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Harald Strittmatter^a; Urs Schwitter^a; Bernd Giese^a

^a Institut für Organische Chemie, Basel, (Switzerland)

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

Harald Strittmatter, Urs Schwitter and Bernd Giese*

Institut für Organische Chemie, St. Johannis-Ring 19, 4056 Basel (Switzerland)

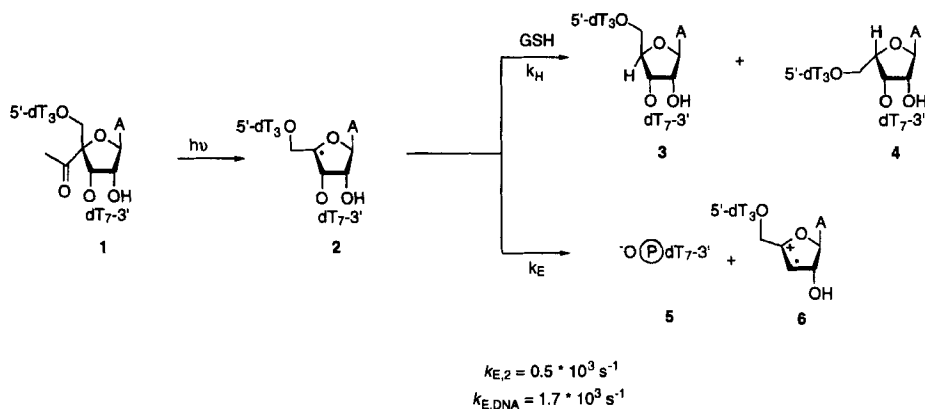
ABSTRACT: The radical-induced RNA cleavage is less efficient than that of DNA. The selectively generated 4'-ribonucleotide radicals show that the 2'-OH group decreases the rate of spontaneous cleavage k_E .

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 Hecht² have shown that bleomycin, which generates 4'-nucleotide radicals, cleaves RNA slower than DNA. Since bleomycin binds better to t-RNA³ 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 $k_H = 1.0 \cdot 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ⁵ the cleavage rate k_E of the 4'-ribonucleotide radical **2** of $0.5 \cdot 10^3 \text{ s}^{-1}$ was determined. The cleavage rate of the corresponding 4'-DNA radical $k_E = 1.7 \cdot 10^3 \text{ M}^{-1} \text{ s}^{-1}$ 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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