reported i.r. spectra,[6] however, show only that the three functional groups are involved in metal-binding, and not necessarily that they bind the same metal atom.

The combination of *X*-ray and neutron structure-analyses of (C) shows that the metal has induced dissociation of the peptide proton, and that the carboxyl group is still protonated. Dissociations of peptide protons occur at pH *ca.* 9 in the presence of Ni^{2+}, [7,8] at pH *ca.* 6 for Cu^{2+}, [9] and at pH 3·5 for Pd^{2+}, [10] but in all these cases the carboxyl protons are titrated at much lower pH's than the peptide protons. Complex (C) crystallises at pH *ca.* 2·5, so that platinum(II) is even more effective than palladium(II) in labilising peptide protons. The carboxyl O–H bond is directed towards a water molecule. The second O(carboxyl) and the O(peptide) atom accept hydrogen bonds from a symmetry-related water molecule. Each water molecule thus forms three hydrogen bonds with two complexes. The two hydrogens on the N(amino) atom take part in intermolecular hydrogen bonds to an O(peptide) and to an O(carboxyl), respectively.

Tetrachloroplatinate(II) has been used extensively to prepare isomorphous heavy-atom derivatives for protein structure analysis. The preferred binding sites appear to be at methionine residues, especially when these are located at the surface of the protein molecule.[11] The electron-density difference map of the $PtCl_4^{2-}$ derivative of cytochrome-*c* has been interpreted as showing that the platinum can occupy two alternative sites near the sulphur atom of Met-65, and that oxidation to octahedral platinum(IV) has taken place.[11] The structure analyses of (A), (B), and (C) show that the interaction of $PtCl_4^{2-}$ with a methionine residue causes a substitution reaction in which a S–Pt bond is formed. There are two equally probable sites for the platinum atom, corresponding to opposite chiralities about the sulphur. Whether the methionyl N(peptide) atom in a protein is also bonded to the Pt atom may depend upon its

accessibility. In the absence of such an interaction, free rotation of the $PtCl_3$ group about the S–Pt bond is to be expected. This would provide an alternative explanation for the appearance of the cytochrome-*c* difference maps.

Crystal data: Crystals of (A) and (B) were prepared by heating K_2PtCl_4 with the free amino-acid in water.[2] Crystals of (C) were grown from a solution which was 0·05M with respect to K_2PtCl_4 and glycyl-L-methionine. After several hours the red solution had turned yellow. It was decanted from a yellow precipitate and allowed to stand. Yellow, truncated tetrahedral crystals formed. Crystals suitable for neutron analysis were grown from a seed.

(A) is monoclinic, $a = 7{\cdot}52(1)$, $b = 9{\cdot}87(1)$, $c = 15{\cdot}85(2)$ Å, $\beta = 118{\cdot}35(5)°$, $\mu = 262$ cm^{-1}, space group $P2_1/c$, $Z = 4$, $D_x = 2{\cdot}67$ g cm^{-3}. 1865 reflections (of which 447 were unobservably weak) were measured on an automated Buerger-Supper equi-inclination diffractometer[12] using Ni-filtered Cu-K_α radiation, λ(Cu-K_1) = 1·5405, λ(Cu-K_2) = 1·5443 Å.

(B) is triclinic, $a = 7{\cdot}34(1)$, $b = 8{\cdot}91(1)$, $c = 8{\cdot}39(1)$ Å, $\alpha = 74{\cdot}47(3)$, $\beta = 78{\cdot}13(3)$, $\gamma = 86{\cdot}40(3)°$, $\mu = 259$ cm^{-1}, space group $P1$, $Z = 2$, $D_x = 2{\cdot}64$ g cm^{-3}. 1506 reflections (of which 23 were unobservably weak) were measured as for (A).

(C) is orthorhombic, $a = 10{\cdot}63(1)$, $b = 16{\cdot}96(2)$, $c = 6{\cdot}95(1)$ Å, μ(*X*-rays) = 249 cm^{-1}, μ(neutrons) = 2·0 cm^{-1}, space group $P2_12_12_1$, $Z = 4$, $D_x = 2{\cdot}41$ g cm^{-3}. 1352 reflections (of which 198 were unobservably weak) were recorded as for (A). The neutron data, comprising 1187 reflections (460 below threshhold intensity), were measured on a four-circle diffractometer. The neutron flux at the specimen was 2×10^5 neutrons cm^{-2} s^{-1}, with $\lambda = 1{\cdot}165$ Å.

The residuals R at the present stage of full-matrix least-squares refinement are: (A) 0·055, (B) 0·062, (C) *X*-ray data, 0·043, and (C) neutron data, 0·095.

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[1] J. F. Blount, K. A. Fraser, H. C. Freeman, J. T. Szymanski, and C.-H. Wang, *Acta Cryst.*, 1967, **22**, 396.
[2] L. M. Volshtein and M. F. Mogilevkina, *Doklady Akad. Nauk S.S.S.R.*, 1962, **142**, 1305; *Proc. Acad. Sci.* (*U.S.S.R.*), 1962, **142**, 129.
[3] C. A. McAuliffe, *J. Chem. Soc.* (*A*), 1967, 641.
[4] N. C. Stephenson, J. F. McConnell, and R. Warren, *Inorg. Nuclear Chem. Letters*, 1967, **3**, 553.
[5] S. E. Livingstone and J. D. Nolan, *Inorg. Chem.*, 1968, **7**, 1447.
[6] L. M. Volshtein, L. F. Krylova, and M. F. Mogilevkina, *Doklady Akad. Nauk S.S.S.R.*, 1968, **178**, 595; *Proc. Acad. Sci.* (*U.S.S.R.*), 1968, **178**, 63.
[7] A. R. Manyak, C. B. Murphy, and A. E. Martell, *Arch. Biochem. Biophys.*, 1955, **59**, 373.
[8] R. B. Martin, M. Chamberlin, and J. T. Edsall, *J. Amer. Chem. Soc.*, 1960, **82**, 495.
[9] S. P. Datta and B. R. Rabin, *Trans. Faraday Soc.*, 1956, **52**, 1123.
[10] E. W. Wilson and R. B. Martin, *Inorg. Chem.*, 1970, **9**, 528.
[11] R. E. Dickerson, D. Eisenberg, J. Varnum, and M. L. Kopka, *J. Mol. Biol.*, 1969, **45**, 77.
[12] H. C. Freeman, J. M. Guss, C. E. Nockolds, R. Page, and A. Webster, *Acta Cryst.*, 1970, **A26**, 149.