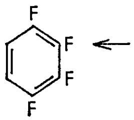
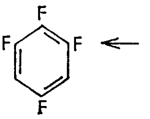
1176. *Aromatic Polyfluoro-compounds. Part XXVI.*[1] *Nucleophilic Replacement Reactions of the Tetrafluorobenzenes*

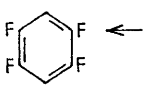
By J. BURDON and W. B. HOLLYHEAD

Nucleophilic attack on 1,2,3,4-tetrafluorobenzene by sodium methoxide, hydrazine, or lithium aluminium hydride replaces the 2-fluorine; 1,2,3,5-tetrafluorobenzene reacts with the same reagents with replacement of the 1-fluorine. These orientations can be rationalised if fluorine is taken as electron-repelling in π-electron systems.

THE nucleophilic replacement reactions of C_6F_5X compounds have been extensively studied,[1,2] but little work has been done on C_6F_4XY compounds. We now report an investigation of the nucleophilic replacement reactions of the three tetrafluorobenzenes.







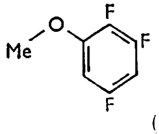
There are, of course, orientational problems with only the 1,2,3,4- and 1,2,3,5-tetrafluoro-isomers. These compounds reacted at the arrowed positions with lithium aluminium hydride, hydrazine, and sodium methoxide, and in all six reactions no other isomeric products were detected. Lithium aluminium hydride reacts as though it were a source of hydride ion,[3] and in both cases the product was the known 1,2,4-trifluorobenzene. Treatment of the trifluorophenylhydrazines from 1,2,3,4- and 1,2,3,5-tetrafluorobenzene with aqueous copper sulphate, a reaction [4] which replaces the hydrazino-group by hydrogen, also gave 1,2,4-trifluorobenzene in both cases.

1,2,3,4-Tetrafluorobenzene gave a monomethoxy-compound with sodium methoxide; proton magnetic resonance spectroscopy indicated [5] that the methoxyl group was flanked by two *ortho*-fluorines (it showed a triplet) and therefore that the 2-fluorine was again the one replaced. Proton magnetic resonance apparently indicated that the methoxy-compound from 1,2,3,5-tetrafluorobenzene was the one in which the 5-fluorine had been replaced, as the methoxyl resonance was a single sharp peak. Fluorine resonance, however, was unambiguous and showed that the compound was, in fact, the expected 2,3,5-trifluoroanisole (I). A similar phenomenon occurred with the 2,4,5-trifluoroanisole (II)

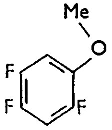
---

[1] Part XXV, J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J.*, 1965, 5152.
[2] J. C. Tatlow, *Endeavour*, 1963, **22**, 89.
[3] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J.*, 1962, 3253.
[4] J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *J.*, 1962, 4966.
[5] J. Burdon, *Tetrahedron*, 1965, **21**, 1101.

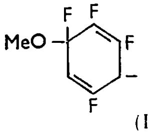
from 1,2,4,5-tetrafluorobenzene; again the methoxyl resonance was a single peak and not the doublet expected[5] from a compound with one *ortho*-fluorine. In this case the methoxy-compound can only be (II) as there is no real possibility of any other isomer from 1,2,4,5-tetrafluorobenzene.



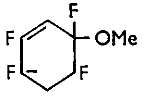
(I)



(II)



(III)



(IV)

Previous work[5] on polyfluoro-aromatic compounds with XCH_3 [$X = O,N,S,SO_2,Sn$] side-chains had shown that protons in such side-chains always couple with the *ortho*-fluorines. However, no case was then known of a compound with an *ortho*-hydrogen, as well as an *ortho*-fluorine. If the coupling were through space, and if the anisoles existed in the configurations shown, (I), (II), possibly for steric reasons, then no coupling would be expected. In the other cases[5] with an *ortho*-substituent besides fluorine, the configurations preferred on steric grounds would be those where the methyl group was nearer the fluorine.

A tentative rationalisation for our results and also for those on pentafluorobenzene [which reacts with nucleophiles[3,6] only (>90%) at the position *para* to the hydrogen] is possible if resonance forms which have a negative charge on the carbon *para* to the site of replacement are taken as the major contributors to the transition state. In the following discussion, no account will be taken of contributors with a negative charge on the *ortho*-carbon.

The major contributor to the transition state in the reaction of methoxide ion with 1,2,3,5-tetrafluorobenzene should then resemble compound (III), that is, have a negative charge on a carbon bearing a hydrogen. The analogous contributors for replacement at the other two positions will have negative charges on carbons bearing fluorines. The same applies to the reactions of 1,2,3,4-tetrafluorobenzene and pentafluorobenzene; in both cases the major contributor to the transition state leading to the only (>90%) product formed has a negative charge on a hydrogen-bearing carbon. Again, replacement at any other position would necessitate the contributors having negative charges on fluorine-bearing carbons. Moreover, 1,2,4,5-tetrafluorobenzene reacts with methoxide very much more slowly than the other two tetrafluorobenzenes and in this case the contributor resembling compound (IV) has a negative charge on a carbon bearing a fluorine.

These arguments imply, therefore, that *in a π-electron system*, other things being equal, carbon bearing a negative charge is less stable when it is attached to a fluorine than when it is attached to a hydrogen, *i.e.*, fluorine is electron-repelling in π-systems. This effect (I_π repulsion[7]) has been suggested before in connection with spectroscopic properties of halogenobenzenes and has been attributed both to simple electrostatic repulsion between the fluorine lone pairs and the π-electrons on the neighbouring carbon,[7] and also to unfavourable penetration of the filled orbitals containing the same electrons.[8]

Deactivation of nucleophilic replacement of aromatic chlorine by a *para*-fluorine has been noted before;[9] the rationalisations offered by these earlier workers, however, were based on a mesomeric effect and not I_π repulsion.

EXPERIMENTAL

Reactions with Sodium Methoxide.—(*a*) 1,2,3,4-*Tetrafluorobenzene.* The benzene (3·9 g.) was refluxed with sodium methoxide in methanol (0·7N; 40 ml.) for 70 hr. The mixture was

---

[6] G. M. Brooke, J. Burdon, M. Stacey, and J. C. Tatlow, *J.*, 1960, 1768.

[7] D. T. Clark, J. N. Murrell, and J. M. Tedder, *J.*, 1963, 1250.

[8] D. P. Craig and G. Doggett, *Mol. Phys.*, 1963, **8**, 485.

[9] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.*, 1952, **74**, 1574; R. L. Heppolette and J. Miller, *ibid.*, 1953, **75**, 4265.

poured into water and the product extracted with ether. Most of the ether was removed by fractionation through a 6-in. column packed with glass helices and the residue (5·3 g.), which showed only one product peak on gas chromatography (g.l.c.), was distilled from phosphoric oxide to give ether (1·7 g.), 1,2,3,4-tetrafluorobenzene (0·6 g.) [identified by infrared spectroscopy (i.r.)], and 2,3,6-*trifluoroanisole* (2·7 g.), b. p. 146° (Found: C, 52·3; H, 3·3. $C_7H_5F_3O$ requires C, 51·9; H, 3·1%). The ^1H n.m.r. spectrum (in carbon tetrachloride) of the last compound showed a triplet (J = 1·2 c./sec.) at 4·00 (OMe).

(*b*) 1,2,3,5-*Tetrafluorobenzene.* The benzene (5·0 g.) was refluxed with sodium methoxide in methanol (0·8N; 42 ml.) for 64 hr. Again, g.l.c. showed only one product peak. Isolation as in (*a*) gave 2,3,5-*trifluoroanisole* (4·0 g.), b. p. 157°, m. p. 35° (Found: C, 51·7; H, 3·1%). The ^1H n.m.r. spectrum (in methylene chloride) showed a single peak at 3·86 (OMe), and the ^{19}F, three multiplets of equal intensity at 37·7, 60·0, and 95·1.

(*c*) 1,2,4,5-*Tetrafluorobenzene.* The benzene (4·0 g.) was heated at 125° in a sealed tube with sodium methoxide in methanol (1·5N; 20 ml.) for 20 hr. Isolation as in (*a*) gave 2,4,5-*trifluoroanisole* (3·5 g.), b. p. 158°, m. p. 35—37° (Found: C, 51·9; H, 3·2%). The ^1H n.m.r. spectrum (in carbon tetrachloride) showed a sharp peak at 3·80 (OMe).

G.l.c. showed that less than 5% reaction occurred when conditions similar to those in (*a*) and (*b*) were employed.

Reactions with Hydrazine.—(*a*) 1,2,3,4-*Tetrafluorobenzene.* The benzene (4·5 g.), hydrazine hydrate (100%; 10 ml.), water (10 ml.), and ethanol (10 ml.) were heated at 130° in a sealed tube for 16 hr. The mixture was poured into water and the crude product (4·0 g.) isolated by ether extraction; crystallisation from aqueous ethanol gave 2,3,6-*trifluorophenylhydrazine* (3·5 g.), m. p. 72—73° (Found: C, 44·6; H, 3·2. $C_6H_5F_3N_2$ requires C, 44·4; H, 3·1%). This compound gave a *benzaldehyde derivative*, m. p. 117—119° (from aqueous ethanol) (Found: C, 62·4; H, 3·7. $C_{13}H_9F_3N_2$ requires C, 62·4; H, 3·6%).

A solution of copper sulphate (7·5 g.) in water (75 ml.) was added dropwise, with stirring, to a suspension of the crude phenylhydrazine (2·0 g.) in water (50 ml.) at 80°. More aqueous copper sulphate (0·5 g. in 10 ml.) was added and the mixture was refluxed for 1 hr. Steam distillation gave 1,2,4-trifluorobenzene (1·3 g.) (i.r.), uncontaminated ($<$5% by g.l.c.) with other trifluorobenzenes.

(*b*) 1,2,3,5-*Tetrafluorobenzene.* The benzene (5·5 g.) was refluxed with hydrazine hydrate (100%, 10 ml.), ethanol (25 ml.), and water (25 ml.) for 64 hr. Isolation as in (*a*) gave 2,3,5-*trifluorophenylhydrazine* (5·0 g. crude, 3·7 g. pure), m. p. 67—69° (from aqueous ethanol) (Found: C, 44·4; H, 3·3%) and its *benzaldehyde derivative*, m. p. 124—125° (from aqueous ethanol) (Found: C, 62·0; H, 3·6%).

The crude phenylhydrazine (2·05 g.) was treated with aqueous copper sulphate as in (*a*) to give 1,2,4-trifluorobenzene (1·26 g.) (i.r.), uncontaminated ($<$5% by g.l.c.) by the other trifluorobenzenes.

Reactions with Lithium Aluminium Hydride.—(*a*) 1,2,3,4-*Tetrafluorobenzene.* The benzene (4·5 g.) and lithium aluminium hydride (1·5 g.) were refluxed in ether (20 ml.) for 51 hr. Dilute sulphuric acid was added to the reaction mixture and the ether layer was dried ($MgSO_4$) and fractionated (6-in. column packed with glass helices) to remove most of the ether. The residue (5·0 g.) was separated by g.l.c. (column 4·8 m. × 35 mm. diam., packed with dinonyl phthalate on Celite, temp. 90°, N_2 flow-rate 15 l./hr.) into ether (1·1 g.), 1,2,3,4-tetrafluorobenzene (2·0 g.) (i.r.), and 1,2,4-trifluorobenzene (1·2 g.) (i.r.).

(*b*) 1,2,3,5-*Tetrafluorobenzene.* The benzene (2·0 g.) was refluxed with lithium aluminium hydride (1·5 g.) in ether (20 ml.) for 41 hr. Isolation as in (*a*) gave 1,2,3,5-tetrafluorobenzene (0·54 g.) (i.r.) and 1,2,4-trifluorobenzene (0·50 g.) (i.r.).

Nuclear Magnetic Resonance Spectra.—These were measured on a Varian A60 at 60Mc./sec. (^1H spectra) and a Varian HR100 at 94·1 Mc./sec. (^{19}F spectra). Chemical shifts are quoted in p.p.m. downfield from tetramethylsilane as internal reference for the ^1H spectra, and in p.p.m. upfield from trifluoroacetic acid as internal reference for the ^{19}F.

We thank Professor J. C. Tatlow for his interest and advice throughout the course of this work.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, EDGBASTON,
BIRMINGHAM 15.

[*Received, March* 15*th*, 1965.]