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The Role of N(1) Coordinated Thymine in 'Platinum Thymine Blue'

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Introduction

The antitumor activity of complexes of platinum (II) with uracil and thymine as ligands has been reported [1–3] but structural details of these compounds are still rare. This applies in particular for the so-called 'platinum pyrimidine blues' although several properties have been recognized recently [4–9]. Information on the actual binding properties of the uracil and thymine ligands in these compounds is of great importance since the monoanions of these ligands exist in solution in an equilibrium of N(1) and N(3) deprotonated tautomers [10, 11]. It is feasible that complexes of the individual tautomers exhibit different biological activity.

Experimental

Upon HCl decomposition of a 'platinum thymine blue' a crystalline compound of composition $[Pt(NH_3)_2(C_5H_5N_2O_2)Cl]\cdot H_2O$ (*1*) had been obtained [4]. A structure determination by X-ray analysis has not been possible due to insufficient crystal size. We have thus synthesized better crystallizable derivatives by replacing the chloro ligand with 1-methylcytosine.

1 has now been synthesized alternatively by reaction of *cis*-$Pt(NH_3)_2Cl_2$ with 1 equivalent of $AgNO_3$ in dimethylformamide, DMF, filtration of AgCl and subsequent reaction with 1 equivalent of potassium thyminate [12] (72 h, room temp.). The resulting DMF adduct was recrystallized from hot water to give *1* in 54% yield, identical with *1* obtained by HCl decomposition of a 'thymine blue' both from infrared spectra and elemental analysis (C 14,84, H 3.11, N 13.69, Pt 48.2, Cl 8.64, O 11.50; theory: C 14.73, H 3.22, N 13.74, Pt 47.84, Cl 8.69, O 11.77).

This compound was then suspended in H_2O and reacted with 1-methylcytosine in 1:1 ratio for several days at 40 °C. To the resulting solution 1.1 mol of $NaClO_4$ were added, the solution concentrated by rotary evaporation to a small volume, filtered hot and the solution (pH = 5.5) allowed to evaporate at room temperature. Crystals of the title compound *cis*-$[Pt(NH_3)_2(C_5H_5N_2O_2)(C_5H_7N_3O)]ClO_4\cdot 3H_2O$ were obtained as colorless transparent columns in 50% yield, stable only in a water atmosphere. When brought on air, the crystals rapidly lose transparency to give the monohydrate. Elemental analysis of the trihydrate: C 19.04, H 3.82, N 16.21, Pt 30.86; theory: C 18.97, H 3.83, N 15.49, Pt 30.82; monohydrate: C 20.53, H 3.44, N 16.97, O 21.51; theory: C 20.12, H 3.38, N 16.43, O 21.45.

Several isolated coproducts are presently under investigation.

A transparent column of the title compound was sealed in a capillary together with a drop of water and the space group and the unit cell dimensions determined as follows: monoclinic, $P2_1/c$, $a = 6.93(2)$, $b = 13.81(2)$, $c = 22.03(3)$ Å, $\beta = 102.07(8)°$, $Z = 4$, $V = 2061.4$ Å^3, mol. mass = 633.0. $d_{cal} = 2.04$ g/cm^3, $\rho = 73.6$ cm^{-1}. A total of 3728 independent reflections were measured on a Syntex $P2_1$ diffractometer (Mo-Kα, $\lambda = 0.71069$ Å, graphite monochromator). Using the Syntex-XTL program the structure was solved by the heavy atom method without absorption correction. The platinum atom was located from Patterson synthesis and all other nonhydrogen atoms were found in difference Fourier syntheses (the hydrogen atoms were not determined). Full matrix refinement with anisotropic temperature factors for all nonhydrogen atoms gave an R value of 0.085 (2163 reflections with $|F| > 5.5\sigma$ were used for the final structure refinement).

Results

A pair of molecular cations is shown in Fig. 1. The perchlorate anions, the oxygens of which are disordered, are omitted for clarity. Pt binds to thymine via N(1) and to 1-methylcytosine via N(3) with bond lengths of 1.90(2) and 2.02(2) Å, respectively. Both rings are practically planar and lie roughly at right angles to each other. The thymine ring forms a 114° angle with the Pt coordination plane, the cytosine ring a 72° angle. Both rings are oriented in such a way that the exocyclic NH_2 group of 1-methylcytosine and the C(2) oxygen of thymine are both at the same side of the Pt coordination plane. The errors in bond lengths and angles within the two heterocycles are such that no statements concerning significant differences with reported structures of thymine [12–15] or 1-methylcytosine [16, 17] compounds can be made. The cations are arranged in centrosymmetrically related pairs with strong hydrogen bonds (2.85(3) Å) via N(3)–H(3)–O(2) between neighbouring thymine ligands. Similar arrangements are also observed in other thymine and uracil structures [12, 18, 19]. Additional strong hydrogen bonds

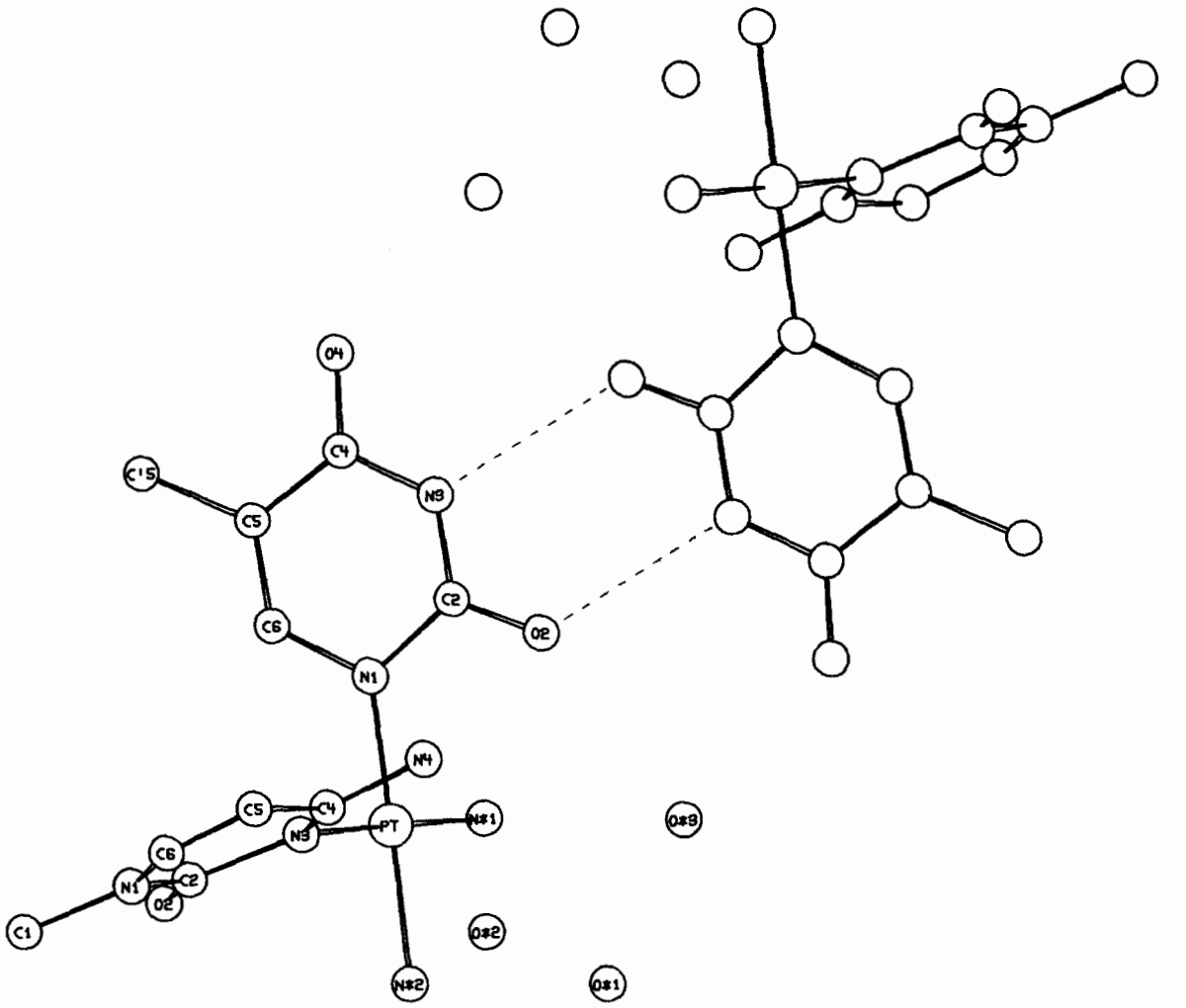

Fig. 1. A pair of molecular cations of *cis*-$[Pt(NH_3)_2(C_5H_5N_2O_2)(C_5H_7N_3O)]^+$ with hydrogen bonds between N(3)H and C(2)O of the thymine ligands. N*1, N*2 represent NH_3 groups, O*1, O*2, O*3 represent water of crystallization.

($\leqslant$ 2.9 Å) are found between H_2O molecules and the two NH_3 groups and between H_2O and O(4) of thymine, weaker hydrogen bonds ($\sim$ 3.1 Å) between H_2O and ClO_4^- as well as H_2O and C(2)O of 1-methylcytosine.

Discussion

The crystal structure of the title compound shows platinum to be coordinated to thymine via N(1). This allows the conclusion that in the precursor, *cis*-$[Pt(NH_3)_2(C_5H_5N_2O_2)Cl]\cdot H_2O$, platinum is bound to the same donor atom and further, that 'platinum thymine blues' contain N(1) bound Pt as well. However, there are strong indications that N(1) coordination is not the exclusive type of Pt binding in the 'blues'. First, a quantitative decomposition of a 'thymine blue' [20] (1 N HCl, 70 °C, 3 min) gives the N(1) coordinated complex *1* in a 40% yield together with thymine, *cis*-$Pt(NH_3)_2Cl_2$ and *cis*-$Pt(NH_3)_2Cl_4$. *1* is very stable towards HCl; only 6 N HCl treatment at 100 °C breaks the Pt–N(1) bond. This means that the 40% yield of *1* is real and is not due to further acid decomposition of *1*. Incidentally, the high stability of N(1) coordinated complexes of uracil and thymine is also observed in the ethylenediamineplatinum(II) system. Such complexes have recently been isolated from solutions of pH $\sim$ 0 and investigated by X-ray analysis. The uracil complex even crystallizes with HCl rather than is decomposed [21]. Second, these findings are in contrast to the situation in the 1-methyluracil and 1-methylthymine systems. The corresponding 'blues' are totally decomposed into starting materials under identical experimental conditions. This indicates a marked decrease in stability of Pt complexes with donor atoms other than N(1). Third, Japanese scientists have isolated both N(1) and N(3)

coordinated complexes of uracil with the triammineplatinum(II) moiety in roughly equal yields from aqueous solution [22]. This is not unexpected since N(1) and N(3) deprotonated tautomers of uracil and thymine are present in approximately 1:1 ratio in this medium [10]. Fourth, compound *1* cannot be transferred back into a 'blue', [4]. Moreover, 3-methylated uracils do not form 'blues' either [1, 5]. It thus appears that N(1) platination neither is a necessary nor a sufficient condition for the formation of a blue colour. Several studies on related blue [8, 23] as well as non-blue [24] compounds have demonstrated the importance of platinum interaction via a ring nitrogen and an adjacent carbonyl oxygen. This kind of coordination permits Pt–Pt distances sufficiently short for metal–metal interaction as observed in the 'blues' [4, 7]. C(2)O of uracil and thymine represents a potentially suitable donor atom next to N(1), yet formation of a blue colour is not observed. Therefore it is concluded that 'platinum blues' of unsubstituted 2,4-dihydroxopyrimidines contain both ligands with N(1) as well as ligands with another donor – most likely N(3) – as primary binding sites.

With regard to the antitumor activity of Pt-uracil and Pt-thymine complexes, the potential differences between complexes of the corresponding tautomeric ligands should be considered and investigated. In particular it should be interesting to find out whether N(1) coordination of thymine (or uracil) retains the biological activity of the *cis*-diammineplatinum(II) moiety or whether it leads to a deactivation similar to that found in triammineplatinum(II) systems.

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