A Carbohydrate-Linked Cisplatin Analogue Having Antitumor Activity**

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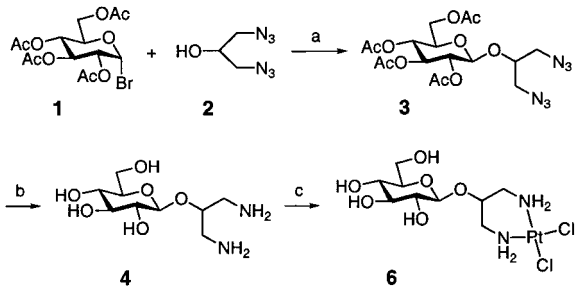
Since the antitumor activity of cisplatin was first discovered by Rosenberg et al.,[1] much effort has been devoted to investigating the interaction of platinum compounds with cellular targets (especially DNA)[2] and developing more potent cisplatin analogues with improved pharmacological properties.[3] Of particular interest is the synthesis of platinum(II) complexes with biologically important ligands[4] because of their reduced toxicity. Although carbohydrates play a key role in various biological processes,[5] their usage in platinum-based cancer chemotherapy has remained virtually unexplored; this is especially true of complexes in which an intact carbohydrate moiety is connected to platinum through an appropriate linker.[6] Here we report on the synthesis, characterization, and cytotoxicity of a novel carbohydrate-linked cisplatin analogue, *cis*-dichloro[(2-β-D-glucopyranosidyl)propane-1,3-diamine]platinum (**6**, see Scheme 1).

Glycosylation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) with 1,3-diazidopropan-2-ol (**2**)[7] was promoted by $HgO/HgBr_2$ in CH_2Cl_2 to give glycoside **3** (Scheme 1).



Scheme 1. Synthesis of complex **6**. Reagents and conditions: a) **1** (1.0 equiv), **2** (1.5 equiv), $HgBr_2$ (0.2 equiv), HgO (1.0 equiv), CH_2Cl_2, RT, 2 d in the dark, 63% of **3**; b) cat. NaOMe, MeOH, RT, 6 h, then Pd/C (12 wt%), H_2 (1810 Torr), RT, 8 h, 96% of **4**; c) $K_2[PtCl_4]$ (**5**, 1.0 equiv), H_2O, RT, 2 d, 75% of **6**.

Deacetylation of **3** and subsequent hydrogenation afforded the diamino ligand **4** with an unprotected glucose unit. Compound **4** was treated with a stoichiometric amount of $K_2[PtCl_4]$ (**5**) in water to give **6** within two days. After the coordination reaction was complete, however, the carbohydrate-linked cisplatin analogue remained dissolved in the solution together with the resulting KCl salt. Complex **6** was isolated from the mixture by use of a gel filtration column with Bio-gel P2 resin (yield 75%). Colorless single crystals were obtained from solutions of purified **6** in D_2O at room temperature.

Complex **6** was characterized by ^1H and ^{13}C NMR spectroscopy,[8] which confirms complex formation in water. New peaks occur at $\delta = 4.23$, 2.86, and 2.68 in the ^1H NMR spectrum, and at $\delta = 46.2$, 45.1 in the ^{13}C NMR spectrum for **6** as compared with the noncoordinated ligand **4**.

The X-ray crystal structure analysis of **6**[9] (Figure 1) reveals that there are two independent molecules in the crystal. In

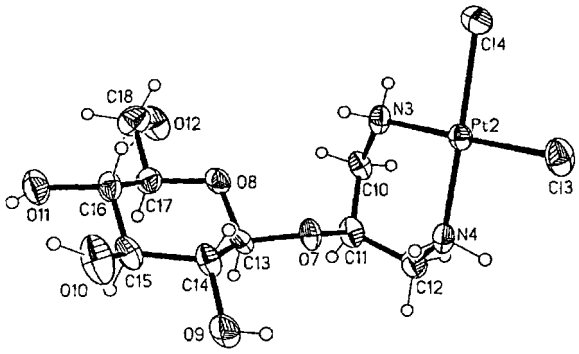


Figure 1. Molecular structure of one of the two molecules of **6** in the crystal. Selected bond lengths [pm] and angles [°]: Pt2–N3 202.3(7), Pt2–N4 202.6(8), Pt2–Cl3 230.2(2), Pt2–Cl4 232.0(2), N3–C10 148.2(12), N4–C12 148.1(12), C10–C11 152.2(13), C11–C12 149.5(14); N3-Pt2-N4 93.3(3), N3-Pt2-Cl3 175.4(2), N4-Pt2-Cl3 87.4(2), N3-Pt2-Cl4 86.3(2), N4-Pt2-Cl4 177.9(2), Cl3-Pt2-Cl4 92.72(9), C10-N3-Pt2 120.9(6), C12-N4-Pt2 118.8(6), N3-C10-C11 111.9(7), C12-C11-C10 113.7(8), N4-C12-C11 111.8(8).

both molecules, the intact and unprotected β-D-glucopyranose moiety is connected to platinum through the 2-propane-1,3-diamine linker group, which acts as a neutral bidendate ligand and coordinates through the two amino groups. The coordination about platinum is roughly square planar as expected, and the six-membered chelate ring is in a chair conformation as is the glucopyranose ring. The mean Pt–Cl and Pt–N distances (231 and 202 pm, respectively) are consistent with those found in $PtCl_2N_2$ systems.[10] However, the Cl-Pt-Cl and N-Pt-N angles (92.7 and 93.3°, respectively) present a major difference from those forming five-membered chelate rings,[11] in which the "bite" of the diamine ligand reduces the N-Pt-N angle to less than 90° with an accompanying increase of the Cl-Pt-Cl angle to more than 90°. The two independent molecules adopt very similar structures except for the conformation of the CH_2OH moiety from the glucose ring, which very likely results from molecular packing controlled by intermolecular hydrogen-bonding interactions. From the crystal structure two types of hydrogen-bonding interactions can be identified: direct hydrogen bonding between two ligand hydroxyl groups, and water-bridged hydrogen bonding from a ligand hydroxyl group to a water molecule and then to another ligand hydroxyl group.

The in vitro antitumor activity of complex **6** (Table 1) shows that it is as active as cisplatin against human ovarian cancer cell A2780S and human melanoma cancer cell MeWo, but less active against human ovarian cancer cell A2780cP. Thus with the attachment of an intact and unprotected carbohydrate moiety, **6** exhibits cytotoxicity comparable to that of the parent compound. While more detailed pharmacokinetic study regarding in vivo behavior is underway, the retained activity of **6**, together with its improved solubility in water,[13]

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Table 1. In vitro antitumor activity[a] of complex **6**.

Cell line	Tumor of origin	MED[b] [μM]	
		6	Cisplatin
A2780S[c]	ovarian	2.5	3.3
A2780cP[c]	ovarian	112	36
MeWo[d]	melanoma	11.2	8

[a] Cytotoxicity was assessed by clonogenic survival assay as described.[12] [b] Median effect dose. [c] A2780S and its cisplatin-resistant variant, A2780cP, were obtained from Dr. Marshal Sklar (University of Miami) and maintained in Paul G. Braunschweiger's laboratory. [d] Obtained from Dr. Jorgen Fogh and maintained in Paul G. Braunschweiger's laboratory.

should open new avenues to explore this important area of cancer chemotherapy.

Moreover, complex **6** is, to the best of our knowledge, the first example of a carbohydrate-containing transition metal complex in which the carbohydrate moiety is not only unprotected, but also unbound to the metal center.[6, 14] Such complexes should be obtainable as single crystals, which can then be used to determine the solid-state structure of intact and unprotected carbohydrates.

Experimental Section

6: A mixture of **1** (2.2 g, 5.36 mmol), **2** (1.14 g, 8.0 mmol), and 4-Å molecular sieves (3.5 g) was stirred under Ar for 1 h at RT in CH_2Cl_2 (50 mL), and $HgBr_2$ (0.39 g, 1.07 mmol) and HgO (1.16 g, 5.36 mmol) were added. After being stirred in the dark for 2 d, the mixture was filtered through a layer of Celite. The filtrate was washed with aqueous $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue in hexanes/ethyl acetate (1/1) on silica gel afforded **3** (1.59 g, 63 %). Compound **3** (0.78 g, 2.56 mmol) and a catalytic amount of NaOMe were stirred in MeOH (30 mL) for 6 h at RT. The mixture was neutralized by addition of Dowex H^+ ion-exchange resin and filtered, and Pd/C (60 mg) was added. After being stirred under H_2 (35 psi) for 8 h, the mixture was filtered through a layer of Celite, and the filtrate concentrated. The residue was redissolved in H_2O and lyophilized to give **4** (0.4 g, 96 %). Compound **4** (0.18 g, 0.71 mmol) and **5** (0.3 g, 0.71 mmol) were stirred in H_2O (10 mL) for 2 d at RT, and concentrated. Chromatography of the residue on a gel filtration column with Bio-gel P2 resin afforded **6** (0.28 g, 75 %).

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[7] Compound **2** was prepared from 1,3-dibromo-2-propanol by reaction with NaN_3 in DMF.
[8] **6**: ^{1}H NMR (500 MHz, D_2O): $\delta = 4.39$ (d, J(H1,H2) = 8.0 Hz, 1H; H1), 4.23 (m, 1H; C*H*$(CH_2NH_2)_2$), 3.70 (dd, J(H6a,H6b) = 12.5, J(H5,H6a) = 2.0 Hz, 1H; H6a), 3.55 (dd, J(H6a,H6b) = 12.5, J(H5,H6b) = 5.0 Hz, 1H; H6b), 3.34 – 3.23 (m, 3H; H3, H4, H5), 3.17 (dd, J(H2,H3) = 9.5, J(H1,H2) = 8.0 Hz, 1H; H2), 2.89 – 2.84, 2.72 – 2.65 (2m, 2 × 2H; CH(C*H*$_2$NH$_2$)$_2$); ^{13}C NMR (125 MHz, D_2O): $\delta = 102.2$ (C1), 76.5, 76.2 (C3, C5), 74.1 (*C*H$(CH_2NH_2)_2$), 73.7 (C2), 70.1 (C4), 61.2 (C6), 46.2, 45.1 (CH$(CH_2NH_2)_2$).
[9] Crystal structure data (Bruker P4/CCD diffractometer) for **6** · 1.5 H_2O: $C_9H_{23}Cl_2N_2O_{7.5}Pt$, $M_r = 545.28$, crystal dimensions $0.32 \times 0.22 \times 0.06$ mm^3, $T = 295(2)$ K, monoclinic, space group $P2_1$, $a = 690.390(10)$, $b = 3174.58(6)$, $c = 809.74(2)$ pm, $\beta = 115.0650(10)^\circ$, $Z = 4$, $V = 1.60758(6)$ nm^3, $\rho_{calcd} = 2.253$ g cm^{-3}, $Mo_{K\alpha}$ radiation ($\lambda_0 = 0.71073$ Å), $\mu = 9.096$ mm^{-1}, $2\theta = 2.56 – 56.68^\circ$; of 9952 reflections collected, 6498 were independent (R(int) = 0.031); refinement method: full-matrix least squares on F^2, 397 refined parameters, empirical absorption correction (SADABS software, T_{min} and T_{max} undefined), GOF = 1.008 (based on F^2), $R1 = 0.0383$, $\omega R2 = 0.0915$ ($\sigma > 2\sigma(I)$), absolute structure parameter 0.007(8), residual electron density $-2.559/3.782$ e Å^{-3}. The structure was solved and refined with the programs SHELXS-93 and SHELXTL. The hydrogen atoms were placed in their geometric positions (riding model), except that no hydrogen atoms were placed in the solvent molecules. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-113805. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Mixed Crossed Aldol Condensation between Conjugated Esters and Aldehydes Using Aluminum Tris(2,6-diphenylphenoxide)

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Crossed aldol condensation between two different carbonyl compounds is one of the earliest and synthetically most significant reactions for carbon – carbon bond formation.[1]

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