

Notes on the Synthesis of Porphin

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Porphin is the parent compound of the porphyrins and as such its properties and behavior are extremely important. Unfortunately, because of the poor syntheses which are available for this compound, relatively few chemical studies have been reported. Fischer and Gleim (1) first synthesized porphin by addition of 2-pyrrole aldehyde (pyrrole-2-carboxaldehyde) to refluxing formic acid. Rothmund (2) extended his studies of the general reaction of pyrrole with aldehydes and found that form-aldehyde condenses with pyrrole to produce porphin in

yields of approximately 0.1%. Krol (3) apparently was the first worker to give the chemistry of these condensation reactions serious consideration. He realized that the conversion of pyrrole or pyrrole derivatives into porphyrins requires oxidation of pyrrole. By use of peroxidizing agents, Krol was able to obtain yields of 5% by the condensation of pyrrole alcohol (2-hydroxymethylpyrrole) in glacial acetic acid. In addition, he was aware of the chief impediment to obtaining high yields: "Yields much in excess of 5% would seem unlikely in a

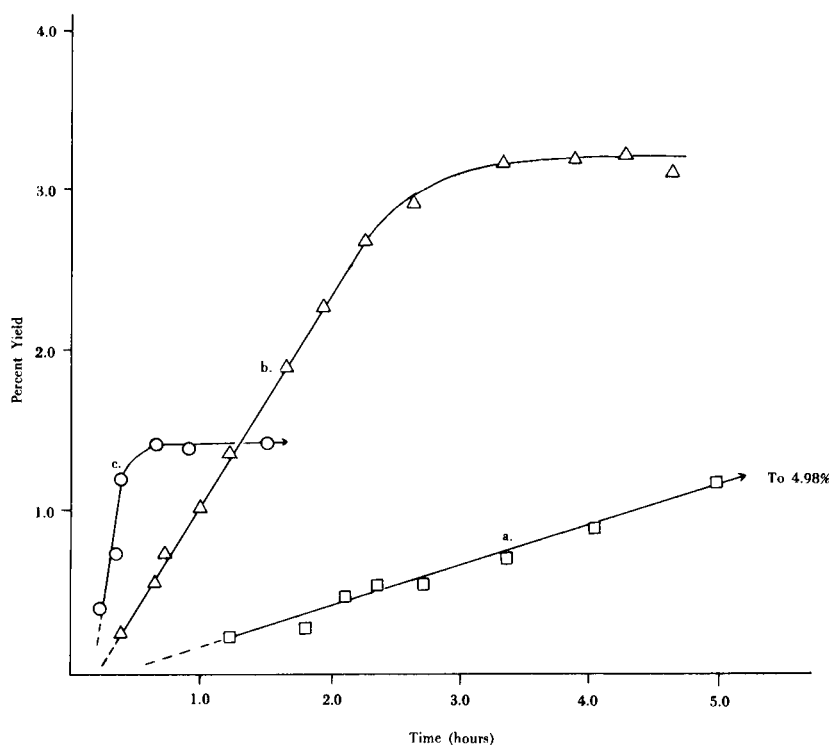


Figure 1

reaction of this type in which polymerization of macromolecules and cyclization in 4-ring units are equally possible." Alder and Bietchman (nee Dym) (4) developed a synthesis involving the acid-catalyzed condensation of 2-pyrrole alcohol which gives slightly higher yields than Krol's method, but more importantly, it allows much easier separation of the porphin.

Results.

In this paper we report the results of rate and yield studies on the condensation of 2-pyrrole alcohol, the stoichiometry of which is:



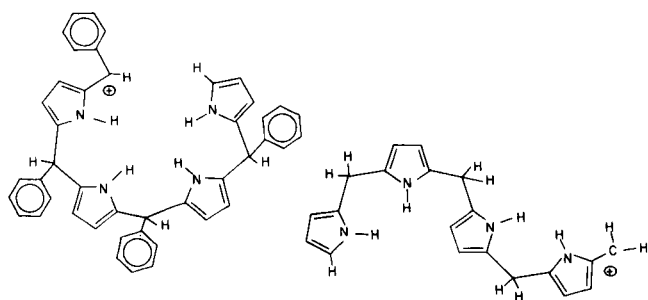
We examined the effects of various solvent media (water, *N,N*-dimethylformamide, benzene, toluene, ethanol, xylene, propionic acid, and glacial acetic acid) on the rate and yield of the reaction described by equation 1. Generally speaking, the highest yields were obtained in the aromatic solvents and the highest rates were obtained in acidified aromatic solvents.

Specifically, our highest yield was obtained in ethylbenzene and our highest rates were obtained in acidified xylenes.

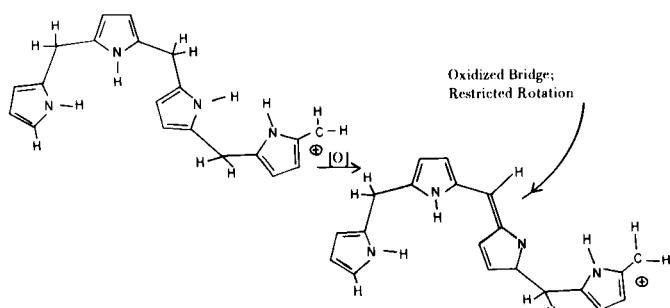
Table 1
Synthesis of Porphin

Entry	Pyrrole Alcohol	T, °C	Solvent	% Yield (b)	Remarks
1	0.001	80	Xylenes (a)	0.0	
2	0.001	90	Xylenes	1.0	Red fluorescence observed
3	0.001	95	Xylenes	12.3	
4	0.001	100	Xylenes	13.8	
5	0.001	120	Xylenes	5.9	
6	0.002	100	Xylenes	9.4	
7	0.010	100	Xylenes	4.0	
8	0.001	100	Xylenes	17.3	Reactant added dropwise; 2×10^{-6} mole/hour in DMF solution (c)
9	0.001	100	Xylenes	16.6	Reaction run in vacuum for first 100 hours
10	0.001	100	10% Acetic Acid in Xylenes	3.1	
11	0.001	100	<i>o</i> -Xylene	8.6	
12	0.001	100	<i>m</i> -Xylene	8.3	
13	0.001	100	<i>p</i> -Xylene	13.3	
14	0.002	60	0.32 Benzoic Acid in Xylenes	4.98	
15	0.002	75	0.32 Benzoic Acid in Xylenes	3.17	
16	0.002	90	0.32 Benzoid Acid in Xylenes	1.47	
17	0.001	100	Ethylbenzene	15.77	
18	0.001	100	Ethylbenzene chromatographed on neutral alumina (Camag)	18.02	The time required to reach maximum yield was 11.5 days

(a) Xylenes refers to the commercial product which is a varying mixture of aromatic compounds predominantly *o*-xylene, *m*-xylene, ethylbenzene with traces of phenol and thiophene. (b) Each entry is the average of the results obtained from a minimum of three different experiments. (c) We added reactant pyrrole alcohol as a stock solution: 0.0001 mole of pyrrole alcohol per 50 ml. of DMF. Pyrrole alcohol is not very soluble in our reaction solvents at room temperature and we have shown that these amounts of DMF have no effect on the rates and yields.



a. The TPP open chain tetrapyrrole

b. The porphyrin open chain tetrapyrrole
Figure 2

Oxidation of the Porphyrin Tetrapyrrolylmethane

Figure 3

The results of our investigation of the yields of the condensation reaction (equation 1) are given in Table 1. Note that no rate data are tabulated since the rates are very erratic in the absence of added acid catalyst. In some experiments porphyrin could be detected in 12 hours; in other experiments, run under what we believe to be the same conditions, we could not detect porphyrin for 8 days.

While the rates of the reactions studied in non-acidified media were erratic, the yields were reproducible. Generally, purification of the solvents by chromatography on basic or neutral alumina caused no change in yields, nor in the erratic rate behavior, nor did irradiation with light or near ultraviolet have any noticeable effect. However, purification of commercial ethylbenzene (entries 17 and 18) does increase the yield and decrease the rate of the reaction. An increase in concentration of reactant (entries 4, 6, and 7) causes a decrease in percent yield.

The optimum temperature for the reaction (entries 1-5) appears to be near 100°. At 120°, the reaction rate is very rapid but the percent yield is much lower. Entries 14 to 16 show that the yields in acidified media decrease with increasing temperature while the rates (*vide infra*) increase with increasing temperature. (Rates and yields are reproducible in acidified media).

The presence of acid (entries 10, 14 to 16) causes the reaction to proceed faster but the percent yield is appreciably reduced. Dropwise addition of the reactant pyrrole

alcohol (entry 8) causes a definite increase in yield as does exclusion of oxygen (entry 9) during the early part of the reaction. We do not understand the results that we obtain when separated xylene isomers are used as solvent (entries 11-13).

We also notice that no absorption peak at 635 nm ever develops during reactions in non-acidified media. Then, unlike the synthesis in acidified xylenes (4), no chlorin is formed. We have tried many solvents, for the reaction, e.g., acetic acid, propionic acid, benzene, toluene, DMF, water, but the highest yields are obtained in the xylenes and in ethylbenzene, in the absence of added catalysts and at moderate temperatures. A general conclusion which we have derived from these studies is that any condition which increases the reaction rate appears to decrease the percent yield. Unfortunately, below 90° the activation energy barrier appears to be so great that no appreciable reaction occurs in non-acidified media.

Table 2
Effect (a) of Temperature on the
Rates and Yields of Porphyrin

T., °C	% Yield	Rate Constant (M/s)
60	4.98	3.7×10^{-10}
75	3.17	1.5×10^{-9}
90	1.47	2.6×10^{-9}

(a) All reactions were carried out in xylenes acidified with benzoic acid, 0.32 M.

A kinetic study of the condensation reaction was carried out spectrophotometrically in a solution of xylenes with a concentration of benzoic acid of 0.32 M, at three different temperatures. The concentration of product porphyrin initially increases linearly with time and a plot of the log of the "zero" order rate constant for the formation of porphyrin vs $1/t$ were linear. The kinetic results are summarized in Table 2 and Figure 1.

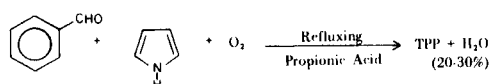
Discussion.

The results of the kinetic studies are similar to the results obtained for the acid catalyzed condensations of *ms*-tetraphenylporphyrin and other *ms*-tetraarylporphyrins. This suggests that the mechanism of the condensation of pyrrole derivatives must involve the same rate controlling steps as the self-condensation of pyrrole alcohol and, in fact, we had previously postulated that the carbinol is an important intermediate in the condensation of pyrrole with various aldehydes (5). Since the condensation reaction is so complicated and we have only monitored the rate of the last step any further analysis of the kinetic data seems unwarranted.

The erratic rates of the condensation reactions in solvent media to which no acid was added are attributed to varying concentrations of trace acid impurities. We

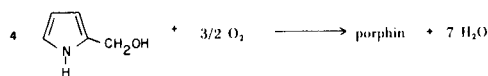
have learned from the supplier (Fisher) that the commercial xylenes and ethylbenzene contain traces of phenol and benzoic acid. The observation that chromatography of the ethylbenzene decreases the rate and increases the yield (entries 17 and 18) also supports this hypothesis.

A consideration of the chemical condensation leading to the formation of synthetic porphyrins suggests the explanation of results which are presented in Table 1. The modified Rothmund synthesis of *ms*-tetraphenylporphin (TPP):



gives a much higher yield of TPP than any reaction reported for the synthesis of porphin, itself. An examination of accurate models shows that the probability of cyclization as opposed to continued chain growth is quite high in a chain which contains four residues each of pyrrole and benzaldehyde because as indicated in Figure 2a, the phenyl groups cause the co-polymer to bend into a cycle.

The synthesis of porphin involves the condensation of pyrrolealcohol:

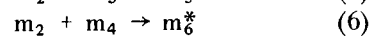
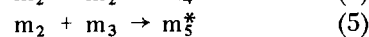
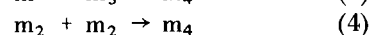
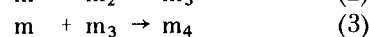
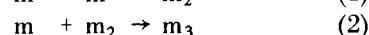
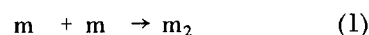


As shown in Figure 2b, for this case the bridge carbons of the open chain tetrapyrrolymethane carry hydrogen atoms. Therefore, there is hardly any hindrance to rotation about the bridge carbon atoms. The corresponding open chain tetrapyrrole is not forced into a conformation favorable to cyclization, and chain lengthening is more probable.

There is another deleterious effect due to the relatively free rotation about the bridge carbon atoms in the open chain tetrapyrrole porphin-precursor: oxidation of the methane to a methene bridge may fix the pyrrole residues in a *trans*-conformation. As shown in Figure 3, a two equivalent oxidation of the growing chain extends the conjugation so that a large portion becomes rigid and planar. If the pyrrol residues are not properly oriented at the time of oxidation the growing chain can never form porphin. Since the oxygen oxidation of the growing chain may freeze the polypyrrolycarbinol into a conformation which can never produce porphin exclusion of oxygen during an initial period of the reaction would prevent oxygen oxidation of the methane bridges and increase the probability that the tetrapyrroly chain would achieve a configuration suitable for formation of the cyclic-tetrapyrrole precursor of porphin. Entry 9, Table 1 supports this reasoning.

Ideally, one would like to cause the condensation of pyrrole alcohol to occur quickly until the tetrapyrrole is formed and then to cease completely allowing the tetrapyrrole to cyclize. Unfortunately, there appears to be no way to stop chain growth at the tetrapyrroly stage, but the condensation reaction can be slowed so that the average time between the individual addition steps will be increased. In this manner all the polymers, the dipyrrolyl, tripyrrolyl, and importantly, the tetrapyrrolyl chains will have longer lifetimes. As the lifetime of the tetrapyrrolyl-methane increases, the probability of cyclization increases and probability of yield-reducing chain growth decreases. We can exercise control over the lifetimes of the porphin intermediates in three obvious ways: (1) eliminate or reduce the catalyst concentration, (2) reduce the reactant (pyrrole alcohol) concentration, and (3) decrease the reaction temperature. Our results show that the yields do increase as we make these changes.

The detailed condensation reactions leading to chain growth include the following steps.



etc.

In this scheme *m* represents pyrrole alcohol, *m*₂ the dipyrrolycarbinol, *m*₃ the tripyrrolycarbinol, *etc.* As can be seen the products of the first four reactions are intermediates which can eventually be converted into porphin. The products of the reactions represented by equations 5 and 6 are not intermediates; these reactions represent chemical routes which never produce the essential tetrapyrrolyl chain. In order to insure that all chains will grow to the tetrapyrrolyl state all condensation reactions would have to involve monomeric pyrrole alcohol and only reactions like 1, 2, and 3, would occur. It is impossible to constrain this chemical system to such reactions, but by slow, continuous addition of pyrrole alcohol to the solvent medium it is possible to increase the probability of reactions like 1, 2, and 3, because, under these conditions, the concentration of monomeric pyrrole alcohol is always relatively high. Entry 8 of Table 1 shows that slow addition of the reactant causes an appreciable increase in yield.

We now hope to use the results of this study to develop a practical synthesis of porphin by combining high dilution methods and vacuum system techniques with automation. At present, the most practical method for the synthesis of porphin is a simple modification of the

synthesis reported by Beitchman and Adler: Replace their solvent with chromatographed ethylbenzene; add 0.1 ml. of pyrrole alcohol twice a day to 3 liters of ethylbenzene thermostated at $100 \pm 2^\circ$ until 2.0 ml. have been added. A maximum of 8-10% yield is reached in 14 to 16 days.

EXPERIMENTAL

Except where indicated we used reagent grade solvents and chemicals without further purification. Pyrrole alcohol was prepared for us by Dr. John E. Drach from pyrrole aldehyde (Aldrich) by the method of Silverstein (7). Spectrophotometric measurements were performed with the Cary 14 and the Beckman DK-1 Spectrophotometers. All other experimental techniques have been previously described (5, 8-10).

REFERENCES AND NOTES

- (1) H. Fischer and W. Gleim, *Ann. Chem.*, **521**, 157 (1936).
- (2) P. Rothmund, *J. Am. Chem. Soc.*, **58**, 625 (1936).
- (3) S. Krol, *J. Org. Chem.*, **24**, 2065 (1959).
- (4) A. D. Adler and S. Beitchman, Ph. D. Thesis by S. Beitchman, "Physical Chemical Study of Porphin," 1966, University of Pennsylvania.
- (5) A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli and M. G. Finarelli, *J. Heterocyclic Chem.*, **5**, 669 (1968).
- (6) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).
- (7) R. M. Silverstein, R. M. Ryskiewicz and S. Chaikin, *J. Am. Chem. Soc.*, **76**, 4485 (1954).
- (8) A. D. Adler, F. R. Longo and W. Shergalis, *J. Am. Chem. Soc.*, **86**, 3145 (1964).
- (9) F. R. Longo, M. Finarelli and J. B. Kim, *J. Heterocyclic Chem.*, **6**, 927 (1969).
- (10) J. B. Kim, J. J. Leonard and F. R. Longo, *J. Am. Chem. Soc.*, **94**, 3986 (1972).