NMR Study of the Intercalation Geometry of a Psoralen in Oligonucleotides

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Psoralens have been used for skin photosensitization in the clinical treatment of skin deseases and as crosslinking probes in nucleic acid research. Dark binding of the drugs to DNA by intercalation has been postulated as an important intermediate in the photochemical reactions underlying the biological activities (1). We investigated the dark interaction of 8-Methoxy-Psoralen (MOP) with $d(pApT)_4$ by 270 MHz proton NMR experiments. As a result we propose an unsymmetrical intercalation model and discuss its photochemical implications.
The six proton resonances of MOP in the presence of excess oligonucleotide were identified by a difference technique based on the fact that at low temperatures MOP can be kept in aqueous solution for a limited time of some hours, after which it precipitates. The double helical oligomer at low temperatures, $0 - 15^{0}$, shifts the MOP resonances to high field. The shifts for the 6 protons vary between 0.3 and 0.9 ppm. The magnitude of the shifts suggests intercalation of MOP between the base pairs (2).

The experimental intercalation shifts were compared to theoretical ring current shifts from the four adjacent bases (3) arranged parallel to the drug 3.4 A above and below it according to various theoretical and experimental base overlap projections reported in the literature for intercalation in B-DNA (4) and ribodinucleotides (5, 6). Invariably unsymmetrical intercalation leads to a much better fit of the experimental shifts than the symmetrical arrangements published for other drugs (2, 4, 6). In our unsymmetrical model the 4', 5'- double bond of MOP is stacked between the bases close to the double bond of the thymine whereas the 3, 4-double bond of MOP sticks out from the bases and is far removed from any thymine double bond. This position of the drug may be responsible for the preferential increase of the yield of 4', 5'- over 3, 4-photoadducts with DNA as compared to free thymine (7).

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