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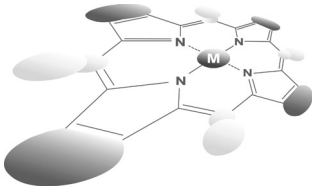

The exhaustive reduction of formylporphyrins to methylporphyrins using dimethylformamide/water as reductant under microwave irradiation

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ABSTRACT: The reduction of *meso*-formyl derivatives of 5,15-diaryl- and 5,10,15-triphenylporphyrin (and their nickel(II) complexes) to the corresponding *meso*-methyl porphyrins is achieved in high yield by microwave heating of the substrate in dimethylformamide (DMF) in the presence of acids such as trifluoroacetic acid, or even just with added water. The reactions are complete in less than 30 min at 250 °C. The reaction is strongly suppressed in very dry DMF in the absence of added acid. The *meso*-hydroxymethyl porphyrins are also reduced to the methyl derivatives, suggesting the primary alcohols may be intermediates in the exhaustive reduction. UV-visible spectra taken at intervals during reaction at 240 °C indicated that at least one other intermediate is present, but it was not identified. In d_7-DMF, the methylporphyrin isolated was mainly Por-CD_2H, showing that both of the added hydrogens arise from the solvent, and not from the added water or acid.

KEYWORDS: methylporphyrins, formylporphyrins, microwave, reduction, dimethylformamide.

INTRODUCTION

Functional group interconversions on the periphery of porphyrins and metalloporphyrins are important for investigating in detail the effects of substituents on the electronic structures and spectra of porphyrins [1]. Porphyrins (and more generally, porphyrinoids) are macrocyclic tetrapyrrole pigments of fundamental importance in biology, but they also provide an unsurpassed platform for studies of electronic structures of non-benzenoid aromatics, electronic absorption and emission spectra, and lately for supramolecular chemistry. Furthermore, the ability of porphyrinoids to complex a huge variety of metal ions, either inside or on the periphery of the macrocycle, adds another dimension of synthetic opportunities. The present results arose from our quest to delineate interporphyrin interactions in diporphyrins linked by short covalent bridges [2]. Porphyrin scientists have been pursuing for many years the goal of understanding the electronic properties of macrocyclic pigment molecules held in close proximity, as a tool for mimicking the natural light-harvesting and photosynthetic pigments. Moreover, conjugated diporphyrins have excited interest as possible highly efficient non-linear optical dyes [3].

One of the systems we were targeting was the diporphyrin imine **$H_4$1a** (Chart 1), a type of porphyrin dyad known for only one previous analog, namely **$Zn_2$1b**, reported by Anderson and co-workers in 2002 [4]. The formation of this imine by classical aldehyde/amine condensation under protic acid catalysis is a frustratingly difficult reaction, and in our hands the conversions are invariably very low. Our preferred *meso*-substituted porphyrin is the very convenient 5,10,15-triphenylporphyrin (H_2TriPP) (Scheme 1). We decided to try the reaction under microwave irradiation at elevated temperatures, initially in toluene, then in *N*,*N*-dimethylformamide (DMF), in the presence of trifluoroacetic acid (TFA). Subjecting equimolar quantities of the aldehyde **2a** and primary aminoporphyrin **2b** (Chart 2) to microwave irradiation at

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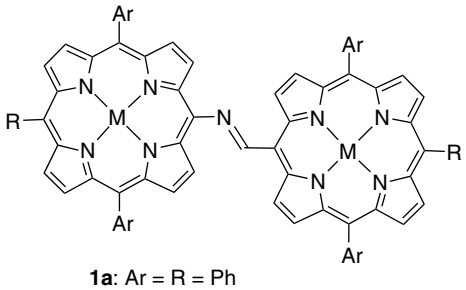
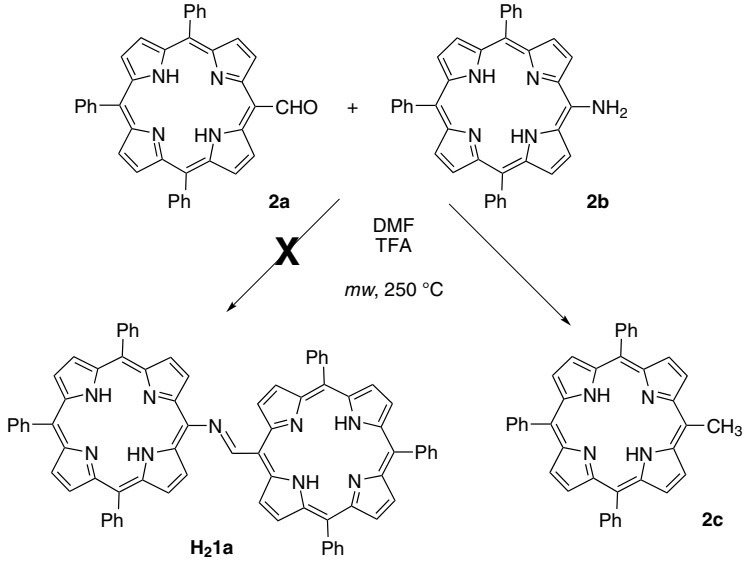


Chart 1. The target imine dyad **1a** (M = Ni, Zn, H_2)



Scheme 1. Attempted synthesis of imine dyad **H$_2$1a** using microwave heating

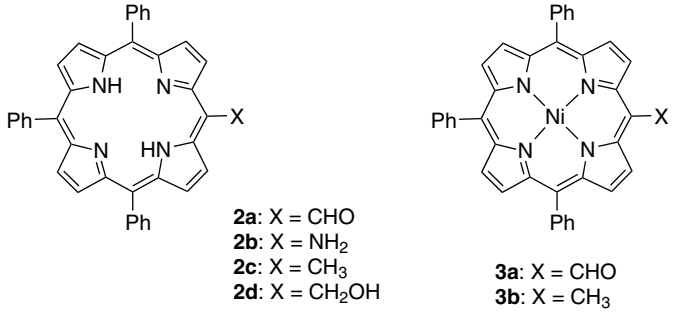


Chart 2. 5,10,15-triphenylporphyrin (TriPP) derivatives used in this study

250 °C in DMF with 4 equivalents of TFA, led to 100% conversion of the aldehyde, with no consumption of the amine. However, TLC analysis of the product mixture showed the formation of a very mobile red product, which was easily separated and identified as the new porphyrin derivative *meso*-methylH$_2$TriPP **2c**. Although there was no sign of the target imine **H$_4$1a** in the product mixture, this curious finding prompted us to study this new reaction for its intrinsic interest, and also as a possible useful addition to the armoury of synthetic transformations around the porphyrin periphery. Recently, we have succeeded in preparing the imine dimer using Lewis acid catalysis; this work will be reported elsewhere [5].

EXPERIMENTAL

General

All solvents were AR grade, distilled on a rotary evaporator to avoid high-boiling residues. Column chromatography was performed using LC60A 40–63 Micron DAVISIL silica gel. Thin-layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and Grace UV254 plates. NMR experiments were conducted on a Bruker Avance 400 spectrophotometer equipped with a QNP probe or a Varian VR400 spectrophotometer fitted with an Auto X probe, operating at 400 MHz for protons. Samples were prepared in $CDCl_3$, unless otherwise stated, with oven dried glassware. Spectra were referenced to $CHCl_3$ at 7.26 ppm for ^{1}H and $CDCl_3$ at 77.0 ppm for ^{13}C. Coupling constants are reported in Hz. Deuterium NMR spectra of **Ni4c** (Chart 3) were recorded in $CHCl_3$ at 61.4 MHz on the Varian instrument, using broadband proton decoupling, and $CDCl_3$ as internal reference. Accurate mass electrospray ionization (ESI) mass spectra were recorded on a Kronos-G6520B QTOF mass spectrometer using a flow rate of 0.4 mL/min and MeOH as eluent. Source temperature at 325 °C and capillary voltage at 4.0 kV were employed. Solvent aspiration was accomplished by nitrogen gas flowing at 5 L/min. Matrix-assisted laser desorption/ionisation (MALDI) spectra were obtained at The University of Queensland, Brisbane. Analysis was performed with an Applied Biosystems Voyager-DE STR BioSpectrometry workstation. The instrument was operated in positive polarity in reflectron mode for analysis. The samples were spotted on a stainless steel sample plate in toluene solutions using 2,5-dihydroxybenzoic acid as the matrix. Data from 100 laser shots (337 nm laser) were collected, signal-averaged, and processed with the instrument manufacturer's Data Explorer software. UV-visible spectra were recorded in $CHCl_3$ solutions on a Shimadzu UV-1800 spectrophotometer.

DMF was Merck AR grade, dried to constant water content (but not "anhydrous") by standing over 3 Å molecular sieves. To investigate the influence of water,

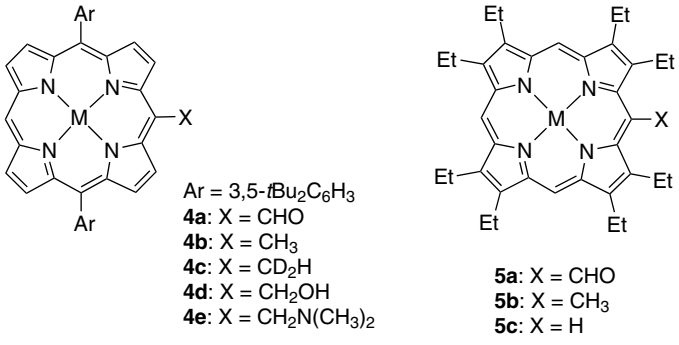


Chart 3. 5,15-Bis(di-*t*-butylphenyl)porphyrin (DAP) and octaethylporphyrin (OEP) derivatives used in this study

either Aldrich Sure-Seal™ or AR DMF distilled under vacuum from CaH_2 directly into the microwave vial were used. TFA was Ajax LabChem "specially pure for peptide work".

Preparation of porphyrin starting materials

The following porphyrin starting materials were prepared by standard methods used in our laboratories and reported previously: NiTriPPCHO (**3a**) [6], NiDAPCHO (**Ni4a**) [6], NiOEPCHO (**Ni5a**) [7], H_2OEPCHO (**$H_2$5a**) [8].

5-Formyl-10,15,20-triphenylporphyrin 2a. NiTriPPCHO (**3a**, 79 mg, 0.13 mmol) was dissolved in a mixture of H_2SO_4 and TFA (1:9, 5 mL) and stirred at room temperature. After 30 min the starting material was seen by TLC to be consumed ($CHCl_3$ with a drop of triethylamine; micro-work-up of TLC samples was performed to deprotonate the porphyrin dication prior to spotting on TLC plate). The reaction mixture was neutralized with saturated sodium bicarbonate (250 mL) and the product extracted into dichloromethane (DCM). The organic layer was then washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered and solvents removed. Recrystallization from $CHCl_3$/MeOH gave dark purple crystals of **2a** (52 mg, 72%). ^{1}H NMR: δ_H, ppm 12.50 (1H, s, CHO), 10.03 (2H, br d, β-H), 9.00 (2H, d, *J* 5.0, β-H), 8.78 (2H, d, *J* 4.8, β-H), 8.71 (2H, d, *J* 4.7, β-H), 8.28–8.18 (6H, m, *o*-Ph), 7.85–7.75 (9H, m, *m,p*-Ph), -1.97 (2H, bs, inner N *H*). These data agree with those published by Dahms *et al*. [9], who prepared it by a different route. The compound was also reported by Ishkov *et al*., using selenous acid oxidation of the methyl derivative, itself prepared by cyclocondensation [10]; the chemical shift of the CHO proton is apparently mis-reported as 11.14 ppm.

5-Hydroxymethyl-10,20-bis(3,5-di-*t*-butylphenyl)-porphyrinatonickel(II) Ni4d. This was prepared by reduction of the aldehyde **Ni4a**, according to the general procedure of Inhoffen *et al*. [8] NiDAPCHO **Ni4b** (100 mg, 0.129 mmol), $NaBH_4$ (196 mg, 5.19 mmol) and anhydrous THF (20 mL) were added to a round bottomed flask and stirred. The reaction progress was monitored by TLC and the mixture was diluted with deionized water (50 mL) upon completion. The product was then extracted with DCM (3 × 20 mL), dried over anhydrous Na_2SO_4 and filtered through cotton wool prior to solvent evaporation. The product was recrystallized from DCM/pentane to yield burgundy, paper-like crystals of **Ni4d** (58 mg, 75%). ^{1}H NMR: δ_H, ppm 9.81 (1H, s, *meso*-H), 9.51, 9.12, 8.94, 8.93 (each 2H, d, *J* = 4.8 Hz, β-H), 7.88 (4H, br s, *o*-Ar-H), 7.76 (2H, br s, *p*-Ar-H), 6.63 (2H, d, *J* = 6.0, CH_2), 2.58 (1H, t, *J* = 6.0, OH), 1.50 (36H, s, *tert*-butyl-H). UV-vis: λ_{max}, nm (ε, 10^3 $M^{-1}.cm^{-1}$) 410 (177), 524 (15.2), 554 (6.3). MS (MALDI): *m/z* 773.9 (calcd. for $[M + H]^+$ 773.4), 756.8 (calcd. for $[M - OH + H]^+$ 756.4).

5-Formyl-10,20-bis(3,5-di-*t*-butylphenyl)-porphyrin $H_2$4a. NiDAPCHO **Ni4a** (49 mg, 63 μmol) was dissolved in a mixture of H_2SO_4 and TFA (1:9, 5 mL) and stirred at room temperature for 15 min and monitored by TLC ($CHCl_3$ with a drop of TEA; micro-work-up of TLC sample was performed to neutralize prior to spotting on TLC plate) until the reaction was complete. The solution was neutralized with saturated sodium bicarbonate solution (50 mL) and transferred to a separating funnel. DCM (3 × 20 mL) was used to extract the product and the combined organic layers were washed with deionized water (2 × 75 mL). The extract was then dried over anhydrous Na_2SO_4 prior to the evaporation of solvent. The product was purified by vacuum filtration of a chloroform solution through a plug of silica gel; evaporation to small volume and trituration with pentane yielded fine, dark crystals of H_2DAPCHO (**$H_2$4a**, 26 mg, 58%). ^{1}H NMR: δ_H, ppm 12.64 (s, 1H, CHO), 10.27 (s, 1H, *meso*-H), 10.10 (br d, 2H, β-H), 9.9.30 (d, 2H, *J* 4.4, β-H), 9.13 (d, 2H, *J* 4.8, β-H), 8.96 (d, 2H, *J* 4.8, β-H), 8.10 (d, 4H, *J* = 2.0, *o*-Ar-H), 7.88 (t, 2H, *J* = 1.6, *p*-Ar-H), 1.59 (s, 36H, *tert*-butyl-H), -2.32 (2H, br s, inner N *H*). These data agree with those published by Takanami *et al*. [11], who prepared it by a different route. UV-vis: λ_{max}, nm (ε, 10^3 $M^{-1}.cm^{-1}$) 424 (205), 523 (12.7), 564 (10.7), 596 (7.6), 652 (9.3).

General procedure for microwave-heated reactions of formylporphyrins

To a 2.0–5.0 mL microwave vial, a small stirrer bar and porphyrin aldehyde (10–12 μmol) were added. DMF (2 mL) and TFA or water were added to the vial, which was then fitted with a septum. The solution was degassed with N_2 and sealed with the microwave vial cap. The solution, which was a pink/red colour, was placed in the microwave reactor for 30 min at 250 °C. It was cooled to 50 °C in the microwave and then removed. The brown/red reaction mixture was diluted with DCM (20 mL) in a separating funnel and washed with deionized water (5 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered through cotton wool into a 100 mL round bottom flask, from which the solvent was

evaporated. The resulting residues were separated on a silica gel column with hexane:chloroform (1:1). The first eluted and major product, the methylporphyrin, was recrystallised from DCM/methanol. For the small-scale trial reactions, the product composition was assessed semi-quantitatively by recording the ^{1}H NMR spectrum of the total crude product after removal of the DMF. For the experiment with DMF-d_7, the procedure was modified slightly, as follows. NiDAPCHO (5 μmol) was added to a 0.2–0.5 mL microwave vial with a small stirrer bar. Water (1 μL) and d_7-DMF (0.4 mL) were added and the solution was degassed with N_2. The vial was placed in the microwave reactor for 2 h at 250 °C with TLC assessment being conducted at 30, 60 and 120 min. The mixture was diluted with water (20 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with deionized water (3 × 20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered through cotton wool into a 50 mL round bottom flask and the solvents evaporated. The products were separated on a silica gel column with chloroform and ^{1}H NMR showed methylporphyrin to be the major product. The ^{2}H NMR spectrum of the sample was then recorded.

Data for new methylporphyrin derivatives isolated from microwave reactions but for which typical yields were not quantified, are as follows.

5-Methyl-10,15,20-triphenylporphyrinatonickel(II) 3b. ^{1}H NMR: δ_H, ppm 9.36, 8.81 (each 2H, d, J = 4.8 Hz, β-H), 8.70 (s, 4H, β-H), 7.99–8.04 (6H, m, *o*-H on 10,15,20-phenyl), 7.67–7.73 (9H, m, *m*, *p*-H on 10,15,20-phenyl), 4.29 (3H, s, CH_3). UV-vis: λ_{max}, nm (ε, 10^3 $M^{-1}.cm^{-1}$) 416 (170), 530 (12.5). MS (MALDI): *m/z* 609.2 (calcd. for $[M + H]^+$ 609.1).

5-Methyl-10,15,20-triphenylporphyrin 2c. ^{1}H NMR: δ_H, ppm 9.54, 8.93, (each 2H, d, J = 4.8 Hz, β-H), 8.81 (4H, second order AB, β-H), 8.15–8.25 (6H, m, *o*-H on 10,15,20-phenyl), 7.75–7.95 (9H, m, *m*, *p*-H on 10,15,20-phenyl), 4.71 (3H, s, CH_3), -2.67 (2H, br s, NH). These data agree for the most part with those reported by Ishkov *et al*. [10] MS (ESI): *m/z* 553.2440 (calcd. for $[M + H]^+$ 553.2387), 575.2258 (calcd. for $[M + Na]^+$ 575.2206).

5-Methyl-10,20-bis(3,5-di-*t*-butylphenyl)porphyrin $H_2$4b. ^{1}H NMR: δ_H, ppm 10.10 (s, 1H, *meso*-H), δ 9.61, 9.28, 9.03, 9.02 (each 2H, d, J = 4.4 Hz, β-H), 4.78 (s, 3H, CH_3), 1.58 (s, 36H, *tert*-butyl-H), -2.82 (s, 2H, NH). UV-vis: λ_{max}, nm (ε, 10^3 $M^{-1}.cm^{-1}$) 416 (153), 512 (9.9), 547 (6.5), 586 (5.1), 643 (4.4). MS (ESI): *m/z* 701.4582, (calcd. for $[M + H]^+$ 701.4578).

5-Methyl-10,20-bis(3,5-di-*t*-butylphenyl)-porphyrinatonickel(II) Ni4b. ^{1}H NMR: δ_H, ppm 9.70 (s, 1H, *meso*-H), 9.38, 9.06, 8.88, 8.87 (each 2H, d, J = 4.8 Hz, β-H), 7.87 (d, 4H, J = 1.6, *o*-Ar-H), 7.74 (t, 2H, J = 1.6, *p*-Ar-H), 4.32 (3H, s, CH_3), 1.50 (s, 36H, *tert*-butyl-H). UV-vis: λ_{max}, nm (ε, 10^3 $M^{-1}.cm^{-1}$) 409 (224), 525 (18.7). MS (MALDI): *m/z* 757.9, (calcd. for $[M + H]^+$ 757.4).

Preparative scale microwave synthesis of Ni4b

To a 2.0–5.0 mL microwave vial, a small stirrer bar and NiDAPCHO (22.8 mg, 29.5 μmol) were added. DMF (2 mL) and water (5 μL) were added to the vial, which was then fitted with a septum. The solution was degassed with N_2 and sealed with the microwave vial cap. The solution, which was a pink/red color, was placed in the microwave reactor for 30 min at 250 °C. It was cooled to 50 °C in the microwave and then removed, now brown/red in color. The reaction mixture was diluted with DCM (20 mL), placed in a separating funnel and washed with deionized water (5 × 50 mL). The organic layer was dried with anhydrous Na_2SO_4 and filtered through cotton wool into a 100 mL round bottom flask, from which the solvent was evaporated. The resulting residues were separated on a silica gel column with hexane:chloroform (1:1). The first eluted and major product, NiDAPCH_3 (**Ni4b**, 14 mg, 18 μmol, 61%), was recrystallized from DCM/methanol to yield fine, red/brown crystals.

Experiment to examine intermediates

NiDAPCHO **Ni4a** (30 mg, 39 μmol) was added to a microwave vial (2.0–5.0 mL) with a small stirrer bar. DMF (3 mL) was added, followed by water (7.5 μL, 0.42 mmol). The red-pink solution was degassed with N_2 and placed in the microwave reactor for 5 min at 240 °C. A 35 μL sample was taken and added to a 5 mL volumetric flask. The flask was made up to the mark with chloroform and the UV-vis spectrum was recorded. The DMF solution was then degassed with N_2 and placed in the microwave for a further 5 min at 240 °C, after which a sample was taken as described earlier. The process was repeated until a total of eight samples had been taken and the reaction appeared to have reached completion.

RESULTS AND DISCUSSION

After testing the reproducibility of the new observation in the presence of the aminoporphyrin, we embarked on a series of microwave reactions to investigate the conditions that favor clean conversion to the methylporphyrin. Reactants, catalysts/additives, time and temperature were varied as shown by the entries in Table 1. As the aminoporphyrin **2b** was recovered unchanged from experiment 1, the first control experiment was to omit this reactant, and as expected, the reduction to methyl porphyrin **2c** was just as successful (entries 2 and 3). Thenceforth, the amine was omitted. Entry 3 shows a scale-up of the reaction to 68 μmol (42 mg), indicating the success of this method for larger-scale preparative use. We next changed the porphyrin substrate, to the corresponding Ni(II) complex NiTriPPCHO **3a** (entries 4, 5) including extending the heating time to 3 h to assess the stability of the product **3b** at 250 °C. These reactions were also successful in achieving almost quantitative formyl to methyl conversion.

Table 1. Summary of representative results of microwave heating of formylporphyrins in DMF under various conditions[a]

Experiment	Porphyrin substrate	Time, min	Additive	Result[b]	Comment
1	H_2TriPPCHO **2a**	60	TFA (5 µL)	40:60	+ H_2TriPPNH$_2$ **2b** ca. 1:1
2	H_2TriPPCHO **2a**	60	TFA (5 µL)	0:100	unidentified minor products present
3	H_2TriPPCHO **2a**	60	TFA (5 µL)	0:100	larger scale: 68 µmol porphyrin
4	NiTriPPCHO **3a**	60	TFA (5 µL)	75:25	—
5	NiTriPPCHO **3a**	180	TFA (5 µL)	0:100	—
6	NiDAPCHO **Ni4a**	60	TFA (5 µL)	0:100	—
7	H_2TriPPCHO **2a**	60	H_2O (2 µL)	0:100	unidentified minor product present
8	NiDAPCHO **Ni4a**	60	H_2O (2 µL)	0:100	—
9	NiDAPCHO **Ni4a**	60	H_2O (5 µL)	0:100	larger scale: 28 µmol porphyrin
10	NiDAPCHO **Ni4a**	30	H_2O (5 µL)	0:100	—
11	NiDAPCHO **Ni4a**	30	H_2O (5 µL)	0:100	23 µmol porphyrin; isolated recrystallized yield **Ni4b** 63%
12	NiDAPCHO **Ni4a**	30	—	100:0	"super-dry DMF": CaH_2 distillation directly into vial
13	NiDAPCHO **Ni4a**	30	H_2O (50 µL)	0:100	—
14	NiDAPCHO **Ni4a**	30	D_2O (2 µL)	100:0	"100%" D_2O
15	NiDAPCHO **Ni4a**	120	H_2O (1 µL)	0:100	0.4 mL d_7-DMF; 5 µmol porphyrin; 4 × 30 min with TLC checks; product NiDAPCHD$_2$
16	NiDAPCH$_3$ **Ni4b**	30	H_2O (1 µL)	n/a	0.4 mL d_7-DMF
17	H_2OEPCHO **$H_2$5a**	60	TFA (5 µL)	—	major product H_2OEP **$H_2$5c**
18	H_2OEPCHO **$H_2$5a**	45	H_2O (2 µL)	—	major product H_2OEP **$H_2$5c**
19	NiOEPCHO **Ni5a**	30	H_2O (2 µL)	—	major product NiOEP **Ni5c**
20	NiDAPCH$_2$OH **Ni4d**	30	H_2O (2 µL)	0:100[c]	precipitate formed on cooling, minor product **Ni4e**
21	NiDAPCH$_2$OH **Ni4d**	20	H_2O (5 µL)	60:40[c]	precipitate formed on cooling; **Ni4e** not observed
22	NiDAPCH$_2$OH **Ni4d**	60	TFA (7.5 µL)	0:100[c]	unidentified minor products formed
23	NiDAPCHO **Ni4a**	—	H_2O (7.5 µL)	0:100	240 °C, sampling of product mixture at 5 min intervals with examination by UV-vis (see Fig. 3)

[a] Standard conditions: 10–15 µmol porphyrin, 2 mL DMF. [b] Result: ratio of unreacted formylporphyrin to methylporphyrin product, estimated by integration of the methyl and aldehyde peaks in the ^{1}H NMR spectrum of the crude reaction mixture; n/a = not applicable as this was a control H/D exchange experiment. [c] Ratio **Ni4d**:**Ni4b**.

The method was extended to 5-formyl-10,20-bis(3,5-di-*t*-butylphenyl)porphyrinatonickel(II) (NiDAPCHO) **Ni4a**, and the corresponding methylporphyrin was formed in high yield (entry 6). To study the effects of the acid, the TFA was replaced with water for both **2a** and **Ni4a**, and the latter was also reacted in a larger scale, with isolation and purification of the product **Ni4b** in 61% recrystallized yield (entries 7–11). Under these conditions, only 30 min was sufficient to consume the aldehyde.

The need for the presence of water and/or acid(s) was assessed by using DMF that was vacuum distilled from CaH_2 directly into the microwave vial before sealing and subjecting **Ni4a** to the usual conditions. However, the methyl porphyrin **Ni4b** was not detected (entry 12). The reaction was found to tolerate ten times the amount of water (entry 13). On the other hand, use of 2 µL of nominally "100% deuterated" water gave no **Ni4b** after the time indicated, perhaps indicating a strong deuterium isotope effect (entry 14).

To investigate the source of the reducing Hs in this reaction, we then employed d_7-DMF, scaled down in volume (entry 15), and checked the reaction progress by heating for four 30 min periods, with sampling and TLC analysis. The reaction progressed normally, but more slowly. The methylporphyrin **Ni4b** was isolated as usual, and the product was examined by ^{1}H and ^{2}H NMR spectroscopy; the former indicated deuteration to

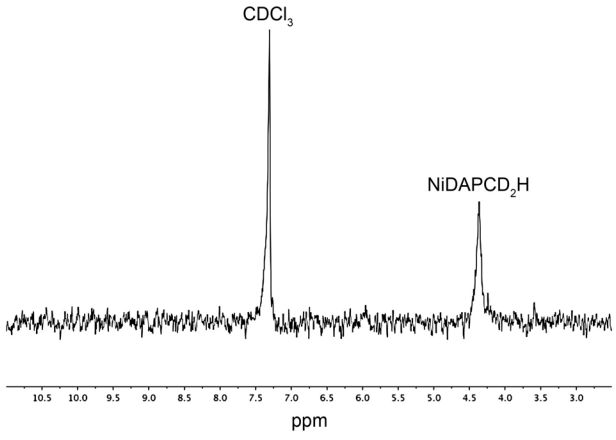


Fig. 1. The ^{2}H NMR spectrum of NiDAPCD$_2$H (**Ni4c**) from the microwave-heated reaction of **Ni4a** in d_7-DMF at 250 °C

the extent of *ca*. 1.75 deuterium atoms per porphyrin, *i.e*. the product was mostly NiDAP-CD$_2$H **Ni4c**. Attempted examination at higher resolution showed the broadening expected due to H–D coupling, but clear separation was not achieved. The ^{2}H NMR spectrum is shown in Fig. 1, and it shows that there was no concomitant deuteration of the porphyrin or aryl positions. A control experiment with the **Ni4b** in d$_7$-DMF showed no exchange occurred over the normal time period of the process (entry 16).

Finally, we also tried the OEP (H$_2$OEP = 2,3,7,8,12,-13,17,18-octaethylporphyrin) aldehydes, both free base and Ni(II) complex. The starting materials **H$_2$5a** and **Ni5a** were consumed over periods of 30–60 min, but no methyl products **H$_2$5b** and **Ni5b** were detected. NMR spectra showed the only products were the corresponding deformylated porphyrins **H$_2$5c** and **Ni5c** (entries 17–19).

Considering the mechanism of the exhaustive reduction, a possible intermediate is the primary alcohol, *e.g*. **Ni4d**. This compound was prepared readily by reduction of the aldehyde **Ni4a** with NaBH$_4$ in THF, and was then substituted for the aldehyde in our usual conditions (entries 20–22). The results were a little inconsistent: in two of the runs, a red precipitate appeared on cooling. After the first experiment, the solid was collected and NMR spectroscopy showed it to be a mixture of the methylporphyrin **Ni4b** and the *meso*-dimethylaminomethyl (DMAM) porphyrin **Ni4e**, in a ratio of 5:1. The latter was identified by comparison with the spectrum of a sample prepared previously in our laboratory by the route of Ponomarev and co-workers [12]. However, in the two subsequent runs, only very small amounts of this product were observed, along with a variety of other, unidentified porphyrins, all in very small quantities compared with the major product, the methylporphyrin **Ni4b**. So the hydroxymethylporphyrin could be an intermediate in the reduction, but the role (if any) of the DMAM porphyrin is still unclear.

To assess whether intermediates could be identified during the reaction time, a run was conducted at the lower temperature of 240 °C, and the vial was cooled, removed from the microwave reactor, and sampled at intervals, beginning with 5 min (entry 23). Aliquots were removed and diluted to a fixed volume with CHCl$_3$, before examination by UV-vis spectroscopy. Standards of **Ni4a**, **Ni4b** and **Ni4d** were recorded quantitatively at similar concentrations, and these spectra are plotted in Fig. 2. The results of the sampled run are shown in Fig. 3. It is

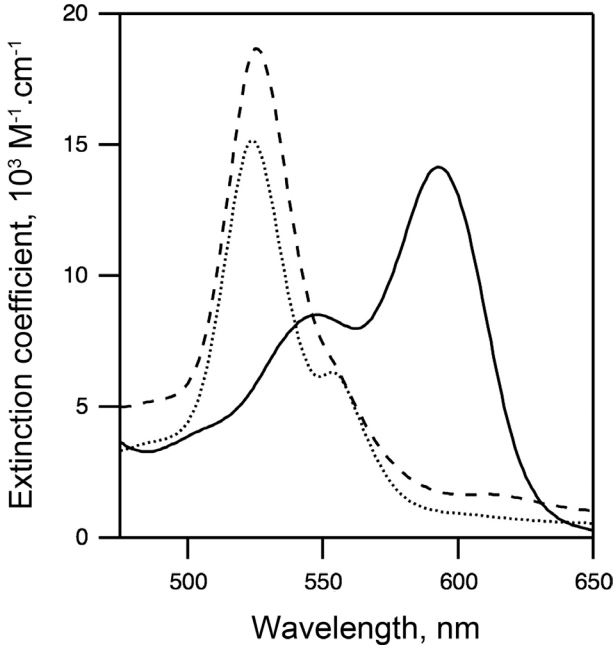


Fig. 2. The UV-visible spectra of NiDAPCHO (**Ni4a**, solid), NiDAPCH$_3$ (**Ni4b**, dashed), and NiDAPCH$_2$OH (**Ni4d**, dotted)

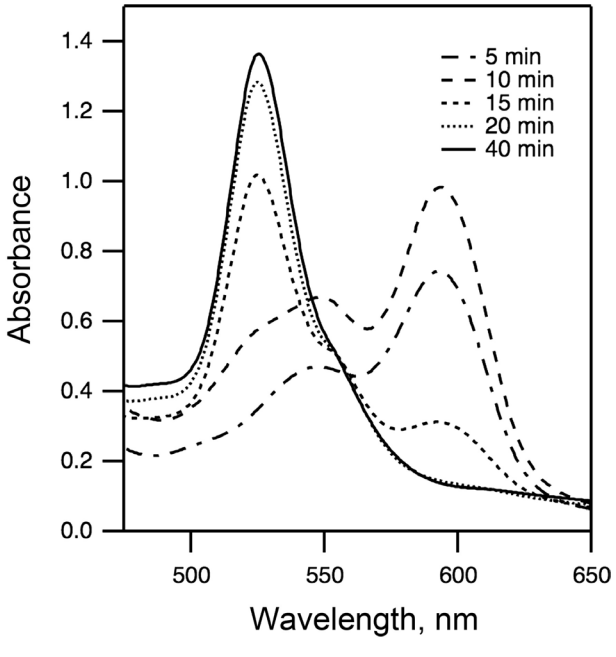
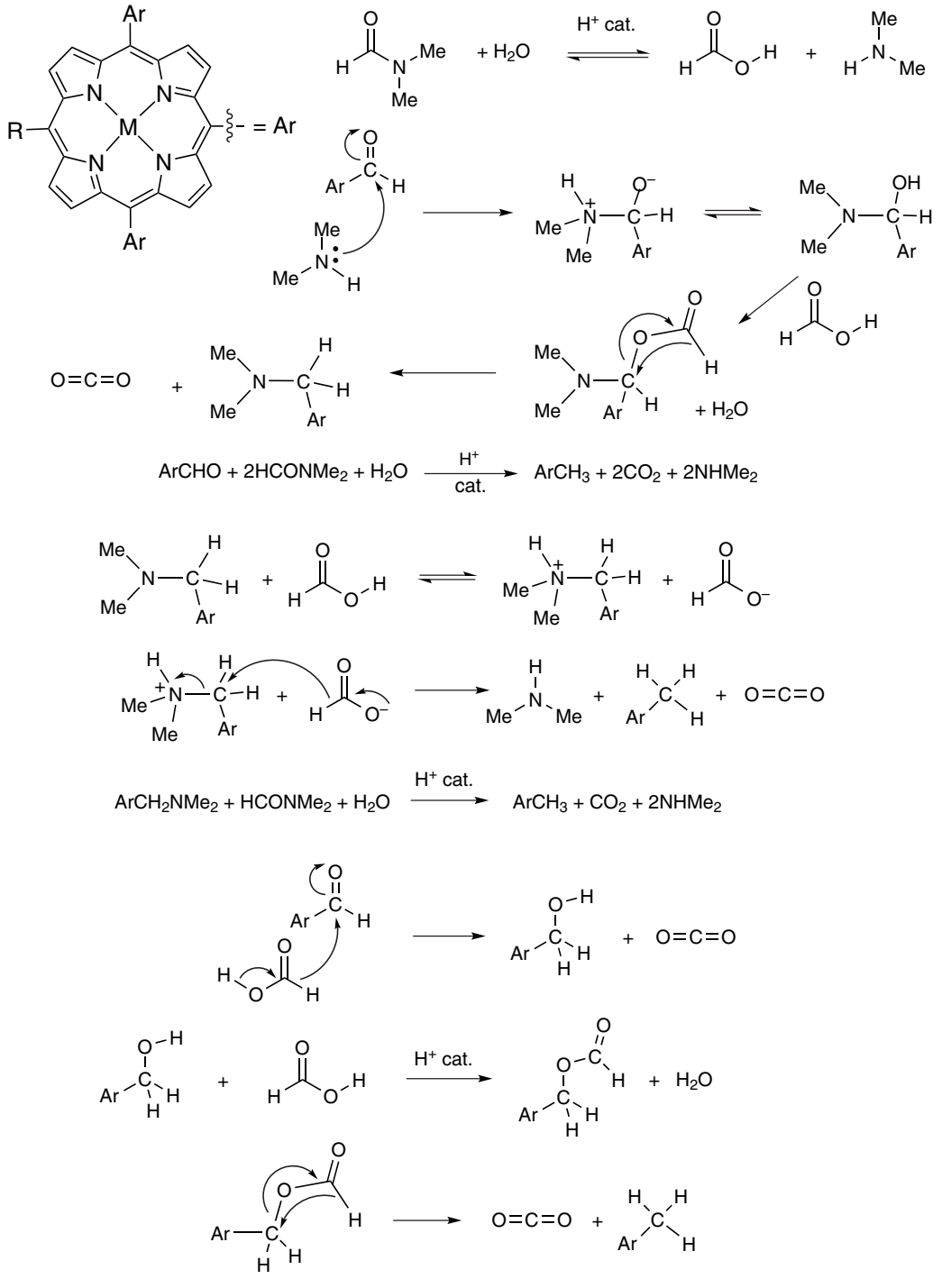


Fig. 3. The UV-visible spectra recorded after sampling at the intervals shown, during the microwave heating of **Ni4a** at 240 °C in DMF



Scheme 2. Possible mechanisms for the reductions of formyl-, dimethylaminomethyl- and hydroxymethylporphyrins to methylporphyrins in DMF in the presence of water and an acid catalyst

apparent that at least one intermediate is present, as no isosbestic point remained through the run. Moreover there was an initial *rise* in absorbance in the region of the band maximum of the formyl starting material. Furthermore, at around 15 min, the absorbance near 600 nm has fallen dramatically, but absorbance near 550 nm is prominent. This is the region where the hydroxymethyl **Ni4d** absorbs, but equally, this could indicate the presence of the DMAM porphyrin **Ni4e**. Later in the run, when almost all **Ni4a** is consumed, the profile is largely the same as that of the final product **Ni4b**. The results are by no means definitive, as the absorbance apparent near 550 nm is higher than would be expected if only **Ni4d** were present. Because of the impossibility of sampling totally *in situ*, and the non-specific nature of the analytical method, we conclude only that more than one intermediate is involved.

meso-Methylporphyrins have been prepared previously by a variety of reductive methods, usually from the

corresponding *meso*-formyl derivatives [7, 13–15], or occasionally by other means, such as the cleavage of *meso*-triphenylphosphinomethyloctaalkylporphyrins [16]. Both metalated and free base methylporphyrins have been prepared for *octaalkyl*porphyrins, but the derivatives of 5,15-diaryl- or 5,10,15-triarylporphyrins, which are the more commonly used frameworks in recent years, were not reported until 1993 [17]. Since then, almost all reports of such structures have involved synthesis of 5-mono- or 5,15-dimethylporphyrins by cyclocondensations, and only the metal-mediated synthesis of Therien and co-workers [17], and the Pd-catalyzed methylation of *meso*-bromoporphyrins using potassium organotrifluoroborates by Senge and co-workers [18], have used pre-formed porphyrins to which the methyl substituents were then attached. Since 5,15-diaryl- or 5,10,15-triarylporphyrins with a huge variety of possible aryl groups are readily available, a simple route to *meso*-methylporphyrins should be useful.

The question of the detailed mechanism of this CHO to CH_3 exhaustive reduction is a complex one. It is clear from our experiments that DMF is providing the reducing Hs (as shown by the deuteration results), and either free acid(s) or water or both are involved, presumably in catalytic roles. We note that using specially dried DMF completely curtails the reduction. DMF has been reported frequently as a reductant [19], especially as an adjunct in the preparation of metal nanoparticles, but as far as we are aware, not for the exact conversion we have studied. There is a multitude of methods in the literature for this reduction in non-porphyrinic substrates (*e.g.* the Clemmensen or Wolff–Kischner reactions, amongst many more modern methods) [20], but we have not uncovered this precise use of a DMF/catalyst or DMF/water system for CHO to CH_3 conversion. It is certainly possible that the primary alcohol is an obligate intermediate, as suggested by entries 20–22 and the UV-visible spectra recorded in our sampled run (entry 23). This reaction bears some resembance to the Leuckart–Wallach suite of reactions, whereby aldehydes and ketones are converted to dialkylaminomethyl derivatives using amine sources (including DMF) and reducing equivalents in the form of formate sources [21]. In very few of the numerous references to this reaction type, the corresponding carbinols were isolated and/or observed during the reactions [22].

Numerous mechanisms for the CHO to CH_2OH/CH_2NMe_2 transformation and their subsequent conversion to CH_3, perhaps involving free radicals (as recently suggested for some DMF reactions [23]), or the Por$CH_2OC(O)H$ ester, are conceivable. At this stage, the details are not clear, but one plausible ionic mechanism is presented in Scheme 2. We have recently discovered that with simple *arylaldehydes*, the dimethylaminomethyl product is exclusively formed under some conditions, which represents a new version of the Leuckart–Wallach-type reaction of carbonyls [24]. Our studies of this reaction are continuing, but meanwhile the present results represent a new resource in the armamentarium of porphyrin chemists.

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Supporting information

^{1}H NMR spectra ($CDCl_3$) of previously unreported porphyrins are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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