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

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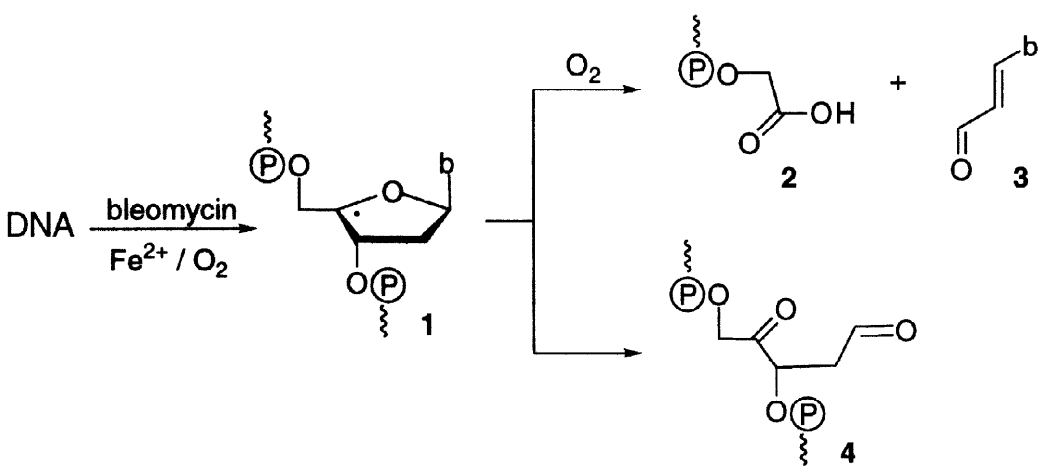
Abstract: *Selective generation of the 4'-deoxyribonucleoside radical* ***8*** *in the presence of* $Mn(OAc)_3$ *gave acetal* ***9*** *in 91% yield. This reaction models the function of the antibiotic bleomycin under diminished* O_2 *concentrations. In the presence of* O_2 *a peroxy radical is formed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

4'-DNA radicals are crucial intermediates in the DNA strand cleavage induced by bleomycin/Fe^{2+}/O_2 complexes.[1] Depending upon the concentration of O_2 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 O_2 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**→**6**). Hydrolysis of the cyclic hemiacetal **6** yields the ketoaldehyde **4**. The oxidation step (**1**→**6**) is suggested to be performed by the bleomycin/Fe^{2+}/O_2 complex after the H-abstraction from DNA.

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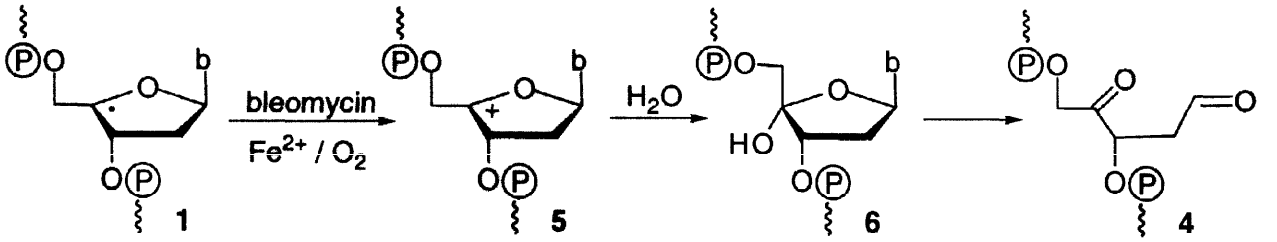
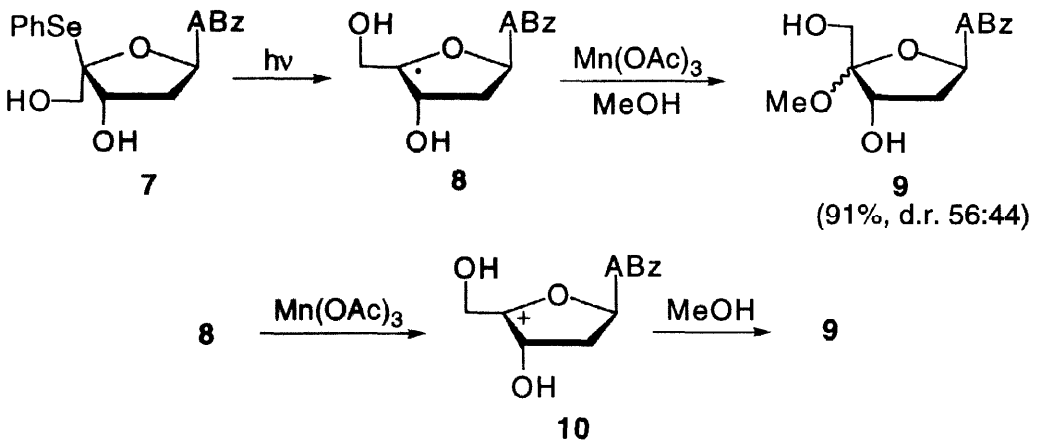
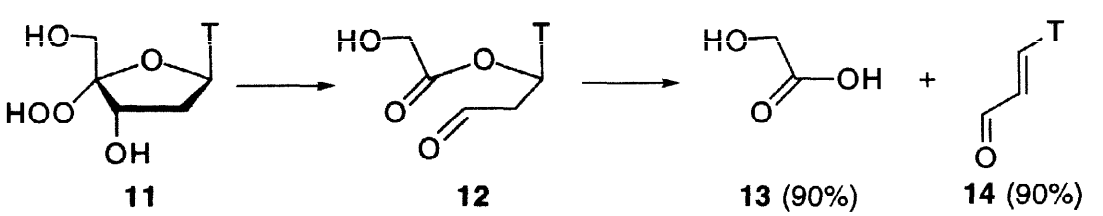


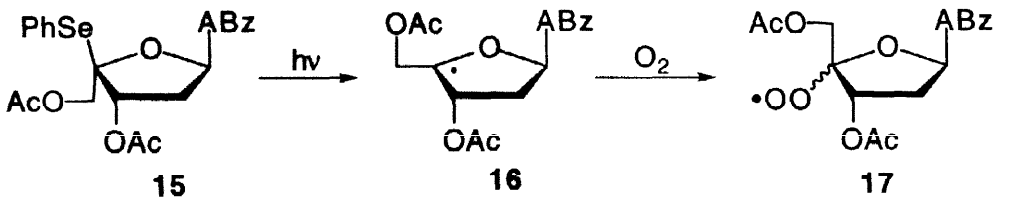
In order to check this mechanism in model experiments, we generated the 4'-nucleoside radical **8** by photolysis of selenide **7**[2] in the presence of $Mn(OAc)_3$[3] as oxidant and MeOH as solvent.[4] Oxygen was excluded by freeze-thaw cycles under argon. This photolysis afforded 91% of the cyclic 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**→**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]



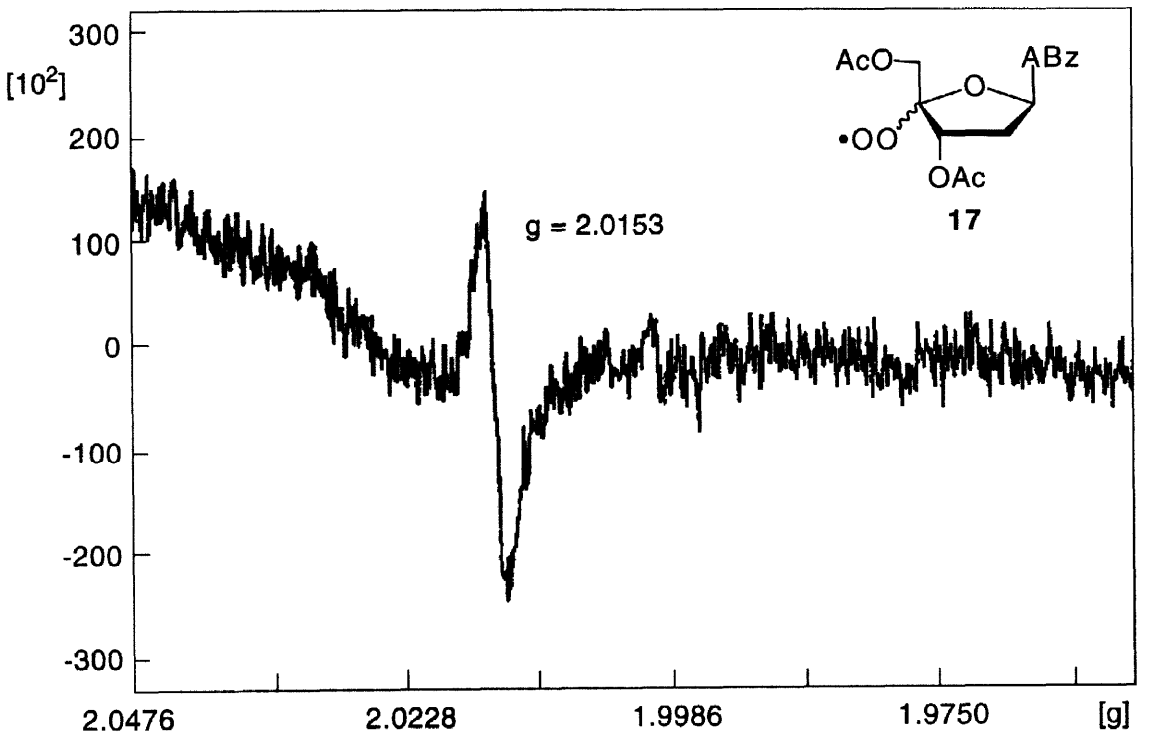
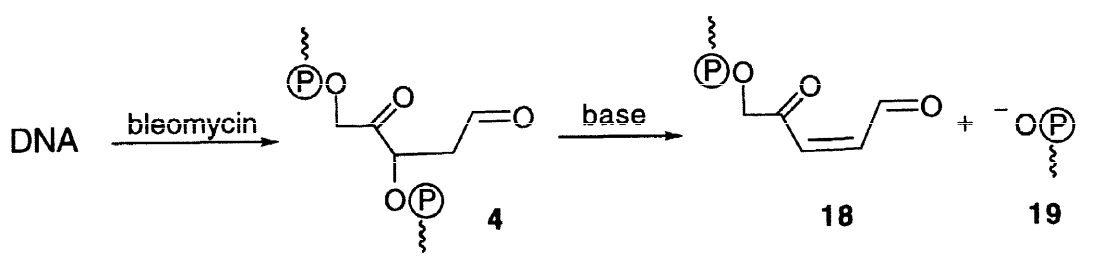


Fig. 1: ESR spectrum of radical **17**.

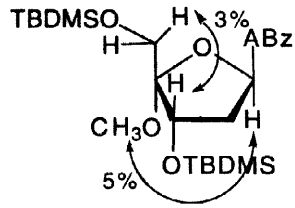
These experiments support the mechanism of J. Stubbe: Oxygen does not oxidizes 4'-nucleoside radicals to 4'-nucleoside cations but metal oxides or their derivatives can easily induce this oxidation step (**1**→**5** or **8**→**10**). Trapping of these cations by protic solvents leads to hemiacetals (**5**→**6**) or acetals (**10**→**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**→**18** + **19**).



Acknowledgment: This work was supported by the Swiss National Science Foundation.

References and Notes

1. For a recent review, see: J. Stubbe, J. W. Kozarich, W. Wu, D. E. Vanderwall, *Acc. Chem. Res.* **1996**, *29*, 322.
2. B. Giese, A. Dussy, C. Elie, P. Erdmann, U. Schwitter, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1861. B. Giese, P. Erdmann, T. Schäfer, U. Schwitter, *Synthesis* **1994**, 1310.
3. 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.
4. Selenide **7** (50 mg, 0.098 mmol) and $Mn(OAc)_3$ (88 mg, 0.29 mmol, 3 equiv.) were solved in dry 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: CH_2Cl_2/CH_3OH: 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-L-*threo* isomers were isolated as minor products. Spectroscopic data: *6-N-Benzoyl-4'-methoxy-2'-deoxyadenosine* **9a**: ^{1}H NMR (300 MHz, $CDCl_3$): 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, C*H*$_3$O), 3.04 (m, H–2'a); 2.54 (ddd, $J_{2'a,2'b}$=13.2 Hz, H–2'b). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 164.20 (*C*OPh); 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 (O*C*H$_3$); 40.02 (C–2'). *6-N-Benzoyl-1-(2'-deoxy-4'-methoxy-α-L-*threo*-pentofuranosyl)adenine* **9b**: ^{1}H NMR: δ (ppm) 9.08 (s br, NH); 8.83 (s, H–2); 8.25 (s, H–8); 8.07 (d, H–2,6$_{Bz}$); 7.63 (m, H–4$_{Bz}$); 7.54 (m, H–3,5$_{Bz}$); 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, C*H*$_3$O), 2.97 (m, H–2'a); 2.68 (dd, $J_{2'a,2'b}$=13.6 Hz, H–2'b). ^{13}C NMR: δ (ppm) 165.40 (*C*OPh); 152.72 (C–2); 151.84 and 149.83 (C–4, C–6); 141.14 (C$_t$, C–8); 133.59 (C–1$_{NBz}$); 132.74–128.05 (C$_{arom}$); 122.48 (C–5); 111.23 (C–4'); 83.82 (C–1'); 75.61 (C–3'); 57.43 (C–5'); 49.20 (O*C*H$_3$); 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.
5. B. Giese, X. Beyrich-Graf, P. Erdmann, L. Giraud, P. Imwinkelried, S. N. Müller, U. Schwitter, *J. Am. Chem. Soc.* **1995**, *117*, 6146.
6. ESR measurements (Bruker ESP-300): A solution of **7** in benzene was saturated with O_2 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.
7. K. U. Ingold, *Acc. Chem. Res.* **1969**, *2*, 1.