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INTERACTIONS OF WATER SOLUBLE PORPHYRINS WITH Z-POLY(dG-dC)

Two water soluble porphyrins, tetrakis(4-*N*-methylpyridyl)porphine and its copper(II) derivative (H₂TMpyP and CuTMpyP, respectively) have

been shown to interact with Z-poly(dG-dC) and to convert it back to the B-form. The fraction of Z-poly(dG-dC) remaining in a mixture depends linearly on the concentration of porphyrin per nucleotide base pair. Thus, there appears to be no "drug-drug" interaction in the conversion.

The kinetics of the conversion of Z- to B-DNA were studied via circular dichroism and ultraviolet absorption. The kinetics are biphasic and independent of porphyrin concentration until near-saturation conditions are approached. A very high order dependence on porphyrin ($n > 10$) is obtained under these conditions.

The kinetics of interaction of the porphyrins with Z-DNA were studied via stopped-flow with monitoring in the Soret region. At comparable concentrations of porphyrin and base pairs, the kinetic profile is monophasic and simple first order. As the concentration of base pairs is raised, the kinetics become second-order. These results will be interpreted in the poster.

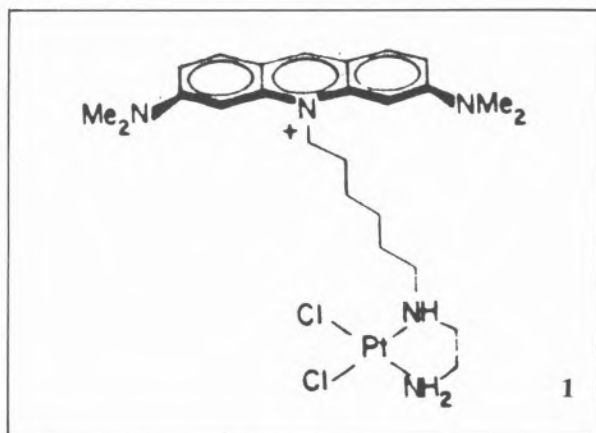


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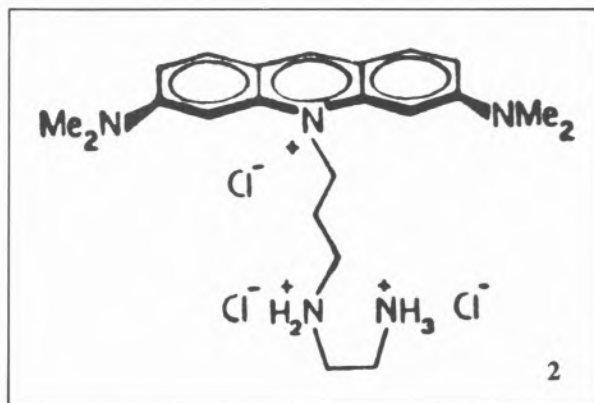
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EFFECTS OF LINKED AND EXTERNAL INTERCALATORS ON THE BINDING OF PLATINUM ANTITUMOR DRUGS TO DNA

Previously we showed that DNA intercalators, such as ethidium bromide, could alter the mode and position of binding of the platinum antitumor drug, *cis*-diamminedichloroplatinum(II) (*cis*-DDP), to the double helix [1]. These results led us to synthesize a molecule with an intercalative drug linked to a platinum complex by a hexamethylene chain [2], **1**, as a more sensitive probe of these effects. We have more recently synthe-



sized the related platinum binding ligand, **2**, in which a trimethylene chain links the acridine orange and ethylenediamine portions of the molecule [3]. When attached to platinum this new compound will allow us to probe the effects of chain length on the interaction of both ends of the molecule with DNA.



Exonuclease III mapping [4] was used to obtain information about the DNA binding sites of compound **1** on the same 165 base-pair (bp) restriction fragment from plasmid pBR322 employed in our previous *cis*-DDP/DNA mapping experiments [1a,4]. As a control we studied the binding sites of dichloroethylenediamineplatinum(II), [Pt(en)Cl₂], which is closely related to **1**, on the 165 bp fragment. We find that [Pt(en)Cl₂] binds to this restriction fragment at virtually the same oligo(dG) regions as does *cis*-DDP. Data for compound **1** also reveal binding at the same oligo(dG) sequences. Two other interesting results are observed, however. The 165 bp fragment contains a G₆CG₂ sequence near the 3'-end which is not observed as an exonuclease III stop at low levels of bound *cis*-DDP or [Pt(en)Cl₂] per nucleotide. Only when bound in the presence of the intercalator ethidium bromide are low levels of *cis*-DDP able to stop Exo III digestion at this sequence. Low levels of compound **1**, bound in the absence of ethidium bromide, definitely show stopping at this site. Thus the attached intercalator enhances platinum binding in this region in a manner similar to that by which externally added ethidium bromide enhances *cis*-DDP binding. This result probably involves relaxation of the steric requirements for platinum binding at this sequence through the conformational changes induced by intercalator binding to the DNA.

The other intriguing result is that additional stops are seen with compound **1** that correlate with (dG)₂ sequences on the unlabeled strand. For *cis*-DDP binding to the 165 bp restriction fragment, Exo III was found to map only those oligo(dG) binding sites on the labeled strand. The presence of the linked intercalator facilitates detection of