First Synthesis and Characterization of Platinum(II) Complexes of Amino Sugars having Anti-tumour Activity; Crystal Structure of [$PtCl_2$(methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside)]·H_2O

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Two novel platinum(II) complexes containing a diamino sugar have been prepared and characterized, including the crystal structure of [$PtCl_2$(methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside)]·H_2O (**1**), and the anti-tumour activity of the complexes has been demonstrated.

Many platinum complexes have been examined since the anti-tumour activity of cisplatin was shown by Rosenberg *et al.*[1] Much work has been devoted to decreasing their toxicity and increasing their solubility. Many complexes including various anionic leaving groups instead of chloride ions have been prepared, but in almost all complexes ammine or simple alkylamines, which are toxic themselves, have been used as the neutral ligands.[2] Recently, many anti-cancer reagents that have sugar residue(s) (*e.g.* bleomycin, adriamycin, and many antibiotics) have been widely used clinically. Therefore it was of interest to examine the action of platinum compounds having sugar residues *in vivo*. In addition, metal complexes containing sugar residues are expected to exhibit fairly good solubility since sugars contain hydroxy groups.

As a significant part of our programme to elucidate the nature of sugar–transition metal interactions,[3] we have synthesized and fully characterized cisplatin type complexes of two amino sugars for the first time. In this study, methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside (Me-ManNN), and 2,3-diamino-2,3-dideoxy-D-glucose (GlcNN) were chosen (Figure 1).

Me-ManNN·2HCl was synthesized by the acid hydrolysis of methyl 2-acetamido-3-amino-2,3-dideoxy-α-D-mannopyranoside[4] (1 M hydrochloric acid, 70 °C, 1 h). GlcNN was prepared and isolated as its dihydrochloride by the method of Meyer zu Reckendorf.[5] The platinum(II) complexes were easily prepared by a method analogous to that of Appleton and Hall,[6] as follows. To a saturated solution of $K_2[PtCl_4]$ was added an equimolar amount of the diamino sugar dihydrochloride and the solution was partially neutralized with KOH. Yellow crystals were obtained from solutions kept in a refrigerator: 33% yield for complex (**1**), [$PtCl_2$(Me-ManNN)]·H_2O, and 40% for complex (**2**), [$PtCl_2$-(GlcNN)]·H_2O, both of which gave good elemental analyses. These complexes, especially complex (**2**), are reasonably soluble in water.† Both complexes, especially complex (**2**), show good anti-tumour activity *in vivo* against sarcoma S180 in mice: *T/C* 229% for complex (**1**) and 411% for complex (**2**) (ICR/CRJ mice, 10^6 cells. Schedule day 1; dose 50 mg/kg, i.p.). The *T/C* value for cisplatin is 237% (dose, 8 mg/kg, other conditions are the same).‡

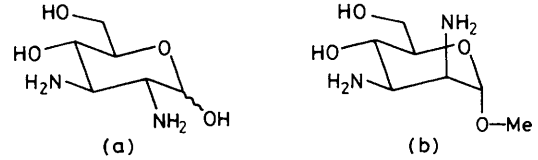

Figure 1. Structures of (a) GlcNN and (b) Me-ManNN.

† Solubility >20 mg/ml for complex (**2**) and >2 mg/ml for (**1**) at 35 °C.

‡ Anti-tumour activity was tested by Ajinomoto Co. Ltd.

The structure of compound (**1**) was determined by *X*-ray crystallography.§ Figure 2 shows a perspective drawing of the [$PtCl_2$(Me-ManNN)] molecule. Two chloride ions and a bidentate Me-ManNN ligand complete square planar co-ordination around platinum. The diamino sugar is bound to platinum through N(1) and N(2). The pyranose ring of the

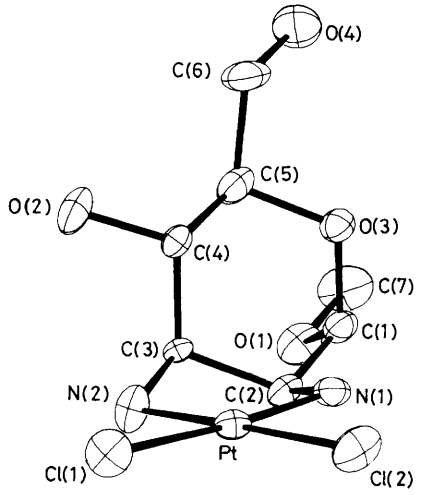

Figure 2. ORTEP drawing of [$PtCl_2$(Me-ManNN)]·H_2O. Selected bond distances (Å): Pt–Cl(1) 2.305(4), Pt–Cl(2) 2.310(4), Pt–N(1) 2.02(1), Pt–N(2) 2.03(1), N(1)–C(2) 1.49(2), N(2)–C(3) 1.51(1); selected bond angles (°): Cl(1)–Pt–Cl(2) 92.8(1), N(1)–Pt–N(2) 83.8(5), Cl(1)–Pt–N(1) 174.8(3), Cl(2)–Pt–N(2) 174.7(3).

§ *Crystal data:* $C_7H_{18}N_2O_5Cl_2Pt$, yellow prism (0.21 × 0.22 × 0.25 mm^3), M_r = 476.2, monoclinic, space group $P2_1$, a = 10.048(2), b = 8.725(2), c = 7.584(2) Å, β = 90.67(2)°, U = 664.8(3) Å^3, D_m = 2.37, D_c = 2.39 g cm^{-3}, Z = 2, μ = 110.8 cm^{-1}. Diffraction data were collected with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å), on a Rigaku Denki AFC-4 four-circle diffractometer. The structure was solved by standard Patterson and Fourier methods by the UNICSIII program (T. Sakurai and K. Kobayashi, *Rikagaku Kenkyuusho Houkoku*, 1979, **55**, 69). 1510 Unique reflexions with 2θ < 55° were corrected for absorption by a numerical integration procedure with a Gaussian grid (6 × 6 × 6) (W. R. Busing and H. A. Levy, *Acta Crystallogr.*, 1957, **10**, 180). Refinement of positional and anisotropic thermal parameters of all non-hydrogen atoms, positional parameters of hydrogen atoms, and an extinction parameter has converged at R = 0.028 and R_w = 0.030 by full-matrix least-squares (RADIEL program, P. Coppens, T. N. Guru Row, P. Leung, E. D. Stevens, P. J. Becker, and Y. W. Yang, *Acta Crystallogr., Sect. A*, 1979, **35**, 63) with $w = \{[\sigma(|F_o|)]^2 + (0.015F_o)^2\}^{-1}$. Full details will be reported elsewhere. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

Me-ManNN unit has the α-$^4C_1$ chair conformation. The amino groups on C(2) and C(3) are axial and equatorial respectively with respect to the pyranose ring. The Pt–N(1)–C(2)–C(3)–N(2) chelate adopts the λ-*gauche* conformation. All bond distances and angles are normal. Although intermolecular hydrogen bonds are found between solvated water molecules, chloride ions, hydroxy groups, and amino groups, no intermolecular interaction between platinum atoms is observed.

We assume that the structure of complex (**2**) is similar to that of complex (**1**), with a bidentate GlcNN ligand and two chloride ions co-ordinating to the platinum atom.¶ The c.d. spectra of the two compounds (**1**) and (**2**) in the d–d transition

$$[PtCl_2(Me\text{-}ManNN)]\cdot H_2O$$
(**1**)

$$[PtCl_2(GlcNN)]\cdot H_2O$$
(**2**)

region have opposite signs.¶ This result is attributable to the chelate conformations of the two diamino sugars: β and γ in the Me-ManNN and GlcNN complexes, respectively.

This study thus confirms that platinum complexes containing sugar residues may be prepared easily, and promises that a number of novel anti-cancer complexes containing amino sugars could be prepared since many amino sugars have widespread occurrence in nature.

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¶ ^1H N.m.r. spectroscopy showed that this compound was a mixture of two anomers in solution. Two doublets were observed for complex (**2**) at δ 5.40 [1H, d, $J(H^1H^2)$ 3.3 Hz, α-anomer] and 4.88 [1H, d, $J(H^1H^2)$ 7.9, β-anomer] (D_2O, 297 K). The ratio of α- and β-anomers is *ca.* 65 : 35 at 297 K. The co-ordination structure of the chelate rings are the same for the α- and β-anomers. For (**1**) c.d. (water): $10^{-3} \times \tilde{\nu}_{max.}$ (Δε) 27.5 (+0.18) and 37.2 (+0.43) cm^{-1}. For (**2**) c.d. (water): $10^{-3} \times \tilde{\nu}_{max.}$ (Δε) 26.8 (−0.32) and 36.5 (−0.93) cm^{-1}.