

## ELECTROPHILIC SUBSTITUTION OF N-METHYLOCTAETHYLPORPHYRIN

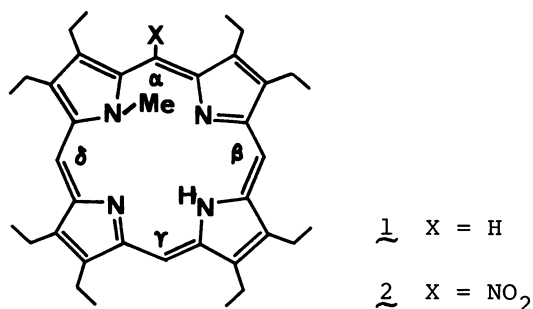
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Nitration of N-methyloctaethylporphyrin (1) takes place at the meso positions adjacent to the N-alkylated pyrrole ring (so-called  $\alpha$ - or  $\delta$ -position). Deuteration with  $\text{CF}_3\text{COOD-D}_2\text{SO}_4$  suggests preferential electrophilic substitution at  $\alpha$ - or  $\delta$ -position on the basis of  $^1\text{H-nmr}$  investigation.

The meso-reactivity of porphyrins is particularly interesting in relation to the biological degradation of the prosthetic heme in hemoproteins. Electrophilic substitution at the meso position such as nitration,<sup>1,2)</sup> formylation,<sup>2,3)</sup> methylation,<sup>3)</sup> and deuteration<sup>2,4)</sup> have been investigated for porphyrin free bases and metalloporphyrins. Methyl substituent on pyrrolic nitrogen lowers molecular symmetry relative to the parent porphyrin to provide two different reaction sites. It is expected that the electron-donating N-alkyl group and its steric constraint cause a marked effect on the electrophilic substitution. Very recently, N-alkylated porphyrins and their metal complexes have been found in the abnormal catabolism of heme enzymes and proteins; destruction of hepatic cytochrome  $\text{P}_{450}$  by a variety of olefinic<sup>5)</sup> and acetylenic<sup>6)</sup> agents and phenylhydrazine-induced hemolytic anemia.<sup>7)</sup> We wish to report briefly the reaction behavior of N-methylporphyrin towards electrophiles in acidic media.

N-Methyloctaethylporphyrin (1, N-Me-OEP) was prepared by treatment of octaethylporphyrin with an excess amount of methyl fluorosulfonate in dry chloroform at  $0^\circ\text{C}$ .<sup>2)</sup> Column chromatography on alumina gel and crystallization from chloroform-methanol gave N-Me-OEP in 40% yield. Nitration of N-Me-OEP was performed by the reaction with fuming nitric acid in glacial acetic acid (1:9) at room temperature for 2 min. The reaction mixture was treated with water and extracted with ether.



Mononitro-N-Me-OEP (2) was obtained in 60% yield after purification by means of column chromatography. Formation of a small amount of the dinitro-derivative was confirmed by TLC. The following spectral data indicate evidently that the porphyrin was mono-nitrated;<sup>8)</sup> IR, 1521 and 1369 cm<sup>-1</sup>; absorption spectrum, 410 ( $\epsilon=9.0 \times 10^4$  M<sup>-1</sup>cm<sup>-1</sup>, Soret), 509 ( $1.1 \times 10^4$ ), 539 ( $6.1 \times 10^3$ ), 590 ( $4.7 \times 10^3$ ), and 646 nm ( $3.7 \times 10^3$ ); mass, m/e 593 (M<sup>+</sup>); <sup>1</sup>H-nmr ( $\delta$  ppm from TMS in CDCl<sub>3</sub>) 10.0 (2H, meso-H), 9.9 (1H, meso-H), 4.15-3.53 (16H, -CH<sub>2</sub>CH<sub>3</sub>), 1.92-1.35 (24H, -CH<sub>2</sub>CH<sub>3</sub>), and -4.70 (3H, N-CH<sub>3</sub>).

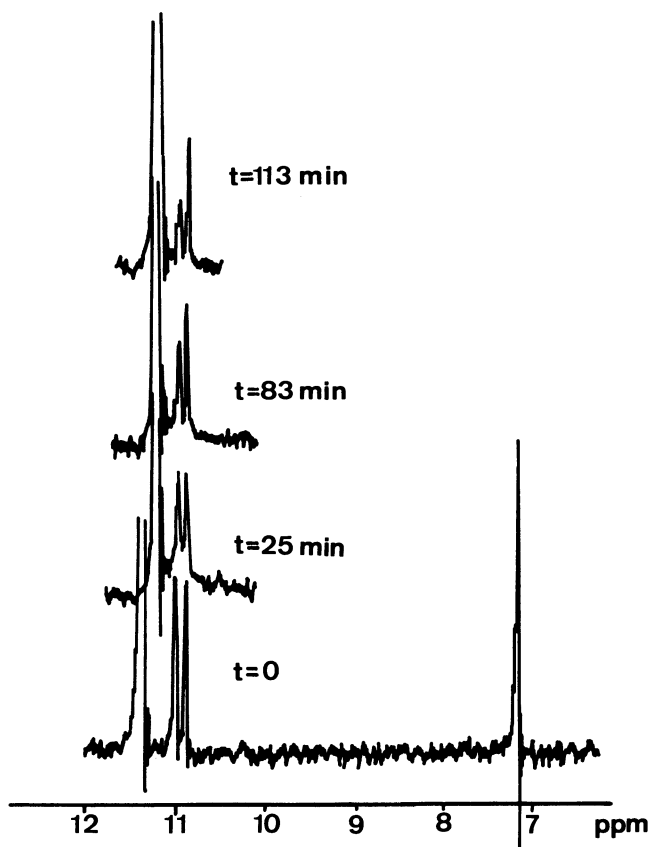


Fig. 1 Time dependent <sup>1</sup>H-nmr spectra of the meso protons of N-Me-OEP. The figure denotes the time after addition of D<sub>2</sub>SO<sub>4</sub>. The signals at 7.2 and 11.2-11.6 ppm are due to CHCl<sub>3</sub> and CF<sub>3</sub>COOH, respectively.

Anisotropic effect due to the meso-substituted nitro group gives up-field shifts of the  $-\text{CH}_2-$  protons of the adjacent ethyl groups.<sup>1b)</sup> The chemical shifts assigned to these  $-\text{CH}_2-$  protons are centered at 3.69 ppm in the case of meso-nitro-octaethylporphyrin. Small changes in chemical shifts and the complicated spectral pattern for the  $-\text{CH}_2-$  protons did not allow us to determine orientation in nitration. The chemical shifts of the meso  $-\text{CH}=\text{}$  protons of 2 shows signals at 9.9 (1H) and 10.0 ppm (2H). The former is tentatively assignable to the  $\delta$   $-\text{CH}=\text{}$  proton in comparison with those of 1.<sup>9)</sup> The  $\alpha$ -nitro group seems to give an almost similar effect on the  $\beta$ - and  $\gamma$ -positions.

For further support for  $\alpha$ -substitution, the  $^1\text{H}$ -nmr of N-Me-OEP was measured in a mixture of trifluoroacetic acid- $\text{d}_1$  and sulfuric acid- $\text{d}_2$  at  $35^\circ\text{C}$  (the temperature of the nmr cavity). Fig.1 shows the nmr spectral change of the meso protons with time. Monitoring of the nmr spectrum indicates decrease in the signal intensity at the lower magnetic field. The signals due to the  $\alpha$ - and  $\delta$ -meso protons in  $\text{CDCl}_3$  appear at higher field than those of the  $\beta$ - and  $\gamma$ -meso protons.<sup>9)</sup> In fact, after neutralization with sodium bicarbonate, the relative signal intensity of these  $-\text{CH}=\text{}$  protons in  $\text{CDCl}_3$  was reversed (Fig.2), while the other signals showed no change from those of the starting porphyrin both in the chemical shifts and in the relative intensities. Thus, it was evidenced that the  $\alpha$ - or  $\delta$ -hydrogen was substituted by deuterium.

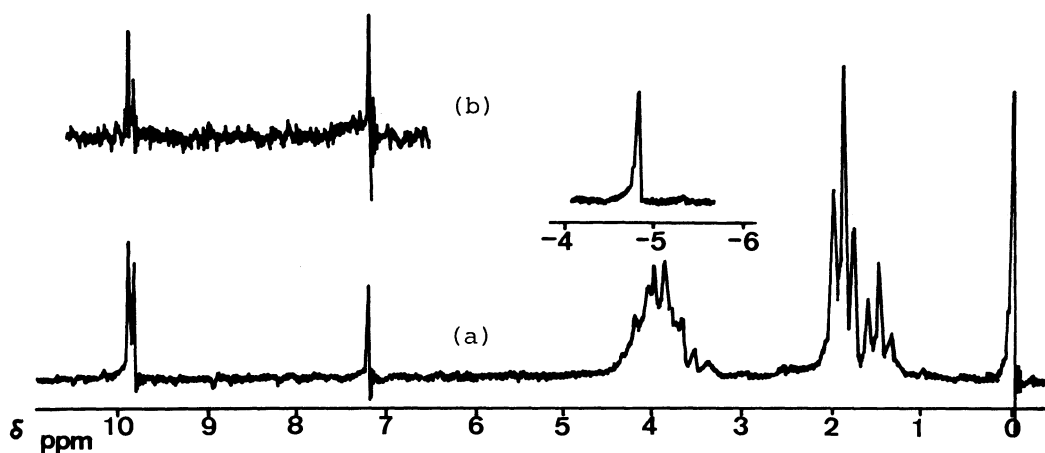


Fig. 2  $^1\text{H}$ -nmr spectra of N-Me-OEP (a) and deuteration product of N-Me-OEP (b) in  $\text{CDCl}_3$ . The higher field portion of the spectrum of (b) is omitted.

The absorption spectrum of N-Me-OEP in the reaction mixture of nitration agrees with that in the reaction mixture in deuteration. These spectra under

acidic conditions imply the formation of diacid of N-Me-OEP. The methyl group on the nitrogen atom is expected to increase the electron density on the  $\alpha$ - and  $\delta$ -meso carbons. The electron-donating character of the N-methyl group causes the preferential electrophilic attack to the  $\alpha$ - or  $\delta$ -position even under acidic condition. The reactions of N-alkylporphyrins and their metal complexes are currently investigated.

#### Acknowledgement

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#### References

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