Pergamon

Tetrahedron, Vol. 53, No. 37, pp. 12339-12360, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00770-9

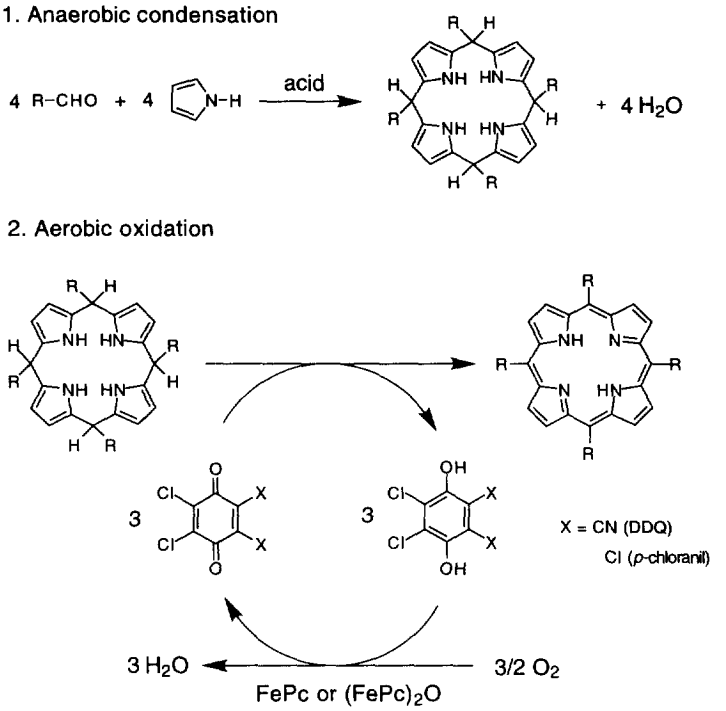
Beneficial Effects of Salts on an Acid-Catalyzed Condensation Leading to Porphyrin Formation[1]

Feirong Li, Kexin Yang, John S. Tyhonas, Kristy A. MacCrum, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204

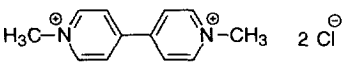
Abstract: Addition of one of a variety of salts to the room temperature, two-step, one flask reaction at 0.1 M forming tetraphenylporphyrin (TPP) gave yield increases of up to 2-fold. Among 21 insoluble salts, 12 gave increased yields, 6 had no effect, and 3 gave diminished yields. The salts that gave increases encompassed diverse cations but were restricted to the anions Cl^-, Br^-, I^-, and Ph_4B^- while SO_4^{2-}, F^-, or BF_4^- did not give improved yields. All 7 soluble tetraalkylammonium or tetraphenylphosphonium salts (F^-, Cl^-, Ph_4B^-, PF_6^-, or HSO_4^- counterions) that were surveyed gave yield increases of > 1.5 fold. Thus a 10^{-1} M pyrrole-benzaldehyde condensation catalyzed with 10^{-2} M $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 containing 0.1 equiv of NaCl (5.85 mg/10 mL CH_2Cl_2) or 0.0031 equiv of benzyltributylammonium chloride ($Bu_3BzlNCl$) (based on [benzaldehyde]) gave ~50% yield compared with ~25% in the reaction without salt. The pyrrole-aldehyde condensation is much faster in the presence of salt, as measured by the rate of disappearance of benzaldehyde and the rate of formation of the porphyrin. Yield increases in the presence of salt were observed with catalysis by $BF_3{\cdot}O(Et)_2$, $BF_3{\cdot}2H_2O$, and CF_3CO_2H. Significant salt effects also were observed with $BF_3{\cdot}O(Et)_2$ or CF_3CO_2H in the solvent diethyl ether, but the maximum yield was 15%. A survey of nine aldehydes showed yield improvements of up to 2-fold in six cases in the presence of salt. During the pyrrole-aldehyde reaction in CH_2Cl_2 either in the presence or absence of soluble salts, the medium becomes heterogeneous (measured by nephelometry). The addition of water to $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 also yields a heterogeneous medium; in the presence of salt this medium affords twice the yield of porphyrin as that formed in the absence of salt. ^{11}B NMR and ^{19}F NMR experiments failed to unveil any new species formed by interaction of chloride-containing salts with $BF_3{\cdot}O(Et)_2$. The complexity of the reaction medium, as well as insufficient information about the nature of the pyrrole-aldehyde condensation, preclude an assignment of mechanisms underlying the salt effects. However, a rank ordering of salts in the porphyrin reaction does not correlate with their desiccative power, and the generality of the salt effects is at odds with the selective anion templating of tetrapyrrolic macrocycles. Irreversible features of the pyrrole-aldehyde condensation have been identified via exchange experiments during the course of the reaction and ^{13}C NMR labeling experiments. The improved reaction conditions can be used for preparative-scale syntheses, as 720 mg tetraphenylporphyrin (47% yield) was obtained from a 100 mL-scale reaction with 0.1 M reactants at room temperature. © 1997 Elsevier Science Ltd.

The synthesis of porphyrins provides a basis for modeling the reactions of porphyrins in biological systems and for preparing a wide variety of molecular devices. In order to synthesize porphyrins bearing sensitive substituents, we introduced a mild, two-step process (Scheme 1) involving an acid-catalyzed pyrrole-aldehyde condensation followed by oxidation with DDQ or *p*-chloranil.[2-5] We found that reactant concentrations of 10^{-2} M afforded optimal yields. These modest concentrations were suitable for preparing 100-mg quantities of porphyrins but were inconvenient for large-scale preparative work. Recently we showed that pyrrole-aldehyde condensations performed at 10^{-1} or 2 x 10^{-1} M in the presence of elevated quantities of acid afforded porphyrin yields that were within a factor of two of those obtained at 10^{-2} M. We also developed an aerobic oxidation process for converting the porphyrinogen to the porphyrin that uses a stoichiometric amount of O_2 and catalytic amounts of *p*-chloranil and iron phthalocyanine.[6] Subsequently we found that the μ-oxo dimer of iron phthalocyanine is the source of activity in the aerobic oxidation.[7] This catalytic oxidation system avoids stoichiometric amounts of organic oxidants (DDQ or *p*-chloranil) and is advantageous with reactions at high concentration. The high-concentration aerobic synthesis has been used to prepare gram quantities of *ortho*-disubstituted tetraarylporphyrins.[8]



Scheme 1. Two-step one-flask synthesis of *meso*-substituted porphyrins.

During the development of the aerobic oxidation process, we surveyed redox-active compounds that could shuttle electrons from the porphyrinogen to various bulk oxidants. When paraquat dichloride was examined in conjunction with *p*-chloranil, the yield of porphyrin was elevated significantly compared with that expected upon stoichiometric oxidation using DDQ or *p*-chloranil alone.



paraquat dichloride

Ultimately we found that the increased yield stemmed not from paraquat serving as an electron shuttle but rather from the fact that paraquat dichloride is a salt. This finding prompted us to investigate the effects of salts in the porphyrin-forming reaction. In this paper we first present a survey of the effects of different salts with various acid catalysts in the reaction of pyrrole and benzaldehyde, focusing primarily on reactions at 0.1 M in order to enable large-scale preparative work. Second, we report the application of the best reaction conditions identified to a handful of aldehydes. Third, we examine the reversibility of the pyrrole-aldehyde condensation under these conditions. Fourth, we describe an initial investigation of the properties of the heterogeneous reaction media. These experiments are aimed at defining the scope of the salt effects rather than determining mechanisms by which salts increase yields in the pyrrole-aldehyde condensations.

RESULTS

Unless noted otherwise, the "standard reaction" for investigating the salt effects in this paper is performed with 10^{-1} M pyrrole and 10^{-1} M aldehyde in 10 mL CH_2Cl_2 with 10^{-2} M $BF_3{\cdot}O(Et)_2$ at room temperature, and yields are determined spectroscopically upon oxidation with DDQ after 15 min of condensation (see Experimental section). The amount of salt (in equiv) is relative to the concentration of aldehyde. Each reported datum is the average from two or more experiments; typical variation among batches is ± 5%.

Effects of salt on tetraphenylporphyrin (TPP) formation

Studies with NaCl. Pyrrole-benzaldehyde condensations were performed in CH_2Cl_2 with $BF_3{\cdot}O(Et)_2$ catalysis in the presence of powdered NaCl. The NaCl does not dissolve and the reaction mixture is heterogeneous. Samples were removed after 15 min and oxidized with DDQ, which gives rapid conversion of porphyrinogen to the porphyrin. Figure 1 shows results from reactions using various amounts of NaCl and $BF_3{\cdot}O(Et)_2$. In each case the yield peaks at around 0.1 equiv NaCl (5.85 mg NaCl/10 mL CH_2Cl_2), with net increase in yield of 2-fold compared with the reaction without salt.

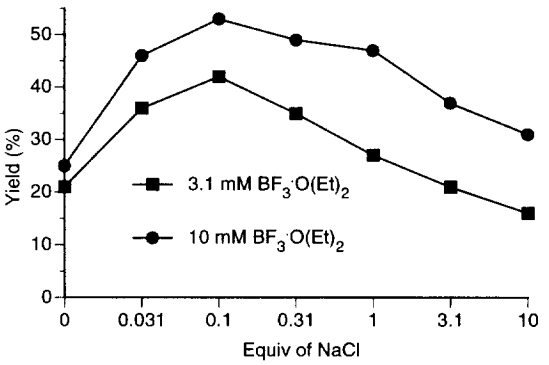


Figure 1. Effects of NaCl on TPP yields in the standard reaction.

Studies with other insoluble salts. The previous experiment was performed with powdered NaCl, prepared by pulverizing granular NaCl. Prior to surveying diverse salts, we investigated the effect of particle size by comparing granular and powdered NaCl (Table 1). The yields only differed slightly. Nonetheless, for consistency all insoluble salts were pulverized and desiccated prior to experimentation.

Table 1. Effect of surface area of salt in the standard reaction.

	% yield of TPP equiv of NaCl added			
	0	1	3.1	10
granular NaCl [a]	21	29	33	46
powdered NaCl [a]	21	38	45	53
granular NaCl	25	51	46	37
powdered NaCl	25	47	37	31

[a]Reactions were carried out with 10^{-2} M benzaldehyde, 10^{-2} M pyrrole, and 10^{-3} M $BF_3{\cdot}O(Et)_2$ at room temperature.

The conditions found optimal for NaCl were applied in a survey of various salts in order to identify those cations and anions that give increased TPP yields. Among possible salts, we have avoided the use of metals that could insert into the free-base porphyrin. Several magnesium-containing salts have been investigated but magnesium insertion does not occur under these acidic reaction conditions.[9] As shown in Table 2, 12 of the 21 salts tested gave enhanced yields of TPP. The origin of the yield enhancement has greater specificity for the anion than the cation. For example NaCl, $NaBPh_4$ and NaBr gave increased yields but Na_2SO_4 and $NaBF_4$ gave no change in yield. Every salt with a chloride counterion (with the exception of triethylamine hydrochloride) gave at least 1.8-fold increase regardless of the cation (LiCl, NaCl, KCl, CsCl, NH_4Cl, $CaCl_2$, $MgCl_2$, Me_4NCl, and paraquat dichloride). The salts NaBr, KI and $NaBPh_4$ showed at least 1.6-fold yield increases. On the other hand, the salts containing SO_4^{2-} (excepting guanidine sulfate), F^-, or BF_4^- did not alter the yield. In summary, the insoluble salts giving yield increases were composed of an indiscriminate cation and Cl^-, Br^-, I^- or BPh_4^-.

Table 2. Survey of insoluble salts on TPP yields in the standard reaction.[a]

Positive effect		No effect		Negative effect	
Salt	Yield (%)	Salt	Yield (%)	Salt	Yield (%)
LiCl	47	No salt	25	TEA·HCl[b]	19
NaCl	52	Na_2SO_4	24	Molecular sieves[c]	20
KCl	47	$MgSO_4$	26	Guanidine sulfate	0
CsCl	48	$CaSO_4$	28		
$MgCl_2$	47	$NaBF_4$	27		
$CaCl_2$	45	Me_4NBF_4	27		
Paraquat·$2Cl^-$	47	KF	25		
NH_4Cl	46				
Me_4NCl	51				
$NaBPh_4$	50				
NaBr	45				
KI	41				

[a] Reactions were performed in the presence of 0.1 equiv of salt. [b] Triethylamine hydrochloride. [c] Reaction was performed with 20 mg of molecular sieves.

Studies with organic-soluble salts. We investigated seven organic-soluble salts, each of which afforded homogeneous solutions in CH_2Cl_2 (Figure 2). Though initially homogeneous, in each case the reaction mixture rapidly became turbid (vide infra). The salts $Bu_3BzlNCl$, $BzlMe_2RNCl$ (R = C_8H_{17}-$C_{18}H_{37}$, molecular weight taken as the average of this range), Ph_4PCl or Bu_4NBPh_4 gave the same 2-fold yield increases (46-50%) as NaCl, though only 0.001-0.031 equiv was required, which is 10 - 100 times less than with NaCl. Nearly identical yields were observed at each concentration with each of these soluble salts (± 3% variation), and the results are grouped in a single curve. A 2-fold yield increase also was observed with Bu_4NF (50%). Yield increases of 1.8-fold were observed for Bu_4NPF_6 (45%) and 1.5-fold for $Bu_4N(HSO_4)$ (39%) though more of each salt was required. In summary, every soluble salt that was examined, regardless of the anion (Cl^-, BPh_4^-, F^-, PF_6^- or HSO_4^-), gave at least a 1.5-fold yield increase.

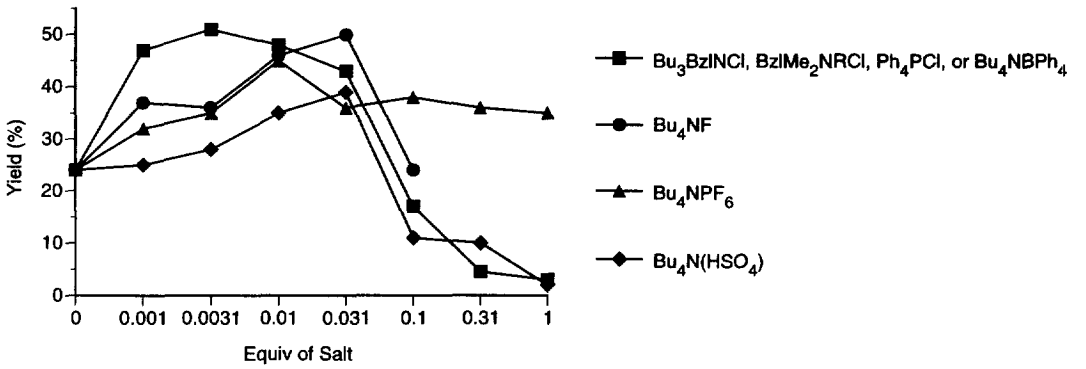


Figure 2. Effects of soluble salts on TPP yields in the standard reaction. Yields at 15 min (shown above) were nearly identical with those obtained at 30 min.

Rate of reaction. The rate of the pyrrole-benzaldehyde condensation was measured by removing samples periodically and oxidizing with DDQ (Figure 3). The yields obtained with added NaCl (0.1 equiv) or $Bu_3BzlNCl$ (0.0031 equiv) were identical after 3 min. However, the rise in porphyrin yield at early times was much faster with $Bu_3BzlNCl$ (33% at 15 sec) compared with NaCl (7% at 15 sec) or no salt (5% at 15 sec). After 15 min in the presence of salt, or 60 min in the absence of salt, the yields steadily declined.

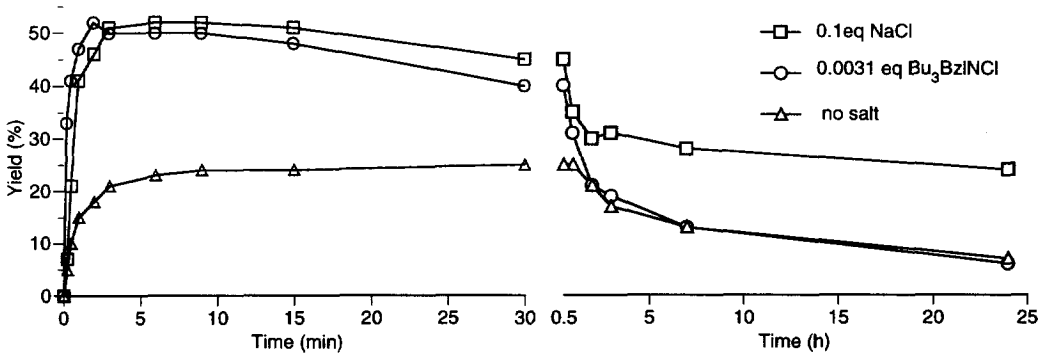


Figure 3. Effects of salts on the time-course of TPP formation in the standard reaction. The graph is divided to display the rapid rise in porphyrin formation (left, in minutes) and the much slower decline (right, in hours). The first three timepoints were at 15 sec, 30 sec, and 1 min.

We also monitored the disappearance of benzaldehyde by TLC through careful use of standards of known concentrations to bracket the observed samples. The results are summarized in Figure 4. The limit of detection is 10^{-4} M = 0.1% unreacted benzaldehyde (see Experimental section). Benzaldehyde disappears at a rate ~10 times faster with salt than without salt (NaCl or $Bu_3BzlNCl$).

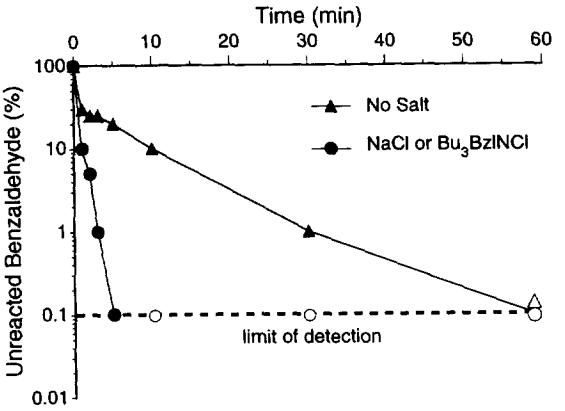


Figure 4. Effects of salt (0.1 equiv NaCl or 0.0031 equiv $Bu_3BzlNCl$) on the disappearance of benzaldehyde in the standard reaction. Open symbols indicate samples where the amount of benzaldehyde was below the limit of detection.

We also used ^{13}C NMR spectroscopy to monitor the pyrrole-benzaldehyde condensation. ^{13}C-(formyl) labeled benzaldehyde and pyrrole (10^{-1} M each) were condensed with 10^{-2} M $BF_3{\cdot}O(Et)_2$ in the presence of 0.0031 equiv of $Bu_3BzlNCl$ in an NMR tube and spectra were collected periodically (3-6 min acquisition time). After 5 min of reaction, the ^{13}C NMR spectrum was collected. The benzaldehyde peak (190 ppm) had decreased to ~3% of its initial value. In addition, a set of at least four new (overlapping) intense peaks appeared ranging from 44.2-45.2 ppm. No other change was observed in the spectrum. These peaks can be compared with that from the *meso*-carbon of *meso*-phenyldipyrromethane[10] (44.5 ppm). After 10 min of reaction, the benzaldehyde peak had completely disappeared and the peaks centered at 44.2-45.2 ppm remained unchanged. In the absence of salt, the rate of disappearance of ^{13}C-labeled benzaldehyde was much slower (15% residual benzaldehyde after 10 min and 4% after 30 min). However, other than differences in the rate of change of peak intensities, the spectra collected with or without salt were indistinguishable. Within the limits of the experiment, the different rates of consumption of benzaldehyde measured by ^{13}C NMR mirror those observed with TLC (Figure 4). The slightly slower consumption rate of benzaldehyde measured by ^{13}C NMR may be due to differences in mixing methods (the NMR tube is spun continuously at 21 Hz but is not stirred).

The reactions performed in the presence of NaCl give noticeably darker mixtures than those without NaCl. The absorption spectra of samples from the condensation mixture (without DDQ oxidation) exhibit absorption in the 450-500 nm region characteristic of dipyrrins, which can be formed oxidatively or via tautomerization at sites in the saturated oligo-pyrromethane (or porphyrinogen).[3,5] After 15 min in a 10^{-1} M benzaldehyde-pyrrole condensation, the yield of dipyrrins was 1% when 0.1 equiv of NaCl was present compared with 0.5% in the absence of NaCl. Thus the presence of NaCl increases the extent of reaction yielding porphyrinogen as well as the products having dipyrrin chromophores.

Breadth of reaction conditions. We performed a variety of experiments to establish whether the salt effects occurred with diverse reaction conditions (Table 3). Salt alone is not a catalyst (entry 1). Moderate increases in TPP yield were observed with TFA in the presence of 1 equiv LiCl (entries 2-8), while no improvement was observed in one trial with $Bu_3BzlNCl$ (entry 9). No yield increases were observed with other acids (entries 10-17), change in temperature (entries 18,19), different solvents (entries 20-22), or use of ultrasound (entry 23). These results show that the salt effects are most pronounced with $BF_3{\cdot}O(Et)_2$.

Table 3. Investigation of diverse reaction conditions on the yields of TPP.[a]

entry	acid[b]	salt	equiv of salt	other conditions	time (min)	yield
1	None	NaCl	0.1		60	0%
2	TFA	none			15	1%
3	TFA	LiCl	0.1		15	1%
4	TFA	LiCl	1		15	6%
5	TFA[c]	none			15	21%
6	TFA[c]	LiCl	0.1		15	24%
7	TFA[c]	LiCl	1		15	36%
8	TFA[c]	LiCl	10		15	27%
9	TFA[c]	$Bu_3BzlNCl$	0.0031		15	25%
10	CH_3SO_3H	none			15	17%
11	CH_3SO_3H	NaCl	0.1		15	17%
12	$B(OH)_3$	none			120	0%
13	$B(OH)_3$	NaCl	0.1		120	0%
14	BCl_3	none			15	11%
15	BCl_3	NaCl	0.1		15	11%
16	BCl_3	$Bu_3BzlNCl$	0.0031		15	9%
17	BCl_3	Bu_4NF	0.031		15	10%
18	$BF_3{\cdot}O(Et)_2$	NaCl	0.1	0 °C	30	15%
19	$BF_3{\cdot}O(Et)_2$	NaCl	0.1	39 °C	1	34%
20	$BF_3{\cdot}O(Et)_2$	NaCl	0 or 0.1	THF[d]	60	0%
21	$BF_3{\cdot}O(Et)_2$	none		toluene[d]	60	6%
22	$BF_3{\cdot}O(Et)_2$	NaCl	0.1	toluene[d]	60	6%
23	$BF_3{\cdot}O(Et)_2$	NaCl	0.1	sonication	30	33%
24[e]	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$ $Bu_4N(HSO_4)$	0.0031 (50%)[f] 0.031 (40%)[f]		15	51%
25[e]	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$ $Bu_4N(HSO_4)$	0.0031(50%)[f] 0.016 (37%)[f]		15	45%
26[e]	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$ $NaBPh_4$	0.0031 (50%)[f] 0.031 (55%)[f]		15	53%
27[e]	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$ $NaBPh_4$	0.0031 (50%)[f] 0.016 (48%)[f]		15	55%
28[e]	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$ Bu_4NPF_6	0.0031 (50%)[f] 0.031 (42%)[f]		15	39%
29	$BF_3{\cdot}O(Et)_2$	none		0.2 M reactants[g]	30	19%
30	$BF_3{\cdot}O(Et)_2$	NaCl	0.05	0.2 M reactants[g]	30	26%
31	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$	0.0016	0.2 M reactants[g]	30	31%
32	$BF_3{\cdot}O(Et)_2$[h]	NaCl	31	0.01 M reactants[g]	30	53%

[a]In CH_2Cl_2 at 25 °C with 10^{-1} M benzaldehyde and pyrrole. [b]10 mM unless noted otherwise. [c]64 mM. [d]Instead of CH_2Cl_2. [e]Co-addition of two salts. [f]Yield in parentheses is for the salt individually. [g]Pyrrole and benzaldehyde. [h]10^{-3} M $BF_3{\cdot}O(Et)_2$.

No synergistic effects were obtained upon co-addition of different salts (entries 24-28), as might occur if different salts increase the yield by different mechanisms. Beneficial effects of individual salts were observed at other concentrations of pyrrole and benzaldehyde. A 1.5-fold yield increase was achieved at 0.2 M (entries 29-31), and similar increases were observed at 0.01 M (entry 32). In other experiments at 0.01 M, the yields were in the range of 42 - 53% in the presence of 1-100 equiv of NaCl (10^{-3} M $BF_3{\cdot}O(Et)_2$) or 100-300 equiv of NaCl (3.1 x 10^{-3} M $BF_3{\cdot}O(Et)_2$). Larger quantities of salts were required at 0.01 M reactants than at 0.1 M. For example, 31 equiv of NaCl (entry 32) corresponds to 181 mg/10 mL CH_2Cl_2, which is far more than the 0.1 equiv of NaCl (5.85 mg/10 mL CH_2Cl_2) in the reactions at 10^{-1} M.

Scope of application with various aldehydes

A wide variety of salts give comparable increases in the yield of TPP. Early in the course of experimentation we focused on Cl^--containing salts. The reaction conditions for benzaldehyde (0.1 equiv of NaCl or 0.0031 equiv of $Bu_3BzlNCl$, 10^{-2} M $BF_3{\cdot}O(Et)_2$) were applied to a set of nine aldehydes (Table 4). Yield increases of ≥ 1.5-fold were obtained in four cases. In each case, the yield increases observed with NaCl or $Bu_3BzlNCl$ were approximately the same. The condensation of mesitaldehyde and pyrrole (10^{-2} M each) exhibits cocatalysis by $BF_3{\cdot}O(Et)_2$ and ethanol, affording tetramesitylporphyrin in 25% yield.[5] No significant improvement in yield was obtained for mesitaldehyde in the presence of salts using $BF_3{\cdot}O(Et)_2$ catalysis or $BF_3{\cdot}O(Et)_2$-ethanol cocatalysis regardless of the mesitaldehyde-pyrrole concentration. The only alkyl aldehyde examined, n-hexanal, gave very slight improvement, and the yields (4-6%) were substantially less than the 25% yield when the reaction is performed at 10^{-3} M n-hexanal-pyrrole with trifluoroacetic acid catalysis.[3]

Table 4. Survey of salt effects with various aldehydes in the standard reaction.[a]

	% Yields of porphyrin		
Aldehyde	No salt	0.1 equiv NaCl	0.0031 equiv $Bu_3BzlNCl$
benzaldehyde	25	50	54
p-methoxybenzaldehyde	7	22	23
p-tolualdehyde	17	38	40
p-bromobenzaldehyde	42	56	55
methyl *p*-formylbenzoate	21	28	33
o-tolualdehyde	37	58	61
o-chlorobenzaldehyde	19	21	24
2,6-dichlorobenzaldehyde	15	17	19
mesitaldehyde[b]	3[c]	7	6
mesitaldehyde[d]	0	0[e]	0
mesitaldehyde (+ ethanol)[f]	20[g]	12[e]	8
n-hexanal	4	6	6

[a]Yields were determined spectroscopically assuming ε_{Soret} = 500,000 $M^{-1}cm^{-1}$. [b]10^{-1} M mesitaldehyde and pyrrole with 3.3 x 10^{-2} M $BF_3{\cdot}O(Et)_2$. [c]Previously the yield was 10% (based on ε_{Soret} = 427,000 $M^{-1}cm^{-1}$).[4] [d]10^{-2} M mesitaldehyde and pyrrole with 3.3 mM $BF_3{\cdot}O(Et)_2$. [e]Using 10 equiv NaCl. [f]10^{-2} M mesitaldehyde and pyrrole with 0.75% v/v ethanol and 3.3 mM $BF_3{\cdot}O(Et)_2$. [g]Literature value is 25%.[5]

Preparative scale syntheses

A preparative reaction was performed to check the scalability of the previous results, which were performed in 10 mL CH_2Cl_2 with spectroscopic monitoring. The condensation of a 100 mL solution of 10^{-1} M pyrrole and benzaldehyde was initiated with 10^{-2} M $BF_3{\cdot}O(Et)_2$ in the presence of 0.0031 equiv Ph_4PCl. After 15 min, DDQ was added, and after 60 min the reaction mixture was worked up by column chromatography. The isolated yield of TPP (720 mg, 47%) is nearly identical with those observed in the 10 mL survey reactions.

We combined the optimal condensation conditions with a refined aerobic oxidation procedure.[7] A 100 mL solution of 10^{-1} M pyrrole and *p*-tolualdehyde containing 0.0031 equiv $Bu_3BzlNCl$ was treated with 10^{-2} M $BF_3{\cdot}O(Et)_2$ at room temperature. After 10 min, a catalytic amount (1 mol %) of the μ-oxo dimer of iron(III) phthalocyanine, $(FePc)_2O$, and 1 mol % of DDQ were added and the mixture was gently bubbled with O_2 for 2 h. Subsequent workup afforded *meso*-tetrakis(*p*-tolyl)porphyrin in 39% yield. These results demonstrate the compatibility of the salt-enhanced condensation and aerobic oxidation processes.

Investigation of the nature of the catalyst in the heterogeneous reaction medium

A turbid medium formed in the pyrrole-aldehyde condensation with every soluble salt that was examined, though at the outset each reaction was homogeneous. (With insoluble salts, the occurrence of turbidity is hard to discern.) We measured the extent of precipitation during the course of the reaction using a nephelometer, which measures scattered light. Precipitation occurs rapidly upon addition of 10^{-2} M $BF_3{\cdot}O(Et)_2$ to the CH_2Cl_2 solution containing 10^{-1} M pyrrole and benzaldehyde, and 0.0031 equiv of the soluble salt $Bu_3BzlNCl$. In the absence of salt, precipitation occurs much more slowly (Figure 5). Each curve was reproduced several times (although the spikes are random). These curves result from differences in extent of precipitation with and without salt and are not due to absorption by organic reaction byproducts (see Experimental for description).

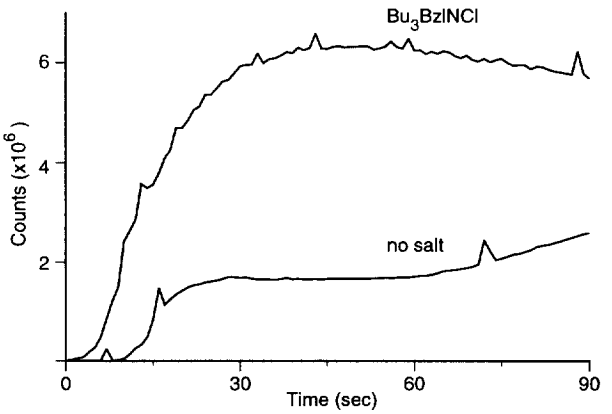


Figure 5. Nephelometry data recorded during pyrrole-benzaldehyde condensations. A 3 second delay occurred between the addition of the acid catalyst and the start of data collection.

These results show that the reaction medium changes markedly during the course of the condensation. Liberation of water as the pyrrole-aldehyde condensation proceeds is one source of change in the reaction medium. Upon complete reaction of 0.1 M pyrrole and aldehyde, the water content will be ~0.11 M, given that the background concentration of water in CH_2Cl_2 is ~8-10 mM (measured by Karl Fischer titration; see Experimental section). This concentration of water in CH_2Cl_2 is near the saturation point[11-13] and is 10 times greater than the concentration of $BF_3{\cdot}O(Et)_2$. These considerations prompted us to examine the effects of salts on the pyrrole-aldehyde condensation in CH_2Cl_2 containing significant amounts of water.

In order to simulate the medium composition toward the end of the reaction, a 10 mL solution of 10^{-2} M $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 was treated with 18 μL H_2O (corresponding to a quantitative 10^{-1} M pyrrole-aldehyde condensation) either in the presence or absence of 0.0031 equiv $Bu_3BzlNCl$. A white milky medium formed in each case. Centrifugation of the white milky medium (with or without salt) afforded a biphasic system comprised of a small liquid beadlet at the bottom and a large upper liquid volume; each liquid layer was homogeneous and colorless. The layer at the bottom requires a density greater than that of CH_2Cl_2 (1.34 g/mL).[14] This result is consistent with the presence of some $BF_3{\cdot}nH_2O$ species with high density; for reference $BF_3{\cdot}2H_2O$ has density 1.63 g/mL[15] while $BF_3{\cdot}O(Et)_2$ has density only of 1.15 g/mL.[14] (In contrast, centrifugation of the turbid medium formed in the pyrrole-aldehyde reaction medium afforded a small amount of a solid.)

Formation of the white milky medium as described in the previous paragraph followed by the addition of pyrrole and benzaldehyde afforded TPP in 13% yield (entry 1, Table 5). If NaCl or $Bu_3BzlNCl$ was added after the milky medium formed, the yield of TPP was 11% or 17%, respectively (entries 2 and 3). When water and NaCl or $Bu_3BzlNCl$ were present prior to the addition of $BF_3{\cdot}O(Et)_2$, the yield of TPP was 28% or 33%, respectively (entries 4 and 5). These results show that the condensation proceeds in the presence of significant amounts of water. Furthermore, the presence of salt prior to the exposure of $BF_3{\cdot}O(Et)_2$ to water results in higher yields than when salt is added after the exposure of $BF_3{\cdot}O(Et)_2$ to water.

The lifetime of the catalyst upon exposure to water was assessed by mixing $BF_3{\cdot}O(Et)_2$ and H_2O in CH_2Cl_2, then after a defined wait period (1-6 h), pyrrole and benzaldehyde were added and the yield of TPP was determined. During the 1-6 h period of stirring, phase separation occurred affording a small amount of a more dense viscous layer separated from the upper layer of CH_2Cl_2. A slight decline in activity occurred over 6 h in the absence of salt, from the already depressed level of 14% (entries 6-8, Table 5). A one-third decline in activity occurred in 1 h, reaching one-half over 6 h, in the presence of salt (entries 9-11). These results show that the catalyst, which is highly active initially in the presence of salt, is slowly inactivated in the presence of water.

Table 5. Effects of combining water and $BF_3{\cdot}O(Et)_2$ on the pyrrole-benzaldehyde condensation.[a]

	Order of addition to 10 mL CH_2Cl_2				
entry	first	second	third	fourth	yield
1	$BF_3{\cdot}O(Et)_2$	H_2O; w30	BA, pyrrole; w15		13%
2	$BF_3{\cdot}O(Et)_2$	H_2O; w30	NaCl; w30	BA, pyrrole; w15	11%
3	$BF_3{\cdot}O(Et)_2$	H_2O; w30	$Bu_3BzlNCl$; w30	BA, pyrrole; w15	17%
4	H_2O	NaCl; w30	$BF_3{\cdot}O(Et)_2$	BA, pyrrole; w15	28%
5	H_2O	$Bu_3BzlNCl$; w30	$BF_3{\cdot}O(Et)_2$	BA, pyrrole; w15	33%
6	$BF_3{\cdot}O(Et)_2$	H_2O	BA, pyrrole; w15		14%
7	$BF_3{\cdot}O(Et)_2$	H_2O; w60	BA, pyrrole; w15		9%
8	$BF_3{\cdot}O(Et)_2$	H_2O; w360	BA, pyrrole; w15		11%
9	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$	H_2O	BA, pyrrole; w15	33%
10	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$	H_2O; w60	BA, pyrrole; w15	21%
11	$BF_3{\cdot}O(Et)_2$	$Bu_3BzlNCl$	H_2O; w360	BA, pyrrole; w15	16%

[a]The amounts of the various components are as follows: 10^{-2} M $BF_3{\cdot}O(Et)_2$, 18 μL H_2O, 0.1 equiv NaCl, 0.0031 equiv $Bu_3BzlNCl$, and 0.1 M benzaldehyde (BA) and pyrrole. A wait period with stirring is signified by "w" and the duration in minutes.

We examined these heterogeneous media by ^{11}B NMR spectroscopy.[16] The inclusion of a sample of $B(OCH_3)_3$ in an internal tube in the sample tube enabled quantitative spectroscopy. A crude sample from the standard reaction (without salt) after 30 min afforded a peak at -1.4 ppm in the ^{11}B NMR spectrum, while the spectrum obtained after 5 min with salt (0.0031 equiv $Bu_3BzlNCl$) showed several peaks in the range -1.0 to -1.5 ppm. In each case the $BF_3{\cdot}O(Et)_2$ peak at 0 ppm had completely disappeared. The ^{11}B NMR spectrum of the white milky medium formed by adding water to $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 (with or without salt) gave two new overlapping signals (~-1.4 ppm, ~-1.7 ppm; 1:2 ratio) and no peak at 0 ppm due to $BF_3{\cdot}O(Et)_2$. Note that adding $BF_3{\cdot}O(Et)_2$ or $BF_3{\cdot}2H_2O$ (50 mM each) to H_2O gives peaks at -1.6 ppm and at 0.2 to -0.3 ppm in ~1:1 ratio (neat $BF_3{\cdot}2H_2O$ exhibits a singlet at -1.8 ppm). In one instance, the $B(OMe)_3$ standard (18.3 ppm) was omitted, and no peaks were observed in the range 18-20 ppm corresponding to $B(OH)_3$. In all cases, the total integrated areas of the boron peaks remained constant upon addition of water or upon reaction. These results indicate the presence of new boron entities in the heterogeneous media. Additional studies are underway to characterize the distribution and identity of the catalytic species in these media.

We performed a variety of NMR experiments to examine the interaction of salts with $BF_3{\cdot}O(Et)_2$. Pertinent precedents for the formation of new catalytic species include BF_3-ethanol cocatalysis in the reaction of mesitaldehyde and pyrrole[5] or in the exchange of pyrrolic protons,[17] and BF_3-ROH cocatalysis in polymerization reactions.[18-22] In addition, halogen addition and exchange occurs upon treatment of 1 M BF_3 (alone, not the etherate) in CH_2Cl_2 with equimolar $Et_4N^+Cl^-$, affording BF_4^-, BF_3Cl^-, and $BF_2Cl_2^-$.[23] These species are readily distinguished by ^{11}B NMR spectroscopy, with BF_4^- and BF_3Cl^- having chemical shifts in CH_2Cl_2 at -1.6 ppm and +1.7 ppm relative to $BF_3{\cdot}O(Et)_2$, respectively.[16,23] Our findings include the following: (1) A solution of 10^{-1} M $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 gave a singlet, as expected. However, no change in the chemical shift of boron was observed upon treatment with up to 10 equiv $Bu_3BzlNCl$, or treatment of a $BF_3{\cdot}O(Et)_2$ stock solution (concentrated) with NaCl. (2) A solution of 10^{-2} M $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 exhibited a singlet at -151.3 ppm in the ^{19}F NMR spectrum, as expected.[24] Upon treatment with 0.0031 equiv $Bu_3BzlNCl$, no change was observed in the spectrum. With 1.8 M $Bu_3BzlNCl$, the main peak remained (-151.4 ppm) and was accompanied by weak peaks at -150.3 and -152.1 ppm. The origin of these weaker peaks is not known, as BF_3Cl^- is expected at -124.6 ppm,[24] and no such peak was observed. Thus no significant new species could be detected, either by ^{11}B or ^{19}F NMR spectroscopy, due to interaction of $BF_3{\cdot}O(Et)_2$ with chloride-containing salts. (3) Upon treatment of $BF_3{\cdot}O(Et)_2$ with $Bu_4NF{\cdot}H_2O$ (10^{-2} M each) in CH_2Cl_2, a sharp singlet at -1.39 ppm was observed, consistent with BF_4^-.[16,23] Nonetheless, the absence of new boron species formed upon interaction with chloride, an anion present in over half of the salts affording increased yields, indicates that enhanced catalytic activity with salts does not necessitate direct interaction of anions with $BF_3{\cdot}O(Et)_2$ (unless transient catalytic species form that are not detected by these NMR experiments).

A commercially-available sample of $BF_3{\cdot}2H_2O$, whose structure is believed to be best represented as $H_3O^+BF_3{\cdot}OH^-$,[25] was examined for catalytic activity in the pyrrole-aldehyde condensation. $BF_3{\cdot}2H_2O$, a possible product upon exposure of $BF_3{\cdot}O(Et)_2$ to water, is believed to be catalytically inactive in some electrophilic processes.[20] $BF_3{\cdot}2H_2O$, a liquid, is immiscible with CH_2Cl_2. With stirring, $BF_3{\cdot}2H_2O$ is dispersed throughout the reaction medium. Upon addition of pyrrole and benzaldehyde, the reaction medium gradually turns cloudy. The yields obtained after 15 min are shown in Figure 6. $BF_3{\cdot}2H_2O$ was less active than $BF_3{\cdot}O(Et)_2$ at 10 mM each, but the yields were greater in the presence of soluble or insoluble salts. With a slightly larger amount of $BF_3{\cdot}2H_2O$ (3.1×10^{-2} M), the yield of TPP is comparable with 0.0031 equiv $Bu_3BzlNCl$ (48%) to that using 10^{-2} M $BF_3{\cdot}O(Et)_2$ (52%).

These results show that $BF_3{\cdot}2H_2O$ is either a catalyst itself or is a source of a catalyst for the pyrrole-aldehyde condensation. However, $BF_3{\cdot}2H_2O$ and $BF_3{\cdot}O(Et)_2$ have some clear differences. The former is immiscible in CH_2Cl_2 (forming two liquid layers) and yields an emulsion upon addition of 0.1 M H_2O, but doesn't yield precipitates even upon standing overnight. In contrast, $BF_3{\cdot}O(Et)_2$ is miscible with CH_2Cl_2, immediately yields precipitates upon addition of 0.1 M H_2O, and then slowly affords two liquid layers. It is noteworthy that in neat H_2O, $BF_3{\cdot}O(Et)_2$ and $BF_3{\cdot}2H_2O$ exhibited identical ^{11}B NMR spectra.

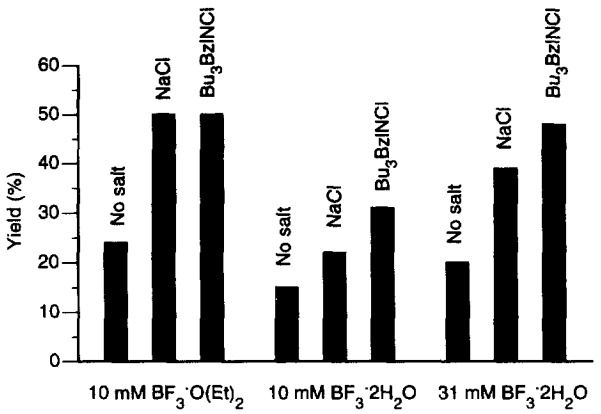


Figure 6. Comparison of $BF_3 \cdot 2H_2O$ and $BF_3 \cdot O(Et)_2$ in the standard reaction (NaCl, 0.1 equiv; $Bu_3BzlNCl$, 0.0031 equiv).

Finally, it has been observed that a catalytic amount of $LiClO_4$ can improve the yield in the DDQ oxidation of allyl ethers.[26] To ensure that the salt effects originated in the condensation process rather than the oxidation, aliquots from a benzaldehyde-pyrrole condensation were removed and added to a solution of DDQ in toluene in the presence or absence of NaCl. Similar yields of TPP were obtained in each case.

Investigation of salt effects in other media

A common organic solvent-salt combination involves $LiClO_4$ in diethyl ether. This homogeneous salt solution affords enhanced yields in Diels-Alder reactions.[27] We performed pyrrole-benzaldehyde condensations in diethyl ether solutions containing various amounts of $LiClO_4$ and $BF_3 \cdot O(Et)_2$, TFA, or p-$TsOH \cdot H_2O$. The major results are shown in Tables 6 and 7. The highest yield (15%) occurred with 2.5 M $LiClO_4$ and 3.2 mM TFA. Except with the highest concentrations of $LiClO_4$, the reactions were homogeneous.

Table 6. Effect of various amounts of $LiClO_4$ and several acids in diethyl ether on TPP yield.[a]

$[LiClO_4]$ (M)	$BF_3 \cdot O(Et)_2$[b]	TFA[c]	p-$TsOH \cdot H_2O$[d]
0	NE	0%	1.1%
0.01	0.8%	0%	1.2%
0.032	2.0%	0.5%	3.1%
0.1	2.9%	1.7%	0.7%
0.32	4.2%	3.6%	0%
1.25	8.5%	8.8%	0%
2.5	9.5%	15.3%[e]	0%
3.75[f]	9.5%	10.2%	NE[g]
5.0[f]	8.6%	6.7%	NE

[a]Reactions were performed at room temperature with 0.1 M benzaldehyde and pyrrole. Yields were obtained after 15 min. [b]10^{-3} M. [c]3.2 x 10^{-3} M. [d]0.1 M p-$TsOH \cdot H_2O$. All reactions were heterogeneous. [e]In refluxing diethyl ether, the yield was 9.3%. [f]$LiClO_4$ was not completely soluble at these concentrations. [g]Not examined.

Table 7. Effect of acid concentration and several salts in diethyl ether on TPP yield.[a]

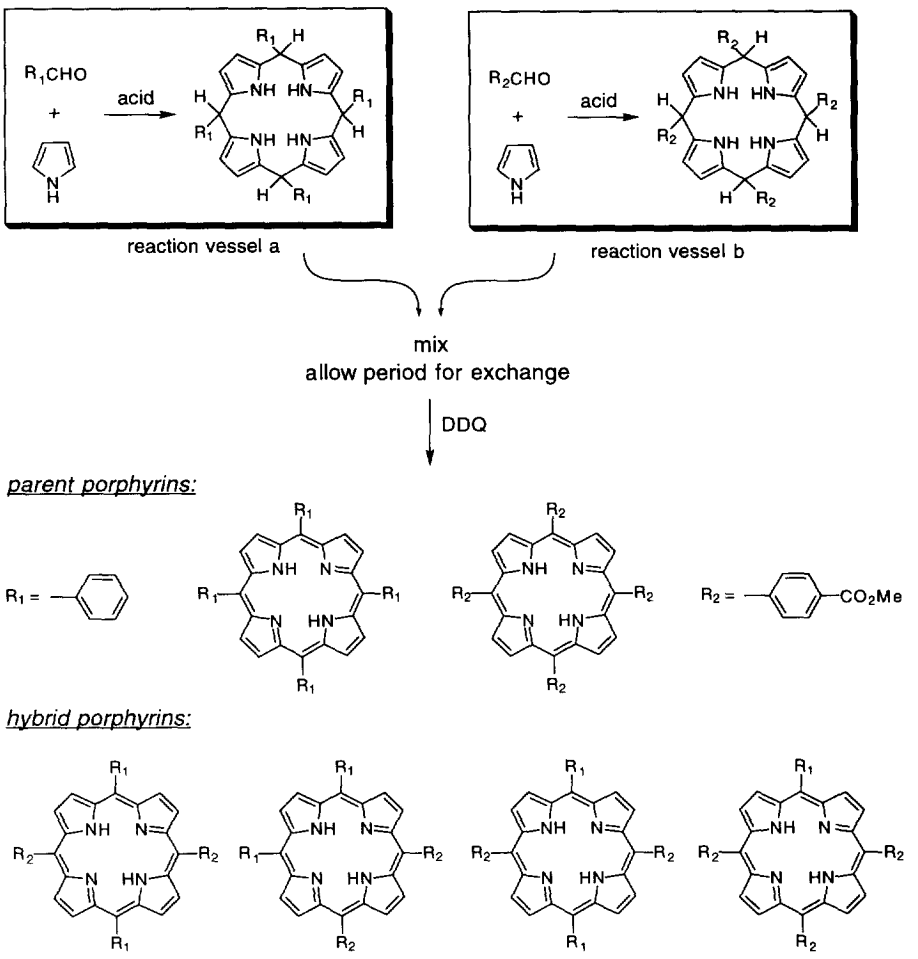
Salt: [Acid] (M)	$LiClO_4$[b] $BF_3{\cdot}O(Et)_2$	$LiClO_4$[b] TFA	NaCl[c] $BF_3{\cdot}O(Et)_2$	LiCl[c] $BF_3{\cdot}O(Et)_2$
0.001	8.5%	4.7%	0%	NE[d]
0.0032	9.5%	8.8%	0%	NE
0.01	8.7%	7.6%	0%	0%
0.032	0.6%	7.7%	1.2%	0.6%
0.1	0%	4.3%	2.9%	2.5%
0.32	0%	1.1%	4.2%	5.3%

[a]Reactions were performed at room temperature with 0.1 M benzaldehyde and pyrrole. Yields were obtained after 15 min. [b]1.25 M. [c]10 equiv (1 mmol/mL). All reactions were heterogeneous. [d]Not examined.

We also examined reactions in the heterogeneous medium of NaCl or LiCl in diethyl ether (Table 7). The presence of large amounts of salt gave increased yields, but the highest yield obtained was 5.3%. In summary, higher yields are obtained in acidified diethyl ether containing $LiClO_4$, NaCl, or LiCl than without any salt, but the yields are far less than those observed with $BF_3{\cdot}O(Et)_2$ and other salts in CH_2Cl_2.

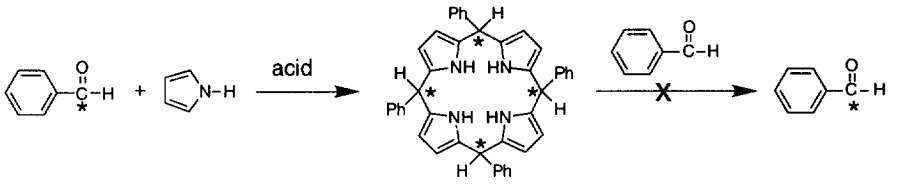
Exchange experiments addressing reversibility in the pyrrole-aldehyde condensation

We previously reported the reversibility of porphyrinogen formation in the 10^{-2} M pyrrole-benzaldehyde condensation catalyzed with 10^{-3} M $BF_3{\cdot}O(Et)_2$.[2,3] To investigate whether porphyrinogen formation is reversible upon reaction at higher concentration in the presence of salt, we performed several exchange experiments (Scheme 2). Condensations of pyrrole-benzaldehyde (reaction vessel a), and of pyrrole-methyl 4-formylbenzoate (reaction vessel b), were performed separately with 10^{-2} M $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 in the presence of 0.1 equiv NaCl. After 10 min, the concentrations of the unreacted benzaldehyde and methyl 4-formylbenzoate were below the limits of detection by TLC analysis. Equal volumes from the two pyrrole-aldehyde condensations were then combined and NaCl was added (0.1 equiv of total [pyrrole] in the mixture). At later times, the reaction mixture was oxidized and analyzed by TLC to assess the distribution of porphyrin products. After 10 min, no increase in total porphyrin yield was observed. However, the distribution consisted of the two parent porphyrins and the four hybrid porphyrins, and the extent of the exchange was ~50% by visual inspection. After 30 min following combination of the two reaction mixtures, the same amount of exchange was detected. When the individual condensations were performed without NaCl, the extent of the exchange was ~20%. However, when the individual reactions were allowed to proceed for 45 min (rather than 10 min) and then mixed, the extent of exchange was only about 10% (with or without NaCl). These results show that porphyrinogen exchange occurs early in the course of reaction but quickly subsides.



Scheme 2. The porphyrinogen exchange experiment.

We sought to determine whether porphyrinogen exchange involves reversion to the starting materials (benzaldehyde and pyrrole) or proceeds via other intermediates. An exchange experiment was performed using ^{13}C NMR spectroscopy to monitor the reaction of ^{13}C-(formyl) labeled benzaldehyde (indicated by the asterisk in Scheme 3). A solution of 10^{-1} M pyrrole and ^{13}C-(formyl) labeled benzaldehyde containing 0.0031 equiv of $Bu_3BzlNCl$ was treated with 10^{-2} M $BF_3{\cdot}O(Et)_2$ in an NMR tube. After 20 min, benzaldehyde had been consumed. A sample of 2 x 10^{-2} M benzaldehyde (unlabeled) was added to the reaction mixture. No reappearance of the formyl carbon signal was observed after 30 min (note that the natural abundance of ^{13}C in unlabeled benzaldehyde was not detected in this experiment). The same experiment was performed in the absence of salt, though the reaction was allowed to proceed for 75 min before adding unlabeled benzaldehyde. Again, no reappearance of the formyl carbon signal was observed after 30 min. These results indicate that benzaldehyde is not reformed as a consequence of porphyrinogen exchange either in the presence or absence of salt.



Scheme 3. Experiment testing the reversible formation of benzaldehyde from the porphyrinogen.

Other experiments probed whether any increase in yield would occur upon addition of salt following the acid catalyst. A sample of 0.1 equiv NaCl was added to a reaction mixture formed after 10 min of condensation of pyrrole and benzaldehyde with 10^{-2} M $BF_3{\cdot}O(Et)_2$. No subsequent change in the yield of porphyrin was observed over 20 min. If 0.1 equiv NaCl and an additional amount of 10^{-2} M $BF_3{\cdot}O(Et)_2$ were added, the porphyrin yield was decreased slightly after 20 min. Thus the increase in yield due to salts is only observed when the salt is present at the outset of the reaction. Taken together, these results indicate that there are significant irreversible reactions accompanying the pyrrole-aldehyde condensation.

DISCUSSION

The presence of one of a wide variety of salts during the pyrrole-aldehyde condensation results in a substantial acceleration in rate and up to 2-fold increase in the yield of porphyrin. Knowledge of the mechanism(s) of the salt effects could aid in the design of further improved reaction conditions. In this discussion, we enumerate the major findings concerning salt effects, summarize new observations concerning the porphyrin reaction, consider mechanisms by which salts can cause yield increases, and outline a number of open issues.

Any model explaining the mechanisms by which salts increase the yield of porphyrin must incorporate the following observations.

(1) Every soluble salt that was examined with $BF_3{\cdot}O(Et)_2$ gave nearly a 2-fold increase in yield, and only a few insoluble salts gave no increase. The soluble salts include diverse anions (Cl^-, F^-, Ph_4B^-, HSO_4^-, or PF_5^-) and R_4N^+ or Ph_4P^+ cations. The successful insoluble salts encompass the anions (Cl^-, Br^-, I^-, or Ph_4B^-) and the cations (Li^+, Na^+, K^+, Cs^+, Ca^{2+}, Mg^{2+}, NH_4^+, Me_4N^+, and paraquat^{2+}), while the insoluble salts giving no improvement encompass a few anions (F^-, SO_4^{2-}, BF_4^-) and cations (guanidine); omitting triethylamine hydrochloride. The only discrepancy between soluble and insoluble salts involved the yield improvement with Bu_4NF and the lack of any response with KF. The result with molecular sieves, an aluminosilicate widely used as a desiccant, constitutes a notable failure. In total, 19 of 28 salts examined gave increases in yield of the porphyrin.

(2) Salt effects are observed with several acids, including $BF_3{\cdot}O(Et)_2$, $BF_3{\cdot}2H_2O$, and TFA in CH_2Cl_2, and $BF_3{\cdot}O(Et)_2$ and TFA in diethyl ether.

(3) A precipitate forms during the course of condensation in CH_2Cl_2 with $BF_3{\cdot}O(Et)_2$, but not with TFA, in the presence or absence of soluble salts. Precipitation occurs more rapidly in the presence of salts than in their absence.

(4) The salts must be present at the outset of the reaction to afford yield increases.

(5) The rate of reaction is significantly faster in the presence of salt, as measured by the disappearance of benzaldehyde or the formation of the porphyrin.

(6) NMR experiments showed a new species formed from $BF_3{\cdot}O(Et)_2$ and high concentrations of F^-, but not with Cl^-.
(7) The soluble salts exhibit maximal effects at low concentrations (0.0031 equiv for 0.1 M reaction, = 0.31 mM) and inhibit the reaction at higher concentrations. Larger amounts of insoluble salts are required (0.1 equiv), and these also inhibit the reaction in higher quantities.
(8) Neither synergistic nor inhibitory effects were observed when various salts were examined together.
(9) The presence of a significant amount of water does not terminate the pyrrole-aldehyde condensation, as shown by performing the reaction in CH_2Cl_2 to which 0.1 M water had been added, or by using $BF_3{\cdot}2H_2O$ as the catalyst. The amount of water present at the end of the pyrrole-aldehyde condensation (~0.11 M) is near the saturation point in CH_2Cl_2.

Observations concerning the porphyrin reaction

Part of the challenge in ascribing a mechanism to the salts originates from insufficient knowledge concerning the two-step one-flask reaction yielding the porphyrin. In our previous studies, we showed that some, but not all, porphyrinogens undergo exchange under the conditions of the pyrrole-aldehyde condensation, and that superimposed on the pyrrole aldehyde condensation are irreversible side reactions (e.g., dipyrrin shunt). The development of the two-step strategy was motivated by the reaction themes in the biosynthesis of porphyrins,[28] where condensation yielding the macrocycle and oxidation of the macrocycle occur separately. Because literature precedent established the thermodynamic stability of uroporphyrinogens (albeit in hot acid),[29] our search for appropriate condensation conditions was motivated by the Jacobson-Stockmayer theory of equilibrium condensation polymerization.[30] This theory shows that the yield of macrocycle formation can be quantitative if reaction is performed at appropriate dilution and bond formation is driven to completion. We felt that finding conditions in the pyrrole-aldehyde condensation where equilibrium could be attained without concurrent oxidation, and finding the appropriate concentration of reactants to favor the cyclic product, would give a high yield of porphyrinogen.

Now it is apparent that the separate condensation and oxidation procedures, and the mild conditions of each, rather than an equilibrium condensation per se, are more important for enabling the synthesis of porphyrins in good yield. Several findings are pertinent:

(1) Porphyrinogen exchange does not involve reformation of a detectable quantity of aldehyde. Thus the initial step(s) of pyrrole-aldehyde condensation are irreversible.
(2) Porphyrinogen exchange occurred to a significant extent (~50%) within minutes following the leveling off of the condensation. However, after pyrrole-aldehyde condensation for 1 h, little exchange could be detected.
(3) The addition of salt to the reaction medium following pyrrole-benzaldehyde condensation does not cause an increase in yield, which would be expected if all reaction processes were completely reversible.
(4) The pyrrole-aldehyde condensation at 0.1 M is extremely rapid, yielding the maximum amount of porphyrin in 2 min.
(5) Porphyrinogen exchange occurs with some aldehydes (including hydroxy benzaldehydes in aqueous micellar media)[31] but not with others,[32,33] yet respectable yields of porphyrin are obtained in all cases.

These data present a picture of irreversible steps early in the pyrrole-aldehyde condensation (presumably involving formation of the pyrrole-carbinol), a set of reversible reactions underlying porphyrinogen exchange, superimposed on which are irreversible processes whose nature is not known (these may include dipyrrin formation,[2-7] β-pyrrole substitution, inactivation of the catalyst, change in reaction medium, polymer formation,[34] etc.). Collectively, these results show that the scrambling observed in the porphyrinogen exchange experiments, or in 2 + 2 dipyrromethane condensations,[10,35] provides a window on only a part of the pyrrole-aldehyde condensation. It is likely that the acid-catalyzed scrambling reactions of porphyrinogens and dipyrromethanes proceed via azafulvene intermediates.

Possible mechanisms of the salt effects and open issues

This survey of salt effects has been aimed primarily at defining scope and limitation rather than mechanism. Numerous mechanisms have been proposed to account for effects of salts in organic reactions.[36] The data presented here are insufficient to distinguish between several well-known mechanisms by which salts exert beneficial effects, including stabilization of polar intermediates, increased internal pressure of the medium, or suppression of side reactions. However, these data can be compared with the extensive literature on salt effects involving water desiccation and templating in other organic reactions.[36]

(1) Salts as desiccants. The facts that the pyrrole-aldehyde condensation liberates water and that salts increase the porphyrin yield point beguilingly to the conclusion that salts function as desiccants. However, the yield data do not correlate with desiccating power ($CaSO_4 > CaCl_2 > MgSO_4 > Na_2SO_4$)[37] where trends are available. Furthermore, the hardest cations tend to be most extensively hydrated. However, the yield data appeared to be indiscriminate with respect to cation rather than correlating with hardness of the cation.[38] Though some desiccation by each of the salts cannot be ruled out, this cannot be the dominant effect as most of the salts that afforded increases in yield are not typical desiccants, and powerful desiccants such as molecular sieves showed no yield increase.

(2) Ions as templating agents. Cations can give increased yields of macroheterocycles via a template effect.[39] However, comparable yields of porphyrin with 13 different cations show that the condensation is not sensitive to the size of the cation. Sessler *et al.* have prepared a family of expanded porphyrins that bind anions,[40] and a linear hexapyrrin binds chloride by hydrogen bonding to three pyrrolic N-H groups.[41] The association of tetrabutylammonium salts with porphyrinogens in solution showed stability constants ranging over 1000-fold in the order of HSO_4^-, $I^- < Br^- < H_2PO_4^- < Cl^- < F^-$.[42] In our survey, the rank ordering of anions across all insoluble and soluble salts is SO_4^{2-}, BF_4^- (25%) < I^-, PF_6^-, HSO_4^- (40%) < Br^-, Cl^-, BPh_4^- (~50%). Comparable yields were generally obtained for each anion in conjunction with a variety of cations, as shown for SO_4^{2-} (Na^+, Mg^{2+}, Ca^{2+}, excepting guanidine), BF_4^- (Na^+, Me_4N^+), Cl^- (13 different cations), and BPh_4^- (Na^+, Bu_4N^+), though only one cation was examined for I^- (K^+), PF_6^- (Bu_4N^+), HSO_4^- (Bu_4N^+) and Br^- (K^+). Fluoride gave anomalous results depending on the nature of the cation, as seen with KF (25%) and Bu_4NF (50%). Thus our rank ordering of anions based on yields somewhat resembles the rank ordering based on stability constants, with the critical exception of fluoride. However, the salts cause at most a doubling of yield, while the stability constants for binding to the porphyrinogen vary from < 10 to 17,000 M^{-1}.[42] Furthermore, the generality of the salt effects appears at odds with the relative selectivity of anion templating.

This study raises a large number of questions. Clearly the nature of the reaction medium changes dramatically during the course of the pyrrole-aldehyde condensation. Whether salts accelerate the phase-separation process which in turn accelerates the reaction, or accelerate the condensation which yields the more rapid phase separation, or shift any equilibria in the overall transformation, is not clear. Additional open issues include the nature of the precipitates (with and without salt), nature of the catalytic species formed upon interaction of $BF_3{\cdot}O(Et)_2$ with water and salt, whether the changes in reaction medium have any correspondence to reactions using clays as catalysts,[32,43] the extent to which porphyrinogens are in equilibrium with oligopyrromethanes, the nature of the processes at longer times that prevent porphyrinogen exchange, whether other media (solvents, catalysts, salts) might afford even higher yields, and the scope of salt effects with a much wider variety of aldehydes. It also remains to be determined if the salt effects in the reactions with $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 share common mechanisms with those in diethyl ether. Though numerous important mechanistic questions remain, the effects of salts are clear: the reactions at 0.1 M are complete in a few minutes and the yield in over half the cases examined is nearly double that without salts. Given the simplicity and utility of adding salts to the reaction, more extensive investigations of the effects of salts on the reactions leading to porphyrin formation are warranted.

EXPERIMENTAL

The aldehydes, pyrrole, acid catalysts, and salts were obtained from Aldrich with the exception of triethylamine hydrochloride (Eastman), guanidine sulfate (Pfaltz and Bauer), and benzaldehyde (formyl-^{13}C, 99%) (Cambridge Isotope Laboratories, Inc.). Pyrrole was distilled from CaH_2, and CH_2Cl_2 (Fisher) was distilled from $LiAlH_4$. The insoluble salts (except for TEA·HCl, Me_4NCl, $NaBF_4$, Me_4NBF_4 and $NaBPh_4$) were ground into a fine powder with a mortar and pestle, dried at 140 °C for at least 2 h, cooled to room temperature in a desiccator, and then stored in a sealed container. The soluble salts were prepared in stock solutions of 0.01 M and 0.1 M in CH_2Cl_2 and used for the 10^{-2} M and 10^{-1} M condensations, respectively, when the reaction called for less than 3 mg of the salt. Reaction sampling was performed with syringes equipped with teflon-tipped plungers (Hamilton Co., Reno, Nevada). Centrifugation of samples was performed at 9000 rpm (MicroD, Fisher). All reported NMR results were obtained at 300 MHz (General Electric GN300 or Varian Gemini 300). Mass spectra of porphyrins were obtained in neat form with *p*-benzoquinone by laser desorption mass spectrometry[44] using a Bruker Proflex II. Absorption spectra were collected routinely with HP 8453.

General procedure for investigation of reaction conditions. The condensations were carried out in 20 mL scintillation vials containing magnetic stir bars. Equimolar amounts of aldehyde and pyrrole were mixed with a specified amount of salt in 10 mL of CH_2Cl_2 at room temperature. The condensation was then initiated by adding $BF_3{\cdot}O(Et)_2$ to the stirred reaction mixture. The progress of the reaction was monitored by taking aliquots periodically from the reaction mixture via syringe and oxidizing with DDQ solution, followed by absorption spectroscopy. In particular, for 10^{-1} M reactions, 5 μL aliquots were removed from the reaction vessel and injected into 300 μL of a 10^{-2} M DDQ solution in toluene. Then 25 μL of this oxidized solution was diluted in 3 mL of CH_2Cl_2/EtOH (3:1) and the visible absorption spectrum was recorded. For 10^{-2} M reactions, 25 μL aliquots were removed from the reaction vessel, injected into 150 μL of 10^{-2} M DDQ solution in toluene, and then 50 μL of this oxidized solution was diluted with 3 mL of CH_2Cl_2/EtOH (3:1) and the visible absorption spectrum was recorded. The yield of porphyrin was determined by the intensity of the Soret band (420 nm, ε = 500,000 $M^{-1}cm^{-1}$) measured from the apex to the base of the red edge of the band. This eliminated the contribution of the polypyrromethene and quinone components which exhibit a broad absorption in the 400-500 nm region. The extinction coefficient of the porphyrin Soret band is not altered by treating a solution of TPP or the crude TPP reaction mixture in CH_2Cl_2 with $Bu_3BzlNCl$.

Assessment of the unreacted benzaldehyde. Stock solutions of 10^{-1} M, 10^{-2} M, 10^{-3} M and 10^{-4} M benzaldehyde in CH_2Cl_2 were prepared as TLC standards. Various volumes (2-10 μL) of the standard benzaldehyde solutions and 2 μL reaction aliquots were spotted on a TLC plate (silica). The amount of the unreacted benzaldehyde in a reaction mixture was assessed by the intensity of the benzaldehyde spot after developing with hexanes/CH_2Cl_2 (2:1). Using ^{13}C NMR spectroscopy, the unreacted benzaldehyde was assessed by monitoring the height of the peak due to the formyl carbon (190 ppm).

^{11}B, ^{13}C, and ^{19}F NMR spectroscopy. The ^{13}C and ^{11}B NMR spectra were obtained on a GN-300 NMR spectrometer. For ^{13}C NMR spectroscopy, CD_2Cl_2 or a mixture of CH_2Cl_2/CD_2Cl_2 (2:1) was used as solvent. 256 scans were collected and spectra were referenced to external TMS. For ^{11}B NMR spectroscopy, the operating frequency was set at the ^{11}B frequency of 96.3688 MHz. 32 to 256 scans were accumulated using 2 μs pulses with 2 s pulse delays and a 50,000 Hz sweep width. The spectrometer was locked on external $CDCl_3$ in a 5 mm tube inserted in a 10 mm NMR tube (Suprasil from Wilmad Glass, < 0.01 ppm boron by weight) containing the sample dissolved in CH_2Cl_2. Spectra were referenced to external $B(OMe)_3$ (δ = 18.3 ppm) or $BF_3{\cdot}O(Et)_2$ (δ = 0.0 ppm) which was dissolved in $CDCl_3$ in the inner 5 mm tube.

^{19}F NMR spectroscopy[23,24] was performed on a Varian Gemini 300 spectrometer using α,α,α-trifluoromethylbenzene (δ = -63.9 ppm) as a standard in CD_2Cl_2.

Titration of water content in CH_2Cl_2. Karl Fischer titration was performed following standard methods.[45] A 25 mL burette equipped with a drying tube was filled with Hydranal® Composite/5 (Fisher).[46] In order to develop a calibrated standard, samples of 20-30 mL of methanol and 5 mL of Hydranal® Buffer (Fisher) were added to the 250 mL titration vessel. The burette tip was placed deeply into the opening of the titration flask. The opening of the flask was protected against atmospheric moisture by parafilm. The methanol in the flask was then titrated till the brown end point was reached and maintained for 20 s. To the flask was then added a known amount of water (usually 50 μL) with a syringe. Care was taken to minimize excessive exposure of the solvent to atmospheric moisture. Titration was continued to the end point. This standard sample established a correlation between the volume of spent Hydranal® Composite/5 and the amount of water added. The same titration was performed using 20-30 mL of methanol and 5 mL of Hydranal® Buffer, but adding 100 mL of CH_2Cl_2 rather than a known amount of water. The standard sample correlation was then used to infer the amount of water present in the 100 mL of CH_2Cl_2.

The solubility limit of water in CH_2Cl_2 (w/w) at 25 °C has been reported to be 0.167%,[11] 0.198%,[12] and 0.184%,[13] corresponding to ~0.13 M. However, in our hands, the addition of 18 μL H_2O to 10 mL CH_2Cl_2 (corresponding to 0.1 M) results, by visual inspection, in a number of beadlets of water adhering to the walls of the reaction flask.

Nephelometry measurements. In order to monitor precipitate formation during the pyrrole-aldehyde condensation, a simple nephelometer was constructed using a Spex Fluoromax spectrometer. Scattered light was measured as a function of time with 1 sec data intervals. The photomultiplier voltage was set at 750 V, giving the counts per second ranging from 1500 (no precipitate) to 6.5 x 10^6 (milky precipitate). The reactions were performed in a 1 cm-pathlength fluorescence cuvette (3 mL). Magnetic stirring at a modest rate (no vortex formation) was performed using a Variomag stirrer (Florida Scientific Services). Excitation and emission monochromators were both set at 800 nm (1 mm slit widths) in order to minimize direct absorption by pyrrole-aldehyde condensation products.

The nephelometry data are interpreted in a straightforward way in the regime of low light scattering (which is equivalent to high transmittance). The intensity of transmitted light at 800 nm diminishes steadily with reaction. The diminished transmittance stems from absorption by dipyrrin chromophores (due to the tail of the band that peaks around 480 nm) as well as light-scattering due to the precipitate. After 90 sec, the transmittance (T) of the mixture in the presence of $Bu_3BzlNCl$ at 800 nm was 56%. Filtration of this mixture afforded an orange filtrate with T = 89% at 800 nm. Thus, most of the diminished transmittance is due to the precipitate, not absorption by the pyrrole-aldehyde byproducts. After 90 sec in the absence of $Bu_3BzlNCl$, the mixture gave T = 89% and the filtrate gave T = 98% (800 nm). The data collected in ≤ 90 sec clearly show differences in the composition of the reaction media in the presence and absence of salt. [The decline in light-scattering observed with salt from 60-90 sec in Figure 5 is likely due to obscured illumination of the sample in the cuvette (diminished transmittance) that accompanies increased precipitate formation.] As the reaction proceeded, the transmittance of the reaction mixtures declined substantially. For example, after 10 min, the mixture in the presence of $Bu_3BzlNCl$ exhibited T = 2.5% at 800 nm. Nephelometry data at these longer times are difficult to interpret under the conditions of these experiments and have not been reported.

Exchange experiment. The reactions of pyrrole with benzaldehyde (0.1 M each), and pyrrole with methyl 4-formylbenzoate (0.1 M each), were performed at the 20 mL scale in separate reaction vessels in the presence of 0.1 equiv NaCl (11.7 mg) and 10^{-2} M $BF_3{\cdot}O(Et)_2$. After 10 min, TLC analysis indicated that benzaldehyde and methyl 4-formylbenzoate were undetectable. Then 10 mL samples were drawn via syringe from each reaction and combined in a reaction vessel containing 11.7 mg NaCl. The extent of porphyrinogen

exchange was monitored by periodic removal of a reaction aliquot and oxidation with DDQ, followed by TLC analysis (silica, CH_2Cl_2/ethyl acetate 50:1). After 10 min, TLC analysis of the oxidized reaction sample showed four new porphyrin products bracketed by the fast moving tetraphenylporphyrin and the slow moving *meso*-tetrakis[4-(methoxycarbonyl)phenyl] porphyrin.[3] By visual inspection of the TLC profile, the extent of porphyrinogen exchange was estimated to be ~50%.

Preparative-scale synthesis of *meso*-tetraphenylporphyrin.[3] Samples of benzaldehyde (1.06 g, 10 mmol), pyrrole (671 mg, 10 mmol) and Ph_4PCl (11.6 mg, 0.031 mmol) were added to 100 mL of CH_2Cl_2 in a 250 mL round bottom flask. Then 1 mL of a stock solution of $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 (1 M, 1.0 mmol, 10^{-2} M) was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by taking aliquots periodically from the reaction mixture via syringe and oxidizing with DDQ solution (10^{-2} M in toluene) followed by absorption spectroscopy. The porphyrin yield reached 48% after 10 min and remained unchanged at 15 min. DDQ (1.71 g, 7.5 mmol) was then added, the dark brown mixture was stirred for 60 min, and then neutralized with 1 mL triethylamine. The mixture was concentrated, dissolved in CH_2Cl_2, and passed over a short silica column (3.5 x 10 cm, CH_2Cl_2) to remove the dark baseline materials. The majority of the porphyrin collected was pure by TLC (silica, CH_2Cl_2/hexanes 1:1). The impure fractions were combined and rechromatographed (silica, CH_2Cl_2/hexanes 1:1). The impure material from the second column was then washed with hexanes until pure by TLC (silica, CH_2Cl_2/hexanes 1:1). The total yield was 720 mg (47% yield, >98% purity).

Preparative-scale synthesis of *meso*-tetrakis(4-methylphenyl)porphyrin employing aerobic oxidation.[47] Pyrrole (671 mg, 10 mmol), *p*-tolualdehyde (1.2 g, 10 mmol) and $Bu_3BzlNCl$ (9.7 mg, 0.031 mmol) were added to 100 mL of CH_2Cl_2 in a 250 mL round bottom flask. Then 1 mL of a stock solution of $BF_3{\cdot}O(Et)_2$ in CH_2Cl_2 (1 M, 1.0 mmol, 10^{-2} M) was added and the mixture was stirred at room temperature. The reaction was monitored by taking aliquots periodically from the reaction mixture and oxidizing with DDQ solution (10^{-2} M in toluene) followed by absorption spectroscopy. The porphyrin yield reached 46% after 5 min and remained unchanged after 10 min. Samples of 17 mg DDQ (0.075 mmol, 1 mol %) and 86.5 mg iron(II) phthalocyanine μ-oxo dimer (0.075 mmol, 1 mol %)[7] were added and a steady stream of O_2 was gently bubbled through the reaction mixture for 2 h. At the end of the 2 h period, 1 L of CH_2Cl_2 was added to the dark mixture to re-dissolve the precipitated porphyrin. The dark mixture was filtered (Fisher filter paper, 09-801B) to remove the insoluble phthalocyanine material. The filtrate was concentrated to *ca.* 200 mL and subjected to a second filtration (Fisher filter paper, 09-801B) to remove the precipitated porphyrin. The porphyrin obtained in this manner was then washed with two portions of CH_2Cl_2 (300 mL) and collected. The CH_2Cl_2 wash was combined with the filtrate from the second filtration. The combined material was purified by passing through a short silica gel column with elution via CH_2Cl_2/hexanes 1:1. The total yield was 660 mg (39% yield, >98% purity). ^1H NMR ($CDCl_3$) δ -2.78 (s, 2 H, NH), 2.70 (s, 12 H, *o*-$ArCH_3$), 7.55 (AA'BB', 8 H, ArH), 8.09 (AA'BB', 8 H, ArH), 8.85 (m, 16 H, β-pyrrole); $C_{48}H_{38}N_4$ calcd mass 670.3, obsd 669.2; λ_{abs} (toluene) 421, 516, 551, 592, 650 nm.

ACKNOWLEDGMENT

This work was supported by the NIH (GM-36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the Facility was obtained from the North Carolina Biotechnology Center and the NSF.

REFERENCES

(1) Presented in part at the 212th National meeting of the American Chemical Society, Orlando, Florida, August 1996.
(2) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969-4970.
(3) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827-836.
(4) Wagner, R. W.; Lawrence, D. S.; Lindsey, J. S. *Tetrahedron Lett.* **1987**, *28*, 3069-3070.
(5) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828-836.
(6) Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y. Y. *J. Org. Chem.* **1994**, *59*, 579-587.
(7) Ravikanth, M.; Achim, C.; Munck, E.; Lindsey, J. S. *J. Porph. Phthalocy.*, **1997**, in press.
(8) Chorghade, M. S.; Dolphin, D.; Dupre, D.; Hill, D. R.; Lee, E. C.; Wijesekera, T. P. *Synthesis* **1996**, 1320-1324. Wijesekera, T.; Dupre, D.; Cader, M. S. R.; Dolphin, D. *Bull. Soc. Chim. Fr.* **1996**, *133*, 765-775.
(9) Lindsey, J. S.; Woodford, J. N. *Inorg. Chem.* **1995**, *34*, 1063-1069. O'Shea, D. F.; Miller, M. A.; Matsueda, H.; Lindsey, J. S. *Inorg. Chem.* **1996**, *35*, 7325-7338.
(10) Lee, C. H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427-11440.
(11) Staverman, A. J. *Rec. Trav. Chim. Pays-Bas* **1941**, *60*, 836-841.
(12) McGovern, E. W. *Ind. Eng. Chem.* **1943**, *35*, 1230-1239.
(13) Horvath, A. L. *Halogenated Hydrocarbons*, Marcel Dekker, Inc., New York, 1982, p. 543.
(14) Fieser, L. F. and Fieser, M. *Reagents for Organic Synthesis,* John Wiley and Sons, Inc., New York, 1967.
(15) Weast, R. C. *Handbook of Chemistry and Physics*, 52nd Ed., The Chemical Rubber Co., Cleveland, OH, 1971.
(16) Nöth, H. and Wrackmeyer, B. in *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds,* P. Diehl, E. Fluck and R. Kosfeld, Eds.; Springer-Verlag, Berlin, 1978, pp. 387-389.
(17) Gross, Z.; Kaustov, L. *Tetrahedron Lett.* **1995**, *36*, 3735-3736.
(18) Farthing, A. C.; Reynolds, R. J. W. *J. Polymer Sci.* **1954**, *12*, 503-507.
(19) Rose, J. B. *J. Chem. Soc.* **1956**, 546-555.
(20) Eastham, A. M. *J. Am. Chem. Soc.* **1956**, *78*, 6040-6042.
(21) Miki, T.; Higashimura, T.; Okamura, S. *Bull. Chem. Soc. Jpn* **1966**, *39*, 2480-2485.
(22) Collins, G. L.; Greene. R. K.; Berardinelli, F. M.; Ray, W. H. *J. Polymer Sci.: Polymer Chem. Ed.* **1981**, *19*, 1597-1607.
(23) Hartman, J. S.; Schrobilgen, G. J. *Inorg. Chem.* **1972**, *11*, 940-951.
(24) Wray, V. in *Annual Reports on NMR Spectroscopy*, G. Webb, Ed., Vol. 14, Academic Press Inc., London, 1983, pp. 1-406.
(25) Wamser, C. A. *J. Am. Chem. Soc.* **1951**, *73*, 409-416.
(26) Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **1987**, 1811-1814.
(27) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595-4596. Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663-2666. Faita, G.; Righetti, P. *Tetrahedron* **1995**, *51*, 9091-9102.
(28) Porra, R. J. *Photochem. Photobiol.* **1997**, *65*, 492-516.
(29) Mauzerall, D. *J. Am. Chem. Soc.* **1960**, *82*, 2601-2605. Mauzerall, D. *J. Am. Chem. Soc.* **1960**, *82*, 2605-2609. Mauzerall, D. in *The Porphyrins*, D. Dolphin, Ed., Academic Press, New York, Vol. IIB, 1978, pp. 91-101.
(30) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600-1606.
(31) Bonar-Law, R. P. *J. Org. Chem.* **1996**, *61*, 3623-3634.
(32) Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Tetrahedron Lett.* **1993**, *34*, 2625-2628.

(33) Takeda, J.; Sato, M. *Chem. Lett.* **1994**, 2233-2236.
(34) DiMagno, S. G.; Williams, R. A.; Therien, M. J. *J. Org. Chem.* **1994**, *59*, 6943-6948.
(35) Lee, C. H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothner-By, A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645-11672.
(36) Loupy, A.; Tchoubar, B. *Salt Effects in Organic and Organometallic Chemistry*, VCH Verlagsgesellschaft mbH, Weinheim, Federal Republic of Germany, 1992.
(37) Perrin, D. D. and Armarego, W. L. F. Eds. *Purification of Laboratory Chemicals,* 3rd Ed, Pergamon Press, 1988, p. 49. Gordon, A. and Ford, R., Eds. *The Chemist's Companion,* John Wiley & Sons, New York, 1972, p. 446.
(38) Parr, R.; Pearson, R. *J. Am. Chem. Soc.* **1983**, *105*, 7512-7516. Pearson, R. *Inorg. Chem.* **1988**, *27*, 734-740.
(39) Thompson, M. C.; Busch, D. H. *J. Am. Chem. Soc.* **1964**, *86*, 213-217. 127. Thompson, M. C.; Busch, D. H. *J. Am. Chem. Soc.* **1964**, *86*, 3651-3656.
(40) Sessler, J. L.; Cyr, M.; Furuta, H.; Kral, V.; Mody, T.; Morishima, T.; Shionoya, M.; Weghorn, S. *Pure Appl. Chem.* **1993**, *65*, 393-398.
(41) Sessler, J. L.; Weghorn, S. J.; Lynch, V.; Fransson, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1289-1290.
(42) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140-5141.
(43) Cady, S. S.; Pinnavaia, T. J. *Inorg. Chem.* **1978**, *17*, 1501-1507. Jackson, A. H.; Pandey, R. K.; Rao, K. R. N.; Roberts, E. *Tetrahedron Lett.* **1985**, *26*, 793-796. Petit, A.; Loupy, A.; Maillard. P.; Momenteau, M. *Syn. Commun.* **1992**, *22*, 1137-1142. Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Chem. Lett.* **1993**, 117-120. Laszlo, P.; Luchetti, J. *Chem. Lett.* **1993**, 449-452. Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245-7257. Xie, H.; Lee, D. A.; Senge, M. O.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1994**, 791-792. Pichon, C.; Scott, I. A. *Tetrahedron Lett.* **1994**, *35*, 4497-4500. Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 493-494. Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 495-496. Shinoda, T.; Izumi, Y.; Onaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1801-1802.
(44) Srinivasan, N.; Sanford, J. H. Jr.; Haney, C. A.; Lindsey, J. S. *45th Proceedings of the ASMS*, **1997**, in press.
(45) Mitchell, S. and Smith, D. M. *Aquametry*, Interscience, New York, 1980.
(46) Scholz, E. *Hydranal® Manual*, Riedel-de Haën, Seelze, Germany, 1995.
(47) Meot-Ner, M.; Adler, A. D. *J. Am. Chem. Soc.* **1975**, *97*, 5107-5111.

(*Received in USA* 13 *May* 1997; *accepted* 1 *July* 1997)