

platinum bound on the unlabeled strand. This difference is ascribed to the more extensive interactions, both covalent (Pt) and intercalative (acridine), of compound 1.

In summary, exonuclease III mapping of compound 1 binding to DNA has shown that the attached intercalator alters the binding pattern of the platinum moiety in a manner analogous to that of an externally added intercalator. The presence of the attached intercalator also allows detection of binding sites on the unlabeled strand.

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## BINDING OF CIS-PLATINUM COMPOUNDS TO NUCLEOBASES, NUCLEOTIDES AND OLIGONUCLEOTIDES

For a better understanding of the specific interactions of *cis*-platinum(II) and *cis*-platinum(IV) compounds with DNA, detailed studies of the binding of such Pt compounds to nucleobases,

nucleotides and oligonucleotides are of great interest [1].

Although it is now generally accepted that binding of platinum compounds has a kinetic preference to guanine N7 sites, other bindings do also occur and may play an important rôle under certain conditions [2]. Using 9-ethylguanine as a simple analog of the GMP part in DNA, it was possible to study Pt(II) binding to guanine N1 and the — unexpected — rapid isomerisation to the N7 binding mode at acid pH values. Studying reactions of Pt(IV) compounds with 9-methylhypoxanthine and 5'-GMP, the major products appeared to be N7-coordinated Pt(II) adducts, although in a few cases spectroscopic indications for Pt(IV) adducts were found. Although it is not yet clear whether the reduction occurs before, during or after the platinum coordination to 5'-GMP, these results support the idea that *in vivo* reduction is essential for the antitumor activity of potential Pt(IV) antitumor drugs. To obtain more information about the chelation and kinetics of the so-called «GNG-*cis*Pt chelates» (platinum bound to both G's with a non-coordinating nucleobase in between), the DNA-trinucleotides pGpGpG, GpApG and GpTpG were reacted with *cis*-PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub> (*cis*Pt). NMR studies indicate that the pGpGpG trimer yields only pGpGpG(N7(1),N7(3)) while GpApG gives 80% GpApG(N7(1),N7(3)) and 20% GpApG(N7(2),N7(3)). HPLC studies showed that this ratio is temperature independent. Reaction of the monofunctional platinum compound [Pt(dien)Cl]Cl with these two trimers gives 100% pGpGpG(N7(1)), while 30% GpApG(N7(1)) and 70% GpApG(N7(3)) was obtained in the second case. *cis*Pt reaction with GpTpG resulted in only one chelate: GpTpG(N7(1),N7(3)). Apparently a GG-chelate is preferred by *cis*Pt over a GNG-chelate, but if no neighbouring G is available after the first binding, kinetic preference determinates the ultimate chelate, *i.e.* binding to AG may occur.

*In vitro* studies concerning *cis*Pt-DNA interactions indicate that next to GG-, AG-chelation is most favoured [3]. This led to the study of the reactivity of *cis*Pt towards the decamer TpCpTpCpApGpTpCpTpC, and the stability of this decamer with its complement GpApG-

pApCpTpGpApGpA as compared to the unplatinated decamer duplex. Enzymatic degradation, atomic absorption spectroscopy together with HPLC showed that the AG-chelate is the major product.

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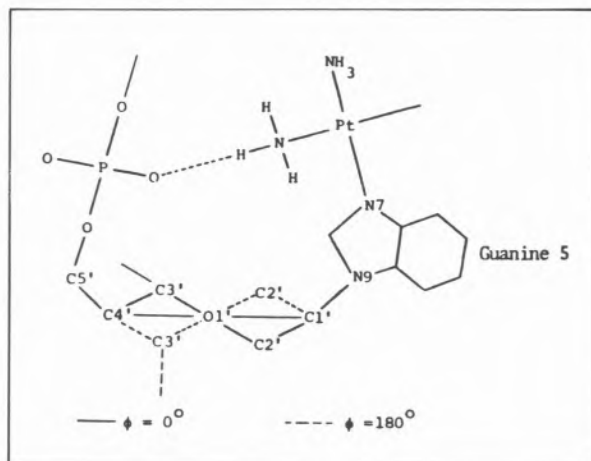
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## MOLECULAR MECHANICS CALCULATIONS ON *cis*-DIAMMINEDICHLOROPLATINUM(II) ADDUCTS OF TWO d(GpG)-CONTAINING OLIGONUCLEOTIDE DUPLEXES

There is increasing evidence that the antitumor drug *cis*-diamminedichloroplatinum(II) (*cis*-DDP) [1] binds predominantly to d(GpG) units of DNA

[2,3]. Since *cis*-DDP binding to DNA destroys substrate recognition for nucleases [3] and shortens the double helix [4], severe structural changes (e.g., unwinding) of DNA have been suggested [4]. On the other hand, NMR work on platinated octa- and decanucleotides, while confirming d(GpG)-Pt binding, offered evidence for duplex structure up to 28°C [5]. We have performed molecular mechanics calculations on two oligonucleotides, [d(GGCCGGCC)]<sub>2</sub> and d(TCTCGGTCTC)•d(GAGACCGAGA) in both A- and B-DNA conformations, as well as on adducts in which a [Pt(NH<sub>3</sub>)<sub>2</sub>]<sup>2+</sup> fragment is coordinated to the N7 atoms of adjacent guanosine residues. The main results of the calculations are: i) the 5'-end coordinated guanine is predicted to tilt out of the base stack, destroying at least one of the amino hydrogen bonds involved in GC base pairing and considerably weakening the imino hydrogen bond; ii) a hydrogen bond, formed between one ammine ligand of the platinum atom and the 5'-phosphate group of the d(pGpG) unit, is indicated for both A- and B-DNA. This hydrogen bond closes a ring (shown below) in which the 5'-sugar is constrained to either of two twisted conformations with phase angles [6] close to 0° or



180°, respectively; iii) in B-DNA models, the coordination of *cis*-[Pt(NH<sub>3</sub>)<sub>2</sub>]<sup>2+</sup> on a d(GpG) unit causes the 5'-guanosine to switch the sugar pucker to C(3')-endo. This conformation is stabilized by a stronger attraction between the platinum residue and the phosphate of d(GpG); iv) in B-DNA models, formation of a non-Watson-Crick inter-strand hydrogen bond between two guanines is