Synthesis and Structure of Dinuclear Complexes of Platinum(IV) Having *cis*-Diamine Geometry

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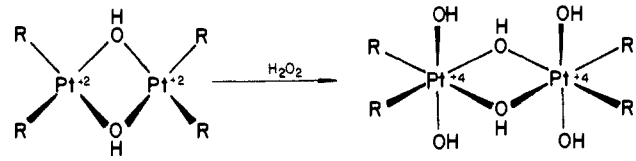
The antitumor agent *cis*-$Pt(NH_3)_2Cl_2$ (**1**) is clinically used for the treatment of various types of cancer.[1] The compound is believed to exhibit its cytotoxic effects through loss of the bound chloride ions followed by ligation of the platinum nucleus to cellular DNA.[2] Studies of the solution properties of the compound in the absence of DNA have revealed that under certain conditions the complex can undergo oligomerization to produce hydroxo-bridged dimers and trimers which have been characterized by X-ray crystallography.[3] Although these compounds are themselves active as antitumor agents, they are more toxic than the parent compound **1**.[4] In light of the observation that a number of mononuclear platinum(IV) complexes such as *cis,cis,trans*-$Pt(NH_2CH(CH_3)_2)_2(Cl)_2(OH)_2$ (**2**) are active as antitumor agents but generally less toxic than platinum(II) compounds,[1] we have attempted to moderate the toxicity of a group of platinum(II) dimers by oxidizing them to Pt(IV).

In this paper we describe the preparation of dinuclear Pt(IV) complexes produced by oxidation of platinum(II) dimers with hydrogen peroxide.[5] In addition to characterizing the compounds using elemental analysis and infrared, and ^{195}Pt NMR spectroscopies, we have determined the structure of one of the complexes using single-crystal X-ray analysis.

The necessary precursor dinuclear platinum(II) complexes shown in Figure 1, $[Pt^{II}(R)_2(\mu\text{-}OH)]_2(NO_3)_2$ where R is NH_3, $NH_2CH(CH_3)_2$, and $NH_2CH_2CH_3$ (**3-5**), were prepared by a modification[6] of the procedure of Boreham.[7] Dissolution of ~1 mmol of a platinum(II) dimer in 3 mL of water followed by addition of 2 mL of 30% aqueous H_2O_2 resulted in the formation of a yellow solution from which **6-8** crystallized as pale yellow needles.[8] No evidence for oligomers higher than order 2 which may be formed in the synthesis was obtained.



3, NH_3
4, $NH_2CH(CH_3)_2$
5, $NH_2CH_2CH_3$

6, NH_3
7, $NH_2CH(CH_3)_2$
8, $NH_2CH_2CH_3$

Figure 1. Structures of the dinuclear platinum complexes are shown.

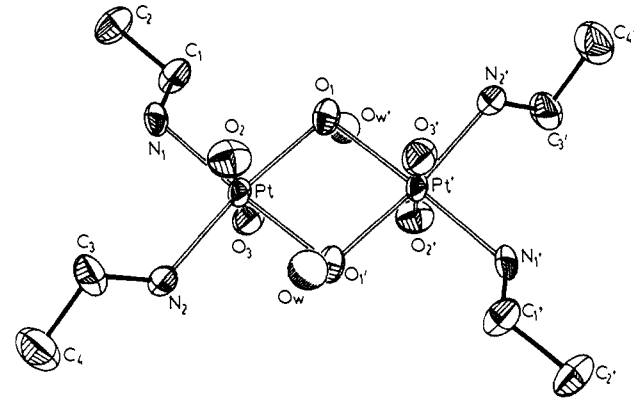


Figure 2. ORTEP Plot of $[cis,trans\text{-}Pt^{IV}(CH_3CH_2NH_2)_2(OH)_2(\mu\text{-}OH)]_2^{2+}$. The oxygen atoms of the two symmetry-equivalent water molecules of hydration are shown as spheres w and w' for the purpose of clarity. All non-hydrogen atoms are represented by thermal vibrations ellipsoids drawn to encompass 50% of their electron density. Atoms labeled with a prime are related to those labeled without a prime by the crystallographic inversion center at $^1/_2$,0,0 in the unit cell.

Compound **5**, containing [^{15}N]ethylamine, exhibited a three-line ^{195}Pt NMR spectrum centered at -1326 ppm.[9] The pattern of the lines and their relative intensities (1:2:1) indicated platinum coupling with a value of $J(^{195}Pt\text{-}^{15}N)$ of 370 Hz, to two symmetry-equivalent nitrogen-15 nuclei ($I = ^1/_2$). The ~150 ppm upfield shifts of the resonance of both **4** and **5** relative to **3** is due to the inductive effects of the alkyl amines on the platinum nucleus.

Although the ^{195}Pt NMR resonances for the **6-8** were in a region expected for a Pt(IV) complexes having two nitrogen and four oxygen atoms as donor ligands, e.g., *cis*-Pt-$((CH_3)_2CHNH_2)_2(OH)_4$,[10] they were shifted 400 ppm to lower field relative to the resonances of their mononuclear counterparts. This shift, which has been observed for other dinuclear Pt(II) and Pt(IV) compounds,[5a,7] appears to be due to the presence of the strained four-membered, Pt-O-Pt chelate ring. The three-line coupling pattern with relative line intensities of 1:2:1 observed for ^{15}N-enriched **8** is consistent with the presence of Pt(IV) ($J(^{195}Pt\text{-}^{15}N)$ = 317 Hz) and two symmetry-equivalent nitrogen nuclei per platinum. As expected the Pt-O-H bending mode which occurs at ~1040 cm^{-1} in the infrared spectra of the divalent dimers[11] shifts to lower energy upon oxidation to Pt(IV).[8]

The structure of the complex ion $[cis,trans\text{-}Pt^{IV}(CH_3CH_2NH_2)_2(OH)_2(\mu\text{-}OH)]_2^{2+}$ is shown in Figure 2.[12,13]

(1) Prestayko, A. W.; Crooke, S. T.; Carter, S. K. *Cisplatin: Current Status and New Developments*; Academic Press: New york, 1980.

(2) (a) Lippard, S. J. *Science (Washington, D.C.)* **1982**, *218*, 1075. (b) Marcelis, A. T. M.; Reedijk, J. *Recl. Trav. Chim. Pays-Bas* **1982**, *103*, 121. (c) Rosenberg, B. *Biochemie* **1978**, *60*, 859.

(3) (a) Lock, C. J. L.; Bradford, J.; Faggiani, R.; Speranzini, R. A.; Turner, G.; Zvagulis, M. *J. Clin. Hematol. Oncol.* **1977**, *7*, 63. (b) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B. *Inorg. Chem.* **1978**, *17*, 1941. (c) Lippert, B.; Lock, C. J. L.; Rosenberg, B.; Zvagulis, M. *Inorg. Chem.* **1978**, *17*, 2971. (d) Macquet, J.; Cros, S.; Beauchamp, A. L. *J. Inorg. Biochem.* **1985**, *25*, 197.

(4) (a) Broomhead, J. A.; Fairlie, D. P.; Whitehouse, M. W. *Chem. Biol. Interact.* **1980**, *31*, 113. (b) Roos, I. A.; Fairlie, D. P.; Whitehouse, M. W. *Chem.-Biol. Interact.* **1981**, *35*, 11. (c) Aggarwal, S. K.; Broomhead, J. A.; Fairlie, D. P.; Whitehouse, M. W. *Cancer Chemother. Pharmacol.* **1980**, *4*, 249.

(5) Examples of other dinuclear Pt(IV) complexes: (a) Agnew, N. H.; Appleton, T. G.; Hall, J. B. *Aust. J. Chem.* **1982**, *35*, 881. (b) Kretschner, V. M.; Heck, L. *Z. Anorg. Allg. Chem.* **1982**, *490*, 205.

(6) In the modification it was found advantageous to isolate the mononuclear *cis*-dinitrato salts which upon redissolution in water and adjustment of the pH to 6.0 gave high yields (80%) of the divalent dimers in 10 h. Synthesis of ^{15}N enriched **5** required 95% mol enriched ^{15}N ethylamine hydrochloride.

(7) Boreham, C. J.; Broomhead, J. A.; Fairlie, D. P. *Aust. J. Chem.* **1981**, *34*, 659.

(8) Anal. Calcd for **6**$(NO_3)_2$: H, 2.63; N, 12.27; Pt, 57.02; O, 28.06. Found: H, 2.65; N, 12.00; Pt, 57.33; O, 27.96. Yield 54%. Calcd for **7**$(NO_3)_2 \cdot 2H_2O$: C, 16.21; H, 5.18; N, 9.46. Found: C, 15.86; H, 5.07; N, 9.47. Yield 62%. Calcd for **8**$(NO_3)_2$: C, 12.06; H, 4.27; N, 10.55; Found: C, 11.99; H, 4.33; N, 10.53. Yield 78%. Analysis showed these compounds to be hydroscopic and to take up a maximum of two water molecules of hydration. IR data in Nujol mulls using KBr disks, δ(Pt-O-H), cm^{-1}: **3**, 1038 m; **4**, 1040 m; **5**, 1035 m; **6**, 1025 m; **7**, 1035 w; **8**, 1020 m.

(9) The ^{195}Pt NMR data were collected in 50-60 mM aqueous solutions with a homemade NMR spectrometer equipped with a 10-mm probe operating at 53.8 MHz. The chemical shifts relative to aqueous Na_2PtCl_6 and values of $J(^{195}Pt\text{-}^{15}N)$, in parentheses: **3**, -1161;[7] **4**, -1322; **5**, -1326 (370 Hz); **6**, 2066; **7**, 2053; **8**, 1925 (317 Hz).

(10) Ismail, J. M.; Sadler, P. J. *ACS Symp. Ser.* **1983**, *No. 209*, 171.

(11) Stanko, J. A.; Hollis, L. S.; Schreifels, J. A.; Hoeschele, J. D. *J. Clin. Hematol. Oncol.* **1977**, *7*, 140.

(12) The space group is $P2/n$—an alternate setting of $P2/c\text{-}C_{2h}^4$ with a = 13.834 (3) Å, b = 5.262 (1) Å, c = 15.524 (3) Å, β = 102.06 (2)°, and Z = 2 for D_{calcd} = 2.45. Least-squares refinement on the basis of 1947 observed reflections converged to a final $R = \sum(|F_o| - |F_c|)/\sum|F_o| = 0.045$. Hydrogen atoms were not included in the refinement.

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Reference to the crystal structure of the divalent dimer [*cis*-$Pt^{II}(NH_3)_2(\mu\text{-}OH)]_2^{2+}$ [3a,c] revealed that oxidation to Pt(IV) has little effect on the geometry of the bridging four-membered ring. Comparative Pt-Pt distances and Pt-O-Pt bond angles for the two dimers respectively are 3.090 (1) Å, Pt(IV), 3.085 (1) Å, Pt(II), and 98.2 (3)°, Pt(IV), and 99 (1)°, Pt(II). Each of the water molecules of hydration shown in Figure 2 is within hydrogen-bonding distance of the bridging hydroxo group (3.332 Å) and the two terminal hydroxy ligands (O_w-O_2, 2.771 Å; O_w-O_3', 3.067 Å).

In this work we show that it is possible to oxidize μ-hydroxo Pt(II) dinuclear compounds to dinuclear Pt(IV) species having the *cis*-diamine geometry. The antitumor and DNA binding properties of the new compounds will be reported subsequently.

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Supplementary Material Available: Tables of crystal data, bond distances, angles, atomic coordinates, and a numbered ORTEP plot of $[Pt(OH)_3(NH_2CH_2CH_3)_2]_2[NO_3][NO_2]\cdot 2H_2O$ (5 pages); table of observed and calculated structure factors for $[Pt(OH)_3(NH_2CH_2CH_3)_2]_2[NO_3][NO_2]\cdot 2H_2O$ (9 pages). Ordering information is given on any current masthead page.

(13) The intensity of six reflections dropped uniformly as a nearly linear function of exposure time, 14% at the end of the first shell ($3° \leq 2\theta(\text{Mo K}\alpha) \leq 43°$) and 30% at the end of the second shell ($43° \leq 2\theta(\text{Mo K}\alpha) \leq 55°$). Reference to earlier work[11] and observation of the NO_3^- groups in the complex revealed that most likely one of the nitrate ions had undergone photolysis to NO_2^- in the X-ray beam.

Catalytic Effect of Nickel(II) Chloride and Palladium(II) Acetate on Chromium(II)-Mediated Coupling Reaction of Iodo Olefins with Aldehydes

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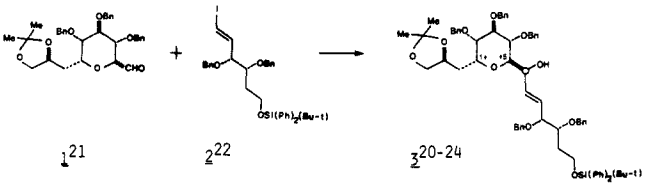
During the synthetic studies on the marine natural product palytoxin,[1-3] we were faced with a problem to transform the aldehyde **1** or its derivative into the trans-allylic alcohol **3**, which seemed possible by using routine synthetic operations. However, we soon realized that standard synthetic routes such as Wittig and aldol approaches were not as practical as we hoped.[3] Among many possibilities attempted, a coupling using organocuprates gave

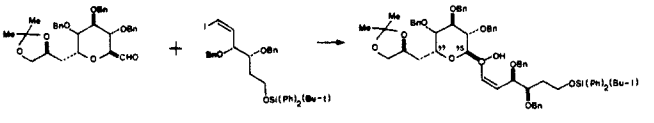


1[21] **2**[22] **3**[20-24]

1	2	$NiCl_2$(0.1%)-$CrCl_2$/DMSO	3 (ratio of 16α:16β stereoisomers)
1.0 eq	1.5 eq	ca. 1.5 eq	55% (1.3:1)
1.0 eq	1.5 eq	ca. 3 eq	60% (1.3:1)
1.0 eq	3.0 eq	ca. 6 eq	71% (1.3:1)
1.0 eq	10 eq	ca. 10 eq	80% (1.3:1)
1.0 eq	1.5 eq	3 eq of $Pd(OAc)_2$ (1%)-$CrCl_2$/DMSO	54% (1:1)
1.0 eq	3.0 eq	$CrCl_2$ (excess) with no added $NiCl_2$	0 ~ 80% (1.3:1)

very promising results at least in the model series.[4] However, in spite of extensive efforts, we were unable to generate the desired organocuprate reagent from **2**.

The clue to the solution came from the work of Nozaki and his co-workers on chromium(II)-mediated addition of alkenyl halides to aldehydes.[5] After much trial-and-error experimentation, we were able to accomplish the required coupling by adding $CrCl_2$ to a DMSO solution of aldehyde **1** and trans-iodo olefin **2** at room temperature in the absence of oxygen. This reaction warrants several additional comments. First, we have examined a large number of highly oxygenated molecules, including α-oxygenated aldehydes and iodo olefins or β-iodo enones[6] and found the coupling to be remarkably effective even for multifunctional substrates. Functional groups tested include esters (methyl, ethyl), amides, nitriles, ketones, acyls (acetate, benzoate), acetals, ketals, ethers (benzyl, *p*-methoxybenzyl), silyl ethers [(*t*-Bu)$(Me)_2$Si, (*t*-Bu)$(Ph)_2$Si], alcohols, and olefins. Second, the stereochemistry of trans- as well as cis-iodo olefin is retained at least in the cases of disubstituted iodo olefins such as **2** and **4**.[7] Trisubstituted



1 **4**[22] **5**[20-24]

1	4	$NiCl_2$(0.1%)-$CrCl_2$/DMSO	5 (ratio of 16α:16β stereoisomers)
1.0 eq	3.0 eq	ca. 6 eq	58% (1.6:1)
1.0 eq	3.0 eq	$CrCl_2$ (excess) with no added $NiCl_2$	0 ~ 60% (1.6:1)

trans-iodo olefins and trans-iodo enones such as **6** and **10** gave the expected products; however, trisubstituted cis-iodo olefins and cis-iodo enones such as **9** and **12** yielded exclusively the trans olefins instead of the expected cis olefins.[8] Third, with respect to the newly introduced chiral center, this process produces a

(1) For the gross structures of palytoxin, see: (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781 and references cited therein. (b) Moore, R. E.; Bartolini, J. *J. Am. Chem. Soc.* **1981**, *103*, 2491 and references cited therein. For the structures of minor constituents, see: Uemura, D.; Hirata, Y.; Iwashita, T.; Naoki, H. *Tetrahedron* **1985**, *41*, 1007.

(2) For the stereochemistry assignment primarily based on organic synthesis, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369 and preceding papers. For the sterochemistry assignment primarily based on spectroscopic methods, see: Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.

(3) For synthetic studies on palytoxin, see: (a) Kishi, Y.; Christ, W. J.; Taniguchi, M. *Natural Products and Biological Activities*; Imura, H., Goto, T., Murachi, T., Narajima, T., Ed.; University of Tokyo Press: Tokyo, 1986; p 87 and references cited therein. (b) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774.

(4) The aldehyde **1** readily eliminates benzyl alcohol even under weakly basic conditions to yield the corresponding α,β-unsaturated aldehyde. This instability limited choices of reagents and conditions. Experimentally, we observed only organocuprates [$LiCu(CH_3)_2$, $LiCu(C_4H_9)_2$, $LiCu(c\text{-}CH{=}CHC_4H_9)_2$] yielded the desired products in satisfactory yield. Furthermore, the addition of organocuprates almost exclusively gave the product with the desired stereochemistry at C16.

(5) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.

(6) This excludes α-acyloxy aldehydes; reductive elimination is the major side reaction for α-acyloxy aldehydes.

(7) Disubstituted trans-iodo enones gave exclusively expected trans enones. However, experiments using disubstituted cis-iodo enones still need to be done to conclude the stereospecificity of disubstituted β-iodo enones.

(8) The reaction of **9** with **7** in the presence of $NiCl_2$-$CrCl_2$ was very sluggish to yield only the trans olefin. It is interesting to note that the recovered iodo olefin from this reaction was pure **9**. There are examples known for the cis-trans isomerization during nickel-catalyzed reactions. See ref 17 and also: Zembayashi, M.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1975**, 1719.

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