Facile, Temperature-Dependent Formation of Gaseous C_1 and C_2 Perfluoroalkyl Hypofluorites. Applications as Electrophilic Fluorinating Agents[1]

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A convenient method for continuous-flow production of gaseous C_1 and C_2 fluoroxyperfluoroalkanes (R_fOF) was developed. Passage of 10% F_2 through short columns of CF_3CO_2Na resulted in the formation of the following hypofluorites: CF_3CF_2OF, CF_3OF, $CF_3CF(OF)_2$, and $CF_2(OF)_2$. No other significant oxidizing side products or residual F_2 were present in the column effluent under normal conditions. Identifications of the hypofluorites were made through direct ^{19}F NMR measurements at -40 °C of the -196 °C condensate of the column effluent and also on the basis of stilbene trapping experiments. Hypofluorites were formed rapidly at temperatures at least as low as -110 °C but no reaction occurred at -160 °C. The ratios of hypofluorites formed strongly depended on the temperature of the salt column. Yields of $CF_3CF(OF)_2$ exceeding 90%, based on input F_2, were obtained at salt temperatures between -110 and -78 °C. At moderate temperatures (-20 to +20 °C) CF_3CF_2OF was the predominant product, accompanied by significant amounts of CF_3OF and $CF_3CF(OF)_2$ and traces of $CF_2(OF)_2$. CF_3OF was the major hypofluorite formed at high (60 to 100 °C) temperatures. No hypofluorites were detected when the column temperature was above 135 °C. A minimum of specialized equipment is required to produce hypofluorites by this method. It makes expensive or previously exotic, little-studied fluoroxy compounds readily available for synthetic applications. Fluorinations of anisole, 3,4,6-triacetyl-D-glucal, phenylmercuric acetate, and *N,N*-dimethylphenylacetamide *tert*-butyldimethylsilyl enolate were carried out to demonstrate the synthetic utility of R_fOF and to compare its chemical reactivity with acetyl hypofluorite, an electrophilic fluorinating agent currently in wide use. R_fOF, used as a homogeneous reagent, was comparable in fluorinating ability but was less regio- and stereoselective than acetyl hypofluorite in the cases examined.

Introduction

Organic fluoroxy compounds or hypofluorites are an interesting class of energetic oxidants which contain the O–F group.[2] Several members of the class have received attention as so-called electrophilic fluorinating agents.

Hypofluorites, provided they can be safely handled, offer an attractive general method for controllably introducing fluorine into organic compound which complements more traditional procedures involving nucleophilic fluoride. Hypofluorites react with nucleophilic carbon centers including electron-rich aromatics,[3] olefins,[4] organometallics,[5] and enol derivatives[6] to yield fluorinated products of a regiochemistry consistent with attack by "F^+" (i.e., an F^+ donor). High regio-[3c] and stereoselectivity[4c,d,6a,e,7] of fluorine addition is observed in some cases. Under free radical conditions even "nonnucleophilic" haloalkenes[8] or alkanes[9] undergo controlled fluorine addition by certain hypofluorites.

There has been keen interest in using hypofluorites,[10] particularly acetyl hypofluorite (AcOF),[6d,7,11] as a radiosynthetic tool to rapidly label medical tracer drugs with short-lived ^{18}F radioisotope. Special constraints are imposed in this application: (1) The ^{18}F hypofluorite ($RO^{18}F$) should be formed efficiently from a *limiting quantity* of $[^{18}F]F_2$. (2) The $RO^{18}F$ must be prepared and used quickly because of ^{18}F's short half-life (110 min). (3) To minimize radiation exposure, synthesis and handling of $RO^{18}F$ must be simple and suited for remote operation.

Workers from this laboratory recently reported a simple continuous-flow, room-temperature synthesis of gaseous AcOF from solid KOAc and dilute F_2.[12] This "gas–solid-phase" procedure is reasonably safe and has been adapted to both radiochemical[13] and preparative scale[14]

$$F_2 + KOAc \rightarrow AcOF + KF$$

(1) A preliminary report of this work was presented at the 188th National ACS Meeting Fluorine Section, Philadelphia, Aug 1984.

(2) Reviews: (a) Shreeve, J. M. *Adv. Inorg. Chem. Radiochem.* **1983**, *26*, 119. (b) Mukhametshin, E. M. *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49* (7), 668. (c) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60. (d) Lustig, M., Shreeve, J. M. *Adv. Fluorine Chem.* **1973**, *7*, 175.

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application. Unfortunately the high thermal instability[15] of AcOF somewhat restricts the usefulness of this reagent. Acetyl hypofluorite steadily undergoes a Hunsdiecker-like breakdown to CO_2 and CH_3F,[15,16] even at low temperatures. Violent decomposition of AcOF may occur in the condensed state.[15,17] Because of this instability, the best yields of AcOF (based on input F_2) by the "gas–solid" (or any other)[6d] method are not more than 80%. Yields of 50–70% are normal in preparative procedures and require the input of highly dilute (<1%) F_2.

The C_1 and C_2 perfluoroalkyl hypofluorites (R_fOF) have certain advantages over AcOF as potential synthetic reagents. While comparable to AcOF in fluorinating ability, R_fOFs possess greater thermal stabilities. R_fOFs appear to be indefinitely stable at room temperature in glass[18,20] in the absence of initiators or oxidizable substances. CF_3OF and $CF_2(OF)_2$ survive temperatures of 150 °C and can withstand extended contact with moisture or strong acids.[2b,d,18–20]

CF_3OF, the prototype electrophilic fluorinating agent, is the simplest and best studied member of this class.[2] Although expensive it is commercially available in the United States. Other members, including CF_3CF_2OF,[18] $CF_2(OF)_2$,[19,20] and $CF_3CF(OF)_2$,[21,22] have been known for some years, but there have been few reported applications of these compounds as fluorinating agents.[4c,6b] They have remained largely unexploited in the face of expanding interest in organofluorine chemistry in part because existing preparative procedures do not readily lend themselves to convenient and safe synthetic use of these compounds.

The most general route of R_fOFs is by static fluorination of carbonyl compounds in the presence of alkali fluorides. High yields are characteristic but it is a batch process usually requiring the use of excess fluorine, pressure vessels, and a vacuum line. For safety reasons, it is strictly limited to small-scale preparations of hypofluorites. While $[^{18}F]CF_3OF$ has been synthesized in this way,[10] the method appears to be to tedious to be practical for radiosynthetic application.

The other common method of preparing R_fOF has been by direct fluorination of salts of alcohols or carboxylic acids under slurry[4c,d,6b] or continuous-flow[18,19,21] conditions. Although experimentally simple, such procedures have suffered from inefficient fluorine utilization, low yields, and complex product mixtures.[2b] Probably because of these problems, no $[^{18}F]R_fOF$ radiochemical syntheses by this approach have heretofore been reported.

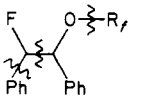
We decided to examine the fluorination of trifluoroacetate salts under conditions analogous to those used for "gas–solid-phase" AcOF production. We report in this paper the development and optimization of an efficient gas–solid-phase continuous-flow R_fOF production system, constructed from Teflon chromatography tubing and fittings, which allows convenient and reasonably safe access to four C_1 and C_2 R_fOF compounds. This paper also includes several examples of fluorinations using the hypofluorites produced by this system.

Results and Discussion

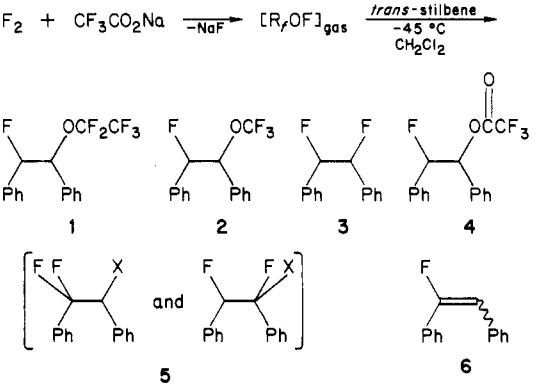
When 0.5–10% F_2 in N_2 or He carrier was passed through a short glass column containing dry NaO_2CCF_3 an exotherm was noted and a gas with about half the oxidizing capacity (KI) as the input F_2 was detected in the column effluent stream. This oxidizing gas was produced at a relatively constant level until more than two-thirds of the NaO_2CCF_3 had been consumed (measured by weight loss). More than 95% of this oxidizing activity condensed from the carrier stream on passage through a −160 °C (N_2–$CFCl_3$) teflon cold trap thus demonstrating the virtual absence of unreacted F_2 (bp 188 °C) in the column effluent. The reaction of F_2 with the salt was very rapid since even at the highest flow rates tested (600 mL/min of 0.5% F_2) little or free F_2 was present in the column effluent. Later experiments using $[^{18}F]F_2$ (0.1%, 300 mL/min) confirmed this fact: Nearly all fluorine reacted (indicated by deposition of $Na^{18}F$) within a 3-cm zone at the front of a 1 × 7 cm salt column.

The oxidative condensate could be revolatilized without significant loss of oxidizing activity by warming the trap under constant carrier purge. The presence of fluoroxy compounds in this gas was indicated by smooth formation of fluoroanisoles when it was bubbled into a solution of anisole (see below).

Trapping Experiments. Addition of hypofluorites across the double bond of stilbenes is a rapid and well-investigated process.[4] We initially employed this reaction to identify indirectly the potentially hazardous hypofluorite species in the column effluent. The R_fOF–stilbene adducts are nonexplosive and have characteristic, easily interpreted mass fragmentation patterns.



In most trapping experiments the effluent gas was passed directly from the column into cold stilbene solutions. Identical results were seen when the effluent gas was first condensed at −196 °C and then revolatized under carrier purge into stilbene solution. Identification of adducts was made chiefly on the basis of GC–MS analysis of the reaction solution.[23] The following products 1–6, in



order of decreasing amount, were observed from the reaction of excess stilbene with the effluent from a tri-

(15) Reflective of this instability is the fact that, in spite of its wide usage, no direct physical or spectral properties of AcOF had been reported prior to submission of this manuscript. However, an excellent report of the full characterization of AcOF has subsequently appeared. See: Appelman, E. H.; Mendelsohn, M. H.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 6515.

(16) (a) Grakauskas, V. *J. Org. Chem.* **1969**, *34*, 2446. (b) Unpublished observations.

(17) See: *Chem. Eng. New* **1985**, Feb. 18, 2.

(18) Prager, J. H.; Thompson, P. G. *J. Am. Chem. Soc.* **1965**, *87*, 230.

(19) Thompson, P. G. *J. Am. Chem. Soc.* **1967**, *89*, 1811.

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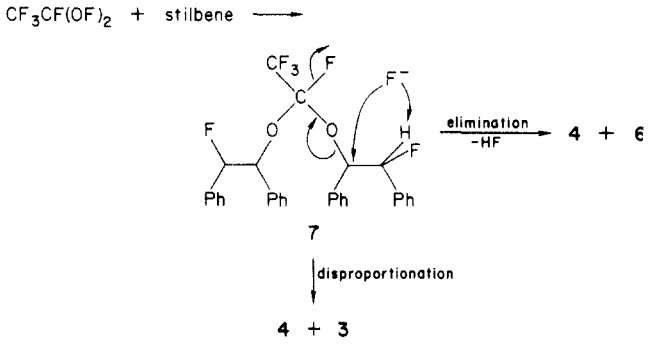
(22) Sekiya, A.; Desmarteau, D. D. *Inorg. Chem.* **1980**, *19*, 1328.

(23) Efforts to obtain more complete characterizations were frustrated by preparative separation problems for the large number of chromatographically similar and, in some cases, hydrolytically labile products on silica. The stereochemistry of hypofluorite addition to stilbene has been well investigated and is known to be predominately syn.

Scheme I



fluoroacetate column maintained at 0 °C (0°R_fOF).

The combined amount of adducts **1** and **2** usually exceeded 70% of the total observed products.[24] It was noted that, over the life of a given column charge of NaO_2CCF_3 at 0 °C, the amount of observed CF_3OF adduct **2** gradually rose and eventually surpassed the amount CF_3CF_2OF adduct **1**. More will be said later about this "old salt" effect.

The 1,2-difluoro compound **3** and the fluoro-trifluoroacetoxy adduct **4** were observed in roughly parallel quantities. Together they amounted to 15–20% of the products seen.

Adduct **1**, isolated by preparative GC, was found by ^{19}F NMR to consist of a 60:40 threo (syn addition) erythro (anti addition) isomeric mixture. The relatively weak preference for syn addition under these conditions is in marked difference to high (≥5:1) syn/anti adduct ratios observed from reaction of slurry-formed CF_3CF_2OF with stilbenes at −75 °C in $CFCl_3$.[4c] Adducts **2–4** were not preparatively separated.[23] Nevertheless, the presence of threo/erythro (*dl*/meso in the case of **3**) mixtures of these adducts was plainly evident from GC–MS data. The isomeric ratios ranged between 3:1 and 1:1 by GC integration and suggested again a lack of strong preference for syn addition by gaseous R_fOF in CH_2Cl_2.

A number of minor products with the general structures **5** (X = OCF_2CF_3, OCF_3, F, O_2CCF_3) were also observed. The total amount of these secondary fluorination products became significant (>5%) only after more than 75% of the stilbene had been consumed. Compounds **5** eventually displaced adducts **1–4** as major products upon treatment with excess R_fOF. Under such conditions, no mass peaks indicative of nuclear fluorination (i.e., $[PhF]^+$ *m/e* 95), nor of chlorinated stilbene resulting from oxidative attack by R_fOF on the CH_2Cl_2 solvent were apparent from GC–MS data.

Traces of **6** were also detected (M^+ 198),[28] however, it was uncertain whether **6** was a real product (see Scheme I) or a GC artifact resulting from thermal elimination reactions of adducts **1–4**.

The possibility that significant amounts of fluorinated stilbene products escaped GC detection because of "sticking" or breakdown on the GC column was ruled out by radiochemical experiments in which 0°[^{18}F]R_fOF was reacted with stilbene. More than 85% (decay corrected) of the radioactivity from an aliquot of this reaction solution injected onto the GC was recoverable from the column exit within the span of expected retention times. Furthermore, the radioactive peaks (obtained by γ- counter measurement of timed GC column exit gas samples collected on charcoal) matched the "cold" GC values in terms of retention times and qualitative intensities. No significant noncoincident radioactive peaks were seen.

The observation of adducts **1** and **2** clearly indicated the major presence of CF_3CF_2OF and CF_3OF in the CF_3CO_2Na column effluent. The large amount of CF_3OF was surprising since previous investigators have failed to note[4c,6b] or report only traces[2d,19] of CF_3OF formation from fluorination of CF_3CO_2Na.

Difluoro adduct **3** was also formed in a hypofluorite-mediated process, as it had been shown conclusively that no significant F_2 escaped the 0°CF_3CO_2Na column. CF_3OF is known to react with stilbene to form some **3**.[2c] It will become apparent that other less thoroughly investigated hypofluorites also produce **3**.

Observation of adduct **4** [the reality of which was bolstered by the IR (C=O 1801 cm^{-1}) of the reaction solution immediately following hypofluorite treatment], was initially interpreted as evidence for the existence of trifluoroacetyl hypofluorite, CF_3CO_2F, as an additional component of the oxidizing gas. However, this apparent result contradicted several independent reports that ruled out CF_3CO_2F formation from trifluoroacetate salts in the absence of water.[4c,d,6d,22]

A less obvious alternate explanation of the formation of **4** is through breakdown of a transient dimeric adduct (**7**) of $CF_3CF(OF)_2$ (Scheme I). 1,1-Bisfluoroxytetrafluoroethane is a well-characterized product of fluorination of trifluoroacetate,[21,22] but little is known of its reactions with organic or inorganic compounds. Hypothetical intermediate **7** (which we were unable to detect even at −45 °C in CH_2Cl_2 by ^{19}F NMR) is analogous to certain alkene adducts of $CF_2(OF)_2$.[25] The suggested mechanism accounts for the occurrence of **6** and the roughly parallel amounts of **3** or **4** among the 0°R_fOF–stilbene adducts.

^{19}F NMR of R_fOF Mixture. Conclusive identification of the hypofluorite species formed at 0 °C was obtained through direct ^{19}F NMR measurements. A sample of gaseous 0°R_fOF, produced by passage of a measured amount of F_2 through a fresh NaO_2CCF_3 column, was condensed out of carrier at −196 °C. The condensed materials carefully were vacuum transferred to an NMR tube and the spectrum was taken at −40 °C in $CFCl_3$. The results were clear-cut: CF_3CF_2OF, 41%; CF_3OF, 30%; $CF_3CF(OF)_2$, 25%; $CF_2(OF)_2$, 5%.[2d] No other significant fluorinated materials were visible within a range 300 ppm

(24) Because pure samples of adducts **1–4** could not readily be isolated, GC calibration curves were not possible. However, in view of the structural similarity among the adducts, use of the following mathematical response correction approach was considered justified. The reported quantities were arrived at by multiplying the raw GC thermal conductivity peak areas for each adduct by a molecular weight dependent factor which compensated for mass effects in detector response. The weighting factor for **3** (MW 218) was set at 1.0 (218/218). For **1** (MW 334) the weighting factor was 0.653 (218/334). The factors for **2** (MW 384) and **4** (MW 312) were 0.768 and 0.70, respectively.

(25) Hohorst, F. A.; Shreeve, J. M. *Inorg. Chem.* **1968**, *7*, 624.

(26) It is interesting to compare these results with those of Prager and Thompson (U.S. Patents 3 415 865, 3 420 866, 3 442 927, 3 692 815 and ref 18, 19, 21). Using all metal flow systems they exhaustively fluorinated CF_3CO_2Na and found, among the products, the same four hypofluorites, albeit in low yield (based on CF_3CO_2Na) and differing ratios: CF_3CF_2OF, 10%; $CF_3CF(OF)_2$, 10%; $CF_2(OF)_2$, 1%; CF_3OF, <1%. They also isolated and identified a number (10) of unique perfluoroalkyl peroxides, trioxides, and fluoroxy peroxides not produced in our (Teflon and glass) system. We speculate that catalytic effects on the surfaces of their metal system caused the differing results.

(27) Sealed reaction solutions develop significant pressure on standing at 3 °C for several hours.

(28) Two isomers of were observed by GC–MS. One coeluted with the *trans*-stilbene peak. The other isomer had a 30% shorter retention time and was hidden within the peak of one of the **4** isomers. By examining computerized GC–mass fragmentogram patterns, which are plots of the intensity of selected ion masses vs. GC retention time, the compounds **6** could be distinguished from obscuring peaks. Treatment of the R_fOF–stilbene adduct mixture with wet pyridine hydrolytically removed the obscuring **4** and allowed a clean mass spectrum of the less retained isomer of **6**, *m/e* (relative intensity): 198 (M + 100), 197 (75), 196 (47), 183 (30), 178 (20), 170 (10), 109 (14), 98 (12).

downfield to 250 ppm upfield of $CFCl_3$. [Slight traces of CF_4 (δ_{CFCl3} −62.8), coproduced in the formation of CF_3OF and $CF_2(OF)_2$, were also present, but most CF_4 formed in these reactions was apparently noncondensable under the collection conditions.]

After recording the ^{19}F NMR spectrum, the NMR sample tube contents carefully were allowed to react with aqueous KI and the liberated iodine was titrated. Excellent agreement was observed between the measured amount of oxidant in the NMR tube (55% of the input F_2 level) and the theoretical maximum amount of formed oxidant possible (59%), calculated as a weighted average using the NMR percentages and the following stoichiometries:

$$\frac{F_2 \text{ consumed}}{OF \text{ bonds formed}}$$

$$2F_2 + CF_3CO_2Na \xrightarrow{-NaF} CF_3CF(OF)_2, \quad 1.0$$

$$3F_2 + CF_3CO_2Na \xrightarrow{-NaF} CF_2(OF)_2 + CF_4, \quad 1.5$$

$$2F_2 + CF_3CO_2Na \xrightarrow{-NaF} CF_3CF_2OF + {}^1/_2O_2, \quad 2.0$$

$$3F_2 + CF_3CO_2Na \xrightarrow{-NaF} CF_3OF + {}^1/_2O_2 + CF_4, \quad 3.0$$

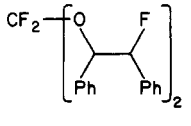
$$F_2 + 2I^- \rightarrow I_2 + 2F^-$$

$$RO\text{–}F + 2I^- \rightarrow I_2 + RO^- + F^-$$

The combined NMR and oxidation data confirmed the reaction of F_2 with CF_3CO_2Na was rapid and complete to yield the four indicated hypofluorites and eliminated the possibility of significant formation of other oxidants such as $R_fO\text{–}OR_f$ in this system.[26]

The ^{19}F NMR of a 0°R_fOF sample, prepared as above but from an "old" (50% consumed) trifluoroacetate column, revealed the following molar ratio of products: CF_3OF, 60%; CF_3CF_2OF, 28%; $CF_3CF(OF)_2$, 7%; $CF(OF)_2$, 5%. The rise of CF_3OF observed by NMR was in qualitative agreement with the "old salt" effect noticed from the stilbene trapping experiments. It may be noteworthy that $CF_2(OF)$ levels appeared to remain constant at around 5% over the life of a column charge of CF_3CO_2Na at 0 °C; more samples must be examined before firm conclusions can be made on this point. The reason for the shift toward increased CF_3OF formation is not known. It is conceivable that the gradual accumulation of NaF[40] or HF causes subtle changes in the surface chemistry or that catalytically active impurities in the salt matrix which favor CF_3OF formation are progressively "uncovered" with the consumption of CF_3CO_2Na.

In retrospect, the direct ^{19}F NMR results pointed out the limitations of the R_fOF–stilbene adduct GC analysis method. First, the method failed to indicate $CF_2(OF)_2$, apparently because of spontaneous breakdown of presumed intermediates **8** or **9** (by analogy to *4*) to **3** and



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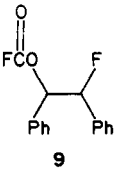

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CO_2.[27] Second, the estimates of CF_3CF_2OF, CF_3OF, and $CF_3CF(OF)_2$ on the basis of trapping experiments varied considerably from the direct NMR values. Part of the reason for this discrepancy was significant participation by these hypofluorites in side reactions (i.e., formation of **3**, **5**, and **6**) in which eliminative loss of OR_f fragments as COF_2, CF_3COF, or CF_3CO_2H[27] occurred. No doubt there were also systematic errors introduced because of the GC detector response correction method used.[24]

Table I. Effect of CF_3CO_2Na Temperature on R_fOF-Stilbene Adduct Ratio and Yield of Formed Oxidizing Activity

CF_3CO_2Na[a] temp, °C	observed R_fOF adducts,[b] rel %				% yield of formed oxidizing activity[c]
	1	2	3	4	
135					0
105	40	53	5	<1	10–30
60	42	44	7	5	30–40
20	59	31	8	8	40–50
0	61	21	9	7	50–60
0[d]	31	37	18	13	40–45
−23	50	6	18	26	60+
−45	26	7	23	43	75
−70	13	<2	26	59	85
−78	6	<1	29	63	90+
−78[d]	8.5	4	30	54	85
−110	3.5	<1	30.5	64	96+
−110[d]	11	4	31	51	85
−160			100		0

[a] Fresh samples of CF_3CO_2Na were used except where noted otherwise. [b] GC yields. See ref 24. [c] Amount of salt column effluent oxidizing activity condensing from carrier stream at −196 °C, expressed as a percentage of input F_2 capacity. [d] "Old" (~50% consumed by weight loss) CF_3CO_2Na columns used.

Mindful of these shortcomings, R_fOF adduct GC analysis was still a useful tool for rapid qualitative detection and assessment of CF_3OF, CF_3CF_2OF, and $CF_3CF(OF)_2$ production and, in fact, offered certain advantages over direct R_fOF NMR measurements in terms of convenience, safety, and sensitivity. For these reasons it was utilized extensively in the optimization experiments now to be described.

Effect of Temperature on Hypofluorite Formation. At an early stage in this work it was noticed that changes in F_2 concentration or flow rate through the CF_3CO_2Na column did not markedly affect R_fOF–adduct ratios or the amount of formed effluent oxidizing activity unless column exotherms occurred, in which case CF_3OF adduct **2** increased and total oxidizing activity dropped off. Deliberately heating the column while passing F_2 at a rate that normally would not generate an exotherm produced these same effects, which additionally included a decrease in the relative amount of CF_3CF_2OF adduct **1** and loss of $CF_3CF(OF)_2$ adduct **4** (Table I). The relative amount of difluoro adduct **3** remained roughly constant over the high-temperature range. The amount of effluent oxidizing activity fell precipitously above 110 °C. At 135 °C essentially no oxidizing activity escaped the salt column.

Reduction of salt column temperature from 20 to −110 °C (caution[29]) led to progressive increase in the amounts of $CF_3CF(OF)_2$ adduct **4** and difluoro adduct **3**. CF_3CF_2OF formation appeared to be maximized between salt temperature of 20 and −20 °C, judging from the amount of adduct **1**. CF_3OF dropped off rapidly below −20 °C and no CF_3OF was detectable in the direct ^{19}F NMR of a −78 °C generated sample of R_fOF (Table II). It showed only $CF_3CF(OF)_2$ (89%) and CF_3CF_2OF (11%). No other hy-

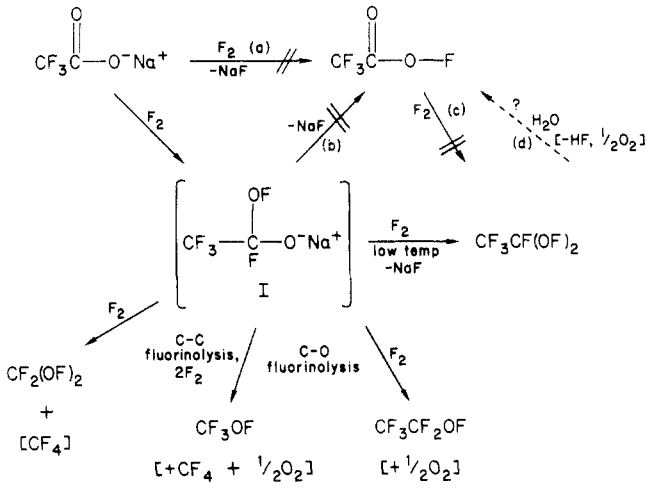
(29) It must be cautioned that $CF_3CF(OF)_2$ (bp −34 °C) and CF_3CF_2OF (bp −50 °C) will condense on the salt column at low temperatures. The accumulation of large amounts of hypofluorites is a potentially hazardous situation to be avoided. Continuous carrier purge should be maintained through the column as long as R_fOF is present. Briefly withdrawing the cooling bath (preferrably by means of a remotely operated jack) while maintaining purge will liberate R_fOF without loss of activity. We have routinely carried out this procedure on scales up to 5 mmol (input F_2) without mishap. Larger scale demands are easily accommodated by cycling the process. See Experimental Section for further precautions.

Table II. Direct ^{19}F NMR Determination[a] of R_fOFs Formed at Different Salt Column Temperatures

CF_3CO_2Na temp, °C	% formation			
	CF_3CF_2OF	CF_3OF	$CF_3CF(OF)_2$	$CF_2(OF)_2$
0	40.5	29.5	24.6	5.4
0[b]	28	60	7	5
−78	11		89	
−110	5.5		94.5	

[a] By comparison with literature[2d] values. [b] "Old" (~50% consumed) sample of CF_3CO_2Na.

Scheme II. Proposed Mechanism of Reaction of F_2 with Solid NaO_2CCF_3



pofluorites or fluorine-containing materials were apparent by NMR. However, small amounts of CF_3OF adduct **2** could be seen by GC after trapping −78°R_fOF with stilbene. At a salt column temperature of −110 °C, $CF_3CF(OF)_2$ formation was better than 94% by NMR with barely detectable amounts of CF_3CF_2OF persisting. R_fOF formation was still complete and rapid at this temperature; no column breakthrough of F_2 occurred.

As the cooling bath temperature was lowered below −120 °C, increasing levels of fluorine breakthrough were observed. Ten percent fluorine at a flow rate of 50 mL/min passed through a −160 °C 1 × 15 cm U-shape glass salt column without significant reaction.

A comparatively minor though still significant "old salt" effect was present at −110 °C. At this salt temperature, increases in CF_3CF_2OF as well as CF_3OF (inferred from adducts) formation occurred as the salt was consumed beyond 50% of capacity.

The amount of condensable effluent oxidizing activity, which can be viewed as a measure of the efficiency of O–F bond formation vs. trifluoroacetate C–O or C–C bond fluorinolysis, rose from 50% of input F_2 activity at 20 °C to virtually 100% at −110 °C.

Mechanism of Hypofluorite Formation. The Scheme II is suggested by these results. It appears that F_2 initially adds to the carbonyl of trifluoroacetate forming intermediate I, which remains ionically attached to the salt surface. Further fluorination of this intermediate at low temperatures leads only to F_2 insertion between the O–Na ionic bond to form $CF_3CF(OF)_2$. At somewhat higher temperatures, C–O bond fluorinolysis of I leading to CF_3CF_2OF becomes the favored route. Competing rates of C–C and C–O bond fluorinolysis occur at still higher temperatures, resulting in an increased proportion of C_1 fluoroxycompounds.

The idea of a nonvolatile, anchored intermediate, I, is proposed to help explain why, in view of the quite narrow

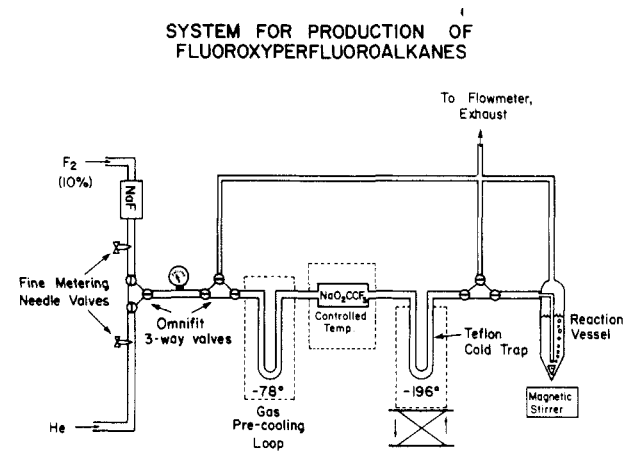


Figure 1.

fluorine reaction zone on the column indicated from radiochemical experiments, wide variations of F_2 flow rate and concentration through the salt column do not alter the ratios of hypofluorites formed. If pathways a–c, involving the intermediacy of volatile CF_3CO_2F, were operative one might expect that when very dilute F_2 was passed through the column at very high flow rates, some amount of CF_3CO_2F would be swept out of the column and be detected before it had a chance to react with a second F_2 molecule. However, under such conditions no CF_3CO_2F could be observed. On these grounds pathways a–c have been ruled out.

CF_3CO_2F has been suggested, based on stilbene trapping experiments, as the major hypofluorite produced by low-temperature slurry fluorination of CF_3CO_2Na in the presence of moisture or HF.[4d] However, other investigators have found (static) fluorination of CF_3CO_2Cs·HF complex to give only $CF_3CF(OF)_2$, even when only half the equivalent amount of F_2 is used.[22] To reconcile these apparently contrasting results we suggest the possibility that in slurry fluorination, CF_3CO_2F forms secondarily from $CF_3CF(OF)_2$ by partial reduction with water (pathway d). We are currently exploring the feasibility of making CF_3CO_2F indirectly from $CF_3CF(OF)_2$ in this way.

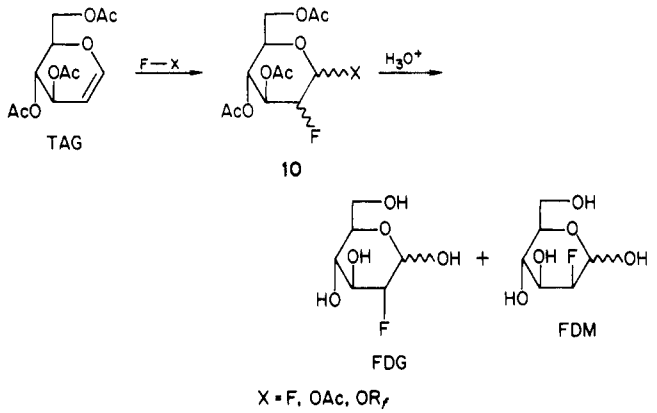
Effect of Cations. Two other trifluoroacetate salts were briefly examined. Dry $Ca(O_2CCF_3)_2$ at 0 °C gave results very similar to NaO_2CCF_3, but the powdery state of this salt caused unacceptable column back pressures to develop. Vacuum sublimed $NH_4O_2CCF_3$ was ineffective in producing hypofluorites. Dilute fluorine reacted vigorously with this salt, but little effluent oxidizing activity was formed.

Fluorinations with R_fOF. Fluorinations were carried out by using the apparatus shown in Figure 1. For the sake of convenience, only the 0 and −78 °C generated R_fOF mixtures were used in these experiments.

Fluorination of Anisole. R_fOF readily fluorinated anisole at −78 °C in $CFCl_3$ in the absence of direct light to give a 3:1 ortho:para ratio of fluoroanisoles. No meta fluorination was observed. In comparison, AcOF gave a >8:1 ortho:para ratio.[3c] Interestingly, an intense purple color developed during reactions of R_fOF with anisole in $CFCl_3$ which persisted after R_fOF addition was stopped. The color disappeared within a few seconds upon exposure of the reaction solution to air. This behavior, not observed with AcOF, is consistent with the presence of free radicals.

Fluorination of 3,4,6-Triacetal-D-glucal (TAG). Reaction of TAG with F_2 or AcOF is a widely used synthetic approach to the radiopharmaceutical [^{18}F]-2-fluoro-2-deoxyglucose (^{18}F-FDG), a positron-emitting glucose mimic used to observe brain metabolic activity.

Depending on the conditions and electrophilic agent used in the synthesis, varying amounts of undesired 2-fluoro-2-deoxymannose (FDM) also may form.



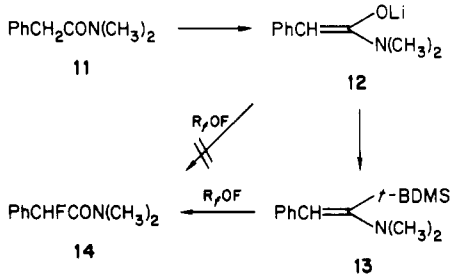
The stereoselectivity of addition of −78 and 0 °C generated R_fOFs to TAG under different reaction conditions was examined and compared with existing procedures (Table III). Stoichiometric addition of R_fOF to TAG (1 equiv of O–F bond per TAG molecule) took place to yield adducts **10** (X = OC_2F_5, OCF_3, F, O_2CCF_3; two isomers of each, observed by GC–MS chemical ionization – CH_4). The mixtures were hydrolyzed (refluxing 50% CF_3CO_2H, 30 min) directly to α,β-FDG and α,β-FDM.

Under optimal conditions a 5:1 ratio of gluco:manno fluorination of TAG was observed with R_fOF. This is comparable to results reported for CF_3OF[6a] but falls short of the 20:1 gluco:manno selectivity attainable with AcOF. With each of these hypofluorites, greatest gluco-selectivity of fluorine addition to TAG was obtained using low reaction temperatures and nonpolar solvents.

Fluorodemercuration. Phenylmercuric acetate reacted in the expected way[5a] with −78°R_fOF to afford fluorobenzene. Conversion efficiency, based on input O–F bond equivalents, was about 50% under unoptimized conditions.

$$\text{PhHgOAc} \xrightarrow{-78°R_fOF} \text{PhF}$$

α-Fluorination of Carbonyl Compounds. CF_3OF is known to react with silyl enolates to form good yields of α-fluoro-carbonyl compounds.[6c] We have found that the same transformation may be effected using either 0°R_fOF or −78°R_fOF as a homogeneous reagent. Thus *t*-BDMS enolate **13**, with one O–F equivalent of R_fOF, was converted to **14** in 40% overall yield from **11**. However, reaction of lithio enolate amide **12** with R_fOF failed to afford measurable amounts of **14**. The presumed reason for



failure in the latter case was that acyl fluorides derived from breakdown of R_fO^- (i.e., $CF_3CF_2O^- \rightarrow F^- + CF_3COF$) reacted with **12** before significant fluorination could occur.

Conclusions

A simple, efficient, and safe on-line method for producing synthetically useful amounts of perfluoroalkyl hypofluorites was described. High yields of nearly pure $CF_3CF(OF)_2$ *based on input* F_2 of nearly pure $CF_3CF(OF)_2$ can be formed readily and isolated under low-temperature conditions. The mixture of four hypofluorites produced at moderate temperatures may be used as a homogeneous reagent with reactivity essentially identical with that of CF_3OF alone. The regio- and stereochemistry of fluorine addition by R_fOF to organic compounds was analogous to, but less selective than, that attainable with AcOF. The major synthetic advantage of R_fOF lies in the greater thermal stability which makes R_fOF safer to handle in preparative-scale syntheses than AcOF. We find that R_fOF solutions in $CFCl_3$ show no decomposition after 8 months stored in sealed NMR tubes at −20 °C. Another preparative advantage of R_fOF over AcOF is that R_fOF can be efficiently formed using relatively concentrated F_2 provided adequate cooling is applied to the column to moderate exotherms.

Original work by Kollonitsch[9] showed remarkably selective and clean photofluorinations of unprotected amino acids, alkyl amines, and other biologically significant molecules to be possible using CF_3OF and CF_3CF_2OF in strong acid. However, to date little follow-up work using this chemistry has been reported, in spite of numerous potential applications; the presumed reasons being the expense and hazards associated with hypofluorite reagents. We believe the described on-line R_fOF synthesis in the future will allow easier access and further exploration of this interesting and unique approach to fluorinating organic compounds.

The use of [^{18}F]R_fOF for radiofluorinations was mentioned only briefly in this paper. A detailed study has been carried out and will appear elsewhere. However, it can be said at this time that, with minimal modifications, this gas–solid-phase system efficiently produces [^{18}F]R_fOF from cyclotron-formed [^{18}F]F_2 at the tracer levels normally used in radiosyntheses of PET imaging agents.

Experimental Section

CAUTION. A review of pertinent literature references[2d,21,22,30] is strongly recommended before beginning work with hypofluorites. While the R_fOFs described in this paper are among the most thermally stable fluoroxy compounds known, they still are potentially explosive and present a toxicity hazard similar to F_2. All work should be carried out in an efficient hood and an upper working limit of 4–5 mmol of fluoroxy bond equivalents (e.g., 2–2.5 mmol of $CF_3CF(OF)_2$) should be observed when handling concentrated forms of R_fOF. Proper safety equipment[31] is required to handle these amounts.

Careful attention should be paid to the material composition and cleanliness of equipment and the purity of reagents because certain metals or organic substances can initiate chain-reaction self-decomposition of R_fOF,[2d] in the process liberating about 2 mol of toxic gaseous products for each mole of R_fOF. We use an R_fOF production apparatus (Figure 1) in which *all contact surfaces downstream from the* CF_3CO_2Na *column are of fluoropolymer or glass construction* and have never experienced a mishap. A 0–20-1b pressure gauge located upstream of the salt column is an important safety feature to indicate any obstructions in the system. Vacuum line handling of R_fOFs, in our opinion, should be kept to the minimum because of the likely presence of mercury or hydrocarbon residues which could trigger an explosion. When vacuum techniques are absolutely required, a dedicated line of proper construction should be used.

(30) Cady, G. H.; Kellogg, K. B. *J. Am. Chem. Soc.* **1953**, *75*, 2501; **1955**, *77*, 6110.
(31) Face shields, leather gloves and coats, 6 mm iri acrylic lab shields, and nonflammable cooling baths are recommended.[21]
(32) Ido, T.; Wan, C.-N.; Casella, V.; Fowler, J. S.; Wolf, A. P.; Reivich, M.; Kuhl, D. E. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 175.
(33) Korytnyk, W.; Valentekovic-Horvath, S.; Petrie, C. R. *Tetrahedron* **1982**, *38*, 2547.

Table III. Fluorination of TAG under Various Conditions

F–X	rxn solvent	rxn temp, °C	2-FDG, %	2-FDM, %
−78° R_fOF	$CFCl_3$	−78	85[a]	15[a]
0° R_fOF	$CFCl_3$	−78	76[a]	24[a]
−78° R_fOF	$CFCl_3$	0	73[a]	27[a]
−78° R_fOF	1:1 CH_3CO_2H/CH_2Cl_2	0	59[a]	41[a]
CF_3OF[b]	$CFCl_3$	−78	81[b]	19[b]
AcOF[c]	$CFCl_3$	−78	>95[a]	<5[a]
AcOF[c]	CH_3CO_2H	20	82[a]	18[a]
F_2[d]	$CFCl_3$	−78	80[d]	20[d]
XeF_2–BF_3[e]	Et_2O–C_6H_6	20	93[e]	7[e]

[a] Relative percentages based on GC and NMR measurements. [b] Taken from ref 6a. [c] By the procedure in ref 12. [d] Taken from ref 32. [e] Taken from ref 33.

Fluorinations always should be conducted by passing the gaseous R_fOF into a solution of the substrate. The reverse mode of addition creates a potentially dangerous situation in which a large amount of accumulated oxidant briefly encounters a small amount of readily oxidizable material.

It must be reemphasized that R_fOFs will condense on the salt column at temperatures below −50 °C. *Carrier purge should be maintained as long as R_fOFs are in the system.* See ref 29.

It has been our experience that the R_fOFs described in this paper can be safely and routinely used as laboratory-scale synthetic reagents provided the above guidelines are observed.

General Procedure. The apparatus shown in Figure 1 was used to generate and use R_fOF. Fluorine gas, 9–10% in N_2, and further diluted as desired with supplemental helium (GC grade), was passed at rates between 0.1 and 0.2 mmol of F_2 min^{-1} through U-shaped 1 × 25 cm borosilicate columns loosely packed with CF_3CO_2Na (6–10 g). Back pressure on the column during gas passage was never permitted to exceed 2 psi. Commercial CF_3CO_2Na (Aldrich 97%) dried at 100 °C and stored in a P_2O_5 desiccator gave the same results as material obtained by neutralization of NaOH with redistilled CF_3CO_2H followed by vacuum drying (160 °C, 1 torr). Column temperatures were measured externally and were maintained by immersion in the appropriate (preferably nonflammable) cooling bath. The column effluent stream was routed via Teflon tubing through an optional −196 °C Teflon cold trap and thence could be directed either to the reaction vessel or the exhaust port by a Teflon three-way valve. Gas flow rates were measured with a bubble flowmeter at the exhaust port. Oxidizing capacities were determined by bubbling the oxidizing gases through aqueous KI (1% HOAc) and titrating with 0.1 N thiosulfate.[36] Ideal gas behavior was assumed in calculations.

In preparative-scale applications, the NaF scrubber, gas precooling loop, and −196 °C cold trap were usually omitted without adverse effects. In this mode, R_fOF could be generated continuously as long as the salt column temperature was warmer than −50 °C. At lower salt temperatures, purge–warm cycling was required to free condensed hypofluorites[29] from the salt solution.

Instrumentation and Analysis. GC analyses were carried out on a Varian 4600 with thermal conductivity detector, using 2 m × 3.2 mm nickel columns (3% OV-17 on Gaschrom Q, He carrier gas, 20 mL min^{-1}), except where otherwise indicated. GC–MS data were obtained with a Finnigan 4021 mass spectrometer with GC inlet, operated either in electron impact (70 eV) or chemical ionization (CH_4) modes. ^1H NMRs were obtained on Varian EM360A (60 MHz) or JEOL FX90Q (90 MHz) spectrometers. ^{19}F NMRs were obtained at 84.26 MHz on the latter instrument. A Beckman Acculab 8 (KBr liquid cells, $CHCl_3$) or a Nicolet 60 SX FTIR with GC inlet were used to record infrared (IR) spectra. ^{18}F samples were counted with a Beckman 8000 γ counter (511-KeV window). Thin-layer chromatography (TLC) was carried out on glass-backed silica plates (Merck 0.25 mm). Merck Silica 60 (40-63 μm) was used for column chromatography. Chromatographic solvent mixture proportions are reported on volume volume basis. Melting points were determined on a Mel-Temp capillary tube apparatus and are uncorrected. Microanalysis was performed by Spang Microanalytical Laboratory Eagle Harbor, MI 49951. Values found for the indicated elements are within 0.4% of theory unless noted otherwise.

Fluorination of Anisole. A 1 M solution of anisole in $CFCl_3$ at −78 °C was treated with 0.5 O–F equiv of R_fOF. Consumption of 36% of the initial quantity of anisole occurred and a mixture of 2- and 4-fluoroanisoles were formed in 68% and 23% respective yields, on the basis of reacted anisole. Yields based on input R_fOF were 49% and 16.5%, respectively. Analysis was performed by GC (6-m Carbowax 20 M, 100 °C) using authentic monofluoroanisoles (Aldrich) for comparison.

Fluorodemercuration of Phenylmercuric Acetate. PhHgOAc (440 mg, 1.31 mmol) was suspended in 20 mL of 19:1 CH_2Cl_2/HOAc, cooled to 0 °C, and treated with 0 °C R_fOF (1.0 O–F equiv). GC analysis (Carbowax 20 M, 50 °C) showed a 56% yield of fluorobenzene on the basis of O–F.

Reaction of 0° R_fOF with *trans*-Stilbene. This example typifies the procedure used in trapping experiments. Fluorine gas, 9% (50 mL min^{-1} flow, 1 mmol/5 min), was passed through a 0 °C trifluoroacetate column. The column effluent (~0.5 mmol of O–F bond) was passed directly into a −45 °C solution of *trans*-stilbene (180 mg, 1 mmol) in 10 mL of CH_2Cl_2. Consumption of slightly less than 50% of the stilbene took place as indicated by GC (3% OV-17, 100 °C programmed to 220 °C 8 °C at min^{-1}). The following major products were observed, in order of retention time relative (rRT) to *trans*-stilbene (rRT for a particular peak equals its retention time divided by the retention time of the reference compound—in this case, *trans*-stilbene). **1** (rRT 0.55) was observed as an unresolved 60:40 threo/erythro mixture. **1** was isolated by preparative GC (10% OV-17, 3 m × 6.4 mm Ni column) in 30% yield, based upon reacted stilbene, as a crystalline, white solid, mp 68–72 °C: ^1H NMR δ (multiplicity, *J*, assignment), 5.2–6.0 (m, 2 H, PhC*H*FC*H*(OC_2F_5)Ph), 7.2 (m, 10 H, Ph). ^{19}F NMR ($CDCl_3$, $CFCl_3$ internal reference) −186.07 (dd, $J_{FH_{gem}}$ = 48 Hz, $J_{FH_{vic}}$ = 14 Hz, *erythro*-PhCH*F*CH(OC_2F_5)Ph), −181.52 (dd, $J_{FH_{gem}}$ = 49, $J_{FH_{vic}}$ = 10 Hz, *threo*-PhCH*F*CH(OC_2F_5)Ph); integration, 60% threo, 40% erythro, −88.70 (m, 2F, OCF_2CF_3), −86.47 (S, 3F, OCF_2CF_3). FTIR 3100, 3050, 1273, 1227 (s), 1060. Mass spectrum, *m/e* (relative intensity), 334 (M^+, 0.5), 225 ($C_2F_5OCFPh^+$, 75), 119 ($C_2F_5^+$, 19), 109 ($PhCHF^+$, 100). These data agree with literature values.[4c] Compound **2**[4b] (two isomers, 2:1 ratio, rRT 0.59, 0.60) mass spectrum, *m/e* (relative intensity) 284 (M^+, 0.6), 175 ($PhCHOCF_3^+$, 100), 109 ($PhCHF^+$, 90). Compound **4**[4d] (two isomers, 1:2 ratio, rRT 0.72, 0.73): Mass spectrum, *m/e* (intensity no. 1, intensity no. 2) 312 (M^+, 0.2, 0.4), 203 ($PhCHOCOCF_3^+$, 36, 46), 109 ($PhCHF^+$, 100, 100) 105 ($PhCO^+$, 18, 25), 91 (40, 5), 83 (10, 15), 77 (10, 15), 69 (22, 25). FTIR 1801, 1230, 1145. Compound **3**[4b] (two isomers, 3:1 ratio, rRT 0.79, 0.81) mass spectrum, *m/e* (intensity) 218 (M^+, 6, 6), 109 (100, 100), 83 (15, 13).

A small amount of **6** (see text and ref 28) was also detected.

Treatment of stilbene with excess R_fOF led to the appearance of significant amounts of the following isomers of **5**: **$PhCF_2CH(OC_2F_5)Ph$** (rRT 0.48) mass spectrum, *m/e* (intensity), 352 (M^+, 0.5), 243, (0.6), 225 ($PhCHOC_2F_5^+$, 55), 127 ($PhCF_2^+$, 100), 119 ($C_2F_5^+$, 20), 109 (25), 105 (15), 77 (20), 69 (10). **$PhCF_2CH(OCF_3)Ph$** (rRT 0.50) mass spectrum, *m/e* (intensity), 302 (M^+, 1), 243 (2.3), 175 ($PhCHOCF_3^+$, 75), 127 ($PhCF_2^+$, 100), 109 (25), 105 (10), 77 (20), 69 (CF_3^+, 20). **$PhCHFCF(OC_2F_5)Ph$** (rRT 0.52) mass spectrum, *m/e* (intensity), 352 (M^+, 0.1), 243 ($PhC(F)OC_2F_5^+$, 45), 119 ($C_2F_5^+$, 30), 109 ($PhCHF^+$, 100), 105 ($PhCO^+$, 80), 77 (Ph^+, 20), 69 (15). **$PhCF_2CH(O_2CCF_3)Ph$** (rRT 0.62) mass spectrum, *m/e* (intensity) 330 (M^+, 1), 203 ($PhCHO_2CCF_3^+$, 25), 127 ($PhCF_2^+$, 100), 77 (10), 69 (10). **$PhCHFCF(O_2CCF_3)Ph$** (rRT 0.66) mass spectrum, *m/e* (intensity), M^+ absent, 221 ($PhCF(O_2CCF_3)^+$, 45), 109 ($PhCHF^+$, 73), 105 ($PhCO^+$, 100), 83 (10), 77 (15), 69 (19). **$PhCHFCF_2Ph$** (rRT 0.69) mass spectrum, *m/e* (intensity), 236 (M^+, 15), 127 ($PhCF_2^+$, 100), 109 ($PhCHF^+$, 50), 83 (8), 77 (8).

^{19}F NMR of R_fOF Mixtures. The R_fOF mixture formed by passage of 3 mmol of F_2 through a fresh, 0 °C trifluoroacetate column was condensed at −196 °C in a glass cold trap. The condensate was vacuum-transferred in a dedicated all glass and Teflon line (scrupulously clean and passivated with 10% F_2) to an NMR tube containing $CFCl_3$ (0.3 mL) and a sealed coaxial capillary tube of acetone-d_6 (lock). The NMR tube was flame-sealed (**caution**) and the spectrum was recorded at −40 °C. ^{19}F chemical shifts are reported in ppm from $CFCl_3$ internal standard.

Values downfield from $CFCl_3$ are *positive*: δ (multiplicity, J, assignment), −111.96 (t, 27 Hz, $CF_3CF(OF)_2$), −97.55 (d, 11 Hz, CF_3CF_2OF), −84.00 (t, 38 Hz, $CF_2(OF)_2$), −81.71 (d, 11 Hz, CF_3CF_2OF), −77.08 (t, 11 Hz, $CF_3CF(OF)_2$), −71.80 (d, 33 Hz, CF_3OF), +139.04 (d, 11 Hz, CF_3CF_2OF), +146.78 (q, 33 Hz, CF_3OF), +149.93 (m, $CF_3CF(OF)_2$), +158.80 (t, 38 Hz, $CF_2(OF)_2$). Integration of assigned peak intensities gave the following values: 40.5% CF_3CF_2OF,[18] 29.5% CF_3OF,[18] 24.6% $CF_3CF(OF)_2$,[21,22] and 5.4% $CF_2(OF)_2$.[19]

Fluorination of 3,4,6-Triacetyl-D-glucal (TAG) with R_fOF. Synthesis and Measurement of 2-Fluoro-2-deoxy-D-glucose (FDG) and 2-Fluoro-2-deoxy-D-mannose (EDM). Representative Procedure. A 1.0 M solution of TAG in the indicated solvent at the indicated temperature (Table III) was treated with 1 O–F equivalent of gaseous 0°R_fOF. Rapid and nearly complete consumption of TAG occurred and the following eight discrete addition products were detected by GC–MS (3% OV-17, 100 °C programmed to 250 °C at 8 °C min^{-1}). rRT = retention time relative to TAG. **TAG-CF_3CF_2OF** (two isomers, rRT 0.73, 0.87) mass spectrum CI, m/e (intensity), 455 (M + 29, 0.21, 0.12), 427 (M + 1, 1.60, 0.06), 385 (12, -), 367 (M − OAc, 58, 8) 291 (M − OCF_2CF_3, 100, 100), 231 (80, 17), 189, 171, 109. **TAG-CF_3OF** (two isomers, rRT 0.80, 0.90) mass spectrum CI, m/e (intensity) 405 (M + 29, 0.22, 0.17), 377 (M + 1, 1.79, 0.08), 355 (19, -), 317 (M − OAc, 80, 13), 291 (M − OCF_3, 100, 100), 231 (87, 17), 189, 171, 109 **TAG-F_2** (two isomers, rRT 0.98, 1.10) mass spectrum CI, m/e (intensity), 339 (M + 29, 0.21, 0.05), 311 (M + 1, 3.0, 0.17), 291 (M − F, 56, 100), 269 (31, 0.12), 251 (M − OAc, 100, 25), 231, 189, 171, 148, 129, 109. **TAG-CF_3CO_2F** (two isomers, rRT, 0.89, 1.05) mass spectrum EI, m/e (intensity) 345 (M − OAc, 0.18, 0.11), 291 (M − CF_3CO_2, 1.25, 0.48) 284 (0.68, 0.52), 259 (2.14, 1.07), 242 (4.81, 6.65), 126 (1.5, 6.7), 115 (6.6, 3.2), 103 (5, 3.75), 97 (3, 6.4), 69 (3, 3), 43 (100).

After evaporation of the reaction solvent under reduced pressure, the product mixture (1.2 g) from a 3-mmol scale reaction of TAG (817 mg) with R_fOF was hydrolyzed in 40 mL of refluxing 1:1 CF_3CO_2H/H_2O for 30 min or until TLC (SiO_2, 95:5, CH_3CN/H_2O) indicated complete hydrolysis (one major spot R_f 0.4). The solvent was then evaporated at 70 °C under reduced pressure. A 20-mL portion of H_2O was added to the residue and it was evaporated under reduced pressure to remove traces of acid. This step was repeated. The residue was taken up into 10 mL of H_2O and the resultant suspension was filtered sequentially through two short columns (each 1.5–2 cm^3) containing 1:4 activated charcoal/neutral alumina and poly(4-vinylpyridine). The columns were then sequentially washed with a single 10-mL portion of water and the combined filtrate and washings were evaporated in vacuo at 70 °C to a syrup which appeared homogeneous by TLC. Vacuum drying (20 C, 1 torr) over P_2O_5 afforded 500 mg (91%) of a foamy solid mixture of FDG and FDM.

The relative amounts of FDG and FDM were routinely determined by GC analysis (3% OV-17 150 °C, 2-min hold, programmed to 250 °C at 10 °C min^{-1}) of a silylated portion (30 mg of fluorohexose, 0.5 mL of pyridine, 0.4 mL of hexamethyldisilazane, 0.2 mL of Me_3SiCl, 70 °C, 5 min) of the mixture. This GC system was able to analytically separate all anomers of silylated mixtures of authentic FDG (Calbiochem Lot 410012) and FDM,[34] as well as 2-deoxy-D-glucose (Aldrich), a minor hydrolysis product of TAG.[35] The relative retention times (rRT) compared to (trimethylsilyl)-[β]-2-deoxy-D-glucose (rRT 1.00) were (trimethylsilyl)-[α]-2-deoxy-D-glucose (rRT 0.85), (TMS-[α]-FDG (rRT 0.91), (TMS)-[α]-FDM (rRT 0.93), (TMS)-[β]-FDG (rRT 1.05), and (TMS)-[β]-FDM (rRT 1.11). In most cases GC quantifications were also checked by ^{19}F NMR of either (a) the free fluorohexoses[39] [(D_2O, C_6F_6 external reference): [β]-FDG δ −32.33, [α]-FDG −32.51, [α]-FDM −37.84, [β]-FDM −56.32) or (b) the fully acetylated derivatives[6a,7b] [(acetone-d_6, C_6F_6 internal reference): Ac_4-[β]-FDG −37.71 (J_{F-H2} 51.02, J_{F-H3} 14.3, J_{F-H1} 3.4 Hz), Ac_4-[α]-FDG −38.87 (J_{F-H2} 48.1, J_{F-H3} 12.4 Hz), Ac_4-[α]-FDM to −40.04–41.05 (multiplet), Ac_4-[β]-FDM −55.76 (septuplet)]. Results of GC and ^{19}F NMR quantifications agreed to within 5% of each other.

Fluorination of 13. Formation of 14. Compound **13** was prepared by a literature procedure.[37] To a solution of lithium diisopropylamide (1.07 g, 10 mmol) under inert atmosphere in 20 mL of THF at 0 °C was added **11** (1.63 g, 10 mmol) dissolved in 10 mL of THF. After stirring magnetically for 10 min, a solution of t-BDMSCl (1.65 g, 11 mmol) in 5 mL of THF was added via syringe and the resulting mixture was stirred at RT for 4 h. The solvent was removed in vacuo at 30 °C while guarding against possible intrusion of moisture. A fresh portion of THF (20 mL) was added to the residue and the solvent was again evaporated in vacuo. The residue was dissolved in 10 mL of dry CH_2Cl_2. This solution was quickly pressure filtered (N_2) through a short column of activated SiO_2 (100–200 mesh, 5 g) to remove chloride salts, and the column was rinsed with fresh CH_2Cl_2 (30 mL). The combined filtrate and washings were cooled to −45 °C and treated with 1 equiv of 0°R_fOF (10 mmol of O–F bond). The reaction solution was poured into an equal volume of cold 1 N HCl and shaken, and the organic layer was separated, dried (Na_2SO_4), and evaporated to an oily residue. The product **14** (R_f 0.35 on silica, 1:1 hexane/EtOAc) was separated from unidentified high R_f materials and **11** (R_f 0.25) by low-pressure LC to give 750 mg (41%) of **14**, as an oil which solidified on standing. Crystallization from hexane–Et_2O gave **14** as colorless crystals mp 58–59 °C (lit. 60–61 °C[38]). ^1H NMR ($CDCl_3/Me_4Si$) δ (multiplicity, J assignment) 2.90, 3.00 (2 S, 6 H, $-N(CH_3)_2$), 6.05 (d, 50 Hz, 1 H, PhC*H*F+) 7.45 (m, 5 H, Ph). ^{19}F NMR ($CDCl_3/CFCl_3$) −172.2 (d, 49 Hz) (lit. −175.5, 50 Hz[6e]). Anal. $C_{10}H_{12}FNO$ (C, H, N, F).

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(34) Prepared by reaction of AcOF with D-glucal in water which gives 55% FDM, 45% FDG.[7] These products were preparatively separated as the fully acetylated derivatives on silica (1:1 hexane/EtOAc): Ac_4-(α,-β)-FDM R_f 0.4; Ac_4-(α)-FDG R_f 0.5; Ac_4-(β)-FDG R_f 0.54. Acid hydrolysis (50% TFA, 80 °C) of the Ac_4-FDM containing fractions regenerated free FDM in 30% overall yield before crystallization, which was contaminated by less than 5% FDG by ^{19}F NMR. The ^{19}F NMR[39] and melting point (129–131 °C)[6a] of a crystallized form (MeOH–EtOAc) of this FDM agreed with literature values.

(35) Most unreacted TAG polymerizes under the conditions of acid hydrolysis.

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(40) On this point the "old salt" effect could not be mimicked by adding dry NaF (2 parts by weight) to fresh CF_3CO_2Na (1 part) nor by passing the R_fOF mixture from a fresh column through a second column of NaF.