CHEMISTRY LETTERS, pp. 529-532, 1993.

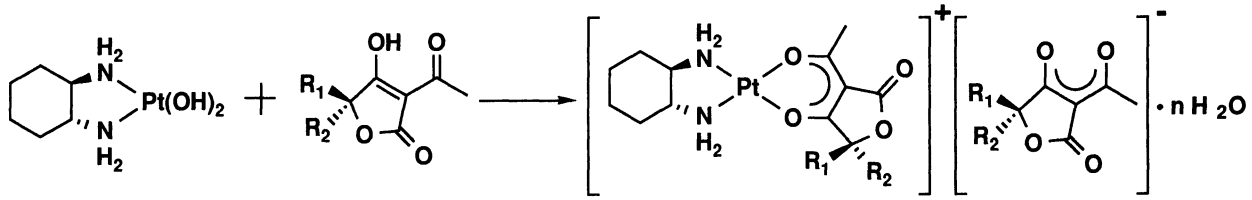
Synthesis and Antitumor Activity of [3-Acetyl-2,4(3*H*, 5*H*)-furandionato-O^3,O^4] [(1*R*, 2*R*)-cyclohexanediamine]platinum(1+) Ion Complex and Its Derivatives

Go HATA,* Hideki KAWAI, Tatsuya KANEKO, Takayuki IMAOKA,
Yukishige KITANO,† Masato MUTOH, and Hideyo IMANISHI
Basic Research Laboratories, Toray Industries Inc., 1111 Tebiro, Kamakura, Kanagawa 251
†Toray Research Center, 3-2-1 Sonoyama, Ohtsu, Shiga 520

The reaction of dihydroxo[(1*R*,2*R*)-cyclohexanediamine]platinum(II) with 3-acetyl-2,4-(3*H*, 5*H*)-furandiones gave salts consisting of [3-acetyl-2,4(3*H*, 5*H*)-furandionato-O^3,O^4] [(1*R*, 2*R*)-cyclohexanediamine]platinum(1+) ions and enolates of 3-acetyl-2,4-(3*H*, 5*H*)-furandiones. The complexes show high solubility, and antitumor activity at low doses against murine leukemia L1210 sensitive and resistant to *cis*-dichlorodiammineplatinum(II).

cis-Dichlorodiammineplatinum(II)(CDDP)[1] has been proven to be effective to human solid tumors. There is still a great need for new platinum complexes which demonstrate no cross resistance to CDDP and different antitumor spectra from those of CDDP besides decreased renal toxicity. With such purposes, much effort has been made to obtain new type platinum(II) complexes. (1,2-Cyclohexanediamine)platinum(II) complexes are reported to be effective against murine leukemia L1210 which acquires resistance to CDDP.[2] Non-ionic antitumor (1,2-cyclohexanediamine)platinum(II) complexes with bidentate leaving groups such as oxalic,[3] glycolic,[4] mandelic,[5] and quinic acid[6] have been reported but there has been no report on ionic ones with antitumor activity.

We report here the preparation, structure determination and antitumor activity of a new type of cationic platinum complexes **3** which contains (1*R*, 2*R*)-cyclohexanediamine and 3-acetyl-2,4-(3*H*, 5*H*)-furandiones **2** as bidentate leaving groups.



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2a ; R_1=R_2=H
2b ; R_1=(*S*)-Me, R_2=H
2c ; R_1=H, R_2=(*R*)-Me
2d ; R_1=R_2=Me

3a ; R_1=R_2=H n=4
3b ; R_1=(*S*)-Me, R_2=H n=4
3c ; R_1=H, R_2=(*R*)-Me n=0
3d ; R_1=R_2=Me n=2

Scheme 1.

The complexes **3a-d** were synthesized by the reaction of dihydroxo[(1*R*, 2*R*)-cyclohexanediamine)]-platinum(II) (**1**)[6] with 2 equiv. of **2a-d** [7,8] as shown in Scheme 1.

A typical example is shown below. To **2b**(71.1 mmol) in H_2O(200 ml) was added **1** (33.6 mmol) in H_2O(500 ml) at 0 °C and kept for 5 h at room temperature. The solution was concentrated to dryness. After washing the residual solid with THF, the resultant powder was submitted to column chromatography on MCI GEL(CHP20P) with H_2O-MeOH(7:3). Twice recrystallization from water gave a colorless crystal **3b** as tetrahydrate (24 %).[9]

The ^1H NMR spectra of **3a-d** show that the complexes consist of two molecules of **2a-d**. The presence of a pair of ^1H NMR signals due to acetyl group and γ-substituted methyl group(s) of the complexes and a rapid release of one molecule of **2** from the complexes in ODS reverse phase HPLC using H_2O-MeOH-CH_3COOH as a mobile phase suggest that one molecule is in an anionic form. The crystal of **3b** was subjected to X-ray structure analysis to determine the configuration of the complex. [10]

An ORTEP drawing of **3b** with four molecules of water is shown in Fig. 1. The practically same bond lengthes of Pt-O(1)(2.02 Å) and Pt-O(2)(2.00 Å) show the chelation of one molecule of **2b** to platinum(II). The complex is defined as a salt consisting of [(5*S*)-3-acetyl-5-methyl-2,4(3*H*, 5*H*)-furandionato-O^3,O^4] [(1*R*, 2*R*)-cyclohexanediamine]platinum(1+) ion and an enolate of **2b**. The distance between Pt and O(6) of the enolate is 4.18 Å. The chiralities of (1*R*, 2*R*)-cyclohexanediamine and **2b** are kept.

The solubilities of **3a, 3b, 3c**, and **3d** are about 50, 30, 30, and 7 mg/ml, respectively. Substitution of methyl group(s) on the γ-C atom of **2a** decreases the solubility of the corresponding complexes. The complexes are stable in water.

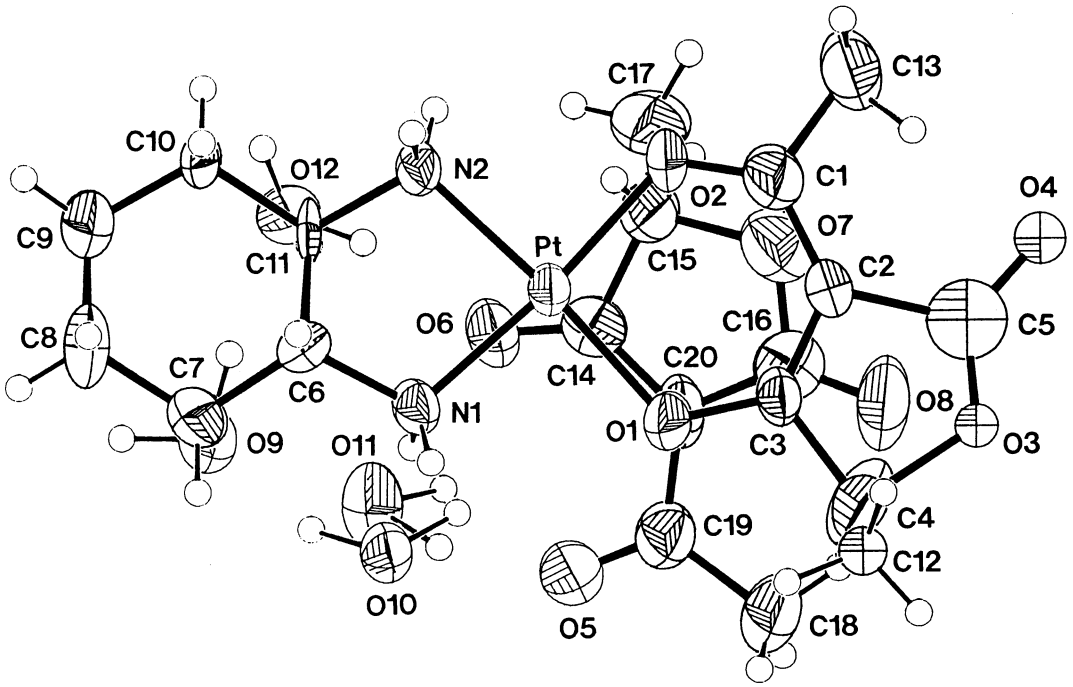


Fig. 1. ORTEP Drawing of Complex **3b**.

Antitumor activity of the complexes **3a-d** against murine leukemia L1210 and L1210 resistant to CDDP was tested *in vivo*. The results are summarized in Tables 1 and 2. The complexes are characteristic of showing antitumor activity at low doses (Table 1). The chilarity of 3-acetyl-5-methyl-2,4(3*H*, 5*H*)-furandionato part did not affect antitumor activity. The complexes **3a** and **3b** have higher antitumor activity for the resistant cells than for the parent sensitive cells (Table 2).

Table 1. Antitumor Activity of **3a-d** against Murine Leukemia L1210 in Mice [a)]

Complex	T/C(%) [b)]						
	Dose(mg/kg)						
	3.2	6.3	10	12.5	25	50	100
3a		163		173	154	119	79
3b	137	145		151	198	159	81
3c	120	130		140	165	155	76
3d			113	139	139	165	88

Table 2. Antitumor Activity of **3a** and **3d** against Murine Leukemia L1210 resistant to CDDP in Mice [a)]

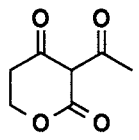
Complex	T/C(%) [b)]									
	Dose(mg/kg)									
	2.5	3.2	5	6.3	10	12.5	20	25	50	100
3a		104		181		156		110	74	55
3b		119		115		178		223	143	88
CDDP	102		91		96		79			

a) L1210 cells (10^5 cells) were inoculated *i.p.* into CDF_1 mice on day 0. Platinum complexes were inoculated *i.p.* on day 1, 5,and 9.

b) From the mean suvival times of treated and control mice (T and C), T/C(%) were calculated as indicators of the activity. T/C(%) value over 125 is evaluated as active.

The effects of structural changes in leaving groups on antitumor activity were investigated. The complex coordinated with acetylacetone did not show any activity. Neither the complex coordinated with 3-acetyl-5, 6-dihydro-2*H*-pyrane-2,4-(3*H*)-dione **4** (insertion of CH_2 between β– and γ–C atom of **2a**) nor the one coordinated with 2-acetyl-1;3-cyclopentanedione **5** (displacement of O atom of **2a** by CH_2) showed antitumor

activity. These structural changes of the leaving groups would cause an increase in electron density on the coordinated oxygen atoms. These facts suggest that the electron density on the coordinated oxygen atoms gives a great effect on antitumor activity in the platinum(1+) ion type of complexes.



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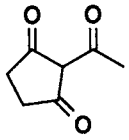

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9) **3b**: Anal. Found: C, 34.75; H, 5.20; N, 4.05; Pt, 28.22 %. Calcd for $C_{20}H_{28}N_2O_8Pt \cdot 4H_2O$: C, 34.74; H, 5.25; N, 4.05; Pt, 28.21 %. ^1H NMR (500 MHz, D_2O) δ 4.79(1H, q, J=7 Hz), 4.58(1H, q, J=7 Hz), 2.62(2H, m), 2.39(3H, s), 2.37(3H, s), 2.15(2H, bd), 1.67(2H, m), 1.49(3H, d, J=7 Hz), 1.43(2H, m), 1.42(3H, d, J=7 Hz), 1.25(2H, bt).
10) Crystallographic data **3b** : Fw=691.60, orthorhombic, $P2_12_12_1$, a=13.519(2), b=24.433(3), c=8.006(6) Å, V=2644(2) $Å^3$, Z=4, Dc=1.737 g cm^{-3}, T=23 °C, R=0.038, Rw=0.040 for 1773 reflections ($I>3.00\sigma(I)$) with monochromated Mo-Kα radiation.

(Received December 14, 1992)