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1:1 and 1:2 Complexes of Bu_4NF and BF_3·Et_2O: Unique Properties as Reagents for Cleavage of Silyl Ethers

Shun-ichi Kawahara, Takeshi Wada and Mitsuo Sekine*

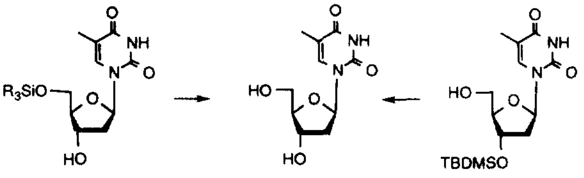
Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 226, Japan

Abstract: A new method for removal of trialkylsilyl groups from silyl ethers using Complex A and Complex B, generated from tetrabutylammonium fluoride (TBAF) and BF_3·Et_2O has been developed. The desilylation by use of these boron complexes is significantly affected by the steric factor on the Si atom and the reagent.

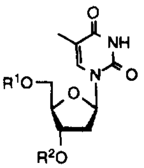
Silyl ethers have been widely used to protect hydroxyl groups in organic synthesis, because they can be prepared easily under mild conditions and selective silylation of primary hydroxyl groups can be utilized in the presence of secondary and/or tertiary alcoholic functions.[1] Sterically hindered trialkylsilyl groups such as TBDMS and *t*-butyldiphenylsilyl (TBDPS) have been often used as protecting groups that are stable under various conditions and cleaved by treatment with fluoride-ion sources such as tetrabutylammonium fluoride (TBAF) and HF-pyridine.[2] Silyl ether linkages have been also cleaved by using a variety of reagents involving Lewis acids and fluoride species such as BF_3·Et_2O,[3] SiF_4,[4] H_2SiF_6,[5] and $LiBF_4$.[6] A comprehensive review of silicon protecting groups has appeared in a book by Green and Wuts.[1b]

In this paper, we report unique properties of 1:1 and 1:2 complexes of TBAF and BF_3·Et_2O as reagents for removal of trialkylsilyl groups from silyl ethers.

In connection with our oligoribonucleotide synthesis, we have needed milder reagents prescribed for removal of the 2'-TBDMS group from protectecd oligoribonucleotide blocks. Our particular interest was focused on the use of complexes of TBAF and BF_3·Et_2O which was first reported as reagents for deprotection of enol ether derivatives by Gevorgyan and Yamamoto.[7,8] Consequently, we found that 1:1 and 1:2 complexes of TBAF and BF_3, *i.e.*, complex **A** (Bu_4NF-BF_3·Et_2O) and complex **B** (Bu_4NF-2(BF_3·Et_2O)), exhibited intrinsic behavior different from the well known desilylating reagents above mentioned.



1a-f **2** **3**



4: $R^1 = R^2$ = TBDMS
5: R^1 = Tr, R^2 = H
6: R^1 = TBDMS, R^2 = THP
7: R^1 = H, R^2 = THP

First, desilylation rate of 5'-*O*-TBDMS-thymidine (**1a**)[8] in CH_3CN was examined under various conditions using 10 equiv of complex **A** or **B**. These results are summarized in Table 1. As the result, it was found that complex **A** cleaved **1a** faster (t_{comp} = 10 min) than TBAF, but more slowly than BF_3 and complex **B** (Entries 1, 2, 5, and 6). When the reaction was prolonged, some byproducts were considerably formed in the case of BF_3·Et_2O and complex **B** (Entries 2, 3, and 6). However, the use of the latter at a concentration of 0.1 M resulted in not only complete depression of such side reactions but also still rapid removal of the TBDMS

Table 1. Time Required for Removal of the TBDMS Group from 5'-O-TBDMS-T (1a) under Various Conditions[a]

	Reagent			Reaction time (min)	
Entry		Conc. (M)	Solvent	t_{comp}	t_{dec}
1	TBAF	1.0	MeCN	40	
2	$BF_3 \cdot Et_2O$	1.0	MeCN	<0.5	$5^b/12\ h^c$
3	$BF_3 \cdot Et_2O$	0.1	MeCN	<0.5	60^b
4	$Bu_4N^+BF_4^-$	1.0	MeCN	no reaction (48 h)	
5	Complex **A**	1.0	MeCN	10	
6	Complex **B**	1.0	MeCN	<0.5	120^b
7	Complex **B**	0.1	MeCN	<0.5	
8	TBAF	1.0	THF	60	
9	$BF_3 \cdot Et_2O$	1.0	THF	24 h	
10	Complex **A**	1.0	THF	180	
11	Complex **B**	1.0	THF	180	

[a] All reactions were carried out in CH_3CN at r.t.

[b] the time when a byproduct was detected.

[c] the time required for complete decomposition.

Table 2. Time Required for Removal of Silyl Groups from 5'-O-Silylated-T (1a-f)[a]

		t_{comp} (min.)		
Entry	Silyl Ether	TBAF	Complex **A**	Complex **B**
1	$tBuMe_2Si$ **1a**	40		
2			10	
3				<0.5
4	Ph_2MeSi **1b**	<0.5		
5			<0.5	
6				<0.5
7	Ph_3Si **1c**	<0.5		
8			10	
9				<0.5
10	$ThexylMe_2Si$ **1d**	60		
11			60	
12				2
13	iPr_3Si **1e**	20		
14			600	
15				20
16	$tBuPh_2Si$ **1f**	60		
17			$t_{1/2} = 12$ h	
18				300

[a] All reactions were carried out in CH_3CN at r.t.

group (Entry 7). In the present boron complex mediated desilylation, a remarkable solvent effect was observed. When THF was used as the solvent, the rate of desilylation using BF_3, complex **A**, or complex **B** was extremely decreased (Entries 9–11). The reason of this solvent effect might be due to unfavorable coordination of these boron reagents with THF having lone pair electrons.

Next, the relationship between the reaction time and the steric factor on the silicon atom was studied (Table 2). Diphenymethylsilyl and triphenylsilyl ethers (**1b** and **1c**) were so unstable that cleavage of the O-Si bonds was too fast to detect an obvious difference in reaction rate between TBAF and complex **B**. Desilylation using complexes **A** and **B** was affected significantly by the steric hindrance on silicon. For example, complex **A** could cleave the O-Si bond of **1a** faster than TBAF (Entries 1, 2), but was considerably less reactive toward the 5'-*O*-triisopropylsilyl (TIPS) thymidine (**1e**) (Entries 13 and 14) and 5'-*O*-TBDPS-thymidine (**1f**) (Entries 16 and 17). On the other hand, complex **B** cleaved very effectively the O-Si bonds of **1a** (Entries 1 and 3) and 5'-*O*-dimethylthexylsilylthymidine (**1d**) (Entries 10 and 12), but slowly in the case of **1f** (Entries 16 and 18). These substituent effects can be explained in terms of the steric hindrance around the oxygen atom of silyl ethers ($tBuMe_2Si \leq ThexylMe_2Si < iPr_3Si < tBuPh_2Si$) as well as the bulkiness of nucleophiles ($F^- \ll BF_4^-$ and $B_2F_7^-$).

The rates of cleavage of the O-Si bond of 5'-*O*-TBDMS-thymidine (**1a**) and 3'-*O*-TBDMS-thymidine (**3**) were compared (Table 3). In both cases, complex **A** or **B** cleaved faster than TBAF (Entries 1 and 3 or Entries 5 and 7) even though the steric effect of desilylation on the rate is bigger in these boron complexes than in TBAF, so that the TBDMS group attached to the secondary hydroxyl group of **3** was removed much more slowly than that attached to the primary hydroxyl group of **1a** (Entries 6–8).

The remarkable effect of substituents on the Si atom could be applied to the selective Si-O bond cleavage of organic molecules having different silyl ethers. To test this possibility, chemoselective desilylation[4,5b,6] of a 1:1 mixture of two silyl ethers was examined (Table 4). The rate of desilylation using complex **B** was so fast that the selective desilylation was achieved neither between **1a** and **3** (Entry 2) nor between **1a** and **1e** (Entry 4). Nonetheless, satisfactory selective desilylation of the TBDMS ether **1a** from a 1:1 mixture of **1a** and **1f** was conducted (Entry 6), resulting in 86% recovery of **1f**. It should be noted that complex **A** is more suitable for the selective removal of the TBDMS group of **1a** from a mixture of **1a** and **3**, as shown in Entries 1 and 2 of Table 5, because it reacts more slowly with silyl ethers. Similarly, 87% of **1e** could be recovered from a

Table 3. Comparison of the Time Required for Removal of the TBDMS Group from 5'-O-TBDMS-T (1a) with That of 3'-O-TBDMS-T (3)^a

Entry	Compd.	Reagent	Conc. (M)	t_{comp} (min.)
1	**1a**	TBAF	1.0	40
2	**1a**	Complex **A**	1.0	10
3	**1a**	Complex **B**	1.0	<0.5
4	**1a**	Complex **B**	0.1	<0.5
5	**3**	TBAF	1.0	60
6	**3**	Complex **A**	1.0	120
7	**3**	Complex **B**	1.0	10
8	**3**	Complex **B**	0.1	20

^{a}All reactions were carried out in CH_3CN at r.t. using 10 equiv of reagent.

Table 4. Selectivity in Desilylation by Boron Complexes^a

Entry	Compd.	Reagent	Conc. (M)	Time min	Recovered compd. (%)
1	**1a** + **3**	Complex **A**	1.0	15	**3** (72)
2	**1a** + **3**	Complex **B**	1.0	1	**3** (22)
3	**1a** + **1e**	Complex **A**	1.0	15	**1e** (87)
4	**1a** + **1e**	Complex **B**	1.0	1	**1e** (30)
5	**1a** + **1f**	Complex **A**	1.0	15	**1f** (89)
6	**1a** + **1f**	Complex **B**	1.0	1	**1f** (86)
7	**4**	Complex **A**	1.0	15	**3** (76)
8	**1a** + **5**	Complex **A**	1.0	15	**5** (9)
9	**6**	Complex **A**	1.0	15	**7** (52)

^{a}All reactions were carried out in CH_3CN at r.t. using 10 equiv of reagent. The reactions were quenched in the case of Entries 1-6 and 8 when one of the two components disappeared.

mixture of **1a** and **1e** after treatment with complex **A** for 15 min, when **1a** disappeared completely. Treatment of a mixture of **1a** and **1f** with complex **A** gave also 89% recovery of **1f**. Compound **3** was obtained in 76 % yield by reaction of 3',5'-*O*-bis(*t*-butyldimethylsilyl)thymidine (**4**) with complex **A** (Entry 7).

The trityl group was lost considerably when the 5'-TBDMS group of **1a** was deprotected from a mixture of **1a** and 5'-*O*-tritylthymidine (**5**) by complex **A**, but ca. half of the 3'-THP group of 5'-*O*-TBDMS-3'-*O*-THP-thymidine (**6**) remained under the same conditions as shown in (Entries 8 and 9).

Before we started this study, *ab initio* calculations of BF_3, BF_4^-, and $B_2F_7^-$, the latter two of which might be produced from the 1:1 and 1:2 mixtures of TBAF and $BF_3 \cdot Et_2O$, were carried out at the MP2/6-31+G* level, in an attempt to expect the possibility of the present desilylation.[10] The results of these calculations are summarized in Table 5.

Table 5. Eigenvalues of HOMO and LUMO and Net Atomic Charges of Boron Reagents of *ab initio* Calculation at the Level of MP2/6-31+G*

Reagent	Eigenvalues (au)		Net Atomic Charges (e)	
	HOMO	LUMO	B	F
BF_3	-0.67	0.05	1.49	-0.35
BF_4^-	-0.39	0.22	1.80	-0.70
$B_2F_7^-$	-0.45	0.18	1.83	-0.64^a, -0.65^a -078^b

^{a} [$\underline{F}_3$B-F-B$\underline{F}_3$]- ^{b}[F_3B-$\underline{F}$-BF_3]$^-$

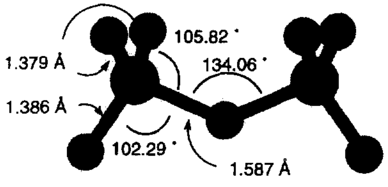


Fig. 1 The structure of $B_2F_7^-$ proposed by *ab initio* calculation (MP2/6-31+G*)

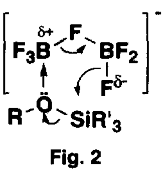


Fig. 2

The calculation of the ionic species $B_2F_7^-$ converged to an optimized structure as shown in Fig. 1. Although BF_4^- and $B_2F_7^-$ do not have unoccupied orbitals which can coordinate with the oxygen atom of silyl ethers, the atomic charges of the boron atoms in BF_4^- (1.80 e) and $B_2F_7^-$ (1.83 e) are as electron-deficient as that of BF_3 (1.49 e). As the result, such a strong possitive charge on the boron complexes enables the facile approach of the boron atom of BF_4^- or $B_2F_7^-$ to the electron-rich oxygen atom of silyl ethers by electrostatic interaction. On the other hand, $B_2F_7^-$ has two kinds of electronegative fluorines (-0.64 and -0.65 e) similar to that of BF_4^- (-0.70 e). Moreover, it is likely that $B_2F_7^-$ can form a six-membered ring intermediate with a silyl ether as shown in Fig 2. This study was actually done on the basis of these results and expectation.

However, it was found that commercially available Bu_4NBF_4 had no ability of cleaving **1a**, as shown in Entry 4 of Table 1.[11] Addition of Et_2O to Bu_4NBF_4 gave a similar result. These results imply that the active species in complex **A**, prepared by addition of $BF_3{\cdot}Et_2O$ to Bu_4NF, is not Bu_4NBF_4 but something like TBAF-$BF_3{\cdot}Et_2O$ containing an ether ligand, as proposed originally by Gevorgyan and Yamamoto.[7,11] Complex **B** might be composed of similar components having ether ligands. Moreover, the above *ab initio* calculation suggested that complex **B** might involve a new species having the B-F-B linkage as a possible component for the present desilylation.

The ^{19}F NMR (56.45 Hz, $CFCl_3$ as reference) spectrum of complex **B** in CD_3CN exhibited a broad resonance signal at -153.47, while complex **A** showed a similar but less broad resonance signal at -149.41 ppm. Contrary to these results, $BF_3{\cdot}Et_2O$ exhibited a sharp resonance signal at -153.35 ppm. The broadening of the signals observed in complexes **A** and **B** implies that the complex **B** is in rapid equilibrium between the parent $BF_3{\cdot}Et_2O$ and complex **A**, which is also in equlibrium between TBAF and $BF_3{\cdot}Et_2O$. These results also suggested that the real species responsible for the present desilylation might be either the complexes themselves or two dissociated ones.

In conclusion, TBAF, complexex **A** and **B** reacted with compounds having silyl ethers in the following order: TBAF (iPr_3Si > TBDMS > $ThexylMe_2Si$ = $tBuPh_2Si$); complex **A** (TBDMS > $ThexylMe_2Si$ > iPr_3Si >> $tBuPh_2Si$); complex **B** (TBDMS > $ThexylMe_2Si$ > iPr_3Si >> $tBuPh_2Si$). These inherent properties of the boron complexes described in this paper would provide a combined use of different silyl protecting groups for conversion of functional groups. Complex **B** would be a useful reagent for rapid emoval of the TBDMS group, while complex **A** would be highly useful for selective removal of TBDMS ethers in the presence of iPr_3Si or $tBuPh_2Si$ ethers.

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