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NUCLEOPHILIC DISPLACEMENT IN POLYHALOGENOAROMATIC COMPOUNDS. PART 12.[1] ADDITIVITY OF FLUORINE SUBSTITUENT EFFECTS IN METHOXYDEFLUORINATION

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SUMMARY

The rates of methoxydefluorination of all twelve polyfluorobenzenes in dimethyl sulphoxide-methanol mixtures (DMSO-MeOH; 9:1, v/v; 298.2 K) have been measured. Three substituent rate factors (f_o, 60; f_m, 180; f_p, 0.75) are sufficient to reproduce the effect of the fluorine substituent in this reaction upon each member of the series. The solvent effect, comparing these results with an earlier and more limited study in methanol is predominantly a simple acceleration. The effects of substituents upon the rate of methoxydefluorination of fluorobenzene itself are slightly greater (ρ^-, 6.9) than in the corresponding reaction of pentafluorobenzene derivatives (ρ^-, 5.8), but the change in sensitivity is much less than that found with nitrobenzene derivatives.

INTRODUCTION

The rates of methoxydefluorination of some polyhalogenofluorobenzenes in methanol have been reported to show additivity in the effects of fluorine and chlorine substituents [2]. A less precise relationship was found with bromine and iodine substituents [3], and a general lack of additivity occurred in the effect of a nitro group [5]. The derived s.r.f s [3] suggested a second-order rate constant for the methoxydefluorination of fluorobenzene in methanol at 323.2 K (k_{PhF}, 2×10^{-12} l mol^{-1} s^{-1}) in good

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agreement with that found by extrapolating the Arrhenius plot derived from studies at 390-422 K [6] (3×10^{-12} l mol^{-1} s^{-1}), but there is no other direct evidence of the applicability of these substituent rate factors throughout the series of polyfluorobenzenes. In contrast, it has been held [4] that the less fully activated substrates are more sensitive to substituent effects in aromatic nucleophilic substitution than are systems such as chloro-2,4-dinitrobenzene.

We now report a study of the rates of methoxydefluorination of the twelve polyfluorobenzenes, and of some derivatives of fluorobenzene, in DMSO-MeOH (9:1, v/v; 298.2 K) to determine the generality of fluorine substituent effects and to investigate the effect of activating substituents upon the rate of attack of fluorobenzene.

DISCUSSION

The mean observed second-order rate constants for methoxydefluorination of the polyfluorobenzenes are shown in Table 1. The constants agreed to within 10% upon changing the concentration of methoxide or of fluoro-arene, usually by a factor of two, and the range of individual values in each run did not exceed 5% of the average. Some loss of reproducibility was found with the very fast ($k_2 > 1$ l mol^{-1} s^{-1}) and very slow ($k_2 < 10^{-6}$ l mol^{-1} s^{-1}) processes, but never past these limits of error. The methoxydefluorination of fluorobenzene was a special case in which the course of the reaction was followed to less than 1% completion, even though unusually high concentrations of fluoro-arene was present ($[PhF]_o$, 0.6 *M*). However, (i) different samples of fluorobenzene gave the same rate constant (ii) different concentrations of fluorobenzene added to the solvent mixture up to 5% by volume has no effect upon the rate of methoxydefluorination of 1,2,3,4-tetrafluorobenzene and (iii) fluorobenzene which had been treated with sodium methoxide in DMSO at the boil (150^{o}) for a day gave the same rate constant after recovery and purification. On this evidence we concluded that the value obtained truly represented the attack of methoxide ion upon fluorobenzene, and not upon some impurity.

The rate constants, which range over a factor of 10^{8}, give substituent rate factors of $f_{o\text{-}F}$, 60; $f_{m\text{-}F}$, 180; and $f_{p\text{-}F}$, 0.75. These figures reproduce the experimental rate constants to an average error of ±25%;

correspondingly the slope and correlation coefficient of the graph of log (experimental rate constant) *vs.* log (calculated rate constant) are 0.997 and 0.998 respectively. The similarity between these substituent rate factors and those found in the methoxydefluorination of the polyfluorobenzenes by sodium methoxide in methanol at 232.2 K [3] indicates that the effect of the change of solvent is substantially to raise all rates of methoxydefluorination by a factor of *ca.* 10^4 on moving to the DMSO-MeOH mixture used in the present work.

The methoxydefluorination of two of the polyfluorobenzenes deserves comment. The orientation of attack of 1,2,3-trifluorobenzene has not

TABLE 1

Second-order rate constants for methoxydefluorination of polyfluorobenzenes*

Substrate	Site attacked	k_2/l $mol^{-1}s^{-1}$ (experimental)	k_2/l $mol^{-1}s^{-1}$ (calculated)
Hexafluorobenzene	C-1	7.4	7.45
Pentafluorobenzene	C-3	1.66	1.63
1,2,3,4-Tetrafluorobenzene	C-1	3 x 10^{-4}	2.0 x 10^{-4}
	C-2	3.0 x 10^{-2}	1.8 x 10^{-2}
1,2,3,5-Tetrafluorobenzene	C-1	4.3 x 10^{-2}	5.4 x 10^{-2}
	C-2	4 x 10^{-4}	4.0 x 10^{-5}
1,2,4,5-Tetrafluorobenzene	C-1	6.7 x 10^{-4}	4.6 x 10^{-4}
1,2,3-Trifluorobenzene	C-1	3.8 x 10^{-4}	3.0 x 10^{-4}
	C-2	8.6 x 10^{-5}	5.0 x 10^{-5}
1,2,4-Trifluorobenzene	C-1	4 x 10^{-6}	6 x 10^{-7}
	C-2	4.3 x 10^{-4}	1.5 x 10^{-4}
	C-4	4 x 10^{-6}	2 x 10^{-6}
1,3,5-Trifluorobenzene	C-1	1.35 x 10^{-3}	1.36 x 10^{-3}
o-Difluorobenzene	C-1	1.2 x 10^{-6}	1.68 x 10^{-6}
m-Difluorobenzene	C-1	7.3 x 10^{-6}	5.0 x 10^{-6}
p-Difluorobenzene	C-1	2.0 x 10^{-8}	2.0 x 10^{-8}
Fluorobenzene	C-1	1.4 x 10^{-8} (standard)	

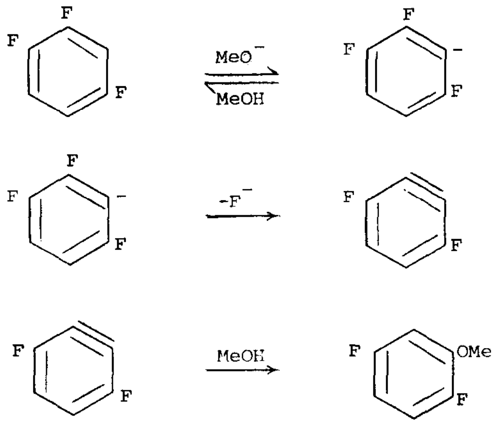
(*) NaOMe; DMSO-MeOH, 9:1, v/v; 298.2 K. Calculated rate constants were based upon the experimental k_2 of fluorobenzene and the derived substituent rate factors (see text).

previously been reported, although a simple M.O. calculation [7] suggests equal extents of attack at the isomeric sites. The substituent rate factors suggest that the relative rates of attack at C-1 and C-2 are given by the ratio

$$(f_{o\text{-}F}\cdot f_{m\text{-}F}\cdot k_{PhF})/(f^{2}_{o\text{-}F}\cdot k_{PhF}) = f_{m\text{-}F}/f_{o\text{-}F}$$

which suggests a value of 6:1 for the relative yields of 2,3-difluoroanisole and 2,6-difluoroanisole; the experimental value is 4:1.

Secondly, Table 1 shows that the rate of attack of 1,2,4-trifluorobenzene proceeds at three times the predicted rate and that this difference is the greatest of all the discrepancies found in the polyfluorobenzenes. A second mechanism of displacement of fluoride ion could be envisaged, involving the rapid [8] formation of the conjugate base of the substrate:



This S_NCB mechanism is more likely in the methoxydefluorination of 1,2,4-trifluorobenzene, since the hydrogen atom at C-3 is strongly activated by two *o*-fluorine substituents towards attack by bases. The derived anion may lose fluoride ion to give 3,6-difluorobenzyne and 3,4-difluorobenzyne, and the observed reaction products may be formally derived from the former aryne. This proposal was disproved by studying the methoxydefluorination of 2,4-difluorochlorobenzene, the derived aryne from which (3-chloro-6-fluorobenzyne) is not symmetrical, and therefore allows the formation of two isomeric ethers by the addition of methanol. However, at 70% conversion, the reaction products are 2-chloro-5-fluoroanisole (95%) and 3-fluoro-4-chloroanisole (5%), but without 2-fluoro-5-chloroanisole which is the second product of addition of methanol to the putative aryne intermediate.

TABLE 2

Second-order rate constants for methoxydefluorination of fluorobenzene derivatives[*]

Substituent	$10^{7}k_{2}$/l mol^{-1}s^{-1}	Substituent	$10^{7}k_{2}$/l mol^{-1}s^{-1}
Hydrogen^{a}	0.14 ± 0.01^{b}	2-Bromo-	97 ± 4^{b}
	4.7 ± 0.2^{c}	3-Bromo-^{f}	100 ± 3^{b}
2-Fluoro-^{d}	6.1 ± 0.1^{b}		3200 ± 200^{c}
	230 ± 10^{c}	4-Bromo-	20.5 ± 0.4^{b}
3-Fluoro-	37 ± 2^{b}	3,4-Dichloro-	1500 ± 200^{c}
4-Fluoro-	0.10 ± 0.01^{b}	3-Trifluoromethyl-^{g}	340 ± 20^{b}
2-Chloro-	99 ± 7^{b}		8800 ± 400^{c}
3-Chloro-^{e}	69 ± 2^{b}	3-Nitro-	13000 ± 1000^{b}
	2000 ± 100^{c}	4-Benzoyl-	87000 ± 4000^{b}
4-Chloro-	14 ± 1^{b}		

(*) NaOMe; DMSO-MeOH (9:1, v/v).

(*a*) ΔE, 27 Kcal mole^{-1}; ΔS, -4 e.u.

(*b*) At 298.2 K

(*c*) At 323.2 K

(*d*) ΔE, 27 Kcal mole^{-1}; ΔS, 4 e.u.

(*e*) ΔE, 26 Kcal mole^{-1}; ΔS, 4 e.u.

(*f*) ΔE, 26 Kcal mole^{-1}; ΔS, 4 e.u.

(*g*) ΔE, 25 Kcal mole^{-1}; ΔS, 3 e.u.

Methoxydefluorination of derivatives of fluorobenzene

Table 2 shows that the rates of methoxydefluorination of a number of derivatives of fluorobenzene under our conditions show a slightly larger dependence upon the substituent effect (ρ^-, 6.9±0.2) than that found in the analogous reaction of derivatives of pentafluorobenzene (ρ^-, 5.8±0.6) [4]. Fluorine substituents showed a sensibly similar effect in the two systems, but the heavier halogens showed a greater substituent effect in the less fully fluorinated system. A number of explanations of this may be proposed, and we have discussed many of them in earlier papers [3]. However, there are two important deductions. The first is that, of the groups studied so far, only the fluorine substituent shows the necessary constancy of activating effect to be used as an activating group in kinetic studies of electronic effects; other such groups e.g. NO_2, either in benzene systems or in other aromatic systems such as quinoline [9] or pyridine [10], show a variety of effect which is inimical to the measurement of 'absolute' substituent effects. The second is that the change of reaction constant observed on increasing the number of activating groups arises because of the interaction between the activated aromatic system and the substituent. Where activation is brought about by fluorine substituents, and not by the polarisable nitro-group, the difference between the sensitivity towards substituents in highly activated systems and in slightly activated systems is comparatively little.

EXPERIMENTAL

Dimethyl sulphoxide (A.R.) was purified by fractional distillation under reduced pressure, rejecting the first and last 15%; fractional freezing raised the m.p. of the middle fraction to 18.45 - 18.55° (lit. [11], 18.55°). Methanol, b.p. 64.5°/757 mmHg, was obtained by previously reported methods from A.R. commercial material. Concentrated (2*M*) solutions of sodium methoxide in methanol were made by dissolving the metal in the purified alcohol; these were diluted with nine volumes of purified DMSO after the precipitation of small amounts of sodium carbonate was complete. The alkoxide content was measured by titration of the diluted (boiled-out distilled water) sample with standard acid (0.05*M*-sulphuric acid; phenolphthalein). Stock mixtures of DMSO-methanol (9:1, v/v) were made by weighing a quantity of purified DMSO, deducing its volume from this weight

(d^{20}_{4}, 1.100 g cm^{-3} [11]), and adding by pipettes the appropriate volume of methanol. New batches of solvent were checked by measuring the rate of a methoxydefluorination of known rate constant in them. The disagreement between rate constants under these circumstances did not exceed 10%.

The methoxydefluorinations followed second-order kinetics, as measured by the rate of formation of fluoride ion (Orion 94-09 specific ion electrode measuring over the range $10^{-5}M < [F^{-}] < 10^{-2}M$) and shown by changing the initial concentrations of both reactants which generally were between $1 - 5 \times 10^{-3}M$. Rate constants agreed internally to ±5% and between runs by no more than 10%. Large amounts of fluorobenzene (0.6*M*) made no discernible effect upon the rate of methoxydefluorination of 1,2,3,4-tetrafluorobenzene; this was taken to show that, within these limits, the fluoro-arenes showed no solvent effect upon the observed rates. With the exception of 1,2,3-trifluorobenzene (prepared from 2,6-difluoroaniline) other organic substrates were commercial samples, purified by fractional distillation. The ^{19}F-NMR spectrum was taken as a primary criterion of purity, and the constancy of rate constant found when two or more samples, purchased and purified at different times, were studied was taken to confirm the purity of each fluorocarbon. The physical properties of the polyfluorobenzenes closely agreed with those reported [12].

The reaction products were isolated from reactions carried out under the kinetic conditions and usually progressing over between one and five half-lives, with the exception of fluorobenzene and *p*-difluorobenzene, where no attempts were made to identify the products. The ^{19}F-NMR spectrum showed that only methoxydefluorination occurred, and that the bromofluorobenzenes had not lost bromine by protiodebromination or by methoxydebromination; tests for bromide ion in the inorganic components were also negative in these cases. The reaction products were identified by their chemical shifts, both in isolation and, where possible, by comparison with authentic materials, using a Jeol FX 90Q NMR spectrometer; these deductions were confirmed by m.s. studies (VG-Micromass 12B).

TABLE 3

Details of kinetic studies of methoxydefluorination of polyfluorobenzenes (DMSO-methanol, 9:1 (v/v), 298.2 K).

Polyfluorobenzene	$10^3[\mathrm{ArF}]_o$	$10^3[\mathrm{OMe}^-]_o$	n^a	Range^b	k_2 ($\mathrm{l\ mol^{-1}s^{-1}}$)
Hexafluorobenzene	2.60	2.34	9	80%	7.7 ± 0.6
	1.94	2.05	8	88%	7.5 ± 0.4
	3.59	2.05	9	84%	7.3 ± 0.2
Pentafluorobenzene	4.28	1.44	12	93%	1.62 ± 0.05
	3.11	2.05	12	60%	1.72 ± 0.05
	2.14	2.05	14	50%	1.90 ± 0.07
	1.71	1.71	12	70%	1.48 ± 0.06
	1.56	1.56	12	55%	1.96 ± 0.07
1,2,3,4-Tetrafluorobenzene	20.0	20.0	14	65%	$2.84 \pm 0.05 \times 10^{-2}$
	10.0	20.0	10	53%	$2.98 \pm 0.13 \times 10^{-2}$
	10.0	10.0	11	37%	$3.14 \pm 0.07 \times 10^{-2}$
	10.0	10.0	8	23%^{c}	$2.75 \pm 0.11 \times 10^{-2}$
1,2,3,5-Tetrafluorobenzene	40.0	20.5	10	22%	$4.0 \pm 0.1 \times 10^{-2}$
	29.6	41.0	5	59%	$4.7 \pm 0.2 \times 10^{-2}$
	20.0	10.3	12	39%	$4.3 \pm 0.2 \times 10^{-2}$
	10.0	41.0	10	29%	$4.3 \pm 0.2 \times 10^{-2}$
	1.8	11.8	7	15%	$4.3 \pm 0.2 \times 10^{-2}$
1,2,4,5-Tetrafluorobenzene	67.0	60.0	7	17%	$6.7 \pm 0.1 \times 10^{-4}$
	61.3	61.5	6	17%	$6.3 \pm 0.2 \times 10^{-4}$
	57.6	58.5	6	17%	$6.5 \pm 0.2 \times 10^{-4}$
	49.0	102.5	7	20%	$7.1 \pm 0.3 \times 10^{-4}$
1,2,3-Trifluorobenzene	40.2	205	11	56%	$4.6 \pm 0.1 \times 10^{-4}$
	40.2	102.5	14	38%	$4.5 \pm 0.1 \times 10^{-4}$
1,2,4-Trifluorobenzene	200	41	7	21%	$4.4 \pm 0.1 \times 10^{-4}$
	80	205	9	45%	$4.3 \pm 0.3 \times 10^{-4}$
	50	205	8	53%	$4.1 \pm 0.2 \times 10^{-4}$
1,3,5-Trifluorobenzene	170	185	6	71%	$1.43 \pm 0.4 \times 10^{-3}$
	60	57	8	21%	$1.33 \pm 0.06 \times 10^{-3}$
	57	59	8	33%	$1.12 \pm 0.17 \times 10^{-3}$
	34	102.5	6	80%	$1.28 \pm 0.01 \times 10^{-3}$

Polyfluorobenzene	$10^3[ArF]_o$	$10^3[OMe^-]_o$	n^a	$Range^b$	$k_2(l\ mol^{-1}s^{-1})$
o-Difluorobenzene	204	58.5	6	0.35%	$1.08\pm0.02 \times 10^{-6}$
	101	103	8	0.32%	$1.22\pm0.06 \times 10^{-6}$
	40	164	10	0.57%	$1.41\pm0.12 \times 10^{-6}$
m-Difluorobenzene	77.5	58.5	5	0.31%	$2.8 \pm0.4 \times 10^{-6}$
	75	205	8	0.54%	$2.7 \pm0.1 \times 10^{-6}$
p-Difluorobenzene	198	57	6	0.06%	$2.1 \pm0.3 \times 10^{-8}$
	428	197	14	0.22%	$2.1 \pm0.1 \times 10^{-8}$
	513	195	9	0.20%	$2.0 \pm0.2 \times 10^{-8}$
Fluorobenzene	536	195	9	0.15%	$1.4 \pm0.1 \times 10^{-8}$
	640	58.5	7	0.07%	$1.4 \pm0.2 \times 10^{-8}$

a Number of points comprising the kinetic plot

b Percentage reaction to which the reaction was studied

c In the presence of 5% v/v fluorobenzene (see text)

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