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# REACTIVITY OF HALOGEN SUBSTITUENTS OF p-HALOGENOPERFLUOROANILINES IN ACID MEDIA

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### SUMMARY

Replacement of a halogen substituent by hydrogen in the reaction of a perfluorophenyl halide which has a basic nitrogen substituent at the <u>para-position</u> with an aqueous hydrogen halide was investigated. The reaction behavior of <u>p-halogeno-N,N-dimethylperfluorophenyltrimethylammonium</u> trifluoromethanesulfonates with nucleophiles and electron-transferring agents indicated two plausible reaction mechanisms for the dehalogenohydrogenation in acid media: a reaction route via positive halogen transfer resulting from nucleophilic attack on the halogen substituent (S<sub>N</sub>X process) and that via electron-transfer and unimolecular elimination of halide ion (S<sub>RN</sub>1 process). The ammonio group and perfluoro substituents on the aromatic ring were found to be indispensable to allow this dehalogenohydrogenation.

#### INTRODUCTION

As is well known, a halogen substituent on an aliphatic side chain of an Fphenyl compound [1] can be replaced with hydrogen by positive halogen trans-

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fer resulting from nucleophilic attack on the halogen substituent (S $_{\rm NI}{\rm X}$  reaction) A halogen substituent on an F-benzene ring is also replaced by hydrogen, [2]. when p-halogeno-F-phenylhydraan acid medium; for instance, even in zine (1) is heated with hydriodic acid, an appreciable amount of p-hydryl-F-aniline (2) is always formed along with the corresponding p-halogeno-F-aniline (3) [3]. It should be noted that in this reaction the fluorine substituent is replaced by hydrogen (Scheme 1).



Scheme 1

In our preliminary study on the dehalogenohydrogenation of p-halogeno-Fphenylhydrazines (1) and p-halogeno-F-anilines (3) in aqueous hydrogen halides [see Experimental], hydriodic acid was the most effective among aqueous hydrogen halides, irrespective of the kind of halogeno substituent. On the other hand, although the iodo substituent of ordinary p-iodoaniline was replaced with hydrogen in aqueous hydriodic acid, p-fluoroaniline remained completely intact under similar conditions. Obviously, the four other ring-fluorine substituents of F-aniline seem to activate the defluorohydrogenation of F-aniline (3a). Hydrobromic acid could also convert the iodo, bromo, and chloro substituents into the hydryl one, although the fluoro substituent gave an extremely low yield. Hydrochloric acid seemed much effective, it less but still gave an appreciable yield of the p-hydrylperfluoro product (2) from the corresponding iodo (1d), bromo (1c), and chloro (1b) compounds, while the p-fluoro compound (1a) yielded only a trace amount of the hydryl product (2).

Such dehalogenohydrogenations by hydriodic acid occurred also in the hydrocarbon analogues, some of which are thought to proceed <u>via</u> electrophilic addition of a proton to the ipso-carbon to form a Wheland-type complex, followed by elimination of the triiodide ion [4]. In the perfluoroaromatic compounds, however, such electrophilic protonation seems less likely to occur in an aqueous medium under conventional conditions.

Deiodohydrogenation of iodo-2,4,6-trinitrobenzene with iodide ion was thought to occur <u>via</u> positive halogen transfer resulting from a nucleophilic attack of iodide ion on the iodo substituent [5]. Some reactions of substituted perfluoroaromatics with hydriodic acid, in which a heteroatom substituent is replaced with hydrogen, have been described in the literature: 4-lodo-F-pyridine gave the corresponding 4-hydryl one [6], and  $\underline{p},\underline{p}'$ -di(phenylthio)-F-azobenzene yielded p-hydryl-F-aniline via the intermediary <u>p-hydryl-p'-phenylthio-F-</u> azobenzene [7]. These reactions were also thought to proceed via nucleophilic attack by the iodide ion on the heteroatom substituent. Such an  $S_N^X$  process is, however, not regarded as the mechanism by which the <u>p-fluorine</u> of F-aniline (3a) is replaced by hydrogen in hydriodic acid, because the displacement of a positive fluorine is most unlikely.

The present article describes a systematic investigation of the reaction behavior of  $\underline{p}$ -halogeno-F-anilines with aqueous hydrogen halides, and proposes two possible mechanisms for the dehalogenohydrogenation in acid media.

## **RESULTS and DISCUSSION**

In contrast to ordinary aniline, highly fluorinated anilines are only slightly soluble in aqueous mineral acids due partly to the decreased basicity of amino nitrogen [8] and partly to the hydrophobic effect of the fluorocarbon Kinetic studies of F-aniline derivatives in a solution system theremoiety. fore require the use of an organic or aqueous organic solvent to form a homogeneous solution phase. Aqueous methanol was used in the present studies as a simple and water-soluble organic solvent stable in aqueous acid. The reactions of p-halogeno-F-anilines (3) in aqueous methanol were, however, accompanied by methylation at the amino nitrogen in the presence of mineral acid, to give a complicated mixture of N-methylated derivatives of the starting phalogeno compound and the resulting p-hydryl one. Kinetic investigations were, therefore, carried out conveniently by use of p-halogeno-N,N-dimethyl-F-aniline (4) in place of the parent p-halogeno-F-aniline (3) to avoid complexities in the product analysis. p-Halogeno-N,N-dimethyl-F-anilines (4) [3, 9] were prepared from the corresponding halogeno-F-benzene (5) and dimethylamine.

# Reactions of p-halogeno-N,N-dimethyl-F-aniline (4) with aqueous hydrogen halide

<u>p</u>-lodo-N,N-dimethyl-F-aniline (4d), when heated with hydrobromic acid in aqueous methanol, yielded <u>p</u>-hydryl-N,N-dimethyl-F-aniline (6) [10]. Kinetics of the reaction were followed under pseudo-first-order conditions in 4d at 100°C. The kinetic plots at various acid concentrations showed good linear pseudo-first-order relationships with correlation coefficients of more than 0.99 within a half-life period of the substrate [11], and an example is shown in Fig. 1.



Fig. 1. Reaction of <u>p-iodo-N,N-dimethyl-F-aniline</u> (4d) at 100°C with hydrobromic acid, 0.57 mol  $dm^{-3}$  in aq. methanol.



Fig. 2. Plotting of pseudo-first-order rate constant,  $k_1'$ , versus acid concentration in the reactions of p-iodo-N,N-dimethyl-F-aniline (4d) with hydrobromic acid at 100°C.

The apparent first-order rate constants,  $k_1'$ , which were obtained at various acid concentrations, were linearly proportional to the acid concentration. The gradient of the correlation line gave an apparent second-order rate constant,  $k_2$ , of 0.10 dm<sup>-3</sup> mol<sup>-1</sup> h<sup>-1</sup>, as shown in Fig. 2. <u>p</u>-Bromo-N,N-dimethyl-F-aniline (4c), on the other hand, remained intact under the same conditions,

to give no <u>p</u>-hydryl product (6). When the temperature was elevated to 150°C, the replacement of the <u>p</u>-bromo substituent proceeded slowly with hydrobromic acid, the  $k_2$  being 0.081 dm<sup>3</sup> mol<sup>-1</sup> h<sup>-1</sup>. At the same temperature, the reaction with hydriodic acid proceeded approximately four times faster, the  $k_2$  increasing to 0.36 dm<sup>3</sup> mol<sup>-1</sup> h<sup>-1</sup>, while hydrochloric acid caused no reaction at all.

The reaction rate varied according to the kind of <u>p</u>-halogeno substituent and halide ion in the reaction medium; the <u>p</u>-iodo-derivative (4d) was the most labile, and iodide ion the most effective. No reaction proceeded in a neutral medium even when more than an equimolar amount of halide ion was present.

Thus the dehalogenohydrogenation of <u>p</u>-halogeno-N,N-dimethyl-F-aniline (4) proceeded at the rate proportional linearly to the substrate and the acid concentration, and one could notice a tendency for the reaction rate to increase with decreasing C-X bond energy and with decreasing electron affinity of the halogen with respect to the aqueous hydrogen halide.

# Mechanisms of dehalogenohydrogenation of p-halogeno-N,N-dimethyl-Fanilines (4)

Regarding the formation of <u>p</u>-hydryl-N,N-dimethyl-F-aniline (6) from the parent <u>p</u>-halogeno compounds (4), one could assume the following two possible paths compatible with the observed reaction kinetics in aqueous hydrogen halide.

Path 1. A route via positive halogen transfer, S<sub>N</sub>X process (Scheme 2).



Scheme 2

Since the reaction is promoted in proportion to the acid concentration, one might presume that <u>p-halogeno-N,N-dimethyl-F-aniline</u> (4) is protonated at the amino group to form an ammonium ion, which is considered to be the reactive species. The highly electron-withdrawing ammonio group would activate the p-halogeno substituent to be susceptible to the  $S_{NI}X$  process.

The great dependence of the reaction rate on the kind of <u>p</u>-halogeno substituent and hydrogen halide indicates that the nucleophilic attack of halide ion on the <u>p</u>-substituent in an  $S_N X$  manner was concerned in determining the rate, while protonation of the following intermediate (A) was rapid to give the <u>p</u>hydryl product (6).

Although a precise kinetic investigation has not been done on the defluorohydrogenation of F-aniline (3a) in aqueous hydriodic acid, an activated <u>p</u>-fluoro substituent might be replaced at first in an  $S_N^{Ar}$  manner by the iodide ion to give <u>p</u>-iodo-F-anilinium ion (3dH<sup>+</sup>) in preference to the  $S_N^X$  replacement, because direct defluorination by iodide ion in an  $S_N^X$  manner might be energetically unfavorable (Scheme 3).



Scheme 3

The difference in the reactivity in defluorohydrogenation between F-ani line (3a) and p-fluoroaniline indicates that the four ring-fluorine substituents of F-aniline (3a) are indispensable for the  $S_N$ Ar reaction to proceed.

Path 2. A route via electron-transfer and unimolecular elimination of halide ion,  $S_{\rm RN}^{}1$  process (Scheme 4) [12].

If the highly electron-withdrawing polyfluorophenylammonium ion were present together with an electron-donating halide ion such as the iodide ion in a reaction system, electron-transfer from the latter to the former would be likely to occur, initiating displacement of the <u>p</u>-halogen in an  $S_{RN}$  manner to yield a <u>p</u>-hydryl-F-aniline (6). The reaction would be facilitated by the electron-donating capability of the halide ion as well as the nucleofugicity of the p-halogeno substituent.



Scheme 4

In the above two paths, the ammonium form is regarded as the reactive species and both reactions proceed via the benzenide intermediate (A), which would be stabilized by the ammonio group in the acid medium and four fluoro substituents on the aromatic ring.

# Reactions of (p-halogeno-F-phenyl)trimethylammonium trifluoromethanesulfonate (7) with nucleophilic and electron-transferring agents in nonacidic media

According to the above presumption, the protonation of the amino group seemed to be indispensable for the reaction to proceed. If it were true, the equivalent effect could be expected in the reaction of a quarternary ammonium derivative under neutral conditions in place of the aniline in mineral acid. The quarternary ammonium derivatives could be prepared by the methylation of the p-halogeno-N,N-dimethyl-F-aniline (4) with methyl trifluoromethanesulfonate (methyl triflate) in dichloromethane at room temperature (Scheme 5). Otherwise, for example with iodomethane, none of the expected product would be obtained.

$$X - F - N(CH_3)_2 + CH_3OSO_2CF_3 \longrightarrow X - F - N(CH_3)_3 \cdot CF_3SO_3^{-1}$$

$$(4a - d) \qquad (7a - d)$$

$$a: X = F, b: X = Cl \qquad a: X = F, b: X = Cl$$

$$c: X = Br, d: X = 1 \qquad c: X = Br, d: X = 1$$

Scheme 5

The reaction path of dehalogenohydrogenation, if actually one of the above two, might be differentiated by knowing whether an electron-transferring agent or a nucleophilic one could promote the reaction.

At first, on the analogy of the reaction with hydriodic acid, (<u>p</u>-halogeno-F-phenyl)trimethylammonium triflate (7) was heated with aqueous potassium iodide. The reaction caused only demethylation of the ammonio group, which reverted to the original dimethylamino group quantitatively. The nucleophilic attack by iodide ion would be directed toward the methyl group on the positive nitrogen prior to the <u>p</u>-halogeno substituent, and a methyl group irreversibly removed to yield an uncharged <u>p</u>-halogeno-N,N-dimethyl-F-aniline (4) in which the p-halogeno substituents were no longer reactive under neutral conditions.

In the case of <u>p</u>-halogeno-F-aniline (3) in an acid medium, a proton can transfer reversibly between the ammonium and the iodide ion, and the reactive ammonium species can be always retained to give the p-hydryl product.

Although the result of the reaction with potassium iodide was not informative regarding the mechanistic studies, it provided a useful process in that the trimethylammonio group reverts quantitatively to the original dimethylamino one without any side reactions.

Secondly, the reaction with sodium dithionite was examined. This reagent has been used quite often as a two-electron reducing agent (Scheme 6).



Scheme 6

The <u>p</u>-iodo-F-phenylammonium salt (7d) gave 92% of the <u>p</u>-hydryl product (6) as a sole product within 24 h. Sodium dithionite was hardly soluble in methanol at room temperature, and the reaction was performed in a liquid-solid two-phase system taking a rather longer reaction period of time. The bromo and chloro compounds (7c and b) gave the <u>p</u>-hydryl product (6) in yields of 62 and 1%, respectively, after 7-days stirring at room temperature. The results indicated the reactivities of dehalogenohydrogenation decreasing in the order of iodo, bromo, and chloro substituents, consistent with the increasing C-X bond strength. The formation of the <u>p</u>-hydryl product (6) in this reaction might be regarded as an indication of a reaction path via an electron-transfer process.

Uncharged <u>p-iodo-N,N-dimethyl-F-aniline</u> (4d) remained intact in the reaction in methanol, neither did the unfluorinated <u>p-iodophenyltrimethylammo-</u>nium iodide yield the corresponding p-hydryl product.

These results indicated that the quarternary ammonio group and perfluorosubstituents on the aromatic ring were both indispensable for the reaction to proceed with dithionite, presumably playing an important role in promoting the electron-acceptance or in stabilizing the intermediary benzenide form (8).

In the case of <u>p</u>-chloro and <u>p</u>-bromo compounds, methoxylation at the ortho-position occurred simultaneously, and the yields of the <u>o</u>-methoxyl byproducts (9) seemed to increase in a reverse manner to those of the <u>p</u>-hydryl product (Table 9 in Experimental). Regarding the formation of these <u>o</u>methoxyl by-products (9), it was presumed that since dithionous acid is a rather weak acid, a proton transfer between dithionite and methanol generates a certain concentration of methoxide ion in methanol, which would react with the trimethylammonium compound (7) to give the corresponding <u>o</u>-methoxyl byproduct (9). In fact, the (<u>p</u>-halogeno-F-phenyl)trimethylammonium compound (7) gave the corresponding <u>o</u>-methoxyl compound (9) in the presence of sodium methoxide, except for the <u>p</u>-fluoro compound (7a), in which <u>p</u>-methoxylation occurred.

The <u>p</u>-fluoro compound also gave no <u>p</u>-hydryl product. One peculiar thing was that the <u>p</u>-fluoro compound gave no <u>p</u>-methoxyl compound in the reaction with dithionite, instead the methyl thioether (10) and the disulfide (12) were formed (see Experimental). It is obvious that this sulfide sulfur should come from the dithionite and that the sulfide moiety is introduced at the <u>p</u>-position prior to the methoxylation; the reaction sequence leading to the methyl thioether, however, remained uncertain at the present stage.

Thirdly, in order to clarify another question on the  $S_N X$  process involved with the reaction, triphenylphosphine was used as a highly nucleophilic reagent [2]. (p-Halogeno-F-phenyl)trimethylammonium triflate (7) was heated with twice molar amounts of triphenylphosphine. The (p-iodo-F-phenyl)trimethylammonium salt (7d) yielded the p-hydryl product (6) in 75% yield together with p-iodo-



Scheme 7

N,N-dimethyl-F-aniline (4d) (Scheme 7). Under the same conditions, the uncharged <u>p</u>-iodo-N,N-dimethyl-F-aniline (4d) gave the p-hydryl one (6) only in 7% yield. The formation of the two kinds of products in the above reaction therefore indicated that triphenylphosphine attacked two electrophilic centers: One was the attack on a methyl on the ammonio nitrogen, and it resulted in the <u>p</u>-halogenodimethylamino compound (4), which was much less reactive under neutral conditions. The other was the attack on the <u>p</u>-iodo substituent, followed by the subsequent attack on the ammonio methyl group. The later reaction mode would afford most of the p-hydryl product (6).

In a similar manner, 96% of the <u>p</u>-bromo substituent of 7c was converted into the <u>p</u>-hydryl ones, about a half of which was the ammonium form (11) and another half was the uncharged one (6), and the demethylated <u>p</u>-halogeno product (4c) was formed in 4% of the theoretical yield.

The <u>p</u>-fluoro substituent remained completely intact in the reaction, instead the nucleophilic attack by triphenylphosphine occurred only at the ammonio methyl site. The fluoro substituent was confirmed to be inert in the  $S_N X$ reaction with triphenylphosphine, as expected. It should be noted again that the quarternary ammonio group was indispensable for the reaction to proceed, seemingly playing an essential role in activating the <u>p</u>-halogeno substituents or stabilizing the resulting intermediary benzenide form (8) in the reaction.

#### EXPERIMENTAL

Melting points were uncorrected. The spectral data are those obtained on the following instruments: <sup>1</sup>H-NMR spectra, Hitachi R-24B and JEOL FX-100 against the internal TMS reference. <sup>19</sup>F-NMR spectra, Hitachi R-24F and JEOL FX-100 as the positive value downfield from the internal F-benzene reference. Mass spectra, JEOL JMS-07 and JMS-01SG.

### p-Substituted F-anilines (2) and (3)

<u>p</u>-Halogeno-F-phenylhydrazines (1a - c), which were prepared according to the literature [3, 13, and 14], were heated at 140 - 150°C for 3 h with 2 - 4 times molar amounts of hydrochloric acid (6 mol dm<sup>-3</sup>) in a stainless steel bomb. The resulting mixture was steam-distilled and the product (3a - c) solidified in the distillate was separated by filtration. The reaction conditions and the results are summarized in Table 1.

<u>p</u> -Halc phenylh	ogeno(X)-F- ydrazine (1)	HCl / (1) mole ratio	Reaction temp. (°C)	Yield %	Mp °C
(a)	X = F	4	150	75	36.4 - 37.1 (34*)
(b)	Cl	4	150	93	54.3 - 55.4
(c)	Br	2.2	140	59	59.7 ~ 61.0 (61*)

Table 1 Preparation of p-halogeno-F-anilines (3)

\* lit. [15].

<u>p-</u>Iodo-F-aniline (3d) was prepared by heating iodo-F-benzene with 6 times molar amounts of 95% methanolic ammonia in a stainless steel bomb at 150°C for 8 h. The resulting mixture was steam-distilled and worked up in a similar manner as above. Yield 48% and mp 76.9 - 77.7°C (lit. [15] 77°C).

<u>p-Hydryl-F-aniline</u> (2) was prepared according to the literature [3] by heating <u>p-bromo-F-phenylhydrazine</u> (1c) with 10 times molar amounts of 55% hydriodic acid for 6 h under reflux. Yield 77% and mp  $35^{\circ}$ C (lit. [3] 30 - 31°C).

Spectral data of 2 and 3 are shown in Table 2.

# Reaction of p-halogeno-F-phenylhydrazine (1) with aqueous hydrogen bromide and hydrogen chloride

<u>p</u>-Halogeno-F-phenylhydrazine (1a - c) (3.86 mmol) in 20 times molar amounts of 47% hydrobromic acid or hydrochloric acid (12 mol dm<sup>-3</sup>) was heated in a stainless steel bomb at 200°C for 3 h. The yields of products, (2) and (3a - c), which were measured by the <sup>1</sup>H-NMR spectra of the reaction mixture, are summarized in Table 3.

# Reaction of F-aniline (3a) with aqueous hydriodic acid

F-Aniline (3a) (0.467 g, 2.55 mmol) was refluxed in 57% hydriodic acid (5.7 g, 26 mmol) under a nitrogen atmosphere for 6 h. The reaction mixture was neutralized by aqueous sodium bicarbonate on an ice-cold water bath and extracted with ether. After the ethereal extract was dried over magnesium sulfate, evaporation of ether gave a pale-yellow oil (0.43 g). <sup>1</sup>H-NMR spectrum of the reaction mixture showed the presence of <u>p</u>-hydryl-F-aniline (2) (10%) and F-aniline (3a).

<u>p</u> -Substitu F-aniline	ted M <sup>+</sup> e m/e	<sup>19</sup> F-NMR (MeOH)	<sup>1</sup> H-NMR (CCI <sub>4</sub> )
( <b>3</b> a) X = 1	F 183	-1.3(m, 2F), -4.5(tdd, 2F) -13.3(tt, 1F)	4.30(br. s)
( <b>3b</b> ) C	Cl 199, 201	0.0(ddd, 2F), 15.5(ddd, 2F)	4.35(br. s)
( <b>3c</b> ) E	Br 243, 245	3.3(ddd, 2F), 16.7(ddd, 2F)	4.10
( <b>3d</b> ) I	291	2.3(m, 2F), 36.6(m, 2F)	4.30
( <b>2</b> ) F	ł	1.2(m, 2F), 28.8(m, 2F)*	4.1(br. s, 2H) 6.4(tt, 1H)

Mass and NMR spectral data of p-substituted F-anilines (2) and (3)

\* in CCl<sub>4</sub> solvent.

## Table 3

Yields of <u>p</u>-hydryl-F-aniline (2) and <u>p</u>-halogeno-F-aniline (3) in the reaction of p-halogeno-F-phenylhydrazine (1) with aqueous hydrogen halide

p-Halogeno(X)-F-	Aq. hydrogen	Yiel		
phenylhydrazine (1)	halide	(2)	(3)	
(a) X = F	HCI	<1	(a) 88	
	HBr	<1	(a) 69	
(b) Cl	HCI	7	(b) 85	
	HBr	7	( <b>b</b> ) 79	
(c) Br	HCl	52	(c) 38	
	HBr	63	-	

Similar reaction of 3a (0.969 g, 5.29 mmol) with 57% hydriodic acid (34,0 g, 151 mmol) under reflux for 12 h gave a product mixture (0.914 g) of 2 (40%) and 3a (60%).

Reaction of 3a (0.961 g, 5.25 mmol) with potassium iodide (8.13 g, 48.9 mmol) and 57% hydriodic acid (34.0 g, 151 mmol) under the same reaction conditions gave a mixture (0.782 g) of 2 (45%) and 3a (55%).

Table 2

## Reaction of p-iodoaniline and p-fluoroaniline with aqueous hydriodic acid

p-lodoaniline (0.42 g, 1.92 mmol) was refluxed in 57% aqueous hydriodic acid (8.63 g, 38.4 mmol) for 3 h. After the addition of aqueous sodium bisulfite at ice-bath temperature, the reaction mixture was neutralized by sodibicarbonate. The resulting mixture was adjusted to pН 10 with um aqueous potassium hydroxide, and extracted with ether; the ethereal extract was dried over magnesium sulfate, and evaporated off to give a reddish oil (0.23 g), GLC of which showed aniline as the sole product.

On the other hand, in a similar heating of <u>p</u>-fluoroaniline (0.53 g, 4.77 mmol) in 57% aqueous hydriodic acid (10.7 g, 47.7 mmol) under reflux for 6 h, p-fluoroaniline was recovered unchanged.

## p-Halogeno-N,N-dimethyl-F-anilines (4) [3, 9]

Halogeno-F-benzene (5) was heated with 2 - 3 times molar amounts of 43.3% dimethylamine in methanol at 100°C in a stainless steel bomb for 5 h. The product was fractionated by distillation under reduced pressure. Results are summarized in Table 4. The structures of the products were assigned by <sup>19</sup>F- and <sup>1</sup>H-NMR spectral data, which are summarized in Table 5.

### p-Hydryl-N,N-dimethyl-F-aniline (6) [10]

The Grignard reagent, which was prepared from <u>p</u>-bromo-N,N-dimethyl-Faniline (4c) in THF by an ordinary method, was hydrolyzed in 5 mol dm<sup>-3</sup> hydrochloric acid. The resulting mixture was worked-up as usual, to give a colorless oil, yield 76% GLC pure. The structure was assigned by <sup>19</sup>F- and <sup>1</sup>H-NMR spectral data given in Table 5.

# (p-Halogeno-F-phenyl)trimethylammonium trifluoromethanesulfonate (triflate) (7) (n.c.)

Into a chilled solution of methyl trifluoromethanesulfonate (2.25 g, 13.7 mmol) in dichloromethane (10 cm<sup>3</sup>) was dropwise added N,N-dimethyl-F-aniline (4a) (2.29 g, 10.8 mmol) dissolved in dichloromethane (10 cm<sup>3</sup>). The resulting solution was kept stirred for 2 days at room temperature. The resulting precipitates were collected by filtration, washed with dichloromethane and recrystallized from water or methanol to give 3.76 g of colorless needles. The reaction conditions, <sup>19</sup>F- and <sup>1</sup>H-NMR data, and elemental analyses are summarized in Tables 6, 7 and 8, respectively.

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Preparation of  $\underline{p}$ -halogeno-N,N-dimethyl-F-anilines (4)

\* lit. [9], 160 - 161°C/760 torr.

\*\* lit. [3], o-, m-, and p-isomer ratio = 10 : 3 : 87.

¶ lit. [3], 216°C/760 torr.

+ lit. [3], 108 - 109°C/15 torr.

Table 5

NMR spectral data of <u>p</u>-substituted N,N-dimethyl-F-anilines (4 and 6)

p-Sul	ostituted	<sup>19</sup> F-NM	R (ppm),	(CCl <sub>4</sub> )	<sup>1</sup> H-NMR (ppm) (CCl <sub>4</sub> )
anilii	nes	<u>o</u> -F	<u>m</u> -F	<u>p</u> -F	N(CH <sub>3</sub> ) <sub>2</sub>
(4a)	X = F	12.5 (m)	-2.1 (m)	-3.6 (tt)*	2.83 (t, $J = 1.8$ Hz)
( <b>4</b> b)	Cl	12.5 (m)	19.5 (m)		3.00 (t, J = 2.0 Hz)
(4c)	Br	12.5 (m)	27.0 (m)		2.85 (t, J = $2.0$ Hz)
(4d)	Ι	14.3 (m)	41.2 (m)*		3.0 (t, $J = 2.2 Hz$ )
(6)	Н	10.7 (m)	21.7 (m)		2.92 (t, 6H, J = $2.0$ Hz)
				6.50	(tt, 1H, J = 7 and 10 Hz)**

\* measured neat. \*\* assigned to p-H.

Table 4

# Reaction of p-halogeno-N,N-dimethyl-F-anilines (4) with hydrogen halide in aqueous methanol

The reaction was followed in the following manner; the required numbers of glass ampoules, each of which contained a mixture of <u>p</u>-iodo-N,N-dimethyl-F-aniline (4d) (0.180 g, 0.563 mmol) and hydrobromic acid (a prescribed amount) in 65% aqueous methanol (1.5 cm<sup>3</sup>), were started to be heated at the same time on an oil bath kept at 100°C. The acid concentrations were adjusted so as to be 2.29, 1.15, 0.573, 0.344, and 0.2299 mol dm<sup>-3</sup> in the reaction mixtures. At each scheduled interval, one ampoule was taken out to be opened, and the contents were neutralized with methanolic dimethylamine and analyzed by GLC. The reaction of <u>p</u>-bromo-N,N-dimethyl-F-aniline (4c) with hydrobromic acid at 100 and 150°C and with hydriodic acid at 100°C were followed in a similar manner as above.

# Reaction of (p-iodo-F-phenyl)trimethylammonium triflate (7d) and potassium iodide

A solution of 7d (0.534 g, 1.11 mmol) and potassium iodide (0.932 g, 5.62 mmol) in water (10 cm<sup>3</sup>) was heated under reflux for 2 h. The resulting mixture was extracted with ether and the ethereal extracts were dried over magnesium sulfate and evaporated off to give a pale yellow oil (0.342 g). The retention time of the single GLC peak and the <sup>19</sup>F- and <sup>1</sup>H-NMR spectra were identical with those of <u>p</u>-iodo-N,N-dimethyl-F-aniline (4d), yield 97%. (F-Phenyl)trimethylammonium triflate (7a) was treated with potassium iodide in a similar manner to give N,N-dimethyl-F-aniline (4a) in 97% yield.

# Reaction of (p-halogeno-F-phenyl)trimethylammonium triflate (7b, c, and d) with sodium dithionite

Into a solution of 7d (0.329 g, 0.68 mmol) in methanol (20 cm<sup>3</sup>) under a deoxygenated nitrogen atmosphere was added finely pulverized sodium dithionite (0.902 g, 5.18 mmol). The mixture was stirred at room temperature for 24 h. Products were analyzed by GLC after the trimethylammonio group was transformed into a dimethylamino form by treating with potassium iodide under neutral conditions; namely aqueous potassium iodide (1.345 g, 20 cm<sup>3</sup> of water) was added and then the mixture was heated for 6 h. The resulting mixture was extracted with dichloromethane. GLC analysis of the extract indicated that the p-hydryl compound (6) was obtained in 92% yield, and the majority

		Reaction	Yield		
Pro	duct (7)	time (days)	%	Mp* (°C)	
(a)	X = F	2	93	151.9 - 153. 7	
(b)	Cl	3	66	171.1 - 172.3	
(c)	Br	2	81	187.0 - 188.1	
(d)	1	2	86	205.8 - 206.5	

Preparation of (p-halogeno-F-phenyl)trimethylammonium triflates (7)

\* recrystallized from methanol, as colorless needles.

Table	7					
NMR	spectral	data	of	$(\underline{p}-halogeno-F-phenyl) trimethylammonium$	triflates	(7)

Prod	uct (7)	<sup>1</sup> H-NMR $^{19}$ F-NMR (ppm) (DMSO act (7) ppm, (DMSO-d <sub>6</sub> )		D-d <sub>6</sub> )		
		N(CH <sub>3</sub> ) <sub>2</sub>	F(2,6)	F(3,5)	F(4)	CF <sub>3</sub>
(a)	X = F	3.80 (t, J = 2.0 Hz)	26.6	3.5	11.9	87.2
(Ь)	Cl	3.82 (t, J = 1.7 Hz)	28.4	24.5		87.3
(c)	Br	3.85 (t, J = 2.4 Hz)	28.2	33.2		87.0
(d)	Ι	3.80 (t, J = 2.0 Hz)	27.2	43.8		87.0

# Table 8

Elemental analyses of (p-halogeno-F-phenyl)trimethylammonium triflates (7)

Product (7)			Observed			Calcd for $C_{10}H_9O_3NF_7SX$		
		C(%)	H(%)	N(%)	C(%)	H(%)	N(%)	
(a)	X = F	31.82	2.43	3.91	32.00	2.42	3.73	
(Ь)	Cl	30,58	2.56	2.38	30.64	2.58	2.32	
(c)	Br	27.53	2.20	3.28	27.49	2.08	3.21	
(d)	Ι	24.87	1.91	2.84	24.84	1.88	2.90	

Table 6

# Reaction of (F-phenyl)trimethylammonium triflate (7a) with sodium dithionite

A mixture of (F-phenyl)trimethylammonium triflate (7a) (0.250 g, 0.67 mmol) and sodium dithionite (0.560 g, 3.22 mmol) in methanol (10  $\mathrm{cm}^3$ ) was stirred at room temperature for 48 h under a nitrogen atmosphere. Potassium iodide (1.27 g, 7.63 mmol) in water (20  $\text{cm}^3$ ) was then added and the solution was refluxed for 5 h. The mixture was extracted with dichloromethane, and the extract was dried over magnesium sulfate. Evaporation of the solvent gave a colorless liquid (0.235 g).  $^{1}$ H- and  $^{19}$ F-NMR and GC-MS data of the product mixture indicated the formation of p-methylthio-N,N-dimethyl-F-aniline (10) and bis(4-N,N-dimethylamino-F-phenyl)disulfide (12) in addition to a trace amount of N,N-dimethyl-F-aniline (9a) (10 :  $12 \approx 80$  : 20). No p-hydryl product was detected. TLC separation of 10 and 12 on silica gel was not successful. 10: <sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  = 2.41 (s, SCH<sub>3</sub>) and 2.97 ppm (t, N(CH<sub>3</sub>)<sub>2</sub>, J<sub>HF</sub> = 2.20 Hz); <sup>19</sup>F-NMR (CDCl<sub>3</sub>),  $\delta$  = 10.58 (m, o-F) and 24.90 ppm (m, m-F); GC-HMS, Found, m/e = 239.0382 (M<sup>+</sup>),  $C_{q}H_{q}F_{4}NS$  requires 239.0391; MS (70 eV), m/e(relative intensity) = 239 (78), 238 (27), 224 (100), 223 (31), and 208 (22). 12: <sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta = 3.04$  (t, N(CH<sub>3</sub>)<sub>2</sub>, J<sub>HF</sub> = 2.44 Hz); <sup>19</sup>F-NMR (CDCl<sub>3</sub>),  $\delta = 10.58$  (m, 3- and 5-F) and 26.66 ppm (m, 2- and 6-F); MS (70 eV), m/e (relative intensity) = 448 (14) (M<sup>+</sup>), 224 (100), 223 (11), and 208 (14).

## p-Methylthio-N,N-dimethyl-F-aniline (10) (n.c.)

The reaction of N,N-dimethyl-F-aniline (9a) (1 mmol) with methanethiol (3 mmol) under reflux for 6.5 h in the presence of sodium hydride (1 mmol) in methanol (10 cm<sup>3</sup>) afforded quantitatively <u>p</u>-methylthio-N,N-dimethyl-F-aniline (10), whose <sup>1</sup>H- and <sup>19</sup>F-NMR spectra and GLC retention time were identical with those of the product from the reaction of 7a with sodium dithionite. Analysis: Found: C, 45.38; H, 3.87; N, 5.58%.  $C_9H_9F_4NS$  requires C, 45.19; H, 3.79; N, 5.86%.

Ct and in a	<b>D</b>	Produ	ict analysis,* y	rield (%)
Compound (7)	Reaction time (h)	<u>p</u> -hydryl- (6)	p-halogeno- (4)	<u>o</u> -methoxy- <u>p</u> - halogeno- ( <b>9</b> )
$(\mathbf{b})  \mathbf{X} = \mathbf{C}1$	168	1	68	30
(c) Br	168	62	20	13
	96	32	67	-
(d) I	228	100	-	-
	24	92	7	-

Reaction of (p-halogeno-F-phenyl)trimethylammonium triflate (7) with sodium dithionite in methanol

\* Product analysis was carried out by GLC after the products were transformed into the respective dimethylaniline forms (4) by treating with aqueous potassium iodide.

# Reaction of (p-halogeno-F-phenyl)trimethylammonium triflate (7) with triphenyl-phosphine

(<u>p</u>-Iodo-F-phenyl)trimethylammonium triflate (7d) (0.470 g, 0.973 mmol) and triphenylphosphine (0. 499 g, 1.90 mmol) were dissolved in deoxygenated methanol (20 cm<sup>3</sup>) and the solution was refluxed under a nitrogen atmosphere for 6 h. After the reaction, the solvent was evaporated off and the precipitated triphenylphosphine was filtered off.

The products and yields, which were assigned by  ${}^{19}$ F-NMR spectra of the resulting mixtures, are summarized in Table 10. 11:  ${}^{19}$ F-NMR (DMSO-d<sub>6</sub>-meth-anol);  $\delta$  = 25.6 (br. m, o-F, 2F) and 28.2 ppm (m, m-F, 2F).

# Reaction of p-iodo-N,N-dimethyl-F-aniline (4d) with triphenylphosphine

A methanol solution of <u>p</u>-iodo-N,N-dimethyl-F-aniline (4d) (0.537 g, 1.68 mmol) and triphenylphosphine (0.952 g, 3.65 mmol) was refluxed for 6 h under a nitrogen atmosphere. GLC analysis of the resulting mixture gave two peaks, which indicated that <u>p</u>-hydryl-N,N-dimethyl-F-aniline (6) was obtained in 7% yield and the rest was the unreacted starting compound (4d).

Table 9

#### Table 10

_			Product analysis, y	rield (%)	
Starting compound (7)		<u>p</u> -hydryl ( <b>6</b> )	<u>p</u> -hydryl-F-phenyl- ammonium salt (11)	p-halogeno (4)	unchanged (7)
(a)	X = F	none	none	58	42
(c)	Br	41	55	4	none
(d)	Ι	75	none	25	none

Reaction of  $(\underline{p}-halogeno-F-phenyl)$  trimethylammonium triflate (7) with triphenyl-phosphine in methanol

## p-lodophenyltrimethylammonium iodide [16]

Into a mixture of <u>p</u>-iodoaniline (0.78 g, 3.4 mmol) and potassium carbonate (1.04 g, 7.5 mmol) in acetone (20 cm<sup>3</sup>) was added iodomethane (2.46 g, 17.33 mmol). The mixture was stirred for 36 h, and the resulting solid was washed with ether and water successively to give pale gray <u>p</u>-iodophenyltrimethylammonium iodide (1.15 g, 83%), mp (decomp.) 193°C. <sup>1</sup>H-NMR (DMSOd<sub>6</sub>);  $\delta = 3.59$  (s, 9H) and 7.85 ppm (d, 4H).

## Reaction of p-iodophenyltrimethylammonium iodide with sodium dithionite

A mixture of p-iodophenyltrimethylammonium iodide (0.475 g, 1.22 mmol)and sodium dithionite (1.19 g, 6.83 mmol) in methanol (20 cm<sup>3</sup>) was stirred for 168 h at room temperature in a similar manner as above. No reaction occurred, the starting compound being recovered quantitatively.

#### p-Halogeno-o-methoxy-N,N-dimethyl-F-aniline (9)

About 2 mmol of  $(\underline{p}$ -halogeno-F-phenyl)trimethylammonium triflate (7) was dissolved in methanolic sodium methoxide (2.1 mmol in 20 ml) and allowed to stand at room temperature for one day. The resulting mixture was treated with aqueous potassium iodide as usual, and the product distribution was analyzed by GLC. The results are summarized in Tables 11 and 12.

# Table 11

Sta	Starting compd.	Yield	(%)	
	(7)	<u>o</u> -Methoxy- ( <b>9</b> )	Unreacted (7)	
(a)	X = F	16 (18)*	13	
		71¶ (82)*		
(b)	Cl**	85	10	
(c)	Br	86	14	
(d)	I	85	15	

Reaction of (p-halogeno-F-phenyl)trimethylammonium triflate (7) with methanolic sodium methoxide

\* relative yield of the o- and p-methoxyl products.

¶ yield of the <u>p</u>-methoxyl product.

\*\* polymethoxyl products occurred.

# Table 12

 $^{1}$ H-NMR spectral data of <u>p</u>-halogeno-<u>o</u>-methoxy-N,N-dimethyl-F-anilines (9) in carbon tetrachloride

<u>o</u> -Methoxyl compd. (8)		-OCH <sub>3</sub>		-N(CH <sub>3</sub> ) <sub>2</sub>	
		δ <b>(ppm)</b>	J <sub>HF</sub> (Hz)	δ (ppm)	J <sub>HF</sub> (Hz)
(a) X = F		3.80 (d)	1.0	*	· · · · · · · · · · · · · · · · · · ·
		3.90 (t)**	0.8**	2.85 (t)**	1.5**
(Ь)	C1	3.68 (d)	0.9	2.93 (d)	2.4
(c)	Br	3.79 (d)	0.8	2.90 (d)	2.1
(d)	I	3.81 (d)	1.0	2.97 (d)	2.2

\* overlapped with the signals of the p-methoxyl isomer.

\*\* <sup>1</sup>H-NMR signal of the <u>p</u>-methoxyl isomer.

Uncharged <u>p</u>-halogeno-N,N-dimethyl-F-aniline, for example, the <u>p</u>-bromo compound (4c), was treated with methanolic sodium methoxide under similar conditions for 7 days and resulted in no reaction: 4c remained practically intact.

### CONCLUSION

To summarize the above results, aromatic p-halogeno substituents, except fluorine, when activated with perfluoro substituents and the ammonio group which is formed in acid media, are shown to be quite susceptible to both  $S_{RN}^{1}$  and  $S_{N}^{X}$  reactions, and are replaced with hydrogen in a protic medium, while the fluoro substituent is inert to both processes, as expected. Defluorohydrogenation of F-aniline with hydriodic acid is, therefore, understood to proceed via  $S_{n}Ar$  replacement of the aromatic fluorine with iodide ion, followed by the  $S_M X$  and/or  $S_{PM} 1$  process. The role of the iodide ion in the second of the reaction may stage be either a nucleophilic agent and/or an electron-transferring one, but this still remains to be defined.

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