(L1210/dach) were cultured in McCoy's 5A medium supplemented with 10% fetal bovine serum and glutamine. Both cell lines were grown in a humidified atmosphere to 5% CO_2/95% air at 37 °C. For testing purposes, cells were diluted to 5×10^4 cells/mL and 1 mL of cell suspension was aliquoted to disposable tissue culture tubes. Test compound was then added to the appropriate tubes (40 μL/tube) to attain final concentrations of 0.01, 0.1, 1.0, and 10 μg/mL. After 72 h of drug exposure, the cell concentrations of all tubes were determined by using a Coulter counter. The percent growth inhibition for each drug concentration was then calculated and the ID_{50} (concentration of drug required to inhibit cell growth by 50%) was derived. The resistance factor for each compound was obtained by dividing the ID_{50} (L1210/DDP) by the ID_{50} (L1210/0).

In Vivo Efficacy Studies. Male BDF_1 mice weighing 18–20 g were purchased from the National Cancer Institute and housed in an environment having controlled humidity, temperature, and photoperiods. The animals had food and water available ad libitum, and wood chip bedding was changed daily. The L1210/0 and P388 murine leukemias were maintained as ascites tumors by weekly intraperitoneal (ip) inoculations of 10^6 cells. For testing purposes, 10^6 tumor cells were inoculated ip (day 0) and mice were administered test compound ip on days 1, 5, and 9. Animals were observed daily for signs of toxicity, and deaths and the day of death were recorded for each animal that died during the 60-day observation period. The efficacy of each dose of compound tested was evaluated by calculating the percent increased life span determined by dividing the mean survival time of treated mice (using the day of death of only those animals that died during the 60-day period) by the mean survival time of nontreated tumor-bearing control animals (%T/C). Compounds exhibiting a %T/C > 140 are considered to have significant antitumor activity. An additional index of antitumor activity is the number of long term survivors defined as treated animals alive at the end of the study.

DNA Synthesis Studies. L1210 cells (5×10^4 mL^{-1}) were treated for 2 h with the $5 \times ID_{50}$ dose calculated for each drug by the method outlined above. The cells were then centrifuged, washed twice with ice-cold phosphate buffered saline (pH 7.4), and resuspended in fresh, drug-free medium at a concentration of 5×10^4 cells/mL. At appropriate times (2, 4, 6, 22 h) 10 mL of cells was exposed to ^{3}H-thymidine (0.25 μCi/mL) for 2 h and the cells were harvested on glass fiber filters. After washing twice each with ice-cold PBS, 5% trichloroacetic acid, and 95% ethanol, the filters were air-dried, and the radioactivity was measured by using a Beckman LS7000 liquid scintillation counter.

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Antitumor and DNA-Binding Properties of a Group of Oligomeric Complexes of Pt(II) and Pt(IV)

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The antitumor and DNA-binding properties of a group of oligomeric platinum(II) and platinum(IV) complexes are described. The compounds, having the stoichiometry $[cis\text{-}Pt^{II}(X)_2(\mu\text{-}OH)]_2(NO_3)_2$, where X is NH_3, $NH_2CH_2CH_3$, and $NH_2CH(CH_3)_2$, were found to be inactive or only weakly active against L-1210 leukemia. In vitro studies involving PM2-DNA show that these compounds bind to and unwind closed circular DNA in a manner similar to $cis\text{-}Pt^{II}(NH_3)_2Cl_2$. The Pt(IV) complexes produced by hydrogen peroxide oxidation of the Pt(II) dimers are inactive as antitumor agents and are incapable of unwinding PM2-DNA. The cyclotrimer $[cis\text{-}Pt^{II}(RR\text{-DACH})(\mu\text{-}OH)]_3(NO_3)_3$, where *RR*-DACH is (*R*,*R*)-1,2 diaminocyclohexane, exhibits potent antitumor activity against L-1210 leukemia and modest activities with B-16 and M5076 tumor lines. This compound platinates DNA, causing DNA unwinding and mobility shifts.

Since the initial report of the anticancer properties of *cis*-diamminedichloroplatinum(II) (**1**,[1] cisplatin) and the subsequent introduction of the compound into the clinic, a large number of Pt(II) as well as Pt(IV) compounds have been examined for their antitumor effects.[2,3] Studies focusing on the mechanism of action of the compound have strongly suggested that the cytotoxicity of the agent is related to its ability to bind to cellular DNA.[4-7] In examining the aqueous solution chemistry of **1**, it was discovered that the compound readily undergoes oligomerization to yield a μ-oxo bridged dimer $[cis\text{-}Pt^{II}(NH_3)_2(\mu\text{-}OH)]_2^{2+}$ (**2**) and trimer $[cis\text{-}Pt^{II}(NH_3)_2(\mu\text{-}OH)]_3^{3-}$ (**3**), both of which have been characterized via ^{195}Pt NMR and X-ray structural analysis.[8-11] Although no detailed in vivo antitumor test data for oligomeric platinum complexes have appeared, it has been reported that both **2** and **3** are more toxic than **1**, but that they are devoid of antitumor effects.[12,13] On the other hand, the dimer and trimer

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analogous to **2** and **3** containing the racemic form of 1,2-diaminocyclohexane have been reported to be active as antitumor agents.[14]

Previously,[15,16] we demonstrated that it is possible to oxidize **2** and the related Pt(II) dimers containing ethyl and isopropylamine, [*cis*-$Pt^{II}(NH_2CH_2CH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**4**) and [*cis*-$Pt^{II}(NH_2CH(CH_3)_2)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**5**), with hydrogen peroxide to dinuclear Pt(IV) complexes. In addition to characterizing one of the Pt(IV) complexes using single-crystal X-ray analysis, the mechanism of the oxidation of the Pt(II) dimers was investigated via ^{195}Pt NMR spectroscopy.[16] In this report we present the antitumor activities and cytotoxicites of a group of oligomeric complexes of Pt(II) and Pt(IV) against a number of different tumor lines. In light of the fact that DNA binding is important for antitumor activity of the platinum-based anticancer agents, we also investigated the ability of the compounds to interact with supercoiled PM2-DNA in vitro.

Experimental Section

The Platinum Complexes. The ^{195}Pt NMR spectrum of the Pt(II) trimer containing the *RR*-DACH ligand (*RR*-DACH is (*R,R*)-1,2-diaminocyclohexane) was obtained on a 50–60 mM aqueous solution with a homemade NMR spectrometer equipped with a 10-mm probe operating at 53.8 MHz. The combustion analysis of the compound was carried out by the Bristol Myers Co.

The compounds [*cis*-$Pt^{II}(NH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**2**), [*cis*-$Pt^{II}(NH_3)_2(\mu\text{-}OH)]_3(NO_3)_3$ (**3**), [*cis*-$Pt^{II}(NH_2CH_2CH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**4**), [*cis*-$Pt^{II}(NH_2CH(CH_3)_2)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**5**), [$Pt^{IV}(NH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**6**), [$Pt^{IV}(NH_2CH_2CH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**7**), and [$Pt^{IV}(NH_2CH(CH_3)_2)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**8**) were synthesized as previously described.[8-11,15,16]

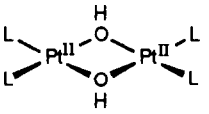
Preparation of [Pt^{II}(*RR*-DACH)(μ-OH)]$_3(NO_3)_3$ (9). This compound was prepared by using optically active *RR*-DACH in a manner analogous to that employed for the synthesis of the trimer containing the racemic form (*RR* + *SS*-DACH) of the ligand.[17] Anal. C, H, N, Pt. ^{195}Pt NMR (aqueous Na_2PtCl_6) δ −1754 ppm.

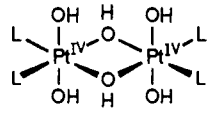
Biological Effects of the Complexes. Cytotoxicity tests were performed by using the microtitre assay described by Catino et al.[18] Established cell lines of murine human tumors were used with five or six such lines represented in each test. Cisplatin (**1**) was used as a control in every experiment and the relative cytotoxicity between the test compound and **1** was initially determined based on the minimum dose in μg/mL to inhibit cell growth by 50% (ID_{50}). This value was then converted through the molecular weights of the compounds to the quantities given in Tables I and II.

Experiments using L-1210 leukemia in ascitic form were performed as previously described.[19] Compound **1** was included as a positive control in each test.

DNA-Binding Studies. Lyophilized PM2-DNA, suppled by Boehringer Mannheim, was dissolved in 500 μL of H_2O and extensively dialyzed against the buffer used in the studies, 20 mM tris(hydroxymethyl)aminomethane (Tris) nitrate, pH 7. The platinum-DNA binding studies were carried out in the aforementioned buffer in a total volume of 10 μL containing 38 μM DNA (base pairs) at 37 °C. The amount of compound added, expressed as the ratio of compound to DNA base pairs, r_t, and the conditions used for various experiments are given in the figure captions. After incubation of the compound–DNA mixture, the solutions were loaded on an 0.8% agarose gel and electrophoresed overnight. To visualize the DNA, the gel was soaked in an ethidium bromide solution for 1 h, placed on an ultraviolet light box, and photographed with a Polaroid camera using Polaroid 55 or 57 film.

Table I. Antitumor and Toxicity Data for the Pt(II) and Pt(IV) Dinuclear Platinum Complexes





compound	mol weight	antitumor (L-1210)[a] OD or MTD[b]	MST[c] T/C	rel cytotox[d]
[*cis*-$Pt^{II}(NH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**2**)	616	5 (10)	121 (193)	2.9
[*cis*-$Pt^{II}(NH_2CH_2CH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**4**)	728	1 (10)	100 (200)	0.7
[*cis*-$Pt^{II}(NH_2CH(CH_3)_2)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**5**)	784	120 (8)	143 (186)	48
[$Pt^{IV}(NH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**6**)	684	5 (10)	121 (193)	14
[$Pt^{IV}(NH_2CH_2CH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**7**)	796	>80 (10)	114 (200)	20
[$Pt^{IV}(NH_2CH_2(CH_3)_2)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**8**)	818	>160 (6)	100 (150)	*e*

[a] The values in parentheses are for *cis*-diamminedichloroplatinum(II) (**1**). Treatment: single dose ip on day 1 in mg/kg. [b] OD is the optimum dose producing the greatest prolongation of survival. If not active, T/C <125. MTD is the maximum tolerated dose. The highest dose tested is indicated by >. [c] MST is the median survival time in days; T/C = (MST treated)/(MST control) × 100. $T/C > 125$ was considered active. [d] The value given is the molar ID_{50} for a particular compound divided by the molar ID_{50} of *cis*-diamminedichloroplatinumII), MW 300.1 (**1**). [e] Not tested.

Results and Discussion

Antitumor Properties of the Compounds. The relative cytotoxicity of the platinum(II) and -(IV) dimers is shown in Table I. For compounds containing the same amine ligands, but having different oxidation states, the platinum(II) compounds were more cytotoxic than their platinum(IV) counterparts. In vivo only **5**, the platinum-(II) compound containing isopropylamine ligands, had slight antitumor activity at a dose 15 times that of cisplatin in the same experiment. All other compounds were inactive. It is interesting to point out that **2**, **6**, and especially **5** were as potent or more so than cisplatin in toxicity to the host animals.

Detailed in vivo antitumor test results with platinum oligomers have not been published. However, Rosenberg reported that amine dimer **2** the trimer **3** were more toxic than cisplatin and devoid of antitumor effects.[12] The values given in Tables I and II confirm these observations. On the other hand, the Pt(II) dimer and trimer containing the racemic form of 1,2-diaminocyclohexane have been reported to be active antitumor agents both in purified form[14] and when they are present as impurities with other compounds.[20] Thus, it is not surprising that the trimer

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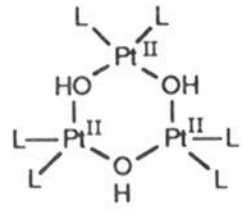
Table II. Antitumor and Toxicity Data for the Trinuclear Complexes



compound	mol weight	antitumor[a] tumor	OD or MTD[b]	MST[c] T/C	$T - C$[d]	MIW[e]	rel cytotox[f]
[*cis*-$Pt^{II}(NH_3)_2(\mu\text{-}OH)]_3(NO_3)_3$ (**3**)	924	L-1210	4 (8)	107 (167)			0.5
		L-1210[g]	6 (10)	143 (186)			
		B-16	0.4 (1.6)	124 (213)			
		M5076	1.6 (4.8)	127 (200)			
		M5076[h]	1.6 (4.8)	106 (166)	6 (32)	46 (2)	
[*cis*-Pt^{II}(*RR*-DACH)$(\mu\text{-}OH)]_3(NO_3)_3$ (**9**)	1164	L-1210	10 (8)	250 (164)			0.7
		L-1210[g]	10 (10)	243 (186)			
		B-16	0.8 (1.6)	174 (213)			
		M5076	3.6 (4.8)	155 (200)			
		M5076[h]	4.8 (4.8)	143 (166)	27 (32)	2 (2)	

[a] The values in parentheses are for *cis*-diamminedichloroplatinum(II) (**1**). Treatment: in mg/kg; L-1210 day 1; B-16 QD 1–9; M5076 days 1 and 4. [b] If active, OD is the optimum dose producing the greatest prolongation of survival. If not active, <125 for L-1210 and M5076 and <140 for B-16, MTD is the greatest maximum tolerated dose. [c] The median survival time in days; T/C = (MST control) × 100. [d] Treated minus control time (in days) for tumors to reach 1 g. [e] Mean tumor weight; % T/C with T/C < 42% considered active. [f] The value given is the molar ID_{50} for a particular compound divided by the ID_{50} of *cis*-diamminedichloroplatinum(II), MW 300.1 (**1**). [g] Experiments were done concurrenely. [h] Subcutaneously implanted.

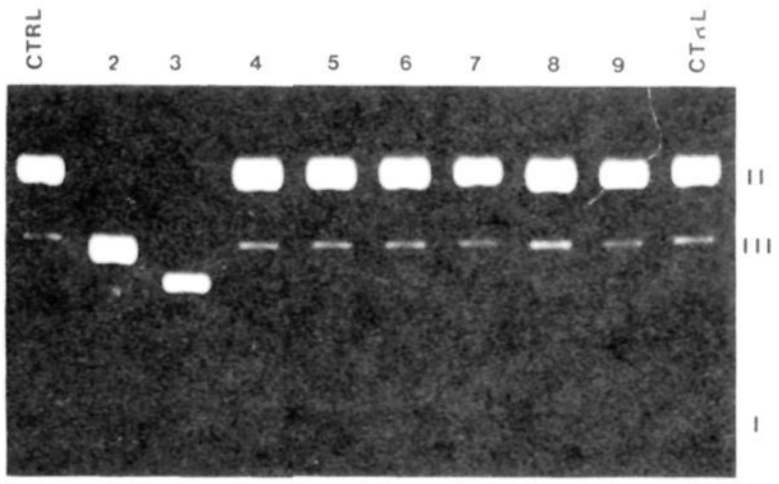


Figure 1. The results of experiments with cisplatin (**1**) (lanes 2 and 3), [$Pt^{IV}(NH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**6**) (lanes 4 and 5), [$Pt^{IV}(NH_2CH_2CH_3)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**7**) (lanes 6 and 7), [$Pt^{IV}(NH_2CH(CH_3)_2)_2(OH)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**8**) (lanes 8 and 9), and PM2-DNA are shown. Controls are lanes 1 and 10; r_t of 0.5 for lanes 2, 4, 6, 8; r_t of 5.0 for lanes 3, 5, 7, 9. The incubations were for 8 h at 37 °C.

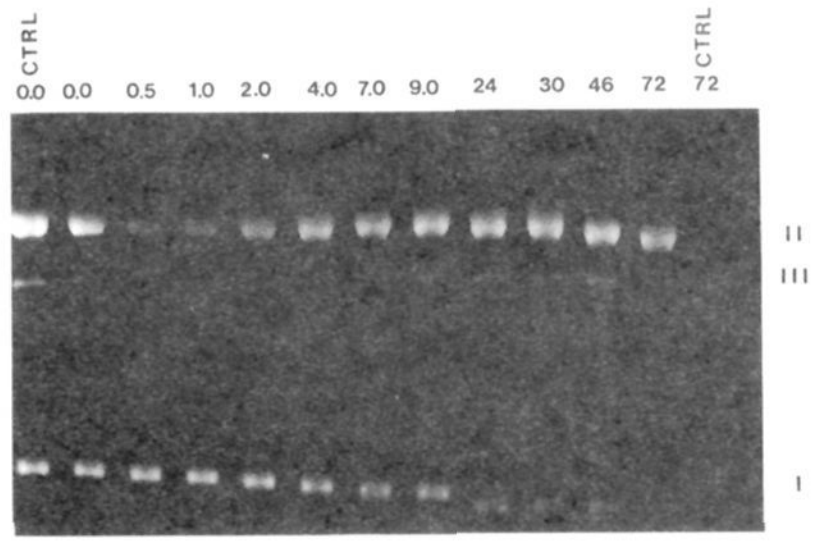


Figure 2. The results of experiments with the compound [*cis*-$Pt^{II}(NH_2CH(CH_3)_2)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**5**) and PM2-DNA are shown. The control lane, CTRL, is lane 1. The incubation times (h) at r_t of 1.0 at 37 °C are given above the lanes.

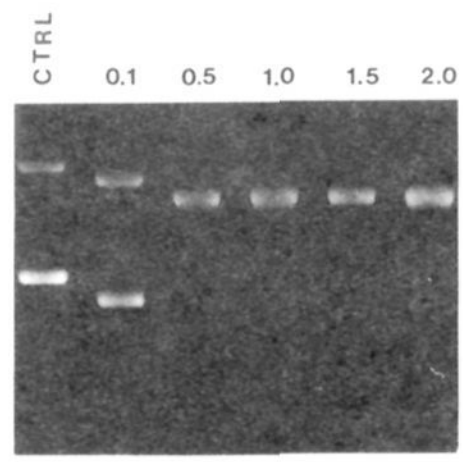


Figure 3. The results of experiments with the compound [*cis*-$Pt^{II}(NH_2CH_2CH_3)_2(\mu\text{-}OH)]_2(NO_3)_2$ (**4**) and PM2-DNA are shown. The value of r_t is given above each lane. Incubation was for 8 h at 37 °C.

containing the optically active form of the ligand RR-DACH, compound **9**, is active against all of the tumor lines tested (Table II).

DNA-Binding Properties of the Compounds. PM2-DNA is a convenient substrate for studying drug–DNA interactions. For antibiotics such as bleomycin which cause DNA strand scission, incubation of the covalently closed circular form of PM2-DNA (form I) with the drug results in the conversion of form I DNA to the nicked circular (II) and linear (III) forms of the polymer. Since the three forms can be readily separated with agarose gel electrophoresis, the effects of drug action on DNA can be easily detected. Visualization of DNA present in the gel after separation can be accomplished by staining with a DNA intercalating dye, e.g. ethidium bromide. Since the intercalated form of the dye is strongly fluorescent, the location of DNA in the gel can be seen under ultraviolet light. For drugs which do not cleave DNA, but bind to DNA in a manner which alters the local DNA structure, e.g., cisplatin, drug binding causes a significant change in the shape of the covalently closed circular form I DNA. The origin of the shape change is due to an alteration of the superhelical density in the polymer, which in turn causes it to have reduced electrophoretic mobility in the electrophoresis experiment. An additional consequence of the binding of **1** to DNA is that the platinum ions reduce the ability to visualize DNA in the gel by blocking ethi-

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Figure 4. The results of experiments with the compound $[Pt^{II}(RR\text{-DACH})(\mu\text{-OH})]_3(NO_3)_3$ (**9**) and PM2-DNA are shown. The lane number and values of r_t are as follows: 1, 0; 2, 0.5; 3, 1.0; 4, 1.5.

dium bromide intercalation sites.[4]

The results of binding studies with PM2-DNA and the oligomeric platinum complexes are summarized in Figures 1–4. As is shown in Figure 1, incubation of PM2-DNA with **1**, for 8 h at two different values of drug to DNA base pair ratios, r_t, results in changes in mobility of all three forms of DNA. This behavior is consistent with platinum binding to DNA.[21] On the other hand, incubation of DNA with the dinuclear Pt(IV) complexes did not affect the relative amounts of the three DNA forms nor their electrophoretic mobilities. Although the experiment shown in Figure 1 was for 8 h, incubation for extended periods of time, e.g. compound **7** for 168 h at an r_t of 1.0 (data not shown), had no effect on the DNA forms, indicating that the Pt(IV) dinuclear compounds neither bind to nor cleave DNA. The lack of DNA platination with these compounds is consistent with the documented slow exchange kinetics of Pt(IV)[22] and with the results of earlier DNA-binding studies with the mononuclear Pt(IV) antitumor agents *cis,cis,trans*-$Pt^{IV}(NH_3)_2Cl_2(OH)_2$ and *cis,cis,trans*-$Pt^{IV}[NH_2CH(CH_3)_2]_2Cl_2(OH)_2$.[23]

Both of the Pt(II) dinuclear complexes studied, **4** and **5**, bind to and unwind the closed circular form of PM2-DNA (Figures 2 and 3). However, one of the compounds, isopropylamine analogue **5**, appeared to be less effective at altering the mobility of DNA than its counterpart **4** (Figures 2 and 3). This may be due to a reduced degree of platination and/or a change in the DNA twist angle when platination occurs. The various mechanisms proposed for dimer binding to DNA indicate that steric effects, in this case ethyl versus isopropylamine, may be important in DNA platination by the dinuclear compounds.[24] Efforts to obtain reproducible results with the dimer **2** and trimer **3** interacting with PM2-DNA were unsuccessful. Although agarose gel studies indicated that the compounds can platinate DNA, the degree of platination appeared to not only depend on r_t and incubation time but also on the time elapsed between synthesis of the compounds and their involvement in studies with DNA. Efforts to detect any impurities which may be present with ^{195}Pt NMR by dissolving "aged" solids in aqueous media or by examining "aged" solutions of the compounds were unsuccessful. Only signals corresponding to **2** or **3** were observed.

The effects of the Pt(II) trimer containing (*R*,*R*)-1,2-diaminocyclohexane (*RR*-DACH) (**9**) on DNA are shown in Figure 4. Extensive studies by Kidani and co-workers[25] have shown that mononuclear Pt(II) complexes containing the various isomeric forms of the DACH ligand can platinate DNA and that the type of interaction which takes place may be dependent on the DACH ligand stereochemistry. Although stereochemical arguments involving DNA have been used to explain the antitumor effects of optically active DACH compounds, other factors, e.g. the nature of the tumor line and the method of compound administration, may also influence the antitumor effects of these agents.[26] In spite of the fact that the question of stereochemistry was not directly addressed in these studies, it is apparent that the cyclotrimer containing the *R*,*R* form of the diamine can bind to and unwind form I PM2-DNA (Figure 4). It is also evident that it is difficult to visualize DNA which has been platinated with the DACH cyclotrimer with ethidium bromide as a stain. This effect may be caused by the trimer binding to DNA with all or part of the trinuclear platinum system intact. This occurrence would give rise to increased steric bulk on the polymer thereby reducing ethidium binding and fluorescence. It is also possible that this compound binds so as to produce local duplex melting or kinking which may also influence the ability of ethidium bromide to intercalate into DNA. The reduced ability to stain may in part be caused by DNA precipitation in the presence of the compound. However, some portion of the precipitated DNA would be expected to make its way to the loading well of the agarose gel and to stain with ethidium bromide in the soaking process. The fact that no fluorescence was found in or above the well after electrophoresis infers that platinum-induced precipitation is probably not occurring.

Comments on the Mechanism of Action of the Compounds. Without directly addressing the pharmacokinetics and other factors associated with drug delivery, it is difficult to correlate the in vivo antitumor activity with the DNA-binding studies which were done in vitro. However, the reduced antitumor activity of the Pt(IV) compounds and their reluctance to bind to DNA is probably directly related to the fact that the ion is slow to undergo substitution reactions. The ion, with a d^6 electronic configuration, possesses considerable crystal field stabilization energy.[22] The transition states obtained via S_N1 or S_N2 substitution processes involve 5-coordinate and 7-coordinate intermediates, respectively, which lie at considerably higher energy than the starting 6-coordinate structure. Thus, as earlier pointed out,[3,23,27,28] it is likely that the antitumor properties of platinum(IV) compounds are the result of in vivo reduction to platinum(II) species which readily undergo substitution processes. Thus, the compounds act as prodrugs, producing other agents which react with nucleic acids and various components in the cell, ultimately producing cell death. An interesting and detailed account of the intracellular biotransformation of platinum(II) complexes containing the DACH ligand can

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Without additional information the mechanism by which the Pt(II) dimers and cyclotrimers exert their antitumor effects is unknown. However, these compounds would be expected to undergo substitution reactions, most likely via an S_N2 process,[22] initially producing acyclic compounds which could react with DNA and other cellular components. The fact that two or three platinum(II) centers are involved suggests that the compounds are potentially more disruptive on a molecular basis to biological processes than are mononuclear platinum species. Studies in progress are attempting to more clearly define the substitution chemistry of the Pt(II) dimers and trimers in solution.

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Brain Targeting of Anti-HIV Nucleosides: Synthesis and in Vitro and in Vivo Studies of Dihydropyridine Derivatives of 3′-Azido-2′,3′-dideoxyuridine and 3′-Azido-3′-deoxythymidine

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A significant number of patients with AIDS and AIDS-related complex develop neurological complications. Therefore, it is critical that anti-HIV agents penetrate the blood–brain barrier and suppress viral replication in the brain. In an effort to increase the brain delivery of anti-HIV nucleosides, in vitro and in vivo pharmacokinetics of dihydropyridine derivatives of 3′-azido-2′,3′-dideoxyuridine (AzddU, AZDU, or CS-87) and 3′-azido-3′-deoxythymidine (AZT, Zidovudine) have been studied. In vitro studies of the prodrugs (AzddU-DHP and AZT-DHP) in human serum, mouse serum, and mouse brain homogenate indicated that the rates of serum conversion from prodrugs to parent drugs are species dependent: mouse brain homogenate > mouse serum > human serum. Half-lives in human serum, mouse serum, and mouse brain homogenate are 4.33, 0.56, 0.17 h, respectively, for AzddU and 7.70, 1.40, and 0.18 h, respectively, for AZT. In vivo studies of AzddU-DHP and AZT-DHP showed that the prodrugs have areas under the serum concentration–time curves (AUC) similar to those of the parent drugs. The AUC in serum for AzddU following prodrug administration is 25.79 μg h/mL, which is similar to the value of 25.83 μg h/mL when AzddU was administered. Analogously, the serum AUCs for AZT when AZT-DHP and AZT were administered are 25.38 and 26.64 μg h/mL, respectively. However, the brain AUCs for both AzddU and AZT derived from prodrugs, being 11.43 and 11.28 μg h/mL, respectively, are greater than the brain AUCs for AzddU (2.09 μg h/mL) and AZT (1.21 μg h/mL) when the parent drugs were administered. Thus, the relative brain exposure (r_e) for AzddU (5.47) and AZT (9.32) indicate a significant increase in exposure to the anti-HIV nucleosides following prodrug administrations. The results of extended half-lives of the synthesized prodrugs in human serum along with the higher r_e values in vivo warrant studies in larger animals to determine the potential usefulness of the prodrugs in humans.

A significant number of patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex develop neurological complications.[1-8] Human immunodeficiency virus (HIV) can replicate in the brain and the infected brain serves as a reservoir for the virus.[5] It is well documented that HIV has been isolated from the cerebrospinal fluid (CSF) of AIDS patients[9,10] as well as from brains of postmortem AIDS patients. Although the mechanism of HIV-induced central nervous system (CNS) dysfunction is still unclear, it has been proposed that the virus is carried into the brain by infected macrophages/monocytes.[5,6,11] The neurological disorder associated with the HIV infection may be the result of interference of endogenous neurotropic substances by gp120 of HIV.[12] Regardless of the mechanism by which HIV causes the CNS disorders, it is critical that anti-HIV agents penetrate the blood–brain barrier and suppress viral replication in the brain. However, most available chemotherapeutic agents either do not cross the blood–brain barrier or cross to only a small extent. Despite this general rule, there is evidence that 3′-azido-3′-deoxythymidine (AZT) can penetrate into cerebrospinal fluid (CSF),[13] although it has not been demonstrated that AZT is actually able to cross the blood–brain barrier in humans. Patients receiving AZT

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