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SECONDARY REACTION IN IRRADIATED NUCLEOTIDES: POSSIBLE SIGNIFICANCE FOR CHEMICAL "REPAIR" MECHANISMS

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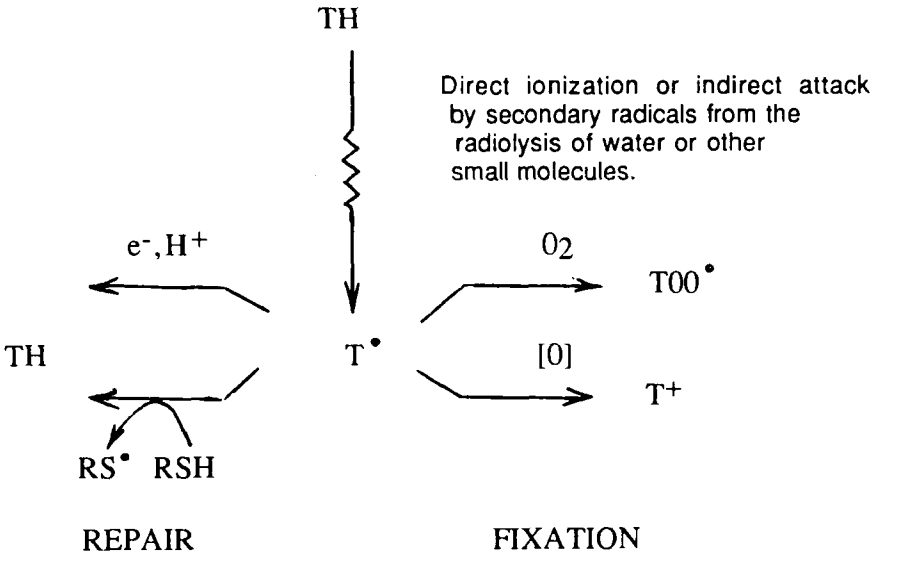
The sequence of events leading to the biological effects of ionizing radiation includes a chemical phase. This phase is characterized by the appearance of ionized molecules and free radicals. A simple competition model describes the consequences of the chemical events in terms of free radicals formed in critical cellular molecules such as DNA (TH):



SCHEME I

The allure of the model is its simplicity, the fact that it is kinetically feasible[1] and that it could account for the oxygen effect in radiobiology.[2] Furthermore, the model has been of value in the development of hypoxic cell radiosensitizers.[2] However, in principle, the model has a serious shortcoming on the repair side. Reduction by hydrogen atom or electron donation to a radical formed at a chiral centre in a target molecule can lead to inversion of configuration. This is not repair but misrepair of damage. There are three such centres on the sugar phosphate backbone of DNA at C-1', C-3' and C-4'.

This aspect of DNA free radical chemistry has received very little attention in the literature. Cadet *et al.*[3] have reported that epimerization occurs at C-1' in frozen

aqueous solutions of nucleosides but the addition of the hydrogen atom donating thiols have no effect on the process. Kochetkov *et al.* had earlier reported that epimerization occurs in irradiated frozen aqueous solutions of carbohydrates and proposed a redox mechanism for the process.[4] Gold and coworkers studied radiation-induced hydrogen atom exchange and epimerization reactions in polyols in tritiated water. They concluded that sequential hydroxyl radical and hydrated electron attack within spurs created by β-particle ionization of water was the underlying mechanism of epimerization. In a microcosm this would be analogous to the free radical "repair" mechanism incorporated in the competition model described above. Raleigh *et al.*[6] and Lesiak and Wheeler[7] have independently reported that epimerization occurs in dilute solutions of polyadenylic acids irradiated with Co-60 gamma rays.

Solutions containing 0.7 mg/mL of polyadenylic acid (poly A) at pH 7.0 in deionized and purified (Barnstead NANOpure system) distilled water were irradiated up to 1000 Gy with Co-60 gamma rays. The solutions were deaerated by bubbling with either N_2 or N_2O. The irradiated poly A was hydrolyzed to the nucleoside level with nuclease P1 and alkaline phosphatase. The mixture of nucleosides was analyzed with coupled high performance liquid chromatography — mass spectroscopy.[8] A number of radiolysis products of poly A were identified including the C-1' epimerization product, α-adenosine ($G = 0.3$ under N_2 or N_2O). The relatively high yield of α-adenosine was somewhat surprising given that it appears to be formed by sequential, single electron oxidation and reduction at the same carbon atom in the ribose ring. This is reminiscent of the formation of 8,5'-cyclo-5'-deoxy-5'-dihydrocycloadenosine by electron attack on 8,5'-cycloadenosine-5'-monophosphate in the absence of oxygen.[8,9]

We shall discuss the analogy between the formation of α-adenosine and 8.5'-cyclo-5'-deoxy-5'-dihydroadenosine and attempt to account for what appears to be sequential radical attack at a single carbon atom in the precursors to these two products. We believe that the interesting mechanistic problem of how radiation-induced epimerization occurs has important implications not only for radiation damage to nucleic acids but also the the competition model of radiation damage and repair in cells irradiated with ionizing radiation.

References

1. Michael, B.D., Held, K.D. and Harrop, H.A. Biological aspects of DNA radioprotection. In *Radioprotectors and Anticarcinogens*.Nygaard, O.F. and Simic, M.G. (eds.), Academic Press, New York, pp. 325, (1983).
2. Adams, G.E. Molecular mechanisms of cellular radiosensitization and protection. In *Radiation Protection and Sensitization*. Moroson, H.L. and Quintiliani, M. (eds.), Taylor and Francis, London, pp. 3, (1970).
3. Cadet, J., Berger, M. and Shaw, A. The radiation chemistry of the purine bases within DNA and related model compounds. In *Mechanisms of DNA Damage and Repair*. Simic, M.G., Grossman, L. and Upton, A.C. (eds.), Plenum Press, New York, pp. 69, (1986).
4. Kochetkov, N.K., Kudrjashov, L.I., Chlenov, M.A. and Livertovskaya, T. Ya. the epimerization of monosaccharides by γ-irradiation in frozen and aqueous solutions. *Carbohydr. Res.*, **28**, 86, (1973).
5. Gold, V. and McAdam, M.E. Radiation-induced organic hydrogen isotope exchange reactions in aqueous solution. *Acc. Chem. Res.*, **11**, 36, (1978).
6. Raleigh, J.A., Fuciarelli, A.F. and Kulatunga, C.R. Potential limitation to hydrogen atom donation as a mechanism of repair in chemical models of radiation damage. In *Anticarcinogenesis and Radiation Protection*. Cerutti, P.A., Nygaard, O.F. and Simic, M.G. (eds.), Plenum Press, New York, pp. 33, (1987).
7. Lesiak, K.B. and Wheeler, K.T. Radiation damage to deoxyadenosine in solutions of double stranded

poly (dA.T) *Abstract (Ei-2) Radiation Research Society, Thirty-Fifth Annual Meeting, Atlanta, Georgia, February 21-26, 1987,* (1987).

8. Alexander, A.J., Kebarle, P., Fuciarelli, A.F. and Raleigh, J.A. Characterization of radiation-induced damage to polyadenylic acid using high performance liquid chromatography/tandem mass spectrometry. *Anal. Chem.*, **59**,2484, (1987).
9. Raleigh, J.A. and Whitehouse, R. Evidence for reductive radiolytic dephosphorylation in the nucleotide analogue 8,5'-cycloadenosine 5'-monophosphate. *J. Chem. Soc., Chem. Commun.*, 305, (1975).