Unusual Sensitivity to the Concentration of Ethanol in the Boron Trifluoride/Ethanol-Catalyzed Synthesis of 5,10,15,20-Tetrakis-(4-cyano-2,6-dimethylphenyl)porphyrin by the Lindsey Method

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The boron trifluoride/ethanol-catalyzed condensation of 4-cyano-2,6-dimethylbenzaldehyde **1b** with pyrrole by the Lindsey method to give the new, *ortho*-disubstituted 5,10,15,20-tetrakis(4-cyano-2,6-dimethylphenyl)porphyrin **2** was found to be highly sensitive to the concentration of ethanol. In the absence of ethanol the yield of porphyrin is only 1%. Yields can be increased to 20-25% with ethanol concentrations of 0.05-0.1% (v/v) but they decrease rapidly at higher concentrations of ethanol. Optimized procedures for the preparation of both **1b** and **2** are described and the newly synthesized molecules are characterized by nmr (^{1}H and ^{13}C), mass spectra and elemental analysis.

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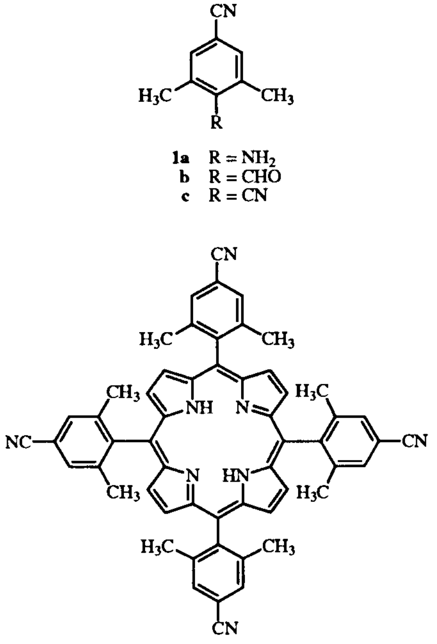
Introduction.

In recent work directed at the synthesis of catalysts for the reduction of dioxygen to water at electrodes, we have prepared a series of cobalt porphyrins with substituents at the four *meso* positions of the porphyrin ring that can serve as ligands for back-bonding transition metal complexes [1-5]. For the purpose of mechanistic diagnoses we became interested in phenyl substituents that contained methyl groups in the 2 and 6 positions of the ring in order to diminish electronic interactions between the π-system of the porphyrin and that of the substituent. We were drawn to the new synthetic procedure of Lindsey and co-workers [6,7] for the preparation of *ortho*-substituted tetraphenylporphyrins because of its demonstrated success in the preparation of "sterically hindered" porphyrins in much higher yields than are available using more classical methods. In applying the Lindsey method to the reaction of 4-cyano-2,6-dimethylbenzaldehyde **1b** with pyrrole, we were surprised to find that the yields of the desired porphyrin exhibited a much higher sensitivity to the concentration of the ethanol cocatalyst than was reported for the analogous reaction of mesitaldeyde with pyrrole [7]. We examined the effect of the ethanol concentrations on the reaction yield in some detail and determined the optimum concentration of the ethanol cocatalyst in the Lindsey reaction of **1b** with pyrrole to obtain the new, sterically hindered 5,10,15,20-tetrakis(4-cyano-2,6-dimethylphenyl)porphyrin **2**. A synthetic procedure for **1b** is also described.

Results and Discussion.

A lengthy procedure for the synthesis of 4-cyano-2,6-dimethylbenzaldehyde **1b** has been reported recently by Lindsey and co-workers [8]. Kubota and coworkers [9] apparently also prepared **1b** in two steps by cyano-de-bromination of 4-bromo-2,6-dimethylaniline followed by conversion to the corresponding aldehyde *via* the Beech reaction [10]. However, experimental details were not provided. We elected to utilize a reaction scheme of this type: The cyano-de-bromination of 4-bromo-2,6-dimethylaniline with cuprous cyanide (Aldrich, greenish powder) in *N,N*-dimethylformamide according to Matsukawa and coworkers [11] gave 4-cyano-2,6-dimethylaniline **1a** in 80% yield. (The source of cuprous cyanide had a major effect on the yield. Cuprous cyanide (white powder) prepared according to Barber [12] gave **1a** in only 32% yield.) The aniline **1a** was converted to the aldehyde **1b** in 23% yield by the Beech reaction using a modified version of the procedure described for the preparation of 3-nitrobenzaldehyde [10] in which the hydrolysis of the intermediate oxime is carried out by heating with ferric ammonium sulfate instead of with hydrochloric acid. (Using hydrochloric acid for the hydrolysis step decreased the yield of **1b** to only 3.5% while the yield of 1,4-dicyano-2,6-dimethylbenzene **1c** was 19%.) Extraction of the crude aldehyde into chloroform was substituted for steam-distillation. The extract was chromatographed and the product was further purified through formation of the bisulfite adduct. (The dinitrile **1c** was isolated in 4.5% yield as a side product.) The reaction of **1b** with pyrrole, using the reaction conditions described by Lindsey for the synthesis of tetramesitylporphyrin [6], afforded a yield of porphyrin **2** (Figure 1) of only 3%.

Investigation on a small scale of the dependence of the yield on the concentration of the ethanol cocatalyst revealed that the yield of **2** could be increased to 25% if much lower concentrations of ethanol were employed (Figure 2). The reaction survey shown in Figure 2 was obtained by following the Lindsey procedure with 3.3 *mM* boron trifluoride diethyl etherate and 10 *mM* substrates (**1b** and pyrrole) in 25 ml of dichloromethane at room temperature. The yields of **2** were determined spectrophotometrically after 1 hour by removing reaction aliquots and oxidizing them with excess 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature. The maximum yield of **2** occurred at a much lower concentration of ethanol (0.05-0.1% v/v) than



1a R = NH_2
b R = CHO
c R = CN

2

Figure 1. Structure of the compounds described in this study.

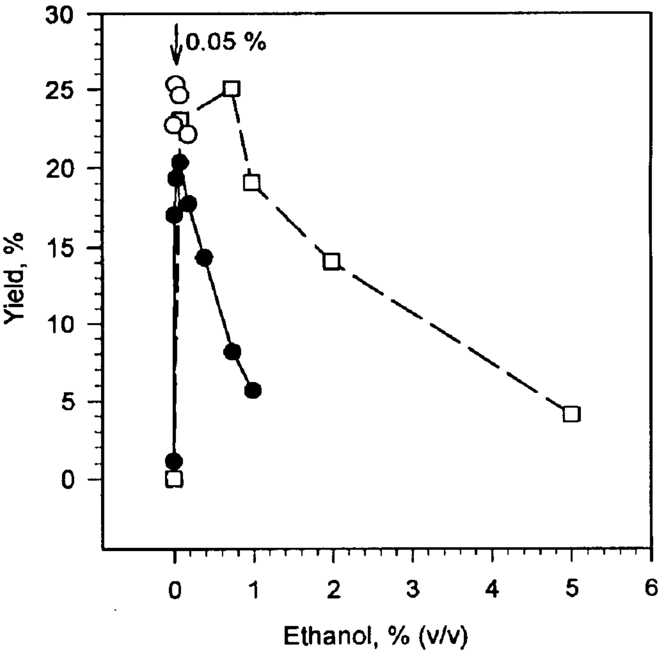


Figure 2. Comparison of the yields of porphyrin **2** (●) and tetramesitylporphyrin (□) [7] as a function of the concentration of the ethanol cocatalyst. Reactions were carried out with 3.3 *mM* boron trifluoride diethyl etherate and 10 *mM* substrates in 25 ml of dichloromethane at room temperature. The yields were determined spectrophotometrically after 1 hour (see Experimental). (O) Effect of increasing the concentration of boron trifluoride diethyl etherate to 6.6 *mM* after 1 hour and continuing the reaction for an additional hour.

the 0.75% concentration found by Lindsey and co-workers [7] to produce the largest yields in the synthesis of the corresponding tetramesityl porphyrin. Prolonging the reaction time beyond one hour did not significantly alter the yields of **2**. However, increasing the concentration of boron trifluoride diethyl etherate to 6.6 *mM* after the reaction had proceeded for 1 hour increased the porphyrin yields substantially, *e.g.* from 19% to 25% at 0.05% (v/v) ethanol (Figure 2). Further increases in the concentration of boron trifluoride diethyl etherate or of the reaction time left the yields essentially unchanged. Beginning the reaction with 6.6 *mM* instead of 3.3 *mM* boron trifluoride diethyl etherate resulted in a somewhat lower yield of **2** (20%) after 1 hour. Using chloroform instead of dichloromethane as solvent produced little change in the yields. The use of 2,3,5,6-tetrachloro-1,4-benzoquinone at 61° in place of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature as oxidant did not result in better yields although Lindsey often obtained somewhat higher yields of other porphyrins using the former oxidation conditions [7].

Using the conditions found optimal in the reaction survey studies of Figure 2a preparative scale reaction of **1b** with pyrrole was carried out. After chromatography and recrystallization, the porphyrin 2 was obtained in a yield of 25%.

EXPERIMENTAL

A stock solution (2.5 *M*) of boron trifluoride diethyl etherate, (Aldrich, purified, redistilled) was prepared in dichloromethane. 4-bromo-2,6-dimethylaniline (Aldrich, camel brown powder) was dissolved in hexane (30 g/600 ml, room temperature), the solution filtered, the solvent evaporated, and the resulting wheat brown crystals dried, mp 50-51°. Chloroform (EM Science, GR) was depleted of ethanol according to [7]. Pyrrole (Aldrich) was distilled from calcium hydride. The following chemicals were used as received: carbon tetrachloride (Aldrich, anhydrous), dichloromethane (EM Science, OmniSolv), cuprous cyanide (Aldrich), copper sulfate (EM Science, GR), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Aldrich), *N,N*-dimethylformamide (EM Science, GR), ethylenediamine (EM Science), ether (EM Science, GR, anhydrous), ethanol (Quantum, 200 proof), ferric ammonium sulfate dodecahydrate (Mallinckrodt, ACS, reagent), hexane (EM Science, OmniSolv), hydroxylamine hydrochloride (Spectrum, ACS, reagent), sulfuric acid (EM Science, GR), methanol (EM Science, OmniSolv), sodium bisulfite (Mallinckrodt, ACS, reagent), sodium nitrite (Spectrum, ACS, reagent), sodium acetate (EM Science, GR), sodium sulfite (Baker, ACS, reagent), paraformaldehyde (Aldrich), silica gel (Baker, for flash chromatography), 2,3,5,6-tetrachloro-1,4-benzoquinone (Aldrich), toluene (EM Science, OmniSolv), triethylamine (Mallinckrodt, ACS, reagent).

Procedures.

Thin-layer chromatography (tlc) was performed on precoated plates (EM Science, silica gel 60 F-254). Filtrations were carried out using Buchner funnels with 4.5-5 µm fritted glass disks. Melting points are uncorrected. Electron impact mass spectrometry and fast atom bombardment (fab) mass spectrometry were performed on a VG/Fisons ProSpec. The matrix for fab mass spectroscopy was 3-nitrobenzyl alcohol.

The ^{1}H-nmr and ^{13}C-nmr were obtained at 500 and 125.7 MHz, respectively, on a Bruker AM-500 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane at ambient temperature. Carbon assignments were made on the basis of DEPT experiments; the multiplicity is given in parentheses following the chemical shift value. Infrared spectra were taken in potassium bromide pellets with a FTIR spectrometer (Perkin-Elmer 1600, and Mattson Polaris). The uv-visible spectra were obtained on a Hewlett Packard 8450A or 8452A diode array spectrophotometer.

Reaction Survey [7].

A flame-dried 50-ml three-neck round-bottom flask equipped with a magnetic stirring bar under an argon atmosphere was charged with 25 ml of dichloromethane or chloroform, containing 0, 0.025, 0.05, 0.1, 0.2, 0.4, 0.75, or 1.0% (v/v) of ethanol, **1b** (39.8 mg, 0.25 mmole), and pyrrole (17.4 µl, 0.25 mmole). 33 µl of 2.5 *M* boron trifluoride diethyl etherate (82.5 µmoles) were added *via* syringe, the flask was shielded from light, and the solution was stirred for 1 hour at room temperature. To determine the yield of porphyrin after 1 hour, a 50-µl aliquot of the reaction solution was injected into 300 µl of 10 *mM* 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in toluene/ethanol (3:1); 50 µl of the resulting oxidized solution was added to 3 ml of dichloromethane/ethanol (3:1) and the absorbance of the solution was determined. The extinction coefficient of the Soret-band (λ = 418 nm) was measured as 4.70 x 10^5 M^{-1} cm^{-1}. Bulk oxidation of reaction mixtures was performed by adding 2,3,5,6-tetrachloro-1,4-benzoquinone as described in [7].

4-Cyano-2,6-dimethylaniline (**1a**) [11].

In a 250-ml round-bottom flask equipped with a reflux condenser and a stirring bar, 60 ml of *N,N*-dimethylformamide, 4-bromo-2,6-dimethylaniline (25 g, 0.125 mole), and cuprous cyanide (13.43 g, 0.15 mole) were refluxed for 4 hours. Ethylenediamine (125 ml) was added to the hot reaction mixture. After stirring for an additional 2 hours, the dark blue-green mixture, which contained elemental copper, was filtered and the solid washed with *N,N*-dimethylformamide. The filtrate was added to 500 ml of ice-water, the resulting precipitate was filtered, washed thoroughly with water and dried to give 15 g of a brownish powder which was dissolved in dichloromethane and purified by column chromatography on silica gel to yield 14.61 g (80%) of a yellowish crystalline material that was pure enough to be used in the next step. Recrystallization from carbon tetrachloride gave 13.71 g (75%) of white **1a**, mp 111-112° (110-111° [11]); tlc (silica gel, dichloromethane): R_f = 0.46; ir (potassium bromide): ν 3484, and 3395 (NH), 2209 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.17 (s, 6H, CH_3), 4.04 (br, s, 2H, NH_2), 7.22 (s, 2H, H-3 and H5); ^{13}C-nmr (deuteriochloroform): δ 17.2 (q, CH_3), 99.5 (s, C-4), 120.5 (s, CN), 121.5 (s, C-2 and C-6), 132.0 (d, C-3 and C-5), 147.3 (s, C-1); hrms: (70 eV, electron impact) Calcd. for $C_9H_{10}N_2$: (M^+) 146.0844. Found 146.0841.

4-Cyano-2,6-dimethylbenzaldehyde (**1b**).

The aniline **1a** (13.6 g) was converted to the aldehyde **1b** following Beech's procedure for the preparation of 3-nitrobenzaldehyde [10]. The brown, powdery oxime was filtered, washed with water and heated with aqueous ferric ammonium sulfate. Instead of isolating the crude aldehyde by steam-distillation as in [10], it was extracted five times with 150 ml aliquots of chloroform. After rotoevaporation of the solvent, the residue was redissolved in 80 ml of toluene (sonication) and separated by flash chromatography on a column (4 x 30 cm) of silica gel using toluene as solvent. The solvent from the combined product fractions was rotoevaporated and the residue was dried *in vacuo* at room temperature for 1 hour to give 7.13 g of a reddish powder. The aldehyde was then converted to the bisulfite addition compound by dissolution in 245 ml of 10% sodium bisulfite in water at 60° (some reddish material did not dissolve). The aqueous phase was extracted with 60 ml of ether to remove non-aldehydic impurities (including **1c**) and filtered. Then 60 ml of a 1:1 mixture of concentrated sulfuric acid and water were added slowly to the filtrate (foaming!), which produced immediate crystallization of the aldehyde **1b**. The mixture was allowed to stand at room temperature for 1 hour before the product was collected on the filter funnel and washed with water. Additional product was obtained by allowing the filtrate to stand at room temperature for an additional 2 hours. The combined product was dried *in vacuo* at room temperature for 12 hours to give 3.42 g (23%) of the aldehyde **1b**, mp 121-123° (mp 124-125° [8]); tlc (silica gel, toluene): R_f = 0.22; ir (potassium bromide): ν 2888 and 2788 (aldehyde CH), 2226 (CN), 1699 (aldehyde CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.62 (s, 6H, CH_3), 7.39 (s, 2H, H-3 and H-5), 10.62 (s, 1H, CHO); ^{13}C-nmr (deuteriochloroform): 20.0 (q, CH_3), 116.0 (s, C-4), 117.9 (s, CN), 132.8 (d, C-3 and C-5), 135.9 (s, C-1), 141.5 (s, C-2 and C-6), 192.5 (s, CHO); hrms (70 eV, electron impact) Calcd. for $C_{10}H_9NO$: (M^+) 159.0684. Found 159.0678.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.10; H, 5.70; N, 8.83.

1,4-Dicyano-2,6-dimethylbenzene (**1c**).

This side-product was obtained as colorless needles (ether, or sublimed at 110°/23 torr) mp 167-169° (sublimed) (mp 172° [13]); tlc (silica gel, toluene): Rf = 0.25; ir (potassium bromide): ν 2230 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.59 (s, 6H, CH_3), 7.44 (s, 2H, H-3 and H-5); ms: (70 eV, electron impact) m/z 156 (M^+).

Anal. Calcd. for $C_{10}H_9N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.66; H, 5.15; N, 17.59.

5,10,15,20-Tetrakis(4-cyano-2,6-dimethylphenyl)porphyrin (**2**).

A flame-dried 500-ml round-bottom flask equipped with a magnetic stirring bar was charged with 250 ml of dichloromethane containing 0.05% (v/v) ethanol, **1b** (398 mg, 2.5 mmoles), and pyrrole (174 µl, 2.5 mmoles). After the solution was purged with dry argon for 5 minutes, 330 µl of 2.5 *M* boron trifluoride diethyl etherate (825 µmoles) were added *via* syringe, the flask was shielded from light, and the solution was stirred for 1 hour at room temperature. At that time a second 330 µl aliquot of 2.5 *M* boron trifluoride diethyl etherate (825 µmoles) was added *via* syringe, and the stirring continued for 1 hour at room temperature. The reaction was quenched by the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (426 mg, 1.88 mmoles) in powder form, and the reaction mixture was stirred for an additional 1 hour at room temperature. The solution was neutralized with 230 µl of triethylamine (1.65 mmoles), and rotoevaporated to dryness. The crude product was scraped from the flask (residual material was collected in methanol by sonication), placed on a Buchner funnel and washed with methanol until the filtrate was clear. The residue was washed several times with small amounts of dichloromethane containing 1% of ethanol until all porphyrinic material was extracted, and the combined filtrates were placed on the top of a silica gel column (60 g, 2 x 34 cm). The product was eluted with dichloromethane containing 1% of ethanol. The main band containing the product was collected and the solvent was rotoevaporated. The resulting solid was recrystallized from dichloromethane/methanol, and dried *in vacuo* at 100° for 6 hours to give 131 mg (25%) of a deep purple, crystalline powder; tlc (silica gel, dichloromethane containing 1% of ethanol): $R_f = 0.45$; ir (potassium bromide): ν 3320 (NH), 2225 (CN) cm^{-1}; uv-visible: (dichloromethane/ethanol 3:1): λ_{max} in nm (log ε): 402 (sh), 418 (5.67), 480 (sh), 512 (4.36), 544 (3.74), 588 (3.83), 646 (3.34); ^{1}H-nmr (deuteriochloroform): δ -2.54 (s, 2H, NH), 1.92 (s, 24H, CH_3), 7.81 (s, 8H, H-3 and H-5), 8.58 (s, 8H, β-pyrrole); ^{13}C-nmr (deuteriochloroform): δ 21.7, 112.9, 116.4, 119.0, 125.0, 130.6 (br), 130.8, 141.2, 145.7; hrms (fab) Calcd. for $C_{56}H_{42}N_8$ (M^+): 826.3532. Found 826.3561.

Anal. Calcd. for $C_{56}H_{42}N_8 \cdot 1/2\ H_2O$: C, 80.46; H, 5.18; N, 13.40. Found: C, 80.70; H, 5.10; N, 13.48.

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