Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3507-3510, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00676-X

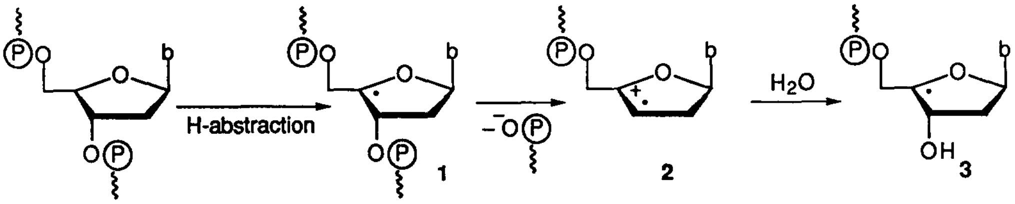
ESR Evidence for a Heterolytic C,O-Bond Cleavage in Models of 4'-DNA Radicals

Stefan Peukert, Rohit Batra and Bernd Giese*

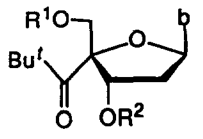
Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Abstract: *Photolysis of ketone* ***6b*** *generates allylic radical* ***9****. The decisive step in this transformation is a heterolytic C,O-bond cleavage from radical* ***7b*** *that generates radical cation* ***8*** *from radical* ***7b****. This ESR study models the anaerobic strand scission of 4'-DNA radicals.* © 1997 Elsevier Science Ltd.

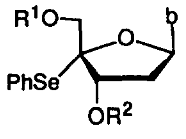
The radical induced DNA strand scission by antitumor antibiotics of the bleomycin or enediyne families is achieved by H-atom abstraction from the deoxyribose moiety.[1] Among the deoxyribose radicals the 4'-DNA radical **1** plays an important role since it can cleave the DNA strand even in the absence of O_2 and under neutral conditions.[2] This spontaneous DNA strand scission is believed to occur via radical cation **2** that reacts with H_2O and generates radical **3**.



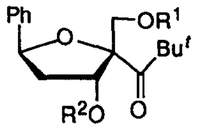
In spite of the importance of this reaction mechanism there is no ESR spectroscopic evidence for 4'-DNA radical intermediates. Even our attempts to observe ESR spectra using 4'-substituted deoxyribonucleosides **4** and **5** as radical precursors failed.[3] However, we have now found that a replacement of the heterocycle b in **4** and **5** by a phenyl group (compound **6**) yields a suitable precursor for these ESR experiments.[4]



4

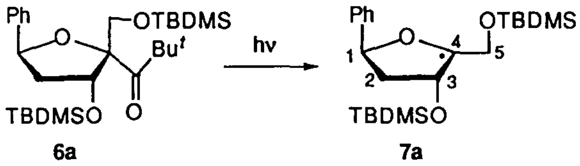


5



6

Figure 2 shows that by photolysis of **6a** an ESR spectrum of the modified deoxyribosyl radical **7a** can be obtained.[5] For the assignment of the coupling constants the geometry of radical **7** (R=TMS) was optimized with the UHF/3-21G* ab initio method, and the Fermi contacts were calculated with the density functionals BLYP/6-31G* at the unrestricted level of theory.[6]



Coupling Constants (a_H) of **7a** in Gauss:

	1–H	2a,b–H	3–H	5a–H	5b–H
obs.	8.2	0.95	3.6	10.4	11.6
calc.	7.1	0.95	4.7		

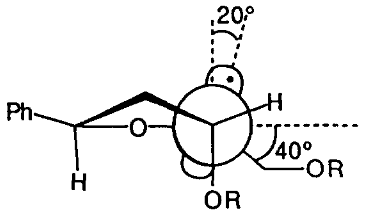


Fig.1: Calculated conformation of radical **7** (R = TMS).

The small β-coupling constant of 3.6 G (4.7 G calc.) demonstrates the equatorial orientation of the C,H-bond at 3–C. Thus, the C,O-bond at 3–C is in axial position.[7] The large γ-coupling constant of 8.2 G (7.2 G calcd.) for 1–H can be explained by the axial orientation of the C,H-bond that facilitates the interaction with the spin of the cyclic oxyalkyl radical. Therefore, the phenyl group at 1–C adopts the equatorial position. The quantum chemical calculations also suggest a pyramidalization at the radical carbon center of **7** (Figure 1).[6]

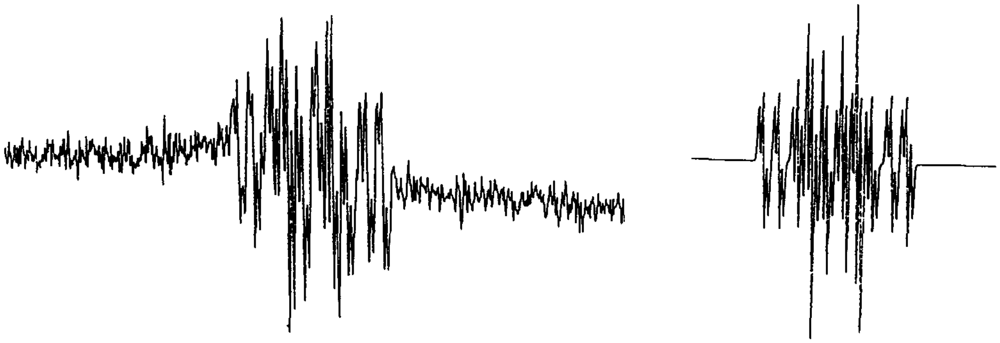
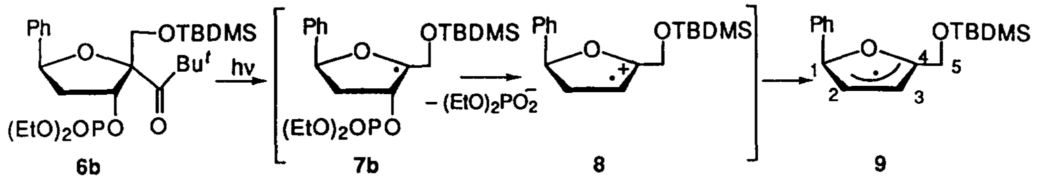


Fig.2: ESR spectrum of **7a** (left) measured in benzene at 7°C and the simulation (right) of this spectrum.

A spontaneous, heterolytic cleavage of the C,O-bond at 3–C can occur only with good anionic leaving groups like phosphates.[8] In order to get more informations about this reaction step, we photolyzed the phosphorylated derivative **6b** in the ESR cavity and observed the formation of the allylic radical **9** (Figure 3).[5]



Coupling Constants (a_H) of 9 in Gauss:

	1-H	2-H	3-H	5a,b-H
obs.	32.8	13.3	2.0	8.6
calc.	29.8	14.2	1.8	7.4

The structure of **9** can be unequivocally confirmed by the ESR coupling constants. The small coupling constant of 2.0 G (1.8 G calc.) is typical for a hydrogen at the central carbon of an allylic radical.[9] The large coupling constant of 32.8 G demonstrates that the C,H-bond at 1–C is in the plane of the allylic π-system so that the phenyl group adopts an equatorial position.

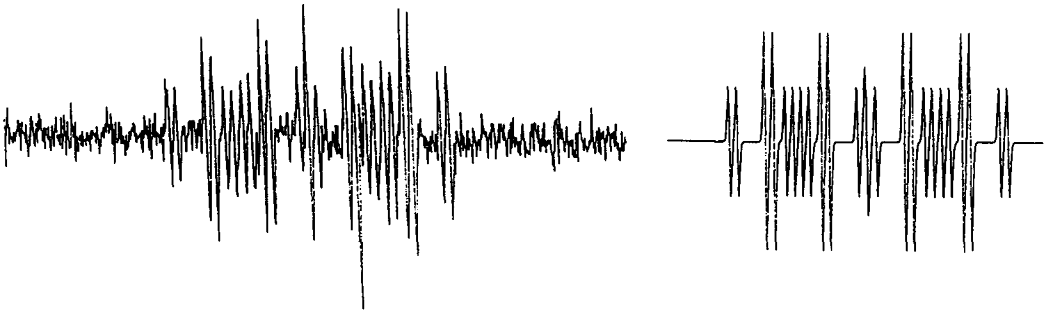


Fig. 3: ESR spectrum of **9** (left) measured in benzene at 7°C and the simulation (right) of this spectrum.

The observation of the allylic radical **9** supports the assumption that radical cation **8** is formed by heterolytic C,O-bond cleavage from radical **7b** since is well known that radical cations are acids that deprotonate easily and yield allylic radicals.[10] These ESR spectroscopic measurements were carried out in benzene. Using methanol as solvent the radical cation **8** was trapped by the nucleophilic alcohol.[4]

Conclusion: The ESR spectroscopic measurements using ketone **6** as a precursor for a model of 4'-deoxyribonucleoside radicals provide further evidence for a heterolytic strand cleavage of 4'-DNA radicals (1→2) under anaerobic conditions.

Acknowledgment: This work was supported by the Swiss National Science Foundation. S. P. thanks the Fonds der Chemischen Industrie for a Kekulé-Stipendium.

References and Notes

1. For recent reviews, see: J. Stubbe, J. W. Kozarich, W. Wu, D. E. Vanderwall, *Acc. Chem. Res.* **1996**, *29*, 322. P. C. Dedon, I. H. Goldberg, *Chem. Res. Toxicol.* **1992**, *5*, 311.
2. B. Giese, A. Dussy, C. Elie, P. Erdmann, U. Schwittter, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1861. D. Schulte-Frohlinde, *CHIUZ*, **1990**, *37*, 1.
3. We tried to observe ESR spectra starting from the precusors **4** and **5** in several solvents, at various temperatures, with the addition of radical starters, or with light. All these experiments were unsuccessful. To our knowledge, ESR spectra of deoxyriboses with the radical center at 4–C have not been observed until now.
4. Compound **6** is the enantiomer of the phenyl analogues of **4** and **5**. We used **6** because it can be synthesized easily: S. Peukert, B. Giese, *Tetrahedron Lett.* **1996**, *37*, 4365.
5. ESR experiments were carried out by irradiation (Hanovia Hg-high pressure burner) of **6** (20-40 mg in 0.5 ml O_2-free benzene) in suprasil quartz tubes at 7°C. In addition to the radicals **7a** and **9**, the ESR spectra showed the *tert*-butyl radical. These lines were substracted in order to obtain the ESR spectra of radicals **7a** and **9** in Figures 2 and 3. The g-values of radicals **7a** and **9** are 2.0030.
6. R. Batra, B. Giese, M. Spichty, G. Gescheid, K. N. Houk, *J. Phys. Chem.* **1996**, *100*, 18371. This procedure proved to be a reliable method for obtaining hyperfine coupling constants of organic radicals.
7. The axial orientation of the C,O-bond at 3–C can be explained by the anomeric effect of α,β-dioxyalkyl radicals: J. Dupuis, B. Giese, D. Rüegge, H. Fischer, H.-G. Korth, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896. H. G. Korth, R. Sustmann, J. Dupuis, B. Giese, *J. Chem. Soc. Perkin Trans. II* **1986**, *1453*.
8. B. Giese, X. Beyrich-Graf, J. Burger, C. Kesselheim, M. Senn, T. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1742.
9. L. Lunazzi, G. Placucci, L. Grossi, *Tetrahedron* **1983**, *39*, 159.
10. Some recent publications: A. Albini, M. Mella, M. Freccero, *Tetrahedron* **1994**, *50*, 575. A. Faucitano, A. Buttafava, F. Martinotti, R. Sustmann, H.-G. Korth, *Tetrahedron Lett.* **1992**, *33*, 2223. D. R. Arnold, S.A. Mines, *Can. J. Chem.* **1989**, *67*, 689.

(*Received in Germany* 3 *April* 1997; *accepted* 4 *April* 1997)