1184. *Kinetics of Nucleophilic Substitution in Polyfluoro-aromatic Compounds. Part I. The Reaction of Sodium Methoxide with Some Pentafluorophenyl-compounds*

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Arrhenius parameters for the reaction of several C_6F_5X compounds ($X = H, F, Cl, NMe_2, Me, CO_2^-, CF_3, NO_2$) with sodium methoxide in methanol have been determined; all the reactions obeyed a second-order kinetic expression. Electron-attracting X-groups increased the rate of reaction and electron-donating groups decreased it; these rates were parallelled more by the activation energies than by the pre-exponential factors. Errors in the parameters have been considered in terms of statistical confidence limits.

As part of our programme [1-4] on the nucleophilic replacement reactions of aromatic polyfluoro-compounds, we have measured the Arrhenius parameters for the reaction of sodium methoxide in methanol with several C_6F_5X compounds ($X = H, F, Cl, NMe_2, Me, CO_2^-, CF_3$, or NO_2). Each of these compounds, with the exception of chloropentafluorobenzene,[5] is known [2-4] to react with this nucleophile to give over 90% of a product in which the fluorine para to X has been replaced. Chloropentafluorobenzene is said [5] to give about 70% *para*- and 25% *ortho*-replacement with refluxing sodium methoxide in methanol, although measurements by us,[6] and the kinetic data reported here, would suggest that the amount of *ortho*-replacement is a little less than this. A preliminary Note on the hexafluorobenzene–sodium methoxide reaction has already appeared.[7]

Experimental

No impurities were detected in any of the liquid substrates by gas-chromatography. Commercial pentafluorobenzoic acid was twice recrystallised from water to m. p. 102·5—103·5° (lit.,[8] 103°).

In all kinetic experiments equal concentrations of the two reactants were used.

For all the substrates except octafluorotoluene and pentafluoronitrobenzene, the following method was employed. The substrate was weighed into a flask, and to this was pipetted the required volume of sodium methoxide in methanol, whose concentration was determined immediately before use by titration with hydrochloric acid. The mixtures were diluted to the desired concentrations (0·25—0·45 mole $l.^{-1}$) with dry methanol. Aliquot parts (2 or 5 ml.) of the stock solutions of the reaction mixtures were pipetted after preparation into sample tubes [6—9 (8—11 for C_6F_5Cl) at each temperature] which were kept in " Drikold "–ethanol for at least 15 min. and then sealed. One tube was opened, and its contents were titrated against aqueous hydrochloric acid with phenolphthalein as indicator; this titre was taken as the value at zero time. The remaining tubes were immediately transferred to a water thermostat ($\pm 0·1°$) and at subsequent intervals they were removed and their contents titrated with hydrochloric acid. In the chloropentafluorobenzene experiments only, the contents of the last two tubes (when reaction had proceeded to about 80%) at each temperature were analysed for 2- and 4-chloro-tetrafluoroanisole by gas-chromatography using a Perkin-Elmer gas Fractometer (stationary phase, silicone gum on Celite) with a hot wire detector. The relative amounts of the isomeric anisoles were determined by peak area measurements by comparison with results obtained with standard mixtures; five chromatograms were taken for each tube, and the mean of the ten area ratios was used to calculate the results.

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[1] J. C. Tatlow, *Endeavour*, 1963, **22**, 89.

[2] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J.*, 1962, 3253.

[3] J. G. Allen, J. Burdon, and J. C. Tatlow, *J.*, 1965, 6329.

[4] J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J.*, 1965, 5152 and 6336; J. G. Allen, J. Burdon, and J. C. Tatlow, *J.*, 1965, 1045; D. J. Alsop, J. Burdon, and J. C. Tatlow, *J.*, 1962, 1801; and other Parts in this Series.

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

[6] J. Burdon, P. L. Coe, and C. R. Marsh, *Tetrahedron*, to be published.

[7] J. Burdon, W. B. Hollyhead, and C. R. Patrick, *J.*, 1964, 4663.

[8] E. Nield, R. Stephens, and J. C. Tatlow, *J.*, 1959, 166.

The experiments on pentafluorobenzoic acid, which presumably reacts as the anion, were carried out in the concentration range 0·29—0·31 mole $l.^{-1}$ to avoid difficulties due to differing ionic strengths.

Owing to their vastly great rate of reaction, octafluorotoluene and pentafluoronitrobenzene were studied in a refrigerated methanol thermostat (±0·2°). The apparatus consisted of two bulbs, one above the other, joined by a wide-bore tap and connected with ground-glass joints. A magnesium perchlorate-packed guard-tube was attached by a ground-glass joint to the upper bulb. A standard solution of the substrate in methanol was pipetted into the lower bulb, and the required volume of sodium methoxide in methanol into the upper one. The whole apparatus was immersed in the thermostat, and after about 15 min. the tap was opened and the reactants were mixed thoroughly by shaking; concentrations of the reaction mixture were 0·10—0·30 mole $l.^{-1}$. After the sodium methoxide solution had drained into the lower bulb, the tap was closed and an excess of hydrochloric acid in methanol was pipetted into the upper bulb. After the required time had been allowed for reaction, the tap was opened, the solutions were mixed thoroughly, and the apparatus was removed and the contents of the lower bulb were titrated against aqueous sodium hydroxide. This procedure was carried out for five different reaction times at each temperature.

RESULTS

All the rates obeyed second-order kinetic expressions. Reactions were allowed to proceed to between 40 and 85% completion. The results are given in Table 1.

TABLE 1

Rates of reaction of C_6F_5X compounds with sodium methoxide in methanol

Compound	10^4k (in l. $mole^{-1}$ $sec.^{-1}$) (temp. in brackets)				
$C_6F_5NMe_2$	0·081 (50·2°)	0·083 (52·1°)	0·130 (55·9°)	0·211 (59·0°)	0·277 (62·3°)
$C_6F_5CH_3$	0·438 (50·0)	0·569 (53·1)	0·923 (57·0)	1·30 (60·0)	1·52 (62·9)
C_6F_5H	0·570 (45·0)	1·04 (50·4)	1·82 (55·2)	3·19 (60·7)	3·22 (61·3)
$C_6F_5CO_2^-$ [a]	2·14 (50·2)	2·59 (53·0)	3·75 (57·2)	5·60 (61·9)	
C_6F_6 [b]	5·09 (52·9)	6·08 (55·4)	7·85 (57·9)	10·1 (60·0)	13·2 (62·0)
C_6F_5Cl [c]	0·48 (30·6)	0·80 (34·8)	1·24 (38·7)	1·82 (42·1)	2·20 (43·3)
C_6F_5Cl [d]	2·62 (30·6)	4·18 (34·8)	6·24 (38·7)	8·74 (42·1)	10·3 (43·3)
$C_6F_5CF_3$	1·37 (−4·7)	2·42 (−40·3)	4·36 (−35)	12·0 (−25·5)	27·0 (−19·7)
$C_6F_5NO_2$	14·4 (−60·5)	23·2 (−57·0)	40·6 (−54·8)	78·0 (−50·0)	

[a] Concentration of reactants 0·29—0·31 mole $l.^{-1}$; at 53·0° the rate constant was 2·41 l. $mole^{-1}$ $sec.^{-1}$ at a concentration of 0·18 mole $l.^{-1}$, and 3·24 at a concentration of 0·40 mole $l.^{-1}$. [b] Measured rates (not divided by six). [c] Replacement of *ortho*-fluorine. [d] Replacement of *para*-fluorine.

TABLE 2

Arrhenius parameters and relative rates for reactions of C_6F_5X compounds with sodium methoxide in methanol

Compound	Relative rate at 60° [a]	E[b] ± 95% confidence limit [c] (kcal. $mole^{-1}$)	log A[b] ± 95% confidence limit [c]
$C_6F_5NMe_2$	0·10	23·5 ± 1·45	10·8 ± 0·95
$C_6F_5CH_3$	0·63	22·0 ± 0·95	10·5 ± 0·65
C_6F_6	0·90 [d]	22·4 ± 0·80	11·0 [e] ± 0·55
C_6F_5H	1	22·9 ± 0·50	11·4 ± 0·35
$C_6F_5CO_2^-$	2·5	19·1 ± 1·00	9·3 ± 0·65
C_6F_5Cl [f]	4·6	22·5 ± 0·80	11·8 ± 0·55
C_6F_5Cl [g]	19	19·9 ± 1·10	10·7 ± 0·80
$C_6F_5CF_3$	$4·5 \times 10^3$	13·1 ± 0·45	8·6 ± 0·40
$C_6F_5NO_2$	$2·3 \times 10^6$	14·9 ± 1·05	12·5 ± 1·05
C_6H_5F [9]	$5·2 \times 10^{-8}$	36·4 [h]	13·0 [h]
o-$FC_6H_4NO_2$ [9]	19	19·9 ± 0·2 [i]	10·7 [h]
p-$FC_6H_4NO_2$ [9]	28	20·1 ± 0·2 [i]	11·0 [h]

[a] Two significant figures. [b] Nearest 0·1. [c] See Appendix. Rounded to nearest 0·05 above. [d] Actual relative rate = 5·4. [e] Measured log A = 11·8. [f] Replacement of *ortho*-fluorine. [g] Replacement of *para*-fluorine. [h] No error limits quoted by authors. [i] Estimated errors, not 95% confidence limits.

[9] C. W. L. Bevan and G. C. Bye, *J.*, 1954, 3091.

For chloropentafluorobenzene, the measured rate is equal to the sum of the rates for attack *ortho* and *para* to the chlorine. The ratio of these rates is given by the ratio of 2- and 4-chlorotetrafluoroanisole formed at each temperature. The percentages of *ortho*-isomer were (temperature in parentheses): 15·5% (30·6°), 16·1% (34·8°), 16·3% (38·7°), 17·2% (42·1°), 17·6% (43·3°).

The Arrhenius parameters were not calculated from the figures in Table 1. Instead, a rate constant was calculated from every titration value (except the first, which is the zero) at each temperature (20—40 rate constants in all). These constants were then fitted by a least squares treatment, (which assumed that the temperatures were known far more accurately than the rate constants), to the Arrhenius equation relating log k and $1/T$. The results are given in Table 2, together with those obtained for fluorobenzene and *ortho*- and *para*-fluoronitrobenzene by other workers.[9] Errors are given in terms of 95% confidence limits (see Appendix). This means that in any repetition of our experiments, there is a 95% chance of the parameters falling within the limits given. The relative rates (at 60°) have been calculated from the Arrhenius parameters and are included in Table 2.

With the exception of chloropentafluorobenzene, no allowance has been made for the replacement of fluorine atoms *meta* or *ortho*, rather than *para*, to the group X. Such replacement has been observed in some of the cases studied, but it never exceeds 10% of the overall reaction.[2,3] It is possible to justify the ommission of an allowance for these small percentages in the following way:

$$\frac{\mathrm{d(OMe^-)}}{\mathrm{d}t} = k_{\mathrm{measured}}\,[\mathrm{C_6F_5X}][\mathrm{OMe^-}]$$

$$= (k_{\mathrm{para}} + k_{\mathrm{r}})\,[\mathrm{C_6F_5X}][\mathrm{OMe^-}]$$

where $k_{\mathrm{r}} = k_{\mathrm{ortho}} + k_{\mathrm{meta}}$

Thus the second-order kinetic behaviour is not affected. Writing the second-order rate constant as:

$$k_{\mathrm{measured}} = k_{\mathrm{para}}(1 + \beta) \text{ when } \beta = k_{\mathrm{r}}/k_{\mathrm{para}}$$

and, by definition:

$$E_{\mathrm{measured}} = \frac{\boldsymbol{R}T^2\mathrm{d}(\ln k_{\mathrm{measured}})}{\mathrm{d}T}$$

then

$$E_{\mathrm{measured}} = \frac{\boldsymbol{R}T^2\mathrm{d}(\ln k_{\mathrm{para}})}{\mathrm{d}T} + \frac{\boldsymbol{R}T^2\mathrm{d}\ln(1 + \beta)}{\mathrm{d}T}$$

If $\beta \ngtr 0{\cdot}1$

$$E_{\mathrm{measured}} = E_{\mathrm{para}} + \frac{\boldsymbol{R}T^2\mathrm{d}\beta}{\mathrm{d}T}$$

For example, if the minor isomers comprise 5% of the product at the low end of the temperature range and 10% at the high end, and if the temperature range is 43—58°, then

$$E_{\mathrm{measured}} = E_{\mathrm{para}} + 0{\cdot}7 \text{ kcal./mole}$$

A similar treatment for log A gives

$$\log A_{\mathrm{measured}} = \log A_{\mathrm{para}} + 0{\cdot}5$$

Even these differencies, which are grossly exaggerated (the minor isomers are most unlikely to change by such a large relative amount), are less than most of the experimental errors. A more realistic change, say from 4 to 5% over the 15° temperature range, changes E by 0·1 kcal./mole and leaves log A almost unaffected. Neglect of the minor isomers is therefore justified, as is the neglect of the slight curvature they presumably impart on the Arrhenius plot, in view of the other experimental errors.

The parameters for hexafluorobenzene are different from those given in our earlier Note.[7] We have recalculated the previous figures by our present statistical procedure, after allowing (by taking the first reading as the zero) for the small amount (*ca.* 3%) of reaction, which we previously neglected, which had occurred before temperature equilibrium had been reached; the revised values are $E = 24{\cdot}3 \pm 2$ kcal. mole^{-1}, and log $A = 12{\cdot}2 \pm 1{\cdot}25$. Although the ranges of these figures overlap those given in Table 2, the parameters are significantly greater. We are unable to explain this, but in view of the greater accuracy of the titrimetric procedure, we suggest that the values given in Table 2 are more nearly correct.

No allowance has been made for ionic strength in the pentafluorobenzoic acid case, since preliminary experiments over the concentration range 0·18—0·40 mole $l.^{-1}$ showed that extrapolation to zero ionic strength [10] had little effect on E and lowered log A by 0·5 at most. The rate constants changed in the usual manner, being higher at the higher concentrations (Table 1, footnote *a*).

DISCUSSION

The relative rates of reaction of the C_6F_5X compounds depend qualitatively on X in the expected manner; electron-donor groups (X = Me or NMe_2) decrease the rate, and electron-attracting groups (X = CF_3 or NO_2) increase it. It appears that an *ortho*- or *para*-nitro-group is roughly equivalent to five fluorines in activating fluorine towards nucleophilic displacement. A plot of log(relative rate) (except for *ortho*-attack on C_6F_5Cl) against the Hammett σ *para* value (insufficient σ^- values are available) for the group X gives a fairly good line (correlation coefficient, 0·86) with the exception of the NMe_2-point. This is in agreement with other work [3] which suggests that the dimethylamino-group in pentafluoro-*NN*-dimethylaniline is bent or twisted out of the ring plane by steric interaction with the *ortho*-fluorines. Since the other compounds fall more nearly on the Hammett plot, steric interactions between their X-groups and the *ortho*-fluorines would seem to be smaller. The ρ value for the C_6F_5X–sodium methoxide in methanol reaction is about seven.

The errors involved in the determination of Arrhenius parameters are important factors in any discussion about them. Most workers give error limits, but Peterson has recently pointed out [11] that they are usually unrealistically low. Our procedure, involving 95% confidence limits, appears to meet Petersen's objections, and since our titrimetric method is similar to that used by other workers in the nucleophilic aromatic substitution field, we suggest that their 95% confidence limits would be about the same as ours, that is about ±1 kcal. $mole^{-1}$ in E and ±1 in log A. It must be emphasised, however, that these are statistical limits; additional systematic errors due to chemical factors are not included, and are more difficult to assess.

It is clear from Table 2, therefore, that many of the activation energies and even more of the pre-exponential factors cannot be distinguished with any certainty. With this proviso, it appears that the activation energies parallel to relative rates more than do the pre-exponential factors, and this is implicit in most electronic interpretations of the differences in reactivity of aromatic compounds. In view of the small and seemingly random scatter of the pre-exponential factors, there is little point at present in discussing them in detail. It may also not be reasonable to compare the pre-exponential factors of octafluorotoluene and pentafluoronitrobenzene with those of the other compounds, because the kinetic experiments were carried out in temperature ranges some 70—100° apart. Log A values are usually associated, in part, with solvation effects, and these would presumably be different in different temperature ranges; there are other factors which might also affect the comparison of log A values. Activation energies determined in widely differing temperature ranges would also be influenced by all such factors, but probably to a lesser extent.

An isokinetic plot [12] of log A against E for the data in Table 2 gave a very poor line, most of the points being distributed randomly in a small region of the graph.

APPENDIX

Treatment of Errors in Arrhenius Parameters.—Most workers give error limits when quoting Arrhenius parameters but none, as far as we have been able to ascertain, state the error in terms of statistical confidence limits. We recommend that the quoting of confidence limits in presenting kinetic data should become standard practice. We acknowledge the

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[10] B. A. Bolto and J. Miller, *Austral. J. Chem.*, 1956, **9**, 74.

[11] R. C. Petersen, *J. Org. Chem.*, 1964, **29**, 3133; R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Amer. Chem. Soc.*, 1961, **83**, 3819.

[12] J. E. Leffler, *J. Org. Chem.*, 1955, **20**, 1202.

clearly defined relationship between standard deviations, which are often quoted by workers in this field, and confidence limits, but emphasise that the relationship cannot be utilised without knowledge of the number of observations included in the study. This is seldom quoted, but should generally be specified, particularly where standard deviations rather than confidence limits are presented.

We calculated log A and E by a least squares treatment as described in the experimental section. We also calculated the standard errors in these parameters from the following formulæ [where $\mathrm{y} = \log k$, $\mathrm{x} = 1/T$, $\bar{\mathrm{y}}$ = mean y, $\bar{\mathrm{x}}$ = mean x, $\boldsymbol{R} = 1{\cdot}98$ cal. mole^{-1}, and n = number of rate constants (about 20—40 in the present work; 5—8 at each of 4—5 temperatures)]:

$$s^2 = \sqrt{\frac{\Sigma(\mathrm{y} - \bar{\mathrm{y}})^2}{n - 1}}$$

$$\text{S.E. in } E = \frac{s}{\sqrt{\Sigma(\mathrm{x} - \bar{\mathrm{x}})^2}}$$

$$\text{S.E. in } \log A = s \cdot \sqrt{1 + \frac{\bar{\mathrm{x}}^2}{\Sigma(\mathrm{x} - \bar{\mathrm{x}})^2}}$$

A confidence limit of $100(1 - 2\alpha)\%$ in E, say, is given by $E \pm t_{\alpha}{\cdot}$(S.E. in E), where t_{α} is the value of "Student's" t at probability α for $n - 2$ degrees of freedom. For $\alpha = 0{\cdot}025$ (*i.e.*, 95% confidence limits), t is about 2 for 20—40° of freedom. This treatment, and tables of t, can be found in most text-books of statistics; it is based on the assumption that the errors in the rate-constants are normally distributed, or approximately so. A confidence limit of $100(1 - 2\alpha)\%$ means that if an experiment is repeated, there is a $100(1—2\alpha)\%$ chance that the results will fall within the calculated limits; it does not make any allowance for systematic errors, chemical or otherwise.

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