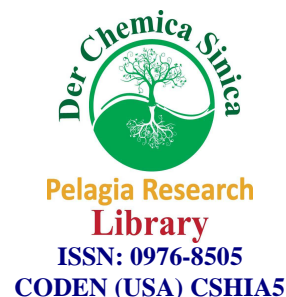




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### Interaction of cis-[Pt(DMSO)<sub>2</sub>Cl<sub>2</sub>] with nucleic acid constituents

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#### ABSTRACT

Complexes of types [Pt(DMSO)(Cl)(nucl-H)], have been synthesized and characterized by elemental and thermal analyses, electronic, infrared, <sup>1</sup>H NMR spectral and single crystal XRD studies. The nucleobases act as anionic bridging bidentate ligand through N3 and N9. The single crystal XRD studies revealed the dimeric nature in Pt (DMSO)(Cl)(CH<sub>3</sub>-tmn-H) with a Pt-Pt distance of 2.96Å.

**Keywords:** Metal-nucleobase complexes, TG, Electronic, NMR, IR and XRD measurements

#### INTRODUCTION

It has been well established that certain platinum and palladium complexes are of biological importance due to their carcinogenic activity. Pd(II) complexes are moderately labile, while those of Pt(II) are inert<sup>1-3</sup>. The X-ray structures of the complexes [Pt(en)Cl(tmn-H)]<sup>4</sup> and [Pt<sub>2</sub>(NH<sub>3</sub>)<sub>4</sub>(CH<sub>3</sub>-tmn)<sub>2</sub>]<sup>5</sup> showed that the thyminato anion coordinates through N1 to platinum to the former and N3 to the latter. In [{Pd(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]ado]Cl<sub>2</sub> a bridging mode of coordination of adenosine through N1 and N7 to palladium has been observed<sup>6</sup>. The <sup>1</sup>H NMR studies on the interaction of Pt(II) with nucleic acid derivatives are useful mainly in elucidating the binding site of the nucleobases in the Pt(II) complexes. The <sup>1</sup>H NMR spectra of [Pt(NH<sub>3</sub>)<sub>3</sub>(CH<sub>3</sub>-ade)] X<sub>2</sub>, X=Cl, ClO<sub>4</sub> and of trans [Pt(NH<sub>3</sub>)<sub>3</sub>(OH)<sub>2</sub>(CH<sub>3</sub>-ade)] X<sub>2</sub> indicated that N7 of CH<sub>3</sub>-ade is coordinated to Pt(II) as evidenced by the coupling between H8 of the adenine ring and <sup>195</sup>Pt.

cis-[Pt(DMSO)<sub>2</sub>Cl<sub>2</sub>] is not an antitumour compound but it was worth comparing the reaction mechanism of the two complexes cis-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] and cis-[Pt(DMSO)<sub>2</sub>Cl<sub>2</sub>] with nucleic acid derivatives in order to understand the variations in the antitumour activities of the platinum compounds. The present note reports the synthesis and characterization of the complexes of Pt(II) with nucleic acid derivatives.

#### MATERIALS AND METHODS

Nucleic acids and potassium tetrachloroplatinate used were commercially available samples. The complex cis-Pt(DMSO)<sub>2</sub>Cl<sub>2</sub> was prepared by reported method. The elemental analyses were carried out using Heraeus CHN-O-RAPID analyser. Thermoanalytical studies were made on a Stanton simultaneous thermal analyses instrument (model 781) in static air at a heating rate of 100C/min. The infrared and electronic spectra were recorded on Shimadzu IR-470 and UV-3100 spectrophotometers respectively. The <sup>1</sup>H NMR data were obtained on a JEOL JNM-JSX 400 MHz spectrometer at room temperature in DMSO-d<sub>6</sub> with TMS as the external reference. Single Crystal X-ray diffraction studies has been carried out using Enraf Nonius CAD4 Diffractometer.

Dichlorobis(dimethylsulphoxide)bis(6-chloroguaninato-N3,N9) diplatinum (II)  $[\text{Pt}(\text{DMSO})(\text{Cl})(\text{Cl-gua-H})]_2$  cis- $[\text{Pt}(\text{DMSO})_2\text{Cl}_2]$  (1.0 mmol in 15 ml of  $\text{H}_2\text{O}$ ) aqueous solution is added to the solution containing Cl-gua (1.0 mmol in 30 ml of  $\text{H}_2\text{O}$ ) with constant stirring for 12h. The precipitated complex is filtered, washed with hot water, acetone and air-dried. The complexes of dichlorobis(dimethylsulphoxide)bis(1methylthyminato-N3,S2)diplatinum(II),  $[\text{Pt}(\text{DMSO})(\text{Cl})(\text{CH}_3\text{-trmn-H})]$  was prepared by the reaction of  $[\text{Pt}(\text{DMSO})_2\text{Cl}_2]$  with the pyrimidines nucleobase,  $\text{CH}_3\text{-trmn}$  gave yellow coloured complex,  $[\text{Pt}(\text{DMSO})(\text{Cl})(\text{CH}_3\text{-trmn-H})]_2$ . The better yield and good quality of the product are achieved by adjusting the PH of the solution to 9.0 with 0.1 M KOH.

## RESULTS AND DISCUSSION

### Platinum(II) Complexes with DMSO and Nucleobase

The complexes are insoluble in water and in common organic solvents like acetone, alcohol, chloroform and benzene. However, they are soluble in DMSO and DMF while the complex of 6-thioguanine is very sparingly soluble in DMSO and that of N6-benzyl adenine is completely insoluble in DMSO. The nucleoside complexes 6 and 7 show a molar conductance of ca.  $96 \text{ ohm}^{-1}\text{cm}^2$  in  $10^{-3}\text{M}$  concentration suggesting them in Table 1 to be 1:2 electrolytes. The magnetic measurements suggest that all the complexes are diamagnetic as expected for square planar platinum(II).

Table :1 Analytical and Conductivity Data

S.No.	Complexes	C%	H%	N%	Cl%	Pt%	Molar conductance $\text{ohm}^{-1}\text{cm}^2$
1	$[\text{Pt}(\text{Me}_2\text{SO})(\text{Cl})(\text{C}_6\text{H}_5\text{CH}_2\text{-ade-H})]$	31.55 (32.24)	2.08 (3.10)	13.15(13.38)	6.65 (7.06)	36.61(37.17)	-
2	$[\text{Pt}(\text{me}_2\text{SO})(\text{Cl})(\text{Cl-gua-H})]$	17.62 (16.29)	2.11 (1.98)	14.68(13.92)	7.43 (8.23)	40.88(40.81)	4
3	$[\text{Pt}(\text{Me}_2\text{SO})(\text{Cl})(\text{S-gua-H})]$	17.71 (18.23)	2.12 (2.32)	14.75(13.69)	7.47 (7.66)	41.18(41.78)	-
4	$[\text{Pt}(\text{ME}_2\text{SO})(\text{Cl})(\text{S-uril-H})]$	21.31 (17.80)	3.39 (2.15)	6.94(6.64)	6.29 (8.12)	34.63(31.29)	3
5	$[\text{Pt}(\text{Me}_2\text{SO})(\text{Cl})(\text{CH}_3\text{-trmn-H})]$	16.02 (15.90)	2.91 (3.23)	6.23(6.11)	7.88 (7.66)	43.37(42.81)	8
6	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}]_2\text{ado}]\text{Cl}_2$	19.45 (19.22)	3.52 (3.29)	6.30(5.77)	12.76(11.86)	35.09(34.50)	96
7	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}]_2\text{ado}]\text{Cl}_2$	18.21 (18.42)	3.11 (3.10)	6.21(5.97)	11.88(12.18)	34.03 (32.91)	97

Table 2 IR Spectral Data of the Complexes of Pt(II) with DMSO and Nucleobases ( $\text{cm}^{-1}$ )

S.No.	Complexes	$\nu_{\text{NH}_2}$	$\nu_{\text{C=O}}$	$\delta_{\text{NH}_2}$	$\nu_{\text{C=C}}$	$\nu_{\text{C=N}}$ $\nu_{\text{C=N}}$ (Pyrimidine)	$\nu_{\text{C=N}}$ $\nu_{\text{C=N}}$ (Imidazole)	$\nu_{\text{NH}}$	$\nu_{\text{NH}}$	$\nu_{\text{NH}}$	$\nu_{\text{NH}}$
1	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{C}_6\text{H}_5\text{CH}_2\text{-ade-H})]$	3350 s 3230 s	1110 s	-	-	1574 m 1510 m 1399 m	1334 sh 1300 w	360 m	520 m	343 w	-
2	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{Cl-gua-H})]$	3290 s 3180 s	1110 s	1665 sh	-	1570 m 1491 w 1395 m	1330 sh 1290 w	365 m	525 m	340 m	-
3	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{s-gua-H})]$	3290 s 3180 s	1115 s	1660 sh	-	1590 sh 1459 sh 1402 m	1331 sh 1290 w	360 m	520 m	340 w	-
4	$[[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{s-uril-H})]$	3104 s	1115 s	-	1670 s	1490 m 1420 m 1350 m	--	360 m	525 m	340 w	412 w
5	$[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{CH}_3\text{-trmn-H})]$	3008 s	1117 s	-	-	1488 m 1417 m 1373 m	--	365 m	520 m	343 w	410 w
6	$[[\text{Pt}(\text{Me}_2\text{SO})_2\text{Cl}]_2\text{ado}]\text{Cl}_2$	3350 s 3230 sh	1110 sh	1665 sh	1665 sh	1591 m 1540 m	1450 m 1305 m	360 m	530 m	345 m	-
7	$[[\text{Pt}(\text{Me}_2\text{SO})_2\text{Cl}]_2\text{Cl-guo}]\text{Cl}_2$	3320 s 3190 sh	1110 sh	1665 sh	1665 sh	1590 m 1575 m 120 m	1448 m 1330 s	365 m	528 m	340 m	-

s - strong, sh - shoulder, m - medium, w - weak

Table 3 Crystal Data and Structure refinement for  $[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{CH}_3\text{-tmn-H})_2]$ 

Molecular Formula	$[\text{Pt}(\text{Me}_2\text{SO})\text{Cl}(\text{CH}_3\text{-tmn-H})_2]$
Formula Weight	895.61
Temperature	293(2)K
Wavelength	0.71073Å
Crystal system	Monoclinic
Space group	C2/C
Unit cell dimensions	$a=16.671(3)$ , $b=7.8151(12)$ and $c=19.512(3)$ Å
Volume	$\alpha = 90$ , $\beta = 104.36$ , $\gamma = 90^\circ$
Z	$2462.8(8) \text{ \AA}^3$
Calculated Density	4
Absorption coefficient	$2.415 \text{ mg/m}^3$
F(000)	$11.774 \text{ mm}^{-1}$
Crystal size	1680
Theta range for data collection	$0.2 \times 0.1 \times 0.1 \text{ mm}$
Index ranges	$2.15 \text{ to } 24.98^\circ$
Reflections collected	$0 \leq h \leq 19, 0 \leq k \leq 9, -23 \leq l \leq 22$
Independent reflections	2239
Absorption correction	$2159 (R(\text{int}) = 0.0341)$
Maximum and minimum transmission	Psi scan
Refinement method	0.996 and 0.256
Data/restraints/parameters	Full-matrix least-squares on $F^2$
Goodness-of-fit on $F^2$	2159/0/146
Final R indices [ $>2 \text{ sigma}(I)$ ]	1.118
R indices	$R1 = 0.0291$ , $wR2 = 0.0694$
Extinction coefficient	$R1 = 0.0398$ , $wR2 = 0.0788$
Largest difference peak and hole-	$0.00007(4)$
	$1.248 \text{ and } -0.672 \text{ e. \AA}^{-3}$

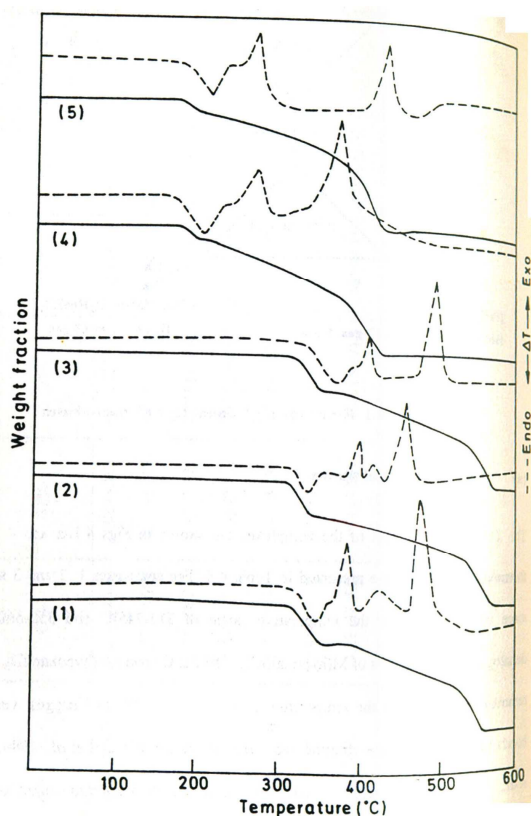


Figure : 1 Thermo Analytical Data Studies

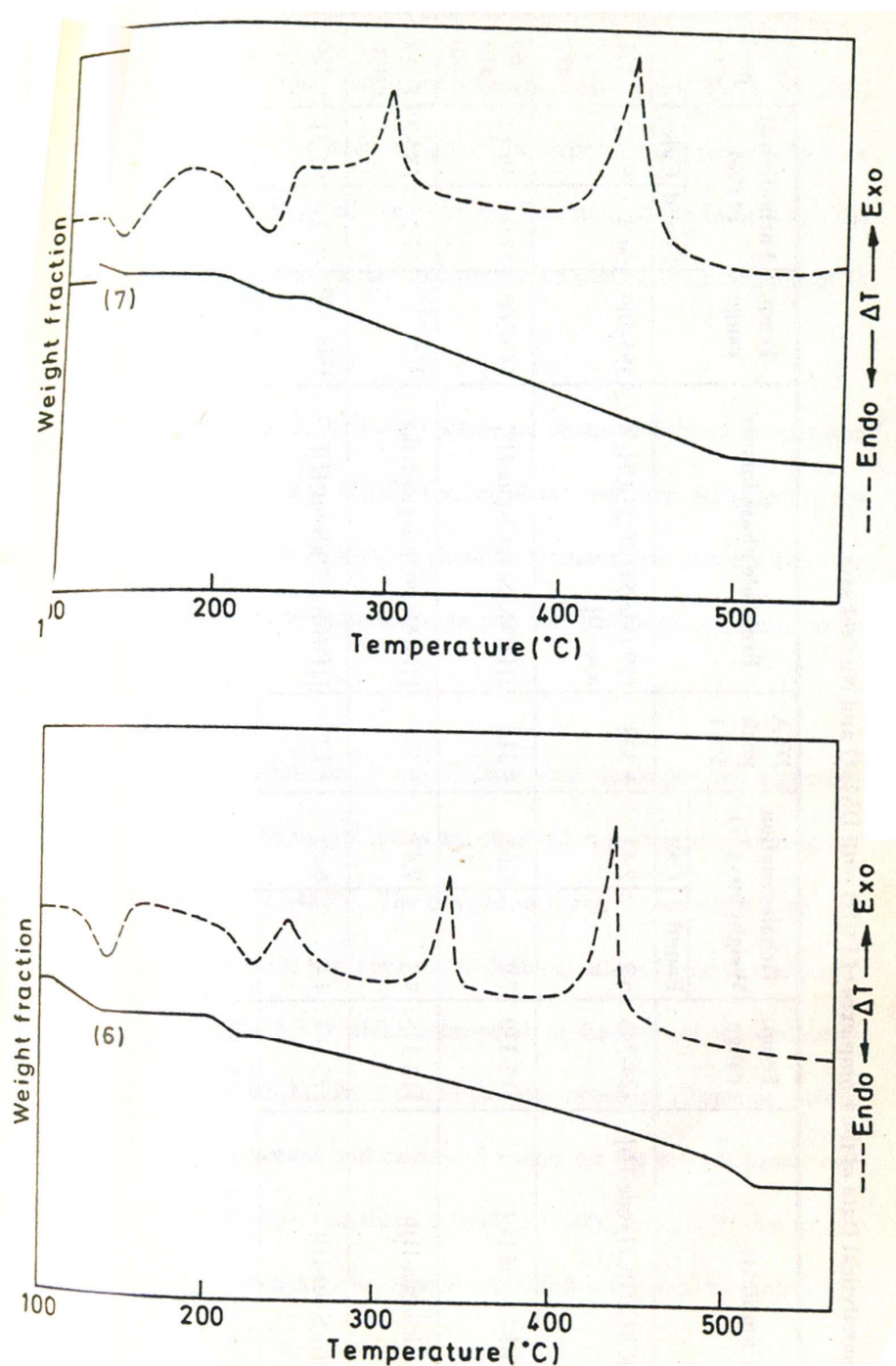


Figure : 2 and 2 (A) Thermo Analytical Data Studies

#### Thermoanalytical studies

The TGA and DTA plots showed that the complexes 1, 2 and 3 show two stage weight losses in the temperature range of 315-345°C and 350-560°C. The dehalogenation processes of  $M(\text{hypoxan})\text{Cl}_2$ ;  $M=\text{Pd, Cu}$  and  $\text{Rh}(\text{hypoxan})\text{Cl}_3$  show the removal of chloride in the temperature range 235 to 350°C and suggest very strong bonds between palladium-chlorine and rhodium-chlorine<sup>7</sup>. In the present study, the complexes 1, 2 and 3 undergo weight

loss of 6.2, 7.0 and 8.3% of the initial mass by 345<sup>o</sup>C respectively and is attributed to the removal of a chloride moiety, as the calculated weight loss for the dehalogenation process are 7.43, 6.65 and 7.47% respectively. This is further confirmed by endothermic peaks observed at 328, 315 and 320<sup>o</sup>C in their DTA plots. The organic moieties in the complexes undergo oxidative decomposition in air as suggested by the observed exothermic peak maxima. The final residues obtained around 550<sup>o</sup>C are found to be 35.1, 42.1 and 42.8% of the initial weight of the respective complexes which are in good agreement with the calculated values for the formation of Pt.

In complexes 4 and 5, the weight losses are observed at lower temperature regions of 175 to 185<sup>o</sup>C and 190 to 420<sup>o</sup>C. The calculated and observed weight loss around 185<sup>o</sup>C corresponds to the removal of chloride and the final residue is found to be platinum.

Complexes 6 and 7, three step decomposition pattern is observed in the TG curves. The weight losses are observed in the temperature range of 110-130<sup>o</sup>C, 200-215<sup>o</sup>C and 220-480<sup>o</sup>C. The weight losses are respectively 5.3 and 6.2% of the initial mass in the first stage due to dehalogenation. In the second stage, the weight loss observed is ca. 5.3% which corresponds to the removal of coordinated chloride. The third stage of weight loss is due to the decomposition of organic moiety leading to Pt metal. Both observed and calculated values for the process agree well. The DTA plots show endothermic peaks at 110<sup>o</sup>C and 210<sup>o</sup>C due to the removal of ionic and coordinated chloride respectively which is followed by exothermic peak maxima around 430<sup>o</sup>C for the oxidative decomposition.

#### Electronic and infrared spectral studies

In all the complexes, the absorption bands around 280 nm and 340 nm are assigned to  $\pi \rightarrow \pi^*$  transition of the nucleobase<sup>8</sup> and  $d \rightarrow d$  transition of Pt(II) respectively, the latter suggesting a square planar geometry around the metal.<sup>9</sup>

The infrared spectra of the complexes and the principal spectral frequencies with the probable assignments are given in Table 2. The imidazole ring frequencies (1415, 1330 and 1305  $\text{cm}^{-1}$ ) and pyrimidine ring frequencies (1600 and 1445  $\text{cm}^{-1}$ ) in the spectrum of  $\text{C}_6\text{H}_5\text{CH}_2\text{-ade}$  are shifted by 30  $\text{cm}^{-1}$  in its complex. The vibrational frequencies around (1600, 1540, 1480, 1430 and 1370  $\text{cm}^{-1}$ ) of free nucleobases, Cl-gua and S-gua are also shifted by about 35  $\text{cm}^{-1}$  in the spectra of the complexes. Thus, the larger negative shift of frequencies due to pyrimidine and imidazole moieties indicate the deprotonation of NH9 and the involvement of N3 and N9 nitrogens in coordination<sup>10</sup> to the metal. The ring vibrational frequencies  $\nu_{\text{C=N}}$  and  $\nu_{\text{C=C}}$  vibrations undergoes shift suggesting N1 and N7 as the probable binding sites[. In the S-ur1 complex, the ring vibrational frequencies and thiocarbonyl bands underwent negative shift indicating N1/N3 and sulfur coordination to the metal. In the methyl thymine complex, the  $\text{NH}_2$  frequency at 1665 $\text{cm}^{-1}$  in the spectrum of free ligand appears at 1648 $\text{cm}^{-1}$  in its complex indicating the deprotonation of HN3 and coordination N3 to platinum [II]. The ring stretching frequency vibrations are shifted to lower wave numbers suggesting N3 coordination to platinum(II).

#### <sup>1</sup>H NMR spectral studies

The <sup>1</sup>H NMR spectra of the complexes having free solubility in DMSO showed that a three bond coupling satellites of the methyl proton resonances due to the <sup>195</sup>Pt. Thus the magnitude of coupling constant value is 32.1 Hz for Cl-gua, 29.8 Hz for ad, 29.7 Hz for CH<sub>3</sub>-tmm and S-ur1 complexes suggest that sulfur atom of DMSO is coordinated to platinum.

The <sup>8</sup>H proton of the Cl-gua undergo downfield shift by 0.23 ppm suggesting coordination through N9 or N7. The HN9 signal is observed at 2.0 ppm in the free Cl-gua and it disappears after complexation. Thus, absence of the signal confirms the coordination has occurred through N9 Site. These results suggest two alternate possibilities of binding of Cl-gua either through N9 and N1 or N9 and N3. However, it is suggested that N9 and N3 nitrogens of Cl-gua are bonded in the bridging fashion to two platinum (II) centres because of steric factors. In the CH<sub>3</sub>-tmm N3 site is used for coordination to the metal. In the S-ur1 complex the broadening of H5 and H6 resonance in the spectrum are probably due to formation of polymeric and dimeric complex. A downfield shift of 0.2 ppm of H2 and H8 indicates coordination of adenosine to metal through N1 and N7.

#### Crystal and molecular structure of dichlorobis(dimethylsulphoxide)bis(-1-methylthyminato-N3,O2) diplatinum(II)

The crystal data and structure refinement parameters for the complex are given in Table 3. The ORTEP plot of the complex is given in Fig.2. The final R-factor is 2.9%.

The structure consists of dimeric  $[\text{Pt}(\text{DMSO})(\text{Cl})(\text{CH}_3\text{-tmn-H})]_2$  unit with platinum (II) bonded through S of DMSO and chloro ligand. The methylthymine anion bridges two platinum (II) centres through N3 and O2 thus satisfying square planar geometry around each platinum (II). The Pt-ligand bond distances vary from 2.041 Å (Pt-N3, shortest) to 2.291 Å (Pt-Cl, longest). The angles at platinum vary from the smallest 88.4° (N-Pt-O) to the largest 92.6° (N-Pt-S). The O-Pt-S and N-Pt-C are 171.9 and 175.0° respectively. The C-N and C-C bond distances and the corresponding bond angles in the thymine group are all of expected values.

In the structure, half of the molecule forms the crystallographic asymmetric unit. The two halves are related through a two-fold rotation axis. The geometry around the metal atom is almost square planar with the sum of the angles around Pt as 359.76°. The Pt atom is 0.0894 Å out of the mean plane formed by N3, O2, Cl and S atoms. The ring atoms C2, N1, C6, C5, C4, N3 of 1-methylthymine are nearly planar, whereas the exocyclic atoms C7(0.063 Å), C8 (-0.1213 Å), O4 (-0.0399 Å), O2 (-0.1246 Å) are considerably out of the ring plane. However, the Pt metal atom is in the plane of the ring.

The Pt-S bond length (2.189 Å) is slightly shorter than the average value (2.21 Å) reported for Pt-DMSO complexes<sup>11</sup>. Rochon and his co-workers suggested that the Pt-S bond which is located in trans position to the Pt-O (CH<sub>3</sub>-tmn) bond is slightly shorter than normal, indicating a greater p-character of the Pt-S bond. The Pt-Cl, Pt-N, Pt-O bond lengths (2.291 Å,

2.041 Å and 2.061 Å) are normal<sup>12</sup>. The ligand CH<sub>3</sub>-tmn acts as anionic bidentate bridging ligand in the complex. It bridges two Pt atoms through N3 and O2 atoms. Two dimethyl sulphoxide molecules bonded to platinum through S, are in trans positions to the CH<sub>3</sub>-tmn oxygen atoms while the chloride ligands are trans to the CH<sub>3</sub>-tmn nitrogen atoms. The dimer is found to be in a head-to-tail manner with Pt...Pt distance of 2.956 Å. A comparison of Pt...Pt distances of similar dimeric platinum(II) complexes are listed in Table 4.16. The values range from 2.898 to 3.083 Å and in all those cases, there is no direct Pt-Pt bonding. The distance of 2.956 Å found in the present complex is thus not to be considered as resulting from Pt-Pt interactions.

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