Improved Protocols for the Synthesis and Halogenation of Sterically Hindered Metalloporphyrins

M.S. Chorghade,[†a] D. Dolphin,*[b] D. Dupré,[b] D.R. Hill,[a] E.C. Lee,[a] T.P. Wijesekera[††b]

[a] D-54P Chemical and Agricultural Products Division, Abbott Laboratories, North Chicago, Illinois 60064-4000, USA
[b] Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, B.C., Canada V6T 1Z1
Fax +1(604)8224571

Received 26 February 1996

Improved procedures are described for the synthesis of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin and for subsequent perhalogenation of the porphyrin ring.

The synthesis of perhalogenated metalloporphyrins and their use in oxidative reactions of organic substrates are of interest in porphyrin model system studies and such compounds have shown potential as industrial catalysts. The past decade has seen considerable advances in the development of synthetic metalloporphyrin complexes.[1–9] In particular, iron and manganese complexes of tetraphenylporphyrins bearing halogens both on the phenyl rings and at the β-porphyrin positions have been shown to be highly robust and effective catalysts in oxidation reactions.[10] In this context, commercially viable procedures for the preparation of *ortho*-halogenated tetraphenylporphyrins would be highly desirable. One major class of porphyrins used in this field are the metal complexes of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin **(1)**. These can be halogenated on the β-positions and can undergo further electrophilic substitution on both the phenyl and porphyrin rings, such as sulfonation, to give water soluble catalysts.[11,12]

The efficient synthesis of porphyrins bearing bulky substituents at the *ortho* position of the *meso*-aryl groups poses a major challenge. The free base **1** was originally prepared by Kim and co-workers,[13] using a modification of the original Adler condensation,[14] affording a yield of only 0.7%! A better route to the synthesis of **1** was the Hill[15]/Rothemund[16] method, modified by Dolphin and his colleagues[9,17,18] which requires subsequent oxidation of the chlorin impurity using DDQ,[16,19–21] giving an overall yield of **1** of about 4–5% based on pyrrole and this has been successfully scaled up to multigram amounts in our laboratories. While the methods of Lindsey[22–25] have been used recently to prepare **1** in higher yields,[26,27] (from 10% to 30% depending on the reaction conditions) the volume of solvent involved is impractical when multigram quantities are required.

However, Lindsey et al. recently published[28] an "Electron Transport Chain" method (where *meso*-tetraarylporphyrins are prepared at room temperature and at high concentration) which sheds new light on porphyrin synthesis and prompted us to apply this new approach to the large scale preparation of **1**. Of the two synthetic methods reported by Lindsey et al., we chose to use the "Two-Step Aerobic Synthesis" using tetrachloro-1,4-benzoquinone (TCQ), phthalocyanine-iron(II) (FePc), 2,6-dichlorobenzaldehyde and pyrrole. This reaction was investigated at concentrations of pyrrole varying from 0.1 M to 1.0 M (equimolar with the aldehyde), in order to obtain the optimum yield of porphyrin under the most suitable reaction conditions. The concentration of the acid catalyst was adjusted in order to maintain an almost constant $BF_3{\cdot}Et_2O$/pyrrole ratio (0.32–0.40) (except for the "1.0 M" experiment), since a decline in yield with increasing reactant concentrations was partially offset by increased acid concentration.[28]

The initial reaction carried out with a pyrrole concentration of 0.1 M was run at room temperature. However, the purification was more difficult since, in addition to a short silica column to remove polymer, two other chromatographies were necessary (silica, then alumina) before we were able to precipitate the porphyrin cleanly, with a yield of 7.4%.

For the second reaction, the concentration of pyrrole and aldehyde was increased to 0.2 M, with an acid catalyst concentration set to 0.08 M. The time allowed for the porphyrinogen formation step was increased to 45 min (from 30 min), and the oxidation time was also increased (to 120 min from 90 min). After quenching the acid catalyst with water and evaporating to dryness, the crude product was prepurified on an alumina column (which retains the black tar), and the eluate containing the porphyrin was chromatographed on silica. After crystallization, the porphyrin was obtained in 10.0% yield.

Pursuant to our goal of optimizing the process, a third experiment, conducted at 0.32 M for aldehyde and pyrrole, and 0.13 M for $BF_3{\cdot}Et_2O$ (other parameters unchanged), gave a slightly improved porphyrin yield of 11.3%. It is to be noted that this higher yield has been attained in a medium where the concentration of the reactants was similar, or even slightly higher, than that of Adler's[14] original condensation method (0.26 M).

Two other experiments at even higher concentrations were less successful. At 0.47 M (pyrrole, aldehyde) and 0.15 M ($BF_3{\cdot}Et_2O$), the porphyrin yield decreased dramatically to 6.7%. At 1.0 M (pyrrole, aldehyde) and 0.8 M ($BF_3{\cdot}Et_2O$), the reaction mixture was very viscous (suggesting increasing polymerization, hence air bubbling was inefficient) and after a difficult workup the porphyrin-containing fraction exhibited a UV-visible spectrum with an additional band at 658 nm, suggesting contamination with chlorin, which was not detected in the other experiments. The presence of chlorin was confirmed as treatment of the sample with DDQ resulted in the complete disappearance of the 658 nm band, affording the pure porphyrin with a 1.8% yield. These results are summarized in Table 1.

The eight *o*-halogens of **1** provide considerable steric protection on both sides of the porphyrin ring since the phenyl groups are essentially orthogonal to the plane of the porphyrin ring (Figure 1). However, the electron-withdrawing properties of the *o*-halogens are weakly

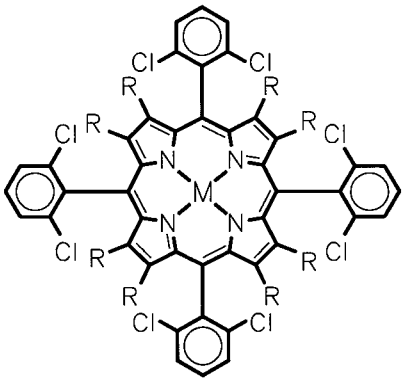
Downloaded by: National University of Singapore. Copyrighted material.

Table 1. Conditions and Yields for the Preparation of **1**

[Pyrrole] (M)	[BF_3·Et_2O] (M)	Cyclization (min)	Oxidation (min)	Yield (%)
0.10	0.033	30	90	7.4
0.20	0.080	45	120	10.0
0.32	0.13	45	120	11.3
0.47	0.15	45	120	6.7
1.0	0.8	45	90	1.8

transmitted to the porphyrin ring and even less to a coordinated metal; thus the difference in the Fe(II)/Fe(III) couple between **2** (the iron complex of **1**) and iron *meso*-tetraphenylporphyrin (FeTPP) is only 60 mV. The porphyrin ring itself is readily oxidized and a robust porphyrin-based oxidation catalyst needs more electronic deactivation than is provided by just the *o*-phenyl halogens. We have shown that the β-positions of the porphyrin ring can be halogenated.[17,18,29] Once all eight β-positions are halogenated the electron-withdrawing power is felt strongly by the porphyrin ring and even a coordinated metal, indeed in the β-octachloro derivative **3** the redox potential of the Fe(II)/Fe(III) couple changes by more than 500 mV compared to FeTPP.[29] The overall result of placing sixteen halogens around the porphyrin ring is to generate an electronically activated sterically protected robust catalyst. Indeed the "steric crowding" in **3** causes the porphyrin to take up a saddle shape conformation[30,31] which is even better sterically protected than its flat conformer (Figure 1).

Traylor and Tsuchiya[32,33] reported the bromination of **4** (the zinc complex of **1**) with *N*-bromosuccinimide (NBS) in CCl_4 to give the β-octabromo derivative **5** in 71% yield. However, this was subsequently challenged by Rocha Gonsalves and co-workers[34] who report no observable bromination under the same conditions. In a related study, bromination of *meso*-tetrakis(2,4,6-trimethylphenyl)porphinato-zinc(II) (ZnTMP) using a twenty fold excess of NBS has been shown to take place in refluxing methanol.[35]



1 R=H, M=2H
2 R=H, M=FeCl
3 R=Cl, M=FeCl
4 R=H, M=Zn
5 R=Br, M=Zn
6 R=Cl, M=Zn

We now report that **4** can be readily halogenated in methanol as illustrated:

$$\underset{\mathbf{6}}{ZnTPPCl_8\beta Cl_8} \xleftarrow[CH_3OH]{NCS\ or\ Cl_2} \underset{\mathbf{4}}{ZnTPPCl_8} \xrightarrow[CH_3OH]{NBS\ or\ Br_2} \underset{\mathbf{5}}{ZnTPPCl_8\beta Br_8}$$

Our initial efforts focused on improving the procedure described by Traylor and Tsuchiya.[32,33] However, we were only able to observe partial bromination. In contrast, when bromination was carried out with NBS in

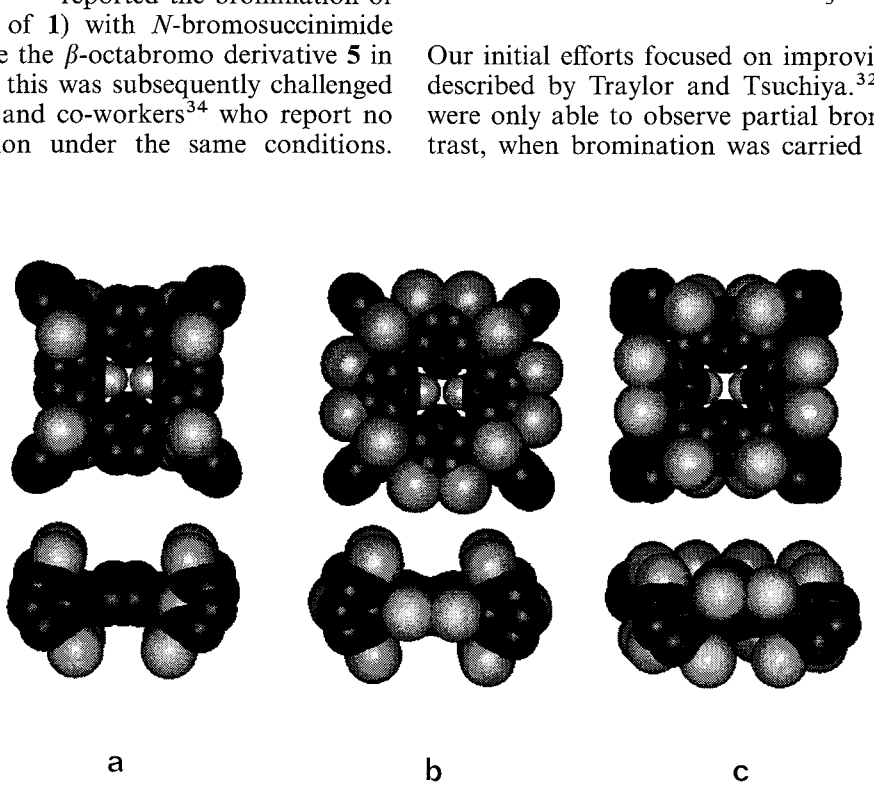


Figure 1 Planar and side views of **1** showing a minimized "flat" porphyrin ring (a), the corresponding flat unminimized free base of **3** (b), and the minimized (Biosym Insight II) saddle shaped free base of **3** (c).

Downloaded by: National University of Singapore. Copyrighted material.

refluxing methanol for 1 h, the desired octabrominated product **5** was obtained in fair yield after chromatography over alumina. FAB mass spectrometry showed the correct molecular ion cluster centered at $m/e = 1585$. It is noteworthy that chromatographic purification could be completely avoided by refrigerating the crude reaction mixture overnight. The crystalline octabromo derivative **5** was obtained in a 63% yield. Meunier and co-workers have also reported use of methanol as solvent for β-halogenation (β-bromination[5,35] with NBS, β-chlorination[5] with NCS), but only with zinc *meso*-tetramesitylporphyrin.

Further experimentation revealed that NBS could be effectively replaced by molecular bromine, thus rendering the process more economical. Moreover, conducting the reaction at room temperature gave a clean, high-yielding reaction (79%) whereas heating at reflux gave the same octabromo derivative in much lower yield and was accompanied by substantial decomposition.

Interestingly, a mixture of Br_2 in CCl_4 did not furnish the octabrominated porphyrin but yielded material with a Soret band ($\lambda_{max} = 429$ nm) indicative of incomplete bromination. In addition, a longer reaction time (at room temperature) or heating the mixture at reflux led to decomposition of the porphyrin. Since Br_2 did not give the same products in CCl_4 and CH_3OH, one can postulate participation of the solvent. Molecular bromine may not be the actual brominating species in CH_3OH; a reaction of bromine with methanol could yield CH_3OBr as the ultimate brominating agent. Rapoport and co-workers have used *N*-bromoacetamide (NBA) in CH_3OH to generate methylhypobromite;[36] therefore we tried to brominate the porphyrin **4** with this reagent. The reaction effectively took place, giving **5** with a respectable yield of 75%, after 1 h reflux.

Dolphin and co-workers have reported[29] that attempted perchlorinations of $ZnTPPCl_8$ with NCS in a variety of solvents failed to give any β-chlorinated products even after 5 h at 140 °C. In contrast, when $ZnTPPCl_8$ and NCS were refluxed in CH_3OH, a very clean reaction ensued giving $ZnTPPCl_8\beta Cl_8$ **(6)** in high yield. Moreover, NCS could be replaced by Cl_2 (gas) giving the β-octachloro derivative in high yield after 20 min at 0 °C. However, in this case it is difficult to control the process and to ensure that the reaction proceeds to add 8 chlorine atoms without under- or overchlorination.

Using the novel method of Lindsey and co-workers, a one-pot preparation of chlorin-free *meso*-tetrakis(2,6-dichlorophenyl)porphyrin **(1)** with an improved yield (up to ~ 3 times the yields generally obtained using the modified Hill/Rothemund method) and a simplified processing and purification, at a concentration similar to that of the original Adler method, has been achieved on a relatively large scale. Furthermore, the corresponding zinc complex can be brominated and chlorinated on the β-pyrrole positions leading to high yields in an easy and clean manner, with simple workup procedures.

UV-visible spectra were recorded in CH_2Cl_2, using either Hewlett-Packard 8452A or Shimadzu UV-2101PC spectrophotometers; λ_{max} are given in nm followed by their relative intensities (100 for the most intense band). Mass spectra were obtained either on a Finnigan MAT 95 (Abbott) or a Kratos MS 50 (UBC) spectrometer. The peak corresponding to the center of the molecular ion cluster is reported followed by the peak intensity relative to the largest ion in the mass range of interest.

Lindsey et al. in their synthesis had difficulties with one particular batch of FePc, suggesting that the efficiency of the reaction is dependent on the quality of FePc.[28] The experiments described here utilized FePc purchased from Eastman (Art. 10575). Boron trifluoride–diethyl ether complex was distilled according to Zweifel.[37] Pyrrole and 2,6-dichlorobenzaldehyde (from Aldrich), and TCQ (from Eastman) were used without further purification.

Chromatographic separations were performed using 70–230 mesh silica gel from BDH, or neutral alumina Brockman activity I (Fisher 60–325 mesh), which was also used after deactivation by addition of 4% H_2O. Reactions were followed by thin-layer chromatography (TLC) using silica gel plates (0.2 mm thickness) and Merck Kieselgel 60 A F_{254} precoated plates.

meso-Tetrakis(2,6-dichlorophenyl)porphyrin (1) by the Electron Transport Chain Method

To ethanol-stabilized $CHCl_3$[22] (300 mL) placed in a 500 mL three-necked round-bottom flask (RBF) was added absolute EtOH (4 mL). The solvent was deoxygenated under a slow stream of Ar (20 min bubbling) through a septum, using a stainless steel needle, then TCQ (0.92 g, 3.74 mmol) and FePc (2.13 g, 3.74 mmol) were added with stirring, and the solution was deoxygenated again for 8 min. 2,6-Dichlorobenzaldehyde (17.5 g, 0.1 mol, 0.32 M) and pyrrole (7 mL, 0.1 mol, 0.32 M) were then added. After a further 8 min deoxygenation, pure freshly distilled $BF_3{\cdot}Et_2O$ (5 mL, 41 mmol, 0.13 M) was added using an air-free syringe. The color of the solution turned purple (an aqueous "$KMnO_4$ color") within a few min. The solution was stirred for a further 45 min with Ar bubbling. At this point Ar line was switched to dry air (filtered through $CaCl_2$) and bubbling was continued for 2 h, during which time the solution turned dark bluish-purple. At the end of this time the acid catalyst was quenched with H_2O (5 mL) and the mixture was taken to dryness on a rotary evaporator and dried under high vacuum. The solid residue was dissolved in a minimum amount of CH_2Cl_2 (~ 100 mL was used; a smaller volume gave too viscous a solution) and the resulting solution was introduced onto the top of an alumina (deactivated) column prepared with CH_2Cl_2/hexanes 1 : 1 (v/v) (850 g, 6.3 × 38 cm; for larger scale preparations, it is possible to dramatically decrease the quantity of alumina, and just "filter" the crude product through it using the solvent mixture). The column was eluted using CH_2Cl_2/hexanes 1 : 1. The porphyrin moved together with a blue byproduct absorbing at 590 nm. This eluate was collected until it became nearly colorless. Attempts at crystallization or precipitation at this stage (CH_2Cl_2/hexanes 1 : 1) resulted in a mixture of the porphyrin and the already mentioned blue byproduct. The combined eluates were evaporated to dryness and the residue redissolved/dispersed in $CHCl_3$ (250 mL) (compound **1** is several times more soluble in $CHCl_3$ than in CH_2Cl_2). The mixture was chromatographed on silica; the column was prepared with CH_2Cl_2/hexanes 1 : 1, using 500 g of silica gel 70–230 mesh (6.3 × 41 cm). The porphyrin was readily separated as a fast moving red band, using CH_2Cl_2/hexanes 1 : 1 (v/v).

The product was recrystallized from CH_2Cl_2/hexane, affording 2.51 g (2.82 mmol, 11.3%). The purple crystals should be shiny; if not, or if they appear dark, rinsing with methanol helps to eliminate any remaining trace of impurities. Spectral characteristics were identical to those previously published.[9,13,17,18,26,27]

meso-Tetrakis(2,6-dichlorophenyl)porphyrin (1) by the Modified Hill/Rothemund Method: Laboratory Scale

Isolation of the Crude Zinc Complex 4:

2,6-Dichlorobenzaldehyde (52.5 g; 0.30 mol), anhyd $Zn(OAc)_2$ (20 g; 0.11 mol), and 2,6-dimethylpyridine (150 mL) were placed in a 1 L RBF fitted with a Soxhlet extractor surmounted by a reflux condenser. Anhyd Na_2SO_4 was placed in a 6 × 17 cm thimble as a

Downloaded by: National University of Singapore. Copyrighted material.

drying agent and the mixture was heated. When the temperature reached 100 °C, pyrrole (21.0 mL; 0.30 mol) was added dropwise (within 10 min); the condenser was removed, allowing the evaporation of some water, formed as droplets in the reaction. The condenser was replaced about 5 min later and the solution was refluxed for 6 h. After evaporating the solvent in vacuo the resulting tarry residue was triturated with toluene (375 mL) then CH_3OH (75 mL) was added; the mixture was allowed to stand in the refrigerator overnight. The porphyrin precipitated as its Zn complex mixed with zinc acetate. It was filtered, rinsed with a small amount of CH_3OH and dried under vacuum in a desiccator, yielding 12.83 g. This powder was redissolved/dispersed in hot $CHCl_3$ (250 mL), and CH_3OH (250 mL) was added; $CHCl_3$ was slowly evaporated under vacuum and the zinc complex was isolated as fine purple crystals which were filtered, washed with H_2O and MeOH, and finally rinsed with pentane and dried, affording 3.59 g (3.76 mmol, yield = 5.0%) of **4** (contaminated with some chlorin). A second crop of 70 mg (7.34×10^{-5} mol, yield = 0.1%) could be obtained from the filtrate.

UV-vis: λ_{max} (rel. int.): 400 sh (13), 420 (100), 430 sh (66), 558 (7), 630 (2).

LRMS (Kratos): (peak of maximum intensity within each isotopic cluster) 664 (6.4), 702 (6.6), 738 (8.2), 772 (10.3), 810 (6.0), 846 (6.1), 882 (10.1), 918 (7.3), 954 (M^+, 100).

Demetallation:

The impure zinc complex **4** (1.19 g; 1.25 mmol) was dissolved in $CHCl_3$ (300 mL), TFA (10 mL) was added and the mixture was stirred; the progress of the reaction was monitored by UV-vis spectroscopy in CH_2Cl_2 after neutralization of the sample by Et_3N: the main Q band at $\lambda = 562$ disappeared in favor of two new bands at $\lambda = 512$ (Q-IV) and $\lambda = 587$ (Q-II). After 1 h the crude product was washed with H_2O (350 mL), aq $NaHCO_3$ (350 mL), H_2O (2×250 mL), and dried ($MgSO_4$). After filtration, the volume was reduced to about 100 mL, and the compound was crystallized by addition of MeOH (50 mL) followed by partial evaporation of $CHCl_3$, affording 0.91 g (1.02 mmol, yield = 81.7%) of **1** (contaminated with chlorin). A second crop of 58 mg (6.51×10^{-5} mol, yield = 5.2%) was obtained from the filtrate.

UV-vis: λ_{max} (rel. int.): 418 (100), 482 sh (2), 512 (9), 540 sh (2), 588 (3), 658 (2; chlorin peak may vary ± 10%).

Oxidation of the Chlorin Impurity:[16,19–21]

The chlorin-contaminated free base **1** (1.83 g; 2.06 mmol) was dissolved in pentene-stabilized $CHCl_3$ (600 mL) and heated to reflux in a 1-L RBF. A solution of DDQ (1.6 g) in benzene (75 mL) was added dropwise over 20 min and the reflux was continued for 2 h (after 90 min, the relative intensity of $\lambda_{658}/\lambda_{587}$ decreased to 0.44 from 0.68), then stirred overnight at r.t. At this point the intensity ratio of the same bands was 0.24; after an additional 1 h refluxing the chlorin peak disappeared completely and the hot solution was passed quickly through alumina (160 g) placed in a 7 cm wide sintered funnel. It was thoroughly rinsed with hot $CHCl_3$, the solution concentrated to 250 mL, and the compound was crystallized by addition of CH_3OH (200 mL) followed by slow evaporation of $CHCl_3$, affording 1.74 g (1.95 mmol; yield = 95.1%) of **1**. Overall yield: 4.2% (based on pyrrole).

UV-vis: λ_{max} (ε, $mol^{-1}mL\,cm^{-1}$): 400 sh (86), 417 (393), 479 (3), 512 (22), 540 (3), 587 (7), 643 (0.4).

LRMS (Kratos): (peak of maximum intensity within each isotopic cluster) 855 (26), 890 (M^+, 100); details for the M^+ cluster) 886 (30), 887 (16), 888 (82), 889 (40), 890 (M^+, 100),[38] 891 (44), 892 (66), 893 (31), 894 (30), 895 (13), 896 (9), 897 (4), 898 (2).

^1H NMR (CD_2Cl_2, 400 MHz) δ (ppm): 8.71 (8 H, s, H pyrrole), 7.87–7.72 (12 H, m, H *meta*, *para* phenyl), −2.57 (2 H, s, NH).

^{13}C NMR (10% TFA/$CDCl_3$, 75 MHz, decoupled spectrum) δ (ppm): 145.25 (α), 138.90 (*ipso*), 135.59 (*o*), 132.92 (*p*), 129.42 (*m*), 128.89 (β), 116.67 (*meso*).

Anal. Calcd (found) for $C_{44}H_{22}N_4Cl_8$: C, 59.36 (59.45); H, 2.49 (2.53); N, 6.29 (6.35).

The reaction has been repeated on a much larger scale as described below.

***meso*-Tetrakis(2,6-dichlorophenyl)porphinato-Zinc(II) (4):**

The free base **1** (0.31 g, 0.35 mmol), $Zn(OAc)_2 \cdot 2H_2O$ (1.00 g, 4.56 mmol), and DMF (100 mL) were refluxed in a 250 mL RBF (color changed from yellowish-purple to reddish-purple). The progress of the reaction was monitored by UV-vis. Within 15 min the visible region changed from $\lambda = 512$, 587 to $\lambda = 520$ (hump), 562. Heating was discontinued after 30 min, the volume reduced to one-half by rotary evaporation, and H_2O (150 mL) was added. The complex was collected by filtration, washed thoroughly with H_2O then rinsed with MeOH, redissolved in hot $CHCl_3$ then recrystallized by addition of CH_3OH and dried, to afford 286 mg (0.30 mmol, yield = 86.2%) of **4**.

UV-vis: λ_{max} (ε, $mol^{-1}\,mL\,cm^{-1}$): 400 (45), 420 (371), 512 (2), 550 (21), 534 (2).

***meso*-Tetrakis(2,6-dichlorophenyl)porphyrin (1) and *meso*-Tetrakis (2,6-dichlorophenyl)porphinato-Zinc(II) (4); Scale-up:**

Isolation of the Crude Zinc Complex 4:

2,6-Dichlorobenzaldehyde (1.5 kg; 8.6 mol), anhyd $Zn(OAc)_2$ (580 g; 3.2 mol), 2,6-dimethylpyridine (5.0 L) and pyrrole (600 mL; 8.6 mol) were placed in a 12-L RBF; the solution was refluxed for 18 h. After evaporation, the tarry residue was triturated with 6 L of toluene then CH_3OH (500 mL) was added, and the mixture was refrigerated overnight. The precipitated crude zinc complex was collected and further purified by recrystallization, as follows: the solid obtained was dissolved/suspended in hot $CHCl_3$ (6.0 L), and CH_3OH (6.0 L) was added; $CHCl_3$ was slowly evaporated in vacuo and the resulting purple precipitate was collected by filtration, washed with H_2O (0.5 L) and MeOH (0.5 L), and finally rinsed with pentane (0.4 L) and dried in vacuo, affording 357 g of **4** (still contaminated with $Zn(OAc)_2$.

Purification of a 30 g Batch of Crude $ZnTPPCl_8$:

Crude **4** was dissolved in $CHCl_3$ (1.5 L) and demetallated by addition of TFA (150 mL). After overnight stirring under N_2, H_2O (1.5 L) was added; after washing and drying the precipitate, oxidation of the chlorin impurity was carried out using TCQ (30 g, 0.12 mol), refluxing for 3 h. Then the hot solution was passed through alumina and rinsed with hot $CHCl_3$. The volume was then reduced to 200 mL and CH_3OH (200 mL) was added. $CHCl_3$ was slowly removed in vacuo and the resulting suspension was filtered giving the free base porphyrin **1** as a dark purple solid (9.4 g; 10.6 mmol); overall yield = 5.8%, relative to pyrrole). It was then dissolved in DMF (750 mL) and $Zn(OAc)_2 \cdot 2H_2O$ (20.0 g; 91.2 mmol) was added. The mixture was refluxed for 2 h, then the volume was reduced to 200 mL by rotary evaporation and H_2O (200 mL) was added. The resulting precipitate was collected as described above, affording 9.13 g (9.6 mmol, yield = 5.3%, relative to pyrrole) of zinc complex **4**. This equates to 108.6 g of pure porphyrin from 357 g of crude material.

UV-vis: λ_{max}: 400 sh (23), 420 (100), 550 (12).

Bromination of 4 with NBS/CH_3OH:

The zinc complex **4** (1.0 g, 1.05 mmol) was dissolved/suspended in CH_3OH (100 mL) and treated with NBS (3.73 g, 21.0 mmol). The resulting mixture was heated at reflux for 1 h, then evaporated to dryness and the residue was chromatographed on alumina, eluting with $CHCl_3$. The dark green band was collected and the solvent removed in vacuo giving a green solid **5** (0.75 g, 4.73×10^{-4} mol; 45.1% yield).

UV-vis: λ_{max} (rel. int): 461 (100), 589.5 (10.5).

LRMS (MAT95) (*m/e*): 1585 (center of molecular ion cluster)

Bromination of 4 with Br_2/CH_3OH

The zinc complex **4** (2.0 g, 2.097 mmol) was dissolved/suspended in CH_3OH (400 mL) and treated with Br_2 (40 mL, 0.78 mol). The resulting mixture was stirred at ambient temperature for 2 h and then refrigerated overnight (4 °C). The resulting precipitate was collected and washed with a small quantity of CH_3OH to furnish the green solid **5** (2.63 g, 1.66 mmol, 79%).

Downloaded by: National University of Singapore. Copyrighted material.

UV-vis: λ_{max} (rel. int): 368.5 (11.5), 463 (100), 594 (7).

LRMS (MAT95): (*m/e*): 1585 (center of molecular ion cluster).

Bromination of 4 with NBA/CH_3OH:

The zinc complex **4** (100 mg, 0.105 mmol) was dissolved/suspended in CH_3OH (50 mL) and NBA (0.29 g; 2.1 mmol) was added. The mixture was heated at reflux for 1 h, then allowed to cool. The resulting mixture was refrigerated overnight and the precipitated green solid was collected giving **5** (125 mg; 75%).

UV-bis: λ_{max} (rel. int): 365.5 (13), 461 (100), 592 (8), 643 (2).

LRMS (MAT95): (*m/e*): 1585 (center of molecular ion cluster).

Chlorination of 4 with Cl_2/CH_3OH:

The zinc complex **4** (250 mg, 0.262 mmol) was dissolved/suspended in CH_3OH (50 mL) and the mixture cooled to 0 °C with an ice bath. Cl_2 gas was bubbled through the mixture at such a rate that the temperature was maintained below 5 °C. After 5 min the mixture had changed color from purple to green. TLC indicated complete disappearance of the starting material. The solvent was then evaporated in vacuo to give a purple solid (283 mg, 88%) with a green luminescence, which gives a green solution in CH_2Cl_2.

UV-vis: λ_{max} (rel. int): 421 sh (63), 433.5 (100), 484 (3), 564 (6), 632.5 (5.5).

LRMS (MAT95) (*m/e*): 1230 (center of molecular ion cluster, 50), 1195 (βCl_7, 100), 1160 (βCl_6, 100), 1125 (βCl_5, 55), 1089 (βCl_4, 37).

Subjecting the product to further chlorination (20 min, < 5 °C) afforded material whose UV spectrum reflected only incremental changes. However some degradation was seen by TLC. In addition, the mass spectrum (FAB) revealed the major component to be the desired βCl_8 derivative **6**. This is accompanied by molecular ions corresponding to additional chlorination of the molecule, presumably on the aromatic rings.

UV-vis: λ_{max} (rel. int): 436 (100), 485 (50), 523 (9.5), 575 (9.5), 625 (9.5).

LRMS (MAT95) (*m/e*): 1338 (center of molecular ion cluster, $\beta Cl_8 + 3Cl$, 25), 1305 ($\beta Cl_8 + 2Cl$, 45), 1266 ($\beta Cl_8 + Cl$, 50), 1230 (βCl_8, 100), 1195 (βCl_7, 60), 1160 (βCl_6, 55).

Chlorination of 4 with NCS/CH_3OH:

The zinc complex **4** (100 mg, 0.105 mmol) was suspended in CH_3OH (50 mL) and treated with NCS (140 mg, 1.05 mmol). The resulting mixture was heated at reflux for 6 h. A second portion of NCS was then added and the mixture refluxed for an additional 5 h. The mixture was then evaporated to dryness and the residue was washed with hot H_2O to give the purple solid **6** (110 mg, 85% yield).

UV-vis: λ_{max} (rel. int): 360.5 (12.5), 440 (100), 573 (7.5), 632 (2).

LRMS (MAT95) (*m/e*): 1230 (M^+, 100), 1195 (38).

Anal. Calcd (found) for $C_{44}H_{12}N_4Cl_{16}Zn$: C, 42.99 (42.26); H, 0.98 (1.34); N, 4.56 (4.30); Cl, 44.15 (44.60).

This work was supported in part by the Natural Sciences and Engineering Research Council of Canada.

† Current address: C.P. Consulting, 43323 N. Oakcrest Lane, Zion, Illinois 60099-9413, U.S.A.

†† Current address: Research and Development Department, Sun Company Inc., P.O. Box 1135, Markus Hook, PA 19061-0835, U.S.A.

(1) Collman, J.P.; Zhang, X.; Lee, V.J.; Uffelman, E.S.; Brauman, J.I. *Science* **1993**, *261*, 1404.
(2) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411 and references therein.
(3) Battioni, P.; Bartoli, J.F.; Mansuy, D.; Byun, Y.S.; Traylor, T.G. *J. Chem. Soc., Chem. Commun.* **1992**, 1051.
(4) Traylor, T.G.; Hill, K.W.; Fann, W.; Tsuchiya, S.; Dunlop, B.E. *J. Am. Chem. Soc.* **1992**, *114*, 1308.
(5) Hoffmann, P.; Robert, A.; Meunier, B. *Bull. Soc. Chim. Fr.* **1992**, *129*, 85.
(6) Nakano, T.; Traylor, T.G.; Dolphin, D. *Can. J. Chem.* **1990**, *68*, 1504.
(7) Ellis Jr., P.E.; Lyons, J.E. *Catal. Lett.* **1989**, *3*, 389.
(8) Renaud, J.P.; Battioni, P.; Bartoli, J.F.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1985**, 888.
(9) Traylor, P.S.; Dolphin, D.; Traylor, T.G. *J. Chem. Soc., Chem. Commun.* **1984**, 279.
(10) Grinstaff, M.W.; Hill, M.G.; Labinger, J.A.; Gray, H.B. *Science* **1994**, *264*, 1311.
(11) Dolphin, D. In *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*, D.H.R. Barton, Ed., Plenum: 1993, 287.
(12) Artaud, I.; Ben-Aziza, K.; Mansuy, D. *J. Am. Chem. Soc.* **1993**, *58*, 3373–3380.
(13) Kim, J.B.; Leonard, J.J.; Longo, F.R. *J. Am. Chem. Soc.* **1972**, *94*, 3986.
(14) Adler, A.D.; Longo, F.R.; Finarelli, J.D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
(15) Hill, C.L.; Williamson, M.M. *J. Chem. Soc., Chem. Commun.* **1985**, 1228.
(16) Badger, G.M.; Jones, R.A.; Laslett, R.L. *Aust. J. Chem.* **1964**, *17*, 1028.
(17) Dolphin, D.H.; Nakano, T.; Maione, T.E.; Kirk, T.K.; Farrel, R.L.; Wijeskera, T.P. Int. Patent No. 1988, 88/078988; *Chem. Abstr.* **1989**, *111*, 71441.
(18) Wijeskera, T.P.; Dupré, D.; Cader, M.S.R.; Dolphin, D. *Bull. Soc. Chim. Fr.*, in press.
(19) Barnett, G.H.; Hudson, M.F.; Smith, K.M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1401.
(20) Rousseau, K.; Dolphin, D. *Tetrahedron Lett.* **1974**, 4251.
(21) Barnett, G.H.; Hudson, M.F.; Smith, K.M. *Tetrahedron Lett.* **1973**, 2887.
(22) Lindsey, J.S.; Wagner, R.W. *J. Org. Chem.* **1989**, *54*, 828.
(23) Kihn-Botulinski, M.; Meunier, B. *Inorg. Chem.* **1988**, *27*, 209.
(24) Wagner, R.W.; Lawrence, D.S.; Lindsey, J.S. *Tetrahedron Lett.* **1987**, *28*, 3069.
(25) Lindsey, J.S.; Schreiman, I.C.; Hsu, H.C.; Kearney, P.C.; Marguerettaz, A.M. *J. Org. Chem.* **1987**, *52*, 827.
(26) Turk, H.; Ford, W.T. *J. Org. Chem.* **1991**, *56*, 1253.
(27) van der Made, A.W.; Hoppenbrouwer, E.J.H.; Nolte, R.J.M.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 15.
(28) Lindsey, J.S.; MacCrum, K.A.; Tyhonas, J.S.; Chuang, Y.-Y. *J. Org. Chem.* **1994**, *59*, 579.
(29) Wijesekera, T.; Matsumoto, A.; Dolphin, D.; Lexa, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1028.
(30) Ochsenbein, P.; Ayougou, K.; Mandon, D.; Fischer, J.; Weiss, R.; Austin, R.N.; Jayaraj, K.; Gold, A.; Terner, J.; Fajer, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 348.
(31) Mandon, D.; Ochsenbein, P.; Fischer, J.; Weiss, R.; Jayaraj, K.; Austin, R.N.; Gold, A.; White, P.S.; Brigaud, O.; Battioni, P.; Mansuy, D. *Inorg. Chem.* **1992**, *31*, 2044.
(32) Traylor, T.G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338.
(33) Traylor, T.G.; Tsuchiya, S. *Inorg. Chem.* **1988**, *27*, 4520.
(34) Rocha Gonsalves, A.M.D.; Johnstone, R.A.W.; Pereira, M.M.; Shaw, J.; Sobral, A.J.F.D.N. *Tetrahedron Lett.* **1991**, *32*, 1355.
(35) Hoffmann, P.; Labat, G.; Robert, A.; Meunier, B. *Tetrahedron Lett.* **1990**, *31*, 1991.
(36) Rapoport, H.; Lovell, C.H.; Reist, H.R.; Warren, Jr.; M.E. *J. Am. Chem. Soc.* **1967**, *89*, 1942.
(37) Zweifel, G.; Brown, H.C. *Org. React.* **1963**, *13*, 28.
(38) Arnold, L.J. *J. Chem. Educ.* **1992**, *69*, 811.

Downloaded by: National University of Singapore. Copyrighted material.