Durene-capped porphyrins: synthesis and characterization

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This paper is dedicated to Professor Charles A. McDowell on the occasion of his 70th birthday


The synthesis of porphyrins having a fully hydrophobic cavity capped by a durene moiety is described. The size of the cavity is adjusted by varying the number of methylene -(CH₂)ₙ- groups linking the tetramethylphenylene cap with the diametrically opposite β-positions of the porphyrin. Bis(chloromethyl)durene (1) was first converted to durene-bisalkanoic acids 11 (n = 4), 13 (n = 5), and 18 (n = 7) using standard chain extension methods. The dialcyl chlorides were then used to acylate two equivalents of a β-unsubstituted pyrrole to give a chain-linked bipyrrole. Each pyrrole, following appropriate manipulation of the α-substituents, was condensed with an α-unsubstituted pyrrole and the resulting chain-linked dipyrromethane dimer was cyclized intramolecularly under high dilution to give the capped porphyrin 34 (n = 4, 5, or 7).


On décrit la synthèse de porphyrines portant une cavité complètement hydrophobe et qui sont cappées par une portion de durene. On ajuste la grandeur de la cavité en faisant varier le nombre de groupements méthylènes -(CH₂)ₙ- reliant le tétraméthylphénylène servant de cap avec les positions β diamétralement opposées de la porphyrine. Dans la première étape, on transforme le bis(chloromethyl)durene (1) en acides durene-bis-alkanols (11, n = 4; 13, n = 5 et 18, n = 7) en utilisant des méthodes standards pour l'extension de la chaîne. On utilise alors les chlorures de diacides pour acylérer deux équivalents d'un pyrrole substitué en position β afin d'obtenir un bispyrrole lié par une chaîne. Après une manipulation appropriée des substituants en α, on a condensé chacun des pyrroles avec un pyrrole substitué en α et, utilisant la technique des grandes dilutions, on a ensuite procédé à une cyclisation intramoléculaire du dipyrrométhane lié par une chaîne qui en résulte afin d'obtenir la porphyrine cappée désirée (34, n = 4, 5 ou 7).

Introduction

Synthetic heme models all necessarily incorporate an active site comparable to that of deoxymyoglobin that has an iron(II) atom coordinated to the four nitrogen atoms of a porphyrin dianion and an axial imidazole. The use of simple ferrous porphyrins as models for reversible oxygen-carrying hemoproteins has been thwarted for two main reasons. First, the addition of a nitrogen-donor base to four coordinate ferrous porphyrins in solution usually leads to a six-coordinate complex incapable of binding oxygen (1). Second, coordination of oxygen to the five coordinate species at room temperature leads rapidly and irreversibly to the formation of bridged oxo-iron(III) species (2, 3). Autoxidation of the iron centre proceeds via the initial formation of a monomeric iron-dioxygen adduct, followed by the reaction with a second iron(II) porphyrin unit (4).

Attempts to achieve reversible dioxygen binding at ambient temperature gave rise to model designs incorporating sterically bulky on one face of the porphyrin. This not only retards the ligation of the nitrogenous base at the sixth site, thus facilitating dioxygen binding, but also prevents "dimerization" of the initially formed dioxygen adduct which leads to oxidation of the metal centre. The best known sterically hindered porphyrins are the "picket-fence" (5) and "pocket" (6) porphyrins of Collman et al., the "capped" (7) porphyrins of Baldwin and co-workers, and the "cyclophane hemes" (8) of Traylor et al. Model systems with sterically hindrances on both faces of the porphyrin (the "basket-handle" porphyrins (9) of Momentau et al.), as well as those with protective structures on one and appended imidazole on the other face have also been prepared (10, 11). This area has recently been reviewed (12) and a survey of the synthesis and structure of these systems has been presented (13).

Two basic synthetic strategies have been used to obtain these hindered porphyrins. The first involves the condensation of a benzaldehyde derivative with pyrrole in a manner analogous to the synthesis of meso-tetraphenylporphyrin (14). The protective structure is introduced either by the modification of an appropriate ortho-substituent on the phenyl group (5, 6) or by carrying it in the aldehyde component prior to condensation with pyrrole (7, 9, 10). The second and the more widely used strategy is to condense, via ester or amide linkages, a diagonally binding may be evaluated in the absence of the distal sterle effects on the reference series where the influence of the distal sterle effects on the synthesis of sterically hindered porphyrins (16-18), which utilizes more flexible and reactive dipyrromethene precursors (15). However, the synthetic route originally developed by some of us to construct permanently deformed porphyrins (16-18), which utilizes more flexible and reactive dipyrromethene intermediates, appeared ideally suited for the synthesis of sterically hindered porphyrins having small fully hydrophobic cavities.

A preliminary communication outlining the synthesis of the durene-capped parent porphyrin and the crystallographic characterization of a chloroiron(III) derivative has appeared (19).

Results and discussion

The bis(chloromethyl)durene (1) was used as starting material for the introduction of the tetramethylphenylene protecting
group for the porphyrin. The synthetic strategy involved the elaboration of 1 into durene bisalkanoic acids (Scheme I; 11, 13, and 18), which could be employed to acylate, simultaneously, two \( \beta \)-unsubstituted pyrroles. Such chain-linked bispyrroles could then be transformed efficiently into the durene-capped porphyrins using the chemistry perfected for the synthesis of deformed porphyrins (16–18).

It was uncertain as to how reactive compound 1 might be, given a significant potential for steric hindrance by the ortho-methyl groups. However, in absolute ethanol containing excess sodium ethoxide and diethyl malonate, bis(chloromethyl)durene reacted rapidly and exothermically to give durene-bismethylene malonic ester (2) nearly quantitatively. Compound 2 could be isolated as a crystalline solid by aqueous dilution of the reaction mixture. However, we found it convenient to saponify the tetraester \( \text{in situ} \) by the addition of water and further alkali. The resulting durene-bismethylene malonic acid (3) was isolated by acidification of the reaction mixture. Its decarboxylation to the
durene-bispropanoic acid (4) was initially effected by the addition of 3 to boiling quinoline, but N,N-diethylformamide was subsequently found to be an equally effective solvent.

Although diborane reduction of the diacid 4 was effective on a small scale, solubility problems were encountered upon scale-up, which led to incomplete reduction of the carboxyl groups, thus producing, in addition to the bis(hydroxypropyl)durene (5), the mono(hydroxypropyl)monocarboxyethyl-durene (6). The use of this incompletely reduced material in the subsequent bromination reaction with 48% aqueous HBr led to the formation of an ester-linked durene dimer 7 as a significant by-product that was difficult to separate from the desired bis(bromopropyl)durene (8). However, these problems were avoided by prior esterification of the diacid 4, which improved the solubility of both the starting material and intermediates of the diborane reduction. The bis(hydroxypropyl)durene (5) isolated in greater than 95% yield was converted to the bis(bromopropyl)durene (8) in over 90% yield. Had these problems been anticipated in the diborane reduction of 4, the tetramethyl ester could have been isolated and its direct conversion to the diester 9 attempted. Decarbalkoxylations of similar geminal diesters have been reported by Krapcho et al. (20).

To generate the durene-bisbutanoic acid (11), bis(bromopropyl)durene (8) was reacted with KCN in ethanol and the resulting durene-bisbutyronitrile (10) hydrolyzed with alkali. The bispentanoic acid (13) and the bisheptanoic acid (18) were prepared by similar malonate syntheses and functional group modifications as shown in Scheme 1.

Examination of space-filling models suggested that two five-carbon chains would allow a durene moiety to be held close to the macrocycle, without significant deformation of the porphyrin core. It was to this species that we first directed our efforts (series a). The reaction sequence was then repeated using the bisbutanoic acid (11) (series b) and the bisheptanoic acid (18) (series c). The experimental methods and yields for all the intermediates in both series b and c were entirely comparable and are provided as supplementary material.

The subsequent synthetic strategy involved the intramolecular cyclization of the chain-linked 5'-unsubstituted-5-formyldipyromethane dimers. Only two basic pyrroles were used in this synthesis. 2-Ethoxycarbonyl-3,5-dimethylpyrrole (20) was pre-
pared by the reductive condensation (21) of diethyloximinomalonate with 2,4-pentanediione in the presence of zinc and acetic acid. The other pyrrole, 2-ethoxycarbonyl-4-ethyl-3-methylpyrrole (30), was prepared by improved procedures (16) of standard degradations (22) of 2-ethoxycarbonyl-4-ethyl-3,5-dimethylpyrrole.

The synthesis of the durene-capped porphyrin was initiated by the acylation of the pyrrole 20 with the diacid chloride 19 in methylene chloride - nitromethane using stannic chloride as catalyst (Scheme 2). The resulting durene-bisoxoalkylidene pyrrole 21 was subjected to the usual diborane reduction, to convert the ketonic carbonyl to methylene groups. For ease of manipulation, the bispyrrole ethyl ester 22 was transbenzylated (18) to give the bispyrrole benzyl ester 23, which was then transformed into the synthetically useful bisformylpyrrole 27 by standard methods (18). The benzyl ester 23 was cleaved by catalytic hydrogenation in tetrahydrofuran and, after removal of the catalyst and the solvent, the acid 24 was decarboxylated in refluxing dimethylformamide. Vilsmeier formylation with phosphorus oxychloride was effected in dimethylformamide without isolation of the bis α-free pyrrole 25, and the resulting iminium salt 26 was hydrolyzed in aqueous bicarbonate to produce the formylpyrrole 27. This was converted to its dicyanovinyl (23) derivative 28 primarily for the purpose of protecting the formyl group during the subsequent oxidation of the α-methyl group. This also served as a method of purification by chromatography, which was essential at this stage since none of the intermediates 24–27 was isolated.

Modification of the α-methyl groups of 28 to monochloroethyl groups was now required in order to condense them with the α-unsubstituted pyrrole 30 to produce the dipyromethane dimers (Scheme 3). The possibility that the durene-methyl
groups might compete with the pyrrole α-methyl groups for the oxidant, sulfuryl chloride, made this reaction the most crucial step in the entire reaction sequence. However, in practice, sulfuryl chloride reacted exclusively with the pyrrole α-methyl groups, and the chloromethyl derivative 29 so produced gave the desired dipyrromethane dimer 31 in the excellent yield of ca. 90% overall for two reactions. The deprotection of the formyl groups and the saponification of the esters of 31 were effected in 90% yield. 

The solvent was evaporated under reduced pressure causing the product to separate out as a white solid. More water (ca. 1 L) was added and the product was collected by filtration. The crude product was recrystallized from DMSO-water (2:1) and then from methanol to constant m.p. The starting material did not dissolve, but turned into a pale yellow solid. The yield of the porphyrin was 14.1 g (94.7%). 

A significant nuclear Overhauser effect was observed in the NMR spectra of the porphyrin 34.

The 1H NMR spectra of 34a-c exhibit significant upfield shifts for the durene methyl and chain-CH2- resonances, resulting from the shielding effect of the porphyrin diamagnetic ring current. The durene methyl protons, usually observed at δ 2.2, are shifted, for example for 34c, to δ 0.2-0.20 ppm, and the chain-CH2-resonances for 34a-c are spread over the range δ = +4 to +2 ppm.

The porphyrin methine protons appear as two singlets in the 1H NMR spectra of 34a-c. The assignment of the upfield resonance to the 5- and 15-methine protons for 34a-c in 11-16% and 9-13% yield, respectively.

Experimental

The NMR spectra were obtained in the indicated solvents, using a Varian HA-100 or XL-100 instrument for proton (5-mm tube) or a Varian CFT-20 (at 25.2 MHz) or Bruker WH-400 (at 100.6 MHz) instrument for carbon-13 (10-mm tube). Melting points were obtained using a Thomas Hoover Unimelt apparatus, and are uncorrected. Microanalyses were performed by P. Borda of this department. Reagents were employed as obtained, unless otherwise noted.

1,4-Bis(2,2-dicarboxyethyl)-2,3,5,6-tetramethylbenzene (3)

Freshly cut metallic Na (12.85 g, 0.56 mol) was dissolved under N2, in anhydrous ethanol (600 mL) in a 2-L Erlenmeyer flask. Diethyl malonate (152 mL, 160.4 g, 1.0 mol) was added followed by 1,4-bis(chloromethyl)-2,3,5,6-tetramethylbenzene (bis(chloromethyl)durene) (I) (57.8 g, 0.25 mol), which was washed down with another 50 mL of anhydrous ethanol. The mixture was refluxed on a stirrer hot plate for 0.5 h; the starting material dissolved on reaction, with precipitation of NaCl.

Ethanol (approximately 200 mL) was distilled off, the reaction mixture cooled to room temperature, and a solution of KOH (200 g, 3.04 mol) in water (400 mL) added. Distillation of ethanol was continued until the temperature reached 100°C, more water (ca. 1 L) added until all of the solid dissolved, and the solution reheated to boiling. This was treated, dropwise, with concentrated HCl (ca. 300 mL). The white solid that precipitated out was collected by filtration, washed well with water, and dried in air to give 86.8 g (94.9%) of analytically pure material, mp 278.0-280.0°C (dec.).

1,4-Bis(2-carboxyethyl)-2,3,5,6-tetramethylbenzene (4)

Durene-bis(methylenemalonic acid) 3 (86.5 g, 0.24 mol) was added in portions to boiling quinoline (150 mL) over 20 min. The resulting thick mixture was heated until gas evolution ceased and then poured into 6 M HCl (400 mL). The product that crystallized out was collected by filtration and washed well with water under suction.

The crude solid was purified by dissolving in hot saturated aqueous NaHCO3, filtering through Celite, and reprecipitating with concentrated HCl. Yield, 62.9 g (94.7%); mp 284.0-286.0°C. 1H NMR (δ 0.56-1.05, 3H, -CH2-CH3); 3.78 (t, 4H, -OCH2CH3); ms m/e: 278 (72) (M-2 CO2), 219 (100), 205 (54). Anal. calcd for C16H22O4: C 71.82, H 6.05; found: C 71.95, H 5.92.

1,4-Bis(2-ethoxycarbonyl-ethyl)-2,3,5,6-tetramethylbenzene (5)

1,4-Bis(2-carboxyethyl)-2,3,5,6-tetramethylbenzene (4) (158.9 g, 0.57 mol) was esterified with ethanol (400 mL) and concentrated H2SO4 (27 mL) using toluene (200 mL) to azetropze out the water (Dean-Stark trap). Yield, 170.5 g (89.4%); mp 118-120°C. 1H NMR (δ 0.22-0.24, 3H, -CH2-CH3); 3.42 (t, 4H, -OCH2CH3); 3.78 (t, 4H, -OCH2CH3); ms m/e: 278 (40), 205 (47), 191 (100), 170 (100), 161 (63), 147 (100). Anal. calcd for C16H24O4: C 75.21, H 6.92; found: C 75.42, H 6.91.
analysis of the reaction mixture after 30 min indicated that the reaction was complete.

The solution was cooled to room temperature, CH₂Cl₂ (100 mL) added, and the acid extracted out with saturated aqueous NaHCO₃ (2 × 30 mL) and water (30 mL). The organic layer was dried (Na₂SO₄) and evaporated in vacuo after adding CH₂OH. The product crystallized out as silvery white needles, yield 9.4 g (83.3%). The mother liquors were concentrated to give a second crop of 2.7 g (8.5%).

1.4-Bis(3-cyanopropyl)-2,3,5,6-tetramethylbenzene (10)

1.4-Bis(3-cyanopropyl)-2,3,5,6-tetramethylbenzene (10) (12.5 g, 39.0 mmol) was treated with HCl (30 mL) and water (30 mL). After being stirred for 1 h, the reaction mixture was poured into water (300 mL) and acidified with concentrated HCl to give 15.9 g (99%) of the desired product, mp 193.5–195.0°C (dec.). IH nmr (0, CDC₆D₅): 1.57–1.72 (m, 4H, side-chain 2,2’-CH₂), 2.12, 2.06–2.38 (s, m, 16H, durene CH₃), 2.80–2.97 (m, 4H, side-chain 1,1’-CH₂), 4.13 (q, 4H, J = 7 Hz, CH₂-CN); l3C nmr (0, CDC₆D₅): 131.98 (4C, durene 2,3,5,6), 33.69 (2C, CH₂ Br), 32.71 (2C, side-chain 1,1’), 30.60 (2C, side-chain 2,2’), 29.73 (2C, side-chain 3,3’), 26.37 (2C, side-chain 4,4’), 16.34 (4C, durene CH₃); ms m/e: 390 (M⁺, 55), 295–297 (M⁺-2CO₂, 45), 275 (100). Anal. calcd. for C₂₅H₂₃NO₂: C 78.30, H 6.31, N 5.81; found: C 78.47, H 6.37, N 5.82.

1.4-Bis(6,6-dicarboxyhexyl)-2,3,5,6-tetramethylbenzene (12)

The bismalonic acid 17 was decarboxylated in refluxing diethylether to give the diacid 18 in near quantitative yield, mp 147–149°C (dec.). IH nmr (0, TFA/CDC₁₅): 1.35 (br, 16H, side-chain 2,2’-CH₂), 1.28–1.70 (m, 14H, side-chain 1,1’-CH₂), 2.12 (s, 12H, durene CH₃), 2.33–2.73 (m, 4H, side-chain 1,1’-CH₂); ms m/e: 390 (M⁺, 100), 275 (50), 253 (30), 170 (100). Anal. calcd. for C₂₄H₂₁O₄: C 73.81, H 7.45, found: C 73.77, H 7.42.

Chains-linked bispyrroles

1.4-Bis[5-(5-ethoxycarbonyl-2,4-dimethylpyrrol-3-yl)-oxo-pentyl]-2,3,5,6-tetramethylbenzene (21a)

Durene-bispentalenic acid (13) (16.7 g, 0.05 mol) and SOCl₂ (3.8 g, 0.02 mol) were refluxed on a steam bath until the mixture was homogeneous and gas evolution had ceased (ca. 30 min). The excess SOCl₂ was removed by evacuation in vacuo and by codistillation with CCl₄ (4 × 30 mL). The resulting crude dicarboxylic acid (19e) and 2-ethoxybenzyl-3,5-dimethylpyrrole (20) (18.0 g, 0.11 mol) were dissolved in CH₂Cl₂ (175 mL); CH₃NO₂ (100 mL) and anhydrous SnCl₄ (38.9 g, 0.15 mol) were added dropwise at room temperature under moisture-exclusion conditions.

After being stirred for 1 h, the reaction mixture was poured into water (300 mL) acidified with concentrated HCl (10 mL), stirred for 15 min, and filtered to collect the solid product (18.3 g, 57.9%). Evaporation in vacuo of the organic phase from the filtrate afforded a second crop of 2.7 g (8.5%).

An analytical sample was obtained by adding ethanol to a concentrat-
ed solution of the crude solid in CH₂Cl₂ and minimum trifluoroacetic acid; mp 207.5–209.0°C. ¹H nmr (δ, %, TFA/CDCl₃): 1.46, 1.38–2.10 (t, br, 14H, OCH₂CH₃, chain 2,2',3,3'-CH₂), 2.24 (s, 12H, durene CH₃), 2.39 (s, 6H, pyrrole-4-CH3), 2.42 (s, 6H, pyrrole-2-CH₃), 2.58–2.85 (m, 4H, chain 1,1'-CH₂), 2.96 (t, 4H, J = 7.5 Hz, chain 4,4'-CH₂), 4.47 (q, 4H, J = 7 Hz, OCH₂CH₃), 10.20 (bs, 2H, NH); ¹C nmr (δ, 10%, TFA/CDCl₃): 204.11 (2C, ketonic C=O), 142.27 (2C, chain 2), 136.59 (2C, durene 1,4), 132.37 (6C, pyrrole 4, durene 2,3,5,6), 123.03 (2C, pyrrole 3), 118.61 (2C, pyrrole 5), 62.57 (2C, -OCH₂CH₃), 42.27 (2C, chain 4,4'), 30.62, 29.88 (4C, chain 1,1',2,2'), 26.12 (2C, chain 3,3'), 16.41 (4C, durene CH₃), 15.44 (2C, pyrrole-2-CH₃), 14.26 (2C, -OCH₂CH₃), 13.03 (2C, pyrrole-4 CH₃); ms m/e: (M⁺, 19), 209 (100), 194 (71), 148 (62). Anal. calcd. for C₅₈H₆₃N₂O₇: C 72.10, H 8.08, N 4.63.

(ii) Decarboxylation. The above yellow solid was dissolved in DMF (100 mL) and refluxed under N₂ until the uv absorption maximum at 284 nm was reduced to a minor shoulder (ca. 2.5 h).

(iii) Formylation. The decarboxylation mixture above was added dropwise to an ice-cooled solution of the Vilsmeyer reagent (prepared by adding POCl₃ (30 mL) in CH₂Cl₂ (10 mL) to DMF (25 mL) in CH₂Cl₂ (80 mL)); the reaction mixture was stirred for 30 min, when the CH₂Cl₂ was removed in vacuo and the remaining solution poured onto crushed ice (500 g).

Solid NaHCO₃ was added cautiously (with effervescence) until the solution was weakly basic. The solution was heated on a steam bath (further bicarbonate being added if the solution became acidic) until the remaining CH₂Cl₂ evaporated, and a clear brown single-phase solution was formed (pH should remain around 8).

The solution was suction filtered to remove insoluble tars, the volume adjusted to ca. 1 L with water, and heating continued for a further 24-30 min. The bisformylpyrrole 27a separated out as a grey solid and was filtered, washed with water, and dried to give 7.1 g. The crude solid was reacted with malonitrile to afford the bisdicyanovinyl-pyrrole 28a (vide infra). After purification by chromatography, a sample of this was deprotected with KOH in aqueous propanol to produce 27a for analysis; mp 233.0–234.0°C. ¹H nmr (δ, CDCl₃): 1.46 (br, 12H, 2,2',3,3',4,4'-CH₂), 2.20 (s, 12H, durene CH₃), 2.22, 2.26 (s, 12H, pyrrole-2,4-CH₃), 2.30–2.43 (m, 4H, 5,5'-CH₂), 2.56–2.69 (m, 4H, 1,1'-CH₂), 8.99 (bs, 2H, NH), 9.44 (s, 2H, CHO); ms m/e: 516 (M⁺, 42), 488 (33), 473 (18), 136 (100), 108 (76). Anal. calcd. for C₅₈H₆₁N₆O₇: C 78.87, H 9.47, N 5.43.

1.4-Bis[5-(5-ethoxy carbonyl-2,4-dimethylpyrrolyl-3-yl)pentyl]-2,3,5,6-tetramethylbenzene (22a)

The diethyl ester 21a (17 g, 0.027 mol) and NaBH₄ (3 g, 0.079 mol) were suspended in dry THF (400 mL) under N₂ and treated dropwise (ice-bath) with BF₃·Et₂O (14 mL, 0.11 mol). When tlc examination showed the absence of starting material or intermediates (more NaBH₄ was added), the reaction mixture was quenched by careful dropwise addition of glacial acetic acid (500 mL). Water (1.5 L) was added causing the separation of the product, which was filtered and washed with water. The solid was redissolved by heating in THF (500 mL), the undissolved impurities were removed by filtration, and the filtrate was then diluted with CH₂Cl₂ and concentrated in vacuo to give 14.3 g (98.1%) of a white powdery solid, in two parts, mp 182.5–207.5°C; ¹H nmr (δ, TFA/CDCI₃): 1.46, 1.44 (s, 12H, chain 2,2' ,3,3' ,4,4'-CH₂), 2.19, 2.22, 2.30, 2.22–2.50 (s,s,s,m, 28H, pyrrole 2-CH₃, durene CH₃, pyrrole 4-CH₃, chain 5,5'-CH₂), 2.50–2.78 (m, 4H, chain 1,1'-CH₂), 3.51 (s, 4H, OCH₂CH₃), 7.30–7.52 (m, 10H, C₅H₅), 8.68 (bs, 2H, NH); ¹C nmr (δ, 10% TFA/CDCl₃): 164.53 (2C, C=O), 137.17 (2C, durene 1,4), 135.81 (2C, benzene 1), 134.25 (2C, pyrrole 2), 132.35 (4C, durene 2,3,5,6), 131.03 (2C, pyrrole 4), 128.91, 128.69, 128.39 (10C, benzene 2,3,4,5,6), 123.96 (2C, pyrrole 3), 115.57 (2C, pyrrole 5), 67.37 (2C, -OCH₂CH₃), 30.96, 30.82, 30.24, 30.07 (8C, chain 1,1',2,2',3,3',4,4'), 24.20 (2C, chain 5,5'), 16.49 (4C, durene CH₃), 11.69, 11.34 (4C, pyrrole-2,4-CH₃); ms m/e: 728 (M⁺, 88), 620 (36), 242 (32), 108 (100), 91 (68). Anal. calcd. for C₅₈H₆₁O₄: C 77.98, H 8.30, N 3.84; found: C 77.91, H 8.47, N 3.83.

1.4-Bis[5-(5-formyl-2,4-dimethyl pyrrolyl-3-yl)pentyl]-2,3,5,6-tetramethylbenzene (27a)

This compound was prepared from the foregoing dibenzyl ester 23a in three steps without the isolation and characterization of the intermediates.

(i) Debenzylation. The dibenzyl ester 23a (10.0 g, 13.8 mmol) and 10% Pd/C (0.9 g) were stirred under H₂ (1 atm, room temperature), in

THF (250 mL) containing triethylamine (5 drops). When the H₂ uptake ceased (ca. 3 h), the solution was checked by tlc for the absence of starting material and the catalyst was filtered. The solvent was then removed in vacuo below 40°C, affording the crude bisbcarboxypyrrole as a pale yellow solid.
the bischloromethyl derivative 29a to crystallize as a lemon yellow powdery solid. This was collected by filtration, washed with 10% CHCl₂ in ether, air dried, and used in the following reaction without further purification.

(ii) Formation of the bisdipyromethene. The above bischloromethyl derivative 29a and 2-ethoxy carbonyl-4-ethyl-3-methylpyrrole 30 (1.2 g, 6.6 mmol) were warmed (water bath) in glacial acetic acid (600 mL), under N₂ to 80°C. The yellow starting material dissolved with reaction and the solution turned orange-red. Thin-layer chromatographic analysis indicated that the reaction was complete in 1 h.

The solution was cooled to room temperature, concentrated to ca. 25 mL in vacuo, CH₂OH (100 mL) was added, and it was allowed to stand overnight under refrigeration. The product crystallized as a dark yellow solid, which was collected by filtration and washed with CH₂OH; yield 1.74 g (89.2%). An analytical sample was recrystallized from CH₂Cl₂-CH₂OH, mp 186.0–190.0°C. *¹H nmr (8, CDCl₃): 1.02 (t, 6H, J = 7.5 Hz, 3°CH₂(CH₃)₂), 1.32 (t, 6H, J = 7 Hz, -OCH₂CH₃), 1.44 (br, 12H, chain 2.2, 3.3, 4.4°CH₂), 2.13 (s, 6H, -CH₃), 2.20 (s, 12H, durene CH₂), 2.26 (s, 6H, pyrrole 4°-CH), 2.33–2.48 (m, 8H, 4°-CH₂CH₃, chain 1.5°-CH₂), 2.56–2.69 (m, 4H, chain 1°-CH), 3.94 (s, 4H, meso CH₂), 4.23 (q, 4H, J = 7 Hz, OCH₂CH₃), 7.28 (s, 2H, (CH) = (C)N₂), 8.75 (br, 2H, 1°-NH), 11.97 (br, 2H, 1°-NH); *¹C nmr (8, 10% TFA/CDCl₃): 164.74 (2C, C=O), 142.93 (2C, (CH) = (C)N₂), 141.89 (2C, pyrrole 2), 138.78 (2C, pyrrole 4), 136.89 (2C, durene 1°-CH₂), 132.21 (4C, durene 2.3.5.6), 129.82, 128.98, 126.51, 126.11 (8C, pyrrole 3°, 3°, 3°, 4°, 125.19 (2C, pyrrole 3°-CH₂), 118.09 (2C pyrrole 3°), 117.65 (2C, C=CN), 115.67 (2C, C=CN), 61.97 (2C, -OCH₂CH₃), 60.99 (2C, (CH) = (C)N₂), 30.82 (2C, chain 1°-CH₂), 30.19, 29.97 (4C, 2C, chain 2°, 2°, 3°, 4°, 4°, 24.20 (4C, meso CH₂, chain 2°), 17.44 (2C, pyrrole 3°-CH₂CH₃), 16.42 (4C, durene CH₂), 15.29 (2C, pyrrole 3°-CH₂CH₃), 14.24 (2C, -OCH₂CH₃), 10.85 (2C, pyrrole 4°CH₂), 9.76 (2C, pyrrole 4°CH₂); ms; m/e 970 (0.2), 924 (1.6), 878 (2.6), 745 (26). Anal. calcd. for C₉₇H₇₅N₃O₃: C 74.20, H 7.68, N 11.54; found: C 73.99, H 7.51, N 11.60.

1. 4,8-Bis[5'-2-[[5-(carboxy-3-ethyl-4-methylpyrrol-2-yl)-methyl]-5-formyl-4-methylpyrrol-3-yl]phenyl]-2,3,5,6-tetramethylbenzene (32a)

The dimeric dicyanovinyl dipyrromethene ester 31a (1.2 g, 1.1 mmol) was dissolved in a solution of KOH (7.5 g) in water (100 mL) and the mixture heated under N₂. At reflux, n-propanol (60 mL) was added; the yellow starting material dissolved promptly giving a pale brown solution. Reflux was continued and the reaction was monitored by uv–visible spectroscopy. The starting material was absorbed strongly by 407 nm, and moderately at 275 nm, while the product absorbed strongly at 270 nm and 320 nm. Propanol was then boiled off while replenishing with water (total volume 300 mL) until the reaction temperature reached 100°C. The solution was cooled to room temperature under N₂, acidified with acetic acid, and the product isolated and dried to give 1.01 g (99%) of analytically pure material, mp 158.0–160.0°C (dec.); *¹H nmr (6, DMSO-d₆): 0.84 (t, 6H, 3°CH₂CH₃), 1.32 (br, 12H, chain 2.2, 3.3, 4.4°CH₂), 1.96–2.54 (br, 36H, durene CH₂, pyrrole 2.4°-CH₂, chain 1.1°, 5°-CH₂, 3°-CH₂CH₃), 3.78 (br, 4H, meso CH₂), 9.48 (s, 2H, CHO), 10.94 (bs, 2H, 1°-NH), 11.48 (bs, 2H, 1°-NH); ms: m/e 818 (M⁺, 5), 816 (15), 730 (40). Anal. calcd. for C₉₇H₇₅N₃O₃: C 73.32, H 8.12, N 6.84; found: C 73.28, H 8.22, N 6.80.

7,17-Diethyl-2,8,12,18-tetramethyl-3,13-(2,3,5,6-tetramethyl-phenylene)-1.4-bis(pentamethylenylene)porphyrin (34a)

(i) Decarboxylation. The chain-linked bisdipyromethane 32a (901 mg; 1.1 mmol) was decarboxylated in refluxing DMF (100 mL) under N₂. The reaction was monitored by uv spectroscopy; the absorption band at 280 nm decayed relative to the band at 320 nm and the reaction was complete in 2–3 h.

The solution was cooled under N₂, concentrated in vacuo to approximately 50 mL, and diluted with CH₂Cl₂ (200 mL). This was washed with water (3 × 60 mL) to remove most of the remaining DMF, dried (Na₂SO₄), filtered, and diluted to 500 mL with CH₂Cl₂ in preparation for the next step.

(ii) Intramolecular 2 + 2 coupling. The cyclization was carried out in two 2-L Erlenmeyer flasks (covered with aluminum foil to exclude light) each containing p-toluenesulfonic acid (4.0 g) in CH₂OH (25 mL) – CH₂Cl₂ (600 mL). The CH₂Cl₂ solution from the above decarboxylation step was added to the catalyst solution by means of a syringe pump; the entire addition was complete in 6 days.

The reddish violet solution was concentrated in vacuo to approximately 150 mL, extracted with saturated aqueous NaHCO₃ (3 × 50 mL) to remove the acid catalyst, and then dried over anhydrous sodium sulfate. The residue was taken up in minimal CH₂Cl₂ and chromatographed as described below.

(iii) Chromatographic purification of porphyrin. The crude porphyrin was initially chromatographed on silica gel (Woelm, act. I. 70–150 mesh, 100 g) using CH₂Cl₂ to elute most of the nonfluorescent impurities. The porphyrin was eluted with 2% CH₂OH in CH₂Cl₂ and rechromatographed on activity IV silica gel (35 g). The impurities were removed with CH₂Cl₂ and the porphyrin was eluted cleanly using 1% CH₂OH in CH₂Cl₂, and crystallized from CH₂Cl₂ to give a yield of 239 mg (31.4% overall for decarboxylation–cyclization). Typically, the yield varied between 22 and 31% and appeared to depend to a large extent on the particular sample of the starting material 32a; mp 273.0–274.5°C. Visible spectrum (CH₂Cl₂, λₚₚₚₚₚₚₚₚₚₚ) found by high resolution mass spectrometry: 692.4866; [¹²CaoH₂N₃O₃]⁺ required 692.4818. Anal. calcd. for C₉₇H₇₅N₃O₃: C 81.22, H 8.84, N 7.73; found: C 81.50, H 8.90, N 7.72.
7,17-Diethyl-2,8,12,18-tetramethyl-3,13[2,3,5,6-tetramethyl-phenylene-1-4-bis(heptamethylen)]porphyrin (34c)

This was synthesized in a manner similar to that described for its analogue 34a. The second chromatographic purification of this material was performed on activity III neutral alumina. Some fore­

running brown impurities were removed by using 25% hexane-toluene initially. The porphyrin product was then eluted cleanly using 20% CH2Cl2-toluene and was crystallized from CH2Cl2-CH3OH. Yields varied between 9 and 13%, mp 314.5-315.5. Visible spectrum (CH3Cl), 34a.

1,4), 12.19, 11.66 (4C, 2,8,12, 18-CH3)' Mol Wt. found by high resolution mass spectrometry: 748.5446; 12C521H6S14N4 requires 748.5444. Anal. calcd. for C52H6sN4'112H20: C 82.38, H 9.17, N 7.39; found: C 82.58, H 9.34, N 7.30.

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