LETTERS

Synthesis, Characterization, and Reactivity of Thermally Stable Anhydrous Quaternary Ammonium Fluorides

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Supporting Information

ABSTRACT: The synthesis and properties of a new class of anhydrous quaternary ammonium fluorides, based on the rigid skeleton azabicyclo[2.2.2]octane, is described. Compounds 2a-d were easily prepared by passing the corresponding ammonium iodides over fluoride-based resin followed by drying their hydrated form at 100 or 140 °C under reduced pressure. The stability (experimental and theoretical study), solubility, reactivity, and characterization by solution and solid-state MAS NMR are discussed.

C ubstitution of functional groups by a fluoride ion remains a Central tool in the synthesis of compounds containing fluorine atom/s for various purposes.¹ Yet, accomplishing chemo- and stereoselective transformations under mild conditions is a challenge.² One way to dramatically enhance the reactivity of a fluoride ion is to "divest" it from its hydrates and perform the reaction in an anhydrous aprotic solvent. The term "naked" fluoride was first introduced by Liotta for the complex KF/[18]crown-6 in MeCN.³ However, true "naked" fluoride can only exist in the gas phase, and therefore, the more accepted term for such a nonhydrated ion is anhydrous fluoride. Indeed, it has been shown that anhydrous fluoride ions, mainly of tetraalkylammonium salts, enable fluorination under much milder conditions than those of their hydrous counterparts.⁴ However, these quaternary ammonium compounds when bearing a β hydrogen atom are unstable and easily undergo a Hofmann elimination (HE) upon hydrate removal conditions, forming the corresponding trialkylamine, olefin, and bifluoride ion (HF_2^{-}) . For example, upon drying of tetrabutylammonium fluoride (TBAF) such decomposition occurs even at rt.⁵ Therefore, achieving an anhydrous quaternary ammonium fluoride is a significant challenge (several approaches including that of the current work are presented in Figure 1). Christe et al. reported the first synthesis and characterization of the anhydrous tetramethylammonium fluoride (TMAF, Figure 1a) and later described the synthesis of the less stable anhydrous 1methylhexamethylenetetramine fluoride, both lacking a β hydrogen.^{6,7} DiMagno et al. reported the in situ preparation of anhydrous TBAF upon nucleophilic aromatic substitution of hexafluorobenzene with tetrabutylammonium cyanide (Figure 1b).⁴ Although unstable, this highly reactive fluoride (anhydrous TBAF) was successfully used for various synthetic purposes, for example, the synthesis of fluoropyridines under mild conditions.⁸ Sanford et al. studied the formation of fluoropyridines using anhydrous acyl azolium fluoride (Figure 1c)⁹ and later anhydrous





Figure 1. Anhydrous ammonium fluorides.

TMAF.¹⁰ Harmon et al. described the synthesis of anhydrous thermally stable *N*,*N*,*N*-trimethyladamantylammonium fluoride.¹¹ Although this compound contains β -hydrogens, it resists HE according to Bredt's rule, as the β -hydrogen is located in proximity to the bridgehead. However, no properties such as stability, reactivity, or even solubility were reported.

Following our ongoing studies on the reactivity of fluoride ions,¹² we hypothesized that ammonium fluoride compounds based on the rigid azabicyclo[2.2.2]octane skeleton would present relatively high tolerance toward HE (E2 requires antiperiplanar geometry of the H–C–C–N bonds).¹³ Herein



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we disclose our results on the synthesis (Figure 1d), stability (using combined theoretical and experimental studies), solubility, NMR characterization (in both solution and solid state), and reactivity of such anhydrous ammonium fluorides.

To evaluate this hypothesis, high-level calculations were performed using the Gaussian 09 program,¹⁴ studying the structure and energetic properties toward HE of these rigid systems (quinuclidinium **2a** and Me-DABCO **2b**) vs the flexible tetraethylammonium fluoride (TEAF, **3**). Gas phase geometries of the initial salt's ground states, the HE products, and the corresponding transition states¹⁵ were fully optimized at the B3LYP/6-311G+(d,p) level (Table 1 and Supporting Information (SI)).

Table 1. Calculated Gas Phase Molecular Structures of 3, 2a, and 2b (GS) and Their Transition States toward HE $(TS)^a$



^{*a*}Calculated at B3LYP/6-311G+(d,p) (gray = carbon, blue = nitrogen, cyan = fluorine). ^{*b*}Dihedral angle. ^{*c*}Transition states in kcal/mol.

In all three salts the distance between the quaternary N and F atom was found to be 2.94–2.99 Å. As expected, each salt possess H-bonds between the fluoride and three hydrogens (located at the α methylenes).¹⁶ Next, we addressed the ability of these salts to undergo HE for which an anti conformation between the nitrogen and the β -hydrogen is essential, i.e. a dihedral angle (DA) of ca. 180° . While for 3 this conformation is readily accessible in both the GS and TS, it is clear that a very large distortion would be necessary in the bicyclic systems 2a and 2b (Table 1). In fact, the initial angle in the latter compounds was calculated to be $\sim 121^{\circ}$ (almost 60° smaller than the optimal angle, and \sim 54° smaller than that of 3). Furthermore, these DAs can be enlarged only by $\sim 20^{\circ}$ in the corresponding transition states to \sim 141°, which is by all means far from ideal. Clearly, HE in these systems would be energetically costly. Next, we computed the gas phase energies of this elimination process for all three compounds using single-point MP2 calculation at the MP2/6-31G+(d)//B3LYP/6-311G+(d,p) level. The calculations revealed that, kinetically, there is a much higher activation barrier for the bicylic systems, as the ΔG^{\ddagger} for 3 was calculated to be 22.4 kcal/mol while for 2a and 2b we calculated these values to be 29.1 and 34.4 kcal/mol, respectively (Table 1). Thermodynamically, the HE was found to be a favored process

for all three compounds, albeit, for **2a** and **2b** the ΔG would be reduced (6.5 and 10.7 kcal/mol, respectively), relative to 23.4 kcal/mol for 3. To study the energetics also in solution, we used the IEF-PCM continuum solvation model as embedded in the G09 package. First, we reoptimized all calculated structures in acetonitrile (polar) and heptane (nonpolar) at the previous DFT level of theory using this solvation model. Next, we calculated the MP2 single-point energies as described above. The nonpolar solvent heptane exhibited kinetic results which were similar to those in the gas phase. The free activation energies for 3, 2a, and 2b were calculated to be 21.4, 32.8, and 37.8 kcal/mol, respectively. On the other hand, in acetonitrile, a much larger increase in ΔG^{\ddagger} values was observed (28.3, 43.7, and 46.6 kcal/ mol, respectively), as can be expected.¹⁷ Thermodynamic considerations in solution revealed more marked results. While 3 may undergo a favored HE in both solvents (16.7 kcal/mol in heptane and 3.5 kcal/mol in acetonitrile), for **2a** we found $\Delta G >$ 0 in both solvents (0.3 kcal/mol in heptane and 15.3 kcal/mol in acetonitrile). For 2b we found the elimination to be still favored in heptane ($\Delta G = -8.3 \text{ kcal/mol}$) but unfavored ($\Delta G = 4.6 \text{ kcal/}$ mol) in acetonitrile. Notably, based on frequency calculations at the DFT level we found that these HE processes are entropy driven, as may be expected from the dissociation reactions. This observation is more pronounced for 3 than for 2a-b as ΔS is at least doubled in the gas phase and solutions. According to these findings, one may conclude that indeed HE in the bicyclic systems may be an unfavored process in comparison to other quaternary ammonium salts such as 3, due to both geometrical and energetic considerations.

Encouraged by these results, we proceeded to investigate the synthesis, thermal stability, and characterization of 2a-d as representatives of a potentially diverse family of compounds. We started the synthesis with methylation of the commercially available free amines using iodomethane to obtain ammonium iodides 1a-d, which were then passed through a column equipped with an ion-exchanged resin (Amberlite IRA 900 F) to give the hydrated form of 2a-d quantitatively (Figure 1d). This procedure avoids the common methods for halide substitution by a fluoride, using silver fluoride or hydrofluoric acid, which have their disadvantages. To dehydrate 2a-d, a drying process that includes three cycles of azeotroping off the water by heating and reduced pressure (isopropyl alcohol, 2×60 °C, 1×100 °C, oil pump) under inert conditions was performed. ¹H and ¹⁹F NMR analyses in solution showed no decomposition of the substances up to 100 °C. According to ¹⁹F and ¹³C solid-state MAS NMR, they exhibited signals that fall relatively close to those of the related anhydrous TMAF 4 (ca. -85 to -95 ppm, Figure S1 in SI). We assume that the rigidity of compounds 2a-dcauses broadening of the signals. It should be noted that although ¹⁹F solid-state MAS NMR shifts are not a measure for the "nakedness" of the fluoride ion,¹⁸ this analytical technique can serve as an indication for the dryness, as the chemical shift is governed by the specified drying state (for 2a, see Figure S2 in SI). To confirm that 2a-d are in the anhydrous state, they were subjected to Karl Fischer titrations and showed a water content of 1.78, 2.04, 8.08, and 2.5 wt %, respectively, values that in all cases indicate the presence of less than one water molecule per ammonium salt (A monohydrate should exhibit 11, 11, 9.1, and 7.5 wt % of water, respectively). We concluded that the drying temperature should be raised. For further stability studies, we conducted DSC thermal measurements which showed that these materials are stable up to 160 °C (Figures S3-S7 in SI). Therefore, we continued to further dry these materials by heating

Table 2. ¹⁹ F NMR Chemic	al Shifts and Solubility	ty (ppm) in Various Solvents"
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	2a	$2b^b$	2d	TMAF ^c	TBAF ^d
ACN	-75 (0.09 M)	-74 (0.05 M)	-74 (0.06 M)	-74	-72
DMSO	-71 (0.07 M)	-74 (0.07 M)	-72 (0.06 M)	-75	-75
DMSO-THF ^e	-74 (0.03 M)	-73 (0.01 M)	-76 (0.05 M)	nd ^f	nd ^f
DCM ^g	-100 (0.08 M)	-102 (0.06 M)	-100 (0.05 M)	-97	nd ^f
CHCl ₃ ^g	-116 (0.03 M)	-100 (0.02 M)	-(0.03 M)	-113	nd ^f
MeOH	-150	-150	-149	-148	nd ^f

^{*a*}Internal standard solutions (0.1 M). ^{*b*}Applied for the substance which was dried at 100 °C. ^{*c*}Reference 5. ^{*d*}Reference 7a. ^{*e*}1:1 mix. ^{*f*}Not determined. ^{*g*}Solubility extent in these solvents was determined by the sum of all observed species resulting from a reaction with these solvents.

them to 140 °C. Compounds 2a and 2d were heated for 11-15 h (oil pump), and according to ¹H and ¹⁹F NMR analyses in solution, no decomposition of these substances was observed. Karl Fischer titrations showed a water content as low as 0.12 and 0.59 wt %, respectively, and hence these compounds may be considered as anhydrous. However, 2b and 2c decomposed upon heating to 140 °C for several hours and, therefore, cannot be obtained as fully anhydrous compounds at this temperature.¹⁹ We assume that in the diazabicyclooctane derivatives 2b,c the neighboring N atom at the β -position may contribute to this instability at 140 °C by an anchimeric effect (note that 2c may first undergo a retro-Menshutkin reaction). Next, we proceeded to examine the solubility of anhydrous 2a,d and also the dried compounds **2b,c** (less than monohydrate) using $\alpha_{,}\alpha_{,}\alpha_{-}$ trifluorotoluene as the standard (0.1 M). All four compounds showed high solubility in methanol, exhibiting a ¹⁹F NMR signal at -150 ppm. It should be noted that, in cases in which an alcoholic solvent is used to solubilize anhydrous fluoride, formation of a H-bonded complex $2 \cdot (MeOH)_n$ is expected. Table 2 displays the solubility in ACN, DMSO, the DMSO/THF mixture (1:1), DCM, CHCl₃, and methanol, and the corresponding chemical shifts. It can be shown that for 2a,b,d good solubility was observed in these solvents. No solubility was observed in DMF, THF, chlorobenzene, and less polar solvents. In some cases the ¹⁹F NMR measurements showed an additional doublet signal at -149 ppm (ACN, DCM, or CHCl₃) or -143 ppm (DMSO) with a J value of 120 Hz that is attributed to HF_2^- (up to 12%), emphasizing the high basicity of the anhydrous fluoride specie.⁶ Interestingly, in both CHCl₃ and DCM the formation of HF₂⁻ is accompanied by chlorine-fluorine exchange (likely, via carbene). However, while the reaction of 2a with CHCl₃ is very fast, the related reaction with DCM is relatively slow, and therefore, the latter solvent can serve as a suitable medium for fast reactions.

To explore reactivity, the simplest compound 2a was chosen. First, we studied the reaction of 1.2–1.5 equiv of 2a, with benzyl bromide, which allows only a substitution product (but not elimination). It was found to be almost immediate in anhydrous ACN, DMSO, and even in the less typical solvent DCM (Table 3, entries 1, 3, and 5, respectively). Control reactions conducted under the same conditions using the hydrated 2a in ACN or DMSO were also performed. Much longer reaction times were required to achieve full conversion (5 days or 7 h, respectively), and additionally, the undesired benzyl alcohol byproduct (*ca*. 6%) was obtained (Table 3, entry 2).

Following these results, we examined the reactivity of **2a** toward a less reactive and more challenging substrate, 2-chloropyridine. A very common reaction in the chemical industry is nucleophilic aromatic fluorination for the preparation of heteroaryl fluorides.²⁰ Alkali metal fluorides (MF) are generally used, requiring harsh conditions. The reaction was

Table 3. Reaction of 2a with Benzyl Bromide^a

	$\langle \rangle$	Br 2a	F	
entry	equiv of $2a$	conditions	$\operatorname{conv}(\%)^{b}$	yield (%) ^c
1	1.5	anhydrous ACN, <2 min	100	72
2	1.5	hydrous ACN, 5 days	90 ^d	79
3	1.5	anhydrous DMSO, <2 min	100	70
4	1.5	hydrous DMSO, 7 h	91	66
5	1.5	anhydrous DCM, <2 min	100	66

^{*a*}Anhydrous **2a** (0.6 M). ^{*b*}Conversion was determined by ¹H NMR. ^{*c*}Yield was determined by ¹⁹F NMR using 1,3,5-trifluorobenzene as an internal standard. ^{*d*}Benzyl alcohol was formed (6%).

conducted in DMSO at 80 $^{\circ}$ C, and sample aliquots were taken and quenched by MeOD. The desired product 2-fluoropyridine was obtained in 68% yield (Table 4, entry 1). In addition, 77%

Table 4. Fluorination of 2-Chloropyridine with 2a

	ĺ		2a ─────────── rt or 80 °C		L _F	
entry	equiv of 2a		conditions		conv (%) ^c	yield (%) ^d
1 ^{<i>a</i>}	2	anhydrou	us DMSO, 4 h, 8	80 °C	93	68
2 ^b	1.2	anhydrou	us DMSO, 2 wee	eks, rt	77	64
3 ^b	1.2	hydrous	DMSO, 2 mont	hs, rt	0	0
^a Anhydrous 2a (0.6 M). ^b Anhydrous 2a (1 M). ^c Conversion was						

determined by ¹H NMR. ^dYield was determined by ¹⁹F NMR using 1,3,5-trifluorobenzene as an internal standard.

conversion was achieved after stirring the reaction mixture at rt for 2 weeks using 1.2 equiv of 2a (entry 2). A control reaction using 2a hydrate in DMSO gave 0% conversion even after two months, highlighting the significance of maintaining an overall anhydrous environment (entry 3).

These results demonstrate **2a** as a highly reactive yet thermally stable fluorinating agent which exhibits comparable yields of fluorination products to the previously reported anhydrous fluoride materials (TBAF and TMAF).^{4b,10}

It is well-known that anhydrous fluorides can act as strong bases as we also demonstrated here. Iododecane can serve as a suitable substrate for studying the products distribution resulting from the competition between substitution vs elimination. As expected, ^{4a,21} reaction of this compound with **2a** in a DMSO/ THF mixture (1:1) led selectively to the elimination product 1-decene after <3 min (Table 5, entry 1). A control experiment using the hydrated **2a** gave no selectivity after 48 h (entry 2). Kim et al. reported that a complex between TBAF and *tert*-butanol significantly reduces the basicity of the fluoride ion but increases its nucleophilicity, and therefore, this compound leads selectively

Table 5. Substitution vs Elimination of Iododecane Using 2a^a

M_7	$\checkmark I \xrightarrow{3 \text{ equiv. of } 2a} \checkmark 7 \xrightarrow{F}$	+ \H_7
entry	conditions	$S_N 2: E_2^{b}$
1	anhydrous DMSO–THF, ^c <3 min	1:6.7 ^d
2	hydrous DMSO–THF, ^c 48 h	1:0.6 ^e
3	anhydrous tert-butanol, 10 days	1:0.1 ^e
4	hydrous tert-butanol, 6 weeks	1:0 ^e
5	anhydrous DCM, 30 min	1:0.6 ^d
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^{*a*}Anhydrous **2a** (0.6 M). ^{*b*}Ratios were determined by ¹H NMR. ^{*c*}1:1 mix. ^{*d*}Full conversion was obtained. ^{*e*}95% (entry 3) and 42% (entry 4) conversions were obtained. Starting material and some solvent impurity were observed (Figures S38 and S40 in the SI).

to the substitution product.²² Inspired by this work, we proceeded to investigate the reactivity of **2a** using anhydrous *tert*-butanol as a solvent (but not as a complex). Although much slower, this reaction led almost exclusively to the substitution product fluorodecane after 10 days at rt (95% conversion, entry 3). Conducting a control experiment using the hydrated **2a** in *tert*-butanol under the same conditions gave after 6 weeks exclusively fluorodecane (entry 4), albeit only 42% conversion was achieved. Interestingly, when DCM was used, the H-bond interactions of the anhydrous **2a** with the solvent indeed reduced the basicity of the fluoride ion yielding almost a 2:1 ratio of the aforementioned products after 0.5 h (entry 5).

In summary, this report demonstrates the facile synthesis of a new family of highly reactive anhydrous ammonium fluorides and their stability, solubility, and reactivity. The high thermal stabilities of 2a-d (100 or 140 °C) are attributed to the distortion formed at the transition state toward HE (DFT studies). Their solubility in solvents such as CH₃CN, DMSO–THF, and DCM and high reactivity (differences in orders of magnitude between the anhydrous vs hydrous counterparts) open the opportunity to accomplish innovative materials (e.g., chiral or amphiphilic) that may exhibit excessive potential for organofluorine chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03864.

Experimental procedures, analytical data, absolute energies, number of imaginary frequencies, and Cartesian coordinates of all stationary points (PDF)

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Notes

The authors declare no competing financial interest.

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