Adduct Formation of *cis*-$(NH_3)_2PtX_2$ ($X = Cl^-, I^-$) with Formamides and the Crystal Structures of *cis*-$(NH_3)_2PtCl_2\cdot(CH_3)_2NCHO$. Application for the Purification of the Antitumor Agent Cisplatin

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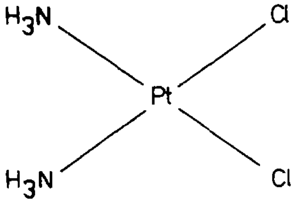
Abstract

The formation of solvates of *cis*-$(NH_3)_2PtCl_2$ and *cis*-$(NH_3)_2PtI_2$ with formamide, FA, and substituted formamides (N-methylformamide, NMF, N,N-dimethylformamide, DMF, and N,N-diethylformamide, DEF) has been studied. Crystalline NMF and DMF adducts have been isolated with both the dichloro and the diiodo species. The infrared spectra of these solvates have been recorded, but only with *cis*-$(NH_3)_2PtCl_2\cdot$DMF are there major changes as compared to the two components, *cis*-Pt(II) and DMF. These spectral changes are discussed and attributed to hydrogen bonding interactions between the NH_3 groups and the DMF molecule. The crystal structure of this compound has been determined. *Cis*-dichlorodiammineplatinum(II) dimethylformamide, *cis*-$(NH_3)_2PtCl_2\cdot(CH_3)_2NCHO$, crystallizes in the orthorhombic space group $Pca2_1$, $Z = 4$. The unit cell dimensions are $a = 11.372(2)$ Å, $b = 7.723(2)$ Å, $c = 11.165(3)$ Å and the volume is 980.5(4) $Å^3$. The density of the crystal was calculated to be 2.53 g cm^{-3}. The crystal structure was determined by standard methods to $R_1 = 0.0637$ on the basis of 2542 unique reflections. The molecular structure of the platinum complex shows normal bond lengths and angles, with the platinum atom in a square planar environment. The DMF molecule is disordered as indicated by the large temperature factors on the atoms, but the disorder could not be resolved.

The reported solvates of *cis*-$(NH_3)_2PtCl_2$ are of interest with regard to methods of an efficient purification of the antitumor drug Cisplatin. Removal of DMF from the isolated DMF solvate by vacuum evaporation yields a highly pure product as judged from UV-visible spectra. Precipitation of *cis*-$(NH_3)_2PtCl_2$ from a saturated DMF solution through addition of aqueous 0.1 N HCl solution also leads to a product meeting the well defined spectral criteria established for *cis*-$(NH_3)_2PtCl_2$. Finally, the solution behavior of *cis*-$(NH_3)_2PtI_2$ has been studied. The compound is unstable in H_2O, in aqueous KI, and in aqueous HI. Both with KI and in aqueous HI there is a release of NH_3 from *cis*-$(NH_3)_2PtI_2$ as a consequence of the *trans*-effect of I.

Introduction

Cis-dichlorodiammineplatinum(II), *cis*-$(NH_3)_2PtCl_2$, is a classical metal coordination compound (Scheme 1), used in many studies on geometrical isomerism, *trans*-influence and vibrational spectroscopy, for example [1]. It was first described by Peyrone in 1844 [2], and its planar structure recognized by Werner fifty years later [3], as confirmed by a crystal structure determination in 1966 [4]. The discovery of the antitumor activity of *cis*-$(NH_3)_2PtCl_2$ by Rosenberg and coworkers in the late sixties [5] and the notable clinical success of Cisplatin [6], as it is now referred to, has led to a renewed interest in the chemistry of this compound [7]. Because of its significance as an antitumor agent, the purity of Cisplatin is of utmost impor-



Scheme 1.

tance. In previous reports [8, 9] we have addressed this aspect and have shown that crystallization or reprecipitation of Cisplatin from N,N-dimethylformamide or N,N-dimethylacetamide dramatically improves the quality of the product.

This paper describes the formation of adducts of *cis*-$(NH_3)_2PtX_2$ (X = Cl^-, I^-) with formamides RR'NCHO and an efficient way of purifying Cisplatin by precipitation from N,N-dimethylformamide solution. In addition, the crystal structure of the N,N-dimethylformamide adduct, *cis*-$(NH_3)_2PtCl_2\cdot(CH_3)_2NCHO$ is reported.

Experimental

Materials and Preparation of Compounds

cis-$(NH_3)_2PtCl_2$ has been prepared from K_2PtCl_4 (Degussa) by any of the methods described by Dhara [10], Kauffman and Cowan [11], or Lebedinskii and Golovnya [12]; *cis*-$(NH_3)_2PtI_2$ was prepared according to Dhara [10]. The amides used (formamide, FA; N-methylformamide, NMF; N,N-dimethylformamide, DMF; N,N-diethylformamide, DEF) were of PROSYNTH quality.

Cis-$(NH_3)_2PtCl_2\cdot(CH_3)_2NCHO$ was prepared as previously described by us [9]. The yield of the crystalline DMF adduct can be increased up to 80% (based on Pt) if, after filtration of the first crop of crystals, ether is added to the DMF filtrate (in two portions of 50% of the DMF volume each) and the solution kept at 3 °C for another 5 d.

Cis-$(NH_3)_2PtI_2\cdot 2[(CH_3)_2NCHO]$: 5 g of crude *cis*-$(NH_3)_2PtI_2$ were dissolved in 6 ml DMF, filtered from undissolved material, and 20 ml ether were added. After 8 h at 4 °C orange-yellow cubes were collected on a filter, washed with a small amount of ether and briefly air dried. 1.46 g yield. Addition of more ether (20 ml) and cooling gave a second crop of product (1.0 g). *Anal.* Calcd. for $Pt(NH_3)_2I_2\cdot 2(C_3H_7NO)$: C, 11.45; H, 3.21; N, 8.91; I, 40.34. Found: C, 11.25; H, 3.19; N, 8.54; I, 40.34%. The crystals are stable at 4 °C but rapidly lose DMF when kept in air.

When 50 ml acetone instead of ether was used as precipitating agent, the adduct-free compound *cis*-$(NH_3)_2PtI_2$ was obtained as thin, orange-yellow plates. 2.05 g yield. Addition of excess acetone (350 ml) and cooling to −20 °C did not produce any more product. *Cis*-$(NH_3)_2PtCl_2\cdot(CH_3)HNCHO$: 300 mg of crude *cis*-$(NH_3)_2PtCl_2$ were dissolved in 10 ml NMF and 10 ml ether were layered on top of the NMF solution. Within several hours at 3 °C orange-yellow needles are formed. After 5 d at 3 °C the crystals were collected on a filter paper, washed with a small amount of ether and briefly air dried. Addition of more ether (10 ml) to the NMF filtrate and cooling did not result in an increased yield. *Anal.* Calcd. for $Pt(NH_3)_2Cl_2\cdot(C_2H_5NO)$: C, 6.69; H, 3.09; N, 11.70. Found: C, 7.34; H, 3.27; N, 11.97%.

If no ether is added to the NMF solution, the yield of the NMF adduct is much smaller, approximately 1/3. Crystals of *cis*-$(NH_3)_2PtCl_2\cdot$NMF rapidly lose NMF when kept in air at 22 °C, but are stable at −20 °C.

Cis-$(NH_3)_2PtI_2\cdot 1.3[(CH_3)HNCHO]$: 250 mg of crude *cis*-$(NH_3)_2PtI_2$ were dissolved in 1 ml NMF and 3 ml of ether were added. After 5 days at 4 °C 100 mg of orange needles were collected on a filter and briefly air dried. The crystals rapidly lose NMF when kept in air. Elemental analysis was performed 2 days after isolation with the sample kept in a sealed vial at room temperature. *Anal.* Calcd. for $Pt(NH_3)_2I_2\cdot 1.3(C_2H_5NO)$: C, 5.58; H, 2.26; I, 45.34; Pt, 34.85. Found: C, 5.37; H, 2.38; I, 45.18; Pt, 34.7%.

It is assumed that the non-integral number of solvent molecules derived from elemental analysis is due to a partial loss of NMF under the conditions of the sample storage.

With unsubstituted formamide, NH_2CHO, and with crude *cis*-$(NH_3)_2PtCl_2$ yellow products which were occasionally crystalline were isolated in low yield. These products rapidly darkened in air. Frequently a partial decomposition (reduction to Pt(0)?) was observed in solution for both the chloro and the iodo species.

No crystalline products were obtained with *cis*-$(NH_3)_2PtI_2$ dissolved in DEF (250 mg in 2 ml), even after addition of ether (1 ml). *Cis*-$(NH_3)_2PtCl_2$ was poorly soluble in DEF (approx. 300 mg in 30 ml) and did not reprecipitate on cooling to 4 °C.

Purification of cis-$(NH_3)_2PtCl_2$ through Precipitation from DMF/HCl

Crude *cis*-$(NH_3)_2PtCl_2$ was dissolved in a minimum of DMF (*ca.* 1 g/50 ml). After any undissolved particulate matter was removed by filtration or centrifugation, *cis*-$(NH_3)_2PtCl_2$ was reprecipitated following addition of 2 or 3 volumes of 0.1 N HCl to the DMF solution. The 0.1 N HCl–DMF solution was chilled to, and maintained at, 0 °C for 2 h and then filtered, washed separately with cold 0.1 N HCl and acetone and then dried in air. The unsolvated form of Cisplatin was obtained using this method. Yield 55 ± 5%.

Apparatus and Spectroscopy

IR spectra (Nujol mulls, CsI windows) were recorded on a Perkin Elmer 580 grating spectrometer and Raman spectra were recorded on a Coderg PH 1 spectrometer with krypton laser excitation (647.1 nm) and slit width between 4 and 6 cm^{-1}. UV-visible spectra were taken on a Cary 17D and a

Pye Unicam SP8-100 spectrophotometer with samples in 1 cm cells. The solutions were protected from light, both while the samples were dissolved and in the interval between spectral measurements. HPLC studies were done on a Philips Pye Unicam instrument with a LiChrosorb RP 18 column and a UV 220 nm detector. Samples of 15–20 mg *cis*-$(NH_3)_2PtCl_2 \cdot (DMF)_x$ ($0 \leqslant x \leqslant 1$) were suspended in 1 ml of aqueous 0.1 N NaCl and the supernatant injected. The eluant was distilled water, and DMF was identified by comparison with the peak obtained from a sample of DMF in 0.1 N NaCl solution. Ascending paper chromatography (Schleicher, Schüll 2043 b) was performed in a closed jar with samples dissolved in DMF and eluted with acetone/water mixtures (9:1) at 22 °C. The chromatograms were developed over I_2 vapor [13].

Solutions of *cis*-$(NH_3)_2PtI_2$ and HI, respectively, were analyzed qualitatively for I_2 with starch reagent. NH_3 was determined quantitatively by addition of 400 mg KOH to solutions of *cis*-$(NH_3)_2$-PtI_2 (volume 50 ml, $c_{Pt} = 1.03 \times 10^{-3}$ M) and distillation of 75% of the solution into a jar containing a known amount of 0.1 N HCl. Titration of this solution with 0.1 N NaOH to pH 6 (methyl-red as indicator) allowed calculation of the amount of NH_4^+ present. There is a 10% loss of NH_3 from *cis*-$(NH_3)_2PtI_2$ dissolved in H_2O, which we attribute to a partial decomposition of the Pt species during the distillation of NH_3 (2 h at 100 °C). As mentioned in the discussion section, the UV-visible spectra agree fairly well with a 70% loss of NH_3 if *cis*-$(NH_3)_2PtI_2$ is dissolved in 0.1 N HI, even if 10% loss is due to decomposition under the experimental conditions. When dissolved in 0.1 N KI, a 55% loss of NH_3 was measured and with 1 N KI solution a loss of 65% (samples 7 d, 22 °C). The results of UV-visible spectra (taken at 22 °C) clearly indicate that considerably less NH_3 is actually displaced by KI at room temperature, suggesting that only at 100 °C is the loss of NH_3 substantial. Unfortunately a direct measurement of NH_3 concentration by means of Nessler's reagent in solutions of *cis*-$(NH_3)_2PtI_2$/KI fails due to the presence of I^-.

Collection of X-ray Data

Crystals of *cis*-$(NH_3)_2PtCl_2 \cdot (CH_3)_2NCHO$ are rectangular blocks which decompose slowly by the loss of DMF from the lattice. A crystal of size 0.24 mm × 0.21 mm × 0.18 mm was selected after examination under a polarizing microscope and was sealed in a Lindemann capillary. The systematic absences observed in precession photographs corresponded to those of the orthorhombic space group *Pcca* ($0kl$, $l = 2n$; $h0l$, $l = 2n$; $hk0$, $h = 2n$). The crystal was placed on a Nicolet P3 diffractometer and the data were collected using graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å) at room temperature. The unit cell parameters were obtained from a least squares fit of χ, ϕ and 2θ for 15 reflections in the range $17.4° < 2\theta < 23.8°$. The crystal data are: $a = 11.372(2)$ Å, $b = 7.723(2)$ Å, $c = 11.165(3)$ Å, $\alpha = \beta = \gamma = 90°$, $Z = 4$, $\mu = 155.38$ cm^{-1}, $\rho_{calc} = 2.53$ g cm^{-3}. Attempts at measuring the density failed: The crystal, which originally floated in bromoform, slowly sank to the bottom of the test-tube. Removal of the crystal from the bromoform solution yielded a yellow powder. Reflections, consisting of $h, k \pm l$, were collected up to a maximum 2θ value of 55°. 2652 reflections were measured, of which 2542 were unique. No equivalent reflections were collected. The stability of the crystal was monitored by measuring two standards every 48 reflections: 2, 1, 2 (e.s.d. = 1.48%) and 4, 4, 0 (e.s.d. = 1.75%). Intensities were measured with the use of a coupled θ (crystal)–2θ(counter) scan for all reflections. The choice of scan rate for each reflection has been described in detail elsewhere [14, 15]. Two types of absorption correction were made on the crystal: an empirical absorption correction by the ψ-scan method using 10 reflections in the range $5.26° \leqslant 2\theta < 54.67°$ to correct for the crystal shape and a 2θ absorption correction to account for the difference in path length of the beam through the crystal as θ changes. μR was calculated (1.86) using an average radius for the crystal and the appropriate A^* values for a cylindrical absorption correction were applied to the intensities (A^* range = 11.9081–9.2576). Corrections were also made for Lorentz-polarization effects.

Solution of the Structure

The systematic absences observed corresponded to those for the space group *Pcca*. Reflections with $l = 2n$ were of much higher intensity than those with $l = 2n + 1$, indicating that the platinum atom sits on special position d or e, at ¼, 0, z or ¼, ½, z, respectively. These positions were verified by a three dimensional Patterson synthesis. A full-matrix least-squares refinement, minimizing $\Sigma w(|F_o| - |F_c|)^2$, followed by a three-dimensional difference synthesis, revealed the ligands of the *cis*-$(NH_3)_2PtCl_2$ complex. Some of the atoms of the DMF molecule could not be found and a systematic search of possible space groups showed that the packing of the molecules belonged to the space group *Pca*2_1. The structure was then solved by a series of refinements followed by difference synthesis, as described above, in *Pca*2_1, until all the non-hydrogen atoms were obtained. No attempts were made to locate the hydrogen atoms. 55 parameters were refined from 2085 non-zero reflections to a final $R = 0.0637$ and $Rw = 0.0388$. Refinement was terminated when the maximum shift/error (average shift/error) was 0.015 (0.004). The highest peak in the final difference map was 4.20 eÅ^{-3} and the lowest valley was –3.16

TABLE I. Atomic Parameters and Isotropic or Equivalent Temperature Factors ($\times 10^3$) for *cis*-$(NH_3)_2PtCl_2 \cdot DMF$.

Atom	x	y	z	U_{iso} or U_{eq}[a]
Pt	−11.66(3)	−9.15(8)	0	25.7(2)[a]
Cl(1)	128.5(6)	−158.7(9)	109.2(7)	41(4)[a]
Cl(2)	129.4(6)	146.0(8)	−102.6(8)	42(4)[a]
N(1)	−138(2)	123(2)	−85(2)	24(4)
N(2)	−137(2)	−154(2)	92(2)	38(5)
O(1)	394(1)	491(2)	956(1)	74(4)
C(1)	492(2)	457(2)	914(2)	62(5)
N(3)	504(1)	391(2)	810(1)	49(4)
C(2)	612(4)	357(5)	760(3)	70(4)
C(3)	389(4)	336(5)	736(3)	70(4)

[a] $U_{eq} = 1/3(U_{11} + U_{22} + U_{33})$.

$e\text{Å}^{-3}$; these lie close to the platinum atom position and are probably caused by termination errors in the Fourier series. A secondary extinction correction was applied by the method listed in SHELX (x = 0.00077). Scattering factors were from Cromer and Waber [16] and the corrections applied for anomalous dispersion were from Cromer [17].

All calculations were carried out on a CYBER 170/730 computer. The programs DATCO5, ABSORB and DATRDN from the XRAY76 program [18] were used for the preliminary data treatment. The structure was solved with SHELX [19]. Plane and dihedral angle calculations were made with NRC-22 [20]. Diagrams were prepared with the program ORTEP II [21].

Crystal Structure of cis-$(NH_3)_2PtCl_2 \cdot DMF$

The positional parameters and temperature factors for the atoms in *cis*-$(NH_3)_2PtCl_2 \cdot (CH_3)_2NCHO$ are listed in Table I. The bond lengths and angles are listed in Table II and the labelling of the atoms of the platinum complex and the DMF molecules is shown in Fig. 1. The geometry around the platinum atom is square planar with the platinum atom sitting out of the plane defined by the four ligands by 0.015(1) Å. The Pt–N and Pt–Cl bond lengths are normal for these types of complexes.

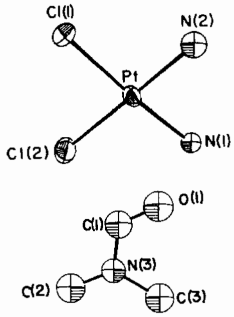


Fig. 1. The Pt complex and the solvate molecule showing the atom numbering.

The DMF molecule is planar with the nitrogen atom being farthest away from the mean plane of the molecule at 0.04(1) Å. The DMF molecule is disordered, as indicated by the large thermal parameters of its atoms compared to those of the atoms of the platinum complex. This type of effect has been observed in many structures containing lattice DMF molecules [22–25]. Such disorder often results in bond lengths and angles which vary from the normal values [24, 25]. This is observed in this structure with C(3)–N(3), 1.56(5) Å and C(2)–N(3), 1.33(5) Å. Any attempts made at resolving the disorder led to solutions which were implausible.

The Cisplatin molecules pack in the same way in *Pcca* as they do in *Pca*2_1. In *Pcca*, the DMF molecules were disordered about the two-fold rotation along y at z = ¼. This simply adds to the

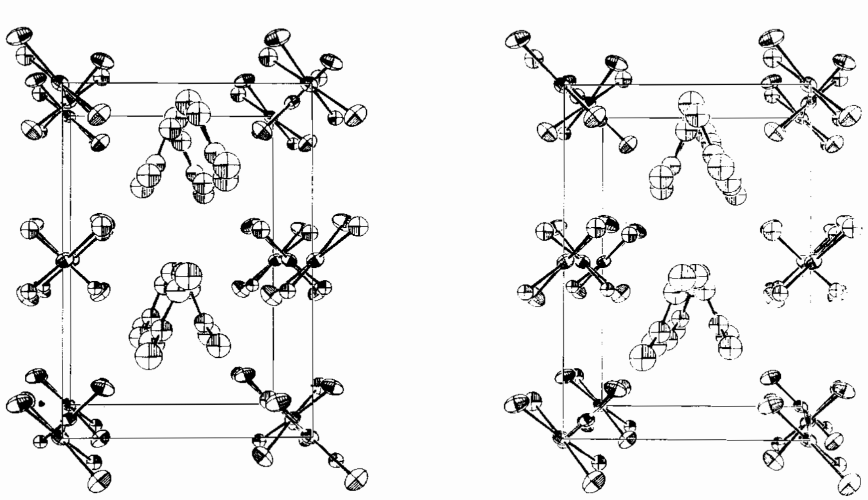


Fig. 2. Packing within the unit cell. b and c are parallel to the bottom and side of the page respectively, and the view is down a.

TABLE II. Bond Lengths (Å) and Bond Angles (Deg) for *cis*-$(NH_3)_2PtCl_2 \cdot C_3H_7NO$.

Pt–N(1)	2.00(2)	Pt–N(2)	2.08(2)	Pt–Cl(1)	2.315(7)
Pt–Cl(2)	2.306(7)	O(1)–C(1)	1.24(2)	C(1)–N(3)	1.36(2)
N(3)–C(2)	1.33(5)	N(3)–C(3)	1.56(5)		
N(1)–Pt–N(2)	91.0(7)	N(1)–Pt–Cl(1)	176.4(5)	N(1)–Pt–Cl(2)	89.9(5)
N(2)–Pt–Cl(1)	86.8(6)	N(2)–Pt–Cl(2)	178.7(6)	Cl(1)–Pt–Cl(2)	92.4(3)
O(1)–C(1)–N(3)	122(2)	C(1)–N(3)–C(2)	120(2)	C(1)–N(3)–C(3)	116(2)
C(2)–N(3)–C(3)	124(2)				
Hydrogen Bonds					
	O(1)–N(2)^{i}	3.03(3)			
	O(1)–N(2)^{ii}	3.04(2)			
	N(1)–Cl(1)^{iii}	3.43(2)			
	N(2)–Cl(2)^{iv}	3.42(2)			
	N(1)–Cl(2)^{v}	3.37(2)			
	N(2)–Cl(2)^{v}	3.43(2)			

i–v. Atom positions are related to those in Table I by the following symmetry operations:
i) $\frac{1}{2} + x, -y + 1, z + 1$; ii) $\frac{1}{2} + x, -y, z + 1$; iii) $-x, -y, z - \frac{1}{2}$; iv) $-x, -y, z + \frac{1}{2}$; v) $x - \frac{1}{2}, -y, z$.

disorder of the solvent molecules since the thermal parameters on the atoms of the DMF molecule were still much larger than those on the atoms of the platinum complex.

The packing of the molecules in the unit cell is shown in Fig. 2. The packing can be described as layers of Cisplatin molecules at $y = 0$ and layers of DMF molecules at $y = \frac{1}{2}$. The interactions between the two layers occur through weak hydrogen bonds between the oxygen atom of the DMF molecule and N(2) of a platinum complex and N(1) of a second platinum molecule, related to the first by a translation along *b* (refer to Table II). The hydrogen bonding interactions between the Cisplatin and DMF molecules are strong enough to affect the positions of the NH_3 modes in the vibrational spectra and to influence the loss of the solvent from the lattice; they are not strong enough to prevent the large thermal motion of the atoms in the DMF molecule, particularly of its oxygen atom.

Within the layers at $y = 0$, the interactions of the Cisplatin molecules along the *c* direction occur through long hydrogen bonds (N(1)——Cl(1), 3.43(2) Å and N(2)——Cl(2), 3.42(2) Å; the molecules are related by a two-fold screw axis and this leads to a zig-zagging chain of platinum molecules. In the *a* direction, the intermolecular interactions occur through long hydrogen bonds between the N(2) and Cl(2) (3.43(2) Å) and the Cl(2) and N(1) (3.37(2) Å) atoms of molecules related by the *c*-glide. The chloride ligand of one molecule and the nitrogen atoms of a symmetry related molecule form loosely interlocked chains.

In the DMF layer at $y = \frac{1}{2}$, the interactions between DMF molecules are weak van der Waals' interactions; this again accounts for the disorder of the DMF moieties.

Results and Discussion

Vibrational Spectra

Infrared spectra of *cis*-$(NH_3)_2PtCl_2$, *cis*-$(NH_3)_2PtI_2$, of the various formamides, and of the isolated adducts were recorded as Nujol mulls and compared. Raman spectra were recorded for DMF (solution), *cis*-$(NH_3)_2PtCl_2$, and *cis*-$(NH_3)_2PtCl_2 \cdot$DMF (both polycrystalline). The assignment of the *cis*-$(NH_3)_2PtX_2$ modes follows that of Nakamoto *et al.* [26], which is in general agreement with values published by other groups [27]; the DMF modes are assigned according to Miyazawa *et al.* [28] and Kaufmann and Leroy [29]. The IR spectra of FA and NMF were found to agree with literature data [30].

All isolated adducts lose the solvent molecules rapidly when kept in air, except the DMF adduct of *cis*-$(NH_3)_2PtCl_2$, which loses solvent more slowly. This observation can be correlated directly with the positions of the NH_3 modes in the solid state vibrational spectra: for *cis*-$(NH_3)_2PtCl_2$ the NH_3 modes are clearly shifted by DMF in the lattice, but there are no such shifts for the other adducts. For the latter, the spectra represent good superpositions of the individual spectra for *cis*-$(NH_3)_2PtX_2$ and the formamides. With DMF as solvent, however, infrared frequencies of the $\delta_s NH_3$ modes of *cis*-$(NH_3)_2PtCl_2$ are shifted +15–20 cm^{-1} from 1300, 1320 cm^{-1} to 1315, 1340 cm^{-1} and the ρNH_3 modes +60–90 cm^{-1} from 790, 800 cm^{-1} to 850,

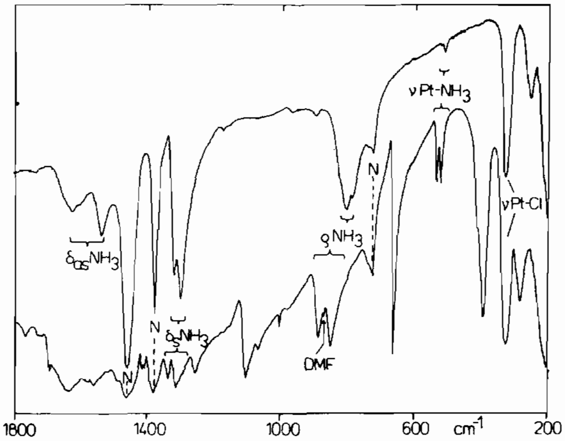


Fig. 3. IR spectra of *cis*-$(NH_3)_2PtCl_2$ (top) and *cis*-$(NH_3)_2$-$PtCl_2 \cdot DMF$ (bottom) between 200 and 1800 cm^{-1}. Nujol absorptions (N) are indicated. The strong increase in intensity of the $Pt-NH_3$ modes is a sensitive indicator of participation of NH_3 in hydrogen bonding with O of DMF. With FA and NMF solvates no such intensity increase is observed.

890 cm^{-1}. Of the skeletal modes, $\nu Pt-NH_3$ absorptions shift +8–12 cm^{-1} from 512, 520 cm^{-1} to 520, 532 cm^{-1} and at the same time substantially increase in intensity in the IR (Fig. 3), and the $\delta_{ip}NPtN$ mode at 254 cm^{-1} is shifted +28 cm^{-1} to 282 cm^{-1} in the DMF adduct. These changes are consistent with an alteration of the hydrogen bonding pattern of the ammine protons in the *cis*-$(NH_3)_2PtCl_2 \cdot DMF$ complex. This conclusion is fully supported by the results of the X-ray structure determination: the Cl···N hydrogen bond distances found in this work are relatively long and are about 0.1 Å longer than those observed in the non-adduct *cis*-$(NH_3)_2PtCl_2$ (3.30(4) Å and 3.34(4) Å) [4]. In addition, there are considerably shorter hydrogen bond distances between the oxygen atom of the DMF molecule and the amine group attached to the platinum atom ($O(1)-N(2)^{i}$ = 3.03(3) Å and $O(1)-N(2)^{ii}$ = 3.04(2) Å, see Table II). Thus, the shift in the NH_3 modes seen in *cis*-$(NH_3)_2PtCl_2 \cdot DMF$ must be caused by the hydrogen bonding of the Cisplatin molecule to the DMF molecule present in the lattice. The expected decrease in νNH_3 frequencies on hydrogen bonding [31] is less well pronounced, though there is an extension of the νNH_3 absorptions to lower wavenumbers in the IR spectrum of the DMF adduct (3280–3100 cm^{-1} in the DMF adduct, 3280 and 3200 cm^{-1} in the non-adduct). The $\delta_{as}NH_3$ modes, which occur at 1620 and 1540 cm^{-1} in the solvent free compound, overlap in the DMF adduct with solvent absorptions and cannot be identified.

The effect of solvate formation on the DMF vibrations is conveniently studied by a comparison of the solution spectra of DMF (IR and Raman) with the solid state spectra of *cis*-$(NH_3)_2PtCl_2 \cdot$ DMF and a closely related compound containing a DMF molecule coordinated to Pt through O, *cis*-$[(NH_3)_2PtCl(DMF)]NO_3$ [32]. Only four very intense (both in IR and Raman) and easily identifiable bands shall be considered: νCO, δOCN, $r(CH_3-N)$, and $\delta(CH_3-N-C)$. The νCO mode, at 1655 cm^{-1} in liquid DMF, is shifted to 1640 cm^{-1} in the DMF adduct and 1650 cm^{-1} in the complex with coordinated DMF. This change seems small considering the fact that metal coordination should affect this mode much more than hydrogen bonding. However, similar small shifts have previously been reported for a variety of metal–DMF complexes [33, 34] and are explained by the fact that this mode is not a pure νCO but is coupled to other modes [29, 33]. The δOCN mode generally is considered the most reliable vibration for diagnosis concerning the state of DMF: It absorbs at 657 cm^{-1} in liquid DMF and, depending on the metal, between 670 and 730 cm^{-1} in complexed DMF [33, 34], *e.g.* 728 cm^{-1} in *cis*-$[(NH_3)_2PtCl(DMF)]NO_3$. In the solvate discussed here, this band occurs at 662 cm^{-1}, close to a position found in free DMF and consistent with hydrogen bonding of the O atom. The third band, a $r(CH_3-N)$ mode, occurs at 1107 cm^{-1} (solvate), also between that observed in liquid DMF (1092 cm^{-1}) and that in *cis*-$[(NH_3)_2PtCl(DMF)]NO_3$ (1125 cm^{-1}). The $\delta(CH_3-N-C)$ mode of DMF at 353 cm^{-1} (solution) is shifted only slightly more by complexation (394 cm^{-1}) than by solvate formation (390 cm^{-1}) and, for this reason, is not suitable for diagnostic purposes.

Purification of Cisplatin

Via Isolated Solvate

The preparation of *cis*-$(NH_3)_2PtCl_2 \cdot DMF$, its conversion into the solvent-free Cisplatin complex, and the UV spectrum of this Cisplatin have been reported by us before [9]. Instead of applying a high vacuum to remove the solvent DMF, the sample can be simply kept in air at 22 °C or 40 °C and the solvent DMF is removed within 3 days. The loss of DMF can be followed conveniently by means of HPLC. The UV spectra of samples of Cisplatin with DMF removed at standard pressure differ somewhat from those of samples with DMF removed under high vacuum; the absorbance ratios (max 301 nm/min 246 nm) being 4.6 and 4.9 respectively, and (max 301 nm/max 363 nm), 5.8 *vs.* 5.3 respectively. Nevertheless, samples with DMF removed at standard pressure are chromatographically pure.

Via HCl Precipitation from DMF Solution

The purification of Cisplatin via the DMF/0.1 N HCl method is, like the adduct formation, particularly effective because the common impurities (Magnus-type salts) are insoluble in DMF and there-

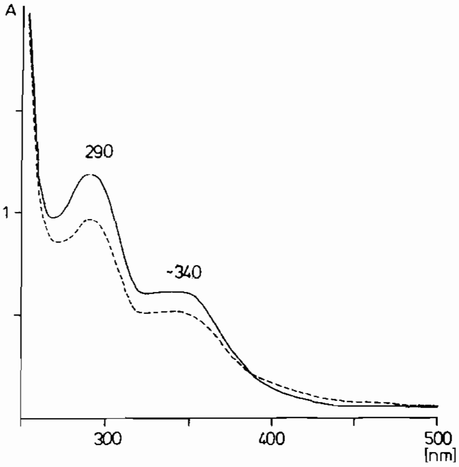


Fig. 4. UV-visible spectrum of *cis*-$(NH_3)_2PtI_2$ (precipitated from DMF with acetone) in H_2O, pH 6, c_{Pt} = 1.03 × 10^{-3} M initially. (a) After all material dissolved (2.5 h at 22 °C) (solid line); (b) after 3 d at 22 °C (dotted line).

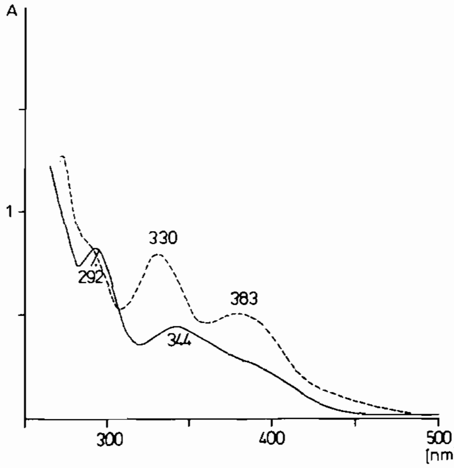


Fig. 5. UV-visible spectrum of *cis*-$(NH_3)_2PtI_2$ (precipitated from DMF with acetone) in 1 N KI, pH 6.5, c_{Pt} = 2.07 × 10^{-4} M. (a) 3 h after beginning of the dissolving process (22 °C) (solid line); (b) after 4 d at 22 °C (dotted line).

fore can be removed by filtration. Use of DMF in the purification process of Cisplatin is particularly desirable for Cisplatin samples prepared by the Kauffman and Cowan [11] and Lebedinskii and Golovnya [12] methods, which tend to produce significant amounts of these salts. Likewise, minor amounts of *trans*-$(NH_3)_2PtCl_2$ which may be produced in these same two preparations are readily removed because of appreciable solubility in the DMF/0.1 N HCl medium. Satisfactory purification of crude Cisplatin containing the Magnus-type impurities is not achieved via recrystallization from 0.1 N HCl alone.

Samples purified via the DMF/0.1 N HCl method meet the well-defined spectral criteria established for Cisplatin samples [35–37], namely, (a) an absorption maximum at 301 nm (±1 nm), (b) a minimum at 246 nm, and (c) an absorbance ratio As (301 nm/246 nm) $\geqslant$ 4.5. The latter parameter for samples purified by the DMF/0.1 N HCl method typically varies between 4.6 and 4.9.

Solution Behavior of cis-$(NH_3)_2PtI_2$

It was our intention to find UV-visible spectroscopic criteria for the purity of *cis*-$(NH_3)_2PtI_2$ similar to those established for Cisplatin, for example [8, 35–37]. As will be shown, these attempts failed because *cis*-$(NH_3)_2PtI_2$ proved to be unstable under our conditions. In particular, unlike Cl^- in the case of *cis*-$(NH_3)_2PtCl_2$, addition of iodide ions did not stabilize the diiodo complex but rather caused its destruction.

The UV-visible spectrum of an aqueous solution (pH 6) of *cis*-$(NH_3)_2PtI_2$ (crude material or precipitated from DMF with acetone) changed over several days; in this time period, the yellow color faded and a cloudy, brown precipitate was formed (Fig. 4). The spectral changes, which occur in the initial phase after dissolution, occur faster with the crude product than with the purified material from the DMF solution, and there appears to be more precipitate in the former. The IR spectrum of the precipitate (*ca.* 5% of the dissolved material) suggests it to be *cis*-$(NH_3)_2PtI_2$, but it is clear that this amount cannot account for the loss of intensity observed in the absorption spectrum.

If aqueous KI was used as the solvent, the UV-visible spectrum again underwent changes with time. As compared to the spectrum in H_2O, there was a shift of the 343 and 292 nm bands to higher energy which was accompanied by an increase in intensity, and at the same time a new band appeared at 383 nm. Since these changes were accelerated with increasing concentration of KI, they could not be attributed to the hydrolysis of the iodo ligands of *cis*-$(NH_3)_2PtI_2$ (Fig. 5).

The most dramatic spectroscopic changes occurred when *cis*-$(NH_3)_2PtI_2$ was dissolved in 0.1 N HI solution (Fig. 6). The spectrum obtained after 2 d at room temperature was quantitatively identical with that of $[PtI_4]^{2-}$ with maxima at 330, 387, and 445(sh) nm and minima at 300 and 360 nm [38]. Thus NH_3 is released from *cis*-$(NH_3)_2PtI_2$ as a consequence of the high *trans*-effect of I. Since NH_3 is immediately protonated to give NH_4^+, the equilibria for the following reactions lie well to the right:

$$(NH_3)_2PtI_2 + HI \longrightarrow (NH_3)PtI_3^- + NH_4^+$$

and

$$(NH_3)PtI_3^- + HI \longrightarrow PtI_4^{2-} + NH_4^+$$

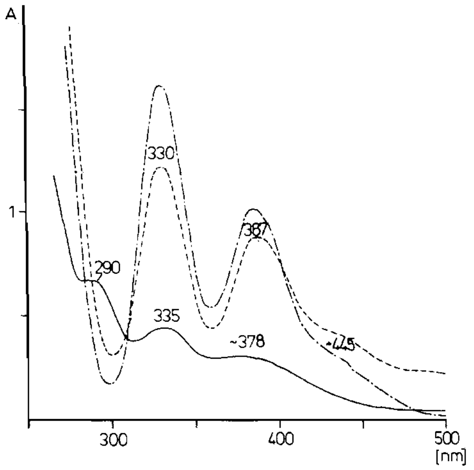


Fig. 6. UV-visible spectrum of *cis*-$(NH_3)_2PtI_2$ (precipitated from DMF with acetone) in 0.1 N HI. pH 1.1, c_{Pt} = 2.07 × 10^{-4}. (a) After all material dissolved (2 h at 22 °C) (solid line); (b) after 2 d at 22 °C (dotted line); (c) K_2PtI_4 in 1 N KI, pH 6, c_{Pt} = 2.0 × 10^{-4} (dots and lines).

A comparison of the extinction coefficients of the three maxima with those of PtI_4^{2-} (obtained on dissolving K_2PtCl_4 in 1 N KI solution) showed that approximately 70% of *cis*-$(NH_3)_2PtI_2$ had been converted into K_2PtI_4 after several days at room temperature. This finding is in excellent agreement with the results obtained from a quantitative analysis of the liberated NH_3 (see Experimental).

The use of HI as solvent of *cis*-$(NH_3)_2PtI_2$ produced another interesting aspect. It is well established that in the presence of even small amounts of oxygen HI is readily oxidized to molecular I_2. As expected, I_2 is detectable in 0.1 N HI solution. However, no I_2 could be detected if *cis*-$(NH_3)_2PtI_2$ was present in solution. Apparently any I_2 formed immediately underwent an oxidative addition with either *cis*-$(NH_3)_2PtI_2$ and/or K_2PtI_4 according to:

$$cis\text{-}(NH_3)_2PtI_2 + I_2 \longrightarrow cis\text{-}(NH_3)_2PtI_4$$

and/or

$$PtI_4^{2-} + I_2 \longrightarrow PtI_6^{2-}$$

NH_3 was also released from *cis*-$(NH_3)_2PtI_2$ when dissolved in aqueous KI solution. From a comparison of Figs. 5 and 6 it is evident that KI causes considerably less release of NH_3 than does HI. This is not unexpected considering the fact that the preparation of *cis*-$(NH_3)_2PtI_2$ involves the addition of NH_3 to a solution of PtI_4^{2-}. On the other hand, a quantitative determination of the amount of free NH_3 in solution of *cis*-$(NH_3)_2PtI_2$ in KI gave rather high values. As outlined in the Experiments, this is because additional NH_3 is displaced under the conditions of the distillation of NH_3.

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