Communications to the Editor

[Chem. Pharm. Bull.]
35(7)3074—3077(1987)

PHOTOCHEMICAL SYNTHESIS OF ANTITUMOR PLATINUM PYRIMIDINE GREENS;
POSSIBLE CONTRIBUTION OF SINGLET OXYGEN

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A method is given for the selective synthesis of antitumor platinum greens in a reaction of the hydrolysis products of cis-diiododiammineplatinum (II) and nucleosides via visible-light induced oxidation. A role of singlet oxygen in the green formation is indicated by the sensitized reactions with methylene blue and rose bengal and by experimental quenching of singlet oxygen with 1,4-diaza-bicyclooctane (DABCO).

KEYWORDS — platinum pyrimidine green; antitumor activity; photosensitized reaction; singlet oxygen; DABCO quenching

Much attention has been focused on the synthesis of potent anticancer platinum complexes and the mechanism of their biological actions. One promising way to reduce such strong side effects as nephrotoxicity and emesis, which occurs in the best known cis-dichlorodiammineplatinum (II), (cis-DDP), is, other than the methods of administration, to develop its oligomer chelates with pyrimidine derivatives.²⁾

Our recent findings confirm this.³⁾ The complexes can be prepared by treating the diaquo derivative of cis-diiododiammineplatinum (II), (cis-DIDP),⁴⁾ with pyrimidines under air. The reaction produces several kinds of characteristic colors including blue, green, violet and yellow. We have reported that the uridine green species had remarkably high anticancer activity against L1210 cells, employing SO_4^{2-} as a counter anion.³⁾ Since then our efforts have been focused on developing selective methods for synthesizing the green complexes by hydrogen peroxide oxidation.^{5,6,7)} Here, we report the first direct formation of Pt-greens by photo-sensitized reactions, which may involve a contribution of singlet oxygen.

When a mixture of hydrolysis products of cis-DIDP (0.3 mmol), uridine (0.3 mmol) and methylene blue⁸⁾ (0.3 μmol) in 3 ml of water (pH 4.3) was irradiated with a 60 W tungsten bulb under air or oxygen atmosphere at 60°C,

Fig. 1. A Time Course of Visible Absorption Spectra in the Formation of Platinum Uridine Green Sensitized by Methylene Blue (path length, 2 mm)

Fig. 2. A Difference Spectrum after 90 h Illumination (Mb) (path length, 2 mm)

Fig. 3. Photochemical Formation of Platinum Uridine Green Sensitized by Rose Bengal

1: (—) 0 h; 2: (—•—) After 3 h irradiation; 3: (—) After 21 h irradiation; 4: (----) Purified platinum green in water (arbitrary scale)

the absorption maxima at 730 nm, corresponding to typical green chelates in the visible region, increased with reaction time. An example is shown in Fig. 1. Though the absorption between 600 and 700 nm due to the sensitizer decreased to some extent (ca.20% after 1 day) during the reaction, the mixture turned green after 25 h. A difference spectrum after 90 h using the corresponding mixture kept in the dark as a reference clearly showed exclusive formation of the green complex, and there was no blue absorption maximum around 570 nm (Fig. 2). Gel filtration (Toyopearl HW-40) showed a single zone on the column, and mostly the same green substance was isolated⁹⁾ [Yield: 22.4 mg, mp>300°C, UV-VIS (water): $\lambda_{\text{max}}(\epsilon)$ nm; 268(28,700), 730(1,140); Circular Dichroism (water): $[\theta](\lambda_{\text{max}} \text{ nm})$; 37,800(272), -37,800(219)].^{3,10)} There were no significant changes in absorption spectra in water solutions of the isolated complexes after 24 h in the presence or absence of the tungsten light under air.

The above observations indicate a contribution of singlet oxygen in the formation of the platinum greens, since it is widely accepted that reactions sensitized by methylene blue efficiently produce singlet oxygen (cf. quantum yield >0.23).⁸⁾

When this photo-oxidation was carried out in D₂O, the rate of the green formation, which was monitored by visible spectra, was 27-29% higher than that in H₂O. The stability of singlet oxygen is known to increase ca.10 times more in D₂O¹¹⁾ than in H₂O. This tends to substantiate our idea about singlet oxygen.

Further support has come from reactions employing rose bengal as a sensitizer, which gives singlet oxygen very efficiently (cf. quantum yield = 0.76).⁸⁾ A solution containing uridine (146.4 mg, 0.6 mmol), the diaquo-complex (6 ml, 0.6 mmol) and rose bengal (0.6 μ mol) was illuminated at room temperature with stirring for 21 h at pH 5. The reaction proceeded very cleanly (see Fig. 3). Gel filtration (a single zone on the column) gave a platinum green. With further purification by reprecipitation from water-acetone, the yield was 74.4 mg.

Another source of supporting data utilizes quenching experiments. For example, using 1,4-diazabicyclooctane (DABCO, 0.3 mmol), known as an efficient quencher of singlet oxygen,^{12,13,14)} completely suppressed the green formation.

The present results are in sharp contrast with simple air oxidation in the dark which produces mostly blue materials.³⁾

Though the experimental findings described here are still somewhat preliminary,¹⁵⁾ we have found novel photochemical methods for the synthesis of anticancer platinum greens. And it appears that singlet oxygen is responsible for selective synthesis of the platinum green complexes. Further work including biological activities against other malignant cells are in progress.

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(Received May 14, 1987)