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Synthesis, structural characterization, and antitumor activity of palladium(II) complexes containing a sugar unit

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Abstract—Six palladium(II) complexes as cisplatin derivatives with a sugar unit (D-glucose, D-galactose, D-mannose, D-xylose, and maltose) have been prepared. The structural features of the complexes have been characterized by NMR spectroscopy, elemental analysis, mass spectroscopy, and X-ray crystallography. The complexes have been tested for in vivo cytotoxicity against P388 cells implanted in mice. All of Pd compounds are apparently nontoxic. A T/C value of 120% was obtained for maltose derivative at the dose of 400 mg/kg, which indicates that the compound may be endowed with antitumor activity.

The discovery of anticancer activity of *cis*-diamminedichloroplatinum(II) (cisplatin) was a breakthrough in the fight against cancer.[1] Although cisplatin is a valuable antitumor drug, it has several disadvantages including side effects such as nephrotoxicity, neurotoxicity, ototoxicity, and emetogenesis.[2–4] In addition, some tumors are resistant to cisplatin.[5,6] Furthermore, cisplatin has limited solubility in aqueous media. All these drawbacks force the limitation of the dose as well as further use of cisplatin in clinical treatment.

To achieve lower undesirable toxicity, enhanced solubility, and tumor selectivity, significant amount of work have been devoted to the preparation of modified platinum complexes. Various amine ligands instead of ammonia as well as other leaving groups replacing chloride ions have been employed.[7–9] Another way to design the new antitumor agent related to cisplatin is to change the nature of central metal ion.[10–13] The consequence of similar coordination behavior of platinum(II) and palladium(II) is of great interest for development of the antitumor palladium(II) complexes.[14–16]

We have investigated in vivo activity of several platinum(II) complexes containing a sugar residue.[17–19] In the present study, we synthesized analogous palladium(II) complexes. With the aim to investigate the biological properties, we report here synthetic and structural studies of new Pd(II) complexes (Fig. 1) and screening of their antitumor activity against P388 cells implanted in mice.

Palladium(II) complexes **1**–**6** were synthesized by mixing equimolar amount of sugar–diamine ligand[20] and potassium tetrachloropalladate(II) in water. Several hours later, appeared precipitates were collected as yellow powders (24–49% yield).[21]

Recrystallization of **5** from water–methanol afforded single crystals suitable for X-ray crystallography. The crystal structure of **5**[22] (Fig. 2) shows that palladium atom is surrounded by four donor atoms: two nitrogens and two chlorides in a *cis*-configuration. As expected, the geometry around the metal center is approximately square planar. The distances and angles around palladium atom are analogous to those found in Pd(II) complexes with related structure.[23] The β-D-xylopyranose moiety is attached to palladium atom by the propane-1,3-diamine group, coordinated through the two amino groups. The six-membered chelate ring adopts chair conformation locating O-glycoside group in an axial position.[19]

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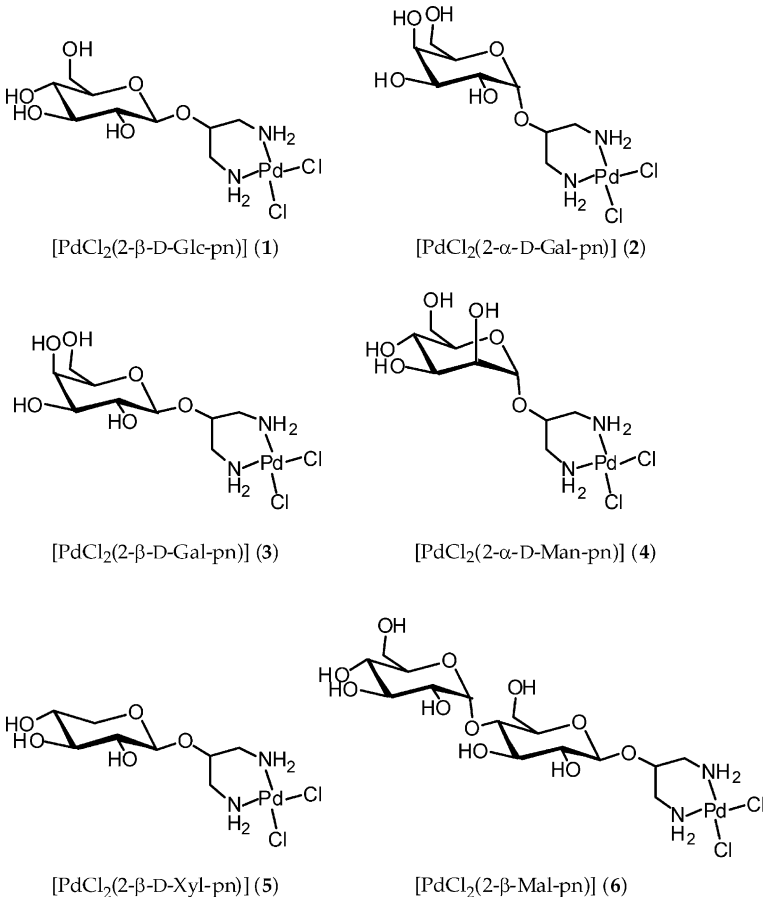

Figure 1. Structures of complexes used in this study.

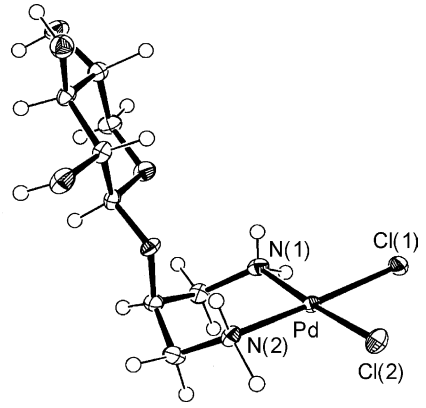

Figure 2. ORTEP drawing of complex **5**. Selected bond lengths (Å) and angles (°): Pd–Cl(1) 2.324(1), Pd–N(1) 2.045(3), Pd–Cl(2) 2.310(1), Pd–N(2) 2.028(4); Cl(1)–Pd–Cl(2) 91.84(4), Cl(2)–Pd–N(2) 87.9(1), Cl(1)–Pd–N(1) 87.2(1), N(1)–Pd–N(2) 92.9(1).

Solution structure of complex **5** was characterized by ^{1}H NMR spectroscopy in D_2O (Fig. 3). Coupling constants ($^3J_{H-H}$) for protons in the sugar part are consistent with those expected for $^4C_1$ chair conformation. The most significant difference between ligand and metal complex was found in downfield shift of the α proton signal in the Pd(II) complexes. It is not electronic but configuration effect because no chemical shift of the β protons was observed upon complexation with palladium atom. As discussed in the previous section, the α proton is fixed in the equatorial position, which causes downfield shift of this proton.[24] All these features in solution are consistent with the solid-state structure determined by X-ray crystallography.

Antitumor activity of Pd(II) compounds **1**–**6** were tested in vivo against P388 leukemia cells implanted in mice.[25] Results are shown in Table 1. Most of palladium complexes did not show any significant activity, except for compound with maltose unit (**6**): T/C value of 120% was obtained at the dose of 400 mg/kg. As shown in Table 1 (footnote), the T/C value for compound **6** is indicative of antitumor activity. No other relationship between activity and type of sugar was observed. In comparison with the results obtained from the same test for analogous Pt(II) complexes,[19] all of Pd compounds are apparently nontoxic. It could be associated with very low genotoxicity of divalent palladium complexes contrary to platinum compounds.[26] Central metal ion, as well as ligand tuning, induces significant changes in the cytostatic activity of the complex. These data shows also, that sugar residue decreases the toxicity of metal ion significantly, as seen in case of analogous platinum(II) complexes.[19] This effect as well as completely different activity pattern of palladium(II) compounds from platinum(II) derivatives can indicate: (i) the different type of DNA damage caused by palladium(II)

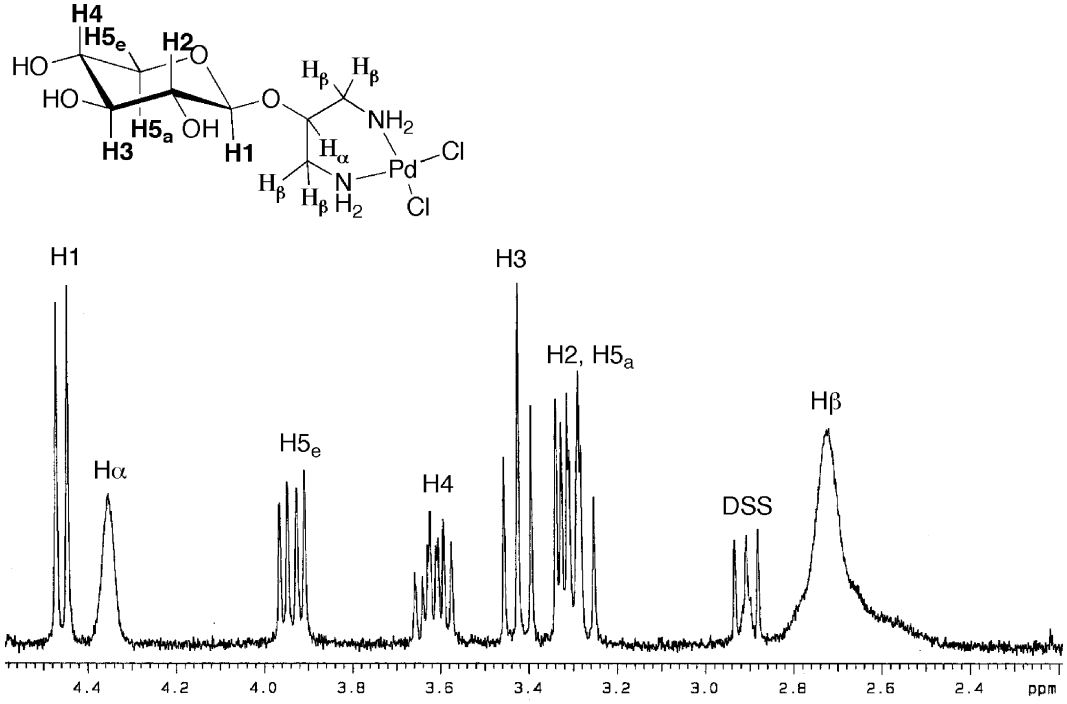

Figure 3. ^{1}H NMR (300 MHz) spectrum of complex **5** in D_2O.

Table 1. Antitumor activity of Pd(II) complexes **1**–**6** against P388 leukemia tumor in CDF1 mice

Compound	Dose (mg/kg)	T/C (%)[a]
1·H_2O	100	112
	200	111
2·H_2O	100	94
	200	102
	400	67
3·2H_2O	100	100
	200	110
	400	108
4·2H_2O	100	111
	200	116
	400	112
5·H_2O	100	102
	200	108
	400	115
6·2H_2O	100	101
	200	110
	400	120

Values of T/C (%) $\geqslant$ 120% are taken as indicators of antitumor activity.

[a] $\mathrm{T/C}\ (\%) = \dfrac{\text{median survival days of treated mice}}{\text{median survival days of control mice}} \times 100.$

compounds; (ii) the DNA damage caused by palladium(II) compounds is processed in a different manner from that induced by the platinum(II) complexes.[27,28] Possible explanation for observed very low activity of Pd(II) complexes is that tested palladium(II) compounds decomposed before entering the cell and reaching the cellular target because of their extremely high lability in biologic fluids.[29,30]

These results inspired us to extend the study to Pd(II) complexes with another carbohydrates and such study is under investigation in our laboratory.

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21. Elemental analyses and mass spectra data for $\mathbf{1}\cdot H_2O$ ($PdCl_2C_9H_{20}N_2O_6\cdot H_2O$): Anal. Calcd (found) C, 24.15 (24.33); H, 4.95 (4.70); N, 6.26 (6.23); ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_9H_{20}O_6N_2Cl_2NaPd$, 450.9631; found, 450.9632. For $\mathbf{2}\cdot H_2O$ ($PdCl_2C_9H_{20}N_2O_6\cdot H_2O$): Anal. Calcd (found) C, 24.15 (24.20); H, 4.95 (4.70); N, 6.26 (6.16)%; ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_9H_{20}O_6N_2Cl_2NaPd$, 450.9631; found, 450.9615. For $\mathbf{3}\cdot 2H_2O$ ($PdCl_2C_9H_{20}N_2O_6\cdot 2H_2O$): Anal. Calcd (found) C, 23.22 (23.09); H, 5.20 (5.13); N, 6.02 (6.17); ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_9H_{20}O_6N_2Cl_2NaPd$, 450.9631; found, 450.9636. For $\mathbf{4}\cdot 2H_2O$ ($PdCl_2C_9H_{20}N_2O_6\cdot 2H_2O$): Anal. Calcd (found) C, 23.22 (23.58); H, 5.20 (4.82); N, 6.02 (6.24); ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_9H_{20}O_6N_2Cl_2NaPd$, 450.9631; found, 450.9646. For $\mathbf{5}\cdot H_2O$ ($PdCl_2C_8H_{18}N_2O_5\cdot H_2O$): Anal. Calcd (found) C, 23.01 (23.05); H, 4.83 (4.52); N, 6.71 (6.54); ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_8H_{18}O_5N_2Cl_2NaPd$, 420.9526; found, 420.9525. For $\mathbf{6}\cdot 2H_2O$ ($PdCl_2C_{15}H_{30}N_2O_{11}\cdot 2H_2O$): Anal. Calcd (found) C, 28.70 (28.82); H, 5.46 (5.32); N, 4.16 (4.54); ESI-HRMS $(m/z)=[M+Na]^+$ calcd for $C_{15}H_{30}O_{11}N_2Cl_2NaPd$, 613.0159; found, 613.0155.
22. Crystal structure data (Rigaku Mercury CCD) for $\mathbf{5}\cdot H_2O$: $C_8H_{20}Cl_2N_2O_6Pd$, $M_r=417.58$, crystal dimensions $0.382\times0.255\times0.032\,mm^3$, $T=173\,K$, monoclinic, space group $C2(\#5)$, $a=14.4480(13)$, $b=6.6687(5)$, $c=14.2882(11)\,Å$, $\beta=91.222(5)°$, $Z=4$, $V=1376.3(2)\,Å^3$, $\rho_{calc}=2.005\,g\,cm^{-3}$, MoK_α radiation ($\lambda_0=0.71070\,Å$), $\mu=17.60\,cm^{-1}$, $2\theta_{max}=54.9°$; of 5372 reflections collected 1694 were independent ($R_{int}=0.027$); refinement method: full-matrix least squares on F^2, 186 refined parameters, GOF = 0.902, $R=0.021$, $R_w=0.052$. The structure was solved by direct methods (SIR88) and expanded using Fourier techniques (DIRDIF-99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 214335. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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