

A Mechanistic Study of the Synthesis of *meso*-Tetraphenylporphin (1)

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In continuation of an earlier preliminary study, some further physical and synthetic studies on the homogenous phase condensation of pyrrole and benzaldehyde to *ms*-tetraphenylporphin in acidic media were undertaken. The role of atmospheric oxygen in the reaction was studied in some detail. The effects of acidity, solvent, concentration, and other constraints on both the rate and yield of the reaction were also investigated. Details of the mechanism, including possible intermediate structures, have been clarified and a reaction scheme accounting for the data is presented.

INTRODUCTION

The combustion tube synthesis of *ms*-tetraphenylporphin (here-after abbreviated as TPP) has been studied by several groups of investigators (3a-5). As this route of synthesis is not readily amenable to physical study (5), we have developed a modified synthesis in acidic media open to the atmosphere that is suitable for mechanistic investigation (6). This preliminary study has resulted in an improved synthesis for TPP (7) specifically and for other *meso*-porphyrins in general (7-9). Recently the condensation of pyrrole and benzaldehyde to TPP has also been investigated electrochemically by anodic oxidation of pyrrole in the presence of aldehydes (10). The experiments reported below are aimed at further clarification of the details of these reactions.

Under the conditions of our preliminary study (6), the condensation of pyrrole and benzaldehyde to TPP showed the following characteristics: (a) there was no detectable reaction in the absence of acid, (b) an oxidant was required for TPP formation, (c) water appeared quickly as a reaction product, (d) both the rate and yield of the reaction were generally depressed in the presence of metallic ions (e) zero-order behavior for TPP formation was observed from about 2% to 75% of the time course of the reaction, (f) tests for surface catalysis were negative, (g) a linear Arrhenius plot was obtained, (h) optical absorbance at 480 $m\mu$ could be identified with reaction intermediates, (i) *ms*-tetraphenylchlorin (here-after abbreviated as TPC) appeared concomitantly with TPP and (j) yields of 35-40% could be obtained in refluxing acetic acid in 6-8 hours.

MATERIALS AND METHODS

All chemicals employed were reagent grade. Pyrrole and benzaldehyde were both freshly distilled under reduced pressure prior to use. For certain experiments the acetic and propionic acids were dehydrated by refluxing with the corresponding anhydrides for several hours prior to use.

The spectrophotometric and kinetic methods employed were those used previously (6). The spectra were taken on either a Beckman DK-1 or a Bausch and Lomb 505. Literature values for the extinction coefficients were employed (5, 11, 12). Standard high vacuum and glove box techniques were used in the oxygen experiments.

EXPERIMENTAL AND RESULTS

Role of Oxygen.

Formerly we were unable to unequivocally identify atmospheric oxygen or benzaldehyde as the possible source of the required oxidizing equivalents for TPP formation (6). Therefore a number of experiments to determine the possible role of oxygen were undertaken.

Firstly, it was noted in the synthetic preparation that the highest yields were always obtained for equimolar ratios of pyrrole and benzaldehyde for a given set of otherwise identical reaction conditions (*cf.* Table 3). Increasing the molar ratio in favor of the benzaldehyde decreases the yield. This observation has been confirmed by an independent investigator (8).

Secondly, we found that the yield of TPP drops to 5% when a refluxing acetic acid reaction 0.02 *M* in each reagent was run under a stream of tank nitrogen rather than open to the atmosphere. Ordinarily the yield for these conditions, *i.e.*, open to the atmosphere, is about 35-40%. Next, two duplicate reactions in acetic acid and 0.02 *M* in each reagent were carried out at room temperature ($22^\circ \pm 2^\circ$) and at an estimated 1×10^{-2} torr oxygen pressure using vacuum system techniques. The reagents were purified by several distillations and then degassed on the vacuum line and sealed into frangible ampules. These were

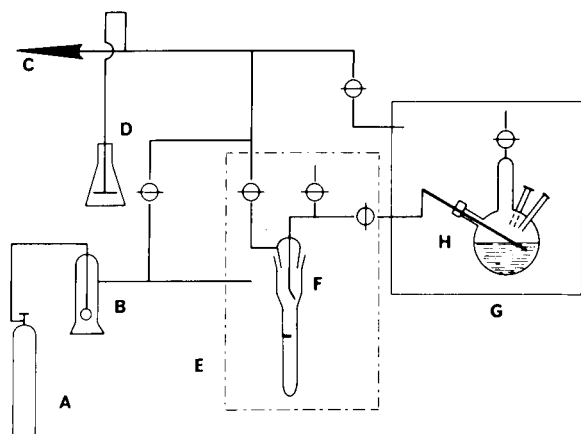


Fig. 1. Schematic diagram of experimental apparatus employed in the glove box experiments (not scaled). (A) N_2 gas tank, (B) alkaline pyrogallol wash, (C) vacuum pump lead, (D) manometer and pressure valve, (E) plastic glove bag assembly, (F) aliquot transfer assembly with 1.00 ml. calibrated receiver, (G) evacuable glove box, and (H) reaction vessel assembly.

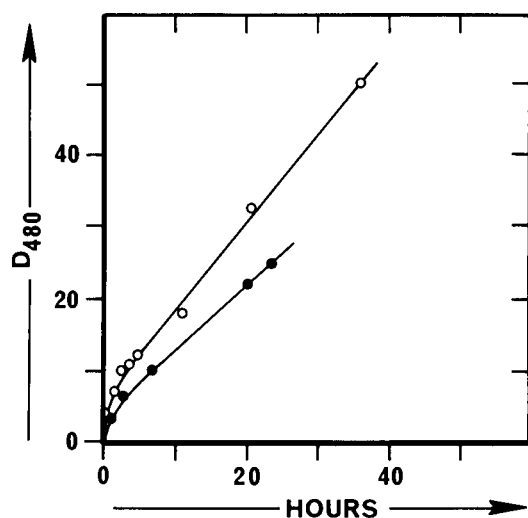


Fig. 2. Time rate of change of absorbance at $480\text{ m}\mu$ in experiments with relatively high oxygen tensions. D_{480} is observed optical density times dilution factor. Experimental conditions given in text. Open circle data for $P_{O_2} = 1$ and solid circle data for $P_{O_2} = \frac{1}{5}$.

transferred into a reaction vessel containing acetic acid and the system was then evacuated and flushed with nitrogen repeatedly before it was sealed off. The reactions were initiated with a magnetic hammer and allowed to proceed for 70 hours. Although the solutions gradually darkened to a red-orange color, no Soret excited fluorescence could be detected at any time, nor could any typical TPP or TPC visible bands be detected with a hand spectroscope.

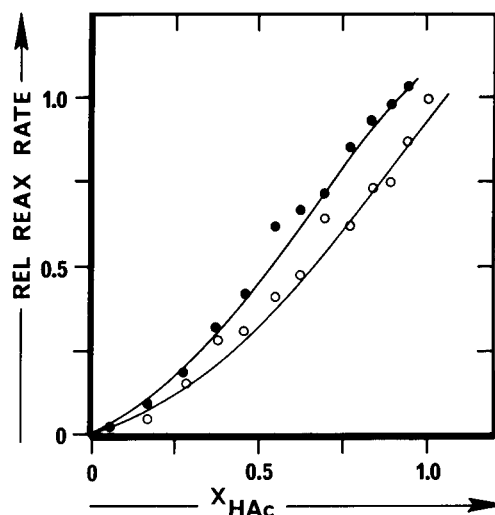


Fig. 3. Effect of acidity on time rate of change of absorbance at $480\text{ m}\mu$ (open circles) and on rate of formation of TPP at $420\text{ m}\mu$ (solid circles). Data given as relative rates versus mole fraction acetic acid in benzene. Other conditions given in text. The rates are relative to the rates at $X_{HAc} = 1$, where $k_{420}^{\circ} = 6.6 \times 10^{-7}\text{ M sec}^{-1}$ and $k_{480}^{\circ} = 0.192\text{ absorbance units sec}^{-1}$ for the zero-order portions of the observed kinetics.

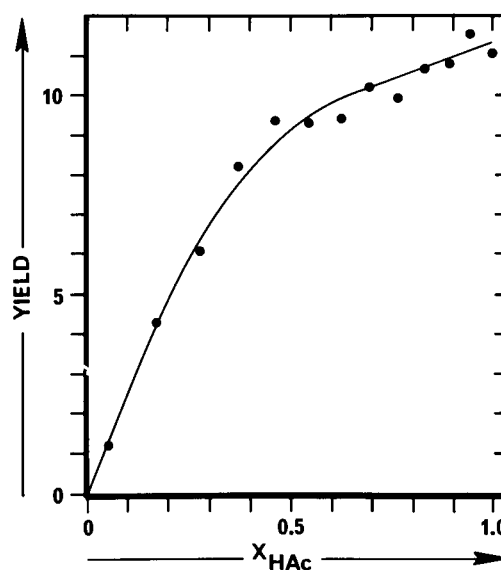


Fig. 4. Effect of acidity on yield of TPP. Data given as % yield versus mole fraction acetic acid in benzene. Conditions given in text.

At the completion of the first experiment the vessel was unsealed under nitrogen and an aliquot removed. This was diluted 1:25 with benzene, transferred to a cuvette, and followed spectrophotometrically. Initially only a broad absorption peak at $480\text{ m}\mu$ could be observed. However, after ten minutes exposure to the atmosphere, absorption at $420\text{ m}\mu$ could be detected along

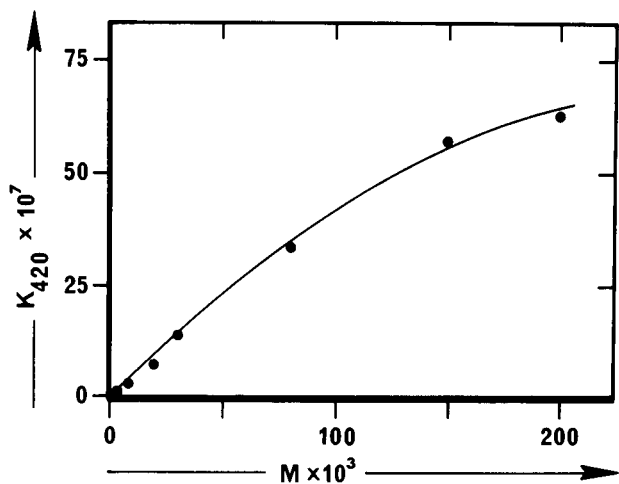


Fig. 5. Effect of concentration on observed zero-order rate constant of formation of TPP (k_{420}° versus molar concentration of the initial reagents). Conditions given in text.

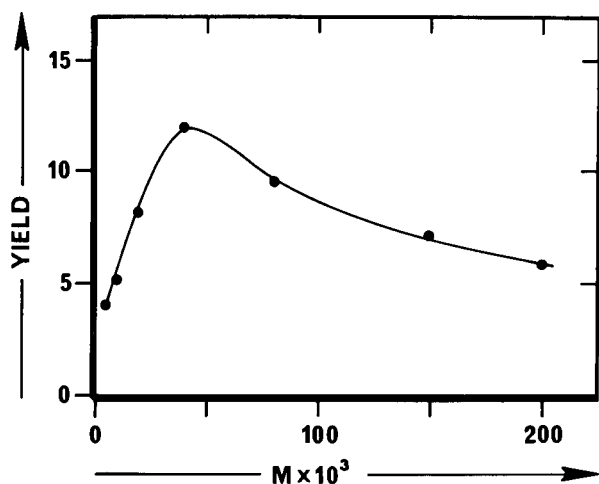


Fig. 6. Effect of concentration on yield of TPP. Data given as % yield versus molar concentration of the initial reagents. Conditions given in text.

with a concomitant increase in Soret excited red fluorescence, both indicative of TPP formation. Over a period of the next four hours, the absorption at both 420 and 480 $m\mu$ gradually increased to relatively stable values.

The second experiment proceeded identically as the first. At its completion the reaction vessel was unsealed, exposed to the air and then connected to a manometer. The pressure gradually fell by a fifth and Soret excited fluorescence gradually increased. Over a period of four hours the system was repeatedly reopened to the air and closed; each time the pressure stabilized at the nitrogen level. While these experiments established oxygen, and precluded benzaldehyde, as the source of the oxidizing equivalents

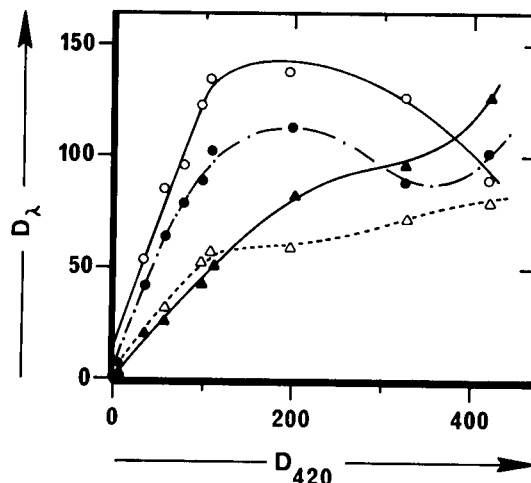


Fig. 7. Absorbance at 420 $m\mu$ versus absorbance at other wave lengths at given times of reaction in the course of the same reaction (see text). Conditions of reaction were 90°, 0.02 M initial reagent concentrations, glacial acetic acid as solvent, open 500 ml. flask as reaction vessel. Absorbance data shown for following wavelengths: 480 $m\mu$ (open circles), 455 $m\mu$ (solid circles), 395 $m\mu$ (solid triangles), and 510 $m\mu$ (open triangles).

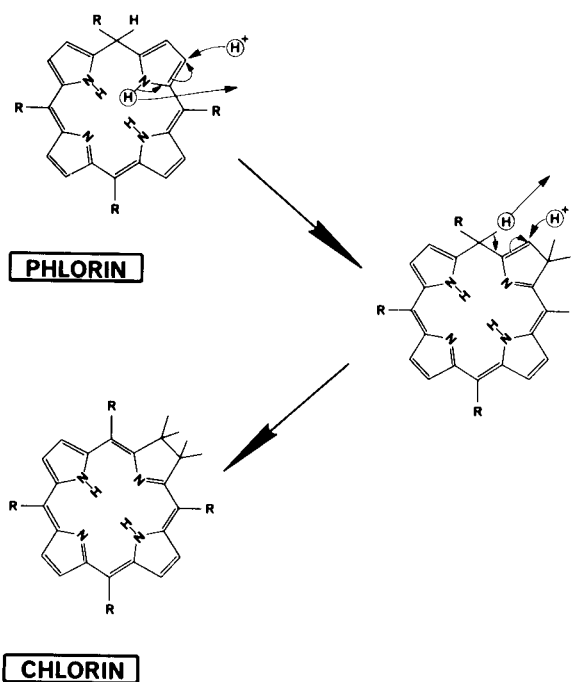


Fig. 8. A proposed mechanism for the conversion of a phlorin into a chlorin in acidic media. Isomerization is in the direction of increased conjugation.

required for TPP formation, they left the matter still unsettled for the formation of the intermediates.

Therefore, two duplicate sets of experiments were carried out using evacuable glove box techniques to test this point. The arrangement (see Fig. 1) allowed measured reaction aliquots to be taken at times intervals, diluted, and transferred to cuvettes all in a controlled atmosphere. The stoppered cuvettes could then be transferred from the apparatus and the kinetics of the reaction could be followed spectrophotometrically. The alkaline pyrogallol-scrubbed tank nitrogen was constantly passed into the glove box system throughout the experiment, giving an estimated average oxygen tension of 1×10^{-2} torr. The reaction conditions and procedures were those of the previous two experiments.

To within the experimental uncertainties both experiments gave identical results. In the first few minutes of reaction the UV absorption band of benzaldehyde decreased very rapidly, while broad absorption peaks began to appear in the region of 350-360 $m\mu$. There was a steady increase of absorption at 480 $m\mu$. However, over a period of four days no TPP or TPC absorption peaks could be detected, nor was any Soret excited red fluorescence observable. The absorbance at 480 $m\mu$, D_{480} , increased linearly with time following a zero-order rate law and, also, extrapolated to zero at initial time. The observed "rate constant", $d(D_{480})/dt$, was 4×10^{-6} absorbance units sec^{-1} .

The effects of oxygen tension, P_{O_2} , on this rate constant could now be examined. For this purpose two reactions similar to the glove box experiments were performed, but with increased oxygen tensions. The first was conducted under a slow stream of compressed air and the second under a stream of tank oxygen. These were metered for the same rate of flow as in the glove box experiments. Plots of D_{480} vs. time for these reactions showed zero-order portions (see Figure 2) from which rate constants were determined and compared with the glove box value (see Table 1). From these data it is seen that the rate of formation of 480 $m\mu$ intermediates is also oxygen limited and shows an approximate fourth root dependence on oxygen concentration. This suggests that the production of 480 $m\mu$ material involves a one electron oxidation as the limiting step.

Note that for the higher oxygen tensions that the zero-order portions do not extrapolate to zero at initial time. The data for these initial time regions do not follow any simple order laws. It was also observed that the TPP yields in these two experiments were somewhat greater, than those found in previous similar experiments in which the reaction system was merely left open to the atmosphere.

Finally, the effect of oxygen on the yield under synthetic conditions (7) was investigated. This end was achieved by carrying out the reaction in a variety of different vessels permitting the independent variation of volume, depth and air-solution interfacial area. For this series of experiments the reactions were run at 0.2 M in each reagent in refluxing propionic acid for 30 minutes. The yield of TPP could be determined directly in these experiments by weighing (7). The yields were found to increase with increase in surface area available for diffusion/constant depth and to decrease with increase in diffusion/constant air-exposed surface area. Unfortunately, there was too much scatter in the data to determine an exact value for the power dependence of yield on these quantities.

We conclude from all of the above experiments that molecular oxygen is the source of the oxidizing equivalents required in this reaction and that it exerts either kinetic or diffusion control throughout the entire course of the reaction for all the conditions we have explored.

TABLE I

Observed Zero-Order Rate Constants of Formation at 480 $m\mu$ (22°)

P_{O_2} (atmos.)	$P_{O_2}^{1/4}$	k'_0 (absorbance units sec^{-1})
1	1	3.6×10^{-4}
$\frac{1}{5}$	0.67	2.5×10^{-4}
$\sim 10^{-5}$	$\sim 5.5 \times 10^{-2}$	4×10^{-6}

TABLE II

Observed Activation Parameters for TPP Formation

	ΔH^* (Kcal/mole)	ΔS^* (e.u.)
Acetic Acid	15 ± 1	-60 ± 5
Propionic Acid	13 ± 1	-47 ± 5

Effect of Acidity.

To test the effect of acidity on this reaction, a series of experiments were conducted in benzene-acetic acid solvent media with mole fractions varying from 0 to 1.0. They were all carried out at $52^\circ \pm 0.2^\circ$ in open 500 ml. flasks and at 0.02 M all each reactant in a total volume of 250 ml. Rates and yields were determined spectrophotometrically, correcting the data for total TPP, i.e., TPP and $TPPH_2^{+2}$. The results of this study are shown in Figures 3 and 4. The kinetic behavior exhibited is that generally expected for an acid catalyzed reaction where several conjugate acids and bases yield products at different rates and at several steps in the mechanism, i.e., more than one pK appears to be operative at different times in the course of reaction.

Effect of Solvent.

For a preliminary assessment of the effect of solvent, synthetic reactions were run at reflux in propionic and butyric acids and compared to the acetic acid reflux data. The butyric acid reactions in comparison to an equivalent acetic acid reaction showed greatly decreased yields and a concomitant increase in impurities. However, while the propionic acid reaction also gave decreased yields (20% as opposed to 40% for acetic acid), it was also noted that it gave a faster reaction and a purer product. The solubility of TPP in propionic acid at room temperature is much less than in acetic acid and the tendency to form the acid salt is also greatly decreased. As these factors offered a number of synthetic advantages, a more extensive study was made of the reaction in propionic acid.

The kinetic behavior of the reaction in propionic acid is identical in all respects to that in acetic acid, except that the rates are faster for comparable conditions in concentration, temperature, volume, etc. Therefore a series of kinetic experiments were carried for 0.02 M concentration at five temperatures from room temperature to reflux. The rates of formation of TPP were

determined and these were found to give a linear Arrhenius plot. A comparison of the observed activation parameters for propionic and acetic acids is shown in Table 2.

Acetic and propionic acids have nearly identical aqueous pK 's and pK -temperature dependences (13) and, also, generally similar physical properties (14). These differences in reaction behavior, therefore, cannot be simply ascribed to differences in acidity, viscosity, dielectric constant and other properties of the solvent. It was noted that oxygen is generally more soluble in organic acids than in other organic solvents (15), which might be at least partially responsible for the differences in yields in such media. However, the data for propionic acid itself is not available and the comparison to acetic acid cannot be made.

Effect of Concentration.

A series of experiments was conducted at $52^\circ \pm 0.2^\circ$, in acetic acid to study the effect of the concentration of the reactants on the yield and on the observed rate constant. The reaction employed 0.005 mole each of pyrrole and benzaldehyde and the concentrations were varied by varying the total volume of reaction solvent. The reaction vessels were chosen to maintain a constant surface area available for diffusion/unit volume and, also, a constant depth of diffusion. The data were obtained spectrophotometrically and the results are shown in Figures 5 and 6.

Note that the effect of concentration on the zero-order rate constant for formation of TPP is non-linear and that the yield of TPP goes through a maximum with increasing concentration. This type of strong concentration dependence is found in reactions involving aggregative changes (16). In this particular reaction monopyrroles condense to linear polypyrroles that either continue to grow or to close to form macrocyclic rings, such as the desired product. A maximum in yield in the system therefore represents competition between chain propagation and chain termination prior to tetrapyrroles at the lower concentrations and competition between further chain propagation and ring closure to TPP at the higher concentrations. The maximum represents the compromise for TPP formation between these competing interactions, as they have an inverse dependence on concentration relative to one another.

Intermediates.

In order to learn more about the number and nature of the intermediates in this reaction an extensive column chromatographic study of the reaction mixture at different times was undertaken. Several solvents and various combinations thereof (chloroform, benzene, pyridine, acetic acid, methanol, ethanol, carbon tetrachloride, ethyl acetate, dioxane, and petroleum ether) were explored on five different supports (alumina, silica, Fuller's earth, Florasil, and Whatman Cellulose). While several of these combinations initially permitted up to ten bands to be clearly distinguished on the column under UV, we were unable to successfully isolate any materials other than TPP, TPC, or large "polypyrrole" polymers. This arises from the fact that conditions that favor separation and rapid elution of these bands also unfortunately favor conversion of these reactive species to final products. Attempts to obtain spectra of these bands directly on the columns were unsuccessful.

Some further information on the reaction intermediates was obtained from further analysis of our spectrophotometric data on kinetic studies. By parametrically plotting absorbancies at different wavelengths against one another for the same times for a given kinetic study, errors in absolute time, concentration, dilution, etc, can be eliminated and very small changes in absorbance

throughout the reaction at specific wavelengths and relative times can be detected. Changes in curvature and intersections of such plots can be used to identify regions of the spectrum in which such small changes occur. These spectral regions may then be identified with particular structures and correlated with time of appearance in the reaction sequence.

Some such representative plots are shown in Figure 7. By such analysis we have located eight spectral regions that can be attributed to various general pyrrolic structure types (mono, di, and tetra). This analysis corroborates the conclusion drawn from the chromatographic study, that there are about ten different reactive species present in the course of the reaction.

The air oxidation of purified TPC and CuTPC under conditions comparable to those employed in the kinetic studies was also studied. No detectable conversion of CuTPC to CuTPP took place in 24 hours in a benzene solution maintained at 72° under a stream of compressed air. Conversion took place slowly when this benzene solution was acidified with acetic acid to 6.7% by weight. In pure acetic acid, however, conversion was relatively rapid and comparable to the rates required for CuTPP formation in our previous study (6).

In a set of similar experiments with TPC, again no detectable reaction took place in the absence of acid. However, even in acetic acid, complete conversion of TPC to TPP at concentration levels found in the kinetic studies required 16 days at 72° . This is not comparable to the rates required for TPP formation under these reaction conditions. Thus TPC cannot be the main reduced intermediate in the path to TPP for these reactions in the absence of metal ions, as we had suggested earlier (6). This is a significant observation, as it immediately suggests the possible importance of reduced bridge intermediates, as opposed to only reduced ring intermediates.

Miscellaneous Observations.

No effect of visible or ultraviolet irradiation could be detected on the rates or yields of these reactions under any of the conditions studied. However, the relatively slow oxidation of TPC to TPP was photosensitive as previously reported (6,17).

Some of the precipitates formed during the acetic acid reactions in the presence of metals (6) were examined for the presence of covalently bound metals. Strong positive spot tests (18) on the Ag, Hg and Zn materials were only obtained after digestion with concentrated nitric acid. This both supports our previous suggestion concerning the inhibitory role of such metals under our reaction condition (6) and also supports the observation that such metal complexes may serve as intermediates in the conditions of the Rothmund route of synthesis (5).

Finally, all the above information was used to develop an improved synthesis of TPP (7). The effect of many parameters on the yield under synthetic conditions was tested. These experiments are summarized in Table 3. Some of the most significant findings are here noted.

Dehydrants under some conditions tended to improve the yield, but not substantially. Oxygen proved to be the best of several oxidants tested. Pure propionic acid provided the most convenient preparative solvent in that it directly yielded relatively pure filterable product. Slow addition of reagents did not improve the yield or product. Accessibility to atmospheric oxygen and removal of water seemed to be the most important factors controlling the yield of the reaction. If a stoichiometric amount of water is initially added to the reaction mixture the yield is sharply decreased. However, if the reaction is run for half its normal time, product rapidly removed by filtration and then

TABLE III

Influence of Various Factors on the Synthesis of TPP

#	Pyrrole (moles)	Benzaldehyde (moles)	Solvent	Volume (ml)	Temp.	Time of Reaction	Additional Variations	Yield (a)	Comments
1	0.005	0.005	Acetic Acid	250	reflux	8 hr.	-----	38%	-----
2	0.0025	0.005	Acetic Acid	250	reflux	8 hr.	-----	35%	-----
3	0.005	0.010	Acetic Acid	250	reflux	8 hr.	-----	32%	More byproducts, more difficult to purify
4	0.05	0.05	Propionic Acid	250	reflux	6 hr.	-----	22%	About 2% TPC present
5	0.05	0.05	Propionic Acid	250	reflux	30 min.	-----	20%	Cleaner product, less TPC and easier to purify than 6 hr.
6	0.05	0.10	Propionic Acid	250	reflux	6 hr.	-----	20%	-----
7	0.05	0.10	Propionic Acid	250	reflux	30 min.	-----	19%	-----
8	0.05	0.20	Propionic Acid	250	reflux	30 min.	-----	17%	-----
9	0.20	0.20	Propionic Acid	250	reflux	30 min.	-----	12%	More byproducts
10	0.05	0.05	Propionic Acid	250	reflux	30 min.	2 ml. propionic anhydride	21%	Cleaner product
11	0.05	0.05	Propionic Acid	250	reflux	30 min.	3 ml. acetic anhydride	21%	Cleaner product
12	0.05	0.05	Propionic Acid	250	reflux	30 min.	15 ml. distilled water	5%	-----
13	0.05	0.05	Propionic Acid	250	reflux	30 min.	30 ml. distilled water	trace	-----

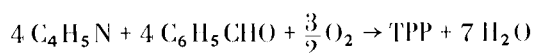
14	0.05	0.05	Propionic Acid	250	reflux	30 min.	10 ml. propionic anhydride	18%	-----
15	0.05	0.05	Propionic Acid	250	reflux	30 min.	2 g. boric anhydride	trace	-----
16	0.05	0.05	Propionic Acid	250	reflux	30 min.	2 g. phosphoric anhydride	trace	-----
17	0.05	0.05	Propionic Acid	250	reflux	30 min.	4 ml. dimethoxypropane	8%	-----
18	0.05	0.05	Propionic Acid	250	reflux	6 hr.	Compressed air slowly bubbled into reaction	22%	More byproducts, harder to purify
19	0.05	0.05	Propionic Acid	250	reflux	6 hr.	Tank oxygen slowly bubbled into reaction	23%	More byproducts, very difficult to purify
20	0.05	0.05	Propionic Acid	250	reflux	6 hr.	4 g. sodium peroxide	20%	Cleaner product
21	0.05	0.05	Propionic Acid	250	reflux	6 hr.	5 g. sodium persulfate	12%	-----
22	0.05	0.05	Propionic Acid	250	reflux	6 hr.	5 g. potassium permanganate	trace	-----
23	0.05	0.05	Propionic Acid	250	reflux	4 hr.	Reagents added dropwise over reaction course	20%	Cleaner product
24	0.04	0.05	Propionic Acid	250	reflux	6 hr.	Reagents added in four aliquots at 1-hour intervals	21%	-----
25	0.05	0.05	Propionic Acid	250	reflux	30 min.	Reagents added dropwise over 20 minutes	20%	-----
26	0.05	0.05	Propionic Acid	250	reflux	1 hr.	Reaction stopped at 15 min, product filtered then filtrate continued to react	20%	-----
27	0.05	0.05	Xylene	200	reflux	4 hr.	15 g. chloroacetic acid	18%	-----
28	0.05	0.05	Xylene	200	reflux	4 hr.	5 g. benzoic acid	trace	-----
29	0.05	0.05	Benzyl alcohol	250	reflux	4 hr.	5 g. benzoic acid	trace	-----
30	0.05	0.05	Benzyl alcohol	250	reflux	4 hr.	2 g. trichloroacetic acid	no yield	-----

Yield based on pyrrole; trace means less than 1% yield, but Soret excited red fluorescence obtainable; no yield means no Soret band or fluorescence detectable.

reaction continued, no increase in total yield is observed. This demonstrates that the reaction is not equilibrium limited, but in fact kinetically controlled even under the synthetic conditions.

DISCUSSION

In our initial studies we had demonstrated that this reaction required an oxidant (6). This present study shows that all these oxidizing equivalents are provided by molecular oxygen. Therefore, the overall stoichiometric reaction can be written as:



In this reaction the oxygen exerts kinetic control throughout the mechanism on both rates and yields. Since the reaction $O_2 + 4H^+ + 4e^- = 2H_2O$ has a standard reduction potential of + 1.23 volts/equiv (19), its efficiency in this regard is not very surprising. It is of some interest to note that the best estimate for the reduction potential for the reaction $C_6H_5CHO + 2H^+ + 2e^- = C_6H_5CH_2OH$ is +0.20 volts/equiv (20,21) or 23 kcal/mole less Gibbs free energy than the oxygen reaction for the same conditions.

Since we have been unable to identify specific structures and since detailed thermodynamic data on most of the reactions in our mechanism are unavailable, and since this reaction seems to be general for all aldehydes so far tested (7), we propose the following general reaction scheme implying the appropriate *ms*-phenyl derivatives for a mechanism for the conditions under which we have studied the reaction:

- (I) pyrrole + aldehyde \rightleftharpoons pyrrole-2-carbinol (A)
- (II) 2(A) \rightarrow dipyrromethane carbinol (B) + H₂O
- (III) (B) + $\frac{1}{2} O_2 \rightarrow$ dipyrromethene carbinol (C) + H₂O
- (IV) (B) + (A) \rightarrow corresponding tripyrryl or (C) carbinol derivatives (D) + H₂O
- (V) tripyrryl derivatives + (A) or 2-dipyrryl derivatives \rightarrow corresponding tetrapyrpyl carbinol derivatives + H₂O
- (VI) saturated tripyrryl or tetrapyrpyl derivatives + $\frac{1}{2} O_2 \rightarrow$ next corresponding unsaturated derivatives + H₂O (and continued oxidation)
- (VII) 2 tripyrryl or tetrapyrpyl + (A) or tetrapyrpyl + (B) etc. \rightarrow polypyrpyl byproducts containing more than 4 pyrrole units
- (VIII) tetrapyrpyl carbinols \rightarrow corresponding ring struc-

tures (porphorinogen, chlorin, phlorin, dihydrochlorin, dihydrophlorin or porphyrin) + H₂O

(IX) saturated ring structure + $\frac{1}{2} O_2 \rightarrow$ next corresponding unsaturated ring structure + H₂O

(X) phlorins \rightarrow chlorins

(XI) phlorins (and chlorins) + $\frac{1}{2} O_2 \rightarrow$ porphyrin + H₂O

This scheme accomodates all of our observations. The equilibrium in (I) and acid catalysed pyrrole carbinol condensation to dipyrromethanes (II) and then oxidation to methenes (III) are well known (22,23). Our observation of the rapid disappearance of the UV band of benzaldehyde suggests that the equilibrium in (I) is established very quickly. That further oxidative and chain building steps of the type indicated (IV-VII) must take place is obvious; however, our present studies do not permit a detailed specification of the relative importance of such intermediate structures. This part of the scheme is supported, though, by our studies on the role of oxygen and on the rapid formation of water as a reaction product.

Considering this, the continuation of a carbinol function as the reactive coupling group throughout this series of reactions is quite reasonable. This point will be further clarified by our studies on the synthesis of porphyrin (24). Competition between reaction of the type in (VII) and (VIII), *i.e.*, chain propagation and ring closure is supported by our concentration studies. Increasing concentration does increase the yield of long chain polymeric byproducts and decrease the yield of porphyrin. This occurs in the higher concentration range as the probability of intermolecular *vs.* intramolecular collisions, and therefore condensation, is increased.

The relative importance of phlorins (reduced bridge structures) as possible intermediates in preference to chlorins (reduced ring structures) is necessitated in (XI) by our studies on the sluggishness of chlorin oxidation under these conditions. Comparing previous investigations on the stability of chlorins (4,25) with corresponding studies on phlorins (26,27), it is clear that the reduced bridge species are, in fact, more readily convertible to porphyrins.

It is of some interest to note that the biosynthesis of chlorins is accomplished by the reduction of a porphyrin which itself has been biosynthesized via reduced bridge intermediates (28). In view of our own studies this raises the point that chlorins in this reaction may be derived from phlorins as shown in (X). A tautomeric equilibrium of this type has been observed for the ZnTPC, Zn phlorin system (29) and has also been suggested in the mechanism

of the Rothmund reaction (5). A mechanism for this rearrangement is shown in Figure 8. A study of these structures with precision atomic models (30) and the available structural data (31,32,33) shows that this mechanism is quite feasible and could take place readily in acidic media without any steric hindrance to the transformation. This transformation is in the direction of increasing conjugation and would be favored on these grounds.

There remains the problem of explaining our observation of zero order kinetics in so many features of this reaction. We have already shown that this does not arise from surface catalysis (6), the usual mechanism for such behavior. If there were a mechanistic step involving a prior equilibrium early in the reaction and if this step was diffusion controlled in oxygen, then one can readily show that this would lead to observed zero-order kinetics. In the reaction scheme proposed above, there are several steps where such a mechanism could operate and accommodate all the data. Unfortunately, assigning this to a particular step requires a better knowledge of the 480 $m\mu$ absorbing materials. Absorption in this region is quite typical for dipyrromethenes (34) and a mechanism of the sort described above applied to step (I) as the prior equilibrium, with diffusion controlled oxidation at step (III) would readily explain all the data and give the required zero-order behavior. However, our studies indicate that more than one intermediate is producing the 480 $m\mu$ absorption (*e. g.*, a tetrapyrrole structure composed of two dipyrromethenes joined by a methane bridge would also absorb here). This complication prevents an unambiguous assignment of the position of the rate controlling step in our reaction scheme.

Further studies on this and similar porphyrin reactions are in progress in our laboratories. The information from these investigations should continue to contribute to our understanding of the reactivity of these interesting molecules and should enable a comparison of this particular reaction with similar reactions of interest such as the Rothmund reaction and the biosynthetic reaction (35).

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