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 develope 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 SO42- 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): λ max (ε) nm; 268(28,700), 730(1,140); Circular
Dichroism (water): [θ](λ max 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 µmol) 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.
REFERENCES AND NOTES

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9) Though the green complex is considered to be an oligomer chelate, its molecular weight is provisionally calculated as a tetranuclear complex with an overall charge of 5. See ref. 3 for more details.
10) cf. Uridine in water: \( \lambda_{\text{max}} (\epsilon) \text{ nm: } 262(10,300); \ [\theta] (\lambda_{\text{max}} \text{ nm): } 8,800(268), -5,500(215). \)
15) Chemical generation of singlet oxygen by NaOCl/H\(_2\)O\(_2\) produced yellow materials, probably cis-DDP via reaction between the diaquo derivative and NaOCl.

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