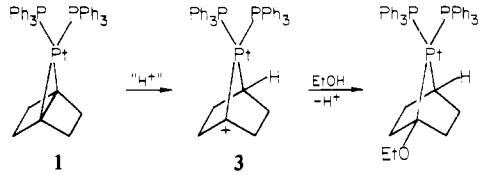
an amine or ether with a Pt–C σ bond trans to the C–N or C–O bond.[17,18]

Few electrophilic additions to either platinum(0)– or platinum(II)–olefin complexes have been observed, as indicated in the review by Hartley.[14] However, the addition of a strong acid such as hydrochloric or trifluoromethanesulfonic acid, to a platinum(0)–acetylene complex results in a σ-bonded alkenylplatinum complex.[19,20]

Hartley and others have pointed to the fact that the stability of platinum(0)–olefin complexes increases as the substituents on the olefin become more highly electron withdrawing.[14] The indication is that back-donation through the *b*-symmetry orbitals, as drawn by McGinnety,[21] is more important than in similar platinum(II) complexes. Thus electron density is built up on the olefinic ligand in strong Pt(0)–olefin bonds. To the extent that this statement follows from the substituent effects on Pt(0)–olefin bond strengths, one would expect these complexes to exhibit enhanced reactivity toward electrophiles and diminished reactivity to nucleophiles.

The reaction of $\Delta^{1,4}$-bicyclo[2.2.0]hexenebis(triphenylphosphine)platinum(0) to give the title compound can thus be envisioned as the protonation of one of the olefinic carbons leaving a cation of structure **3**, which reacts with the solvent



1 **3** **2**

to give the ether complex. This reaction has a direct analogy in the addition of acids to many propellanes.[22-24] Propellanes are subject to reaction with both electrophiles and radicals at one of the bridgehead carbons with simultaneous cleavage of the central bond. It is interesting to note that as a class of compounds they are stable to bases and nucleophiles.

Sensitivity of Pt(0)–olefin complexes to ethanol is in no way a common property. In fact cyclopropene[25] and strained allene complexes are commonly recrystallized from ethanol. It is hoped that this report will create interest in the relationship between the reactivity of metal–ligand complexes and the strain inherent in the ligand.

Acknowledgment. M.E.J. wishes to thank the NSF for a predoctoral fellowship (1971–1974). Also, warm thanks are expressed to the Chemistry Department of Cornell University, particularly Mel Goldstein, Jon Clardy, and Barry Carpenter, for their help in the preparation of this manuscript.

Registry No. **1**, 54071-60-2; **2**, 54071-61-3.

Supplementary Material Available: Tables of group parameters (Table III) and thermal parameters and derived fractional coordinates of phenyl group carbon atoms (Table IV) in $Pt[C_6H_9OC_2H_5][P(C_6H_5)_3]_2$, root-mean-square components of thermal displacement along principal axis R (Table V), and observed and calculated structure factors (Table VI) (11 pages). Ordering information is given on any current masthead page.

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Contribution from Bell Laboratories, Murray Hill, New Jersey 07974

Melting Profiles of *cis*- and *trans*-Dichlorodiammineplatinum(II) Poly(dA-dT) Complexes in Solution

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Numerous spectroscopic studies have investigated the interaction of dichlorodiammineplatinum(II) (DDP) with DNA[1] since the discovery that *cis*-DDP (but not *trans*-DDP) is an active antitumor agent.[2] Both DDP isomers bind strongly to DNA, and the antitumor activity of *cis*-DDP has been related to its ability to inhibit DNA synthesis. Recent extended X-ray absorption fine structure (EXAFS) studies from our laboratory suggest that the local structure of the complexes formed by *cis*- and *trans*-DDP with calf thymus DNA contains no distinct metal–metal bonds.[3] We report here our optical and ^{1}H NMR studies of the thermal melting (duplex to strand transition) profiles of the complexes formed by *cis*- and *trans*-DDP with the synthetic DNA poly(dA-dT) in an attempt to understand the differences in the binding of these complexes to DNA.

Experimental Section

Optical Melting Studies. The lyophilized sodium salt of poly(dA-dT) was purchased from Collaborative Research and dialyzed against two changes of 5 mM cacodylate buffer (pH 7.0). Cacodylate buffer was used to avoid coordination to the platinum complexes or interference in the ^{1}H NMR studies (vide infra) by the buffer material. No other salts were added in the buffer in order to avoid raising the melting temperature(s) of the resulting complexes too close to the boiling point (vide infra). The polynucleotide concentration was based on an extinction coefficient, $\epsilon_{260} = 6.7 \times 10^3$ in phosphates. Solutions of *cis*- or *trans*-DDP and poly(dA-dT) were mixed in 5 mM buffer (final synthetic DNA concentration of 0.15 mM in phosphates) and allowed to react in the dark at 25 °C with constant agitation for 2–3 days. It should be mentioned that at the BP/M ratios employed, the concentrations appropriate for optical measurements, and the reaction times allowed in the present study, all solubilized DDP complexes would have reacted. Control reactions run for a longer period of time (5 days) or dialyzed against the buffer at the end produced essentially the same optical melting data reported here. The thermal melting of the complex with base pair/metal (BP/M) ratios of 64, 32, 24, 16, 8, 4, and 2 was measured as the relative changes in absorbance at 260 nm (ΔA_{260}) with the use of a Gilford 2400-2 spectrometer equipped with a thermoelectric device for heating the sample cell, a thermoprogrammer, and a reference compensator. The samples were held in separate 5-mm quartz cells and were heated at a constant rate of 1 °C/min from 25 to 80 °C. Each set included a poly(dA-dT) control along with the *cis*- and *trans*-DDP·poly(dA-dT) complexes at the same BP/M ratio.

^{1}H NMR Studies. The DDP·poly(dA-dT) samples for the NMR studies were prepared by reacting *cis*- and *trans*-DDP with poly(dA-dT) at BP/M ratios of 8 and 4 in 5 mM cacodylate buffer in the dark at 25 °C with constant agitation for 2–3 days. The samples (volume 8 mL) were subsequently dialyzed against 5 mM NaCl, 0.5

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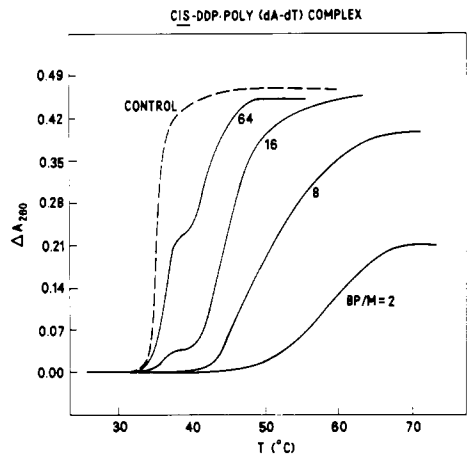

Figure 1. Thermal melting curves (260 nm) for the complex of *cis*-DDP with poly(dA-dT) in 5 mM cacodylate buffer at BP/M ratios of 64, 16, 8, and 2.

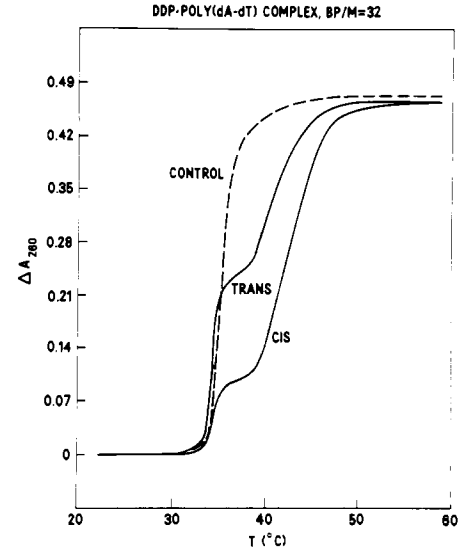

Figure 2. The thermal melting curves (260 nm) for the poly(dA-dT), *cis*-DDP·poly(dA-dT) complex, BP/M = 32, and *trans*-DDP·poly(dA-dT) complex, BP/M = 32 in 5 mM cacodylate buffer.

mM cacodylate buffer to remove any unreacted DDP. The complexes were lyophilized repeatedly from D_2O and dissolved finally in 0.4 mL of 100% D_2O (20-fold concentration of sample and buffer). The proton NMR spectra of the complexes in 0.1 M NaCl, 10 mM cacodylate were recorded on an HX-360 Bruker spectrometer, and the chemical shifts are referenced relative to standard sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS).

Results and Discussion

Optical Melting Studies. The melting curves (first heating cycle) for the complexes formed by *cis*-DDP with poly(dA-dT) at base pair/metal (BP/M) ratios of 2,8,16, and 64 in 5 mM buffer are presented in Figure 1. A comparison of the melting behavior of the *cis*- and *trans*-DDP·poly(dA-dT) complexes at BP/M = 32 in 5 mM buffer is presented in Figure 2. The *cis* and *trans*-DDP complexes with poly(dA-dT) exhibit biphasic melting transitions as monitored by the 260-nm nucleic acid absorbance at BP/M ratios greater than 4 (Figures 1 and 2). Since the extent of the high-temperature phase correlates directly with the metal content, we assign the low-temperature cooperative phase to the "platinum-free" base pair region and the high-temperature cooperative phase to the base pair region stabilized by the covalently bound platinum. While the melting of free poly(dA-dT) is completely reversible, we found no renaturation for the high-temperature phase of the platinum complexes. A direct consequence is that the second and

Table I. Melting Data of the Complexes Formed by *cis*- and *trans*-DDP with Poly(dA-dT) in 5 mM Cacodylate Buffer (pH 7) at Room Temperature

complex	BP/M[a]	b[b]	α[c]
I (cis)	2	1	2
	4	1	4
	8	0.98 (3)[d]	7.98 (3)
	16	0.91 (7)	14.6 (12)
	24	0.84 (6)	20.1 (13)
	32	0.79 (5)	25.2 (15)
	64	0.50 (2)	31.8 (11)
II (trans)	2	1	2
	4	0.99 (7)	4.0 (3)
	8	0.90 (7)	7.2 (5)
	16	0.74 (5)	11.9 (9)
	24	0.58 (6)	14.3 (18)
	32	0.48 (4)	15.5 (14)
	64	0.21 (2)	13.4 (13)

[a] Base pair to metal ratio. [b] Fractional increase in ΔA_{260} of the "stabilized" region. [c] $\alpha = b(\mathrm{BP/M})$; it is the number of base pairs stabilized by bound DDP. [d] The numbers in parentheses are estimated errors of the last significant figure.

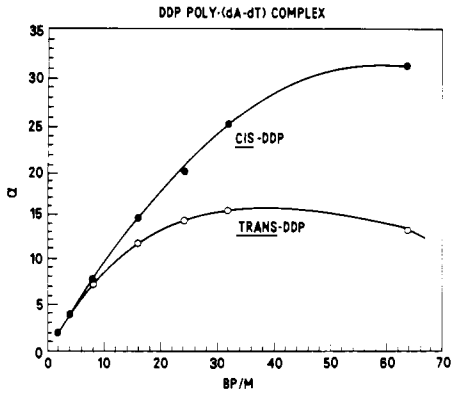

Figure 3. Plot of the number of base pairs stabilized per bound platinum ligand, α, in the *cis*-DDP·poly(dA-dT) complex and the *trans*-DDP·poly(dA-dT) complex as a function of the base pair to metal (BP/M) ratio.

subsequent heating cycles are different from the first one. These observations are similar to that observed by Harder[4] for the reaction product of *cis*-$Pt(NH_3)_2Cl_2$ with poly(dA-dT). For example, Harder[4] observed a biphasic melting curve of roughly equal ΔA_{260} for $BP/M = 10$ with melting temperatures of 35° and 42° for poly(dA-dT) incubated with *cis*-DDP for 16 h at 21 °C in 5 mM $NaClO_4$. The high-temperature transition, which is not renaturable, is considerably broader than the low-temperature transition, which occurs at about the same temperature as free poly(dA-dT). At BP/M = 2, a broad transition occurs with T_m of ca. 46 °C. As the drug level increases, the absorbance change, ΔA_{260}, decreases significantly.[4] The differences (melting temperatures, ratio of the two phases, etc.) between our results and those of Harder[4] are conceivably due to the different buffer systems used. Melting behavior of DNA bound with *cis*- and *trans*-DDP have also been studied.[5,6] We note, however, only poly(dA-dT) shows a distinct biphasic structure in the melting profile when reacted with the platinum complexes.

As is evident from Figure 2, there is a larger increase in the transition midpoint (T_m) of the base pair regions stabilized by bound *cis*-DDP compared to *trans*-DDP at the same BP/M ratio, suggesting that greater stabilization is associated with

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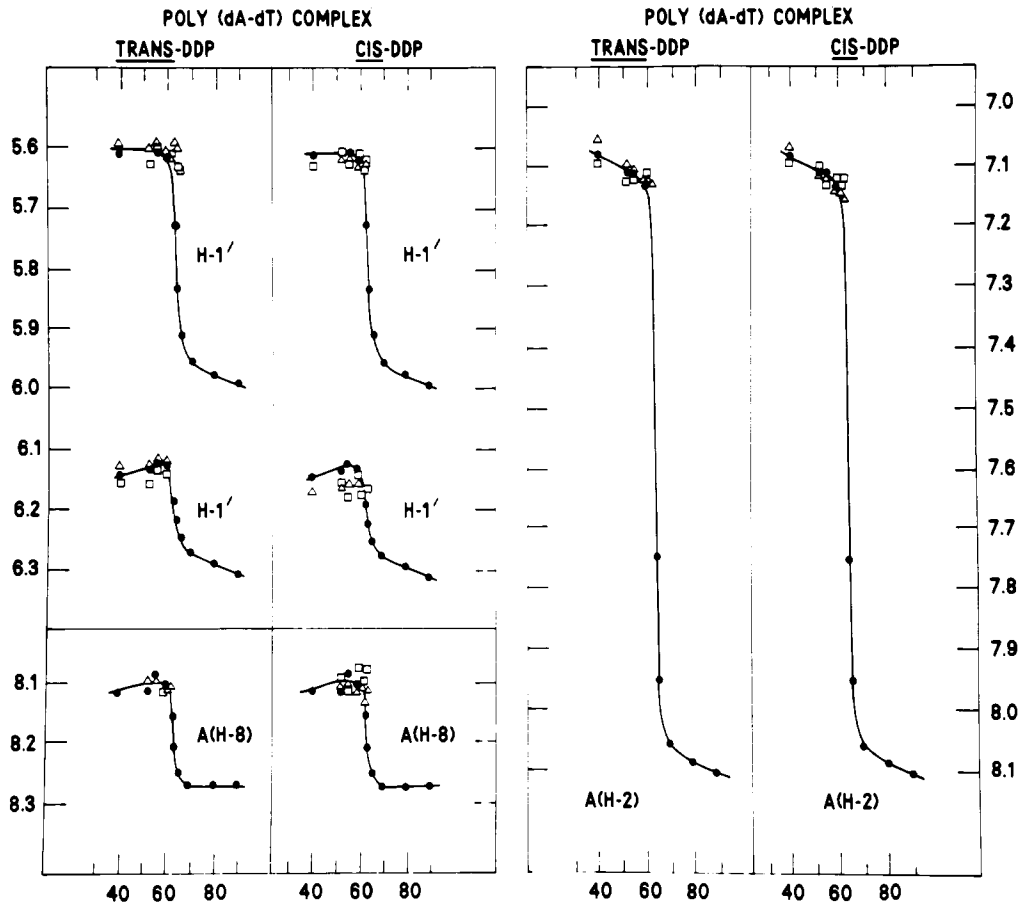

Figure 4. Temperature-dependent proton NMR chemical shifts of poly(dA-dT) (●) and the DDP·poly(dA-dT) complexes, BP/M = 8 (△), and BP/M = 4 (□), in 0.1 M NaCl, 10 mM cacodylate, D_2O solution.

the binding of the *cis* vs. the *trans*-DDP to the duplex state.

We can estimate the number of base pairs stabilized by bound DDP, $\alpha = b(\mathrm{BP/M})$, where b is the fractional increase in ΔA_{260} of the higher temperature cooperative transition in the biphasic melting curve (Table I). The number of base pairs stabilized by bound DDP, α, is plotted as a function of BP/M values for the *cis*- and *trans*-DDP·poly(dA-dT) complexes in Figure 3. The results demonstrate that covalent binding of platinum stabilizes a large number of base pairs adjacent to its binding site (Figure 3). The stabilization extends over more base pairs in the *cis*-DDP·poly(dA-dT) complex and is most pronounced at high base pair/metal ratios (Figure 3).

Proton Nuclear Magnetic Resonance Studies. Proton NMR spectra have been recorded on the poly(dA-dT) complexes with *cis*- and *trans*-DDP at BP/M ratios of 8 and 4 in 0.1 M NaCl, 10 mM cacodylate solution. The base and sugar protons of poly(dA-dT) shift as average peaks during the duplex to strand transition (midpoint, $t_{1/2}$ = 62.5 °C) in this buffer (Figure 4). As expected, the melting temperatures in the buffer employed in the NMR study (0.1 M NaCl, 10 mM cacodylate) are substantially higher than those in the buffer employed in the optical study (5 mM cacodylate) due to the increased ionic strength. The chemical shift data is reported for the adenosine H-8 and H-2 and the sugar H-1′ protons attached to the adenosine and thymidine rings.[7]

The duplex to strand transition of the DDP·poly(dA-dT) complexes (BP/M = 8 and 4) occurs in two steps as monitored by proton NMR spectroscopy.[8] The transition midpoint for the opening of Pt–*free* base pair regions is ~64 °C with the resonance in *slow exchange* between duplex and strand states. This indicates that the opening of the Pt–free base pair regions in the complex becomes slow ($<10^2$ s^{-1}) on the NMR time scale in contrast to fast exchange ($\sim 10^3$ s^{-1}) for the dissociation of the poly(dA-dT) duplex in 0.1 M NaCl solution. The spectra of the complex at ~67 °C are a superposition of the narrow resonances from Pt–free base pair regions that have opened up and broad resonances from intact Pt–bound base pair regions. The broad resonances gradually disappear on raising the temperature further indicative of the melting of the Pt–bound base pair regions.

The base (adenosine H-8 and H-2) and the sugar (H-1′ protons attached to the adenosine and thymidine rings) protons of the DDP·poly(dA-dT) complexes (BP/M = 8 and 4) in the duplex state are compared with the corresponding values in the duplex state of poly(dA-dT) in Figure 4. The chemical shifts of the base resonances are similar for the synthetic DNA, and the complexes which indicates that the base pair overlaps[9,10] as monitored at the adenosine H-8 and H-2 protons are little perturbed on formation of the covalent Pt complexes.

The two sugar H-1′ protons of poly(dA-dT) are unperturbed on formation of the *trans*-DDP complexes while the sugar H-1′ proton at 6.1 ppm selectively shifts downfield on formation of the *cis*-DDP complex (Figure 4). The sugar H-1′ protons are sensitive to changes in the glycosidic torsion angles so that formation of the *cis*-DDP·poly(dA-dT) complex results in a change in one (either adenosine or thymidine) glycosidic torsion angle. The same selective shift was observed when the

(7) The thymidine H-6 resonance is superimposed under the narrow adenosine H-2 resonance, and the thymidine CH_3-5 resonance is close to the strong cacodylate CH_3 signal. Hence neither thymidine base resonance could be monitored accurately in the duplex state.

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NMR spectra of the complexes were recorded in 1 M NaCl solution.

It has been established previously that *cis*-DDP is an effective anticancer agent while its trans analogue lacks activity.[1,2] The optical binding studies on DDP·poly(dA-dT) complexes show significant differences between the two isomers, with the cis isomer stabilizing twice the number of base pairs (reaching of number of ~32 per bound Pt for the reaction conditions specified in this work) about its binding site compared to the trans isomer. Further, the transition midpoint for the opening of base pairs centered about bound Pt occurs at a much higher temperature for the cis isomer compared to the trans isomer, indicative of the formation of a more stable complex with the cis isomer.

It has been proposed that the covalent interaction between dichlorodiammineplatinum(II) and the nucleic acid involves nitrogen and/or oxygen atoms on the base pair edges though the exact nature of binding is still a subject of controversy.[11-14] The NMR studies suggest that the base pair overlaps in poly(dA-dT) are not significantly perturbed on formation of the DDP·(synthetic DNA) complexes. However, the selective change in one of the sugar H-1′ chemical shifts on formation of the *cis*-DDP·poly(dA-dT) complex suggests that the covalent interaction does result in a perturbation in either the adenosine or thymidine glycosidic torsion angle.

Registry No. *cis*-DDP, 15663-27-1; *trans*-DDP, 14913-33-8; dA, 958-09-8; dT, 3416-05-5.

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Synthesis of Bis(*cis*-dichloro(diamine)platinum(II)) Complexes with Variable Bridges and Study of Their Binding with Poly(dA-dT) by Melting Profiles

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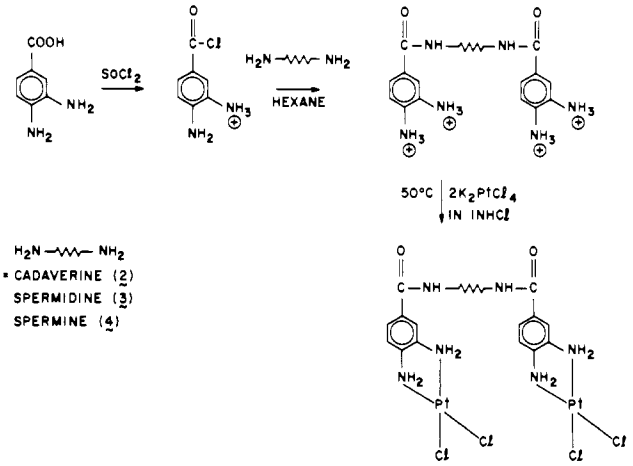
Since Rosenberg's discovery of the anticancer activity of *cis*-dichlorodiammineplatinum(II) (DDP) (whereas the trans analogue is ineffective), there has been a considerable amount of work aimed at synthesizing new platinum compounds with more desirable properties.[1-5] While these studies have produced many new active antitumor agents, they generally involve monomeric platinum complexes. We report here the synthesis of a series of new bis(*cis*-dichloro(diamine)platinum(II)) complexes with a variable and flexible bridge.[6] The design of these platinum complexes allows us to investigate the effect of the bridging chain length on their binding to DNA, particularly in light of the fact that their antitumor activity is related to their ability to interact with DNA. This is accomplished by a study of melting profiles of the reaction products of these bis(platinum) complexes with the synthetic DNA, poly(dA-dT).

Scheme I



Since *cis*-[Pt(diamine)Cl_2] where diamine = *o*-phenylenediamine was shown to be an active antitumor agent against ADJ/PC6 plasma cell tumor,[5c] the compound with diamine = 3,4-diaminobenzoic acid (DAB) was chosen for the synthetic convenience of bridging two such units via two amide linkages with diamines such as cadaverine ($H_2N(CH_2)_5NH_2$), spermidine ($H_2N(CH_2)_3NH(CH_2)_4NH_2$), and spermine ($H_2N$-$(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$). These diamines possess the following desirable characteristics: (1) they span roughly

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