Table I. ^{31}P NMR Analysis of the ATPβS (B) Derived from Chiral Thiophosphates

Ps_i samples	% intensity[a] a	b	c	d	"F" value	configuration
$PS^{18}O_3^{3-}$	41.3 ± 1.2	24.6 ± 0.1	22.1 ± 0.0	11.8 ± 1.2	1.11	
7	8.8 ± 0.5	42.8 ± 0.6	28.1 ± 0.5	20.3 ± 0,5	1.52	*S*
8	12.2 ± 0.5	26.5 ± 1.6	38.8 ± 0.1	22.4 ± 2.0	0.68	*R*

[a] Obtained from peak-height measurements for the Pβ signal of ATPβS. The errors represent deviations between the two nonoverlapping halves of the two doublets.

"*F*" value. The relative intensities are dependent on isotopic enrichments. However, any nonchirally labeled Ps_i should contribute equally to b and c to give $F = 1.0 \pm 0.1$ (reproducibility of peak heights is ±10%).

Table I lists the relative heights of the peaks corresponding to a–d from various Ps_i samples. While this work was in progress, Webb and Trentham had determined that the phosphoryl transfer catalyzed by PGK proceeds with inversion of configuration[13] by use of a similar NMR analysis. On the basis of this finding, (*R*)-Ps_i should give rise to c ($F < 1$) whereas (*S*)-Ps_i should give rise to b ($F > 1$). Since **7** and **8** gave *F* values of 1.52 and 0.68, respectively, the configurations of **7** and **8** are "*S*" and "*R*", respectively. These results indicate that hydrolysis of AMPS by 5′-nucleotidase proceeds with inversion of configuration. Thus, unlike alkaline phosphatase,[14] the reaction of 5′-nucleotidase seems to be a single displacement without involving a phosphorylenzyme intermediate.

On the basis of the enrichments of the isotopes used, the optimal optical purity of **7** and **8** is 50% and the optimal *F* values are 2.0 and 0.5, respectively. Since hydrolysis is accompanied by an exchange of 0.5 atom % oxygen, the observed *F* values suggest an almost complete stereospecificity.

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(13) Webb, M. R.; Trentham, D. R. *J. Biol. Chem.*, in press.
(14) Jones, S. R.; Kindman, L. A.; Knowles, J. R. *Nature (London)* **1978**, *275*, 564–565.

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An Unexpected G–G Base Pairing Caused by the Coordination of Platinum(II) at the N(7) Position of 9-Ethylguanine

Sir:

The mechanism of the anticancer action of *cis*-$Pt(NH_3)_2Cl_2$[1] is thought to involve interaction of the drug with the bases of DNA.[2] There is good evidence for such an interaction both in vitro[3-6] and in vivo,[7-9] probably with guanine,[10] or at least with the guanine–cytosine base pair.[11] Suggested models include interstrand cross-linking,[12] an intrastrand clip,[13,14] an N(7)–O(6) chelate to guanine which interferes with hydrogen bonding,[15-17] and costacking of pairs of *cis*-Pt(II) complexes monofunctionally bound to adjacent bases on one strand.[18] The isolation of hydroxo-bridged Pt(II) amine complexes[19,20] and their peculiar interactions with DNA bases[21-23] lends credence to the postulate of an interaction of two platinum atoms at N(1) and O(6) of guanine[24] or alternately at N(7) and O(6).[25] All these models are based on the assumption that it is necessary to interfere with the replication process of DNA by interfering with the hydrogen-bonding sites used for producing base pairing between DNA strands. These models are consistent with recent ideas that cancer cells are deficient in their ability to excise defects from the DNA strand, and, thus, one can selectively kill a cancer cell chemically by introducing further defects into the DNA strand which cannot be excised.[2]

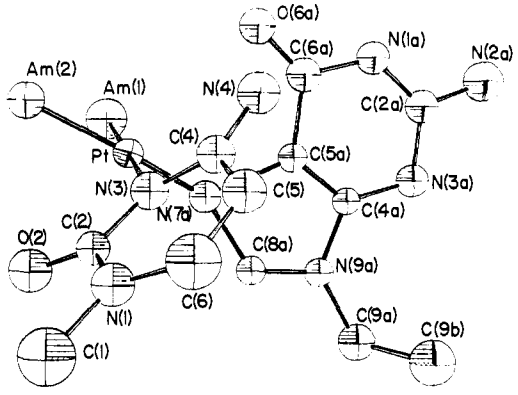

Figure 1. The molecular cations $[Pt(NH_3)_2(1\text{-MeC})(9\text{-EtG})]^{2+}$ or $[Pt(NH_3)_2(1\text{-MeC})(9\text{-EtG-H})]^{+}$.

The problem is that all crystallographic studies of model compounds of the *cis*-diammineplatinum(II) moiety combined with guanosine[26-28] show interaction at the N(7) site only, and this site

(1) Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature (London)* **1969**, *222*, 385.
(2) Rosenberg, B. *Biochimie* **1978**, *60*, 859, and references therein.
(3) Wakelin, L. P. G. *Biochem. Soc. Trans.* **1974**, *2*, 866.
(4) Macquet, J. P.; Theophanides, T. *Biopolymers*, **1975**, *14*, 781.
(5) Howle, J. A.; Gale, G. R.; Smith, A. B. *Biochem. Pharmacol.* **1972**, *21*, 1465.
(6) Roos, I. A. G.; Arnold, M. C. *J. Clin. Hematol. Oncol.* **1977**, *7*, 374.
(7) Harder, H.; Rosenberg, B. *Int. J. Cancer* **1970**, *6*, 207.
(8) Howle, J.; Gale, G. *Biochem. Pharmacol.* **1970**, *19*, 2757.
(9) Howle, J.; Gale, G. *J. Bacteriol.* **1970**, *103*, 259.
(10) Janowski, J. P.; Macquet, J. P.; Butour, J. L. *Biochimie* **1978**, *60*, 901.
(11) Stone, P. J.; Kelman, A. D.; Sinex, F. M. *Nature (London)* **1974**, *251*, 736.
(12) Roberts, J. J.; Pascoe, J. M. *Nature (London)* **1972**, *235*, 282.
(13) Stone, P. J.; Kelman, A. D.; Sinex, F. M.; Bhargava, M. M.; Halvorson, H. O. *J. Mol. Biol.* **1976**, *104*, 793.
(14) Kelman, A. D.; Buchbinder, M. *Biochimie* **1978**, *60*, 901.
(15) Macquet, J. P.; Theophanides, T. *Inorg. Chim. Acta* **1976**, *18*, 189.
(16) Goodgame, D. M. L.; Jeeves, L.; Phillipes, F. L.; Skapski, A. C. *Biochim. Biophys. Acta* **1975**, *378*, 153.
(17) Dehand, J.; Jordanov, J. *J. Chem. Soc., Chem. Commun.* **1976**, 598.
(18) Srivastava, R. C.; Froehlich, J.; Eichhorn, G. L. *Biochimie* **1978**, *60*, 879.
(19) (a) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B. *J. Am. Chem. Soc.* **1977**, *99*, 777: (b) *Inorg. Chem.* **1977**, *16*, 1192: (c) *Ibid.* **1978**, *17*, 1941.
(20) Lippert, B.; Lock, C. J. L.; Rosenberg, B.; Zvagulis, M. *Inorg. Chem.* **1978**, *17*, 2975.
(21) Lock, C. J. L.; Peresie, H. J.; Rosenberg, B.; Turner, G. *J. Am. Chem. Soc.* **1978**, *100*, 3371.
(22) Faggiani, R.; Lock, C. J. L.; Pollock, R. J.; Rosenberg, B.; Turner, G., submitted for publication in *Inorg. Chem.*
(23) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Speranzini, R. A., submitted for publication in *J. Am. Chem. Soc.*
(24) Barton, J. K.; Rabinowitz, H. N.; Szalda, D. J.; Lippard, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 2827.
(25) Chu, G. Y. H.; Mansy, S.; Duncan, R. E.; Tobias, R. S. *J. Am. Chem. Soc.* **1978**, *100*, 593.

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is outside the hydrogen-bonding region. We have now discovered a way in which coordination of a platinum(II) complex at the N(7) position may interfere with the hydrogen-bonding region and cause unusual base pairing.

We have been studying a series of complexes containing the *cis*-$Pt(NH_3)_2^{2+}$ unit attached to 9-ethylguanine (9-EtG) and 1-methylcytosine (1-MeC), crystallizing at various pHs. The compound crystallizing from water at pH 7 is $[Pt(NH_3)_2(9\text{-EtG})(1\text{-MeC})]^{2+}[Pt(NH_3)_2(9\text{-EtG-H})(1\text{-MeC})]^{+}(ClO_4)_3$, where 9-EtG-H is the deprotonated base. The compound was prepared by dissolving $[Pt(NH_3)_2(9\text{-EtG})(1\text{-MeC})]^{2+}(ClO_4)_2$ in water (solution pH 4.5) and titrating the solution with 0.2 N NaOH to pH ~8.4 under N_2. Evaporation gives the desired product in 65% yield. Crystals were obtained by heating the product in a little water to 75 °C and slowly cooling the resulting solution.[29] Crystal data for $C_{24}H_{43}Cl_3N_{20}O_{16}Pt_2$: M_r 1364.3; monoclinic; $C2/c$; a = 23.16 (8), b = 11.971 (3), c = 16.140 (4) Å; β = 106.45 (2)°; Z = 4; d_{calcd} = 2.08 g cm^{-3}. Intensity data were collected by using a Syntex $P2_1$ diffractometer with Mo Kα radiation. The platinum atom was located from a Patterson map, and the other nonhydrogen atoms were located by successive electron-density difference syntheses. Full-matrix least-squares refinement with anisotropic temperature factors for Pt and Cl converged to a conventional R value of 0.055 for 2536 reflections with $I > 3\sigma(I)$.

The molecular cation is shown in Figure 1. Bonding in the cations is normal, Pt being attached to N(7) of 9-EtG and N(3) of 1-MeC. The arrangement of ligand atoms about each platinum atom is essentially a square, and the Pt–N distances [Pt–Am(1), 2.06 (1); Pt–Am(2), 2.06 (1); Pt–N(3), 2.02 (1); Pt–N(7a), 2.04 (1) Å] and N–Pt–N angles [(Am(1)–Pt–Am(2), 88.8 (4); Am(1)–Pt–N(7a), 90.2 (4); Am(2)–Pt–N(3), 90.4 (4); N(3)–Pt–N(7a), 90.6 (4)°] are similar to those we have observed previously in other ammonia–base complexes of Pt(II).[21-23,30,31] Bond lengths and angles within 1-methylcytosine and 9-ethylguanine do not differ significantly from the average values listed by Voet and Rich.[32]

Significant features of the structure are the large dihedral angles between the planes of the bases and the square plane (N_2PtN_2–1-MeC, 68°; N_2PtN_2–9-EtG, 74°; 1-MeC–9-EtG, 79°). Because there are only four formula units in the unit cell, one perchlorate ion sits at a twofold axis and is disordered. The protonated and deprotonated cations are related by the twofold axis at $x = 0$, $z = {}^1/_4$, and we assume that the hydrogen atom attached to N(1a) is disordered about this position. The interaction between the two cations is represented schematically in Figure 2. Hydrogen-bond distances are O(6a)–N(2a)′, 2.99 (2) Å; N(1a)–N(1a)′, 2.77 (2) Å. Thus, the coordination of Pt(II) at the N(7) position has shifted the pK of the N(1) position sufficiently to produce significant amounts of both protonated and deprotonated guanine at pH 7 and allow the G–G base pairing (Figure 2b), which is quite unlike that observed in poly(G) and poly(dG) helices,[33-35] guanosine and guanine gels,[36] or the Donohue structures.[37] The hydrogen bonding is very much like the Watson–Crick[38] hydrogen bonding between G–C pairs (Figure 2a). There are differences concerning the arrangement of the deoxyribose positions, and there is the difference in distance between these positions (13.11 Å in the G–G compound, 10.85 Å for a G–C pair[39]) which would make packing a G–G pair within a molecule very difficult.

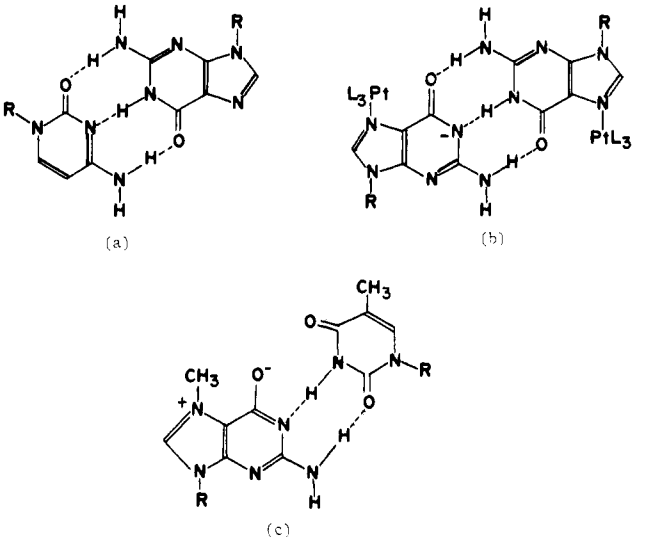

Figure 2. A comparison of the (a) Watson–Crick G–C pair, (b) the platinated G–G pair, and (c) the methylated G–T pair.

There is, however, an alternate way that base mispairing in DNA could be induced. The guanine in the deprotonated cation looks very much like the N(7) methylated guanosine which can bond in the manner shown in Figure 2c to thymine to give a G–T pair.[40] Thus, we have a very simple model of how a pK shift caused by platinum coordination at N(7) of guanine might give rise to a G–T mispairing in DNA. It will be necessary to do further work to see whether other cis or trans complexes can induce the same effect.

(26) Gellert, R. W.; Bau, R. *J. Am. Chem. Soc.* **1975**, *97*, 7379.
(27) Bau, R.; Gellert, R. W.; Lehovec, S. M; Louie, S. *J. Clin. Hematol. Oncol.* **1977**, *7*, 51.
(28) Cramer, R. E.; Dahlstrom, P. L. *J. Clin. Hematol. Oncol.* **1977**, *7*, 330.
(29) Analytical figures agree best with the formulation of the compound as a dihydrate (Anal. Calcd: C, 20.6; H, 3.4; N, 20.0; O 20.6. Found: C, 21.1; H, 3.2; N, 20.2; O, 20.3; Pt, 27.7.) although individually C and H agree best with anhydrous material, N with the monohydrate, and O and Pt with the dihydrate. No water was found in the structure examined crystallographically. No residual peak >1 e/Å^3 was found in the final difference map.
(30) Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1980**, *19*, 295.
(31) Lippert, B.; Lock, C. J. L.; Speranzini, R. A., submitted for publication in *Inorg. Chem.*
(32) Voet, D.; Rich, A. *Prog. Nucleic Acid Res. Mol. Biol.* **1970**, *10*, 183.
(33) Arnott, S.; Chandrasekaran, R.; Mattilla, C. M. *Biochem. J.* **1944**, *141*, 537.
(34) Gellert, M.; Lipsett, M. N.; Davies, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **1962**, *48*, 2013.
(35) Guschlbauer, W. "Nucleic Acid Structure", Springer-Verlag: Heidelberg, 1976; p 72.
(36) Tougard, P.; Chantot, J-F.; Guschlbauer, W. *Biochim. Biophys. Acta* **1973**, *308*, 9.
(37) Donohue, J. *Proc. Natl. Acad. Sci. U.S.A.* **1956**, *42*, 60.
(38) Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737.
(39) Arnott, S. *Prog. Biophys.* **1970**, *21*, 265.
(40) Shapiro, R. *Prog. Nucleic Acid Res. Mol. Biol.* **1968**, *8*, 73.

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Cleavage of DNA by Coordination Complexes. Superoxide Formation in the Oxidation of 1,10-Phenanthroline–Cuprous Complexes by Oxygen—Relevance to DNA-Cleavage Reaction

Sir:

The 1,10-phenanthroline–cuprous complex, $(OP)_2Cu^+$, cleaves DNA in an oxygen-dependent reaction.[1] Cleavage of 10 μg/mL of poly(dA-T) by micromolar levels of coordination complex can be readily measured within 1 min because the products of the degradation are effective inhibitors of *E. coli* DNA polymerase I. The blockage of the reaction by catalase and the failure of the oxidatively stable 2,9-dimethyl-1,10-phenanthroline–cuprous complex[2] to degrade DNA indicate that intermediates formed

(1) D. S. Sigman, D. R. Graham, V. D'Aurora, and A. M. Stern, *J. Biol. Chem.*, **254**, 12269 (1979).
(2) J. R. Hall, N. K. Marchant, and R. A. Plowman, *Aust. J. Chem.*, **15**, 480 (1962).

0002-7863/80/1502-5419$01.00/0