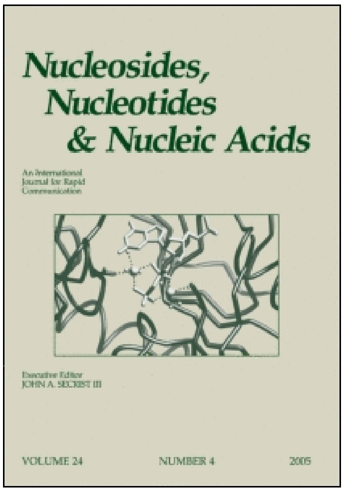

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Spontaneous Cleavage of Single and Double Stranded 4'-DNA Radicals Under Aerobic Conditions

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SPONTANEOUS CLEAVAGE OF SINGLE AND DOUBLE STRANDED 4'-DNA RADICALS UNDER AEROBIC CONDITIONS

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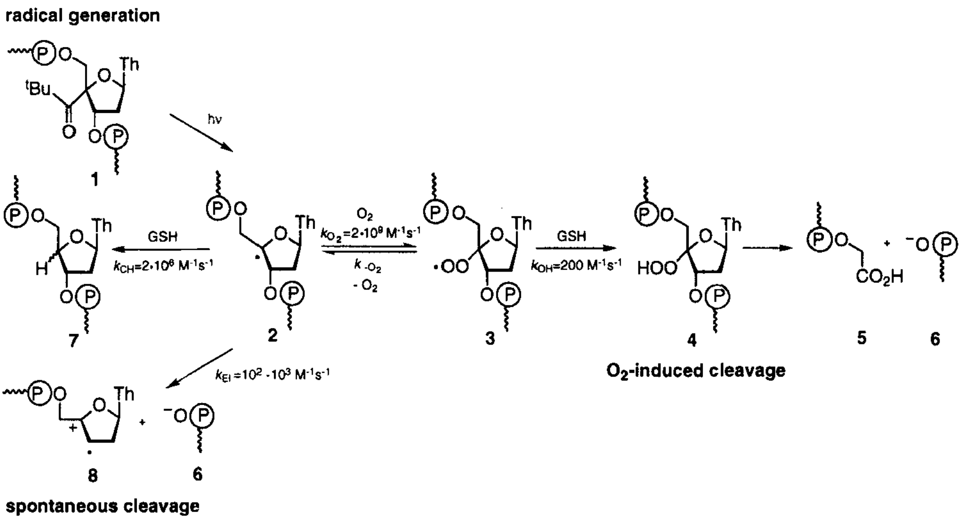
ABSTRACT: The O_2-induced strand scission of 4'-DNA radicals is initiated by a reversible O_2 addition reaction. The rate coefficient of the O_2 release from the 4'-DNA peroxyl radical is 1.00 s^{-1} in single strands and 0.05 s^{-1} in double strands at 20°C. Because of this reversibility, an O_2-dependent strand cleavage occurs only in the presence of H-donors which trap the 4'-DNA peroxyl radicals yielding DNA hydroperoxides. At very low H-donor concentrations the strand scission is the result of an O_2-independent, spontaneous reaction even under aerobic conditions.

Recently we described the synthesis of 4'-pivaloylthymidine and its incorporation into DNA. 4'-DNA radical **2** can be generated selectively by photolysis of the modified oligonucleotide **1**.[2] We have already determined the spontaneous cleavage rate k_{EI} of single stranded 4'-DNA radicals to be 10^3 s^{-1} and that of double stranded 4'-DNA radicals to be 10^2 s^{-1} under anaerobic conditions.[3] We have now measured the rate of formation of the O_2-dependent products, 5'-phosphate **6** and 3'-phosphoglycolate **5**, by pseudo-first order competition experiments with glutathione (GSH) under aerobic conditions with single[4] and double stranded DNA. We found that the O_2-induced strand scission of 4'-DNA radicals is initiated by a reversible O_2 addition (Scheme). The long-lived peroxylradical **3** is either trapped by GSH with $k_{OH} = 200\ M^{-1}s^{-1}$ to hydroperoxide **4** which via a Criegee-rearrangement forms 5'-phosphate **6** and 3'-phosphoglycolate **5** or it goes back to the 4'-radical **2** with $k_{-O_2} = 1.00\ s^{-1}$ for single and with 0.05 s^{-1} for double stranded DNA. As a consequence of this reversibility, the O_2-induced cleavage (**2** + $O_2 \rightarrow$ **3** + GSH $\rightarrow$ **4** $\rightarrow$ **5** + **6**) needs a sufficiently high amount of H-donor in order to trap the peroxylradical **3**.



At low H-donor concentrations the H-trap to the hydroperoxide **4** is so slow that the spontaneous cleavage reaction (**2** → **8** + **6**) can become dominant even under aerobic conditions. Because the O_2 elimination (**3** → **2** + O_2) is 20 times slower in double than in single stranded 4'-radicals **2**, less GSH is needed in double strands to favor the spontaneous cleavage. Obviously, the importance of oxidative cleavage also depends on the O_2 concentration. Since the nucleus can be a poorly oxygenated cellular compartment the spontaneous cleavage of single and double stranded 4'-DNA radicals is more significant in biological systems than assumed until now.

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