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A Simple Procedure for Purifying the Antitumor Agent *cis*-$Pt(NH_3)_2Cl_2$ (Cisplatin)

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Since *cis*-$Pt(NH_3)_2Cl_2$, Cisplatin, is a widely used antitumor agent [1, 2], the question concerning the purity of this compound is of considerable interest. The synthesis of Cisplatin via any of the common procedures – the methods of Dhara [3], Kauffman and Cowan [4], or Lebedinskii and Golovnya [5] – yields products which may require extensive purification before being clinically acceptable. As has been shown by one of us [6], recrystallization of crude *cis*-$Pt(NH_3)_2Cl_2$ from N,N-dimethylformamide/HCl results in a dramatic improvement in the quality of the product, and a similar procedure with N,N-dimethylacetamide, DMA, instead of N,N-dimethylformamide, also gives a very pure material [7].

We have now found that isolation of a crystalline N,N-dimethylformamide adduct of Cisplatin, *cis*-$Pt(NH_3)_2Cl_2 \cdot C_3H_7NO$, and subsequent removal of DMF at high vacuum yields a product which is purer than the product obtained from a DMF solution on addition of aqueous HCl, and of comparable quality with the purest samples of Cisplatin described so far.

Experimental

cis-$Pt(NH_3)_2Cl_2$, prepared according to Dhara [3], was dissolved in N,N-dimethylformamide at room temperature (2 g/90 ml) and the solution filtered. The yellow filtrate was stored in a stoppered flask for 15 h at 3 °C, which resulted in the formation of bright lemon-yellow, transparent cubes. After filtration, crystals were washed with a small amount of DMF and then briefly air-dried on a filter paper. Yield: 1.5 g (60% based on Pt). *Anal.* Found: C, 9.58; H, 3.46; N, 11.41; Pt, 52.2. Calcd. for $Pt(NH_3)_2Cl_2 \cdot C_3H_7NO$: C, 9.66; H, 3.52; N, 11.26; Pt, 52.28.

When exposed to the air, the crystals gradually lose their transparency to give the yellow *cis*-$Pt(NH_3)_2Cl_2$. A quantitative removal of DMF is achieved if the DMF adduct is kept under high vacuum (utilizing a mercury diffusion pump) for 20 h. The IR spectrum of the product obtained does not give any indication of the presence of DMF (Nujol mull). Visible–ultraviolet spectra were recorded on a Cary 17 D spectrophotometer using 1 cm cells. Samples of crude and purified *cis*-$Pt(NH_3)_2Cl_2$ were dissolved in 0.1 *N* HCl (Titrisol, Merck) at concentrations of $c_{Pt} = 3.3 \times 10^{-3}$ *M*. A spectrum of the solvent alone was taken using the identical cell. Absorbance values were obtained by subtraction of $A_{solvent}$ from $A_{solution}$.

Results

Formulation of the isolated crystals as DMF adduct, *cis*-$Pt(NH_3)_2Cl_2 \cdot DMF$, rather than a DMF complex, *cis*-$[Pt(NH_3)_2Cl(DMF)]Cl$, is straightforward on the basis of combined solid state IR and Raman spectroscopy as well as solution ^1H NMR spectroscopy. For example, the position of the characteristic OCN deformation mode of DMF at 662 cm^{-1} (IR: vs; Ra: s) is close to the value of free DMF at 655 cm^{-1} (IR: s; Ra: vs) and distinctly different from that found in metal complexes containing the DMF coordinated through O [8, 9]. In DMF-d_7 solution, the resonances of the DMF adduct occur at positions close to those of free DMF (δ 2.79, 2.96, 8.03 ppm), whereas in DMF complexes of platinum both CH and CH_3 resonances are observed at lower field (shifts of 0.2–0.3 ppm) with additional $^{195}Pt-^1H$ coupling of the CH resonance [10]. As a means of evaluating the purity of *cis*-$Pt(NH_3)_2Cl_2$ after removal of DMF, the established criteria of visible–uv absorption spectra were applied [11, 12], which include the molar absorptivity of the 301 nm maximum, the position of the minimum (246 nm), and the absorbance ratios of the maximum at 301 nm to the minimum at 246 nm as well as to the maximum at 363 nm. The visible–uv spectrum of a sample of *cis*-$Pt(NH_3)_2Cl_2$, obtained from the crystalline DMF adduct under high vacuum, in 0.1 *N* HCl is shown in Fig. 1. The molar absorptivity, ϵ_{301} nm, is 132 M^{-1} cm^{-1}. The absorbance ratio A (301 nm/246 nm), which is the most reliable indicator of the purity of Cisplatin, is 4.9 and the absorbance ratio A (301 nm/363 nm) is 5.3. With crude

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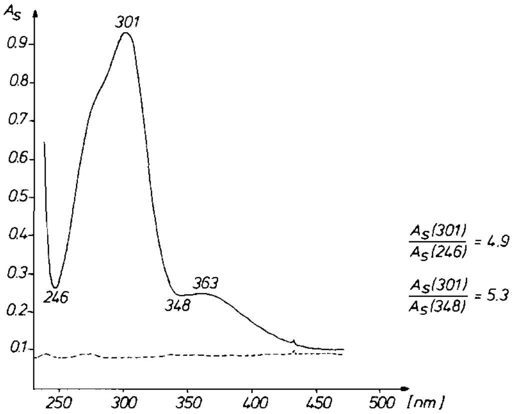

Fig. 1. UV–visible spectrum of *cis*-$Pt(NH_3)_2Cl_2$ obtained from *cis*-$Pt(NH_3)_2Cl_2 \cdot DMF$ after 20 h at high vacuum. C_{Pt} = 3.3 × 10^{-3} *M* in 0.1 *N* HCl; 1 cm cell, abs. range, 0.5. ------ solvent only.

cis-$Pt(NH_3)_2Cl_2$ absorbance ratios, A (301 nm/246 nm), of 2–4 are usually found which increase up to 4.7 after recrystallization from DMF/HCl [6], and up to 4.9 on recrystallization from DMA/HCl [7]. With samples of Cisplatin purified by DMA/HCl treatment the other spectral features are as follows: λ_{max} = 301 nm, λ_{min} = 246 nm, ϵ_{301} nm = 131, A (301 nm/365 nm) = 5.5 ± 0.1. In summary, isolation of crystalline *cis*-$Pt(NH_3)_2Cl_2 \cdot DMF$ and subsequent removal of DMF at high vacuum is a simple and efficient way to substantially improve the purity of Cisplatin.

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