SELECTIVE CLEAVAGE OF *O*-(DIMETHOXYTRITYL) PROTECTING GROUP WITH SODIUM PERIODATE

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Sodium periodate in aqueous organic solvents selectively removes, under mild reaction conditions, the *O*-(dimethoxytrityl) protecting group. Selectivity of the cleavage was studied using the nucleoside derivatives protected by various types of groups commonly used in nucleoside and nucleotide chemistry.

Keywords: Dimethoxytrityl; Periodate anions; Oxidations; Solvent effects; Catalysis; Lewis acids; Nucleosides; Deprotection; Protective functions.

There is a number of variations on the oxidative cleavage of alkoxy-activated aromatic protecting groups. Thus, ceric ammonium nitrate has been used to deprotect bis(4-methoxyphenyl)methyl[1] and 4-methoxyphenyl groups[2,3] whereas potassium persulfate has been employed for the cleavage of 2,4-dimethoxybenzyl group[4]. As to silyl groups, their stability under various oxidative conditions was reviewed[5]; *tert*-butyl(diphenyl)silyl (TBDPS) group was stable under treatment with RuO_2/$NaIO_4$ whereas a single note[6] mentions $NaIO_4$ without RuO_2 to cleave triethylsiloxy group. The use of KO_2/DMSO/18-crown-6 in the cleavage of TBDMS and TBDPS ethers[7] and the cleavage of *O*-TBDMS group by *N*-bromosuccinimide[8] were also reported.

We report here the cleavage of *O*-(dimethoxytrityl) group using neutral sodium periodate. During the oxidation of thioether bond[9] in 2-*N*-(2-methylpropanoyl)-5′-*O*-(dimethoxytrityl)-6-*O*-{2-[(4-nitrophenyl)sulfanyl]ethyl}-2′-deoxyguanosine (**7**) to sulfoxide derivative with sodium periodate ($NaIO_4$) in aqueous methanol, we have observed a quantitative cleavage of *O*-(dimethoxytrityl) linkage (*O*-DMTr) (Scheme 1). $NaIO_4$ has been extensively used in sugar chemistry to cleave especially diols[10] but we found no reference in the literature on its use with the dimethoxytrityl substituent.

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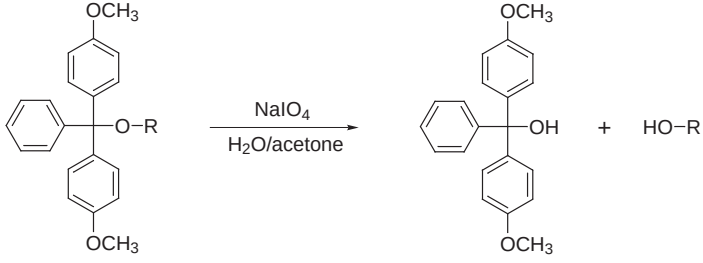
To learn more about it, we subjected various dimethoxytrityl derivatives of nucleosides to the treatment with sodium periodate in aqueous water-miscible solvents. The results of this study are summarized in Table I. Under conditions specified in Table I, the *O*- and *N*-(dimethoxytrityl) groups in compounds **1**–**11, 20** and also TBDMS groups in compounds **19** and **20** were quantitatively cleaved off. The *O*-(methoxytrityl) group exhibited a



1-10 R = nucleoside residue

SCHEME 1

much higher stability (compounds **12, 13**) than the *O*-DMTr group which suggests a possibility, in particular cases, to discriminate between these types of groups. In contrast, a small extent of the cleavage of trityl (**15**, **16**), isopropylidene (**19**), TBDPS (**12**, **13**, **17**, **18**) and benzyl (**6**) protecting groups was observed only at elevated temperatures. Also the tetrahydropyranyl group at the secondary hydroxy group in compound **23** was reasonably stable at room temperature but it was cleaved off completely at 50 °C. Finally, the 3′,5′-tetraisopropyldisiloxanyl group in uridine derivative **22** was cleaved selectively at the 5′-end of the protected nucleoside so that the 3′-hydroxy group remained protected by (di)siloxanyl moiety. These findings could be of practical importance in partial selective deprotection of nucleoside derivatives. In our laboratory we successfully utilized the described $NaIO_4$ cleavage in the purine 2′-deoxynucleoside series to avoid depurinations occuring under acidic conditions. We also succeeded in an IO_4-driven detritylation of thymine nucleoside **8** which proceeded without any anomerization that was otherwise encountered when detritylation was performed in 80% aqueous acetic acid[11].

Our attempts to gather more facts to understand possible mechanism of the cleavage with $NaIO_4$ provided the following important findings (as performed with compound **1**). The rate of cleavage of (dimethoxytrityl)oxy bond rises both with concentration of $NaIO_4$ in the reaction mixture and with polarity of the solvent. Although aqueous methanol and ethanol seem to be better solvents for the cleavage than aqueous acetone or dioxane,

careful analysis of 0.5 M solutions of $NaIO_4$ in 70% aqueous acetone, 70% aqueous ethanol (or methanol), and water, after standing at room temperature for 36 h, revealed the presence of substantial amounts of $NaIO_3$ in aqueous acetone (10 mole %) and aqueous ethanol (50 mole %); no $NaIO_3$ was found in water. Obviously, the organic solvent itself or its trace impurities caused, acting in a catalytic manner, a considerable reduction of $NaIO_4$ to $NaIO_3$. In addition, we have found that the cleavage of methyl [4-*N*-benzoyl-2′-deoxy-5′-*O*-(dimethoxytrityl)cytidin-3′-*O*-yl]methylphosphonate (**9**) with 20 equiv. of $NaIO_4$ (12 h at room temperature) in aqueous solution free from organic solvents provided 7 equiv. of $NaIO_3$ (clearly a non-stoichiometric amount). On the other hand, treatment of $NaIO_4$ (20 equiv.) with 2′-deoxythymidine in water for 16 h left both $NaIO_4$ and nucleoside unchanged; no $NaIO_3$ was formed. It can be concluded that the presence of a non-stoichiometric amount of $NaIO_3$ formed in the cleavage of the *O*-DMTr linkage in water free from organic solvent must be caused by catalytic redox reactions between dimethoxytrityl-containing species and $NaIO_4$. This "catalysis" hypothesis seems to be supported by the findings that no other DMTr-containing species except DMTr-OH were found in the reaction mixture after the cleavage.

Furthermore, we have found that pH value of the reaction mixture remains slightly acidic (pH 4.7 in water) during the reaction but the pH value *per se* affects the DMTr group stability only a little. Thus, the cleavage of the *O*-DMTr bond in compound **1** performed in aqueous ethanol went to completion in 10 h with $NaIO_4$ (10 equiv.) but not in 0.25 M formic acid (10 equiv. relative to the DMTr derivative) where only *ca* 5% of the starting compound was cleaved after the same time. In addition, the presence of various organic and inorganic bases (see Table I, note *c*) completely prevents the cleavage.

To clarify more the nature of the cleavage, we performed experiments in a two-phase system composed of a saturated aqueous solution of $NaIO_4$ and an ethyl acetate or dichloromethane solution of 5′-*O*-DMTr-T **1**, both in the absence and in the presence of $Bu_4N^+HSO_4^-$ as the phase-transfer catalyst (PTC). A small extent of detritylation, not exceeding 10% after 16 h for both solvent systems, was found without PTC while the addition of PTC increased the cleavage to 60–70% after 20 h. We also investigated the cleavage under exclusion of water. It was found that the presence of water is strictly required for the cleavage reaction; no cleavage of the *O*-DMTr bond was observed in absolute ethanol, dichloromethane or benzene without or with 18-crown-6 used as an $NaIO_4$ solubilizer.

Last but not least, we have found that a direct sunlight does not influence the rate of the cleavage, and no free iodine is released during the cleavage.

Since there were reasons for the rationalization that the cleavage of the *O*-DMTr linkage proceeded in an oxidative manner, we performed additional experiments with the use of other types of oxidation agents. Thus, neither hydrogen peroxide, lead tetraacetate nor sodium perchlorate caused the cleavage of the (dimethoxytrityl)oxy bond in compound **1**. On the other hand, potassium persulfate worked as efficiently as $NaIO_4$ itself in the cleavage reaction with compound **1** (14 h at room temperature), but its acidity is much higher than the acidity of $NaIO_4$. On the basis of all these observations, a fundamental question emerges: Is the cleavage of *O*-DMTr linkage a simple $NaIO_4$-mediated hydrolytic reaction or a redox reaction associated with the reduction of $NaIO_4$ to $NaIO_3$?

Although the formation of $NaIO_3$ in the cleavage of the *O*-DMTr linkage could support an oxidative (probably non-radical) mechanism of the cleavage reaction, the experiment performed with compound **9** in water strongly suggests that the formation of a non-stoichiometric amount (excess) of $NaIO_3$ is caused by the dimethoxytrityl-containing species serving as a catalyst for the $NaIO_4$ reduction. This fact seems to be unambiguously confirmed by the experiment with 2′-deoxythymidine and $NaIO_4$ in water where no $NaIO_3$ was formed. We can conclude that $NaIO_4$ reduction could be a side reaction that need not necessarily be connected with the cleavage of the *O*-DMTr linkage.

What could be then the most likely mechanism of the cleavage? It is known that periodate ion IO_4^- coordinates in aqueous solutions two molecules of water to form the hypervalent iodine species $H_4IO_6^-$ (ref.[12]). This ionic compound could be a relatively strong Lewis acid (working in water) responsible for the cleavage of the ether and acetal (ketal) linkages. This assumption seems to be strongly supported by the finding that no cleavage occurred under strictly anhydrous conditions. Although the aqueous solution of $NaIO_4$ is slightly acidic (pH 4.7), the acidity of the $H_4IO_6^-$ ions does not seem to be a single factor sufficient to cleave the *O*-DMTr linkage as proved in the experiment in which the pH *per se* affected the cleavage only a little. These findings suggest that $H_4IO_6^-$ ion has to be coordinated to the electron-rich oxygen atom of the cleaved linkage either *via* replacement of one molecule of water in the $H_4IO_6^-$ ion for the oxygen atom with highest electron density, or *via* formation of hydrogen bond to the same oxygen atom. In both cases the coordination of the $H_4IO_6^-$ ion (probably a rate-limiting factor) would have a destabilizing effect on the C–O linkage result-

TABLE I
Stability of the selected protected nucleosides in the presence of $NaIO_4$

Compound (0.05–0.1 M solution in MeOH–water 7 : 3)		$NaIO_4$ equiv.	Time h	Cleavage, %	
				20 °C	50 °C
2′-Deoxy-5′-*O*-DMTr-thymidine	(**1**)	0.25	16	0	0
	(**1**)	1	16	0	5[a]
	(**1**)	3	16	5[a]	95[a]
	(**1**)	20	6/16	95[a]/100[a]	–
	(**1**)	0.25	16	0	0[b]
	(**1**)	3	16	0[c]	–
2′-Deoxy-3′-*O*-DMTr-thymidine	(**2**)	3	16	50[a]	–
	(**2**)	10	16	100[a]	–
2′-Deoxy-5′-*O*-DMTr-6-*N*-(1-dimethylaminoethylidene)adenosine	(**3**)	20	8	100[a]	–
2′-Deoxy-5′-*O*-DMTr-2-*N*-(2-methylpropanoyl)guanosine	(**4**)	20	8	100[a]	–
4-*N*-Benzoyl-2′-deoxy-5′-*O*-DMTr-cytidine	(**5**)	20	6/16	80[a]/100[a]	–
3′-*O*-Benzyl-2′-deoxy-5′-*O*-DMTr-thymidine	(**6**)	13	48	100[a]	–
2′-Deoxy-5′-*O*-DMTr-2-*N*-(2-methylpropanoyl)-6-*O*-{2-[(4-nitrofenyl)-sylfanyl]ethyl}guanosine	(**7**)	2	16	100[a]	–
1-(2-Deoxy-5-*O*-DMTr-β-D-*threo*-pentofuranosyl)thymine	(**8**)	6	16	100[a]	–
Methyl(4-*N*-benzoyl-2′-deoxy-5′-*O*-DMTr-cytidine-3′-*O*-yl)methyl-phosphonate[d]	(**9**)	20	8	100[a]	–
2-(2-{-[(Dimethoxytrityl)oxy]ethoxy}ethoxy)ethanol	(**10**)	3	16	100[a]	–
6-[Methoxy(trityl)amino]hexanol	(**11**)	3	16	100[e]	–
3′-*O*-[*tert*-Butyl(diphenyl)silyl]-2′-deoxy-5′-*O*-(methoxytrityl)thymidine[f]	(**12**)	20	16	20[e]	–
5′-*O*-[*tert*-Butyl(diphenyl)silyl]-2′-deoxy-3′-*O*-(methoxytrityl)-thymidine[f]	(**13**)	20	16	5[e]	–
1,3-di-*O*-Tritylglycerol[f]	(**14**)	4	16	0	0
	(**14**)	20	16	0	–
2′-Deoxy-5′-*O*-tritylthymidine	(**15**)	2	16	0	0
1-(3-Azido-2,3-dideoxy-5-*O*-trityl-β-D-*erythro*-pentofuranosyl)thymine	(**16**)	20	20	0	10[g]
3′-*O*-[*tert*-Butyl(diphenyl)silyl]-2′-deoxythymidine	(**17**)	20	20	0	–
5′-*O*-[*tert*-Butyl(diphenyl)silyl]-2′-deoxythymidine	(**18**)	20	20	0	–
5′-*O*-[*tert*-Butyl(dimethyl)silyl]-2′,3′-*O*-isopropylideneuridine	(**19**)	2	16	10[h]	30[h]
	(**19**)	12	16	50[h]	100[h]
3′-*O*-[*tert*-Butyl(dimethyl)silyl]-2′-deoxy-5′-*O*-DMTr-thymidine	(**20**)	20	20/72	100[a]/50[h]	–
3′-*O*-[*tert*-Butyl(diphenyl)silyl]-2′-deoxy-5′-*O*-DMTr-2-*N*-(2-methyl-propanoyl)guanosine[i]	(**21**)	17	120	70[a]	–
3′,5′-*O*-(Tetraisopropyldisiloxan-1,3-diyl)uridine	(**22**)	4	16	10[j]	30[j]
	(**22**)	12	16	–	100[j]
4-*N*-Benzoyl-1-(2,3-di-*O*-tetrahydropyran-2-yl-β-D-arabinofuranosyl)-cytosine	(**23**)	2	16	0	10[k]
	(**23**)	20	16	5[k]	90[k]

[a] (Dimethoxytrityl)oxy bond cleavage; [b] in the presence of AIBN; [c] in the presence of triethylamine, sodium hydrogencarbonate, triethylammonium hydrogencarbonate, 4-methoxypyridine-1-oxide or 2,6-lutidine; [d] 0.025 M solution in water; [e] (methoxytrityl)oxy bond cleavage; [f] 0.05–0.1 M solution in acetone–water 7 : 3; [g] trityl cleavage; [h] *tert*-butyl-(dimethyl)silyloxy bond cleavage; [i] further details in Experimental; [j] (tetraisopropyl-disiloxan-1,3-diyl)oxy bond cleavage (only at the 5′-end); [k] (tetrahydropyran-2-yl)oxy bond cleavage. Note: the extent of the cleavage was determined by RP HPLC or estimated from TLC; the products were compared with authentic samples.

ing in its immediate hydrolysis. As it can be seen from the Table I, the more polarized is the C–O linkage the faster is its cleavage.

In our opinion, the gathered knowledge seems to favor the $NaIO_4$-mediated mechanism of the *O*-DMTr linkage hydrolysis; a detailed study to support the suggested course is under way. Still, at this point we have the reason to believe that the described cleavage reaction can be of practical importance in the nucleoside and nucleotide chemistry and in other areas as an alternative to classic acid hydrolysis if a problem is encountered. The findings included in Table I suggest that the use of $NaIO_4$ enlarges the number of available selective deprotecting reactions.

EXPERIMENTAL

The protected nucleosides **1**–**8**, **10**–**23** and the phosphonate derivative **9** (see Table I) as well as all products of the cleavage (for comparative study) were prepared earlier in our laboratory. Sodium periodate (purum) purchased from Lachema Brno, Czech Republic was used in all experiments.

Typical Preparative Procedures

In the following preparative experiments we used an aqueous acetone as the solvent instead of aqueous ethanol (or methanol) because of much better solubility of starting protected nucleosides.

3′-O-[tert-Butyl(diphenyl)silyl]-2′-deoxy-2-N-(2-methylpropanoyl)guanosine[13]. Powdered $NaIO_4$ (74 g, 346 mmol) was added in five unequal portions (32 g, 16 g, 2 × 10 g, 6 g; each after 16 h) to the vigorously stirred solution of 2′-deoxy-3′-*O*-[*tert*-butyl(diphenyl)silyl]-5′-*O*-(dimethoxytrityl)-2-*N*-(2-methylpropanoyl)guanosine[13] (**21**) (17.6 g, 20 mmol) in 70% aqueous acetone (800 ml). The suspension was filtered, the filtration cake washed with acetone, and the combined filtrates were evaporated to dryness. The residue was dissolved in acetone, and the turbid solution filtered through Celite to remove traces of inorganic salts. Chromatography on silica gel in 5% ethanol in chloroform afforded 9.52 g (85%) of 3′-*O*-[*tert*-butyl(diphenyl)silyl]-2-*N*-(2-methylpropanoyl)guanosine and 1.7 g (10%) of the starting material.

3′-O- Benzyl-2′-deoxythymidine[14]. 3′-*O*- Benzyl-2′-deoxy-5′-*O*-(dimethoxytrityl)thymidine[14] (332 mg, 0.5 mmol) in 70% aqueous acetone (10 ml) was treated for 48 h with $NaIO_4$ (1.39 g, 6.5 mmol) added in two portions (1.07 g and 0.32 g within a period of 16 h). TLC in 10% ethanol–chloroform revealed complete detritylation. The workup as described above afforded 130 mg (78%) of 3′-*O*-benzyl-2′-deoxythymidine.

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