Inorganica Chimica Acta, *190* (1991) 285–289

Metal-stabilized rare tautomers of nucleobases

3. (1-Methylthyminato-*N3*)(1-methylthymine-*N3*)-*cis*-diammineplatinum(II) hemihexachloroplatinate(IV) dihydrate

Oliver Renn, Bernhard Lippert*
Fachbereich Chemie, Universität Dortmund, D-4600 Dortmund (FRG)
and Alberto Albinati*
Istituto Chimico Farmaceutico della Università di Milano, I-20131 Milan (Italy)

(Received March 27, 1991, revised September 2, 1991)

Abstract

The crystal structure of *cis*-$[(NH_3)_2Pt(1\text{-}MeT)(1\text{-}MeTH)][PtCl_6]_{0.5}\cdot 2H_2O$, where 1-MeTH = neutral 1-methylthymine, $C_6H_8N_2O_2$, and 1-MeT is the corresponding anion, is reported. The compound contains both heterocyclic bases bound to Pt via the N3 positions, with the neutral 1-MeTH protonated at 04. It hence represents the rare enol tautomeric structure of this nucleobase. The compound crystallizes in the space group $P2_1/n$ with cell dimensions $a = 11.814(4)$, $b = 13.270(3)$, $c = 14.738(3)$ Å, $\beta = 74.02(2)°$, $Z = 4$.

Introduction

The proper tautomeric structure of a nucleobase and the *anti* conformation of the base about the glycosyl bond are basic requirements for the correct storage of genetic information [1]. Metal ions are known to affect the structure and function of nucleic acids [2] and there are many reports that metal ions and/or metal coordination compounds are mutagenic [3]. The mechanisms by which these metals exercise their mutagenic effects are still speculative. One feasible way of achieving base mispairing is a shift in tautomer equilibrium as a consequence of metal coordination to a nucleobase. In two previous reports [4, 5] we have provided structural evidence for metal-stabilized rare tautomers and speculated on the possible biological relevance. As a follow-up to a paper dealing with the spectroscopy of the rare 2-oxo-4-hydroxo form of 1-methylthymine (1-MeTH) platinated at the N3 position [6] we herewith report on the X-ray structure of (1-methylthyminato-*N*3)-(1-methylthymine-*N3*)-*cis*-diammineplatinum(II) hemihexachloroplatinate(IV) which contains the neutral nucleobase in its unusual tautomeric form.

Experimental

Preparation

cis-$(NH_3)_2Pt(1\text{-}MeT)_2\cdot H_2O$ was prepared according to a modified version of a previously published procedure [7] as follows. *cis*-$(NH_3)_2PtCl_2$ was reacted with slightly less than the stoichiometric amount of $AgNO_3$ to prepare *cis*-$[(NH_3)_2Pt(H_2O)_2](NO_3)_2$. 2.5 Equiv. of 1-methylthymine and 2 equiv. of NaOH were added and the resulting mixture (0.15 M based on Pt) was kept in a stoppered flask for 3 days at 70 °C. The resulting solution wa filtered (occasionally very small amounts of Pt^0 are present) and brought to pH ≈ 6 with 1 N HNO_3. The solution was concentrated by rotary evaporation to a very small volume, the precipitate then filtered off and stirred in excess MeOH. After 3 days *cis*-$(NH_3)_2Pt(1\text{-}MeT)_2\cdot H_2O$ was filtered and washed with a few ml of icewater and acetone (yield 80%). According to its ^1H NMR spectrum, the product is free of 1-MeTH. Recrystallization from H_2O yields colorless columns of an *n*-hydrate (*n* = ?) which rapidly loses part of the water when in air and then analyzes as a 2.5-hydrate [7].

The title compound was prepared by reacting 0.3 mmol of *cis*-$(NH_3)_2Pt(1\text{-}MeT)_2\cdot H_2O$ in 6 ml H_2O with 0.3 mmol of Na_2PtCl_6. After filtration from yellow *cis*-$[(NH_3)_2Pt(1\text{-}MeT)_2Na](PtCl_6)_{0.5}$ the acidic solution (pH ≈ 2) was allowed to crystallize at 4 °C

---

*Authors to whom correspondence should be addressed.

0020-1693/91/$3.50

by slow evaporation. Orange single crystals were isolated in 32% yield. *Anal.* Calc. for $[(NH_3)_2Pt(1\text{-}MeT)(1\text{-}MeTH)][PtCl_6]_{0.5} \cdot 2H_2O$: C, 19.26; H, 3.36; N, 11.23. Found: C, 19.00; H, 3.30; N, 11.10%.

Crystallography

A polyhedral crystal was mounted on a glass fiber at random orientation on an Enraf-Nonius CAD4 diffractometer for the unit cell and space group determination and for the data collection. Unit cell dimensions were obtained by least-squares fit of the 2ϑ values of 25 high order reflections ($9 \leqslant \vartheta \leqslant 15°$) using the CAD4 centering routines. Selected crystallographic and other relevant data are listed in Table 1.

Data were measured with variable scan speed to ensure constant statistical precision on the collected intensities; no significant variation in the intensities was detected by monitoring 3 standards every hour. Data have been corrected for Lorentz and polarization factors and for adsorption using azimuthal (ψ) scans of three reflections ($\chi > 85.4$; $12.7 < \vartheta < 18.5°$). The standard deviations on intensities were calculated in terms of statistics alone; an $F_o = 0.0$ was given to those reflections having negative net intensities.

The structure was solved by a combination of Patterson and Fourier methods and refined by full matrix least-squares [8] (the function minimized was $[\Sigma w(|F_o| - 1/k|F_c|)^2]$). No extinction correction was applied.

The scattering factors used, corrected for the real and imaginary parts of the anomalous dispersion were taken from the literature [9]. Anisotropic temperature factors were used for all but the hydrogen atoms. The contribution from the hydrogen atoms in their idealized positions (C–H = 0.95 Å, $B = 5.0$ Å^2) was taken into account but not refined.

Upon convergence (no parameter shift $> 0.2\sigma(p)$) the Fourier difference map showed no significant feature.

To check the possibility that due to the pseudobinary axis through atoms N3 and C6 of both rings, atoms N1 and C5, O2 and O4 could be interchanged, both possible models were refined, using isotropic temperature factors for the above mentioned atoms. For both refinement R, R_w and the *GOF* were the same, while the B_{iso} for the atoms N1A, N1B, C5A, C5B were 4.8(3), 5.1(3), 1.8(2), 2.1(2) Å^2, respectively, for the model reported in Table 2 and 2.9(2), 3.2(3), 3.2(2) and 3.5(2) Å^2 for the other. In this context we note that: (i) even though the latter model gives a more uniform distribution of values for the thermal factors, the differences between the B parameters of the atoms in the ring obtained from the refinement of the first model (e.g. in Table 2 the values of B_{eq} for C4B and C5B: 2.9(3) and 2.2(3) Å^2, respectively) are, at the best, only marginally significant; (ii) static disorder caused by the presence of both head–head and head–tail arrangements of the two rings with respect to 1-MeT (cf. Fig. 1) would also affect the thermal parameters of C5 and N1. Thus an unambiguous differentiation between the two orientations of the rings is not possible using the diffraction data alone.

TABLE 1. Experimental data for the X-ray diffraction study of *cis*-$[(NH_3)_2Pt(1\text{-}MeT)(1\text{-}MeTH)][PtCl_6]_{0.5} \cdot 2H_2O$

Formula	$C_{12}H_{25}Cl_3O_6N_6Pt_{1.5}$
Molecular weight	748.34
Crystal dimensions (mm)	0.10 × 0.15 × 0.40
Data collection T (°C)	23
Crystal system	monoclinic
Space group[a]	$P2_1/n$
a (Å)	11.814(4)
b (Å)	13.270(3)
c (Å)	14.738(3)
β (°)	74.02(2)
V (Å^3)	2221.3
Z	4
ρ (calc.) (g cm^{-3})	2.229
μ (cm^{-1})	99.35
Radiation	Mo Kα (graphite monochromated $\lambda = 0.71069$ Å)
Measured reflections	$\pm h$, $+k$, $+l$
ϑ range (°)	$2.20 < \vartheta < 25.0$
Scan type	$\omega/2\vartheta$
Scan width (°)	$1.20 + 0.35 \tan \vartheta$
Max. counting time (s)	70
Background time (s)	0.5* scan-time
Max. scan speed (° min^{-1})	10.5
Prescan rejection limit	0.55 (1.8 σ)
Prescan acceptance limit	0.03 (33.3 σ)
Horizontal receiving slit (mm)	$1.80 + \tan \vartheta$
Vertical receiving slit (mm)	4.0
No. independent data collected	3891
No. observed reflections (n_o) ($|F_o|^2 > 2.0\sigma(|F|^2)$)	2386
Transmission factors	0.6011–0.9930
No. parameters refined (n_v)	259
R[b]	0.035
R_w[c]	0.042
GOF[d]	1.256

[a] The $P2_1/n$ space group may be converted to $P2_1/c$ by the transformation matrix: [1 0 −1; 0 1 0; 0 0 −1]. [b] $R = \Sigma||F_o| - 1/k|F_c||/\Sigma|F_o|$. [c] $R_w = [\Sigma w|F_o| - 1/k|F_c|)^2/\Sigma w|F_o|^2]^{1/2}$ where $w = [\sigma^2(F_o)]^{-1}$ and $(F_o) = [\sigma^2(I) + f^2(F_o^4)]^{1/2}/2F_o$ with $f = 0.045$. [d] $GOF = [\Sigma w(|F_o| - (1/k)|F_c|)^2/(n_o - n_v)]^{1/2}$.

All calculations were carried out by using the SDP crystallographic package [8]. Final atomic coordinates and thermal factors are given in Table 2. See also 'Supplementary material'.

TABLE 2. Final positional coordinates and isotropic equivalent thermal factors (Å^2) for *cis*-[$(NH_3)_2$Pt(1-MeT)(1-MeTH)][$PtCl_6$]$_{0.5}\cdot 2H_2O$

Atom	x	y	z	B (Å^2)
Pt1	0.11644(4)	0.11009(3)	0.06465(3)	2.267(8)
Pt2	0.000	0.500	0.000	2.83(1)
Cl1	0.0982(4)	0.4162(3)	0.0930(3)	6.1(1)
Cl2	0.0816(4)	0.3892(3)	−0.1209(3)	5.7(1)
Cl3	−0.1600(3)	0.3953(3)	0.0567(3)	4.45(8)
O2A′	0.0301(8)	−0.0451(7)	0.2246(6)	3.8(2)
O2B′	0.1762(7)	−0.1039(6)	−0.0145(6)	3.3(2)
O4A′	0.2852(8)	0.2214(7)	0.1589(6)	3.9(2)
O4B′	0.3658(7)	0.1947(6)	−0.0142(6)	3.7(2)
N1A	0.247(1)	0.147(1)	0.3083(8)	5.0(3)
N1B	0.469(1)	0.065(1)	−0.1088(9)	5.2(3)
N3A	0.1572(8)	0.0878(7)	0.1889(6)	2.4(2)
N3B	0.2700(8)	0.0465(7)	−0.0136(6)	2.4(2)
N10	0.0712(8)	0.1370(8)	−0.0581(7)	3.1(2)
N11	−0.0377(8)	0.1789(8)	0.1390(7)	3.3(2)
C1A′	0.322(1)	0.223(1)	0.3381(9)	3.6(3)
C1B′	0.576(1)	0.132(1)	−0.147(1)	5.3(4)
C2A	0.098(1)	0.0136(8)	0.2479(9)	3.0(3)
C2B	0.267(1)	−0.0516(9)	−0.0430(8)	2.8(3)
C4A	0.228(1)	0.1506(9)	0.2163(8)	3.0(3)
C4B	0.366(1)	0.107(1)	−0.0435(7)	2.9(3)
C5A	0.1192(9)	0.0033(8)	0.3353(7)	1.9(2)
C5A′	0.058(1)	−0.078(1)	0.3987(9)	4.1(3)
C5B	0.3703(9)	−0.0922(8)	−0.1023(8)	2.2(2)
C5B′	0.369(1)	−0.197(1)	−0.132(1)	5.5(4)
C6A	0.187(1)	0.068(1)	0.3651(9)	3.5(3)
C6B	0.466(1)	−0.034(1)	−0.139(1)	3.9(3)
OW1	−0.2088(9)	−0.0243(9)	0.2224(8)	6.5(3)
OW2	−0.119(1)	0.1425(8)	0.3597(8)	6.1(3)

Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as: $(4/3)[a^2B(1,1)+b^2B(2,2)+c^2B(3,3)+ab(\cos\gamma)B(1,2)+ac(\cos\beta)B(1,3)+bc(\cos\alpha)B(2.3)]$.

Results

Figure 1 provides a view of the cation of the title compound, *cis*-[$(NH_3)_2$Pt(1-MeT)(1-MeTH)]$^+$. Interatomic distances and angles are listed in Table 3. The coordination sphere of Pt is square-planar with minor deviations from the ideal case. Rings a and b refer to the neutral 1-MeTH ring and the anionic 1-MeT, respectively. Because of the pseudo-twofold axis of 1-methylthymine, a rigorous differentiation of atoms at the 1 and 5 as well as 2 and 4 positions is not unambiguous (see preceding discussion in 'Experimental'). However, we assign the atom denoted O(4a′) as the site of protonation for the following reasons. First, in the related 1-methyluracil system O4 is protonated initially [5] and in all cases of metal binding [10] except with *trans*-$(NH_3)_2$Pt(1-MeU)$_2$ [11], O4 appears to be distinctly more basic than O2. We are aware that the crystallographic evidence is indeed insufficient to prove this point beyond doubt. Second, the C(4a)–O(4a′) distance of 1.32(1) Å is significantly longer (5–7σ) than any of the other CO bond lengths and therefore clearly indicates protonation of the carbonyl oxygens O(4a′). Other bond lengths and angles do not differ significantly in the two rings. They are also similar to those in closely related 1-methylthymine complexes [12]. The orientation of the anionic 1-MeT ring b in Fig. 1 is head-to-head with respect to 1-MeTH (a) and follows the finding in the 1-MeU/1-MeUH system as crystallographically there is no way of differentiating a head–head from a head–tail arrangement. The geometry of the $PtCl_6^{2-}$ anion is normal [5].

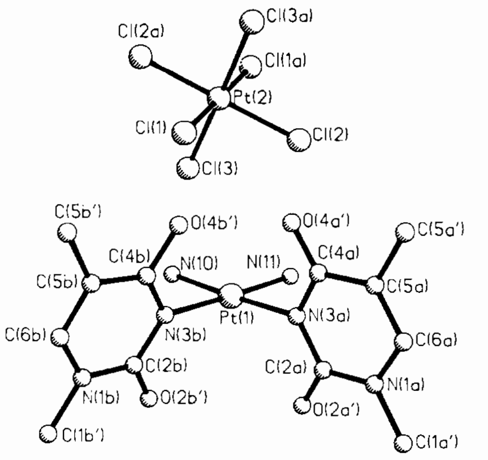

Fig. 1. View of *cis*-[$(NH_3)_2$Pt(1-MeTH)(1-MeT)]$^+$ cation and [$PtCl_6$]$^{2-}$ anion with atom numbering scheme.

As expected, there is a short (2.49(1) Å) intramolecular hydrogen bond between O(4b′) and the protonated O(4a′) atom of the 1-MeTH ring. The molecular packing is dictated by a complex network of hydrogen bonds involving both intermolecular interactions between the NH_3 groups and the oxygen atom O(2b′), NH_3 and water, as well as the two water molecules (Table 4). Only weak interactions may be assumed between the [$PtCl_6$]$^{2-}$ anion and the water molecules (3.3–3.5 Å).

Spectroscopic data (^{1}H NMR, UV, IR) of the title compound are closely similar to those of the corresponding Cl^-, NO_3^- and ClO_4^- salts [6]. Likewise, the solution behaviour (cleavage of the Pt–N(3) bond of the 1-MeTH ligand) confirms our earlier findings.

A recent observation [13] on base pairing between two thymines in the crystal of a hairpin hexadecanucleotide has tentatively been interpreted as occurring between the rare enol and the preferred dioxo tautomer of thymine. It seems to confirm our previous speculation [5, 6] that a rare thymine tautomer might be sufficiently long lived to accomplish

TABLE 3. Interatomic distances (Å) and angles (°) in the title compound

Pt coordination sphere			
Pt(1)–N(10)	2.065(9)	N(11)–Pt(1)–N(3b)	177.5(4)
Pt(1)–N(11)	2.056(9)	N(3a)–Pt(1)–N(3b)	93.1(3)
Pt(1)–N(3a)	2.041(9)	N(10)–Pt(1)–N(11)	89.2(4)
Pt(1)–N(3b)	2.048(9)	N(10)–Pt(1)–N(3a)	177.8(3)
		N(10)–Pt(1)–N(3b)	88.9(3)
		N(11)–Pt(1)–N(3a)	88.9(3)
Thymine ligands			
	Ring a	Ring b	
N(1)–C(1′)	1.46(2)	1.49(1)	
N(1)–C(2)	1.43(2)	1.44(2)	
C(2)–O(2′)	1.23(1)	1.25(1)	
C(2)–N(3)	1.33(1)	1.36(1)	
N(3)–C(4)	1.37(1)	1.38(1)	
C(4)–O(4′)	1.32(1)	1.24(1)	
C(4)–C(5)	1.39(2)	1.40(1)	
C(5)–C(6)	1.33(2)	1.35(1)	
C(6)–N(1)	1.40(2)	1.39(2)	
C(5)–C(5′)	1.48(1)	1.46(2)	
C1′–N1–C6	125.0(11)	121.5(12)	
C1′–N1–C2	120.8(11)	119.1(10)	
C6–N1–C2	119.1(10)	119.3(11)	
O2′–C2–N1	116.8(11)	121.2(11)	
O2′–C2–N3	120.4(11)	121.2(11)	
N1–C2–N3	122.8(11)	117.5(11)	
Pt1–N3–C2	120.6(8)	118.1(8)	
Pt1–N3–C4	118.0(7)	118.1(7)	
C2–N3–C4	121.0(10)	123.3(10)	
O4′–C4–N3	122.3(11)	121.0(10)	
O4′–C4–C5	119.7(10)	121.1(10)	
N3–C4–C5	118.0(10)	117.9(10)	
C4–C5–C6	121.5(10)	121.1(10)	
C5–C6–N1	122.4(11)	120.4(11)	
C4–C5–C5′	118.6(10)	118.3(10)	
C6–C5–C5′	119.8(10)	120.2(10)	
Anion			
Pt2–Cl1	2.312(4)	Cl1–Pt2–Cl2	88.9(2)
Pt2–Cl2	2.310(4)	Cl1–Pt2–Cl3	89.4(1)
Pt2–Cl3	2.312(3)	Cl2–Pt2–Cl3	91.3(1)
		Cl1–Pt–Cl2 (a)	91.1(2)
		Cl1–Pt–Cl3 (a)	90.5(1)
		Cl2′–Pt–Cl3 (a)	88.7(1)

Chlorine atoms labelled (a) are related to the others in the cation by the symmetry operation: $\bar{x}$, $1-y$, $\bar{z}$.

mispairing, e.g. with a guanine, thereby causing a premutagenic lesion. While a mutation mechanism involving a metalated thymine nucleobase is a rather unlikely event for *cis*-$(NH_3)_2PtCl_2$ [14], metals with a more pronounced affinity for T–N(3) might very well make use of such a pathway. The advantage of applying Pt(II), however, is in slow kinetics of the ligand displacement reaction which permits the isolation of species containing rare tautomers.

TABLE 4. Some hydrogen bond distances (Å) in the title compound

Cl2–OW1*	3.40(1)	(a)
Cl3–OW1*	3.38(1)	(b)
O4a′–O4b′	2.49(1)	
O4b′–OW2*	2.83(1)	(a)
O2a′–OW1	2.85(1)	
O2b′–N10*	2.86(1)	(c)
O2b′–N11*	2.95(1)	(c)
N10–OW1*	2.93(1)	(c)

Starred atoms are related to those unstarred by the symmetry operations given in parentheses: (a) $\frac{1}{2}-x$; $\frac{1}{2}+y$; $-\frac{1}{2}-z$; (b) $x-\frac{1}{2}$; $\frac{1}{2}-y$; $\frac{1}{2}+z$; (c) $-x$; $-y$; $-z$.

Supplementary material

Lists of calculated and observed structure factors and of anisotropic displacement parameters may be obtained from the authors upon request.

Acknowledgements

This work has been supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Degussa (loan of K_2PtCl_4). A.A. acknowledges partial financial support from M.U.R.S.T., Italy.

References

1 (a) M. D. Topal and J. R. Fresco, *Nature (London), 263* (1976) 285, 189; (b) W. Saenger, *Principles of Nucleic Acid Structure,* Springer, New York, 1984.

2 (a) G. L. Eichhorn, in G. L. Eichhorn and L. G. Marzilli (eds.), *Metal Ions in Genetic Information Transfer,* Elsevier, New York, 1981, p. 1; (b) T. G. Spiro (ed.), *Nucleic Acid–Metal Ion Interactions,* Wiley, New York, 1980.

3 (a) A. Furst, *Adv. Med. Biol., 91* (1978) 1; (b) C. P. Flessel, A. Furst and S. B. Radding, *Met. Ions Biol. Syst., 10* (1980) 23; (c) L. A. Loeb and R. A. Zakour, in T. G. Spiro (ed.), *Nucleic Acid–Metal Ion Interactions,* Wiley, New York, 1980, p. 116.

4 B. Lippert, H. Schöllhorn and U. Thewalt, *J. Am. Chem. Soc., 108* (1986) 6616.

5 H. Schöllhorn, U. Thewalt and B. Lippert, *J. Am. Chem. Soc., 111* (1989) 7213.

6 B. Lippert, *Inorg. Chim. Acta, 55* (1981) 5.

7 B. Lippert and D. Neugebauer, *Inorg. Chim. Acta, 46* (1980) 171.

8 *Enraf-Nonius Structure Determination Package (SDP),* Enraf-Nonius, Delft, Netherlands, 1980.

9 *International Tables for X-ray Crystallography,* Vol. IV, Kynoch, Birmingham, UK, 1974.

10 B. Lippert, *Prog. Inorg. Chem., 37* (1989) 1.

11 (a) I. Dieter, B. Lippert, H. Schöllhorn and U. Thewalt, *Z. Naturforsch., Teil B, 45* (1990) 731; (b) H. Schöllhorn, U. Thewalt and B. Lippert, *J. Chem. Soc., Chem. Commun.,* (1984) 769.

12 (a) O. Renn, B. Lippert, H. Schöllhorn and U. Thewalt, *Inorg. Chim. Acta, 167* (1990) 123; (b) H. Schöllhorn, U. Thewalt and B. Lippert, *Inorg. Chim. Acta, 106* (1985) 177.

13 R. Chattopadhyaya, S. Ikuta, K. Grzeskowiak and R. E. Dickerson, *Nature (London), 334* (1988) 175.

14 (a) D. Burnouf, C. Gauthier, J. C. Chottard and R. P. P. Fuchs, *Proc. Natl. Acad. Sci. U.S.A., 87* (1990) 6087; (b) D. Burnouf, M. Daune and R. P. P. Fuchs, *Proc. Natl. Acad. Sci. U.S.A., 84* (1987) 3758.