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Oxidation of 4'-Deoxyribonucleoside Radicals to 4'-Deoxyribonucleoside Cations. A Model for the Function of Bleomycin.

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Abstract: Selective generation of the 4'-deoxyribonucleoside radical 8 in the presence of $Mn(OAc)_3$ gave acetal 9 in 91% yield. This reaction models the function of the antibiotic bleomycin under diminished O_2 concentrations. In the presence of O_2 a peroxy radical is formed that leads to completely different products. © 1998 Elsevier Science Ltd. All rights reserved.

4'-DNA radicals are crucial intermediates in the DNA strand cleavage induced by bleomycin/Fe²⁺/O₂ complexes.¹ Depending upon the concentration of O₂ either glycolate 2 and base propenal 3 or ketoaldehyde 4 are produced. For the formation of cleavage products 2 and 3 the 4'-DNA radical is trapped by O₂ and the resulting hydroperoxide undergoes a Criegee rearrangement with subsequent elimination and hydrolysis steps.



According to the mechanism of J. Stubbe *et al.*¹, the ketoaldehyde 4 is produced by oxidation of the 4'-DNA radical 1 to the 4'-DNA cation 5 that is trapped by $H_2O(5\rightarrow 6)$. Hydrolysis of the cyclic hemiacetal 6 yields the ketoaldehyde 4. The oxidation step $(1\rightarrow 6)$ is suggested to be performed by the bleomycin/Fe²⁺/O₂ complex after the H-abstraction from DNA.

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In order to check this mechanism in model experiments, we generated the 4'-nucleoside radical 8 by photolysis of selenide 7^2 in the presence of $Mn(OAc)_3^3$ as oxidant and MeOH as solvent.⁴ Oxygen was excluded by freeze-thaw cycles under argon. This photolysis afforded 91% of the cyclic acetal 9 which is a precursor of the ketoaldehyde. Under non-photolytical conditions the oxidation reaction did not occur and the starting material 7 was recovered.⁴ Thus, selenide 7 is stable against $Mn(OAc)_3$ whereas radical 8 is oxidized to the nucleoside cation 10.



The formation of a hydroperoxide as intermediate could be excluded because the reactions were carried out in the absence of O_2 . Furthermore, we have shown recently that a hydroperoxide 11 yields glycolate 13 and base propenal 14 by Grob fragmentation (11 \rightarrow 12) and subsequent elimination.⁵



In the presence of O_2 the first step of the 4'-nucleoside radical is the formation of a peroxy radical. Fig. 1 shows the ESR spectrum of a radical which was generated by photolysis of selenide 15 in the presence of O_2 .⁶ The g-value of 2.0153 is typical for a peroxy radical and the absence of a hyperfine coupling is in accord with the peroxy radical 17.⁷



Fig. 1: ESR spectrum of radical 17.

These experiments support the mechanism of J. Stubbe: Oxygen does not oxidizes 4'-nucleoside radicals to 4'-nucleoside cations but metal oxides or their derivatives can easily induce this oxidation step $(1\rightarrow 5 \text{ or } 8\rightarrow 10)$. Trapping of these cations by protic solvents leads to hemiacetals $(5\rightarrow 6)$ or acetals $(10\rightarrow 9)$ that can be hydrolyzed to the ketoaldehydes. In DNA the ketoaldehyde 4 is not a direct strand cleavage product, but its treatment with base induces the strand scission through an elimination reaction $(4\rightarrow 18 + 19)$.



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References and Notes

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- For recent reviews on the use of Mn(OAc)₃ in radical chemistry, see: B. B. Snider, Chem. Rev. 1997, 97, 339. G. G. Melikyan, Synthesis 1993, 833.
- Selenide 7 (50 mg, 0.098 mmol) and Mn(OAc)₃ (88 mg, 0.29 mmol, 3 equiv.) were solved in dry 4. methanol (10 ml) and treated with Ar in three freeze-thaw cycles. After irradiation under Ar with a mercury high-pressure lamp (150 W) for 1.5 h at 25°C, the reaction mixture was filtered and chromatographed on silica gel (eluent: CH₂Cl₂/CH₃OH: 98:2 to 90:10). The two diastereomers of **9** (25 mg, 65%, d.r. 56:44) were isolated together with the corresponding non-benzoylated products (7 mg, 26%, d.r. 55:45). The main products were the N-benzoylated or non-benzoylated 2'-deoxy-4'-methoxyadenosines, and the α -Lthreo isomers were isolated as minor products. Spectroscopic data: 6-N-Benzoyl-4'-methoxy-2'deoxyadenosine 9a: ¹H NMR (300 MHz, CDCl₃): δ (ppm) 9.10 (s br, NH); 8.78 (s, H-2); 8.10 (s, H-8); 8.03 (s, H-2,6_{Bz}); 7.63 (m, H-4_{Bz}); 7.54 (m, H-3,5_{Bz}); 6.45 (dd, $J_{1',2'a}$ = 6.6 Hz, $J_{1',2'b}$ = 3.5 Hz, H-1'); 4.79 (dd, $J_{2'a,3'}=3.9$ Hz, $J_{2'b,3}=5.7$ Hz, H-3'); 4.12 (d, $J_{5'a,5'b}=11.6$ Hz, H-5'a); 3.74 (d, H-5'b); 3.51 (s, CH₃O), 3.04 (m, H–2'a); 2.54 (ddd, $J_{2'a,2'b}$ =13.2 Hz, H–2'b). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 164.20 (COPh); 152.31 (C-2); 150.73 and 150.19 (C-4, C-6); 142.14 (C-8); 133.44 (C-1_{NBz}); 132.97-127.90 (C_{arom}); 124.33 (C-5); 107.34 (C-4'); 86.22 (C-1'); 72.70 (C-3'); 62.83 (C-5'); 51.46 (OCH₃); 40.02 (C-2'). 6-N-Benzoyl-1-(2'-deoxy-4'-methoxy- α -L-threo-pentofuranosyl)adenine 9b: ¹H NMR: δ (ppm) 9.08 (s br, NH); 8.83 (s, H-2); 8.25 (s, H-8); 8.07 (d, H-2,6_{B2}); 7.63 (m, H-4_{B2}); 7.54 (m, H-3,5_{B2}); 6.85 (t, $J_{1',2'a} = J_{1',2'b} = 7.1$ Hz, H-1'); 4.55 (d, $J_{2'a,3'} = J_{2'b,3'} = 4.9$ Hz, H-3'); 3.93 (s, H-5'a, H-5'b); 3.24 (s, CH₃O), 2.97 (m, H-2'a); 2.68 (dd, $J_{2'a,2'b}$ =13.6 Hz, H-2'b). ¹³C NMR: δ (ppm) 165.40 (COPh); 152.72 (C-2); 151.84 and 149.83 (C-4, C-6); 141.14 (C_p, C-8); 133.59 (C-1_{NBz}); 132.74-128.05 (C_{aron}); 122.48 (C-5); 111.23 (C-4'); 83.82 (C-1'); 75.61 (C-3'); 57.43 (C-5'); 49.20 (OCH₃); 39.13 (C-2'). The stereochemistry was elucidated by NOE experiments of the O-silylated compound:



Treatment of selenide 7 with $Mn(OAc)_3$ without light (5h, 30°C) led to a quantitative recovery of the selenide that was debenzoylated by 10%. Obviously, debenzoylation occurs in the presence of Lewis acid as a side reaction.

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- ESR measurements (Bruker ESP-300): A solution of 7 in benzene was saturated with O₂ and irradiated in a Suprasil quartz tube (5.0 mm) with the filtered light (water-cooled Schott filter UG-5) of a Hanovia 977-B1, 1 kW, Hg-Xe high-pressure lamp.
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