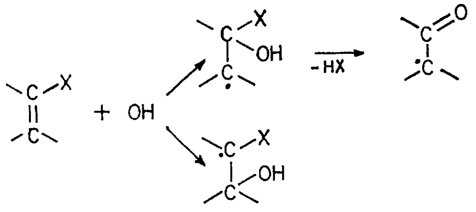
Oxidative Denitration of 5-Nitrouracil and 5-Nitro-9-furoic acid by Hydroxy Radicals

By Pedatsur Neta*
(*Radiation Research Laboratories and Center for Special Studies, Mellon Institute of Science, Carnegie Mellon University, Pittsburgh, Pennsylvania* 15213)

and Clive L. Greenstock
(*Medical Biophysics Branch, Whiteshell Nuclear Research Establishment, Atomic Energy of Canada Limited, Pinawa, Manitoba Canada*)

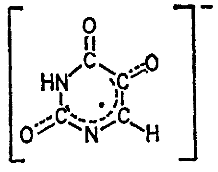
Summary The radicals initially produced by addition of OH to the carbon atom bearing the nitro-group in 5-nitrouracil and 5-nitro-2-furoic acid have been found to undergo rapid elimination of nitrous acid, and the resulting radicals are identical to those produced by oxidative debromination of the corresponding bromo-derivatives.

Addition of OH radicals to α-halogenated double bonds has been found to result in a partial dehalogenation *via* the general mechanism in Scheme 1. These reactions have been studied for 5-halogeno-uracils[1,2] and for chlorinated ethylenes.[3] We report here an oxidative denitration by a similar mechanism. We studied 5-nitrouracil and 5-nitro-2-furoic acid because of their biological importance as possible radiosensitizers. E.s.r. and kinetic spectrophotometric pulse-radiolysis experiments have been carried out with aqueous solutions of these compounds under conditions where only OH radicals are present in high yield to react with the solutes. The resulting radicals have been identified from their e.s.r. and optical absorption spectra by comparison with those obtained from the corresponding bromo-derivatives. The experimental details are similar to those described previously.[2,4]

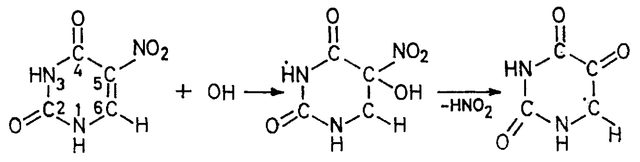


Scheme 1

The e.s.r. spectrum recorded with an irradiated neutral aqueous solution of 5-nitrouracil (1×10^{-3} M and saturated with N_2O) was that of one radical. The e.s.r. parameters determined in the present study for radical (A) are: $g = 2{\cdot}00471$, $a_1^{\mathrm{N}} = 2{\cdot}21$, $a_3^{\mathrm{N}} = 1{\cdot}105$, $a_3^{\mathrm{H}} = 0{\cdot}20$, and $a_6^{\mathrm{H}} = 4{\cdot}96$ G, and are in very good agreement with those determined previously[2] for all the 5-halogeno-uracils and can be assigned to the same radical. The mechanism of formation is reasonably attributed to the sequence in Scheme 2. The resulting radical exists in neutral solution in the singly dissociated form[2] and it undergoes another proton dissociation at pH > 10.



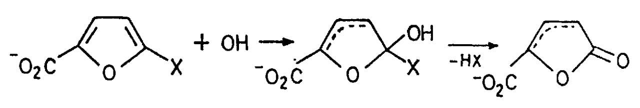
(A)



Scheme 2

The optical absorption spectrum obtained immediately after the reaction of OH with 5-nitrouracil was also very similar to that for 5-bromouracil. The rate of increase of this absorption and the rate of destruction of the parent compound absorption both give a rate constant of $6{\cdot}5 \pm 1 \times 10^{9}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for the reaction of OH with 5-nitrouracil, which shows that elimination of HNO_2 is very rapid. However, the yields of the radicals observed with the nitro- and the bromo-compounds are different. Because OH can add to either C-5 or C-6, oxidative dehalogenation and denitration account for only a portion of the OH reactions. In the case of 5-bromouracil this portion was found to be 0·55.[1] By comparison with this result the efficiency of oxidative denitration of 5-nitrouracil is found to be 0·25.

Similar experiments have been carried out with 5-bromo-2-furoic acid and 5-nitro-2-furoic acid in neutral solutions where the carboxy-group is dissociated. In both cases the observed e.s.r. spectrum can be analysed in terms of two proton hyperfine constants of 9·67 and 1·14 G with $g = 2{\cdot}00361$. These parameters can be reasonably[5] assigned to an allyl-type radical formed, respectively, by oxidative dehalogenation or denitration (Scheme 3; X = Br or NO_2).



Scheme 3

The transient absorption spectra obtained with solutions of these two compounds are also similar. The relative efficiency of the process, *i.e.* the fraction of OH which add to the C-5 position compared with all other OH reactions, was determined from the optical absorbance, and denitration was found to be as efficient as debromination.

Oxidative denitration is of major importance in compounds such as those reported here and its efficiency is equal to the portion of OH which add to the carbon atom bearing the *nitro*-group. The loss of nitrous acid is found to be a fast process. Addition to other positions does not appear to result in denitration. A small loss of the nitro-group from nitroaromatic compounds reacting with OH has been previously reported[6,7] and we suggest that this can also be explained by the same mechanism. The low yield in the nitroaromatics is, therefore, a direct result of the larger number of positions susceptible to OH attack, as compared with 5-nitrouracil or 5-nitrofuroic acid.

This work was supported in part by the U.S. Atomic Energy Commission and by Atomic Energy of Canada Limited.

(*Received*, 15*th January* **1973**; *Com.* 044.)

---

[1] K. M. Bansal, L. K. Patterson, and R. H. Schuler, *J. Phys. Chem.*, 1972, **76**, 2386.

[2] P. Neta, *J. Phys. Chem.*, 1972, **76**, 2399.

[3] R. Köster and K.-D. Asmus, *Z. Naturforsch.*, 1971, **26**, 1108.

[4] J. W. Hunt, C. L. Greenstock, and M. J. Bronskill, *Internat. J. Radiation Phys. Chem.*, 1972, **4**, 87.

[5] R. H. Schuler, G. P. Laroff, and R. W. Fessenden, *J. Phys. Chem.*, 1973, **77**, 456.

[6] J. H. Fendler and G. L. Gasowski, *J. Org. Chem.*, 1968, **33**, 1865.

[7] K. Eiben, D. Schulte-Frohlinde, C. Suarez, and H. Zorn, *Internat. J. Radiation Phys. Chem.*, 1971, **3**, 409.