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Investigation of a Synthesis of *meso*-Porphyrins Employing High Concentration Conditions and an Electron Transport Chain for Aerobic Oxidation

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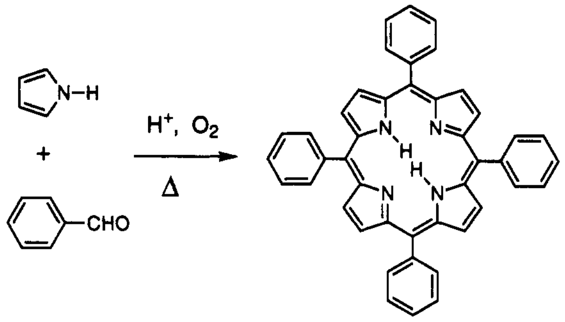
The room-temperature synthesis of *meso*-porphyrins has been investigated at aldehyde and pyrrole concentrations ≥0.1 M using tetraphenylporphyrin (TPP) and tetramesitylporphyrin (TMP) as models. The decline in yield that occurs at higher reactant concentrations can be offset partially with higher acid catalyst concentrations. Reactions of 0.1 M benzaldehyde and pyrrole afford 20–30% yields of TPP at appropriate concentration of three acids, trifluoroacetic acid, $BF_3{\cdot}OEt_2$, or methanesulfonic acid, using the two-step process of acid-catalyzed condensation followed by quinone oxidation. A one-step synthesis of porphyrins has been investigated where aldehyde, pyrrole, acid catalyst, and oxidant are present simultaneously. Among five quinones examined only *p*-chloranil (TCQ) provides successful oxidation. The one-step synthesis performed at concentrations of 0.1 M affords TPP in 10–20% yields. Both the one- and two-step syntheses at high concentrations involve slurries due to the amount of TCQ required for oxidation. An electron transport chain employing TCQ and iron(II) phthalocyanine (FePc) in catalytic amounts and O_2 as the terminal electron acceptor has been adapted for the porphyrin synthesis. FePc activates O_2 and recycles reduced TCQ at room temperature. This electron transport chain provides mild aerobic oxidation. The aerobic oxidation process is cleaner than oxidation with stoichiometric amounts of TCQ and can be implemented as part of a one-step or two-step porphyrin synthesis. Reaction of 0.1 M benzaldehyde and pyrrole with acid catalysis in the presence of 5 mol % TCQ and 5 mol % FePc with gentle aeration affords TPP in 11% (one step) or 24% (two step) yield. Mesitaldehyde is converted to tetramesitylporphyrin upon reaction at a concentration of 0.1 M with BF_3–ethanol cocatalysis and aerobic oxidation. The two-step synthesis with aerobic oxidation proceeds under mild ambient conditions, affords ~100 mg porphyrin from 50-mL reactions, and should prove generally useful for preparative scale syntheses of *meso*-porphyrins.

Introduction

Advances in porphyrin model systems are closely tied to methods for preparing synthetic porphyrins. In the Adler method, pyrrole and aldehyde (0.1–0.3 M each) are combined in refluxing propionic acid (141 °C) in an open beaker for 30 min, and then upon cooling the crystalline porphyrin is isolated by filtration (Scheme 1).[1-6] The Adler method is attractive in many ways: implementation is simple, the reaction is performed at high concentration, and the porphyrin usually is obtained in crystalline form without chromatography. However, the severe reaction conditions are incompatible with aldehydes bearing sensitive substituents.

In order to broaden the scope of model systems, we developed a room temperature synthesis of *meso*-porphyrins that is complementary to the Adler method.[7,8] Aldehyde and pyrrole react at room temperature under mild acid catalysis to form the porphyrinogen. Then, in a second step, a quinone (DDQ or *p*-chloranil) is added to oxidize the porphyrinogen to the porphyrin (Scheme 2). Modified catalysis conditions support the reactions of 2,6-disubstituted benzaldehydes via the same strategy.[9-11] The gentle conditions of this two-step one-flask synthesis are compatible with a diverse array of sensitive, highly-functionalized aldehydes.[12] One drawback of this method is that optimal yields are obtained with 0.01 M pyrrole and aldehyde concentrations, requiring large solvent

Scheme 1. Adler Synthesis of Tetraphenylporphyrin



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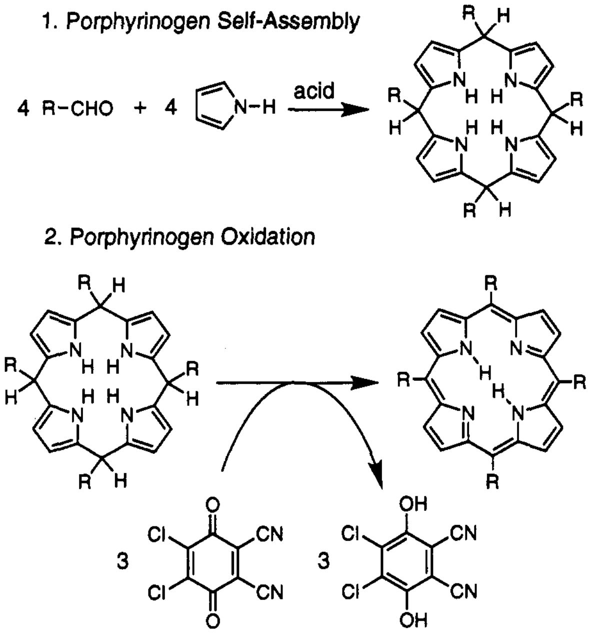
Scheme 2. Two-Step Room-Temperature Synthesis of *meso*-Porphyrins



volumes for gram-scale preparations of porphyrins. In addition, isolation of the porphyrin usually requires two chromatographic procedures.

We have sought to develop an eclectic procedure that combines the high concentration and simple workup of the Adler method with the gentle conditions, moderate yields, and broad applicability of the room-temperature synthesis. In this paper we describe our efforts toward such a method, using the syntheses of tetraphenylporphyrin (TPP) and tetramesitylporphyrin (TMP) as models.

Results

I. Two-Step Synthesis at High Concentration. Previously we reported that the porphyrin yield declines at reactant (aldehyde and pyrrole) concentrations above 0.01 M.[8,10] However, recent studies showed that the decline in yield with increasing concentration is less pronounced upon reaction with an increased acid concentration.[13,14] The condensation of benzaldehyde and pyrrole at ≥0.1 M concentrations was examined using $BF_3{\cdot}OEt_2$ (BF_3), trifluoroacetic acid (TFA), or methanesulfonic acid (MSA) (Table 1). MSA exhibits activity at low concentrations in the porphyrin synthesis.[13] Samples were removed at 45 min and oxidized with DDQ, and the yield of porphyrin was determined spectroscopically.[8] Yields of 20–30% were obtained for each acid catalyst with reactants at 0.1 M. Similarly, 0.1 M mesitaldehyde and pyrrole with BF_3–ethanol cocatalysis[10] afforded TMP in yields reaching 15%. The highest yields in all 0.1 M reactions were obtained with acid concentrations greater than those in 0.01 M reactions.

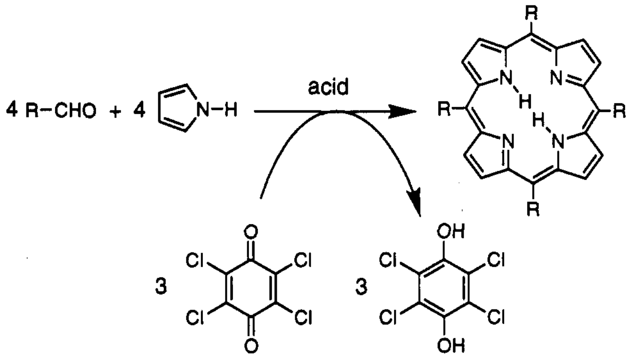
II. One-Step Synthesis at High Concentration. In the Adler method the catalyst (propionic acid at reflux, 141 °C) and oxidant (O_2) are present simultaneously. We investigated a one-step synthesis of porphyrins where aldehyde, pyrrole, acid, and oxidant are combined at the same time in CH_2Cl_2 at 25 °C (Scheme 3).

Table 1. Two-Step Syntheses at High Concentration[a]

[aldehyde]	*% yields of porphyrin at various* [*acid*]		
		[BF_3]	
[benzaldehyde]	0.001	0.0032	0.01
0.1	*23*	*30*	*29*
		[BF_3]	
	0.002	0.0064	0.02
0.2	*9.3*	*15*	*24*
		[BF_3]	
	0.1		
0.32	*13*		
		[MSA]	
[benzaldehyde]	0.001	0.0032	0.01
0.1	*9.2*	*13*	*17*
		[TFA]	
[benzaldehyde]	0.064	0.2	
0.1	*25*	*12, 23*[b]	
		[MSA]	
[mesitaldehyde]	0.0032	0.01	0.032
0.01	*0.5*	*1.0*	
0.1	*1.0*	*2.6*	*3.5*
		[BF_3][c]	
[mesitaldehyde]	0.01	0.033	0.1
0.1	*8.5*	*12*	*15*
		[BF_3][c]	
	0.02	0.066	0.2
0.2	*5.7*	*7.9*	*10*

[a] Reactions (10 mL) were performed at room temperature in CH_2Cl_2 in loosely capped vials with magnetic stirring with equimolar [pyrrole] and [aldehyde]. The reaction solutions were dark red but no precipitates were evident. Samples (15–25 μL) were obtained via syringe at 45 min and oxidized with DDQ in toluene; then yields were determined spectroscopically.[8] [b] Yield determined at 5 min. [c] Reactions were performed in $CHCl_3$ containing 0.75% ethanol.

Scheme 3. One-Step Room-Temperature Synthesis of *meso*-Porphyrins



A survey of several oxidants and catalysts was performed (Table 2). The reaction vessel was charged with oxidant, CH_2Cl_2, benzaldehyde, and pyrrole in that order. Then acid was added and samples were removed periodically for spectroscopic analysis of the porphyrin yield. All reactions were heterogeneous due to the insolubility of the quantity of oxidant required for 0.1 M benzaldehyde and pyrrole. Among five quinones only TCQ succeeded, affording porphyrin in 10–20% yields within 10 min. Several inorganic oxidants were examined but no results better than those with TCQ were obtained.

Factorial design experiments were performed to identify optimal catalyst and reactant concentrations for the one-step synthesis with TCQ (Table 3). Yields of 10–20%

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Table 2. Oxidants for the One-Step Synthesis with Benzaldehyde and Pyrrole (0.1 M)[a]

oxidant	% yields of porphyrin BF_3 (0.01 M)	 MSA (0.01 M)	 TFA (0.18 M)
DDQ	0	0	0
TCQ (*p*-chloranil)	18	12	16
2-chlorobenzoquinone	0[b]		
p-benzoquinone	0[c]	0	<0.1
duroquinone	0[d]	0	0.4
dimethyl fumarate	0		
$Ce(NH_4)_2(NO_3)_6$	2.9	1.9[e]	14
$FeCl_3$	0	0[e]	0.9

[a] Reactions (10 mL) were performed at room temperature in CH_2Cl_2 with magnetic stirring in open vials. The order of addition of reagents was oxidant, CH_2Cl_2, benzaldehyde, pyrrole, and then acid. Stoichiometric quantities of oxidant (corresponding to 0.075 M) were employed. Samples were collected via syringe typically at 10–30 min after initiating the reaction with acid. Yields were determined spectroscopically. [b] A sample removed after 30 min from the dark reddish solution and treated with DDQ showed 1.6% yield of porphyrin. [c] A sample removed after 30 min from the dark greenish solution and treated with DDQ showed <0.1% yield of porphyrin. [d] Samples removed after 5, 27, or 55 min and treated with DDQ showed 15–17% yield of porphyrin. [e] 0.1 M acid.

Table 3. One-Step Syntheses at High Concentration[a]

[aldehyde]	% *yields of porphyrin at various* [*acid*]			
		[TFA]		
[benzaldehyde]	0.018	0.18	0.59	
0.01	*8.1*	*32*	*19*	
0.1	*1.4*	*15*	*23*	
0.32	*0.5*	*2.3*	*7.7*	
		[MSA]		
[benzaldehyde]	0.001	0.01	0.1	
0.01	*10*	*21*	*9.1*	
0.032		*25*	*8.7*	
0.1		*16*	*16*	
0.32		*1.4*	*3.2*	
			$[BF_3]$	
[benzaldehyde]	0.001	0.01	0.1	0.32
0.01	*13*	*2.0*	*0*	
0.1	*3.1*	*18*	*5.2*	
0.32	*1.0*	*3.2*	*18*[b]	*16*[b]
		[MSA]		
[mesitaldehyde]	0.01	0.1	0.32	
0.1	*2*	*7*	*6*	
0.32	*3.5*	*7*	*6*[b]	
		$[BF_3]$[c]		
[mesitaldehyde]	0.01	0.033	0.1	
0.1	*0.8*	*3.0*	*13*	
		$[BF_3]$[c]		
	0.02	0.066	0.2	
0.2	*2.1*	*3.0*	*11*	

[a] Reactions (10 mL) with equimolar [aldehyde] and [pyrrole] were performed at room temperature in CH_2Cl_2 with magnetic stirring in open vials. The order of addition of reagents was TCQ, CH_2Cl_2, benzaldehyde, and pyrrole, which usually formed a red mixture. Stoichiometric quantities of TCQ were employed (quantity of TCQ = 0.75[aldehyde]). Samples for spectroscopic yield monitoring were collected 10–30 min after initiating the reaction with acid. In general the reactions were complete within 10 min. [b] Refluxing in 20-mL vial due to reaction exothermicity. [c] Reactions were performed in $CHCl_3$ containing 0.75% ethanol.

Table 4. Order-of-Addition Effects in One-Step Syntheses[a]

initial components	observation (time)	last component	% porphyrin yield
pyrrole + TCQ + MSA	red mixture (10 s)[b] black precipitates (15 min)	BA[c]	2.3
pyrrole + BA + TCQ	red mixture (10 s) brown mixture (15 min)	MSA	6.7
BA + TCQ + MSA	yellow TCQ mixture (10 s, 15 min)	pyrrole	6.8
pyrrole + BA + MSA	orange-red solution (10 s) red-black solution, no precipitates (15 min)	TCQ	21[d]

binary mixtures	observations (15 min)
pyrrole + TCQ	red mixture
pyrrole + MSA	cloudy, yellow mixture[e]
pyrrole + BF_3	yellow-orange, orange precipitates
TCQ + BA	yellow TCQ mixture
TCQ + MSA	yellow TCQ mixture

[a] Reactions were performed at room temperature in CH_2Cl_2 using 0.1 M benzaldehyde (BA) and 0.1 M pyrrole, 0.01 M methanesulfonic acid (or BF_3), and an amount of TCQ corresponding to 0.075 M (not all the TCQ dissolves). The initial three components were combined and stirred for 15 min and observed visually, and then the last component was added. Then 20 min later the reactions were sampled and yields were determined spectroscopically. [b] Red mixture consists of a clear red solution containing undissolved TCQ. [c] BA stands for benzaldehyde. [d] Identical to the two-step synthesis where porphyrinogen formation occurs during the 15-min waiting period; then TCQ addition oxidizes porphyrinogen to porphyrin. [e] Orange precipitates formed after several hours.

were readily obtained at 0.1 M pyrrole and benzaldehyde or mesitaldehyde. In general the highest yields were obtained with acid concentrations up to 3 times those employed in the two-step syntheses (compare Tables 1 and 3). Two limitations were encountered in attempting reactions at very high concentrations (≥0.32 M). First, the reactions at 0.32 M with high acid concentrations were exothermic and caused rapid vigorous refluxing of CH_2Cl_2 (bp 39 °C), compared with slight warming for the 0.1 M reactions. Second, the formation of black precipitates in conjunction with the insoluble quinone components (TCQ and $TCQH_2$) rendered sampling and workup quite difficult.

The sequence of addition of the four components (benzaldehyde, pyrrole, TCQ, MSA) was examined through omission and reconstitution experiments (Table 4). Three of the components were combined and stirred for 15 min before adding the fourth, thereby providing sufficient time to accentuate any deleterious reactions among the three components. Pyrrole, TCQ, and acid together form a black mixture within 15 min. The subsequent addition of benzaldehyde results in only 2.3% yield, a 7-fold decline from the one-step synthesis (16%, Table 3). The side reactions do not require the presence of three components; pyrrole alone with acid or with TCQ resulted in red mixtures. These results indicate the importance of order and timing of additions. The exposure of pyrrole to TCQ and acid in one-step syntheses is minimized by charging a reaction vessel first with TCQ, CH_2Cl_2, and benzaldehyde, followed by pyrrole, and then immediately by acid.

The participation of insoluble TCQ in the oxidation process was studied by reacting 0.1 M benzaldehyde and pyrrole with varying amounts of TCQ (Figure 1A). The amount of TCQ that is soluble (0.016 M) corresponds to 21% of the stoichiometric quantity, but higher yields were obtained with 50 mol % TCQ. Similar results were obtained at concentrations of 0.32 M mesitaldehyde and pyrrole with MSA catalysis, where only one-tenth of the necessary TCQ is dissolved (Figure 1B). The solubility of

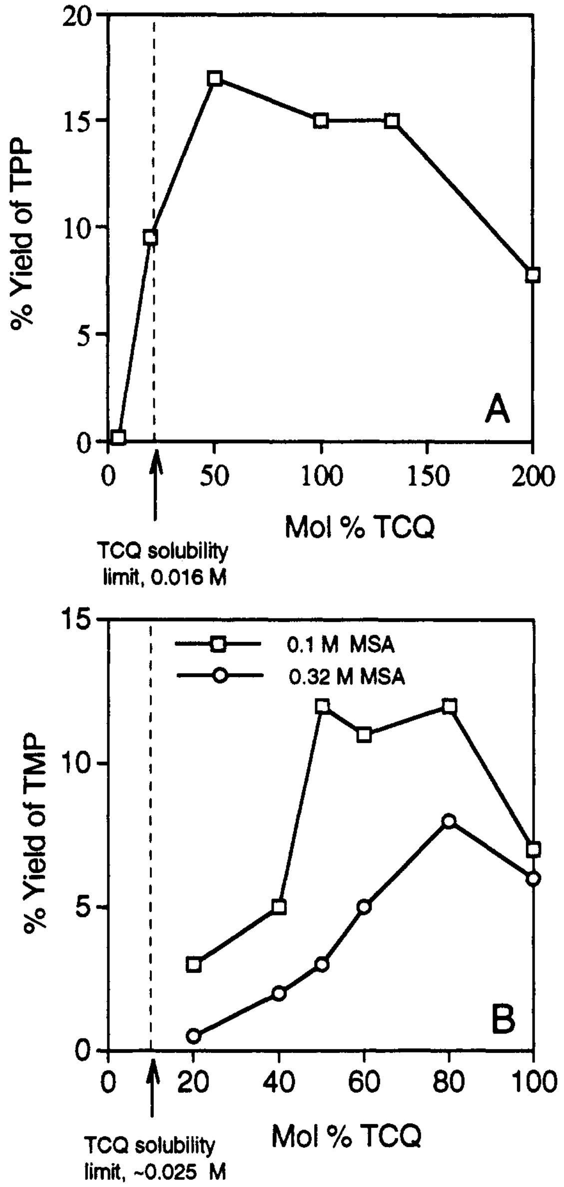

Figure 1. Yield dependence on the quantity of TCQ in one-step syntheses. Samples were removed via syringe for yield determinations. (A) 0.1 M benzaldehyde and pyrrole (0.01 M BF_3, 20 min data points) in CH_2Cl_2 at room temperature. The soluble TCQ (0.016 M) corresponds to 21.3 mol % of the stoichiometric quantity (0.075 M); at higher percentages the reactions are heterogeneous. (B) 0.32 M mesitaldehyde and pyrrole in CH_2Cl_2 at room temperature with MSA catalysis. The solubility of TCQ in the presence of 0.1 M MSA falls between 0.02 and 0.03 M and is shown at 0.025 M.

TCQ increased ~2-fold with 0.1 M MSA. These experiments show that initially-insoluble TCQ participates in the one-step synthesis. A tangential finding is that the highest yields were obtained with ~50–80 mol % of the stoichiometric quantity of TCQ.

The rates and yields of the one-step and two-step syntheses were compared for 0.1 M benzaldehyde and pyrrole using a stoichiometric amount of TCQ (Figure 2). The one-step synthesis is essentially complete at the 5-min timepoint and gives ~17% yield. The two-step synthesis with 30- and 90-min condensation periods also gives rapid oxidations upon addition of TCQ but the yields are 29% and 26%, respectively.

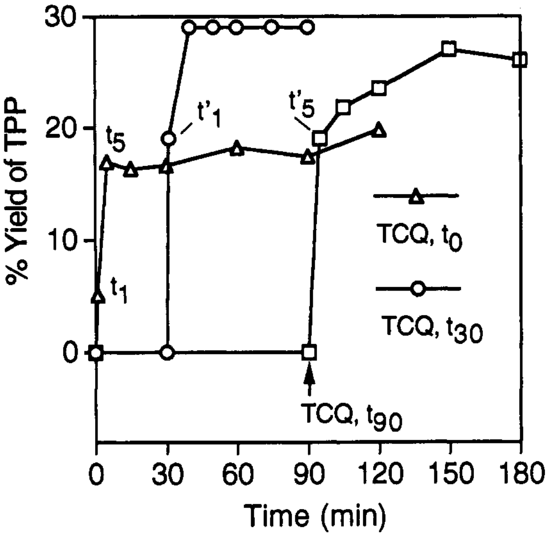

Figure 2. One-step and two-step porphyrin syntheses with oxidation by a stoichiometric amount of TCQ. Reactions were performed with 0.1 M benzaldehyde and pyrrole with 0.01 M BF_3 in CH_2Cl_2 at room temperature. The one-step synthesis is performed with all four components present simultaneously (△). The two-step synthesis is performed by adding TCQ at 30 min (○) or 90 min (□). Samples were removed via syringe for yield determinations. t_1, t'_1, t_5, and t'_5 indicate timepoints after start of oxidation.

III. Electron Transport Chain for Aerobic Oxidation. In order to decrease the quantity of TCQ required at high concentrations, we sought to design an electron shuttle employing a small amount of TCQ as a soluble recyclable oxidant. Backvall et al.[15-18] have employed metal complexes to activate molecular oxygen for oxidation of hydroquinone, thereby allowing O_2 to serve as the terminal electron acceptor in oxidation processes. The best metal complex was found to be iron(II) phthalocyanine (FePc).[16,17] We have extended this approach to a process that incorporates catalytic TCQ for oxidation of the porphyrinogen, O_2 for the stoichiometric oxidizing equivalents, and catalytic FePc for activating O_2 and regenerating TCQ (Scheme 4).

A reaction vessel was charged with 5 mol % TCQ (3.75 mM), 5 mol % FePc (corresponding to 3.75 mM but little FePc dissolved), CH_2Cl_2, and 0.1 M benzaldehyde and pyrrole. The reaction was initiated by addition of 0.01 M BF_3 and the mixture was aerated with a steady stream of air. Samples were removed periodically for yield monitoring. The porphyrin yield reached 11% over 1 h (Figure 3). This constitutes a one-step porphyrin synthesis with aerobic oxidation.

Similar reactions were performed with a 30–90-min argon purge during the pyrrole–aldehyde condensation followed by aeration to achieve oxidation. During the anaerobic condensation the yield of porphyrin was <0.2%. Upon aeration following 30- or 90-min argon purges, the porphyrin yield steadily climbed to 19% or 24%, respectively (Figure 3). These constitute two-step porphyrin syntheses with aerobic oxidation. In both one-step and two-step aerations the $t_{1/2}$ for the oxidation process is ~20–30 min.

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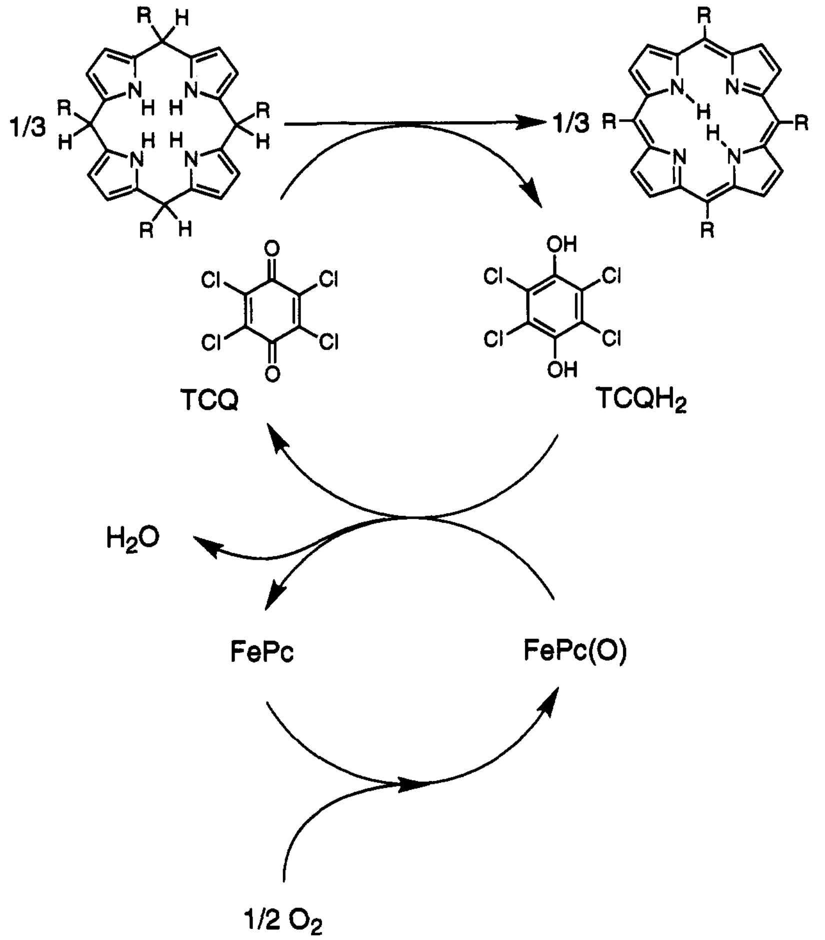
Scheme 4. Electron Transport Chain for Aerobic Oxidation of the Porphyrinogen



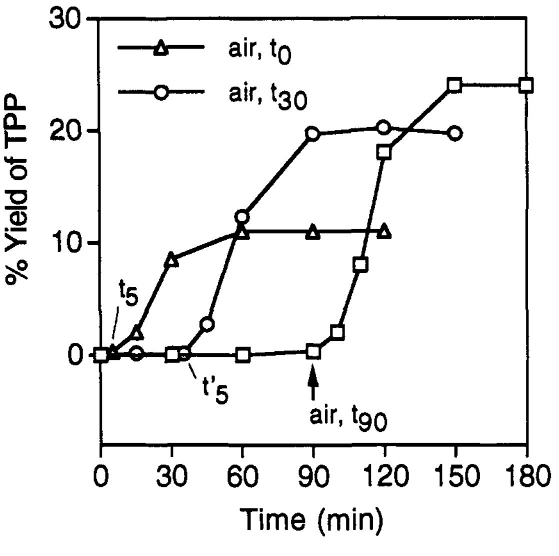


Figure 3. One-step and two-step porphyrin syntheses with aerobic oxidation. Reactions were performed with 0.1 M benzaldehyde and pyrrole, 5 mol % TCQ, 5 mol % FePc, and 0.01 M BF_3 in CH_2Cl_2 at room temperature. The one-step synthesis is performed with aeration upon adding acid (△). The two-step synthesis is performed under argon followed by aeration at 30 min (○) or 90 min (□). Samples were removed via syringe for yield determinations. t_5 and t'_5 indicate 5-min timepoints after start of aeration.

The resilience of the aerobic oxidation process was probed through systematic alterations (Table 5). The aerobic oxidation is tolerant toward several acids, higher concentrations, replacement of TCQ with DDQ or $TCQH_2$, and reaction of mesitaldehyde. The reaction course forming TMP closely mirrored that of TPP. These experiments indicate the aerobic oxidation process is quite robust. However, when any one component of the electron transport chain was omitted, the yields were ≤1%. All three components are essential for the aerobic oxidation process, and electron transport is "turned on" only when O_2 is present.

The solubility of each component in the aerobic oxidation process was characterized (Table 6). The aerobic oxidation is a heterogeneous process because FePc is poorly soluble in CH_2Cl_2. Although the solubility of FePc increases 10-fold in 0.01 M acid, over 99.5% of the FePc employed at the 5 mol % level (for 0.1 M reactants) remains insoluble. Reactions performed with 0.1 mol % FePc, an amount still involving undissolved FePc, were extremely sluggish and only 2% porphyrin was found after 16 h (Table 5). These results indicate that suspended FePc participates in the oxidation processes. The soluble FePc in acidified CH_2Cl_2 exhibits an absorption maximum nearly identical with (BF_3 or TFA) or red-shifted only 36 nm (MSA) from that of neutral FePc,[19] which is distinct from the absorption maximum at 780 nm of tetraprotonated FePc in 96% H_2SO_4.[20] The quinone components of the electron transport chain (TCQ or $TCQH_2$) are soluble at the 5 mol % level for 0.1 M reactants.

Some oxidation occurs during the pyrrole–aldehyde condensation under argon. The reaction mixtures are a

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Table 5. Alterations of Components in the Electron Transport Chain[a]

specific alteration	argon purge (min)	% porphyrin yield
no alteration	0[b]	11[c]
no alteration	30	19[c]
no alteration	90	24[c]
O_2 instead of air	30	18[d]
DDQ instead of TCQ	90	19
MSA (0.01 M) instead of BF_3	90	11
0.2 M reactants,[e] 0.02 M BF_3	90	17
TCQ, FePc (5 mol % each) added at 30 min	30	18[f]
$TCQH_2$ instead of TCQ	30	25
expose to air but without bubbling	0	15[g]
0.1 M mesitaldehyde[h]	30	11
0.1 M mesitaldehyde[h] and $TCQH_2$ instead of TCQ	30	12
0.75 mol % FePc (8 mg/25 mL reaction)	30	1[i]
0.1 mol % FePc (1 mg/25 mL reaction)	30	0[j]
omission of TCQ	0[b]	<1
omission of FePc	0[b]	1
omission of air[k]	0[b]	<1

[a] The standard reaction consists of adding FePc (5 mol %), 25 mL of CH_2Cl_2, TCQ (5 mol %), benzaldehyde (0.1 M), pyrrole (0.1 M), and $BF_3{\cdot}OEt_2$ (0.01 M) in that order to a 50-mL flask. The mixture is purged with argon for a defined period of anaerobic condensation ("argon purge") before switching to aeration. The yield is determined spectroscopically 30–90 min after beginning aeration of the mixture. [b] Aeration started without an argon purge, thus constituting a one-step synthesis. [c] See Figure 3. [d] A 10% yield obtained at 5 min timepoint following start of aeration. [e] Reactants = benzaldehyde and pyrrole; 5 mol % FePc and 5 mol % TCQ were employed based on 0.2 M reactants. [f] $t_{1/2}$ 30–60 min. [g] $t_{1/2}$ 1–2 h. [h] Mesitaldehyde instead of benzaldehyde, and 0.033 M BF_3 in $CHCl_3$. [i] 27% after 47-h aeration. [j] 2% after 16-h aeration. [k] Argon was used in place of air throughout the reaction.

Table 6. Solubilities in CH_2Cl_2 at Room Temperature

compound	solubility
TCQ (*p*-chloranil)	1.6×10^{-2} M[a]
$TCQH_2$	$4–5 \times 10^{-3}$ M[b]
FePc	2×10^{-6} M[c]
FePc (+ 0.01 M acid[d])	2×10^{-5} M
O_2	2.2×10^{-3} M[e]
TPP	0.025 M
TMP	0.09 M

[a] The solubility increased slightly (0.02–0.03 M) upon acidification with 0.01 M MSA but was not significantly affected upon acidification with BF_3 (0.01 M). [b] The solubility in 0.01 M BF_3 increased slightly to 5–6 mM. [c] The extinction coefficient ($\epsilon_{650\ \mathrm{nm}}$ = 69 200 M^{-1} cm^{-1}) for FePc in *o*-dichlorobenzene was used.[19] [d] BF_3, TFA, or MSA. BF_3 and TFA gave λ_{max} 654 nm; MSA gave 690 nm; $\epsilon_{\lambda_{max}}$ = 69 200 M^{-1} cm^{-1} was employed in each case. [e] Under an air atmosphere.[21]

reddish purple with a distinctive absorption at ~500 nm characteristic of dipyrromethenes. The yield of dipyrromethenes ranges from 0.1% with neither TCQ nor FePc to 3% when both are present (Table 7). This measure of oxidation encompasses dipyrromethenes in side products and as components of partially oxidized porphyrinogens.

IV. Workup Procedure. At the end of the 30–90-min aerations the reaction mixtures have turned from reddish purple to deep brownish black. The absorption spectrum is dominated by the characteristic Soret band with clearly observable visible bands and comparatively little absorption characteristic of FePc (650 nm). TLC analysis (silica) showed the rapidly migrating porphyrin (TPP or TMP), ~15% unreacted aldehyde (benzaldehyde or mesitaldehyde), a few pigmented bands, and a large amount of black material at the origin. The large separation of the porphyrin from the other components made for an easy purification. Passage of the crude mixture over a short silica column, evaporation of the porphyrin band to a slightly damp solid, and washing with methanol afforded porphyrin crystals. In general, 50-mL reactions (0.1 M) with aerobic oxidation afforded ~100 mg of TPP. In comparison, a 50-mL Adler reaction with 0.25 M reactants affords 420 mg of TPP (20% yield).[2] This workup procedure is effective for one-step or two-step syntheses with stoichiometric TCQ or aerobic oxidation. However, reactions performed with stoichiometric quantities of TCQ afforded viscous mixtures with poorer recoveries of porphyrin.

Table 7. Oxidation during Pyrrole–Aldehyde Condensation Due to Components of the Electron Transport Chain[a]

oxidation components	% dipyrromethene yields
5 mol % TCQ	2
5 mol % TCQ + 5 mol % FePc	3
5 mol % $TCQH_2$ + 5 mol % FePc	1
5 mol % $TCQH_2$	0.2
no components[b]	0.1

[a] Reactions were performed using 0.1 M benzaldehyde and pyrrole in CH_2Cl_2 with 0.01 M BF_3 under argon at room temperature. Samples were obtained via syringe at 30 min and analyzed by absorption spectroscopy (λ_{max} ~ 500 nm). The effects of scattering and absorption due to particles of FePc were subtracted. Yields are based on $\epsilon_{\lambda_{max}}$ = 60 000 M^{-1} cm^{-1} and a theoretical yield of 0.05 M for 0.1 M benzaldehyde and pyrrole.[8] [b] Benzaldehyde, pyrrole, and BF_3 only.

Discussion

The room temperature synthesis of *meso*-porphyrins has previously been carried out as a two-step procedure at modest concentration (0.01 M). The new features introduced here include condensing aldehyde and pyrrole at concentrations ≥0.1 M, performing the synthesis as either a one-step or two-step procedure, and employing an electron transport chain for aerobic oxidation.

I. Condensation at High Concentration. Three trends emerge from the investigation of various acid and reactant concentrations in the two-step syntheses (Table 1). First, at a given concentration of reactants (aldehyde and pyrrole) the porphyrin yield tends to increase with increasing [acid] across the concentrations investigated. This general trend occurred with all four acids examined, TFA, MSA, BF_3, and BF_3–ethanol. Second, at a given acid concentration the yield of porphyrin declines as the reactant concentrations are increased from 0.1 to 0.32 M, as found in the benzaldehyde–pyrrole (BF_3 catalysis) and mesitaldehyde–pyrrole (BF_3–ethanol cocatalysis) reactions. These yield-declines at 0.1–0.32 M concentrations extend similar trends observed in the 0.01–0.1 M concentration regime.[8,10] Third, the sharp decline in yield with increasing reactant concentrations is partially, though not entirely, offset by increased acid concentration. The 30% yield obtained with 0.1 M benzaldehyde and pyrrole (3.2 mM BF_3) declines by over half (9.3–15%) with 0.2 M reactants and the same acid concentration, but with 0.2 M reactants and 20 mM BF_3 the yield is 24%. Similarly, the 12% yield obtained with 0.1 M mesitaldehyde and pyrrole (0.033 M BF_3) declines by at least one-third (5.7–7.9%) with 0.2 M reactants and the same acid concentration, but with 0.2 M reactants and 0.2 M BF_3 the yield

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is 10%. Similar trends are observed in the one-step syntheses (Table 3). Thus elevated acid concentrations provide increased yields at higher reactant concentrations.

One limitation to the use of high acid concentrations involves the acid-catalyzed polymerization of pyrrole. Exposure of 0.1 M pyrrole to 0.01 M BF_3 for 15 min led to orange precipitates (Table 4). Such "pyrrole-red" species[22] are known to form in the presence of strong acids, though their structures have not been determined. Pyrrole-red does not form under the conditions used in the 0.01 M porphyrin synthesis.[8] Further studies are required to assess the detriment caused by pyrrole-red formation to the overall yields in the high concentration reactions.

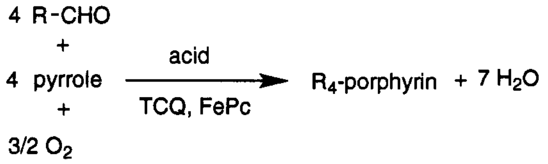
II. Aerobic Oxidation. Molecular oxygen has many attractive features as an oxidant, including availability, strong oxidizing ability, and formation of water as an innocuous product of oxidation. A special attraction is the ability to deliver excess O_2 without affecting the workup procedures, as occurs with the slurries caused by organic oxidants such as TCQ. Molecular oxygen is the oxidant in the Adler reaction (120–141 °C) but reacts slowly with *meso*-porphyrinogens at room temperature. We have built on the pioneering work of Backvall and co-workers[15–18] in developing a room-temperature aerobic oxidation process in the synthesis of *meso*-porphyrins.

The artificial electron transport chains of Backvall and co-workers employ palladium to oxidize an organic substrate, benzoquinone to recycle the palladium, and a metal–macrocyclic complex to activate molecular oxygen and regenerate benzoquinone. This "triple catalytic system" has been applied to three reactions, the 1,4-diacetoxylation or dialkoxylation of conjugated dienes, oxidation of terminal olefins to methyl ketones, and allylic acetoxylation of cyclic olefins.[17] Each of these reactions requires slightly acidic conditions. FePc was found to be superior among several oxygen-activating complexes due in part to its ability to withstand the acidic conditions. All three redox couples are essential and the flow of electrons from substrate to O_2 via the specific series of redox couples is a kinetically-controlled process.

In the aerobic oxidation of the porphyrinogen there are two redox couples, $TCQ/TCQH_2$ and FePc(O)/FePc, that mediate electron flow from the porphyrinogen to O_2 (Scheme 4). Direct evidence that $TCQH_2$ is formed in this cycle is not available, however $TCQH_2$ can be used in place of TCQ with comparable results (Table 5). Because the conversion of porphyrinogen to porphyrin requires removal of 6 e^- and 6 H^+, and TCQ is a 2 e^-, 2 H^+ carrier, the redox couples must turn over three times per porphyrin formed.

The oxygenated derivatives of FePc formed under the conditions of the aerobic porphyrin synthesis have not been characterized. FePc(O) in Scheme 4 indicates an oxidized FePc molecule but is not meant to imply a specific molecular entity, as catalytic dioxygen activation processes typically involve several intermediates.[23] The kinetics of each individual reaction have not been determined, though switching to 100% O_2 rather than air gave a much faster rate of oxidation ($t_{1/2}$ ~5 min). The bulk of the FePc is comprised of finely dispersed particles. The small amount of FePc that dissolves in acidified CH_2Cl_2 is not tetraprotonated as occurs in 96% H_2SO_4, a medium in which the interaction of FePc and O_2 has been studied extensively.[24,25] Oxygenation in 96% H_2SO_4 yielded the phthalocyanine decomposition product phthalimide.[25] In contrast, oxygenation of FePc suspended in DMF for 24–48 h yielded the μ-oxo derivative $(FePc)_2O$.[26,27] Moreover, Backvall showed that FePc recovered following a 12-h diacetoxylation in an acidified organic medium could be reused with little decrease in catalytic activity.[17] Thus FePc is a robust heterogeneous catalyst under neutral or moderately acidic conditions.

Scheme 5. Presumed Stoichiometry in the Aerobic Porphyrin Synthesis



$$4\ \text{R-CHO} + 4\ \text{pyrrole} + 3/2\ O_2 \xrightarrow[\text{TCQ, FePc}]{\text{acid}} R_4\text{-porphyrin} + 7\ H_2O$$

The aerobic oxidation of the porphyrinogen occurs only if components of the two electron relays (TCQ, FePc) and molecular oxygen are present. TCQ and FePc are present only in catalytic quantities, but omission of either results in ≤1% yield of porphyrin (Table 5). These results indicate that direct porphyrinogen oxidation by O_2, or by FePc(O), is slow and that oxidation of $TCQH_2$ directly by O_2 also is slow. Though each of these oxidations is permissible thermodynamically, the flow of electrons from porphyrinogen to O_2 occurs in a kinetically-controlled sequential manner via the redox couples $TCQ/TCQH_2$ and FePc(O)/FePc. TCQ, FePc, O_2, and their redox counterparts constitute a self-organizing electron transport chain that enables aerobic oxidation of the porphyrinogen.

The overall porphyrin synthesis including aerobic oxidation is summarized in Scheme 5. This scheme assumes molecular oxygen serves as a 4 e^-, 4 H^+ acceptor, in which case $^3/_2\ O_2$ is sufficient to convert porphyrinogen to porphyrin. In this scheme, 4 H_2O derive from pyrrole–aldehyde condensation and 3 H_2O derive from porphyrinogen oxidation. On the basis of this stoichiometry, a 1-mmol aldehyde–pyrrole reaction would produce 31.5 μL of H_2O and consume 9.2 mL of O_2. Aeration is essential since the O_2 dissolved in CH_2Cl_2 under an air atmosphere[21] is 17 times less than the stoichiometric requirement for a 0.1 M reaction.

The aerobic oxidation process provides an effective method for converting the porphyrinogen to the porphyrin. The rate of aerobic oxidation is significantly slower than that with a stoichiometric amount of TCQ ($t_{1/2}$ 20–30 min vs ~2 min, respectively), as seen in comparing the traces in Figures 2 and 3. These rates are significantly faster than those observed by Backvall and co-workers in various triple catalytic systems, which often required 10 h or more for completion. The yields are slightly less than those obtained with a stoichiometric amount of TCQ for either one- or two-step methods (Figures 2 and 3). Oxidation with stoichiometric TCQ gives higher yields, but aerobic oxidation affords a reaction mixture that is significantly easier to workup. Both approaches are heterogeneous but

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the small quantity of finely dispersed FePc is readily filtered, in contrast with the thick slurries obtained with stoichiometric quantities of TCQ at high reaction concentrations.

III. One-Step and Two-Step Syntheses. The two-step syntheses with oxidation either aerobically or with a stoichiometric amount of TCQ give higher porphyrin yields than the corresponding one-step syntheses. The superiority of the former accrues from allowing porphyrinogen self-assembly to proceed before initiating the oxidation. Delaying oxidation prevents premature termination of condensation processes leading to the porphyrinogen. How then do one-step syntheses succeed? One picture is that underlying the "all-at-once" one-step synthesis is a timed sequence of reactions involving porphyrinogen self-assembly and porphyrinogen oxidation. In this kinetic interpretation, the success of one-step syntheses requires balanced rates of condensation and oxidation, where porphyrinogen self-assembly is faster than oxidation of precursors to the porphyrinogen. Indirect evidence for this picture stems from studies of different quinones in one-step syntheses.

The one-step synthesis at room temperature exhibits a striking selectivity for TCQ (Table 2). The quinones examined span a 1-V range of oxidant strength as measured by their 1 e^- reduction potentials (DDQ, +0.51 V; TCQ, +0.01 V; 2-chlorobenzoquinone, −0.34 V; benzoquinone, −0.51 V; duroquinone, −0.84 V; in CH_3CN vs saturated calomel electrode at 25 °C).[28] These values may not be directly applicable, since quinone reduction potentials shift to more positive values in the presence of acid,[29] but the relative reactivity of quinones in hydrocarbon dehydrogenations parallels the electrochemical ordering.[30] The failure of DDQ is attributed to its rapid oxidation of precursors to the porphyrinogen, including pyrrole, relative to the rate of porphyrinogen self-assembly. At the other extreme, the weak oxidant duroquinone could be expected to oxidize the porphyrinogen and its precursors slowly if at all. Indeed, duroquinone gave no porphyrin, but upon treating a sample from the reaction with DDQ, the yield of porphyrin was 15–17% (Table 2). Thus duroquinone does not oxidize the porphyrinogen at a significant rate, nor does it interfere with the pyrrole–aldehyde condensation. Benzoquinone and 2-chlorobenzoquinone could be expected to oxidize the porphyrinogen at rates intermediate between those of duroquinone and TCQ. Instead, neither gave the porphyrin. When a sample from a one-step synthesis with benzoquinone or 2-chlorobenzoquinone was removed and oxidized with DDQ, the yield of porphyrin was <0.1%, indicating that the pyrrole–aldehyde condensation had been subverted. We attribute the subversion of the one-step synthesis with benzoquinone or 2-chlorobenzoquinone to side reactions of the quinones with pyrrole and linear polypyrromethanes. In the presence of strong acids, benzoquinone, but not TCQ, undergoes Michael addition with pyrrole.[31] Reactions between pyrrole and quinones in the presence of acid form the basis for a quinone color test.[32] Unsubstituted quinones also undergo Michael addition under neutral conditions with pyrroles bearing alkyl substituents.[33] In summary, TCQ succeeds as it reacts slower than DDQ with pyrrole and intermediates along the path to the porphyrinogen, does not engage in the side reactions that cause failure with benzoquinone and 2-chlorobenzoquinone, and reacts faster than duroquinone in oxidizing the porphyrinogen.

An ideal oxidant would selectively oxidize only the porphyrinogen and leave the precursors to the porphyrinogen untouched. In such a case, a one-step synthesis would give the same results as a two-step synthesis when the oxidant is added at the point of maximal porphyrinogen yield. Several pieces of data indicate that TCQ does not selectively oxidize the porphyrinogen. First, the two-step synthesis with a stoichiometric amount of TCQ gave higher yields than the one-step synthesis (29% vs 11%, respectively). The reactions are terminated rapidly (porphyrin formation $t_{1/2} \sim 2$ min) in both cases (Figure 2). If TCQ did not react with precursors of the porphyrinogen, these yields should ultimately be the same. Second, TCQ reacts with pyrrole in the presence of acid, forming black precipitates and giving only 2.3% yield of TPP upon subsequent addition of benzaldehyde (Table 4). Such "pyrrole-black" species[34] are known to form by polymerization of pyrrole under oxidative conditions, provided electrochemically[35] or by chemical oxidants.[36] These results show that TCQ reacts with precursors to the porphyrin, including pyrrole, but the rate of reaction evidently is slower than that of pyrrole–aldehyde condensation. In the absence of a perfectly selective oxidant, the success of a one-step synthesis relies on achieving balanced rates for pyrrole–aldehyde condensation, oxidation of the precursors to the porphyrinogen, and oxidation of the porphyrinogen. The temporally distinct condensation and oxidation reactions in a two-step synthesis avoid the difficulties of achieving balanced rates and afford higher yields of porphyrin.

Summary

The goal of this work, to develop a mild, room-temperature, high concentration, robust, simple synthesis of *meso*-porphyrins, has been partially achieved. Increased acid concentrations in conjunction with 0.1–0.3 M aldehyde and pyrrole provide effective condensations. An electron transport chain enables air to serve as the oxidant. The electron transport chain utilizes catalytic TCQ for porphyrinogen oxidation, catalytic FePc to activate O_2 and recycle reduced TCQ, and O_2 as the stoichiometric oxidant. The best synthetic method involves a two-step process of acid-catalyzed pyrrole–aldehyde condensation followed by aerobic oxidation of the porphyrinogen. This methodology has been developed for TPP and TMP. Further study of the individual reactions and refinement of the overall synthetic process should yield an attractive preparative-scale method for preparing *meso*-porphyrins.

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Experimental Section

Benzaldehyde, mesitaldehyde, $BF_3{\cdot}OEt_2$, TFA, and MSA were obtained from Aldrich. All mentions of BF_3 in this paper refer to $BF_3{\cdot}OEt_2$. Pyrrole was distilled from CaH_2. CH_2Cl_2 (Fisher) and $CHCl_3$ (Fisher, Certified ACS grade containing 0.75% ethanol) were distilled from K_2CO_3. Tetrachlorohydroquinone (2,3,5,6-tetrachloro-1,4-benzenediol, $TCQH_2$) was obtained from Sigma. Argon (CGA grade E; 99.997%, $\leq$5 ppm O_2) was obtained from Airco.

Two 10-g bottles of FePc (iron(II) phthalocyanine, 90%) were obtained from Aldrich. The first batch of FePc was used as received and gave most of the results presented here. The second batch exhibited no activity in the porphyrin synthesis and interfered with the acid-catalyzed pyrrole–aldehyde condensation. This material had a noticeable amine-like odor; washing with acetic acid (brown eluant) followed by 95% ethanol (green eluant) until a turquoise eluant was obtained and then vacuum desiccating produced a material that had 60% the normally-observed catalytic activity. A more rigorous activation was performed as described[37] with two significant changes. First the NH_4OH wash was omitted, and after the first vacuum desiccation the dark brown solid was pulverized with mortar and pestle and vacuum desiccated again (45% recovery). The FePc purified in this manner exhibited 100% of the catalytic activity observed with the first batch.

Solubilities of porphyrins and TCQ were determined by stirring a slurry of the solid in CH_2Cl_2 for 3 h. After standing for 3 days, the mixture was filtered and the solid obtained upon evaporation of the filtrate was dried and weighed. Solubilities of FePc were determined by filtering a mixture of excess FePc in the desired solvent through glass wool in a Pasteur pipette and then diluting an aliquot of the filtrate into the same solvent in a cuvette and recording the absorption spectrum. Solubilities of $TCQH_2$ were bracketed by stepwise addition of solvent until dissolution occurred.

Reaction sampling was performed with syringes equipped with Teflon-tipped plungers. Clogging of the syringes at the higher reactant concentrations ($\geq$0.1 M) occurred frequently with all acids but was most pronounced with MSA.

Method for Surveying the Two-Step Aerobic Synthesis, Given for TPP. Samples of TCQ (23 mg, 5 mol %) and FePc (53 mg, 5 mol %) were placed in a 50-mL three-necked round-bottom flask equipped for magnetic stirring and fitted with a glass air bubbler equipped with a rather porous tip, a gas outlet valve, and a rubber septum. Then 25 mL of CH_2Cl_2 was added to the reaction flask. The mixture was purged with argon by steady bubbling into the flask for 5 min. Then 0.254 mL of benzaldehyde (0.1 M) and 0.173 mL of pyrrole (0.1 M) were added via syringe. After a further 2–3-min purge, $BF_3{\cdot}OEt_2$ (0.10 mL of a 2.5 M stock solution, 0.01 M) was added and the condensation was allowed to proceed at room temperature under a steady flow of argon for 30 min. Samples (typically 25 μL) were removed via syringe, diluted to 3 mL (CH_2Cl_2:ethanol 3:1), and analyzed by absorption spectroscopy (assuming $\epsilon_{420\ \mathrm{nm}} = 500\,000$ M^{-1} cm^{-1}). During the argon purge, the yield of TPP was <1%. At the end of the 30 min, the argon line was changed to filtered house air. The reaction mixture was steadily bubbled at the same flow rate with filtered air for 90 min. The removal and assay of samples showed a rapid rise in TPP yield, reaching 19% at the end of the 90 min. Though FePc particles are taken up in the syringe, the spectroscopic yield monitoring was not affected. The gas purge caused a slight but continual decrease in reaction volume, which was compensated for by occasional addition of 1–2 mL of CH_2Cl_2 via syringe as required prior to acquisition of samples (total volume ~6 mL over 120 min). In reactions of very high acid concentrations, triethylamine was added to the cuvette to confirm that no protonated porphyrin was present, but this step was generally not necessary for reactions at 0.1 M aldehyde and pyrrole concentrations. Reactions forming tetramesitylporphyrin were performed identically using $\epsilon_{\mathrm{Soret}} = 500\,000$ M^{-1} cm^{-1}.

Two exemplary procedures are shown for preparative scale syntheses.

One-Step Synthesis of TPP (at 0.32 M) Using a Stoichiometric Amount of TCQ. A sample of 2.95 g of TCQ (0.24 M) was placed in a 100-mL one-necked round-bottom flask. Then 50 mL of CH_2Cl_2 was added and the mixture was stirred magnetically. Then benzaldehyde (1.626 mL, 0.32 M) and pyrrole (1.110 mL, 0.32 M) were added via syringe and the resulting mixture was allowed to stir for a few minutes. Then $BF_3{\cdot}OEt_2$ (2 mL of a 2.5 M stock solution, 0.1 M) was added 1 mL at a time in rapid succession. The mixture immediately turned dark purple and refluxed for 1 min. The reaction was allowed to proceed for 45 min. A sample removed via syringe for spectroscopic analysis (CH_2Cl_2/ethanol, 3:1) indicated a 16.5% yield. Then the reaction flask was placed directly on the rotary evaporator and solvent was removed until a fluid slurry of ~10 mL remained. Then ~10 mL of hexanes was added and the mixture was evaporated to dryness. A short column was prepared from a thin silica layer (1 cm) sandwiched between two sand layers (0.5 cm) in a fritted glass funnel (6 cm × 7 cm diameter). The column was washed with 25 mL of CH_2Cl_2/hexanes (1:1), then the crude product (without neutralization) was placed on top of the column and eluted with CH_2Cl_2/hexanes (1:1). The porphyrin band appeared to be the only mobile component. A total of 200 mL of CH_2Cl_2/hexanes (1:1) was used for elution, though some porphyrin remained on the column. The fractions were collected in a 250-mL round-bottom flask, rotary evaporated to dryness, methanol was added (20 mL), and the crystals were collected in a Buchner funnel. The crystals were washed with ~10 mL of methanol, yielding 226 mg of TPP (9% yield). The chlorin content of the product was <1%. Analytical data were identical with those obtained for an authentic sample of tetraphenylporphyrin.[8]

Two-Step Aerobic Synthesis of TMP (at 0.1 M). Samples of 138.3 mg of TCQ (5 mol %) and 319.7 mg of FePc (5 mol %) were placed in a 250-mL three-necked round-bottom flask fitted with a glass air bubbler equipped with a rather porous tip, a gas outlet valve, and a rubber septum. Then 150 mL of $CHCl_3$ (containing 0.75% ethanol) was added and the mixture was stirred magnetically. The reaction mixture was purged with argon for 10 min. Then mesitaldehyde (2.212 mL, 0.1 M) and pyrrole (1.041 mL, 0.1 M) were added via syringe and the resulting mixture was allowed to stir for a few minutes. Then $BF_3{\cdot}OEt_2$ (1.98 mL of 2.5 M stock in $CHCl_3$, 0.033 M) was added. The condensation was allowed to proceed under argon for 30 min, at which point the mixture exhibited a dark pinkish tint. Then the gas inlet line was switched to filtered house air and the mixture was aerated for 90 min, during which time the mixture became dark purple. A sample removed via syringe for spectroscopic analysis (CH_2Cl_2/ethanol, 3:1) indicated a 10% yield. Then the contents were transferred to a 250-mL round-bottom flask and concentrated on the rotary evaporator to a damp solid which was allowed to dry for 5 min. Then 50 mL of CH_2Cl_2 was added to wash down material on the walls of the reaction flask and then 60 mL of hexanes was added. A short column was prepared as a slurry from a thin silica layer (2.5 cm) sandwiched between two sand layers (0.5 cm) in a fritted glass funnel (6 cm × 7 cm diameter). The crude product (without neutralization) was then poured on top of the column and eluted with hexanes/CH_2Cl_2 (6:5). A green material eluted first followed by TMP. A total of 200 mL of hexanes/CH_2Cl_2 (6:5) was used for elution, with little porphyrin remaining bound on the silica. The fractions were collected in a 250-mL round-bottom flask, rotary evaporated to dryness, methanol was added (90 mL), and the crystals were collected in a Buchner funnel. The crystals were washed with 30 mL of methanol, yielding 455 mg of TMP (15.7% yield). The chlorin content of the product was <1%. Analytical data were identical with those obtained for an authentic sample of tetramesitylporphyrin.[10]

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