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Design of Multidentate Pyrrolic Ligands by *N*-Modification: Synthesis of *N*-Monomethyl, Monoethyl, Dimethyl, Trimethyl, and Tetramethylporphyrinogens

Yoshio Furusho, Hiroaki Kawasaki, Saburo Nakanishi, Takuzo Aida[†] and Toshikazu Takata*

Department of Applied Chemistry, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 599-8531, Japan
† Department of Chemistry and Biotechnology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

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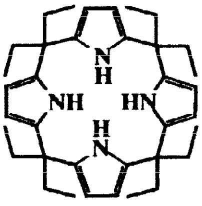
Abstract: Five possible *N*-methylated and *N*-monoethylated *meso*-octaethylporphyrinogens were prepared by *N*-alkylation of lithiated *meso*-octaethylporphyrinogens with alkyl iodides in the presence of crown ether. The crystal structure of **3b** was established by X-ray crystal structure analysis.

Recently *meso*-octaalkylporphyrinogen has attracted much attention as a tetraanionic N_4 ligand, which is suitable for complexation of transition metal ions in high oxidation state. It coordinates to a metal ion in σ and/or π forms depending on the nature of the metal ion.[1] In order to serve as useful ligands for metal ions in low oxidation state, it is essential to modify nitrogen atoms of porphyrinogen. However, Sessler has reported that the reaction of *N, N', N", N'"*-tetralithioporphyrinogen with an alkyl halide results in selective β-alkylation of the pyrrole ring without *N*-alkylation.[2] Herein we report the synthesis of *N*-alkylated *meso*-octaethylporphyrinogens (**2**-**6**).



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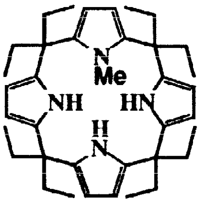

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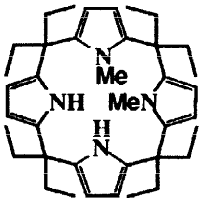
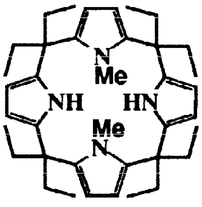
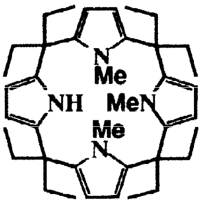


3a



3b



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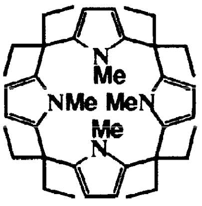

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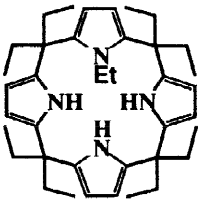

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meso-Octaethylporphyrinogen (**1**) was prepared in 52 % yield by the acid-catalyzed condensation of pyrrole and diethylketone in ethanol.[1] In *N*-methylation attempted with *n*-butyllithium (4 eq.) and methyl iodide (MeI), no *N*-methylated porphyrinogen was obtained, but formation of a complicated mixture of

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various β-methylated porphyrinogens was confirmed by the intensities of β- and *N*-H signals as well as the absence of the *N*-CH_3 signals in the ^{1}H NMR spectrum. Similar results were obtained with other metalating agents such as NaH, KH and metal K. However, a mixture of *N*-methylated porphyrinogens was obtained by using NaH and MeI in the presence of 18-crown-6 ether in THF, without formation of any β-methylated one as similarly confirmed by ^{1}H NMR spectrum.[3] The mixture was chromatographed over silica gel ($CHCl_3$: *n*-hexane = 1 : 3, then, toluene : *n*-hexane = 1 : 3) to give *N*-mono- (**2**), neighboring-*N, N*'-di-(**3a**), opposite-*N, N*'-di- (**3b**), *N, N', N*"-tri- (**4**), and *N, N', N", N'"*-tetra- (**5**) methylated porphyrinogens (Figure 1), which were characterized by the ^{1}H NMR and FAB-MS spectra.[4,5] The distribution of the *N*-alkylated porphyrinogens was varied with the amount of MeI used as shown in Table 1. When 1eq. of MeI was used, the main product was **2**. On the other hand, use of 2 eq. of MeI resulted in the predominant formation of **3b**, **4**, and **5**, where **3b** was isolated predominantly. The low isolated yields of **4** and **5** were mainly due to their lower solubility to the eluent.

Table 1. Distributions of the products in the *N*-methylation of *meso*-octaethylporphyrinogen[a]

Reactant molar ratio MeI : **1**	Product distribution / %[b]					Recovery / %
	2	**3a**	**3b**	**4**	**5**	**1**
1 : 1	29	0.8	5.0	<1	<1	66
2 : 1	0.6 (<1)	0.8 (<1)	37 (30)	23 (13)	22 (5)	17

[a] The reaction was conducted as described in the endnote.[4] [b] Product distributions were estimated on the basis of the ^{1}H NMR (500 MHz) spectra of the reaction mixtures. Isolated yields based on **1** are given in parentheses.

Single crystals of **3b** were grown in toluene solution at room temperature, and subjected to X-ray crystal structure analysis.[6] Figure 1 shows the ORTEP drawing of **3b**, in which the four pyrrole rings are pointing up and down alternately, like a saddle structure, in a conformation tilted by *ca.* 60 ° to the average plane defined by four *meso*-carbon atoms. The two *N*-methyl groups are oriented toward the same direction. The distance between the two carbon atoms of *N*-methyl groups is 3.930 Å. Hydrogen atoms of the two *N*-methyl groups are contacted to each other in the space-filling model closely enough to shield one side of the two possible ligation sites (*N*-H groups) produced by the non-methylated pyrrole nitrogens. On the other side, the cavity with *ca.* 3 Å diameter is provided, where the distance between the two non-methylated nitrogens was 4.971 Å.

N-Ethylation of **1** with ethyl iodide was carried out under similar conditions described above. Only *N*-monoethylated porphyrinogen (**6**) was isolable in 16 % yield, which was characterized by the ^{1}H NMR and FAB-MS spectra.[7] Attempts to alkylate the nitrogen atoms with other alkyl halides, such as benzyl chloride, dichloroethane, and *m*-xylylene dibromide caused the formation of complicated mixtures, which apparently involved β-alkylated products from the ^{1}H NMR spectra.

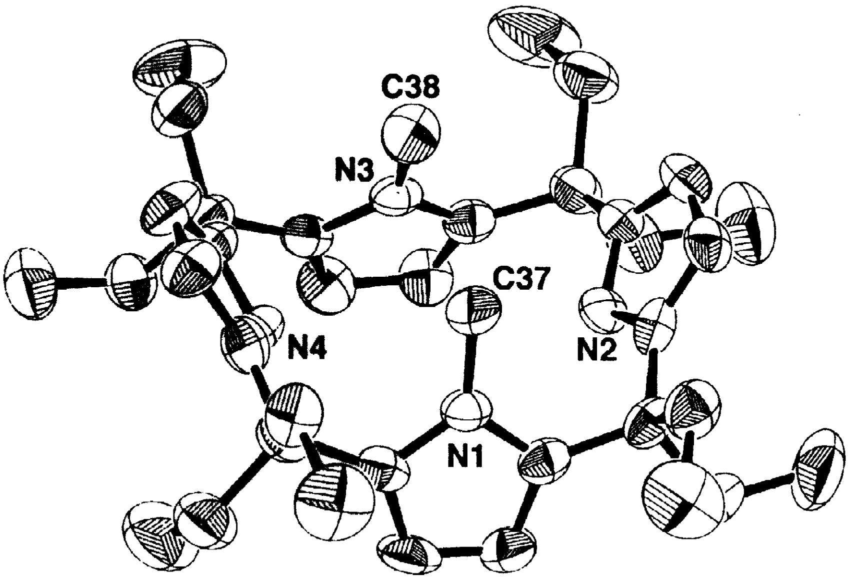

Figure 1. The crystal structure of dimethyl derivative (**3b**): N1-C37 1.468 Å, N3-C38 1.452 Å, C37···C38 3.930 Å, N2-N4 4.971 Å. Thermal ellipsoids are scaled to the 50 % probability level. Hydrogen atoms are omitted for clarity.

Thus, the synthesis of *N*-polyalkylated *meso*-octaethylporphyrinogens were achieved in this work. It was found that crown ether added to the reaction systems is indispensable. Besides their use as ligands, they are promising building blocks for sophisticated supramolecules.[8, 9] Further study on complexation of these porphyrinogens with various metal ions is ongoing.

Acknowledgment

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References and Notes

1. Floriani, C. *J. Chem. Soc., Chem. Commun.*, **1996**, 1257-1263, and references cited therein.
2. Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *J. Chem. Soc., Chem. Commun.*, **1997**, 665-666.
3. The x-ray crystal structure analysis of *N*, *N'*, *N''*, *N'''*-tetralithio-*meso*-octaethylporphyrinogen revealed the formation of a very tight ion-pair complex between lithium and the tetraanion, in which four lithium cations bind nitrogen and α-carbon atoms strongly.[1] It suggests that β-alkylation is likely to occur. We speculate that separation of the tight ion-pair in the presence of crown ether resulted in *N*-alkylation.
4. A THF (50 mL) suspension of *meso*-ocataethylporphyrinogen (**1**) (0.54 g, 1.0 mmol) and sodium hydride (60 % oil dispersion, 0.16 g, 4.0 mmol) was stirred under Ar atmosphere at 50 °C for 1 h, and cooled to room temperature. 18-Crown-6 ether (1.1 g, 4.0 mmol) was added to the mixture, and the mixture was stirred for 30 min. To this mixture was added methyl iodide (1.0

mmol or 2.0 mmol), and the resulting mixture was stirred for 3.5 h at room temperature. The mixture was poured into sat. NH_4Claq. and extracted with ether. The extract was washed with sat. $NaHCO_3$aq., H_2O, and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed over silica gel (eluent; toluene : *n*-hexane = 1 : 3, then, toluene : *n*-hexane = 1 : 3) to separate *N*-methylated porphyrinogens: *N*-Monomethyl derivative (**2**): white crystals, m.p. 215-219 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.16 (1H, br s, N*H*), 6.88 (2H, br s, N*H*), 5.95 (2H, s, H_β), 5.94 (2H, d, J = 2 Hz, H_β), 5.86 (2H, t, J = 4 Hz, H_β), 5.85 (2H, t, J = 4 Hz, H_β), 2.55 (3H, s, CH_3N), 2.1-1.6 (16H, m, CH_2CH_3), 0.8-0.4 (24H, m, CH_2CH_3); FAB-MS (mNBA matrix): m/z 554.4 [M^+]. Neighboring-*N*, *N*'-dimethyl derivative (**3a**): white crystals, m.p. 232-235 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.08 (2H, br s, N*H*), 6.00-5.85 (8H, m, H_β), 2.46 (6H, s, CH_3N), 2.1-1.6 (16H, m, CH_2CH_3), 0.7-0.5 (24H, m, CH_2CH_3); FAB-MS (mNBA matrix): m/z 568.5 [M^+]. Opposite-*N*, *N*'-dimethyl derivative (**3b**): white crystals, m.p. 288-293 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 6.85 (2H, br s, N*H*), 5.98 (4H, s, H_β), 5.84 (4H, d, J = 2 Hz, H_β), 2.82 (6H, s, CH_3N), 2.0-1.6 (16H, m, CH_2CH_3), 0.7-0.4 (24H, m, CH_2CH_3); FAB-MS (mNBA matrix): m/z 568.5 [M^+]. *N*, *N*', *N*''-Trimethyl derivative (**4**): white crystals, m.p. >300 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.05 (1H, br s, N*H*), 5.98 (2H, d, J = 4 Hz, H_β), 5.94 (2H, d, J = 4 Hz, H_β), 5.90 (2H, s, H_β), 5.89 (2H, d, J = 4 Hz, H_β), 2.82 (6H, s, CH_3N), 2.36 (3H, s, CH_3N), 2.1-1.6 (16H, m, CH_2CH_3), 0.7-0.4 (24H, m, CH_2CH_3); FAB-MS (mNBA matrix): m/z 582.4 [M^+]. *N*, *N*', *N*'', *N*'''-Tetramethyl derivative (**5**): white crystals, m.p. > 300 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 5.94 (8H, s, H_β), 2.80 (12H, s, CH_3N), 2.1-1.8 (16H, m, CH_2CH_3), 0.57 (24H, t, J = 8 Hz, CH_2CH_3); FAB-MS (mNBA matrix): m/z 596.3 [M^+]; The simple pattern in the ^1H NMR spectrum indicates that **5** exists in a single conformer, either 1, 3-alternate or cone.

5. Cyclic oligomers such as **5** were not isolated by acid-catalyzed condensation of *N*-methylpyrrole and diethylketone. Similar result obtained with *N*-phenylpyrrole and acetone was reported by Sessler *et al.*; Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140 - 5141 (Supporting Information).

6. Crystal data for **3b**: $C_{38}H_{56}N_4$, M = 568.89, *triclinic*, a = 12.979 (4), b = 13.296 (4), c = 11.959 (4), α = 95.20 (3), β = 63.45 (2), γ = 63.45 (2) V = 1714 (1) $Å^3$, space group $P\bar{1}$ (#2), Z = 2, D_{calcd} = 1.102 g cm^{-3}, μ (MoKα) = 0.64 cm^{-1}. A total of 6673 reflections (in the range 22.04 < 2θ < 24.06°) were collected at room temperature on a Rigaku AFC5R diffractometer with graphite monochromated Mo-Kα radiation and a rotating anode generator. The structure was solved by direct methods (SIR 92) and refined with 1841 reflections ($I > 3.00\ \sigma(I)$); GOF = 1.71, R = 0.045, Rw = 0.029. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ (UK) on quoting the full journal citation.

7. Monoethyl derivative (**6**): white crystals, 882 mg (1.6 mmol, 16 %), m.p. 170-173 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.15 (1H, br s, N*H*), 6.85 (2H, br s, N*H*), 5.98 (2H, s, H_β), 5.94 (2H, d, J = 3 Hz, H_β), 5.88 (2H, t, J = 3 Hz, H_β), 5.85 (2H, t, J = 3 Hz, H_β), 2.93 (2H, br s, NCH_2CH_3), 2.10-1.55 (16H, m, CH_2CH_3), 0.75-0.50 (27H, m, CH_2CH_3); FAB-MS (mNBA matrix): m/z 598.5 [M^+].

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