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Tris(Nucleobase) Complexes Derived from *cis*-$Pt(NH_3)_2Cl_2$

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Introduction

Preservation of the *cis*-configuration of the two ammine groups of the *cis*-$Pt(NH_3)_2^{2+}$ moiety during its reaction with DNA or nucleobases generally has not been questioned. Exceptions have been reports on the interconversion of *cis*-$[Pt(NH_3)_2CCl]Cl$ into *trans*-$Pt(NH_3)CCl_2$ [a], observed in a mass spectroscopic study at high temperature [1], and suggestions based on elemental analysis results that NH_3 might be released from adenine complexes [2] and from 'platinum pyrimidine blues' [3].

We recently found that the above interconversion of *cis*-$[Pt(NH_3)_2CCl]Cl$ into *trans*-$Pt(NH_3)CCl_2$ takes place under very mild conditions in aqueous solution at room temperature, and unambiguously verified this by performing X-ray structures of both the starting and the end product [4]. Our findings open up an interesting alternative to the generally accepted principle of a bifunctional attack of *cis*-$Pt(NH_3)_2Cl_2$ with replacement of the two chloride ligands. With the possibility of two additional chlorides to be replaced in *trans*-$Pt(NH_3)CCl_2$, three biomolecules could simultaneously be bound by a single Pt atom. Thus both inter- and intrastrand crosslinking of DNA or/and bidentate DNA- plus protein crosslink could occur. This possibility, a consequence of the kinetic *trans*-effect of chloride, would be unique for *cis*-$Pt(NH_3)_2ClX$ (X = H_2O, OH, ...) compounds and could neither be expected for *cis*-$Pt(NH_3)_2X_2$ (X = H_2O, OH, ...) nor for any *trans*-$Pt(NH_3)_2X_2$ (X = Cl, H_2O, OH, ...) species.

In order to evaluate the possibility of tris(nucleobase) complex formation from *cis*-$Pt(NH_3)_2^{2+}$ complexes, such complexes were prepared and studied using ^1H NMR spectroscopy.

Experimental

Trans-$Pt(NH_3)CCl_2 \cdot 0.5H_2O$ was obtained from *cis*-$[Pt(NH_3)_2CCl]Cl \cdot 1H_2O$ as previously described [4].

[a] Abbreviations used: C = 1-methylcytosine; G = 9-ethylguanine.

[Pt(NH$_3$)C$_3$](ClO$_4$)$_2$

0.15 mmol *trans*-$Pt(NH_3)CCl_2$ and 0.3 mmol $AgClO_4 \cdot 1H_2O$ were suspended in 15 ml H_2O at 40 °C. After 1–2 h 0.3 mmol C were added and the reaction mixture kept at 40 °C for 40 h. Filtration of AgCl, concentration and slow crystallization gave 80 mg of the desired compound—colorless, transparent cubes, losing water of crystallization on exposure to air. *Anal.* Found: C, 21.98; H, 3.33; N, 17.55. Calcd. for $[Pt(NH_3)(C_5H_7N_3O)_3](ClO_4)_2 \cdot 1.5H_2O$: C, 22.14; H, 3.35; N, 17.22.

Trans-*[Pt(NH$_3$)CG$_2$](ClO$_4$)$_2$*

Preparation analogous to the above complex with G added instead of C. Yield 130 mg. Recrystallization from water gave tiny, colorless crystal plates, rapidly losing water of crystallization on exposure to air. *Anal.* Found: C, 24.67; H, 3.36; N, 21.21. Calcd. for $[Pt(NH_3)(C_5H_7N_3O)(C_7H_9N_5O)_2](ClO_4)_2$: C, 24.52; H, 3.47; N, 21.08.

Results and Discussion

The ^1H NMR spectrum of $[Pt(NH_3)C_3](ClO_4)_2$ in DMSO-d_6 is shown in Fig. 1. The assignment of the NH_3 and C resonances is based on comparison with a number of related compounds [5]. Relative intensities of the NH_3 and the C signals agree with the above formulation, as does elemental analysis. The integrated intensity of the CH_3/H_2O peak shows 1.5–2H_2O to be present. The occurrence of ^{195}Pt satellites (J ≃ 14 Hz) of the H5 resonances, though not perfectly resolved, clearly indicates N3 binding of the C ligands. The 2:1-splittings of the H5 and H6 doublets, well observable for H6 only, is a con-

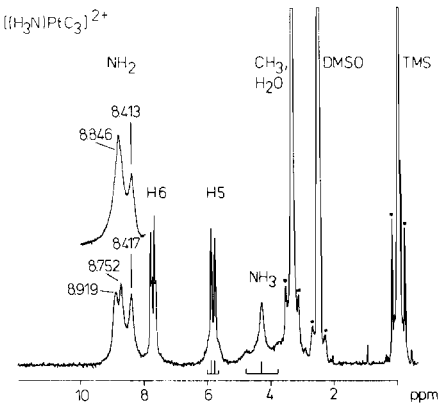

Fig. 1. ^1H NMR spectrum of $[Pt(NH_3)C_3](ClO_4)_2 \cdot 1.5H_2O$ (0.1 *M*) in dimethylsufoxide-d_6. Inset: C-NH_2 resonances of sample dried over 4 Å molecular sieves. Jeol JNM-FX 60 Fourier transform spectrometer; 30 °C; TMS internal standard. * spinning side bands.

sequence of the magnetic inequivalence of the three C ligands: while the two C ligands *trans* to each other are equivalent (free rotation about the Pt–N3 axis is assumed), the third C *trans* to NH_3 is different from the other two. The relative intensities (1:1:1) of the NH_2 signals either indicate non-equivalence of all three NH_2 signals or that the NH_2 resonances of the two C ligands *trans* to each other are split, whereas this is not the case with the third C. Addition of 4 Å molecular sieves, which removes the water, also changes the NH_2 signal pattern: in the absence of H_2O, two broad singlets with relative intensities of 2:1 are observed. Although this finding must be a consequence of the loss of hydrogen bonding between C–NH_2 and H_2O, it is unclear at present if the spectral changes are the result of an upfield shift of the original 8.919 ppm resonance, or are due to the removal of the splitting of the NH_2 signal of the two equivalent C ligands. As has been shown [6], inequivalence of the C–NH_2 protons may be caused by hydrogen bonding interactions and is not necessarily a consequence of metal coordination at N3.

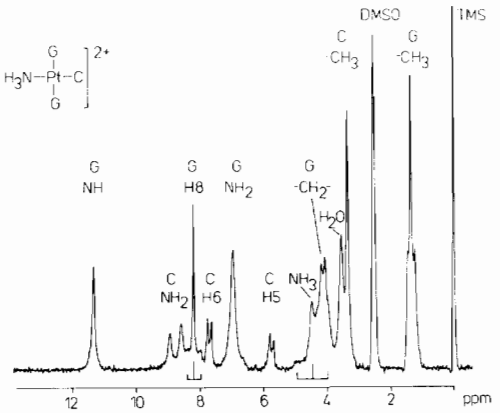

Fig. 2. ^1H NMR spectrum of *trans*-$[Pt(NH_3)_2CG_2](ClO_4)_2 \cdot 2H_2O$ (0.1 *M*) in dimethylsulfoxide-d_6.

In Fig. 2 the ^1H NMR spectrum of *trans*-$[Pt(NH_3)CG_2](ClO_4)_2$ in DMSO-d_6 is given. The assignment is based on comparison with related compounds [5]. Relative intensities and elemental analysis are consistent with the above formulation. The G ligands are coordinated to Pt through N7 as evident from ^{195}Pt coupling bands of the H8 resonance ($J \simeq 21$ Hz). No ^{195}Pt satellites of the H5 doublet of C are resolved, but since the starting compound contained C bound to Pt via N3, this way of coordination appears to be certain*. Removal of H_2O by means of molecular sieves causes only minor shifts of NH and NH_2 resonances. In particular, the C-NH_2 resonance remains split.

*The somewhat reduced intensity of the H5 doublet compared to the H6 doublet certainly agrees with this assumption.

A crystalline complex containing three different nucleobases, C, G, and 9-methyladenine has been isolated as well. NMR results thus far are puzzling, but it is hoped that further studies will clarify the solution behaviour of this compound.

Conclusion

As to the possible biological relevance of tris-(nucleobase) complexes derived from *cis*-Pt(II), two aspects can be seen which, admittedly, are somewhat speculative since they are based on uncertainties such as kinetics and cell-uptake.

(1) Because of the low cellular chloride concentration and the resulting high tendency of Pt bound chloride to become aquated, a chloride induced release of NH_3 from *cis*-$Pt(NH_3)_2^{2+}$ moieties inside a cell appears very unlikely.

(2) However, within the plasma with its high chloride concentration a similar reaction pathway as with the model complex *cis*-$[Pt(NH_3)_2CCl]Cl$ is feasible. It is well established that *cis*-$Pt(NH_3)_2Cl_2$ readily reacts with plasma components such as proteins, erythrocytes [7] and so far unspecified low molecular weight nucleophiles [8]. Thus a species *cis*-$Pt(NH_3)_2ClX$ (X being a plasma component) might very well undergo NH_3 release in the plasma with formation of *trans*-$Pt(NH_3)Cl_2X$. Once inside the cell, such a species could react with binding of two more molecules *trans* to each other or with substitution of both chlorides and X.

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