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## Nucleosides, Nucleotides and Nucleic Acids

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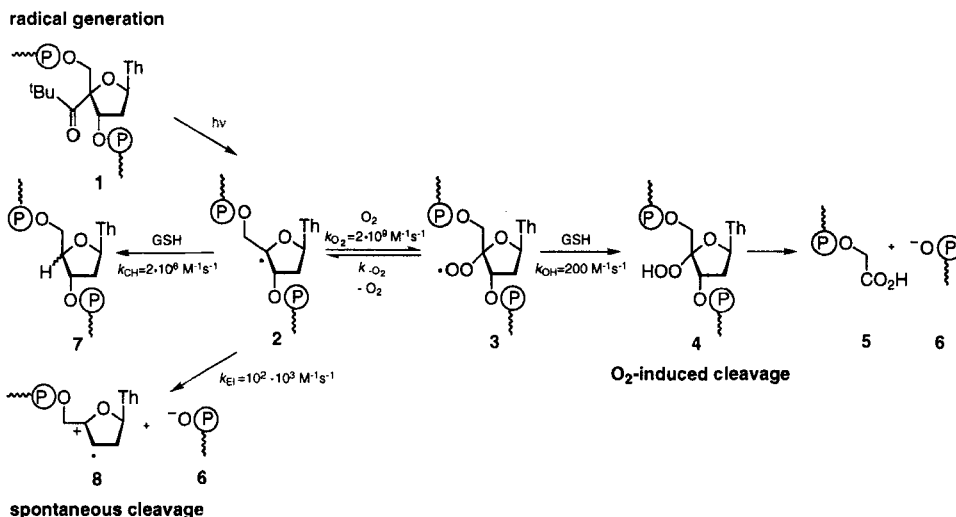
## SPONTANEOUS CLEAVAGE OF SINGLE AND DOUBLE STRANDED 4'-DNA RADICALS UNDER AEROBIC CONDITIONS

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**ABSTRACT:** The O<sub>2</sub>-induced strand scission of 4'-DNA radicals is initiated by a reversible O<sub>2</sub> addition reaction. The rate coefficient of the O<sub>2</sub> release from the 4'-DNA peroxy radical is 1.00 s<sup>-1</sup> in single strands and 0.05 s<sup>-1</sup> in double strands at 20°C. Because of this reversibility, an O<sub>2</sub>-dependent strand cleavage occurs only in the presence of H-donors which trap the 4'-DNA peroxy radicals yielding DNA hydroperoxides. At very low H-donor concentrations the strand scission is the result of an O<sub>2</sub>-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**.<sup>[2]</sup> We have already determined the spontaneous cleavage rate  $k_{EI}$  of single stranded 4'-DNA radicals to be 10<sup>3</sup> s<sup>-1</sup> and that of double stranded 4'-DNA radicals to be 10<sup>2</sup> s<sup>-1</sup> under anaerobic conditions.<sup>[3]</sup> We have now measured the rate of formation of the O<sub>2</sub>-dependent products, 5'-phosphate **6** and 3'-phosphoglycolate **5**, by pseudo-first order competition experiments with glutathione (GSH) under aerobic conditions with single<sup>[4]</sup> and double stranded DNA. We found that the O<sub>2</sub>-induced strand scission of 4'-DNA radicals is initiated by a reversible O<sub>2</sub> addition (Scheme). The long-lived peroxy radical **3** is either trapped by GSH with  $k_{OH} = 200 \text{ M}^{-1}\text{s}^{-1}$  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  $k_{O_2} = 1.00 \text{ s}^{-1}$  for single and with 0.05 s<sup>-1</sup> for double stranded DNA. As a consequence of this reversibility, the O<sub>2</sub>-induced cleavage (**2** + O<sub>2</sub> → **3** + GSH → **4** → **5** + **6**) needs a sufficiently high amount of H-donor in order to trap the peroxy radical **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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