THE PHOTOLYTICAL PRODUCTS OF AQUEOUS CARBOPLATIN SOLUTION

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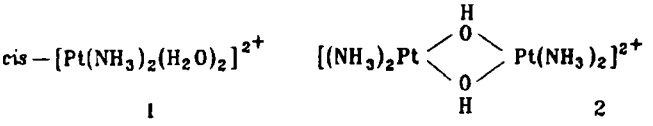
Carboplatin, an abbreviation for 1,1-cyclobutanedicarboxylatodiamine platinum (II), is the second generation platinum anticancer drug[1]. The stability of its aqueous solution is of great importance to clinical effects. It has been known that the solution is relatively stable with $t_{1/2}$ being about three months when kept in dark place, and unstable to light as shown by the rapid change in the UV spectrum[2]. But, the photolytic products remain unidentified. As a knowledge of the products plays an important role in understanding the influence of photolysis of carboplatin on the clinical effects, we have recently studied the photolytical products of aqueous carboplatin solution upon 313 and 254 nm irradiation, and now report our results here.

EXPERIMENTAL

The irradiation equipment consists of a light source, filter and reaction cell, all in line along an optical axis. The reaction cell is a standard spectrophotometer cell. Light beams at 313 and 254 nm were obtained by using the filter reported in the literature[3]. The photoreactions were followed by an established HPLC measurement[4]. The solutions of compounds 1 and 2 were prepared according to the reported methods[5] as the reference standards for HPLC measurement.



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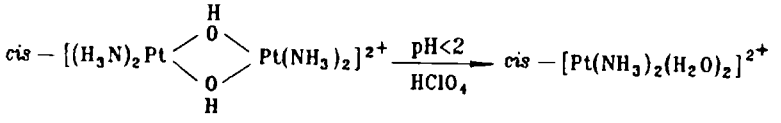
RESULTS AND DISCUSSION

Upon UV irradiation at 313 nm, two new peaks developed in the chromatogram (Fig 1.a) with retention time 1.093 and 6.435 min. Compared with the standards, these peaks correspond to compounds 1 and 2, respectively. So, UV irradiation of 313 nm results in the production of these two compounds from aqueous solution of carboplatin. Acidification of the irradiated solution with $HClO_4$ will cause the peak of compound 2 to disappear due to the reaction:



本文于 1994 年 11 月 1 日收到。

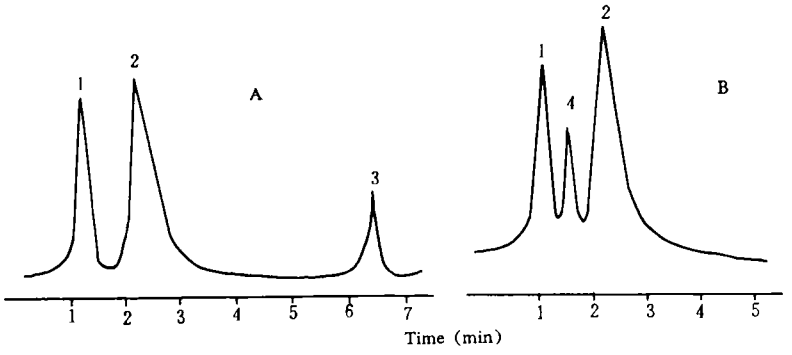
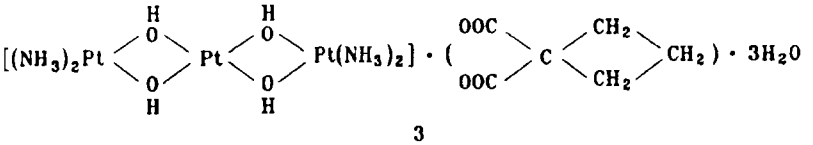


Fig 1 Chromatograms of aqueous carboplatin upon 313 nm (A) and 254 nm (B) irradiation. 1. Compound 1; 2. Carboplatin; 3. Compound 2; 4. Compound 3.

Upon UV irradiation at 254 nm a brownish product crystallized gradually from the solution. After separation and air-drying, it was submitted for structure analyses. The remaining solution was tested by HPLC. Besides a new peak at 1.085 min corresponding to compound 1, there was another new peak with the same retention time (1.465 min) as the aqueous solution of the pure brown product, therefore, it should correspond to it. The results of elemental analysis, mass spectrum and DTA/TG of this product are in good agreement with the molecular formula $C_6N_4O_8H_{22}Pt_3 \cdot 3H_2O$ in which platinum was determined by photoelectron spectroscopy to be in a bivalent state, for (1) the largest fragment of FAB-MS was m/z 863, due to $M^+ - 3H_2O$; (2) the weight loss from 54℃～116℃ was 6%, corresponding to the loss of three molecules of crystallized water; (3) elemental analysis showed Pt 63.51%, C 8.20%, N 5.97% H 2.86%, consistent with the calculated value Pt 63.79%, C 7.90%, N 6.10%, H 3.05%.

The IR data and assignments are listed in Table 1. The absorption near 261 cm^{-1} is characteristic of hydroxo-bridged platinum complexes[6]. As the product has no absorption at 340 cm^{-1} which is the characteristic band for Pt-OOCR in carboplatin[7], we believe that it does not contain such complex bond. Based on these results, we propose that the brownish product should have the following structure:



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So, 254 nm irradiation leads to the formation of compounds 1 and 3 in aqueous carboplatin solution.

Tab 1 IR bands of compound 3*

cm^{-1}	IR intensity	Assignment
3436	vs	γ(OH)
3287	s	γ(OH)+γ(NH)
2957	m	γ(CH)
2922		
1619	vs	γ_s(COO)
1368	s	γ_{as}(COO)+δ(CH)
1340		
1076	m	δ(PtO—H)
530	m	γ(Pt—NH_3)
400	m	γ(Pt—OH)
261	w	δ(Pt  Pt)

* In KBr pellets

When aqueous carboplatin solution is exposed to sunlight or UV light, photolysis will take place forming toxic hydrolyzed species. Therefore, we recommend that aqueous carboplatin solution for clinical injection should be prepared, kept and used in a room without direct sunlight or UV irradiation.

Key words Carboplatin; Photolysis

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卡铂水溶液的光分解产物

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摘要 卡铂是第二代铂族抗癌药物,其水溶液有见光分解的不稳定特性。本文用 HPLC 定性方法及红外光谱、热重分析和光电子能谱对光解产物进行了检测。结果表明卡铂水溶液在光的作用下发生水解反应,生成有害的水解产物,因此建议在临床备制和使用卡铂注射液时要避光。

关键词 卡铂;光解