# Reactivity of Perfluoroalkyl Groups and of Halogen in (Perfluoroalkyl) Halobenzenes

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In analogy to the superior reactivity of vinylic fluorides over other vinylic halides toward nucleophilic reagents, activated aromatic fluorine compounds have been known for some time to be considerably more reactive than the corresponding chlorides, bromides or iodides when exposed to certain nucleophiles. This was demonstrated conclusively by Bevan[1], who found that the reactivities of the p-nitrohalobenzenes toward alkoxide ion at 90.8° C corresponded to the ratios F : Cl : Br : I = 3,100 : 13.6 : 11.8 : 1, the fluoride being by far the most reactive. This is explained by a one-step mechanism alternate to the established S_N2 type mechanism, whereby the formation of a discrete intermediate is the rate-determining step.

$$k_2 \gg k_{-1}$$
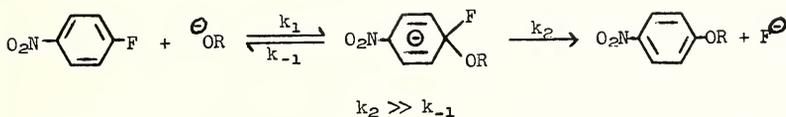
The considerable strength of the carbon-fluorine bond is now of relatively little importance, whereas the high electronegativity of fluorine, rendering the adjacent carbon atom positive and subject to nucleophilic attack, becomes the dominant factor. Although the reactivity sequence can be changed to ArBr > ArCl > ArF, by modifying the reaction conditions in order to increase the extent to which the carbon-halogen bond is broken in the transition state[2], under normal conditions the superior reactivity of the fluorides prevails.

This high reactivity of activated aromatic fluorides toward nucleophiles is also encountered in polyfluorobenzenes. Thus, hexafluorobenzene very readily undergoes nucleophilic displacement[3,4,5], yielding, for example, pentafluorophenol, dihydroxytetrafluorobenzene and the corresponding ethers[4,5]. Apparently the activating atoms do not cancel each other out.

The question arises, how does a mixed halobenzene behave when activated by a haloalkyl side chain, and are there specific reactions for both ring and side chain halogens? Interesting results were obtained upon hydrolysis with methanolic base of the chlorotetrafluoro- and the dichlorotrifluoro(trifluoromethyl)benzenes, obtained by the method of McBee, Lindgren and Ligett[3] after fluorination of pentachloro-(trifluoromethyl)-benzene with bromine trifluoride and subsequent dehalogenation.
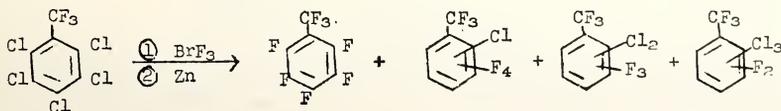
Treatment of the monochloride with an equimolar amount of base gave a chlorotrifluoro (trifluoromethyl) anisole. This product was very stable; subsequent photochlorination and exchange of chlorine for fluorine with antimony trifluoride resulted in exclusive substitution on the methoxy group.

More challenging, however, was the hydrolysis of the dichloride with excess base. Mainly dichlorotrimethoxy (trifluoromethyl) benzene, some starting material and a very small amount of methyl dichlorotrimethoxybenzoate were obtained. This complete retention of the chlorine atoms can be assumed to be caused by faster substitution of the fluorine atoms whereby one or more compounds are obtained which do not allow transition states of type A to be formed because of steric hindrance.
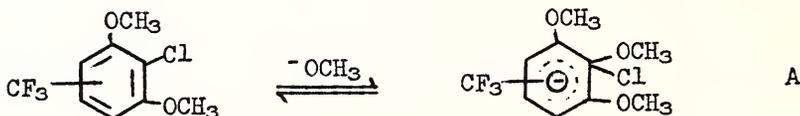

Table 1 lists rate coefficients obtained by Miller and Wrightson who subjected several trifluoromethylbenzene halides to nucleophilic displacement by ethoxide ion[6].

TABLE 1

Nucleophilic substitution of activated halobenzenes
in 1.0 N sodium ethoxide[6]

Compound	Reacting	Non-reacting	$K_{(av.)}$ 1.mole^{-1} sec^{-1}
p-CF$_3$C$_6$H$_4$F	F	CF$_3$	4.44×10^{-3}
p-CF$_3$C$_6$H$_4$Cl	Cl	CF$_3$	5.83×10^{-6}
m-CF$_3$C$_6$H$_4$F	F	CF$_3$	1.08×10^{-4}
m-CF$_3$C$_6$H$_4$Cl	Cl	CF$_3$	5.83×10^{-7}
o-ClC$_6$H$_4$F	F	Cl	8.06×10^{-5}

It is unfortunate that the value for o-fluoro (trifluoromethyl) benzene is not known, since it is very possible that substitution of fluorine ortho to the bulky trifluoromethyl group meets with considerable steric hindrance, rendering the rate coefficient smaller than for p-chloro (trifluoromethyl) benzene. Should this be found true, our results would place the chlorine atoms in the *ortho* positions.

If, however, this should not be the case, the values show that chlorine would react slower in all three positions and thus could be situated anywhere in the ring. Unfortunately the presence of isomers could not be established at the time this research was performed. Nevertheless, the results are interesting because of the probability that forces participate in these reactions which are stronger than the *ortho-para*-directing influence of the trifluoromethyl group, known for its inductive and resonance polar effects. The reactions will be further investigated.

It was shown that basic hydrolysis affects the trifluoromethyl group only slightly. A different picture is obtained with acid hydrolysis; the ring halogens are not attacked whereas the trifluoromethyl group is con-

verted to a carboxyl function. This was demonstrated by Wertyporoch who prepared various chlorobenzoic acids from the corresponding trifluoromethylbenzene chlorides with 60-80% sulfuric acid[7].

Bis-(trifluoromethyl)benzenes[8] and their chloro compounds[9] can also be hydrolyzed, but concentrated sulfuric acid is required.
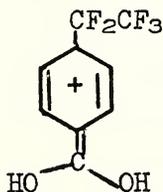
Bis-(pentafluoroethyl)benzenes and their chloro compounds do not react[9].

When extending these reactions to compounds with one fluoromethyl group and one larger side chain, surprising results were obtained. 4-(Trifluoromethyl)pentafluoroethylbenzene and 4-trifluoromethyl)heptafluoro-*iso*propylbenzene were hydrolyzed to 4-(pentafluoroethyl)- and 4-(heptafluoro*iso*propyl)benzoic acid, respectively. As before, the longer side chain was not attacked.

That the longer side chain is not unreactive, however, because of e.g. steric hindrance, can readily be seen from the fact that 3-chloro(pentafluoroethyl)benzene was hydrolyzed to 3-chloro(trifluoroacetyl)benzene.
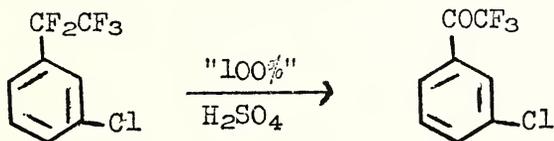
It can be argued that with the compounds having mixed side chains, the trifluoromethyl group is attacked first because of steric hindrance of the α-carbon in the pentafluoroethyl side chain. Protonation of the ensuing carboxyl group would withdraw electrons from the pentafluoroethyl substituent, rendering it inactive.

However, no explanation can be given for the total inactivity of the bis-pentafluoroethyl benzenes and the relative ease with which 3-chloro-(pentafluoroethyl)benzene is hydrolyzed, under the *m*-chlorine atom activates the carbon-fluorine bond sufficiently to permit hydrolysis.
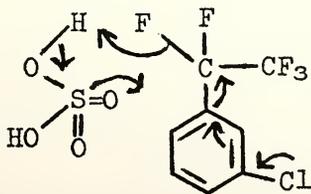
Reactions of this very interesting nature will be further investigated.

Experimental

Chlorotrifluoro(trifluoromethyl) anisole. A solution of 54 g. of potassium hydroxide in 300 ml. of methanol was added slowly, with stirring, to 203 g. of chlorotetrafluoro(trifluoromethyl)benzene. Stirring was continued until the mixture cooled to room temperature. It was poured into one liter of water. The organic layer was separated, washed with water, dried and rectified to give 17 g. of starting material and 100 g. (51% yield) of chlorotrifluoro(trifluoromethyl) anisole, having the following properties: bp. 63/6 mm, mp. –42 to –44, n_D^{25} 1.4360, d_4^{25} 1.595. *Anal.* Calc. for $C_8H_3OCl F_6$: Cl, 13.4; F, 43.2. Found: Cl, 13.8; F, 42.7.

A small amount of higher-boiling residue remained, indicating the presence of polymethoxy compounds.

Chlorination of chlorotrifluoro(trifluoromethyl) anisole. Chlorotrifluoro(trifluoromethyl) anisole (97 g.) was illuminated by three 200-watt incandescent lamps while chlorine was bubbled through it for 30 hrs. at a temperature below 50°. Air was blown through the liquid to remove dissolved gases, leaving 123 g. of a pale yellow liquid. *Anal.* Calc. for 22 mol % $C_8O Cl_4F_6$ + 78 mol % $C_8HOCl_3F_6$: Cl, 33.6; F, 33.4. Found: Cl, 33.6; F, 33.6.

Chlorotrifluoro(trifluoromethoxy)(trifluoromethyl)benzene. The product from the chlorination of chlorotrifluoro(trifluoromethyl) anisole (412 g.) was refluxed for 1.5 hrs. with 250 g. of antimony (III) fluoride and 74 g. of antimony (V) chloride. The organic product was decanted from the antimony salts, washed with hydrochloric acid and water, dried and rectified to give 104 g. of a fraction boiling at 135°, 115 g. of crude chlorotrifluoro(trifluoromethoxy)(trifluoromethyl) benzene (bp. 146-150), and 67 g. of residue. A purified sample of chlorotrifluoro(trifluoromethoxy)-(trifluoromethyl)benzene was found to have the following properties: bp. 150, mp. –56 to –57, n_D^{25} 1.3875, d_4^{25} 1.710. *Anal.* Calc. for $C_8OCl F_9$: Cl, 11.2; F. 53.7; MW, 318. Found: Cl, 13.2; F, 54.9; MW 316.

The fraction boiling at 135° was found to contain 15.9% Cl and 51.0% F. This boiling point and composition suggest that the material may be chlorotrifluoro(trifluoromethyl)benzene or chlorotetrafluoro(trifluoromethyl)benzene.

Dichlorotrifluoro(trifluoromethyl)benzene and methanolic potassium hydroxide. Potassium hydroxide (300 g.) was dissolved in a small amount of water, and methanol was added to make 500 ml. of solution. This solution was added, with stirring, to 404 g. of dichlorotrifluoro(trifluoromethyl)benzene, at such a rate that a steady reflux was maintained. After the addition was complete, the mixture was refluxed for another three hrs. The organic layer was separated, washed with water, dried and rectified to give 50 g. of dichlorotrifluoro(trifluoromethyl)benzene and 183 g. (42% yield) of dichlorotrimethoxy(trifluoromethyl)benzene, bp. 106-117/7 mm. (*Anal.* Calc. for $C_{10}H_9O_3Cl_2F_3$: Cl, 23.3; F, 18.7. Found: Cl, 23.7; F, 16.9), and 38 g. of a semi-solid fraction, bp. 117-127/7 mm. Recrystallization of the last fraction from ethanol-water gave 6 g. of crystalline methyl dichlorotrimethoxybenzoate. *Anal.* Calc. for $C_{11}H_{12}O_5Cl_2$: Cl. 24.1; F, 0.0. Found: Cl, 23.3; F. 0.0.

4-(Pentafluoroethyl)benzoic acid. Fifty grams of 4-(trifluoromethyl)-(pentafluoroethyl)benzene[3] was refluxed with 250 ml. of concentrated

sulfuric acid[1] for 24 hours. When cool the mixture was poured on to ice, the solid acid removed by filtration, and washed with water; m.p. 155-6° (after one recrystallization from ethanol); b.p. 242-3° (748 mm.).

Anal. Calcd. for $C_9H_5F_5O_2$: F, 39.1; M. W., 240. Found: F, 39.3; M. W., 233.

4-(Heptafluoroisopropyl)benzoic acid. In a similar manner 4-(trifluoromethyl)-(heptafluoro*iso*propyl)benzene[10] was hydrolyzed to 4-(heptofluoro*iso*propyl)benzoic acid; m.p. 102.5-103.5; b.p. 246-246.5 (748 mm.). *Anal.* Calcd. for $C_{10}H_5F_7O_2$: F, 45.9; M. W., 290. Found: F, 45.7; M. W., 286.

3-Chloro-(trifluoroacetyl)benzene. Fifty grams (0.22 mole) of 3-chloro-(pentafluoroethyl)benzene and 300 g. of concentrated sulfuric acid (95.5%, sp. gr. 1.84) were heated at a temperature sufficient to reflux the organic compound vigorously. After two hours hydrogen fluoride was being evolved. The experiment was stopped at the end of 15 hours and when cool the mixture was poured on to ice. The organic oil, the bottom layer, was separated, washed with water and dried. Distillation gave 29 g. (0.14 mole) of 3-chloro(trifluoroacetyl)benzene[8], 64%; b.p. 182.5-183° (751 mm.); n_D^{25} 1.4250; d_4^{25} 1.406. *Anal.* Calcd. for $C_8H_4ClF_3O$: Cl, 17.0; F, 27.3; M. W., 208. Found: Cl. 17.4; F. 27.6; M. W., 203.

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1. In reference to previous work[9] it has been pointed out by Scheurer and Le Fave[8] that 60-80% sulfuric acid is not suitable for the hydrolysis of the bis(trifluoromethyl) benzenes. On checking the original work of McBee and Fredrick[9] it has been found that concentrated sulfuric acid (95.5%) was the reagent actually used and that the 60-80% figure got into the paper by error in abstracting the thesis.