Tetrahedron Letters, Vol. 33, No. 8, pp. 1069-1072, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

meso-Perfluorination of Porphyrins with *N*-Fluoropyridinium Triflate

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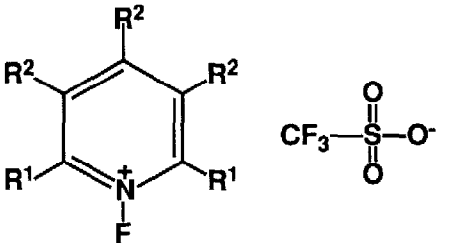
Abstract: Octaethylporphyrin was perfluorinated at its *meso*-positions with *N*-fluoropyridinium triflate in 67% of a total yield.

Fluorinated porphyrins are expected to be unique in their physico- and biochemical properties. They are potentially useful for diagnosis and phototherapy of cancer[1] and also applied for the structural study of the heam-requiring enzymes as a prosthetic group, e.g. myoglobin, heamoglobin, cytochromes.[2] Reported methods, however, for the preparation of fluorinated porphyrins are limited and inefficient: Synthesis of fluoro-containing pyrroles is tedious, and the yields of their electrophilic condensation to tetrapyrroles are generally low because of their reduced electron density on the pyrrole α-carbons.[3] Direct fluorination of porphyrins is considered to be the most promising strategy, but not fully developed.[4]

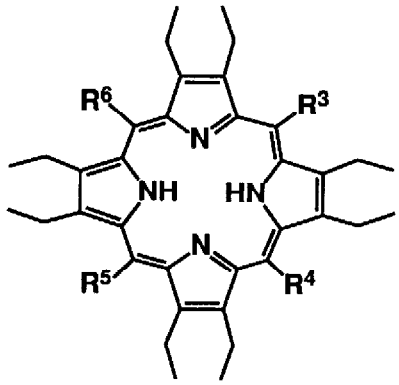
N-Fluoropyridinium salts are recently shown to have a reasonable fluorinating power, especially for aromatic ring, and their enough stability allows easy handling in a conventional organic synthesis.[5] We report herein the efficient perfluorination of porphyrins by these reagents.



***N*-Fluoropyridinium triflate**

1: $R^1=R^2=Cl$
2: $R^1=CO_2Me$, $R^2=H$

Free base of octaethylporphyrin (**3**) (OEP, 20 mg, 37 mmol) was heated at 50 °C overnight with *N*-fluoro-2,3,4,5,6-pentachloropyridinium triflate (**1**) (140 mg, 336 mmol) in hexafluorobenzene (10 ml) under an argon atmosphere. After the formation of the desired compounds was ascertained by means of TLC and FAB-mass spectroscopy, the reaction mixture was washed successively with aqueous sodium thiosulfate and water, dried, and evaporated to dryness. The resulting residue was subjected to silica-gel flash column chromatography (hexane-CH_2Cl_2 as an eluent; 10:1~1:1, v/v),[6] the more fluoro-substituted, the less polar. Their ^1H and ^{19}F NMR and FAB mass spectra[7] substantiated the assigned structures by comparing with the reported data.[4a] The isolated yields of the *meso*-fluorinated derivatives are shown in Table 1. In a reported work,[4a] the yield of tetrafluorination of OEP with ceasium fluorooxysulphate was only 2%. On the other hand, the yields 20% observed in the present method is high enough for synthetic fluorination of porphyrin compounds.[8]



3: $R^3=R^4=R^5=R^6=H$
4: $R^3=F$, $R^4=R^5=R^6=H$
5: $R^3=R^4=F$, $R^5=R^6=H$
6: $R^3=R^5=F$, $R^4=R^6=H$
7: $R^3=R^4=R^5=F$, $R^6=H$
8: $R^3=R^4=R^5=R^6=F$
9: $R^3=Cl$, $R^4=R^5=R^6=H$
10: $R^3=R^4=R^5=R^6=Cl$
11: $R^3=Br$, $R^4=R^5=R^6=H$

This reaction is very critical in the choice of solvents. Fluorinating power of *N*-fluoropyridinium salts is dependent upon the polarity of solvent used.[5] Polar and coordinative solvents decrease the reactivity of the reagents by stabilizing the N-F bond. In acetonitrile, the corresponding *meso*-chlorinated products concomitantly formed (~10% to the fluorination), confirmed by FAB mass spectroscopy. Chlorine atoms are considered to be derived from the hydrolysis of the reagent,[9] which would be enhanced by the considerable polarity of acetonitrile. When CH_2Cl_2 was used as a solvent, polar and complex by-products were dominantly observed. Initial single electron transfer[5] caused by the most powerful reagent **1** could be responsible for the chlorine atom abstraction from the solvent through a radical pathway. Chlorinated organic solvents, which are generally used in the reported reactions,[5] are not suitable for this reaction. Hence, hexafluorobenzene is a choice, since it is stable, nonpolar, and able to solubilize reasonable amounts of porphyrin derivatives.

Oxidation potentials of these fluorinated porphyrins were measured in CH_2Cl_2 at 25 °C with 0.1 M tetrabutylammonium perchlorate as a supporting electrolyte on a platinum electrode (Table 1). Well-defined reversible voltammograms were obtained in all the compounds. No significant potential shift was observed upon the fluorination.

Table 1. Yields and Physical Properties of Halogenated OEP

		UV-vis λmax. (nm, in CH_2Cl_2)					1st oxidation
compound	yield (%)	Soret	IV	III	II	I	$E_{1/2}$ (V)[a]
3		398	497	531	566	620	0.85
4	19	401	499	532	571	622	0.89
5,6	13	402	501	528	577	629	0.90
7	15	402	500	528	578	633	0.89
8	20	404	503	543	592	646	0.87
9[b]		406	507	540	578	628	
10[b]		446	550	597	634	712	
11[b]		409	510	543	580	630	

[a] Against SCE. [b] From ref. 10, in $CHCl_3$.

In contrast to the manifested bathochromic shifts of chloro- and bromo-substituted octaethylporphyrins in UV-vis absorption spectrum[4a,10] (Table 1), the relative small shifts of the fluorinated ones indicate that such perturbation will be derived mainly from the steric effects and suggest that they are ideal probes for the aforementioned biochemical studies on account of their minimized perturbations in both electronic and steric senses.

As an extension of this fluorination, 5,15-diphenyl-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (**12**), which has two reactive *meso* positions, was treated with *N*-fluoro-2,6-biscarbomethoxypyridinium triflates (**2**) in hexafluorobenzene to give a mixture (6:1) of the parent **12** and the monofluoro derivative, which was ascertained by ^1H and ^{19}F NMR and FAB mass spectroscopy.[11] More reactive **1** was not suitable for this reaction because of its concomitant chlorination of **12** and appreciable side reactions even when hexafluorobenzene was used as a solvent. On the other hand, β-free porphyrins, e.g. *meso*-tetraphenylporphyrin, were not be fluorinated with these *N*-fluoropyridinium salts.

Thus, *N*-fluoropyridinium triflates are shown to be effective for the *meso*-selective fluorination of porphyrins. Improved fluorination by using new types of *N*-fluoropyridinium salts and of other porphyrin compounds is now under way.

Acknowledgment: We are grateful to Dr. M. Okamura, Chemical Institute of Kyoto University, for the measurement of ^{19}F NMR spectra, and to Dr. S. Okazaki for his aid in the cyclic voltammetry.

References and Notes

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6 Two regio-isomers, 5,10- and 5,15-difluoro derivatives could not be separated.

7 ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$, chemical shifts being reported on the δ scale relative to TMS and $CFCl_3$, respectively.

4: δ_H -3.59 (2 H, br s, NH), 1.88 (24 H, m, CH_3), 4.08 (16 H, m, CH_2), 9.88 (3 H, s, *meso*-H); δ_F -136.2 (s, *meso*-F); *m/z* 553 ($M+H^+$).

5, 6: δ_H -3.80 (2 H, br s, NH), 1.86 (24 H, m, CH_3), 4.05 (16 H, m, CH_2), 10.07 (2 H, s, *meso*-H); δ_F -139.9 (s, *meso*-5,15-F), -134.4 (s, *meso*-5,10-F); *m/z* 570 (M^+).

7: δ_H -3.66 (2 H, br s, NH), 1.82 (24 H, m, CH_3), 4.00 (16 H, m, CH_2), 9.81 (1 H, s, *meso*-H); δ_F -138.2 (2 F, s, *meso*-5,15-F), -132.1 (2 F, s, *meso*-10-F); *m/z* 588 (M^+).

8: δ_H -3.59 (2 H, br s, NH), 1.88 (24 H, m, CH_3), 4.08 (16 H, m, CH_2); δ_F -136.3 (s, *meso*-F); *m/z* 606 (M^+).

8 Metal complexes (Ni, Cu, and Zn) of OEP were also tested for the reaction, but the free base gave the most successful results.

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11 δ_H -2.31 (2 H, br s, NH), 1.72 (12 H, m, CH_3), 2.39 (6 H, s, CH_3), 2.40 (6 H, s, CH_3), 3.92 (8 H, m, CH_2), 7.80 (6 H, m, phenyl-H), 8.05 (4 H, m, phenyl-H), 9.92 (1 H, s, *meso*-H); δ_F -136.1 (s, *meso*-F); *m/z* 649 ($M+H^+$).

(Received in Japan 14 October 1991)