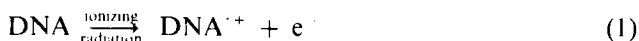


THE SO_4^- -INDUCED OXIDATION OF 1,3,6-TRIMETHYLURACIL AND 1,3-DIMETHYLTHYMINE BY POTASSIUM PEROXODISULPHATE AND OXYGEN IN AQUEOUS SOLUTION: AN INTERESTING CONTRAST

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In living cells, DNA damage may be caused either by the "direct effect" (energy absorbed by the DNA) or the "indirect effect" (energy absorbed by the water surrounding the DNA). On a model level the indirect effect can be studied by irradiating dilute aqueous solutions of DNA. The direct effect is more difficult to mimic. One major event in the direct effect must be the formation of radical cations (reaction 1).



One of the most powerful one-electron oxidants is the SO_4^- radical whose reaction with the DNA nucleobases may lead to the formation of the corresponding nucleobase radical cations.¹ The SO_4^- radical is most conveniently formed by reacting the solvated electron (generated in the radiolysis of water) with peroxodisulphate anion. The OH radical which is also formed during radiolysis can be scavenged by t-butanol.¹

The reaction of the sulphate radical with uracil leads to an N(1)-centred radical which may result from the deprotonation of an intermediate radical cation.² In 1,3-dimethyluracil the first product identified by pulse radiolysis is the C(5)-OH-6-yl radical, whose formation can be rationalized assuming that water reacts with the intermediate radical cation at the C(5) position.³ At this point a cautionary remark is in order. In the case of the reaction of the sulphate radical with 1,3-dimethylthymine a short-lived sulphate radical adduct could be ascertained by pulse conductometry (Deeble, private communication). Thus, a sulphate radical adduct might be a precursor common to all the species actually observed. This would be in line with the detection of such adduct radicals in other olefinic systems.⁴ Moreover, the postulate of an intermediate radical cation finds support in the observation that in the case of 1,3,5,6-tetramethyluracil a relatively long-lived radical cation (Steenken, to be published) is formed.⁵

We have now extended our studies to 1,3-dimethylthymine (1,3-Me₂T) and to 1,3,6-trimethyluracil (1,3,6-Me₃U). Both react very rapidly with SO_4^- ($k = 5 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$). While 1,3,6-Me₃U resembles 1,3-dimethyluracil,³ 1,3-Me₂T behaves very differently:

In the case of 1,3,6-Me₃U, a chain reaction sets in which results in the formation of sulphuric acid, the glycols (2/3) and the isobarbituric acid (1/3). Typically at $[1,3,6\text{-Me}_3\text{U}] = 5 \times 10^4$, $[\text{S}_2\text{O}_8^{2-}] = 4 \times 10^{-2}$, and $[\text{t-BuOH}] = 10^{-2} \text{ mol dm}^{-3}$, $G(\text{H}^+) = 22 \mu\text{mol J}^{-1}$ is found at a dose rate of 0.0022 Gy s^{-1} . The main features of

this chain reaction are interpreted as follows: The sulphate radical adds to 1,3,6-Me₃U and the adduct rapidly loses sulphate anion, thereby forming the 1,3,6-Me₃U radical cation. This reacts with water yielding a proton and the reducing 1,3,6-Me₃U-5-OH-6-yl radical which reacts with peroxodisulphate and continues the chain. In this oxidation process a carbocation is formed which can either react with water yielding the glycols, or deprotonate yielding the isobarbituric acid.

Now to the 1,3-Me₂T system. No chain reaction of any significance is induced. In the presence of oxygen an allyl-type radical can be trapped, as shown by the subsequent formation of 1,3-dimethyl-5-hydroxymethyluracil ($G = 0.03 \mu\text{mol J}^{-1}$) and 1,3-dimethyl-5-formyluracil ($G = 0.27 \mu\text{mol J}^{-1}$). Corresponding products are not observed in the 1,3,6-Me₃U system. It is concluded that in contrast to the 1,3,6-Me₃U radical cation, the 1,3-Me₂T radical cation deprotonates efficiently at C(5)-methyl, apart from also being able to react with water.

It is recalled that our results are supported by experiments where the radical cation of thymidine was produced with help of photoexcited menadione.⁶ Again the radical at C(5)-methyl is a major intermediate.

Quantum-chemical model calculations (undertaken with uracil, thymine and 6-methyluracil) show why these two isomers should behave the way they do. The C(5)-methylsubstituted radical cation should differ from the C(6)-methylsubstituted one in the following respects:

- 1) The tendency to undergo deprotonation should be greater for the methyl group substituted at C(5), than at C(6).
- 2) The reactivity with respect to water addition (to form the OH-adduct radical upon deprotonation of the hydrated radical cation) should be greater in the case of the C(6)-methyl compound than for the thymine compound. Moreover, the selectivity of this hydration reaction in favour of water addition at C(5) vs. C(6) should be greater in the case of the C(6)-methyl compound than in the substituted thymine.

In the irradiation of DNA in cells, 5-hydroxymethyluracil has been found among the products.⁷ Our results suggest that it may well be possible that this product arises from the direct effect. In comparison with the radical cation route. OH radical attack produces only a low yield of C(5)-methyl radicals (Schuchmann, Wagner and von Sonntag, unpublished results).

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