observed in the resulting product mixture were $[PtCl_2(dmpe)]$, *cis*-$[PtCl_2(PPh_3)_2]$, and $[Pt(dmpe)_2]Cl_2$. No evidence for the cationic complex $[PtCl(PPh_3)(dmpe)]^+$ was obtained.

Reaction of $[PtCl_2(dmpe)]$ with $PMePh_2$. (a) $[PtCl_2(dmpe)]$ (0.037 g, 0.088 mmol) was mixed with $CDCl_3$ in a 5-mm NMR tube. After the tube had been flushed with argon, $PMePh_2$ (16.3 μL, 0.088 mmol) was added. $^{31}P\{^1H\}$ NMR analysis of the resulting mixture indicated that the predominant platinum-containing species was $[PtCl(PMePh_2)(dmpe)]Cl$.

(b) When $[PtCl_2(dmpe)]$ (0.032 g, 0.077 mmol) was reacted with $PMePh_2$ (28.8 μL, 0.16 mmol) in $CDCl_3$ in the same way as above, the $^{31}P\{^1H\}$ NMR spectrum indicated that the predominant platinum-containing species in solution was $[PtCl(PMePh_2)_3]Cl$.

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Solvolysis Reactions of *cis*- and *trans*-Diamminedichloroplatinum(II) in Dimethyl Sulfoxide. Structural Characterization and DNA Binding of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$

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Dimethyl sulfoxide, Me_2SO, is commonly used to dissolve *cis*- and *trans*-diamminedichloroplatinum(II), *cis*- and *trans*-DDP, prior to use in experiments comparing their biological activities. The solvolysis reactions of *cis*- and *trans*-DDP in Me_2SO have been investigated in this study. Me_2SO substitutes for a single chloride ligand in both cases to form *cis*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (**1**-Cl) and *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (**2**-Cl). The half-lives of the cis and trans isomers in Me_2SO at 37 °C are 60 and 8 min, respectively, as determined by both optical and ^{195}Pt NMR spectroscopy. Kinetic studies gave activation parameters for *cis*-DDP solvolysis of $\Delta H^* = 18.9$ (1) kcal mol^{-1} and $\Delta S^* = -14.5$ (2) eu (optical spectroscopy) and $\Delta H^* = 19.8$ (3) kcal mol^{-1} and $\Delta S^* = -11.6$ (3) eu (^{195}Pt NMR spectroscopy). Activation parameters for solvolysis of *trans*-DDP were $\Delta H^* = 15.5$ (1) kcal mol^{-1} and $\Delta S^* = -21.4$ (2) eu (optical spectroscopy) and $\Delta H^* = 16.9$ (3) kcal mol^{-1} and $\Delta S^* = -17.7$ (4) eu (^{195}Pt NMR spectroscopy). The mixed perchlorate/chloride salt of **2**, *trans*-$[Pt(NH_3)_2(Me_2SO)Cl](ClO_4)_{0.8}Cl_{0.2}$, has been crystallized and its structure determined by single-crystal X-ray diffraction methods. The compound crystallizes in the orthorhombic space group *Pnma* with $a = 10.554$ (3) Å, $b = 7.446$ (1) Å, $c = 14.161$ (2) Å, $V = 1111.79$ Å^3, and $Z = 4$. The final R_1 value was 0.0395 for 799 observed reflections. The geometry of platinum is square planar, with Pt–S, Pt–N, and Pt–Cl distances of 2.204 (4), 2.11 (2) and 2.03 (1), and 2.307 (5) Å, respectively. Since **2** is formed rapidly enough to be a significant contaminant in studies in which *trans*-DDP has been dissolved in Me_2SO, reactions with DNA substrates of *trans*-DDP dissolved in either Me_2SO or aqueous buffer were compared. Use of Me_2SO instead of aqueous buffer to dissolve *trans*-DDP increases the rate of platinum binding to calf thymus DNA. Moreover, significant changes occur in the spectrum of products, as revealed in reactions with the model DNA substrate d(GpTpG). These results are consistent with the conversion of *trans*-DDP in Me_2SO to *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$ and the subsequent reaction of this complex with DNA. The use of Me_2SO to dissolve *cis*- or *trans*-DDP in biological studies is therefore strongly discouraged.

Introduction

cis-Diamminedichloroplatinum(II), *cis*-DDP,[2] is a clinically important anticancer drug that apparently acts by binding to DNA and inhibiting replication.[3] Bidentate coordination of DNA to *cis*-DDP is preceded by hydrolysis of at least one labile chloride ligand.[4] Interestingly, the trans isomer, which can bind DNA in a different bifunctional manner, is far less cytotoxic at equimolar doses. A number of studies have focused on the different biological activities of the two isomers in an attempt to explain the detailed mechanism of *cis*-DDP cytotoxicity.[5]

While reviewing data on the different biological effects of *cis*- and *trans*-DDP we became concerned that a number of laboratories[6] employ dimethyl sulfoxide, Me_2SO, as a solvent to dissolve these platinum complexes prior to use in biological experiments, despite the well-known affinity of divalent platinum for sulfur donor ligands.[7] In particular, substitution of a chloride ligand by Me_2SO is expected to occur much faster for *trans*-DDP than for *cis*-DDP, owing to the greater trans-labilizing effect of chloride vs. ammonia.[8] Use of Me_2SO as a solvent may therefore change

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(2) Abbreviations: *cis*- and *trans*-DDP, *cis*- and *trans*-diamminedichloroplatinum(II); Me_2SO, dimethyl sulfoxide; en, ethylenediammine; dach, 1,2-diaminocyclohexane; HPLC, high pressure liquid chromatography; $(D/N)_f$ and $(D/N)_b$, formal and bound drug-to-nucleotide ratios.

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the observed biological activity of *trans*-DDP.[9] The reaction of *cis*-DDP with Me_2SO to form *cis*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (**1**-Cl) and, eventually, other products has been investigated by ^{195}Pt NMR spectroscopy.[10] We now wish to report a study of the solvolysis reaction of *trans*-DDP in Me_2SO to form *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (**2**-Cl) and the structure determination of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl](ClO_4)_{0.8}Cl_{0.2}$ by single-crystal X-ray diffraction methods. We also report a comparison of the reactions of *trans*-DDP, dissolved in either Me_2SO or aqueous buffer, with calf thymus DNA and with the synthetic oligonucleotide d(GpTpG).

Experimental Section

Materials. *cis*- and *trans*-DDP were synthesized according to literature procedures[11] from K_2PtCl_4. Calf thymus DNA (Sigma) was extracted with chloroform/isoamyl alcohol, 24:1 (3x), and precipitated with ethanol (2x) before dialysis into 1 mM phosphate, containing 3 mM sodium chloride, at pH 7.4 (aqueous buffer) and quantitation by UV spectroscopy (ϵ_{260} = 6600 M_{phos}^{-1} cm^{-1}). d(GpTpG) was synthesized by the solution phosphotriester method,[12] purified by reversed-phase HPLC, and converted to the sodium salt by cation-exchange chromatography (Bio-Rad). The product was characterized by ^1H NMR spectroscopy and quantitated by UV spectroscopy (ϵ_{260} = 30 300).[13]

Physical Methods. ^1H NMR spectra were obtained on a Bruker WM 250 spectrometer, and positive chemical shifts are reported downfield from internal $Si(CH_3)_4$. IR spectra were obtained on a Beckman Acculab 10 spectrometer. Atomic absorption spectroscopy was performed on a Varian 1475 spectrophotometer with a GTA 95 graphite furnace and an automatic sample injector. HPLC was performed on a Perkin-Elmer Series 4 LC, using a Phenomenex Bondex C-18 column, and recorded with an LC-95 UV–vis spectrophotometric detector.

^{195}Pt NMR Studies. The kinetics of the solvolysis reactions of both *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ in Me_2SO-d_6 were monitored by ^{195}Pt NMR spectroscopy using a Varian XL 200 spectrometer operating at 42.935 MHz. ^{195}Pt spectra were collected by using a sweep width of 80 kHz, a pulse width of 9 μs, and an acquisition time of 0.06 s. To follow the reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with Me_2SO, 200 mg of the complex was dissolved in 3.0 mL of Me_2SO-d_6 (0.22 M). Spectra were accumulated for 7.5 min at various time intervals. In the case of the trans isomer, 25 mg of solid was dissolved in 3.0 mL of Me_2SO-d_6 (28 mM). Spectra were collected at either 4-min (at 26 and 33 °C) or 2-min (37, 40, and 49 °C) intervals. First-order rate constants were derived by monitoring the decrease in ^{195}Pt signal intensity for the reactants. Reactions were monitored within the temperature range $26 \leq T \leq 49$ °C, and activation parameters were derived from the Arrhenius plot of ln (k_1) vs T^{-1}.

UV–Visible Spectroscopic Studies. Electronic absorption spectra were obtained on a Perkin-Elmer Lambda 7 UV–visible spectrophotometer interfaced with a PE 3600 data station. Temperature-controlled, jacketed cuvettes were used for kinetic experiments, and the temperatures within the cuvettes were monitored with a thermocouple. A 10–12 mg portion of *cis*- or *trans*-DDP was dissolved in 4 mL of Me_2SO and the spectrum recorded at regular time intervals through three reaction half-lives. First-order rate constants were derived by monitoring the increase in absorption at 276 nm for *cis*-DDP and 302 nm for *trans*-DDP. Reactions were studied within the temperature range 23 °C $\leq T \leq$ 46 °C, and activation parameters were derived from Arrhenius plots of ln k_1 vs. T^{-1}.

Preparation of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (2-Cl). *trans*-DDP (300 mg, 1 mmol) was dissolved in 10 mL of Me_2SO (Mallinckrodt) and stirred for 1.5 h at ambient temperature. The resulting nearly colorless solution was treated with 20 mL of ethanol, and diethyl ether was added until the solution became cloudy. After 24 h, the white microcrystalline product was filtered and washed with ethanol and diethyl ether. Isolated yield was 333 mg (88%). Anal. Calcd for $PtCl_2SON_2C_2H_{12}$: Cl, 18.75; S, 8.48; N, 7.41; C, 6.35; H, 3.20. Found: Cl, 18.90; S, 8.45; N, 7.40; C, 6.44; H, 3.21. IR (KBr pellet): 3411 (m), 3226 (m), 3039 (s), 1556 (m), 1357 (m), 1314 (m), 1122 (s), 1021 (s) cm^{-1}. ^1H NMR (CD_3OD): δ 3.52 (J_{Pt-H} = 23.9 Hz). ^{195}Pt NMR (Me_2SO-d_6): δ −3112 (vs. H_2PtCl_6). Electronic absorption spectrum (0.1 M HCl), λ_{max} (ϵ, M^{-1} cm^{-1}): 303 (152), 244 (736) nm.

Table I. Experimental Details of the X-ray Diffraction Study of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl](ClO_4)_{0.8}Cl_{0.2}$

(a) Crystal Parameters[a] at 23 °C

a, Å	10.554 (3)	Z	4
b, Å	7.446 (1)	space group	*Pnma*
c, Å	14.161 (2)	ρ_{calcd}, g/cm^3	2.564
V, Å^3	1111.79	ρ_{obsd}, g/cm^3	2.55 (2)

(B) Measurement of Intensity Data[b]

instrument	Enraf-Nonius CAD-4F κ-geometry diffractometer
radiation	Mo Kα (λ_α = 0.710 73 Å), graphite monochromatized
temp, °C	23
takeoff angle, deg	2.3
stds (measd every 1 h)[c]	(422), (221), (051)
no. of reflcns collcd	2168
data collcn range, deg	$3 \leq 2\theta \leq 50$
measd reflcns	$h,k,\pm l$

(C) Treatment of Data[d]

linear abs coeff	127 cm^{-1}	no. of unique data	1056
averaging, R_{av}	0.0198	no. of obsd data, $I > 2\sigma(I)$	799
R_1[e]	0.0395	R_2[f]	0.0502

[a] From a least-squares fit to the setting angles of 25 reflections with $2\theta \geq 40°$. [b] For typical procedures, see: Silverman, L. D.; Dewan, J. C.; Giandomenico, C. M.; Lippard, S. J. *Inorg. Chem.* **1980**, *19*, 3379. [c] No decay in intensities was observed. [d] F_o and $\sigma(F_o)$ were corrected for background, attenuation, and Lorentz–polarization effects of X-radiation as described in footnote *b*. [e] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [f] $R_2 = [\sum w(|F_o|^2 - |F_c|^2)/\sum w|F_o|^2]^{1/2}$.

Reaction of *trans*-DDP and *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (2-Cl) with Calf Thymus DNA. Freshly prepared solutions (1.0×10^{-3} M) of *trans*-DDP in aqueous buffer, *trans*-DDP in Me_2SO, and **2**-Cl in aqueous buffer were incubated at ambient temperature for exactly 5 min before reaction with calf thymus DNA. A 50-μL portion of each solution was added to 10 mL of DNA solution (1.0×10^{-4} M in aqueous buffer) and allowed to react at 37 °C (final concentrations: [DNA] = 1.0×10^{-4} M; [Pt] = 5.0×10^{-6} M; $(D/N)_f$ = 0.05). Aliquots of the reaction mixtures were removed at various times and quenched by addition of NaCl (0.5 M final concentration) and rapid cooling to 4 °C. Unbound platinum was removed by dialysis at 4 °C for 16 h against aqueous buffer. DNA concentrations were determined by UV spectroscopy and platinum concentrations by atomic absorption spectroscopy.

Reaction of *trans*-DDP and *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]Cl$ (2-Cl) with d(GpTpG). Platinum-containing solutions were prepared and incubated as described above prior to reaction with d(GpTpG) in aqueous buffer, except that *trans*-DDP/Me_2SO was initially 10 mM to minimize the amount of Me_2SO added to the DNA reaction mixture (final concentrations: d(GpTpG) = 1.0×10^{-4} M; [Pt] = 1.0×10^{-4} M). Reactions were allowed to proceed at 37 °C and were monitored by reversed-phase HPLC. Products were eluted with a 30-min gradient of 0–15% CH_3CN in 0.1 M ammonium acetate, pH 6.8. The primary product of the reaction of *trans*-DDP with d(GpTpG), a G(1)–G(3) intrastrand cross-link with coordination at the N-7 positions of guanine,[14] was confirmed by ^1H NMR spectroscopy.

X-ray Crystallography. Crystals of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl](ClO_4)_{0.8}Cl_{0.2}$ were grown by slow evaporation of **2**-Cl and 2 equiv of $NaClO_4$ from a solution of 2-propanol/water. A colorless crystal with approximate dimensions 0.11 mm × 0.10 mm × 0.09 mm was mounted with epoxy resin on the end of a glass fiber. Open-counter ω scans of several strong, low-angle reflections revealed structureless profiles with acceptable peak widths ($\overline{\Delta\omega_{1/2}}$ = 0.19°). Intensity data and unit cell parameters were measured with a single-crystal diffractometer, details of which are presented in Table I. The crystal was found to belong to the orthorhombic system, with either space group $Pn2_1a$ (C_{2v}^9, No. 33 in a nonstandard setting) or *Pnma* (D_{2h}^{16}, No. 62), as determined from systematic absences in the data.[15] The structure was successfully solved in the latter, centrosymmetric space group. The platinum atom was located from a Patterson map, and the remaining non-hydrogen atoms were found in subsequent difference Fourier maps. Neutral-atom scat-

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Table II. Kinetic Data for the Solvolysis Reactions of *cis*- and *trans*-DDP in Me_2SO

	cis-DDP		*trans*-DDP	
T, °C	k_1, s^{-1}	$t_{1/2}$, min	k_1, s^{-1}	$t_{1/2}$, min
	^{195}Pt NMR Spectroscopy[a]			
26	6.24 (7)[b] × 10^{-5}	185	4.9 (3) × 10^{-4}	24
33	1.35 (3) × 10^{-4}	86	9.1 (5) × 10^{-4}	13
37	2.00 (3) × 10^{-4}	58	1.3 (1) × 10^{-3}	9
40	2.88 (4) × 10^{-4}	40	1.7 (1) × 10^{-3}	7
49	6.6 (4) × 10^{-4}	18	...	...
	UV–Visible Spectroscopy[c]			
23	4.36 (4) × 10^{-5}	265	4.84 (1) × 10^{-4}	24
30	9.33 (4) × 10^{-5}	124	9.10 (1) × 10^{-4}	13
37	1.87 (1) × 10^{-4}	62	1.60 (1) × 10^{-3}	7
46	4.41 (2) × 10^{-4}	26	3.20 (2) × 10^{-3}	4

[a] Monitored by disappearance of the resonances at −2087 and −2086 ppm for *cis*-DDP and *trans*-DDP, respectively. [b] The numbers in parentheses refer to the errors in the last digit(s). [c] Monitored at 276 and 302 nm for *cis*-DDP and *trans*-DDP, respectively.

Table III. Final Positional Parameters of Non-Hydrogen Atoms in *trans*-$[Pt(NH_3)_2(Me_2SO)Cl](ClO_4)_{0.8}Cl_{0.2}$[a]

atom	x	y	z
Pt	0.14304 (7)	0.2500	0.05681 (5)
S	0.1825 (4)	0.2500	0.2098 (3)
Cl1	0.1122 (5)	0.2500	−0.1046 (4)
Cl2	0.1499 (4)	0.2500	0.5735 (3)
O1	0.3171 (11)	0.2500	0.2350 (10)
O2	0.1478 (14)	0.2500	0.4497 (10)
O3	0.0823 (19)	0.388 (2)	0.5997 (15)
O4	0.271 (2)	0.2500	0.6002 (17)
N1	−0.0557 (16)	0.2500	0.0734 (11)
N2	0.3322 (13)	0.2500	0.0307 (11)
C	0.1095 (11)	0.4392 (17)	0.2650 (8)
Cl3	0.1488 (11)	0.1441 (17)	0.4797 (8)

[a] Numbers in parentheses refer to errors in the last digit(s). Atoms are labeled as shown in Figure 1. Atom Cl2 is the perchlorate chlorine atom and Cl3 is the partially occupied chloride ion (see text).

Table IV. Interatomic Distances (Å) and Angles (deg) for the *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$ Cation (**2**)[a]

Pt–N2	2.03 (1)	Pt–N1	2.11 (2)
Pt–S	2.204 (4)	Pt–Cl1	2.307 (5)
S–O1	1.46 (1)	S–C	1.79 (1)
N2–Pt–N1	175.9 (6)	N2–Pt–S	89.6 (5)
N2–Pt–Cl1	87.6 (5)	N1–Pt–S	94.5 (4)
N1–Pt–Cl1	88.3 (4)	S–Pt–Cl1	177.2 (2)
O1–S–C	108.2 (5)	O1–S–Pt	114.9 (6)
C–S–O1	108.5 (6)	C–S–C′	103.8

[a] See footnote *a* in Table III.

tering factors and anomalous dispersion corrections for the non-hydrogen atoms were obtained from ref 16. Anisotropic thermal parameters were used for the non-hydrogen atoms. Hydrogen atoms were placed at their calculated positions, constrained to "ride" on the atoms to which they are attached, and assigned a common isotropic thermal parameter.

Full-matrix least-squares refinement was carried out on 75 variable parameters by using SHELX-76.[17] Toward the end of the refinement, some residual electron density (2.2 e $Å^{-3}$) was evident in the region of the counterion, which, up to that point, was believed to be a full-occupancy perchlorate group. Attempts to account for this peak in terms of ClO_4^- disorder were unsuccessful. Since the observed crystal density of 2.55 (2) g cm^{-3} was lower than the 2.641 g cm^{-3} value calculated for *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]ClO_4$, it occurred to us that not all of the chloride ion in **2**-Cl had been replaced by perchlorate. A model was therefore introduced in which both ClO_4^-, with a partial occupancy of 0.80, and Cl^-, with 0.20 occupancy, were refined. This model both resolved the residual electron density problem and gave a calculated crystal density (2.564 g cm^{-3}) in agreement with that observed. The final difference Fourier map was clean (<1 e $Å^{-3}$), and the refinement converged at R_1 = 0.0395 and R_2 = 0.0502.[18] The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1.3945/[\sigma^2(F_o) + 0.000625(F_o)^2]$ and the maximum parameter shift in the final refinement was 0.002σ.

Final non-hydrogen atom positional parameters are given in Table III, and bond lengths and angles within the cation are given in Table IV. Listings of observed and calculated structure factors, anisotropic thermal parameters, and final hydrogen atom positional and thermal parameters are available in Tables S1–S3, respectively, supplied as supplementary material. An ORTEP drawing showing the molecular geometry and atom-labeling scheme is given in Figure 1.

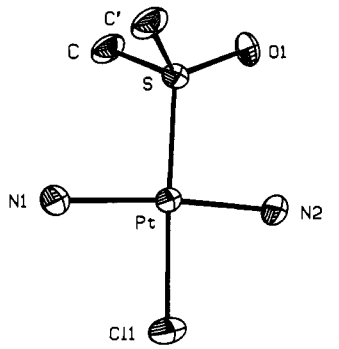

Figure 1. Structure of the *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$ cation, showing the 40% probability thermal ellipsoids and atom-labeling scheme.

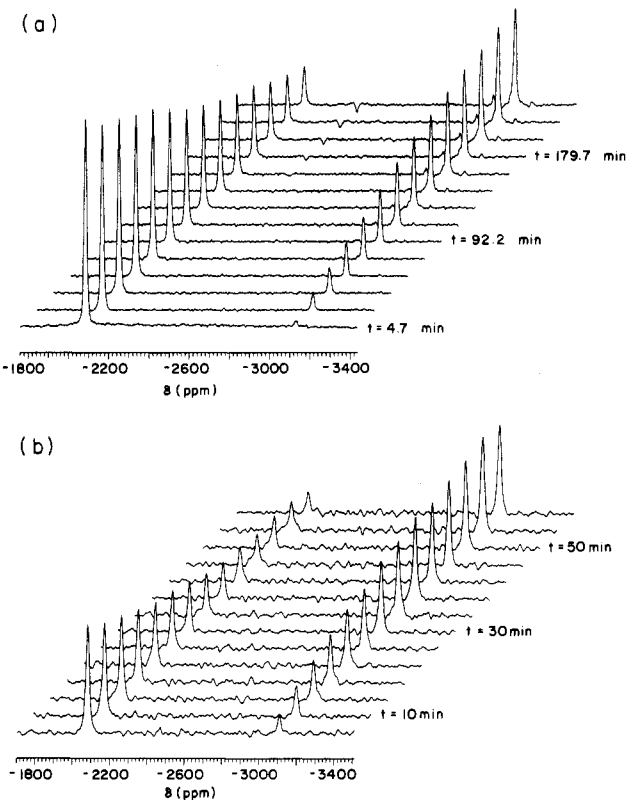

Figure 2. Time-dependent ^{195}Pt NMR spectra of the solvolysis of (a) *cis*-DDP, recorded every 17.5 min, and (b) *trans*-DDP, recorded every 4 min, in Me_2SO-d_6 at 26 °C. Spectra were taken at 42.935 MHz and chemical shifts are reported relative to H_2PtCl_6 (δ 0).

Results and Discussion

Kinetics of Solvolysis of *cis*- and *trans*-DDP in Me_2SO. The solvolysis reactions of both the cis and trans isomers of $[Pt(NH_3)_2Cl_2]$ in Me_2SO were monitored by ^{195}Pt NMR and UV–vis absorption spectroscopy. The kinetic data for both isomers conform to first-order rate equations, and the results are summarized in Table II. Activation parameters, obtained from plots

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(18) $R_1 = \sum w||F_o| - |F_c||/\sum|F_o|$; $R_2 = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

of ln k_1 vs. T^{-1}, were as follows: for *cis*-DDP, $\Delta H^{\ddagger}$ = 18.9 (1) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −14.5 (2) eu (optical spectroscopy) and $\Delta H^{\ddagger}$ = 19.8 (3) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −11.6 (3) eu (^{195}Pt NMR spectroscopy); for *trans*-DDP, $\Delta H^{\ddagger}$ = 15.5 (1) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −21.4 (2) eu (optical spectroscopy) and $\Delta H^{\ddagger}$ = 16.9 (3) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −17.7 (4) eu (^{195}Pt NMR spectroscopy). Figure 2a shows the time-dependent ^{195}Pt NMR spectra of *cis*-DDP in Me_2SO-d_6. The resonance due to *cis*-DDP (δ −2087) gradually diminishes ($t_{1/2}$ = 185 min at 26 °C) with a concomitant increase in the resonance due to *cis*-[$Pt(NH_3)_2(Me_2SO)Cl$]Cl (**1**-Cl). The chemical shift of the latter species (δ −3145) is in good agreement with that reported in the literature.[10]

At longer reaction times (3–24 h), five additional species were observed in the Me_2SO solution of *cis*-DDP by ^{195}Pt NMR spectroscopy. These products, which were identified in a previous NMR study of the reaction of Me_2SO with *cis*-[$Pt(^{15}NH_3)_2Cl_2$],[10] are [$Pt(NH_3)_3Cl$]$^+$, [$Pt(NH_3)_3(Me_2SO)$]$^{2+}$, *cis*-[$Pt(NH_3)(Me_2SO)Cl_2$], *trans*-[$Pt(NH_3)(Me_2SO)Cl_2$] and *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]$^+$. These complexes form as a result of ammonia exchange reacions, which are promoted by the large kinetic trans effect of the sulfur-bound Me_2SO ligand.[8b]

The solvolysis of *trans*-DDP in Me_2SO proceeds more rapidly ($t_{1/2}$ = 24 min at 26 °C) than that of *cis*-DDP and produces the analogous product, *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]Cl (**2**-Cl). Figure 2b shows the time dependence of the ^{195}Pt NMR spectra. The resonance due to *trans*-DDP (δ −2086) diminishes as the resonance due to **2** (δ −3112) grows in. *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]$^+$ is the only product observed in solution by ^{195}Pt NMR spectroscopy, even after long reaction times (24–48 h). Apparently, ammonia exchange products do not result from cis labilization of the ammonia ligands in this case. The much faster rate of solvolysis for the trans isomer is due to the greater kinetic trans-labilizing effect of chloride versus ammonia.

The reactions of *cis*- and *trans*-DDP in Me_2SO were also monitored by UV–vis spectroscopy, and the observed rate constants (Table II) are in agreement with those of the ^{195}Pt NMR spectroscopic studies. The solvolysis reactions can be more accurately followed by UV–vis spectroscopy at temperatures above 35 °C owing to the acquisition times required for ^{195}Pt NMR spectroscopy.

Synthesis of *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]Cl (2-Cl). In order to demonstrate unequivocally that **2** forms in the reaction of *trans*-DDP and Me_2SO, this compound was synthesized on a preparative scale and characterized by chemical analysis and by IR and NMR spectroscopy. The reaction of *trans*-DDP and Me_2SO produces **2** in high yield (88%). In complexes of divalent platinum with Me_2SO, the latter usually coordinates through its sulfur atom.[19] In the present case, sulfur coordination is confirmed by the observed ^{195}Pt–H coupling for the CH_3 protons on the Me_2SO ligand (δ 3.52, $^3J_{Pt-H}$ = 23.9 Hz) and by the characteristic ^{195}Pt NMR chemical shift (δ −3112).[10] The S–O stretch is observed at 1122 cm^{-1} in the IR spectrum, shifted to higher energy than in the free ligand (1050 cm^{-1}). This result is again consistent with sulfur coordination.[20]

Solid-State Structure of *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]-$(ClO_4)_{0.8}Cl_{0.2}$. The cation **2** lies on a crystallographically imposed mirror plane that contains the platinum and all of its coordinating atoms, Cl1, S, N1, and N2 (Figure 1). The arrangement of the ligands around the platinum atom does not deviate substantially from the idealized square-planar geometry; the largest angle (N1–Pt–S) is 95°. The N1 ammonia ligand is in van der Waals contact with the methyl groups of the Me_2SO ligand (N1–C = 3.5 Å), and the 95° angle may be a consequence of the intramolecular packing.

The Me_2SO ligand is bonded to the platinum through its sulfur atom, as expected from the spectroscopic evidence presented above.

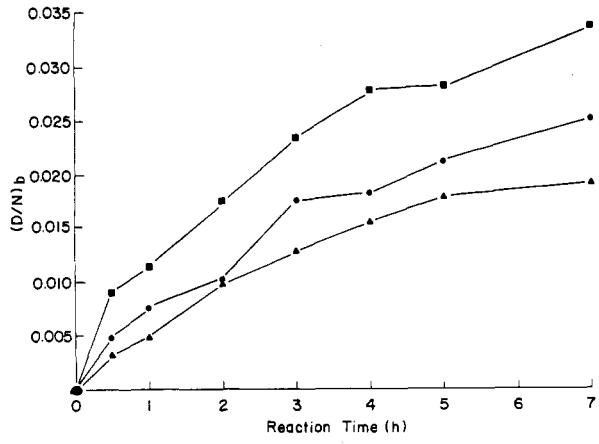

Figure 3. Time dependence of the binding to calf thymus DNA of *trans*-DDP dissolved in buffer (▲), *trans*-DDP in Me_2SO (●), and *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]Cl (■), plotted as the ratio of bound platinum per nucleotide, $(D/N)_b$.

The Pt–S distance of 2.204 (4) Å is well within the range reported for other Me_2SO–Pt complexes.[19] The environment around the sulfur atom is nearly tetrahedral with angles ranging from 104 to 115°, again in good agreement with previously reported values. The Pt–Cl distance of 2.307 (5) Å is also normal. Although Me_2SO exerts a relatively large trans influence, it does not appear to have a major effect on the trans Pt–Cl bond length, which is 2.30 Å in *trans*-DDP itself.[21]

Reaction of *trans*-DDP and *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]$^+$ (2) with DNA. In order to determine the effect on reaction rate of *trans*-DDP binding to DNA when Me_2SO is used to dissolve the platinum complex, DNA-bound platinum was measured as a function of time when the following species were allowed to react with calf thymus DNA dissolved in aqueous buffer: (1) *trans*-DDP in aqueous buffer (1.0 mM) (abbreviated *trans*-DDP/buffer); (2) *trans*-DDP dissolved in Me_2SO (1.0 mM) (abbreviated *trans*-DDP/Me_2SO); (3) **2** dissolved in aqueous buffer (1.0 mM). All dissolved compounds were incubated for 5 min at 25 °C prior to 200-fold dilution into the 0.1 mM DNA reaction mixture, producing a formal drug-to-nucleotide ratio, $(D/N)_f$, of 0.05. Aliquots from the reaction mixtures were quenched at different time intervals, the unbound platinum was removed by dialysis, and the level of bound platinum, $(D/N)_b$, was determined by atomic absorption spectroscopy. As is evident from Figure 3, **2** binds to DNA significantly more rapidly than *trans*-DDP/buffer. At short time intervals, the difference is threefold, leveling off to a twofold difference at longer time periods. This result may be explained by the greater labilization of the chloride ligand trans to Me_2SO in **2**. The *trans*-DDP/Me_2SO reaction rate is intermediate, as would be expected for a mixture of *trans*-DDP and *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]Cl.

Reaction of *trans*-DDP and *trans*-[$Pt(NH_3)_2(Me_2SO)Cl$]$^+$ (2) with d(GpTpG). We also investigated the reactions of *trans*-DDP and **2** with the oligonucleotide d(GpTpG). This reaction is particularly relevant, since one of the major adducts formed when *trans*-DDP binds to DNA is an intrastrand cross-link of two guanines separated by an intervening nucleotide.[22] Reactions between d(GpTpG) and *trans*-DDP/buffer or *trans*-DDP/Me_2SO at 37 °C were monitored by reversed-phase HPLC (Figure 4). The major reaction product (species III) when *trans*-DDP was dissolved in aqueous buffer is the 1,3-bis(guanine) adduct, in which the platinum is coordinated to the N-7 positions of the two guanine bases.[14] We have previously isolated this product and confirmed its identity by ^{1}H NMR spectroscopy.[23] This species accounts for 92% of the products after 42 h. An intermediate species II (5% at 42 h), which is probably a monofunctional Pt–DNA ad-

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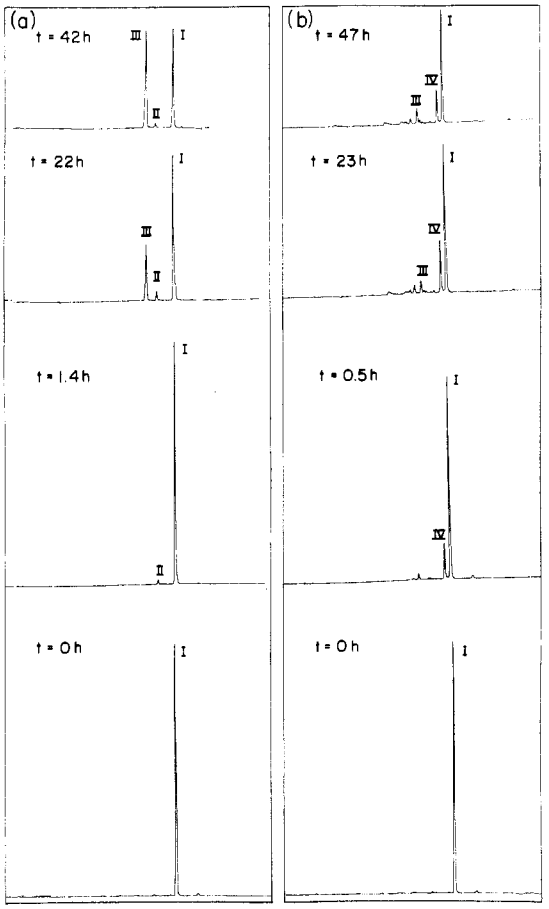

Figure 4. HPLC traces showing the time course of the appearance and disappearance of species formed in the reactions with d(GpTpG) of (a) *trans*-DDP dissolved in buffer and (b) *trans*-DDP dissolved in Me_2SO at 37 °C. Labels are as follows: I, d(GpTpG); II, intermediate species; III, *trans*-$[Pt(NH_3)_2\{d(GpTpG)\}]$; IV, unidentified product.

duct, is observed and disappears as the reaction progresses beyond 42 h (data not shown).

The reaction of d(GpTpG) with *trans*-DDP/Me_2SO, however, does not proceed nearly as cleanly (Figure 4b). A number of products are evident after 47 h, and *trans*-$[Pt(NH_3)_2\{d(GpTpG)\}]$ accounts for only 17% of the total adducts formed. The other HPLC-detectable products were also observed when **2**, *dissolved in aqueous buffer*, was allowed to react with d(GpTpG).

These results clearly reveal that when *trans*-DDP is dissolved in Me_2SO, even for a time as short as 5 min, and subsequently allowed to react at 37 °C with d(GpTpG), the majority of products obtained result from the formation of **2** in solution, which subsequently reacts with the oligonucleotide. At earlier time points, **2** is seen to react more quickly than *trans*-DDP with d(GpTpG), as was the case for the reactions with calf thymus DNA.

Implications for Biological Work. The results presented demonstrate that the reaction of *trans*-DDP in Me_2SO measurably alters the subsequent rate of DNA binding, as well as the spectrum of Pt–DNA adducts formed. This effect is significant even when *trans*-DDP is dissolved in Me_2SO for only 5 min, which would almost certainly be the case in a typical experiment. At the physiological temperature of 37 °C, the half-life of *trans*-DDP in Me_2SO is 8 min, rather than the recently reported value of 19 min.[6h] Moreover, the reaction of *trans*-DDP with Me_2SO undoubtedly continues even after dilution of the initial Me_2SO solution in aqueous buffer.

It is interesting that in several of the biological studies[6] in which Me_2SO was used to dissolve the platinum complexes, unusual activities were observed for *trans*-DDP. For example, *trans*-DDP that had been dissolved in Me_2SO was reported to be cytotoxic and to retard TA3Ha tumor cell growth in combination with hypothermia treatment.[6g] Such results may be due to the formation and subsequent reaction of *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$, rather than the reaction of *trans*-DDP itself. The *trans*-$[Pt(NH_3)_2(Me_2SO)Cl]^+$ complex might be expected to form primarily monofunctional DNA adducts, similar to those made by $[Pt(dien)Cl]^+$. The strong cis-labilization effect of Me_2SO,[8] however, could conceivably result in loss of an ammonia ligand with concomitant bifunctional DNA coordination with cis stereochemistry.

Finally, although use of Me_2SO as a solvent is especially problematic for *trans*-DDP, Me_2SO also reacts at an appreciable rate with *cis*-DDP, especially at the higher temperatures (Table II), and should react even faster with the commonly studied *cis*-DDP analogues $[Pt(en)Cl_2]$ and $[Pt(dach)Cl_2]$. We therefore conclude that the affinity of platinum for sulfur donor ligands makes Me_2SO unsuitable for use in biological studies of the mechanism of action of platinum antitumor drugs and that the results of biologically related experiments employing this solvent for *cis*- and, especially, *trans*-DDP must be viewed with caution.

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Registry No. **2**-Cl, 62850-81-1; *cis*-$[Pt(NH_3)_2Cl_2]$, 15663-27-1; *trans*-$[Pt(NH_3)_2Cl_2]$, 15663-27-1.

Supplementary Material Available: Listings of anisotropic thermal parameters (Table S2) and hydrogen atom parameters (Table S3) for **2**-$(ClO_4)_{0.8}Cl_{0.2}$ (2 pages); a table of observed and calculated structure factors for **2**-$(ClO_4)_{0.8}Cl_{0.2}$ (Table S1) (4 pages). Ordering information is given on any current masthead page.