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DNA Binding and Chemistry of Dinuclear Platinum Complexes

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DNA Binding and Chemistry of Dinuclear Platinum Complexes

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This Comment summarises the chemistry and DNA binding of dinuclear platinum–amine, or bis(platinum), complexes, a new class of potent antitumor agents. In these structures, the Pt coordination spheres are bridged by variable-length diamine chains. The DNA binding of these species produces an array of structurally distinct adducts not available to mononuclear analogs such as cis-$[PtCl_2(NH_3)_2]$. The possibility of tri- and tetra-substitution inherent in the dinuclear structure poses interesting challenges for design of complexes capable of specific DNA binding. Besides the utility of the dinuclear structure in design of novel antitumor agents, the unique DNA binding modes of these species allow their use as probes of DNA structure and conformation.

Key Words: *dinuclear platinum complexes, DNA binding, antitumor activity*

INTRODUCTION

The clinical utility of the anticancer agents cisplatin and carboplatin is by now well established.[1,2] The more widespread and efficacious use of these agents is limited by the development of drug resistance (reduced efficacy upon repeated treatment). The principal factors

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responsible for cellular resistance to cisplatin include altered cellular uptake and/or efflux, and modulation of the Pt–DNA interaction, either as a result of enhanced sequestering of platinum by intracellular thiols or by enhanced DNA repair.[3–5] A current exciting challenge in platinum medicinal chemistry is to use the detailed knowledge of the *cis*-DDP-DNA interaction[6,7] to design new and more effective agents with a wider spectrum of antitumor activity and capable of overcoming *cis*-DDP resistance.

The empirical structure–activity relationships for platinum complexes stressed the need for the *cis*-$[PtX_2(amine)_2]$ geometry (X = leaving group, amine = primary amine or bidentate diamine). Direct structural analogs of *cis*-DDP have not, however, shown a greatly altered spectrum of clinical efficacy in comparison to the parent drug.[8,9] The mechanistic explanation for this finding is that all *cis*-$[PtX_2(amine)_2]$ compounds produce an array of adducts very similar to those of *cis*-DDP, with intrastrand d(GpG) and d(ApG) adducts predominating. Thus, the biological consequences of these adducts are also expected to be similar. We have proposed that alteration of the mode of DNA binding of platinum complexes in comparison to *cis*-DDP may result in an altered spectrum of antitumor activity and enhanced activity in cisplatin-resistant cells. DNA adducts structurally distinct from those of *cis*-DDP may have different conformational features and may be inherently more cytotoxic or more difficult to repair. Two classes of complexes we have discovered which appear to have biological properties distinct from those of *cis*-DDP are dinuclear platinum (or bis(platinum)) and novel *trans* platinum complexes containing planar heterocyclic ligands.[10–14] In particular, both series retain activity in cells resistant to *cis*-DDP and act on DNA in manners distinct to the "parent" *cis*-DDP.[15,16] These results mean that *cis*-DDP-like lesions are not the unique arbiters of cytotoxicity as previously thought. In this Comment, I wish to summarise the chemistry and DNA-binding of dinuclear platinum complexes and demonstrate their utility as antitumor agents and versatile probes of DNA structure and function.

DINUCLEAR PLATINUM COMPLEXES AS DNA-BINDING AGENTS

The study and application of metal complex interactions with DNA covers a wide area of interests, including mechanisms of antitumor

activity, their use as sequence and conformational probes, the participation of metal-binding domains of proteins in DNA recognition, control of gene expression by metals, sequence-specific DNA cleavage and design of artificial endonucleases and restriction enzymes. (For recent major reviews see Refs. 17 and 18). In general, the examination of all these aspects has involved mononuclear complexes containing only one metal center. DNA binding of mononuclear complexes may be modulated by chemical factors such as geometry (*cis/trans*-DDP), number of leaving groups (mono, bifunctional), redox ability (Fe, Cu, Co, Ru to effect DNA cleavage) and chirality (Ru(tris-phenanthrolines), etc.). Dinuclear metal complexes present a different and intriguing set of chemical and structural questions to answer. Our studies to date have made it clear that the structure of dinuclear complexes is an extremely powerful one for design of DNA–DNA and DNA–protein cross-linking agents. Figure 1 summarizes, in a schematic manner, the limiting binding modes available to dinuclear species, while Table I summarizes the principal structural classes studied to date, their binding properties, and the abbreviations used to designate these species.

SYNTHESIS AND PROPERTIES OF BIS(PLATINUM) COMPLEXES

The most general formula for the dinuclear complexes we have studied is $[\{PtCl_m(NH_3)_{3-m}\}\mu\text{-}H_2N\text{-}R\text{-}NH_2\text{-}\{PtCl_n(NH_3)_{3-n}\}]^{\{(2-m)+(2-n)\}+}$ (m or n = 0–3 and R is a linear or substituted aliphatic linker). The wide class of complexes covered by this general formula may be divided into two groups—those containing equivalent coordination spheres (m = n) and those in which the two coordination spheres are inequivalent (m ≠ n). Further, complexes containing either monofunctional or bifunctional coordination spheres are possible. Indeed the complexes containing two *cis*-$[PtCl_2(amine)_2]$ units are unique examples of potentially tetrafunctional antitumor and DNA-binding agents. Complexes with only one leaving group on each platinum are thus formally bifunctional with modes of DNA binding distinct from the bifunctional *cis* or *trans*-$[PtCl_2(NH_3)_2]$. Figure 2 shows the principal structures studied to date. Note the possibility of geometric isomers within the bis (platinum) framework. Indeed, all three possible 2,2 isomers (both

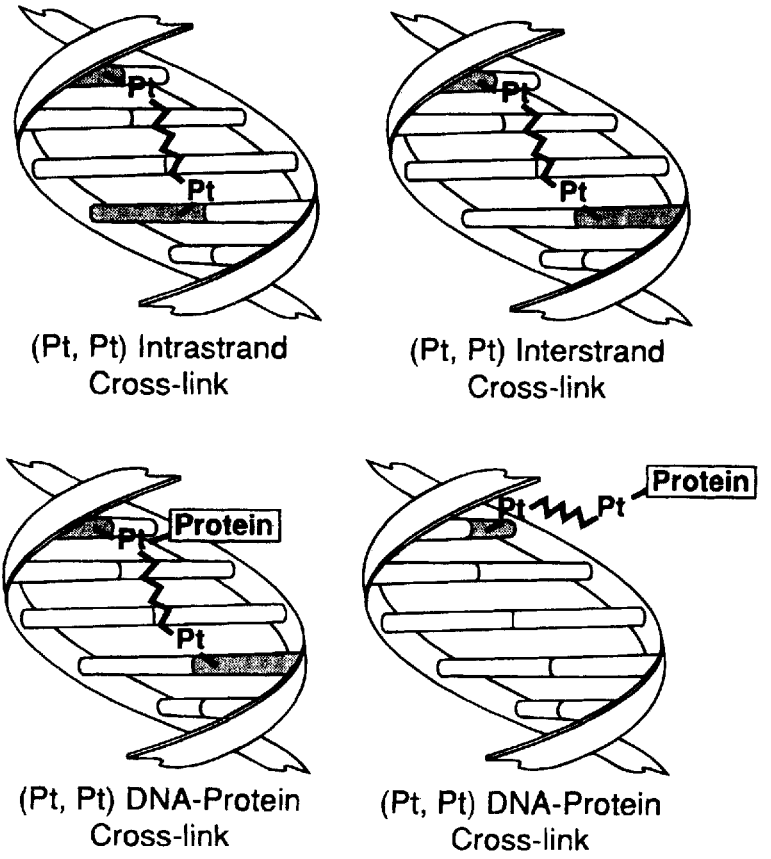

FIGURE 1 Schematic limiting modes for possible DNA–DNA and DNA–protein cross-linking induced by dinuclear platinum complexes.

coordination spheres *cis*, both *trans*, and the situation in which one coordination sphere is *cis* and one is *trans*) have been synthesized and characterised.[19,10]

Bis(Platinum) Complexes with Equivalent Coordination Spheres

$[\{cis\text{-}PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)](2,2/c,c)$. These are usually prepared by reaction of two equivalents of a suitable mononuclear

TABLE I

Summary of properties and DNA binding of dinuclear bis(platinum) complexes studied to date.

Coordination Spheres	Isomers Studied	Relevance
$[PtCl_2(am)_2]$/ $[PtCl_2(am)_2]$	2,2/c,c;t,t;t,c	For 2,2/c,c: Tetrafunctional Anti-tumor Compound. DNA–Protein Cross-Linking Agent.
$[PtCl(am)_3]$/ $[PtCl(am)_3]$	1,1/c/c;t,t	Bifunctional Antitumor Compounds with Mono-functional coordination spheres. No cis-DDP adduct. Interstrand cross-linking agents. (Pt,Pt) Intrastrand Adduct for 1,1/t,t. Induces B → Z change.
$[Pt(am)_4]/[PtCl(am)_3]$	0,1/t	First step of interstrand cross-link formation. Steric and electrostatic effects on monofunctional binding. Induces B → Z change.
$[Pt(am)_4]/[Pt(am)_4]$	0,0	Effect of charge. No covalent binding. Induces B → Z by charge effects.

Abbreviations. For a convenient abbreviation of bis(platinum) complexes we have adopted a system where the numbers refer to the number of chlorides (or anionic leaving groups) on each platinum atom. Where there are two chlorides on the same Pt, the lettering specifies their mutual geometries (*cis* or *trans*). For those possibilities where there is only one chloride in a coordination sphere, the lettering refers to the geometry with respect to the nitrogen of the bridging diamine. Once these two parameters are specified, the geometry of the overall complex is automatically fixed. Thus $[\{cis\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$ is 2,2/c,c, $[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2$ is 1,1/t,t etc. The 0,0 therefore refers to a species with tetra-amine coordination spheres. The chlorides in the 2,2/c,c complexes may be substituted by dicarboxylates such as malonate etc.

cis-DDP = cisplatin, *cis*-$[PtCl_2(NH_3)_2]$; carboplatin = $[Pt(CBDCA)(NH_3)_2]$; CBDCA = 1,1-cyclobutanedicarboxylate; r_b = the number of bound platinum complexes per nucleotide; terpy = 2,2′:6,2″-terpyridine; DMF = dimethylformamide; BOC = tert-butoxycarbonyl; 5′-GMP = 5′-guanosinemonophosphate.

platinum complex with the diamine.[20] Synthetic routes are dependent on chain length. Thus:

$$2\ K[PtCl_3(NH_3)] + NH_2(CH_2)_nNH_2 \rightarrow [\{cis\text{-}PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)]\ (n > 4).$$

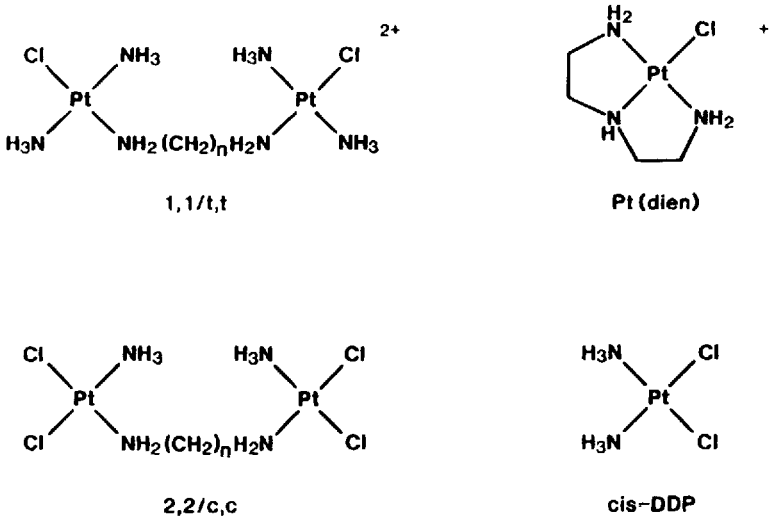

FIGURE 2 The principal dinuclear platinum complexes studied to date and their mononuclear analogs. Note that geometric isomerism exists in both dinuclear structures. For abbreviations see Table I.

Substitution of the chlorides with water-solubilizing groups such as malonate, etc. is straightforward.[12] Direct routes to short-chain complexes are not yet available.[21] Instead, chelate formation is preferred over bridging and "double" salts are formed:

$$2\ K[PtCl_3(NH_3)] + NH_2(CH_2)_nNH_2 \rightarrow [PtCl(NH_3)(NH_2(CH_2)_nNH_2)][PtCl_3(NH_3)]\ (n = 2,3).$$

The synthesis and mechanism of formation of the *trans* isomer (2,2/t,t) from tetra-amine bis(platinum) complexes has also been reported.[19]

$[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]^{2+}$ *(1,1/t,t).* In contrast to the 2,2/c,c case above, the direct route for 1,1/t,t complexes is best for n = 2–4:

$$2\ \textit{trans}\text{-}[PtCl_2(NH_3)_2] + H_2N(CH_2)_nNH_2 \rightarrow [\{\textit{trans}\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2\ (n = 2\text{–}4).$$

For n = 5, an interesting *trans*-chelate is formed because upon complexation of the diamine the other end is at the right distance to bind to the *trans* position rather than form a dimer[22]:

$$\textit{trans}\text{-}[PtCl_2(NH_3)_2] + H_2N(CH_2)_nNH_2 \rightarrow \textit{trans}\text{-}[Pt(NH_3)_2(H_2N(CH_2)_nNH_2)]Cl_2\ (n > 5).$$

The 1,1/t,t complexes for n > 5 are best obtained by preparing in situ the cation *trans*-$[PtCl(DMF)(NH_3)_2]^+$. The DMF is selectively displaced giving the desired dimer:

$$\textit{trans}\text{-}[PtCl_2(NH_3)_2] + AgNO_3 \rightarrow \textit{trans}\text{-}[PtCl(DMF)(NH_3)_2]^+(NO_3)^-,$$

$$2\ \textit{trans}\text{-}[PtCl(DMF)(NH_3)_2]^+ + H_2N(CH_2)_nNH_2 \rightarrow [\{\textit{trans}\text{-}PtCl(NH_3)\}_2H_2N(CH_2)_nNH_2](NO_3)_2.$$

The routes to the alternative 1,1/c,c isomer are similar.[23] The potent antitumor activity of these charged species[15] violates all known structure–activity relationships of platinum complexes.

Bis(Platinum) Complexes with Inequivalent Coordination Spheres

This case is an interesting one because suitable design can allow specific reactions to take place at one Pt center. For complexes with inequivalent coordination spheres, a general approach is to prepare a precursor monomer containing a "dangling" H_2N–R–NH_2, with one end uncomplexed in the form of either a protected amine or a

NH_3^+ salt. Subsequent reaction with a suitable target in the presence of base gives the dinuclear species:

$$Pt(a)–H_2N–R–NH_3^+ + Pt(b) \rightarrow Pt(a)–H_2N–R–NH_2–Pt(b).$$

This chemistry potentially gives a very wide range of complexes. The target molecule, Pt(b), should be chosen so as to have only one major mode of substitution to avoid competitive reactions. Specific examples of products formed in this way are the complex [{*cis*-$PtCl_2(NH_3)$}-μ-$NH_2(CH_2)_4NH_2$-{*trans*-$[PtCl_2(NH_3)$}], a unique example containing two coordination spheres differing only in geometry,[10] and the complex [*cis*-{$PtCl_2(NH_3)$}-μ-$NH_2(CH_2)_4NH_2$-{*cis*-$PtCl_2(Me_2SO)$}], where the two coordination spheres differ in the nature of the ligands attached.[24]

Bis(platinum) complexes with inequivalent coordination spheres are of interest for two main reasons:

(i) The possibility of designing complexes susceptible to selective attack on one coordination sphere, thus also allowing us eventually to dictate DNA-binding modes in a polyfunctional complex. Bis(platinum) complexes with two equivalent coordination spheres (such as the 2,2/c,c) are equally likely to react at either metal center. In a substitution reaction this equivalence is broken when the first Pt center reacts. There is now the possibility of competitive interaction between the two inequivalent platinum centers, and the final products will depend on the nature of the incoming group and the ligands bound to the platinum atoms. This aspect of substitution reactions on bis(platinum) complexes has been exemplified in the formation of the complex with two *trans*-$[PtCl_2(amine)_2]$ coordination spheres, [{*trans*-$PtCl_2$-(NH_3)}$_2(NH_2(CH_2)_nNH_2)$], from doubly bridged tetra-amines[19] and in the reactions of 5′-GMP with the tetra-aqua species derived from [{*cis*-$PtCl_2(NH_3)$}$_2(NH_2(CH_2)_nNH_2)$].[25]

(ii) The preparation of monofunctional and trifunctional species as DNA-binding agents and as intermediates in bis(Pt)–DNA adduct formation. The synthesis of the formally monofunctional bis(platinum) complex [{$Pt(NH_3)_3$}μ-$H_2N(CH_2)_4NH_2$-{*trans*-

$PtCl(NH_3)_2\}]^{3+}$ (1,0/t) was achieved as described in Fig. 3.[26] This compound was useful for examining the mechanism of Z-DNA induction of poly(dG-dC).poly(dG-dC) as well as the kinetics of sequence preference of bis(platinum) complexes.

Tri(platinum) Complexes. The linking concept has been extended to prepare tri(platinum) complexes containing three *cis*-$Pt(amine)_2$ units.[27] In this case, the general preparation involves the following steps: synthesis of a suitable precursor containing two mono-protected diamines; treatment with acid to give the protonated amine $RNH_3^+Cl^-$, which may then be used as a source for further metallation; and reaction with two equivalents of an appropriate target molecule to afford the desired product (Fig. 4).

Heterodinuclear (Ru,Pt) Complexes. At the most general level, bis(-platinum) complexes may be considered the first examples of an entirely new set of DNA-binding agents: *dimetallic cross-linking agents*. A logical extension is thus the preparation and study of complexes containing two non-platinum (homobimetallic, e.g., M,M) centers or one Pt and one other metal center (heterobimetallic, e.g., Pt,M). We have further extended the linking concept to the preparation of heterodinuclear complexes containing one Pt atom and another metal, preferably ruthenium. In this case, the linking was achieved by preparing a dangling amine on the Ru atom.[28] Ruthenium was

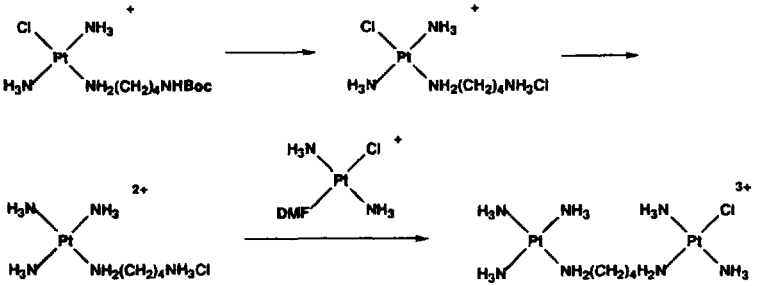

FIGURE 3 Synthetic scheme for formation of a dinuclear platinum complex with inequivalent coordination spheres. In this case a formally mono-functional derivative is linked to a tetra-amine complex.

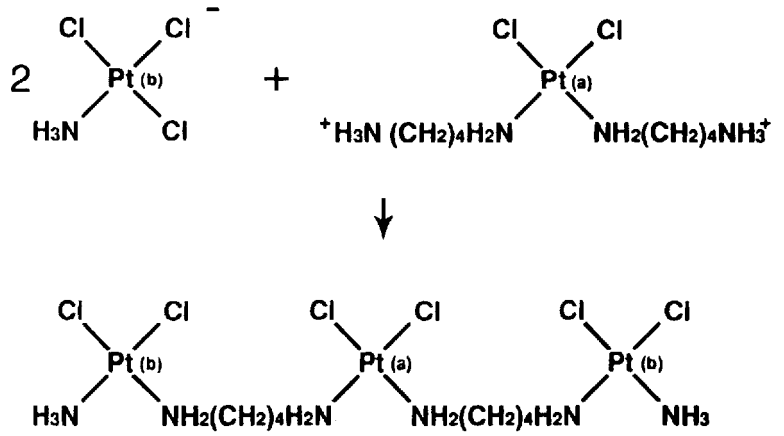

FIGURE 4 Synthetic scheme for formation of triplatinum complexes.

chosen as the second metal because of the anti-tumor activity of a large number of complexes.[29–31] A further consideration is that Ru complexes have been used extensively to site-specifically label proteins involved in electron transfer reactions.[32] Since, in general, Ru complexes are less reactive than Pt complexes, the combination may be used to impart reactivity to particular DNA sequences and to facilitate cross-linking of unique proteins with DNA.

DNA Interactions of Bis(Platinum) Complexes

Upon initial monofunctional binding, further reaction of the second Pt site may lead to a series of structurally distinct adducts including (i) DNA (Pt,Pt) interstrand cross-links by binding of one Pt atom to each strand of DNA, (ii) (Pt,Pt) intrastrand cross-links by binding of the two Pt atoms to the same strand as well as DNA–protein cross-links. The DNA–DNA and DNA–protein binding modes shown in Fig. 1 are minimal in the sense that they require only one leaving group (chloride) on each Pt atom. A fully reacted bis(platinum) complex with *cis*-DDP like coordination spheres is in fact tetrafunctional. In this case the second step of binding to DNA is important because a competition arises between formation of (Pt,Pt) interstrand cross-links or a cisplatin-like intrastrand adduct by preferential reac-

tion of one *cis*-Pt unit (Fig. 5). In the following sections the binding preferences and conformational changes in bis(Pt)–DNA interactions are summarized.

1. Kinetics of Binding of Bis(platinum) Complexes.

Early studies indicated that bis(platinum) complexes reacted faster than *cis*-DDP with DNA.[20] Sequencing studies also showed binding to alternating purine–pyrimidine GCGC runs.[33] The initial rates of reaction of bis(platinum) complexes with small self-complementary oligonucleotides 5′-ATATAGCGCATATAT-3′ (GCGC) and 5′-ATATATGGCCATATAT-3′ (GGCC) were calculated to determine the kinetic preferences between the two sequences. For both mononuclear and dinuclear platinum complexes, the GGCC oligonucleotide reacted faster than the GCGC counterpart. The bis(platinum) complexes are, nevertheless, much more reactive with GCGC sequences

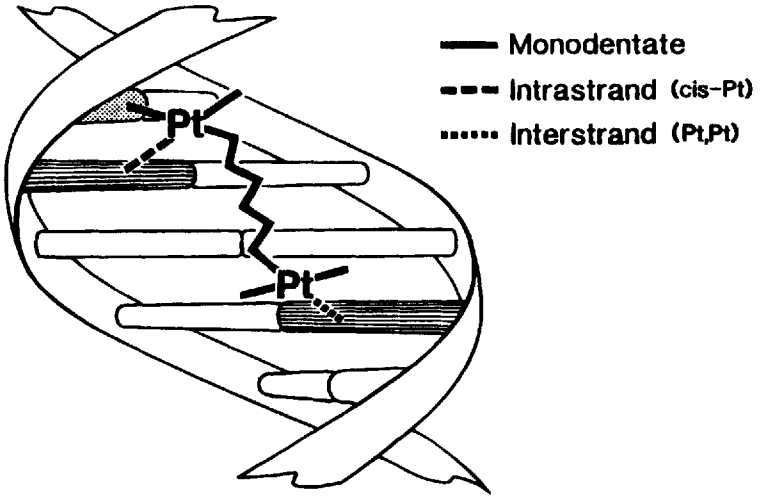

FIGURE 5 Schematic demonstration of competitive binding of a dinuclear platinum complex containing bifunctional (*cis*-DDP like, 2,2/c,c) coordination spheres. Once the first Pt–purine bond is formed, a competition is automatically set up between *cis*-DDP like intrastrand cross-link formation and a (Pt,Pt) interstrand cross-link. Suitable modification of coordination sphere or backbone may affect the reaction pathways.

than *cis*-DDP.[26] The presence of GCGC runs in many promoter sequences of DNA suggests that dinuclear species may be designed to specifically modify such regions. The kinetic results indicate that differences in antitumor activity between dinuclear and monomeric platinum complexes are dictated, to a first degree, by the nature of the adducts within a similar sequence (i.e., GGCC) rather than a different sequence specificity.

2. The (Pt,Pt) Intrastrand Cross-Link.

The (Pt,Pt) intrastrand cross-link is currently being studied by a combination of NMR studies on model dinucleotides, sequencing on oligonucleotides of defined sequence, and protein recognition of bis(platinum)-damaged DNA.[34]

NMR Studies on Model Dinucleotides. We have reported on the characterization by NMR spectroscopy of the unique macrochelate formed from d(GpG) and $[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_6NH_2]^{2+}$ (1,1/t,t, n = 6).[35] This structure represents a model for the (Pt,Pt) intrastrand cross-link and is the direct dinuclear analog of the major intrastrand adduct of *cis*-DDP with DNA. The important features are a separation of 1.8 Hz for the two independent (5′ and 3′) H8 protons and a complicated NMR pattern for the H1′ protons of the sugar groups. Kinetic studies showed that the rate of formation (and proportion relative to other products) of the chelate is dependent on the chain length with n = 6 > 4 > 2. The H(8) separation is also dependent on chain length.[36]

Sequencing of Bis(Pt)–DNA Lesions. The assignment of intrastrand and interstrand cross-links caused by platinum complexes was aided by development of a new assay taking advantage of the fact that 3′ → 5′ exonuclease digestion of randomly platinated DNA produces a pool of fragments of different length.[37] We reasoned that termination of exonuclease activity prior to an interstrand cross-linking site would leave a fragment with complementary base pairs at the cross-linking site which may act as a primer template for extension upon subsequent treatment with a DNA polymerase. On the other hand, degradation of intrastrand adducts will not produce fragments with complementary base pairs and the fragments will not act as templates for DNA replication. Using these properties of Pt–DNA adducts we can distin-

guish intrastrand from interstrand cross-linked fragments, and the formation of the (Pt,Pt) intrastrand cross-link in a 49-bp duplex DNA was confirmed.[37]

Conformational Changes Due to the (Pt,Pt) Intrastrand Cross-Link. How similar is the (Pt,Pt) intrastrand cross-link to that of *cis*-DDP? A principal feature of the *cis*-DDP intrastrand cross-link is a kink or bend of the double helix toward the major groove.[38] Recent exciting studies have implicated this conformational change as responsible for the recognition of *cis*-DDP-damaged DNA by the family of HMG proteins.[39,40] Molecular modelling showed that the (Pt,Pt) intrastrand cross-link also results in kinking caused by the relative orientations of the two guanine bases. Interestingly, HMG proteins recognize DNA damaged by bis(platinum) complexes but not as efficiently as for *cis*-DDP-damaged DNA.[41] The protein recognition thus implies that conformational changes similar to those induced by *cis*-DDP are also induced by the dinuclear compound. Quantitation of the binding of the dinuclear complexes to DNA showed that at equal r_b and equal concentrations of protein, recognition of the bifunctional 1,1/t,t complex is 30% of that for *cis*-DDP. Thus the possibility arises that the dinuclear structure allows us to *systematically* modify important cellular processes such as protein recognition of damaged DNA from those induced by *cis*-DDP.

3. The (Pt,Pt) Interstrand Cross-Link.

cis-DDP, and indeed most alkylating agents, give rise to only 1,2-interstrand cross-links. In contrast, the sequencing work described above and previous studies[37,42] suggest that both the length and the flexibility of the diamine chain in dinuclear compounds allow the targeting of much larger DNA sequences for cross-link formation. For binding between guanines on opposite strands, in addition to 1,2 cross-links, 1,3 and 1,4 DNA interstrand cross-links may also form. In 1,3 and 1,4 cross-links the guanines are separated by one and two base pairs, respectively, whereas a 1,2 cross-link is formed from guanines on neighboring base pairs.[37]

Conformational Changes Caused by the Interstrand Cross-Link. An interesting demonstration of the differences between mononuclear and dinuclear complexes involves stabilization of Z-form DNA. Bis-

(platinum) complexes $[\{PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]^{2+}$ are especially efficient at inducing the B → Z transition in poly(dG.dC)–poly(dG.dC).[43] The effect of different adduct structures on conformational changes within a similar sequence may be appreciated by the fact that *cis*-DDP stabilizes B-form poly(dG.dC)–poly(dG.dC).[44,45] Studies with a series of dinuclear compounds (tetra-amine complexes capable of only electrostatic interactions and the formally monofunctional complex depicted in Fig. 3) have delineated the mechanistic scheme for Z-DNA formation shown in Fig. 6.[26,43] The interesting result emerges that bifunctional binding is not a prerequisite for the B → Z transition. Rather, bifunctional binding or interstrand cross-linking "locks" the DNA in the left-handed conformation. In agreement with this, ethidium bromide does *not* reverse the Z-conformation caused by the interstrand cross-linking agents.[46]

4. Cross-Linking of Platinated DNA to Repair Proteins.

The excision repair UVrABC complex[47,28] also recognizes bis(Pt)–DNA adducts formed by either tetrafunctional (2,2/c,c) or bifunctional (1,1/t,t) complexes. The polyfunctional nature of the bis(platinum) complexes suggested to us that the availability of multiple coordination sites (> 2) could be used to induce covalent cross-

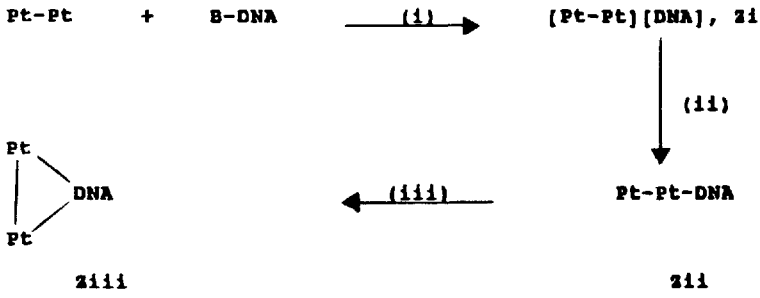

FIGURE 6 Proposed mechanism of Z-form DNA induction by dinuclear platinum complexes. Z_i, Z_{ii} and Z_{iii} refer to different forms of left-handed DNA as indicated by C.D. spectroscopy (Refs. 26 and 43). Thus, Z_i is induced by purely electrostatic interactions from tetra-amine bis(platinum) cations and Z_{ii} is induced by monofunctional binding from only one Pt unit of a bis(platinum) complex. Finally, Z_{iii} is caused by covalent binding of the second Pt unit resulting in bifunctional binding on the polynucleotide. Note that the cross-linked form (Z_{iii}) is irreversible.

linking of protein to platinated DNA. This possibility was recently confirmed for both homodinuclear (Pt,Pt) and heterodinuclear (Ru,Pt) complexes using a radiolabeled 49 bp DNA fragment combined with native and denaturing polyacrylamide gel electrophoresis.[28] The DNA lesion responsible for efficient protein–DNA cross-linking is most probably a DNA–DNA interstrand cross-link in which each metal atom is coordinated with one strand of the DNA helix (Fig. 7). The cross-linking efficiency is significantly greater than for mononuclear complexes such as *cis* and *trans*-DDP and suggests novel ways for designing specific DNA-protein cross-linking agents. The formation of ternary DNA–protein adducts could have significance in developing "suicide" agents capable of inactivating repair proteins as well as in the isolation of DNA-bound proteins from cells.

SUMMARY

The dinuclear structure produces an array of adducts structurally different from those obtainable from mononuclear complexes. Compared to the classical mononuclear complexes, the dinuclear complexes have considerable application from the point of view of the development of drugs as well as new and powerful probes of DNA structure. The chemistry we have developed allows for systematic exploration of the factors affecting specific binding. Besides the uses

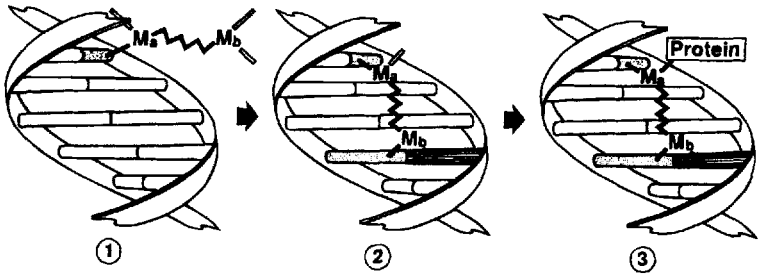

FIGURE 7 Scheme for formation of ternary Pt–DNA–protein cross-linking. Cross-linking of UVrAB proteins probably occurs through a pre-formed DNA–DNA interstrand cross-link (1 → 2 → 3). This mode of DNA–protein cross-linking is only available through a polyfunctional complex, such as a dinuclear species.

described above, the basic dinuclear structure has utility in anti-sense chemistry and in triple-helix formation.[41] Some similar approaches in dinuclear platinum chemistry have been published, altering both coordination sphere[48,49] and type and rigidity of the linker chain.[50–52] A dinuclear complex based on the intercalating Pt(terpy) unit and tethered to a Fe(EDTA) molecule[53] is simply a variation on the theme of intercalation plus strand breakage exemplified by the well-known methidium–Fe(EDTA) complexes.[54]

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