meso-Reactivity of Porphyrins and Related Compounds. Part 10.[1] Direct Fluorination of Octaethylporphyrin with Caesium Fluoroxysulphate

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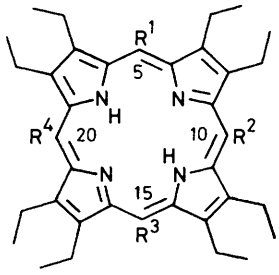
The reaction of octaethylporphyrin with caesium fluoroxysulphate in dioxane for a limited period at room temperature leads to *meso*-fluorination, the major product being 5-fluoro-octaethylporphyrin with the 5,10-difluoro, 5,15-difluoro, 5,10,15-trifluoro, and 5,10,15,20-tetrafluoro derivatives being formed in smaller amounts. The electronic absorption and n.m.r. (^1H,^{19}F) spectra of this suite of substitution products show features of considerable interest which are discussed. Caesium fluoroxysulphate appears to be a convenient source of electrophilic fluorine for aromatic substitution and, in the porphyrin series at least, its use shows some marked advantages over the multi-step Schiemann procedure.

In previous parts of this series we have examined electrophilic and other substitution processes at the *meso*-positions of macrocyclic tetrapyrroles, and the subject has recently been reviewed in detail.[2-4] Early examples of porphyrin halogenation were confined to chlorination and bromination:[5] in Part 2 of this series[6] we investigated the chlorination of octaethylporphyrin and octaethylchlorin as convenient model systems. It was shown that chlorination of octaethylporphyrin gave a mixture of *meso*-substituted derivatives (5-chloro-, 5,15-dichloro-, 5,10,15,20-tetrachloro-), the distribution of products being sensitive to reaction conditions. Chlorination of octaethylchlorin occurred preferentially at the *meso*-positions flanking the reduced ring. Direct bromination of the chlorin (but not the porphyrin) was described.[6]

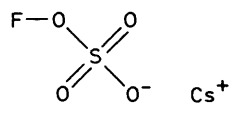
The earlier failure to detect direct bromination of octaethylporphyrin was attributed to steric factors.[6] Such factors would be unlikely to impede direct *meso*-fluorination, since direct chlorination does occur readily. However, direct fluorination of organic substrates, while highly desirable, is experimentally a difficult operation if fluorine itself is used as reagent. Fluorinated porphyrins have only been prepared in the past by indirect procedures. Thus *meso*-fluoro derivatives of deuterioporphyrin dimethyl ester were obtained in low yield (5%) by the thermal decomposition of the corresponding diazonium tetrafluoroborates (Schiemann reaction).[7]

The fluoroxysulphate ion was identified in 1979 in the form of its caesium and rubidium salts, which can be handled safely in gram quantities at room temperature.[8] These salts are prepared by the reaction of fluorine with aqueous solutions of the corresponding sulphates, and with these new reagents the direct fluorination of alkenes,[9] aromatic compounds,[10-12] and uracil derivatives[13] has been observed. The reaction with aromatics is acid catalysed and has been interpreted in terms of the fluoroxysulphate ion acting as a source of electrophilic fluorine, although oxidative processes, leading to oxygen and fluorine containing dimers and polymers, are complicating side reactions.[11] Cleavage of the carbon–tin bond of aryltrialkylstannanes with caesium fluoroxysulphate generates fluoroaromatics in good yields.[14]

We have examined the direct fluorination of octaethylporphyrin (**1**) with caesium fluoroxysulphate (**2**). Preliminary experiments with various solvent systems led to the selection of dioxane as the solvent of choice, since it was a satisfactory solvent for the porphyrin and undesirable side-reactions were minimised. It has to be recognised that the fluoroxysulphate ion



(**1**) $R^1 = R^2 = R^3 = R^4 = H$
(**3**) $R^1 = F$, $R^2 = R^3 = R^4 = H$
(**4**) $R^1 = R^2 = F$, $R^3 = R^4 = H$
(**5**) $R^1 = R^3 = F$, $R^2 = R^4 = H$
(**6**) $R^1 = R^2 = R^3 = F$, $R^4 = H$
(**7**) $R^1 = R^2 = R^3 = R^4 = F$



(**2**)

is a powerful oxidant, the SO_4F^-–HSO_4^- couple having a standard electrode potential of about 2.5 V.[15]

Reaction of octaethylporphyrin in dioxane for 8—10 min at room temperature with a ten-fold excess of caesium fluoroxysulphate freshly dissolved in a small quantity of water gave, besides some recovered starting material (*ca.* 20%), a suite of five less polar porphyrins which were separated with difficulty by preparative t.l.c. The five new compounds were crystallised and identified by n.m.r. spectroscopy as the *meso*-fluorinated compounds. The R_F values of the fluoro-substituted porphyrins on normal silica increased with increasing substitution: this correlates with the decreasing basicity expected as substitution is increased. The derivatives obtained were, in order of decreasing polarity on the plate, 5-fluoro (**3**), (28%), 5,10-difluoro (**4**), (11%), 5,15-difluoro (**5**), (9%), 5,10,15-trifluoro (**6**), (4%), and 5,10,15,20-tetrafluoro (**7**), (2%). With increasing substitution the solutions became more yellow-brown (rather than red) in hue, and fluorescence (on the t.l.c. plate) became increasingly less apparent.

Prolongation of the reaction time led to diminished yields with an increase in polar by-products (presumably oxidation products). With a reaction time of 2 h the less polar products (*i.e.* the *meso*-fluoroporphyrins) had completely disappeared.

Table 1. ^{1}H N.m.r. spectra of octaethylporphyrin and its *meso*-fluoro derivatives ($CDCl_3$)

Porphyrin	*meso* (s)	CH_2 (q)[a]	CH_3 (t)[a]	NH (br s)
Octaethyl (**1**)[16]	10.07	4.11	1.92	−3.65
5-Fluoro (**3**)	9.89 (1 H) 10.03 (2 H)	4.07 (m)	1.86 (6 H) 1.90 (18 H)	−3.58
5,10-Difluoro (**4**)	9.82	4.03 (m)	1.84 (12 H) 1.97 (6 H) 1.88 (6 H)	−3.45
5,15-Difluoro (**5**)	10.36	4.03 (8 H) 4.07 (8 H)	1.85 (12 H) 1.89 (12 H)	−3.80
5,10,15-Trifluoro (**6**)	9.81	4.00 (m)	1.82 (18 H) 1.85 (6 H)	−3.70
5,10,15,20-Tetrafluoro (**7**)[b]		3.99	1.81	−3.94

[a] Signal multiplicities ($J \sim 7$ Hz). [b] Hydrocarbon impurities revealed in n.m.r. spectrum.

Table 2. Electronic spectra of *meso*-fluoroporphyrins [$\lambda_{max.}$/nm (ε)]

	Chloroform solution (free base)						$CHCl_3$ + trace H_2SO_4 (diprotonated form)	
Porphyrin	Soret	IV	III	II	I	R[a]	α	β
Octaethyl (**1**)	401 (167 000)	499 (13 300)	534 (10 300)	566 (6 600)	618 (4 900)	—		
5-Fluoro (**3**)	401 (152 000)	498 (12 900)	532 (7 750)	566 (8 125)	621 (1 300)	1.64	552 (13 800)	588 (5 400)
5-Chloro[6]	406 (161 000)	507 (14 800)	540 (5 300)	578 (5 600)	628 (1 600)	1.65		
6-Bromo[6]	409 (184 000)	510 (13 900)	543 (6 000)	580 (5 700)	630 (1 800)	1.49		
5,10-Difluoro (**4**)	398 (186 000)	497 (14 800)	530 (3 000)	571 (5 150)	627 (1 450)	2.68	554 (13 400)	599 (5 300)
5,15-Difluoro (**5**)	398 (153 000)	497 (12 800)	528 (4 500)	573 (4 100)	627 (2 500)	1.42	559 (7 500)	612 (7 400)
5,10,15-Trifluoro (**6**)	398 (164 000)	498 (14 600)	529 (2 750)	577 (4 200)	631 (2 700)	2.39	562 (6 800)	612 (10 800)
5,10,15,20-Tetrafluoro (**7**)	400 (178 000)	466/501 (3 600)/(12 100)	531 (5 080)	584 (3 630)	642 (7 020)	1.12	671 (5 200)	618 (12 000)

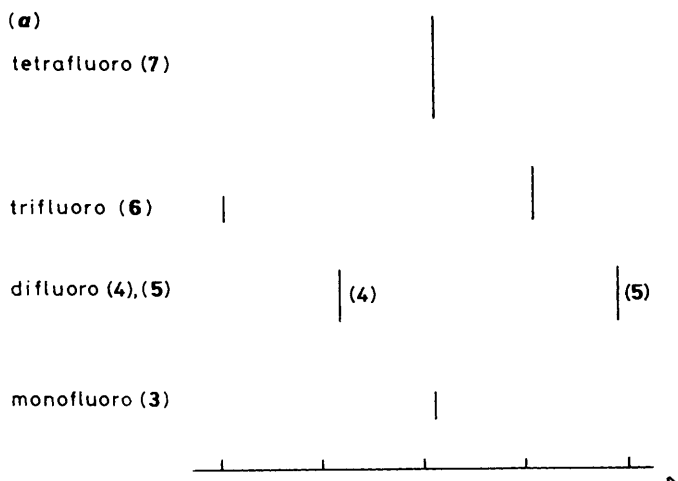
[a] $R = \frac{\varepsilon_{IIIp}/\varepsilon_{IIp}}{\varepsilon_{IIIm}/\varepsilon_{IIm}}$, where subscript Roman numerals refer to visible band notation, p refers to parent porphyrin, and m to *meso*-substituted porphyrins.

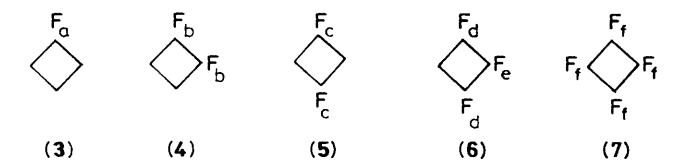
Acid catalysis of the reaction, which had been shown to be useful in the fluorination of carbocyclic aromatic compounds,[11] was not helpful with octaethylporphyrin, possibly because of protonation and deactivation of the porphyrin system. Only traces of the monofluoro derivative, as well as polar by-products, were detected in the presence of an acid catalyst. Attempts to increase yields by insertion of a metal were also unsuccessful. Thus zinc(II) octaethylporphyrin gave only 5% of the monofluoro derivative on treatment with caesium fluoroxysulphate under similar conditions.

The mass spectra of the *meso*-fluoro derivatives, observed in the electron impact mode, all showed the molecular ion as the base or prominent peak, the accurate mass measurement of which allowed molecular formulae to be determined. The ^{1}H n.m.r. spectra (Table 1) substantiated the assigned structures, and allowed the 5,10-difluoro and 5,15-difluoro compounds to be distinguished. The 5,15-difluoro compound (**5**) has the more symmetrical structure and the spectrum showed only two types of ethyl group, with equal integration values. The 5,10-difluoro compound (**4**) had a more complex spectrum, the ethyl groups being of three types. Irradiation at δ 4.1 decoupled the methyl signals, which then appeared as three singlets with an integration ratio of 2:1:1 in the direction of higher field. As with the corresponding chloro compounds, proximity to a *meso*-substituent was associated with shielding of a β-alkyl group, an effect attributed to the buckling of the periphery in the region of substitution, with the subsequent diminution of the deshielding ring current effect.

The ^{19}F n.m.r. spectra showed considerable substituent-induced shift effects and an interesting relationship between chemical shift and substitution pattern, as shown in Figure 1. The spectrum of the 5-fluoro derivative (**3**) showed a singlet at δ − 136.24: introduction of a second fluorine at an adjacent *meso*-position, as in (**4**), shifted the signal about 2 p.p.m. downfield, while introduction of the second fluorine at the opposite *meso*-position, as in (**5**), shifted the signal *ca.* 3.6 p.p.m. *upfield.* Introduction of a third *meso*-fluoro substituent into (**5**) caused a deshielding of both signals with respect to the chemical shifts in (**4**) and (**5**), while in the tetrafluoro compound (**7**) symmetry is restored, and a single resonance was observed at a chemical shift similar to that observed for compound (**3**). Thus the chemical shift values show a simple additivity relationship with respect to fluorination at adjacent or opposite *meso*-positions: with respect to the chemical shift of *meso*-fluorine an adjacent *meso*-fluoro substituent causes a downfield shift ($\Delta F_{adj.} = +1.91 \pm 0.16$), while an opposite *meso*-fluoro substituent causes an upfield shift ($\Delta F_{opp.} = -3.88 \pm 0.27$).

The electronic spectra of the *meso*-fluoro porphyrins for neutral and acidic chloroform solutions are summarised in Table 2. Interestingly, the absorption maxima of the monofluoro compound in neutral solution are scarcely shifted from those of the parent (**1**), in contrast to the monochloro and





Additivity: $F_a = \delta - 136.24$, $\Delta F_{adj.} = +1.91$, $\Delta F_{opp.} = -3.88$

	Observed δ	Calc. δ
F_b	−134.35	−134.33 ($F_a + \Delta F_{adj.}$)
F_c	−139.85	−140.12 ($F_a + \Delta F_{opp.}$)
F_d	−138.18	−138.21 ($F_a + \Delta F_{opp.} + \Delta F_{adj.}$)
F_e	−132.10	−132.42 ($F_a + 2\Delta F_{adj.}$)
F_f	−136.27	−136.30 ($F_a + 2\Delta F_{adj.} + \Delta F_{opp.}$)

Figure 1. ^{19}F N.m.r. spectra of *meso*-fluoro-octaethylporphyrins in $CDCl_3$ ($CFCl_3$, δ = 0): (*a*) schematic representation of spectra (*b*) chemical shifts and additivity parameters for substituent-induced shifts.

monobromo derivatives, in which a bathochromic shift is found (*ca.* 8 nm for chloro, 10 nm for bromo). Indeed, with respect to $\lambda_{max.}$ values, bands III, IV and the Soret band are rather similar for the parent and *all* the fluoro derivatives. This suggests to us that the bathochromic shifts observed with other *meso*-substituents are due principally to steric effects rather than to electronic ones. With respect to intensity effects, *meso*-substitution is known to be correlated empirically with a relative diminution in band III, leading to spectra of the phyllo type ($\varepsilon_{III} < \varepsilon_{II}$).[17] This shows up most clearly for the 5,10-difluoro (**4**) and 5,10,15-trifluoro (**6**) derivatives. The other spectra are not of the phyllo type, but a consideration of the $\varepsilon_{III}/\varepsilon_{II}$ ratio compared with that of the parent (**1**) (R in Table 2)[18] shows a tendency to relatively lower ε_{III} values even where the spectrum is not formally of the phyllo type. The 5,10,15,20-tetrafluoro derivative (**7**) has an atypical visible spectrum where band I, usually the weakest of the four, is second in intensity to band IV. There is clearly a very delicate interplay of factors affecting the probabilities of electronic transitions here which deserves further consideration.

Overall, it is evident that caesium fluoroxysulphate is a useful reagent for the direct *meso*-fluorination of the porphyrin nucleus. In spite of disadvantages with respect to cost and oxidative properties, it may offer a convenient approach to the direct small-scale fluorination of other heteroaromatic systems.

Experimental

General.—Spectroscopic measurements were made with the following equipment. Electronic spectra: Perkin-Elmer 552 with holmium glass calibration. I.r. spectra: PE225, CsI discs. ^1H N.m.r. spectra: Bruker AM250, $CDCl_3$, with TMS as internal reference. ^{19}F N.m.r. spectra, Bruker WM250, $CDCl_3$, with $CFCl_3$ as reference. Mass spectra: AEI MS902, direct insertion, ionising voltage 70 eV, probe temperature indicated, calibrated with heptacosafluorotributylamine. Where spectroscopic data are not given below they are collected in the tables.

M.p.s were determined on a Kofler block. T.l.c. was used throughout for investigating reaction progress and sample purity (Merck Kieselgel 60; $CHCl_3$–light petroleum b.p. 60—80 °C, 1:1). Caesium fluoroxysulphate, prepared as previously described,[19] was 98 ± 1% pure by iodometric assay; it was stored at −20 °C.

Fluorination of 2,3,7,8,12,13,17,18-*Octaethylporphyrin.*—Octaethylporphyrin (100 mg) was dissolved in dioxane (redistilled; 350 ml) with heating (90 °C, 2 h). The solution was treated at room temperature with an excess of freshly prepared aqueous caesium fluoroxysulphate (500 mg in 3 ml) with vigorous stirring. After 10 min the solution was poured into water (800 ml) and extracted with chloroform (2 × 100 ml). The chloroform extract was washed with water (3 × 200 ml), dried (Na_2SO_4), concentrated, and subjected to preparative t.l.c. (chloroform–light petroleum, 1:2) to give six bands, as follows.

R_F = 0.20, recovered octaethylporphyrin, 19.8 mg.

R_F = 0.37, 2,3,7,8,12,13,17,18-*octaethyl*-5-*fluoroporphyrin* (**3**) (29 mg, 29%), red hair-like needles from chloroform–methanol, m.p. 235—237 °C (Found: M^+, 552.364. $C_{36}H_{45}FN_4$ requires M 552.363); $\nu_{max.}$(CsI) 1 598, 1 050, 1 010, 955, and 828 cm^{-1}. The next two bands (R_F 0.60 and 0.62) were initially isolated together and required separation and purification by further t.l.c. (two stages).

R_F = 0.60, 2,3,7,8,12,13,17,18-*octaethyl*-5,10-*difluoroporphyrin* (**4**) (12 mg, 11%), red-brown hair-like needles, m.p. 280—282 °C from chloroform–methanol (Found: M^+, 570.354. $C_{36}H_{44}F_2N_4$ requires M, 570.353).

R_F = 0.62, 2,3,7,8,12,13,17,18-*octaethyl*-5,15-*difluoroporphyrin* (**5**), (10 mg, 9.5%) red-brown hair-like needles. m.p. 290—292 °C, from chloroform–methanol (Found: M^+, 570.355); $\nu_{max.}$ (CsI) 3 300, 1 495, 1 262, 1 244, 1 165, 1 135, 1085, 1 052, 1 012, 942, and 832 cm^{-1}.

R_F = 0.75, 2,3,7,8,12,13,17,18-*octaethyl*-5,10,15-*trifluoroporphyrin* (**6**), isolated after further chromatography on silica as brown hairs (5 mg, 4%), m.p. 232—234 °C (Found: M^+, 588.346. $C_{36}H_{43}F_3N_4$ requires M, 588.344).

R_F = 0.85, 2,3,7,8,12,13,17,18-*octaethyl*-5,10,15,20-*tetrafluoroporphyrin* (**7**), rechromatographed on silica, and crystallised from chloroform–methanol as brown plates (3 mg, 2%), m.p. 208—209 °C, with decomposition. The sample was not obtained pure: the n.m.r. spectrum in $CDCl_3$ revealed the presence of hydrocarbon impurities (Found: M^+. 606.333. $C_{36}H_{42}F_4N_4$ requires M, 606.335).

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