

## A Potential Approach to Porphyrins with $\beta$ -Pyrrole Electron-withdrawing Substituents

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*Amination of 3,4-pyrroledicarbonyl chloride with either dimethyl or diethylamine led to the synthesis of 3,4-bis(N,N-dialkylcarboxamide)pyrrole. When 3-carbomethoxy-4-pyrroledicarbonyl chloride was reacted with diethylamine in a similar manner, 3-carbomethoxy-4-(N,N-diethylcarboxamide)pyrrole was synthesized.*

*Condensation of 3,4-bis(N,N-diethylcarboxamide)pyrrole with formaldehyde in the presence of hydrobromic acid in ethanol led to a novel, highly soluble 1,2,3,4,5,6,7,8-octakis(N,N-diethylcarboxamide)porphyrin. Metallation of this new porphyrin with metal salts in N,N-dimethylformamide produced metalloporphyrins.*

*When the cobalt porphyrin was dissolved in acetone and dry air was bubbled through the solution for 50 hours, the presumed product was a cobalt porphyrin dioxygen adduct. When dry nitrogen was passed for 5 hours through a benzene solution of this dioxygen adduct, the product was the original cobalt porphyrin. Bubbling dry air for 150 hours through an acetone solution of the oxygen-free cobalt porphyrin led irreversibly to what is hypothesized to be a  $\mu$ -oxo-cobalt porphyrin.*

### Introduction

The synthesis and solution study of novel metalloporphyrin compounds continue as an active research area because the porphin skeleton plays an important role in many biological and catalytic systems [1, 2].

One great advantage of using these molecules as catalysts is that their structure can be modified in a controlled way and correlations between catalytic activity and structure can be followed. Catalytic activity has been reported which is dependent on the central metal atoms [3], as well as on substituents

in the *p*-phenyl positions of tetraphenylporphyrin [4].

Octaethylporphyrin is a thermally stable ligand which can be synthesized according to established methods [5]. LeGoff and co-workers have synthesized several meso free octaalkylporphyrins [6-8]. Several porphyrins have been synthesized in order to study the effect of electron-withdrawing groups. These include modified deuteroporphyrins and tetracyanotetraphenylporphyrin [9, 10]. Certain natural porphyrins (heme a, chlorophyll b) can also be considered to fall into this category. In this paper we report results of attempts to synthesize meso free octasubstituted porphyrins having amide electron-withdrawing groups.

### Experimental

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra (in  $\text{CDCl}_3$ , TMS as internal standard) were recorded on a Varian EM 390 instrument. IR spectra were obtained with a Perkin-Elmer 283 spectrophotometer. Electronic absorption spectra were determined at room temperature for solutions in reagent grade acetone ( $\lambda = 350$  to 700 nm) with a HP 8450 A spectrophotometer and HP 7225 S plotter. Mass spectra were obtained on an A.E.I. MS 50 instrument. Elemental analyses were performed by Galbraith Laboratories, Inc.

#### *3,4-Bis(N,N-diethylcarboxamide)pyrrole (1)*

The procedure of Groves *et al.* [11] was scaled up by ten times to produce 3,4-pyrroledicarbonyl chloride (using N-benzoylpyrrole [12, 13] as a starting material to produce A-C). Thus, a mixture of 1.55 g of 3,4-pyrroledicarboxylic acid C (0.01 mol), 250 ml of freshly distilled benzene, 10 ml of oxalyl chloride, and two drops of dimethylformamide (DMF) were heated under reflux until the mixture

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changed to a homogeneous, faintly yellow solution (in 5 hours). Subsequently, excess oxalyl chloride and solvent were distilled off. Crude 3,4-pyrroledicarbonyl chloride *E* was dissolved in freshly distilled tetrahydrofuran (THF). This solution was slowly dripped into 80 ml of THF solution at 0 °C containing 40 ml of freshly distilled diethylamine. The mixture was allowed to reflux for 2 hours, cooled to room temperature, and filtered to remove diethylamine hydrochloride. The light brown filtrate was evaporated and the semi-solid residue was dissolved into a small portion of warm THF and petroleum ether was added. The solid thus obtained was recrystallized from benzene. It gave 2.07 g (78%) of a colorless solid: m.p. 122–123 °C; IR spectrum (CHCl<sub>3</sub>): 3170(NH), 2990(CH) and 1600(C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR, δ: 1.10(12H,t), 3.40(8H,q), 6.64(2H,d), and 10.93 (1H,bs); high resolution mass spectrum, M/e (relative intensity): 265.1780(8%) (molecular ion, calc. 265.3546), 192.2973(32%), 122.0243(27%) and 72.0821(100%). The product 3,4-bis(*N,N*-diethylcarboxamide)pyrrole C<sub>14</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> requires: 63.37% C, 8.74% H and 15.84% N; found 63.22% C, 8.67% H and 15.66% N.

### 3,4-Bis(*N,N*-dimethylcarboxamide)pyrrole (2)

This compound was prepared by the above method with the exception of bubbling excess dimethylamine gas into the THF solution of 3,4-pyrroledicarbonylchloride *E*, and the exothermic reaction was controlled with an ice bath. Recrystallization of product from acetone gave 1.53 g (73%) of 2 as a colorless solid: m.p. 206–207 °C; the IR spectrum (KBr pellet): 3100(NH), 2880(CH), 1625 and 1600(C=O) cm<sup>-1</sup>; <sup>1</sup>H NMR δ: 2.90(12H,s), 6.90(2H,d), and 11.40(1H,bs); high resolution mass spectrum, molecular ion at M/e 209.1166(12%) cal. 209.2474 and other prominent ions at 165.0661 (29%), 164.0586(36%), 122.0245(100%) and 94.0294(19%).

### 3-Carbomethoxy-4-(*N,N*-diethylcarboxamide)pyrrole (3)

This compound was also prepared by the above method using 3-carboxymethoxy-4-carbonylchloride pyrrole *D* with diethylamine at 0 °C. Recrystallization of product from THF–petroleum ether (15:1) afforded 1.54 g (71%) of 3 as a colorless solid: m.p. 110–113 °C; IR spectrum (KBr pellet): 3260(NH),

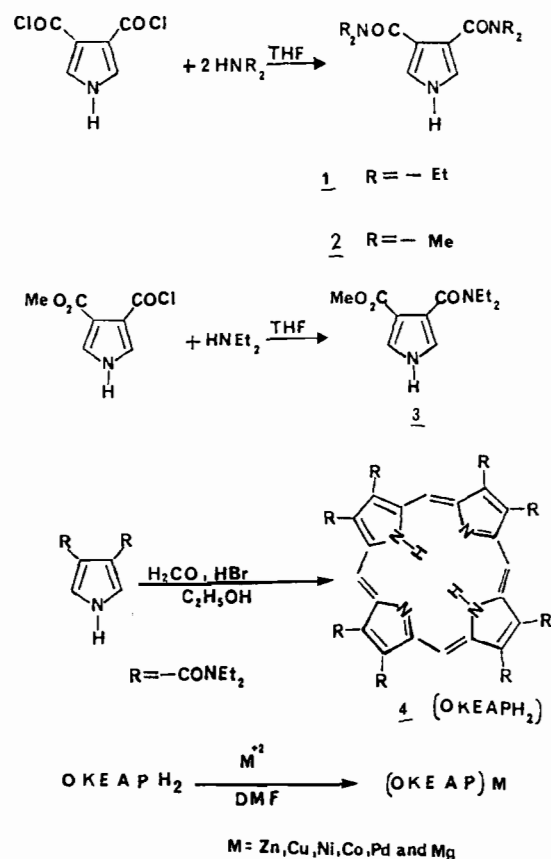
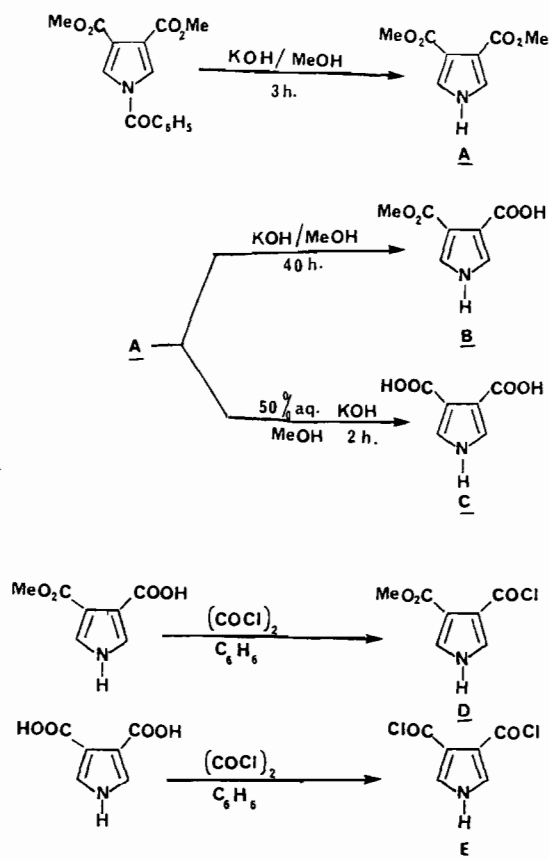


TABLE I. UV/VIS Spectral Results of Metalloporphyrin Complexes in Acetone.

Compound	Color	$\phi(0.0)\lambda_{\max}(\epsilon)^{a,b}$	$\phi(1.0)\lambda_{\max}(\epsilon)^{a,b}$	B(0.0) $\lambda_{\max}(\epsilon)^{a,b}$
Mg(OBEAP)	green yellow		560(1.131 $\times 10^4$ ) <sup>c</sup>	430(1.399 $\times 10^5$ )
Zn(OBEAP)	violet	584(4.020 $\times 10^3$ )	548(8.936 $\times 10^3$ )	418(1.742 $\times 10^5$ )
Cu(OBEAP)	purple	570(1.001 $\times 10^4$ )	534(8.798 $\times 10^3$ )	408(1.196 $\times 10^5$ )
Co(OBEAP)	brown pink	554(1.517 $\times 10^4$ )	526(1.360 $\times 10^4$ )	408(1.395 $\times 10^5$ )
Pd(OBEAP)	brown	550(5.796 $\times 10^3$ )	516(3.067 $\times 10^3$ )	406(4.900 $\times 10^4$ )
Ni(OBEAP)	violet	556(3.571 $\times 10^4$ )	520(1.879 $\times 10^4$ )	402(2.389 $\times 10^5$ )

<sup>a</sup> $\lambda_{\max}$  in nm. <sup>b</sup> $\epsilon$  in  $M^{-1} \text{ cm}^{-1}$ . <sup>c</sup>Uncertain assignment.

2860 and 3110(CH), 1590 and 1705(C=O)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR  $\delta$ : 1.0(3H,t), 1.22(3H,s), 3.16(2H,q), 3.54(2H,q), 3.69(3H,s), 6.39(1H,s) and 7.10(1H,s).

#### Oktakis(N,N-diethylcarboxamide)porphyrin (4) (OKEAPH<sub>2</sub>)

A solution of 1.20 g, 3,4-bis(N,N-diethylcarboxamide)pyrrole 1 (4.5 mmol), 16 ml of 37% aqueous formaldehyde, and 4 ml of 48% hydrobromic acid in 160 ml absolute ethanol was refluxed for 24 hours. The resulting brown solution was cooled to room temperature and transferred to a beaker open to the air for 10 days. The solution was neutralized with 1 M KOH, then 100 ml of water was added and the solution was extracted three times with 75 ml aliquots of methylene chloride. The brown methylene chloride solution was dried (MgSO<sub>4</sub>), and the volume of the solution was reduced to 10 ml. The residue was chromatographed on alumina (0.5% CH<sub>3</sub>OH and 99.5% CH<sub>2</sub>Cl<sub>2</sub>). The porphyrin product appeared as a deep brown band which slowly moved down the column. The brown eluent was reduced in volume to 2 ml, 150 ml of light petroleum ether was added, and dry nitrogen was passed over the solution until the porphyrin precipitated as a red purple solid which was dried over P<sub>2</sub>O<sub>5</sub> in vacuum to afford 0.279 g, (22%). The UV/VIS spectrum in acetone,  $\lambda_{\max}$  ( $\epsilon$ ): 410(1.919  $\times 10^5$ ), 508(1.418  $\times 10^4$ ), 538 (6.400  $\times 10^3$ ), 580(5.333  $\times 10^3$ ) and 632(2.28  $\times 10^3$ ) nm ( $M^{-1} \text{ cm}^{-1}$ ); the IR spectrum (KBr pellet): 3300 (N-H), 2470–2870 (C-H) [14] and 1630  $\text{cm}^{-1}$  (C=O); <sup>1</sup>H NMR,  $\delta$ : 10.08(4H,s), 3.65(16H,bq), 4.00(16H,q), 1.63(24H,t), 1.14(24H,t), -3.34(2H,s); mass spectrum: molecular ion at M/e 1103. The product C<sub>60</sub>H<sub>86</sub>N<sub>12</sub>O<sub>8</sub>, required 65.31% C, 7.86% H and 15.23% N: found 65.20% C, 7.93% H and 15.09% N.

#### Metalloporphyrins

A variety of metalloporphyrins (Cu, Zn, Co, Pd, Mg, Ni and Sn) were prepared following the procedure of Adler *et al.* [15]. The only exception was for dichlorooctakis(N,N-diethylcarboxamide)porphy-

rinatotin(IV) which was prepared according to the Collins and Corwin procedure [16]. The details of a typical DMF reaction are as follows:

Ten ml (in the case of Pd, 50 ml) of reagent grade N,N-dimethylformamide (DMF) was brought to gentle reflux. 22 mg (0.02 mmol) of the porphyrin was added, and later 40 mg (0.02 mmol) of cupric acetate monohydrate (in the case of Pd, a hundred-fold excess of PdCl<sub>2</sub>) was added. The reaction was allowed to proceed for 5 minutes (in the case of Mg and Zn, one minute was enough and further heating led to product decompositions; five hours were required for Pd). Solvent was removed under vacuum, the residue was chromatographed on alumina (2% methanol and 98% methylene chloride) to give 22.6 mg (97%) of the Cu porphyrin after evaporation of solvent. The UV/VIS spectral results for the metalloporphyrin complexes in acetone are shown in Table I. The mass spectra of the zinc and cobalt porphyrins showed molecular ions at M/e 1165.5 and 1160, respectively. The UV/VIS of Sn(OKEAP)Cl<sub>2</sub> in acetone having a violet color revealed peaks at 424, 508, 552 and 588 nm.

## Results and Discussion

### Porphyrins

Condensation of 3,4-dimethylesterpyrrole, A, with aldehydes failed to produce porphyrins [17]. Accordingly, 3,4-dimethylesterpyrrole [11], A, was used to synthesize amide pyrroles (1, 2, 3) with the hope that the less electron-withdrawing amide groups might allow condensation to occur. Amidation of 3,4-pyrroledicarbonyl chloride, E, with dialkylamines produced 3,4-bis(N,N-dialkyl carboxamide)-pyrroles 1, 2 and the condensation of with acidic formaldehyde did produce porphyrin product. However, the reaction of these pyrroles with benzaldehyde or acetaldehyde with hydrobromic acid failed to produce macrocyclic porphyrin products.

Furthermore, a limited number of standard procedures for modifying amide groups were tried on

octakis(N,N-diethylcarboxamide)porphyrin 4 without success [18].

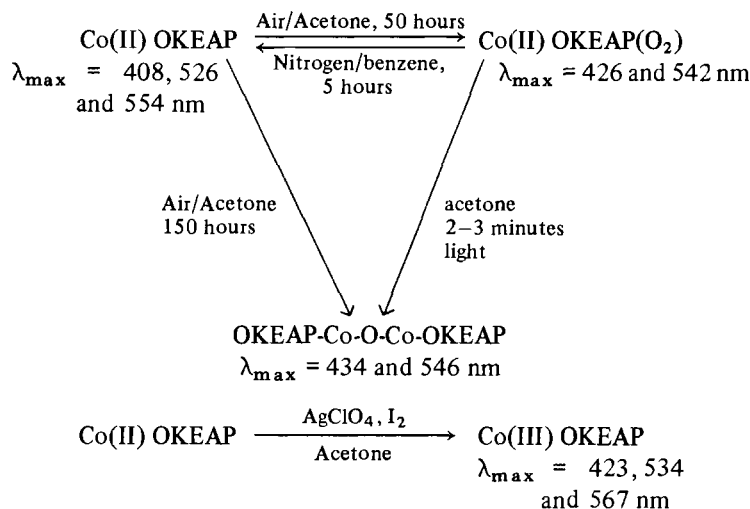
### Metalloporphyrins

The most general and convenient method for the metallation of this porphyrin which was chosen is the procedure employing DMF as the reaction medium. Divalent metal acetates were used successfully to produce Cu, Zn, Ni, Co, Mg, and Pd (palladium chloride) metalloporphyrins. On formation of a metalloporphyrin, the five-banded spectrum of the free porphyrin changed into one containing three bands, with the exception of the Mg complex which showed two bands (Table I). The Soret band shifted to higher (Cu, Co, Pd, and Ni) or lower (Mg and Zn) energy. The data in Table I show that the wavelength of the Soret band B (0,0) increases along the series  $Ni < Pd < Cu = Co < Zn < Mg$ . Both  $\phi$  (with the exception of Ni and Co) and B bands tend to suffer red shifts in concert. The spectra of these metalloporphyrins show a second variation occurring with change of metal. Along the series, the ratio of intensity of  $\phi(0,0)$  to  $\phi(1,0)$  decreases as  $Ni > Pd > Cu > Co > Zn > Mg$ . These types of wavelength shift and intensity variation have been attributed to a weak perturbation by the central metal [19]. Generally a very qualitative stability order for metalloporphyrins can be discerned by consideration of the relative intensities of the  $\phi(0,0)$  and  $\phi(1,0)$  bands. The stable chelates (Ni, Pd, Cu and Co) did show an increased  $\phi(0,0)$  to  $\phi(1,0)$  ratio while in the less stable complexes (Zn and Mg) the ratio was decreased.

### Interaction of Molecular Oxygen

The interaction of molecular oxygen with metalloporphyrin species is important in some naturally occurring oxygen storage (myoglobins) and transport

(hemoglobins) systems. In recent years much attention has been paid to the syntheses of synthetic oxygen carriers using various metal complexes [21]. It has been suggested that the ease of oxygen uptake by metal complexes should depend on the ease of oxidation of the metal in a given complex [22]. This implies that metals which are readily oxidized (e.g., Fe(II)) react with oxygen irreversibly, metals difficult to oxidize (e.g., Ni(II)) do not react with oxygen, whereas metals between the two extremes (e.g., Co(II)) may react reversibly with oxygen. The cobalt hemoglobin [22] species obtained through replacement of the protohemes in hemoglobin by molecules of the low-spin cobalt(II) derivative of protoporphyrin-IX, displays a reversible and cooperative uptake of oxygen that is qualitatively similar to the uptake of oxygen by hemoglobin. Thus the low-spin  $d^7$  cobalt(II) atom serves as a qualitatively acceptable substitute for the  $d^6$  iron atom both in the high-spin five-coordinate hemes of deoxyhemoglobin and in the low-spin oxygenated six-coordinate hemes of oxyhemoglobin. Woodruff *et al.* [23] have studied resonance Raman spectra of oxy and deoxycoboglobin and the structure-sensitive bands show only slight wave number shifts upon oxygenation, indicating small cobalt atom displacement [23]. We studied the interaction of cobalt(II) octakis(N,N-diethylcarboxamide)porphyrin with molecular oxygen. Initial experiments indicated that when a small quantity of this cobalt porphyrin was dissolved in 20 ml of acetone and dry air was bubbled through the solution at room temperature for 50 hours, it changed to the dioxygen adduct cobalt porphyrin. This new complex, in benzene solution at room temperature after 6 hours bubbling with nitrogen, changed to the initial deoxygenated cobalt porphyrin. This is one of the few examples of reversible



oxygen interaction with a metalloporphyrin at room temperature. When air was bubbled through an acetone solution of cobalt(II) porphyrin for 150 hours it changed to what has been hypothesized to be a  $\mu$ -oxodimer, because bubbling dry nitrogen through a benzene solution of this presumed  $\mu$ -oxodimer caused no change. The dioxygen cobalt octakis(N,N-diethylcarboxamide)porphyrin in the presence of light changed to this presumed  $\mu$ -oxodimer form after only 2 to 3 minutes as shown in the Scheme on page 8.

Chemical oxidation of cobalt(II) octakis(N,N-diethylcarboxamide)porphyrin in acetone with excess  $\text{Br}_2$  or  $\text{I}_2$  produced a broad Soret band indicative of a  $\pi$ -cation radical. When an equivalent of iodine in acetone and silver perchlorate in acetone [24] was used the product was cobalt(III) octakis(N,N-diethylcarboxamide)porphyrin having absorptions at 423, 534 and 567 nm. All of the above reactions were monitored by UV/VIS spectroscopy. The characteristic spectral maxima of each species are included in the scheme.

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