The Synthesis and Proton Nuclear Magnetic Resonance Study of some Nitro- and Amino-unsymmetrically *meta*-Substituted Tetraphenylporphyrins

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Procedures for the synthesis of new partially-substituted mesotetraphenylporphyrins (TPP's) are described. The 5-(3-nitrophenyl)-10,15,20-triphenylporphyrin is the primary product from a 1:2:3 molar ratio of *m*-nitrobenzaldehyde, benzaldehyde and pyrrole. The crude reaction product also contained TPP, 5,10-bis-(3-nitrophenyl)-15,20-diphenylporphyrin, 5,15-bis(3-nitrophenyl)-10,20-diphenylporphyrin, and 5,10,15-tris-(3-nitrophenyl)-20-phenylporphyrin. The crude mixture of *m*-nitrophenylporphyrins was reduced to a mixture of the corresponding amino derivatives, which was separated into TPP, 5-(3-aminophenyl)-10,15,20-triphenylporphyrin, 5,10-bis(3-aminophenyl)-15,20-diphenylporphyrin, and 5,15-bis(3-aminophenyl)-10,20-diphenylporphyrin. The products were characterized by uv-visible and ir spectrophotometry, and by high resolution nmr spectroscopy and mass spectroscopy.

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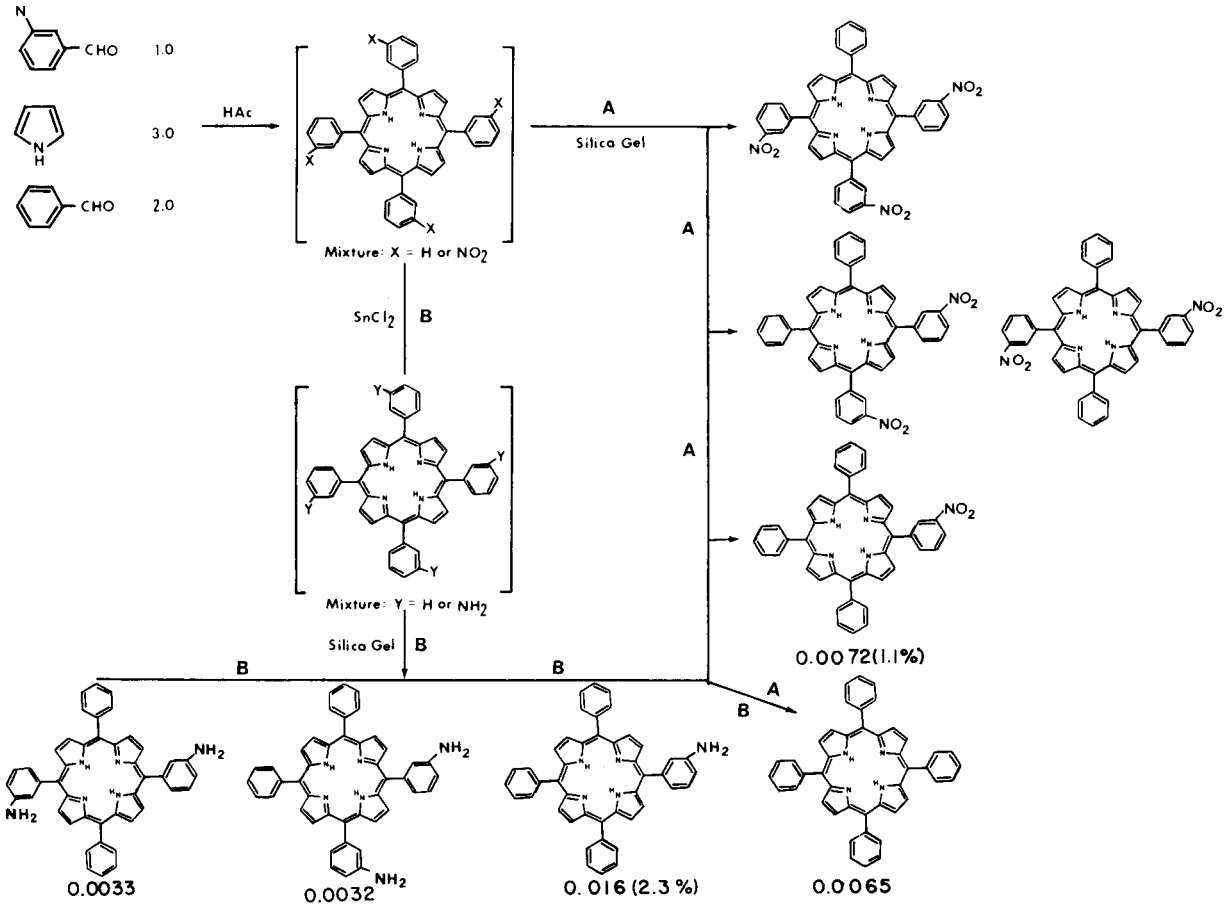
Introduction.

Numerous symmetrically substituted tetraarylporphyrins [1-10] have been used as models for the naturally occurring porphyrins because of their ease of preparation by a one-step synthesis in spite of the characteristically low yields obtained in most cases. On the other hand relatively few unsymmetrically substituted tetraphenylporphyrins [1, 11-22] have been synthesized, especially those with substituents on the *meta* positions of the peripheral phenyl

SCHEME

REACTION ROUTES AND SEPARATIONS FOR THE SYNTHESIS OF PARTIALLY SUBSTITUTED m-AMINO AND m-NITRO TETRAPHENYLPORPHINES



groups.

For the synthesis of tetraarylporphyrin derivatives having more complex substitutents that are built up by stepwise reactions, there are definite advantages in preparing the monosubstituted derivatives. Thus the problem of separation of reaction products resulting from incomplete reactions is greatly simplified. Also, it was found in the present work, that the mono-substituted product generally has higher solubility in polar solvents than the tetra-substituted analogs. If the substituent is a polar multifunctional group, the monosubstituted product is usually more easily purified by column chromatography than are the tetra-substituted prophyrins.

Since Ibers and coworkers [1] reported the mixed aldehyde synthesis of several mono-substituted tetratolylporphyrins, a number of other functional groups have been added to the peripheral phenyl ring of tetraarylporphyrins by this method, such as: carboxy [12,13,14]; 4-pyridyl [18,20]; 4-alkyloxy [19,22] benzoquinonyl [16]; nitro and amino [11,17] benzo-15-crown-5-ether [15]; 2,6-dinitrophenyl [17]; 4-hydrox-3-nitrophenyl, 4-hydroxy-3-methoxy-5-nitrophenyl [17]. Some of these compounds served as precursors for the synthesis of models for myoglobin, the

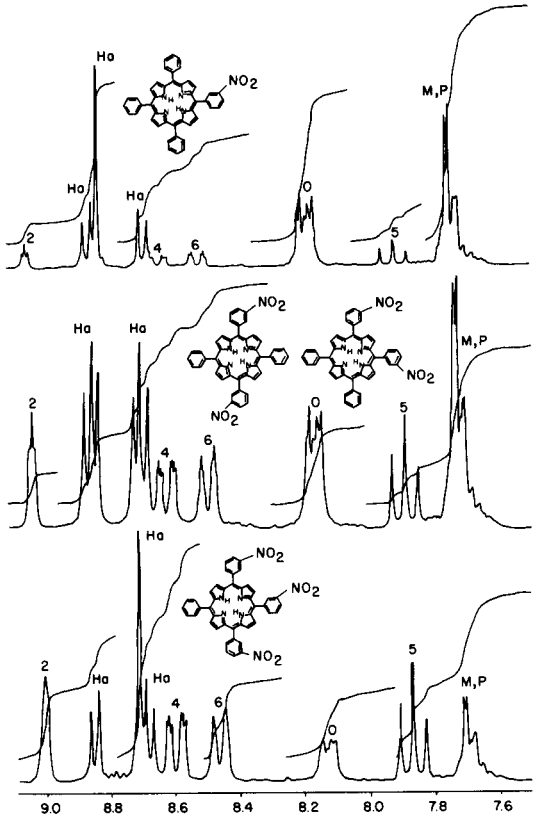


Figure 1 200 Hz proton nmr of some *m*-nitroporphyrins (in deuteriochloroform, see numbering system in Figure 3).

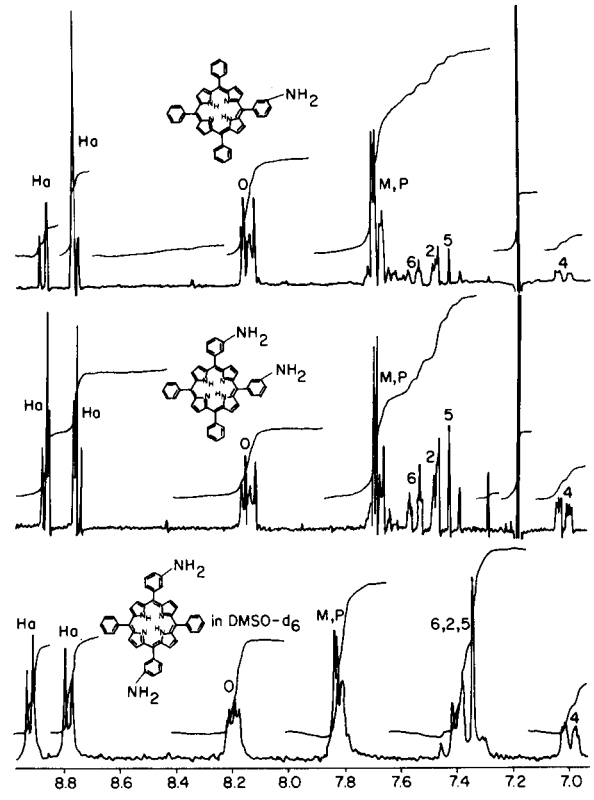


Figure 2 200 Hz proton nmr of some *m*-aminoporphyrins (in deuteriochloroform, see numbering system in Figure 3).

cytochromes, and the photosynthetic active site. This report describes the synthesis of 5-(3-nitrophenyl)-10,15,20-triphenylporphyrin (mono-*m*-nitroTPP) and 5-(3-aminophenyl)-10,15,20-triphenylporphyrin (mono-*m*-aminoTPP) as intermediates for the build-up of more complex substitution products, which may also be further modified by substitution of the para positions. The related di- and tri-substituted derivatives and isomers were also isolated and characterized.

Results and Discussion.

The reaction route and separation for the synthesis of mono-, di- and tri-*m*-nitrotetraphenylporphyrins are shown in the Scheme (route A). Because of the deactivating effect of the nitro group on the activity of the aldehyde function a 2:1 ratio rather than the statistical 3:1 ratio of benzaldehyde and *m*-nitrobenzaldehyde was used. Benzene was employed for the chromatographic separation of mono-, di- and tri-nitrotetraphenyl porphyrins from a dry column. A silica gel column, 2 x 24 in, was used to separate 0.5 g of a mixture with development taking about one hour.

Because the Rf value differences between the aminoporphyrins are larger than those of the nitroporphyrins, for the preparation of aminoporphyrins, the column separa-

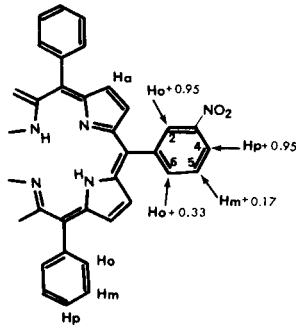


Figure 3 Number system and the chemical shifts (ppm) calculation of mono-*m*-nitroTPP, and mono-*m*-aminoTPP.

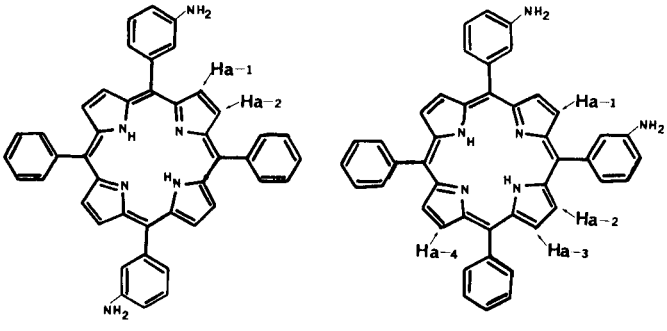


Figure 4 The different β-pyrrol protons (Ha) of *trans*-di(*m*-amino)TPP and *cis*-di(*m*-amino)TPP.

Table I

Shielding Parameters (ppm) for Aromatic Substituents [24]

Substituent	ortho	meta	para
$-NO_2$	+0.95	+0.17	+0.33
$-NH_2$	−0.75	−0.24	−0.63

tion step was best delayed until the reduction of the mixture of nitro porphyrins was completed (Scheme, route B). Thus with a shorter column, less solvent, and less time, a better yield (2.3%) of mono-*m*-aminoTPP based on the starting benzaldehyde was obtained. In Collman's work [11] two column separations were used for the preparation of the monosubstituted ortho isomer with a 1.2% yield of crude reaction product.

The uv-visible spectra of all the porphyrins in this work are nearly the same. The ir spectra of the nitroporphyrins have two peaks at 1530 and 1350 cm^{-1} which are characteristic of the nitro group [11,23]. The intensities of these two peaks increase as the number of nitro groups in the substituted tetraphenylporphyrins increases. Proton nmr, a powerful technique for identification of nitro- and amino-porphyrins, also clearly distinguishes between the structures of the two isomeric disubstituted TPP's. Figures 1 and 2 compare the nmr spectra of some nitro- and aminoporphyrins. By use of the chemical shifts of the unsubstituted TPP [25], Ho, Hm and Hp and the shielding parameters of nitro- and amino-groups for aromatic compounds [24] (Table I), the ppm values of H-2, H-4, H-5 and H-6 were calculated (Fig. 3). The experimental values are consistent with the calculated data (Table II). The expected coupling pattern and coupling constants were also obtained (see Experimental Section). The deshielding effect of the nitrophenyl ring also changes the chemical shifts and coupling patterns of the pyrrole β protons (designated as Ha). Two doublets and one singlet appear in the spectrum of mono-*m*-nitroTPP, whereas for TPP the identical eight Ha's produce a singlet.

The nmr spectra of the amino porphyrins are comparable to those of their nitro analogs (Fig.2), with the only difference being the upfield chemical shifts of the four protons on the aminophenyl rings, as would be expected from the electron-withdrawing and electron release effects of the nitro- and amino-substituents, respectively (Table I).

Table II

Some PMR Chemical Shifts of
Mono-*m*-nitroTPP and Mono-*m*-aminoTPP

	Mono-*m*-nitroTPP		Mono-*m*-aminoTPP	
Proton	Experimental	Calculated	Experimental	Calculated
H-2	9.01	9.15	7.48	7.45
H-4	8.61	8.65	7.02	6.95
H-5	7.88	7.87	7.43	7.46
H-6	8.48	8.53	7.56	7.57

Due to the shielding effect of the aminophenyl ring, the 5,15-bis(3-aminophenyl)-10,20-diphenylporphyrin (*trans*-di(*m*-amino)TPP) has two non-identical Ha's, whereas the *cis* analog (5,10-bis(3-aminophenyl)-15,20-diphenylporphyrin (*cis*-di(*m*-amino)TPP)) has four (Figure 4). Thus the coupling patterns of the former produce two doublets, the latter two doublets and two singlets. Since the disubstituted nitro porphyrins which was isolated is a mixture of two isomers, its nmr shows overlap of these two groups of peaks.

The different symmetries of the two disubstituted amino isomers leads to different solubilities in polar solvents. Thus the *trans* derivative is less soluble in chloroform than its *cis* isomer.

EXPERIMENTAL

Measurements.

The proton nmr spectra were recorded with a Varian XL-200 spectrometer operating at 200 MHz, using a 30° pulse applied every 3 seconds. The spectra were determined using a 4000 Hz spectral window, 24000 data points, and quadrature phase detection, resulting in 0.33 Hz digital resolution. Unless otherwise specified, the solvent is deuterochloroform with tetramethylsilane (TMS) as standard. The shifts are given in ppm from TMS and the coupling constants are in Hz. The infrared spectra were obtained in potassium bromide pellets with a Sargent-Welch Model 3-2000 Infrared Spectrophotometer. The uv-visible spectra of chloroform solutions were obtained with a Cary 14 recording spectrophotometer. The mass spectra were obtained by a Californium-252 Plasma Desorption Mass Spectrometer.

The C, H, N analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Separations.

The chromatographic separations described below were effected by the dry-column procedure using silica gel 40 (70-230 mesh ASTM) purchased from MC/B Manufacturing Company, Inc. (EM Reagent). The tlc was performed with a commercially prepared silica gel 60 F_{254} purchased from Merck (layer thickness 0.2 mm).

Materials.

All solvents and reagents were purchased commercially and used as supplied except for pyrrole, which was distilled before use, and benzene, which was dried over activated 4A molecular sieves.

5-(3-Nitrophenyl)-10,15,20-triphenylporphyrin (mono-*m*-nitroTPP).

Benzaldehyde (17.7 g, 0.167 mole, 17.0 ml) and *m*-nitrobenzaldehyde (12.6 g, 0.083 mole) were dissolved in 500 ml of glacial acetic acid. The mixture was brought to reflux and 17.5 ml of pyrrole (0.25 mole) was added as rapidly as possible without causing excessive evolution of heat. The resulting black solution was heated at reflux for 20 minutes, then cooled to 35°. The solid material was filtered on a coarse sintered glass funnel, and washed repeatedly with methanol until the washings were nearly colorless. The crude product was dried at 105° for several hours. 2.5 g of fine shiny purple crystals were obtained.

A small sample of the crude porphyrin sample was dissolved in chloroform and fractionated by thin layer chromatography. The plate developed with benzene was found to have five spots, with relative Rf values of 0.85, 0.70, 0.50, 0.41, and 0.04. Subsequent work proved that the first spot is TPP, the second is mono-*m*-nitroTPP, the third and fourth spots are the di- and tri-substituted porphyrins, respectively.

Silica gel (600 g) was deactivated by shaking for 3 hours with 72 g of water. The deactivated silica gel was packed into a 2 x 24 in column. The crude porphyrin mixture (0.5 g) was dissolved in 20 ml of chloroform, 20 g of silica gel was added, the solution was vacuum evaporated to nearly dryness at 30-40°. The loaded silica gel was placed at the top of the column, and covered with a 3mm layer of purified sand. About 900 ml of benzene was used as the developing solvent. Of the five bands that were developed, the first and second band had a certain extent of overlap, while the other three components were completely separated. The column was allowed to run dry and tamped down to collect the bands. The second band was placed in a small column, washed with chloroform and an equal volume of methanol was added to the concentrated chloroform solution of the desired mononitrophenylporphyrin. A purple crystalline product was isolated by filtration and washed with methanol. After the solid was dried at 150° for several hours, a yield of 80 mg (16% based on crude porphyrin mixture; 1.1% based on the starting benzaldehyde) was obtained; ir: 1530 cm^{-1} (ν (asym) NO_2), 1350 cm^{-1}(ν (sym) NO_2); visible spectrum (chloroform): 646, 588, 549, 515, 480 nm; pmr [26]: δ 9.01 (t, 1H, H-2, J = 2), 8.82 (d, 2H, Ha, J = 4.8), 8.79 (s, 4H, Ha), 8.65 (d, 2H, Ha, J = 4.8), 8.12-8.17 (m, 6H, Ho), 7.68-7.74 (m, 9H, Hm, Hp), 8.48 (d, d, d, 1H, H-6, J = 8, 2, 2), 8.61 (d, d, d, 1H, H-4, J = 8, 2, 2), 7.88 (t, 1H, H-5, J = 8); ms: m^+/e, 659, 660, m^-/e, 658. F.W. = 659.75.

Anal. Calcd. for $C_{44}H_{29}N_5O_2$: C, 80.1; H, 4.43; N, 10.6. Found: C, 79.8; H, 4.38; N, 10.2.

The porphyrins which were isolated from the first, third and fourth bands were also crystallized and characterized by ir, pmr and visible spectra. The procedures employed for separation and work-up are similar to those described above for mono-*m*-nitroTPP. The porphyrin which was isolated from the first band is TPP (verified by its ir, pmr and visible spectrum). The second band components have the following characteristics: ir: 1530 cm^{-1} (ν (asym) NO_2), 1350 cm^{-1}(ν (sym) NO_2); visible spectrum (chloroform): 645, 590, 550, 518, 482 nm; pmr [26]: δ 9.01 (t, 2H, H-2, J = 2), 8.84-8.80 (d + s, 4H, Ha), 8.65-8.69 (d + s, 4H, Ha), 8.59 (d, d, d, 2H, H-4, J = 8, 2, 2), 8.46 (d, d, d, 2H, H-6, J = 8, 2, 2), 7.85 (t, 2H, H-5, J = 8), 8.10-8.17 (m, 4H, Ho), 7.65-7.72 (m, 6H, Hm, Hp), ms: m^+/e, 705.5 (100), m^-/e, 704.2 (100). F.W. = 704.75. It is a mixture of 5,15-bis(3-nitrophenyl)-10,20-diphenylporphyrin and 5,10-bis(3-nitrophenyl)-15, 20-diphenylporphyrin. The fourth band component is 5,10,15-tris(3-nitrophenyl)-20-phenylporphyrin; ir: 1520 cm^{-1} (ν (asym). NO_2), 1350 cm^{-1}(ν(sym) NO_2), visible spectrum (chloroform): 645, 590, 550, 518, 482 nm; pmr [26]: δ 9.01 (t, 3H, H-2, J = 2), 8.84 (d, 2H, Ha, J = 4), 8.71(s, 4H, Ha), 8.68 (d, 2H, Ha, J = 4), 8.60 (d, d, d, 3H, H-4, J = 8, 2, 2), 8.45 (d, d, d, 3H, H-6, J = 8, 2, 2), 7.87 (t, 3H, H-5, J = 8), 8.10-8.14 (m, 2H, Ho), 7.65-7.72 (m, 3H, Hm, Hp); ms: m^+/e, 749.7 (23), 750.1 (30), m^-/e, 749.5 (100). F.W. = 749.75.

To the filtered porphyrin chloroform solution was added 50 g of silica gel. The mixture was vacuum evaporated to near dryness and was then dried in air. The loaded silica gel was placed on the top of a 4.5 x 26 cm dry silica gel column, which contained 240 g of silica gel which had been pre- equilibrated with the mixture of 28 ml water and 24 ml 95:5 of benzene:ether by volume.

5-(3-Aminophenyl)-10,15,20-triphenylporphyrin (mono-*m*-aminoTPP).

The crude nitroporphyrin mixture (0.53 g) was dissolved in 65 ml of concentrated hydrochloric acid, and 1.6 g of tin(II)-chloride dihydrate was added. The green solution was stirred at room temperature for 45 minutes and then heated to 65° for 45 minutes. After the solution was cooled in ice, 54 g of potassium hydroxide was added to bring the pH of the suspension higher than 10. The brown-violet mixture was stirred with 130 ml of chloroform for 1 hour, the organic layer was separated, and 40 ml of chloroform was used to wash the aqueous layer. All chloroform extracts were combined and washed three times with equal volumes of water and dried over anhydrous sodium sulfate. This aminoporphyrin solution was spotted on a tlc plate. Four spots were developed with benzene-ether (95:5 V/V). Their relative Rf values are 0.91, 0.48, 0.04, 0. High resolution pmr studies showed that they are TPP, mono-*m*-aminoTPP, *cis*-di(*m*-amino)TPP and *trans*-di(*m*-amino)TPP, respectively.

The column was developed and washed with benzene. The rapidly-moving band was identified as TPP by its ir and nmr spectra. After all the TPP had been separated, a more polar solvent, benzene:ether - 9:1, was used to separate the second band. The pmr spectrum and mass spectra data proved that this band contains pure mono-*m*-aminoTPP; pmr [26]: δ 8.76-8.87 (d + s, 8H, Ha), 8.12-8.17 (m, 6H, Ho), 7.65-7.71 (m, 9H, Hm,Hp), 7.43 (t, 1H, H-5, J = 8), 7.48 (t, 1H, H-2, J = 2), 7.02 (d, d, d, 1H, H-4, J = 8, 2, 2), 7.56 (d, t, 1H, H-6, J = 8, 2), 3.8 (b, 2H, $-NH_2$), -2.9 (b, 2H, 21H, 23H of porphine); ms: m^+/e, 629.6 (70), 630.45 (100); m^-/e, 629.6 (91.8), 630.6 (100). F.W. = 629.77.

Anal. Calcd. for $C_{44}H_{31}N_5$: C, 83.8; H, 4.93; N, 11.1. Found: C, 83.6, H, 5.00; N, 10.82.

Two additional (3rd and 4th) bands were separated on the column by continued washing with benzene:ether (9:1 V/V). The proton nmr and mass spectra results proved that these two bands contain separate diaminoporphyrin isomer: 5,10-bis(3-aminophenyl)-15,20-diphenylporphyrin pmr [26]: δ 8.75-8.86 (d + s, 8H, Ha), 8.10-8.16 (m, 4H,Ho), 7.64-7.70 (m, 6H, Hm, Hp), 755 (d, t, 2H, H-6, J = 8, 2), 7.47 (t, 2H, H-2, J = 2), 7.43 (t, 2H, H-5, J = 8), 7.02 (d, d, d, 1H, H-4, J = 8, 2, 2), 3.8 (b, 4H, $-NH_2$), −2.9 (b, 21H, 23H of porphine); ms: m^+/e 645.62 (100), m^-/e = 644 (95), 645 (95), 646 (100). F.W. = 644.28.

Anal. Calcd. for $C_{44}H_{22}N_6$: C, 82.0; H, 4.97; N, 13.0. Found: C, 81.9; H, 5.17; N, 12.6. 5,15-bis(3-aminophenyl)-10,20-diphenylporphyrin; pmr (DMSO-d_6) [26]; δ 8.78-8.92(d,8H, Ha), 8.16-8.22 (m, 4H, Ho), 7.78-7.84 (m, 6H, Hm, Hp), 7.0 (d + m, 2H, H-4, J = 8), 7.30-7.44 (m, 6H, H-2, H-5, H-6), 5.4 (b, 4H, $-NH_2$), -3 (b, 21H, 23H of porphine); ms: m^+/e, 645.11 (79), 645.47 (100), (64). F.W. = 644.78.

Anal. Calcd. for $C_{44}H_{32}N_6$; C, 82.0; H, 4.97; N, 13.0. Found: 82.2; H, 5.11; N, 12.4.

After recrystalization (chloroform-methanol) the following yields were obtained: TPP, 71.5 mg; mono-*m*-aminoTPP, 174.4 mg; *cis*-di(*m*-amino)TPP, 36.2 mg; *trans*-di-(*m*-amino)TPP, 38 mg. Total porphyrins obtained are 320.1 mg, which represents 60% of the crude nitroporphyrins. The yield of 5(3-aminophenyl)-10,15,20-triphenylporphyrin is 2.3% based on the starting benzaldehyde.

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[26] See structure in Figure 3 for numbering system.