

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.

## ACKNOWLEDGEMENTS

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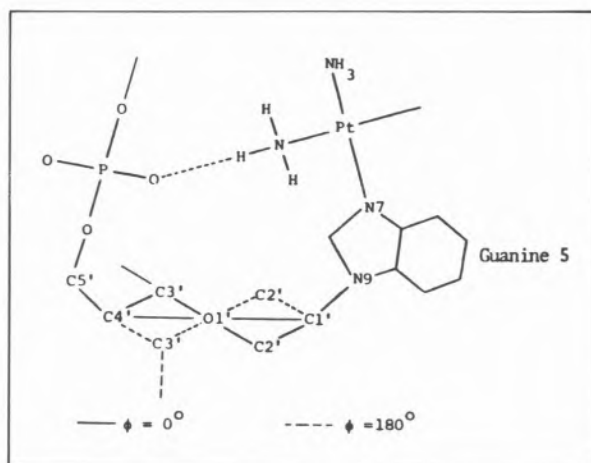
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## MOLECULAR MECHANICS CALCULATIONS ON *cis*-DIAMMINEDICHLOROPLATINUM(II) ADDUCTS OF TWO d(GpG)-CONTAINING OLIGONUCLEOTIDE DUPLEXES

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

indicated. Implications of these results for the interpretation of spectroscopic data on *cis*-DDP-oligonucleotide adducts are discussed.

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## CHIRAL DISCRIMINATION IN THE COVALENT BINDING OF BIS(PHENANTHROLINE)RUTHENIUM(II) COMPLEXES TO DNA

Isomers of bis(phenanthroline)dichlororuthenium(II) display striking enantioselectivity in binding covalently to right-handed B-DNA. Incubation of racemic (phen)<sub>2</sub>RuCl<sub>2</sub> with calf thymus DNA yields ruthenium-bound complexes having a maximum binding ratio of 0.06 ruthenium per nucleotide. Much as for the analogous dichlorodiammineplatinum(II) complexes, binding studies with various synthetic polymers reveal a preference for guanine. Circular dichroism of the supernatants following ethanol precipitation of the ruthenium-DNA complexes show substantial optical activity and, importantly, a sequence dependence in the level of enrichment. Interestingly, in contrast to stereoselective intercalation, covalent binding of (phen)<sub>2</sub>Ru<sup>2+</sup> to simple B-DNA appears to favor the lambda isomer. Coordination of the (phen)<sub>2</sub>Ru<sup>2+</sup> moiety to the helix seems to require a structure of complementary symmetry. Curiously, incubation with poly d(GC) or Z-form polymers leads to the preferential covalent binding of the opposite (delta) ruthenium isomer. The conformation and sequence specificity of these chiral octahedral complexes suggests the possible utility of chiral bis(amine) complexes in DNA site-specific drug design.