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Coordination Chemistry of 7,9-Disubstituted 6-Oxopurine Metal Compounds. 5. Electrostatic Potential Energy Distributions for 7,9-Dimethylhypoxanthine and 7,9-Dimethylguanine and Preparation and Structure of *trans*-Diamminebis(7,9-dimethylhypoxanthine)platinum(II) Nitrate Dihydrate¹

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The synthesis, ¹H NMR spectrum, and molecular and crystal structure of *trans*-diamminebis(7,9-dimethylhypoxanthine)platinum(II) nitrate dihydrate, *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O, are reported. The compound crystallizes in the monoclinic system, space group *P*2₁/*n*, with *a* = 15.859 (10) Å, *b* = 12.913 (6) Å, *c* = 6.107 (3) Å, β = 96.74 (3)°, *V* = 1242.0 Å³, *Z* = 2 (based on a molecular weight of 717.5 for [Pt(NH₃)₂(C₇N₄H₈O)₂](NO₃)₂·2H₂O), *D*_{calcd} = 1.92 g cm⁻³, and *D*_{measd} = 1.91 (2) g cm⁻³. The structural model was obtained by conventional Patterson and Fourier methods and refined by full-matrix least-squares techniques to an *R* value of 0.038. The *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ complex cation is centrosymmetric, and the primary coordination sphere is, therefore, planar. Principal geometric parameters are as follows: Pt-N(amine) = 2.046 (4) Å; Pt-N(1)(7,9-Dmhyp) = 2.035 (3) Å; N(amine)-Pt-N(1) angles 90.1 (1) and 89.9 (1)°; base/PtN₄ coordination plane dihedral angle = 77.9°. The relatively large base/PtN₄ dihedral angle may in part be due to the presence of a weak Pt...O(6) axial interaction of 3.086 (4) Å. The molecular dimensions of the 7,9-Dmhyp ligand are in excellent agreement with those reported previously. The crystal structure exhibits an extensive network of hydrogen bonds as well as electrostatic interactions. The ¹H NMR spectrum of the coordinated 7,9-Dmhyp ligand in this *trans* cation is compared to that for the free base and some other of its complexes with platinum(II). Electrostatic potential energy maps have also been computed for the modified purines 7,9-dimethylhypoxanthine and 7,9-dimethylguanine under the INDO molecular orbital approximation. These computations indicate a broad electrostatic minimum in the N(1)/O(6) cleft of these purine bases. Comparison of these results with those for their pyrimidine analogues clearly shows that the well depths for the purines are about 20 kcal mol⁻¹ more attractive. However, such differences show only small structural manifestations.

Introduction

The numerous solution and solid-state investigations of complexes formed between nucleic acid constituents and *cis*-A₂Pt^{II} cationic moieties, where A is NH₃ or A₂ is a bidentate chelate such as ethylenediamine (en) or trimethylenediamine (tn), reflect the high level of interest directed toward a detailed knowledge of the mode of action of *cis*-Pt antitumor agents.³ These metallo antineoplastic drugs are believed to act by binding to the bases of DNA in such a way as to induce one or more different kinds of "defects" which cancer cells may find difficult or impossible to repair. The paucity of information on the corresponding *trans* analogues is undoubtedly due to their inactivity as antitumor agents, although the *trans* compounds are known to be mutagenic and can apparently readily form metal-mediated interstrand cross-links in polynucleotides and possibly protein-metal-nucleic acid ternary systems.⁴

While there is probably much less information of biochemical significance to be gleaned from model studies based on *trans*-bis(nucleic acid base)platinum(II) compounds than from their *cis* analogues, such systems are not completely devoid of interest, particularly from a stereochemical point of view. Consequently, we have synthesized the compound *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O, where 7,9-Dmhyp is the modified purine 7,9-dimethylhypoxanthine. We have previously utilized such modified bases in our studies on metal binding at the six-membered pyrimidine site N(1) of the purine framework.¹ In this report, the structural and ¹H NMR

Table I. Crystal Data for

trans-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O

| | |
|----------------------------------|--|
| <i>a</i> = 15.859 (10) Å | [Pt(NH ₃) ₂ (C ₇ N ₄ H ₈ O) ₂](NO ₃) ₂ ·2H ₂ O |
| <i>b</i> = 12.913 (6) Å | space group <i>P</i> 2 ₁ / <i>n</i> |
| <i>c</i> = 6.107 (3) Å | mol wt = 717.53 |
| β = 96.74 (3)° | <i>D</i> _{measd} = 1.91 (2) g cm ⁻³ |
| <i>V</i> = 1242.0 Å ³ | <i>D</i> _{calcd} (<i>Z</i> = 2) = 1.92 g cm ⁻³ |

spectroscopic properties of the *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ cation are compared with those of the closely related [Pt(en)(7,9-Dmhyp)₂]²⁺ cation,^{1b,5} where the purine bases are in *cis* positions. The former complex can be thought of as a model for a *trans* N(1)_{5'-IMP}-Pt-N(1)_{5'-IMP} cross-link, while the latter can be considered as a model for a *cis* N(1)_{5'-IMP}-Pt-N(1)_{5'-IMP} lesion.

In addition, we have computed some of the electronic properties, including in-plane electrostatic potential energy distributions and molecular dipole moments, for the 7,9-disubstituted 6-oxopurines 7,9-Dmhyp and 7,9-Dmgua (7,9-dimethylguanine) (Figure 1). This is part of a continuing program to correlate the physical and chemical properties of alkylated nucleobases with their electronic structures.⁶⁻⁸

Experimental Section

Preparation. A suspension of *trans*-[Pt(NH₃)₂Cl₂]⁹ in H₂O was allowed to react with 2 equiv of AgNO₃. The reaction mixture was stirred magnetically, along with gentle heating. Subsequently, the mixture was cooled and filtered through Celite and washed with a minimum amount of water. To the filtrate was added 2 equiv of 7,9-Dmhyp;¹⁰ the resulting solution was put aside to evaporate slowly. After several days, clear, colorless parallelepipeds were collected.

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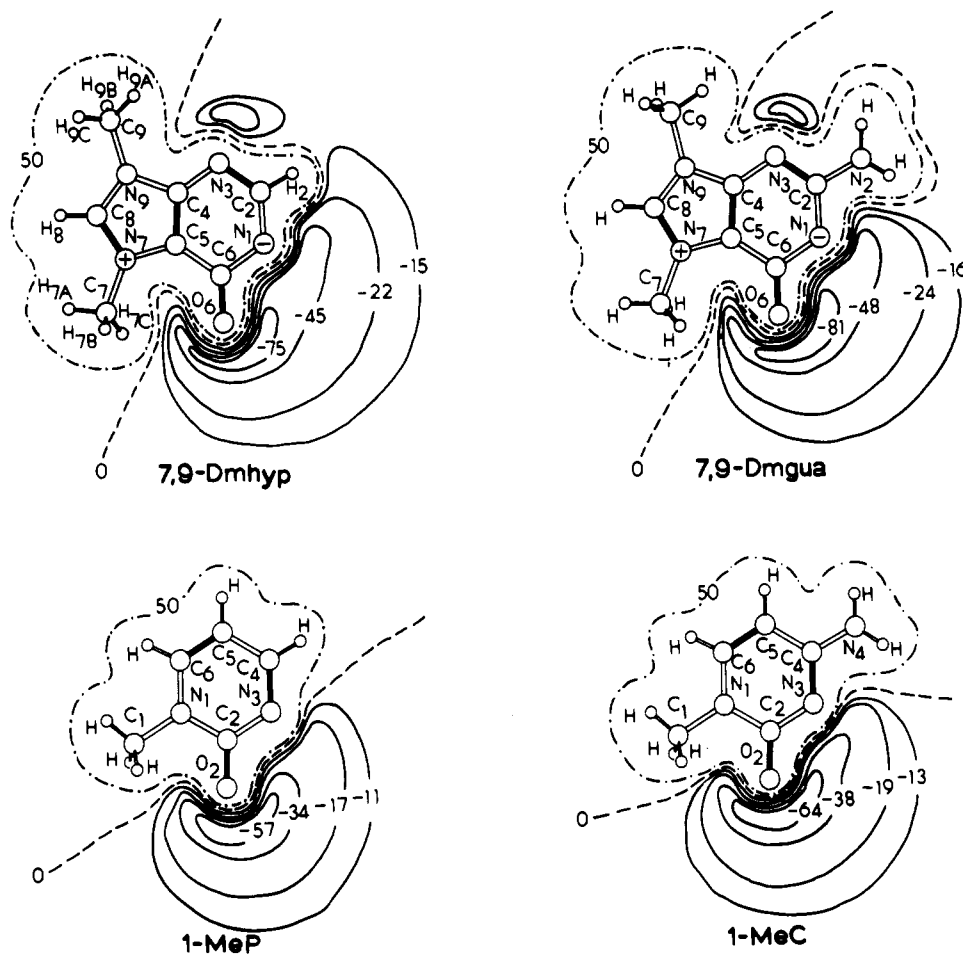


Figure 1. In-plane electrostatic potential energy distributions for the modified purine and pyrimidine bases 7,9-Dmhyp (7,9-dimethylhypoxanthine), 7,9-Dmgua (7,9-dimethylguanaine), 1-MeP (1-methyl-2-pyrimidone), and 1-MeC (1-methylcytosine). Contours are given in kcal mol⁻¹. For each base, shaded bonds indicate double bonds in the resonance form shown.

Crystal density data (CCl₄/CHBr₃, neutral buoyancy method) indicated two phases of formulation [Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·xH₂O, with $x = 1$ or 2. We have selected the dihydrate for our structural investigation.

Collection and Reduction of the X-ray Intensity Data. Oscillation and Weissenberg photography showed that the crystal class was monoclinic; space group $P2_1/n$ was indicated by systematically absent spectra ($h0l$, $h + l = 2n + 1$, and $0k0$, $k = 2n + 1$). A well-formed crystal was selected for intensity data collection and cleaved parallel to the (001) plane to give a parallelepiped with the following faces and interfacial distances: (001)–(00 $\bar{1}$), 0.25 mm; (110)–($\bar{1}\bar{1}0$), 0.19 mm; ($\bar{1}\bar{1}0$)–($\bar{1}10$), 0.15 mm. Precise unit-cell dimensions, along with their estimated standard deviations, were derived from a least-squares fit to the setting angles for 15 carefully-selected reflections on a Syntex P $\bar{1}$ automated diffractometer. The crystallographic c axis was approximately aligned along the ϕ axis of the spectrometer. Pertinent crystallographic data are collected in Table I.

Employing graphite-monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å) and the θ – 2θ scan mode with a constant scan rate of 2° min⁻¹ in 2θ , we surveyed the intensities of 4087 reflections (including measurements for three standards recorded after every 100 reflections) in the $h, k, +l$ quadrant to $2\theta = 60^\circ$. The three monitored standards showed no systematic variation over the course of the experiment. Out of a set of 3639 independent reflections, 3090 had net intensities above zero; these were assigned observational variances based on counting statistics plus a correction term of the form¹¹ $(pI)^2$, where p was chosen as 0.03.

The nonzero intensities and their estimated standard deviations were corrected for Lorentz and polarization effects and for the effect of absorption. On the basis of the above face assignments and crystal dimensions and a calculated linear absorption coefficient of 60.2 cm⁻¹, the maximum and minimum transmission factors were 0.46 and 0.35,

respectively. An approximation to the absolute scale factor was derived by the method of Wilson.¹²

Solution and Refinement of the Structure. The presence of two formula units per cell (Table I) requires the Pt atom to occupy a special position of C_2 symmetry; the inversion site at the center of the unit cell ($1/2, 1/2, 1/2$) was chosen. A Patterson synthesis was utilized to obtain coordinates for the atoms of the 7,9-Dmhyp ligand, and a subsequent structure factor–Fourier calculation allowed the location of the symmetry-independent nitrate anion and water molecule of crystallization. Several cycles of isotropic and anisotropic least-squares refinement, minimizing the quantity $\sum w(|F_o| - |F_c|)^2$, where $w = 4F_o^2/\sigma^2(F_o^2)$, gave an R value ($\sum ||F_o| - |F_c||/\sum |F_o|$) of 0.041. At this stage, a difference-Fourier synthesis yielded coordinates for all H atoms in the asymmetric unit. The isotropic thermal parameters for the H atoms were set at a value ca. 1.0 \AA^2 larger than that of the atom to which they were bonded. Two subsequent cycles of refinement, with the H atom parameters held fixed, led to convergence (maximum shift/error of 0.7) and to a final R value of 0.038. The final weighted R ($(\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$) and goodness of fit ($(\sum w(|F_o| - |F_c|)^2/(\text{NO} - \text{NV}))^{1/2}$, where NO = 3090 nonzero observations and NV = 169 variables) values were 0.039 and 1.4, respectively. A final difference-Fourier map was essentially featureless, showing a maximum peak of $1.2 e \text{ \AA}^{-3}$ near the Pt atom.

Neutral scattering curves for the non-hydrogen¹³ and the hydrogen¹⁴ atoms were taken from standard sources. Anomalous dispersion corrections were applied to the scattering curves for all non-hydrogen atoms.¹⁵ Final atomic coordinates for the nonhydrogen atoms are collected in Table II. Tables of anisotropic thermal parameters,

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Table II. Final Non-Hydrogen Atom Coordinates for *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O

| atom | x | y | z | atom | x | y | z |
|-----------------|----------|----------|----------|-------|----------|----------|------------|
| Pt ^b | 1/2 | 1/2 | 1/2 | C(5) | 2506 (3) | 4457 (3) | 1902 (6) |
| O(6) | 3697 (2) | 5379 (4) | 915 (6) | C(6) | 3360 (3) | 4824 (3) | 2226 (8) |
| N(10) | 4589 (2) | 6007 (3) | 7234 (6) | C(7) | 1834 (4) | 5381 (5) | -1568 (9) |
| N(1) | 3791 (2) | 4480 (3) | 4212 (5) | C(8) | 1179 (3) | 4111 (4) | 772 (8) |
| N(3) | 2651 (2) | 3439 (3) | 5237 (6) | C(9) | 806 (4) | 2875 (5) | 3623 (11) |
| N(7) | 1843 (3) | 4648 (3) | 277 (6) | N(40) | 4017 (4) | 1849 (5) | 11788 (9) |
| N(9) | 1374 (2) | 3586 (3) | 2612 (7) | O(41) | 4546 (3) | 1759 (5) | 13333 (9) |
| C(2) | 3432 (3) | 3828 (3) | 5537 (7) | O(42) | 3994 (3) | 2596 (4) | 10532 (8) |
| C(4) | 2210 (2) | 3791 (3) | 3378 (7) | O(43) | 3366 (5) | 1284 (5) | 11548 (11) |
| | | | | O(W) | 1998 (2) | 2222 (3) | 8847 (6) |

^a Estimated standard deviations in the least significant figures are enclosed in parentheses here and in all the following tables. ^b The Pt atom coordinates are fixed by symmetry; fractional coordinates for all other atoms have been multiplied by 10⁴.

Table III. Electrostatic Minima and Theoretical Dipole Moments for 7,9-Dmhyp, 7,9-Dmgua, 1-MeP, and 1-MeC

| molecule | electrostatic min, kcal mol ⁻¹ | Δ | location of min | calcd dipole moment, D |
|-----------|---|------|------------------------|------------------------|
| 7,9-Dmhyp | -89.5 | 21.3 | O(6)/N(1) ^a | 12.3 |
| 1-MeP | -68.2 | | O(2)/N(3) ^b | 6.7 |
| 7,9-Dmgua | -96.9 | 20.4 | O(6)/N(1) ^a | 11.7 |
| 1-MeC | -76.5 | | O(2)/N(3) ^b | 7.5 |

^a The exact location of the minimum is closer to O(6) than to N(1). ^b The exact location of the minimum is closer to O(2) than to N(2).

parameters for the hydrogen atoms, and final calculated and observed structure factor amplitudes have been deposited. The crystallographic computations were performed with a standard set of computer programs.¹⁶

¹H NMR Data. ¹H NMR spectra were recorded on a Varian CFT-20 spectrometer operating in the proton mode with use of standard Fourier transform techniques. D₂O and Me₂SO-*d*₆ were used as solvents. A spectral width of 1205 Hz, a pulse width of 15 μs, and an acquisition time of 3.4 s (8192 data points) for 125 transients were employed.

Results and Discussion

(a) Electrostatic Potential Energy Calculations. The electronic properties of the substituted 6-oxopurines 7,9-dimethylhypoxanthine and 7,9-dimethylguanine have been explored within the INDO approximate molecular orbital theory.¹⁷ From these computations, the in-plane molecular electrostatic potential¹⁸ and molecular dipole moments for these purine bases have been derived. We have also chosen to compute the electronic properties of 1-methyl-2-pyrimidone (1-MeP) and 1-methylcytosine (1-MeC) as these substituted bases are the pyrimidine analogues of 7,9-Dmhyp and 7,9-Dmgua and, thus, allow insights into the electronic effect of the fused imidazole ring of the 7,9-disubstituted purines. Moreover, 1-MeC is a commonly used base for modeling 5'-CMP metal complexes¹⁹ and 1-MeP is closely related to α-pyridone, for which the structure of a tetrameric "platinum-blau" is known.²⁰ The results of these computations are presented visually for the electrostatic potentials in Figure 1 and collected in tabular form in Table III.

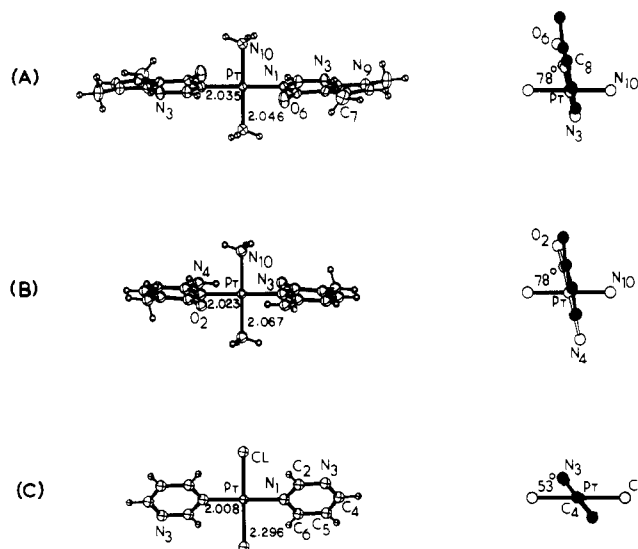


Figure 2. Molecular conformational drawings for (A) *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺, (B) *trans*-[Pt(NH₃)₂(1-MeC)₂]²⁺, and (C) *trans*-[Pt(Pyr)₂Cl₂]. For the latter two complexes, hydrogen atom positions were computed on the basis of stereochemical arguments. In each case, the illustration on the left is approximately normal to the primary coordination plane, and the illustration on the right is parallel to the Pt-N vector of the base (only one ligand is shown as for each case the trans base is required to be parallel by symmetry).

First, it is noted that the calculated molecular dipole moments for the substituted purines are on the order of twice those for the substituted pyrimidines (Table III). This is not particularly surprising as there are several resonance forms that can be written for the 7,9-disubstituted purines (one of which is illustrated in Figure 1) that involve substantial charge separation between the imidazole and the pyrimidine rings.¹⁰ Second, and important to their relative coordinating strengths,⁶⁻⁸ it is found that, while all four bases exhibit molecular electrostatic potentials that show broad attractive regions near N(1)/O(6) for the purines or N(3)/O(2) for the pyrimidines, the well depths for the purines are about 20 kcal mol⁻¹ deeper than for the pyrimidine analogues. It is to be expected then, all else being equal, that electrophiles will have a greater affinity for the N(1)/O(6) regions of the 7,9-disubstituted purine bases than for the N(3)/O(2) regions of the pyrimidines examined here.

(b) Molecular Geometry of the *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ Cation. A projection of the *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ cation viewed along the normal to the coordination plane is presented in Figure 2A. The complex cation is centrosymmetric, which requires that the primary coordination sphere be planar. The four coordination sites are occupied by the N(1) atoms of two *trans* 7,9-Dmhyp ligands (which are arranged in a parallel head-to-tail fashion) and by the N atoms of two amines. The plane of the 7,9-Dmhyp

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Table IV. Molecular Geometry for *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O

(a) Primary Coordination Sphere about the Pt Atom

| Bond Lengths, Å | | | |
|------------------|-----------|----------------|-----------|
| Pt-N(1) | 2.035 (3) | Pt-N(10) | 2.046 (4) |
| Bond Angles, Deg | | | |
| N(10)-Pt-N(1) | 90.1 (1) | N(10')-Pt-N(1) | 89.9 (1) |

(b) 7,9-Dimethylhypoxanthine Base

| Bond Lengths, Å | | | |
|------------------|-----------|----------------|-----------|
| N(1)-C(2) | 1.341 (6) | N(7)-C(8) | 1.325 (6) |
| N(1)-C(6) | 1.393 (6) | N(9)-C(4) | 1.380 (6) |
| N(3)-C(2) | 1.329 (6) | N(9)-C(8) | 1.318 (6) |
| N(3)-C(4) | 1.340 (6) | N(9)-C(9) | 1.471 (7) |
| N(7)-C(5) | 1.381 (6) | O(6)-C(6) | 1.241 (6) |
| N(7)-C(7) | 1.470 (7) | C(4)-C(5) | 1.369 (6) |
| | | C(5)-C(6) | 1.426 (6) |
| Bond Angles, Deg | | | |
| Pt-N(1)-C(2) | 121.3 (3) | N(1)-C(2)-N(3) | 127.5 (4) |
| Pt-N(1)-C(6) | 117.0 (3) | N(3)-C(4)-N(9) | 127.4 (4) |
| C(2)-N(1)-C(6) | 121.7 (4) | N(3)-C(4)-C(5) | 125.9 (4) |
| C(2)-N(3)-C(4) | 111.9 (4) | N(9)-C(4)-C(5) | 106.7 (4) |
| C(5)-N(7)-C(7) | 127.1 (4) | N(7)-C(5)-C(4) | 107.1 (4) |
| C(5)-N(7)-C(8) | 107.5 (4) | N(7)-C(5)-C(6) | 132.2 (4) |
| C(7)-N(7)-C(8) | 125.2 (4) | C(4)-C(5)-C(6) | 120.7 (4) |
| C(4)-N(9)-C(8) | 108.1 (4) | O(6)-C(6)-N(1) | 122.7 (4) |
| C(4)-N(9)-C(9) | 126.0 (4) | O(6)-C(6)-C(5) | 125.2 (4) |
| C(8)-N(9)-C(9) | 125.8 (4) | N(1)-C(6)-C(5) | 112.1 (4) |
| | | N(7)-C(8)-N(9) | 110.5 (4) |

base forms a dihedral angle of 77.9° to the PtN₄ coordination plane. The base/PtN₄ dihedral angle is also illustrated in Figure 2A, where the cation is viewed along the N(1)-Pt bond. Since the 7,9-Dmhyp planes are required by symmetry to be parallel, only the base nearest the viewer has been included in this latter illustration. Bond lengths and angles for the complex cation are collected in Table IV. The Pt-N atom bond lengths for *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ are also included in Figure 2, where illustrations of the other two *trans*-bis(nucleic acid base)platinum(II) complexes reported to date^{21,22} and the Pt-N bond lengths for these systems are presented as well.

The unique Pt-N(1) distance to the Dmhyp ligand of the *trans* cation of 2.035 (3) Å falls in about the middle of the range of Pt-N(1) bond lengths we have reported earlier for [Pt(en)(7,9-Dmhyp)₂]²⁺, 2.020 (5) Å,⁵ [Pt(dien)(7,9-Dmgua)]²⁺, 2.044 (5) Å,^{1a} and [Pt(dien)(7,9-Dmhyp)]²⁺, 2.051 (6) Å^{1a} (dien = diethylenetriamine). Interestingly, it is observed that the Pt-N(1) bond length in the *trans*-diammine complex is longer, by 0.015 Å (ca. 3-4σ), than that found in the *cis*-en cation. The lengthening of the Pt-N(1) bond length for the *trans* complex could indicate a stronger structural *trans* effect²³ for the N(1)-bound 7,9-Dmhyp base over that of an en ligand. This notion is buttressed by the fact that the Pt-N(en) bond length in the [Pt(en)(7,9-Dmhyp)₂]²⁺ cation of 2.059 (6) Å is slightly over 0.03 Å (5-6σ) longer than the Pt-N(en) bond lengths reported for complexes containing the N(7)-bound 6-oxopurine base 1,3,9-trimethylxanthine (2.012 (4) and 2.026 (3) Å for the nitrate salt of [Pt(en)-(1,3,9-trimethylxanthine)₂]²⁺ and 2.029 (5) Å for the unique Pt-N(en) bond length in the hexafluorophosphate salt of this same cation).²⁴ Similarly, it can be seen in Figure 2 that the Pt-N(nucleic acid base) bond lengths increase noticeably on going from *trans*-[Pt(Pyr)₂Cl₂] (2.008 (5) Å,²² Pyr = pyri-

Table V. Least-Squares Planes and the Deviation of Individual Atoms (Å) from These Planes for*trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O^{a,b}

(a) Imidazole Ring (0.3502X - 0.7761Y - 0.5244Z = -3.7289 Å)

| | | | |
|------|--------|------|---------|
| N(7) | -0.000 | C(8) | -0.001 |
| N(9) | 0.002 | C(7) | -0.107* |
| C(4) | -0.002 | C(9) | 0.052* |
| C(5) | 0.001 | | |

(b) Pyrimidine Ring (0.3812X - 0.7825Y - 0.4924Z = 3.5926 Å)

| | | | |
|------|--------|------|--------|
| N(1) | -0.015 | C(5) | -0.016 |
| N(3) | 0.014 | C(6) | 0.024 |
| C(2) | -0.004 | O(6) | 0.094* |
| C(4) | -0.003 | | |

(c) Full Purine Plane
(0.3652X - 0.7807Y - 0.5071Z = -3.6943 Å)

| | | | |
|------|--------|------|---------|
| N(1) | -0.032 | C(6) | 0.035 |
| N(3) | 0.015 | C(8) | -0.025 |
| N(7) | -0.016 | Pt | -0.119 |
| N(9) | 0.003 | O(6) | 0.108* |
| C(2) | -0.024 | C(7) | -0.145* |
| C(4) | 0.025 | C(9) | 0.054* |
| C(5) | 0.018 | | |

^a In each of the equations of the planes, X, Y, and Z are coordinates referred to the orthogonal axes *a*, *b*, and *c**. Atoms designated by an asterisk were given zero weight in calculating the planes; the atoms used to define the planes were given equal weight.

^b The primary coordination sphere, defined by the atoms Pt, N(1), N(1'), N(10), and N(10'), is required by symmetry to be exactly planar. The equation of this plane is -0.0692X + 0.6987Y - 0.7121Z = 1.8276 Å.

midine) to *trans*-[Pt(NH₃)₂(1-McC)₂]²⁺ (2.023 (8) Å)²¹ to the present *trans* 7,9-Dmhyp cation (2.035 (3) Å). Although the differences noted here are small (especially for the series of *trans* complexes of Figure 2), they parallel the expected increase in the electrostatic component of the ligand binding strength of these ligands (vide supra) and perhaps, then, an expected increase in structural *trans* effect.²⁵

In the present complex there is also a hint of a significant Pt...O(6) axial interaction, Pt...O(6) distance 3.086 (4) Å, consistent with similar distances reported for other Pt-N(1)-bound 6-oxopurine complexes, 3.07-3.14 Å,¹ and M...O(2) distances, 3.01-3.07 Å, for N(3)-bound cytosine complexes of Pt(II)²⁶ and Pd(II).²⁷ As will be suggested below, the presence of this Pt...O(6) interaction in the *trans*-7,9-Dmhyp cation may well favor the large base/PtN₄ dihedral angle of 77.9°.

(c) **Molecular Dimensions of the 7,9-Dimethylhypoxanthine Ligand and the Nitrate Anion.** Bond lengths and angles for the coordinated 7,9-Dmhyp base are compiled in Table IV. The observed values are in excellent agreement with those for the [Pt(dien)(7,9-Dmhyp)]²⁺ and [Pt(en)(7,9-Dmhyp)₂]²⁺ cations^{1a,5} and the [Cu(glycylglycinato)(7,9-Dmhyp)] complex²⁸ reported earlier. The nine-atom framework of the purine base shows a measurable degree of nonplanarity (Table V), which is typical for free and coordinated purine bases.²⁹ The dihedral angle between the highly planar five-membered imidazole ring and the six-membered pyrimidine ring (which retains a degree of nonplanarity) is 2.6°. The displacement of the Pt atom from the plane of the purine ligand is 0.12 Å

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- (25) We find a strong correlation between the well depth in the molecular electrostatic potential energy for a base and the stability (see the recent work on Pd(II) complexes by: Scheller, K. H.; Scheller-Krattiger, V.; Martin, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 6833) of its metal-nucleic acid base complexes.
 (26) See, for example: Lock, C. J. L.; Speranzini, R. A.; Powell, J. *Can. J. Chem.* **1976**, *54*, 53.
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Table VI. Distances (Å) and Angles (Deg) in the Interactions of the Type D-H...A

| D | H | D-H | A ^a | H...A | D...A | ∠D-H...A |
|-------|--------|------|--------------------|-------|-----------|----------|
| N(10) | H[100] | 0.95 | O(W) ^b | 2.04 | 2.974 (8) | 166 |
| N(10) | H[101] | 0.85 | O(6) ^c | 2.12 | 2.908 (8) | 153 |
| N(10) | H[102] | 0.90 | O(42) ^d | 2.18 | 3.073 (8) | 171 |
| O(W) | H[W1] | 0.81 | O(43) ^e | 2.17 | 2.838 (8) | 140 |
| O(W) | H[W2] | 1.00 | N(3) ^e | 2.00 | 2.990 (8) | 166 |

^a Symmetry transforms (space group $P2_1/n$) are given in the following footnotes. ^b $1/2 - x, 1/2 + y, 3/2 - z$. ^c $x, y, 1 + z$. ^d $1 - x, 1 - y, 2 - z$. ^e x, y, z .

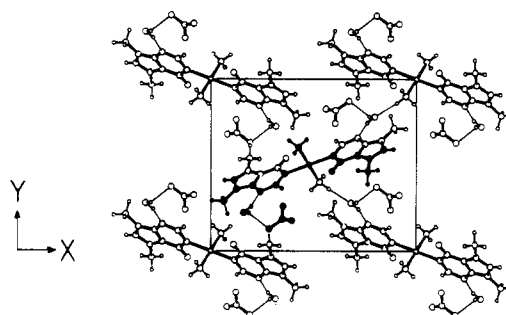
and toward the weakly bound pseudoaxial O(6) group. The deviations of the other exocyclic substituents are as expected and detailed in Table V.

The nitrate anion is relatively firmly fixed in the structure through hydrogen-bonding interactions and general electrostatic forces and shows only limited evidence of librational disorder. The average N-O bond length is 1.23 (4) Å (range 1.19–1.26 Å), and the average O-N-O bond angle is 119 (4)° (range 115–123°).

(d) Crystal Packing. The (001) projection of the extended crystal structure for *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O is presented in Figure 3. The structure is characterized by a network of hydrogen bonds involving the water molecule of crystallization, the exocyclic O(6) atom and the endocyclic N(3) atom of the 7,9-Dmhyp base, and the ammine ligands. Possible hydrogen-bonding interactions are collected in Table VI, and some of these interactions are illustrated in Figure 3. There are no interbase hydrogen bonds or base-stacking interactions in the present system, although additional crystal stability is afforded by the stacking of the nitrate anions over the plane of the coordinated purine base (Figure 3). The dihedral angle between the plane of the 7,9-Dmhyp ligand and that of the nitrate anion is 29°.

(e) Conformational Features. To our knowledge, *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ is the first *trans*-Pt(II) complex of a purine derivative to be subjected to X-ray structural analysis, although three *trans*-Pt(II) complexes with pyrimidine ligands have been structurally characterized, *trans*-[Pt(NH₃)₂(1-MeC)₂](NO₃)₂²¹ and *trans*-[Pt(Pyr)₂X₂], where X = Cl⁻ or Br⁻.²² In Figure 2, the molecular structures of these *trans* complexes are compared, with the base/coordination plane dihedral angles illustrated in the right-hand column of the figure. The dihedral angles for the 7,9-Dmhyp and the 1-MeC complexes are identical at 78°, while that for the pyrimidine complex is considerably smaller at 53°. Any attempt to rationalize the differences in the conformations of these three complexes (as well as mono(nucleic acid base)-platinum(II) systems) requires consideration of the competition between intramolecular and intermolecular forces.

A compendium of the likely intramolecular and intermolecular forces and their tendencies to favor a large or a small base/coordination plane dihedral angle is as follows: (i) *Pt...O(exocyclic) axial binding*—in isolation, this interaction is likely to prefer a large dihedral angle (close to 90°) so as

**Figure 3.** Projection of the crystal structure of *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂](NO₃)₂·2H₂O onto the (001) plane. Thin lines denote hydrogen bond interactions (see the text).

to maximize potential overlap between orbitals on the Pt center and the lone-pair density on the exocyclic oxygen atom; (ii) *interligand hydrogen bonding*—such interactions are expected to favor a small dihedral angle (50–60°) in order to minimize the distance between the donor or acceptor atom of the coordinated base and the acceptor or donor atom on an equatorial ligand of a square-planar Pt(II) system; (iii) *interligand steric effects*—when bulky ligands are present in the primary coordination sphere or bulky substituents appear as functional groups on the coordinated base, unfavorable interligand interactions will almost certainly favor a dihedral angle near 90°; (iv) *crystal packing forces*—in solids, the presence of specific intermolecular interactions (intercomplex, solvent, or counterion mediated) can surely influence the observed base/coordination plane dihedral angle,⁸ although it is difficult to a priori suggest whether these interactions would favor any particular dihedral angle.

In Table VII, we list various *trans*-bis(nucleic acid base)- and mono(nucleic acid base)platinum(II) complexes along with their solid-state base/coordination plane dihedral angle and comment on the intramolecular interactions in each system. The possible dominance of one or more of the forces indicated above (i–iv) may be suggested by analyzing the information of Table VII. For example, the small base/PtN₄ dihedral angle of 48° in [Pt(dien)(7,9-Dmhyp)]²⁺ is likely^{1a} a result of the relatively strong interbase hydrogen bond formed between the exocyclic O(6) atom of the base and one of the terminal amino groups of the chelate ligand. On the other hand, in [Pt(dien)(7,9-Dmgua)]²⁺, it has been argued^{1a} that the repulsive interaction between the amino group next to N(1) (Figure 1) mitigates against a small dihedral angle, consistent with the observed enlargement of the dihedral angle by 15° compared to the angle in the 7,9-Dmhyp complex. The INDO calculations lend support to this conclusion since the electronic differences between the 7,9-Dmhyp and 7,9-Dmgua ligands are negligible.

For the *trans*-[Pt(NH₃)₂(7,9-Dmhyp)₂]²⁺ and *trans*-[Pt(NH₃)₂(1-MeC)₂]²⁺ cations, the respective Pt...O(6) and Pt...O(2) distances of 3.086 (4) and 3.037 (7) Å²¹ possibly represent significant enough interactions to favor the large dihedral angles of 78°. The INDO calculations would suggest

Table VII. Metal-Ligand and Ligand-Ligand Interactions in Various Bis- and Mono(base) Complexes

| complex | ref | M-N dist, Å | M...O(6) dist, Å | B/CP dihedral angle, deg | comments |
|---|-----------|-------------|------------------|--------------------------|------------------------------|
| <i>trans</i> -[Pt(NH ₃) ₂ (7,9-Dmhyp) ₂] ²⁺ | this work | 2.035 (3) | 3.086 (3) | 77.9 (2) | weak Pt...O(6) |
| <i>trans</i> -[Pt(NH ₃) ₂ (1-MeC) ₂] ²⁺ | 21 | 2.023 (8) | 3.037 (7) | 78.2 | weak Pt...O(2) |
| [Pt(dien)(7,9-Dmhyp)] ²⁺ | 1a | 2.051 (6) | 3.145 (5) | 47.7 (3) | O(6)...HN and weak Pt...O(6) |
| [Pt(dien)(7,9-Dmgua)] ²⁺ | 1a | 2.044 (5) | 3.021 | 62.4 (3) | weak Pt...O(6) and O(6)...HN |
| <i>trans</i> -[Pt(Pyr) ₂ Cl ₂] ⁰ | 22 | 2.008 (5) | | 52.5 (3) | weak CH...Cl |
| <i>trans</i> -[Pt(Pyr) ₂ Br ₂] ⁰ | 22 | 2.014 (7) | | 54.3 (4) | weak CH...Br |
| [Cu(glygly)(7,9-Dmhyp)] ⁰ | 28 | 1.997 (3) | 2.970 (2) | 63.4 (2) | intra Cu...O(6) |
| | | | 2.769 (2) | | inter Cu...O(6) |

Table VIII. Proton Chemical Shift Data for Various 7,9-Dmhypp Complexes

| compd | H(8) | H(2) | -CH ₃ | N-H |
|---|------|-------------------|------------------|-------------------|
| (A) In D ₂ O (δ , Downfield from <i>p</i> -Dioxane) | | | | |
| 7,9-Dmhypp | | 4.36 | 0.14, 0.38 | |
| [Pt(dien)(7,9-Dmhypp)] ²⁺ | | 4.96 ^a | 0.20, 0.45 | |
| [Pt(en)(7,9-Dmhypp) ₂] ²⁺ | | 4.95 ^b | 0.17, 0.44 | |
| <i>trans</i> -[Pt(NH ₃) ₂ (7,9-Dmhypp) ₂] ²⁺ | | 4.97 ^c | 0.21, 0.46 | |
| (B) In Me ₂ SO- <i>d</i> ₆ (δ , Downfield from Me ₄ Si) | | | | |
| [Pt(dien)(7,9-Dmhypp)] ²⁺ | 9.52 | 8.47 | 3.88, 4.14 | 5.84 |
| [Pt(en)(7,9-Dmhypp) ₂] ²⁺ | 9.56 | 8.56 | 3.91, 4.20 | 5.90 |
| <i>trans</i> -[Pt(NH ₃) ₂ (7,9-Dmhypp) ₂] ²⁺ | 9.37 | 8.41 | 3.88, 4.08 | 4.20 ^d |
| ^a $J_{\text{Pt-H}} \approx 22$ Hz. ^b $J_{\text{Pt-H}} \approx 28$ Hz. ^c $J_{\text{Pt-H}} \approx 27$ Hz. | | | | |
| ^d $J_{\text{Pt-H}} \approx 56$ Hz. | | | | |

that this effect is more important in 7,9-Dmhypp than in 1-MeC, although it must be noted that the N(3)-bound 1-MeC base, like the N(1)-bound 7,9-Dmgua base, possesses an exocyclic amino group next to the metal binding site (Figure 1) and the unfavorable interaction of this amino group with the *cis* ammine ligand surely encourages a large dihedral angle for the 1-MeC complex. For the *trans*-[Pt(Pyr)₂X₂] complexes,²² it is possible that interactions of the type C-H...X (observed at 3.29 and 3.41 Å for X = Cl⁻ and Br⁻, respectively), involving the carbon atoms adjacent to the base binding site, favor the small dihedral angles found in these complexes.

Although a degree of rationalization for the base/coordination plane dihedral angles may be achieved by the arguments presented above, such reasoning must be viewed cautiously since there is always the possibility that intermolecular effects are competitive with these rather weak intramolecular forces. For example, the large dihedral angle for *trans*-[Pt(NH₃)₂(7,9-Dmhypp)₂]²⁺ has been suggested to follow from the presence of the Pt...O(6) intramolecular interaction. In this context, it is noted that the complex of Table VII for which the M...O(6) intramolecular distance is the shortest is [Cu(glycylglycinato)(7,9-Dmhypp)],²⁸ where the Cu...O(6) distance is 2.970 (2) Å. However, the observed base/coordination plane dihedral angle at 63° is rather small and probably dictated in large measure by the shorter intermolecular Cu...O(2) interaction at 2.769 (2) Å.

(f) ¹H NMR Studies. We have studied the solution ¹H NMR spectrum of crystals of *trans*-[Pt(NH₃)₂(7,9-Dmhypp)₂](NO₃)₂·2H₂O in D₂O and Me₂SO-*d*₆. In Table VIII, a comparison of chemical shift data is given for the N(1)-bound 7,9-Dmhypp base in the *trans* complex to that for the free base and several other of its Pt(II) complexes, notably [Pt(en)(7,9-Dmhypp)₂]²⁺, where the purine bases are in *cis* positions.

In D₂O, only the H(2) ring proton signal and those for the exocyclic methyl substituents at N(7) and N(9) of the purine ligand are easily observable as the H(8) ring proton and the ammine protons are readily exchanged. For all of the complexes studied in D₂O (Table VIII), there is a large chemical shift difference (ca. 0.6 ppm downfield) between the H(2) signal for the platinated base and that for the free base. The unassigned methyl resonances are, as expected,²⁴ much less sensitive to platination at N(1) and experience downfield shifts

of only a few hundredths of a ppm. In addition, in D₂O, ¹⁹⁵Pt splitting of the H(2) signal is discernible. For the [Pt(dien)(7,9-Dmhypp)]²⁺ cation, the ¹⁹⁵Pt-H(2) coupling constant is 22 Hz, whereas this coupling constant rises to 27–28 Hz for [Pt(en)(7,9-Dmhypp)₂]²⁺ and *trans*-[Pt(NH₃)₂(7,9-Dmhypp)₂]²⁺. The presence of ¹⁹⁵Pt coupling to the H(2) proton is indicative, as expected for the highly substituted 7,9-Dmhypp base, of N(1) binding in solution.

The ¹H NMR spectra of the Pt complexes in Me₂SO-*d*₆ is richer in detail (due to the absence of exchange effects) than in D₂O as the base H(8) and the ammine resonances are also observable. Unfortunately, the free Dmhypp base is insoluble, preventing a direct comparison of coordinated and uncoordinated chemical shifts. The chemical shift and ¹⁹⁵Pt-H(NH₃) coupling constant for the ammine ligands of *trans*-[Pt(NH₃)₂(7,9-Dmhypp)₂]²⁺ are typical of *cis*- and *trans*-diammineplatinum(II) systems (for a recent report, see ref 30). As in D₂O, the methyl resonances show an absence of a significant trend in chemical shift over the range of complexes studied. For the H(8) (and possibly the H(2)) resonance, however, there appears to be a slightly smaller (0.1–0.2 ppm) downfield shift for the *trans* complex relative to the dien and the en complexes (Table VIII). However, this effect is too small to be easily interpreted.

Summary

The preparation and some of the physical properties of this first example of a *trans*-bis(purine)platinum(II) coordination compound, *trans*-[Pt(NH₃)₂(7,9-Dmhypp)₂](NO₃)₂·2H₂O, are reported and discussed. Indications are given that N(1)-bound 6-oxopurine bases, typified by 7,9-dimethylhypoxanthine, possess fairly strong structural *trans* effects, consistent with their electronic properties and binding affinities. The present complex can be considered as a model for a *trans* DNA cross-link of the type N(1)_{5'-IMP}-Pt-N(1)_{5'-IMP}. Intramolecular forces are not expected to play a dominant role in determining the degree of deformation of a polynucleotide by such a cross-link. In contrast, intramolecular forces (especially base-base interactions) are expected to be stronger for *cis* DNA cross-links. In particular, interbase steric factors are probably dominant factors in determining the degree of deformation introduced by a *cis* cross-link of the type N(1)_{5'-IMP}-Pt-N(1)_{5'-GMP} or N(3)_{5'-CMP}-Pt-N(3)_{5'-CMP} as has been suggested elsewhere.^{19b}

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Registry No. *trans*-Diamminebis(7,9-dimethylhypoxanthine)-platinum(II) nitrate dihydrate, 82456-45-9; 7,9-dimethylhypoxanthine, 5752-16-9; 7,9-dimethylquanine, 524-35-6; 1-methyl-2-pyrimidone, 3739-81-9; 1-methylcytosine, 1122-47-0; [Pt(dien)(7,9-Dmhypp)]²⁺, 76900-58-8; [Pt(en)(7,9-Dmhypp)₂]²⁺, 82456-46-0.

Supplementary Material Available: Tables of non-hydrogen atom anisotropic thermal parameters, parameters for the hydrogen atoms, and calculated and observed structure factor amplitudes (21 pages). Ordering information is given on any current masthead page.

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