Mechanisms for Reactions of Halogenated Compounds. Part 5.[1] Orientating Effects of Fluorine Substituents on Nucleophilic Substitution in Naphthalene and Other Polycyclic Systems

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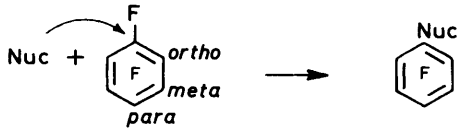
Separate activating effects have been determined for fluorine atoms as substituents at *ortho*-positions and at sites in the remote ring, relative to the position of attack by methoxide in methanol, in polyfluoronaphthalenes. Fluorine activates at sites in the remote ring that are adjacent to the centres of high charge density in the transition state, but is slightly deactivating when attached directly to these sites. Fluorine at *ortho*-positions activates. These results enable a simple model, which accounts for orientation of nucleophilic aromatic substitution, to be extended to perfluoropolycyclic compounds.

In this series of papers, we have been developing an empirical experimental approach to the problems of orientation and reactivity arising from reactions of nucleophiles with various halogenated aromatic systems. We consider this to be a significant study because it could be argued that these problems are analogous to the classical ones of orientation and reactivity, for electrophilic aromatic substitution, posed by hydrocarbon systems.

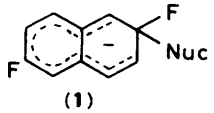
So far, we have established (for benzene and pyridine derivatives) the separate activating effects of fluorine atoms as substituents, that are *ortho*-, *meta*-, and *para*- to the site of



nucleophilic attack and, consequently, this led to a general empirical explanation of the orientation of substitution in a variety of highly fluorinated systems. Rationalization of the basis of these separate effects has also been attempted,[2,3] and more will be said about this later.[4]

In spite of the fact that there seems little need for argument on this empirical experimental approach, nevertheless, some workers continue with other approaches that do not take into account the experimentally established data. In a recent communication,[5] it was reported that calculations predict 9,10-substitution in perfluoroanthracene, whereas 2-substitution is actually observed. Unfortunately, the model used for the calculations does not include the now well established fact that fluorine *ortho*- to the site of attack is *activating*, since it is implicit in that approach [5] that fluorine atoms at sites *ortho*- and *para*- to the position of nucleophilic attack are *deactivating*. In fact, 9,10-attack in perfluoroanthracene should be the *least* likely sites of attack, since these sites are without any activating effect arising from *ortho*-fluorine substituents.

We now set out to extend our approach, which accounts for the orientation of substitution in monocyclic systems, to some fused-ring derivatives, including perfluoroanthracene, but we recognise that we have not yet established the separate effects of fluorine atoms as substituents in rings that are remote from the reaction site, *e.g.* structure (**1**), and in this paper we set out to do so.

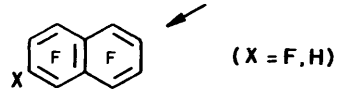


(**1**)

It is, however, quite unrealistic to make such a study beyond the naphthalene system but we now demonstrate that the principles established earlier[2,3] for monocyclic aromatic compounds may, in fact, be usefully applied to at least di- and tricyclic systems.

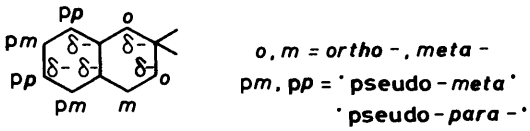
Results and Discussion

Our approach requires the comparison of rate constants for substitution in systems that differ only by having fluorine or hydrogen at the appropriate sites. Therefore, the type of comparison required in this study is illustrated by compound (**2**), where we would be able to compare the effect of fluorine,



(**2**)

relative to hydrogen as a substituent, on the rate constant for nucleophilic substitution at the arrowed position. For the purposes of this discussion, we have defined fluorine at remote sites as 'pseudo-*meta*' and 'pseudo-*para*' [see structure (**3**)], in



(**3**)

order to emphasise the fact that we would expect the order, if not magnitude, of these effects to relate to those of fluorine as substituents in monocyclic systems.

We have measured rate constants for reactions of sodium methoxide in methanol, at 25.0 °C, with the naphthalene derivatives (**4**)—(**7**), which have mostly been synthesized by established procedures.[6,7] 2,6-Dihydrohexafluoronaphthalene (**7**) has not been characterised previously and this was obtained after reaction of lithium aluminium hydride with octafluoronaphthalene (**4**) in dry tetrahydrofuran (THF). Rate constants are given in Table 1 and the orientation of substitution was determined in each case by ^{19}F n.m.r. spectroscopy. Three inseparable isomers (**7a**—**c**) were obtained from compound (**7**) and were clearly identified and

Table 1. Rate constants for reactions of sodium methoxide in methanol with some polyfluoronaphthalenes at 25.0 °C

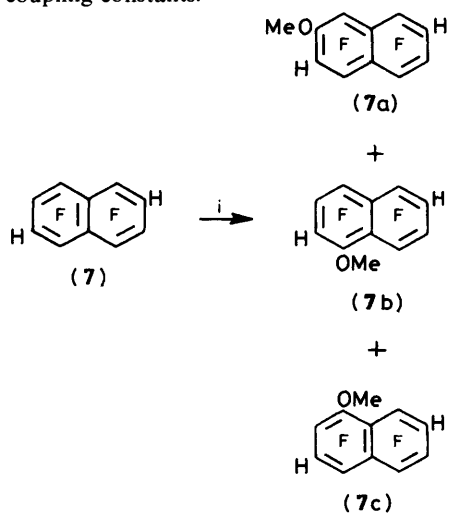
Naphthalene	Position of substitution	k/l mol^{-1} s^{-1}
F_8 (**4**)	2-	(1.12 ± 0.01) × 10^{-3} [a]
1,3,4,5,6,7,8-F_7 (**5**)	6-	(1.38 ± 0.01) × 10^{-3}
3,4,5,6,7,8-F_6 (**6**)	6-	(4.55 ± 0.03) × 10^{-5}
1,3,4,5,7,8-F_6 (**7**)	3- (**7a**)	*ca.* 1.4 × 10^{-6} [a,b]
	1- (**7b**)	*ca.* 4.0 × 10^{-7} [a,b]
	4- (**7c**)	*ca.* 2.0 × 10^{-7} [a,b]
1,3,4,5,6,7,8-F_7 (**5**)	3-	*ca.* 4.6 × 10^{-5} [c]

[a] Corrected for statistical factor. [b] Separate k values calculated from n.m.r. integrations. [c] Rate constant estimated from the value for compound (**7**) × 30.3 *i.e.* making allowance for the activation from an additional pseudo-*meta* fluorine (see Table 2).

Table 2. Activating influence of fluorine in the naphthalene ring system

Comparison	Effect determined	k_F/k_H
(**4**) *vs.* (**5**)	pseudo-*para* F / pseudo-*para* H	0.81
(**5**) *vs.* (**6**)	pseudo-*meta* F / pseudo-*meta* H	30.3
(**4**) *vs.* (**5**) (Calc.)	*ortho*-F / *ortho*-H	*ca.* 25

distinguished by ^{19}F n.m.r. spectroscopy (proportions 70:20:10). The identity of the major isomer (**7a**) was very easy to establish from the observation of two characteristically large *peri* F–F coupling constants.[8]



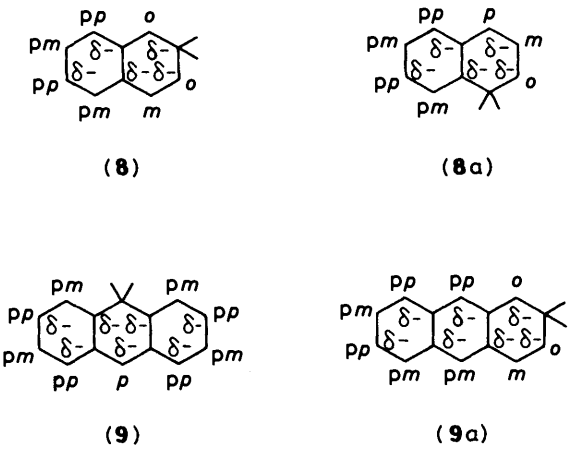
Scheme. *Reagents and conditions:* i, MeO^- – MeOH, 25 °C, 7—10 days. [(**7a**):(**7b**):(**7c**) = 70:20:10]

The minor isomers were also easily distinguished by a combination of chemical shift and *peri* F–F coupling constants. Our assignments were confirmed by ^{19}F–^{19}F COSY experiments.

From these data we were able to establish, simply, the required 'pseudo-*para*' and 'pseudo-*meta*' effects, as shown in Table 2. We would expect the effect of *ortho*-F to be activating, as we have established for benzene and pyridine systems,[3] but we have been unable to determine this directly for naphthalene derivatives. This stems simply from the fact that nucleophilic attack occurs in the fully fluorinated ring in compound (**5**). However, we established the effect of *ortho*-F by using rate constant data for the 2,6-dihydro derivative (**7**) and made allowance for a 'pseudo-*meta*' fluorine substituent, as determined in Table 2, *i.e.* compound (**5**) (Calc.). Unfortunately, we have no procedure for establishing effects of *meta*-F in this system.

We have previously determined that, for benzene and pyridine systems, *ortho*- and *meta*-fluorine substituents are activating, whereas *para*-fluorine is deactivating towards nucleophilic attack. It is clear, therefore, from the effects shown in Table 2, that 'pseudo-*meta*' and 'pseudo-*para*' effects parallel these observations. Consequently, we are justified in extending our previous general rationalisation of orientation of nucleophilic substitution to include systems containing fused rings.

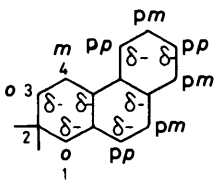
Rationalisation of the observed orientation of nucleophilic substitution in perfluoro-naphthalene and -anthracene follows simply from the requirement that these determined activating influences of fluorine substituents are maximised. If we consider, for example, attack at the 2-(**8**) *versus* 1-(**8a**) positions in



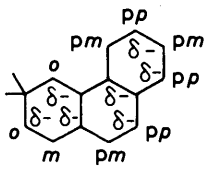
(**8**) 5 Activating F-substituents
(**8a**) 4 Activating F-substituents
(**9**) 4 Activating F-substituents
(**9a**) 6 Activating F-substituents

perfluoronaphthalene, there is a clear difference in reactivity indicated, which is quite sufficient to account for the observed orientation of substitution at the 2-position. Similarly, comparing substitution in the 9,10-(**9**) *versus* the 2-(**9a**) positions in perfluoroanthracene, we see an even greater difference in favour of the observed 2-attack.

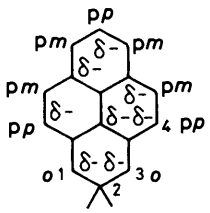
A similar approach can be applied to perfluorobiphenylene which rationalises the observed preferential 2-attack,[9] but our approach does not distinguish between 2-(**10**) and 3-(**10a**) substitution in perfluorophenanthrene. Substitution of the 2-position (**10**) has been observed but other products (which



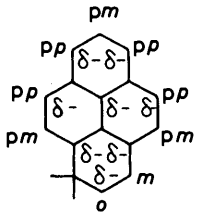
(10)



(10a)



(11)



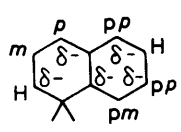
(11a)

(**10**) 6 Activating F
(**10a**) 6 Activating F
(**11**) 6 Activating F
(**11a**) 5 Activating F (observed)

could include the 3-isomer) were not identified.[10] Only in the case of perfluoropyrene is there a clear difference between the observed and predicted orientation of substitution, based on the effects of fluorine. This approach shows that 2-attack is favoured by fluorine substituents (**11**), whereas 1-attack (**11a**) has been observed.[11] It would seem clear, therefore, that at this stage, the effects of fluorine are no longer dominating orientation of substitution but, for this extensively conjugated system, localisation energy is the dominant factor. Calculated localisation energies, for the parent system,[12] predict that attack at the 1-position would be favoured on this basis.

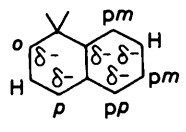
Therefore, we now see little basis for contesting the factual approach to accounting for the gross features that determine the orientation of nucleophilic substitution in perfluorinated benzenoid derivatives as outlined in this paper. Nevertheless, more subtle factors, such as solvent and steric effects, will further affect orientation; some of these effects have already been noted by other workers[13,14] but, clearly, the gross model reviewed here is not intended to take such factors into consideration.

The formation of compound (**7b**), in greater proportion than compound (**7c**), also indicates that this approach becomes less effective as the number of fluorine atoms in the system diminish. In the following paper[4] we establish that the ratios of the effects of *ortho*-F:*meta*-F increase significantly with increase in reactivity of the system and the preferential formation of compound (**7b**) indicates that the converse applies for a relatively *unreactive* system. We conclude that isomer (**7c**) is not preferred over isomer (**7b**) because, in compound (**7**), reactivity is so reduced (see Table 1) that the activating effect of *ortho*-F is now greatly diminished with respect to a *meta*-F [see intermediates (**7b**)* and (**7c**)*].



(7b)*

2 Activating F
(including 1 *m*)



(7c)*

3 Activating F
(including 1 *o*)

Experimental

^{19}F and ^{1}H N.m.r. spectra were recorded on a Bruker HK90 spectrophotometer with Fourier Transform facility; chemical shifts are quoted in p.p.m. with reference to internal $CFCl_3$ and TMS.

Materials.—Octafluoronaphthalene was obtained from Bristol Organics Ltd. 2*H*-Heptafluoro- (**5**)[6] and 1,2-dihydrohexafluoro-naphthalene (**6**)[7] were prepared by established procedures.

2,6-*Dihydrohexafluoronaphthalene* (**7**).—Lithium aluminium hydride (3.42 g, 90.0 mmol) in dry THF (125 ml) was added dropwise over 2 h to a stirred solution of octafluoronaphthalene (20.0 g, 73.5 mmol) in dry THF (50 ml) under nitrogen. The reaction mixture was then stirred at 60 °C for 24 h. After cooling, the mixture was cautiously diluted with water (200 ml) and extracted with ether (8 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a residue which sublimed *in vacuo* to yield a white solid (16.52 g) shown to contain several components by analytical scale g.l.c. Repeated, preparative scale g.l.c. (column 'O,' 220 °C) gave 2,6-dihydrohexafluoronaphthalene (6.38 g, 37%) as white crystals, m.p. 72–73 °C (Found: C, 50.5; H, 1.0; F, 48.5%; M^+, 236. $C_{10}H_2F_6$ requires C, 50.8; H, 0.9; F, 48.3%; M^+, 236); δ_F 117.6 (1- and 5-F), 136.3 (3-and 7-F), and 149.3, (4- and 8-F); $J_{1F,8F}$ 63, $J_{4F,5F}$ 64 Hz; δ_H 7.2 (2- and 6-H).

Product Identification.—The products were all isolated by the same general procedure. After the kinetic runs were completed, the remaining mixture was poured into an excess of water and extracted with ether. The ether fraction was washed with water, dried ($MgSO_4$), and the ether distilled to give the product residue. Before further purification, the products were analysed by g.l.c. and n.m.r. to determine the number and relative amounts of any isomers formed. The products from octafluoro- (**4**), 2*H*-heptafluoro- (**5**), and 1,2-dihydrohexafluoro-naphthalene (**6**) were identified as the 2-, 6-, and 6-methoxy derivatives, respectively, from their ^{19}F n.m.r. spectra, in agreement with the literature.[7]

From 2,6-*Dihydrohexafluoronaphthalene.*—A mixture containing 2,6-dihydrohexafluoronaphthalene (1.50 g, 6.35 mmol), methanol (5 ml), and sodium methoxide in methanol (0.75M; 9 ml, 6.75 mmol), contained in a sealed Carius tube, was heated at 25 °C for 7—10 days. The contents of the tube were poured into water (150 ml), and extracted with ether (4 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a solid product (1.63 g) shown by analytical g.l.c. to contain one component in addition to starting material; this was separated by preparative scale g.l.c. (column 'O,' 240 °C). However, analysis of this separate component by ^{19}F n.m.r. showed it to be a mixture (7:2:1 by integration) of three isomers. The major component was identified as 1,4,5,6,8-pentafluoro-2-methoxy-naphthalene (**7a**); δ_F(mixture) 118.6 [8 F, d (*J* 67.0 Hz) of d (*J* 19.2 Hz) of d (*J* 11.3 Hz) of d (*J* 2.3 Hz)], 119.4 [4 F, d (*J* 61.6 Hz) of m], 140.0 (6 F, m), 146.8 [1 F, d (*J* 67.0 Hz) of d (*J* 19.2 Hz), t (*J* 5.1 Hz)], and 150.8 [5 F, d (*J* 61.6 Hz) of d (*J* 5.7 Hz) of m]. The next most abundant isomer was identified as 3,4,5,7,8-pentafluoro-1-methoxynaphthalene (**7b**); δ_F(mixture) 119.0 [5 F, d (*J* 67.4 Hz) of m], 137.9 (3 F, m), 138.8 (7 F, m), 145.8 (8 F, m), and 156.6 [4 F, d (*J* 67.4 Hz) of d (*J* 18.8 Hz) of t (*J* 5.0 Hz)].

The third isomer was identified as 2,4,5,6,8-pentafluoro-1-methoxynaphthalene (**7c**); δ_F(mixture) 117.2 [4 F, d (J 62.0 Hz) of m], 118.3 (8 F, m), 135.4 (2 F, m), 150.0 (6 F, m), and 152.4 [5 F, d (J 62.0 Hz) of m].

Pure samples of each component could not be obtained, but elemental analysis of the mixture was consistent with a mixture of isomers of pentafluoromethoxynaphthalenes (Found: C, 53.0; H, 1.7; F, 38.0%; M^+, 248. Calc. for $C_{11}H_5F_5O$: C, 53.2; H, 2.0; F, 38.3%; M^+, 248).

Rate Measurements.—For the reactions of sodium methoxide in methanol, a 2:1 molar excess of the substrate was used and the second-order rate constants, k, determined from the following equation where a = initial concentration of substrate,

$$kt = \frac{1}{a-b} \cdot \ln\left[\frac{b}{a} \cdot \frac{(a-x)}{(b-x)}\right]$$

b = initial concentration of sodium methoxide, and x = concentration of nucleophile reacted at time t. Aliquots (5 ml) of the reaction mixture were removed periodically, quenched with an excess of water, and titrated with a standard acid.

Acknowledgements

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