



## PULSE RADIOLYSIS STUDIES ON DNA-BINDING RADIOPROTECTORS

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Hoechst 33342 and newly-synthesised analogues exhibit radioprotective activity in cultured cells and *in vivo*, as described in accompanying abstracts. These minor groove binding ligands bind at discreet sites in DNA, characterised by 3 to 4 consecutive AT base pairs, and DNA sequencing studies have shown focussed radioprotection at these binding sites (1). There is evidence that the bound ligands also confer more "global" protection including the intervening DNA between the binding sites (2). The observed focussed radioprotection could be explained by H-atom donation from the ligand to radiation-induced carbon-centred deoxyribosyl radicals (1), but this mechanism is unlikely to account for the global radioprotection. We now report pulse radiolysis studies on another possible mechanism, namely reduction of transient radiation-induced oxidising species on DNA by the ligand, which is consistent with the report of reduction of  $G^{•+}$  by TMPD (3). Oxidation of deoxyguanosine (dG) by  $Br_2^{•-}$ , produced by radiolysis of  $Br^-$  in  $N_2O$ -saturated solutions, in the presence of Hoechst 33342 results in the appearance of a transient ligand species which is kinetically resolvable from that obtained from direct oxidation of Hoechst 33342 by  $Br_2^{•-}$ . A plot of reaction rate *versus* ligand concentration indicates that the rate constant for reduction of  $G^{•+}$  is approximately  $3 \times 10^8 \text{ dm}^3 \text{ M}^{-1} \text{ sec}^{-1}$ . Similar experiments with DNA, rather than dG, also revealed a transient species corresponding to oxidation of the ligand, but the absolute rate of oxidation was considerably slower for the DNA-bound ligand compared to that for oxidation of the free ligand by  $G^{•+}$ . These results are clearly consistent with the proposed mechanism of radioprotection by Hoechst 33342 and its analogues, moreover, pulse radiolysis may provide a very useful endpoint for screening new analogues, as a preliminary to radiobiological evaluation.

References

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