IMPROVED SYNTHESES OF 5,10,15,20-TETRAKISARYL- AND TETRAKISALKYLPORPHYRINS

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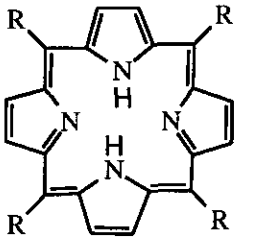
Abstract – Three significant modifications to existing methods for the preparation of the important 5,10,15,20-tetrakisarylporphyrins have improved isolated yields, simplified work-up and made large-scale synthesis feasible. Two tetrakisalkyl-porphyrins were also produced. A two-stage approach using hydrogen peroxide in acetic acid as second stage oxidant gave good yields but for ease of isolation and convenience in working on a large scale, the one-pot approach is preferred. No one method appears to be suitable for all such tetrakisarylporphyrins and, for best yields, the method of preparation needs to be chosen carefully. Application of statistical optimisation techniques (factorial two design and simplex operation) led to considerably enhanced yields for the one-pot method. For one of the two-stage modifications, significant amounts of chlorins were observed, sometimes of such magnitude as to make it suitable as a method for their preparation.

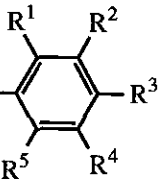
INTRODUCTION

Porphyrins are currently of major interest in a wide variety of fields encompassing catalysis,[1] molecular electronics,[2] energy conversion,[3] modelling of enzymes[4] and photodynamic cancer therapy.[5] Specifically, in oxidative catalysis, mimics of cytochrome P450 and peroxidases are being sought in simple model systems, many of which are based on 5,10,15,20-tetrakisarylporphyrins.[4] Important efforts are being made to synthesize these model compounds by quick short routes from cheap starting materials,

particularly those arylporphyrins having bulky ortho-aryl substituents which can sterically hinder the approach of oxidants to the reactive meso- or α-pyrrole positions at which oxidative attack normally occurs.[6]

Synthesis of both symmetrical and unsymmetrical 5,10,15,20-tetrakisarylporphyrins can be effected conveniently from pyrroles and aromatic aldehydes in "one-" and "two-pot" reactions . The one-pot or one-stage reactions involve mixing a suitable aldehyde with a pyrrole under acidic, oxidising conditions; the required porphyrin often separates directly from the reaction medium, making isolation easy. The two-pot or two-stage process involves condensing the aldehyde and pyrrole under low temperature conditions until a maximum yield of porphyrinogen is attained and then the mixture is oxidised to the porphyrin stage through use of a strong oxidising agent such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Isolated yields are frequently poor or modest or are much less than those expected from initial analysis by visible spectroscopy. Best reaction conditions and work-up vary from porphyrin to porphyrin and there is no one best method for all porphyrins. Many reported yields are not based on actual isolated product porphyrin but are estimates derived from the height of the Soret band in the reaction mixture before isolation. The intrinsic absorption at the Soret wavelength is not constant but varies from porphyrin to porphyrin. More importantly, the Soret band in crude porphyrin preparations is most likely due to additive effects of the required porphyrin, its chlorin and other isomers. This effect has been discussed[7] and exemplified.[8] If normal workup losses are also included, then reported yields of porphyrins based on the height of a Soret band are frequently wildly optimistic and do not match isolated yields. In the present work, three methods are described for synthesis of several tetraarylporphyrins (**1**, ***a–n***) and two tetraalkylporphyrins (**1**, ***o–p***) by taking advantage of the best features of the one- and two-stage syntheses. Three variants are reported and compared for most of the porphyrins synthesised (Table 1). All yields refer to isolated pure porphyrin, averaged over several preparations in each case. For the simplest of these methods (the one-pot synthesis), which is most applicable to large-scale preparations, utilization of statistical factorial two design and a simplex in *n*-fold space led to considerable improvements in attainable yields.





1*a–n*; R =

1*o*; R = *n*-C_3H_7
1*p*; R = *n*-$C_{11}H_{23}$

RESULTS AND DISCUSSION

Both one- and two-pot syntheses appear to proceed through an initial condensation of aldehyde and pyrrole to porphyrinogen followed by its oxidation to porphyrin although, in one variation, pyrrole and aldehyde are first condensed to form an acylpyrrole by a modified Vilsmeier reaction before assembly into the porphyrinogen.[9] In the one-pot reaction, the porphyrinogen occurs at an intermediate, unisolated stage but, in the two-pot type, this first step is separated physically from the second stage oxidation to porphyrin. The earliest[10] and most recently modified[11] one-pot syntheses use a carboxylic acid to catalyse the first condensation step and cheap air (oxygen) and/or a nitroaromatic for the second oxidative step. In two-pot reactions, careful attention to detail has resulted in a first step showing good yields of porphyrinogen, which are based on observation of the Soret band after oxidation of test aliquots from the reaction mixture; at this optimum stage, a standard method of oxidation of porphyinogen to porhyrin has been established using the expensive DDQ.[12] Recently,[11] this oxidative stage has been effected with the much cheaper nitrobenzene but, in some cases, chlorins can be produced in surprisingly large amounts and these are not always readily oxidised to porphyrin by the nitrobenzene.[13] Indeed, in some instances, this approach is more suited to the preparation of chlorins than it is to porphyrins. In the present work, three variants were explored. The first two (methods A, B) were "two-pot" reactions using respectively either cheap hydrogen peroxide or nitrobenzene as second stage oxidants and the third (method C) was a "one-pot" approach in which the statistical Simplex method was used to maximize yields. The advantages of the different modifications enable diverse 5,10,15,20-tetrakisarylporphyrins to be synthesized on a large scale.

Typically, for the first modification of the two-pot procedure (method A, Table 1), pyrrole and the requisite aromatic aldehyde, with BF_3-etherate in $CHCl_3$ were stirred at room temperature until small test samples when reacted with DDQ in toluene revealed that no further increase in porphyrin yield could be expected. This stage was reached usually in 3-4 h. At this point, a slight excess of triethylamine was added to deactivate the BF_3 and was followed by addition of a freshly prepared solution of hydrogen peroxide in acetic acid. After 1 h at room temperature and workup, the reproducible isolated yields of porphyrin shown the Table were obtained. Generally, yields are between 12 and 40%. No evidence for the formation of chlorins was found with this oxidative procedure.[13] Such use of hydrogen peroxide in the synthesis of porphyrins would seem at first to be unreasonable as this reagent is known to oxidise

haem and other natural porphyrins at the meso- and even the α-pyrrole positions.[6] Closer examination of the earlier results with hydrogen peroxide reveals that those oxidations were done either on metallo-

Table 1. Yields of porphyrins (**1*a–p***) obtained by the three methods (A, B, C) and through use of a statistical simplex operation.

Porphyrin (**1**) tetrakis (substituent)[a]	Isolated yield (%), method A[b]	Isolated yield (%), method B[c]	Isolated yield (%), method C[d]
(*a*) phenyl	14	6 (1.5)	20
(*b*) 4-biphenyl	12	20 (15)	40 [46]
(*c*) 4-methoxyphenyl	21	25 (11)	21 [78]
(*d*) 3,4-dimethoxyphenyl	23	25 (0)	18
(*e*) 3,4,5-trimethoxyphenyl	30	-[f]	-
(*f*) 3,4-methylenedioxyphenyl	20	18 (14)	27
(*g*) 3-chlorophenyl	19	30 (0)	22
(*h*) 4-chlorophenyl	27	13 (4)	49 [56]
(*i*) 2,4-dichlorophenyl	-	10 (2)	9
(*j*)2,6-dichlorophenyl	23	5 (13)	5
(*k*)2,4,6-tribromo-3-methoxyphenyl	10	3 (12)-	-
(*l*) 2,6-difluorophenyl	-	7.5 (0.5)	9
(*m*)4-methylthiophenyl	-	-	37
(*n*) 4-methylsulphoxyphenyl	40	-	-
(*o*) *n*-propyl[e]	-	-	12
(*p*)*n*-undecyl[e]	-	-	13

a. 5,10,15,20-Tetrakisarylporphyrins, except for **1*o,p***. All porphyrins were characterized by ^{1}H-nmr, uv/visible and mass spectroscopy (FAB) and elemental analysis, as described in the experimental section.

b. No chlorins were observed by uv/visible or ^{1}H-nmr spectroscopy.

c. Amounts of chlorins were determined from ^{1}H nmr spectra of the crude product mixtures and are shown in parentheses. The total yield of porphyrin plus chlorin is obtained by *addition* of the two figures.

d. The yield using Simplex optimisation is shown in square brackets. The yield obtained with standard conditions is the first figure reported.

e. These are 5,10,15,20-tetrakis*alkyl*porphyrins.

f. In the cases where no preparation was carried out, a dash is shown.

porphyrins in the presence of the strong ligand pyridine or on free porphyrin dissolved in a strong acid. In the oxidation of porphyrinogens described here, there is no metal, no pyridine or other strong ligand and the meso- and α-pyrrole positions are more or less protected by the substituent aryl groups. Yields of isolated product are generally good, even for the sterically hindered ortho-disubstituted compounds

(Table 1). In view of the known acid-catalysed reaction of hydrogen peroxide with carboxylic acids to form peroxycarboxylic acids, it is quite probable that the actual oxidant in this method A is not hydrogen peroxide itself but, rather, peroxyacetic acid. This cheap method of oxidation is much more convenient than the use of DDQ since the latter is expensive on a large scale and its reduction products necessitate careful chromatography to separate them from the required porphyrin.

In the second modification of the two-pot approach, the initial porphyrinogen in $CHCl_3$, formed as in method A, was neutralized with triethylamine and was then dropped into a mixture of acetic acid and nitrobenzene held at 120 °C in air, at such a rate that the lower boiling $CHCl_3$ distilled out as fast as it was added. Yields of isolated products are shown in Table 1. This direct addition of the initial chloroform reaction medium to the hot oxidising nitrobenzene/acetic acid solution was preferred because other experiments had shown that, if the $CHCl_3$ solution was first evaporated to leave a residue which was then added to the oxidising mixture, yields of porphyrin were lower than expected from oxidation of test samples with DDQ, sometimes drastically so. It is thought that this diminution in yield was caused by some reversal of the initial ring closure to porphyrinogen, which occurred during evaporation of the solvent, followed by general oxidative degradation so that there was relatively little residual porphyrinogen to be added to the nitrobenzene oxidant. Although isolation of product is easy with method B since it usually crystallizes out of the reaction mixture directly, for some types of porphyrinogen under the oxidising conditions (nitrobenzene/air) applied to this two-step approach, considerable proportions of chlorins can be formed, as shown by the appearance of their characteristic signals in ^{1}H-nmr spectra of the crude reaction products.[13] These cases are shown in Table 1. Unexpectedly, extended heating of these reaction mixtures in the nitrobenzene/air oxidising medium did not convert the chlorins into more of the corresponding porphyrin. The problem of formation of chlorin did not arise with the same oxidant when used in the one-pot method C (see below). This observation suggests that conversion of porphyrinogen into porphyrin proceeds through more than one pathway, one of which goes through the chlorin stage, for which nitrobenzene/air is not suitable for converting it into porphyrin.[13] The mechanism of oxidation of porphyrinogens to porphyrins *via* chlorins, phlorins and so on has been discussed.[15] Notably in the present experiments, a combined 18% yield of porphyrin plus chlorin was obtained from the reaction of pyrrole with the highly *ortho*-hindered 2,6-dichlorobenzaldehyde but only 5% of this mixture was the desired porphyrin, the remainder being the

corresponding chlorin. In comparison, method A, which is also a two-step process but using hydrogen peroxide (or peroxyacetic acid) as oxidant, does not give chlorins; it gave a comparable 23% yield of product that was entirely the required sterically hindered porphyrin. These yields for methods A, B are in sharp contrast to the approximately 5% yields of porphyrin usually reported in reactions with the ortho-disubstituted 2,6-dichlorobenzaldehyde. It is documented[16] and confirmed[17] that reaction conditions are highly demanding for efficient cyclization of pyrroles and aldehydes to 5,10,15,20-tetrakisporphyrinogens when there are bulky groups in the ortho-positions of the initial aldehydes. The initial dipyrromethane, which is formed at the first stage to formation of porphyrinogen, tends to be oxidized to a stabilized dipyrromethene species.[16] In the present work with method B, for some porphyrinogens, the yield of chlorin is so high compared with porphyrin that the method could be regarded more properly as a good synthesis of chlorins. For example, in the case of 5,10,15,20-tetrakis(2,4,6-tribromo-3-methoxyphenyl)porphyrin (Table 1), approximately 80% of the isolated "porphyrin" was actually the corresponding chlorin. Porphyrins could be isolated from mixtures with the corresponding chlorins most readily by chromatography of their zinc complexes.

The third modification is a "one-pot" reaction[11] in which pyrrole and an aromatic aldehyde are added to a mixture of acetic acid and nitrobenzene preheated to 120 °C. After reaction, it is usually sufficient to cool the solution to room temperature in order to obtain crystals of the product porphyrin in a high state of purity. Yields are given in Table 1. The absence of any chlorins in the products of this one-stage reaction suggests that, although the oxidants (nitrobenzene and air) are the same as for Method B, the oxidation of porphyrinogen to porphyrin must not pass through a chlorin step because chlorins formed in method B were not affected by nitrobenzene and air. Since formation of a chlorin requires a migration of hydrogens from the meso to the β-positions, it is probable that oxidation of any porphyrinogen initially produced by method C occurs almost immediately, before there is time to form a significant quantity of chlorin by rearrangement. A major advantage of the one-pot method C is that the product porphyrin usually crystallises directly in a highly pure form from the cooled reaction mixture. Although overall yields from method C may not be quite as high as those obtained by method A or B, the ease of work-up makes method C very convenient, particularly on a large scale. As shown below, this advantage can be enhanced quite considerably by a statistical methods investigation of optimum experimental parameters for any one porphyrin. This chemometric approach is capable of improving yields considerably.

For maximum yields with method C, it appears that reaction parameters are more critical than for the "two-pot" reactions. Accordingly, the one-pot preparation of three 5,10,15,20-tetrakisarylporphyrins was examined through use of a factorial two statistical design experiment[18] followed by optimization through the Simplex procedure.[19] Temperature, the presence of *both* nitrobenzene and air, and the amounts of nitrobenzene and carboxylic acid were found to be crucial in determining yields of porphyrin. In order to be able to operate at temperatures above the boiling point of acetic acid, higher homologues such as propionic or valeric acid were used, as described in the experimental section. With temperature, amounts of carboxylic acid, nitrobenzene, and the presence or absence of air as parameters for the Simplex, the yield of porphyrin could be maximized. For example, in the case of 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (**1*c***), the best conditions were found to be reaction at 160 °C under aerobic conditions, with a molar ratio of 2.3:1 for the proportions of carboxylic acid (valeric) to nitrobenzene. The yield of isolated porphyrin increased from 21% under standard conditions for method C to 78% under the Simplex optimised conditions. The same procedure applied to 5,10,15,20-tetrakis(4-biphenyl)porphyrin (**1*b***) and 5,10,15,20-tetrakis(4-chlorophenyl)porphyrin (**1*h***) raised the standard yields from 40 to 46% and 38 to 56% respectively.

By way of comparison of the reactivity of alkyl and aryl aldehydes in method C, two tetrakisalkylporphyrins (**1*o,p***) were synthesised. Reaction occurred readily although, in these cases, the products did not crystallise directly from the reaction medium but had to be recovered by chromatography of the crude reaction products on alumina.

CONCLUSIONS

Two-step and one-step conversions of pyrrole and aromatic or alkyl aldehydes into porphyrins have been investigated. The two-step approach has been improved through the use of hydrogen peroxide as second stage oxidant after the first condensation step to porphyrinogen. This second stage was also effected through the use of nitrobenzene and air as joint oxidants but this procedure can lead to exceptionally high yields of chlorins being produced in some cases. A one-pot conversion of pyrrole and aldehyde into porphyrin has been shown to be readily applicable on a large scale, with easy isolation of pure porphyrin. This method normally gives good yields but these can be improved by variation of reaction conditions. A statistical factorial two statistical design experiment has shown that the amounts of nitrobenzene and

carboxylic acids are important and that there is an interactive effect of them that affects yields. The statistical design experiment also showed that the presence of both nitrobenzene and air was necessary for obtaining best yields. With the importance of these reaction parameters known, it is then a simple task to carry out a Simplex optimization on any of the one-pot syntheses so as to afford greatly improved yields of 5,10,15,20-tetrakisarylporphyrins. The one-pot method is particularly suited to large-scale operation. Where the two-step approach is used, hydrogen peroxide in acetic acid is an excellent cheap alternative to the traditionally used DDQ.

EXPERIMENTAL

Mass spectra were determined on a VG 7070E mass spectrometer, using fast atom bombardment with Xenon from a 3-NOBA matrix. Nuclear magnetic resonance spectra were obtained on a Bruker WM 2000 (200 MHz) spectrometer; the solvents were $CDCl_3$ or $(CD_3)_2SO$, unless stated otherwise. Uv/vis spectra were measured on a Hewlett Packard 845A diode array spectrometer, using CH_2Cl_2 or $CHCl_3$ as solvent. All porphyrins reported in Table 1 were checked for purity by elemental analysis, and ^{1}H nmr, mass and uv/vis spectroscopy. Percentages of chlorin found in some reactions were determined from characteristic resonances in their ^{1}H nmr spectra, as set out below. Dichloromethane and chloroform were purified before use by refluxing them over dry potassium carbonate for 2–3 h and then distilling them.

Synthesis of porphyrins

Method A. In a typical reaction, pyrrole (0.35 ml, 5 mmol), the requisite aldehyde (5 mmol) and BF_3 etherate (5 mmol) in $CHCl_3$ (500 ml) were stirred at room temperature until small test samples, when reacted with an excess of 2,3-dichlo-5,6-dicyanobenzoquinone in toluene (10^{-2} M) and examined for a Soret band near 420–430 nm, revealed no further increase in porphyrin yield could be expected (usually after 3–4 h). At this optimum stage, a slight excess of triethylamine (70 µl) was added to deactivate the BF_3, followed by a freshly prepared solution of hydrogen peroxide (1.5–2.0 g; 35% w/v) in acetic acid (100 ml; 98-100%). The mixture was stirred for 1 h at 20-30 °C after which the solution was washed with aqueous 5% sodium hydrogen carbonate and then water. The chloroform was distilled off and the residue was chromatographed on alumina (Woelm Grade II), using $CHCl_3$ as eluant. The porphyrins shown in Table 1 were prepared by this method.

Method B. In the second modification of the two-pot approach, the initial porphyrinogen in $CHCl_3$, prepared as described in Method A, was neutralized with triethylamine and was then added dropwise to a mixture of acetic acid and nitrobenzene held at 120 °C so that the lower boiling $CHCl_3$ distilled off as fast as it was added. After addition of all the $CHCl_3$ solution, the reaction temperature was maintained at 120 °C for 1 h and was then allowed to cool overnight. Usually, the required porphyrin crystallized directly from the reaction medium and was simply filtered off, washed with methanol and dried. For the few cases when the porphyrin did not crystallise or crystallised out in low yield, the solvent was distilled off from the reaction product, which was then chromatographed as described in method A above. Chlorins were produced in some of these experiments. Their presence and concentrations were monitored easily by ^1H nmr spectroscopy of the first crystallized reaction product. The ratios of chlorin to porphyrin were most readily estimated from the relative peak sizes of their NH proton resonances at about δ –1.3 (chlorin) and δ –2.6 (porphyrin). Chlorins were also identified by the presence of their β-proton resonances separate from the normal singlet near δ 8.8 representing β-protons in a porphyrin. For example, in the chlorin accompanying tetrakis(2,6-dichlorophenyl)porphyrin (**1** *j*), there were β-proton signals at δ 8.45 (d, 2H, 5.5 Hz), 8.25 (s, 2H), 8.1 (d, 2H, J 5.5 Hz) and 4.1 (s, 4H). Where formed, chlorins were found only in method B and were not usually separated from the corresponding porphyrin, which could be obtained more readily by method A or C. Where the chlorins were produced in large proportion to porphyrin, they could be separated by chromatography through alumina as for porphyrins; the separation was better if the mixture of chlorin and porphyrin was first converted into their zinc complexes with $ZnCl_2$.

Method C. In a typical "one-pot" reaction,[11] pyrrole (0.7 ml, 10 mmol) and an aromatic aldehyde (10 mmol) were added to a mixture of acetic acid (75 ml, 1.3 mol) and nitrobenzene (50 ml, 490 mmol) preheated to 120 °C. The temperature was maintained for 1 h and then the solution was cooled to room temperature to give crystals of the product porphyrin, which were filtered off and dried. Yields are given in Table 1. No chlorins were produced by this method and isolation was usually simple, with rarely any need for chromatography.

Simplex Procedure. An initial factorial 2 design experiment[18,19] into the factors involved in producing best yields of tetrakis(4-methoxyphenyl)porphyrin was carried out. For this, 4-methoxybenzaldehyde (1

ml, 7.3 mmol) was reacted with pyrrole (0.7 ml, 10 mmol) in each experiment. A mixture of propionic acid, nitrobenzene and 4-methoxybenzaldehyde were heated to the required temperature and then the pyrrole was added all at once. The chosen factorial low and high values of temperature, amount of propionic acid, length of reaction at set temperature after addition of pyrrole, amount of oxygen and amount of nitrobenzene were respectively: 100 and 150 °C; 5 and 50 ml; 30 and 90 min; under argon (absence of air) and in an air atmosphere; 0 and 50 ml. For these preliminary experiments, the yield of porphyrin was estimated from the height of the Soret band at 422 nm. The results revealed that temperature, amount of acid, amount of nitrobenzene, and the presence or absence of oxygen needed to be considered as the most important parameters. Further, there were strong interactions for temperature and the amount of nitrobenzene and for the amount of oxygen with the amount of nitrobenzene.[20] Neither oxygen nor nitrobenzene alone produced the best yields. On the basis of these factorial 2 design results, three parameters (temperature, amount of carboxylic acid, amount of nitrobenzene) were chosen as being most important for implementation of a Simplex analysis[19,20] to optimise yields. The Simplex analysis was applied to the preparation of three porphyrins, all in the presence of air: 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin, 5,10,15,20-tetrakis(4-biphenyl)porphyrin, and 5,10,15,20-tetrakis-(4-chlorophenyl)porphyrin. After about 9–11 moves of the Simplex, best yields were obtained under conditions that were different from the standard ones described for Method C, which is essentially the same reaction but carried out without optimization of yields. The Simplex procedure was highly beneficial and, for large-scale preparations of porphyrins using method C, is highly desirable. The Simplex yields are shown in Table 1 and the experiments are detailed below.

In the following list of details of all the porphyrins synthesized in this work, in structure **1**, the substituents R^1, R^2, R^3, R^4, R^5 = H, unless stated otherwise. All porphyrins were isolated as crystalline solids either directly from the reaction medium or after recrstallisation from methanol or methanol/chloroform. Except for the low melting examples recorded, the porphyrins mostly decomposed on heating or decomposed on melting, as is commonly observed with these ring systems.

5,10,15,20-Tetrakisphenylporphyrin (1*a*). Anal. Calcd for $C_{44}H_{30}N_4$: C, 86.0; H, 4.9; N, 9.1. Found: C, 85.7; H, 4.9; N, 9.0. Ms (FAB), $[M+H]^+$, m/z 615; λ_{max} ($CHCl_3$; log ε): 418 nm(5.66), 516(4.56), 550(4.25), 590(4.08), 646(4.00); ^{1}H-nmr ($CDCl_3$), δ: 8.80 (s, 8H), 8.17 (m, 8H), 7.68(m, 12H), –2.82(s, 2H).

5,10,15,20-Tetrakis(4-biphenyl)porphyrin (1*b*; $R^3 = C_6H_5$). Anal. Calcd for $C_{68}H_{46}N_4$: C, 88.9; H, 5.0; N, 6.1. Found: C, 88.6; H, 5.0; N, 5.9. Ms (FAB), $[M+H]^+$ m/z 919; λ_{max} (CH_2Cl_2; log ε): 424 nm(5.63), 518(4.62), 554(4.41), 592(4.19), 650(4.20); ^{1}H-nmr (CF_3CO_2H), δ: 8.79 (s, 8H), 8.77 (d, 8H, J 9.9 Hz), 8.33 (d, 8H, J 7.7 Hz), 8.05 (d, 8H, J 6.8 Hz) 7.72 (t, 8H, J 8 Hz) 7.60 (t, 4H, J 8 Hz), –0.06 (s, 4H).

For the one-pot Simplex approach, the optimum yield (1.05 g, 46% based on aldehyde used) was obtained from pyrrole (0.7 ml, 10 mmol) and 4-formylbiphenyl (1.76 g, 10 mmol) reacted for 1 h in a pre-heated mixture of valeric acid (84 ml, 770 mmol) and nitrobenzene (42 ml, 410 mmol) at 129 °C; the solution was allowed to cool overnight and the crystals of porphyrin (**1*b***) were filtered off.

5,10,15,20-Tetrakis(4-methoxyphenyl)porphyrin (1*c*; $R^3 = CH_3O$). Anal. Calcd for $C_{48}H_{38}N_4O_4$: C, 78.5; H, 5.2; N, 7.6. Found: C, 78.4; H, 5.4; N, 7.3. Ms (FAB), $[M+H]^+$, m/z 735; λ_{max} ($CHCl_3$; log ε): 422 nm (5.59), 518 (4.34), 556 (4.19), 594 (4.05), 650 (4.07); ^{1}H-nmr ($CDCl_3$), δ: 8.85 (s, 8H), 8.12 (d, 8H J 8.8 Hz), 7.28 (d, 8H, J 8.8 Hz), 4.05 (s, 12H), –2.8 (s, 2H).

For the one-pot Simplex approach, the optimum yield (1.43 g, 78% based on aldehyde used) was obtained from pyrrole (0.7 ml, 10 mmol) and 4-methoxybenzaldehyde (1.36 g, 10 mmol) reacted for 1 h in a pre-heated mixture of valeric acid (41 ml, 376 mmol) and nitrobenzene (11 ml, 107 mmol) at 120 °C; the solution was allowed to cool overnight and the crystals of porphyrin (**1*c***) were filtered off.

5,10,15,20-Tetrakis(3,4-dimethoxyphenyl)porphyrin (1*d*; $R^2 = R^3 = CH_3O$). Anal. Calcd for $C_{52}H_{46}N_4O_8$: C, 73.1; H, 5.4; N, 6.5. Found: C, 73.1; H, 5.4; N, 6.4. Ms (FAB), $[M+H]^+$ m/z 855 ; λ_{max} (CH_2Cl_2; log ε): 424 nm (5.53), 520(4.38), 556(4.29), 594(4.02), 650(4.03); ^{1}H-nmr ($CDCl_3$), δ: 8.9 (s, 8H), 7.78 (s, 4H), 7.74 (d, 4H, J 4.5 Hz), 7.26 (d, 4H, J 4.5 Hz), 4.17 (s, 3H), 3.98 (s, 3H), –2.75 (s, 2H).

5,10,15,20-Tetrakis(3,4,5-trimethoxyphenyl)porphyrin (1*e*, $R^2 = R^3 = R^4 = OCH_3$). Anal. Calcd for $C_{56}H_{54}N_4Cl_{12}$: C, 68.8; H, 5.6; N, 5.8. Found: C, 68.2; H, 5.7; N, 5.3. Ms (FAB), $[M+H]^+$, m/z 975; λ_{max} ($CHCl_3$; log ε): 424 nm(5.45), 516(4.25), 552(3.97), 592(3.87, 648(3.75); ^{1}H-nmr ($CDCl_3$), δ: 8.97 (s, 8H), 7.37 (s, 8H), 4.08 (s, 12H), -2.88 (s, 2H).

5,10,15,20-Tetrakis(3,4-methylenedioxyphenyl)porphyrin (1*f*; R^2, R^3 = -OCH_2O-). Anal. Calcd for $C_{48}H_{36}N_4O_8$: C, 72.9; H, 3.8; N, 7.1. Found: C, 72.9; H, 3.8; N, 7.1. Ms (FAB), $[M+H]^+$, m/z 791; λ_{max} ($CHCl_3$; log ε): 424 nm(5.58), 518(4.39), 554(4.14), 592(3.92), 650(3.90); ^{1}H-nmr ($CDCl_3$), δ: 8.87 (s, 8H), 7.67 (s, 4H), 7.61 (d, 4H, J 7.7 Hz), 7.14 (d, 4H, J 7.7 Hz), 6.21 (s, 8H), –2.85 (s, 2H).

5,10,15,20-Tetrakis(3-chlorophenyl)porphyrin (1*g*; R^2 = Cl). Anal. Calcd for $C_{44}H_{26}N_4Cl_8$: C, 70.2; H, 3.5; N, 7.4. Found: C, 69.4; H, 3.4; N, 7.4. Ms (FAB), $[M+H]^+$, m/z 751-759 (Cl isotopes); λ_{max} ($CHCl_3$; log ε): 418 nm(5.62), 514(4.47), 548(4.09), 588(4.04), 646(4.02); ^{1}H-nmr (CF_3CO_3H), δ: 8.72 (s, 8H), 8.55 (s, 4H), 8.39 (d, 4H, J 2 Hz), 7.92(m, 8H), –0.52 (s, 4H).

5,10,15,20-Tetrakis(4-chlorophenyl)porphyrin (1*h*; R^3 = Cl). Anal. Calcd for $C_{44}H_{26}N_4Cl_4$: C, 70.2; H, 3.5; N, 7.4. Found: C, 70.3; H, 3.6; N, 7.2. Ms (FAB), $[M+H]^+$ m/z 751-759 (752 max:Cl isotopes); λ_{max} (CH_2Cl_2; log ε): 418 nm(5.61), 516(4.49), 550(4.17), 590(4.04), 646(3.93); ^{1}H-nmr ($CDCl_3$), δ: 8.83 (s, 8H), 8.13 (d, 8H, J 8.8 Hz), 7.74 (d, 8H, J 8.8 Hz), –2.87 (s, 2H).

For the one-pot Simplex approach, the optimum yield (1.05 g, 56% based on aldehyde used) was obtained from pyrrole (0.7 ml, 10 mmol) and 4-chlorobenzaldehyde (1.41 g, 10 mmol) reacted for 1 h in a pre-heated mixture of valeric acid (52 ml, 477 mmol) and nitrobenzene (43 ml, 418 mmol) at 141 °C; the solution was allowed to cool overnight and the crystals of the pyrrole (**1*g***) were filtered off.

5,10,15,20-Tetrakis(2,4-dichlorophenyl)porphyrin (1*i*; R^1 = R^3 = Cl). Anal. Calcd for $C_{44}H_{22}N_4Cl_8$: C, 59.4; H, 2.5; N, 6.3. Found: C, 60.1; H, 2.9; N, 6.2. Ms (FAB), $[M+H]^+$, m/z 887–905; λ_{max} (CH_2Cl_2; log ε): 416 nm(5.6), 511(4.34), 586(3.8), 641(3.1); ^{1}H-nmr ($CDCl_3$), δ: 8.15-7.98 (m, atrop isomers, 4H), 7.89-7.85 (m, atrop isomers, 4H), 7.67-7.61 (m, atrop isomers, 4H), –2.76 (s, 2H).

5,10,15-Tetrakis(2,6-dichlorophenyl)porphyrin (1*j*; R^1 = R^5 = Cl). Anal. Calcd for $C_{44}H_{22}N_4Cl_8$: C, 59.3; H, 2.5; N, 6.3. Found: C, 59.3; H, 2.5; N, 6.3. Ms (FAB), $[M+H]^+$, m/z 887–905 (Cl isotopes); λ_{max} ($CHCl_3$; log ε): 418 nm (5.5), 512 (4.5), 588 (4.1), 611 (3.0), 657 (3.1) ; ^{1}H-nmr ($CDCl_3$), δ: 8.62 (s, 8H), 7.68 (m, 12H), –2.59(s, 2H).

5,10,15,20-Tetrakis(2,4,6-tribromo-3-methoxyphenyl)porphyrin (1*k*; R^1 = R^3 = R^5 = Br, R^3 = CH_3O; only method A). Anal. Calcd for $C_{48}H_{26}N_4O_4Br_{12}$: C, 34.3; H, 1.6; N, 3.3. Found: C, 34.7; H, 1.4; N, 3.0. Ms (FAB), $[M+H]^+$, m/z 1671-1692 (Br isotopes), max at 1681; λ_{max} (CH_2Cl_2; log ε): 421 nm (5.5), 515(3.4), 590(4.0), 659(3.6); ^{1}H-nmr ($CDCl_3$; zinc complex) δ: 8.65 (s, 8H), 8.27 (s, 4H), 4.13 (s, 12H).

5,10,15,20-Tetrakis(2,6-difluorophenyl)porphyrin (1*l*; R^1 = R^5 = F). Anal. Calcd for $C_{44}H_{22}N_4F_8$:C, 69.7; H, 2.9; N, 7.38. Found: C, 69.8; H, 2.9; N, 7.1. Ms (FAB), $[M+H]^+$, m/z 759; λ_{max} (CH_2Cl_2; log ε): 413 nm(5.57), 507(4.39), 583(3.89), 654(3.76); ^{1}H-nmr ($CDCl_3$), δ: 8.80 (s, 8H), 7.81 (m, 8H), 7.4 (m, 12H), –2.76 (s, 2H).

5,10,15,20-Tetrakis(4-methylthiophenyl)porphyrin (1*m*; $R^3 = CH_3S$). Anal. Calcd for $C_{48}H_{38}N_4S_4$: C, 72.2; H, 4.8; N, 7.0. Found: C, 72.0; H, 4.8; N, 7.0. Ms (FAB), $[M+H]^+$, m/z 799; λ_{max} (CH_2Cl_2; log ε): 424 nm(5.5), 520(4.1), 556(4.0), 594(3.6), 650(3.7); ^{1}H-nmr (DMSO) δ: 8.82 (s, 8H), 8.07 (d, 8H, J 7.7 Hz), 7.58 (d, 8H, J 7.7 Hz), 2.70 (s, 12H), –2.84 (s, 2H).

5,10,15,20-Tetrakis(4-methylsulphonylphenyl)porphyrin (1*n*; $R^3 = CH_3SO_2$). Anal. Calcd for $C_{48}H_{38}N_4O_8S_4$: C, 62.2 ;H, 4.1; N, 6.0. Found: C, 62.7; H, 4.6; N, 5.7. Ms (FAB), $[M+H]^+$, m/z 927 ; λ_{max} (CH_2Cl_2; relative %): 420 nm(100), 514(7.53), 550(4.01), 590(2.94), 646(2.0); ^{1}H-nmr (DMSO) δ: 8.83 (s, 8H), 8.38 (d, 8H, J 7.7 Hz), 8.05 (d, 8H, J 7.7 Hz), 3.06 (s, 12H), –2.79 (s, 2H).

5,10,15,20-Tetrakis(1-propyl)porphyrin (1*o*). The product was isolated by chromatography of the crude reaction mixture on alumina (Woelm, grade II), eluting with a mixture of $CHCl_3/CH_3OH$ (10:1, v/v). Anal. Calcd for $C_{32}H_{38}N_4$: C, 62.2; H; 6.04; N; 4.1. Found: C; 62.7; H; 5.7; N; 4.5. Ms (FAB), $[M+H]^+$, m/z 479; λ_{max} (CH_2Cl_2; log ε): 416 nm(5.5), 518(4.0), 553(3.8), 599(3.5), 657(3.7); ^{1}H-nmr ($CDCl_3$) δ: 9.50 (s, 8H), 4.90 (t, 8H, J 6 Hz), 1.40 (m, 72H), 0.80 (t, 12H, J 6 Hz), –2.40 (br s, 2H).

5,10,15,20-Tetrakis(1-undecyl)porphyrin (1*p*). The product was isolated by chromatography of the crude reaction mixture on alumina (Woelm, grade II), eluting with a mixture of $CHCl_3/CH_3OH$ (10:1, v/v). Anal. Calcd for $C_{64}H_{102}N_4$: C, 82.8; H; 11.1; N; 6.0. Found: C; 82.2; H; 10.5; N; 6.3. λ_{max} (CH_2Cl_2; log ε): 417 nm(5.6), 519(4.1), 554 (4.0), 600(3.6), 658(3.7); ^{1}H-nmr ($CDCl_3$) δ: 9.40 (s, 8H), 4.71 (t, 8H, J 7 Hz), 2.50 (m, 8H), 1.20 (t, 12H, J 7 Hz), –2.60 (br s, 2H), mp 80–81 °C.

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