Inorganica Chimica Acta, 155 (1989) 21–23

Facile One-pot Synthesis of Anticancer *cis*-Diammineplatinum Pyrimidine Green Analogs

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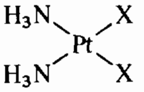
(Received July 7, 1988)

Although the first discovery of *cis*-dichlorodiammineplatinum(II) itself (**Ia**, *cis*-DDP, cisplatin)



Ia; X = Cl
Ib; X = I

was almost 100 years ago [1], it was not studied further in detail. In recent years, however, *cis*-DDP has attracted much interest, since the discovery of its beneficial effects in the treatment of cancer [2, 3]. Platinum pyrimidine blues, which are oligomer compounds derived from the aquo derivative of *cis*-DDP and pyrimidine bases, are reported to show antitumor activities against Sarcoma 180 and L1210 [4]. According to the earlier investigators, the advantage of these platinum blue complexes over the well-known *cis*-DDP is their low nephrotoxicities [4, 5]. But, because of poor reproducibility in their synthesis and the lack of single crystal X-ray diffraction analysis, their structures and activities have long remained vague. We have currently demonstrated that the related green materials are remarkably active against leukemia L1210 cells, but that the corresponding blue compounds are inactive [6–11]. To examine this further in detail, the development of a selective and facile synthesis method for platinum greens was necessary, and we now report their convenient 'one-pot' synthesis.

Experimental

Typical synthetic procedures were as follows. A mixture of *cis*-diiododiammineplatinum(II) [12] (**Ib**, 142.8 mg, 0.3 mmol), Ag_2SO_4 (92.55 mg, 0.3 mmol), uridine (73.69 mg, 0.3 mmol) and hydrogen peroxide (1%, 336 μl) in water (3 ml, deaerated by bubbling He) was stirred at room temperature for 24 h under nitrogen. The precipitates were removed by filtration, and the green filtrate was submitted to gel filtration (a 25 X 200 mm column packed with Toyopearl HW-40) using a 10 mM H_2SO_4 solution as eluant. A single zone with a green color was observed on the column. Acetone (300 ml) was then added to the eluant and the mixture was kept at 4 °C overnight in the dark. The platinum uridine green was collected by filtration and dried over phosphorus pentaoxide for 2 h at 60 °C. The yield was 73.59 mg (46.1%, run 3 in Table 1).

Results and Discussion

With a conventional method, formation of the diaquo complex **III** from **I** and a silver salt (e.g., **II**) in an overnight reaction was required in advance, according to eqn. (1). Then compound **III** was reacted with pyrimidines (e.g., **V**) to produce platinum greens (**VI**, eqn. (2)) [4, 6–9].

$$\underset{\mathbf{I}}{cis\text{-Pt}(NH_3)_2X_2} + \underset{\mathbf{II}}{Ag_2SO_4} \xrightarrow[\text{overnight}]{H_2O,\ \text{r.t.}} \underset{\mathbf{III}}{cis\text{-Pt}(NH_3)_2(H_2O)_2(SO_4)} + \underset{\mathbf{IV}}{2AgX} \qquad (1)$$

$$\mathbf{III} + \underset{\mathbf{V}}{\text{uridine}} \xrightarrow[N_2]{H_2O_2} \underset{\mathbf{VI}}{\text{'platinum pyrimidine green'}} \qquad (2)$$

'platinum pyrimidine green' (2)

However, there seemed no need to carry out the two reactions independently, and eventually the formation of platinum greens proceeded very smoothly in a one-pot reaction. During these procedures, exposure to air was carefully excluded, so that no further oxidized materials (e.g., blue and violet complexes) were formed. A stoichiometric amount of AgI (138.34 mg, 98%) was recovered, which suggested *in situ* generation of the aquo complexes in the present reaction. Quantitative analysis showed a negligible amount of Ag (less than 0.02%) in the platinum green complex, as determined by the ICP method (inductively coupled plasma atomic emission spectrometry; Shimadzu ICPS-2H and CTM-100). Similarly, platinum uridine greens were synthesized under various conditions (Table 1). The present 'one-pot' preparation is of great advantage over the previous method that involved synthesis of the diaquo complex from *cis*-dichlorodiammineplatinum(II) separately (overnight reaction) prior to the formation of green compounds [6, 9]. Isolated yields are much higher (2- to 3.7-fold) with this method in most cases. Consequently, the reaction

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0020-1693/89/$3.50

TABLE 1. One-pot Synthesis of *cis*-Diammineplatinum Uridine Greens[a]

Run	Temperature (°C)	One-pot reaction			
		Time	Yield[b] (%)	Pt:Ud:NH_3[c]	λ_{max} (log ϵ)[d] (nm)
1	2	2 wk	43.8	9:6:16	265(4.76), 721(2.08)
2	2	4 wk	51.0	12:8:23	265(4.80), 722(2.64)
3	25	24 h	46.1	8:6:14	267(4.66), 722(2.07)
4	40	3 h	33.4	8:3:16	264(4.44), 722(1.63)
5	75	3 h	61.0	12:9:21	265(4.71), 722(1.84)
6	75	45 min	74.4	12:8:22	265(4.88), 721(1.71)
7	60	36 h	77	24:26:31	N.D. 567(3.81)

[a]With hydrogen peroxide, except for 7 (air oxidation); 0.1 M substrate concn., except for run 5 (0.01 M). [b]As tetranuclear complex. [c]From microanalysis. [d]Refs. 8 and 9.

TABLE 2. *cis*-Diammineplatinum Green Analogs with Various Ligands by One-pot Reaction[a]

Compound	Substrate	Temperature (°C)	Time	Yield[b] (%)	Pt:Sub:NH_3[c]	Remarks[d]
8	Uracil	37	3 h	38.8	12:3:21	green
9	5FU[e]	75	45 min	34.0	15:7:29	green
10	Guanosine	75	2 d	47.9	1:1:2	yellow
11	Inosine	75	2 d	94.3	2:2:4	colorless
12	UMP[f]	25	24 h	13.9	5:3:9	green
13	Thymidine	75	30 min	22.4	11:4:19	green
15[g]	UMP[f]	75	12 h	39.6	N.D.	yellow
16[g]	Thymidine	2	12.5 d	10.1	N.D.	green
17[g]	Thymidine	75	45 min	20.9	N.D.	blue

[a]Concentration 0.1 M, 1% H_2O_2 used. [b]Calculated as tetranuclear complex. [c]From elemental analysis. [d]Color of compound. [e]5-Fluorouracil. [f]Uridine 5'-monophosphate. [g]By the conventional method; ref. 9.

is faster, more efficient and highly reliable compared with the conventional two-step reaction.

A series of other platinum greens were also synthesized similarly, employing various substrates in lieu of uridine. Typical examples are given in Table 2. *cis*-Diammineplatinum greens with uracil, 5-fluorouracil, uridine 5'-monophosphate (UMP) and thymidine as substrate have been obtained without difficulty (runs 8, 9, 12 and 13, respectively). Silver salts with different anions such as SO_4^{2-}, NO_3^- and ClO_4^- can be used as well. It is notable that a yellow substance resulted with UMP (75 °C, 12 h, 0.05 M, 39.6%) by the previous method (run 14). Furthermore, the conventional method gave the corresponding green compound with thymidine at a relatively low temperature (run 15), but only blue (20.9%) and yellow (trace) materials resulted at 75 °C (run 16). These green complexes were confirmed by both elemental analyses and UV–Vis absorption spectra. *Anal.* Calc. for $[Pt_{12}(C_4H_3N_2O_2)_3(NH_3)_{21}(OH)_5(H_2O)_{16}](SO_4)_{10}$ (compound **8**): C, 3.30; H, 2.52; N, 8.66; S, 7.34. Found: C, 3.37; H, 2.07; N, 9.13; S, 7.72%. λ_{max} (log ϵ) (10 mM H_2SO_4): 259(4.36), 732 nm. Calc. for $[Pt_{15}(C_4H_2N_2O_2F)_7(NH_3)_{29}(OH)_6(H_2O)_{11}](SO_4)_{11}$ (compound **9**): C, 6.04; H, 2.34; N, 10.82. Found: C, 6.10; H, 2.25; N, 10.87%. λ_{max} (log ϵ) (10 mM H_2SO_4): 272(4.74), 738(3.62) nm. Calc. for $[Pt_5(C_9H_{12}N_2O_9P)_3(NH_3)_9(OH)_4(H_2O)](SO_4)_2$ (compound **12**): C, 13.65; H, 2.93; N, 8.84; S, 2.70. Found: C, 13.95; H, 2.94; N, 8.99; S, 3.08%. λ_{max} (log ϵ) (10 mM H_2SO_4): 265(4.43), 722 nm. Calc. for $[Pt_{11}(C_{10}H_{13}N_2O_5)_4(NH_3)_{19}(OH)_5(H_2O)_{12}](SO_4)_8$ (compound **13**): C, 10.67; H, 3.09; N, 8.40; S, 5.69. Found: C, 10.77; H, 2.85; N, 8.55; S, 6.05%. λ_{max} (log ϵ) (10 mM H_2SO_4): 278(4.62), 438(2.80), 714(3.20) nm.

The solution did not show a green color, however, on reaction with purines, even under comparatively rigorous conditions (runs 10 and 11). Microanalysis showed the formation of mono- and dinuclear complexes for guanosine and inosine, respectively.

Antitumor activity against L1210 cells has been tested with these complexes and will be reported elsewhere. In conclusion, one-pot reaction via *in situ* generation of the diaquo complex has been shown to be a very convenient method for preparing anticancer platinum pyrimidine greens with high efficiency.

Acknowledgement

We appreciate help with the ICP measurements received from Dr S. Nakamura of NCLI.

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