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Platinum(IV) Analogues of AMD473 (*cis*-[$PtCl_2(NH_3)$(2-picoline)]): Preparative, Structural, and Electrochemical Studies

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The preparation and oxidation of the anticancer drug AMD473, *cis*-[$PtCl_2(NH_3)$(2-pic)] (2-pic = 2-methylpyridine), has been investigated. *cis*-[$PtCl_2(NH_3)$(2-pic)] is readily oxidized with peroxide to give the *trans*-dihydroxoplatinum(IV) complex *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)]. The crystal structure of this complex reveals that it is highly strained as a result of a steric clash between the methyl group of the 2-picoline ligand and an axial hydroxo ligand, with the Pt–N–C angle adjacent to this clash opened up to an unprecedented 138.6(6)°. Attempts at converting the dihydroxoplatinum(IV) complex to dichloro and diacetato analogues were unsuccessful with reaction with HCl leading to loss and protonation of the 2-picoline ligand to form the salt (2-picH)[$PtCl_5(NH_3)$] and the platinum(II) complex *cis*-[$PtCl_2(NH_3)$(2-pic)], both confirmed by crystallography. Electrochemical studies revealed that *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)] is reduced more readily (–714 mV vs Ag/AgCl) than its pyridine analogue *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(pyridine)] (–770 mV vs Ag/AgCl) consistent with the steric clash in the former complex destabilizing the platinum(IV) oxidation state.

Introduction

Platinum(IV) complexes have potential advantages over the highly successful platinum(II)-based anticancer drugs.[1−3] In particular, they are more inert and can therefore avoid many of the reactions that both deactivate the bulk of the administered platinum(II) complexes[4,5] and contribute to the side effects. Also, the axial ligands provide additional opportunities for the tuning of the lipophilicity of the complexes[6] and can influence the rate at which the platinum(IV) compounds are reduced.[1,7,8] Increased lipophilicity and slowed reaction with deactivating agents, particularly sulfhydryl-containing compounds, should allow platinum(IV) complexes to overcome some of the mechanisms of resistance developed by tumors.

Studies of platinum(II) complexes with bulky planar ligands, such as pyridine and substituted pyridine, have shown that they too can reduce the rate of deactivation by sulfhydryl groups without interfering with the DNA binding or cytotoxic activity.[9] The sterically hindered platinum(II) complex AMD473 (*cis*-[$PtCl_2(NH_3)$(2-pic)], 2-pic = 2-methylpyridine, **1**) entered clinical trials in November 1997 and has proven to be effective in the treatment of ovarian cancer resistant to carboplatin.[10,11] The drug was designed to overcome resistance caused by cytoplasmic thiols, such as glutathione and metallothionein.[9]

Given that both steric bulk and platinum(IV) have the potential for overcoming resistance, we were interested in examining complexes in which the two are combined, specifically, platinum(IV) analogues of *cis*-[$PtCl_2(NH_3)$(2-

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pic)]. To the best of our knowledge, there have been no reports of such compounds in the literature other than in patents covering both platinum(II) and platinum(IV) analogues of *cis*-[$PtCl_2(NH_3)$(2-pic)].[12,13] Here we describe the successful preparation and characterization of one platinum(IV) analogue of *cis*-[$PtCl_2(NH_3)$(2-pic)] and studies that show that most such compounds are unstable.

Experimental Section

Instrumentation and Materials. All compounds used were of technical grade. Potassium tetrachloroplatinate(II) was obtained from Aithaca Chemical Corp. Pyridine and 2-picoline(2-methylpyridine) were obtained from Aldrich. Tetraethylammonium chloride-1-water was obtained from Merck, and all compounds were used without further purification. Hydrogen peroxide (30%) was obtained from Ajax Chemicals and stored in the dark at 5 °C. Diffuse reflectance infrared Fourier transform spectra (DRIFTS) of the complexes were obtained on a Bio-Rad FTS-7 spectrophotometer over the range 400−4000 cm^{-1} using a KBr background and matrix. Elemental analysis (C, H, N) was conducted by the Microanalytical Service of the Australian National University, Canberra. Electrochemical measurements were carried out using a BAS 100W system. Glassy carbon working electrodes, Ag/AgCl reference electrodes, and platinum wire auxiliary electrodes were used. The solutions were degassed prior to measurements using argon gas, which had previously been passed through an oxygen trap. The supporting electrolyte was tetraethylammonium chloride at a concentration of 0.1 M, and the concentration of the complexes was 2 mM. Cisplatin (*cis*-[$PtCl_2(NH_3)_2$]) was prepared as previously described.[14]

Synthesis of *cis*-Amminedichloro(2-picoline)platinum(II). Method 1. This synthesis was adapted and modified from the method previously described for *cis*-amminedichloropyridineplatinum(II) by Abrams et al.[15]

cis-[$PtCl_2(NH_3)_2$] (1.17 g, 3.9×10^{-3} mol) was used to synthesize [Et_4N][$PtCl_3(NH_3)$] dissolved in water (20 mL). One stoichiometric equivalent of 2-picoline (0.38 mL, 3.9×10^{-3} mol) was added slowly, and the mixture was stirred at room temperature in the dark for 72 h. A gray-green precipitate resulted, which was removed by filtration and washed with water. This solid was resuspended in water and stirred at 80 °C until dissolution was complete. The solution was filtered, the solvent removed, and the resulting *cis*-[$PtCl_2(NH_3)$(2-pic)] was collected as a dull yellow solid. Yield 0.35 g, 9.3×10^{-4} mol, 24%.

Method 2. This synthesis was adapted and modified from the method previously described by Kelland.[16] *cis*-[$PtCl_2(NH_3)_2$] (1.17 g, 3.9×10^{-3} mol) was used to synthesize [$(Et)_4N$][$PtCl_3(NH_3)$], dissolved in water (20 mL) as in Method 1. Water (20 mL) was added and the solution stirred before adding 2.1 stoichiometric equivalents of potassium iodide (1.36 g, 8.2×10^{-3} mol). The clear orange solution was stirred in the dark at room temperature until it turned red. Then, 1.1 stoichiometric equivalents of 2-picoline (0.40 g, 4.3×10^{-3} mol) was added slowly, and the mixture stirred until a light brown precipitate of *cis*-[$PtI_2(NH_3)$(2-pic)] formed. The solid was removed by filtration, washed with water, and dried. Yield 1.15 g, 2.1×10^{-3} mol, 53%.

Cis-[$PtI_2(NH_3)$(2-pic)] (1.15 g, 2.1×10^{-3} mol) was suspended in water (50 mL) and stirred with 2.0 stoichiometric equivalents of $AgNO_3$ (0.70 g, 4.1×10^{-3} mol) in the dark at room temperature for 6 h. The silver iodide that precipitated from solution was removed by filtration, and the filtrate was treated with dropwise additions of 1 M HCl to remove any remaining Ag^+. This step was repeated until all the Ag^+ was removed. An excess of KCl (0.56 g, 7.4×10^{-3} mol) was added, and the mixture was stirred at room temperature. After 3 h, a yellow-green precipitate of *cis*-[$PtCl_2(NH_3)$(2-pic)] formed. The solid was collected, washed with cold water, ethanol, and ether, and placed in a desiccator. Yield 0.43 g, 1.1×10^{-3} mol, 55% (29% based on *cis*-[$PtCl_2(NH_3)_2$]).

Method 3. This synthesis was adapted and modified from the method previously described by Davies et al.[17] $K_2[PtCl_4]$ (0.50 g, 1.2×10^{-3} mol) was dissolved in DMF (25 mL) and stirred. One stoichiometric equivalent of 2-picoline (0.12 mL, 1.2×10^{-3} mol) was added slowly, and the mixture was stirred at 50 °C in the dark for 6 h. The mixture changed to a dull orange color, and KCl precipitated from the solution. The KCl was removed by filtration and the DMF removed from the filtrate via rotary evaporation. Diethyl ether was added in excess to the remaining thick orange oil, and K[$PtCl_3$(2-pic)] preciptated as a buff-colored solid. This solid was collected, washed with ether, and dried in a desiccator. Yield 0.43 g, 1.1×10^{-3} mol, 91%.

K[$PtCl_3$(2-pic)] (0.43 g, 1.1×10^{-3} mol) was suspended in water (20 mL) and stirred. KI (0.38 g, 2.3×10^{-3} mol, 2.1 stoichiometric equivalents) was added, and the mixture was stirred for 3 h. The very dark brown precipitate that formed was removed by filtration and suspended in water. Ammonia (30%, 0.20 mL, 1.7×10^{-3} mol, 1.5 stoichiometric equivalents) was added to the stirring precipitate, and the reaction was watched closely until the precipitate changed from dark brown to yellow. The solid was filtered from the mixture before the yellow color turned green (indicating the formation of an aquated species and a loss of yield). The yellow solid, *cis*-[$PtI_2(NH_3)$(2-pic)] was washed with water and ether. Yield 0.45 g, 8.1×10^{-4} mol, 73%. Dry *cis*-[$PtI_2(NH_3)$(2-pic)] (0.45 g, 8.1×10^{-4} mol) was converted to the chloride as described in Method 2. Yield 0.18 g, 4.8×10^{-4} mol, 59%.

Method 4. This synthesis was adapted and modified from the method previously described by Danzeisen et al.[18] $K_2[PtCl_4]$ (0.49 g, 1.2×10^{-3} mol) was dissolved in water (10 mL) and stirred at room temperature. Five stoichiometric equivalents of KI (0.98 g, 5.9×10^{-3} mol) were added, and the solution was stirred in the dark until all the solid had dissolved. One stoichiometric equivalent of 2-picoline (0.12 mL, 1.2×10^{-3} mol) was added slowly while stirring, and the mixture was stirred in the dark, at room temperature, for 12 h. The dark brown precipitate that formed was separated by filtration and suspended in water. Slow addition of 1.5 stoichiometric equivalents of 30% ammonia (0.21 mL, 1.8×10^{-3} mol) followed, and the reaction was watched closely until the brown precipitate turned yellow. The yellow solid *cis*-[$PtI_2(NH_3)$(2-pic)] was collected, washed with cold water and ether, and dried in a desiccator. Yield 0.52 g, 9.3×10^{-4} mol, 79%. *cis*-[$PtI_2(NH_3)$(2-pic)] (0.51 g, 9.3×10^{-4} mol) was converted to the chloride as described in Method 2. Yield 0.21 g, 5.5×10^{-4} mol, 60%. IR (KBr, cm^{-1}) 3195 s, 3065 w, 1610 s, 1566 m, 1479 vs, 1452 m,

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1382 m, 1326 vs, 1293 w, 1156 w, 1112 m, 1036 w, 778 vs, 773 vs, 717 m, 485 vw.

Synthesis of *cis*-Amminedichloropyridineplatinum(II), *cis*-[$PtCl_2(NH_3)(py)$]. The synthesis of this complex follows a method described by Rochon and Kong.[19] $K_2[PtCl_4]$ (0.25 g, 6.0×10^{-4} mol) was dissolved in water (10 mL), and the solution was stirred for 15 min. KI (0.21 g, 1.3×10^{-3} mol, 2.1 stoichiometric equivalents) and 2.1 stoichiometric equivalents of pyridine (0.10 mL, 1.3×10^{-3} mol) were added to the solution, and the mixture was stirred for 6 h at 50 °C. The resultant tan solid, *cis*-$[PtI_2(py)_2]$, was collected, washed with ethanol and ether, and dried in a desiccator. Yield 0.21 g, 3.5×10^{-4} mol, 58%. *cis*-$[PtI_2(py)_2]$ (0.21 g, 3.5×10^{-4} mol) was suspended in water (20 mL) and was stirred. Perchloric acid (70%, 0.086 mL, 1.2×10^{-3} mol, 3.5 stoichiometric equivalents) (Perchlorates are potentially explosive, especially when dry, and should be handled with care.) was added, and the mixture was stirred for 12 h at 50 °C. The resultant dark brown solid was removed by filtration and resuspended in water (20 mL). Under stirring, 1.5 stoichiometric equivalents of ammonia (0.06 mL, 5.3×10^{-4} mol) were added, and the reaction was watched closely until the brown precipitate turned yellow. The yellow *cis*-$[PtI_2(NH_3)(py)]$ was collected, washed with cold water and ether, and dried in a desiccator. Yield 0.15 g, 2.8×10^{-4} mol, 80%. *cis*-$[PtI_2(NH_3)(py)]$ (0.15 g, 2.8×10^{-4} mol) was converted to the chloride as described above in Method 2. Yield 0.06 g, 1.5×10^{-4} mol, 55%. IR (KBr, cm^{-1}) 3272 vs, 3202 s, 3045 w, 1610 m, 1451 s, 1305 s, 1154 w, 1079 vw, 947 vw, 805 m, 772 vs, 691 vs.

***cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)].** *cis*-$[PtCl_2(NH_3)$(2-pic)] (0.10 g, 2.6×10^{-4} mol) was suspended in water (3 mL) and stirred at room temperature. Hydrogen peroxide (3 mL, 30%) was added dropwise, and the mixture was stirred for 24 h. The resultant yellow solution was filtered from any unreacted *cis*-$[PtCl_2(NH_3)$(2-pic)], and the filtrate reduced to near dryness via rotary evaporation. Copious amounts of ethanol were added, and a very pale yellow solid, *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)$(2-pic)], precipitated from the solution. This solid was collected, washed with ether, and dried in a desiccator. Recrystallization from water afforded diffraction-quality crystals. Yield 3.60×10^{-2} g, 8.8×10^{-5} mol, 34%. IR (KBr cm^{-1}) 3500 s, 3308 vw, 3050−2400 br, 1995 vw, 1612 w, 1490 vw, 1371 w, 1308 vw, 1070 m, 772 vs, 558 vs.

***cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(py)].** *cis*-$[PtCl_2(NH_3)$(py)] (0.10 g, 2.5×10^{-4} mol) was suspended in water (10 mL) and stirred at room temperature. Hydrogen peroxide (3 mL, 30%) was added dropwise, and the mixture was stirred for 12 h at 50 °C. The resultant yellow solution was filtered to remove any unreacted *cis*-$[PtCl_2(NH_3)$(py)], and the filtrate was reduced to near dryness via rotary evaporation. Careful additions of both water and ethanol in equal amounts to the mixture produced pale yellow crystals of *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)$(py)]. The solid was collected, washed with ether, and dried in a desiccator. Yield 0.02 g, 4.0×10^{-5} mol, 16%. IR (KBr, cm^{-1}) 3549 w, 3515 w, 3230−2780 br, 1599 w, 1455 w, 1401 w, 1210 w, 1070 m, 1012 m, 768 s, 685 s, 562 vs, 553 s.

Attempted Synthesis of [$PtCl_4(NH_3)$(2-pic)]. To a suspension of *cis*-$[PtCl_2(NH_3)$(2-pic)] (0.10 g, 2.6×10^{-4} mol) in water (3 mL) 30% H_2O_2 (3 mL) was added dropwise, and the mixture stirred at room temperature for 24 h. The resultant yellow solution was filtered from any unreacted *cis*-$[PtCl_2(NH_3)$(2-pic)]. Hydrochloric acid (1 M, 0.57 mL, 5.7×10^{-4} mol, 2.2 stoichiometric equivalents) was added dropwise, and the mixture stirred at 45 °C for 24 h. After 24 h, the resultant pale orange solution was reduced to dryness via rotary evaporation and the solid collected, washed with ether, and dried in a desiccator. Yield 2.50×10^{-2} g. Crystals suitable for X-ray diffraction were grown from water, the analysis showing the product to be (2-picH)[$PtCl_5(NH_3)$]. Other crystals, subsequently shown to be *cis*-$[PtCl_2(NH_3)$(2-pic)], were also obtained from this solution.

Table 1. Crystal Structure Data for the Platinum(IV) Complexes

	(2-picH)[$PtCl_5(NH_3)$]	*cis*,*trans*,*cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)]·H_2O
empirical formula	$C_6H_{11}Cl_5N_2Pt$	$C_6H_{14}Cl_2N_2O_3Pt$
fw	412.99	428.18
space group	*Pnma*	$P2_1/c$
a, Å	6.870(2)	9.806(2)
b, Å	8.009(2)	9.771(2)
c, Å	23.731(6)	12.207(3)
β, deg	90	97.00(3)
V, Å^3	1305.8(5)	1161(2)
Z	4	4
μ, mm^{-1}	11.50	12.53
ρ_{obsd}, g cm^{-1}	2.437	2.450
T, K	293	220
λ, Å	0.71073	0.71073
R (F_o)[a]	0.053	0.029
R_w[a]	0.057	0.030

[a] $R(F_o) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2$, $w = 1/\sigma^2(F_o)$.

Attempted Synthesis of *cis,trans,cis*-[$PtCl_2(OAc)_2(NH_3)$(2-pic)]. *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)$(2-pic)] (0.2 g, 4.9×10^{-4} mol) was suspended in neat acetic anhydride (10 mL) and stirred in a vessel capped with a drying tube to keep moisture from the reaction. The solution was stirred in the dark at room temperature for 2 weeks, after which all solids had dissolved. The mixture was then rotary evaporated to dryness. The resultant black residue was discarded. All subsequent attempts were equally unsuccessful.

X-ray Crystallography. The crystals were attached to glass fibers and mounted on a Bruker Smart 1000 CCD diffractometer using graphite-monochromated Mo Kα radiation. Data reduction, Lorentz, and polarization corrections were applied using SAINT and XPREP,[20] and absorption corrections were carried out using SADABS.[21] Direct methods were employed to solve the structures with SHELXS-86 and SHELXS-97.[22,23] Structure refinement was carried out using full matrix least-squares methods within teXsan[24] or SHELXL97.[25] Hydrogen atoms were included at calculated sites with thermal parameters (U_{iso}) set at 1.5 times that of the parent atoms, excepting those of the 2-picoline ligand in *cis*-$[PtCl_2(NH_3)$(2-pic)], which were refined isotropically. All non-hydrogen atoms were refined anisotropically. Final *R* indices and weighting schemes are as quoted in Table 1 and Table S1 (for *cis*-$[PtCl_2(NH_3)$(2-pic)]).

Results and Discussion

Syntheses. Although *cis*-$[PtCl_2(NH_3)$(2-pic)] is structurally similar to cisplatin, with one ammine ligand replaced by a 2-picoline, the synthesis requires a multistep procedure

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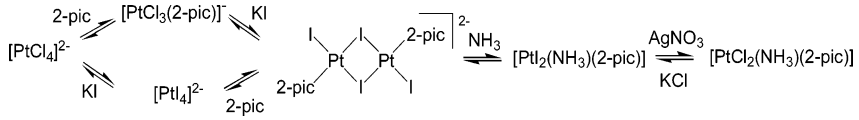
Scheme 1



leading to low yields and high levels of impurities. The preparation of mixed-donor am(m)ine platinum(II) complexes usually follows a route described by Abrams[15] that employs $[Et_4N][PtCl_3(NH_3)]$. Sadler and co-workers[26,27] have used this anion to prepare several mixed-donor platinum(II) species, but they have not reported yields of these products. In our hands, typical yields based on this method were very low, though a method recently reported by Cai et al. for preparing $[PtCl_3(NH_3)]^-$ in situ offers significant improvements.[28] Because of the difficulties, four synthetic schemes[10,15−18] were investigated in an attempt to improve the yield of *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$. All methods did indeed produce the desired product but in varying yields.

Abrams[15] has described the preparation of the ammine-trichloroplatinate(II) anion from cisplatin (Method 1). Addition of 2-picoline to this anion requires heating to 80 °C, causing substantial decomposition of the species to Pt(0) and formation of impurities. Purification of the *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ formed required dissolution in a large volume of water and further heating, giving a final yield for Method 1 of 24% based on the cisplatin starting material. To avoid heating in the previous method, a synthetic pathway first proposed by Kelland[11] using a variation of the Dhara method[14] was carried out at room temperature, in which the 2-picoline replaces an iodo rather than a chloro ligand, a process that is facilitated by the greater trans effect of iodide. However, the yield of 29% for Method 2 based on cisplatin was only slightly higher than that in the previous method, though this method produces a purer product, as evidenced by IR.

Both of these methods require cisplatin as the starting material, and the synthesis of cisplatin itself is a multistep, moderate-yielding procedure. Two other methods using $K_2[PtCl_4]$ as the starting material were therefore investigated. Method 3, adapted from Davies,[17] produces *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ in 59% yield based on $K_2[PtCl_4]$. During the multistep procedure, a platinum dimer (Scheme 1) is formed from $[PtCl_3(2\text{-pic})]$ and iodide. Upon addition of 1.5 stoichiometric equivalents of NH_3, the species is converted to *cis*-amminediiodo(2-picoline)platinum(II) with both the dimer and the product being solids, which contributes to the higher yield.

Method 4, based on a report by Danzeisen and co-workers,[18] also involves the formation of the platinum dimer species (Scheme 1) directly from $[PtI_4]^{2-}$ in water. This method requires fewer steps and affords a higher yield to the previous method, and thus is the method of choice for the synthesis of *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$.

The synthesis of *cis*-$[PtCl_2(NH_3)(py)]$ was nontrivial, as adaptations of the preferred method for the preparation of *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ led to bis-pyridine complexes, even though a stoichiometric amount of pyridine was used. Evidently, the steric bulk of the 2-picoline prevents the formation of the bis ligand complex. The method of choice which afforded the highest yield involved the preparation of *cis*-$[PtI_2(py)_2]$ as an intermediate species, removal of a pyridine ligand using perchloric acid, and addition of ammonia. A similar method has been used recently to prepare $[PtCl_2(NH_3)(\text{cyclohexylamine})]$.[29]

The dihydroxoplatinum(IV) complexes were prepared in water by hydrogen peroxide oxidation of the platinum(II) precursors. This procedure is relatively straightforward, the platinum(IV) species being more soluble than the platinum(II), hence purification by filtration then precipitation by ethanol produced the complex in high purity. An attempt to produce *cis*-$[PtCl_4(NH_3)(2\text{-pic})]$ from *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ using HCl resulted in an unexpected product, (2-picH)$[PtCl_5(NH_3)]$, in which the 2-picoline ligand had been lost and protonated. For other platinum(IV) *trans*-dihydroxo species such as *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)_2]$ and *cis*,*trans*-$[PtCl_2(OH)_2(en)]$, reaction with HCl results in replacement of the hydroxo ligands in the axial positions by chloro ligands.[7] While this was the case here, the 2-picoline ligand was also replaced by a chloro ligand, a process that was probably facilitated by the steric repulsion between an axial chloro ligand and the methyl group of the 2-picoline. Reduction of the platinum(IV) species to *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ was also observed, as evidenced by IR spectroscopy and structural analysis of crystals obtained from the solution. Despite varying the reaction times and temperatures, it was not possible to avoid the reduction and/or decomposition of the platinum(IV) species, and there was no evidence of the desired product, $[PtCl_4(NH_3)(2\text{-pic})]$.

Repeated attempts at synthesising *cis*,*trans*,*cis*-$[PtCl_2(O_2CMe)_2(NH_3)(2\text{-pic})]$ by reaction of the dihydroxo complex with acetic anhydride were also unsuccessful, presumably because of steric interactions between the methyl group of the 2-picoline and the axial site as seen in the crystal structure of the dihydroxo complex. It should be noted that Wong and Giandomenico have reported the synthesis of closely related complexes with acetate ligands in the axial sites.[12,13]

Description of the Crystal Structures. The crystal structures of *cis*,*trans*,*cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ and (2-picH)$[PtCl_5(NH_3)]$ are shown in Figures 1−2 as ORTEP representations, with thermal ellipsoids at the 30% level. Crystal structure data, selected bond lengths, and selected bond angles are given in Tables 1−3. The data for *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ have been deposited as Supporting Information.

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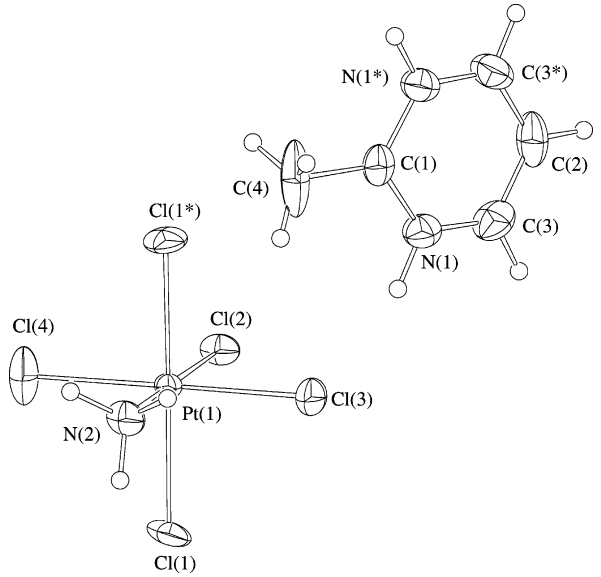

Figure 1. ORTEP representation of (2-picH)[$PtCl_5(NH_3)$], ellipsoids at 30% probability.

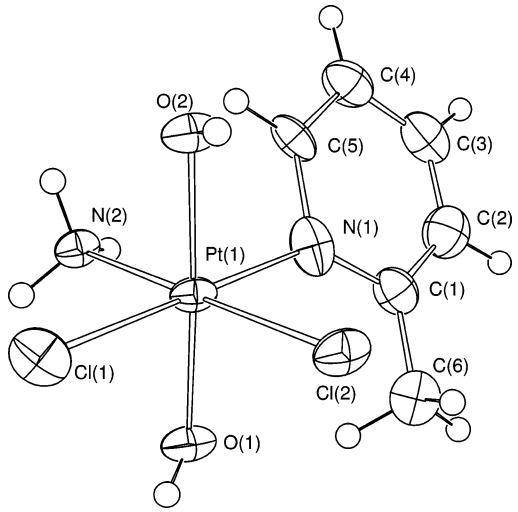

Figure 2. ORTEP representation of *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)], ellipsoids at 30% probability.

Table 2. Bond Lengths (Å) and Angles (deg) for (2-picH)[$PtCl_5(NH_3)$][a]

Pt(1)−Cl(1)	2.311(3)	Pt(1) Cl(3)	2.304(3)
Pt(1)−Cl(2)	2.308(3)	Pt(1)−N(2)	2.06(1)
Pt(1)−Cl(4)	2.307(4)	N(1)−C(3)	1.28(2)
N(1)−C(1)	1.38(1)	C(2)−C(3)	1.37(2)
C(1)−C(4)	1.48(2)		
Cl(1)−Pt(1)−Cl(1*)	176.8(1)	Cl(1)−Pt(1)−Cl(2)	91.61(7)
Cl(1)−Pt(1)−Cl(3)	89.86(8)	Cl(1)−Pt(1)−Cl(4)	90.10(8)
Cl(1)−Pt(1)−N(2)	88.39(7)	Cl(1)−Pt(1)−Cl(2)	91.61(7)
Cl(1)−Pt(1)−Cl(3)	89.86(8)	Cl(1)−Pt(1)−Cl(4)	90.10(8)
Cl(1)−Pt(1)−N(2)	88.39(7)	Cl(2)−Pt(1)−Cl(3)	89.6(1)
Cl(2)−Pt(1)−Cl(4)	91.9(2)	Cl(2)−Pt(1)−N(2)	178.4(4)
Cl(3)−Pt(1)−Cl(4)	178.5(2)	Cl(3)−Pt(1)−N(2)	88.8(4)
Cl(4)−Pt(1)−N(2)	89.7(4)	C(1)−N(1)−C(3)	125(1)
N(1)−C(1)−N(1*)	113(1)	N(1)−C(1)−C(4)	123.6(7)
N(1)−C(1)−C(4)	123.6(7)	C(3)−C(2)−C(3)	117(2)
N(1)−C(3)−C(2)	120(1)		

[a] The asterisk denotes the symmetry operator x, $0.5 - y$, z.

***cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)].** The crystal structure of *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)] reveals that the 2-picoline ring is disordered over two coplanar sites resulting from the co-crystallization of the two forms generated by rotation about the Pt−N(1) bond. Separate sites were refined for all carbon atoms with occupancy factors of 50% each. Pt−N and Pt−Cl bond lengths fall within the expected range. The Pt−Cl bond trans to the picoline is slightly shorter than the bond trans to the ammine, and a similar observation is reported in the structure of the platinum(II) analogue *cis*-[$PtCl_2(NH_3)$(2-pic)].[26] Slight deviation from octahedral geometry is seen in the structure (Table 3). A steric clash between the axial hydroxo ligand and the methyl group of the 2-picoline results in the opening of the Pt−N(1)−C(1′) angle to an unprecedented 138.6(6)°. The O(1)···C(6) distance is 2.945 Å, and the O(2)···C(6′) distance is 2.933 Å. In *cis*-[$PtCl_2(NH_3)$(2-pic)], the distance between the platinum center and the methyl group is 3.224 Å, but it is 3.442 Å in the platinum(IV) structure. This steric clash also contributes to a lengthening of the Pt−N(2-pic) bond length from 2.027(3) to 2.051(5) Å upon oxidation.

Table 3. Bond Lengths (Å) and Angles (deg) for *cis,trans,cis*-[$PtCl_2(OH)_2(NH_3)$(2-pic)]

Pt(1)−O(2)	2.001(4)	N(1)−C(5)	1.43 (5)
Pt(1)−O(1)	2.010(4)	C(1)−C(2)	1.35(2)
Pt(1)−N(2)	2.033(4)	C(1)−C(6)	1.41(2)
Pt(1)−N(1)	2.051(5)	C(2)−C(3)	1.33(2)
Pt(1)−Cl(1)	2.303(2)	C(3)−C(4)	1.38(2)
Pt(1)−Cl(2)	2.334(1)	C(4)−C(5)	1.39 (2)
N(1)−C(1)	1.398(5)		
O(2)−Pt(1)−O(1)	176.94(15)	N(1)−Pt(1)−Cl(2)	90.63(14)
O(2)−Pt(1)−N(2)	90.53(16)	Cl(1)−Pt(1)−Cl(2)	90.54(6)
O(1)−Pt(1)−N(2)	86.45(16)	C(1)−N(1)−C(5)	111.8(8)
O(2)−Pt(1)−N(1)	90.69(16)	C(1)−N(1)−Pt(1)	138.6(6)
O(1)−Pt(1)−N(1)	89.81(16)	C(5)−N(1)−Pt(1)	109.6(6)
N(2)−Pt(1)−N(1)	90.11(18)	C(2)−C(1)−N(1)	119.8(12)
O(2)−Pt(1)−Cl(1)	90.06(12)	C(2)−C(1)−C(6)	129.9(11)
O(1)−Pt(1)−Cl(1)	89.38(12)	N(1)−C(1)−C(6)	110.1(9)
N(2)−Pt(1)−Cl(1)	88.74(13)	C(3)−C(2)−C(1)	127.0(17)
N(1)−Pt(1)−Cl(1)	178.63(13)	C(2)−C(3)−C(4)	118.7(16)
O(2)−Pt(1)−Cl(2)	88.70(11)	C(3)−C(4)−C(5)	114.6(12)
O(1)−Pt(1)−Cl(2)	94.31(12)	C(4)−C(5)−N(1)	128.0(11)
N(2)−Pt(1)−Cl(2)	178.95(12)		

Extensive hydrogen bonds are present in this structure. All of the ammine hydrogen atoms participate in hydrogen-bonding interactions, and these are detailed (along with others) in Table S3. A short hydrogen bond exists between an ammine hydrogen and the water molecule of solvation (O(1w)···H(2c)−N(2) ($+x$, $0.5 - y$, $0.5 + z$) 1.93 Å). The other hydrogen bonds are between the chloro ligands on one complex and the ammine or hydroxyl protons on a neighboring molecule. These are longer and are not atypical of such systems, with the distances between the donor and acceptor atoms being 3.12 Å or greater. These hydrogen bonds result in a continuous, multidimensional lattice, shown in Figure S2.

(2-picH)[$PtCl_5(NH_3)$]. The crystal structure of (2-picH)-[$PtCl_5(NH_3)$] reveals that the 2-picoline has been protonated and acts as the cation for the amminepentachloroplatinate-(IV) anion. The protonated 2-picoline ring is located on a crystallographic mirror plane and is therefore necessarily disordered with the nitrogen atom and a carbon atom interchanged 50% of the time. The platinum(IV) anion adopts the expected octahedral geometry. The Pt−N(ammine) bond is longer than average at 2.06(1) Å, presumably due to the

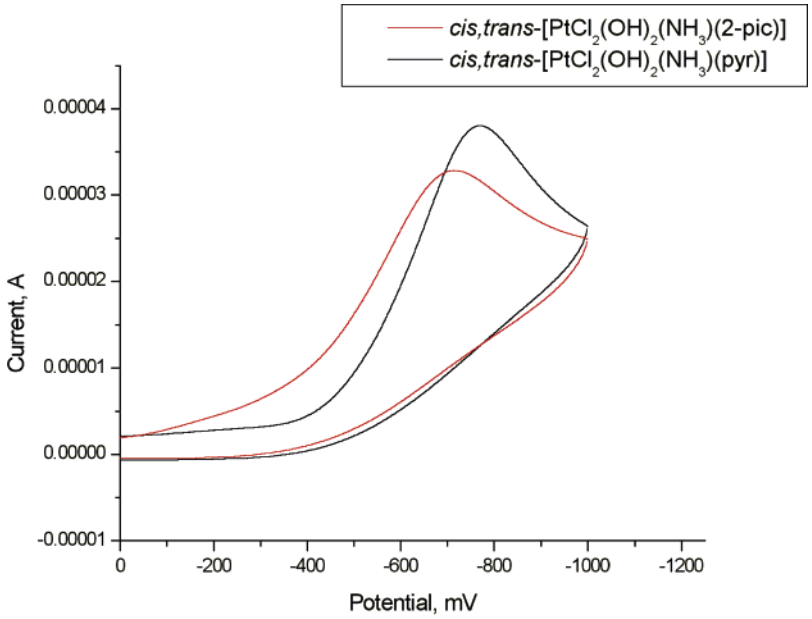

Figure 3. Cyclic voltammograms for *cis,trans*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ and *cis,trans*-$[PtCl_2(OH)_2(NH_3)(pyr)]$ (scan rate 100 mV s^{-1}).

Table 4. Reduction Potentials for Some Platinum(IV) Complexes[a]

complex	E_p vs Ag/AgCl
cis,trans,cis-$[PtCl_2(OH)_2(NH_3)(py)]$	−770
cis,trans,cis-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$	−714
cis,trans,cis-$[PtCl_2(OH)_2(NH_3)_2]$	−802

[a] Scan rate of 100 mV s^{-1}.

electronic and/or steric effects of the five chloro donors. An intermolecular hydrogen bond is seen between Cl(1) and the H(4) atom of N(2) (X−H 2.540 Å (−*x*, 0.5 + *y*, −*z*)).

***cis*-[PtCl$_2$(NH$_3$)(2-pic)].** The room-temperature structure of *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ is indistinguishable from the low-temperature structure reported by Chen and co-workers,[26] with the crystal data parameters, bond lengths, and angles showing very little or no deviation from the low-temperature collection.

Electrochemistry. The cathodic potentials of *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ and *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(py)]$ at −714 and −770 mV (Table 4, Figure 3), respectively, differ by 56 mV, solely as a result of the presence of the methyl substituent of the 2-picoline. The steric clashes between the methyl substituent of the 2-picoline and the hydroxo ligand in the axial position will destabilize the Pt−O bond, facilitating reduction of *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ to platinum(II). However, there is also the expectation of the methyl group having a positive induction effect on the pyridine, strengthening the Pt−N(py) bond, and stabilizing the platinum(IV) oxidation state. Consistent with this expectation is the observation by Sadler and colleagues of chemical reactivity changes arising from the methyl substituent in the 2-position producing an increase in the electron density on the platinum.[30] The destabilizing effect of the methyl substituent due to steric effects must have a greater impact than any possible induction effects, and indeed, without the aforementioned positive induction effects, the differences in reduction potential of the two compounds might have been greater. The effect of steric strain on the reduction of platinum(IV) complexes was also noted by Choi et al.[8]

It is not clear why both *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ and *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(py)]$ are more readily reduced than their diammine analogue ($E_p = -802$ mV), but the ability of the 2-pic and pyridine ligands to act as π-acids may be a contributing factor since the consequent electron depletion would favor the platinum(II) oxidation state.

Conclusions

Oxidation of *cis*-$[PtCl_2(NH_3)(2\text{-pic})]$ to the dihydroxoplatinum(IV) complex *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ occurs readily but results in the formation of a highly strained complex that does not readily undergo substantial transformation. Wong and Giandomenico reported the formation of the trihydroxo complex $[PtCl(OH)_3(NH_3)(2\text{-pic})]$ by reaction with LiOH.[12,13] However, this does not involve reaction at the sterically crowded axial sites. This complex undergoes reduction more readily than its pyridine analogue, probably as a result of the steric clash. Attempted conversion of *cis,trans,cis*-$[PtCl_2(OH)_2(NH_3)(2\text{-pic})]$ to *trans*-dichloro or *trans*-diacetato forms was unsuccessful, resulting in decomposition of the complex. Thus, platinum(IV) analogues of AMD473 are unlikely to be good candidates for development as anticancer agents.

Supporting Information Available: Crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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