Hydrated Tetrabutylammonium Fluoride as a Powerful Nucleophilic Fluorinating Agent

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Lipophilic quaternary ammonium fluorides, in particular tetrabutylammonium fluoride, TBAF (**1**), find widespread use as organic sources of F^- for nucleophilic fluorination reactions in aprotic solvents, even of low polarity.[1] However, the high hygroscopicity of these salts is considered a severe limitation to the use of these compounds. Tetraalkylammonium fluorides are obtained as stable trihydrate products,[2] whereas complete dehydration processes are usually accompanied by extensive decomposition of the quaternary fluoride via a Hofmann-like elimination reaction.[3,4]

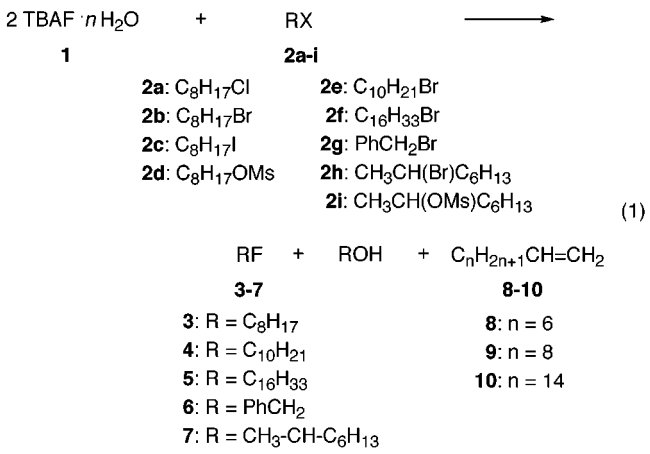
Cox et al.[5] reported that TBAF (**1**) can be prepared "anhydrous" by heating the commercial trihydrate material at ∼ 40 °C under high vacuum for several hours. In fact, this procedure affords **1** still retaining some water and variable amounts of decomposition products.[5,6] These authors showed that the so-called "anhydrous TBAF" in the reactions with alkyl halides and tosylate behaves not only as a good source of nucleophilic fluoride, generating the expected fluoro derivatives **3**, but also as a strong base and hydrolyzing agent, producing substantial amounts of the corresponding alkenes and alcohols, respectively.[5]

In a previous paper,[4] we reported a quantitative study of the influence of the specific hydration *n* on the reactivity (nucleophilicity and basicity) of quaternary ammonium fluorides in nonprotic organic solvents. In particular, we found that in the same hydration range $1.5 < n < 6$ of $R_4N^+F^-\cdot nH_2O$, the F^- basicity is much more decreased than its nucleophilicity by increasing *n*. On the basis of these results, hydrated TBAF·nH_2O (**1**) was anticipated to be an efficient, nonbasic, nucleophilic fluorinating agent; therefore we decided to reinvestigate the nucleophilic fluorination of alkyl halides and sulfonates **2** with **1** (eq 1). A systematic study was conducted by reacting substrates **2** with TBAF·nH_2O in several hydration states ($n = 0.5-10$), in acetonitrile or without solvent, and 1-bromooctane (**2b**) was chosen as a model for the process optimization (Table 1).

Table 1. Effect of Hydration State *n* of Fluoride Ion on Products Distribution in Reaction of 1-Bromooctane (2b) with $Bu_4N^+F^-\cdot nH_2O$ (1)[a]

entry	*n*	solvent	reaction time, h[c]	T, °C	products, %[b] **3**	**8**
1	0.5	CH_3CN	0.5	25	73	27
2	0.5	CH_3CN	0.25	80	56	44
3	0.5	-	0.25	80	63	37
4	1.2	CH_3CN	0.5	80	64	36
5	1.2	-	0.25	80	70	30
6	3.5	CH_3CN	0.5	80	87	13
7	3.5	-	0.25	80	91	9
8	5	CH_3CN	2	80	91	9
9	5	-	0.5	80	94	6
10	10	CH_3CN	9	80	91	9
11	10	-	4	80	93	7
12	5	CH_3CN	26	50	92	8
13	5	-	8	50	93	7
14	5[d]	CH_3CN	12[e]	80	83	11
15	5[d]	-	2	80	91	9
16	5[f]	CH_3CN	8	80	87	13
17	5[f]	-	1	80	90	10

[a] 1-Bromooctane (**2b**), 1 mol equiv; $Bu_4N^+F^-\cdot nH_2O$ (**1**), 2 mol equiv. [b] GLC yields. [c] At 100% conversion. [d] 1.2 mol equiv of **1**. [e] At 94% of conversion. [f] 1.5 mol equiv of **1**.



As expected,[4] we found that the distribution of the reaction products strongly depends on the TBAF hydration state *n*. In particular, the ratio of fluorination/elimination products greatly increased by increasing *n*. Indeed, the reaction of 1-bromooctane (**2b**) (Table 1) with "anhydrous TBAF" ($n = 0.5$) (entries 1−3) gave moderate yields (56−73%) of 1-fluorooctane (**3**) and substantial amounts (27−44%) of 1-octene (**8**). On the contrary, **3** increased up to 94% when the pentahydrate species, $Bu_4N^+F^-\cdot 5H_2O$ (2 mol equiv), was used instead of the anhydrous reagent, by operating without solvent, at 80 °C for 0.5 h (entry 9). The same results, although in longer reaction times, were found in the reactions with decahydrate **1** ($n = 10$) (entries 10, 11). Even commercial TBAF ($n = 3.5$) is a good fluorinating agent,[7] affording 1-fluorooctane (**3**) in 87−91% yields (entries 6, 7). As expected, the reaction time increased by decreasing the

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(6) In our hands this procedure afforded "anhydrous TBAF" (**1**) containing 0.5 mol equiv of water and 6% molar of tetrabutylammonium bifluoride (Karl Fischer and acid−base titration).

(7) Katzenellenbogen and co-workers[1e] reported that haloalkyl trifluoromethanesulfonates react with TBAF·$3H_2O$, affording the corresponding haloalkyl fluorides in 74−90% yields.

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Table 2. Reaction of Substrates 2a−i with $Bu_4N^+F^-\cdot nH_2O$ (1) without Solvent[a]

				products, %[b]	
entry	**2**	*n*	time, h	RF	alkene
1	**a**	3.5	6	**3** (95)	**8** (5)
2	**a**	5	7	**3** (96)	**8** (4)
3	**b**	3.5	0.5	**3** (91)	**8** (9)
4	**b**	5	0.5	**3** (94)	**8** (6)
5	**c**	3.5	0.25	**3** (70)	**8** (30)
6	**c**	5	0.25	**3** (76)	**8** (24)
7	**d**	3.5	0.25	**3** (100)	- -
8	**d**	5	0.25	**3** (100)	- -
9	**e**	5	0.5	**4** (88)	**9** (12)
10	**f**	5	0.5	**5** (86)	**10** (14)
11	**g**	3.5	0.5[c]	**6** (90)[d]	- -
12	**h**	5	1	**7** (32)	(68)[e]
13	**h**	10	6	**7** (40)	(60)[e]
14	**i**	5	0.5	**7** (72)	(28)[e]
15	**i**	5	4[f]	**7** (78)	(22)[e]

[a] Substrates **2a**−**i**, 1 mol equiv; $Bu_4N^+F^-\cdot nH_2O$ (**1**), 2 mol equiv; 80 °C. [b] GLC yields. [c] At 25 °C. [d] Together with 10% of benzyl alcohol. [e] As a mixture of 1- and 2-octenes. [f] At 50 °C.

molar excess of the fluorinating agent **1** or working at 50 °C instead of 80 °C (entries 12−17).

The results obtained for substrates **2a**−**i** are reported in Table 2. Under the better conditions found for **2b** ($n = 5$) or using commercial TBAF ($n = 3.5$), octyl chloride (**2a**) afforded octyl fluoride (**3**) in 95−96% (entries 1, 2), whereas methanesulfonate **2d** gave quantitative conversion to **3** with both TBAF species (entries 7, 8). Lower yields of **3** (76%) together with higher amounts of 1-octene (**8**) (24%) were observed in the reaction of 1-iodooctane (**2c**) (entries 5, 6). A reduced selectivity was found increasing the number of carbon atoms in the alkyl chain: 1-bromodecane (**2e**) and 1-bromohexadecane (**2f**) gave the fluoro derivatives **4** in 88% and **5** in 86% yield, respectively (entries 9, 10). Benzyl bromide (**2g**) quickly reacted with commercial $TBAF\cdot 3.5H_2O$ (**1**) at 25 °C, affording benzyl fluoride (**6**) in excellent yields (90%) and 10% of benzyl alcohol (entry 11). The main reaction product of 2-bromooctane (**2h**) in the presence of $TBAF\cdot 5H_2O$ (entry 12) was a mixture of 1- and 2-octene (68%) together with only a minor quantity of 2-fluorooctane (**7**) (32%). A slight increase of **7** (40%) was obtained in the reaction of **2h** with $TBAF\cdot 10H_2O$ (**1**) (entry 13). Using 2-octyl methanesulfonate (**2i**), the 2-fluoro derivative **7** was obtained in 72% yield, which increased to 78% by performing the reaction at 50 °C (entry 14, 15).

Generally, fluorinations in acetonitrile (Table 3) are slower than those carried out without solvent, the fluoro derivatives being generated in similar yields.

It is worth noting that, differently from that previously reported by Cox et al.,[5] no detectable amounts of the corresponding alcohols were produced in the fluorination reaction of the substrates **2a**−**f**,**h**−**i**, using $TBAF\cdot nH_2O$ in the hydration state range $0.5 < n < 10$.

In conclusion, hydrated tetrabutylammonium fluoride (**1**), in particular the pentahydrate and the commercial species, behaves as a powerful, nonbasic and nucleophilic fluorinating agent, and it is particularly suitable for converting alkyl chlorides, bromides, and methanesulfonates into the corresponding alkyl fluorides.

Experimental Section

General Methods. The ^1H NMR and ^{19}F NMR were run in $CDCl_3$ and acetone-d_6 at 300 and 282 MHz. Chemical shifts are reported in ppm relative to Me_4Si (^1H) and $CFCl_3$ (^{19}F) as external standards. The progress of the reaction was monitored by GLC (50 cm × 1.6 mm OV 101−5% chrom WHP 100−120 mesh and capillary MP19091J-413 30m × 0.32 mm × 0.25 μm columns with a temperature program from 30 °C to 240 °C) and GC-MS (EI 70 eV, J&W 08−3MS 30 × 0.25 mm × 0.25 μm column). The data were evaluated by an internal standard method. In all cases the mass balance of the reaction mixture was ≥ 98% in the expected reaction products.

Table 3. Reaction of Substrates 2a−d,g−i with $Bu_4N^+F^-\cdot nH_2O$ (1) in Acetonitrile[a]

			reaction	products, %[b]	
entry	**2**	*n*	time, h	RF	alkene
1	**2a**	3.5	12	**3** (90)	**8** (10)
2	**2a**	5	16	**3** (94)	**8** (6)
3	**2b**	3.5	1	**3** (87)	**8** (13)
4	**2b**	5	2	**3** (91)	**8** (9)
5	**2c**	3.5	0.25	**3** (60)	**8** (40)
6	**2c**	5	0.25	**3** (77)	**8** (21)
7	**2d**	3.5	0.5	**3** (98)	**8** (2)
8	**2d**	5	0.5	**3** (99)	**8** (1)
9	**2g**	3.5	0.5[c]	**6** (95)	-[d]
10	**2h**	5	2	**7** (38)	(62)[e]
11	**2h**	10	16	**7** (41)	(59)[e]
12	**2i**	5	1	**7** (70)	(30)[e]
13	**2i**	5	1[f]	**7** (76)	(24)[e]

[a] Substrates **2a**−**d**,**g**−**i** 1 mol equiv; $Bu_4N^+F^-\cdot nH_2O$ (**1**), 2 mol equiv; 80 °C. [b] GLC yields. [c] At 25 °C. [d] Together with 5% of benzyl alcohol. [e] As a mixture of 1- and 2-octene. [f] At 50 °C.

Compounds **2d**[8], **2h**[9], and **2i**[8] were prepared as described elsewhere, whereas other substrates **2a**−**c**,**e**−**g** are commercially available and were distilled before use. Acetonitrile over molecular sieves (Fluka) was used throughout the work.

TBAF $3.5\cdot H_2O$ was obtained by Aldrich (Karl Fischer titration).The final hydration state *n* of various $TBAF\cdot nH_2O$ (**1**) ($n =$ 0.5, 1.2, 5, 10) was confirmed by Karl Fischer titration of THF solutions prepared in a dry box.

Typical Procedure for Fluorination with $TBAF\cdot nH_2O$ (1) ($n < 3.5$). $TBAF\cdot 3.5H_2O$ **1** (2 mmol) was gently heated (<40 °C) under sonication and high vacuum (4×10^{-4} Torr) in a round-bottomed flask equipped with an inlet. The loss of weight was monitored at regular intervals after filling with nitrogen. $TBAF\cdot 1.2H_2O$ was obtained after 12 h, whereas 30 h were necessary to prepare $TBAF\cdot 0.5H_2O$.[6]

As soon as the desired hydration state was achieved, the reactions were carried out in the same flask by adding 2-methoxynaphthalene (0.2 mmol) as internal standard, the solvent (2 mL) (if necessary), and the substrate **2** (1 mmol). A reflux condenser equipped with a calcium chloride drying tube was connected and the reaction mixture heated under magnetic stirring.

Typical Procedure for Fluorination with $TBAF\cdot nH_2O$ (1) ($n \geq 3.5$). Method A (Neat). A screw cap vial was charged with $TBAF\cdot 3.5H_2O$ (**1**) (2 mmol), 2-methoxynaphthalene (0.2 mmol), and the water required to obtain the desired hydration state ($n = 5$, 10). After 1 min of stirring, the substrate **2** (1 mmol) was added and the reaction mixture stirred at the specified temperature until completion.

Samples were withdrawn at various times after cooling and centrifuging the vial. The samples were further diluted with CH_3CN and injected.[10]

Method B (CH_3CN). Standardized acetonitrile solutions of $TBAF\cdot nH_2O$ ($n = 5$, 10) (2 M) were prepared by adding the

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(10) When a chlorinated solvent (e.g., CH_2Cl_2) was used instead of CH_3CN, variable amounts of 1-chlorooctane (**2a**) were detected in the reaction mixture of 1-bromooctane (**2b**) with TBAF. As reported,[2] dichloromethane promotes metathesis of TBAF, producing tetrabutylammonium chloride, which is a good chlorinating reagent and reacts with **2b**, generating the less reactive **2a**, thus reducing the overall reaction rate. **2a**, which we identified by GC-MS and ^{13}C and ^1H NMR analyses, can be confused with 1-octanol because of the similar chromatographic retention times and proton resonances. This behavior could be responsible for the differences between the data reported by Cox et al. [5] and our results (i.e., Cox found large amounts of 1-octanol).

calculated amounts of water to the appropriate quantity of commercial TBAF·3.5H_2O (**1**) in a volumetric flask, which was filled to the mark with the solvent. A screw-cap vial was charged with 1 mL of a CH_3CN solution of the substrate **2** (1 M) and 2-methoxynaphthalene (0.2 M) as internal standard, and 1 mL of a standardized CH_3CN solution of TBAF·*n*H_2O (**1**) (n = 5, 10) (2 M). The reaction vial was closed and heated at the desired temperature until completion. Samples were withdrawn at various times after cooling the vial and directly injected.

Typical Procedure for Isolation of Fluoro Derivatives. 1-Fluorooctane (3) (Method A). 1-Bromooctane (1.73 mL, 10 mmol) and water (0.54 mL, 30 mmol) were added to TBAF·3.5H_2O (6.49 g, 20 mmol) and the mixture was stirred for 0.5 h at 80 °C. After cooling to room temperature, pentane was added and decanted after centrifugation. The pentane layers (5 × 10 mL) were combined and treated with bromine dropwise until the orange color remained. The excess bromine was removed by washing with 5% aqueous thiosulfate and the resultant organic phase was dried (Na_2SO_4) and evaporated. The crude fluorooctane **3** was purified by distillation to give 1.07 g (81%) of pure compound (> 99 by GLC), bp 142 °C.[11] ^{19}F NMR ($CDCl_3$) δ −218.2 (septet, $^2J_{HF}$ = 47.8, $^3J_{HF}$ = 24.4).[5]

Benzyl Fluoride (6). (Method B). Benzyl bromide (1.19 mL, 10 mmol) was added to an acetonitrile (20 mL) solution of TBAF·3.5H_2O (6.49 g, 20 mmol). After stirring for 0.5 h at 25 °C, water (5 mL) was added and the reaction mixture was extracted with 5 × 10 mL of pentane. The combined extracts were dried (Na_2SO_4) and evaporated. The crude benzyl fluoride **6** was purified by distillation to give 0.87 g (79%) of pure compound (> 99% by GLC), bp 60 °C/60 mbar. ^{19}F NMR ($CDCl_3$) δ −207.2 (t, $^2J_{HF}$ = 48.2).[12]

1-Fluorodecane (**4**). Bp 189 °C.[13] ^{19}F NMR ($CDCl_3$) δ −218.4 (septet, $^2J_{HF}$ = 47.7, $^3J_{HF}$ = 24.6).[14]

2-Fluorooctane (**7**). Bp 138−139 °C.[11] ^{19}F NMR ($CDCl_3$) δ −170.8 (m).[5]

1-Fluorohexadecane (**5**). Bp 148 °C/2 Torr.[11] ^{19}F NMR ($CDCl_3$) δ −218.5 (septet, $^2J_{HF}$ = 48.7, $^3J_{HF}$ = 24.3).

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