weak and ill-suited to defending free trade for farmers. Renouncing farm exports, however, would mean renouncing export earnings—recently about 25 percent of U.S. farm income. This would cost hundreds of thousands of jobs on U.S. farms and in farm-related industries, while worsening the U.S. balance of trade and weakening economic growth.

The U.S. farm policy of the future must be geared to competing for buyers who have more alternative sources of supply than ever—their own agricultures, competing agricultures all over the globe, and more synthetics and substitutes. This means that our policies must be designed to reduce costs per unit and to provide farmers with the latest technology. Strong efforts are also needed to lower trade barriers; this will not only be good for U.S. farmers but will help the world to benefit from fuller utilization of global comparative advantages. Researchers need to look at farmland not only in the traditional sense but also as a

potential source of biomass and the various kinds of complex chemical feedstocks that could be produced from genetically engineered plant life.

One thing seems certain: the price supports, land diversion, and storage programs that have dominated U.S. farm policy for the past 50 years work against the U.S. farmer in a world of high technology and rising productivity.

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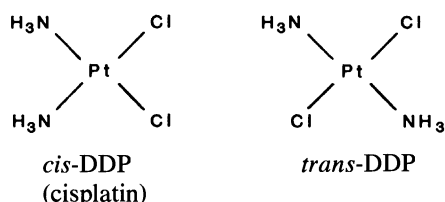9. "Liberian agricultural sector review (Report 4200-LBR, World Bank, Washington, D.C., 1984); "Guinea agricultural sector review" (Report GUI 4672, World Bank, Washington, D.C., 1984); "Sierra Leone agricultural sector review" (Report 4469-SL, World Bank, Washington, D.C., 1984).
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RESEARCH ARTICLE

X-ray Structure of the Major Adduct of the Anticancer Drug Cisplatin with DNA: *cis*-[Pt(NH₃)₂{d(pGpG)}]

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cis-Diamminedichloroplatinum(II), *cis*-DDP or cisplatin, is a clinically important anticancer drug, being especially effective for the management of testicular, ovarian, and head and neck cancers (*1, 2*).

$$H_3N \diagdown \diagup Cl$$
$$Pt$$
$$H_3N \diagup \diagdown Cl$$

cis-DDP (cisplatin)

$$H_3N \diagdown \diagup Cl$$
$$Pt$$
$$Cl \diagup \diagdown NH_3$$

trans-DDP

It is one of the most widely used antitumor drugs at the present time. The *trans* isomer, *trans*-DDP, is inactive. Considerable evidence points to DNA as

being the main target of cisplatin in the tumor cell (*3*). Attention has therefore focused on the nature of, and the differences between, adducts formed by *cis*- and *trans*-DDP with DNA. By using a variety of enzymatic mapping techniques, we and others have shown (*4*) that the most common binding mode of *cis*-DDP with DNA involves loss of two chloride ions and formation of two Pt-N bonds to the N(7) atoms of two adjacent guanosine nucleosides on the same strand. For stereochemical reasons, this intrastrand d(GpG) cross-link cannot be formed by *trans*-DDP. Much structural information about the adduct of *cis*-DDP with synthetic oligodeoxynucleotides has been garnered through nu-

clear magnetic resonance (NMR) spectroscopic investigations (*5, 6*). In addition, recent molecular mechanics calculations on *cis*-[Pt(NH₃)₂{d(GpG)}] adducts in two oligonucleotide duplexes and two single-stranded oligomers have provided theoretical insight about the structure (*7*).

Conspicuously lacking thus far has been structurally definitive single crystal x-ray diffraction information about *cis*-DDP bound to DNA. In attempts to model the binding of the *cis*-{Pt(NH₃)₂}²⁺ fragment to d(GpG), more than a dozen x-ray structural studies have been made on amine complexes of platinum bound to two 6-oxopurine bases, nucleosides, or nucleotides (*8, 9*); however, no oligodeoxynucleotide adduct has yet been crystallographically characterized. Three studies have been directed toward establishing the nature of cisplatin binding to nucleic acids by diffusing the drug into crystals of a B-DNA dodecamer (*10*) or into phenylalanine transfer RNA (tRNA^Phe) (*11, 12*). In all cases, high resolution information was precluded either by low or multiple occupancy (or both) of platinum binding sites in the crystal lattice or by the failure

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of the crystals to scatter beyond 4 to 6 Å resolution. Moreover, although several structures of antitumor drugs complexed with oligonucleotides have been described (13–16), no x-ray crystallographic information is yet available about a covalently linked DNA-drug adduct.

We now describe the synthesis and x-ray structural characterization to atomic resolution of cis-[Pt(NH$_3$)$_2${d(pGpG)}], a study that reveals the molecular geometry of the anticancer drug bound to its putative biological target on DNA. Although the structural analysis was inauspiciously complicated by the occurrence of four such complexes in the asymmetric unit of the cell, once solved we were fortunate in having four crystallographically independent views of the desired structure.

Synthesis and details of the x-ray crystal structure determination. The platinum dinucleotide complex was prepared by allowing the ammonium salt of d(pGpG) (Collaborative Research) to react at ~pH 4.5 with an equimolar amount of a 2 mM aqueous solution of cis-[Pt(NH$_3$)$_2$(NO$_3$)$_2$] at 37°C for 80 minutes. The product, cis-[Pt(NH$_3$)$_2${d(pGpG)}], was purified by anion exchange and reversed-phase high-performance liquid chromatography (HPLC) and characterized by its proton nuclear magnetic resonance (NMR) spectrum (17). An identical NMR spectrum was obtained upon redissolving crystals (see below) of the complex.

Single crystals were grown from solutions that contained 9 mM cis-[Pt(NH$_3$)$_2${d(pGpG)}], 33 mM (pH 3.8) glycine · HCl buffer, 33 mM NaCl, and 9.2 percent 2-methyl-2,4-pentanediol (2-MPD), with equilibration to 70 percent 2-MPD. At this pH, the platinum dinucleotide complex is expected to be neutral with the terminal phosphate being monoprotonated. Upon equilibration, two visually distinct crystal forms were obtained. Initially, long prismatic crystals (crystal type 2) were formed. At longer equilibration times and with higher 2-MPD concentrations and the addition of 17 mM MgCl$_2$, rectangular parallelepipeds (crystal type 1) also deposited.

Both forms were examined by x-ray crystallography (Table 1). A crystal of type 1, having approximate dimensions of 0.6 by 0.5 by 0.4 mm, was sealed in a glass capillary containing a drop of mother liquor. Intensity data were collected at 16°C from one crystal on a Nicolet P3 diffractometer in the ω-scan mode with CuKα radiation. Several data sets were also taken on crystals of type 2, but at this stage we have only a partial solution of the structure, which we do not discuss

further. The two crystal lattices are clearly related to one another, as can be seen from their unit cell dimensions.

The atomic positions of the four independent platinum atoms were obtained by direct methods with MULTAN (18). The remaining nonhydrogen atoms were located from a series of subsequent difference Fourier maps. Unconstrained full-matrix least-squares refinement was carried out in blocks with SHELX-76 (19). Only the platinum, phosphorus, and phosphate oxygen atoms were refined anisotropically, whereas all other atoms were assigned isotropic thermal parameters. After all 192 nonhydrogen atoms of the four independent cis-[Pt(NH$_3$)$_2${d(pGpG)}] molecules were located, one glycine molecule and 26 water molecules were found in the lattice and refined isotropically. At the present stage of refinement, the deoxyribose rings of the 3'-guanosine residues have large thermal parameters, and not all of the solvent molecules have been located. Although work on the structure is continuing, atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre.

Unit cell contents and packing. The four crystallographically independent cis-[Pt(NH$_3$)$_2${d(pGpG)}] molecules, designated 1, 2, 3, and 4 in Fig. 1, form a tightly packed aggregate held together by an extensive network of hydrogen bond-

ing and intermolecular base-base stacking interactions. The platinum-platinum distances range from 5.56 to 7.64 Å. The ammine ligands are oriented toward the center of the aggregate while the sugar-phosphate backbones are directed outward toward solvent channels and neighboring aggregates. A noncrystallographic C$_2$ axis along a relates molecule 1

Abstract. *Crystals of the adduct of the anticancer drug* cis-diamminedichloroplatinum(II), *cis-DDP, with d(pGpG), its putative target on DNA in the cancer cell, have been obtained and used in an x-ray crystallographic study to elucidate the molecular structure to atomic resolution. Each of the four crystallographically independent* cis-[Pt(NH$_3$)$_2${d(pGpG)}] *molecules is comprised of a square-planar platinum atom bonded to two ammonia ligands and two N(7) atoms of guanosine nucleosides from the same chain. Base stacking of the two adjacent guanine rings is completely disrupted by coordination to the* cis-{Pt(NH$_3$)$_2$}$^{2+}$ *unit. Comparison of the backbone and deoxyribose ring torsion angles with those found by previous (nuclear magnetic resonance spectroscopy) studies of this adduct in solution demonstrates that the solid state geometry is substantially the same as that in solution. The relevance of these results to the molecular mechanism of action of* cis-DDP *is discussed.*

with 2 and molecule 3 with 4 (Fig. 1). Around the periphery of the aggregate there are hydrogen bonds [donor-acceptor distances, 2.62(5) − 3.08(5) Å] between terminal 5'-phosphate groups and the N(1)-imino and exocyclic N(2)-amino hydrogen atoms of neighboring molecules. Specifically, the 5'-phosphate groups of molecules 3 and 4 interact with the respective 3'-guanosine hydrogen atoms of molecules 1 and 2, and the 5'-phosphate oxygen atoms of molecules 1 and 2 form hydrogen bonds to the 5'-guanosine residues of molecules 2 and 1, respectively. At the core of the aggregate there is partial stacking of the guanine rings of molecules 1 with 2 and 3 with 4 (Fig. 1). In addition, 20 hydrogen bonds [2.70(4) − 3.34(4) Å] occur between the ammine ligands and the guanine O(6) oxygen atoms of neighboring molecules. Most of these hydrogen bonds are formed between the 5'- and 3'-O(6) atoms of molecules 1, 2, 3, and 4 and the ammine ligands of molecules 3, 4, 2, and 1, respectively.

Table 1. X-ray crystallographic information about cis-[Pt(NH$_3$)$_2${d(pGpG)}].

Property	Crystal type 1	Crystal type 2
Unit cell	a = 31.326 Å b = 35.679 Å c = 19.504 Å Volume = 21,799 Å^3 Z = 16	a = 30.55 Å b = 33.90 Å c = 41.25 Å Volume = 42,709 Å^3 Z = 32
Space group	P2$_1$2$_1$2	C222$_1$ or C222
Reflections (No.)*	14,950 (10,236)	4,677
Resolution	0.94 Å	1.37 Å
Current R factor†	8.4%	

*Number collected and, in parentheses, number used in refinement for which $F_0 > 4$ σ(F_0). †$R = \Sigma \|\ |F_0| - |F_c|\ \| /\Sigma| F_0 |$.

Between tetrameric aggregates, some hydrogen bonding occurs, but the aggregates are largely separated from one another by solvent channels in the crystal lattice. More specifically, hydrogen bonding occurs between the terminal O(3')-hydroxyl protons and terminal phosphate oxygen atoms, and between guanine N(2) amino protons and N(3) nitrogen atoms, of neighboring aggregates. Water and glycine molecules occupy the solvent channels and are hydrogen bonded to the phosphate oxygen atoms, coordinated ammine protons, terminal O(3') hydroxyl groups, and guanine ring heteroatoms. One or two water molecules also form bridges between the two phosphate groups along the sugar-phosphate backbone within each of the four individual platinum complexes.

The molecular geometry of cis-[Pt(NH₃)₂{d(pGpG)}]. The structure of one of the four independent molecules is shown in Fig. 2, and selected geometric information is given in Table 2. In all four molecules the guanosine nucleosides are in the *anti* conformation, and the two O(6) oxygen atoms are on the same side (head-to-head orientation) of the platinum coordination plane. The geometry about each platinum atom is square-planar, with two ammine ligands and two guanosine N(7) atoms comprising the coordination sphere. The average Pt-NH₃ and Pt-N(7) bond lengths are 2.04 and 2.00 Å, respectively. No atom deviates by more than 0.06 Å from the best plane through platinum and its four bonded nitrogen atoms. The dihedral angles between coordinated guanine bases; defined according to conventions (20), range from 76° to 87°. Thus, coordination of cis-{Pt(NH₃)₂}²⁺ to {d(pGpG)}²⁻ completely disrupts the base stacking of the two adjacent nucleotides (Fig. 3b). Dihedral angles between planes through the PtN₄ and guanine rings atoms occur in pairs for the four molecules, reflecting the pseudo-twofold symmetry of the crystal lattice. For pairs of molecules 1 and 2 and 3 and 4, respectively, these angles are 111° and 111° and 80° and 77° for the 5'-guanosine and 86° and 95° and 58° and 60° for the 3'-guanosine nucleoside. With these values the ammine-O(6) contacts exceed 3.1 Å, precluding a significant amount of hydrogen bonding between the ammine ligands and the exocyclic O(6) oxygen atoms of the guanine bases. Intramolecular hydrogen bonding does occur to varying degrees between the coordinated ammines and the oxygen atoms of the 5'-phosphate groups, however, with N $\cdots$ O distances of 2.72(5) (Pt1 in Fig. 3b), 2.83(3) (Pt2), and 3.03(3) (Pt3), and 3.22(5) (Pt4) Å.

From the torsion angles within the five-membered deoxyribose sugar rings we may calculate the pseudorotation angles, P, and amplitudes, ψ (21, 22). In all four molecules the 5'-nucleotide is in the N, or C(3')-endo, conformation. More precisely, there are two classes of sugar puckers. Molecules 1 and 2 have P-5' = −12° and −8° and are characterized by relatively strong hydrogen bonding between the ammine ligands and 5'-phosphate groups. Weaker hydrogen bonding of this kind occurs for the other two molecules, for which the respective pseudorotation angles are P-5' = 23° and 27°. The intramolecular phosphorus-phosphorus distances range from 5.58(4) to 6.18(2) Å. The 3'-nucleotide sugars display a wider range of pseudorotation angles, characteristic of S, or C(2')-endo, conformations but centered about the C(1')-exo conformation, 84° < P < 138°. The larger errors in torsion angles and the greater thermal motion of the 3'-nucleotide sugars in all four molecules suggest that they have greater conformational flexibility than the better behaved 5'-nucleotides in cis-[Pt(NH₃)₂{d(pGpG)}]. Alternatively, there may be some unresolved disorder in these sugars, as reflected by a few unusual bond distances and angles.

Table 2 also lists the sugar-phosphate backbone and glycosyl bond torsion angles, defined according to standard con-

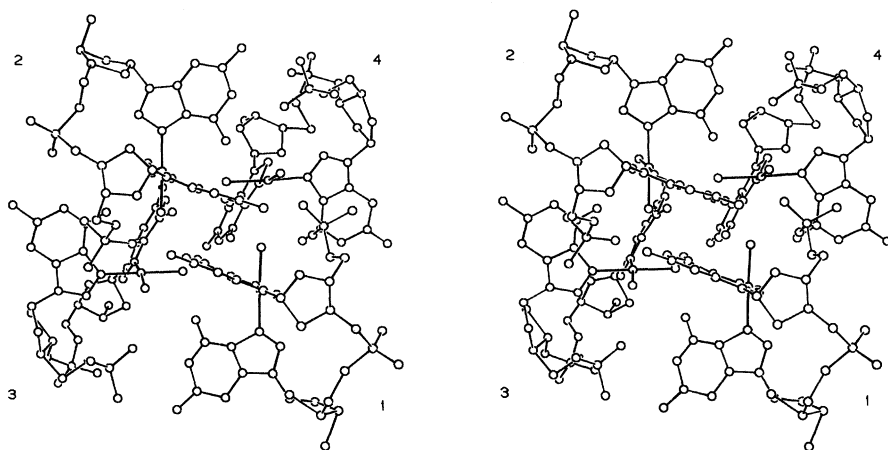Fig. 1. Stereo view of the four crystallographically independent cis-[Pt(NH₃)₂{d(pGpG)}] molecules in the unit cell. The view is down the *a* axis of the unit cell, revealing the pseudo-twofold symmetry of the aggregate. Water and glycine molecules in the lattice are not shown.
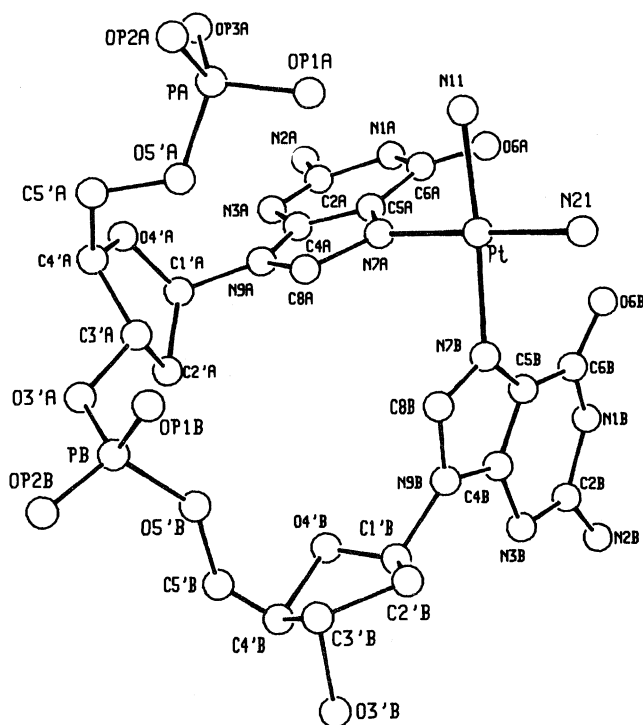

Fig. 2. Molecular structure of one of the four cis-[Pt(NH₃)₂{d(pGpG)}] molecules portraying the atom labeling scheme.

vention (21). Despite their different sugar conformations, the χ-values of all eight nucleotides fall within or close to the "high-*anti*" range (22) except for the 5′ residues of molecules 3 and 4. Coordination of the two N(7) nitrogen atoms to platinum, which closes a large, 17-membered chelate ring (Fig. 3a), undoubtedly contributes to these glycosyl bond torsion angles.

Comparisons. With the crystal structure of a d(GpG)-containing oligonucleotide complex of *cis*-diammineplatinum-(II) in hand, it is interesting to compare the geometrical results with previously made predictions. The most accurate insights were provided by NMR spectroscopic investigations and molecular mechanics calculations. Proton NMR studies of *cis*-[Pt(NH₃)₂{d(pGpG)}] correctly forecast that the chelated complex would have the two guanine bases in an *anti-anti* configuration with corresponding head-to-head disposition of the O(6) oxygen atoms (17). A more detailed analysis of NMR data on the related complex *cis*-[Pt(NH₃)₂{d(GpG)}] revealed that the 5′-nucleoside has the N (C3′-endo) conformation but that the 3′-nucleoside is conformationally more flexible, with ~70 percent S (C2′-endo) character (5). Indeed, the picture constructed from NMR and related model building studies is in good accord with our crystallographic details (Table 2). This agreement suggests that the solid state structures of the four cisplatin-DNA adducts determined here most likely reflect the salient features of their geometry in solution.

One aspect of the *cis*-[Pt(NH₃)₂-{d(pGpG)}] structure not yet identified by NMR spectroscopy, but predicted from molecular mechanics calculations on platinated duplexes as well as single-stranded oligonucleotides (7), is the occurrence of a hydrogen bond between an ammine ligand and the 5′-phosphate group of the coordinated dinucleotide. This intramolecular hydrogen bond is clearly present in at least three of the four molecules that we studied. Hydrogen bonding between an ammine ligand and the 5′-phosphate group of coordinated mononucleotides had been postulated to explain the greater stability of unsubstituted compared to alkylated amines in a series of related palladium(II) complexes (23). Since substitution of protons by alkyl groups diminishes the antitumor activity of platinum coordination compounds (24), the intramolecular NH₃ ··· phosphate hydrogen bond may function in stabilizing the DNA adduct of cisplatin required for its biological mechanism of action.

Molecular mechanics calculations

Table 2. Geometric information about *cis*-[Pt(NH₃)₂{d(pGpG)}] from the crystal structure described in this article, *cis*-[Pt(NH₃)₂{d(GpG)}] from NMR and model building (5), and two *cis*-DDP-oligonucleotide adducts from molecular mechanics calculations (7). Bond lengths are in angstroms and all angles are given in degrees. Dihedral angles between planes are defined according to the conventions in (20), and P and ψ according to (21, 22). The symbol PtN₄ refers to platinum and its four bonded nitrogen atoms. Torsion angles are defined as P≜O5′≜C5′≜C4′≜C3′≜O3′≜P and χ for the glycosyl O4′-C1′-N9-C4. Except when defined, numbers in parentheses are standard deviations.

| Item | Coordination geometry and dihedral angles between planes | | | | |
	< Pt-N > (range)	< N-Pt-N > (range)	3′-Gua/5′-Gua	5′-Gua/PtN₄	3′-Gua/PtN₄
Molecule 1	2.03 (2.01–2.05)	90 (88–92)	76.2 (5)	111.0 (5)	85.6 (6)
Molecule 2	2.02 (1.97–2.08)	90 (89–91)	81.4 (5)	111.1 (6)	95.4 (7)
Molecule 3	2.00 (1.92–2.09)	90 (87–92)	86.7 (6)	80.2 (6)	57.8 (6)
Molecule 4	2.04 (1.94–2.09)	90 (88–94)	80.5 (6)	76.8 (6)	59.7 (6)

| Item | Dinucleotide geometry | | | | | | | | | | | | | | | | |
| | 5′ Nucleotide | | | | | | | 3′ Nucleotide | | | | | | | | |
	P	ψ	χ	β	γ	δ	ε	ζ	P	ψ	χ	α	β	γ	δ
Molecule 1	−12	33	−94 (4)	141 (3)	56 (4)	94 (4)	−142 (3)	−65 (3)	84	38	−93 (5)	−85 (8)	−143 (6)	30 (11)	147 (7)
Molecule 2	−8	35	−89 (3)	209 (2)	65 (4)	104 (4)	−144 (3)	−64 (3)	138	28	−110 (4)	−77 (6)	−141 (4)	84 (16)	108 (15)
Molecule 3	23	46	−138 (4)	143 (3)	55 (4)	91 (5)	−126 (4)	−71 (5)	130	49	−117 (4)	−57 (7)	−168 (6)	47 (8)	150 (7)
Molecule 4	27	48	−142 (3)	166 (3)	36 (6)	101 (5)	−128 (4)	−69 (4)	136	43	−127 (4)	−49 (5)	−161 (4)	42 (7)	137 (6)
NMR + model building:	−1 (7)	37	−110	—	52	87	−157	−53	149	34	−115	−68	−168	58	137
Calculations: d(GpG) − Pt(NH₃)₂*	−3	40	−143	170	59	88	−115	−70	148	39	−132	−65	−176	57	137
Calculations: Pt-decamer†	−2	44	−152	137	55	84	−147	−53	147	29	−126	−63	−161	56	128

*Values computed from coordinates supplied by J. Reedijk.   †Values given are for *cis*-[Pt(NH₃)₂]²⁺ bound to (GpG) in [d(TCTCGGTCTC)·d(GAGACCGAGA)], see (7).
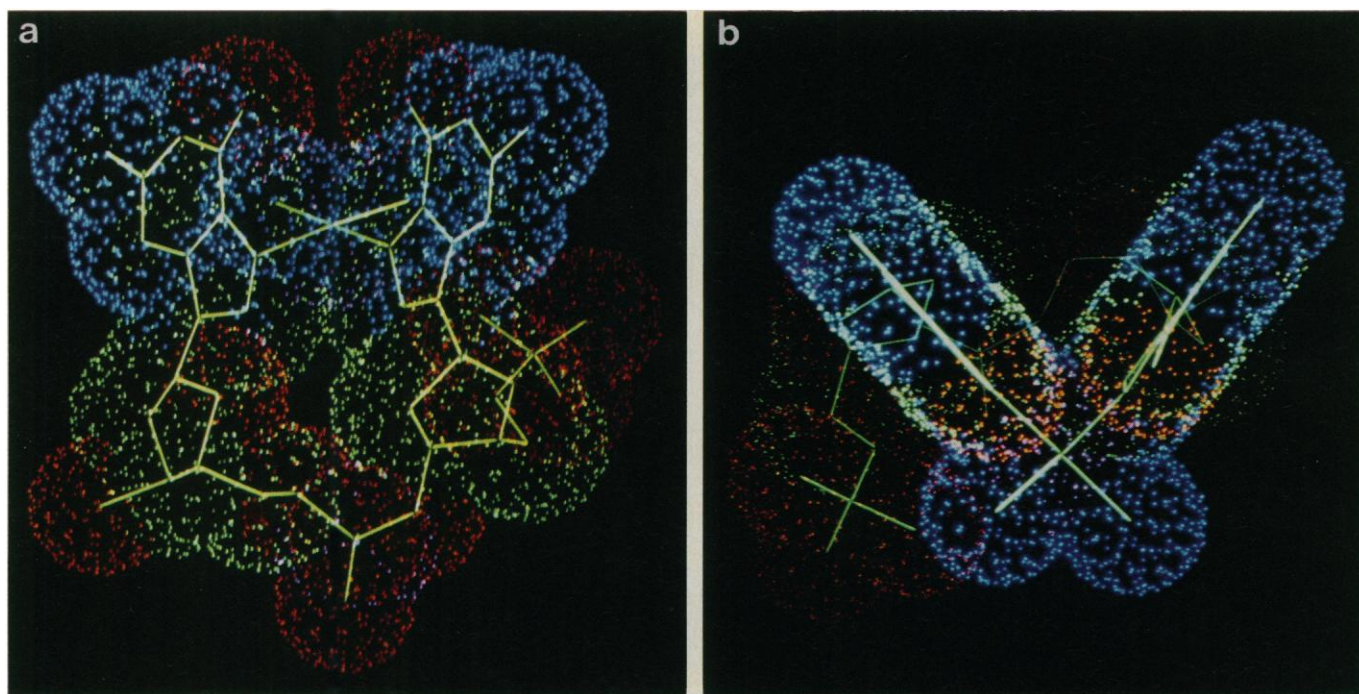
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Fig. 3 (a and b). Two views of the van der Waals spheres of the structure in Fig. 2. The right-hand view clearly reveals the hydrogen bond formed between the terminal 5'-phosphate and coordinated ammine groups as interpenetrating van der Waals spheres.

have been carried out on *cis*-diammine-platinum(II) coordinated to the N(7) atoms of adjacent guanosine nucleosides in d(pGpG), d(ApGpGpCpCpT), and two double helical oligonucleotides, an octameric and a decameric duplex (7). The predicted conformational angles (Table 2) are in relatively good agreement with the values observed from our x-ray study.

This result suggests that the geometry of the platinated d(GpG) fragment elucidated in this work could be retained in double helical DNA, with attendant local disruptions of Watson-Crick base pairing or duplex kinking as described (7). Base pair disruptions have been detected in studies with antibodies to nucleosides (25).

Finally, we inquire which predictions that were based on x-ray crystallographic studies of *cis*-DDP soaked into crystals of DNA or RNA are upheld by our results. The postulated (10) intramolecular hydrogen bond between a platinum-ammine ligand and the O(6) oxygen atom of the guanine base, possibly with an intervening water molecule as a bridge, is not observed. Because of the tight, hydrogen-bonded cluster formed among the four molecules in our crystal structure, however, it is not possible to rule out such a hydrogen-bonding network on platinated duplex DNA. Apart from the conclusion that platinum binds to N(7) of purines, there is little information in the two studies of *cis*-DDP soaked into

tRNA^{Phe} (11, 12) that can be assessed by our results.

Relevance to mechanism of action of *cis*-DDP. Our x-ray structural results, taken alone, offer little insight into the biological mechanism of action. Within the context of several recent findings, however, they do provide an important piece of the puzzle from which a picture of how *cis*-DDP might work has begun to emerge. Studies with an in vivo SV40 model system reveal that equal amounts of *cis*- and *trans*-DDP bound to the SV40 chromosome are equally effective at inhibiting replication, but that an order of magnitude more *trans*- than *cis*-DDP is required in the medium to produce equivalent inhibition of DNA synthesis (26). Furthermore, these results were shown to be the consequence of much more efficient repair of *trans*- versus *cis*-DDP from DNA in this system. What kind of DNA adduct would render *cis*-DDP difficult to repair yet capable of inhibiting replication? The intrastrand cross-linked *cis*-[Pt(NH$_3$)$_2${d(pGpG)}] is a very reasonable candidate. Both molecular mechanics calculations (7) and NMR studies (27, 28) reveal that such an adduct, the structural details of which have been elucidated here, can be accommodated in duplex DNA with only very localized disruption of the double helix. Such local melting of DNA at the site of platination by *cis*-DDP, while lethal to the cell because it inhibits replication, might elude the repair enzymes, espe-

cially if they were repressed in neoplastic cells (29). On the other hand, *trans*-DDP cannot, for stereochemical reasons, link two adjacent guanosine nucleosides in DNA. Studies in vitro reveal that it forms a greater variety of intrastrand cross-links between bases with one or more intervening nucleotides (30). Possibly these or other adducts made by *trans*-DDP in vivo disrupt the duplex more profoundly than the intrastrand cross-linked *cis*-[Pt(NH$_3$)$_2${d(pGpG)}]. The *trans*-DDP adducts may therefore be more readily recognized and repaired by the cell, requiring the addition of very high doses to produce an equivalent effect on DNA replication. Further structural and biological studies of single-stranded and duplex DNA modified by *cis*- or *trans*-DDP will permit evaluation of this model.

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