The Isolation and *X*-Ray Crystal Structure of an Adduct formed between 18-Crown-6 and Cisplatin

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The *X*-ray structure of the crystalline complex formed between 18-crown-6 and 2 mol. equiv. of cisplatin and dimethylacetamide reveals hydrogen bonding which involves all *three* hydrogen atoms on *both* ammine ligands of cisplatin forming bonds to (i) all *six* oxygen atoms of 18-crown-6, (ii) *one* chlorine atom on a symmetry-translated cisplatin, and (iii) *the* carbonyl oxygen atom of dimethylacetamide.

In recent years, *cis*-dichlorodiammineplatinum(II) (cisplatin) and second generation analogues have found[1—5] clinical application against a wide range of tumours, including several (*e.g.* testicular and ovarian carcinomas and certain head and neck cancers) which are particularly resistant to treatment by other methods. Transition metal complexes,[6—9] including neutral platinum ammines,[6,8] may be co-ordinated in their second sphere to crown ethers, principally on account of (N–H · · · O) hydrogen bond formation between the first sphere ammine ligands on the transition metal and the oxygen atoms in the crown ether. Here, we report on (i) the isolation of a crystalline 1:2:2 adduct between 18-crown-6, cisplatin, and dimethylacetamide (one of the solvents employed in the crystallisation process), and (ii) the characterisation of the adduct by *X*-ray crystallography.

Cisplatin [*cis*-$PtCl_2(NH_3)_2$] (300 mg, 1 mmol) was dissolved in $MeCONMe_2$ (10 ml) containing 18-crown-6 (264 mg, 1 mmol). Crystals of {18-crown-6 · [*cis*-$PtCl_2(NH_3)_2$]$_2$·[$MeCONMe_2$]$_2$} were obtained by vapour diffusion[10] using Et_2O. After 48 h, the crystals were filtered off. Yield, 363 mg (40%), m.p. 138—139 °C, ^{1}H n.m.r. data: δ (CD_3SOCD_3, 220 MHz) 1.96 (6H, s, 2 × COMe), 2.78 and 2.95 (12H, 2 × s, 2 × NMe_AMe_B), 3.50 (24H, s, 12 × OCH_2), and 3.95 (12H, br. s, 4 × NH_3). Single crystals, suitable for *X*-ray investigation,† were obtained by liquid diffusion[10] using n-pentane instead of Et_2O. The crystal structure (Figure 1) has features in common with the structures[6—8] formed both by $[Cu(NH_3)_4H_2O]^{2+}$ and [*trans*-$PtCl_2(PMe_3)NH_3$] with 18-crown-6. There is a crystallographic centre of symmetry at the centre of the macrocycle which adopts a characteristic all-*gauche* conformation with pseudo D_{3d} symmetry. The platinum ammine ligands approach more or less axially towards opposite faces of the macrocycle and are bound *via* (N–H · · · O) hydrogen bonds (3.06, 3.10, and 3.17 Å) to the oxygen atoms on each face in a three-point perching arrangement.[11] In addition to these six hydrogen bonds to N(1) and N(1′), there are a further three hydrogen bonds between each equatorial N(2) to (i) O(7) (3.11 Å) of the macrocycle, (ii) O(10) (2.88 Å) of the $MeCONMe_2$ molecule, and (iii) Cl(2′) (3.31Å) of a symmetry-related cisplatin molecule. A similar (N–H · · · Cl) interaction (3.30 Å) was proposed[12] in the crystal structure of cisplatin. Whereas, in the crystal structure of $[Cu(NH_3)_4H_2O$·18-crown-6$]_n^{2+}[PF_6]_{2n}^-$ the axial *trans*-ammine ligands form[7,8] a continuous 1:1 polymeric structure, in the present instance the (N–H · · · Cl) hydrogen bond between the equatorial ammine ligand and the axial chlorine atom on the symmetry-related cisplatin complex creates a continuous 2:1 (cisplatin:18-crown-6) hydrogen bonded stepped-chain copolymer. Finally, a significant feature of the structure of this crystalline adduct is the relative shortness‡ [3.22(3)Å] of the through the ring N · · · N distance.

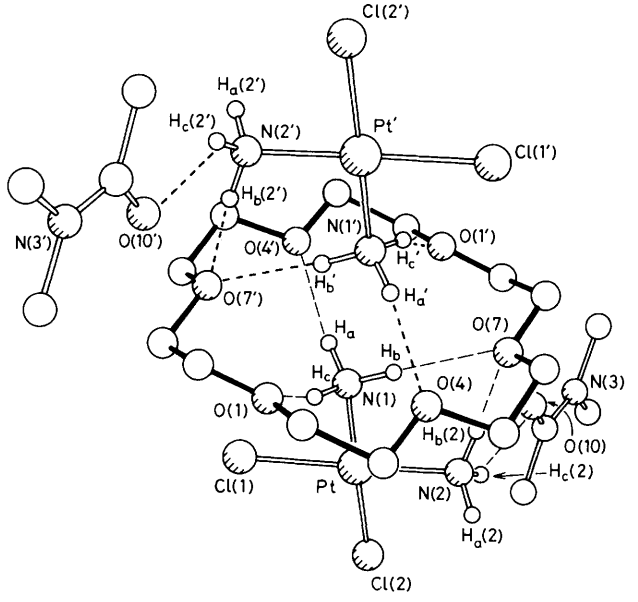

Figure 1. Crystal structure of {18-crown-6·[*cis*-$PtCl_2(NH_3)_2$·-[$MeCONMe_2$]$_2$}. Torsion angles: |O–C–C–O| 65—66, |C–C–O–C| 175—179°. Hydrogen bond distances to the macrocycle, (N · · · O), (H · · · O) (Å), C–H · · · O angles (°) at H atoms, angles (θ°) between COC planes and HO vectors; [N(1) · · · O(4′)] H_a: 3.06, 2.13, 163, 5; [N(1) · · · O(7)] H_b: 3.17, 2.21, 174, 15; [N(1) · · · O(1)] H_c: 3.10, 2.20, 156, 12; [N(2) · · · O(7)] $H_b(2)$: 3.11, 2.17, 164, 40. Other hydrogen bonds from N(2), (N · · · X), (H · · · X) Å, C–H · · · X angles (°) at H atoms; [N(2) · · · O(10)] $H_c(2)$: 2.88, 2.12, 135; [N(2) · · · Cl(2′)] $H_a(2)$: 3.31, 2.36, 172. N(1) lies 1.61 Å from the mean plane of the six ring oxygen atoms. Angle of Pt–N(1) vector to this plane = 11.2°. Through the ring N(1) · · · N(1′) distance = 3.22 Å.

† *Crystal data*: $C_{12}H_{24}O_6[PtCl_2(NH_3)_2C_4H_9ON]_2$, M = 1038.6, triclinic, space group $P\bar{1}$, a = 8.821(3), b = 10.133(4), c = 11.065(4) Å, α = 87.10(3), β = 84.24(3), γ = 69.76(3)°, U = 923 Å^3, z = 1, μ(Cu-K_α) = 172 cm^{-1}, D_c = 1.88 g cm^{-3}. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. The structure was solved by the heavy atom method and refined anisotropically with absorption corrected data. The ammine hydrogen atoms were located in a ΔF map and both ammine ligands were refined as rigid bodies. Refinement was to R = 0.063, R_w = 0.067 for 2188 independent observed reflections [θ ≤ 55°, $|F_o| > 3\sigma(|F_o|)$]. The atomic co-ordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ Compare with values of 3.48(3) Å in [{*trans*-$PtCl_2$-$(PMe_3)NH_3$}$_2$·18-crown-6] (refs. 6,8) and 3.37(1) Å in $[Cu(NH_3)_4H_2O$·18-crown-6$]_n^{2+}$ $[PF_6]_{2n}^-$ (refs. 7,8).

The results of this investigation are important in at least two respects: (i) the consequences that adduct formation between cisplatin and 18-crown-6 could have for the solubility characteristics and transport properties of the drug (*cf.* ref. 13) and (ii) the design of second generation receptor molecules for cisplatin based on the 18-crown-6 constitution.

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