Synthesis, Characterization, and Reactivity of *trans*-[PtCl(R′R″SO)(A)₂]NO₃ (R′R″SO = Me₂SO, MeBzSO, MePhSO; A = NH₃, py, pic). Crystal Structure of *trans*-[PtCl(Me₂SO)(py)₂]⁺

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Trans complexes such as *trans*-[PtCl₂(NH₃)₂] have historically been considered therapeutically inactive. The use of planar ligands such as pyridine greatly enhances the cytotoxicity of the trans geometry. The complexes *trans*-[PtCl(R′R″SO)(A)₂]NO₃ (R′R″SO = substituted sulfoxides such as dimethyl (Me₂SO), methyl benzyl (MeBzSO), and methyl phenyl sulfoxide (MePhSO) and A = NH₃, pyridine (py) and 4-methylpyridine or picoline (pic)) were prepared for comparison of the chemical reactivity between ammine and pyridine ligands. The X-ray crystal structure determination for *trans*-[PtCl(Me₂SO)(py)₂]NO₃ confirmed the geometry with S-bound Me₂SO. The crystals are orthorhombic, space group $P2_12_12_1$, with cell dimensions $a = 7.888(2)$ Å, $b = 14.740(3)$ Å, $c = 15.626(5)$ Å, and $Z = 4$. The geometry around the platinum atom is square planar with $l(\text{Pt}-\text{Cl}) = 2.304(4)$ Å, $l(\text{Pt}-\text{S}) = 2.218(5)$ Å, and $l(\text{Pt}-\text{N}) = 2.03(1)$ and $2.02(1)$ Å. Bond angles are normal with Cl−Pt−S = 177.9-(2)°, Cl−Pt−N₁ = 88.0(4)°, Cl−Pt−N₂ = 89.3(5)°, S−Pt−N₁ = 93.8(4)°, S−Pt−N₂ = 88.9(4)°, and N₁−Pt−N₂ = 177.2(6)°. The intensity data were collected with Mo Kα radiation with $\lambda = 0.710\ 69$ Å. Refinement was by full-matrix least-squares methods to a final R value of 3.80%. Unlike *trans*-[PtCl₂(NH₃)₂], *trans*-[PtCl₂(A)₂] (A = py or pic) complexes do not react with Me₂SO. The solvolytic products of *cis*-[PtCl₂(A)₂] (A = py or pic) were characterized. Studies of displacement of the sulfoxide by chloride were performed using HPLC. The sulfoxide was displaced faster for the pyridine complex relative to the ammine complex. Chemical studies comparing the reactivity of *trans*-[PtCl(R′R″SO)(amine)₂]NO₃ with a model nucleotide, guanosine 5′-monophosphate (GMP), showed that the reaction gave two principal products: the species [Pt(R′R″SO)(amine)₂(N7-GMP)], which reacts with a second equivalent of GMP, forming [Pt(amine)₂(N7-GMP)₂]. The reaction pathways were different, however, for the pyridine complexes in comparison to the NH₃ species, with sulfoxide displacement again being significantly faster for the pyridine case.

Introduction

Trans-planaramine platinum (TPA) complexes of general formula *trans*-[PtCl₂((L)(L′)] (L = L′ = pyridine, thiazole, or L = quinoline, L′ = NH₃ or substituted sulfoxide R′R″SO) display greatly enhanced cytotoxicity in comparison to the geometric isomer of cisplatin, *trans*-[PtCl₂(NH₃)₂] (*trans*-DDP). A significant feature of these new transplatinum complexes is their activity in both murine and human tumor cells resistant to cisplatin.[1−3] To explain these findings, we have begun to explore the chemistry and DNA binding of this potentially important new class of platinum antitumor agents.[4−6] An important structural feature of these newer trans complexes is the presence of a sterically demanding ligand such as pyridine or quinoline.

This paper compares the effect of NH₃ and pyridine groups on the chemistry and reactivity of the sulfoxide ligands in *trans*-[PtCl(R′R″SO)(amine)₂]NO₃ and reports studies on their reaction with a model mononucleotide, guanosine 5′-monophosphate (GMP). The use of sulfoxide as ligands gave cationic complexes that are more water soluble than the starting material *trans*-[PtCl₂(A)₂]. The literature reports antitumor active cationic complexes having some characteristics similar to those described in this paper, [PtCl(R′R″SO)(damch)]⁺ and *cis*-[PtCl(NH₃)₂-(py)]⁺.[7,8] For platinum complexes, the lability of sulfoxide as leaving group depends on the structure of the sulfoxide, with Me₂SO having a lability similar to chloride.[9,10] Further, the mechanism of action of the series *cis*-[PtCl(R′R″SO)(diamine)]⁺ most likely involves displacement of sulfoxide by DNA to give

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bifunctional adducts.[7,11] It was therefore of interest to examine the interactions of the trans complexes with GMP, and the initial results are reported in this paper.

Experimental Section

Starting Materials and Methods. The complexes *trans*-[PtCl$_2$(A)$_2$] where A = NH$_3$[12] and py[13] were prepared by literature methods. *trans*-[PtCl$_2$(pic)$_2$] was prepared by the same procedure used for the pyridine complex.[13] Standard sulfoxides were purchased from Aldrich and used without further purification. Guanosine 5′-monophosphate sodium salt (GMP) was from Aldrich. IR spectra were obtained as KBr disks on Nicolet FT6000 series and Perkin-Elmer 1430 spectrophotometers. NMR spectra were run on Bruker 250- and 270-MHz spectrometers. ^{195}Pt NMR spectra were run in D$_2$O with reference to a 0.1 M Na$_2$-PtCl$_6$ solution in D$_2$O as external reference on a Bruker 250 MHz spectrometer. Samples were run by using a pulse width of 15 μs. Usually a sweep width of 30 kHz was used, and 5000−10000 scans were adequate. All shifts are positive to lower shielding. Elemental analyses were by Robertson Laboratories, Madison, NJ.

Synthesis of Complexes. *trans*-[PtCl(R′R″SO)(NH$_3$)$_2$]NO$_3$. The Me$_2$SO complex, complex **I**, has been described previously.[14,15] The complexes were prepared in basically the same manner with slight modifications in workup and crystallization. The preparation is exemplified for the Me$_2$SO case. To a suspension of *trans*-[PtCl$_2$(NH$_3$)$_2$] (1.0 g, 3.3 mmol) in 30 mL of MeOH was added AgNO$_3$ (0.57 g, 3.3 mmol) and Me$_2$SO (1.3 mL, 1.43 g, 18 mmol). The reaction mixture was stirred at 80 °C overnight. The insoluble AgCl precipitate was filtered off and the filtrate evaporated to dryness. Ethanol and ether were added until the solution became cloudy. Upon cooling, the white solid was filtered off and recrystallized from MeOH/ether. The product was dried in a vacuum with heat. Yield: 85%. Anal. Calcd for C$_2$H$_{12}$-ClN$_3$O$_4$SPt: C, 5.93; H, 2.97; N, 10.38. Found: C, 5.92; H, 3.02; N, 10.43.

***trans*-[PtCl(MeBzSO)(NH$_3$)$_2$]NO$_3$, II.** The same general reaction conditions were used but with stoichiometric equivalents of MeBzSO. Upon evaporation, an oil was obtained, 2 mL of MeOH was added to dissolve the oil, and the product then precipitated out with ether. Upon cooling, the white solid was filtered off and recrystallized from MeOH/ether. Yield: 69%. Anal. Calcd for C$_8$H$_{16}$ClN$_3$O$_4$SPt: C, 19.98; H, 3.33; N, 8.74. Found: C, 19.93; H, 3.41; N, 8.86.

***trans*-[PtCl(MePhSO)(NH$_3$)$_2$]NO$_3$, III**. The same general reaction conditions were used, and in this case the oil obtained upon evaporation was stirred overnight with ether, which resulted in precipitation of a white solid, which was filtered off and recrystallized from MeOH/ether. Yield: 70%. Anal. Calcd for C$_7$H$_{14}$ClN$_3$O$_4$SPt: C, 18.01; H, 3.00; N, 9.00. Found: C, 18.72; H, 2.82; N, 8.93.

***trans*-[PtCl(Me$_2$SO)(py)$_2$]NO$_3$, IV.** To a suspension of *trans*-[PtCl$_2$(py)$_2$] (1.0 g, 2.4 mmol) in 30 mL of MeOH was added AgNO$_3$ (0.4 g, 2.4 mmol) and Me$_2$SO (2 mL, 2.2 g, 28 mmol). The reaction mixture was stirred at 80 °C overnight. The insoluble AgCl precipitate was filtered off, and the filtrate was evaporated down. To the oil was added 2 mL of MeOH, then a white solid precipitated out after stirring for about 10 min. Ether was then added to intensify the precipitation. After cooling overnight, the white solid was filtered off and recrystallized from hot MeOH/ether. The product was dried in a vacuum with heat. Yield: 66%. Anal. Calcd for C$_{12}$H$_{16}$ClN$_3$O$_4$SPt: C, 27.25; H, 3.03; N, 7.95. Found: C, 26.71; H, 2.95; N, 7.56.

***trans*-[PtCl(MeBzSO)(py)$_2$]NO$_3$, V.** The same general conditions were used as for the previous complex but with 2 equiv of sulfoxide ligand. Upon evaporation to an oil, acetone was added to dissolve the excess MeBzSO, and the product was precipitated out with ether. Upon cooling, the white solid was filtered off, recrystallized from MeOH/ether, and washed with acetone to remove any remaining free ligand. The product was dried in a vacuum with heat. Yield: 45%. Anal. Calcd

for C$_{18}$H$_{20}$ClN$_3$O$_4$SPt: C, 35.73; H, 3.31; N, 6.95. Found: C, 35.93; H, 3.11; N, 6.70.

***trans*-[PtCl(Me$_2$SO)(pic)$_2$]NO$_3$, VI.** The same general reaction conditions were used as above. Yield: 68%. Anal. Calcd for C$_{14}$H$_{20}$-ClN$_3$O$_4$SPt: C, 30.19; H, 3.59; N, 7.55. Found: C, 30.51; H, 3.94; N, 7.53.

***trans*-[PtCl(MeBzSO)(pic)$_2$]NO$_3$, VII.** The same general conditions were used as above but again with 2 equiv of sulfoxide ligand. Upon evaporation to an oil, the product was precipitated out with ether. After cooling overnight, the white solid was filtered off, recrystallized from hot MeOH/ether, and washed with acetone to remove the excess free ligand. The product was dried in a vacuum with heat. Yield: 53%. Anal. Calcd for C$_{19}$H$_{22}$ClN$_3$O$_4$SPt: C, 37.94; H, 3.79; N, 6.64. Found: C, 38.08; H, 3.73; N, 6.63.

Displacement Studies. High-pressure liquid chromatography (HPLC) separations were performed on an ISCO equipment consisting of pump model 2350, absorbance detector model V^4, and gradient programmer model 2360. The column was a SPHERISORB ODS-2 5 μm, 250 mm × 4.6 mm C18 from ISCO. The water was double-distilled and deionized. All the solvents used were HPLC pure, filtered over a micropore filter (0.2 μm), and degassed in a sonificator (Branson 3200). The wavelength used for the analyses was 245 nm, where the maximum absorption for free MeBzSO occurs. The complexes were dissolved in 0.7 mL of water and 0.3 mL of MeOH, and a 50-fold excess of NaCl was added. A 15 μL portion of this solution was injected in the column every 10 min. The system of solvents consisted of 50% water and 50% MeOH, in the isocratic mode. The integration of the area under the curve (AUC) of the peak of interest was used to measure the free MeBzSO concentration. A pseudo-first-order kinetics approach was used to calculate the rate constants through plotting ln(AUC$_f$−AUC$_t$) versus time. The slope corresponded to the pseudo-first-order rate constant, k'.

Reactions Followed by NMR Spectroscopy. The solvolysis of *cis*- and *trans*-[PtCl$_2$(amine)$_2$] in Me$_2$SO was followed by ^{195}Pt and ^{1}H NMR spectroscopy using 0.025 M solutions in both cases. For the reactions of *trans*-[PtCl(R′R″SO)(amine)$_2$]NO$_3$ with GMP the following concentrations were used: 10 mM of the complexes and either 10 or 20 mM GMP in 1 mL of D$_2$O. The reactions were performed in an NMR tube, and spectra were recorded at regular time intervals.

Acid−Base Titrations. Solutions of 0.1 and 1 M of NaOD and DCl were used to reach the desired pH. The pH values (uncorrected for deuterium isotope effects) were measured in a Fisher Scientific instrument, model Accumet 925, having an ultrathin pH electrode from Aldrich as reference electrode (Hg/Hg$_2$Cl$_2$).

Crystal Structure Determination. Colorless crystals of *trans*-[PtCl-(DMSO)(py)$_2$]NO$_3$ suitable for structure analysis were grown by slow evaporation of saturated methanolic solutions at room temperature. The crystal was mounted on a glass fiber, and all measurements were made on an Enraf-Nonius CAD-4 diffractometer with graphite monochromated Mo Kα radiation. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 22 carefully centered reflections in the range 12.89 < 2θ < 38.88, corresponded to an orthorhombic cell. A total of 1854 reflections were collected. The intensities of two representative reflections which were measured after every 60 min of X-ray exposure time remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was applied). The data were corrected for Lorentz and polarization effects. Crystal data are given on Table 3. The structure was solved by direct methods. The non-hydrogen atoms were refined either anisotropically or isotropically. Neutral atom scattering factors were taken from Cromer and Waber.[16] Anomalous dispersion effects were included in F_{calc};[17] the values for Δf′ and Δf″ were those of Cromer.[18] All calculations were performed using the TEXSAN[19] crystallographic software package of Molecular Structure Corporation.

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Table 1. NMR Spectroscopy Data for
trans-[PtCl(R′R″SO)(A)$_2$]NO$_3$

complex	$\delta(^1H)^a$ R′R″SO	A	$\delta(^{195}Pt)$
I	3.6 (28.2)		−3123
II	3.54 (28.6), 4.98(dd), 7.56(m), 7.66(m)		−3143
III	3.86 (27.7), 7.78(m), 8.22(m)		−3159
IV	3.28 (27.7)	7.7(t), 8.15(t), 8.9(d)	−2902
V	3.16, 7.57(m)	7.57(m), 8.06(t), 8.5(m)	−2891
VI	3.25 (30.3)	2.52, 7.52(d), 8.67(d)	−2909
VII	3.12, 7.57(m)	2.47, 7.38(d), 8.28(d)	−2890

^{a} See Experimental Section for details. All values in ppm, ^{1}H rel. to TMS, ^{195}Pt rel. to Na$_2$ PtCl$_6$. Singlets except where indicated, d = doublet, dd = double doublet, m = multiplet. Numbers in parentheses refer to ^3J(Pt−H) (Hz) and are given only when observed clearly.

Table 2. Crystallographic Data for *trans*-[PtCl(Me$_2$SO)(py)$_2$]NO$_3$

formula	PtClN$_3$SO$_4$C$_{12}$H$_{16}$
fw	528.88
cryst dimens	0.250 × 0.162 × 0.075 mm
space group	orthorhombic $P2_12_12_1$
a	7.888(2) Å
b	4.740(3) Å
c	15.626(5) Å
V	1817(1) Å^3
Z	4
D_{calc}	1.933 g/cm^3
diffractometer	Enraf-Nonius CAD-4
radiation	Mo Kα ($\lambda = 0.710\,69$ Å)
μ(Mo Kα)	80.78 cm^{-1}
temperature	23 °C
tot. no. of reflns	1854
R, %	3.8
R_w, %	3.9

Table 3. Selected Bond Distances (Å) and Angles (deg) for *trans*-[PtCl(Me$_2$SO)(py)$_2$]$^+$

Bond Lengths

Pt−Cl	2.304(4)	Pt−S	2.218(5)	Pt−N$_1$	2.03(1)	Pt−N$_2$	2.02(1)
S−O$_1$	1.46(1)	S−C$_{11}$	1.80(2)	S−C$_{12}$	1.81(2)		

Bond Angles

Cl−Pt−S	177.9(2)	Cl−N$_1$−C$_5$	118(1)
Cl−Pt−N$_1$	88.0(4)	Pt−N$_2$−C$_6$	129(1)
Cl−Pt−N$_2$	89.3(50	Pt−N$_2$−C$_{10}$	119(1)
S−Pt−N$_1$	93.8(4)	C$_6$−N$_2$−C$_{10}$	120(1)
S−Pt−N$_2$	88.9(4)	N$_1$−C$_1$−C$_2$	126(2)
N$_1$−Pt−N$_2$	177.2(6)	Pt−S−O$_1$	115.1(7)
Pt−S−C$_{11}$	111.8(8)	Pt−S−C12	111.6(9)
N$_1$−C$_5$−C$_4$	120(2)	O$_1$−S−C$_{11}$	107(1)
N$_2$−C$_6$−C$_7$	25(2)	O$_1$−S−C$_{12}$	108(1)
C$_{11}$−S−C$_{12}$	103(1)	Pt−N$_1$−C$_5$	120(1)

Results and Discussion

Figure 1 shows the structures of the sulfoxides and the complexes prepared. The general method used for preparation of the complexes consisted of the reaction of *trans*-[PtCl$_2$(A)$_2$] (A = NH$_3$, py, or pic) with AgNO$_3$ in the presence of the appropriate sulfoxide as follows:

trans-[PtCl$_2$(A)$_2$] + AgNO$_3$ + R′R″SO →

trans-[PtCl(R′R″SO)(A)$_2$]NO$_3$ + AgCl
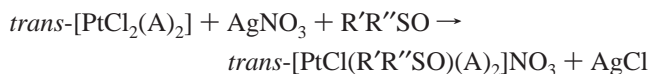
The facile preparation of *trans*-[PtCl(Me$_2$SO)(NH$_3$)$_2$]Cl by simply dissolving *trans*-DDP in Me$_2$SO has been reported.[14,15] Interestingly, this approach did not work for the pyridine derivatives (see also below), and more forcing conditions using chloride abstraction with AgNO$_3$ were necessary. AgNO$_3$ was used to prepare the ammine complexes for consistency and to avoid the presence of excess chloride in the substitution
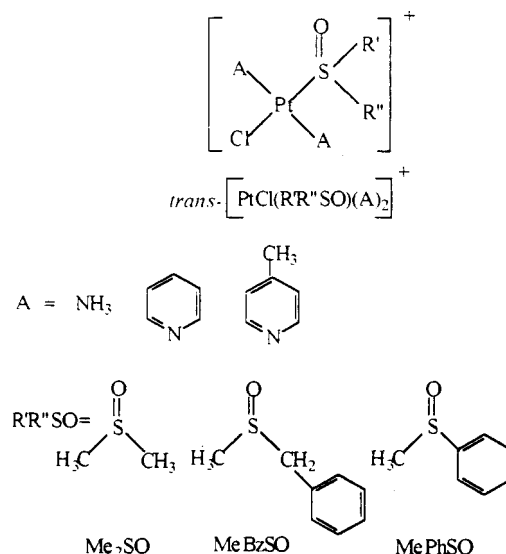
Figure 1. Structures of sulfoxides and their complexes *trans*-[PtCl-(R′R″SO)(A)$_2$]$^+$ used in this study.

reactions. The characterizing data are given in Table 1. The chemical shifts of the sulfoxide protons for all the complexes indicated an S-bonded sulfoxide.[7] For the ammine complexes the signal corresponding to the S-Me protons is shifted 0.90−0.98 ppm to lower field compared to the free ligand. In the case of the aromatic amine complexes this shift is smaller, 0.5−0.6 ppm, which is probably due to the ring current effect.[20] The phenyl protons of the sulfoxide are shifted to lower field as well; for complex **II** these signals occur as two multiplets at 7.66 and 7.56 ppm compared to 7.46 and 7.38 ppm for free MeBzSO. The ^{1}H NMR spectrum for complex **II** also shows a doublet of doublets at 4.98 ppm due to the diasteriomeric methylenic protons of MeBzSO. In the case of complexes **V** and **VII** these signals overlap with the solvent and were not observed. The ^{195}Pt chemical shifts confirm that the sulfoxide is bound through the sulfur. The ^{195}Pt NMR chemical shifts for all the complexes depend mainly on the nature of the amine. Compared to the pyridine complexes, the signals for the ammine complexes occur upfield since the NH$_3$ is a better donor with no back-bonding capacity; for instance, the signal for *trans*-[PtCl$_2$(NH$_3$)$_2$] occurs at −2243 ppm and for *trans*-[PtCl$_2$(py)$_2$] at −1946 ppm. In the ^{195}Pt NMR spectrum for *trans*-[PtCl-(Me$_2$SO)(NH$_3$)$_2$]NO$_3$, it is possible to observe the coupling between the platinum and the nitrogen atoms, $^1J(^{195}$Pt−^{14}N) = 203 Hz.[21,22] The IR spectra of the ammine complexes show a strong ν(SO) around 1130 cm^{-1}. For the aromatic amines this band occurs around 1140 cm^{-1}. No attempt was made to distinguish ν(PtS) and ν(PtCl), which appear around 320 cm^{-1}, as the bands due to vibrations of the sulfoxide occur in this region as well.[23]

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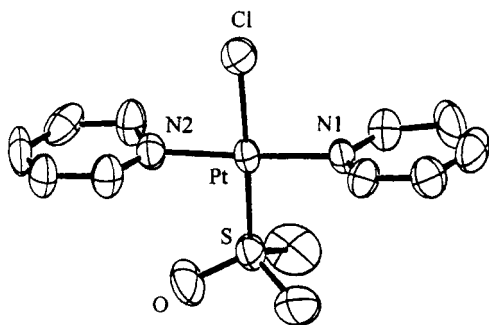
Figure 2. Molecular structure of *trans*-[PtCl(Me₂SO)(py)₂]⁺ in the crystal.

Description of the Structure of *trans*-[PtCl(Me₂SO)(py)₂]-NO₃. To further confirm the structures and to examine structural effects on the reactivity of the Me₂SO ligand, a single-crystal structure determination was performed on *trans*-[PtCl(Me₂SO)-(py)₂]NO₃. The crystal data are given in Table 2 and important distances and angles in Table 3. The structure of the complex is shown in Figure 2, confirming that the sulfoxide is bound to the platinum through the sulfur. The complex displays the expected square-planar configuration about the platinum with N−Pt−S and N−Pt−Cl angles close to 90°. The angle N₁−Pt−S, 93.8°, is a little large; however it can be related to other platinum complexes having sulfoxide as ligands.[23] The geometry around the sulfur is normal. The Pt−S bond length of 2.218 Å is close to those found in the *trans*-[PtCl(Me₂SO)(NH₃)₂]⁺, 2.197 Å[14] and 2.204 Å,[15] determinations. The bond distances and angles in the pyridine rings are about the same as found in *trans*-[PtCl₂(py)₂].[24] The dihedral angles between the pyridine molecules and the coordination plane are 91.6° and 92.9° to minimize the steric hindrance. The Pt−S bond length is slightly longer and the Pt−Cl bond at 2.304 Å is slightly shorter than those found in similar compounds with the same trans influence such as *trans*-[PtCl(Me₂SO)(NH₃)₂]⁺ and *cis*-[PtCl₂(Me₂SO)-(py)].[14,25] Indeed, all the crystallographically determined bond distances and bond angles for both pyridine and NH₃ species are very close to each other, suggesting that any differences in reactivity are not the result of ground-state effects.

Solvolysis of [PtCl₂(A)₂] in Me₂SO. The synthesis of *trans*-[PtCl(R′R″SO)(amine)₂]⁺ complexes required more forcing conditions for pyridine than for NH₃ and provided evidence of differences in reactivity between ammine (NH₃) and aromatic amines. Indeed, we were unable to prepare pyridine complexes with sterically demanding sulfoxides such as MePhSO, and even the synthesis and recrystallization of *trans*-[PtCl(Me₂SO)(pic)₂]⁺ was unpredictable in our hands: on several occasions *trans*-[PtCl₂(pic)₂] precipitated from solution upon workup after the initial metathesis reaction. A reasonable explanation for this observation is that a small amount of Cl⁻ produced from solvolysis of the initially formed *trans*-[PtCl(Me₂SO)(pic)₂]⁺ could displace Me₂SO, giving back the starting material. This effect is reminiscent of the disproportionation in concentrated solutions of *trans*-[PtCl(H₂O)(NH₃)₂]⁺ to *trans*-[PtCl₂(NH₃)₂] and the diaqua cation *trans*-[Pt(H₂O)₂(NH₃)₂]²⁺.[26]

To determine whether steric or electronic factors contributed to the diminished reactivity of complexes containing pyridine ligands, we investigated the solvolytic reactions of the starting

Table 4. ¹⁹⁵Pt and ¹H NMR Spectroscopy Data for Solvolysis of *cis*-[PtCl₂(A)₂] (A = py and pic) in Me₂SO-*d₆*[a]

	δ(¹⁹⁵Pt)		δ(¹H)		
species	A = py	A = pic	H (ortho)	H (meta)	−CH₃
cis-PtCl₂(A)₂	−1954	−1961	8.56(d)	7.30(d)	2.34(s)
free picoline			8.42(d)	7.21(d)	2.31(s)
cis-[PtCl₂(Me₂SO)(A)₂]	−2851	−2862	8.72(d)	7.38(d)	2.40(s)
trans-[PtCl₂(Me₂SO)(A)₂]	−3014	−3023	8.50(d)	7.47(d)	2.43(s)

[a] See Experimental Section for details. ¹H NMR data only for A = pic; d = doublet; s = singlet. All values in ppm, ¹H rel. to TMS.

complexes, *cis*- and *trans*-[PtCl₂(pyr)₂] in Me₂SO. Such investigations have been carried out previously for *cis*- and *trans*-[PtCl₂(NH₃)₂], and both react readily with Me₂SO to give initially the corresponding [PtCl(Me₂SO)(NH₃)₂]⁺.[27] The trans isomer reacts more rapidly than *cis*-[PtCl₂(NH₃)₂], and the substitution of the first chloride by Me₂SO in *trans*-[PtCl₂-(NH₃)₂] is very favored. The solvolysis reactions of *cis*- and *trans*-[PtCl₂(amine)₂] in Me₂SO were followed by ¹⁹⁵Pt NMR spectroscopy for both pyridine and picoline and by ¹H NMR spectroscopy for the picoline derivative. Unlike *trans*-[PtCl₂-(NH₃)₂], the pyridine complexes simply do not react with Me₂-SO. Even up to 24 h after mixing only the signal corresponding to the original complexes was observed. Hoover and Zipp studied the reaction of *trans*-[PtCl₂(py)₂] with Me₂SO in methanol using conductimetry.[28] They reported the displacement of the chloride giving *trans*-[Pt(Me₂SO)₂(py)₂]²⁺ as the purported final product. We did not observe any reaction between the trans complex and Me₂SO. Likewise, no reaction was observed in Me₂SO for *trans*-[PtI₂(py)₂].[29]

The cis compounds [PtCl₂(py)₂] react very rapidly with Me₂-SO, and a signal due to the first product was observed after 1 h. The solvolysis products were characterized as an equilibrium mixture of *cis*- and *trans*-[PtCl₂(Me₂SO)(amine)] by their ¹⁹⁵Pt and ¹H NMR spectra and comparison with literature data (See Table 4 and Supporting Information Figures S1 and S2).[31−33] The ¹⁹⁵Pt NMR chemical shifts for *cis*- and *trans*-[PtCl₂(Me₂-SO)(pyridine)] were −2862 and −3023 ppm, respectively. Marzilli et al.[30] reported chemical shifts for *cis*- and *trans*-[PtCl₂(Me₂SO)(A)] at −2856 and −3018 ppm (A = py) and at −2859 and −3020 ppm (A = pic), similar to those found for *cis*- and *trans*-[PtCl₂(Me₂SO)(quin)] chemical shifts at −2871 and −3016 ppm, respectively.[2] The following scheme represents the solvolysis reaction:

$$\textit{cis}\text{-}[PtCl_2(A)_2] + Me_2SO \rightarrow \textit{cis}\text{-}[PtCl_2(Me_2SO)(A)] \ + \ A$$

$$\downarrow\uparrow$$
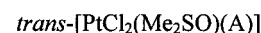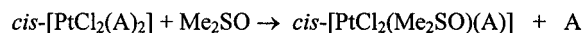
$$\textit{trans}\text{-}[PtCl_2(Me_2SO)(A)]$$

The results on solvolysis may be compared with the reaction of *cis*-[PtCl₂(Me₂SO)₂] with pyridines and other heterocycle donors, which has been extensively studied. The final products are always *cis/trans*-[PtCl₂(amine)(Me₂SO)], through initial formation of the cationic species *cis*-[PtCl(Me₂SO)₂(amine)]⁺. The relative proportions of the cis and trans final products is dependent on the nature of the amine as well as solvent medium.[30,32] Ha et al. also used the reaction of *cis*-[PtI₂(py)₂]

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with Me$_2$SO to obtain *trans*-[PtI$_2$(Me$_2$SO)(py)].[29] The isomerization was explained by postulating the initial displacement of one iodide by Me$_2$SO forming *cis*-[PtI(Me$_2$SO)(py)$_2$]$^+$, with further reaction of the displaced iodide giving the final product *trans*-[PtI$_2$(Me$_2$SO)(py)] plus free pyridine. The solvolysis of the chloride complexes above does not appear to follow this mechanism, but direct initial formation of *cis*-[PtCl$_2$(Me$_2$SO)-(py)] is implied for two main reasons. First, the ^{195}Pt chemical shift for *cis*-[PtCl$_2$(Me$_2$SO)(amine)] agrees with the literature data. For chloride leaving groups, the proposed intermediate *cis*-[PtCl(Me$_2$SO)(amine)$_2$]$^+$ (δ(Pt) = -2957 and -2964 ppm for amine = pyridine and picoline respectively[30]) was never observed in our reactions. In contrast, free picoline was detected by ^{1}H NMR spectroscopy at times when only the *cis*-[PtCl$_2$(Me$_2$SO)(A)] species was present in solution (spectrum run after 1 h, see Figure S1), indicating that Me$_2$SO is displacing the amine. Further possible intermediates may be proposed such as *cis*-[PtCl(Me$_2$SO)$_2$(py)]$^+$ formed from *cis*-[PtCl$_2$(Me$_2$SO)(py)], but these were never detected. If formed, the likelihood is that such a species would be consumed very rapidly due to the mutual cis labilization of two Me$_2$SO groups.[33,34] These solvolysis reactions attest to an important difference in reactivity between ammine and pyridine complexes.

Displacement Reactions of *trans*-[PtCl(MeBzSO)-(amine)$_2$]$^+$. To compare the effects of pyridine and ammine ligands in substitution reactions, the rate of displacement of the sulfoxide in *trans*-[PtCl(MeBzSO)(A)$_2$]NO$_3$ (A = NH$_3$, py, or pic) with excess NaCl was measured. The displacement of the sulfoxide was followed by the appearance of the free sulfoxide HPLC peak. Those experiments were done only for the MeBzSO complexes because their reaction times are more convenient since they react faster than the Me$_2$SO complexes and the appearance of the free sulfoxide peak in the HPLC of the reaction mixture is easily monitored. The following scheme represents the reaction:

$$\textit{trans-}[\text{PtCl(MeBzSO)(A)}_2]^+ + \text{Cl}^- \rightarrow$$
$$\textit{trans-}[\text{PtCl}_2(\text{A})_2] + \text{MeBzSO}$$
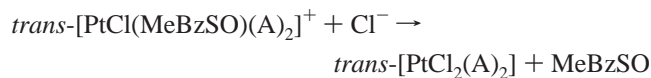
The HPLC peak of the complex decreased in intensity with time with parallel increase in intensity of free ligand as it is displaced by chloride. The other reaction product, *trans*-[PtCl$_2$(amine)$_2$], precipitates from solution and was characterized by IR spectra compared to an authentic sample. The reactions were performed at 298 and 310 K. Since Cl$^-$ was used in excess in all the reactions and the ion concentration remained essentially constant, in general no noncoordinating anions such as ClO$_4^-$ were added. Analysis of appearance of free sulfoxide versus time gave first-order plots. The pseudo-first-order rate constants are given in Table 5. The data show that the sulfoxide is more rapidly displaced for the aromatic amines than for the ammine complexes. There is a 1- to 2-order magnitude increase in rate constant for the pyridine complexes over that of NH$_3$ and a further distinct increase in rate in moving from pyridine to the 4-substituted picoline. The pseudo-first-order rate constants found for the reaction [PtCl(MeBzSO)(diam)]$^+$ + Cl$^-$ → [PtCl$_2$-

Table 5. Pseudo-First-Order Rate Constants for the Reaction of Displacement of Sulfoxide by Cl$^-$ for *trans*-[PtCl(MeBzSO)(A)$_2$]NO$_3$

A	temperature (°C)	k' (s^{-1}) × 10^5
NH$_3$	25	1.57
	37	2.20
pyridine	25	45.60
	37	64.25
4-picoline	37	98.18

Table 6. ^{1}H NMR Data for the Reactions of *trans*-[PtCl(R'R''SO)(NH$_3$)$_2$]NO$_3$ and 2 equiv of GMP

|	δ		
species^a	H8	H1'	SCH$_3$
free 5'-GMP	8.17	5.91(d)	
[Pt(Me$_2$SO)(NH$_3$)$_2$(GMP)]	8.96	6.05(d)	3.71, 3.68
[Pt(MeBzSO)(NH$_3$)$_2$(GMP)]	8.94	6.04(d)	3.58
[Pt(NH$_3$)$_2$(GMP)$_2$]	8.90	6.02(d)	

^{a} All the complexes are trans. Charges omitted for clarity. See Experimental Section for details. ^{1}H NMR data only for A = pic. Singlets except where indicated; d = doublet. All values in ppm, ^{1}H rel. to TMS.

(diam)] + MeBzSO at 37 °C were 0.049 × 10^{-5} s^{-1} for diam = *R,R*-1,2-diaminocyclohexane (dach) and 0.196 × 10^{-5} s^{-1} for diam = 1,1-diaminomethylcyclohexane (damch).[7] Thus, the sulfoxide is displaced faster for all the trans compounds, presumably explained by the presence of the trans chloride.[7] The high values of the rate constants may also explain the difficulties in synthesis noted above.

Reactions with Guanosine 5'-Monophosphate (GMP). To further investigate differences in reactivity between ammine and pyridine complexes, the reactions of *trans*-[PtCl(R'R''SO)(A)$_2$]-NO$_3$ (R'R''SO = Me$_2$SO, MeBzSO and A = NH$_3$ and py) and 1 or 2 equiv of GMP were performed in an NMR tube at 310 K. Interestingly, the patterns were the same, and only the reactions with 2 equiv of the mononucleotide were examined in detail. No buffer was used to avoid complexation with the platinum.[35] The pH was between 7.0 and 6.5 during the entire reaction time. The complex *trans*-[PtCl(Me$_2$SO)(NH$_3$)$_2$]$^+$ has been shown to react faster with DNA and produce more bifunctional adducts (as measured by interstrand cross-linking) than the dichloride.[15,36] For both amines, the reaction pathway was consistent with that previously observed for *cis*-[PtCl-(R'R''SO)(diamine)]$^+$.[7,11] Initial formation of *trans*-[Pt(R'R''SO)(GMP)(amine)$_2$]$^+$ (**1**) appears to be followed by competing reactions of sulfoxide displacement by the displaced chloride or by a further molecule of GMP, giving *trans*-[PtCl(GMP)-(amine)$_2$] (**2**) and *trans*-[Pt(GMP)$_2$(amine)$_2$] (**3**), respectively. The monosubstituted species may then react further by slow displacement of the chloride.[37-39] Because of the difficulty in analyzing these competing reactions, the results of these experiments are discussed only briefly below. Table 6 summarizes the pertinent ^{1}H and ^{195}Pt NMR data.

Reaction of *trans*-[PtCl(R'R''SO)(NH$_3$)$_2$]NO$_3$ with GMP (R'R''SO = Me$_2$SO, MeBzSO). The reactions were very similar for both sulfoxide complexes. Loss of some sulfoxide ligand is

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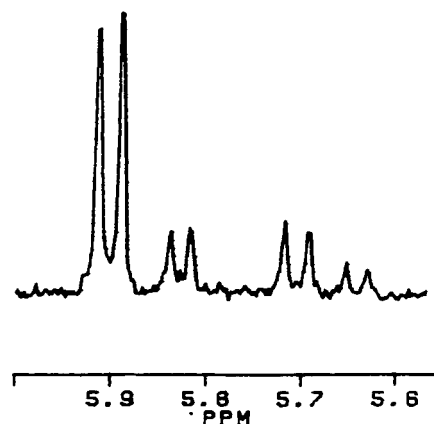(34) Farrell, N. *J. Chem. Soc., Chem. Commun.* **1982**, 331.

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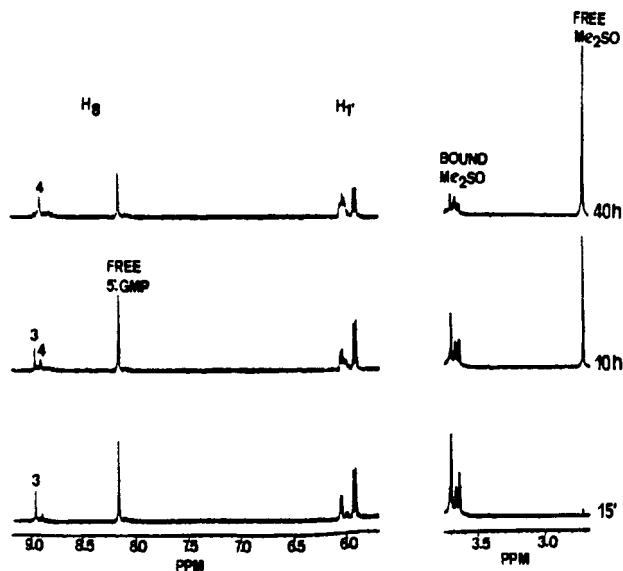
Figure 3. ^{1}H NMR spectra versus time for the reaction of *trans*-[PtCl-(Me$_2$SO)(NH$_3$)$_2$]NO$_3$ and 2 equiv of GMP at 310 K, pH = 7.

Figure 4. ^{1}H NMR spectrum showing the H1′ of 5′-GMP region for the reaction of *trans*-[PtCl(Me$_2$SO)(py)$_2$]NO$_3$ and 2 equiv of GMP after 9 h. The four species are described in the text.

observed immediately, and the intensity of the free sulfoxide ligand increased as the reaction proceeded. Loss of bound sulfoxide did not correlate with disappearance of free GMP, and even after 40 h there was still free GMP and species having bound sulfoxide in solution, Figure 3. Nevertheless, the ^{195}Pt NMR spectrum after 40 h reaction showed only one signal at −2467 ppm assigned to the major product *trans*-[Pt(NH$_3$)$_2$-(GMP)$_2$], in agreement with the literature value of −2469 ppm.[40] Two signals corresponding to the Me$_2$SO methyl protons are observed for the purported initial species *trans*-[Pt(Me$_2$SO)-(GMP)(NH$_3$)$_2$]$^+$ due to inequivalence upon GMP binding to Pt. For the corresponding MeBzSO complex, the ^{1}H NMR spectrum also shows two multiplets at 7.71 and 7.57 ppm corresponding to the aromatic protons of the ligand.

Reaction of *trans*-[PtCl(R′R″SO)(py)$_2$]NO$_3$ with GMP. The analysis of these reactions is more complicated due to overlap of the pyridine signals with the H8 signals of the various species produced and (where used) the phenyl protons of MeBzSO. Therefore, only the picoline/Me$_2$SO complex with the simplest NMR spectrum was examined. The complexity of the reaction is most clearly seen in the case of *trans*-[PtCl(Me$_2$SO)(pic)]$^+$, where the H1′ region shows four doublets after approximately 1 h of reaction, indicating the presence of the species (**1, 2, 3**) listed above along with unreacted GMP, Figure 4. Nevertheless, the increased rate of reaction of the pyridine complexes was inferred by the production of 100% of free sulfoxide after approximately 9 h with no peaks present corresponding to either starting material or *trans*-[Pt(Me$_2$SO)(GMP)(pic)$_2$]$^+$. Again, the appearance of free sulfoxide did not correlate with disappearance of GMP, and indeed unreacted GMP was observed throughout the reactions (followed up to 40 h). After 9 h the main species is most likely to be the 1:2 adduct, *trans*-[Pt(pic)$_2$(GMP)$_2$], since the ^{195}Pt NMR spectrum showed only one peak at −2331 ppm, which is analogous to that of *trans*-[Pt(NH$_3$)$_2$(GMP)$_2$] consider-

ing the observed differences in chemical shift for ammine and pyridine complexes.[40] The identity of the final product was also confirmed by comparison with an authentic sample of *trans*-[Pt(GMP)$_2$(pic)$_2$] prepared from *trans*-[Pt(NO$_3$)$_2$(pic)$_2$] and GMP.[41]

The rapid loss of Me$_2$SO is further testimony to the steric demands of the pyridine ligand in comparison to NH$_3$; in this case three planar ligands, two pyridine and one purine, will create steric crowding around the Pt square plane, which is relieved by loss of the S-bound ligand.

Conclusions. This work was aimed at an understanding of the role of the pyridine ligands in the activation of the trans platinum geometry. Consistently, the sulfoxide ligand in the pyridine complexes is displaced more readily than the corresponding ammine species. Steric effects are likely to explain this difference, as is also the case for the dramatic differences in solvolysis observed for the [PtCl$_2$(py)$_2$] isomers. The inability to observe substitution reactions of the trans isomer by Me$_2$SO may be a result of steric effects caused by the presence of two pyridine ligands and a slower rate of chloride displacement in the presence of planar ligands.[4,6] The reduced kinetic reactivity of the *trans*-[PtCl$_2$(py)$_2$] may thus be manifested in a more suitable pharmacokinetic profile, leading to the observed enhancement of biological activity in comparison to *trans*-[PtCl$_2$-(NH$_3$)$_2$].[1–4] The steric effects of the 2-picoline ligand have also been used to produce the compound *cis*-[PtCl$_2$(NH$_3$)(2-pic)], ZDO473, currently in Phase II clinical trials, whose reactivity toward biomolecules is less than that of cisplatin.[42] The chemical differences are sufficient to impart a profile of biological activity to ZDO473 complementary to that of the clinically used drug.[43] These findings suggest that these approaches may also lead to the development of clinically relevant trans platinum compounds.

Supporting Information Available: Two figures (^{1}H and ^{195}Pt NMR spectra) on the time course of the solvolysis of *cis*-[PtCl$_2$(4-pic)$_2$] in Me$_2$SO. Complete tables of crystallographic data, positional parameters, thermal displacement parameters, intramolecular bond lengths and bond angles, torsion angles, and selected contacts for *trans*-[PtCl(Me$_2$SO)(py)$_2$]NO$_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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