Structure of a Platinum(II) Complex with Morphine

JEAN-PIERRE MACQUET

Laboratoire de Pharmacologie et de Toxicologie Fondamentales du C.N.R.S., 205, route de Narbonne, 31400-Toulouse, France

and ANDRÉ L. BEAUCHAMP

Département de Chimie, Université de Montréal, Montreal, Que. H3C 3V1, Canada

Received August 29, 1983

As part of our continuing interest in platinum complexes likely to exhibit antitumor activity [1, 2], the use of morphine as a ligand to platinum was considered because this molecule could act as a carrier to facilitate the transfer of a platinum entity across the blood-brain barrier.

The zwitterionic [(morphinium)$PtCl_3$] compound was obtained by reacting K_2PtCl_4 with morphine hydrochloride in water. No X-ray studies are available on metal complexes of morphine, and the structure of the $Cr(CO)_3$ compound with the related codeine molecule [3] is not informative in connection with platinum binding. The present crystallographic study was undertaken to identify the site of attachment of platinum and to determine the position of the platinum square plane with respect to the van der Waals envelope of morphine.

The compound was prepared by mixing K_2PtCl_4 (1.0 mmol, 0.415 g) dissolved in 25 ml H_2O with morphine·HCl·$3H_2O$ (1.0 mmol, 0.375 g) dissolved in 25 ml H_2O at room temperature. After 3 h, a light pink precipitate was filtered off and the mixture was left either at room temperature or at 4 °C for 6 days. The yellow solid was washed with H_2O, ethanol and ether, and dried under vacuum. Yield: 0.22 g, 36%. Calcd. for $C_{17}H_{20}Cl_3NO_3Pt$·$2H_2O$: C, 32.73; H, 3.88; N, 2.25; Cl, 17.05, Pt, 31.27. Found: C, 32.75; H, 3.83; N, 2.04; Cl, 16.71; Pt, 31.39.

To grow crystals, the above yellow solid was washed only with water and the wet precipitate was dissolved in acetone. Orange-yellow crystals formed upon slow evaporation at room temperature. The structure revealed the presence of $\frac{1}{2}H_2O$ and 1 acetone molecule per complex molecule. When left in open air, these crystals lost their crystallinity and the analysis was consistent with the formula [(morphinium)$PtCl_3$]·H_2O. Calcd. for $C_{17}H_{20}Cl_3NO_3Pt$·H_2O: C, 33.70; H, 3.66; N, 2.31; Cl, 17.56. Found: C, 33.74; H, 3.85; N, 2.08; Cl, 17.26.

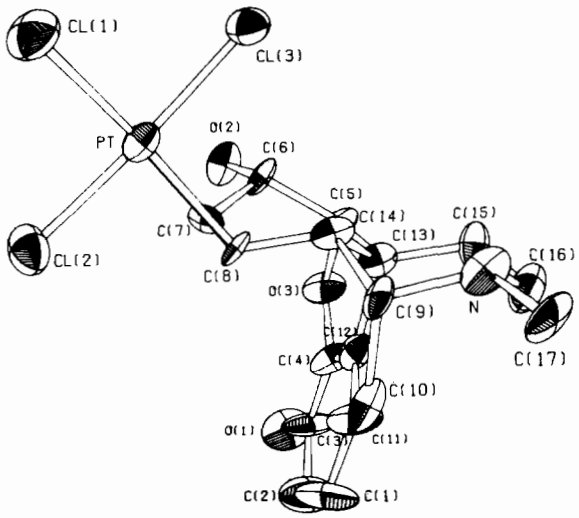

Fig. 1. ORTEP drawing of the [(morphinium)$PtCl_3$] zwitterion. The ellipsoids correspond to 50% probability.

Crystals of [(morphinium)$PtCl_3$]·$\frac{1}{2}H_2O$·Acetone belong to the tetragonal space group $P4_12_12$, with a = 9.468(4) Å, c = 52.30(1) Å and Z = 8 formula units per cell. The structure was solved by the heavy-atom method and refined on 1537 independent non-zero reflections to R = 0.039 and R_w = 0.044.

The [(morphinium)$PtCl_3$] zwitterion is shown in Fig. 1. The $PtCl_3$ unit is π-bonded to the C(7)–C(8) double bond of the morphinium moiety in the same manner as in Zeise's salt [4] and other olefinic complexes. The double bond is perpendicular to the $PtCl_3$ plane, and the Pt–Cl and Pt–C bonds (averaging 2.308(5) Å and 2.15(1) Å, respectively) compare well with those found in Zeise's salt. The C(7)–C(8) bond (1.39(2) Å) seems to be longer than in the uncoordinated molecule (~1.33 Å) [3, 5, 6]. The overall geometry of morphine is not profoundly altered by complexation. The ligand has the usual T shape and the $PtCl_3$ group stands above the edge of one of the T arms. Attack of the C(7)–C(8) bond from underneath would produce excessive steric repulsion between coordinated chlorine atoms and the vertical portion of the molecule. In this position, the $PtCl_3$ unit drastically changes the van der Waals profile of morphine and remains easily accessible for chlorine substitution. It is noteworthy that in the [(morphinium)$PtCl_3$] complex, the important binding sites related with the pharmacological properties of morphine (analgesia and binding to opiate receptors) [7, 8] are not significantly altered by platinum complexation.

0020-1693/84/$3.00

The compound, kindly tested by Dr. S. Cros, revealed no significant antitumor activity on ascites L1210 leukemia cells grafted in CDF_1 mice.

Acknowledgement

A generous gift of morphine hydrochloride trihydrate from Professor J. Cros is gratefully acknowledged. The technical assistance of J. Escalier and Marc J. Olivier is appreciated.

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