A Facile Synthesis of the Lowest Homologues of *meso*-Tetraalkylporphyrin

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Utilization of a less stoichiometric amount of aldehyde in portions and addition of water to the reaction mixture depressed the tar formation, affording much easier isolation of *meso*-tetraalkylporphyrins. The title porphyrins bearing methyl, ethyl, or *n*-propyl substituents were synthesized in isolated yields of 10, 10, and 8%, respectively.

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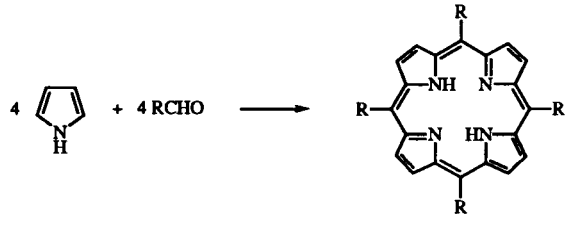
Synthetic porphyrins, in addition to their own interests, are useful in elucidating the structure and function of hemoproteins. The lowest homologues of *meso*-tetraalkylporphyrin with alkyl side-chains of methyl (**1**), ethyl (**2**), or *n*-propyl (**3**) are still less accessible while the syntheses of higher homologues are improved [1]. Compound **1** was first prepared by Rosemund [2] and Eisner [3]. Von Maltzan [4] also synthesized Ni•**1** in a 4.3% yield. Tabushi *et al.* [5] reported an 8.7% yield for **1** after a six-day reaction, although the yield was not always reproduced when checked by others [6]. Ulman *et al.* [6] and Suh *et al.* [7] devised a Ni-assisted template method to afford a 1.6% yield of a Ni•**1**/chlorin mixture. Rocha Gonsalves and Pereira [8] reported a two-step procedure using the preparation of precursory porphyrinogens and the subsequent photo or chemical oxidation. The reported yields of **1-3**, about 8-10% based on the porphyrinogens [8], are indeed higher than those with other procedures [4-6]. However, the necessary porphyrinogens are prepared in approximately 30% yield after time-consuming reaction and column chromatography under oxygen-free conditions [7,9].

Special attention has been paid to the least bulky **1-3** because the iron complexes, owing to their moderately small molecular sizes, can be used as the prosthetic group of myoglobin [10]. Suitable selection for the alkyl side-chains of *meso*-tetraalkylporphyrin allows us to control the magnitude of the heme-globin interactions with ease [11]. The least bulky Fe•**1** dynamically rotates about the iron-histidine bond [10]. In view of the renewed interest on Fe•**1-3** as the novel prosthetic groups of hemoprotein, the direct and simple synthesis will be profitable. We will report here a facile one-pot synthesis of **1-3** from pyrrole and aldehyde (Scheme 1) with reasonable yields and much easier work-up.

Scheme 1



1, R = -CH_3, **2**, R = -CH_2CH_3, **3**, R = -$CH_2CH_2CH_3$

One of the frequently overlooked problems in the conventional *meso*-tetraalkylporphyrin synthesis is the intractable tar formation in large amounts. The inherently low solubility of **1-3** in common organic solvents and the intensive tar formation often necessitate repeated column chromatography with large amounts of the gel and solvents [6]. The mechanistic consideration of the reaction [7,8] suggests several critical modifications to be made. The initial step of the Rosemund reaction is a simple carbinol formation. The monomeric carbinol consequently polymerizes into porphyrin and higher oligomers in rather random manner. Low yield for the *meso*-tetraalkylporphyrins appears to derive not only from the competitive random polymerization of the carbinol but also from self-polymerization of the aldehyde because aldehydes in acid medium are invariably activated toward self-condensation. With addition of water to the reaction mixture and application of the aldehyde in less than a stoichiometric amount, the tar formation could be suppressed. The strategy was applied in our synthesis, and these alterations successfully decreased tar and increased porphyrin. We found that the side-products in the present synthesis are methanol-soluble probably because of lower oligomerization of the reactants whereas the tar formed in the convantional syntheses is hardly soluble in methanol. Owing to the insolubility of the lowest homologues of *meso*-tetraalkylporphyrin and the solubility of the by-products in methanol, **1-3** were readily isolated from the crude reaction mixture after washing with methanol. We obtained pure **1-3** after a single chromatography on a short silica-gel column followed by recrystallization. The yields, 8-10% based on the aldehyde, are comparable with or better than those found in the previous works [6,8]. Washing with methanol was not effective for the *meso*-tetraalkylporphyrins with side-chains longer than *n*-pentyl because they are partially or significantly soluble in methanol, and tedious column chromatography must be repeated for purification. Tanaka *et al.* [12,13], paying attention to the peripheral substitution difference between *meso*-tetraalkyl-

porphyrin iron and protoheme, have characterized the Fe•**1**-**3** in myoglobin by X-ray crystallography.

EXPERIMENTAL

The proton NMR spectra were recorded in deuterated chloroform at 300 MHz on a Varian XL-300 spectrometer with tetramethylsilane as an internal reference. Visible spectra were obtained with Shimadzu MPS-2000 spectrophotometer. Mass spectral and elemental analyses were carried out by the Departmant of Analytical Chamistry, Kyoto Pharmaceutical University. Pyrrole, aldehydes, pyridine and the organic solvents were purchased from Aldrich. Silica gel (Wakogel C-200, 100-200 mesh) was available from Wako Pure Chemical Industries, Osaka.

meso-Tetramethylporphyrin (**1**).

Pyrrole (4.2 ml, 0.0605 mole) and acetaldehyde (1.3 ml, 0.0232 mole) were added to 300 ml of propionic acid containing 12 ml of water and 1 ml of pyridine at 85-88° in an Erlenmeyer flask equipped with magnetic bar and thermometer. A supplementary amount of acetaldehyde (0.5 ml, 0.0089 mole) was added 30 minutes later, and the solution was stirred for another 2 hours at 85-88°. Presence of water, controlled temperature, and utilization of a less than stoichiometric amount of acetaldehyde in portions were essential to suppress tar formation. Chloroform (300 ml) was added to the cooled solution, and the mixture was washed with water (300 ml x 2), 50 m*M* sodium hydroxide (300 ml x 2), and water (300 ml) to remove propionic acid. The chloroform solution was evaporated to dryness. The residue was repeatedly washed with methanol (5 ml x about 10) until colorless on a centrifuge (5000 rpm, 3 minutes) to leave fine crystals at the bottom of the glass tube. The solid was chromatographed once on a silica gel column with chloroform. Dark blue crystals of **1** (293 mg, 10%) with a metallic luster were obtained (chroloform/methanol); ^{1}H nmr (deuteriochloroform): δ 9.48 (s, 8H, β-H), 4.59 (s, 12H, CH_3), and -2.39 (br s, 2H, NH); ms: m/z 366 (M^+); uv (chloroform): λ max 416 nm (ε 410,000), 484 (3,400), 519 (15,000), 553 (9,800), 602 (4,000), and 661 (7,300).

Anal Calcd. for $C_{24}H_{22}N_4$: C, 78.66; H, 6.05; N, 15.29. Found: C, 78.48; H, 5.91; N, 15.60.

meso-Tetraethylporphyrin (**2**).

Pyrrole (4.2 ml, 0.0605 mole) and propionaldehyde (2.1 ml, 0.0291 mole) were added to 300 ml of propionic acid containing 12 ml of water and 1 ml of pyridine at 90-93°. A supplementary amount of propionaldehyde (1.0 ml, 0.0139 mole) was added 30 minutes later, and the solution was stirred for 2 more hours at 90-93°. The same work-up as described for **1** afforded crystalline **2** (432 mg, 10%); ^{1}H nmr (deuteriochloroform): δ 9.51 (s, 8H, β-H), 5.00 (q, J = 9 Hz, 8H, CH_2), 2.14 (t, J = 7 Hz, 12H, CH_3), and -2.65 (brs, 2H, NH); ms: m/z 422 (M^+); uv (chloroform): indistiunguishable from that of **1**.

Anal. Calcd. for $C_{28}H_{30}N_4$: C, 79.59; H, 7.16; N, 13.26. Found: C, 79.32; H, 7.00; N, 13.50.

meso-Tetra(*n*-propyl)porphyrin (**3**).

Pyrrole (4.2 ml, 0.0605 mole) and butyraldehyde (3.0 ml, 0.0333 mole) were added to 300 ml of propionic acid containing 12 ml of water and 1 ml of pyridine at 100-105°. A supplementary amount of butyraldehyde (1.5 ml, 0.0166 mole) was added 30 minutes later, and the solution was stirred for another 2 hours at 100-105°. The same work-up as described for **1** afforded crystalline **3** (503 mg, 8%); ^{1}H nmr (deuteriochloroform): δ 9.48 (s, 8H, β-H), 4.93 (t, J = 7 Hz, 8H, -$CH_2$$CH_2CH_3$), 2.54 (m, 8H, -$CH_2CH_2$$CH_3$), 1.34 (t, J = 7Hz, 12H, -CH_3) and -2.66 (br s, 2H, NH); ms: m/z 478 (M^+); uv (chloroform): indistiunguishable from that of **1**.

Anal. Calcd. for $C_{32}H_{38}N_4$: C, 80.29; H, 8.00; N, 11.70. Found: C, 79.99; H, 7.91; N, 12.00.

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