Synthesis of New Four-Atom-Linked Capped Porphyrins

Wuping Ma, Keith M. Wilcoxen, Jason W. Szewczyk, and James A. Ibers*

Department of Chemistry, Northwestern University, Evanston, Illinois 60208-3113

Received June 26, 1995

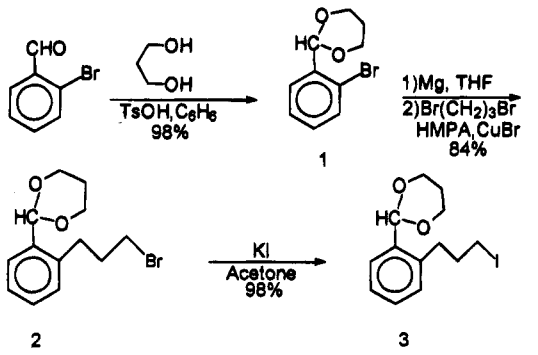
Encumbered porphyrins have served as useful models in some aspects of the chemistry of the hemoproteins.[1] Previously, we have reported the synthesis of four-atom-linked[2] and five-atom-linked[3] benzene-capped porphyrins. Other recent examples of capped porphyrins include "punt-tent" and "crown ether",[4] "strapped cyclam",[5] "porphyrin–quinone cyclophane",[6] "hydrocarbon-capped",[7] and "pendant-capped".[8] When the linkage between porphyrin and cap consists of five or more atoms, the resultant porphyrin is usually only slightly encumbered. However, when that linkage consists of four atoms and there are four such linkages, the resultant porphyrin is severely encumbered. Thus, consider the binding properties for CO and O_2 of Fe(Por)(1-MeIm), where Por are two such porphyrins prepared earlier.[2] With the four-atom linkage $-OCH_2CH_2O-$, the system binds O_2 normally but CO a factor of 10^3 more poorly than in unencumbered systems; with the four-atom linkage $-OCH_2(CO)NH-$, the system binds neither O_2 nor CO up to pressures of 7.7×10^4 Torr.[9] Herein we report the design and synthesis of two new four-atom-linked capped porphyrins, $H_2(OC_3Por)$ **6** and $H_2((CO)OC_2Por)$ **10**.

Results and Discussion

The general methodology for the synthesis of porphyrins **6** (Schemes 1 and 2) and **10** (Scheme 3) follows that reported earlier.[3]

Synthesis of the porphyrin $H_2(OC_3Por)$ **6** started from 2-bromobenzaldehyde and protection with 1,3-propanediol in benzene containing a catalytic amount of toluenesulfonic acid to give the acetal **1** in 98% yield (Scheme 1). The acetal was reacted with Mg in dry THF under N_2 to form the Grignard reagent which was added to 1,3-dibromopropane and a catalytic amount of CuBr in HMPA and THF to afford compound **2** in 84% yield after column chromatography. When compound **2** was reacted with 1,2,4,5-tetrahydroxybenzene and KOH in degassed DMSO, the starting material **2** was recovered in 80% yield and the elimination product 2-allylbenzacetal was obtained in 15% yield. Accordingly, the bromo compound

Scheme 1



2 was converted to the iodo compound **3** by refluxing overnight with KI in dry acetone. Then (Scheme 2) in one pot 1,2,4,5-tetrahydroxybenzene was reacted under N_2, first with powdered KOH in degassed DMSO and then with **3** to afford the tetraacetal **4** in 82% yield after workup. Compound **4** was deprotected cleanly with PPTs/water/acetone to afford compound **5** in 99% yield after recrystallization twice from acetone–water. After considerable experimentation, we found that the 4-fold condensation of the tetraaldehyde **5** with pyrrole to the very sterically unfavorable capped porphyrin **6** could be achieved in 0.2% yield through the use of the method developed by Lindsey and co-workers.[10–12] Application of the high concentration method[13] to obtain more porphyrin **6** was unsuccessful.

Synthesis of the porphyrin $H_2((CO)OC_2Por)$ **10** (Scheme 3) began with the reaction of **1** with Mg in THF to form the Grignard reagent, which was then added to a solution of ethylene oxide, CuBr, and HMPA at −20 °C to afford **7** in 65% yield.[14] The tetraacetal **8** was prepared by the reaction of **7** with pyromellitoyl chloride in THF/Et_3N in 56% yield. Deprotection with PPTs/acetone/water afforded **9** in 99% yield. The condensation of the tetraaldehyde with pyrrole could be carried out with the procedure developed by either Baldwin and co-workers[15,16] or Lindsey and co-workers[10–12] to afford the capped porphyrin **10** in 5% yield after extensive chromatography and recrystallization.

Experimental Section

With the following exceptions, all solvents and reagents were used as purchased. Toluene was distilled over sodium under N_2. THF was distilled under N_2 from sodium benzophenone ketyl. DMSO was deoxygenated with the freeze–pump–thaw technique just prior to use. Propionic acid was refluxed over $K_2Cr_2O_7$ followed by two fractional distillations. HMPA was dried over CaH_2 and distilled. Pyrrole was doubly distilled before use. All reagents were obtained from Aldrich except Mg, KI, and Na_2SO_4 which were purchased from other commercial sources. Melting points were uncorrected. ^1H and ^{13}C NMR

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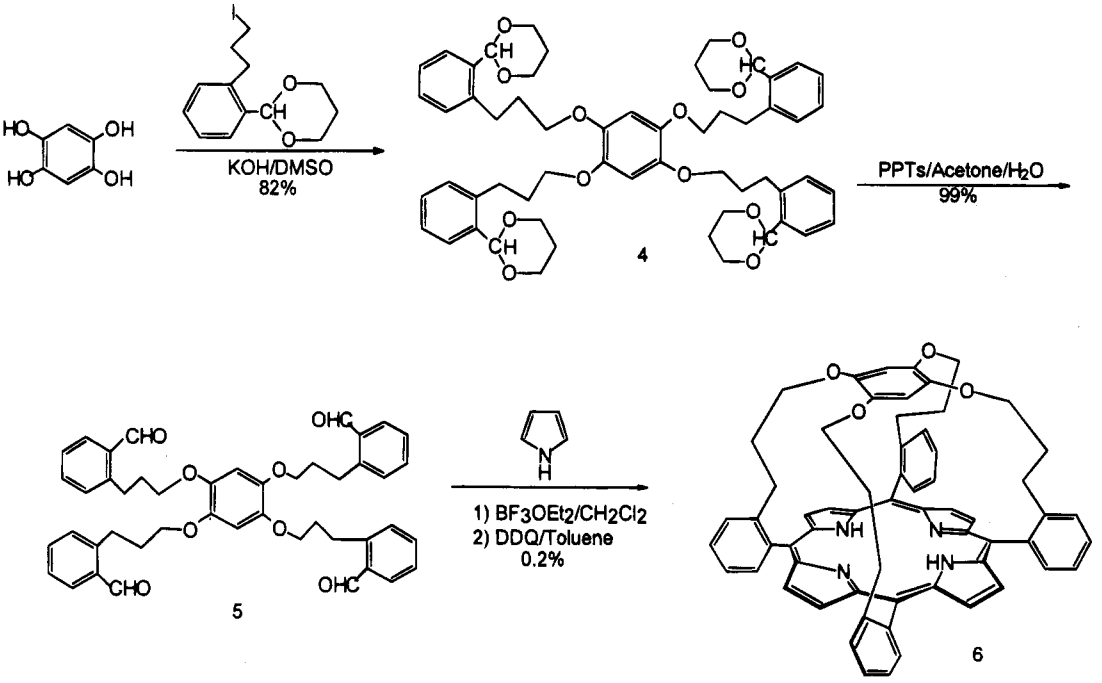
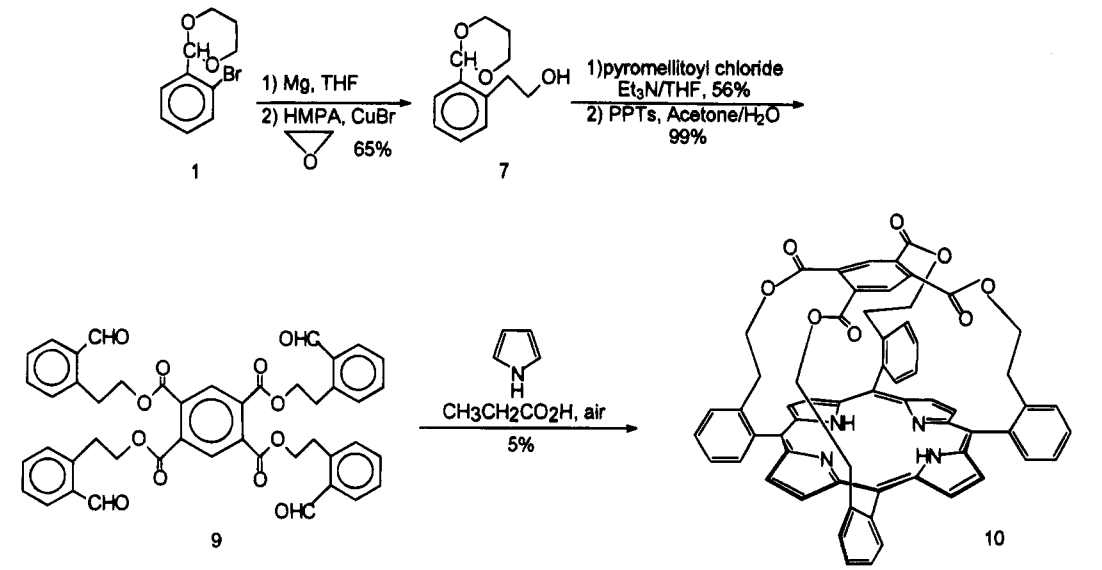
Scheme 2



Scheme 3



measurements were made with $CDCl_3$ as solvent at 300 and 75.4 MHz, respectively.

2-(2-Bromophenyl)-1,3-dioxane (1). To a 500-mL round-bottom flask equipped with a Dean–Stark trap and condenser were added 2-bromobenzaldehyde (50 g, 0.27 mol), 1,3-propanediol (30.8 g, 0.405 mol), *p*-toluenesulfonic acid (1 g), and benzene (300 mL). The mixture was stirred and refluxed overnight. Et_3N (5 mL) was added, and the reaction mixture was cooled. Ethyl acetate (200 mL) was added, and the organic layer was washed with NaOH, water, and brine and dried over Na_2SO_4. Solvent was removed, and **1** was obtained as a colorless solid (64.3 g, 0.265 mol, 98%): mp 44–46 °C; ^1H NMR δ 1.45 (d, 1H), 2.23 (m, 1H), 4.05 (d, 2H), 4.28 (dd, 2H), 5.78 (s, 1H), 7.21 (t, 1H), 7.36 (t, 1H), 7.55 (d, 1H), 7.70 (d, 1H); ^{13}C NMR δ 25.74, 67.66, 100.92, 122.37, 127.64, 128.13, 130.43, 132.66, 137.53; MS *m/e* 244 (73), 243 (93), 242 (75), 241 (88), 186 (50), 185 (86), 184 (52), 183 (82), 163 (46), 105 (30), 87 (100); HRMS calcd for $C_{10}H_{10}BrO_2$ *m/e* 240.9865, found 240.9870.

2-[2-(4-Bromopropanyl)phenyl]-1,3-dioxane (2). This compound was synthesized with the use of a method developed by Zhang et al.[17] Dry Mg turnings (5.4 g, 0.225 mol) and 35 mg of I_2 were added to a 500-mL three-necked flask under N_2. Dry THF (150 mL) was added, and the mixture was warmed to 70–80 °C. One-fourth of **1** (36.2 g total, 0.15 mol) was dissolved in dry THF (100 mL) and added to initiate the reaction. The remainder was added over a 1-h period to maintain a gentle reflux, and the mixture was refluxed for another 1 h after the addition was complete to obtain the Grignard reagent. In another 1-L flask under an N_2 atmosphere, dry CuBr (2.4 g, 16.8 mmol), dry THF (50 mL), dry HMPA (20 mL), and dry 1,4-dibromopropane (30.3 g, 0.15 mol) were stirred vigorously and refluxed gently. The Grignard reagent prepared above was quickly added, and the reaction mixture was refluxed for an additional 4–6 h. The solution was cooled to room temperature, aqueous NH_4Cl was added, and the solution was stirred overnight. The solution was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Solvent was removed, and a blue-brown oily product was isolated. The product was purified by passing it through silica gel with 1:10 ethyl acetate/hexanes as the eluent. Compound **2** was isolated as a light yellow oil (35.8 g, 0.126 mol, 84%): ^1H NMR δ 1.45 (d, J = 13.44 Hz, 1H), 2.17 (q, J = 6.40 Hz, 2H), 2.25 (m, J = 12.78 Hz, 1H), 2.91 (t, J = 7.60 Hz, 2H),

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3.47 (t, J = 6.41 Hz, 2H), 4.01 (dt, J = 11.80 Hz, 2H), 4.25 (dd, J = 11.49 Hz, 2H), 5.68 (s, 1H), 7.19–7.27 (m, 3H), 7.61 (d, J = 7.42 Hz, 1H); ^{13}C NMR δ 25.82, 30.76, 34.13, 34.49, 67.61, 100.04, 126.60, 128.97, 129.87, 136.51, 138.47; MS m/e 287 (14.2), 286 (98.6), 285 (62.7), 284 (100), 283 (49.1), 228 (12.1), 227 (25.3), 226 (12.3), 225 (23.8), 164 (11.8), 163 (72.4), 147 (34.7), 129 (59.4), 117 (52.8); HRMS calcd for $C_{13}H_{17}BrO_2$ m/e 284.0412, found 284.0420.

2-[2-(4-Iodopropanyl)phenyl]-1,3-dioxane (3). KI (43.3 g, 261.1 mmol), **2** (7.10 g, 25 mmol), and dry acetone (100 mL) were placed in a 250-mL round-bottom flask, stirred vigorously, and refluxed overnight. The solution was filtered and the solid residue was washed with ethyl acetate. The organic layer was added to ethyl acetate (100 mL), washed with water (2 × 50 mL), and dried over Na_2SO_4. Solvent was removed, and **3** was obtained as a yellow oil. It was purified by passing through a silica gel column with 1:10 ethyl acetate/hexanes as the eluent to give a yellow oil (8.13 g, 24.5 mmol, 98%): ^{1}H NMR δ 1.45 (d, J = 13.44 Hz, 1H), 2.13 (q, J = 6.44 Hz, 2H), 2.25 (m, J = 12.79 Hz, 1H), 2.86 (t, J = 7.89 Hz, 2H), 3.26 (t, J = 6.45 Hz, 2H), 4.04 (dt, J = 11.81 Hz, 2H), 4.27 (dd, J = 11.51 Hz, 2H), 5.69 (s, 1H), 7.20–7.39 (m, 3H), 7.62 (d, J = 7.42 Hz, 1H); ^{13}C NMR δ 25.83, 31.26, 35.15, 34.40, 67.65, 100.11, 126.93, 127.17, 129.89, 136.01, 138.95; MS m/e 332 (95.1), 331 (100), 205 (67.6), 163 (87.3); HRMS calcd for $C_{13}H_{17}IO_2$ m/e 332.0273, found 332.0269.

1,2,4,5-Tetrakis[3-[2-(1,3-dioxan-2-yl)phenyl]-1-oxypropyl]benzene (Tetraacetal 4). Compound **4** was isolated as a yellow solid (2.46 g, 2.56 mmol, 82%) with the use of a literature procedure[3] involving the reaction of **3** (8.44 g, 25 mmol) and 1,2,4,5-tetrahydroxybenzene (0.44 g, 3.13 mmol) with KOH (2.81 g, 50 mmol) in degassed DMSO (150 mL): mp 98–99 °C; ^{1}H NMR δ 1.46 (d, J = 13.43 Hz, 4H), 2.15 (q, J = 6.43 Hz, 8H), 2.25 (m, J = 12.88 Hz, 4H), 2.95 (t, J = 7.65 Hz, 8H), 4.09 (t, J = 6.11 Hz, 8H), 5.65 (s, 4H), 6.61 (s, 2H), 7.20–7.36 (m, 12H), 7.62 (d, J = 7.42 Hz, 4H); ^{13}C NMR δ 25.82, 30.76, 31.66, 34.18, 34.49, 69.37, 105.13, 126.93, 128.87, 129.89, 131.37, 132.51, 138.05, 143.45, 144.96; FAB MS (3-nitrobenzyl alcohol) m/e 958 (100), 957 (43.7), 884 (26.5); FAB HRMS calcd for $C_{58}H_{70}O_{12}$ m/e 958.4867, found 958.4839.

1,2,4,5-Tetrakis[3-(2-formylphenyl)-1-oxypropyl]benzene (5). In a 500-mL round-bottom flask equipped with a condenser and an Ar inlet, the tetraacetal **4** (3.91 g, 4.08 mmol) was dissolved in acetone with stirring. Water was added until the solution became cloudy white. A minimum of acetone was added to remove the turbidity. The solution was stirred and kept at reflux under Ar overnight. It was then cooled to room temperature, and the acetone was removed. The resultant oil was dissolved in $CHCl_3$, washed with water and brine, and then dried over Na_2SO_4. The solvent was removed to give an orange oil which solidified on standing. The solid was recrystallized in acetone–water or acetone–hexanes to give product **5** (2.93 g, 4.04 mmol, 99%): mp 83–84 °C; ^{1}H NMR δ 2.10 (q, J = 7.62 Hz, 8H), 3.25 (t, J = 7.98 Hz, 8H), 4.01 (t, J = 6.09 Hz, 8H), 6.60 (s, 2H), 7.31 (t, J = 6.39 Hz, 4H), 7.39 (d, J = 6.39 Hz, 4H), 7.48 (t, J = 5.94 Hz, 4H), 7.83 (d, J = 7.62 Hz, 4H); ^{13}C NMR δ 29.06, 31.66, 69.37, 105.13, 126.73, 131.27, 132.50, 133.89, 143.36, 144.50, 192.62; FAB MS (3-nitrobenzyl alcohol) m/e 727 (100), 580 (20.0), 461 (15.1), 281 (50.5); FAB HRMS calcd for $C_{46}H_{46}O_8$ m/e 726.3193, found 726.3187. Anal. Calcd for $C_{46}H_{46}O_8$: C, 76.01; H, 6.38. Found: C, 75.69; H, 6.31.

H_2(OC$_3$Por)-Capped Porphyrin 6. Compound **5** (0.218 g, 3 mmol) was dissolved in $CHCl_3$ (3 L) distilled from K_2CO_3. While N_2 was bubbled through the solution, 0.5 M pyrrole in $CHCl_3$ (2.64 mL, 1.32 mmol) and 0.2 M BF_3·OEt_2 in $CHCl_3$ (1.80 mL, 0.36 mmol) were added. The solution was stirred for 48 h at room temperature in the dark. DDQ (0.116 g) was added, and the solution was refluxed for 1 h. A second aliquot of DDQ (0.116 g) was added, and the solution was refluxed for an additional 2 h. The solvent was removed under reduced pressure, and the dark residue obtained was eluted through silica gel with 3% MeOH in $CHCl_3$. The isolated porphyrin was purified again by preparative plate TLC with 1% CH_3OH in $CHCl_3$ followed by 1% acetone in $CHCl_3$. The solvent was removed, and **6** was isolated as a purple solid (4.7 mg, 5.1 × 10^{-3} mmol, 0.2%): mp >300 °C; UV–vis λ_{max} ($CHCl_3$) 421 (5.65), 519 (4.24), 552 (4.60), 594 (3.70), 687 (3.21); ^{1}H NMR δ −2.91 (br s, 2H), 0.88–2.77 (m, 18H), 4.80 (s, 2H), 7.93–7.43 (m, 16H), 8.72 (d, 8H); ^{13}C NMR δ 22.90, 27.84, 29.96, 31.83, 35.51, 37.60, 67.99, 119.42, 125.07, 128.56, 134.77, 141.86, 142.35, 143.60; FAB MS (3-nitrobenzyl alcohol) m/e 918 (67.9), 410 (100); FAB HRMS (3-nitrobenzyl alcohol) calcd for $C_{62}H_{53}N_4O_4$ m/e 917.4066, found 917.4033. Anal. Calcd for $C_{62}H_{53}N_4O_4$: C, 81.10; H, 5.82; N, 6.10. Found: C, 81.42; H, 5.60; N, 6.36.

2-[2-(2-Hydroxyethyl)phenyl]-1,3-dioxane (7). **1** (10 g, 40.96 mmol) were reacted with 1.48 g (61.44 mmol) of Mg and 10 mg of I_2 in 50 mL of dry THF to afford a Grignard reagent, as in the procedure for **2**. CuBr (0.585 g, 4.1 mmol) and ethylene oxide (2.35 g, 53.25 mmol) were dissolved in 50 mL of dry THF, cooled to −20 °C, and stirred. The Grignard reagent was added, and the solution was stirred overnight. After the solution was slowly warmed to room temperature, 2 M NH_4Cl solution was added slowly, and the reaction mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with water and brine and then dried over Na_2SO_4. The solvent was removed, and the residue was chromatographed with 30% ethyl acetate in hexanes to give **7** as a yellow oil (5.51 g, 26.62 mmol, 65%): ^{1}H NMR δ 1.45 (d, J = 13.77 Hz, 1H), 2.35 (m, J = 12.87 Hz, 1H), 2.61 (s, 1H), 3.05 (t, J = 7.61 Hz, 2H), 3.86 (q, J = 7.30 Hz, 2H), 4.01 (dt, J = 11.80 Hz, 2H), 4.26 (dd, J = 11.49 Hz, 2H), 5.65 (s, 1H), 7.20–7.45 (m, 3H), 7.58 (d, J = 7.43 Hz, 1H); MS m/e 208 (7.9), 207 (25.1), 178 (37.0), 163 (100), 149 (35.5), 132 (36.5), 119 (38.0), 104 (27.3); HRMS calcd for $C_{12}H_{15}O_3$ m/e 207.1021, found 207.1014.

Tetraacetal 8. Pyromellitoyl chloride (3.28 g, 10 mmol) in dry THF (15 mL) was added to a stirred solution of **7** (9.20 g, 44.20 mmol) and Et_3N (4.04 g, 40 mmol) in dry THF (150 mL) at 0 °C. The solution was maintained at 0 °C for 0.5 h and then stirred overnight at room temperature. The reaction mixture was added to ethyl acetate (200 mL), and the organic layer was washed with water and dried over Na_2SO_4. When solvent was removed, an oily gum product was obtained. The oil was eluted through silica gel with 2% methanol in $CHCl_3$ to obtain compound **8** (5.70 g, 5.61 mmol, 56%): ^{1}H NMR δ 1.45 (d, J = 13.77 Hz, 4H), 2.20 (m, J = 12.86 Hz, 4H), 3.21 (t, J = 7.65 Hz, 8H), 3.98 (dt, J = 11.80 Hz, 8H), 4.21 (dd, J = 11.49 Hz, 8H), 4.52 (t, J = 7.48 Hz, 8H), 5.69 (s, 4H), 7.23–7.29 (m, 12H), 7.61 (d, J = 7.43 Hz, 4H), 8.05 (s, 2H); ^{13}C NMR δ 28.71, 31.60, 30.76, 34.18, 34.96, 61.87, 126.69, 128.89, 130.70, 132.11, 133.95, 134.12, 134.79, 140.39, 144.68, 167.08; FAB MS m/e 1015 (100), 677 (41.0), 460 (39.4); FAB HRMS calcd for $C_{58}H_{63}O_{16}$ m/e 1015.4116, found 1015.4105.

1,2,4,5-Tetrakis[2-(2-formylphenyl)ethyl]benzoyl Ester-(9). The tetraacetal **7** (5.70 g, 5.61 mmol) was reacted with PPTs in acetone–water as in the procedure for **5** to give the white solid **9** (4.35 g, 5.55 mmol, 99%): ^{1}H NMR δ 3.47 (t, J = 6.87 Hz, 8H), 4.50 (t, J = 6.87 Hz, 8H), 7.34 (d, J = 7.41 Hz, 4H), 7.50 (m, 8H), 7.82 (d, 4H), 7.85 (s, 2H); FAB MS m/e 784 (50.1), 613 (30.4), 556 (65.5), 528 (100); FAB HRMS calcd for $C_{46}H_{39}O_{12}$ m/e 783.2442, found 783.2424.

H_2((CO)OCCPor)-Capped Porphyrin 10. Compound **9** (0.783 g, 1 mmol), dissolved in doubly distilled propionic acid (1 L), was added to a 1-L three-necked round-bottom flask that was equipped with a condenser, magnetic bar, and air inlet. The solution was heated to reflux, and air was bubbled into the flask. Doubly freshly distilled pyrrole (0.67 g, 10 mmol) was added, and the reaction mixture was refluxed with stirring for 1.5 h. Solvent was removed under reduced pressure, and the residue was purified by eluting through silica gel with 5% MeOH in $CHCl_3$. A fast moving band was isolated and chromatographed again with 1% MeOH in $CHCl_3$ followed by 2% acetone in $CHCl_3$. A purple solid was isolated and recrystallized from MeOH/$CHCl_3$ to give **10** (51.4 mg, 5.0 × 10^{-2} mmol, 5%): mp >300 °C; UV–vis λ_{max} ($CHCl_3$) 421 (5.64), 518 (4.07), 550 (3.61), 590 (3.53), 654 (3.10); ^{1}H NMR δ −3.05 (br s, 2H), 1.61 (m, 8H), 4.23–1.98 (m, 8H), 5.87 (s, 2H), 7.76–7.26 (m, 16H), 8.58 (d, J = 5.51 Hz, 8H); ^{13}C NMR δ 25.52, 31.80, 67.98, 119.41, 123.96, 128.40, 130.11, 130.63, 134.31, 136.73, 140.30, 143.32, 144.71, 193.37; FAB MS m/e 1029 (100), 1028 (64.7); FAB HRMS calcd for $C_{66}H_{53}N_4O_8$ m/e 1029.3863, found 1029.3837. Anal. Calcd for $C_{66}H_{53}N_4O_8$: C, 76.95; H, 5.19; N, 5.44. Found: C, 76.68; H, 5.43; N, 5.46.

Acknowledgment. This research was supported by the National Institutes of Health (Grant HL-13157).

JO951152T