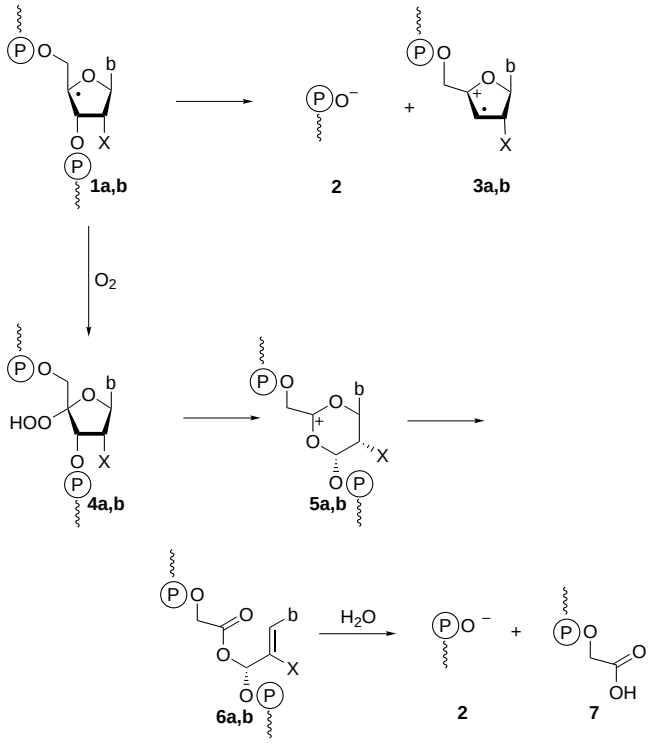
[8] M. Jansen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1975**, *417*, 31.
[9] E. Zintl, H. H. von Baumbach, *Z. Anorg. Allg. Chem.* **1931**, *198*, 88.
[10] H. Klassen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1983**, *497*, 70.
[11] M. Jansen, B. Wolf, *Z. Anorg. Allg. Chem.* **1983**, *497*, 65.
[12] D. Trinschek, M. Jansen, *Z. Naturforsch. B* **1996**, *51*, 711.
[13] D. Trinschek, M. Jansen, *Z. Naturforsch. B* **1996**, *51*, 917.
[14] D. Trinschek, M. Jansen, *Z. Anorg. Allg. Chem.* **1996,** *622*, 245.
[15] M. G. Barker, P. G. Gadd, *J. Chem. Res. Synop.* **1981**, 274.
[16] J. Kissel, R. Hoppe, *Z. Anorg. Allg. Chem.* **1990**, *582*, 103.
[17] P. Hagenmuller, A. Lecerf, M. Onillon, *C. R. Hebd. Seances Acad. Sci. Ser. B* **1962**, *255*, 928.
[18] G. Wagner, R. Hoppe, *Z. Anorg. Allg. Chem.* **1987**, *549*, 15.
[19] R. Hoppe, K. Hestermann, F. Schenk, *Z. Anorg. Allg. Chem.* **1969**, *367*, 275.
[20] G. Tams, H. Müller-Buschbaum, *J. Alloys Compd.* **1992**, *189*, 241.
[21] M. Jansen, *Z. Anorg. Allg. Chem.* **1975**, *417*, 35.
[22] H. Klassen, R. Hoppe, *Z. Anorg. Allg. Chem.* **1982**, *485*, 101.
[23] L. D. Dyer, B. S. Borie, G. P. Smith, *J. Am. Chem. Soc.* **1954**, *76*, 1499.
[24] K. Hestermann, R. Hoppe, *Z. Anorg. Allg. Chem.* **1969**, *367*, 249.
[25] K.-R. Wambach, R. Hoppe, *Z. Anorg. Allg. Chem.* **1978**, *444*, 30.
[26] R. Hoppe, K. Hestermann, F. Schenk, *Z. Anorg. Allg. Chem.* **1969**, *367*, 275.
[27] H. Rieck, R. Hoppe, *Z. Anorg. Allg. Chem.* **1972**, *372*, 193.
[28] T. Hewston, B. Chamberland, *J. Phys. Chem. Solids* **1988**, *75*, 332.
[29] P. Lambert, M. Morrison, P. Edwards, *J. Solid State Chem.* **1988**, *75*, 332.



a: X = H; **b**: X = OH

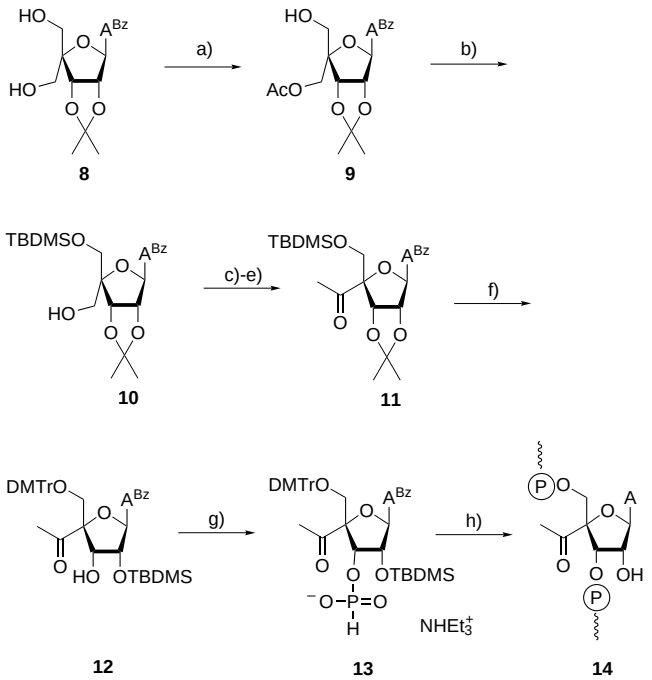
Scheme 1. Nucleotide strand cleavage by 4′-radicals under anaerobic and aerobic conditions. b = nucleobase. wavy line = nucleotide strand.

Differences Between 4′-RNA and 4′-DNA Radicals during Anaerobic and Aerobic Strand Cleavage**

Harald Strittmatter, Adrian Dussy, Urs Schwitter, and Bernd Giese*

The mechanism of DNA strand cleavage by 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 C3′ leads to the 5′-phosphate **2** as the stable cleavage product (Scheme 1). In the presence of O_2 the 4′-DNA radical **1a** is converted first into hydroperoxide **4a**, then to cation **5a**, which after β-elimination (**5a**→**6a**) and subsequent hydrolysis leads to the stable cleavage products 5′-phosphate **2** and 3′-phosphoglycolate **7**.

The mechanism of the corresponding RNA cleavage, however, has been hardly investigated. Nevertheless, studies by Hecht[2] have shown that bleomycin, which generates 4′-nucleotide radicals, cleaves RNA slower than DNA. Since bleomycin binds better to t-RNA[3] than to DNA, the difference in cleavage efficiency might be explained by a difference in the reactivity of the 4′-oligonucleotide radical **1a** relative to **1b**. In order to prove this we have synthesized oligonucleotide **14** in which one ribonucleotide carries an acetyl group at position C4′ (Scheme 2). In analogy to the



Scheme 2. Synthesis of 4′-acetylated RNA. a) $MeC(OMe)_3$, camphorsulfonic acid, 20 °C; HOAc, 0 °C, 42 %; in the second diastereomer (formed in 41 % yield) the acetyl group was cleaved off to reform nucleoside **8**; b) TBDMSCl, imidazole, 40 °C; NaOMe, 20 °C, 5 min, 72 %; c) Dess-Martin periodinane, 80 %; d) MeMgCl, 93 %; e) Dess-Martin periodinane, 85 %; f) CF_3CO_2H; TBDMSCl; CF_3CO_2H; DMTrCl; 68 %; g) PCl_3, 1,2,4-triazole; $Me_3NH^+HCO_3^-$; 78 %; h) DNA synthesizer. A^{BZ} = benzyladenine, DMTr = 4,4′-dimethoxytrityl, dT = 2′-deoxyribosylthymine, TBDMS = *tert*-butyldimethylsilyl.

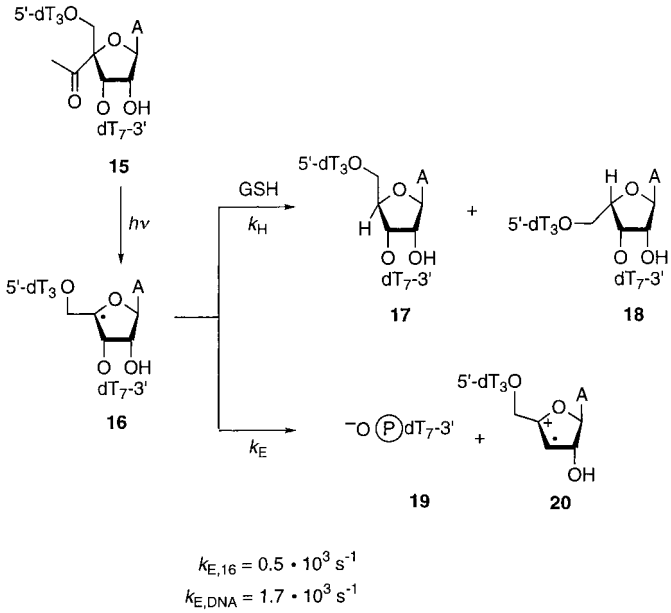
[*] Prof. Dr. B. Giese, Dipl.-Chem. H. Strittmatter, Dipl.-Chem. A. Dussy, Dr. U. Schwitter
Institut für Organische Chemie der Universität
St. Johanns-Ring 19, CH-4056 Basel (Switzerland)
Fax: (+41) 61-267-1105
E-mail: giese@ubaclu.unibas.ch

[**] This work was supported by the Swiss National Science Foundation.

  1433-7851/99/3801-0135 $ 17.50+.50/0

photolysis experiments that were carried out with 4′-acylated deoxyribonucleotides[4] compound **14** is a precursor of 4′-ribonucleotide radicals **1b**.

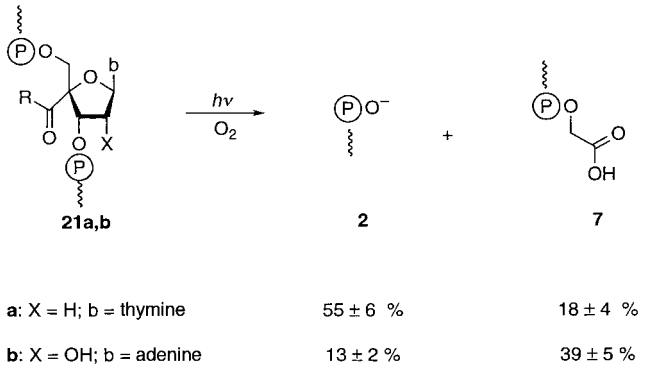
The synthesis starts from the known compound **8**[5] and essentially follows the synthetic route that was worked out for the corresponding modified deoxyribonucleotides (Scheme 2).[6] The 2′,5′-protected phosphite **13** was used so that the oligonucleotide synthesis could be performed on a solid support.[7] The rate of the spontaneous strand cleavage was measured by photolysis of the modified oligomer **15** to the 4′-RNA radical **16**, which was then trapped with an excess of glutathione diethyl ester (GSH; Scheme 3). The ratio of the rate constants k_H/k_E was obtained from the dependence of the product mixture (**17** + **18**)/**19** on the GSH concentration.[8] With the rate of hydrogen abstraction $k_H = 1.0 \cdot 10^7\ M^{-1}s^{-1}$[9] the rate of cleavage k_E of the 4′-ribonucleotide radical **16** was determined as $0.5 \cdot 10^3\ s^{-1}$. The cleavage rate of the corresponding 4′-DNA radical at $k_E = 1.7 \cdot 10^3\ M^{-1}s^{-1}$ was more than three times faster.[10]



Scheme 3. Determination of the relative rate constants of the photoinduced strand cleavage. A = adenine.

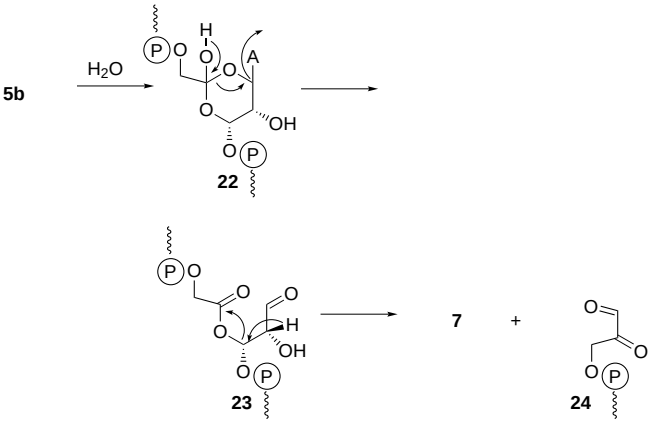
This decrease in the rate of cleavage of 4′-ribonucleotide radicals can be interpreted by a destabilizing effect of the additional OH group on the radical cation **20**. Nevertheless, this effect is very small and we assume that the oligomeric radical cation is probably so well solvated by water molecules that the introduction of a 2′-OH group exerts only a slight destabilizing effect on the transition state of the reaction.[11]

Experiments carried out under aerobic conditions, in which the hydroperoxides **4a, b** are intermediates,[4a] should also be influenced by the presence of an additional 2′-OH group. Stubbe et al.[12] have shown that the deoxyribonucleotide cation **5a**, formed by a Criegee rearrangement, opens the ring stereoselectively (**5a** → **6a**), whereby only the *pro-R* proton at C2′ of **5a** is cleaved (Scheme 1). In the ribonucleotide this position is occupied by the OH group, so that the elimination step (**5b** → **6b**) should be slowed down. Our experiments have now shown that the introduction of the 2′-OH group has a strong influence on the product composition obtained by aerobic cleavage. Whereas oligodeoxyribonucleotide **21a** yields preferentially the 5′-phosphate **2**, the 3′-phosphoglycolate **7** was obtained as the major product from ribonucleotide **21b** (Scheme 4).[13] The preferred formation of 5′-phosphate **2**



Scheme 4. Difference in the product composition after aerobic photolytic strand cleavage.

from deoxyribonucleotides is in accordance with the Stubbe mechanism[12] where intermediate **6a** cleaves the 5′-phosphate **2** in an S_N1 reaction (Scheme 1). The 3′-phosphoglycolate **7** is formed later on in the reaction pathway and thus is obtained in lower yield. In the ribose system **5b** the 2′-OH group slows down the elimination step (**5b** → **6b**) so that cation **5b** can be trapped by water in a competing reaction (**5b** → **22**). Fragmentation (**22** → **23**) and subsequent elimination (**23** → **7** + **24**) then leads to 3′-phosphoglycolate **7** as the cleavage product (Scheme 5). This additional pathway in RNA offers a possible explanation for the preferred formation of 3′-phosphoglycolate **7** during the aerobic strand cleavage of 4′-ribonucleotide radical **1b**.[14]



Scheme 5. Trapping of cation **5b** by water, and subsequent fragmentation and elimination to give **7**.

The 2′-OH group in ribonucleotides influences the rate of the spontaneous cleavage of 4′-ribonucleotide radicals and changes the product composition under aerobic cleavage. Both effects originate from the retardation of reaction steps

  1433-7851/99/3801-0136 $ 17.50+.50/0

1 → **2** + **3** and **5** → **6**, respectively, during RNA strand cleavage. Whereas the 2′-OH group accelerates the ionic cleavage of RNA relative to DNA,[15] it slows down the radical-induced RNA strand cleavage.

Received: August 7, 1998 [Z 12265 IE]
German version: *Angew. Chem.* **1999**, *111*, 238 – 240

Keywords: DNA cleavage · nucleotides · radical ions · RNA

[1] Review: W. K. Pogozelski, T. D. Tullius, *Chem. Rev.* **1998**, *98*, 1089.
[2] a) S. M. Hecht, *Bioconjugate Chem.* **1994**, *5*, 513; b) S. M. Hecht, *Polynucleotide Cleavage and the Expression of Antitumor Activity by Bleomycin* (Ed.: S. M. Hecht), Kluwer Academic, Dordrecht, **1996**, p. 77.
[3] C. E. Holmes, S. M. Hecht, *J. Biol. Chem.* **1993**, *268*, 25 909.
[4] a) B. Giese, X. Beyrich-Graf, P. Erdmann, M. Petretta, U. Schwitter, *Chem. Biol.* **1995**, *2*, 367; b) A. Marx, M. P. MacWilliams, T. A. Bickle, U. Schwitter, B. Giese, *J. Am. Chem. Soc.* **1997**, *119*, 1131.
[5] R. Youssefyeh, D. Tegg, J. H. Verheyen, G. H. Jones, G. H. Moffat, *Tetrahedron Lett.* **1977**, *18*, 435.
[6] The stereochemistry at C4′ of nucleotide **11** was determined by NOE experiments. A medium-sized NOE effect was observed between 5′-H and 3′-H, a small NOE effect between C4′-(acetoxymethyl) and 1′-H, as well as between the methyl group of the acetate and one of the methyl groups of the isopropylidene protecting group.
[7] Phosphite **13** was activated with pivaloyl chloride, subsequently coupled with the oligonucleotide bound to the solid phase, and the oligonucleotide synthesis was finally performed with a synthesizer.
[8] An aqueous solution (100 μL) containing the modified oligonucleotide (about 0.3 nmol) and GSH (10 – 70 nmol) was irradiated for 5 min under argon (Osram 500 W, 320 nm filter, 30 °C). The product separation was performed by HPLC on a reversed-phase column and the product analysis was done by MALDI-TOF MS. The relative ratio of the competing reaction rates k_H/k_E was determined from the ratio of products (**17** + **18**)/**19** and the glutathione concentration, see B. Giese, A. Dussy, E. Meggers, M. Petretta, U. Schwitter, *J. Am. Chem. Soc.* **1997**, *119*, 11 130.
[9] C. Tronche, F. N. Martinez, J. H. Horner, M. Newcomb, M. Senn, B. Giese, *Tetrahedron Lett.* **1996**, *37*, 5845.
[10] These experiments were carried out as described in ref. [8].
[11] In model studies with noncharged phosphate triesters in alcoholic solutions the effect of the 2′-OH group is considerably larger: D. Crich, X. Mo, *J. Am. Chem. Soc.* **1997**, *119*, 245. This shows how risky it is to extrapolate results obtained from model reactions with small molecules in organic solvents to explain biomolecules in water.
[12] a) S. Ajmera, J. C. Wu, L. Worth, Jr., L. E. Rabow, J. Stubbe, J. W. Kozarich *Biochemistry* **1986**, *25*, 6586; b) G. H. McGall, L. E. Rabow, G. W. Ashley, S. H. Wu, J. W. Kozarich, J. Stubbe *J. Am. Chem. Soc.* **1992**, *114*, 4958.
[13] The aqueous solution (200 μL) containing the modified oligonucleotide **21a** (5′-dCGCGT*TACTGCT-3′) or **21b** (5′-d[TCTC]A*d[C-TAACTA]-3′) (0.3 nmol) as well as GSH (about 75 nmol) was saturated with O_2. After photolyzing for 5 – 10 min (Osram 500 W, 320 nm filter, 25 °C) the products were separated by HPLC on a reversed-phase column and the peaks were analyzed by MALDI-TOF MS. The compounds 5′-phosphate **2** and 3′-phosphoglycolate **7** were obtained in all experiments together with 2 – 8 % of 3′-phosphate.
[14] The preferred formation of 3′-phosphoglycolate **7** can also be explained by the Burger mechanism in which the cleavage of intermediate **6a** in DNA leads preferentially to **7**, see R. M. Burger, *Chem. Rev.* **1998**, *98*, 1153.
[15] Review: B. N. Trawick, A. T. Daniher, J. K. Bashkin, *Chem. Rev.* **1998**, *98*, 939.

UF^{3+}—A Thermochemically Stable Diatomic Trication with a Covalent Bond**

Detlef Schröder,* Martin Diefenbach, Thomas M. Klapötke, and Helmut Schwarz*

Dedicated to Professor Heinrich Nöth on the occasion of his 70th birthday

The chemistry and physics of multiply charged ions are attracting ongoing attention. One particular aspect concerns the quest for diatomic, thermochemically stable polycations. Here, thermochemical stability refers to a situation in which the polycation state AB^{n+} is lower in energy than the dissociated fragments due to charge separation, that is $A^{(n-1)+} + B^+$. Since the ionization energies (IEs)[1] of monocations AB^+ are often much larger than those of the separated neutral atoms, IE(A) and IE(B), respectively, many diatomic dications are not thermochemically stable. Nevertheless, a number of thermochemically stable, diatomic dications have recently been studied by theoretical and experimental means.[2] For diatomic trications, however, the energetic situation is even worse, because triple ionization of neutrals often requires enormous amounts of energy such that Coulomb explosion according to reaction (1) is energetically favorable.[3]

$$AB^{3+} \longrightarrow A^{2+} + B^+ \qquad (1)$$

First-principle considerations predict the existence of thermochemically stable diatomic trications for rare gas (Rg) complexes of metals M for which $IE(M^{2+})$ is smaller than IE(Rg). For example, $ThHe^{3+}$ should be stable with respect to charge separation according to reaction (1), simply because $IE(Th^{2+})$ (18.3 eV) is smaller than IE(He) (24.5 eV); in fact, even the existence of $ThHe^{4+}$ has been suggested.[4] However, such highly charged rare-gas complexes offer limited conceptual insight into bonding principles because they are expected to have mostly electrostatic character.

In contrast, we are focussing on the generation of multiply charged molecules having well-defined covalent bonds in which for a diatomic trication it is the $A^{3+}-B$ bond energy which locates the AB^{n+} ground state below the $A^{(n-1)+} + B^+$ asymptote.[5] In this respect the UF^{n+} ($n = 1-3$) cations deem promising, because the combination of uranium and fluorine appears as a good candidate with respect to thermochemical stability (Table 1). Thus, the ionization energies of uranium are moderate,[6] while fluorine is the most electronegative element with a rather high IE (17.4 eV) and a pronounced

[*] Dr. D. Schröder, Prof. Dr. H. Schwarz
Dipl.-Chem. M. Diefenbach
Institut für Organische Chemie der Technischen Universität
Strasse des 17. Juni 135, D-10623 Berlin (Germany)
Fax: (+49) 30-314-21102
Prof. Dr. T. M. Klapötke
Institut für Anorganische Chemie der Universität
Meiserstrasse 1, D-80333 München (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Volkswagen-Stiftung, and the Fonds der Chemischen Industrie.

  1433-7851/99/3801-0137 $ 17.50+.50/0