A Synthesis of Unsymmetric Porphyrin Dimers

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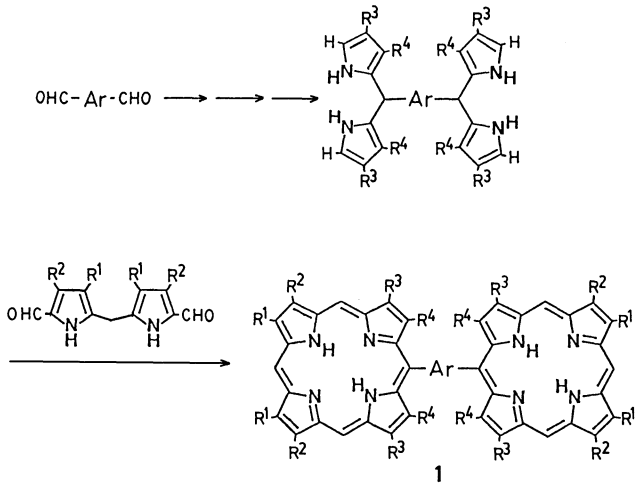
A new synthetic method of porphyrins via bis(hydroxymethyl)dipyrromethanes is described. This new method can be utilized for preparation of several unsymmetric porphyrin dimers.

In recent years, much interest has been focussed on development of conformationally restricted porphyrin dimers as models for photosynthetic reaction center[1] and metalloenzymes such as cytochrome oxidase.[2] Among these, octaalkylporphyrin dimer (**1**) bridged by an aromatic spacer has been shown to be a useful model. The relative geometry of the two porphyrin rings in these compounds is rather restricted because of the steric hindrance between the aromatic spacer and the flanking peripheral alkyl groups.

Symmetric porphyrin dimer **1** is generally prepared by the synthetic routes shown in Scheme 1.[3] However, synthesis of unsymmetric dimers, such as **10a** and **10b**, is not so straightforward as **1**.

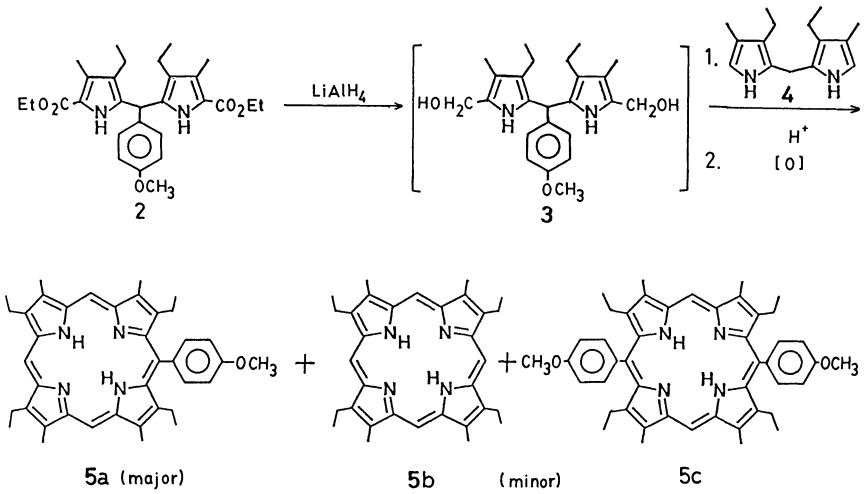


Scheme 1.

We wish to report here a new synthetic method of porphyrins by acid-catalyzed condensation of 5,5′-bis(hydroxymethyl)dipyrromethane and 5,5′-unsubstituted dipyrromethane. Since the conditions are mild enough, this method can be applied for a stepwise synthesis of non-symmetric dimers. It should be noted that this method is an application of the synthesis of octaalkyl- and octaarylporphyrins reported by Ono and Maruyama, in which $LiAlH_4$ treatment of 5-unsubstituted 2-ethoxycarbonylpyrrole followed by acid catalyzed self-condensation is utilized.[4]

Results and Discussion

Dipyrromethane diester **2** was treated with lithium aluminum hydride to give the corresponding diol **3**, which was immediately allowed to react with the 5,5′-unsubstituted dipyrromethane **4** in the presence of acid catalyst. After standing for 1—2 days at room temperature, the reaction mixture was worked up and separated by column chromatography. The desired product **5a** was obtained in a moderate yield. Generally two other porphyrins, **5b** and **5c**, were obtained together with **5a**. These by-products were formed through self-coupling of each dipyrromethane unit. Several cyclization conditions were employed, and the results are summarized in Table 1.



Scheme 2.

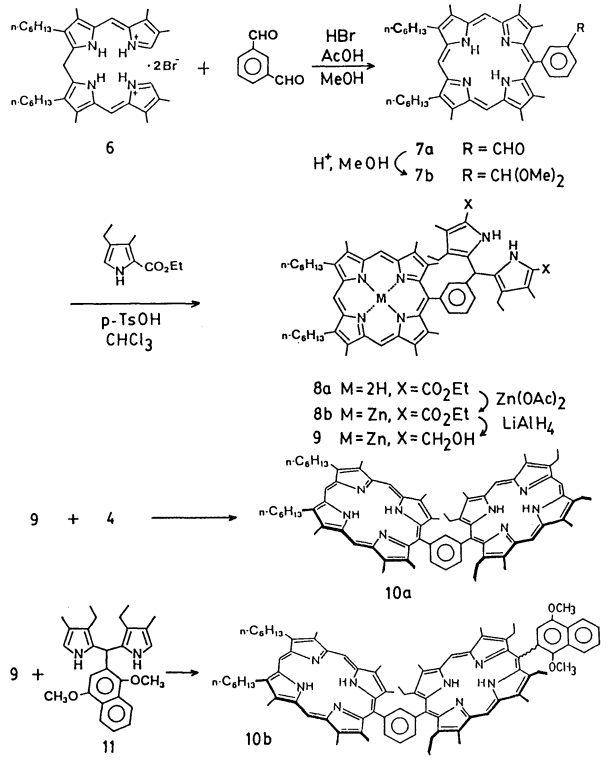
In several cases (Runs 1, 2, and 4), "scrambling" of the peripheral alkyl substituents took place during cyclization. This is probably due to acid-catalyzed redistribution reactions of the porphyrinogens (the saturated precursor of porphyrins).[5] When more weakly acidic conditions were employed, no scrambling was observed (Runs 3, 5, and 6). Thus, it was concluded that acetic acid in methanol or silica gel in dichloromethane was the reagent of choice in the reaction of **3** and **4**.

The present method of porphyrin formation was applied for synthesis of unsymmetric porphyrin dimers. Condensation of 1,19-dideoxybiladiene-ac dihydrobromide **6** with isophthalaldehyde gave a porphyrin bearing a formyl group (**7**),[6] which was allowed to react with ethyl 4-ethyl-3-methyl-2-pyrrolecarboxylate to give **8a**. The porphyrin-dipyrromethane **8a** was converted to the zinc complex **8b**, and treated with $LiAlH_4$ to give the corresponding diol **9**, which was allowed to react with **4** in methanol/dichloromethane (pure methanol did not dissolve the porphyrin) in the presence of silica gel. The dimer **10a** was obtained in a moderate yield (9%).

Table 1. Coupling Reaction of **3** and **4**

Run	Catalyst	Solvent	Yield (%) of **5a**[a]
1	$HClO_4$	MeOH	6[b]
2	pTsOH	MeOH	18[b]
3	AcOH	MeOH	15
4	AcOH	CH_2Cl_2	14[c]
5	C-200[d]	CH_2Cl_2	9
6	AcOH	$MeOH/CH_2Cl_2$(1/1)	13

a) Including scrambled products. b) Scrambling. c) Slight scrambling. d) Silica gel (Wako Pure Chemicals).



Scheme 3.

Coupling of **9** with dipyrromethane **11** similarly gave an unsymmetric porphyrin dimer **10b** in 0.5% yield. The dimer **10b** can be transformed into a quinone-linked porphyrin dimer, which is a very important model compound in the studies of plant- and bacterial photosynthesis. We are currently preparing other quinone-linked porphyrin dimers with restricted conformation by a similar method as described here, and the photophysical properties of these photosynthetic model systems will be presented in the near future.

Experimental

The instruments were as previously reported.[7] Mass spectra were recorded on a JEOL DX-300 spectrometer using the FAB method; the FAB matrix was $CHCl_3$+trifluoroacetic acid/*m*-nitrobenzyl alcohol (NBA)/glycerol unless otherwise stated. High-resolution mass spectrum was recorded on a JEOL JMS-SX102 spectrometer.

5-(4-Methoxyphenyl)-3,7,13,17-tetraethyl-2,8,12,18-tetramethylporphine (5a). Various conditions were employed (see Table 1), and one typical experiment is described here.

To a suspension of $LiAlH_4$ (40 mg) in 2 ml of anhydrous tetrahydrofuran, a solution of dipyrromethane **2**[8] (100 mg, 0.21 mmol) in tetrahydrofuran (10 ml) was dropwise added (under nitrogen, at room temperature). After 40 minutes, water was carefully added, and the mixture was extracted with dichloromethane (quickly!). The extract was washed with water and dried over sodium sulfate.

The resultant solution (**3**) was diluted with 70 ml of methanol, and bis(3-ethyl-4-methyl-2-pyrrolyl)methane[10] (**4**, 48 mg=0.21 mmol) was added. Acetic acid (15 drops) was added, and the mixture was stirred in the dark under nitrogen for 38 hours (room temperature). Chloranil (50mg) was added, and stirring was continued for 24 hours.

Solvent was evaporated from the reaction mixture, 10% aqueous NaOH was added and the mixture was extracted with dichloromethane. The extract was washed with aqueous NaOH and water, dried (Na_2SO_4), and treated with saturated solution of zinc acetate in methanol (1 ml) for 2 hours at refluxing temperature. The reaction mixture was washed with water, dried, evaporated, and separated by flash column chromatography (CH_2Cl_2). The fractions containing zinc porphyrin were collected, shaken twice with 4M HCl (1 M=1 mol dm^{-3}), neutralized, dried, and evaporated. Separation by flash column chromatography (CH_2Cl_2) gave three porphyrinic fractions. The first fraction was porphyrin **5b**, the second was the desired product **5a**, and the third was bis(*p*-methoxyphenyl)porphyrin **5c**. Yield of **5a**: 19 mg (0.032 mmol, 15%). Mp 290—295 °C. ^{1}H NMR ($CDCl_3$): δ=10.17 (s, 2H, 10,20-H), 9.92 (s, 1H, 15-H), 8.08+7.20 (d+d, 2H+2H, aromatic-H), 4.11 (s, OMe), 4.06 (q, 13,17-Et), 3.64+3.57 (s+s, 6H+6H, Me), 2.82 (q, 4H, 3,7-Et), 1.18+1.17(t+t, 6H+6H, Et), −3.0+−3.2 (br, 1H+1H, NH). UV-vis (CH_2Cl_2): 404, 503, 537, 574 and 624 nm. MS (FAB): *m/z* 585 ($M+H^+$).

5-[3-(Dimethoxymethyl)phenyl]-13,17-dihexyl-2,3,7,8,12,18-hexamethylporphine (7b). HBr-catalyzed condensa-

tion[6] of the 1,19-dideoxybiladiene-ac dihydrobromide **6**[11] (286 mg, 0.40 mmol) and isophthalaldehyde (536 mg, 4.0 mmol) gave 5-(3-formylphenyl)-13,17-dihexyl-2,3,7,8,12,18-hexamethylporphine **7a** in 68% yield (185 mg, 0.27 mmol). **7a:** mp 298—301 °C, IR (KBr): 1700 cm^{-1} (C=O). The formylporphyrin **7a** (73mg, 0.11 mmol) was dissolved in chloroform (40 ml). Methanol (10 ml) and *p*-toluenesulfonic acid monohydrate (60 mg) were added, and the resultant mixture was heated under reflux for 5.5 hours. The reaction mixture was cooled, washed with aqueous $NaHCO_3$ and brine, dried, and evaporated. The dimethyl acetal **7b** was obtained in quantitative yield. Mp 271—283 °C. ^1H NMR ($CDCl_3$): δ=10.15 (s, 2H, 10,20-H), 9.95 (s, 1H, 15-H), 5.68 (s, 1H, C<u>H</u>$(OMe)_2$), 4.04 (t, 4H, hex-1), 3.63+3.52+3.49 (s+s+s, 6H+6H+6H, Me and OMe), 2.45 (s, 6H, 3,7-Me), 2.30 (quint, 4H, hex-2), 1.76 (quint, 4H, hex-3), 1.51 (m, hex-4), 1.39 (sext, 4H, hex-5), 0.92 (t, hex-6), −3.15 +−3.30 (s+s, NH); phenyl: 8.18 (s, 1H), 8.01+7.91 (d+d, 1H+1H), 7.75 (t, 1H). UV-vis (CH_2Cl_2): 403, 502, 536, 570, and 623 nm. MS (FAB): *m/z* 713 ($M+H^+$). IR (KBr): no carbonyl. Found: C, 79.28; H, 8.59; N, 7.78%. Calcd for $C_{65}H_{82}O_4N_6$: C, 79.17; H, 8.48; N, 7.76%.

5-(3-[Bis(5-ethoxycarbonyl-3-ethyl-4-methyl-2-pyrrolyl)-methyl]phenyl)-13,17-dihexyl-2,3,7,8,12,18-hexamethylporphine Zinc Complex (8b). The porphyrin dimethyl acetal **7b** (183 mg, 0.26 mmol) and ethyl 4-ethyl-3-methyl-2-pyrrolecarboxylate (183 mg, 1.01 mmol) was dissolved in chloroform (100 ml), *p*-toluenesulfonic acid monohydrate (180 mg, 0.95 mmol) was added, and the resultant mixture was refluxed for 12 hours. The reaction mixture was then cooled, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. The resultant solution was treated with 10 ml of $Zn(OAc)_2$/MeOH solution (reflux, 2 hours). The reaction mixture was separated by flash column chromatography (benzene). After the unreacted pyrrole and non-porphyrinic by-products were eluted, the porphyrin zinc complex **8b** was eluted by benzene/diethyl ether (v/v=95/5). Yield 246 mg (0.23 mmol, 89%). Mp 140—148 °C. ^1H NMR ($CDCl_3$): δ=10.14 (s, 2H, 10,20-H), 10.03 (s, 1H, 15-H), 4.04 (t, 4H, hex-1), 3.62+3.52 (s+s, 6H+6H, Me), 2.3 (m, 4H, hex-2), 2.46 (s, 6H, 3,7-Me), 1.79 (quint, 4H, hex-3), 1.6 (m, hex-4), 1.41 (m, 4H, hex-5), 0.93 (t, 6H, hex-6); phenyl: 7.99 (d, 1H), 7.95 (s, 1H), 7.73 (t, 1H), 7.50 (d, 1H); pyrrole: 8.44 (s, 2H, NH), 5.83 (s, 1H, $(pyrrolyl)_2C\underline{H}$-), 4.34 (q, 4H, $OC\underline{H}_2CH_3$), 2.41 (m, 4H, $C\underline{H}_2CH_3$), 2.31 (s, 6H, Me), 1.39 (t, 6H, $OCH_2C\underline{H}_3$), 0.99 (t, 6H, $CH_2C\underline{H}_3$). UV-vis (CH_2Cl_2): 407, 537, and 572 nm.

5-[3-(3,7,13,17-Tetraethyl-2,8,12,18-tetramethyl-5-porphinyl)-phenyl]-13,17-dihexyl-2,3,7,8,12,18-hexamethylporphine (10a). The dipyrromethane-porphyrin zinc complex **8b** (66 mg, 0.061 mmol) was treated with $LiAlH_4$ (26 mg) in tetrahydrofuran (10 ml) at 4 °C for 1 hour. The reaction mixture was quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. The resultant solids were dissolved in 2 ml of CH_2Cl_2, which was added to the solution of dipyrromethane **4** (30 mg) in 10 ml of methanol. Silica gel (C-100, Wako Pure Chemicals) was added (1.0 g), and the mixture was stirred for 3 days (dark, under nitrogen, room temperature). Chloranil (20 mg) was added and the mixture was stirred for 2 hours.

The silica gel was removed by filtration, and the resultant mixture was treated in the similar manner as in the case of **5a**. The dimer **10a** was obtained. Yield 6 mg (0.005 mmol, 9%). Mp>300 °C. ^1H NMR ($CDCl_3$): δ=10.12+10.01 (s+s, 2H+2H, meso), 9.81+9.80 (s+s, 1H+1H, meso), 3.98+3.95 (q+t, 8H, 13,17-Et+hex-1), 3.62+3.57+3.53+3.46+3.6 (4s+m, 28H, 4Me+3,7-$C\underline{H}_2CH_3$), 2.97 (s, 6H, Me), 2.20 (quint, 4H, hex-2), 1.80 (t, 6H, Et), 1.67 (quint, hex-3), 1.60 (t, Et), 1.43 (quint, hex-4), 1.31 (sext, hex-5), 0.85 (t, 6H, hex-6), −2.5 to −3.3 (br, 4H, NH); phenyl: 9.38 (d, 1H), 8.58 (d, 1H), 8.23 (t, 1H), 7.83 (s, 1H). UV-vis (CH_2Cl_2): 407, 505, 538, 574, and 626 nm. MS (FAB): *m/z* 1116 ($M+H^+$).

5-(1,4-Dimethoxy-2-naphthyl)-15-[3-(13,17-dihexyl-2,3,7,8,12,18-hexamethyl-5-porphinyl)phenyl]-3,7,13,17-tetraethyl-2,8,12,18-tetramethylporphine (10b). The porphyrin dimer **10b** was prepared by the same method as **10a**, starting from **8b** and 2-[bis(3-ethyl-4-methyl-2-pyrrolyl)methyl]-1,4-dimethoxynaphthalene **11**[1c] (0.5% yield). ^1H NMR ($CDCl_3$):[12] δ=10.14 (s, 2H, meso), 9.97 (s, 2H, meso), 9.75 (s, 1H, meso), 3.97—3.86 (m, 7H, hex-1 and OMe), 3.57—3.42 (5s, 27H, Me and OMe), 2.93 (s, 6H, Me), 2.93—2.50 (4m, 4H, Et), 2.3—2.13 (2m, 4H, hex-2), 1.7—1.6 (2m, hex-3), 1.5—1.2 (m, hex-4 and hex-5), 1.08 (t, Et), 0.81 (t, hex-6), −1.8 (br, NH), −3.1 and −3.2 (br, NH); naphthyl: 8.46+8.1 (m+br, 1H+1H, 6- and 7-H), 7.6 (m, 2H, 5- and 8-H), 7.5 (br, 1H, 3-H); phenyl: 9.3+8.55 (br+br, 1H+1H, 4- and 6-H), 8.17 (t, 1H, 5-H), 7.9 (br, 1H, 2-H). UV-vis (CH_2Cl_2): 404, 505, 537, 575, 624 and 654nm. High resolution mass (FAB, $CHCl_3$+NBA). Found: 1301.806 ($M+H^+$). Calcd for $C_{88}H_{101}O_2N_8$: 1301.805.

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8) The compound **2** was prepared by acid-catalyzed condensation (Ref. 3b) of *p*-anisaldehyde with ethyl 4-ethyl-3-methyl-2-pyrrolecarboxylate (Ref. 9).

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12) Since the compound **10b** was obtained as a mixture of two atropisomers, the ^{1}H NMR spectrum of **10b** was complex and somewhat broadened. The peak assignment was based on the 2D (COSY) ^{1}H NMR spectrum.