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Syntheses of Porphyrin-Isoflavonoid Conjugates and Octa-Substituted Porphyrins as a Building Blocks for 3-Dimensional Array of Porphyrins

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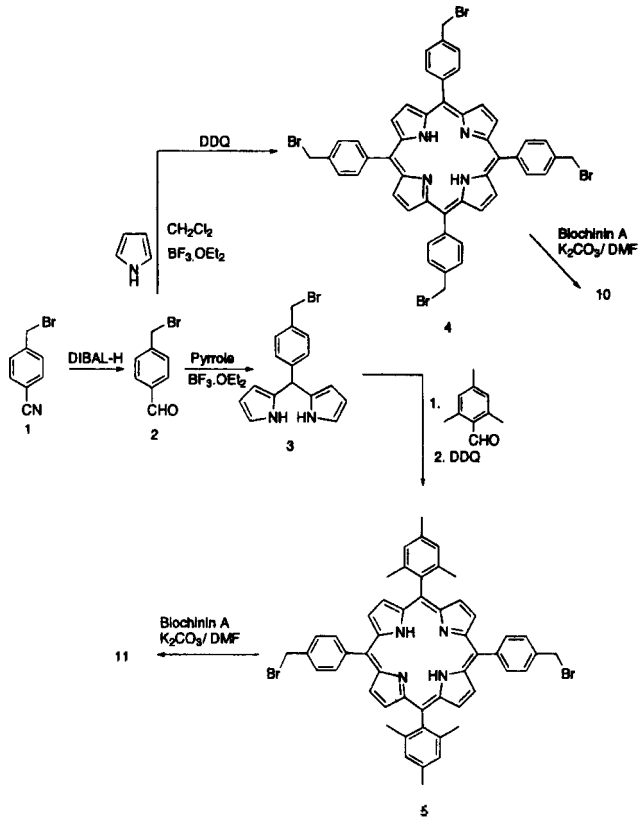
Porphyrins which is one of the most widely studied macrocycles could be a good carrier of drugs.[1a] The meso-substituted porphyrins are especially versatile compounds with regard that meso-position is convenient for functionalization and controlling the substituent geometry.[1b] Moreover wealth of available substituents make meso-substituted porphyrins ideally suited for various purposes. Flavonoid compounds such have been shown to possess various biological activities including antibacterial, anti viral, anti cancer, anti-inflammatory and immuno regulatory activities.[2] Due to the reduced side effects compared to nonsteroidal acidic drug or steroidal anti-inflammatory drug, much interests have been focused on the anti-inflammatory activities of flavonoids. The structure-activity relationship for the simple alkylated biochanin-A derivatives have been reported recently and the results indicates that flavonoids possess some improved activities *in vivo*.[3]

The porphyrins are well known as photosensitizing activities also.[4] The coupling of flavonoids and porphyrins may show compensating activities against inflammation and tumor. The convenience of the synthesis and their unique structural characteristic led us to synthesize various octa-substituted porphyrins including biochin A-porphyrin conjugates as potential anti-inflammatory compounds. A three dimensional array of porphyrins with two connecting bridges has been synthesized.[5] But multi-porphyrin array with four connecting straps are not synthesized. These compounds will have restricted coplanar geometry and thus it might be useful in studying geometry dependence of electronic excitation[6] electron transfer or energy transfer.[7] A specific order of porphyrins are found in many biological substructures including light harvesting complexes and cytochromes.[8] One of the key question would be the extent of interaction between porphyrins with such close contact. With these regards, we report the synthesis of porphyrins coupled with biochinin-A or salicylaldehyde with facial encumbrance.

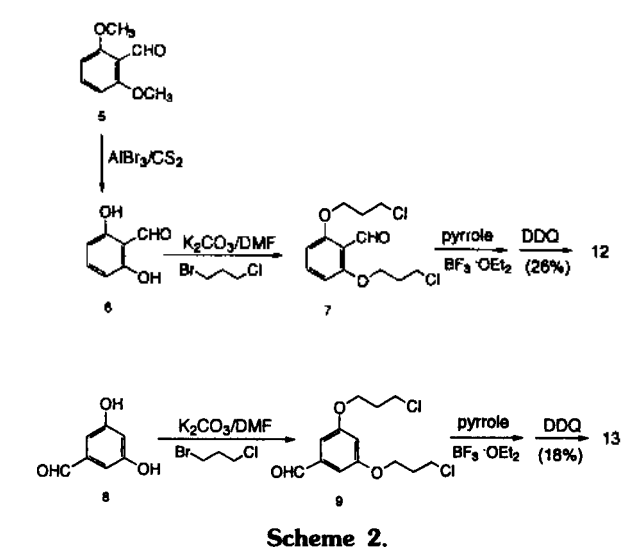
The synthetic work is summarized in Scheme 1 and Scheme 2. α-Bromomethylbenzaldehyde **2** is easily synthesized by reduction of p-(α-Bromomethyl)benzonitrile **1**.[9] The dipyrromethane **3** is synthesized by treatment of aldehyde **2** with excess pyrrole in the presence of borontrifluoride etherate. Simple base wash followed by removal of residual pyrrole usually gave high yield of **3**.[10] The condensation of dipyrromethane **3** with mesityl aldehyde was performed at 0.01 M using BF_3 catalyst in chloroform at room temperature. Oxidation of the resulting porphyrinogen with DDQ afforded the porphyrin **5**. The porphyrin **5** was purified by column chromatography on silica gel in 21% yield. The similar reaction of aldehyde **2** with pyrrole gave porphyrin **4** in 22% yield. The synthesis of the conjugates **10** and **11** was carried out by dissolving proper amount of biochinin-A and **4** or **5** in N,N-dimethylformamide in the presence of K_2CO_3. The coupling reaction did not result any appreciable side reaction. But due to the limited solubility of **10** in organic solvent, the isolated yields was quite low.

Since one of the our objectives is to develop a method that can give a multiporphyrin array and related porphyrin system. we attempted to synthesize a building blocks for



Scheme 1.

these purpose. The porphyrins bearing peripheral functional groups and facial encumbrance will reduce aggregation and enhance solubility in organic media. Alkylation of 2,6-hydroxybenzaldehyde **6**, obtained by demethylation of **5**, was accomplished with 1-bromo-3-chloropropane using potassium carbonate at 50 °C for 2 hr.[11] Similar alkylation of 3,5-dihydroxybenzaldehyde **8** afforded **9**, which upon condensation with pyrrole followed by DDQ oxidation gave porphyrin **13** in 18% yield. The condensation of **7** with pyrrole performed similar condition afforded porphyrin **12** in 26% yield. These results indicate that steric effects of the ortho- substituents in the condensation reaction is minimal in the self assembly of pyrrole and aldehyde. Porphyrin **10** is rarely soluble in organic solvent, but freely soluble in slightly acidic condition. Coupling reaction of **13** with salicylaldehyde is successful affording porphyrin **14** in 10%. But due to limited solubility in organic solvent only small amount (cal. < 5%) of coupled products **15** was isolated and characterized. Mass spectra and proton NMR spectra clearly indicate the desired product is formed without formation of any other products.



Scheme 2.

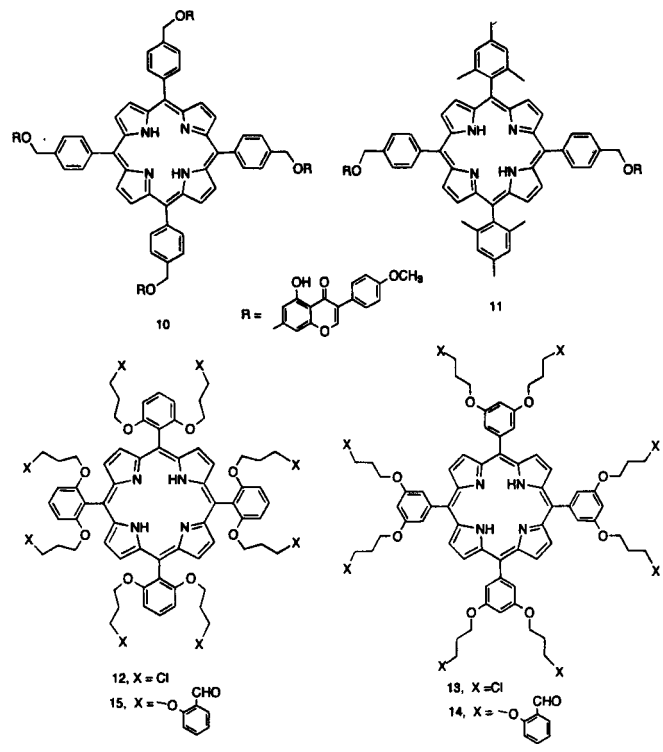


Figure 1.

The UV-Vis absorption spectra of the porphyrins synthesized closely resemble that of meso-tetraphenylporphyrin (TPP). The absorption spectra of the ortho and meta-substituted octakis-(propyloxy)porphyrins exhibit Soret band at 415-420 nm. The eight ortho or *para*-propyl group doesn't perturb the spectral properties of the porphyrins. The spectral feature resembles with those of meso-tetramesitylporphyrins (TMP) in Soret and Q-band. The ability to condense octa-substituted aldehyde to corresponding porphyrins will provide an access to the three dimensional array of porphyrins with tight bridges. Increasing number of bridges is known to result more flexibility and allows each porphyrins come closer.[6]

Experimental

^{1}H NMR spectra (200 MHz, Varian Gemini 200), IR spectra (Perkin Elmer 1430), and absorption spectra (Kontron 941 and Hitachi U-3200) were collected routinely. Mass spectra were obtained at regional center for basic science research. High resolution mass spectra were obtained from KRICT. Column chromatography was performed on silica (Merck, 230-400 mesh) or alumina (Fisher A540, 80-200 mesh). Pyr-

role was distilled at atmospheric pressure from CaH_2. CH_2Cl_2 (Fisher, reagent grade) was distilled from K_2CO_3. $CHCl_3$ (Fisher certified A.C.S.) containing 0.75% ethanol was distilled from K_2CO_3. Trifluoroacetic acid and $BF_3.O(Et)_2$ were used as obtained from Aldrich. All other reagents were obtained from Aldrich unless noted otherwise.

2,6-Bis(3-chloropropyloxy)benzaldehyde (7). The solution containing 2,6-dihydroxybenzaldehyde (0.2 g, 1.45 mmol), K_2CO_3 (3.0 g, 21.7 mmol) and N,N-dimethylformamide (30 mL) was stirred for 10 min then 1-bromo-3-chloropropane (0.32 mL, 3.2 mmol) was added. The whole mixture was stirred for 2 hr at 50 °C. The mixture was combined with water (15 mL) and extracted twice with methylene chloride (50 mL). The organic layer was dried with anhydrous sodium sulfate. The residual solid after evaporation of solvent was purified by column chromatography on silica (hexane/ethyl acetate=7/3). Yield 0.26 g (53%); ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H, aldehyde), 7.44 (t, 1H, Ar-H), 6.60 (d, 2H, Ar-H), 4.21 (t, 2H, methylene), 3.81 (t, 2H, methylene), 2.29 (m, 2H, methylene).

3,5-Bis(3-chloropropyloxy)benzaldehyde (9). 1.45 mmol (0.2 g) of 3,5-dihydroxybenzaldehyde and 3.2 mmol of 1-bromo-3-chloropropane were reacted using the same method for the preparation of **7** affording 0.2 g (47%) of 9. ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H, aldehyde), 7.02 (t, 1H, Ar-H), 6.73 (d, 2H, Ar-H), 4.16 (t, 2H, 3-methylene), 3.75 (t, 2H, 1-methylene), 2.25 (m, 2H, 2-methylene).

5,10,15,20-tetra(*p*-bromomethylphenyl)porphyrin (4). To a solution of p-bromomethylbenzaldehyde (300 mg, 1.5 mmol), pyrrole (100 mg, 1.5 mmol) and methylene chloride (150 mL) was added trifluoroacetic acid (138 μL, 1.2 eqv.). The mixture was stirred for 1 hr at room temperature then DDQ (1.02 g, 3 eqv.) was added and stirred additional 1hr. Solvent was evaporated and the remaining solid was separated by column chromatography on silica (chloroform). Yield 22%; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 8H, β-pyrrolic-H), 8.20 and 7.80 (AA'BB', 16H, Ar-H), 4.87 (s, 8H, benzylic-H), - 2.84 (s, 2H, N-H). MALDI-MS Clacd. for $C_{48}H_{34}N_4Br_4$ 986.44, Found 985.97.

5,15-dimesityl-10,20-di[(*p*-bromomethyl)phenyl] porphyrin (5). 4-Bromobenzaldehyde (74 mg, 0.37 mmol) and meso-mesityldipyrromethane (100 mg, 0.37 mmol) were dissolved in distilled chloroform (20 mL) and degassed for 5 min. Then borontrifluoride therate (36 μL) was added. The mixture was stirred for 1 hr at room temperature then DDQ (134 mg, 0.3 mmol) was added. After stirring additional 1 hr, the mixture was washed with sat. $NaHCO_3$ solution and water. The organic layer was dried on anhydrous sodium sulfate and solvent was removed. The product was isolated from resulting black solid by flash column chromatogtaphy on silica (chloroform/ethyl acetate= 9/1). Yield 21%; ^{1}H NMR ($CDCl_3$) δ 8.82 and 8.70 (AA'BB', 8H, β-pyrrolic-H), 8.20 and 7.77 (AA'BB', 8H, Ar-H), 7.29 (s, 4H, Ar(mesityl)-H), 4.85 (s, 4H, benzylic-H), 2.63 (s, 6H, mesityl-p-methyl), 1.83 (s, 12H, mesityl-o-methyl), - 2.65 (s, 2H, N-H).

5,10,15,20-terakis[p-(5-dihydroxy-4'-methoxyisoflavone-7-oxymethyl)phenyl]porphyrin (10). Biochinin-A (112 mg, 0.394 mmol) and K_2CO_3 (135 mg, 0.984 mmol) were dissolved in DMF (30 mL). The mixture was stirred for 30 min at room temperature then the porphyrin **4** (97 mg, 0.0.098 mmol) was added. The whole mixture was stirred for 82 h at room temperature. The mixture was combined with THF (50 mL), water (30 mL) and methylene chloride (50 mL). The organic layer was separated and the solvent was removed *in vaccuo*. The residual solid was washed with ethylacetate. The compound was pure enough for analysis without further purification. Yield 93 mg (52%); ^{1}H NMR ($CDCl_3$/TFA-d) δ 8.73 (s, 8H, β-pyrrolic-H), 8.63 and 8.12 (AA'BB', 16H, Ar-H), 7.97 (s, 4H), 7.46 and 7.01 (AA'BB', 16H, Ar-H), 6.74 (s, 8H, Ar-H), 5.60 (s, 8H, benzylic-H), 3.87 (s, 12H, methoxy), MS (FAB) Calcd. for $C_{112}H_{78}N_4O_{20}$ 1799.86, Found 1799.

5,15-dimesityl-10,20-di[*p*-(5-dihydroxy-4'-methoxyisoflavone-7-oxymethyl)phenyl]porphyrin (11). The porphyrin 5 (33 mg, 0.037 mmol) and biochinin A (21 mg, 0.074 mmol) were dissolved in DMF (15 mL) then added K_2CO_3 (3 eqv.). The mixture was stirred for 3 hr at room temperature then the solvent was removed *in vacuo*. The product was isolated by column chromatography on silica ($CHCl_3$/ethyl acetate=9/1). Yield 43 mg (90%); ^{1}H NMR ($CDCl_3$) δ 12.98 (s, 2H, Ar-OH), 8.83 and 8.72 (AA'BB', 8H, β-pyrrolic-H), 8.28 and 7.82 (AA'BB', 8H, meso-phenyl-H), 7.95 (s, 2H, Ar-H), 7.52 and 7.29 (AA'BB', 8H, Ar(3-phenyl)-H), 7.30 (s, 4H, Ar(mesityl)-H), 6.70 (s, 2H, Ar-H), 6.69 (s, 2H, Ar-H), 3.87 (s, 6H, methoxy), 2.64 (s, 6H, mesityl-*p*-H), 1.85 (s, 12H, mesityl-o-H), - 2.63 (s, 2H, N-H).

***meso*-5,10,15,20-tetrakis[2,6-bis(3-chloropropyloxy)phenyl]porphyrin (12).** 2,6-Bis(3-chloropropyloxy) benzaldehyde 7 (0.25 g, 0.86 mmol) and pyrrole (0.06 mL, 0.86 mmol) were dissolved in chloroform (86 mL) and degassed for 5 min. Then borontrifluoride etherate (36 μL, 0.29 mmol) was added. The mixture was stirred for 1 hr at room temperature then DDQ (146 mg, 0.64 mmol) was added. After stirring additional 1 hr, triethylamine (40 μL) was added. The solvent was evaporated and the product was isolated by flash column chromatogtaphy on silica (methylene chloride). The fast moving purple band was desired product. Yield 75 mg (26%); ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 8H, β-pyrrolic-H), 7.71 (t, 4H, Ar-H), 7.03 (d, 8H, Ar-H), 4.00 (t, 16H, methylene), 2.57 (t, 16H, methylene), 1.41 (m, 16H, methylene), - 2.65 (s, 2H, N-H).

***meso*-5,10,15,20-tetrakis[3,5-bis(3-chloropropyloxy)phenyl]porphyrin (13).** 1.0 g (3.43 mmol) of 3,5-Bis (3-chloropropyloxy)benzaldehyde **9** and pyrrole (0.24 mL, 3.43 mmol), which were dissolved in chloroform (350 mL), were reacted using the same method for the preparation of **12** affording 0.2 g (18%) of **13**. ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 8H, β-pyrrolic-H), 7.40 (d, 8H, Ar-H), 6.91 (t, 4H, Ar-H), 4.29 (t, 16H, methylene), 3.82 (t, 16H, methylene), 2.32 (m, 16H, methylene), - 2.86 (s, 2H, N-H).

***meso*-5,10,15,20-tetrakis[3,5-bis(3-(o-formylphenoxy) propyloxy)phenyl]porphyrin (14).** Salicylaldehyde (0.14 g, 1.11 mmol) and K_2CO_3 (3.0 g, 21.7 mmol) were dissolved in DMF (10 mL). The mixture was stirred for 50 min at 50 °C then porphyrin **13** (0.15 g, 1.11 mmol) was added. The whole mixture was stirred for 150 h at 50 °C. The progress of reaction was followed by TLC. When no starting porphyrin was observed, the mixture was combined with water (10 mL). The mixture was extracted with methylene chloride and the organic layer was dried

over Na_2SO_4. The residue after evaporation of the solvent was purified by column chromatography on silica (methylene chloride/ethyl acetate=1/1). Yield 22 mg (9.7%); ^{1}H NMR ($CDCl_3$) δ 10.50 (s, 8H, CHO), 8.89 (s, 8H, β-pyrrolic-H), 7.77 (d, 8H, Ar-H), 7.50 (t, 8H, Ar-H), 7.39 (s, 4H, Ar-H), 7.00 (m, 24H, Ar-H), 4.35 (t, 32H, methylene), 2.41 (m, 16H, methylene), − 2.92 (s, 2H, N-H).

meso-5,10,15,20-tetrakis[2,6-bis(3-(o-formylphenoxy)propyloxy)phenyl]porphyrin (15). salicylaldehyde (0.1 g, 0.82 mmol), K_2CO_3 (1.0 g, 7.24 mmol) and porphyrin **12** (30 mg, 0.02 mmol) were dissolved in DMF (5 mL). This was reacted using the same method for the preparation of **14** affording 2 mg (4.5%). ^{1}H NMR ($CDCl_3$) δ 10.04 (s, 8H, aldehyde), 8.71 (s, 8H, β-pyrrolic-H), 7.78 (t, 8H, Ar-H), 7.44 (d, 8H, Ar-H), 7.10 (d, 16H, Ar-H), 6.52 (t, 8H, Ar-H), 6.15 (t, 4H, Ar-H), 3.96 (t, 16H, methylene), 2.62 (t, 16H, methylene), 0.88 (m, 16H, methylene), − 2.30 (s, 2H, N-H). MS (MALDI) Calcd. for $C_{124}H_{110}N_4O_{24}$ 2040.24, Found 2040.64.

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