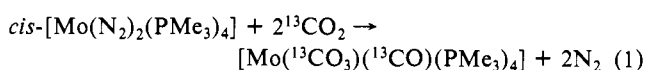


the three central lines of the 1:4:6:4:1 quintet that would be expected for an isotopic mixture of **2** and **2*** containing approximately 50% of molecules of **2** having one $^{13}\text{CO}_2$, 25% with two $^{13}\text{CO}_2$, and 25% with two $^{12}\text{CO}_2$. From the separation of the outer lines a value of 17.5 Hz can be computed for $^2J_{\text{PC}}$, in excellent agreement with the ^{13}C data already discussed. The IR spectrum has a strong band at 1670 cm^{-1} (1620 cm^{-1} in ^{13}C -enriched **2***) in the region expected for coordinated CO_2 .^{7,8}

As reported previously,² the reaction of **1** with CO_2 may yield, in addition to **2**, the disproportionation products **3** and **4**. Using $^{13}\text{CO}_2$, we have now confirmed our initial IR assignments of bands due to coordinated CO and CO_3^{2-} in these complexes and demonstrated that both groups form in a metal-induced CO_2 reductive disproportionation (eq 1). A reasonable mechanism for the



formation of complexes **2-4** should address the question of under what conditions the coordinated CO_2 molecule is "sufficiently activated" to give the disproportionation products and should explain the facts that (a) free PMe_3 drastically diminishes the yield of **2** in favor of **3**, (b) **2** is stable toward disproportionation even under 5 atm of CO_2 and in the presence of free PMe_3 , and (c) polar or aromatic hydrocarbon solvents also favor disproportionation. These observations are consistent with the formation of an intermediate species " $\text{Mo}(\text{CO}_2)(\text{N}_2)(\text{PMe}_3)_4$ ", which would yield **2** by coordination to a second molecule of CO_2 , following prior dissociation of N_2 . Alternatively, N_2 substitution by solvent or PMe_3 blocks the available coordination site at the Mo center and activates the coordinated CO_2 through an increase in the back-donation from the metal, thus favoring disproportionation. This process might involve formation of a Herskovitz type head-to-tail dimer,⁹ but if the coordinated CO_2 is sufficiently activated toward electrophilic attack by free CO_2 , it could be viewed as an O^{2-} transfer¹⁰ from coordinated to free CO_2 , with the subsequent formation of two Mo-O bonds (to yield **3**) providing the additional thermodynamic driving force. Since in **2** the back-donation from the MoP_4 fragment is shared by two CO_2 molecules, it becomes clear that a sufficient perturbation of the electronic structure of the coordinated CO_2 molecule, i.e., sufficient activation, is a necessary requirement for the disproportionation reaction to take place.

In conclusion we believe that the stability of **2** is due to a delicate balance of steric and electronic effects. The importance of the former is shown by the tendency of **2** to decompose by dissociation of PMe_3 (as found for $\text{trans-}[\text{Mo}(\text{C}_2\text{H}_4)_2(\text{PMe}_3)_4]$ ⁵) and by our failure¹¹ to observe adduct formation with the bulkier phosphines PMe_2Ph and PET_3 , while the influence of the electronic factors is demonstrated by the preferred formation of the disproportionation products when the electron density at the metal is increased by solvent or PMe_3 coordination. We also believe that

the remarkable strength of the Mo-CO₂ bonds, as compared to other transition-metal-carbon dioxide bonds,¹ is due to the intense back-bonding from the molybdenum center to the coordinated CO_2 molecules and to the oxophilic nature of molybdenum.

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DNA Breakage by a Perhydrate Complex of *cis,cis,trans*-Pt^{IV}Cl₂(NH₃)₂(OH)₂

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The coordination compound *cis*-dichlorodiammineplatinum(II) (CDDP, **1**) is in wide clinical use for the treatment of various types of cancer.¹ The drug is believed to derive its cytotoxic effects by direct interaction with guanine bases of cellular DNA.² Although the majority of the platinum-based antitumor agents which have been studied to date are platinum(II) complexes, certain complexes of platinum(IV) are also known to exhibit antitumor effects.³ One such compound, *cis,cis,trans*-Pt^{IV}Cl₂((CH₃)₂CHNH₂)₂(OH)₂ (CHIP, **2**), is currently undergoing clinical trials in the United States as a potential second generation CDDP analogue. The results of this study strongly suggest that the DNA breakage observed in the earlier investigations with CHIP (**2**) was due to lattice hydrogen peroxide.⁴⁻⁶

In an effort to more clearly define the chemical and biochemical events which underlie the mechanism of action of platinum-(IV)-based antitumor agents, we have studied the hydrogen peroxide oxidation products of CDDP (**1**). Two products have been isolated: the well-characterized *cis,cis,trans*-Pt^{IV}Cl₂(NH₃)₂(OH)₂^{7,8} (**3**) and a previously unreported perhydrate (**4**) whose formulation includes 1.0 H₂O₂ per platinum(IV) complex.

Reaction of **1** with an excess of 30% H₂O₂ at 50 °C results in the formation of a pale yellow solid (**4**). The IR spectrum of **4**⁹ exhibits strong bands at 3460 and 3475 cm⁻¹ assigned to OH

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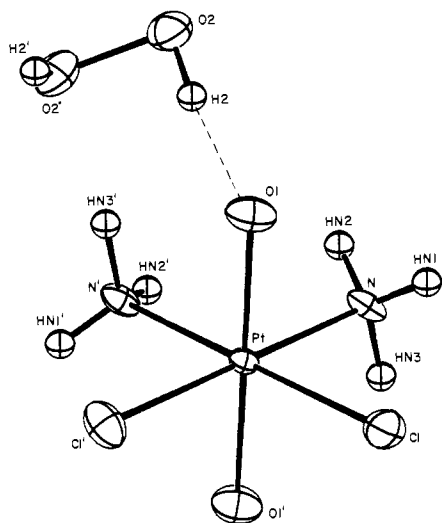


Figure 1. ORTEP plot of *cis,cis,trans*-Pt^{IV}Cl₂(NH₃)₂(OH)₂·H₂O₂ with thermal ellipsoids at the 50% probability level. H atoms are represented by spheres of arbitrary radius. Primed atoms are twofold related. Bond lengths: Pt–Cl = 2.311 (4), Pt–N = 2.05 (1), Pt–O1 = 2.03 (1), O2–O2' = 1.47 (2), and O2...O1 = 2.60 (1) Å. Bond angles: N–Pt–N' = 92.3 (6), Cl–Pt–Cl' = 93.1 (2), O1–Pt–O1' = 177.6 (5), N–Pt–Cl = 87.3 (4), N–Pt–Cl' = 179.5 (3), N–Pt–O1 = 88.9 (5), N–Pt–O1' = 89.4 (5), Cl–Pt–O1 = 90.3 (3) and Cl–Pt–O1' = 91.4 (3)°.

stretching modes of the complex. The hydrogen peroxide moiety gives rise to a strong band at 860 cm⁻¹ (symmetric O–O str) indicative of skewed C₂ symmetry for the peroxide.¹⁰ Subsequent X-ray crystallographic analysis confirmed that **4** was indeed a perhydrate complex.

Crystal Data. *cis,cis,trans*-PtCl₂(NH₃)₂(OH)₂·H₂O₂, monoclinic, space group C2/c (C_{2h}²-No. 15),¹¹ *a* = 11.236 (3) Å, *b* = 10.803 (2) Å, *c* = 7.129 (2) Å, β = 115.25 (2)°, and *Z* = 4. Independent reflections (733) were measured on an Enraf-Nonius CAD 4 diffractometer by using graphite-monochromated Mo Kα radiation and the θ–2θ scan mode, to a maximum of 2θ_{MoKα} of 50°. The structure was solved by using standard Patterson and difference Fourier techniques. It was not possible to locate the hydrogen atom of the independent hydroxyl group. Full-matrix least-squares refinement¹² (five independent nonhydrogen atoms, anisotropic; four independent hydrogen atoms, fixed, isotropic) led to a conventional unweighted residual $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ of 0.051 for the 664 reflections having $I \geq 2\sigma I$.

Figure 1 shows the ORTEP plot of the molecular geometry of the perhydrate complex **4**. Complex **4** has distorted octahedral geometry around the platinum atom (Figure 1). Both the platinum(IV) complex and the hydrogen peroxide molecule have crystallographic twofold symmetry. Molecular geometry and bond lengths of **3**^{7,8} and the platinum(IV) complex in **4** are essentially the same. Differences are derived from the extensive hydrogen bonding network due to the hydrogen peroxide solvate found in **4**. There is a strong hydrogen bond between the peroxide hydrogen atom (H2) and the hydroxyl oxygen atom (O1), reflected in the rather short O2–O1 distance of 2.60 (1) Å. On the basis of this interaction, the lattice structure can be viewed as consisting of chains in which the peroxide molecules act as bridges between twofold related platinum complexes. There is additional hydrogen bonding in this network involving the ammine hydrogen atoms. Two of the ammine hydrogens, HN2 and HN3, are hydrogen bonded to oxygen atoms of different symmetry-related peroxide molecules. In addition, one ammine hydrogen, HN1, is bonded to a symmetry-related hydroxyl oxygen atom.

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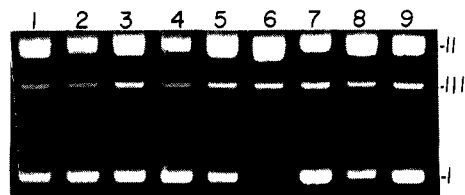


Figure 2. Electrophoresis in a 0.8% agarose gel of 0.46 μg of PM2–DNA following incubation with compounds **2**–**4**. The reactions were carried out for 9 h at 37 °C in a buffer containing 25 mM tricine, 15 mM NaNO₃, 100 mM NaCl, and 87.2 μM DNA–BP. Control lanes are 1, 4, and 7. The lane number and the value of [drug]/[DNA–BP] for the various compounds were as follows: **2**, 2, 0.5; **3**, 5.0; compound **4**, 5, 0.5; **6**, 5.0; compound **3**, 8, 0.5; **9**, 5.0.

Spin-trapping experiments using PBN^{13,14} revealed that thermal decomposition of **4** gives a hydroxyl radical, *g*: 2.005; *A*(H), 3.6 G; *A*(N), 15.9 G, and **3**. Under the same conditions, **2**¹⁵ and **3** did not produce radical species which could be trapped by PBN.

Using the conditions described by Mong et al.^{4–6} we examined the ability of compounds **2**, **3**, and **4**, to cleave PM2–DNA.¹⁶ The results of the DNA breakage experiments show (Figure 2) that, contrary to earlier studies, compound **2** is incapable of breaking DNA. Incubation of PM2–DNA with **2** or **3** at an input drug–DNA BP ratio (*r*_i) of 5.0 for 9.0 h at 37 °C followed by agarose gel electrophoresis and ethidium bromide staining of the DNA resulted in no change in the relative amounts or electrophoretic mobilities of form I (closed circular), form II (open circular), and form III (linear) PM2–DNA. However, incubation of DNA with the perhydrate **4** resulted in DNA breakage (lanes 5 and 6, Figure 2) as evidenced by the decrease in the amount of form I and the increase in the amount of form II PM2–DNA. These observations were confirmed by quantitative microdensitometric scanning of the gel photograph. Increasing temperature, time, or *r*_i for **4** results in the total disappearance of all three forms of PM2–DNA (data not shown), indicating that the aforementioned conditions produce extensive DNA breakage. Studies of the interaction between PM2–DNA and hydrogen peroxide¹⁷ have shown that peroxide itself causes DNA breakage.

These results suggest that the earlier DNA breakage studies with **2**^{4–6} employed samples of the compound containing hydrogen peroxide and that the pure form of **2** is incapable of cleaving DNA.¹⁸

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Supplementary Material Available: Atomic coordinates (Table A), thermal parameters (Table B), and hydrogen bonding parameters (Table C) for *cis,cis,trans*-Pt^{IV}Cl₂(NH₃)₂(OH)₂·H₂O₂ (3 pages). Ordering information is given on any current masthead page.

(13) The X-band EPR spectrum was obtained by heating (100 °C, 2 min) an aqueous solution containing 2 mM **4** and 50 mM PBN. The minor component observed in the EPR spectrum was identified as the thermal decomposition product of PBN, *tert*-butyl hydroxyl radical, *g* = 2.005, *A*(H) = *A*(N) = 14.6 G. Kalyanaraman, B.; Perez-Reyes, E.; Mason, R. P. *Tetrahedron Lett.* **1979**, *9*, 4809.

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(16) Lyophilized PM2–DNA was purchased from Boehringer Mannheim. It was dissolved in 500 μL of H₂O and extensively dialyzed against a buffer containing 25 mM tricine, 15 mM NaNO₃, and 100 mM NaCl at pH 7.1.

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