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AROMATIC POLYFLUORO-COMPOUNDS—XXXII[1]

ISOMER DISTRIBUTIONS IN THE NUCLEOPHILIC REPLACEMENT REACTIONS OF THE PENTAFLUOROHALOGENOBENZENES

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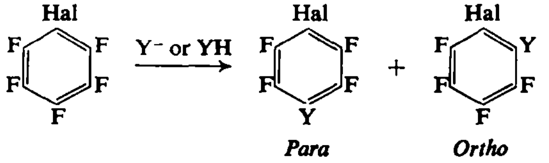
Abstract—The pentafluorohalogenobenzenes react with nucleophiles mainly at the position *para* to the halogen; *ortho* replacement occurs to a lesser extent and diminishes in the order $C_6F_5Cl > C_6F_5Br > C_6F_5I \sim C_6F_5H$. This is rationalized in terms of an electronic effect, which involves electron repulsion by halogens in π-electron systems and also by steric factors.

The first nucleophilic reactions of pentafluorohalogenobenzenes were reported by Wall and by Musgrave and their co-workers.[2,3] The bromo-compound reacted[2] with potassium hydroxide, sodium methoxide and ammonia to give the products in which the fluorine *para* to the bromine had been replaced. A small amount of the product formed by *ortho* fluorine replacement was also isolated from the hydroxide reaction. Only *para* replacement products were found in the reactions of pentafluoroiodobenzene with the same three nucleophiles. A brief report on reactions of chloropentafluorobenzene, with several nucleophiles, stated[3] that the fluorines *ortho*, *meta* and *para* to the chlorine were replaced in the ratios 25:5:70, respectively.

We have now carried out a study of the nucleophilic reactions of the three pentafluorohalogenobenzenes, in which we have attempted to assess accurately the amounts of the various isomers formed.



$Y = OMe, NMe_2, NHNH_2, OH$

Our main results are summarized in Table 1.

The structures of the products from the reactions with sodium methoxide and dimethylamine were determined by PMR measurements; the signals of the methyl groups of the *para* isomers were triplets, indicating two *ortho* fluorines, and those of the *ortho* isomers doublets, indicating one. This method of structural assignment has been found[6] to be valid in a large number of other cases. There is a possible ambiguity in this method as the *para* isomers could be confused with the *meta*. In view of Wall's results,[2] and our own on the hydrazino-compounds (see later), however, it seems certain that the compounds allocated a *para* structure were, in fact, *para* compounds.

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[1] Part XXXI. P. L. Coe, R. G. Plevey and J. C. Tatlow, submitted to *J. Chem. Soc.*

[2] L. A. Wall, W. J. Pummer, J. E. Fearn and J. M. Antonucci, *J. Res. Natl. Bur. Standards* 67A, 481 (1963).

[3] G. M. Brooke, R. D. Chambers, J. Heyes and W. K. R. Musgrave, *Proc. Chem. Soc.* 213 (1963).

[4] R. Stephens and J. C. Tatlow, *Chem. & Ind.* 821 (1957).

[5] J. Burdon, W. B. Hollyhead and J. C. Tatlow, *J. Chem. Soc.* 6336 (1965).

[6] J. Burdon, *Tetrahedron* 21, 1101 (1965).

TABLE 1. ISOMER DISTRIBUTIONS IN THE NUCLEOPHILIC REACTIONS OF C_6F_5X COMPOUNDS

Compound	Nucleophile KOH % ortho[a]	 NaOMe % ortho[a]	 Me$_2$NH % ortho[a]
	The remaining percentage is *para* in all cases unless otherwise stated.		
C_6F_5Cl	—	17[b]	10[b]
C_6F_5Br	15[c]	12[c]	5[c]
C_6F_5I	7	5	0
C_6F_5H[d]	—	3	5

[a] Accuracy ±3%, [b] About 3% *meta* (assumed) isomer also detected. [c] About 1% *meta* isomer (assumed) also detected. [d] These figures were obtained from ^{1}H NMR measurements on mixtures prepared as described previously.[4,5]

The relative amounts of the isomers were determined from these NMR spectra and by GLC; the two methods were always in excellent agreement. It will be seen that our results on chloropentafluorobenzene do not exactly duplicate those of Musgrave,[3] who found about 25% *ortho* replacement with sodium methoxide; the figures in Table 1 are, however, in agreement with our independent kinetic data on chloropentafluorobenzene.[7]

The tetrafluorohalogenophenols (from the reactions with potassium hydroxide) were converted into the methoxy compounds by treatment with diazomethane and so analysed in the same way.

We have also made tetrafluorohalogenophenylhydrazines in high yield from bromo- and iodo- pentafluorobenzene and hydrazine. These compounds were shown to be *para* isomers by treatment with hydriodic acid which converted both of them into the known[8] 2,3,5,6-tetrafluoroaniline. Also, the bromohydrazine, on being treated with aqueous copper sulphate—a reagent which replaces hydrazino groups by hydrogen,[9] gave the known[10] 1-bromo-2,3,5,6-tetrafluorobenzene; treatment of the mother-liquors from the preparation of the bromo-hydrazine in the same way gave a small amount of 1-bromo-2,3,4,5-tetrafluorobenzene, indicating that some 2–3% *ortho* replacement occurred in the bromopentafluorobenzene–hydrazine reaction. For experimental reasons this assessment of *ortho* replacement is not accurate and is almost certainly low. 2,3,5,6-Tetrafluoro-4-iodophenylhydrazine did not react in the usual way with copper sulphate; iodine was removed as well as the hydrazino group. We did succeed, however, in replacing the hydrazino group by hydrogen, without affecting the iodine, by treatment with hypobromite solution; 1,2,4,5-tetrafluoro-3-iodobenzene was formed in 50% yield.

There are three features of the replacement reactions of the pentafluorohalogenobenzenes which we wish to discuss. First, why does nucleophilic attack take place mainly at the position *para* to the halogen; secondly, why does a significant amount of attack occur at the position *ortho* to chlorine (as compared with the insignificant

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[7] J. Burdon, W. B. Hollyhead, C. R. Patrick and K. V. Wilson, *J. Chem. Soc.* 6375 (1965).

[8] G. M. Brooke, J. Burdon, M. Stacey and J. C. Tatlow, *J. Chem. Soc.* 1768 (1960).

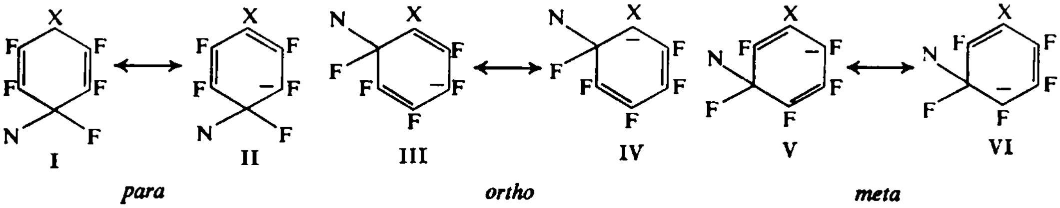
[9] J. M. Birchall, R. N. Haszeldine and A. R. Parkinson, *J. Chem. Soc.* 4966 (1962).

[10] J. F. Tilney-Bassett, *Chem. & Ind.* 693 (1965).

extent of *ortho* attack in most other C_6F_5X compounds[11]) and why does the amount of this *ortho* attack decrease in the order $C_6F_5Cl > C_6F_5Br > C_6F_5I \sim C_6F_5H$; and thirdly, why does dimethylamine lead to less *ortho* replacement than sodium methoxide?

The first two points can be rationalized by the theory recently advanced.[12] The isomer distribution in any nucleophilic substitution reaction of this type depends only on the relative stabilities of the transition states leading to the various products. If Wheland intermediates (represented, for example, by I and II) are taken as models for transition states, then the transition states for *ortho*, *meta* and *para* replacement in any C_6F_5X compound can be represented by I–VI.

N = nucleophile



It was argued previously[12] that the *para* quinonoid forms (I, III, V) were the main contributors to these intermediates, and that, in π-electron systems, the halogens would destabilize a neighbouring negative charge by Iπ-repulsion in the order $\bar{\mathrm{C}}$—F > $\bar{\mathrm{C}}$—Cl > $\bar{\mathrm{C}}$—Br > $\bar{\mathrm{C}}$—I ~ $\bar{\mathrm{C}}$—H. Iπ-repulsion is said to be due either to Coulombic repulsion between the negative charge and the lone pairs on the halogens,[13] or to unfavourable penetration of filled orbitals containing these same electrons.[14] It follows, then, that as Iπ repulsion is greater for fluorine than for the other halogens or hydrogen, that the contributor I is more stable than III or V (i.e. with X = halogen or hydrogen), and therefore that *para* replacement predominates for all the pentafluorohalogenobenzenes and for pentafluorobenzene.

The second point can be rationalized if *ortho* quinonoid forms (e.g. II, IV, VI) are considered as secondary contributors. For all the pentafluorohalogenobenzenes and for pentafluorobenzene, the (I–II) pair is most stable and then the (III–IV) because of the greater stability of the *p*-quinonoid form I over form III. However, the (V–VI) pair is least stable because the *o*-quinonoid form IV is more stable than VI (III and V should be of approximately equal stability). Clearly, the more nearly the Iπ-repulsive effect of a halogen approaches that of fluorine, the more nearly the isomer distribution will approach the statistical *para*:*ortho*:*meta* = 1:2:2, from the direction of *para* > *ortho* > *meta*. Chlorine is most similar to fluorine and therefore gives most *ortho* replacement, whereas iodine and hydrogen are most different and therefore give least *ortho*; that is, there is more difference between (I–II) and (III–IV) for iodine and hydrogen than for chlorine. Further, this argument explains why *meta* replacement also falls off in the order $C_6F_5Cl > C_6F_5Br > C_6F_5I$ (Table 1), although here the experimental facts are far from certain.

A complicating factor in these *ortho* replacements is undoubtedly steric hindrance,

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[11] J. C. Tatlow, *Endeavour* **22,** 89 (1963) and earlier papers in this series.

[12] J. Burdon, *Tetrahedron* **21,** 3373 (1965).

[13] D. T. Clark, J. N. Murrell and J. M. Tedder, *J. Chem. Soc.* 1250 (1963).

[14] D. P. Craig and G. Doggett, *Mol. Phys.* **8,** 485 (1964).

particularly with pentafluoroiodobenzene, and this we suggest is the explanation for the third point. Russian workers[15] have reported a striking example of the effect in the polychloroaromatic field; pentachlorobenzene reacted mainly at the position *para* to the hydrogen with ammonia, but mainly at the more accessible *ortho* position with the larger dimethylamine. With the pentafluorohalogenobenzenes, more *ortho* replacement occurred with hydroxide and methoxide than with the larger dimethylamine. Since, however, pentafluorobenzene—where *ortho* replacement ought to be sterically favoured—gave a smaller amount of *ortho* product than either chloro- or bromo- pentafluorobenzene, we suggest that the electronic factors discussed above do play the major part in determining the *ortho*:*para* ratio in the nucleophilic replacement reactions of the pentafluorohalobenzenes. These electronic and steric factors ought to be applicable generally in the polyhalo-aromatic field, and further work is in progress to study their interplay.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Varian A60 instrument; chemical shifts are in ppm downfield from tetramethylsilane as internal reference.

Reactions with sodium methoxide

(a) *Bromopentafluorobenzene.* The bromo-compound (5·0 g) was refluxed with 1·1N MeONa in dry MeOH (20·5 ml) for 4 hr. The reaction mixture was poured into water and the liquid product (4·97 g) isolated by ether extraction. ^{1}H NMR showed a doublet (J = 1·5 c/s) at 3·99 and a triplet (J = 1·4 c/s) at 4·11 (methoxyl[6]) in intensity ratio 12:88, attributable to the *ortho* and *para* isomers respectively. GLC showed three peaks in intensity ratio 11:1:88. Separation by GLC (4·8 m × 35 mm diam column; packed with silicone gum on Celite; temp 160°; N_2 flow-rate 17 l/hr) gave a trace of *2-bromo-*3,4,5,6-*tetrafluoroanisole.* (Found: C, 32·9: H, 1·2: Br, 31·0. $C_7H_3BrF_4O$ requires: C, 32·5; H, 1·2; Br, 30·9%) and 4-bromo-2,3,5,6-tetrafluoroanisole[2] (3·75 g), b.p. 194–195°. (Found: C, 32·8; H, 1·2; Br, 30·6%). The other, smallest, peak was present in an amount too small to isolate; it could have been 3-bromo-2,4,5,6-tetrafluoroanisole.

(b) *Pentafluoroiodobenzene.* This was carried out as in (a) on 5 g of the iodo-compound to give 5 g crude material. Two products, in the ratio 95:5 were detected by GLC and ^{1}H NMR [doublet (J = 1·5 c/s) at 3·90 and triplet (J = 1·5 c/s) at 4·03]. Only the major one could be isolated by GLC; it was 2,3,5,6-tetrafluoro-4-iodoanisole[2] (2·5 g), b.p. 92–93°/15 mm. (Found: C, 27·1; H, 0·7; I, 40·9. Calc. for $C_7H_3F_4IO$: C, 27·5; H, 1·0; I, 41·5%.) The other component, since it was the one which showed the doublet in the ^{1}H NMR spectrum, has been taken to be 2,3,4,5-tetrafluoro-6- iodoanisole.

(c) *Chloropentafluorobenzene.* This was carried out as in (a). ^{1}H NMR of the product (>90% yield of crude material) showed a doublet (J = 1·6 c/s) and a triplet (J = 1·4 c/s) in intensity ratio 17:83 (cf. Ref 3), attributable to the *ortho* and *para* isomers, respectively. GLC showed three peaks in intensity ratio 17:3:80; the smallest peak has been taken to be the *meta* isomer. 4-$MeOC_6F_4Cl$ was isolated by preparative-scale GLC; it had b.p. 174°. (Found: C, 39·4; H, 1·6. Calc. for $C_7H_3ClF_4O$: C, 39·2; H, 1·4%.) No chloride ion could be detected in the aqueous layer from this reaction.

Reactions with potassium hydroxide

(a) *Bromopentafluorobenzene.* The bromo-compound (5·0 g) was heated at 100° with KOH (1·15 g) in t-butanol (30 ml) for 4 hr. The reaction mixture was poured into dil H_2SO_4 and the product (4·6 g) isolated by ether extraction. GLC indicated that it contained about 40% of unreacted bromopentafluorobenzene. 2N Ethereal diazomethane (30 ml) was added slowly to the crude product in ether (10 ml). After 1 hr the ether solution was washed with dil H_2SO_4, dried (Na_2SO_4) and evaporated. The residue (4·7 g) was analysed by ^{1}H NMR and GLC as in the previous experiment; the results are recorded in Table 1. Separation by GLC as before gave specimens of 2-bromo-and 4-bromotetrafluoroanisole which were identified by IR spectroscopy.

[15] L. S. Kobrina, G. G. Yakobson and N. N. Vorozhtsov, *Zh. Obshch. Khim.* 35, 137 and 142 (1965).

(b) *Pentafluoroiodobenzene*. The iodo-compound (5·0 g) was treated as in (a), but for 16 hr. The product (4·9 g) which, by GLC contained about 40% of unreacted pentafluoroiodobenzene, was methylated and analysed by GLC and ^{1}H NMR as in (a); the results are recorded in Table 1.

Reactions with dimethylamine

(a) *Bromopentafluorobenzene*. The bromo-compound (5·0 g) was heated for 24 hr at 80° in a sealed tube with 33% w/w ethanolic dimethylamine (7·25 ml). The reaction mixture was poured into water and the product (5·1 g) isolated by ether extraction. ^{1}H NMR showed two products and GLC three (ratios in Table 1). Only the *para* isomer, 4-bromo-2,3,5,6-tetrafluoro-N,N-dimethylaniline, b.p. 216°. (Found: C, 35·1; H, 2·5; Br, 29·8. $C_8H_6BrF_4N$ requires; C, 35·3; H, 2·2; Br, 29·4%) could be isolated. It showed a triplet (J = 2·2 c/s) at 2·91 in its ^{1}H NMR spectrum. The second-most abundant component showed only a doublet (J = 2·4 c/s) at 2·81 in its spectrum, and has therefore been assigned the 2-bromo-3,4,5,6-tetrafluoro-N,N-dimethylaniline structure. The minor component could have been 3-bromo-2,4,5,6-tetrafluoro-N,N-dimethylaniline.

(b) *Pentafluoroiodobenzene*. The iodo-compound was treated as in (a) to give a 92% yield of 2,3,5,6-*tetrafluoro-4-iodo*-N,N-*dimethylaniline*, b.p. 108–109°/15 mm. (Found: C, 30·2; H, 1·7; I, 39·3. $C_8H_6F_4IN$ requires: C, 30·1; H, 1·9; I, 39·8%.) It showed a triplet (J = 2·4 c/s) at 3·0 in its ^{1}H NMR spectrum. No other product could be detected (<2%) by GLC or ^{1}H NMR.

(c) *Chloropentafluorobenzene*. Treatment as in (a) gave over 90% of mixed products whose relative amounts are shown in Table 1. The ^{1}H NMR spectrum of the *para* isomer was a triplet (J = 2·2 c/s) at 2·85 and that of the *ortho* isomer a doublet (J = 2·5 c/s) at 2·80. 4-*Chloro*-2,3,5,6-*tetrafluoro*-N,N-*dimethylaniline* was isolated by preparative-scale GLC; it had b.p. 203–204°. (Found: C, 42·3: H, 2·9. $C_8H_6ClF_4N$ requires: C, 42·2; H, 2·7%.)

Reactions with hydrazine

(a) *Bromopentafluorobenzene*. The bromo-compound (5·0 g) was heated at 100° with hydrazine hydrate (2·02 g of 100%) in dry dioxan (25 ml) for 18 hr. The solvent was removed by distillation *in vacuo* and the residue was extracted several times with boiling light petroleum (b.p. 80–100°). 4-*Bromo*-2,3,5,6-*tetrafluorophenylhydrazine* (5·0 g) crystallized from this solvent on cooling; recrystallization from the same solvent gave the pure compound (3·0 g), m.p. 77·5–78·5°. (Found: C, 28·1; H, 1·3; Br, 31·5. $C_6H_3BrF_4N_2$ requires: C, 27·8; H, 1·2; Br, 30·9%.) This compound formed a *benzaldehyde derivative*, m.p. 155–156° from aqueous EtOH. (Found: C, 44·9; H, 2·2; Br, 23·2. $C_{13}H_7BrF_4N_2$ requires: C, 45·0; H, 2·0; Br, 23·0%) and, with HCl in dry ether, a *hydrochloride*, m.p. 247–244° (sealed tube) from EtOH–ether. (Found: C, 24·4; H, 1·3. $C_6H_4BrClF_4N_2$ requires: C, 24·4; H, 1·4%.)

(b) *Pentafluoroiodobenzene*. The iodo-compound (5·0 g) was treated as in (a) to give pure 2,3,5,6-*tetrafluoro-4-iodophenylhydrazine* (4·7 g), m.p. 101–103°, (Found: C, 23·6; H, 1·0; I, 41·0. $C_6H_3F_4IN_2$ requires: C, 23·6; H, 1·0; I, 41·5%) and its *benzaldehyde derivative*, m.p. 148–149°. (Found: C, 39·8; H, 2·0; I, 32·4. $C_{13}H_7F_4IN_2$ requires: C, 39·6; H, 1·8; I, 32·2%) and *hydrochloride*, m.p. 208–209° dec (sealed tube). (Found: C, 20·8; H, 1·4. $C_6H_4ClF_4IN_2$ requires: C, 21·0; H, 1·2%).

2,3,5,6-*Tetrafluoroaniline from the* 2,3,5,6-*tetrafluoro-4-halogenophenylhydrazines*. The bromohydrazine (1·32 g) was refluxed with 55% HIaq (10 ml) for 3 hr. The reaction mixture was poured into water, the solution basified and extracted with ether. The extracts were washed with $NaHCO_3$aq and $Na_2S_2O_3$aq, dried, and evaporated to leave a residue which was sublimed at 48–50°/15 mm to give 2,3,5,6-tetrafluoroaniline (0·77 g), m.p. 30–31° (lit.[8] 23·5–26·5°), identified by IR.

Reduction with Zn dust and 11N HCl gave the same product.

The iodohydrazine also gave 2,3,5,6-tetrafluoroaniline in similar yield on being treated with HI in the same way.

Dehydrazination of the 2,3,5,6-*tetrafluoro-4-halogenophenylhydrazines*

(a) *The bromohydrazine*. Aqueous $CuSO_4$ (5 g in 20 ml) was added slowly to a stirred suspension of this hydrazine (2·3 g) in water (60 ml) at 80°. After a further hr at 100°, the reaction mixture was steam-distilled and the product isolated from the distillate by ether-extraction; it was 1-bromo-2,3,5,6-tetrafluorobenzene (1·15 g), identified by IR.[10]

When this reaction was repeated on the residues (2·5 g) from the crystallization of the bromohydrazine (cf. the preparation of this compound, above), GLC showed two peaks in the ratio 5:95, whose retention times corresponded to 1-bromo-2,3,4,5- and 1-bromo-2,3,5,6-tetrafluorobenzene, respectively. This procedure almost certainly underestimates (it gives a figure of about 2%) the amount of 2-bromo-3,4,5,6-tetrafluorophenylhydrazine formed in the bromopentafluorobenzene–hydrazine reaction, since the residues from the crystallization mother-liquors contained large amounts of coloured impurities as well as the two hydrazines.

(b) *The iodohydrazine.* A mixture of Br_2 (1·04 g) and NaOH (1·04 g) in water (50 ml) was added to a stirred suspension of the crude, unrecrystallized hydrazine (1·0 g) in water (50 ml) at 16°. After being stirred for 2 days, the reaction mixture was steam-distilled and the product isolated as in (a); GLC showed only one peak which was 1,2,4,5-*tetrafluoro*-3-*iodobenzene* (0·45 g), b.p. 54°/15 mm. (Found: C, 25·5; H, 0·5; I, 46·3. C_6HF_4I requires: C, 26·1; H, 0·4; I, 46·0%.)

The $CuSO_4$ procedure, as in (a), liberated iodide ion; oxidations with $FeCl_3$ and CrO_3 gave (GLC) complex mixtures, but no tetrafluoroiodobenzene.