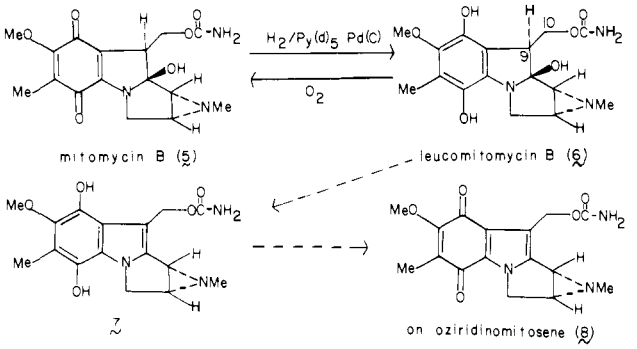
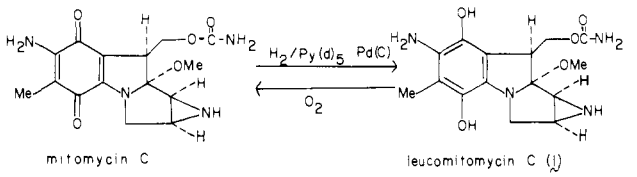
sharply reduced. (At the moment we are unable to carry out the transfer from the NMR tube to the IR cell without incurring some slight oxidation). The infrared spectrum of the material produced by air oxidation of the leuco compound is identical with that of the original **5**. *On the basis of its infrared and NMR spectra,*[13] *and on the basis of its clean reconversion to* **5**, *the leuco compound can be confidently formulated as* **6**.[14]

The leuco compound, **6**, can also be generated by reduction of **5**, in ethanol. Upon proper sensitivity to experimental detail, when an ethanolic solution of compound **6** is evaporated to dryness and the residue redissolved in pyridine-$d_5$, the resulting NMR spectrum is virtually identical with that obtained when the reduction is carried out in pyridine directly. However, the material handled in this way is of lower purity than that generated directly in pyridine **5**. Reoxidation of compound **6** generated in ethanol also restores essentially pure **5**.




An identical reduction in pyridine-$d_5$ was carried out with mitomycin C. Again, a leuco product was produced. The NMR spectrum (at 490 MHz) of this lecuo system is similar to, but clearly different from, that of mitomycin C. In this case, the NMR spectroscopic measurements were complicated both by serious line broadening (possibly due to the aminohydroquinone and secondary (NH) aziridine functionalities) and by the presence of a large $H_2O$–HOD resonance.[15] Though the multiplicities of the various signals are not sufficiently resolved to allow for full assignment of the NMR spectrum, its key features including the signals from the $C_6$ Me ($\delta$ 2.46, s, 3 H), the $C_{9a}$ OMe (3.31, s, 3 H), and the six remaining carbon-bound protons are clearly discerned.[15] Once again, treatment of the leuco solution with oxygen results in the immediate regeneration of essentially pure mitomycin C, as evidenced by its virtually clean NMR spectrum. Adventitious oxidation of the leuco dihydro system **1** is even more facile than the corresponding process in the case of compound **6**. Thus, the act




of transferring compound **1** from the NMR tube to an IR cell resulted in substantial reoxidation back to mitomycin C thereby compromising the value of the infrared spectrum. However, as in the B series, elimination to the indolohydroquinone **2** is by no means automatic. In fact, from an experimental standpoint, avoidance of reoxidation back to the parent mitomycin poses a greater challenge than avoidance of elimination.

The dihydro (leuco) compounds constitute new access points for understanding the biological behavior of the fascinating family of mitomycin drugs. Experiments intended to further that understanding are planned.

**Acknowledgment.** This work was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210. We also thank Dr. K. Shirahata of the Kyowa Chemical Co. for a gift of mitomycin B.

**Registry No.** **1**, 92056-69-4; **5**, 4055-40-7; **6**, 92056-68-3; mitomycin C, 50-07-7.

**Supplementary Material Available:** Experimental procedures for the preparations of dihydro(leuco)mitomycins **1** and **6**, and NMR spectral tabulations (4 pages). Ordering information is given on any current masthead page.

(13) The fully assigned NMR spectrum of compound **6** in conjunction with that of compound **5** is provided in the supplementary material.

(14) Our NMR data[13] do not decisively deal with the question to whether the leuco compound might exist as its azocinone (secondary amino keto valance isomer). The FT IR spectrum does not suggest the presence of an additional ketone.

(15) The chemical shifts of these protons are provided in the supplementary material. However, due to serious line broadening in the NMR spectrum of the leuco compound, a definitive assignment of protons via decoupling is not possible. By running the 490-MHz spectrum at 40 °C, the $H_2O$–HOD absorption is moved upfield and out of the range of the critical methine and methylene protons.

## Synthesis of Prostaglandins via a 2,3-Dioxabicyclo[2.2.1]heptane (Endoperoxide) Intermediate. Stereochemical Divergence of Enzymatic and Biomimetic Chemical Cyclization Reactions

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The view that prostaglandin (PG) biosynthesis from $C_{20}$ polyunsaturated fatty acids occurs by a free radical process through intermediates such as **1**–**3**[1] is supported by the actual isolation of the endoperoxides $PGG_2$ and $PGH_2$.[2] In this paper we report the first realization of a purely chemical synthesis of prostaglandins by a free radical pathway through an endoperoxide intermediate. Evidence is also provided that the enzymatic and purely chemical pathways differ with regard to stereochemical preference in the step that determines the relative orientation of the two appendages on the 2,3-dioxabicyclo[2.2.1]heptane nucleus. A rational explanation is offered for the selective formation of cis oriented appendages (exo,exo and endo,endo) in the nonenzymatic ring closure to the endoperoxide system.

For this study we utilized as substrates the racemic[3] isomeric hydroperoxides **4** and **5** which differ with regard to geometry of the homoallylic 3,4 double bond. These hydroperoxides were obtained in ca. 45% overall yield from the corresponding alcohols by (a) conversion to mesylate using mesyl chloride–triethylamine in $CH_2Cl_2$ at −78 °C for 20 min, (b) reaction of the mesylate with a dry (20%) solution of hydrogen peroxide in ether initially at −110 °C (30 min) then at −110 to −78 °C (30 min) and finally at −78 °C (1 h) and (c) quenching the reaction mixture at −78 °C with deionized water, extraction with ether, and preparative sg TLC[4] at 5 °C using 1:1 ether–hexane containing 1% of triethylamine

(1) Nugteren, D. H.; Beerthuis, R. K.; van Dorn, D. A. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 405.

(2) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 899.

(3) All intermediates and products described herein are racemic. Satisfactory $^1H$ NMR, infrared, ultraviolet and (in the case of thermally stable substances) mass spectral data were obtained for each new compound.

(4) Thin-layer chromtography on silica gel.

(5) The hydroperoxides **4** and **5** were obtained in 90% yield as a 1:1 mixture with the isomeric hydroperoxide having the (*E*,*E*)-diene unit and hydroperoxide function at C(10). The byproduct, apparently formed as a result of a competing $S_Ni$ pathway, was not separated since it did not interfere with either the formation or purification of **6** or **7** in the next step.

(6) For previous use of this methodology, see: Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.

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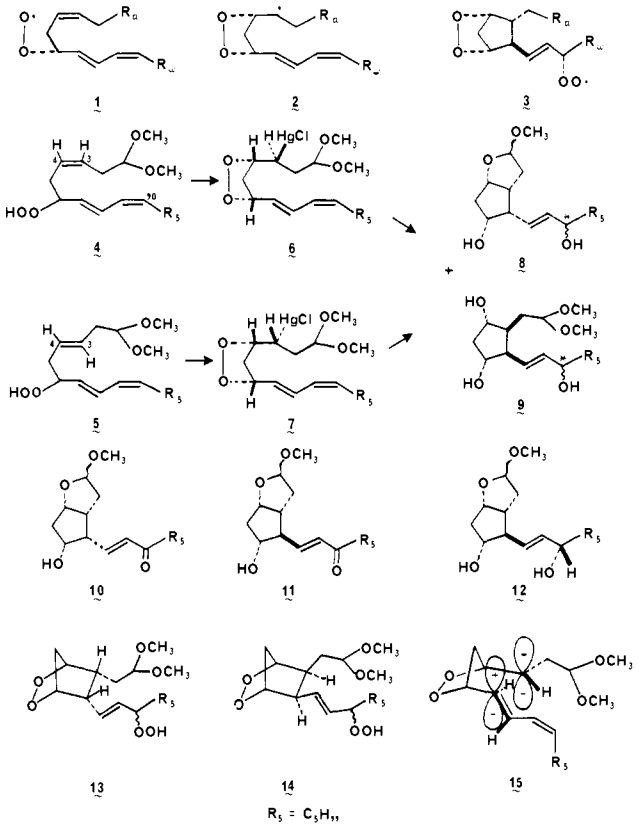
as eluant.[5,6] Separately, **4** and **5** were selectively converted (in 80% and 93% yield) to diastereomeric cis-3,5-disubstituted 1,2-dioxolanes **6** and **7**, respectively, by reaction[7,8] at 0 °C in THF with mercury(II) chloroacetate (1.5 equiv for 1 h and thereafter an additional 0.8 equiv for 1 h) followed by extractive isolation from saturated aqueous sodium chloride and sg TLC (20:1 $CH_2Cl_2$–ether for elution).[9] Conversion of **6** and **7** to endoperoxides was effected by the following process: (1) reaction with 3 equiv of tri-*n*-butyltin hydride in chlorobenzene under argon at −40 °C for 0.5 h to form an unstable reduced organomercurial which could be detected by sg TLC as a strong UV absorbing spot ($R_f$ 0.46 vs. 0.56 for **6** or **7** using 20:1 $CH_2Cl_2$–ether)[10] and (2) bubbling air through the reaction mixture which was allowed to warm from −40 to 0 °C over 1 h and then kept at 0 °C for an additional 2 h.[11] Because the resulting isomeric endoperoxides showed virtually identical chromatographic mobilities, the products were processed by the sequence: (1) endoperoxide reduction[2] at 0 °C with triphenylphosphine in isopropyl alcohol, (2) treatment with 0.02 M pyridinium tosylate in methanol at 23 °C for 24 h to effect internal transacetalization, and (3) purification by sg TLC. In this way there was obtained cyclic acetal **8** (as a separable 1:1 mixture of epimers at C*) and noncyclic acetal **9** (1:1 mixture of epimers at C*). The total yield of **8** and **9** varied from 60% to as high as 90% with a ratio of **8**/**9** of 2:1.[12] *The same mixture of* **8** *and* **9** *was obtained starting from either* **6** (originating from hydroperoxide **4**) *or* **7** (originating from hydroperoxide **5**). $^1$H NMR analysis of **8** and **9** indicated that in the former the cyclopentane substituents are all cis whereas in the latter the carbon substituents are cis to one another and trans to the hydroxyls.[13,14] Independent proof was obtained for **8** by $MnO_2$ oxidation of the mixture to enone **10**, which though readily distinguishable from an authentic sample of enone **11**[15] was cleanly converted to it by heating with 75 equiv of acetic acid and 25 equiv of morpholine in 2:1 dimethoxyethane–water at 70–75 °C for 72 h.[16] Reduction of **11** with Noyori's chiral aluminum hydride reagent[17] to 50% conversion gave the 15*S* alcohol **12** with >95% stereoselectivity by GC analysis (along with unreacted 15-ketone). Diol **12** had been converted to prostaglandins in an earlier synthesis.[18] The first biomimetic route for the synthesis of PGs was thus demonstrated.[19]




These results also show that regardless of whether the initiating radical is generated from *cis*-1,2-dioxolane diastereomer **6** or **7** the same mixture of endo,endo- and exo,exo-4,5-disubstituted 1,2-dioxabicyclo[2.2.1]heptanes (**13** and **14**) is formed. *None* of the more stable diastereomers with the carbon appendages trans to one another could be detected by a careful HPLC analysis of total endoperoxide after peroxide reduction, methanolic pyH$^+$ treatment, and oxidation to enone as described above for intermediates **8** and **10**, an analysis capable of sensing <2% of enones with trans appendages. It has previously been reported[13] that the endoperoxides generated in low yield from linolenic acid by (1) oxidation with soybean lipoxygenase and (2) subsequent autoxidation consist mainly of compounds in which the carbon side chains are cis.

An attractive explanation for the highly selective radical closure to cis-4,5-disubstituted dioxabicyclo[2.2.1]heptanes **13** and **14** is the following. The carbon radical which initiates endoperoxide closure is stabilized by endo n-electron delocalization from the nearest peroxy oxygen[8] and also the $\pi$-orbital of the other carbon appendage into the half filled p-orbital. Because of this delocalization the stable conformer of that radical may be that shown in **15**; i.e., the $\pi$ nodal planes of the carbon radical (assuming $sp^2$ hybridization) and the trans olefinic unit coincide with one another and with dioxolane ring atoms 3 and 5 to which they are attached. With the ring proximal appendage C–H bonds projecting inward as indicated in **15** (to minimize steric repulsions) the (parallel) p-orbitals must be phased as shown for a stabilizing $\pi$ interaction to occur between the side chains. From this minimum-energy conformer ring closure to endoperoxide will involve rotation of syn p-orbital lobes toward one another (disrotatory motion) and must lead to cis, i.e., endo,endo- or exo,exo-oriented appendages. The generality of this stereochemical preference for endoperoxide

(7) Bloodworth, A. J.; Bylina, G. S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2423.

(8) Corey, E. J.; Schmidt, G.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 3169.

(9) The cis orientation of substituents in the 1,2-dioxolanes **6** and **7** follows from subsequent cyclization to 2,3-dioxabicyclo[2.2.1]heptanes. The trans isomers of **6** and **7** were obtained along with **6** and **7** (2:1 ratio trans/cis) when the internal peroxymercuration was carried out in $CH_2Cl_2$ as solvent. The cis and trans chloromercurated 1,2-dioxolanes are quite stable to sg chromatography and storage at 0 °C and are readily purified by sg TLC. The diastereomeric *cis*-1,2-dioxolanes **6** and **7** are clearly distinguished by their 270-MHz $^1$H NMR spectra.

(10) The reduced mercurial is relatively stable at −40 °C but gradually decomposes with formation of elemental mercury at −10 to 0 °C.

(11) The major byproducts accompanying the conversion of **6** and **7** to 1,2-dioxabicyclo[2.2.1]heptanes were the two diastereomeric alcohols corresponding to replacement of HgCl in **6** and **7** by OH (yield ca. 3%), presumably formed by oxygenation of the initially formed radical. Sodium borohydride[8] was not a satisfactory reagent for the conversion of **6** or **7** to endoperoxide.

(12) The ratio of **8**/**9** was found to depend on the medium used for the conversion of **6** or **7** to endoperoxide. Use of 3:1 isopropyl alcohol-chlorobenzene or 50% aqueous methanol–chlorobenzene (3:1) afforded a mixture of **8** and **9** in a ratio of 1:2. Autoxidation[13] of **4** or **5** did not furnish detectable amounts of endoperoxide.

(13) O'Connor, D. E.; Mihelich, E. D.; Coleman, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 223; **1984**, 106, 3577. See also: Porter, N. A.; Zuraw, P. J.; Sullivan J. A. *Tetrahedron Lett.* **1984**, *25*, 807.

(14) Mizsak, S. A.; Slomp, G. *Prostaglandins* **1975**, *10*, 807.

(15) By HPLC or $^1$H NMR. The $^1$H NMR peak due to the $\beta$ enone proton occurs at $\delta$ 7.03 for **10** and $\delta$ 6.66 or 6.69 for the acetal diastereomers of **11**.

(16) This epimerization, thought to occur via reversible dienamine formation, could not be effected by a variety of basic ($Et_3N$, DBU, $K_2CO_3$, KOAc, $Al_2O_3$) or acidic catalysts because of intervening decomposition.

(17) Noyori, R.; Tombino, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843.

(18) Corey, E J.; Noyori R. *Tetrahedron Lett.* **1970**, 307.

(19) The synthesis of the cis or trans homoallylic alcohols corresponding to hydroperoxides **4** and **5** was effected by the addition of 1-nona-1(*E*),3-(*Z*)-dienyllithium to either *cis*- or *trans*-hex-3-enedial mono methyl acetal. The synthesis of the mono methyl acetals of *E*- and *Z*-hept-3-enediol was carried out from the methyl acetal of hept-3-yn-6-enal by catalytic hydroxylation ($OsO_4$–N-methylmorpholine–$H_2O_2$), reduction ($LiAlH_4$ or Lindlar catalyst), and glycol cleavage ($Pb(OAc)_4$). The nonadienyllithium reagent was generated from the corresponding tributyltin compound which was synthesized from non-1-yn-3(*Z*)-ene (Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719) by hydrozirconation and metal exchange with tri-*n*-butyltin triflate (Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2419).

formation is indicated by extensive studies in these laboratories to be described elsewhere which show that the preference is maintained for the full eicosanoid side chains with $\Delta^{12,13}$ cis and $\Delta^{14,15}$ either cis or trans.[20] Clearly the PG synthetase must control stereochemistry in the face of this intrinsic kinetic bias either by preventing the initiating carbon radical from assuming a conformation analogous to **15** or by forcing a conrotatory closure.[21]

**Supplementary Material Available:** $^1$H NMR, IR, UV, and MS data for new compounds (3 pages). Ordering information is given on any current masthead page.

(20) Corey, E. J.; Shih, C.; Shimoji, K. *Tetrahedron Lett.*, in press.

(21) This research was assisted financial by a grant from the National Science Foundation. We thank Drs. John O. Albright and Claude Le Drian for providing samples of the alcohol corresponding to **4**.

## Correlation between Metal–Metal Distances and Optical Spectroscopy in the Platinum Blues: Synthesis, Crystal Structure, and Electronic Spectrum of Ethylenediamineplatinum α-Pyridone Blue

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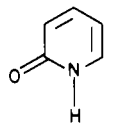
*Received May 29, 1984*

Interest in blue platinum species, known to form by oxidation of a variety of Pt(II) complexes with potentially bridging ligands, remains high.[1] Unfortunately, the paucity of pure samples and single crystals of these often oligomeric complexes leaves basic questions about their chemical nature unanswered. Despite extensive studies of their physical properties, the intriguing colors observed in solid samples of these materials are poorly understood. The only platinum blue that has previously been crystallized and characterized by X-ray diffraction is *cis*-diammineplatinum α-pyridone blue (**1**),[2] an amidate-bridged, mixed-valent, metal–



α-pyridone, $C_5H_5NO$

metal-bonded $Pt_4$ complex with an average platinum oxidation state of 2.25. We now wish to describe the syntheses of two new crystalline platinum blues, the properties of which substantially enhance our understanding of this interesting class of compounds. Here we report the preparation, *x*-ray crystal structure, magnetic properties, and assignment of the visible spectroscopic bands of ethylenediamineplatinum α-pyridone blue ($[Pt_4(en)_4(C_5H_4NO)_4](NO_3)_5\cdot H_2O$ (**2**)). In the accompanying paper[3] we describe the synthesis, properties, and crystal structure of *cis*-diammineplatinum 1-methyluracil blue (**3**), the first structurally

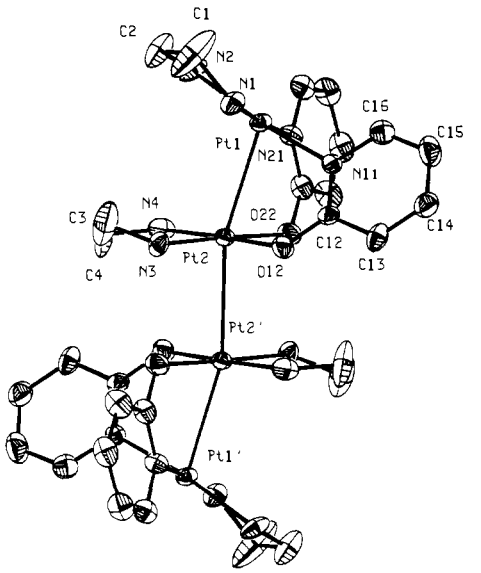



**Figure 1.** Structure of the $[Pt_4(en)_4(C_5H_4NO)_4]^{5+}$ cation (**2**) showing the 40% probability thermal ellipsoids and atom labeling scheme. Hydrogen atoms have been omitted for clarity. Selected interatomic distances: Pt1–Pt(2), 2.8296 (5); Pt2–Pt2, 2.9058 (6); ⟨Pt–N(en)⟩, 2.04 (1); ⟨Pt–N(α-pyridone)⟩, 2.04 (1); ⟨Pt–O⟩, 2.04 (1); Pt1–Pt2 twist angle $\omega$ = 24.3°, tilt angle $\tau$ = 32.1°.

characterized pyrimidine blue. Both the direction and relative magnitude of the shifts of the two principal absorption bands in **1–3** correlate with changes in the Pt–Pt distances and this result is discussed in terms of a model based on a recent SCF-X$\alpha$ calculation for **1**.[4] The relationship between stereochemistry and electronic structure established here should prove valuable in understanding related platinum clusters.

Attempts to modify the synthetic procedure used for **1**[2b] failed to produce **2**, yielding only the known[5] head-to-head Pt(II) complex $[Pt_4(en)_4(C_5H_4NO)_4](NO_3)_4$ (**4**). It was possible, however, to oxidize 70 mg (43 μmol) of **4** dissolved in 15 mL of $H_2O$ with 20 mg (21 μmol) of the binuclear Pt(III) head-to-head complex $[Pt_2(en)_2(C_5H_4NO)_2(NO_2)(NO_3)](NO_3)_2\cdot 0.5H_2O$ (**5**),[6] in 1 mL of 3 M $HNO_3$, to obtain **2** and the head-to-head Pt(II) dimer $[Pt_2(en)_2(C_5H_4NO_2)]^{2+}$ (**6**) eq 1. After the nitric acid concen-

$$2(Pt_4^{II}) + (Pt_2^{III}) \rightarrow 2(Pt_3^{II}Pt^{III}) + (Pt_2^{II}) \qquad (1)$$
$$\mathbf{4} \qquad \mathbf{5} \qquad \mathbf{2} \qquad \mathbf{6}$$

tration of the resulting mixture was adjusted to 0.5 M, the blue solution was immediately frozen. Warming to 4 °C and filtration gave a blue powder in 40% yield which was recrystallized by dissolving in water at 0 °C and adjusting the $HNO_3$ concentration to 0.5 M to form **2**.[7]

X-ray crystallographic study[8] showed **2** to be nearly isomorphous with **1**. The structure of the tetranuclear $[Pt_4(en)_4(C_5H_4NO)_4]^{5+}$ cation, displayed in Figure 1, is very similar to that of **1** except for the Pt(1)–Pt(2) and Pt(2)–Pt(2) distances. These have increased by 0.055 and 0.029 Å, respectively, due mainly to nonbonding steric interactions between ethylenediamine

(1) (a) Lippert, B.; Neugebauer, D. *Inorg. Chem.* **1982**, *21*, 451. (b) Matsumoto, K.; Fuwa, K. *J. Am. Chem. Soc.* **1982**, *104*, 897. (c) Laurent, J.-P.; Lepage, P.; Dahan, F. *J. Am. Chem. Soc.* **1982**, *104*, 7335. (d) Laurent, J.-P.; Lepage, P.; Castan, P.; Arrizabalaga, P. *Inorg. Chim. Acta* **1982**, *67*, 31. (e) Appleton, T. G.; Berry, R. D.; Hall, J. R. *Inorg. Chim. Acta* **1982**, *64*, L229. (f) Woollins, J. D.; Rosenberg, B. *J. Inorg. Biochem.* **1983**, *19*, 43. (g) Arrizabalaga, P.; Castan, P.; Laurent, J.-P. *J. Am. Chem. Soc.* **1984**, *106*, 1300. (h) Matsumoto, K.; Takahashi, H.; Fuwa, K. *J. Am. Chem. Soc.* **1984**, *106*, 2049.

(2) (a) Lippard, S. J. *Science (Washington, D.C.)* **1982**, *218*, 1075. (b) Barton, J. K.; Szalda, D. J.; Rabinowitz, H. N.; Waszczak, J. W.; Lippard, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 1434. (c) Barton, J. K.; Caravana, C.; Lippard, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 7269.

(3) Mascharak, P.; Williams, I. D.; Lippard, S. J. *J. Am. Chem. Soc.*, following paper in this issue.

(4) Ginsberg, A. P.; O'Halloran, T. V.; Fanwick, P. E.; Hollis, L. S.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 5430.

(5) Hollis, L. S.; Lippard, S. J. *Inorg. Chem.* **1983**, *22*, 2600.

(6) O'Halloran, T. V.; Roberts, M. M.; Lippard, S. J., manuscript in preparation.

(7) Chemical anal. Calcd for $Pt_4C_{28}H_{50}N_{17}O_{20}$: C, 19.49; H, 2.92; N, 13.80. Found: C, 19.49, 19.39, H, 2.93, 2.88; N, 13.41, 13.39.

(8) Crystallographic analysis. The compound $[Pt_4(H_2NCH_2CH_2NH_2)_4(C_5H_4NO)_4](NO_3)_5\cdot H_2O$ crystallizes in the triclinic system, space group $P\bar{1}$, with $a$ = 10.652 (1) Å, $b$ = 13.068 (2) Å, $c$ = 9.413 (1) Å, $\alpha$ = 108.14 (2)°, $\beta$ = 96.62 (1)°, $\gamma$ = 68.39(1)°, $V$ = 1157.7 Å$^3$, $\rho_{obsd}$ = 2.485 (5) g cm$^{-3}$, $\rho_{calcd}$ = 2.474 g cm$^{-3}$. By use of 2918 unique observed reflections collected with Mo K$\bar{\alpha}$ (λ 0.7107 Å) radiation out to $2\theta$ = 50° on a CAD-4F single crystal diffractometer, the structure was solved and refined anisotropically to a current value of 0.030 for the discrepancy index $R_1$. Further work is in progress to locate and refine the position of the lattice water molecule suggested by the analytical data. Atomic and thermal parameters are provided as supplementary material.

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