

Heterobimetallic Pt-Ti Complexes: Potential Anticancer Drugs

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Heterobimetallic complexes containing titanocene chloride and *trans*-platinum dichloride-DMSO functional groups have been prepared by bridging the metal centers with hydroxypyridine ligands, in order to explore the possibility that a chelate effect will enhance DNA-metal binding affinity and chemotherapeutic effectiveness. The structure of *trans*-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl) has been determined; crystals are monoclinic, (*Cc*), with unit cell dimensions *a* = 6.958(2) Å, *b* = 18.047(3) Å, *c* = 33.217(5) Å, β = 92.04(2)°, *V* = 4168.5(16) Å³, and *Z* = 4 and density = 2.077 Mg m⁻³. Both metal coordination environments are virtually identical to related monometallic complexes.

Introduction

The pioneering discovery of the anticancer properties of *cis*-diamminedichloroplatinum(II)¹ has inspired a significant effort toward understanding and improving of the therapeutic activity of inorganic molecules for cancer treatment.² The subsequent synthesis and screening of thousands of platinum derivatives led researchers to conclude that platinum drugs required charge neutrality, a divalent metal ion, and a *cis*-geometry, in order to optimize anti-cancer properties.³ These stringent requirements are only recently coming under renewed investigation, with reported activity in a series of triamines⁴ (which appear to act mechanistically quite different than *cis*-platin)⁵ and activity in *trans*-PtCl₂(py)₂⁶ and other *trans*-platinum complexes.⁷ The subsequent screening of non-platinum transition metal complexes has led to the discovery that the metallocenes (C₅H₅)₂MCl₂ (M = Ti, V, Mo) also display substantial therapeutic activity.⁸ The origin of activity in metallocene complexes is different from that of the Pt complexes; while Pt compounds are currently thought to bind DNA internally,⁹ the metallocene compounds are thought to disrupt DNA structure by binding preferentially to the external DNA phosphates.¹⁰

Heterobimetallic compounds containing early and Nobel transition metal centers have been sought after for their potential catalytic applications; the oxophilic nature of the electropositive early metal center would ideally serve to orient an organic ligand for subsequent catalytic processes at the noble metal site. A

similar scenario could be envisioned for the use of heterobimetallic compounds in chemotherapy; if the electropositive metal center of a heterobimetallic complex is bound rapidly to the phosphate backbone of a DNA helix, it could then efficiently deliver a platinum complex into either the major or minor groove of the DNA helix. In this paper, we report the synthesis and characterization of heterobimetallic compounds containing a classical platinum coordination compound linked to an organometallic titanium group *via* a bridging hydroxypyridine ligand and the crystal structure of *trans*-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl).

Experimental Section

Titanocene dichloride was purchased from Strem Chemical and used without any further purification. K₂PtCl₄ was obtained as a gift from Englehard and used to make K[(DMSO)PtCl₃].¹¹ Both the 2-hydroxypyridine and the 3-hydroxypyridine were purchased from Aldrich and used without any further purification. The DMSO was HPLC/spectrograde (Pierce Chemical Co.). Acetonitrile, NaOH, CH₂Cl₂, and MeOH were Fisher ACS grade; the acetonitrile was refluxed over calcium hydride for 24 h, distilled, and stored over 4-Å molecular sieves. Technical grade 4-hydroxypyridine (90%) was purchased from Janseen Chimica and used as received. IR spectra were taken by diffuse reflectance in KBr using a Perkin-Elmer 1720X FTIR at 4-cm⁻¹ resolution from 4000-450 cm⁻¹. NMR spectra were recorded on a Varian XL 400 MHz NMR 24.5 °C, with a TMS reference in either CDCl₃ or acetone-*d*₆, and are reported in ppm. Electronic spectra were recorded in THF on a Beckman DU-65 spectrometer. Recrystallizations of the Ti products were carried out under ultrapure N₂ using standard Schlenk techniques. Elemental analyses were performed by Quantitative Technologies, Inc. (Salem, NJ).

***trans*-PtCl₂(DMSO)(NC₅H₄-2-OH).** A solution of 0.26 g (2.7 mmol) of α-pyridone in H₂O (10 mL) was added to a solution of K[(DMSO)PtCl₃] (1.00 g, 2.39 mmol) in H₂O (30 mL). The bright yellow solution quickly turned cloudy, and solid began to form within 5 min. The reaction was stirred for 24 h and filtered. The light yellow solid was washed with H₂O (2 × 20 mL) and allowed to dry in air. The product was dissolved in ca. 50 mL of boiling MeOH, filtered, and cooled (-20 °C) to yield yellow crystals (0.82 g, 78%), mp 148-150 °C dec. Anal. Calcd for C₇H₁₁Cl₂NO₂PtS: C, 19.15; H, 2.53; N, 3.19. Found: C, 18.90; H, 2.76; N, 2.97. IR: 3555 (s), 3436 (m), 3023 (m), 2926 (m), 2603 (m), 2351 (m), 1615 (s), 1452 (s), 1420 (m), 1331 (s), 1297 (m), 1279 (m), 1163 (m), 1134 (m), 1030 (s), 982 (s), 924 (s), 850 (s), 776 (s), 747 (m), 736 (m), 695 (m), 525 (s) cm⁻¹. ¹H NMR (CDCl₃): 8.24 (1 H, m), 7.79 (1 H, m), 6.99 (2 H, m), 3.49 (6 H, s), 1.26 (1 H, s).

***trans*-PtCl₂(DMSO)(NC₅H₄-3-OH).** To K[(DMSO)PtCl₃] (1.00 g, 2.39 mmol) dissolved in H₂O (30 mL) was added a suspension of 3-hydroxypyridine (0.23 g, 2.39 mmol) in water (15 mL), and the reaction was allowed to stir for 24 h. The mixture was filtered to collect a light

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yellow solid, which was washed with H₂O (2 × 20 mL) and allowed to dry in air. The product was dissolved in minimal boiling MeOH filtered and cooled (-20 °C). Yield 0.70 g (67%); mp 172–174 °C. Anal. Calcd for C₇H₁₁Cl₂NO₂PtS: C, 19.15; H, 2.53; N, 3.19. Found: C, 19.10; H, 2.34; N, 3.15. IR: 3167 (b), 3024 (m), 2912 (s), 2829 (s), 2724 (w), 2664 (w), 2603 (w), 2353 (w), 2312 (w), 1626 (w), 1580 (s), 1483 (s), 1362 (m), 1329 (m), 1297 (s), 1241 (s), 1090 (s), 1030 (s), 986 (m), 927 (m), 898 (m), 807 (s), 744 (m), 693 (s), 551 (w), 463 (m) cm⁻¹. ¹H NMR (acetone-*d*₆): 8.32 (1 H, m), 8.22 (1 H, m), 7.50 (2 H, m), 3.43 (6 H, s).

trans-PtCl₂(DMSO)(NC₅H₄-4-OH). To a solution of K[(DM-SO)PtCl₃] (1.00 g, 2.39 mmol) in H₂O (30 mL) was added a solution of 4-hydroxypyridine (0.27 g, 2.8 mmol) in H₂O (15 mL). The reaction was stirred for 20 h and then filtered. Recrystallization from boiling MeOH (ca. 100 mL) affords yellow crystals (0.73 g, 69%), mp 204–205.5 °C. Anal. Calcd for C₇H₁₁Cl₂NO₂PtS: C, 19.15; H, 2.53; N, 3.19. Found: C, 19.12; H, 2.34; N, 3.12. IR: 3211 (b), 3025 (m), 2907 (m), 2746 (m), 2671 (m), 2603 (m), 2446 (m), 2352 (w), 2155 (w), 1925 (w), 1620 (s), 1589 (s), 1509 (s), 1456 (s), 1377 (m), 1301 (s), 1224 (m), 1200 (m), 1093 (m), 1058 (s), 1023 (s), 918 (m), 841 (s), 699 (s), 577 (m), 541 (m) cm⁻¹. ¹H NMR (acetone-*d*₆): 8.41 (1 H, m), 6.99 (1 H, m), 3.40 (3 H, s).

trans-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl). **Method A.** To PtCl₂(DMSO)(NC₅H₄-2-OH) (0.439 g, 1.00 mmol) suspended in H₂O (2 mL) was added solid NaOH (0.040 g, 1.00 mmol). The mixture was allowed to stir until it turned homogeneous, and then CH₂Cl₂ (75 mL) was added. To this mixture crystalline titanocene dichloride (0.249 g, 1.00 mmol) was immediately added. The reaction was stirred vigorously as the color quickly changed from red to yellow orange. After 15 min, the layers were separated and the CH₂Cl₂ layer was washed with H₂O (30 mL). The CH₂Cl₂ solutions were combined, dried over MgSO₄, and filtered. The CH₂Cl₂ was removed and the resulting orange solid was dried under vacuum, redissolved in acetonitrile (30 mL), filtered, and stored at 15 °C to give a crystalline orange product (80 mg, 12%), mp 201–203 °C dec.

Method B. PtCl₂(DMSO)(NC₅H₄-2-OH) (0.439 g, 1.00 mmol) was added to a solution of sodium (0.023 g, 1 mmol) in MeOH (20 mL). The solution was stirred for 5 min and then concentrated to dryness on a Schlenk line. The resulting oily white solid was stirred under THF (20 mL, 10 min) to remove any residual MeOH and taken to dryness again. Titanocene dichloride (0.249 g, 1.00 mmol) was added to the Schlenk tube, and it was evacuated and filled with nitrogen. THF (100 mL) was added via cannula, and the cloudy orange mixture was stirred for 24 h, during which the solution became homogeneous. The orange solution was concentrated to dryness, the solid was dissolved in CH₂Cl₂ (30 mL), and the solution was filtered. Small portions of hexane were added to the filtrate until the solution became cloudy, and a small amount of yellow material was filtered off. The product was then precipitated with hexane, collected by filtration, redissolved in CH₂Cl₂, and reprecipitated with hexane to yield 0.244 g (37.4%). Anal. Calcd for C₁₇H₂₀Cl₃NO₂PtSTi: C, 31.51; H, 2.93; N, 2.35. Found: C, 31.39; H, 2.93; N, 2.35. IR: 3017 (w), 2988 (w), 2911 (m), 1607 (s), 1558 (m), 1475 (s), 1437 (s), 1346 (s), 1276 (w), 1251 (w), 1135 (m), 1029 (m), 889 (m), 826 (s), 771 (m), 744 (m), 700 (w), 661 (m), 637 (m), 529 (w) cm⁻¹. ¹H NMR (CDCl₃): 7.99 (1 H, m), 7.63 (1 H, m), 6.90 (1 H, m), 6.81 (1 H, m), 6.74 (10 H, s), 3.44 (6 H, s). Crystals suitable for X-ray diffraction were grown by slow evaporation from acetonitrile at -20 °C.

trans-PtCl₂(DMSO)(NC₅H₄-3-OTi(C₅H₅)₂Cl). **trans-PtCl₂(DMSO)(NC₅H₄-3-OH)** (0.439 g, 1.00 mmol) was dissolved with NaOH (0.04 g, 1.00 mmol) in H₂O (2 mL). To this solution was added titanocene dichloride (0.249 g, 1.00 mmol) dissolved in CH₂Cl₂ (30 mL). The two phases were stirred vigorously for 20 min, at which time the red organic layer had turned to a bright orange color. The phases were separated, and the CH₂Cl₂ was washed with H₂O (30 mL). After the orange CH₂Cl₂ solution was dried with MgSO₄, the solvent was removed, and the orange solid was redissolved in THF (10 mL). To this solution was added 60 mL of diethyl ether, slowly in 5-mL portions, as a yellow orange solid formed. The product was removed by filtration, washed with diethyl ether (50 mL), and then recollected to give a yellow orange solid (0.290 g, 44.5%), mp > 110 °C dec. Anal. Calcd for C₁₇H₂₀Cl₃NO₂PtTi: C, 31.51; H, 3.09; N, 2.41. Found: C, 31.42; H, 3.16; N, 2.06. IR: 3937 (w), 3854 (w), 3691 (w), 3104 (w), 2918 (w), 1562 (m), 1461 (s), 1417 (m), 1305 (s), 1254 (m), 1144 (m), 1026 (m), 909 (s), 822 (s), 694 (m), 639 (s) cm⁻¹. ¹H NMR (acetone-*d*₆): 8.08 (2 H, m), 7.38 (1 H, m), 7.25 (1 H, m), 6.59 (10 H, s), 3.43 (6 H, s).

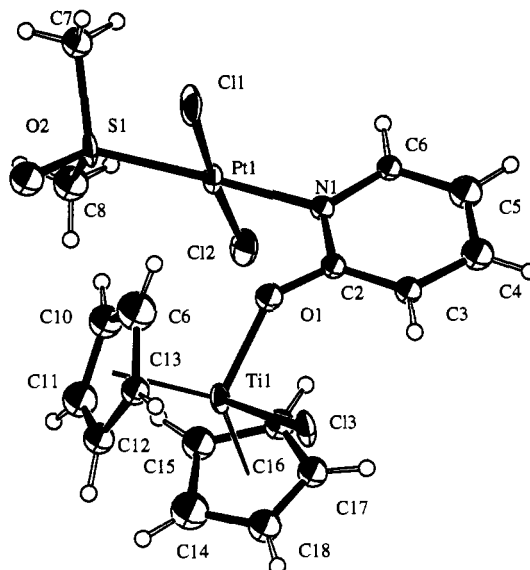


Figure 1. Molecular structure of the first molecule of *trans*-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl), with thermal ellipsoids of non-H atoms drawn at the 30% probability level and H atoms drawn as open circles of arbitrary radii.

trans-PtCl₂(DMSO)(NC₅H₄-4-OTi(C₅H₅)₂Cl). PtCl₂(DMSO)(NC₅H₄-4-OH) (0.414 g, 0.94 mmol) was dissolved in aqueous NaOH (0.040 g, 1.00 mmol in 2 mL). The light green solution was then layered with CH₂Cl₂ (100 mL), and then solid titanocene dichloride was added. The mixture was stirred vigorously for 10 min, at which time the organic phase was separated and washed with H₂O (30 mL). The orange CH₂Cl₂ layer was separated, dried over MgSO₄, and concentrated to 10 mL. Hexane was added dropwise by pipet until the solution remained cloudy. The solution was placed in the freezer at -20 °C for 1.5 h. A small amount of unidentified yellow solid was removed by filtration, and the volume was brought to 20 mL with hexane. The solution was returned to the freezer and chilled again to -20 °C and then refiltered. The filtrate was brought to dryness under vacuum after which 270 mg of yellow orange solid was isolated. Recrystallization from acetonitrile (15 mL) yielded 240 mg (37%) of an orange crystalline material, mp 207 °C dec. Anal. Calcd for C₁₇H₂₀Cl₃NO₂PtSTi: C, 31.51; H, 3.09; N, 2.41. Found: C, 31.53; H, 2.91; N, 2.41. IR: 3107 (w), 1607 (s), 1504 (s), 1340 (s), 1189 (w), 1145 (w), 1061 (w), 1028 (m), 897 (m), 826 (m), 651 (m), 540 (w) cm⁻¹. ¹H NMR (acetone-*d*₆): 8.30 (1 H, m), 6.66 (1 H, m), 6.62 (5 H, s), 3.40 (3 H, s).

[trans-PtCl₂(DMSO)(NC₅H₄-2-O)]₂Ti(C₅H₅)₂. PtCl₂(DMSO)(NC₅H₄-2-OH) (0.439 g, 1.00 mmol) was dissolved with NaOH (0.04 g, 1.00 mmol) in H₂O (2 mL). The solution was layered with CH₂Cl₂ (100 mL), and then solid titanocene dichloride (0.125 g, 0.50 mmol) was added. The mixture was stirred vigorously for 15 min, and then the two layers were separated. The yellow organic layer was washed with water (30 mL), and the CH₂Cl₂ was separated and dried over MgSO₄. The MgSO₄ was filtered off, and the filtrate was layered with hexane (40 mL) and left to sit for 2 days, to give yellow needles (350 mg, 71%; mp 208 °C dec), which were collected, washed with hexane, and dried under vacuum. Anal. Calcd for C₂₄H₃₀Cl₄N₂O₄Pt₂S₂Ti: C, 27.33; H, 2.74; N, 2.55. Found: C, 27.33; H, 2.87; N, 2.66. IR: 3951 (w), 3855 (w), 3650 (w), 3639 (w), 3110 (w), 3013 (w), 2926 (w), 1610 (m), 1554 (m), 1467 (s), 1440 (s), 1340 (s), 1299 (w), 1280 (w), 1145 (s), 1021 (m), 978 (w), 915 (m), 885 (m), 825 (m), 773 (m), 741 (w), 691 (w), 656 (w), 631 (m) cm⁻¹. ¹H NMR (CDCl₃): 8.05 (2 H, m), 7.64 (2 H, m), 6.90 (10 H, m), 6.82 (2 H, m), 6.66 (2 H, m), 3.43 (6 H, m).

X-ray Structural Characterization of trans-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl). The molecular structure of *trans*-PtCl₂(DMSO)(NC₅H₄-2-OTi(C₅H₅)₂Cl) (PtTi, Figure 1) was determined by single-crystal X-ray diffraction methods, which revealed two molecules per asymmetric unit. The crystal structure of PtTi is composed of layers of molecule 1 adjacent to layers of molecule 2 in the *ab*-plane. These two layers are related by an approximate 2-fold along the crystallographic *a*-axis but in a noncrystallographic location.¹²

The crystal structure solution of PtTi (using SHELXS) was nontrivial, due to the twinning and the X-ray target selected (Cu) for this Pt-containing complex. The empirical absorption correction ($\mu = 206$

cm⁻¹) was applied after the structural solution, so the difficulties encountered in solving this structure were entirely the result of poor peak profiles due to many instances of two twin components in single peaks. Since peak profiles were saved during data collection, various schemes for analysis of the asymmetry of peaks were examined, and it was discovered that if peaks with left and right backgrounds differing by more than 40% were omitted, a solution could be found in space group *Cc*. As a check, the refined model from space group *Cc* [with $R(F) = 5\%$] was used in subsequent rotation-translation (PATSEE) searches for alternative structure solutions in all five *C*-centered monoclinic space groups, but only the attempt in space group *Cc* succeeded. Thus, the initial space group, *Cc*, was maintained as the true space group.

Individual reflections collected from each twin component indicated that the ratio of intensities was 1.083 (with respect to the collected versus uncollected twin components) and the 683 $h = 0$ reflections containing intensity from both components were multiplied by 0.52 for consistent scaling with the $h = 1, 2, 4, 5, 7,$ and 8 data collected from one component. The analysis of overlapping peaks (which involved computing the diffractometer angles for all reflections from both twin components) revealed that all $h = 3$ and $h = 6$ reflections were broad with nearly direct overlap between twin components, and all of these data were subsequently omitted. Thus, the two sets of data omitted were as follows: (a) 677 general reflections with very asymmetric backgrounds; (b) 969 reflections with $h = 3$ or $h = 6$. A structure determination summary is given in Table I.¹³

Atomic coordinates and equivalent isotropic displacement coefficients (U_{equiv}) for PtTi are given in Table II. The molecular structure of molecule 1 of PtTi is essentially the same as that of molecule 2 (see Table III for details), and the following discussion is based upon the average geometry of these two molecules. There are no significantly short nonbond contacts (e.g., hydrogen bonding).

After refinement, the cyclopentadiene anion (Cp) and pyridine rings are nearly planar, with deviations from their mean planes of 0.02 Å or less. The C and N atoms that compose these rings were given isotropic thermal parameters. All H atoms were given positional and isotropic thermal parameters consistent with a riding motion on the atom to which they were bonded. The site symmetry of the Pt coordination sphere of each molecule is square planar within 0.05 Å. The C2 and S atoms of the DMSO ligand, the Pt atom, and the N1 and C4 atoms of the pyridine ring describe an approximate plane.

The bonding of the Ti atom to the hydroxypyridine O atom is the major point of departure of this complex from overall mirror symmetry (C_v). The geometries about the Ti-O bonds are described in Table III.

Results

Heterobimetallic complexes containing titanocene and square planar, *trans*-dichloro(DMSO)(hydroxypyridine)platinum(II) can be prepared by deprotonating the platinum hydroxypyridine coordination complex with aqueous NaOH and coupling this functional group to a titanocene chloride ligand in a mixture of H₂O and dichloromethane, or by deprotonating the platinum-hydroxypyridine starting material with methoxide anion in THF. All three hydroxypyridine isomers can function as the bridging ligand, and the resultant orange bimetallic solids can be recrystallized from acetonitrile to give microcrystalline materials.

- (12) In deforming the observed unit cell symmetry from monoclinic to orthorhombic (e.g., as β changes from 92 to 90°), it may be possible to generate the space group *C2cb* (*Aba2*), where the two molecules would be 2-fold-related, such that one unique molecule is obtained. In the present monoclinic structure, however, the two molecules of PtTi can be viewed as a dimer, with each half having approximately the same "handedness" (e.g., the dimer pair is also polar). In this case, the polar space group *Cc* was used, and this selection was based upon systematic absences and normalized intensity statistics.
- (13) Initial photographic studies (Weissenberg) were instrumental in determining that the twinning was 2-fold but would probably not prevent a structure solution (e.g., for most reflections, the two twin components could be resolved if Cu radiation were used—a Cu target was required because of the 33-Å *c*-axis and the twinning in the *ac*-plane). The use of the Cu radiation (a) gave rise to larger absorption effects and (b) provided data only to the $\theta = 70^\circ$ limit of our machine. As it turned out, the absorption effects were well corrected for by the empirical ψ -scan method and the data in the $0 < \theta < 70^\circ$ Cu sphere of diffraction that remained after omitting twin-affected data were of sufficient number (over 2500) to obtain a convergent refinement with fairly low esd's (see Tables I and II).

Table I. Structure Determination Summary for PtTi

| Crystal Data | |
|--|---|
| empirical formula | C ₁₇ H ₂₀ NO ₂ SCl ₃ PtTi |
| fw | 651.76 |
| color/habit | yellow/needle |
| cryst size (mm) | 0.45, 0.25, 0.10 along <i>a, b, c</i> |
| cryst orientation | <i>a</i> -axis nearly along goniometer ϕ |
| cryst system | monoclinic |
| space group | <i>Cc</i> (No. 9) |
| reflens for cell data | 25 |
| θ range for cell data (deg) | 12–15 |
| unit cell dimens (Å, deg) | <i>a</i> = 6.958(2) <i>b</i> = 18.047(3) <i>c</i> = 33.216(5) β = 92.04(2) |
| unit cell vol (Å ³) | 4169(2) |
| Z | 4 |
| calcd density (Mg m ⁻³) | 2.077 |
| abs coeff (cm ⁻¹) | 205 |
| F_{000} | 2496 |
| Data Collection | |
| diffractometer system used | Enraf-Nonius CAD4 |
| radiation (λ , Å) | Cu K α (1.5418) |
| temp (°C) | 20 |
| monochromator | oriented graphite (0,0,2) |
| θ range (deg) | 2.0–69.0 |
| indices colld | $0 < h < 8, 0 < k < 21, -40 < l < 40$ |
| scan type | $\omega:2\theta$ |
| scan range (deg in θ) | $[0.8 + 0.14 \tan(\theta)]$ |
| vertical aperture | $[2.4 + 0.30 \tan(\theta)]$ |
| scan speed (in θ) (deg min ⁻¹) | 1.3–5.5 |
| bkgd counting time | 0.25 of total scan time |
| std reflens | 3 measured every 1 h |
| reflens colld | 4505 |
| Data Reduction | |
| data reduction program | MOLEN (Enraf-Nonius) and local program to remove twinning-affected data and rescale the coincident data ($h = 0$) |
| reflens processed | 2689 |
| decay corr (min/max) | 1.0000/1.0106 |
| abs corr method | ψ -scan |
| transm (min/max): | 0.521/0.994 |
| unique reflens | 2613 (no data avgd) |
| Solution and Refinement | |
| computer programs used | SHELXS, SHELX-76, ORTEP |
| solution method | direct methods |
| refinement method | full-matrix, least squares |
| H atoms treatment | fixed calcd posns and fixed $U(\text{iso})$ |
| quantity minimized | $\sum[w(F_o - F_c)^2]$ |
| weights | $4.579/[\sigma^2(F) + 0.0009F^2]$ |
| obsd reflens | 2427 [$F > 4\sigma(F)$] |
| params refined | 268 |
| data-to-param ratio | 9:1 |
| final param shift/error: | <0.01 |
| <i>R</i> indices (obsd data) | $R(F) = 0.049, R_w(F) = 0.067$ |
| goodness-of-fit | GOF = 4.020 |
| <i>R</i> index (all unique data) | $R(F) = 0.052$ |
| diff-Fourier resid (e/Å ³) | -2.3 to 1.5 |

X-ray quality crystals can be obtained by slowly cooling an acetonitrile solution of the compounds.

The structure of the bridging 2-hydroxypyridine compound was determined by X-ray diffraction, and an ORTEP diagram is shown in Figure 1. In the structure, bond lengths and bond angles are comparable to related monometallic Pt¹⁴ and Ti¹⁵ complexes. The square planar platinum atom retains the *trans*

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Table II. Atomic Fractional Coordinates and Equivalent Isotropic Displacement Coefficients (\AA^2) for PtTi^a

| atom | x | y | z | U_{equiv} |
|------|-------------|------------|------------|--------------------|
| Pt1 | 0.21930 | 0.61021(4) | 0.47100 | 0.0321(5) |
| Cl1 | -0.0415(12) | 0.5515(4) | 0.4410(2) | 0.058(4) |
| Cl2 | 0.4640(12) | 0.6733(3) | 0.5042(2) | 0.056(4) |
| Ti1 | 0.4465(7) | 0.3965(2) | 0.5171(1) | 0.032(2) |
| Cl3 | 0.2928(10) | 0.3103(3) | 0.5596(2) | 0.045(3) |
| O1 | 0.241(2) | 0.468(1) | 0.519(1) | 0.037(3) |
| N1 | 0.130(3) | 0.582(1) | 0.527(1) | 0.028(3) |
| C2 | 0.162(3) | 0.515(1) | 0.543(1) | 0.030(4) |
| C3 | 0.114(3) | 0.498(1) | 0.581(1) | 0.034(4) |
| C4 | 0.027(4) | 0.552(1) | 0.606(1) | 0.050(6) |
| C5 | -0.016(5) | 0.619(1) | 0.589(1) | 0.052(6) |
| C6 | 0.031(3) | 0.634(1) | 0.549(1) | 0.030(4) |
| S1 | 0.3216(11) | 0.6350(3) | 0.4097(2) | 0.041(3) |
| O2 | 0.365(3) | 0.568(1) | 0.386(1) | 0.056(4) |
| C7 | 0.143(4) | 0.689(1) | 0.381(1) | 0.044(5) |
| C8 | 0.524(4) | 0.692(1) | 0.412(1) | 0.059(7) |
| C9 | 0.260(7) | 0.362(2) | 0.458(1) | 0.074(9) |
| C10 | 0.404(4) | 0.413(1) | 0.448(1) | 0.052(6) |
| C11 | 0.583(6) | 0.380(1) | 0.454(1) | 0.058(7) |
| C12 | 0.556(4) | 0.313(1) | 0.468(1) | 0.046(6) |
| C13 | 0.365(4) | 0.297(1) | 0.473(1) | 0.038(5) |
| C14 | 0.778(6) | 0.400(2) | 0.530(1) | 0.071(9) |
| C15 | 0.712(5) | 0.474(1) | 0.521(1) | 0.053(6) |
| C16 | 0.603(4) | 0.494(1) | 0.554(1) | 0.043(5) |
| C17 | 0.595(4) | 0.434(1) | 0.578(1) | 0.043(5) |
| C18 | 0.699(5) | 0.378(1) | 0.566(1) | 0.053(7) |
| Pt2 | 0.26074(19) | 0.12115(4) | 0.76907(3) | 0.0339(5) |
| Cl4 | 0.0099(12) | 0.1819(4) | 0.7987(2) | 0.059(4) |
| Cl5 | 0.4957(13) | 0.0565(3) | 0.7376(2) | 0.060(4) |
| Ti2 | 0.4817(7) | 0.3327(2) | 0.7209(1) | 0.032(2) |
| Cl6 | 0.3141(11) | 0.4191(3) | 0.6793(2) | 0.046(3) |
| O3 | 0.279(2) | 0.262(1) | 0.719(1) | 0.033(3) |
| N21 | 0.151(3) | 0.147(1) | 0.713(1) | 0.035(4) |
| C22 | 0.189(4) | 0.215(1) | 0.696(1) | 0.039(5) |
| C23 | 0.121(4) | 0.229(1) | 0.658(1) | 0.042(5) |
| C24 | 0.027(4) | 0.178(1) | 0.635(1) | 0.048(6) |
| C25 | -0.011(4) | 0.111(1) | 0.651(1) | 0.040(5) |
| C26 | 0.050(4) | 0.097(1) | 0.688(1) | 0.047(6) |
| S2 | 0.3728(10) | 0.0968(3) | 0.8310(2) | 0.042(3) |
| O4 | 0.415(3) | 0.160(1) | 0.855(1) | 0.054(4) |
| C27 | 0.205(4) | 0.042(1) | 0.855(1) | 0.055(6) |
| C28 | 0.564(5) | 0.038(2) | 0.832(1) | 0.068(8) |
| C29 | 0.320(5) | 0.369(1) | 0.781(1) | 0.047(6) |
| C30 | 0.462(4) | 0.315(1) | 0.791(1) | 0.044(5) |
| C31 | 0.642(5) | 0.345(2) | 0.786(1) | 0.062(7) |
| C32 | 0.613(5) | 0.417(2) | 0.769(1) | 0.059(7) |
| C33 | 0.420(4) | 0.430(1) | 0.767(1) | 0.037(5) |
| C34 | 0.817(6) | 0.324(2) | 0.708(1) | 0.063(8) |
| C35 | 0.739(4) | 0.250(1) | 0.715(1) | 0.054(7) |
| C36 | 0.622(4) | 0.235(1) | 0.684(1) | 0.043(5) |
| C37 | 0.593(4) | 0.292(1) | 0.657(1) | 0.048(6) |
| C38 | 0.721(4) | 0.351(1) | 0.673(1) | 0.047(6) |

^a Estimated standard deviations are enclosed in parentheses. $U_{\text{equiv}} = 1/3(U_{11} + U_{22} + U_{33})$.

chloride geometry and sulfur-bound DMSO ligand, with the plane defined by the hydroxypyridine ligand twisted 79° from the plane defined by the atoms surrounding the platinum. The titanium coordination geometry is that of a distorted tetrahedron, similar to other monosubstituted titanocene chlorides. There are no indications of intramolecular metal–metal interactions, nor are there any interactions between the titanium ion and the DMSO oxygen, nor between the titanium chloride ligand and the platinum ion. The Ti–O–C angle of 142° can be interpreted in terms of partial π bonding character between the oxygen ligand and the 16 electron metallocene fragment. The compounds react slowly with water.

Reacting the titanium dichloride with 2 equiv of deprotonated platinum (hydroxypyridine) dichloride DMSO results in the formation of a yellow disubstituted compound which has physical properties that are identical to the properties of a minor product isolated in the synthesis of the 1:1 compound.

Table III. Selected Bond Distances (\AA) and Angles (deg) for PtTi^a

| atoms in mol 1 | distance | atoms in mol 2 | distance |
|----------------|----------|----------------|----------|
| Pt1–C11 | 2.297(7) | Pt2–C14 | 2.311(8) |
| Pt1–C12 | 2.297(8) | Pt2–C15 | 2.290(8) |
| Pt1–S1 | 2.225(6) | Pt2–S2 | 2.219(6) |
| Pt1–N1 | 2.03(2) | Pt2–N21 | 2.04(2) |
| S1–O2 | 1.49(2) | S2–O4 | 1.43(2) |
| S1–C7 | 1.82(3) | S2–C27 | 1.74(3) |
| S1–C8 | 1.75(3) | S2–C28 | 1.70(3) |
| Ti1–C13 | 2.382(7) | Ti2–C16 | 2.364(7) |
| Ti1–O1 | 1.93(2) | Ti2–O3 | 1.90(2) |
| Ti1–C9 | 2.41(4) | Ti2–C29 | 2.42(3) |
| Ti1–C10 | 2.32(3) | Ti2–C30 | 2.37(3) |
| Ti1–C11 | 2.36(3) | Ti2–C31 | 2.40(3) |
| Ti1–C12 | 2.36(3) | Ti2–C32 | 2.36(3) |
| Ti1–C13 | 2.37(2) | Ti2–C33 | 2.39(2) |
| Ti1–C14 | 2.34(4) | Ti2–C34 | 2.39(4) |
| Ti1–C15 | 2.32(3) | Ti2–C35 | 2.34(3) |
| Ti1–C16 | 2.39(2) | Ti2–C36 | 2.38(2) |
| Ti1–C17 | 2.35(2) | Ti2–C37 | 2.40(3) |
| Ti1–C18 | 2.38(3) | Ti2–C38 | 2.37(3) |
| O1–C2 | 1.29(3) | O3–C22 | 1.29(3) |

| atoms in mol 1 | angle | atoms in mol 2 | angle |
|----------------|----------|----------------|----------|
| Cl1–Pt1–C12 | 175.6(3) | Cl4–Pt2–C15 | 176.5(3) |
| C12–Pt1–S1 | 94.8(2) | C15–Pt2–S2 | 95.1(2) |
| C11–Pt1–S1 | 88.3(2) | C14–Pt2–S2 | 86.8(2) |
| C12–Pt1–N1 | 86.1(5) | C15–Pt2–N21 | 87.1(6) |
| C11–Pt1–N1 | 91.0(5) | C14–Pt2–N21 | 91.0(6) |
| C13–Ti1–O1 | 94.1(6) | C16–Ti2–O3 | 94.3(5) |
| N1–Pt1–S1 | 177.2(5) | N21–Pt2–S2 | 177.7(5) |
| Pt1–S1–O2 | 114.1(7) | Pt2–S2–O4 | 115.2(8) |
| Pt1–S1–C7 | 110.3(9) | Pt2–S2–C27 | 109(1) |
| O2–S1–C7 | 108(1) | O4–S2–C27 | 109(1) |
| Pt1–S1–C8 | 112(1) | Pt2–S2–C28 | 113(1) |
| O2–S1–C8 | 109(1) | O4–S2–C28 | 110(2) |
| C7–S1–C8 | 104(1) | C27–S2–C28 | 100(1) |
| C13–Ti1–O1 | 94.1(6) | C16–Ti2–O3 | 94.3(5) |
| Ti1–O1–C2 | 142(2) | Ti2–O3–C22 | 143(2) |

^a Estimated standard deviations are enclosed in parentheses.

Discussion

Our motivation for preparing heterobimetallic compounds containing both square planar platinum and titanocene functional groups originates in the antiproliferative activity displayed by both individual inorganic species. The hydrolytic instability of the titanium alkoxide bond will result in the eventual *in vivo* delivery of both a reactive titanium compound as well as an active platinum compound. If the hydrolysis properties of the molecules are properly designed, the drugs may penetrate the cell wall intact to function as DNA chelators, with the titanium binding to an external phosphate and the platinum ion binding to internal nitrogen donors. The potential benefits from this bimetallic combination differ from previously described heterobimetallic Pt–Fe,¹⁶ Cu,¹⁷ or Ag¹⁸ combinations in that the oxophilic titanium functionality can serve to enhance the effective concentration of the platinum drug in the vicinity of the DNA oligomer by binding selectively to the DNA phosphates.

The use of hydroxypyridine as a binuclear bridging ligand is well established in platinum chemistry, and it has been used to prepare a number of monometallic multinuclear compounds.¹⁹ Similar ligands coordinated to platinum, such as 1-methylcytosine, 1-methyluracil, and 1-methylthymine, have been used to complex other metal ions such as Cu(II) and Ag(I).²⁰ Hydroxypyridine was particularly useful in the present work because the *ortho*,

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meta, and *para* isomers were readily available. Each isomer will create a unique spatial arrangement between the two metal centers, and thus all three bimetallic complexes will differ in the ability to chelate DNA. Molecular models indicate that the 3-substituted complex is ideally suited to having the titanium ion bind to a phosphate oxygen while the platinum ion binds to the nitrogen donor in a monomeric GMP fragment. In addition, it is worth noting that since metallocene compounds have also been found to bind to the basic nitrogens of DNA bases,²¹ there is the potential for binding adjacent bases through solely nitrogen-metal bonds.

The synthesis of bimetallic complexes containing both organo-titanium and square planar platinum functional groups is complicated by the vastly different reactivity and solubility properties of the two central metal ions. The bimetallic product must be approached with the bridging hydroxypyridine ligand bound initially to the platinum ion; attempts to synthesize titanocene chloride hydroxypyridine complexes in dry solvents under nitrogen, by combining the hydroxypyridine anion with an equivalent of titanocene dichloride, resulted in orange red solutions from which no pure material was isolated. This approach is further complicated by the different hydrolysis properties of the two inorganic starting materials: $\text{KPtCl}_3\text{DMSO}$ is water soluble, and the titanium hydroxypyridine complex is hydrolytically unstable (while other simple ligands such as phenoxide and benzoate can be attached to the Cp_2Ti moiety in water, it appears that the presence of the basic nitrogen of the pyridine facilitates hydrolysis of the ligand and the rapid formation of titanium oxides). Attaching the hydroxypyridine to the platinum first allows the isolation of the *trans*-platinum dichloride hydroxypyridine complexes in reasonable yields of 70–80% and also eliminates the hydrolysis problems.

Coupling of the platinum and titanium fragments can be achieved in a straightforward fashion, by deprotonating the phenoxide ion with methoxide and reaction with titanocene dichloride in THF, to give bimetallic complexes in 37% yield. Alternatively, the platinum hydroxypyridine complexes can be deprotonated with NaOH in water, and then the phenoxide anion can be treated with titanocene dichloride dissolved in methylene chloride. The mixed phase reaction medium has been used to prepare simple benzoate and phenolate derivatives of titanocene.²² Hydrolysis of either the second chloride or a cyclopentadiene ring is slow enough to permit isolation of the monosubstituted monochloride product.²³ Substitution of the titanium chloride

by the phenoxide anion is rapid, and relatively rapid extraction of the reaction product into anhydrous solvents affords the bimetallic compounds in 12–45% yield.

Either synthesis approach can be used to link the platinum and titanium fragments with the hydroxy group at the 2-, 3-, or 4-position of the pyridine ring. The bimetallic compounds are extremely soluble in CH_2Cl_2 , THF, or acetonitrile, are moderately soluble in toluene or methanol, and have limited solubility in water. The 4-substituted Pt and Pt:Ti compounds have higher melting points and are considerably less soluble than the 2- and 3-substituted hydroxypyridines.

Both monosubstituted (1:1 Pt:Ti) and disubstituted (2:1 Pt:Ti) compounds are formed in a stoichiometric 1:1 reaction, with the disubstituted product being the minor component (as judged by ^1H NMR). These substitution products were separated by fractional crystallization, and the identity of the minor product was confirmed by reacting the Pt and Ti starting materials in a 2:1 ratio, and crystallizing from chloroform/hexane, in over 70% yield.

The substitution reactions can be monitored visually as well as by UV-visible spectroscopy. Substitution of one chloride by the phenoxide substantially alters the position of the ligand to metal charge-transfer band, which dominates the color of titanocene complexes, turning the solution color from the red dichloride²⁴ to orange, and further substitution of the second chloride has a similar effect, shifting the solution color from orange to yellow as the LMCT band of the titanium functional group shifts into the UV. Similar color changes have been observed previously in titanocene derivative chemistry.

The structure of *trans*- $\text{PtCl}_2(\text{DMSO})(\text{NC}_5\text{H}_4\text{-2-OTi}(\text{C}_5\text{H}_5)_2\text{Cl})$ has been determined by X-ray diffraction, in order to confirm that the hydroxypyridine ligand constituted the only set of atoms spanning the two metal centers. As shown in Figure 1, the molecule consists of Pt and Ti functional groups, bridged only from the titanium bound to the oxygen and the platinum bound to the nitrogen. The platinum coordination environment is square planar, and the chloride ions have maintained their original *trans*-configuration. The titanium fragment is a distorted tetrahedron. The bond distances and angles defining both metal geometries are virtually identical to those of related structures. The Ti–O–C angle of 142° suggests that the oxygen atom is involved in π bonding with the 16 electron titanium fragment.²⁵

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Supplementary Material Available: Tables of additional bond distances and angles, hydrogen atom positions, and calculations of torsional angles and least-square planes (15 pages). Ordering information is given on any current masthead page. Structure factor listings are available from the authors.

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