Nucleobase Displacement from *trans*-Diamineplatinum(II) Complexes. A Rationale for the Inactivity of *trans*-DDP as an Antitumor Agent?

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In 1974, Roos *et al.* published a mass spectroscopic study [1] according to which nucleobase coordinated to either *cis*- or *trans*-$(NH_3)_2Pt(II)$ can undergo displacement of the nucleobase (L) according to

$$cis\text{-}[(NH_3)_2PtLCl]Cl \longrightarrow trans\text{-}Cl_2Pt(NH_3)L + NH_3 \quad (1)$$

and

$$trans\text{-}[(NH_3)_2PtLCl]Cl \longrightarrow trans\text{-}(NH_3)_2PtCl_2 + L \quad (2)$$

The possible significance of this finding with regard to the mode of action of *cis*-diamminedichloroplatinum(II) (*cis*-DDP) as an antitumor agent [2] and the inactivity of the corresponding *trans*-isomer appears to have been widely ignored, probably because the conditions of the experiment (250–300 °C) were considered unlikely to be of any relevance in biological systems. In 1981 it was recognized that reaction (1) with L = 1-methylcytosine (mec) in fact takes place in aqueous solution at room temperature, albeit at a slow rate [3]. As subsequently demonstrated [4, 5], tris(nucleobase) complexes can be obtained via *trans*-$Cl_2Pt(NH_3)L$, a reaction unique for *cis*-DDP and not to be expected for *trans*-DDP.

We have now conclusive evidence that with L = mec, also reaction (2) takes place in aqueous solution at 40 °C. *trans*-$[(NH_3)_2Pt(mec)Cl]Cl\cdot 1.5H_2O$ (**1**) has been prepared from *trans*-$(NH_3)_2PtCl_2$ and mec and identified by elemental analysis and X-ray crystallography [6]. *trans*-$[(CH_3NH_2)_2Pt(mec)Cl]Cl\cdot H_2O$ (**2**) was obtained in a similar way and characterized by elemental analysis and X-ray crystallography as well [7]. The 300 MHz ^1H NMR spectra of both compounds in D_2O show single sets of resonances of the mec ligands with no signs of any other species present immediately after sample preparation. With time (at 40 °C), two new sets of signals appear (Fig. 1) which have now unambiguously been identified as being due to two rotamers of *trans*-$[a_2Pt(mec)_2]Cl_2$, indicating that reaction (3) takes place

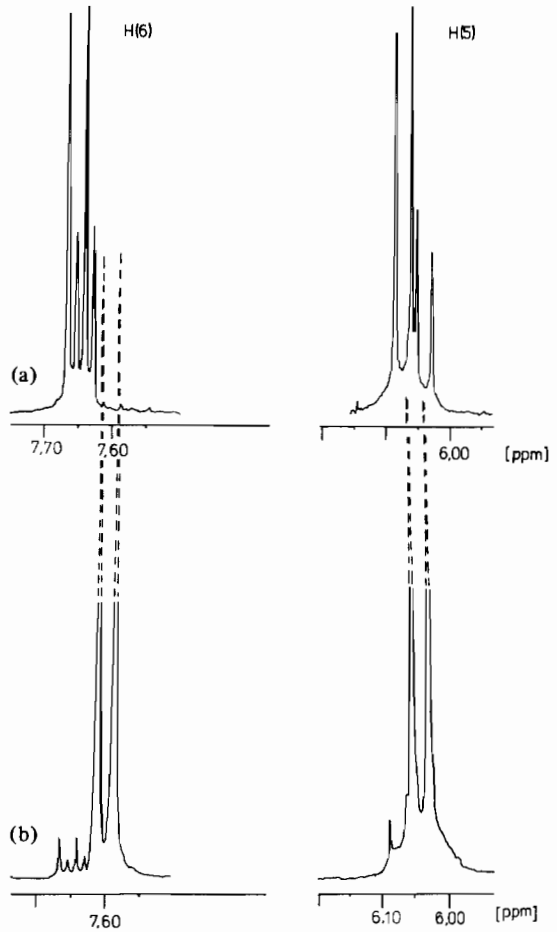

Fig. 1. 300 MHz ^1H NMR spectra (lowfield region only, D_2O, pD 5, 0.02 mmol/l) of *trans*-$[(NH_3)_2Pt(mec)_2]^{2+}$ (a) and *trans*-$[(NH_3)_2Pt(mec)Cl]Cl$ after 4 weeks at 40 °C (b). Resonances due to *trans*-$[(NH_3)_2Pt(mec)_2]^{2+}$ formed after only a few days.

$$2\ trans\text{-}[a_2Pt(mec)Cl]Cl \rightleftharpoons trans\text{-}[a_2Pt(mec)_2]Cl_2 + trans\text{-}a_2PtCl_2 \quad (3)$$

The respective two sets of H5 and H6 resonances of *trans*-$[a_2Pt(mec)_2]Cl_2$, which are of different intensities, are assigned to two rotamers, head–tail and head–head, the former considered to dominate. ^1H NMR spectra of *trans*-$[(NH_3)_2Pt(mec)_2]^{2+}$, a species also characterized by X-ray analysis [3], do not display any marked changes in relative intensities of the two sets of resonances with increasing temperature (up to 85 °C), consistent with a high barrier of rotation about the Pt–N3(mec) bond [8]. In the case of **2**, *trans*-a_2PtCl_2 has been isolated from solution and identified by IR spectroscopy and elemental analysis. We can safely exclude that the poor solubility of the dichloro species in water is the driving force

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of reaction (3) since the NMR spectroscopic changes occur well before precipitation of *trans*-a_2PtCl_2 starts. From the NMR intensities we estimate that K of (3) is $>3 \times 10^{-3}$.

Reaction (3) implies that a monofunctionally bound nucleobase (mec) is displaced from *trans*-$[a_2Pt(mec)Cl]^+$. In a secondary reaction, the liberated nucleobase binds to intact *trans*-$[a_2Pt(mec)Cl]^+$ to give the inert bis(nucleobase) complex.

Our findings appear to be of considerable relevance with regard to the coordination behaviour of *trans*-DDP toward DNA. (i) It is well established, that several hours after incubation of DNA with *trans*-DDP, monofunctional adducts predominate [9], and further that after an initial binding phase, *trans*-DDP is again removed from DNA [10]. Moreover, it has been shown that a much higher *trans*-DDP concentration in the medium is required to achieve the same effect as *cis*-DDP on DNA replication [10], although this finding is not undisputed [11]. Considering our data it would seem likely that monofunctionally bound *trans*-DDP indeed can be removed from DNA by any ligand having a moderately strong *trans* effect. S containing ligands are, of course, particularly suitable, but apparently even Cl^- is capable of achieving this. A similar reaction is not to be expected for monofunctionally bound *cis*-DDP or at most in the presence of very strong nucleophiles such as CN^-, leading eventually to substitution of all Pt bound ligands [12]. (ii) Unlike for *cis*-DDP, a migration of a *trans*-a_2PtClX entity from one donor site on DNA to another, is chemically feasible. Whether such a process is actually occurring, is unknown as yet.

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