Synthesis of Trifluoromethyl-Porphyrins and -Chlorins

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Reaction of zinc 5,15-bis(3,5-di-*tert*-butylphenyl)porphyrin with *S*-(trifluoromethyl)-3,7-dinitrobenzothiophene trifluoromethanesulfonate in tetrahydrofuran gave the 10-trifluoromethylated compound as the major product and 2-CF_3- and 10,20-di-CF_3-porphyrins as the minor products. The direct trifluoromethylation is effective for preparation of longer-wavelength absorbing *meso*-trifluoromethylated porphyrins and chlorins.

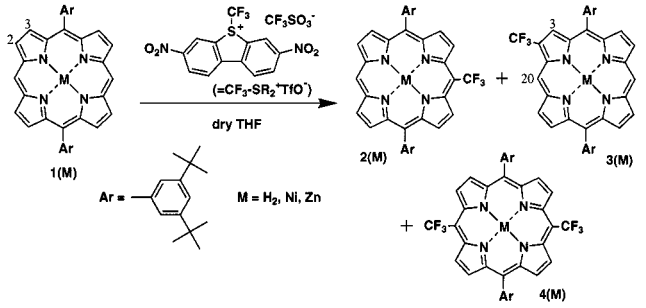
Introduction

Organofluorine compounds have attracted the attention of scientists in many fields including organic, biological, medicinal, environmental and physical chemistry.[1] Perfluoroalkylated porphyrins are especially useful for heme enzymatic models.[2–5] Porphyrins substituted at the β- and *meso*-positions with perfluoroalkyl groups have been prepared from tetramerization of perfluoroalkylated pyrroles[2] and condensation of perfluoroaldehyde hydrate with pyrrole,[3][4] respectively. Here we report on the facile synthesis of trifluoromethylporphyrins and -chlorins by direct trifluoromethylation.

Results and Discussion

5,15-Bis(3,5-di-*tert*-butylphenyl)porphyrin[6] and the metal complexes **1(M)**[7] (Scheme 1) were used for trifluoromethylation. Since the phenyl substituent at the *meso*-position has sterically bulky *tert*-butyl groups, the *meso*-aryl group was less reactive with various reagents, including electrophiles. Moreover, the porphyrin was highly soluble in most organic solvents because π-π interactions in the porphyrin moiety were suppressed by the bulky aryl substituents at the *meso*-position.[8] Many trifluoromethylation reagents are available[1,9,10] and *S*-(trifluoromethyl)-3,7-dinitrobenzothiophene trifluoromethanesulfonate $CF_3-SR_2^+OTf^-$ is one of the most effective trifluoromethylating agents for aromatic compounds.[10] The commercially available $CF_3-SR_2^+OTf^-$ (MEC-12, Daikin Industries Ltd., Japan) is easy to handle, fairly stable solid and useful for direct introduction of the CF_3-group to aromatic systems through an electrophilic substitution; it was thus examined in the present trifluoromethylation of porphyrins.

The zinc porphyrin **1(Zn)** was dissolved in dry tetrahydrofuran (THF) at ca. 6 mM and $CF_3-SR_2^+OTf^-$ (2 equiv.) was added. After stirring for 12 hours at room temperature under nitrogen, the mixture was washed with aqueous 4% $NaHCO_3$ solution and purified by flash column chromatography (FCC) over silica gel with 5% dichloromethane and hexane to give four products. The first eluted greenish-red band was a di-trifluoromethylated compound possessing a C_{2v} symmetrical structure. From mass and $^1H/^{19}F$ NMR spectroscopic analyses it was determined to be the 10,20-trifluoromethyl-porphyrin **4(Zn)** (1.4%). The second eluted purple band gave the metal-free porphyrin **1(H$_2$)** in 35% yield; the demetallation occurred during the reaction. In a normal trifluoromethylation of aromatic compounds by $CF_3-SR_2^+OTf^-$,[10] a base {e.g., 4-(dimethylamino)pyridine} is added to trap the trifluoromethanesulfonic acid produced. Addition of such a base in the present case made the reaction complex and purification of the reaction mixture was so difficult that the pure products could not be separated. The acid-labile zinc porphyrin **1(Zn)** was demetallated with CF_3SO_3H to afford the corresponding metal-free porphyrin **1(H$_2$)**. All unreacted starting material **1(Zn)** was demetallated during the reaction or workup. In contrast, zinc complexes of the trifluoromethylated porphyrins produced were exclusively isolated and the corresponding metal-free porphyrins could not be observed after the same workup. This might be due to the electronic effect of the trifluoromethyl group: the peripheral CF_3 withdraws electron density from the porphyrin π-system[4] and few protons attacked the pyrrolic nitrogen of the zinc porphyrin to induce no demetallation. The third red band contained a mixture of two mono-trifluoromethylated compounds. Careful purification by FCC allowed us to separate the two isomers: the first compound isolated was the minor β-CF_3 compound (4.4%) with the slow moving major *meso*-



Scheme 1. Direct trifluoromethylation of porphyrin

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CF_3-porphyrin **2(Zn)** (16%) following. The 1D/2D ^1H NMR spectra of the former compound revealed that it had been trifluoromethylated at the 2-position as in **3(Zn)**: one proton (3-β-H) at the β-potion was a singlet resonance at δ = 9.45 and did not couple with any of the protons at the *meso*- and other β-positions, including the 20-*meso*-proton. The regioselectivities in the electrophilic trifluoromethylation reactions were attributed to the fact that the *meso*-position is more nucleophilic than the β-position,[7] and that the 3-position of **1(Zn)** is more crowded due to the neighboring *meso*-aryl group and, therefore, less reactive than the 2-position. This explanation was supported by the following experiment: reaction of zinc 5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin[8] with $CF_3-SR_2^+OTf^-$ in THF gave, quantitatively, the corresponding metal-free porphyrin. In such a zinc complex, all the *meso*-positions are substituted by the aryl group and all the β-positions are consequently less reactive due to the neighboring aryl group.

The metal-free porphyrin **1(H_2)** reacted with $CF_3-SR_2^+OTf^-$ to give a 3:1 mixture of **2(H_2)** and **3(H_2)** (3%), and recovery of **1(H_2)** (30%). A similar trifluoromethylation of **1(Ni)** yielded a 4:1 mixture of **2(H_2)** and **3(H_2)** (1%), and **1(Ni)** was also recovered (62%). Both reactions afforded a regioisomeric mixture of mono-trifluoromethylated compounds in which the *meso*-CF_3 compound was the major isomer and the β-CF_3 compound was the minor isomer, although the yields were much lower than those with the zinc porphyrin **1(Zn)**.

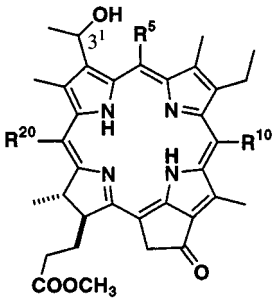
The introduction of trifluoromethyl groups at the *meso*-position of porphyrin chromophores caused the visible absorption and fluorescence emission peaks to move to longer wavelengths and their bands broadened in the order **1(Zn) < 2(Zn) < 4(Zn)** as shown in Table 1 and Figure 1. Molecular modeling (PM3/MM+)[11] indicated that introduction of the CF_3 group at the *meso*-position distorted the porphyrin π-plane: **1(Zn) < 2(Zn) < 4(Zn)** is the calculated deviation from the standard porphyrin π-plane. This is consistent with the previously reported observation[4] that *meso*-perfluoroalkylation distorts the porphyrin plane in the solid state. Therefore, the red-shift and the broadening of these peaks in the *meso*-CF_3-porphryins could be explained by this distortion.[12] Moreover, the introduction of this group increased the intensity of the longer-wavelength absorbing Q-peak (QI) compared to the shorter QII peak; a similar tendency was observed in the ratio of the emission peak heights. Trifluoromethylation at the β-position, as in **3(Zn)**, induced a slight distortion of the porphyrin π-plane from the calculation, indicating that the electronic effect would red-shift the absorption[2] and emission peaks in the β-CF_3-porphyrin rather than the steric effect.

Table 1. Visible absorption and fluorescence emission peaks (nm) of **1**−**4(Zn)** in THF (ca. 3 μM)

	λ_{abs}			Intensity ratio	λ_{em}[b]		Intensity ratio
	Soret[a]	QII	QI	in QII/QI	I	II	in II/I
1(Zn)	413 (550)	544	580	6.6	586	638	2.8
2(Zn)	417 (700)	548	580	2.8	594	647	2.3
3(Zn)	417 (620)	549	586	2.9	592	646	1.6
4(Zn)	419 (830)	556	592	0.6	609	662	0.8

[a] Values in parenthesis are half-height bandwidth (cm^{-1}). − [b] Excited at the Soret peak.

The trifluoromethylation was preliminarily applied to a natural chlorophyll derivative. Similar trifluoromethylation of methyl bacteriopheophorbide-*d* (**5a**, $R^5 = R^{10} = R^{20} =$ H in Figure 2)[13] gave a 1:3:4:2 mixture of **5b** ($R^5 = CF_3$), **5c** ($R^{10} = CF_3$), **5d** ($R^{20} = CF_3$) and **5e** ($R^{10} = R^{20} = CF_3$) as isolable products in 25% yield based on consumed **5a** (not optimized). The 20-mono-trifluoromethylated product **5d** is the $20^1,20^1,20^1$-trifluoride of methyl bacteriopheophorbide-*c* (**5f**, $R^5 = R^{10} = H$, $R^{20} = CH_3$).[13] The magnesium and zinc complexes of the 20-CF_3-chlorins should be good model compounds for bacteriochlorophyll-*c* which is a major light-harvesting pigment of photosynthetic green bacteria.[13][14] Their physical properties, including self-aggregation of the synthetic trifluoromethylated chlorins, will be reported elsewhere.



5a: R^5=R^{10}=R^{20}=H
5b: R^5=CF_3, R^{10}=R^{20}=H
5c: R^5=R^{20}=H, R^{10}=CF_3
5d: R^5=R^{10}=H, R^{20}=CF_3
5e: R^5=H, R^{10}=R^{20}=CF_3
5f: R^5=R^{10}=H, R^{20}=CH_3

Figure 2. Methyl bacteriopheophorbides

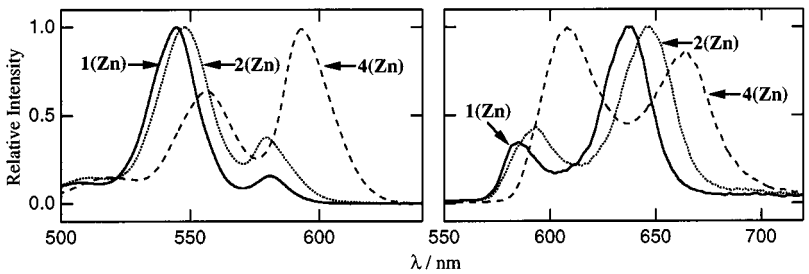


Figure 1. Relative visible absorption (left) and fluorescence emission spectra (right, excited at the Soret peak) of zinc *meso*-$(CF_3)_n$-porphyrins **1**,**2**,**4(Zn)** (n = 0,1,2) in THF (ca. 3 μM), normalized at the larger peak

Conclusion

This direct trifluoromethylation reaction is useful for the preparation of trifluoromethylated porphyrins. Synthetic CF_3-containing porphyrins absorbed and emitted longer wavelengths than the corresponding unsubstituted porphyrins. The synthetic application of other perfluoroalkylated porphyrins and chlorins, as well as the physical properties of such compounds prepared systematically, have now been elucidated.

Experimental Section

Trifluoromethylation of the Zinc Porphyrin 1(Zn): *S*-(Trifluoromethyl)-3,7-dinitrobenzothiophene trifluoromethanesulfonate $CF_3-SR_2^+OTf^-$ (20 mg; MEC-12, Daikin Industries Ltd., Japan) was added to a dry THF solution (3 mL) of zinc 5,15-bis(3,5-di-*tert*-butylphenyl)porphyrin **1(Zn)**[7] (15 mg). After stirring for 12 h in the dark under nitrogen, the reaction mixture was diluted with dichloromethane, washed with H_2O and aq. 4% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The pink residue was dissolved in hexane and purified by flash column chromatography over silica gel with 5% dichloromethane and hexane to give four products, **4(Zn)** (0.25 mg, 1.4%, first elution), **3(Zn)** (0.72 mg, 4.4%, second elution), **2(Zn)** (2.6 mg, 16%, third elution), and **1(H_2)**[6] (4.8 mg, 35%, last elution).

Zinc 5,15-bis(3,5-di-*tert*-butylphenyl)-10-trifluoromethylporphyrin 2(Zn): ^{1}H NMR (300 MHz, $CDCl_3$, chloroform as internal standard) δ = 10.34 (s, 1 H, 20-*meso*-H), 9.79 (m,[15] 2 H, 8,12-β-H), 9.42 (d, *J* = 5 Hz, 2 H, 2,18-β-H), 9.15 (d, *J* = 5 Hz, 2 H, 7,13-β-H), 9.08 (d, *J* = 5 Hz, 2 H, 3,17-β-H), 8.08 (d, *J* = 1 Hz, 4 H, 2,6-Ar-H), 7.84 (t, *J* = 1 Hz, 2 H, 4-Ar-H), 1.56 (s, 36 H, *t*Bu). − ^{19}F NMR (282 MHz, $CDCl_3$, trifluoroacetic acid as external standard) δ = −35.9.[16] − MS (FAB) found: *m*/*z* = 816; calcd. for $C_{49}H_{51}F_3N_4{}^{64}Zn$: M^+, 816.

Zinc 5,15-bis(3,5-di-*tert*-butylphenyl)-2-trifluoromethylporphyrin 3(Zn): ^{1}H NMR ($CDCl_3$) δ = 10.49 (s, 1 H, 20-*meso*-H), 10.32 (s, 1 H, 10-*meso*-H), 9.49 (d, *J* = 5 Hz, 1 H, 18-β-H), 9.45 (s, 1 H, 3-β-H), 9.45, 9.44 (d, *J* = 5 Hz, each 1 H, 8,12-β-H), 9.19 (d, *J* = 5 Hz, 3 H, 7,13,17-β-H), 8.11 (d, *J* = 1 Hz, 4 H, 2,6-Ar-H), 7.87, 7.85 (t, *J* = 1 Hz, each 1 H, 4-Ar-H), 1.58, 1.57 (s, each 18 H, *t*Bu). − ^{19}F NMR ($CDCl_3$) δ = −53.7. − MS (FAB) found: *m*/*z* = 816; calcd. for $C_{49}H_{51}F_3N_4{}^{64}Zn$: M^+, 816.

Zinc 5,15-bis(3,5-di-*tert*-butylphenyl)-10,20-di-trifluoromethylporphyrin 4(Zn): ^{1}H NMR ($CDCl_3$) δ = 9.76 (m,[15] 4 H, 2,8,12,18-β-H), 9.05 (d, *J* = 5 Hz, 4 H, 3,7,13,17-β-H), 8.02 (s, 4 H, 2,6-Ar-H), 7.85 (s, 2 H, 4-Ar-H), 1.55 (s, 36 H, *t*Bu). − ^{19}F NMR ($CDCl_3$) δ = −36.7. − MS (FAB) found: *m*/*z* = 884; calcd. for $C_{50}H_{50}N_4F_6{}^{64}Zn$: M^+, 884.

Trifluoromethylation of Chlorin 5a: A 3^1-*R*/*S*-epimeric mixture of **5a**[13] (15 mg) was reacted with MEC-12 (24 mg) in dry DMF (2 mL) for 1 h. Purification by HPLC (Cosmosil 5C18-AR, Nacalai Tesque, Japan, MeOH) gave **5a** (15%), **5b** (2%), **5d** (8%), **5c** (6%) and **5e** (4%) in this eluted order (yields were not optimized). Selected spectral data of the products (3^1-*R*/*S* = 1/1) are as follows:

5b (5-CF_3): ^{1}H NMR ($CDCl_3$) δ = 9.17 (s, 1 H, 10-H), 8.25 (s, 1 H, 20-H). − ^{19}F NMR ($CDCl_3$) δ = −34.7. − MS (TOF) *m*/*z* = 635 (MH^+).

5c (10-CF_3): ^{1}H NMR ($CDCl_3$) δ = 10.00/9.94 (s, 1 H, 5 H), 8.71/8.70 (s, 1 H, 20-H). − ^{19}F NMR ($CDCl_3$) δ = −37.1. − MS (TOF) *m*/*z* = 635 (MH^+).

5d (20-CF_3): ^{1}H NMR ($CDCl_3$) δ = 10.12/10.01 (s, 1 H, 5-H), 9.39 (s, 1 H, 10-H). − ^{19}F NMR ($CDCl_3$) δ = −41.7/−41.9. − MS (TOF) *m*/*z* = 635 (MH^+).

5e {10,20-$(CF_3)_2$}: ^{1}H NMR ($CDCl_3$) δ = 10.40/10.36 (s, 1 H, 5-H). − ^{19}F NMR ($CDCl_3$) δ = −39.1 (10-CF_3), −42.8/−43.0 (20-CF_3). − MS (TOF) *m*/*z* = 703 (MH^+).

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[12] Compared with *meso*-tetraalkylporphyrins, *meso*-tetrakis(perfluoroalkyl)porphyrins afforded blue-shifted visible peaks in solution.[4] On the assumption of small changes in the distortion of both the π-systems, electron-withdrawing perfluoroalkyl substituents at all the *meso*-positions would induce a blue-shift in the visible spectra. In the present *meso*-CF_3−Zn-porphyrins, the effect of the distortion by steric repulsion of *meso*-CF_3 with β-H might overcome the electronic effect.
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[15] Trifluoromethylation at the *meso*-position split the signal of the neighboring proton at the β-position. The reason for this has still not been determined, but the specific and long-range spin-spin coupling with ^{19}F nuclei situated very close to the β-H (*J* < 1 Hz) should occur in the *distorted* trifluoromethyl-porphyrins, **2(Zn)** and **4(Zn)**.
[16] The ^{19}F NMR spectra were measured with complete decoupling of the ^{1}H-nuclei and all the ^{19}F spectroscopic resonances are singlets.

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