Direct Evidence for the Polymeric Structure of Some Platinum-blue Complexes in Aqueous Solution

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The anticancer active compound, *cis*-dichlorodiammine platinum(II), and the biomolecules cytosine and thymine form paramagnetic complexes in aqueous solution. The electron spin resonance spectra which can be attributed to paramagnetic platinum, exhibit large anisotropy in frozen solution as well as in liquid solution. This fact can be explained by assuming polymeric structures also in liquid solution.

After the discovery of the antitumor potency of *cis*-dichlorodiammine-platinum(II) (PDD) [1], numerous blue colored complexes have been observed on mixing the hydrolysis products of *cis*-PDD with various biomolecules [2–12]. Some of the products seem to be very promising with regard to their activity as antitumor drugs and diminished nephrotoxicity in comparison to the original *cis*-PDD compound [5–7, 10, 14].

The structure of these blue platinum complexes is still uncertain due mainly to the inability to crystallize these products. Amorphous blue powders were obtained only. It is believed that these complexes exist as a mixture of polymers with varying chain length and degrees of stability [2–4, 6–9, 11–13, 15–22) as has been shown by different experimental methods such as molecular weight studies [11], ESR studies [9], a californium-252 plasma desorption mass spectroscopy study [19], and optical studies [17].

Although the existence of a polymeric structure is generally accepted only a few experimental results indicate that these structures exist in solution, too [3, 6, 9, 11, 16, 18].

In this paper, electron spin resonance (ESR) spectra of liquid solutions of a purple platinum complex of cytosin (Cyt) (Fig. 1) and of a blue complex of thymine (Thy) (Fig. 2) are shown which support such an existence. The cytosin complex has been prepared by mixing PDD and cytosin in aqueous solution and incubation at 340 K. The thymine complex has been obtained after reaction of *cis*-diaquodiammine-platinum(II)-ion (PDDa)

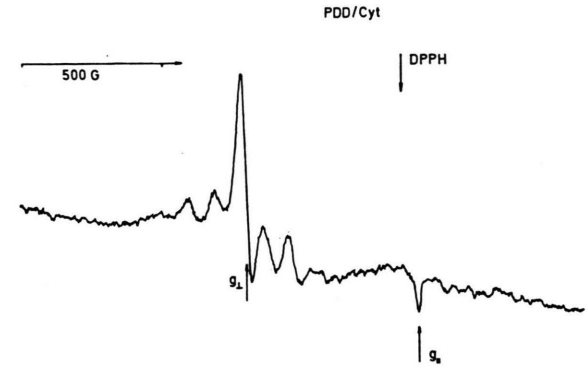

Fig. 1. ESR spectrum of the filtrate of a 0.1 M aqueous solution of *cis*-$Pt(NH_3)_2Cl_2$ containing 0.1 M of cytosine, pH 4.0, after a reaction time of 47 days at 340 K and measured at 294 K.

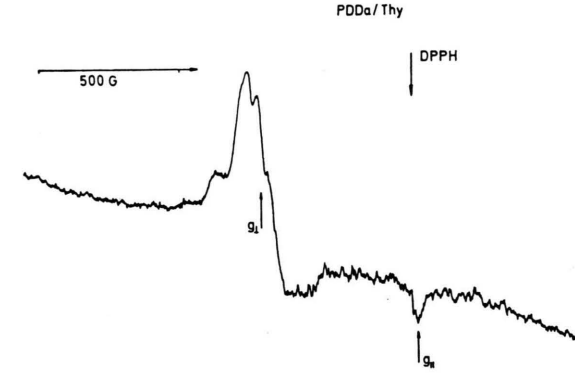

Fig. 2. ESR spectrum of the filtrate of a 0.1 M aqueous solution of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ containing 0.1 M of thymine, pH 1.3, after a reaction time of 15 days at 340 K and measured at 294 K.

and thymine in aqueous solution at 340 K. The ESR measurements have been performed with the filtrate of these samples. Details of the preparation of these complexes and the discussion of the ESR spectra of blue platinum compounds have been described elsewhere [23, 24].

In liquid solution the orientation of the complexes is rapidly changing relative to the magnetic field used in the ESR experiments. If the reorientation frequency is greater than the frequency width of the absorption line obtained in a frozen solution, the spectrum of the liquid solution will exhibit narrow lines and fits an isotropic spin Hamiltonian. If the frozen solution pattern is extended so broad that the tumbling frequency is not sufficient to produce narrow absorption lines, the line pattern will only be changed in such a way, that $g_\parallel$ and $g_\perp$ will approach $g_0 = 1/3\,(2g_\perp + g_\parallel)$ [25, 26]. This can be expected for monomeric or dimeric complexes in aqueous solutions since their tumbling should be fast enough. In aqueous solution a correlation time

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of $\tau \sim 10^{-11}$ s–10^{-10} s was assumed according to relaxation phenomena obtained with metal complexes such as vanadyl and copper complexes and some radicals [26–28]. In these cases, the large asymmetry in the hyperfine parameters results in a spectrum with a large variation in the width of the individual hyperfines lines. The tumbling frequency is high enough to narrow some lines but not others and this gives a solution-like hyperfine spectrum in which each line exhibits a different width.

The g-values of *e.g.* frozen aqueous $Cu(ClO_4)_2$ solutions at liquid nitrogen temperature, are $g_{\parallel} = 2.39$, $g_{\perp} = 2.07$, and $\Delta g = g_{\parallel} - g_{\perp} = 0.32$. At room temperature, this spectrum has changed drastically in the way mentioned above [29]. Figs. 1 and 2 show two typical ESR spectra of blue platinum compounds. The g-values of these complexes at liquid nitrogen temperature and at room temperature are summarized in Table I. Although the anisotropy is about the same as in the case of $Cu(ClO_4)_2$ in frozen aqueous solution, the room temperature spectra exhibit nearly the same g-values as have been obtained at 77 K. The line width has not been narrowed.

Table I. g-Values in frozen and liquid solution.

Pt complex	T	$g_{\parallel}$ ($\pm$ 0.005)	$g_{\perp}$ ($\pm$ 0.005)	$\Delta g = g_{\perp} - g_{\parallel}$
PDD–Cyt	77 K	1.968	2.388	0.420
	RT	1.970	2.394	0.424
PDDa–Thy	77 K	1.983	2.364	0.381
	RT	1.995	2.378	0.383

As a consequence of this, it has to be assumed that the tumbling frequency of the platinum complexes is much smaller than that one of the Cu complexes. The decrease in the tumbling frequency might be caused by bulky complexes. The existence of the very anisotropic ESR spectra in aqueous solution at room temperature can, therefore, be taken as a strong indication, that blue platinum complexes exist and are polymeric also in liquid aqueous solution.

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