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Crystal Structure and Proton NMR of (1,2-Bis(pyridin-2-yl)-ethane-N,N′)(2,2-dimethyl-1,3-diaminopropane-N^1,N^3)platinum(II) Dichloride Monohydrate

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The crystal and molecular structure of the title compound, [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$ (bpe = 1,2-bis-(pyridin-2-yl)ethane; dmdap = 2,2-dimethyl-1,3-diamino-propane) has been studied in the solid state by single-crystal X-ray diffraction. The properties of this compound have been studied in solution by high-resolution proton NMR spectroscopy.

The compound crystallizes in the orthorhombic space group Pnma with cell dimensions at −115 °C of a = 15.012(3) Å, b = 13.555(3) Å and c = 10.247(2) Å and four formula units per unit cell. The structure has been solved by the heavy-atom method and refined by standard least-squares techniques to R = 0.031 and R_w = 0.032 for 2079 independent reflections with $I > 1.96\sigma(I)$.

The compound consists of cations [Pt(dmdap)(bpe)]$^{2+}$, Cl^- anions and water of crystallization. The square-planar coordinated Pt(II) ions have a mean Pt–N distance of 2.032(5) Å and N–Pt–N angles between 87.3 and 92.0°. The chloride anions and water molecules are linked to each other and to the cations through N–H···Cl and O–H····Cl hydrogen bonds. The ethylene bridge between the pyridine rings in the bpe ligand appears to be present in disordered orientations, even at −115 °C. Although refinement with a split-atom model was possible, final values for R and R_w did not improve.

Proton NMR spectroscopy (100 and 300 MHz) between +90 and −90 °C shows that the same structure also occurs in solution (H_2O and MeOH). Even at −90 °C the interconversion between the two possible chair conformations of the Pt–dmdap chelate is fast on the NMR time scale.

Introduction

The chelating ligand 1,2-bis(pyridin-2-yl)ethane (abbreviated as bpe) has been shown to be a useful ligand in the creation of different chemical environments above and below the coordination plane of square planar platinum(II) compounds [1]. With ligands of this type it is possible that rotational processes about Pt–N bonds, such as in platinum–nucleotide and Pt–nucleoside adducts, can be studied in detail. Knowledge of these processes is of great importance for a better understanding of the interaction of Pt-compounds with DNA [2, 3]. Addition of a second nucleic-acid base to Pt(II) appears to be easier if rotation about the Pt–N bond is possible [4].

In the process of further developing the usefulness of bpe as a chelating ligand to introduce asymmetry, we have prepared the cation Pt(dmdap)(bpe)$^{2+}$ (dmdap = 2,2-dimethyl-1,3-diamino-propane). The dmdap ligand was selected because of its relatively simple NMR spectrum, without overlapping signals with bpe. Moreover, the two methyl signals at C(2) might yield information about the flexibility of the chelate rings.

Because initial studies showed quite some thermal motion of the ethylene protons of the bpe ligand, it was decided to determine the crystal structure at −115 °C and to study the NMR spectrum as a function of temperature.

Experimental

Starting Materials

cis-Pt(dmdap)Cl_2 was prepared as described previously [5] from K_2PtCl_4 as starting material. 2,2-dimethyl-1,3-diaminopropane was obtained as a gift from BASF (Arnhem). 1,2-bis(pyridin-2-yl)-ethane (Alfred Bader Chemie) was obtained commercially.

Synthesis

Pt(dmdap)(bpe)$Cl_2 \cdot H_2O$ was obtained by reaction for two days of 0.5 mmol of *cis*-Pt(dmdap)Cl_2 and 0.5 mmol of bpe in 20 ml water at 60 °C. The resulting colorless solution was concentrated by evaporation to about 2 ml. After addition of acetone a white precipitate was formed, analysing (C, H, N, Cl) as $PtCl_2C_{17}N_4H_{28}O$.

Single crystals were obtained by vapour diffusion of a solution in methanol against acetone.

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X-ray Methods and Structure Determination

A colorless crystal (measuring 0.30 × 0.13 × 0.08 mm^3) of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$ was used for the structure determination. X-ray intensity data of 2386 unique reflections were measured on a Syntex $P2_1$ diffractometer equipped with a modified LT-1 cooling unit by the θ–2θ scan mode in the range $3° \leq 2\theta \leq 54°$ at −115 °C using graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å). 2079 reflections with an intensity $I > 1.96\sigma(I)$ were used for the structure determination (crystal data see Table I).

Unit-cell dimensions, with their estimated standard deviations, were derived from a least-squares fit of the setting angles for 15 reflections on a Syntex $P2_1$ diffractometer (−115 °C). Crystal data and information related to data collection are summarized in Table I.

The structure was solved by Patterson methods. A starting model with Pt as a heavy atom on the special position 4c (x, 0.25, z) was found. Subsequent refinement cycles followed by three-dimensional difference Fourier syntheses revealed the positions of the non-hydrogen atoms in the unit cell. Full-matrix least-squares refinements with anisotropic temperature factors using 121 variables and 15 atoms led to final R-values of $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o| = 0.031$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2]^{1/2} = 0.032$. No attempt was made to locate the hydrogen atoms. The weighting scheme used was $1/w = [\sigma(F_o)]^2 + (0.005 \cdot |F_o|)^2$ with $\sigma(F_o) = \sigma(I)/(2 \cdot |F_o| \cdot Lp)$ with Lp = Lorentz and polarization factors. The atomic scattering factors for the neutral atoms were taken from the compilation in the International Tables [6]. The calculations were done with programs of the Syntex EXTL and SHELXTL systems.

TABLE I. Summary of Crystal Data and Intensity Collection of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$.

Compound	$Pt(C_{12}H_{12}N_2)(C_5H_{14}N_2)Cl_2 \cdot H_2O$
Formula	$C_{17}H_{27}ON_4Cl_2Pt$
Mol. weight	570.16
Crystal dimensions	0.30 × 0.13 × 0.08 mm^3
Space group	$Pnma - D_{2h}^{16}$
Systematic absences	0kl: k + l ≠ 2n hk0: h ≠ 2n
a	15.012(3) Å
b	13.555(3) Å
c	10.247(2) Å
X-ray density	1.84 g·cm^{-3}
Temperature	−115 ± 2 °C
Radiation	MoKα (0.71069 Å) from graphite monochromator
Linear absorption coefficient	73.5 cm^{-1}
Minimum transmission factor	0.38
No. of independent refl.	2386
No. of refl. with $I > 1.96(I)$	2079
2θ limit	54°
Final number of variables	121 (averaged model) 114 (split-atom model)
Final R, R_w	
averaged model	0.031, 0.032
split-atom model	0.031, 0.033

In the resulting model an abnormal geometry (apparent bond angles 121.5°) of the C atoms in the ethylene bridge, as well as high temperature factors of this atom were observed, so that a disordered structure was to be suspected. Therefore, isotropic refinements with split-atom positional parameters of the bpe ligand were carried out. The two halves of the ligand occupy the alternate positions of the split-atom sites. The new model shows normal distances and angles of the ethylene bridge. However, it was not possible to refine the split-atoms with anisotropic temperature factors because of high correlation between the coefficients for the closely spaced half-positions (distance 0.28···0.54 Å) of the split-atoms. The refinement of the positional parameters of the split-atoms was stable, but resulted in higher standard deviations. Final refinement with 114 variables and 19 atomic sites led to R-values of R: 0.031 and R_w: 0.033.

Table II shows the atomic positional parameters; the anisotropic temperature factors are given in Table III. The interatomic distances and angles in this structural model of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$ are listed in Table IV. The coordinates, temperature factors, bond distances and bond angles for the split-atom model are given in supplementary Tables. A list of observed and calculated structure factors is also available as supplementary material from the editor.

NMR-spectroscopy

^{1}H-NMR spectra of D_2O (or CD_3OD) solutions were recorded on Bruker WM-300 and JEOL PS-100 spectrometers. Tetramethylsilane (TMS) was used as an internal chemical shift reference.

Results and Discussion

Crystal and Molecular Structure

A drawing of the coordination cation is depicted in Fig. 1, together with the labelling system. Only the structure of the averaged model is discussed here. The platinum ion is square planar coordinated by four nitrogens of the bpe ligand and the dmdap ligand. Relevant distances and angles are given in Table IV. The Pt–N distances are in the range usually observed for square planar coordinated Pt(II) amine compounds. The Pt–N(bpe) distance of 2.025(5) Å is almost identical to the only other Pt–bpe compound, where the distance is 2.017(5) Å [1]. The Pt–N(dmdap) distance of 2.039(5) is slightly larger than the value of 2.022(4) Å reported earlier for Pt(dmdap) malonate [5]. All C–C and C–N distances in bpe and in dmdap have values that are similar to

TABLE II. Coordinates of the Non-Hydrogen Atoms of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$ with Standard Deviations in Parentheses (Averaged Model).

Atom	x	y	z
Pt	0.00969(7)	0.25	0.15400(3)
N1	−0.0465(3)	0.3582(3)	0.0430(5)
N2	0.0704(3)	0.1469(4)	0.2659(5)
C1	−0.1420(4)	0.3436(4)	0.0044(6)
C2	−0.1529(5)	0.25	−0.0756(8)
C3	−0.2591(6)	0.25	−0.1096(9)
C4	−0.1043(6)	0.25	−0.2055(8)
C5	0.1368(4)	0.0941(5)	0.2100(7)
C6	0.1864(4)	0.0259(5)	0.2822(8)
C7	0.1662(5)	0.0132(6)	0.4138(8)
C8	0.0976(5)	0.0682(6)	0.4723(7)
C9	0.0506(5)	0.1356(5)	0.3961(7)
C10	−0.0275(6)	0.1943(5)	0.4506(8)
Cl	0.09141(12)	0.43547(14)	−0.17632(18)
Ow	0.2019(5)	0.25	−0.0564(8)

those found earlier in other Pt–Bpe and Pt–Dmdap compounds [1, 5]. As mentioned above, the disorder in the ethylene bridge (C 10 and C 10′) can also be described by a split-atom model. Space-filling molecular models show that both extremes of the structure are equally likely. The origin for this flexible structure almost certainly is the 7-membered chelate ring formed by Pt and bpe. The pyridine rings definitely allow some motion of the ethylene bridge without disturbing the structure. The twist angles of the pyridine rings from the coordination plane PtN_4 are both 67.9° (Cf. 62.5 and 69.4° in (9-Me-HX)$_2$](NO_3)$_2$; 9-MeHX = 9-methylhypoxanthine [1]).

TABLE IV. Selected Interactomic Distances (Å) and Angles (Deg) of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$.

Pt–N1	2.039(5)	N2–C5	1.354(8)
Pt–N2	2.025(5)	C5–C6	1.398(10)
N1–C1	1.500(7)	C6–C7	1.393(12)
C1–C2	1.532(8)	C7–C8	1.406(11)
C2–C3	1.542(12)	C8–C9	1.395(10)
C2–C4	1.564(12)	C9–C10	1.523(11)
		C9–N2	1.375(9)
		C10–C10′	1.509(10)
N1–Pt–N2′	90.3(2)	Pt–N2–C5	117.2(4)
N1–Pt–N2	177.3(2)	Pt–N2–C9	121.9(4)
N2–Pt–N2′	87.3(2)	C9–N2–C5	120.7(5)
N1–Pt–N1′	92.0(2)	N2–C5–C6	121.2(6)
		C5–C6–C7	118.5(7)
Pt–N1–C1	116.6(3)	C6–C7–C8	120.4(7)
N1–C1–C2	114.2(5)	C7–C8–C9	118.7(7)
C1–C2–C1′	111.8(5)	C8–C9–N2	120.4(6)
C1–C2–C3	106.5(5)	N2–C9–C10	117.7(6)
C3–C2–C4	108.6(6)	C10–C9–C8	121.8(6)
C4–C2–C1	111.6(5)	C9–C10–C10′	121.5(7)

The six-membered chelate ring of Pt and dmdap forms a chair conformation, not flattened at the PtN_2 end, similar to Pt(dmdap)(malonate) [5]. Taking N1, Cl, N1′ and Cl′ as a square, Pt is 0.87 Å above the plane and C2 is 0.72 Å below the plane.

Apart from the hydrogen bonding (*vide infra*) the packing in the molecule shows no unusual features. A stereo drawing is given in Fig. 2.

Hydrogen Bonding

The cations and the anions are held together with water molecules in the lattice, through N–H···Cl

TABLE III. Anisotropic Temperature Factors[a] ($Å^2$) of the Non-Hydrogen Atoms of [Pt(dmdap)(bpe)]$Cl_2 \cdot H_2O$ with Standard Deviations in Parentheses (Averaged Model).

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Pt	1.84(1)	1.57(1)	1.62(1)	0	0.29(1)	0
N1	2.2(2)	1.6(2)	2.0(2)	0.0(2)	0.0(2)	0.1(2)
N2	2.6(2)	1.7(2)	2.3(2)	−0.1(2)	−0.5(2)	−0.2(2)
C1	2.5(2)	1.6(2)	2.1(3)	0.2(2)	−0.1(2)	−0.3(2)
C2	2.1(3)	2.1(4)	2.0(4)	0	0.1(3)	0
C3	2.2(3)	2.7(4)	2.8(4)	0	−0.3(3)	0
C4	3.5(4)	2.6(4)	1.5(3)	0	0.6(3)	0
C5	2.4(3)	2.5(3)	3.6(3)	0.4(2)	−0.7(2)	−0.7(2)
C6	3.2(3)	2.8(3)	4.4(4)	0.1(2)	−1.4(3)	−0.2(3)
C7	3.8(3)	2.9(3)	5.1(4)	−1.2(3)	−2.3(3)	0.5(3)
C8	5.2(4)	3.1(3)	3.2(3)	−1.5(3)	−1.7(3)	0.8(3)
C9	4.1(3)	2.2(3)	2.4(3)	−1.3(3)	−0.2(2)	0.2(2)
C10	7.1(5)	3.1(4)	6.1(5)	−0.4(3)	4.2(4)	0.1(3)
Cl	4.54(8)	3.00(7)	3.94(9)	−1.36(6)	2.12(7)	−1.32(7)
Ow	5.4(4)	12.2(8)	2.8(4)	0	1.1(3)	0

[a] The anisotropic temperature factors are defined as: $\exp[-0.25(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$.

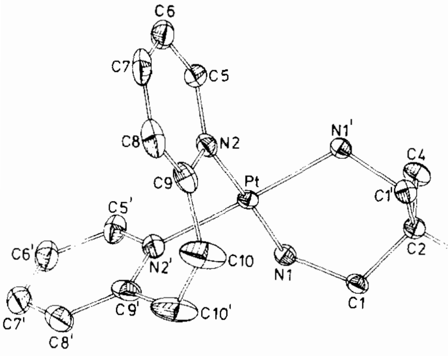

Fig. 1. ORTEP drawing of the cation $[Pt(dmdap)(bpe)]^{2+}$ and the atomic labelling system used. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted.

and O–H···Cl hydrogen bonds. Each Cl^- ion is surrounded by three protons, coming from water and two amines. The water molecule binds to two chlorides, whereas each proton of the amine binds to one chloride ion. These interactions are indicated by dotted bonds in Fig. 2. Relevant information is given in Table V. Compared with other N–H···Cl and O–H···Cl distances, the hydrogen bond interaction can be considered to be of intermediate strength. In the case of strong hydrogen bonding one would expect N···Cl distances below 3.10 Å and O···Cl distances below 3.05 Å [7].

TABLE V. Hydrogen Bond[a] Information of $[Pt(dmdap)(bpe)]Cl_2 \cdot H_2O$.

Hydrogen bond	N(O)···Cl Distances (Å)	Angles	
N1–H···Cl	3.230(5)	Cl···N1···Cl'	98.6(1)
N1–H···Cl'	3.185(5)	Pt···N1···Cl	110.9(2)
Ow–H···Cl	3.253(5)	Pt···N1···Cl'	118.7(2)
		Cl···N1···Cl	118.1(3)
		N1···Cl···N1'	81.4(1)
		N1···Cl···Ow	79.2(1)
		N1'···Cl···Ow	128.6(2)
		Cl···Ow···Cl'	101.2(2)

[a] No attempts were undertaken to locate the proton positions (see experimental part).

NMR Spectrum

The proton NMR spectrum of the title compound has been obtained in aqueous solution, as well as in $MeOH-d_4$ at various temperatures at 100 and 300 MHz. A typical spectrum is given as Fig. 3. The assignments of the several peaks are based on earlier work [1]. From the spectrum it is evident that:

– Both protons of the CH_2 groups in the ethylene bridge are in a different chemical environments, due to the rigid conformation of the Pt–bpe chelate, resulting in a shift difference of the Hα and Hβ protons of ≈ 0.9 ppm.

– Satellites due to the coupling of ^{195}Pt with H6 (observed only at 100 MHz) are hardly seen at 300 MHz. This effect has been attributed to anisotropic terms in the coupling [8].

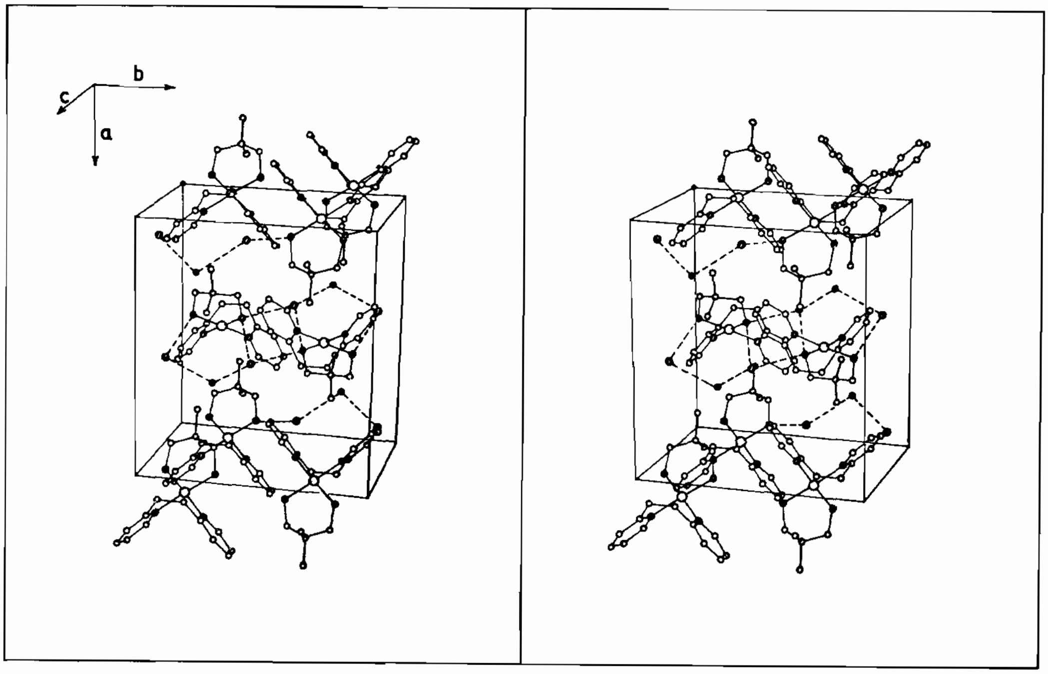

Fig. 2. Stereo drawing of the crystal packing in $[Pt(dmdap)(bpe)]Cl_2 \cdot H_2O$. Hydrogen bonds are indicated by dotted lines.

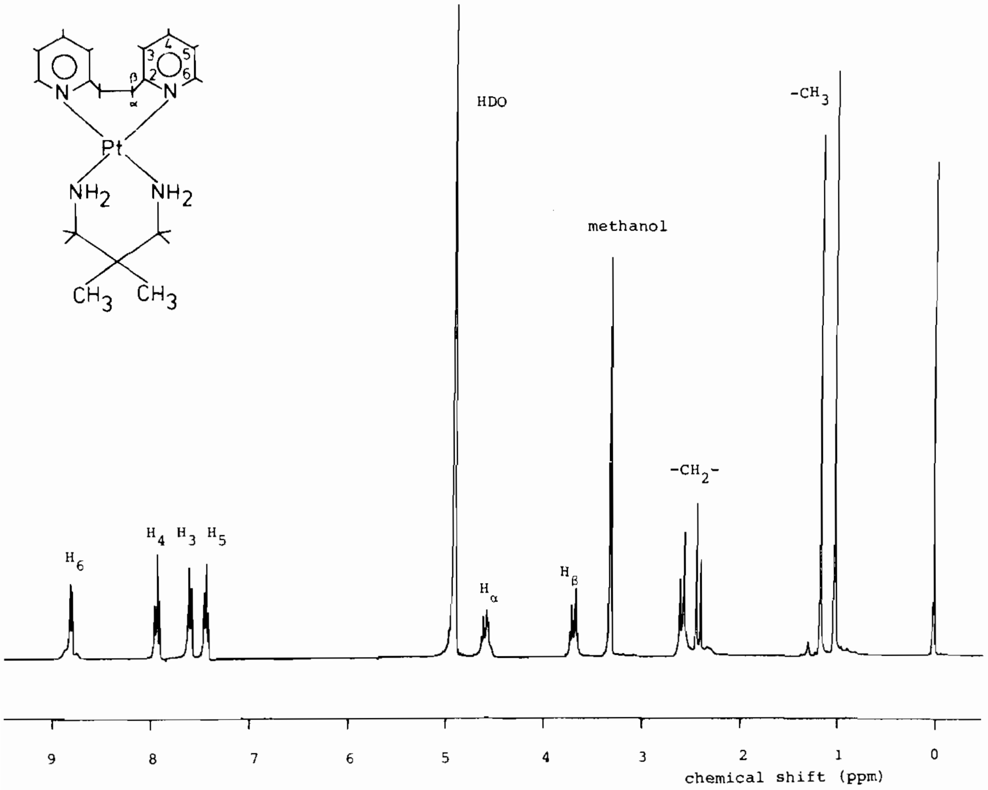

Fig. 3. 300 MHz NMR spectrum of Pt(dmdap)(bpe)$Cl_2 \cdot H_2O$ in CD_3OD at 65 °C. Assignments are given in the figure. The chemical shift is calibrated on TMS.

– Due to the rigid conformation of the Pt–bpe chelate the ring groups of the dmdap ligand are now diastereotopic, and two different CH_3 signals are observed at about 1 ppm. The protons of the $-CH_2$ groups in dmdap are also diastereotopic and give rise to the AB pattern observed at about 2.5 ppm.

None of these signals change upon heating to 90 °C, indicating no decomposition or coalescence. Upon cooling the spectrum remains essentially unchanged; only the chemical shifts of both CH_3 signals change slightly to higher field. Since the Pt dmdap chelate is known to be flexible even at low temperatures, the fact that no broadening or splitting of the CH_3 resonances is observed confirms that even at −90° in CD_3OD the interconversion between the two possible chair conformations is fast on the NMR time scale.

Concluding Remarks

The results described in the present study have shown that:

1. 1,2-bis(pyridine-2-yl)-ethane(bpe) is a very useful ligand for the introduction of asymmetry in *cis*-Pt(II) compounds.

2. Although the ligand bpe forms a rigid chelate with Pt(II), even at −115° the ethylene bridge shows some motional disorder.

3. Even at −90 °C in CD_3OD the interconversion between the possible chair conformations of the Pt–dmdap chelate is still fast on the NMR time scale.

4. Hydrogen bonding of the NH_2 groups of the amine ligands influences the crystal packing. It is interesting to note that this hydrogen bonding seems to be a basic requirement for the anti-tumor activity of *cis*-Pt(amine)$_2^{2+}$ compounds. Such hydrogen bonding may also play a significant role by binding of the drug to DNA and/or other molecules inside the tumor cell [4, 5].

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Supplementary Material

Tables of observed and calculated structure factors, atomic coordinates and bond lengths, and distances obtained with a split-atom model, are all available from the editor.

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