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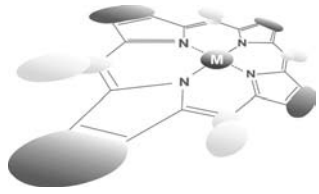

Solvent-free synthesis of *meso*-tetraarylporphyrins in air: product diversity and yield optimization

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Dedicated to Professor David Mauzerall on the occasion of his 80th birthday

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ABSTRACT: The scope and optimization of a solvent-free method for the rapid preparation and facile purification of technologically important *meso*-substituted aryl porphyrins, such as 5,10,15,20-tetraphenylporphyrin is presented. This one-step method involves heating the aromatic aldehyde to ~200 °C in a vial fitted with a septum-lined cap, followed by addition of the pyrrole and maintaining the temperature for about 20 minutes. The dioxygen in air serves as the oxidant. Present results show that the addition of benzoic acid as a catalyst improves the yield of 5,10,15,20-tetraphenylporphyrin from 22% to 32% and of *para* halogenated phenylporphyrins from 10% to ~25%. Herein is also presented an examination of the many factors that influence the yield, the ease of purification, and the ability to scale up the reaction. Since the tarry by-products from this method are much less soluble than in most other synthetic strategies, much less solvent is required for purification; simple extraction is often sufficient. This method can be scaled in the lab to >300 mg, and provides an attractive route to many *meso*-substituted porphyrins because of its minimal waste generation in terms of both solvent and chromatography support.

KEYWORDS: solvent-free, synthesis, green chemistry.

INTRODUCTION

Porphyrins are extremely versatile molecules [1–4]. In addition to their biological functions [5], synthetic derivatives are used for a tremendous variety of applications including photodynamic therapy [6], oxidation catalysis [7, 8], molecular photonic devices, dye-based sensors, inks, and others [9]. Tetraarylporphyrins continue to be a primary focus of research efforts because of the ease by which their various derivatives can be synthesized from pyrroles and arylaldehydes. Combined with appropriate functional groups that enable the aforementioned applications, the molecular topology is poised to drive the self-assembly or self-organization of these chromophores into functional supramolecular materials [10–12].

Tetraarylporphyrins are most commonly synthesized by one of three strategies [4, 13–15]: by Adler-Longo synthesis [16, 17] in propionic or acetic acid in air, by multi-step coupling of dipyrroles based on the MacDonald synthesis [18], or by the Lindsey equilibrium synthesis [19]. There are intermediate two-step methods [20, 21] and many variations for all three. The one-step method is amenable to large-scale synthesis while the latter methods allow for the directed, rational synthesis of less symmetrically substituted porphyrins [22, 23]. The addition of mild oxidants, such as nitrobenzene, to the Adler-Longo procedure increases the yield of many tetraarylporphyrins [21], and the azeotropic removal of water in a tosylate/benzene system increases the yield of *meso*-alkyl porphyrins [24]. Clays and zeolites also have been used

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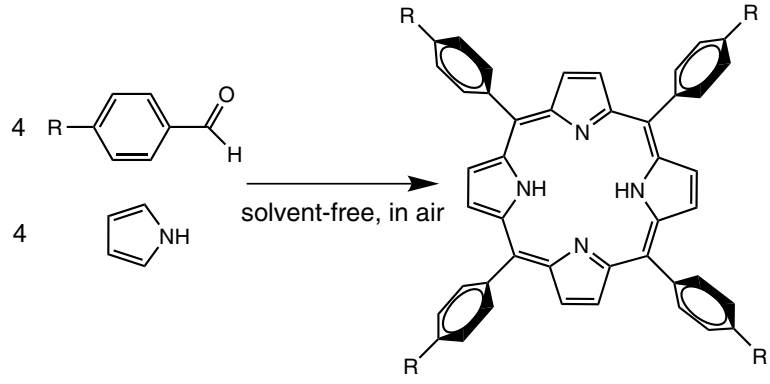
as catalysts for tetraarylporphyrin syntheses [25]. A resurgence in the investigation of new methods to synthesize these versatile compounds began with Lindsey's method whereby the porphyrinogen is formed under anaerobic conditions in an organic solvent with a Lewis acid catalyst, and then oxidized with reagents such as quinones or phthalocyanines [26, 27]. This strategy takes much of its inspiration from the pioneering work of Mauzerall on the biosynthesis of uroporphyrins [28, 29]. The equilibrium method has many advantages such as increased yield and tolerance of many functional groups. Nejad and co-workers reported the use of CF_3SO_2Cl under aerobic conditions and room temperature to make a variety of tetraarylporphyrins in 25–67% yields [30]. Given the widespread use of porphyrins with 1–3 *meso*-pyridyl groups for self-assembled and self-organized multichromophore materials, a direct route to several of the possible isomers and compounds using 1-acyldipyrromethanes and a non-coordinating base catalyst was reported [31].



Scheme 1. A gas-tight septum-capped vial containing two equivalents of benzaldehyde and one equivalent of benzoic acid is heated at 200 °C in air for five minutes at which time one equivalent of pyrrole is injected and the system heated for an additional 20 min. The dioxygen in air is the primary oxidant. Isolated yields of H_2TPP are 32 ± 2%. Abbreviations: R = H, H_2TPP = (5,10,15,20-tetraphenylporphyrin); R = CH_3, H_2TTP = tetrakis(4′-tolyl)porphyrin; H_2TPyP = tetrakis(4′-pyridyl)porphyrin

Green chemical research into solventless (or solvent-free) synthetic methods has been explored over the last decade in an effort to reduce environmental impacts [32]. Our solvent- and catalyst-free method [33] reported in 1997 is akin to the Rothmund [34, 35] and Adler-Longo [16, 17] methods in that the aldehydes and pyrroles are mixed and heated. Subsequently, a similar method was used to prepare corroles using perfluorobenzaldehyde and a 4:3 pyrrole:aldehyde stoichiometry [36]. Using microwave radiation, Momenteau and co-workers synthesized *meso*-tetraphenyl porphyrin in ~9.5% yield by using a silica-gel catalyst [37], and other groups recently explored similar solvent-free reactions for metalation of porphyrins [38–40] and for the preparation of phthalocyanines [39, 41, 42]. It is interesting to note that almost 40 years ago Hodgson reported the synthesis of porphyrin from pyrrole and formaldehyde in a fluid-bed reactor, and from ammonia, graphite and formaldehyde in a plasma reactor [43].

Our solvent- and catalyst-free reaction is complete in minutes, uses temperatures 10–20 °C over the boiling point of the aldehyde used, and uses the dioxygen in air as the oxidant [33]. This method is used to teach principles of green chemistry in an undergraduate laboratory experience [39]. The salient finding of the initial report are summarized: (1) Some of the aryl aldehyde is also oxidized. (2) A significant fraction of the reactions between the pyrrole and aldehyde occur rapidly after the reagents enter the gas phase, as shown by the presence of the porphyrin at the site of condensation on the reaction vial. (3) The elevated temperatures allow for the removal of water from the proximity of the intermediate, as well as for an increase in the rate of oxidation by dioxygen. The oxidative reaction is proposed to be the rate-limiting step in the Adler-Longo method [16]. (4) The reaction is not highly dependent on surface area thus it is not catalyzed by the glass walls of the vessel. (5) This method is general enough to make a cadre of *meso*-substituted porphyrins in yields ranging from 5 to 32%. (6) The soluble portion of the reaction products is mostly the porphyrin.

Herein we report our exploration of the complex interplay between temperature, pressure, concentration, acid catalysts, and oxidants for this solvent-free synthetic strategy (Scheme 1). The present study shows that use of benzoic acid as a catalyst substantially improves yields from 20% to 32% for 4′-alkylphenyl- and many other porphyrins (Fig. 1). Although the physical properties of each aldehyde are different, such as the vapor pressure at 200 °C, there are definite trends and significant considerations that will serve as guides to the utilization of this procedure both in the laboratory and for larger-scale synthesis of aryl porphyrins. Secondly, we show that microwave heating of the pyrrole and aldehyde in solvent-free reactions efficiently produces porphyrins without solid catalysts such as silica gel.

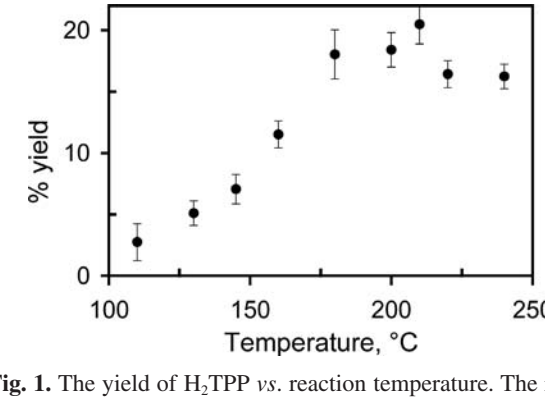


Fig. 1. The yield of H_2TPP *vs*. reaction temperature. The reaction utilized a 3:1 mole ratio of benzaldehyde to pyrrole, and five-minute preheating of the aldehyde. The pressure was kept at approximately 3.6 atm

RESULTS AND DISCUSSION

Temperature, pressure, and aldehyde volatility

Porphyrin formation is believed to be driven by enthalpy changes where entropy favors the macrocycle over the polymer. For volatile aldehydes, much of the present reaction occurs in the gas phase. The thermodynamic values for 5,10,15,20-tetraphenylporphyrin (TPP) formation are estimated in the literature to be: ΔG = -166 kcal.mol^{-1}, ΔH = -212 kcal.mol^{-1}, and ΔS = -153 e.u, while for solution phase reactions ΔG = -171 kcal.mol^{-1}, ΔH = -230 kcal.mol^{-1}, and ΔS = -199 e.u. [44]. If this data is correct, then the favorable value of ΔG is governed by the entropy contribution, and cooler temperatures should favor porphyrin formation. However, under our reaction conditions, the porphyrin yield increased with temperature up to ~175 °C (Fig. 1), thus under these conditions the high-temperature gas phase formation of porphyrins and/or their intermediates appears to represent a kinetically controlled reaction limited by the reaction with dioxygen, as the oxidation studies suggest. The observation that the polymeric by-products are much less soluble, indicating the minimal formation of short pyrromethanes, and the temperature data may also suggest variation in the complex thermodynamics and equilibria between reactants and the intermediates leading to the products. A series of reactions at different temperatures were carried out to test the relationship between temperature and yield. As shown for benzaldehyde (Fig. 1), the yield of H_2TPP increases with temperature, but levels off at ~175 °C. The pressure was maintained at ~3.6 atm, and measured using a pressure gauge attached to the vial.

The rate of porphyrin formation is rapid at these temperatures. About half of the yield is obtained in the first 1.3 minutes, followed by a much slower, ~8 minute time constant. For the benzoic acid catalyzed reactions the time constants are 1.4 and 14 minutes. Thus, most of the porphyrin is formed within the first 20 minutes (Fig. 2). Surprisingly, similar trends for the temperature and the kinetics are observed for the other 4-alkyl benzaldehydes, so the reactivity is not determined solely by the volatility of the starting materials. Of course, the nature of the aldehyde dictates the amount in the vapor phase. However, in virtually every case, some dark red to brown gas is observed in the first few minutes of the reaction. It seems likely that the condensation reactions occur quite rapidly in aerosol dispersions, which then precipitate. This is consistent with the observation of a dark liquid forming on the reaction vessel walls after only about two minutes, and with fractal-like patterns of almost pure porphyrin often found on the sides of the vial after cooling.

The role of reaction pressure was examined. In typical conditions, the reaction pressure is ~3.6 atm. Pressures in a stainless steel reaction vessel with a pressure gauge were increased by addition of N_2 or by an inert solvent such as toluene. Using both methods, pressures

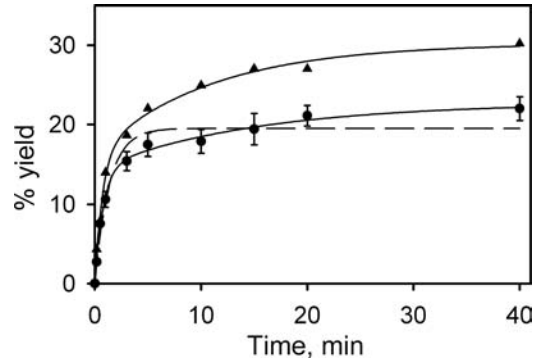


Fig. 2. The yield of H_2TPP *vs.* reaction time. The lower data points ● used 2.5:1 benzaldehyde to pyrrole, and five-minute preheating of the benzaldehyde. The solid line represents a two exponential rise to a constant value (τ_1 = 1.3 ± 0.1 min, τ_2 = 8.3 ± 0.9 min) and the dashed line represents a single exponential rise for comparison. The upper data points ▲ are for reactions used 1:2.5:1 benzoic acid:benzaldehyde:pyrrole. The fit is for a double exponential rise (τ_1 = 1.4 ± 0.2 min, τ_2 = 13.9 ± 1.5 min)

from ~2 atm to ~10 atm at constant temperature were examined. The concomitant decrease in the partial pressure of the reactants, as well as the increased amounts of reactants condensed onto the walls of the reaction vessel both correlate with the observed decrease in porphyrin yield with increasing pressure. Reduced yield of porphyrin was associated with increased yield of polymers and not lower reactivity of the reagents. The yield of H_2TPP decreases at lower pressures as well. Under our standard conditions of ~3.6 atm and 200 °C, the concentration of benzaldehyde and pyrrole in the gas phase is estimated to be ~1.2 mM.

Under these conditions, not all of the aldehyde and perhaps not all of the pyrrole is in the gas phase. Note that the yield is not simply related to the boiling point of the aldehyde, at least for the series of 4-alkylphenyl groups tested (Tables 1 and 2). The yield is essentially the same when R = H, Me, tBu (boiling point at 1 atm = 178, 204, 245 °C, respectively). It is unclear why the yield of the iPr derivative is lower. Other experiments indicate that the reaction does not take place entirely in the vapor phase. Mixing equimolar amounts of tolyl and tBu aldehydes in a 205 °C reaction results in porphyrins with the expected statistical distribution of tolyl and tBu groups determined by NMR and TLC. If aldehyde volatility were the primary consideration, the two populations of porphyrins would be observed: one that contains mostly methyl groups from the gas phase, and one that contains mostly tBu groups from the solution phase.

Aldehyde and carboxylic acid

There is a complex relationship between the total yield and the amount of aldehyde used in the reaction. Some of the aldehyde is converted to the corresponding acid under these conditions. Also, the presence of benzoic acid not only decreases aldehyde oxidation, but increases

Table 1. Other reagents for H_2TPP synthesis[a]

	Reagent	Mole, % relative to pyrrole	Yields, %
Salts	NaCl	20	14
		100	9
	ZnO	800	11
Template	$Zn(Ac)_2$	25	12 (ZnTPP)
Oxidants	$VOCl_3$	20	0
	$C_6H_5NO_2$	150	5.0
	$Na_2S_4O_6$	150	<1
Water		15-fold	12
		55-fold	9.0
Acid Catalyst	X-C_6H_4COOH X = H	100	32
	X = 2-Me	100	26
	X = 3-Cl	100	27
	X = 2,6-Me	100	18
	CCl_3COOH	5	15
	CH_3COOH	8.3	16
		16	19
		100	18
		400	18
	CH_3CH_2COOH	100	17
	CF_3COOH	4.5	6.2
		9.0	2.8
Alcohols	C_6H_5OH	100	11
		10	13
	$C_6H_5CH_2OH$	100	13
		10	16
	2-carboxybenzaldehyde	100	6
	2-carboxybenzaldehyde	200 (no benzaldehyde)	0
	BF_3	4	0
Base	NH_4OH	170	9
		85	11

[a] The yields of H_2TPP using various additives known to enhance the yield in other synthetic methods, see text. A 3:1 ratio of aldehyde to pyrrole is used with a five-minute preheating of the aldehyde. Note that the pK of acetic acid = 4.75, propionic acid = 4.87, benzoic acid = 4.19, 2-toluic acid = 3.91, mesitic acid = 4.49, 3-chlorobenzoic acid = 3.82, and trichloroacetic acid = 0.7. All data represent the average of at least three trials by two different researchers.

the yield of porphyrin. The rate of benzaldehyde oxidation is greatly increased when heated in air at 200 °C for five minutes such that ~1/3 of the aldehyde is converted to its acid as indicated by ^1H NMR. This oxidation process is greatly inhibited by the presence of benzoic acid, as shown by the bi-exponential decrease of aldehyde and concomitant increase in benzoic acid with time constants of ~2 and ~10 min. In all cases, other decomposition products account for <5% of the total.

The amount of time that the aldehyde is preheated prior to pyrrole addition also plays an important role in both porphyrin yields and the ease of purification. Under our standard 3:1 conditions, the yields pass through a maximum at a preheating time ~5 min. Increasing the amount of time the aldehyde is preheated increases the amount of benzoic acid formed, thus there is a trade-off between the oxidation of this reactant *vs.* catalysis by the resulting acid. For costly or synthetically difficult aldehydes, the addition of benzoic acid to the reaction ameliorates degradation of the reactant, but the effectiveness of this modification depends largely on the relative reactivity of the substituted aldehyde to oxidation and

Table 2. Yields of various *meso* aryl porphyrins

R (4′ unless noted)	Yield with no BA catalyst[a]	Yield with 1:2:1 BA:aldehyde:pyrrole[b]	BP aldehyde °C[c]
H	23	32	178
CH_3	20	30	204
$(CH_3)_2CH$	12	24	235
$(CH_3)_3C$	15	33	~245
Mesityl	7	5[d]	237
CH_3O	20	25	~248
CH_3OOC	—	19	—
CH_3S	10	11	~250
Cl	10	25	—
Br	—	26	—
3,4,5 trimethoxy	—	15	—
3,5 dibenzyloxy	—	15	—
Other porphyrins			
Tetrakis (1′-pyrenyl) porphyrin	—	5	—
Tetrakis (4′-pyridyl) porphyrin	10	7[e]	~200
Tetra *n*-heptyl porphyrin	—	2[f]	153

[a]From reference 13. [b]Standard reaction conditions. [c]Estimates for 1 atmosphere. [d]$NH_2OH \bullet HCl$: aldehyde : pyrrole = 1:2:1; [e]propionic acid : aldehyde : pyrrole = 6.8:2:1; [f]0.35 g silica gel added in place of benzoic acid.

porphyrin formation. For arylaldehyde derivatives that oxidize faster than benzaldehyde at these temperatures in air, this synthetic method may be disadvantageous. Pyrrole is relatively stable when heated in air at these temperatures as demonstrated by the ^1H NMR. The porphyrin yield *vs.* the ratio of aldehyde to pyrrole is plotted in Fig. 3, and the optimum ratio is shown to be ~3:1.

The longer the aldehyde is incubated before pyrrole addition, the easier it is to purify the porphyrin, because even though the yield of H_2TPP decreases, the formation of insoluble, polymeric by-products increases at the cost of the smaller, soluble materials. There is no evidence that the benzoic acid is incorporated into any of the porphyrins, nor into the side products. Only H_2TPP is observed by ^1H NMR as the product from experiments using a 4-methylbenzoic acid catalyst with benzaldehyde, and only tetratolylporphyrin (H_2TTP) is observed when benzoic acid is present with 4-methylbenzaldehyde.

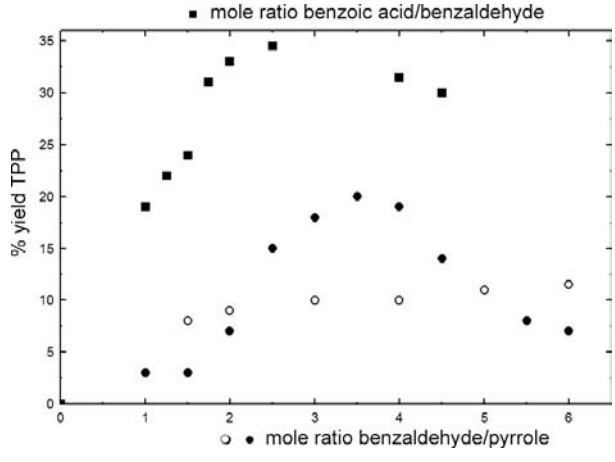


Fig. 3. The complex relation between benzaldehyde and benzoic acid. All reactions are at 200 °C ~3.6 atm. The ○ shows the yield of H_2TPP *vs*. the mole ratio of benzaldehyde and pyrrole with one-minute preheating of the aldehyde so there is minimal benzoic acid formed. The ● shows the results when the aldehyde is preheated five minutes before addition of the pyrrole, so there is ~33% conversion to the corresponding benzoic acid. The ■ shows the effects of adding benzoic acid to the aldehyde, preheating for five minutes, followed by addition of the pyrrole using a 2:1 ratio of benzaldehyde to pyrrole

Effect of acid catalysis

The excess aldehyde increases the yield either from oxidation to benzoic acid which then can serve as a catalyst [14, 16], or compensation for the loss of this reagent due to oxidation. The benzoic acid formed when there is a three-fold excess of the aldehyde still does not bring the yield up to the level of the reaction observed with added benzoic acid. These results suggest that the role of benzoic acid is to retard the aldehyde oxidation, which uses up the oxygen in the closed vial and lowers the porphyrin yield. Unlike the conditions used to obtain ~32% yields (Fig. 3), addition of the aldehyde to the preheated mixture of benzoic acid and pyrrole has only a small effect on the yield, increasing it from ~18% to ~20%. Again, since

most of the benzoic acid remains on the vessel walls even at 200 °C, it is likely that benzoic acid affects the intermediate steps in porphyrin formation rather than the initial, gas phase reactions.

As mentioned above, the presence of the added benzoic acid inhibits the destruction of the aldehyde, but it may also inhibit the destruction of porphyrin intermediates by the radicals involved in the oxidation pathway. Small quantities of other possible aromatic aldehyde decomposition products such as perbenzoic acid, phenol, and benzyl alcohol are found to inhibit porphyrin formation (Table 1). The possibility that some hemiacetal is formed between the aldehyde and the acid is supported by the fact that the presence of 2,6-dimethylbenzoic acid has virtually no effect on the yield (Table 1). As can be seen in Table 1, there is a balance between pKa, the nature of the acid, and the yield. Aromatic acids are effective reagents, whereas alkyl acids are not. The reasons for this are unclear, but may have to do with the stability of the proposed hemiacetal at these temperatures. It is interesting to note that the initial rates for the reactions with and without the benzoic acid catalyst are essentially the same (Fig. 2). Catalytic amounts of ammonium hydroxide, HCl, and BF_3 decrease yields to trace amounts (see Supporting information).

Oxidation

Figure 2 indicates that porphyrin formation occurs very rapidly. Oxidation of the intermediate polypyrromethanes and/or the porphyrinogen is the rate limiting step in the propionic acid synthesis. Oxidation must be occurring rapidly and efficiently under these conditions, since we detect no porphyrinogen and no chlorins even after reaction times of a few seconds. Anaerobic reaction conditions with no benzoic acid result in trace amounts of porphyrin, and some dipyrromethane indicating the crucial role of dioxygen in formation of the porphyrin products. Excess oxygen and some non-volatile oxidants results in little or no detectable porphyrin in the black tarry products (Table 1). At these elevated temperatures, these oxidants probably react with the pyrrole, the aldehyde, and even the porphyrin.

Water

The substantial amount of water needed to reduce the yield of H_2TPP under these reaction conditions is an indication that the rapid removal of water away from the condensing porphyrin (intermediates) is one key to the success of these reactions. When one equivalent of pyrrole is added to 15:3 water:benzaldehyde mixture that has been preheated for five minutes at 200 °C, the yield decreases by about a third, from 18% to 12%. Similarly, if a 55-fold excess of water is added the yield drops to about half (9%). Thus, water is a relatively weak inhibitor. We observed that presence of two equivalents of water significantly quenches porphyrin formation under both Lindsey and Adler conditions [14]. These observations imply that the key water-producing steps, both dehydration and oxidation, occur rapidly and irreversibly because water is removed from the vicinity of the reaction. Some of the reduced yield in the presence of water can be recovered by prolonging the reaction times. Increasing the reaction time from 20 to 40 minutes increases the porphyrin yield from 12% to 16% in the presence of a 15-fold excess of water, using standard reaction conditions. Much longer reaction times, >60 minutes, actually decrease the porphyrin yield.

Other observations

There are several reports that the yield of tetraarylporphyrins can be substantially increased by the addition of various salts and other reagents [4, 7, 14], but these reagents are ineffective under the present conditions. $ZnCl_2$ may increase the pyridyporphyrin yield by templating and/or altering the reactivity of the aldehydes. When the products at various places in the vial are carefully removed and analyzed, it is observed that the porphyrin is found both at the top and the bottom of the vial. In fact, very thin 1–4 mm branched leaflets of nearly pure porphyrin are found on the sides of the glass reaction vessel that are just above the sand bath. Small purple islands of porphyrin in the mist of dark brownish polymer are also observed. These arise from a nucleation process during the reaction and subsequent cooling [45]. The surface of the glass vial does not directly participate in the reaction since control experiments, whereby glass wool is inserted into the reaction vial to increase surface area or the vial has been silanated to reduce surface energy, show similar yields and rates.

Porphyrin formation

The mechanism of porphyrin formation has been well reviewed [4, 14, 16], and we have no evidence that the fundamental condensation reactions or oxidation steps are different under the conditions of this synthesis. The location of the reaction is likely aldehyde-dependent. In this procedure, there are several pathways to TPP formation that are not mutually exclusive: (a) the porphyrin forms in the gas phase and then condenses on the reaction vessel sides; (b) the porphyrin forms in a film coated onto the reaction vial surface; (c) the initial condensation step(s) occur in the gas phase and the final steps on the surface.

The extent of porphyrin formation in the vapor and condensed phases depends on the aldehyde used. Several observations imply that at least the initial reactions take place in the gas phase for TPP formation and when other volatile aldehydes are used. The atmosphere in the vial containing only benzaldehyde remains clear after it is heated for five minutes at 210 °C, but a brown-purple gas forms immediately upon addition of the pyrrole and this begins to liquefy within the next two minutes. Reactions at temperatures much lower than the boiling point of the aldehyde result in significant reduction in porphyrin

formation. Experiments where pyrrole and benzaldehyde are mixed as gases at 210 °C by diffusion from opposite sides of a reaction tube show similar results as when the liquid pyrrole is injected to a preheated vapor of the aldehyde. Quenching the reaction ~10 s after addition of the pyrrole indicates that the dark vapor consists of reactants, dipyrromethanes, and H_2TPP. Assuming ideal solutions, the concentration of the reactants approach 3 M in this solventless film. Small amounts of H_2TPP are known to form at room temperature and pressure [43, 44]. When the reactants are mixed at room temperature and flash-heated to 210 °C, a great increase in insoluble polymer formation is observed.

A third pathway, where the initial reactions take place in the gas phase and the intermediates condense on the walls of the reaction vessel where the porphyrin is formed, is also consistent with our experiments. Several considerations, however, lead us to conclude that the intermediates condensed on the glass are closed macrocycles. Since porphyrinogens rapidly oxidize, it is unlikely that large amounts of this species are formed in any phase of the reaction. At these temperatures, the dipyrromethanes condense so that "2+2" and "3+1" MacDonald-type coupling may occur in both condensed and vapor phases with subsequent oxidation to form the porphyrin. The observation that the yields continue to increase with increasing temperature up to ~175 °C for H_2TPP is consistent with the idea of keeping more of the small pyrrolic multimer intermediates in the gas phase. The fast time constants shown in Fig. 2 may suggest that most of the porphyrin is formed in the initial minutes in the gas phase, and the slower time scale is a result of reactions on the surface and in the condensed phase where the benzoic acid exerts its greatest effects. Note that the initial time-constants are essentially the same for both sets of reaction conditions. Increased reaction temperatures may increase the yield of the higher boiling aldehydes.

EXPERIMENTAL

Materials and instrumentation

Pyrrole and the aldehydes were passed through short pipette columns of basic alumina before use. All other reagents were used as received from Aldrich. ^{1}H-NMR spectra were obtained on 300 MHz Brüker or 400 MHz JEOL spectrometers. UV-visible spectra were taken on a Carey Bio-3 spectrophotometer. All compounds were characterized by NMR, UV-visible spectroscopy, and electrospray ionization mass spectrometry, and were consistent with the structures and data reported in the literature [46].

Synthesis

Preparation of 5,10,15,20-tetraphenylporphyrin (H_2TPP). The reactions were performed in 8.3 mL vials closed by a cap fitted with a gas-tight rubber septum. The bottom 2/3 of the vial was placed in a temperature-controlled sand or oil bath for visual monitoring of the progress of the reaction. The procedure for the acid catalyzed reaction is as follows. Benzoic acid (12.2 mg, 0.1 mmol) was placed in a septum-capped vial, and when the vial reached 200 ± 5 °C, benzaldehyde (20 μL, 0.2 mmol) was injected through the septum in the cap. After 5 min, pyrrole (7μL, 0.1 mmol, 1 equiv.) was injected and the vial kept at 200 °C for another 20 min. Afterward, the vial was removed from the sand bath and cooled in ambient air. Once at room temperature, a minimum volume of chloroform (1–2 mL) was used to wash the vial. Sonication facilitated the extraction of all the porphyrin. The resulting solution was loaded directly onto a pipette column packed with (<1 g) flash silica gel, and eluted with another (5 mL) chloroform. Yields were determined spectroscopically [19] and routinely compared to the isolated yields; interestingly the latter were typically greater. *Caution should be used in this synthesis due to the rapid formation of gases. The flash point of all compounds must be considered.* Under these conditions, there is some benzaldehyde decomposition and little decomposition of the pyrrole. ^{1}H NMR in ($CDCl_3$): δ, ppm (mult, int) 8.85, s, 8H pyrrole βH; 8.24, m, 8H 2,6-phenyl; 7.77, m, 8H 3,5-phenyl; 7.73, m, 4-phenyl; -2.75, s, 2H pyrrole NH. UV-vis (CH_2Cl_2): λ_{max}, nm (log ε) 418 (5.66), 514 (4.20), 549 (3.81), 595 (3.60), 645 (3.49). MS (ES): *m/z* 615, 616, 617. The procedures used for H_2TPP were then used to obtain the porphyrins listed below. The spectroscopic yield is calculated by subtracting the baseline absorbance at 437 nm from that at λ_{max} at 418 nm; Δabs, and using $\varepsilon = 4.27 \times 10^5\ M^{-1}.cm^{-1}$ for the Soret band (see Supporting information).

The reaction was scaled up to afford 0.1–0.3 g H_2TPP by use of a 1.5 × 60 cm glass tube with the ends sealed by glass wool and rubber septa. The tube was heated with heating tape. After the tube was heated to ~200 °C, benzaldehyde (0.75 mL) was injected from one side and pyrrole (0.175 mL) was injected from the other side wherein the reagents diffused and reacted. After 20 min the tube was cooled, washed with ~150 mL $CHCl_3$, loaded directly onto a 2 × 30 cm silica gel column and eluted with $CHCl_3$ to yield pure porphyrins. Alternatively, larger-scale reactions can use jars with lids modified with small rubber septa and heated in a lab oven. We note here, and consistent with previous reports, a standard microwave oven also can be used to heat a solvent-free reaction between benzaldehyde and pyrrole. Mixing of benzaldehyde and pyrrole in a cleaning sonicator also yields some detectable porphyrin.

Preparation of 5,10,15,20-tetrakis(4-pyridyl)porphyrin. To a 8.3 mL vial was added zinc acetate (0.0149 g, 0.075 mmol) and 4-pyridinecarboxaldehyde (30 μL, 0.3 mmol). After the mixture was heated to 200 °C for one minute, pyrrole (7 μL) was injected and the system heated for 20 min. This porphyrin was extracted and

eluted with 9:1 chloroform:methanol. NMR, UV-visible and mass spectra were consistent with those reported in the literature.

CONCLUSION

A new synthetic method has been developed to synthesize commercially important porphyrins. The method tolerates a variety of functional groups, but the specific reaction conditions vary depending on the nature of the aldehyde. Mixed, or combinatorial libraries of porphyrins [38, 47, 48] can be made using this strategy; however as in the traditional Adler synthesis of these libraries, the product distribution is influenced by the relative reactivity of the aldehydes. The 20–30% yields of many of the *meso*-tetraarylporphyrins studied is quite acceptable, the rate of the reactions noteworthy, and the reaction is modestly scalable. Since the reaction utilizes no solvent, and the purification is substantially simplified due to the insolubility of the tarry by-products, there is much less waste generated in terms of solvent, chromatography supports, and heating energy used. The utilization of air in the oxidative steps also substantially reduces the cost of the procedure and is a greener approach. Thus, this is a greener synthesis of purple porphyrins.

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Supporting information

Detailed experimental data and discussion of results are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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