Pergamon

Tetrahedron Letters, Vol. 37, No. 25, pp. 4365-4368, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00782-4

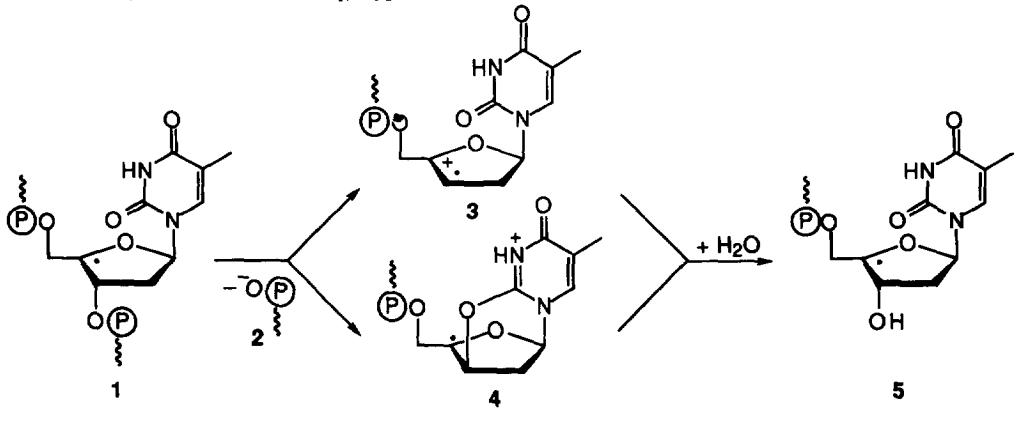
Radical-Induced S_N1 Substitution Reactions

Stefan Peukert, Bernd Giese*

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

Abstract: Solvolysis of radicals **17** and **18** yielded the same products **19–23**. This indicates that the radical-induced substitution of the phosphate group occurs *via* radical cation **24** as common intermediate.

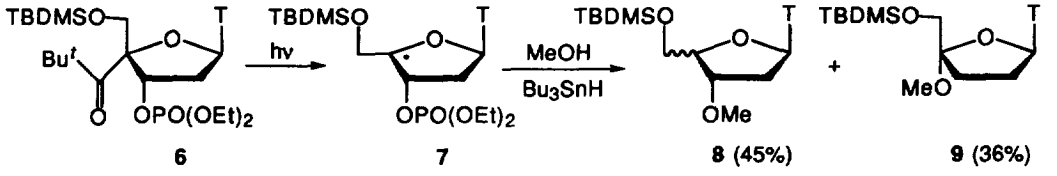
Recently, we have demonstrated that in aqueous solutions the 4'-DNA radical **1** undergoes heterolytic cleavage of the C–O bond at the 3'-position yielding phosphate **2** and the β-hydroxylated radical **5**.[1] As it has been pointed out by Zipse,[2] substitution reactions where H_2O displaces the 3'-phosphate adjacent to a radical center might occur either by spontaneous C,O-bond cleavage *via* radical cation **3** (S_N1 type) or by anchimeric assistance of thymine via radical **4** (S_N2 type).



1 2 3 4 5

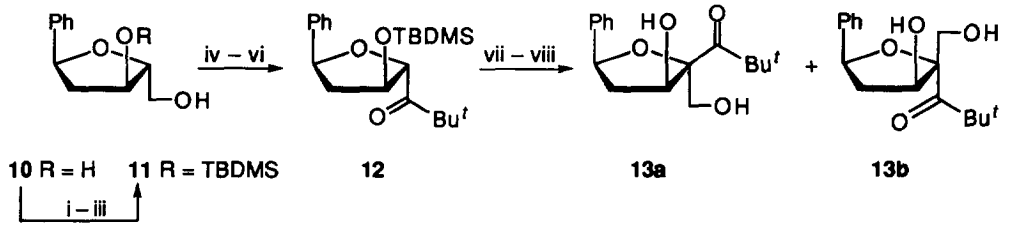
To further investigate this substitution mechanism, we generated radical **7** by irradiation of the 4'-mononucleotide radical precursor **6** in methanol and in the presence of Bu_3SnH.[3] The reaction gave a 1.3:1 mixture of the regioisomers **8** and **9** (81% yield) in which the methoxy group is *trans* to the thymine substituent.[4] As in the DNA case, the stereochemistry can be explained either by a stereoselective S_N1 reaction

with the thymine base shielding the β-face or by S_N2 reactions with a radical species analogous to **4** as an intermediate.



6 **7** **8** (45%) **9** (36%)

In order to exclude the pathway with anchimeric assistance by thymine, we synthesized model compounds where the heterocycle is replaced by a phenyl group. The synthesis started from the known diol **10**.[5] Transformation into **11**, Pfitzner-Moffatt oxidation of the primary alcohol, addition of *t*-BuLi, and subsequent Dess-Martin oxidation afforded ketone **12**. Desilylation, followed by aldol reaction with formaldehyde, yielded compounds **13a** and **13b**.[6]

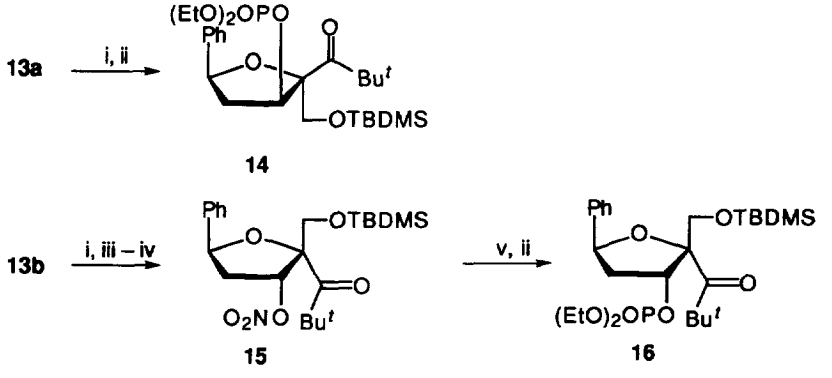


10 R = H **11** R = TBDMS **12** **13a** **13b**

i – iii

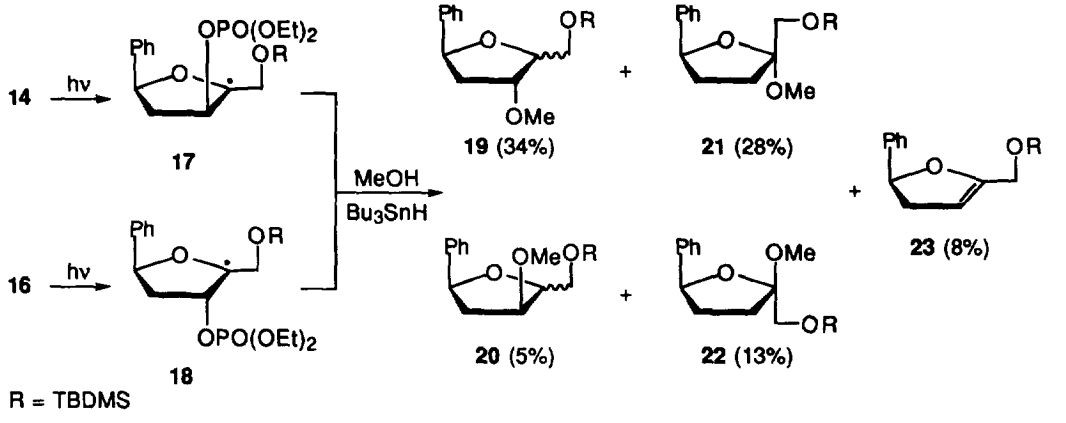
i) DMTrCl, pyridine; ii) TBDMSCl, imidazole, DMF; iii) TsOH, CH_2Cl_2, 78% (3 steps); iv) CMC, pyridine-TFA, DMSO, 97%; v) *t*-BuLi, $CeCl_3$, THF, -78°C, 65%; vi) periodinane, CH_2Cl_2, 98%; vii) TBAF (1M), THF, 0°C, 92%; viii) LDA (2.5 eq.), HCHO, THF, -60°C, 75% based on recovered material.

Compound **13a** was converted into the radical precursor **14** by silylation and phosphorylation. For the preparation of the isomeric radical precursor **16** where the phosphate group is *trans* to the phenyl substituent, **13b** was silylated and treated with Tf_2O. Subsequent reaction with *n*-Bu_4NNO_3 led to nitrate **15** which was cleaved reductively and phosphorylated to give **16**.

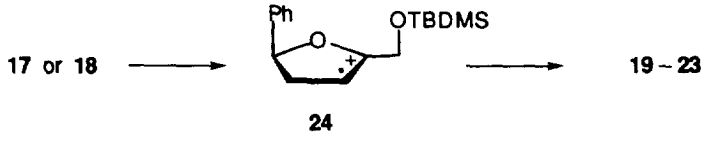


i) TBDMSCl, imidazole, DMF, 62–65%; ii) ClPO(OEt)$_2$, LDA, -78°C, 62–79%; iii) Tf_2O, pyridine, CH_2Cl_2, 0°–25°C; iv) *n*-Bu_4NNO_3, benzene, 40°C, 60% (2 steps); v) Zn, HOAc, CH_2Cl_2, 0°C, 80%.

Photolysis of ketones **14** and **16** gave isomeric radicals **17** and **18**, respectively, in which the phosphate substituents are *cis* or *trans* to the phenyl group. If the phosphate nucleofuges are substituted by S_N2 reactions, one should expect products with opposite stereochemistry. But photolysis of methanolic solutions of **14** and **16** in the presence of Bu_3SnH afforded the same substitution products **19** to **22** and enol ether **23** in a total yield of 85–90%.[7,8] The observation of an identical product mixture for both radical precursors excludes S_N2 reaction mechanisms and suggests the existence of a common intermediate.



The result can be rationalized by assuming a S_N1 type loss of the phosphate group from the radicals **17** and **18** leading to radical cation **24**. Nucleophilic attack of MeOH occurs at the two carbon atoms of the mesomeric radical cation **24**. In comparison to the thymidine derivative **6** the stereoselectivity is lower, yet attack *trans* to the phenyl group is still preferred. Formation of the enol ether **23** can be explained by reduction of this intermediate radical cation *via* single electron transfer.[9]



Conclusion: The results with phenyl substituted nucleotide analoga are in accord with a S_N1 type cleavage of the 4'-DNA radical (**1**→**3**) and subsequent addition of water (**3**→**5**).

Acknowledgement: This work was supported by the Swiss National Science Foundation. S. P. thanks the Fonds der Chemischen Industrie for a Kekulé-Stipendium. We thank M. Zehnder and M. Neuburger for the X-ray crystal structure analysis.

References and Notes

1. a) B. Giese, A. Dussy, C. Elie, P. Erdmann, U. Schwitter, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1861. b) B. Giese, X. Beyrich-Graf, P. Erdmann, M. Petretta, U. Schwitter, *Chem. & Biol.* **1995**, *2*, 367. For pioneering work in this area, see: c) G. Behrens, G. Koltzenburg, D. Schulte-Frohlinde, *Z. Naturforsch. C* **1982**, *37*, 1205.
2. a) H. Zipse, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1985. b) D. P. Curran, *Chemtracts Org. Chem.* **1995**, *8*, 62.
3. The radical precursor **6** was synthesized according to the procedure described in B. Giese, P. Imwinkelried, M. Petretta, *Synlett* **1994**, 1003.
4. The structures of compounds **8** and **9** were determined by comparison of the NMR data of analogous compounds described in: B. Giese, X. Beyrich-Graf, J. Burger, C. Kesselheim, M. Senn, T. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1742.
5. The use of diol **10** leads to radical **18** which is an enantiomeric analog of **7** (thymine is substituted by phenyl). We have used this system because **10** is readily available: E. T. Kool, N. Chaudhuri, *Tetrahedron Lett.* **1995**, *36*, 1795 and corrigendum, *Tetrahedron Lett.* **1995**, *36*, 4910.
6. The stereochemistry of compounds **13a,b** was assigned by NOE-experiments and by X-ray crystal structure analysis of **13b**. The atomic coordinates for **13b** are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. The NMR signals of the methylene protons of the hydroxymethyl group are different in **13a** and **13b**. The *cis* orientation of the vicinal OH function in **13b** leads to a downfield shift of about 0.2 ppm compared to **13a**. Similar shift differences can also be observed in the 4 diastereomers of **19** and **20**.
7. In a typical procedure 10 μmol of the radical precursor in 1 ml degassed methanol was irradiated (Osram Hg high pressure lamp, 500 W, 320 nm filter) for 2 h in the presence of 25 μmol of Bu_3SnH.
8. The product mixture was analyzed by GC and comparison with reference samples prepared independently. Compounds **21** and **22** were prepared by acid-catalyzed addition of MeOH to enol ether **23**. The diastereomers were separated and the stereochemistry assigned by NOE experiments. The four compounds **19** and **20** were synthesized from **10** and its C–1 epimer.[5] Silylation and methylation afforded two of the four diastereomers of **19** and **20**. The other two diastereomers were prepared by silylation of the primary alcohol, inversion of the stereochemistry of the secondary alcohol by Mitsunobu reaction using benzoic acid, ester hydrolysis, and subsequent methylation.
9. Cyclic voltammetry of the enol ether **23** (10 mM in acetonitrile, 0.1 M n-Bu_4NPF_6) gave a redox potential on a glassy carbon electrode of 1.47 V (*vs* Hg/Hg_2Cl_2, 20°C, scan rate 0.4 V s^{-1}). Thus, radical cation **24** is a strong oxidizing agent. The reduction of a similar radical cation is described in: B. Giese, J. Burger, T. W. Kang, C. Kesselheim, T. Wittmer, *J. Am. Chem. Soc.* **1992**, *114*, 7322.

(*Received in Germany* 17 *April* 1996; *accepted* 23 *April* 1996)