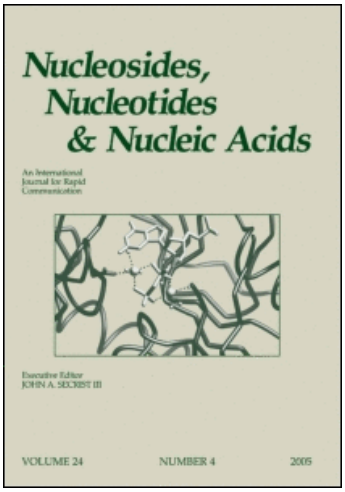

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Differences Between 4'-RNA and 4'-DNA Radicals During Anaerobic Strand Cleavage

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DIFFERENCES BETWEEN 4'-RNA and 4'-DNA RADICALS DURING ANAEROBIC STRAND CLEAVAGE

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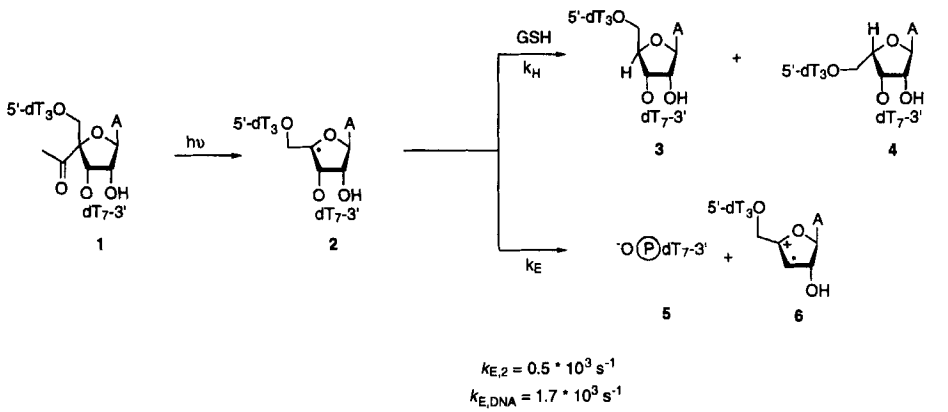
ABSTRACT: The radical-induced RNA cleavage is less efficient than that of DNA. The selectively generated 4'-ribonucleotide radicals show that the 2'-OH group decreases the rate of spontaneous cleavage k_E.

The mechanism of DNA strand cleavage involving 4'-DNA radicals has been elucidated to a large extent in recent years.[1] Under anaerobic conditions, a spontaneous strand cleavage takes place whereby a heterolytic C,O-bond scission at C–3' leads to the 5'-phosphate as stable cleavage product.

The mechanism of the corresponding RNA cleavage has been hardly investigated. Nevertheless, studies by Hecht[2] have shown that bleomycin, which generates 4'-nucleotide radicals, cleaves RNA slower than DNA. Since bleomycin binds better to t-RNA[3] than to DNA, the difference in cleavage efficiency might be explained by a difference in reactivity of both 4'-oligonucleotide radicals. In order to prove this, we have synthesized an oligonucleotide **1** in which one ribonucleotide carries an acetyl group at position C–4'. This compound is a precursor of 4'-ribonucleotide radicals **2** in analogy to the photolysis experiments that were carried out with 4'-acylated deoxyribonucleotides.[4]

In order to measure the rate of spontaneous strand cleavage, the modified oligomer was photolyzed to the 4'-RNA radical **2** and trapped with an excess of glutathione diethyl ester (GSH) (Scheme 1). The ratio of the rate constants k_H/k_E was obtained from the dependence of the product mixture (**3**+**4**)/**5** on the GSH concentration. With a H-abstraction rate $k_H = 1.0 \cdot 10^7$ $M^{-1}s^{-1}$ [5] the cleavage rate k_E of the 4'-ribonucleotide radical **2** of $0.5 \cdot 10^3$ s^{-1} was determined. The cleavage rate of the corresponding 4'-DNA radical $k_E = 1.7 \cdot 10^3$ $M^{-1}s^{-1}$ was more than 3 times faster.

Scheme 1



This decrease of the cleavage rate of 4'-ribonucleotide radicals can be interpreted by a destabilizing effect of the additional OH-group on the radical cation **6**. Nevertheless, this effect is very small and we assume that the oligomeric radical cation is probably so well solvated by water that the introduction of a 2'-OH group exerts only a slight destabilizing effect on the transition state of the reaction.

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