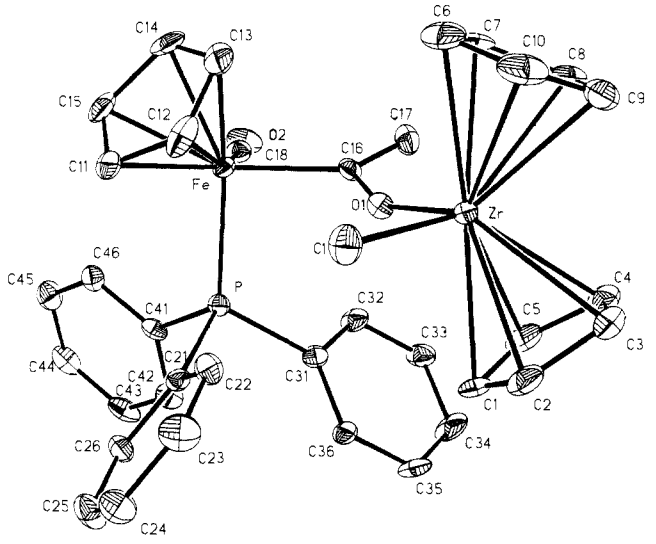

Figure 1. ORTEP diagram of complex I. Bond lengths (Å): Zr–O1 = 1.948 (8), Zr–Cl = 2.479 (3), Zr–cpl = 2.235 (9), Zr–cp2 = 2.239 (8), O1–C16 = 1.364 (14), C16–C17 = 1.331 (12), Fe–C16 = 1.993 (11), Fe–C18 = 1.740 (10), Fe–cp3 = 1.736 (7), Fe–P = 2.219 (3). Bond angles (°): P–Fe–C18 = 90.8 (3), P–Fe–C16 = 92.9 (3), C18–Fe–C16 = 92.1 (4), Fe–P–C31 = 118.1 (2), cpl–Zr–cp2 = 128.1 (3), Cl–Zr–O1 = 99.0 (2).

1555 cm^{-1}, 45 cm^{-1}, removed from that of the parent acyl, $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)C(O)CH_3]$, ν(CO)(acyl) 1600 cm^{-1}. (This band was not seen in the enol form, complex I.) By reaction of the thermally unstable lithium enolate $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)(COCH_2)^-Li^+]$ with organotransition-metal halides, chiral metallo keto [Fe]*—C(=O)—CH_2M and metallo enol [Fe]*—C(=CH_2)—OM′ derivatives have been isolated.

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Supplementary Material Available: Positional and thermal parameters for complex I (Tables SI–SIII) (3 pages). Ordering information is given on any current masthead page.

Novel, Definitive NMR Evidence for N(7), α-PO_4 Chelation of 6-Oxopurine Nucleotide Monophosphates to Platinum Anticancer Drugs

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The nature of compounds formed between diverse metal species and nucleotides has received extensive study.[1-7] Although many early studies sought metal chelation by the base and the α-phosphate group on the *same* nucleotide, no such species has been unambiguously established.[3] Furthermore, multiple products are formed between *cis*-PtA_2Cl_2 (A = amine ligand) and guanosine-type ligands; some of these have not yet been fully characterized.[4-7] Such products have been the subject of several studies because guanine bases are the preferred reaction site on DNA for Pt anticancer drugs.[8] We now report that one of these products is the first unambiguous example of the long sought species in which a nucleotide chelates the same metal via a base N and an α-phosphate O.

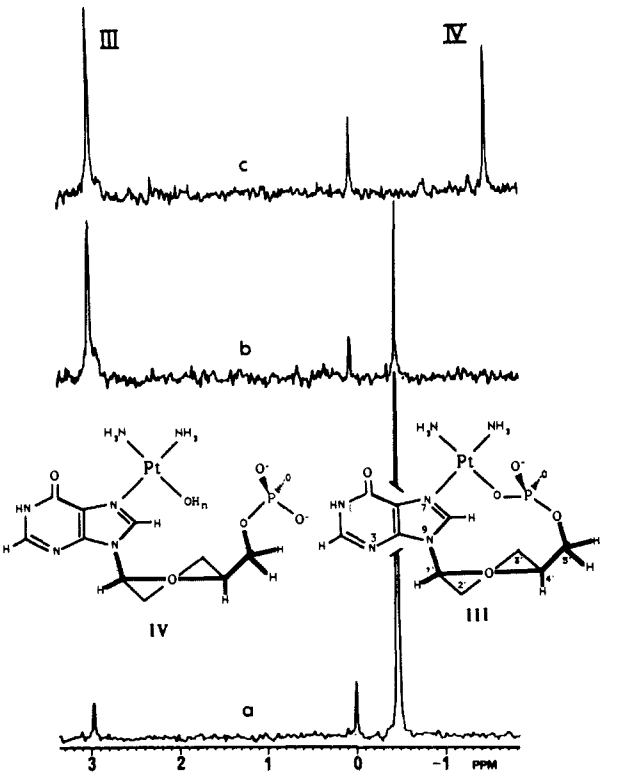

Figure 1. 81.01-MHz $^{31}P\{^1H\}$ NMR spectra of 5 mM 5′-IMP after reaction with 10 mM *cis*-$Pt(NH_2CH_3)_2(OH_2)_2$. All spectra were recorded on the same sample at 25 °C in D_2O, 90° pulse, 15-s RD. The pD was maintained at ~6.8 with 0.010 M PIPES buffer. Shifts were measured from internal trimethylphosphate (central peak). Total elapsed times to midpoint of acquisition were the following: (a) directly after mixing, t = 20 min; (b) after heating at 50 °C for 30 min, t = 90 min; (c) after lowering the pD to 5.8, t = 130 min.

We find that one of the reaction products of "aquated" *cis*-PtA_2 (A = NH_3, NH_2CH_3) with 5′-GMP, 5′-dGMP, 5′-IMP, or 5′-dIMP has spectral characteristics previously interpreted as evidence for dimers such as $[cis\text{-}Pt(NH_3)_2\mu\text{-}(5'\text{-GMP-}N7,O6)]_2$.[7] Our evidence that this species is in fact the N7,PO chelate *cis*-$Pt(NH_3)_2$(5′-GMP-*N7,PO*) (I) and that I is in equilibrium with *cis*-$Pt(NH_3)_2$(GMP-*N7*)(H_2O) (II)[1] is best illustrated by our study of the equilibrium between the species *cis*-$Pt(NH_2CH_3)_2$(5′-IMP-*N7,PO*) (III) and its aquated counterpart IV, where the CH_3 and H2 ^1H NMR signals provide deeper insight into the nature of this unusual compound (see Figure 1).

Our principal findings for monomeric N7,PO chelate compounds are as follows: First, the ^{31}P NMR spectrum of a pD 6.8 solution of IV has a signal at −0.50 ppm in the upfield region

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(3) Good evidence for such chelates has been reported only rarely (Mariam, Y. H.; Martin, R. B. *Inorg. Chim. Acta* **1979**, *35*, 23). However, for labile metals, multiple species can exist (Martin, R. B.; Miriam, Y. H. *Met. Ions Biol. Syst.* **1979**, *8*, 57) and, in contrast to the inert Pt II species studied here, it is difficult to obtain unambiguous evidence of simultaneous direct coordination of both base and phosphate groups.

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characteristic of uncoordinated phosphate groups (Figure 1).[9] Furthermore, on lowering the pD to 5.8 and to 4.7, the signal shifts upfield to −1.55 and to −2.77 ppm, respectively, characteristic of protonation. Heating the pD 6.8 solution produces a mixture of III and IV. The ^{31}P signal for III is at +2.95 ppm—an unusually far downfield shift. Moreover, lowering the pD to 4.7 resulted in an upfield shift of less than 0.1 ppm. Second, addition of base (pH 7.9 in H_2O) converts IV immediately and III readily to *cis*-Pt(NH_2CH_3)$_2$(5′-IMP-*N7*)OH. Similarly, addition of Cl^- (100 mM) converts both I and II to the well-known *cis*-Pt(NH_3)$_2$(GMP-*N7*)Cl[1,4,10] with $t_{1/2}$ of ca. 1 and 8 h, respectively, as monitored by the H8 signals (25 °C, pH 7). Third, no similar complexes were observed when the 5′-NMP was replaced by 3′-GMP, inosine, or the methyl phosphate ester of 5′-GMP (Me-5′-GMP). Fourth, the chemical shift of H8 of III was nearly invariant (<0.03 ppm) between pH 4.5 and 7.5. Previous work[2,10,11] has shown that H8 shifts upfield ca. 0.1–0.3 ppm on primary phosphate protonation both in 5′-NMP's[2] (pK_a ca. 6.7) and in complexes of the type *cis*-PtA_2(5′NMP-*N7*)$_2$ and *cis*-PtA_2(5′NMP-*N7*)X, where X = Cl^- or H_2O and 5′-NMP = 5′-GMP[10] or where X = Br and 5′-NMP = 5′-AMP (pK_a ca. 5.7).[11] Fifth, addition of Cu^{2+} (0.01 Cu/NMP) to a solution of III and IV causes broadening of H8 of IV but no broadening of H8 of III. This result suggests that Pt is bound to both N7 and PO_4, blocking Cu^{2+} coordination. These five points are readily understood only if the 5′-phosphate group is bound to Pt. Sixth, there is no concentration dependence of the equilibrium III ⇄ IV but III is favored between pH 6 and 7; IV is favored at pH > 7 (~2:1 at pH 7.9). The equilibrium condition is established by the ready interconversion of III and IV as the pH is changed. These results rule out a dimer, particularly of the type proposed in the literature, since formation of such a dimer requires a concentration dependence. Seventh, the ^1H NMR spectrum obtained from addition of 2 equiv[12] of *cis*-Pt(NH_2CH_3)$_2$(OH_2)$_2$ to a mixture of 0.5 equiv each of 5′-GMP and 5′-IMP is essentially identical with the sum of the spectra obtained when similar reactions are carried out on the individual 5′-NMPs. Two new sets of resonances could be expected if species such as III were dimers. Finally, two CH_3 signals for III, each ca. 3 times the intensity of the H2 signal, indicate that two amine ligands in different environments and one nucleotide are connected to each Pt.

Several additional observations on III provide information on the relationship of the ribose and purine rings and suggest that the ribose sugar is in an unusual N-type conformation, ^1E or ^1_2T.[13] First, the value of $^3J_{1'2'}$ should be near zero due to an expected Cl′–H1′ to C2′–H2′ torsion angle of near 90° (we observe values of <0.2 Hz for all 5′-NMP's studied). Second, in the 5′-dNMP adducts we expected $^3J_{1'2''}$ of 9.5–10.5 Hz for a pure N conformer.[13] In fact, we observe a sharp doublet for H1′, J = 6.9–7.4 Hz, depending on the complex.[13] Third, an anisotropic downfield shift of H2′ signals due to a positioning of this proton near N3 in the plane of the pyrimidine ring should be observed. Indeed, the H2′ signal appears near 5.25 ppm (ribose) or near 3.25 ppm (deoxyribose), ca. 0.4 ppm downfield from the same signals in the unreacted nucleotide or in II or IV. This signal for I was incorrectly assigned[7] to an *upfield*-shifted H1′. Our assignment of H2′ signals for the 5′-dNMP adducts is unambiguous since H2′ is strongly coupled to H2″ (^2J = 13.5 Hz) but not to H1′ (supplementary material). Signals we assign to H1′ are in the usual shift region. Fourth, it is likely that H5″ is shifted upfield slightly by the anisotropic five-membered ring (we observe a 0.2 ppm upfield shift). Molecular models reveal that coordination of the phosphate group and N7 to Pt would lead to the structural parameters consistent with these four points.

Pt–OP bonds are known,[14] and the inertness of the Pt II center allows identification of this novel chelate.[15] However, the low stability of the chelate with a phosphate monoester suggests that such interactions will be at most transient with phosphodiester groups in DNA. Complexation to polynucleotides leads to ^{31}P signals at ca. −3 ppm which have been attributed to N7,N7 chelates with no Pt–OP interactions.[16] The absence of species III in studies with Me-5′-GMP supports this view.

Acknowledgment. Support for this work by NIH Grant GM 29222 and a loan of K_2PtCl_4 from Johnson-Matthey are greatly appreciated.

Supplementary Material Available: Figures illustrating ^1H NMR spectral studies of the mixed nucleotide reactions, selective ^1H decoupling experiments, and the pH and concentration dependence of the III ⇄ IV equilibrium (3 pages). Ordering information is given on any current masthead page.

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(12) In the preparation of IV from *cis*-Pt(NH_2CH_3)$_2$(OH_2)$_2$ and 5′-IMP, an excess of Pt is required to prevent formation of *cis*-Pt(NH_2CH_3)$_2$(5′-IMP-*N7*)$_2$.[7] Five to ten minutes after the reactants were mixed and the pD adjusted to ~6.7, excess Pt was removed by addition of a slurry of CM-25 Sephadex. The complete removal of excess Pt was verified by the absence of the characteristic CH_3 ^1H NMR signal at 2.35 ppm.
(13) The furanose ring conformation cannot be fully deduced from the observation of $^3J_{1'2'}$ alone. The observation of $^3J_{1'2''}$ of ~7.0 Hz and $^3J_{1'2'}$ of <0.5 Hz precludes a pure N conformer, which requires $^3J_{1'2'} + {}^3J_{1'2''} = \sum{}^3J_{1'}$ = 9.5–10.5 Hz. See Altona, C. *Recueil Travaux Chim. Pays-Bas.*, 1982, *101*, 413. The situation is surprisingly similar to the case of Pt–d(GpG) where G(1)H1′ exhibits a sharp doublet with $^3J_{1'2''}$ (and thereby $\sum{}^3J_{1'}$) = 7.9 Hz. See: den Hartog, J. H. J.; Altona, C.; Chottard, J.-C.; Girault, J. P.; Lallemand, J.-Y.; deLeeuw, F. A. A. M.; Marcelis, A. T. M.; Reedijk, J. *Nucleic Acids Res.* **1976**, *10*, 4715.
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Macroscopically Oriented Copper(II) Chelates in Cast Multibilayer Films

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Bilayer membranes are two-dimensional arrays of molecules and constitute molecular systems useful for preparing ordered functional units.[1] This molecular ordering is readily transformable to macroscopic ordering, as regular multilayer films are obtainable by casting of aqueous bilayer dispersions onto solid supports.[2-4] The cast films retain structural characteristics essentially analogous to those of the original aqueous dispersions, and the bilayers are aligned parallel to the substrate surface.

It occurred to us that the macroscopic ordering in cast films can be used for producing macroscopic orientations of electron spins. For this purpose, we prepared cast films of bilayer membranes in which the Cu(II) chelate moiety is either covalently[5]

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