Chiral Phosphine Ligands Derived from Sugars. 16. Design and Synthesis of Platinum Anticancer Compounds with Carbohydrate Ligand

Ji-Cheng Shi,*[,†] Chi-Hung Yueng,[‡] Da-Xu Wu,[†] Qiu-Tian Liu,[†] and Bei-Sheng Kang[†, §]

State Key Laboratory of Structural Chemistry and Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, 350002 Fujian, China, and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China

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The bis(alkoxo)platinum(II) complex *cis*-[Pt(2-mbpa)$_2$] (**3**) (2-Hmbpa = methyl 4,6-*O*-benzylidene-2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside), which shows the inhibiting ratio against P388 leukemia as high as 60% at 10^{-7} mol/dm^3, has been designed and prepared. Reaction of 2-Hmbpa with [Pt(COD)Cl$_2$] forms *cis*-[Pt(2-Hmbpa)$_2$Cl$_2$] (**1**), in which alcohol ligating species *cis*-[Pt(2-Hmbpa)$_2$Cl]Cl has been observed in solution. When treated with NEt$_3$, **1** converts to the monodeprotonated alkoxoplatinum(II) complex *cis*-[Pt(2-Hmbpa)(2-mbpa)Cl] (**2**). Both **1** and **2** react with NaOMe to give the bis(alkoxo) complex *cis*-[Pt(2-mbpa)$_2$] (**3**). The compounds **1**−**3** have been characterized by infrared, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The Pt−O absorption has been assigned and appears at 349 cm^{-1} for both **2** and **3**. The crystal structure of **3**·3H$_2$O has been determined by X-ray crystallography. Structure analysis shows the pyranose ring in a boat conformation, which is consistent with the NMR observations, while the 4,6-*O*-benzylidene ring remains in a chair conformation. The ligating oxygen donors form a strong hydrogen bond with water and take a proton ion from acetic acid to give the ring-opening compound *cis*-[Pt(2-Hmbpa)(2-mbpa)(AcO)] (**4**), implying that **3** can be protonated in biological medium and can afford a vacant coordination site. The bulky sidearms of chiral 4,6-*O*-benzylidene groups, which are expected to provide steric hindrance around the Pt(II) atom, are hydrolyzed under strong acid to afford the complex *cis*-[Pt(2-mpa)$_2$] (**5**) (2-Hmpa = methyl 2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside).

A strategy to circumvent resistance of "cisplatin"[1] is to choose amine ("chelating or not, hydrogen-bond donor, steric effects, possible sidearms for secondary DNA interactions"[2]) instead of ammonia. Since a large number of phosphine-containing gold complexes including auranofin, an antiarthritic compound in clinical use, are potentially cytotoxic to tumor cells in culture,[3] the strategy to circumvent resistance may be extended to use phosphines instead of amines. Indeed, most recently, it has been found that the chelate ring-opening platinum anticancer complexes with aminophosphine ligands have a much lower resistance factor against an A2780 cell line which has acquired resistance to cisplatin.[4]

It has now been accepted that cisplatin binds to sulfur-containing biomolecules directly as a second-order reaction,[5] which is likely responsible for inactivation and toxic side effects.[2,6] This class of reactions therefore must be suppressed, especially in the blood. Then, a feature among most of the new generation of platinum compounds in clinical trials is to use RCOO$^-$ rather than Cl$^-$ as the leaving group.[2] In addition, it is recommended to increase the steric crowding around the platinum(II) center to decrease the rate of the substitution reaction.[2,5]

Hemilabile P,O ligands occupy an important position in the development of novel homogeneous catalysts, in which the oxygen donors play a key role in the "opening and closing mechanism".[7] The mechanism seems useful in the design of a platinum(II) drug. A closed state with bulky sidearms is likely to prevent the platinum(II) center from binding to sulfur-containing biomolecules; while the oxygen donors ligating to late transition metals, which are extremely electron-rich and have a great tendency to form hydrogen bonds with alcohol or

† Fujian Institute of Research on the Structure of Matter.
‡ The Hong Kong Polytechnic University.
§ Present address: Institute of Physical Chemistry, School of Chemistry and Chemical Engineering, Zhongshan University, Guangzhou, 510275 Guangdong, China.

(1) Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds. *Platinum Coordination Compounds in Cancer Chemotherapy;* Nijhoff: Boston, 1984.
(2) Reedijk, J. *J. Chem Soc., Chem. Commun.* **1996,** 801.
(3) (a) Shi, J. C.; Huang, X. Y.; Wu, D. X.; Liu, Q. T.; Kang, B. S. *Inorg. Chem.* **1996,** *35,* 2742. (b) Shi, J. C.; Cheng, L. J.; Huang, X. Y.; Wu, D. X.; Kang, B. S. *J. Organomet. Chem.* **1997,** *535,* 17.
(4) (a) Habtemariam, A.; Sadler, P. J. *J. Chem. Soc., Chem. Commun.* **1996,** 1785. (b) Margiotta, N.; Habtemariam, A.; Salder, P. J. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 1185.
(5) Djuran, M. I.; Lempers, E. L. M.; Reedijk, J. *Inorg. Chem.* **1991,** *30,* 2648, and references therein.
(6) Borch R. F.; Pleasants, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1979,** *76,* 6611.
(7) Bader, A.; Lindner, E. *Coord. Chem. Rev.* **1991,** *108,* 27.

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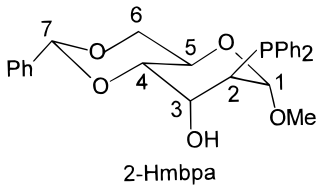
Scheme 1. Structure of the Ligand 2-H-mbpa



2-Hmbpa

water,[8] can to be protonated[9] in biological medium to form the hemilabile species. The hemilabile species can easily afford empty coordination sites, which makes binding to DNA possible. In addition, the leaving hydroxy group in the opened state may form hydrogen bonds and provide secondary interactions with DNA. We report here the synthesis, characterization, and preliminary antitumor activity of the bis(alkoxo)platinum(II) complex *cis*-[Pt(2-Hmbpa)$_2$] (**3**) (2-Hmbpa = methyl 4,6-*O*-benzylidene-2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside; see Scheme 1), with bulky sidearms, and its reaction with acid, along with the compounds *cis*-[Pt(2-Hmbpa)$_2$Cl$_2$] (**1**) and *cis*-[Pt(2-Hmbpa)(2-mbpa)Cl] (**2**).

Experimental Section

Elemental analyses were performed by the Chemical Analysis Division of Fujian Institute. Infrared spectra were measured on either a Nicolet Magna-750 FT spectrometer (in KBr disks, 4000−400 cm^{-1}) or a Digilab FTS-20 E/D-V (in CsI disks, 550−120 cm^{-1}). NMR spectra were measured in $CDCl_3$ on a Varian Unity-500 spectrometer operating at 499.98 MHz for ^{1}H, 125.71 MHz for ^{13}C, and 202.36 MHz for ^{31}P. Chemical shifts are expressed in parts per million (ppm) downfield from internal TMS (^{1}H and ^{13}C) or external 85% H_3PO_4 (^{31}P) standards as positive values. NMR data are listed in Tables 1, 2, and 3, respectively.

Reagent [Pt(COD)Cl$_2$] (COD = 1,5-cyclooctadiene) was prepared according to the literature method.[11] Methyl 4,6-*O*-benzylidene-2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside (2-Hmbpa) was prepared as reported.[12] Sodium methoxide was prepared by dissolving sodium metal in dry methanol; then the solvent was evaporated and the product was dried under reduced pressure. Analytical grade solvents were used without further purification.

***cis*-[Pt(2-Hmbpa)$_2$Cl$_2$] (1).** A suspension of [Pt(COD)Cl$_2$] (37.4 mg, 1.0 mmol) in dichloromethane (10 cm^3) was mixed with the ligand 2-Hmbpa (90.0 mg, 2.0 mmol) in dichloromethane (10 cm^3), and the mixture was swirled until all the solid had dissolved. Partially evaporating the solvent, followed by the addition of *n*-hexane, gave the white complex **1** in nearly quantitative yield. Found: C, 53.73; H, 4.52; Cl, 6.18. Calcd for $C_{52}H_{54}Cl_2O_{10}P_2Pt$: C, 53.52; H, 4.66; Cl, 6.08. IR (cm^{-1}): ν(OH), 3421 (m); ν(C−H), 3056 (w), 2929 (w), 2811 (w); ν(C═C), 1697 (w), 1437 (m); ν(C−O), 1097 (s), 1044 (s); ν(Pt−Cl), 318 (w); ν(Pt−P), 195 (w), 166 (w).

***cis*-[Pt(2-Hmbpa)(2-mbpa)Cl]·H$_2$O (2·H$_2$O).** A solution of **1** (23.3 mg, 0.02 mmol) in dichloromethane (20 cm^3) was treated with an excess of NEt_3 (0.1 cm^3), and the resulting solution was stirred for 1 h at room temperature. The dichloromethane solution was extracted with water (3 × 10 cm^3) and then dried over $MgSO_4$, filtered, and reduced to ca. 3 cm^3. The product **2** was precipitated with *n*-hexane. Yield: 18.8 mg, 82%. Found: C, 53.25; H, 4.90; Cl, 3.21. Calcd for $C_{52}H_{55}ClO_{11}P_2Pt$: C, 53.38; H, 4.83; Cl, 3.09. IR (cm^{-1}): ν(OH), 3419 (m), 3220 (w); ν(C−H), 3056 (w), 2977 (w), 2937 (w); ν(C═C), 1636 (w), 1474 (m), 1434 (m); ν(C−O), 1101 (s), 1048 (s); ν(Pt−Cl), 304 (w); ν(Pt−O), 349 (w); ν(Pt−P), 191 (w), 160 (w).

***cis*-[Pt(2-mbpa)$_2$]·3H$_2$O (3·3H$_2$O).** A suspension of **1** (23.3 mg, 0.02 mmol) or **2** (23.0 mg, 0.02 mmol) was treated with an excess of NaOMe (5.4 mg, 0.1 mmol) in methanol (10 cm^3). After all the solid had dissolved (ca. 0.5 h), the resulting solution was stirred continuously for another 1 h at room temperature. Water (10 cm^3) was added, and the solution was left standing for a few days at 5 °C (yield: 80−90%). The isolated product was recrystallized from aqueous methanol, and crystals suitable for X-ray diffraction were obtained. Found: C, 54.07; H, 5.47. Calcd for $C_{52}H_{52}O_{10}P_2Pt\cdot 3H_2O$: C, 54.40; H, 5.09. IR (cm^{-1}): ν(OH), 3369 (m), 3236 (w); ν(C−H), 3056 (w), 2928 (w), 2668 (w); ν(C═C), 1647 (w), 1438 (m); ν(C−O), 1105 (s), 1051 (s); ν(Pt−O), 349 (w); ν(Pt−P), 194 (w).

***cis*-[Pt(2-Hmbpa)(2-mbpa)(AcO)] (4).** To a solution of **3** in chloroform in an NMR tube was added excess acetic acid at room temperature.

***cis*-[Pt(2-mpa)$_2$] (5).** A solution of **3** (114.8 mg, 1 mmol) in dichloromethane (20 cm^3) and methanol (50 cm^3) was treated with 5% $HClO_4$ (5 cm^3) at room temperature for 48 h. The solution was neutralized with solid Na_2CO_3, filtered, and washed with methanol and dichloromethane. The residue obtained by removing the solvent under reduced pressure at room temperature was dissolved in dichloromethane (50 cm^3) and washed with water (10 cm^3). After drying over Na_2SO_4, the dichloromethane was removed to give the compound **5**, which was dried at 60 °C under reduced pressure for 24 h (yield: 76%). MS(FAB): 940 (M + Na$^+$, 100), 918 (M$^+$ + 1, 50), 900 ((M$^+$ + 1 − H_2O, 2), 784 (15), 765 (10), 379 (8), 307 (18), 154 (80). IR (cm^{-1}): ν(OH), 3350 (s), 3210 (w); ν(C−H), 3055 (w), 2915 (w), 2670 (w); ν(C═C), 1648 (w), 1436 (m); ν(C−O), 1121 (s), 1105 (s).

Crystallographic Measurement. Data collections were performed at 296 K on an Enraf-Nonius CAD 4 diffractometer with Mo Kα radiation (λ = 0.71069 Å) and a graphite monochromator. The unit cell parameters were obtained by least-squares refinements of the θ range of 25 reflections. Crystal and instrument stabilities were monitored with a set of three standard reflections measured every 120 min; in all cases no significant variations were found. The intensity data collected were corrected for *Lp* factors. The structures were solved by the direct methods with the MOLEN/PC program.[13] A total of three atoms were located from an E-map prepared from the phase set with probability statistics: absolute figure of merit = 1.09, residual = 6.05, and psi zero = 3.953. The remaining atoms were located in succeeding difference Fourier syntheses and refined by full-matrix least-squares techniques with anisotropic thermal parameters for all non-hydrogen atoms.[14] Hydrogen atoms were not refined, but added isotropically to the structure factor calculations. The crystallographic data for complex **3** are listed in Table 4 together with the data collection parameters. Selected bond lengths and bond angles are given in Table 5.

Results and Discussion

Synthesis and ^{31}P NMR. The compound methyl 4,6-*O*-benzylidene-2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside (2-Hmbpa)[12] was chosen as the ligand on the

(8) Kapteijn, G. M.; Grove, D. M.; Kooijman, H.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1996,** *35*, 526, and references therein.

(9) Alcock, N. W.; Platt, A. W. G.; Pringle, P. *J. Chem. Soc., Dalton Trans.* **1987,** 2273. (b) Alcock, N. W.; Platt, A. W. G.; Pringle, P. *J. Chem. Soc., Dalton Trans.* **1989,** 139.

(10) Hartwig, J. F.; Lippard, S. J. *J. Am. Chem. Soc.* **1992,** *114*, 5646.

(11) *Inorg. Synth.* **1972,** *13*, 48.

(12) Shi, J. C.; Hong, M. C.; Wu. D. X.; Liu, Q. T.; Kang, B. S. *Chem. Lett.* **1995,** 685.

(13) *MOLEN*, An Interactive Structure Solution Procedure; Enraf Nonius: Delft, The Netherlands, 1990.

(14) Killean, R. C. G.; Lawrence, J. L. *Acta Crystallogr. B* **1969,** *25*, 1750.

Table 1. ^{31}P {^{1}H}NMR Data of the Compounds 1−5

complex		δ^a	$^1J_{PtP}{}^b$	$^2J_{PP}{}^b$	solvent
cis-[Pt(2-Hmbpa)$_2$Cl$_2$] (**1**)	2-Hmbpa	7.6	3732		$CDCl_3$
		9.1	3684		$(CD_3)_2SO$
cis-[Pt(2-Hmbpa)(2-mbpa)Cl] (**2**)	2-Hmbpa	4.6	3118	15	$(CD_3)_2SO$
	2-mbpa	31.9	4009		
cis-[Pt(2-mbpa)$_2$] (**3**)	2-mbpa	29.9	3432		
cis-[Pt(2-Hmbpa)(2-mbpa)(AcO)] (**4**)	2-Hmbpa	5.8	3108	*c*	$CHCl_3$
	2-mbpa	23.7	3745		
cis-[Pt(2-mpa)$_2$] (**5**)	2-mpa	30.4	3500		

[a] Chemical shifts (δ) in ppm. [b] Coupling constants (J) in hertz. [c] Not resolved.

Table 2. ^1H NMR Data of the Compounds 1−3 and 5[a]

		2			
	1	2-Hmbpa	2-mbpa	3	5
aryl−H	7.0−7.8 (m)	6.5−7.8 (m)		7.1−7.7 (m)	7.2−7.6
H(1)	5.30 (d, 6.0)	5.97 (d, 8.0)	3.96 (dd, 9.0, 6.0)	4.01 (dd, 9.0, 5.5)	4.02 (m)
H(2)	3.92 (m, 22.5)	4.42 (d, 16.5)	3.50 (m)	3.52 (m)	3.56 (m)
H(3)	3.93 (m)	3.80 (t, 11.0)	4.31 (dd, 12.5, 9.0)	4.22 (dd, 12.5, 9.0)	4.28 (m)
H(4)	4.34 (m, 7.5)	4.13 (m)	3.79 (t, 9.0)	3.74 (t, 9.5)	3.85 (m)
H(5)	4.06 (dt, 10.5, 5.5)	4.03 (m)	4.15 (dt, 9.5, 4.5)	4.15 (dt, 10.0, 5.0)	3.95 (m)
H(6)	4.14 (dd)	4.12 (dd)	4.26 (dd)	4.30 (dd)	3.85 (m)
	(10.5, 5.5)	(10.0, 4.5)	(10.0, 4.5)	(10.0, 4.5)	
H(6′)	3.15 (t, 10.5)	3.02 (t, 10.0)	3.59 (t, 10.0)	3.63 (t, 10.0)	3.48 (m)
H(7)	5.00 (s)	4.61 (s)	5.50 (s)	5.58 (s)	
CH_3	3.22 (s)	3.55 (s)	2.96 (s)	3.02 (s)	3.05 (s)

[a] ^1H NMR spectra of compounds **1**−**3**, **5** are recorded in $CDCl_3$. Chemical shifts (δ) in ppm. Coupling constants (J) in hertz.

Table 3. ^{13}C NMR Data of the Compounds 1−3 and 5

			3		
	1	2	2-Hmbpa	2-mbpa	5
aryl−C	126−138	126−138	127−138		126−136
C(1)	98.8	100.6	99.5	99.6	98.4
C(2)	47.6 (41.9)	42.6 (34.1)	52.21 (41.0)	51.3 (41.9)	47.6 (41.0)
C(3)	57.9	65.6	72.9	73.5	71.0
C(4)	66.0	69.4	80.3	80.7	75.8
C(5)	75.2	57.3	64.8	64.5	60.4
C(6)	69.3	69.4	70.1	70.1	70.0
C(7)	101.7	101.9	102.9	102.4	
CH_3	55.8	56.2	54.5	54.4	54.8

[a] ^{13}C NMR spectra of compounds **1**−**3**, **5** are recorded in $CDCl_3$. Chemical shifts (δ) in ppm. Coupling constants (J) in hertz.

Table 4. Crystallographic Data for *cis*-[Pt(2-mbpa)$_2$] (3)

empirical formula	$C_{52}H_{52}O_{10}P_2Pt\cdot 3H_2O$
fw	1148.07
cryst dimens, mm^3	0.40 × 0.40 × 0.40
space group	*C*2 (No. 5)
a, Å	24.562(6)
b, Å	11.071(7)
c, Å	21.007(3)
β, deg	98.11(2)
V, Å^3	5655(6)
Z	4
D_{calcd}, g cm^{-3}	1.35
F(000)	2328
μ, cm^{-1}	26.2
θ range for lattice params, deg	13−14
scan mode	$\omega-2\theta$
$2\theta_{max}$, deg	50.0
no. of reflecns collecd	5398
no. of obsd reflecns with $I \geq 3\sigma(I)$	5621
no. of reflecns used	3905
no. of variables	612
S	1.38
$(\Delta/\sigma)_{max}$	0.82
R^a	0.062
$R_w{}^b$	0.076

[a] $R = (\sum||F_o| - |F_c||)/\sum|F_o|$. [b] $R_w = \{[\sum w(|F_o| - |F_c|)^2]/\sum w|F_o|^2\}^{1/2}$. $w = [\sigma^2(F_i) + (0.020F_o)^2 + 1.000]^{-1}$.

basis of the following considerations: (a) it is derived from D-glucose with a hydroxy group, which is a potential alkoxide ligand. (b) It contains the bulky sidearm group 4,6-*O*-benzylidene. (c) Its gold(I) complexes have attracted much interest because many of them possess high antitumor activity.[3]

Treatment of [Pt(COD)Cl$_2$] (COD = 1,5-cyclooctadiene) with the ligand 2-Hmbpa afforded *cis*-[Pt(2-Hmbpa)$_2$Cl$_2$] (**1**) (see Scheme 2). The *cis* assignment is made on the basis of the large $^1J_{PtP}$ coupling constant, which exceeds 3000 Hz (see Table 1). The ^{31}P chemical shift and the $^1J_{PtP}$ coupling constant of **1** are sensitive to the polarity of the solvents used, 7.6 ppm (3732 Hz) in $CDCl_3$ and 9.1 ppm (3684 Hz) in $(CD_3)_2SO$, indicating that species (**1a** and **1b**) with 3-OH coordinating to Pt(II) are present in solution (Scheme 3).[9]

Indeed, in solution **1** converted smoothly to the monodeprotonated alkoxoplatinum(II) species *cis*-[Pt(2-Hmbpa)(2-mbpa)Cl] (**2**), and no bis(alkoxo)platinum(II) species can be observed in the presence of NEt_3. The complex **2** possesses two different ^{31}P chemical shifts at 4.6 ppm ($^1J_{PtP}$ = 3118 Hz) and 31.9 ppm ($^1J_{PtP}$ = 4009 Hz) with a small $^2J_{PP}$ value of 15 Hz in DMSO-d_6. The large Pt−P coupling constants indicate that the two phosphorus atoms remain mutually *cis* to each other in **2**, which is further confirmed by the small P−P coupling constant. The signal at 31.9 ppm in the ^{31}P NMR spectrum of **2** shifting down 22.8 ppm compared to that of **1** in DMSO-d_6 shows the formation of the P:O five-membered chelate ring.[15]

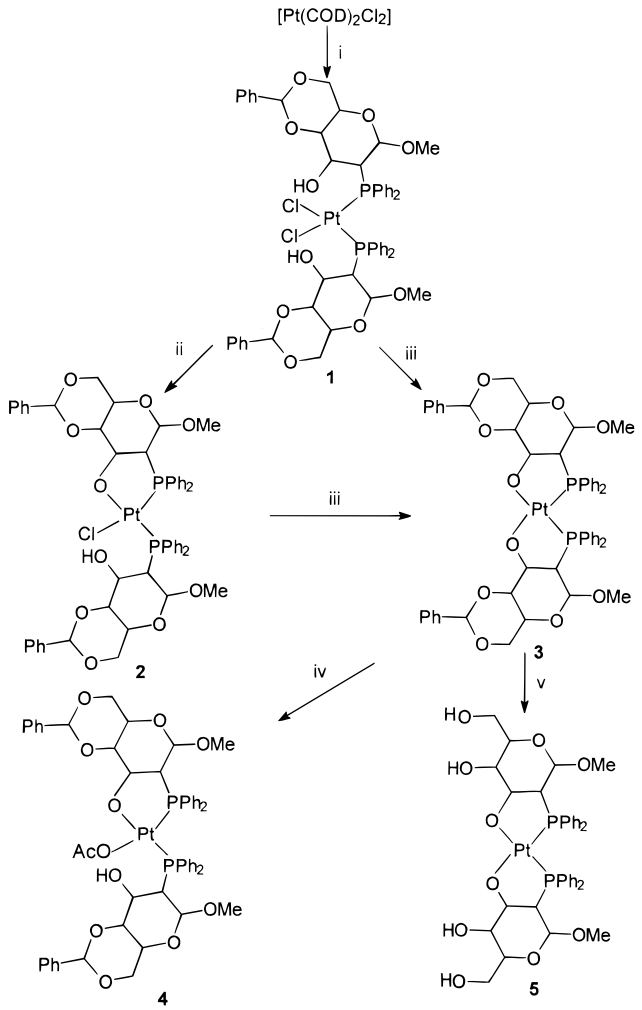
When treated with strong base such as NaOMe, both **1** and **2** gave the bis(alkoxo)platinum(II) complex *cis*-[Pt(2-mbpa)$_2$] (**3**) in high yield, which was deduced from only one set of signals centered at 29.9 ppm with the Pt−P coupling constant of 3432 Hz. The compound **3** is air stable and can be recrystallized from aqueous methanol solution.

(15) Garrou, P. E. *Inorg. Chem.* **1975,** *14,* 1435.

Table 5. Selected Atomic Distances (Å) and Bond Angles (deg) for the Compound 3

Pt−P	2.226(8)	Pt−P′	2.210(8)
Pt−O(3)	1.98(2)	Pt−O(3′)	1.99(1)
P−C(2)	1.83(2)	P−C(21)	1.85(3)
P−C(31)	1.81(2)	P′−C(2′)	1.83(3)
P′−C(21′)	1.76(4)	P′−C(31′)	1.93(3)
P−Pt−P′	103.2(3)	O(3)−Pt−O(3′)	89.2(7)
P−Pt−O(3)	85.5(6)	P−Pt−O(3′)	173.5(5)
P′−Pt−O(3)	171.2(6)	P′−Pt−O(3′)	82.1(5)
Pt−P−C(2)	102.3(8)	Pt−P−C(31)	116.3(9)
Pt−P−C(21)	118(1)	Pt−P′−C(21′)	101.1(9)
Pt−P′−C(21′)	121(2)	Pt−P′−C(31′)	117.3(8)
Pt−O(3)−C(3)	118(2)	Pt−O(3′)−C(3′)	118(1)
P−C(2)−C(1)	119(3)	P−C(2)−C(3)	105(2)
P′−C(2′)−C(1′)	115(2)	P′−C(2′)−C(3′)	102(2)

Scheme 2[a]

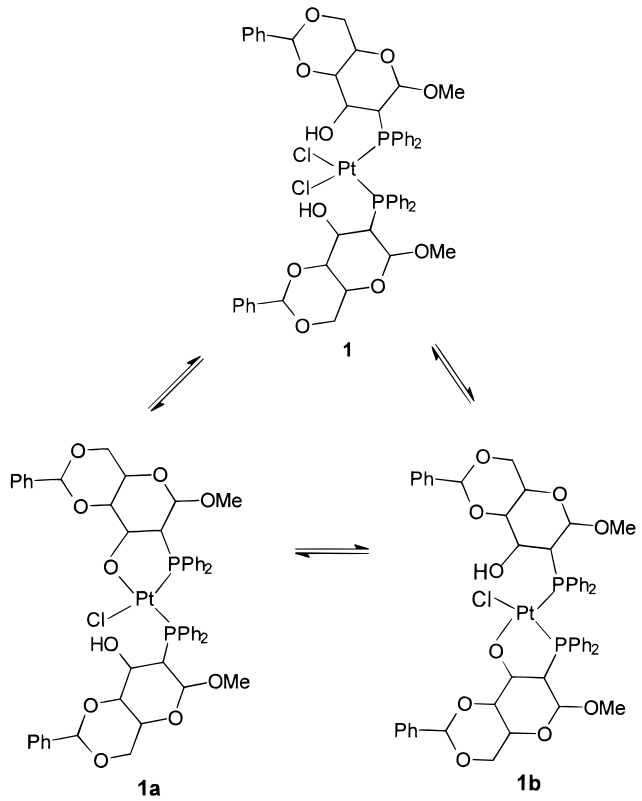


[a] (i) 2 equiv of ligands 2-Hmbpa in dichloromethane; (ii) an excess of NEt_3 in dichloromethane; (iii) an excess of NaOMe in methanol; (iv) an excess of acetic acid in chloroform; (v) 5% $HClO_4$ aqueous solution at room temperature.

The value of $^1J_{PtP}$ is a sensitive function of the σ-bonding ability of the ligand *trans* to the phosphorus donors.[16] The value of $^1J_{PtP}$ for P *trans* to O (3118 Hz) in **2** is smaller than those *trans* to Cl (4009 Hz) in **2**. Similarly, those *trans* to O in **3** (3432 Hz) are smaller than those *trans* to Cl in **1** (3684 Hz). These data suggest that the σ-bonding ability of alkoxide to Pt(II) is larger than chloride.

IR. The absorptions at 318 cm^{-1} for **1** and 304 cm^{-1} for **2** are typical of ν(Pt−Cl) for Cl *trans* to PR_3,[9] which

Scheme 3



are consistent with the assignment of the configuration of **1** and **2** by ^{31}P NMR studies. Although there are no similar ν(Pt−O) values of alkoxoplatinum(II) for comparison, the new absorption at 349 cm^{-1} in **2**, which became stronger in **3**, can be attributed to ν(Pt−O) by careful comparison of the far-IR regions of complexes **1**−**3** with that of the free ligand (2-Hmbpa). The ν(Pt−O) values for **2** and **3** are smaller than ν(Pd−O) (ca. 380 cm^{-1}) for the alkoxopalladium(II) analogue,[17] indicating that the assignment is reasonable. The broad peaks at ca. 3400 cm^{-1} and the absorption at ca. 3200 cm^{-1} combined with elemental analyses indicate the presence of the hydrogen bond interactions between water molecules and **2** and **3**.

^{1}H and ^{13}C NMR. ^{1}H and ^{13}C NMR chemical shifts for the complexes **1**−**3** are listed in Tables 2 and 3, respectively. The spectra cannot be analyzed straightforwardly, mainly due to the long-range and virtual coupling.[18] 2D NMR techniques are necessary for full assignment. In some cases, assignments were further aided by the data from the literature on the relevant compounds.[12,17]

It is often found for the *n*-Hmbpa (n = 2, 3) ligands that when only phosphorus donor coordinates to the metal center, the conformation of the pyranose ring does not change significantly and H(1), H(2), and H(3) atoms remain in equatorial positions.[3] Therefore, the couplings of H(3)−H(2) and H(2)−H(1) are often too weak to be observed and the assignment cannot start from H(1) in the ^{1}H−^{1}H COSY spectrum, which is generally expected

(16) (a) Boere, R. T.; Willis, C. J. *Inorg. Chem.* **1985,** *24,* 1059. (b) Appleton, T. G.; Bennett, M. A. *Inorg. Chem.* **1978,** 17, 738.
(17) Shi, J. C.; Wu, D. X.; Weng, T. B.; Hong, M. C.; Liu, Q. T.; Kang, B. S.; Lu, S. J.; Wang, H. Q. *J. Chem. Soc., Dalton Trans.* **1996,** 2911.
(18) Razi, M. T.; Sadler, P. J. *J. Chem. Soc., Dalton Trans.* **1983,** 1331.

as a doublet peak for pyrano-sugars. Fortunately, only one CH_2 group exists in the *n*-Hmbpa ligands and the two protons are not equivalent, resulting from the CH_2 group linking to the chiral backbone. Assignment of ^1H and ^{13}C resonances of the complexes **1**−**3** can start from the two proton signals correlating to one carbon signal in the $^1H-^{13}C$ HMQC (heteronuclear multiple-quantum coherence) spectrum. There are two sets of two proton signals correlating to one carbon signal in the $^1H-^{13}C$ HMQC spectrum of [Pt(2-Hmbpa)(2-mbpa)Cl] (**2**): 4.12 and 3.02 ppm to 69.4 ppm; 4.26 and 3.59 to 70.1 ppm. This fact is consistent with **2** containing the two types of carbohydrate ligands: (i) the ligand 2-Hmbpa, in which only the phosphorus donor coordinates to Pt(II); (ii) the deprotonated ligand 2-mbpa with chelate P:O donors to Pt(II). From the former set, the correlated peaks in the $^1H-^1H$ COSY spectrum can be found for H(4)−H(3) from H(6) and H(6′) through H(5), implying that the set is contributed from the ligand 2-Hmbpa. Contrarily, the signal at 3.96 ppm of H(1) for the deprotonated ligand 2-mbpa can be assigned from the latter set via the correlated peaks in the $^1H-^1H$ COSY spectrum. The doublet signal ($^3J_{PH}$ = 8.0 Hz) at 5.97 ppm correlating to a downfield ^{13}C signal at 100.6 ppm allows us to assign them to H(1) and C(1) belonging to the ligand 2-Hmbpa, respectively. Similarly, the doublet signal ($^2J_{PH}$ = 16.5 Hz) at 4.43 ppm correlating to the highest-field ^{13}C signal at 42.6 ppm can be assigned to H(2) and C(2) belonging to the ligand 2-Hmbpa, respectively, because the signal of the carbon linking to the phosphorus atom in the ligand 2-Hmbpa should appear at the highest field. After all the proton signals of the pyranose ring have been assigned, the other carbon signals of the pyranose ring are easily assigned through the $^1H-^{13}C$ HMQC spectrum.

The absence of the correlated peaks of H(3)−H(2) and H(2)−H(1) for the ligand 2-Hmbpa of **2** indicates that the conformation of the pyranose ring remains in a chair fashion. For the P:O chelate deprotonated ligand 2-mbpa, however, the correlated peaks for H(3)−H(2) and H(2)−H(1) appear. This indicates that the conformation of the pyranose ring belonging to the ligand 2-mbpa changes significantly when the oxygen donor coordinates also to Pt(II). Since both diphenylphosphino and hydroxy groups are still in axial positions as only the phosphorus donor is ligated to Pt(II), they must twist to equatorial positions in order to make phosphorus and oxygen donors simultaneously coordinate to Pt(II). Because the O(4) and C(6) are fixed by the 4,6-*O*-benzylidene ring, which is in chair conformation, only the methoxy group can change and turn to an equatorial position as the diphenylphosphino and hydroxy groups turn to equatorial positions, consequently, resulting in the pyranose ring of the deprotonated ligand 2-mbpa adopting a boat conformation.

Crystal Structure. The structure of **3** was confirmed by X-ray diffraction methods (Figure 1). The square-planar geometry about Pt is slightly distorted due to the bulkiness of the phosphine ligands, with a P−Pt−P angle of 105.7(1)°, compared to a O−Pt−O of 85.5(6)°. The Pt−P distances (av 2.218(8) Å) have normal values.[9] The Pt−O distances (av 1.98 (2) Å) are slightly shorter than those of bis(3-diphenylphosphino-2-methylpropan-2-olato-*O*,*P*)platinum(II) (av 2.043(3) Å) and bis(3-diphenylphosphinoethoxo-*O*,*P*)platinum(II) (2.039(5) Å).[9] Considering the normal difference of 0.11 Å between single bonds of C−C and C−O, and the Pt−C distances (2.120(1) Å), the Pt−O bonds in **3** have exactly the expected length of a standard single bond. Therefore, the great thermal lability and sensitivity to water for many alkoxoplatinum(II) complexes[19] cannot be ascribed to the fact that Pt−O bond is inherently weak. On the contrary, it is most probably due to the facile *β*-hydrogen elimination effect. Incorporation of the O-donor into a chelating ring makes the conformation of the ligand orient in a way that the *β*-hydrogen will move away from the platinum, thus making it unavailable for hydrogen elimination.[20]

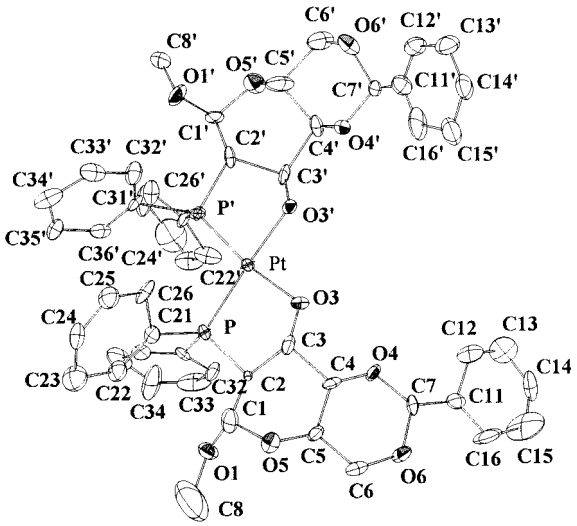


Figure 1. Crystal structure of *cis*-[Pt(2-mbpa)$_2$] (**3**) showing the atom-labeling scheme with 20% probability.

As can be seen from Figure 1, the 4,6-*O*-benzylidene ring remains in a chair conformation and the pyranose rings adopt a distorted boat conformation. The bow atoms are C(2) and C(5). The torsion angles of −34° for P−C(2)−C(3)−O(3), −58° for P′−C(2′)−C(3′)−O(3′), 69° for P−C(2)−C(1)−O(1), and 84° for P−C(2)−C(1)−O(1) indicate clearly that the diphenylphosphino, methoxy, and alkoxo groups are all in equatorial positions. This conclusion has been deduced from NMR studies.

The packing diagram of molecules in the lattice is presented in Figure 2; each molecule contains three H_2O molecules. The significant distances (Å) are O(1w)−O(3), 3.87(3); O(2w)−O(3′), 2.88(6); O(1w)−O(2w), 3.63(3); O(1w)−O(3w), 2.85(3); O(2w)−O(3w), 4.16 (4); and O(3w)−O(6′), 3.36(3). There is a very strong hydrogen-bonding interaction between O(3′) and H_2O(2w) and a weak one between O(3) and H_2O(1w). The strong hydrogen-bonding interaction indicates the oxygen donors ligating to Pt(II) are extremely electron-rich.

Reaction with Acid. The electron-rich character of the oxygen donors in **3** can be expected to take proton ions in biological medium and to form the species ligated by alcohol, which is ready to offer vacant coordination sites. Therefore, the labile species may be comparable to the intermediates of the aqua species of cisplatin. It has been found that on the addition of excess acetic acid

(19) Bryndza, H. E.; Calabrese, J. C.; Marsi, M.; Roe, D. C.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986,** *108,* 4805.
(20) McDermott, J. X.; White, J. F.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976,** *98,* 6521.

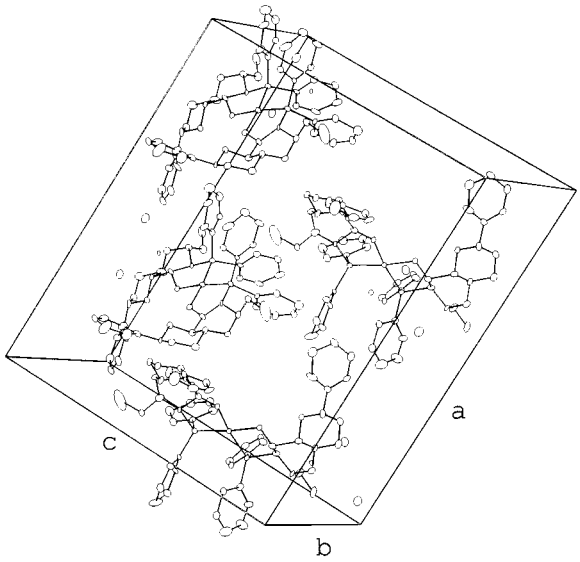


Figure 2. Packing of *cis*-[Pt(2-mbpa)$_2$] (**3**) in the lattice.

to the solution of **3** in chloroform, the ^{31}P peak at 29.9 ppm disappeared and two new sets centered at 23.7 ($^1J_{PtP}$ = 3745 Hz) and 5.8 ($^1J_{PtP}$ = 3108 Hz) ppm appeared, and *cis*-[Pt(2-Hmbpa)(2-mbpa)(AcO)] (**4**) is reasonably assigned on the basis of its chemical shifts and coupling constants. The result supported partially the expectation that **3** may take protons in biological medium.

Both before and after **3** taking proton ions, the bulky sidearms of the chiral 4,6-*O*-benzylidene groups are expected to provide π-stacking[21] and steric control over the recognition of the incoming ligands, resulting in preventing the platinum(II) center from binding to sulfur-containing biomacromolecule.[5] However, the bulky sidearms can also reduce the reactivity toward the target DNA. Therefore, it is necessary to study the hydrolysis of the 4,6-*O*-benzylidene groups. It has been found that the free ligand 2-Hmbpa is stable in weak acids such as acetic acid and 4-methylbenzenesulfonic acid for several days at room temperature, and no hydrolysis of benzaldehyde has been observed.[23] However, the 4,6-*O*-benzylidene group can be removed by strong acid at room temperature. Similarly, it takes 2 days to completely remove the 4,6-*O*-benzylidene groups in **3** by 5% $HClO_4$ aqueous solution at room temperature, and the complex *cis*-[Pt(2-mpa)$_2$] [**5**, 2-Hmpa = methyl 2-deoxy-2-(diphenylphosphino)-α-D-altropyranoside] is isolated after being neutralized. Whether the sidearms will be hydrolyzed in the transporting process is unclear because of the higher temperature, but the long time needed for hydrolysis and the requirement of strong acid at room temperature may imply that the bulky sidearms can be preserved in the early stage of the transporting process to the target DNA molecule after administration. It is desired to remove the sidearms in **3** similar to removing the biscarboxylate in carbolatin when binding to DNA. We are interested in synthesizing the analogues of **3** in which the sidearms have different hydrolysis kinetics.

Antitumor Activity. The general method has been used to detect the antitumor activity of complexes **1**−**3** against P388 leukemia.[22] Complexes **1**−**3** are all effective; for example, the inhibiting ratio of **3** to P388 leukemia is as high as 60% even at 10^{-7} mol/dm^3. The detailed data and further antitumor studies will be reported elsewhere.

Conclusion

A new kind of anticancer compounds with high activities have been designed, synthesized, and characterized. The concept of an "opening and closing mechanism" has been introduced from homogeneous catalysis into medicine design. The electron-rich character of oxygen donors in the alkoxoplatinum(II) complexes has been used to produce the labile species and provide vacant coordination sites. The bulky sidearms 4,6-*O*-benzylidene have been introduced to provide steric hindrance around the platinum(II) center in the closed state, although the arms should to be hydrolyzed when binding to DNA. After binding to DNA, the leaving hydroxy groups may produce a second interaction through hydrogen bonding in opened state. Detailed studies of **3** with biological ligands including DNA in different pH's would be interesting to carry out.

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Supporting Information Available: Tables of atomic coordinates, bond distances and angles, anisotropic thermal parameters, and torsion angles. This material is available free of charge via the Internet at http://pubs.acs.org.

OM990068R

(21) Echavarren, A. M.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989,** *111,* 4994.
(22) Mirabelli, C. K.; Johnson, P. K.; Sung, C. M.; Faucette, L.; Muirhead, K.; Crooke, S. T. *Cancer Res.* **1985,** *45,* 32.
(23) Shi, J. C. Unpublished results.