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1:1 and 1:2 Complexes of Bu₄NF and BF₃·Et₂O: Unique Properties as Reagents for Cleavage of Silyl Ethers

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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 BF₃·Et₂O,³ SiF₄,⁴ H₂SiF₆,⁵ and LiBF₄.⁶ 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 BF₃·Et₂O 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 $BF_3 \cdot Et_2O$ 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 $BF_3 \cdot i.e.$, complex A ($Bu_4NF-BF_3 \cdot Et_2O$) and complex B ($Bu_4NF-2(BF_3 \cdot Et_2O)$), exhibited intrinsic behavior different from the well known desilylating reagents above mentioned.



First, desilylation rate of 5'-O-TBDMS-thymidine $(1a)^8$ in CH₃CN 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 BF₃ and complex B (Entries 1, 2, 5, and 6). When the reaction was prolonged, some byproducts were considerably formed in the case of BF₃·Et₂O 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

	Rea	gent			Reaction	time (min)
Entry		Conc.	(M)	Solvent	t _{comp}	t _{dec}
1	TBAF	1.	.0	MeCN	40	
2	BF3·Et2O	1.	0	MeCN	<0.5	5 ^b /12 h ^c
3	BF3.Et2O	0	.1	MeCN	<0.5	60 ^b
4	Bu₄N ⁺ BF₄ ⁻	1.	.0	MeCN	no rea	ction (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	BF3·Et2O	1.	.0	THF	24 h	
10	Complex	A 1.	.0	THF	180	
11	Complex	B 1.	.0	THF	180	

Table 1. Time Required for Removal of the TBDMS Group

from 5'-O-TBDMS-T (1a) under Various Conditions^a

 Table 2. Time Required for Removal of Slivi Groups

 from 5'-O-Silviated-T (1a-f)^a

Silyl _		t _{comp} (min.)				
	Entry	Ether	TBAF	Complex A	Complex B	
	1 2 3	tBuMe ₂ Si 1a	40	10	<0.5	
	4 5 6	Ph ₂ MeSi 1 b	<0.5	<0.5	<0.5	
	7 8 9	Ph ₃ Si 1c	<0.5	10	<0.5	
	10 11 12	ThexylMe ₂ Si 1 d	60	60	2	
	13 14 15	iPr ₃ Si 1e	20	600	20	
	16 17 18	tBuPh ₂ Si 1f	60	t _{1/2} = 12	h 300	

^a All reactions were carried out in CH₃CN at r.t.

^b the time when a byproduct was detected.

^c the time required for complete decomposition.

a All reactions were carried out in CH3CN 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 (tBuMe₂Si ≤ ThexylMe₂Si < iPr₃Si < tBuPh₂Si) as well as the bulkiness of nucleophiles ($F^- << BF_4^-$ 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. Co	mparison of the	Time Required	for Removal
of the TBD!	MS Group from	5'-O-TBDMS-T (*	a) with That
of 3'-O-TBD	DMS-T (3) ^a		

Entry	Compd.	Reagent Conc. (M)		t _{comp} (min.)
1	1a	TBAF	1.0	40
2	1a	Complex A	1.0	10
з	1 a	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

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		Reager	nt	Time	Recovered	
Entry	Compd.	Con	c. (M)	min	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)	_

^aAll reactions were carried out in CH₃CN at r.t. using 10 equiv of reagent.

^aAll reactions were carried out in CH₃CN 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 BF₃, BF₄⁻, and B₂F₇⁻, the latter two of which might be produced from the 1:1 and 1:2 mixtures of TBAF and BF₃·Et₂O, 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.

Level of MP2/0-31+0						
Descent	Eigenvalues (au)		Net Atomic Charges (e)			
Reagent	номо	LUMO	В	F		
BF3	-0.67	0.05	1.49	-0.35		
BF4	-0.39	0.22	1.80	-0.70		
B ₂ F ₇	-0.45	0.18	1.83	-0.64 ^a , -0.65 ^a -078 ^b		

Table 5. Elgenvalues of HOMO and LUMO and Net Atomic Charges of Boron Reagents of *ab initio* Calculation at the







105.82

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 Et₂O to Bu₄NBF₄ gave a similar result. These results imply that the active species in complex A, prepared by addition of BF₃·Et₂O to Bu₄NF, is not Bu₄NBF₄ but something like TBAF-BF₃·Et₂O 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 ¹⁹F NMR (56.45 Hz, CFCl₃ as reference) spectrum of complex **B** in CD₃CN 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 equilibrium 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 silvl ethers in the following order: TBAF ($iPr_3Si > TBDMS > ThexylMe_2Si = tBuPh_2Si$); complex A (TBDMS > ThexylMe_2Si > iPr_3Si >> tBuPh₂Si); complex **B** (TBDMS > ThexylMe₂Si > iPr₃Si >> tBuPh₂Si). 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 iPr₃Si or tBuPh₂Si ethers.

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- REFERENCES AND NOTES
 1. a) Colvin, E. W. Silicon Reagents in Organic Synthesis; Academic Press: London, 1988. b) Greene, T. W. and Wuts, P. G. M. Protective Groups in Organic Synthesis; John Wiley and Sons, Inc.: New York, 1991.
- a) Corey, E. J.; Venkateswawarlu, A. J. Am. Chem. Soc. 1972, 94, 6190. b) Carpino, L. A.; Sau, A. C. J. Chem Soc., Chem. Commun. 1979, 514. d) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. Tetrahedron Lett. 1979, 20, 3981.
 a) Barton, T. J.; Tully, C. R. J. Org. Chem. 1978, 43, 3649. b) Kelly, D. R.; Robert, S. M. Synthetic Commun. 1979, 9, 295.
 Corey, E. J.; Yi, K. -L. Tetrahedron Lett. 1992, 33, 2289.
 a) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. J. Org. Chem. 1992, 57, 2492. b) Pilcher, A. S.; DeShong, P. J. Org. Chem. 1993, 58, 5130.
 Metcalf, B. W.; Bukhart, J. P.; Jund, K. Tetrahedron Lett. 1980, 21, 35.
 Gevorgyan, V.; Yamamoto, Y. J. Chem. Soc., Chem. Commun. 1994, 59. In this paper, reagents of TBAF-BF3 in which the ratio of TBAF:BF3 varied from 1:0.1 to 1:1.5, were used.

- TBAF-BF₃ in which the ratio of TBAF:BF₃ varied from 1:0.1 to 1:1.5, were used.
- 9.
- TBAF-BF3 in which the ratio of TBAF:BF3 varied from 1:0.1 to 1:1.5, were used. Gevorgyan, V.; Yamamoto, Y. Tetrahedron Lett. **1995**, 36, 7765. Hanessian, S.; Lavalee, P. Can. J. Chem. **1975**, 53, 2975. New compounds **1c** and **1d** have mps of 126 °C and 171-173 °C, respectively (from CH₂Cl₂-hexane). Compound **1b** was obtained as foam. These new compounds have satisfactory elemental analyses and were characterized by ¹H, ¹³C NMR. Compounds **1b**, **1e**, and **1f** were synthesized by the literature method: Ogilvie, K. K. Can. J. Chem. **1973**, 51, 3799; Ogilvie, K. K.; Donald J. I. Tetrahedron Lett. **1973**, 14, 317; Ogilvie, K. K.; Thompson E. A.; Quilliam, M.A.; Westhmore, J. B. Tetrahedron **1974**, 33, 2865. Calculation was performed on a Cray C916/12256 super computer by using Guassian 94, Revision B.3: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J.; R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Pittsburgh PA, 1995. One of the referees kindly suggested this possibility. 10.
- 11. One of the referees kindly suggested this possibility.

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