ANGIL BUTLER
The Synthesis of *meso*-Substituted Porphyrins: Reaction Conditions and Substituent Effects
(Under the Direction of THOMAS E. JOHNSON)

The purpose of this study is to gain a better understanding of the parameters governing the synthesis of *meso*-substituted porphyrins. As a result of doing so, we anticipate that better reaction conditions can be developed, which will afford porphyrins in higher yields. Porphyrins are a large class of deeply colored red or purple, fluorescent crystalline pigments, of natural or synthetic origin, having in common a substituted aromatic macrocyclic ring consisting of four pyrrole-type residues, linked together by four methine bridging groups. The structure of porphyrin has been known since the early 1900's, but discrepancies exist on how the formation of porphyrin actually occurs. Several methods have been developed for the porphyrin reaction under various conditions. Three of the most common methods for the synthesis of *meso*-substituted porphyrins are: the Rothemund Method, the Adler Method, and the Lindsey Method. The conditions for these reactions vary from the harsh conditions where the reaction is completed in 15 minutes to 1 hour. Although each of these methods has their advantages, a convenient procedure for the large-scale synthesis of meso-substituted porphyrins has yet to be developed. Therefore, the demands required by commercial enterprise to prepare new molecules and materials in sufficient quantities as to make their use practical have still not been met. As a result, this led to the investigation of the 2-step, 1-pot synthesis and the proposal of a 2-step, 2-pot synthesis of porphyrins whereby the porphyrinogen intermediate is isolated and oxidized to porphyrin under non-reversible conditions.

INDEX WORDS: Porphyrin, Synthesis, BF_3-Aldehyde Complex

THE SYNTHESIS OF MESO-SUBSTITUTED PORPHYRIN: REACTION CONDITIONS AND SUBSTITUTENT EFFECTS

by

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December 2001

DEDICATION

I would like to dedicate my achievement to my family for being patient and understanding with me in my time of needs. Also for comforting me when I was stressed from all my studies.

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TABLE OF CONTENTS

Page

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

For more than 50 years there has been a struggle to find efficient conditions for the synthesis of porphyrins, but these studies have only provided adaptations of the original method (Rothemund Synthesis), together with extensions and mechanistic studies. Despite all efforts, the struggle still continues.

The word porphyrin has its origin in the classical world of ancient Greece. The Greek word porphura was used to describe the color purple.[1] This immediately tells us something about one of the most obvious features of porphyrins: their intense purple color Porphura was actually derive from an earlier Semitic word used by the Phoenicians to describe mollusks from which they extracted a rare pigment, called Tyrian Purple. Chemically, this substance is known as 6,6-dibromoindigotin (Figure 1.1). The Phoenicians used the color purple to dye the garments of royal families.[2] Even now, the color purple still represents with wealth, power, and privilege.

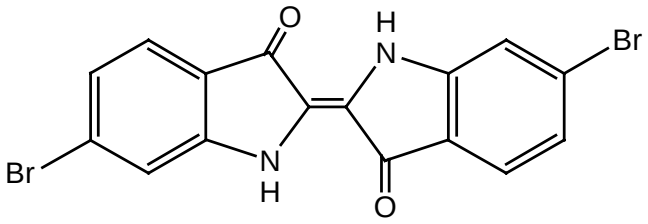


Figure 1.1 The structure of 6,6-dibromoindigotin.

The Structure of Porphyrins

Porphyrins are a large class of deeply colored red or purple fluorescent crystalline pigments, of natural or synthetic origin. The porphyrin structure was first proposed by Küster[3] in 1912, but nobody believed him because such a large ring was thought to be unstable. Years later, Fischer proposed the same structure when he succeeded in synthesizing heme from pyrrolic starting materials.[4] The structure was then confirmed by x-ray crystallography.

The unsubstituted porphyrin macrocycle, porphine, consists of four pyrrole-type residues, linked together by four methine bridging groups (Figure 1.2). Although the carbon atoms that make up the periphery of the porphyrin can be numbered consecutively from 1-20, they are typically referred to as either the β or *meso* positions whereby carbons 2 and 5 on the pyrrole fragments are the α-positions, carbons 3 and 4 are the β-positions, and the carbon atoms bridging the pyrroles are the *meso*-position.

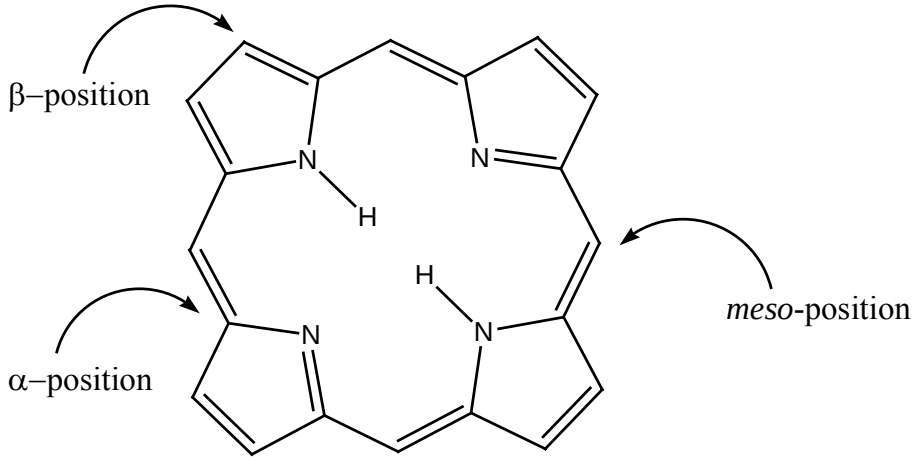
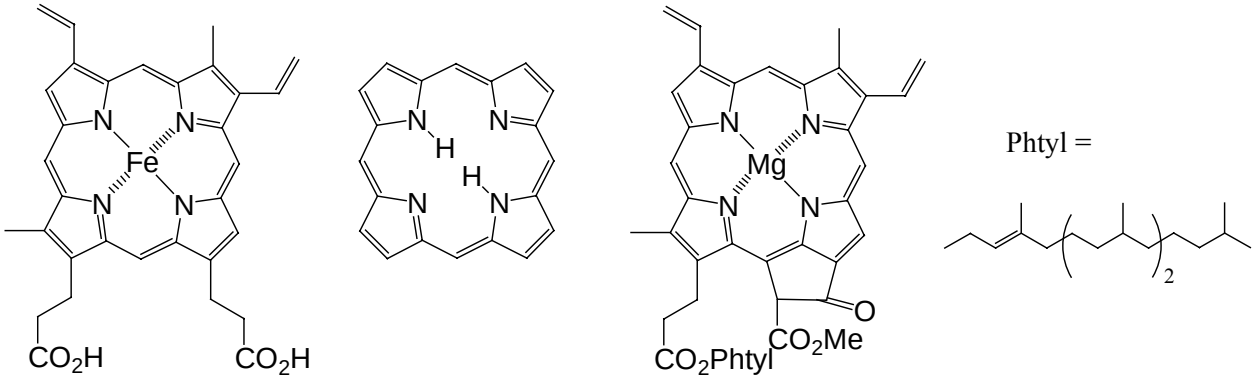


Figure 1.2 The unsubstituted porphyrin macrocycle.

Porphyrins in Nature

Porphyrins are particularly widespread in nature; they appear either as constituents of other pigments, or as the products of the disintegration of these pigments, or else as substances.[5] The quantities of porphyrins found in nature are relatively small and for this reason the study and separation of these pigments is often difficult, but with the aid of fluoroscopic analysis minute quantities of porphyrin may often be revealed by their red fluorescence. However, the appearance of a red fluorescence does not always indicate the presence of porphyrin, as many other substances exhibit a similar fluorescence. Only spectroscopic examination of the red fluorescence can determine the nature of the fluorescent material with exactitude. For instance, according to Neugebauer,[6] chlorophyll and its derivatives, rufin, and rufescin, as well as certain medicinal extracts such as rheum, cascara sagrada, and aloe frangula exhibit a red fluorescence which has no connection with the fluorescence of porphyrins.

The main function of porphyrins and porphyrin-like compounds in nature is to bind to metal atoms, which act as centers for significant biochemical events. Porphyrins are extraordinary because they are components of both heme (from blood), and chlorophyll (from plants). Thus biologically and chemically, porphyrins play a particularly important role in the life of the cell in both the animal and vegetable kingdoms. By comparing the structure of porphyrin and its components side by side (Figure 1.3), one can see that they are related molecules, and indeed they share the same biosynthetic pathway (Scheme 1.1).

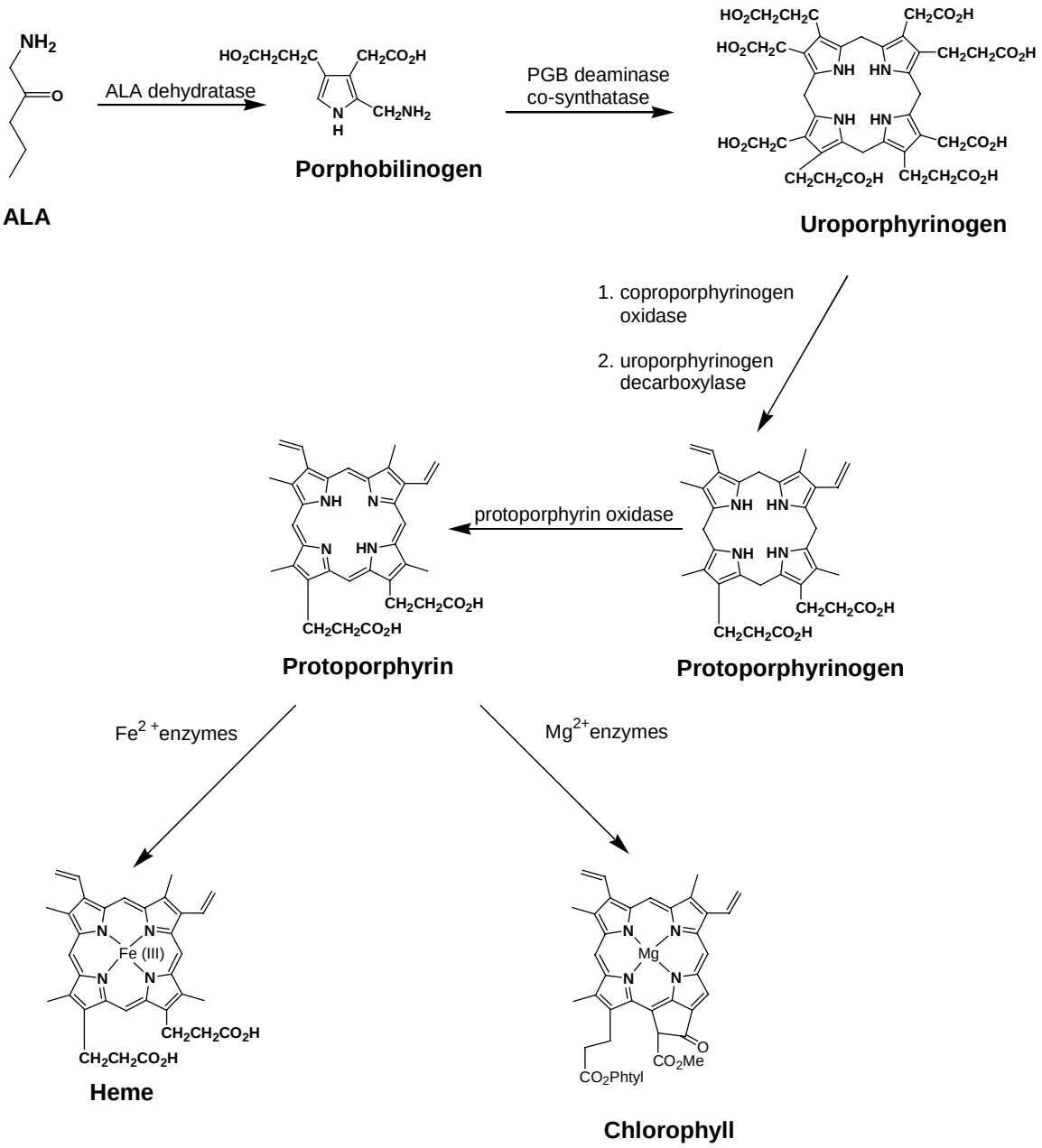


Heme **Porphyrin** **Chlorophyll A**

Figure 1.3 The structural similarities between porphyrin, heme, and chlorophyll A.

The animal pigment, heme, is found in hemoglobin and myglobin, which contains an iron atom (Fe^{2+}) ligated by the four nitrogens of a porphyrin ring system. Hemoglobin is contained in red blood cells and is responsible for transporting oxygen to cells and carbon dioxide away from cells. Without its presence, blood would be able to absorb only a fraction (about 2%) of the oxygen needed by the body.[7] Myglobin is active in the muscle and is responsible for oxygen storage in cells.[8]

The vegetable pigment, chlorophyll a, has a structure similar to that of heme, but is coordinated to magnesium (Mg^{2+}) instead of iron. It orchestrates photosynthesis, without which life, as we know it would be impossible.



Scheme 1.1 Biosynthesis of porphyrins.

δ-Aminolevulinic acid (ALA)[9] is the starting material for all porphyrin biosynthesis. ALA is cyclized to form porphobilinogen (PBG), and through a number of enzymatic reactions this pyrrole is cyclized to uroporphyrinogen III. The

uroporphyrinogen is then subjected to decarboxylation to give the reduced form of protoporphyrinogen IX. Oxidation at this point, followed by metallation of protoporphyrin gives hemin, which can be found as the co-factor in, for instance, hemoglobin and the cytochromes.[10]

Porphyrinic pigments also lie at the heart of the light-harvesting complexes of photosynthetic organisms.[11] The concentration of pigments in the antenna complexes is ~0.1 M,[12] yet structural analysis of one bacteriochlorophyll-protein complex shows that the π-systems of the pigments are not in van der Waals contact.[13] The design of a light-harvesting model system must bring a large number of porphyrins in close proximity yet maintain limited pigment contact. Porphyrinic pigments have a pronounced tendency to undergo face-to-face dimerization, and this aggregation process must be controlled in any model system for light-harvesting.

One approach to the construction of light-harvesting complexes is the synthesis of covalent arrays of porphyrins with the porphyrins held apart by relatively rigid linkers.[14] A second approach, co-crystallizing tetraphenylporphyrin with small organic compounds, has yielded a large family of crystals with regular sponge-like structures.[15] A third approach is to introduce bulky groups on both faces of the porphyrin, thereby establishing a minimum distance of separation of the porphyrin macrocycles in the crystalline state.[16]

Diseases Related to Porphyrins

The photoreactivity of porphyrins is the basis for photosynthesis and it offers the benefits of phototherapy against tumors and the aggravation of photodynamic action in the disease of porphyria. Porphyria is a defect of blood pigment metabolism in which

porphyrins are produced in excess. Porphyrins are present in the blood, and are found in the urine. Saillet[17] is generally credited with the first observation of porphyrin in normal urine. He called the pigment 'urospectrine' and noted that a considerable proportion of the total was excreted in the form of a colorless precursor, an observation that lay neglected for many years. It is now realized that over 95% and possibly all of the urinary coproporphyrin is actually excreted by the kidney in the form of coproporphyrinogen, which oxidizes spontaneously into coproporphyrin.

In 1911, Hans Günther[18] was the first to classify the porphyria disease into 3 groups: congenital, acute intermittent, and cutaneous hepatic. The symptoms that are usually present involve a sensitivity to light in exposed areas of skin, and in extreme cases, to photocutaneous lesions and neurological dysfunction.[19] Porphyria is eliminated through the bile and feces even under sterile conditions is proved by the finding of quite large quantities of porphyrin in meconium in various species.

Congenital porphyria is a very rare disease of porphyrin metabolism in which there is an onset of photosensitivity in early life and a complete absence of abdominal and neurological symptoms; the patient excretes excessive quantities of porphyrins resulting in erythrodonitia – pink–brown teeth and brown discoloration of the bones. In 1874, Schultz[20] reported the first case of congenital porphyria. Schultz's patient was a thirty-three year old weaver who had suffered from skin photosensitivity since the age of three months. His spleen was enlarged, his conjunctivae were icteric, and his urine was wine-red, which contained pigments resembling hematoporphyrin. At autopsy, an enormous quantity of porphyrin was found in his bones and they were very dark in color. Besides this, there was porphyrin fluorescence from many organs in his body. According

to Schmid[21] porphyrins were found to be more concentrated in the bone marrow than in the liver. Liver tissue possesses the enzymes capable of synthesizing porphyrins from porphobilinogen and it is possible that even in adult life this contributes to the total of porphyrins excreted. Heikel[22] suggested that the excessive porphyrin appearing in the liver in cutaneous porphyria might be derived from porphyrinogen, which has become oxidized and thus 'escaped' from the biosynthetic pathway.

Acute intermittent porphyria is the most important member of the group of porphyria diseases and is clinically distinguishable from others by the dominance of gastrointestinal and neurological symptoms and the absence of skin photosensitivity. In the acute and latent phase of the disease and often in states of remission, patients excrete in the urine excessive quantities of porphobilinogen and less of δ-aminolaevulic acid. Waldenström classified a substance in his patients' urine, which gave a red color with Ehrlich's aldehyde reagent (p-dimethyl-aminobenzaldehyde) as porphobilinogen. Porphobilinogen is now known to be the precursor chromogen of most of the uroporphyrin found in these urines and with certain very rare exceptions; its presence in excess in urine is a specific test for acute porphyria.

The first case of cutaneous hepatic porphyria was noted by Harris (1898).[23] He described a woman, aged forty, who had taken a good deal of Sulphonal and had excreted red urine for three years. Her skin showed a patchy pigmentation and bullae filled with a red alkaline fluid. The red pigment in her urine was considered by MacMunn to be porphyrin.

The Legend of Vampirism

Of all the disorders and diseases associated with porphyria, the most bizarre is their association with the myth of vampirism.[24] A person suffering from the following symptoms: 1) a pale complexion, 2) fatigue, 3) fainting spells, 4) shortness of breath, and 5) digestive disorders may have been under suspicion of a vampire attack. This disease would likely cause the victim to only go out at night, in order to avoid the painful rays of the sun. In addition, while garlic stimulates the production of heme in a healthy person, it would only cause the symptoms of porphyria to become more severe. For example, the strong smell of garlic or the sight of a reflection in a mirror would send a rabid person into convulsions. These contractions would mainly involve the muscles of the face and throat, causing growling and a grotesque toothy grin. Therefore, one could protect themselves from vampires by rubbing themselves with garlic or by brandishing a mirror. Experts believe characteristics widely attributed to vampires are the result of many cultural streams flowing together.[25] Whatever the case may be, whether vampires were actual supernatural beings (most unlikely) or legends based on some non-related facts (possible) or pure fabrications of fantasy, ignorance and anxiety mixed with superstition (most likely), the popular image of the vampire will probably reflect the sign of the times.

Synthetic Porphyrins and Their Applications

A large number of naturally occurring and synthetic porphyrin derivates are currently being used in a wide variety of applications, including molecular electronic devices, catalysis, energy conversion, and photodynamic cancer therapy.

In 1913 Meyer-Betz[26]demonstrated the phototoxicity of porphyrins by injecting himself with 200 milligrams of hematoporphyrin. The injection caused pain in the hepatic region for an hour, without any further symptoms as long as he remained sheltered from light. But, ten minutes' exposure to the sun caused a well-defined inflammatory reaction of the exposed skin, with redness and edema. Later, the swelling showed symptoms of a serious infiltration, which slowly disappeared, producing heavy pigmentation and peeling. The photosensitivity remained for several months.

In 1924 Policard[27] had discovered that certain malignant tumors accumulated porphyrins. However, it wasn't until 1975 that such a fortuitous combination was found to be beneficial in detecting and treating cancers. By 1976, the first successful trials with human volunteers in photodynamic therapy (PDT) had been initiated.

PDT is based on the administration of a drug (photosensitizer) combined with light. Light may cause chemical effects in cells exposed to its action and more especially a progressive degradation of the cellular components, the final products of which may be destroyed by oxidation during continued irradiation with light in the visible spectrum and in the presence of oxygen. But this final degradation by oxidation may even take place without oxygen being present if irradiation is by means of ultra-violet rays. According to Tappeiner,[28] all photosensitizing substances should fluoresce, and fluorescence is, therefore, intimately connected with the photodynamic action of these substances. This treatment is effective for cancerous tissues and malignant hemopoetic cells. However, hematoporphyrin is not the most ideal photosensitizer for the photodynamic treatment of cancers. For instance, it is a mixture of compounds, some of which are PDT-inactive. It also localizes, to a lesser extent, in healthy tissues, leading to photosensitivity of the

patient long after injection. There are seven golden rules for what constitutes a good PDT photosensitizer.

1. It must be a pure compound with a reproducible synthesis.
2. It must be activated at wavelengths >650nm to ensure better absorption of tissue-penetrating red light, and so sensitization by an external light source.
3. It must be non-toxic in the absence of light.
4. Its excited states must be long-lived enough to enable it to photosensitize the production of singlet oxygen.
5. It must localize specifically in the tumor.
6. It must clear rapidly from the body after it has done its work.
7. It must be soluble in the body's tissue fluids so that it can be injected and carried around the body to the tumor site.

The hunt for more efficient photosensitizers of PDT has been going on for several years because porphyrins have historically had little large-scale application industry, and therefore the technology to scale up lab bench reactions is lacking.

The Chemical Synthesis of Porphyrins

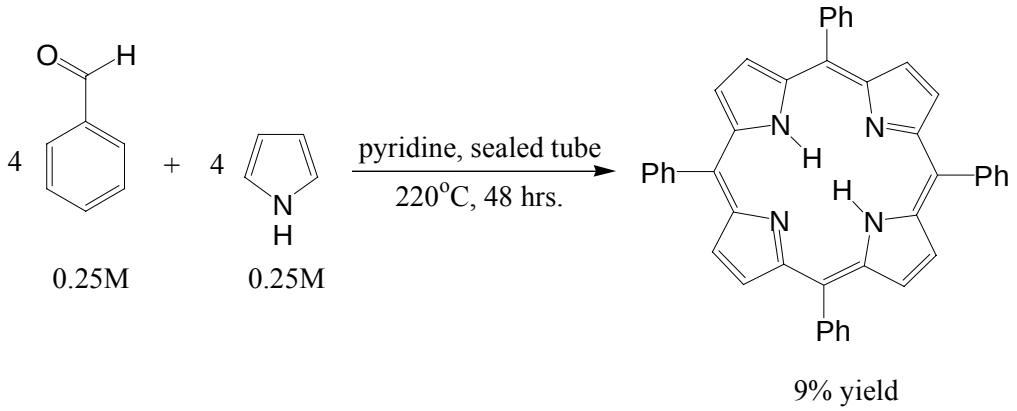
A variety of synthetic methods have been developed for the synthesis of non-natural porphyrins, especially for the *meso* tetra-substituted porphyrins, using pyrrole and aromatic aldehydes. Some of which include:

- Sealed-tube anaerobic reactions in pyridine at 220˚C
- Reactions in propionic or acetic acid under aerobic conditions

- Anaerobic condensation to form the porphyrinogen followed by oxidation to the porphyrin
- MacDonald coupling of dipyrroles
- Reactions without solvents, catalysts or man-made oxidants

The ultimate goal of these methods is to develop improved conditions that will support a convenient procedure for large-scale synthesis of meso-substituted porphyrins. Without easy access to large quantities of porphyrins the potential clinical and technological applications of porphyrins will be limited.

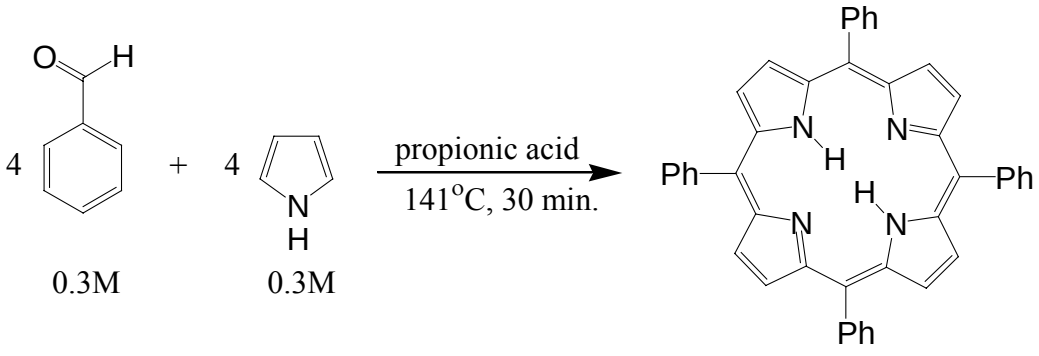
The Rothemund Synthesis. The first synthesis of tetraphenylporphyrin was achieved by Rothemund in 1936.[29] He caused benzaldehyde and pyrrole to react in the presence of pyridine in a sealed tube at 220°C for 48 hours; achieving tetraphenylporphyrin that was isolated as sparkling deep-purple needles from the by products in 9 %yield (Scheme 1.2). In addition to the low and irreproducible yields, the most severe limitation of the Rothemund synthesis was due to the harsh reaction conditions, which resulted in failure with all but a small selection of rather inert aldehydes.



Scheme 1.2 The Rothemund Synthesis of Tetraphenylporphyrin

In the Rothemund reaction, the yields of tetraphenylporphyrins are found to depend substantially on the character of the substituent on the phenyl ring.[30] Electron-acceptor substituents accelerate the reaction and increase the yields of tetraphenylporphyrins, whereas electron-donor substituents retard the reaction and decrease the yields; this is apparently due to preferred polymerization of pyrrole to give polypyrroles.

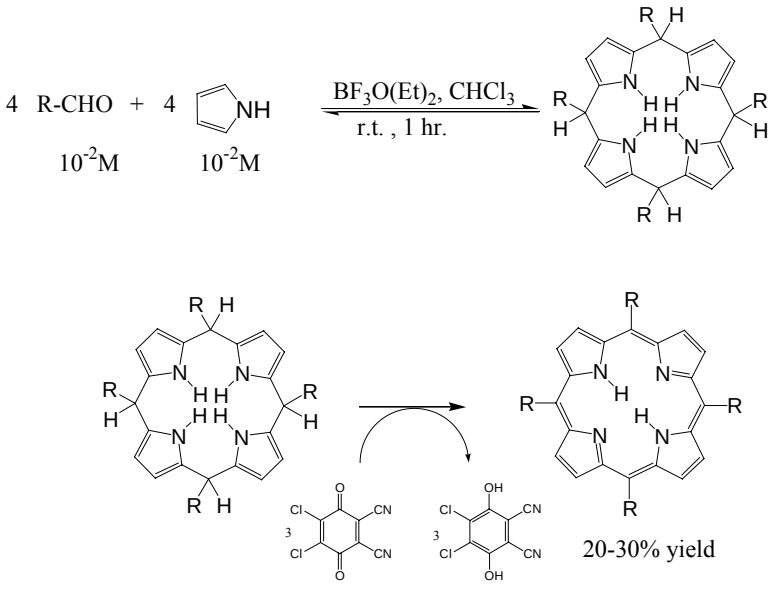
The Adler Synthesis. Adler altered the Rothemund reaction and was able to achieve tetraphenylporphyrin under milder conditions. He reacted benzaldehyde and pyrrole at high concentrations in refluxing propionic acid (141°C) for 30 minutes in the presence of air (Scheme 1.3).[31] The porphyrin crystals were isolated upon cooling by filtration, thus giving a 20% yield. Importantly, the Adler reaction can be performed on a large scale. By using propionic acid as a solvent Adler was able to avoid the hassle and limitations of dealing with sealed bombs. Additionally, these milder reaction conditions were compatible with a wider selection of aldehydes.



Scheme 1.3 The Adler Synthesis of Tetraphenylporphyrin

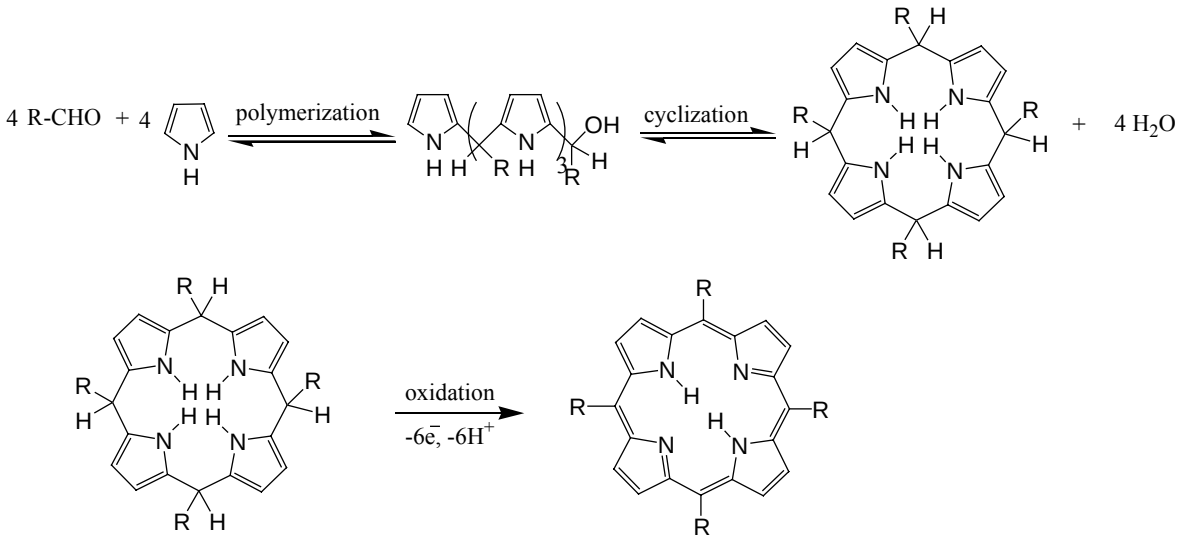
Even though the Adler method works better than the Rothemund method it still has its limitations. Some of which include: 1) the reaction fails completely with benzaldehydes bearing acid sensitive functional groups, 2) purification problems resulting from porphyrins that do not crystallize from propionic acid, and 3) the yields obtained are low and are often not reproducible.[32]

The Lindsey Synthesis. Lindsey developed a two-step, one-flask synthetic procedure for the synthesis of *meso*-substituted porphyrins, which gave an increase in the number of porphyrins being produced. It is an acid-catalyzed pyrrole-aldehyde condensation using low concentrations (10^{-2} M) at room temperature in the presence of $CHCl_3$ for an hour. In this first step the reaction is monitored for the maximum formation of porphyrinogen, an intermediate formed by the cyclization of a tetrapyrromethane, which is then rapidly oxidized to porphyrin in the second step by the addition of 3 equivalents of a high potential quinone oxidant (Scheme 1.4).[33] Isolation of the porphyrin usually requires two chromatographic procedures.



Scheme 1.4 Lindsey's Two-Step, One-Flask Synthesis of *meso*-Substituted Porphyrins.

The steps in the porphyrin-forming reaction presumably involve polymerization of an aldehyde and pyrrole to give tetrapyrromethane with each addition of pyrrole in a series of electrophilic aromatic substitution reactions. The carbonyl carbon is converted from sp^2 to sp^3 and thus becomes the *meso*-carbon in the porphyrin. Cyclization of the tetrapyrromethane affords the porphyrinogen, but does not involve rehybridization. The addition of an oxidant then converts the porphyrinogen to porphyrin in a six proton, six-electron process, thus converting the 4 *meso*-carbons from sp^3 back to sp^2 (Scheme 1.5).[34]

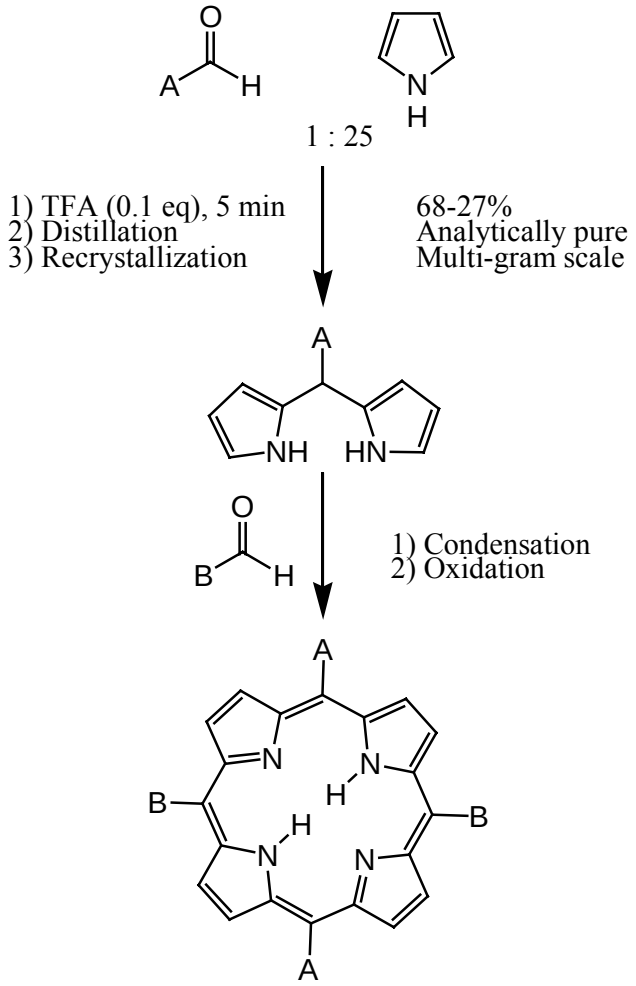


Scheme 1.5 The Lindsey Synthesis in more detail.

In the Rothemund and Adler reactions, the stoichiometric oxidant is presumably oxygen. In the Lindsey reaction, the oxidation of porphyrinogen to porphyrin is performed with p-chloranil or 2,3-dichlor-5,6-dicyano-1, 4-benzoquinone (DDQ). The addition of DDQ at room temperature gives a nearly instantaneous conversion of

porphyrinogen to porphyrin while p-chloranil is a much milder oxidant, requiring an exposure time of 1 hour for a complete reaction. The major disadvantages of using DDQ are 1) it is very expensive, and 2) it destroys some of the porphyrinogen.[35] Two other disadvantages of the Lindsey method include: (1) optimal yields are obtained with 0.01 M pyrrole and aldehyde concentrations, requiring large solvent volumes for gram scale preparations of porphyrins, and (2) the difficulties of purification (through tedious column chromatography) due to the large amount of quinone used as oxidant. For these reasons, this method is only useful for the preparation of milligram quantities of porphyrin.

The MacDonald-Type 2+2 Condensation. Condensation of a 5-disubstituted dipyrromethane with an aldehyde in a MacDonald-type 2+2 condensation[36] has been used to prepare a wide range of meso-substituted trans-porphyrins (Scheme 1.6). This methodology suffers from three major limitations: (1) the condensation is performed in dilute solutions (10 mM), (2) isolated yields of porphyrins are modest (10-30%), and (3) the product of a dipyrromethane-aldehyde condensation is frequently not just the desired trans-A_2B_2-porphyrin but a mixture of porphyrins that can be extremely difficult to separate. As a result, pure trans-porphyrins have typically been available only in limited quantities.



Scheme 1.6 MacDonald-Type 2+2 Condensation

Solventless Reactions. Drain developed a simple way to synthesize many *meso*-substituted porphyrins without solvents, catalysts or man-made oxidants with the reaction being completed in minutes.[37] *meso*-Tetraarylporphyrins were synthesized in 7-23% yield cleanly and efficiently in one step by reacting pyrrole at temperatures 10-15ºC above the boiling point of the starting aldehydes, using air as the oxidant. The advantage of this method is its simplicity and minimal waste production. Major drawbacks include low yields and the formation of similar side products.

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CHAPTER 2

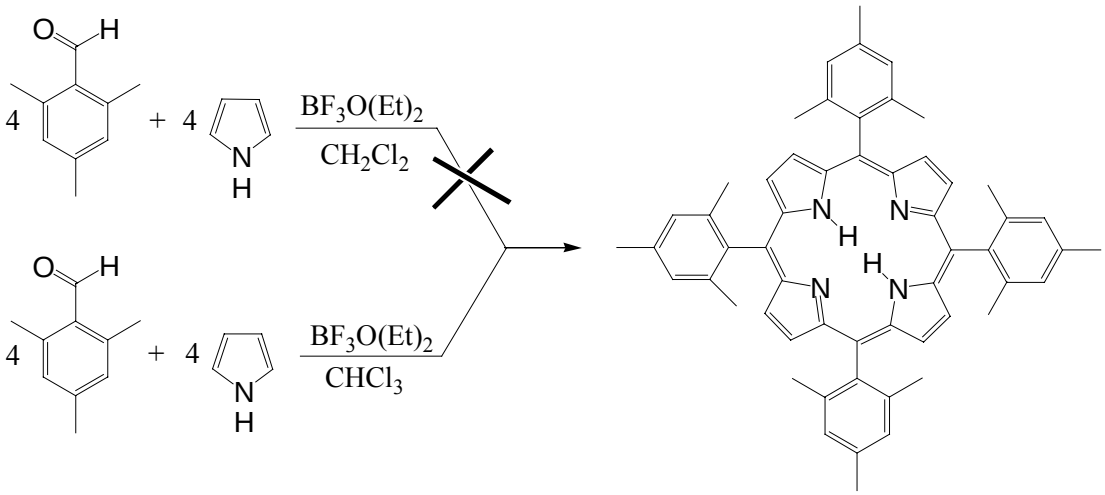
PRECIPITATE OF THE BF_3-ALDEHYDE COMPLEX

Abstract

The success or failure of various aldehydes in the porphyrin-forming reaction has been known to depend on several factors. However, a recent discovery of a previously unidentified precipitate observed when mesitaldehyde, pyrrole and BF_3 were reacted in the presence of CH_2Cl_2 was identified as the BF_3-aldehyde complex has led to a more complete understanding of the porphyrin reaction. The solubility of the BF_3-aldehdye complex has been added as one of the factors that contribute to the yield of porphyrins. By understanding the relationship between the precipitate and the success or failure of various aldehydes, porphyrins may be produced in higher yields.

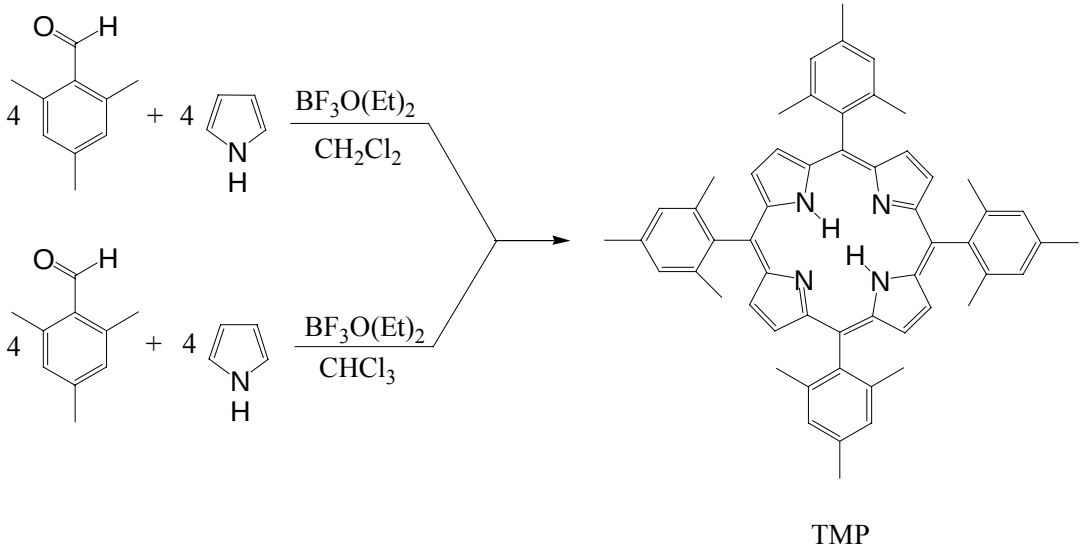
Introduction

The yield of porphyrin has been found to be dependent on a variety of factors, including solvent, concentration of acid, pyrrole, and aldehyde.[1] While the porphyrin reaction involves the use of several solvents, there is still not a clear understanding of the solvent effects. The most striking observation is found in the comparison of $CHCl_3$ and CH_2Cl_2 (Scheme 2.1). Lindsey found that the condensation of mesitaldehyde, pyrrole and $BF_3{\cdot}O(Et)_2$ in the presence of CH_2Cl_2 does not yield porphyrin. However, when the same reaction was performed in $CHCl_3$, tetramesitylporphyrin was produced in 31% yield.[2]



Scheme 2.1 Solvent comparisons for tetramesitylporphyrin (TMP).

By investigating the two solvents, Lindsey found out that the major difference between the two chlorinated solvents was the presence of 0.75% ethanol as a stabilizer in the commercial $CHCl_3$. The addition of 0.75% ethanol to CH_2Cl_2 resulted in a 25% yield of TMP, showing that the solvent effect was due to the presence of ethanol (Scheme 2.2).



Scheme 2.2 CH_2Cl_2 vs. $CHCl_3$.

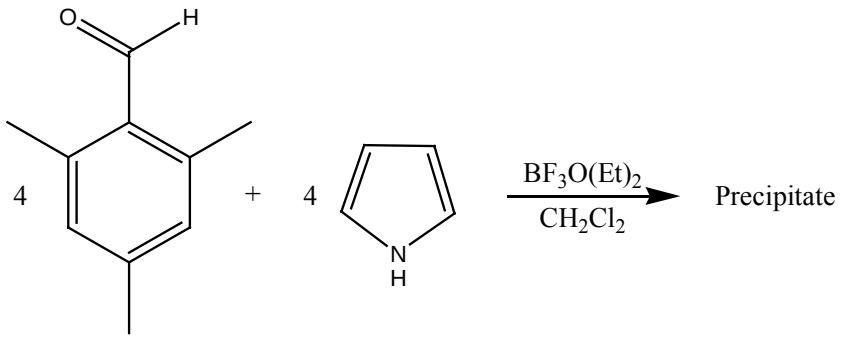
During his investigation of the mesitaldehyde reaction in the presence of CH_2Cl_2, he also observed the formation of a precipitate, but did not explain what the precipitate was. Although he could not account for the action of ethanol, he suggested that ethanol was acting as a co-catalyst by displacing the BF_3-aldehyde complex because mesitaldehyde is more basic than benzaldehyde. He also went one step further and suggested that ethanol is a requirement for the synthesis of all *o*-substituted benzaldehydes.

However, the requirement of added ethanol is not universal for the synthesis of all *o*-TPPs. Even when using conditions found optimal for TMP, for example, some aldehydes still fail to produce porphyrins (Table 2.1). In addition, using Adler's conditions 9-anthraldehyde, and 2,4,6-triphenylbenzaldehyde afford porphyrin, albeit in low yields of 0.2 and 1% yield respectively. Finally, some *o*-TPPs succeed in the Lindsey reaction without added ethanol. This data suggests that there is still no clear understanding of the factors related to solvent in the porphyrin-forming reaction.

Table 2.1 Benzaldehydes that fail to produce porphyrin.

Benzaldehydes	pKa	Lindsey	Adler
9-anthraldehyde	-5.11	0	0.2
2,4,6-triphenyl	-5.51	0	1
2,6-dinitro	-6.30	0	0
2,4,6-triisopropyl	-5.05	0	0
2,4,6-tri-t-butyl	-5.05	0	0
2,6-dichloro	-5.79	50	0
2,6-dimethoxy	-5.37	26	0

One observation in particular peaked our interest. Lindsey observed a precipitate while investigating the synthesis of TMP using CH_2Cl_2, as a solvent, but he failed to explain its origins. This precipitate was generated when mesitaldehyde, pyrrole, and BF_3 was reacted in the presence of CH_2Cl_2 (Scheme 2.3).



Scheme 2.3 The observed precipitate.

Clearly if something was precipitating from the solution this could help to explain why the reaction fails, so to gain a better understanding of this observation we decided to determine the origin of the precipitate by duplicating the conditions in which Lindsey observes the precipitate (Table 2.2). Upon mixing of mesitaldehyde, and pyrrole in the absence of BF_3, we did not observe a precipitate. Likewise, mixing of pyrrole and BF_3 in the absence of mesitaldehyde, failed to afford a precipitate. Finally, we mixed mesitaldehyde and BF_3 without pyrrole and observed the formation of a white precipitate.

Table 2.2 Origin of the precipitate.

Ms-CHO	Pyrrole	BF_3	Precipitate?
Ms-CHO	Pyrrole	-	No
-	Pyrrole	BF_3	No
Ms-CHO	-	BF_3	Yes

Since boron trifluoride complexes of aromatic aldehydes form stable 1:1 solid complexes, which are readily formed by treating a CCl_4 or CH_2Cl_2 solution of the free aldehyde with boron trifluoride gas or etherate[3], we assumed that the precipitate was the mesitaldehyde BF_3-complex (Figure 2.1).

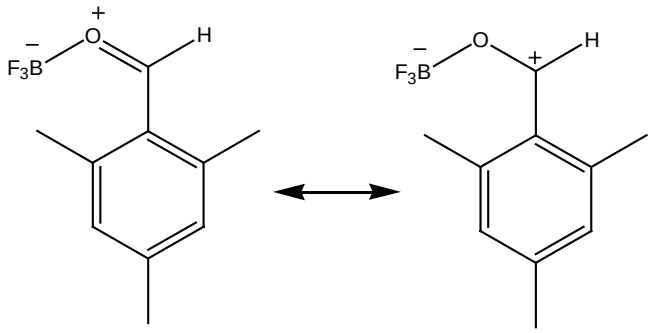
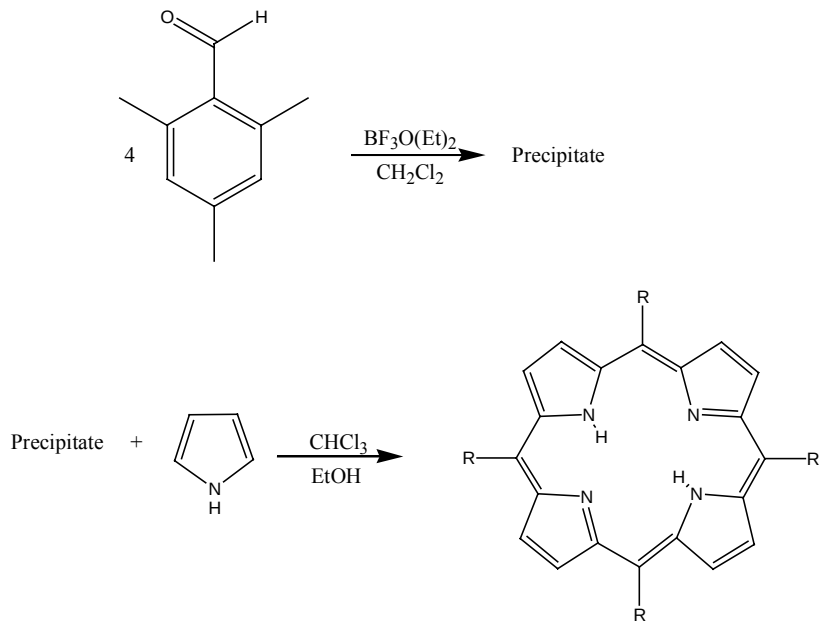


Figure 2.1 The BF_3 Lewis Acid Complex.

Further support of this assumption comes about when we dissolved the precipitate in $CHCl_3$ containing ethanol and added pyrrole. As a result, porphyrin was produced without additional aldehyde or BF_3 (Scheme 2.4).



Scheme 2.4 Precipitate yields porphyrin.

Given that it appears that the failure of the porphyrin-forming reaction is due to the insolubility of the BF_3-aldehyde complex, we looked at several possible factors that may influence the yield of porphyrin including, but not limited to: dihedral angle, pKa, and solubility.

The pKa values of several benzaldehydes were calculated using SPARC[4] (Table 2.3) to see if there was a correlation or cut off point between the aldehydes that worked and those that failed. Although these values were determined using the protonated aldehyde complexes and not the BF_3-aldehyde complex we felt that the trends for the two species would be similar.

Table 2.3 Benzaldehydes with different pKa values.

Benzaldehydes	pKa	% Yield
2,6-difluoromethyl	-6.25	20
2,3,4,5,6-pentafluoro	-6.11	40
2,6-difluoro	-5.73	46
Benzaldehyde	-5.42	50
2,6-dimethoxy	-5.37	15
2,4,6-trimethoxy	-5.23	15
2,4,6-trimethyl	-5.13	31

According to the results there appeared to be no cut off point for aldehydes that succeed or failed in the porphyrin reaction because a variety of benzaldehydes with a range of different pKa values from –6.34 to –5.13 produced porphyrin. Benzaldehydes with similar pKa values were also investigated (Table 2.4). 2-methoxy and 2-methylbenzaldehyde both yield porphyrin, but 2-phenylbenzaldehyde failed to produce porphyrin even though its pKa value was similar to 2-methoxy and 2-methylbenzaldehyde. Thus indicating that there appears to be no correlation between the stability of the complex and suggests that pKa is not an indicator of the success or failure of an aldehyde in the porphyrin-forming reaction. As mentioned earlier in chapter 1, it was suggested that electron-donor substituents retard the reaction and decreases the yield of porphyrin whereas; electron-acceptor substituents accelerate the reaction and increases the yield of porphyrin. Looking at the porphyrins that produced porphyrins and comparing it to those that did not yield porphyrin indicates that these trends are not universal.

Table 2.4 Benzaldehydes with similar pka values.

Benzaldehydes	pKa	% yield
2-methoxy	-5.38	38
2-phenyl	-5.48	0
2-methyl	-5.35	50

Sterics have also been suggested as an alternative explanation for the failure of the aldehydes.[5] Steric effects are dependent on the size and shape of a substituent as well as the environment with which it interacts. The ortho substituent, X faces the *meso* hydrogen and the second substituent, Y fits just below the tetrahedral meso carbon (Figure 2.2). These two interactions are seen in the minimal energy conformation of 5-mesityldipyrromethane, the structural motif of tetramesitylporphyrinogen. One methyl group is packed snugly into the lower groove, and the second methyl group's docks in a cogwheel fashion with the *meso* hydrogen.

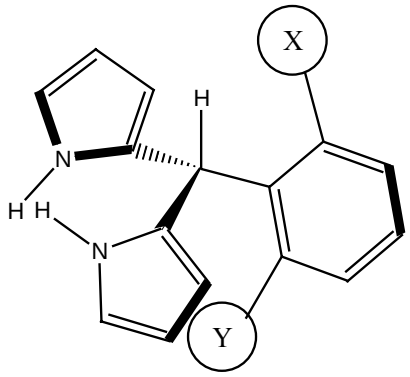


Figure 2.2 Rotational Barriers

One measure of the substituent size, the effective radius was obtained by Bott, by measuring the rotational barriers of various biphenyls (Table 2.5).[6]

Table 2.5 Substituent size and porphyrin yield of various aldehydes

ArCHO substituent	Effective radius*	% Yield
2,6-dimethoxy	1.52	15
2,6-dinitro	1.61	0
2,6-diphenyl	1.62	0
2,6-dichloro	1.73	50
2,6-dimethyl	1.80	32

According to Lindsey, aldehydes bearing ortho substituents "smaller" than the methyl group should react with equal or greater yield. Looking at the nitro, and phenyl groups, both of which are smaller than the methyl group one can see that yield and substituent size are not related and indicates that factors other than steric effects may be the cause of the failure of these aldehydes.

This then led us to an investigation of the dihedral angles of the BF_3 complex of various aldehydes.[7] Given that there seems to be no barrier to the formation of porphyrinogen, we thought that there may be hindered attack of the aldehyde. The dihedral angles involving atoms a, b, c, d were calculated for both mesitaldehyde and 2,6-dichlorobenzaldehyde using Spartan. The BF_3 complex of mesitaldehyde has a dihedral

angle of 90˚, where as 2,6-dichlorobenzaldehyde has a dihedral angle of 180˚ (Figure 2.2).

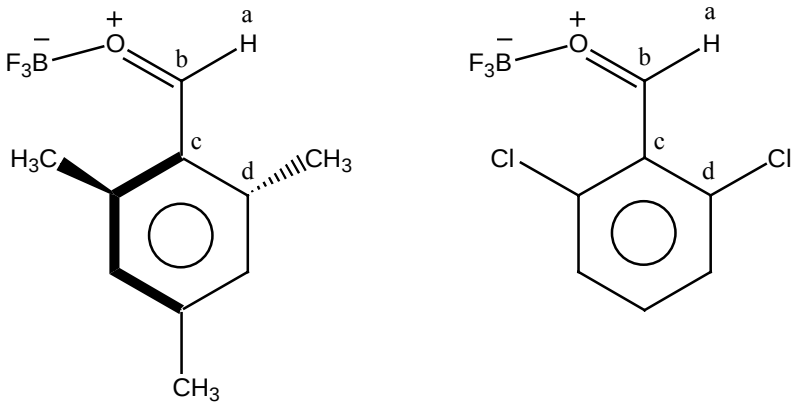


Figure 2.2 Investigation of the dihedral angles for BF_3-aldehyde complex

At first it seemed as if there was no correlation between the success and failure of the porphyrin reaction because both mesitaldehyde and 2,6-dichlorobenzaldedhyde produced porphyrin. However, mesitaldehyde only works with added ethanol, whereas 2,6-dichlorobenzaldehyde, also an ortho substituted aldehyde, works with or without added ethanol. An alternative explanation for these observations is that mesitaldehyde is hindered from solvation, whereas 2,6-dichlorobenzaldehdye is open to solvation. This explanation would also support the observation of a precipitate in solvents, which do not contain ethanol, since both propionic acid and the chlorinated hydrocarbons are relatively large molecules with diffuse charge density. Further support of this assumption can be

seen using Lindsey's data whereby he investigated the success of mesitaldehyde in the porphyrin reaction using other alcohols (Table 2.6).

Table 2.6 The alcohol comparison for several organic solvents.

ROH	% Yield	Dipole Moment	Dielectric Constant
Methanol	19	1.7	33
Ethylene glycol	24	0	0
Ethanol	25	1.69	24
tert-Butyl alcohol	0	0	0
Propionic acid	0	0	0
$CHCl_3$	31	0	0
CH_2Cl_2	0	0	0

According to these results, methanol, ethylene glycol, and ethanol, all primary alcohols, appear to be small enough to solvate mesitaldehyde, however *t*-butyl alcohol appears to be too bulky to solvate the mesitaldehyde BF_3 complex. Since ethanol is required with mesitaldehyde, but not with 2,6-dichlorobenzaldehdye we believe that the 2,6-dichlorobenzaldehyde-BF3 complex is open to solvation from bulkier solvents and also attack by pyrrole.

The data also suggest that solvation is afforded by direct interaction of the solvent with the complex rather than on the bulk properties of the solvent. This is supported by

the fact that the dielectric constants for each of these solvents differ widely, but the dipole moments among the alcohols remain the same.

Finally, additional support for this idea can be found with the comparison of other aldehydes. 2,6-dichloro and 2,6-dimethoxybenzaldehyde, for example, both have a dihedral angle of 180˚ and do not require ethanol. However, 2,6-diphenyl and 2,6-dimethylbenzaldehydes both have a dihedral angle of nearly 90˚ and require ethanol, thus indicating that the BF_3-aldehyde complex is hindered from solvation and attack, and hence fails to produce porphyrin (Table 2.7). Therefore, we believe that ethanol is acting as a co-solvent in the Lindsey reaction rather than a co-catalyst as Lindsey suggested.

Table 2.7 Ethanol requirements for several benzaldehydes with substituents in the 2,6-position.

Benzaldehyde	Ethanol	Dihedral Angle
2,6-dichloro	NR	180º
2,6-dimethoxy	NR	180º
2,6-diphenyl	R	113º
2,6-dimethyl	R	90º

Table 2.8 Calculated pKa values.

pKa	Aldehyde	% Yield
-6.34	2,4-dinitrobenzaldehyde	-
-6.30	2,6-dinitrobenzaldehyde	-
-6.25	2,6-difluoromethylbenzaldehyde	20[d]
-6.21	3,5-difluoromethylbenzaldehyde	10[b], 40[c]
-6.11	2,3,4,5,6-pentafluorobenzaldehyde	-
-6.09	2-chloro, 6-nitrobenzaldehyde	-
-6.09	2-nitro, 5-chlorobenzaldehyde	-
-6.01	2-chloro, 5-fluoromethylbenzaldehyde	-
-6.00	2,3,5,6-tetrafluorobenzaldehyde	-
-5.99	2-chloro, 5-nitrobenzaldedhyde	-
-5.98	2-fluoro, 6-fluoromethylbenzaldehyde	-
-5.96	2,3,6-trichlorobenzaldehyde	-
-5.95	2,3,5-trichlorobenzaldehyde	-
-5.94	4-nitrobenzaldehyde	25[d]
-5.94	2-fluoromethyl, 4-fluorobenzaldehyde	-
-5.92	3-nitro, 4-fluorobenzaldehyde	-
-5.92	2-nitro, 3-methoxybenzaldehyde	-
-5.92	2-nitrobenzaldehyde	27[c], 20[d]
-5.83	2-fluoromethylbenzaldehyde	43[c]
-5.83	2,3,4-trifluorobenzaldehyde	-
-5.82	3-fluoromethylbenzaldehyde	-
-5.81	3,4-dimethoxy, 6-nitrobenzaldehyde	-
-5.79	2,3-dichlorobenzaldehyde	-
-5.79	2,6-dichlorobenzaldehyde	50[c], 7[d]
-5.79	3-nitrobenzaldehyde	9[d]
-5.76	2-chloro, 6-fluorobenzaldehyde	-
-5.76	2,4-dichlorobenzaldehyde	-
-5.75	3,5-dichlorobenzaldehyde	5.1[d]
-5.73	3,4-dichlorobenzaldehyde	-

-5.73	**2,6-difluorobenzaldehyde**	**52[c]**
-5.73	**2-chloro, 4-fluorobenzaldehyde**	**-**
-5.72	**2,5-difluorobenzaldedhyde**	**-**
-5.72	**2,3-difluorobenzaldehyde**	**-**
-5.72	**2,3-difluorobenzaldehyde**	**-**
-5.71	**4-fluoromethylbenzaldehyde**	**-**
-5.70	**2,4-difluorobenzaldehyde**	**-**
-5.70	**3-bromo, 4-fluorobenzaldehyde**	**-**
-5.69	**3-chloro, 4-fluorobenzaldehyde**	**-**
-5.69	**3,5-difluorobenzaldehyde**	**-**
-5.66	**3,4-difluorobenzaldehyde**	**-**
-5.62	**2-chlorobenzaldehyde**	**27[c], 8.5[d]**
-5.61	**2-bromobenzaldehyde**	**30[c]**
-5.59	**3-chlorobenzaldehyde**	**-**
-5.59	**3-bromobenzaldehyde**	**-**
-5.58	**2-fluorobenzaldehyde**	**24[c]**
-5.56	**3-fluorobenzaldehyde**	**-**
-5.56	**4-chlorobenzaldehyde**	**20[b]**
-5.56	**2-methoxybenzaldehyde**	**-**
-5.55	**4-bromobenzaldehyde**	**42[c]**
-5.54	**2-fluoro, 3-methylbenzaldehyde**	**-**
-5.53	**4-fluorobenzaldehyde**	**-**
-5.51	**2,4,6-triphenylbenzaldedhyde**	**1[b], 0.046[c]**
-5.50	**2,3-dimethoxybenzaldehyde**	**-**
-5.49	**2-methyl, 3-fluorobenzaldehye**	**-**
-5.49	**3,4-dimethoxy, 6-bromobenzaldehyde**	**-**
-5.48	**2-phenylbenzaldehyde**	**-**
-5.47	**3,5-dimethoxybenzaldehyde**	**-**
-5.46	**Anthraldehyde**	**0.2[b]**
-5.44	**3-methoxybenzaldehyde**	**10[d]**
-5.42	**3-phenylbenzaldehyde**	**-**
-5.42	**Benzaldehyde**	**9[a], 20[b], 30[c], 18[d]**
-5.41	**2,5-dimethoxybenzaldehyde**	**-**
-5.40	**3-bromo, 4-methoxybenzaldedhyde**	**-**

-5.40	**2,4-dimethoxybenzaldehyde**	**-**
-5.40	**3,4,5-trimethoxybenzaldehyde**	**-**
-5.39	**2,3,4-trimethoxybenzaldehyde**	**-**
-5.39	**4-phenylbenzaldehyde**	**-**
-5.38	**2-methoxybenzaldehyde**	**38[c], 15[d]**
-5.37	**3-methylbenzaldehyde**	**-**
-5.37	**2,6-dimethoxybenzaldehyde**	**26[c], 15[d]**
-5.36	**3-fluoro, 4-methoxybenzaldehyde**	**-**
-5.35	**2-methylbenzaldehyde**	**50[c], 14[d]**
-5.31	**2,5-dimethylbenzaldehyde**	**-**
-5.27	**4-methylbenzaldehyde**	**17[c], 19[d]**
-5.27	**3,4-dimethoxybenzaldehyde**	**-**
-5.27	**2,4,5-trimethoxybenzaldehyde**	**-**
-5.24	**2,4-dimethoxy, 3-methylbenzaldehyde**	**-**
-5.23	**2,4,6-trimethoxybenzaldehyde**	**3.7[c], 15[d]**
-5.22	**4-methoxybenzaldehyde**	**35[c], 45[d]**
-5.22	**2,4-dimethylbenzaldehyde**	**-**
-5.22	**2,4-dimethoxybenzaldedhyde**	**-**
-5.18	**3-methyl, 4-methoxybenzaldehyde**	**-**
-5.14	**2,3-dimethyl, 4-methoxybenzaldehyde**	**-**
-5.14	**2,4-dimethoxy, 5-methylbenzaldehyde**	**-**
-5.13	**2,4,6-trimethylbenzaldedhyde**	**31[c], 2[d]**

Table 2.9 Dihedral angles for the BF_3-aldehyde complex.

BF_3-Aldehdye Complex	**Set at 90º**	**Set at 180º**
2,6-dichlorobenzaldehyde	180	180
2,6-dibromobenzaldehyde	180	180
2,6-dimethoxybenzaldehyde	180	180
2,6-dihydroxybenzaldehyde	180	180
2,6-difluoromethylbenzaldehyde	95	95
2,6-dinitrobenzaldedhyde	90	90
2,6-diphenylbenzaldehyde	88	88
2,4,6-trimethylbenzaldehyde	88	180
2,4,6-tri-tertbutylbenzaldehyde	90	108

Table 2.10 Dihedral angles for the aldehyde and BF_3-aldehyde complex in the 2-position.

BF_3-Aldehyde Complex	Dihedral Angle	Aldehyde	Dihedral Angle
2-chlorobenzaldehyde	180	2-chlorobenzaldehyde	180
2-bromobenzaldehyde	180	2-bromobenzaldehyde	180
2-methoxybenzaldehyde	180	2-methoxybenzaldehyde	180
2-fluoromethylbenzaldehyde	80	2-fluoromethylbenzaldehyde	180
2-nitrobenzaldehyde	109	2-nitrobenzaldehyde	3
2-phenylbenzaldehyde	50	2-phenylbenzaldehyde	180
2-methylbenzaldehyde	90	2-methylbenzaldehyde	-
2-*tert*butylbenzaldehyde	70	2-*tert*butylbenzaldehyde	-

Table 2.11 Dihedral angles for aldehydes in the 2,6-position.

Aldehyde	Dihedral Angle
2,6-dichlorobenzaldehyde	180
2,6-dibromobenzaldehyde	180
2,6-dimethoxybenzaldehyde	180
2,6-di-fluoromethylbenzaldehyde	35
2,6-dinitrobenzaldehyde	90
2,6-diphenylbenzaldehyde	85
2,6-dimethylbenzaldehyde	180
2,6-di*tert*butylbenzaldehyde	180

Conclusion

Although there may be no single factor that contributes to the yield of porphyrin, it appears that the solubility of the BF_3-aldehyde complex plays a major role in determining the success or failure of different aldehydes in the porphyrin reaction rather

than any substituent effects. Thus, the clarification of the role of ethanol points the direct to further studies rather than obscuring them. Studies involving more lipophilic lewis acid catalysts and better co-solvents are currently underway.

Experimental

General Procedure for the synthesis of Porphyrins.

A flame-dried 50mL three-neck round bottom flak equipped with a magnetic stirring bar. 25mL of freshly distilled dichloromethane was charged with a slight stream of argon. Pyrrole (17.3μL, 0.25mmol), mesitaldehyde (37μL, 0.25mmol), and 10μL of 2.5M boron trifluoride diethyl etherate were added in this order using a syringe. The reaction vessel was shielded from light using aluminum foil. To monitor the progress of the reaction, samples were taken at 15 minutes intervals from the reaction vessel. The samples developed as follows: 25μL was removed from the reaction vessel and injected into 150μL of a 10^{-2}M DDQ solution in toluene (an oxidizing solution). The oxidation of porphyrinogen to porphyrin and pyrrylmethanes to pyrrylmethenes occurs instantaneous. Then 50μL of the oxidized solution was diluted in 3mL 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 (λ_{max} = 420nm, ε = 500,000 $M^{-1}cm^{-1}$) measured from the apex to the base of the edge of the band.

Solvents.

CH_2Cl_2 and $CHCl_3$ were distilled from K_2CO_3. The commercially available $CHCl_3$ contained ethanol (0.75%) as a stabilizer. Ethanol was not removed by distillation from

K_2CO_3. Pyrrole was distilled from calcium hydride and stored samples were discarded when discoloration occurred.

Acid Catalysts.

Stock solutions of $BF_3 \cdot OEt_2$ were prepared by diluting the commercially available $BF_3 \cdot OEt_2$ from Aldrich (8.1M) to 2.5M in CH_2Cl_2 of $CHCl_3$ depending on the solvent used in the reaction. Stock solutions remained viable for at least 2 weeks.

Computations.

Computational studies were done on the dihedral angles for various aldehydes using semi-empirical methods at the PM3 level of theory with Spartan (v5.0). The pKa values were calculated using SPARC (SPARC Performs Automated Reasoning in Chemistry). It analyzes the chemical structure relative to a specific reactivity query.

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CHAPTER 3

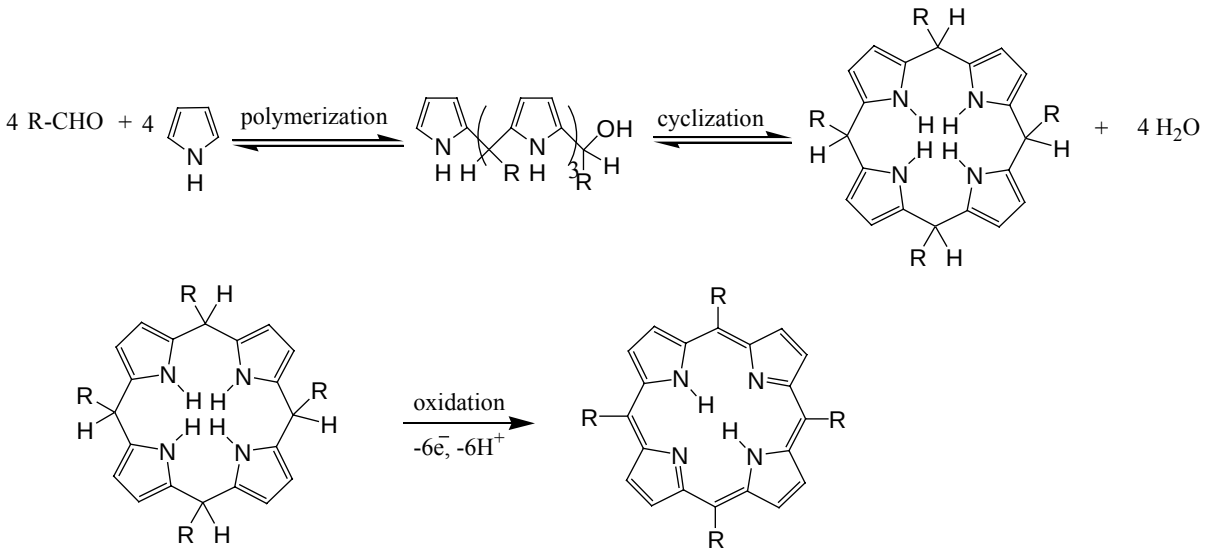
THE FORMATION OF PORPHYRINOGEN

Abstract

The porphyrin reaction presumably fails because of the competition between oligomerization and cyclization. Although low concentration methods have been investigated, they have shown little improvements in the yield of the reaction. However, using different solvents and higher reagent concentrations, porphyrinogen formation was enhanced by precipitation from the reaction mixture and successfully converted to porphyrin.

Introduction

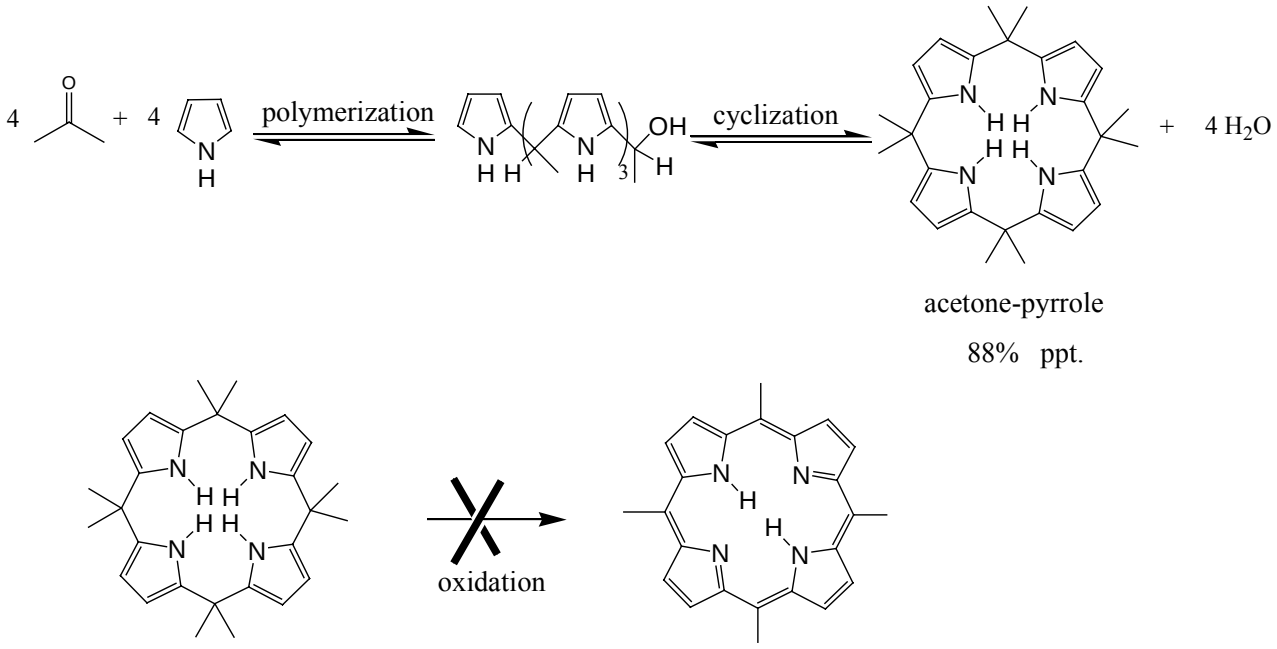
Porphyrins bearing four identical *meso*-substituents can be synthesized by the reaction of an aldehyde and pyrrole in a relatively simple two-step, one flask procedure at high dilution.[1] The first step involves acid-catalyzed condensation yielding oligomers and the cyclic porphyrinogen. The second step involves the oxidative conversion of the porphyrinogen to the porphyrin (Scheme 3.1).



Scheme 3.1 The two-step, one-flak synthetic procedure.

Although the oligomers are critical intermediates along the pathway from starting material to porphyrinogen they are also undesirable reaction by-products.[2] The oligomers are believed to constitute ~50 % or more of the material derived from the starting materials.[3]

In contrast to the low yields of porphyrinogen obtained in the porphyrin reaction, the condensation of pyrroles with ketones gives a cyclic tetramer, calix[4]pyrrole, in high yield, which cannot be oxidized to porphyrin (Scheme 3.2). It has been suggested that the geminal methyl groups tends to force the pyrrole rings into a coplanar conformation, greatly increasing the chances of cyclization of a linear tetrapyrrolic precursor.[4] This effect known as the Thorpe-Ingold Effect or Gem-Dimethyl Effect (GDME) can be used to account for the high yields of cyclization obtain in the synthesis of acetone-pyrrole.



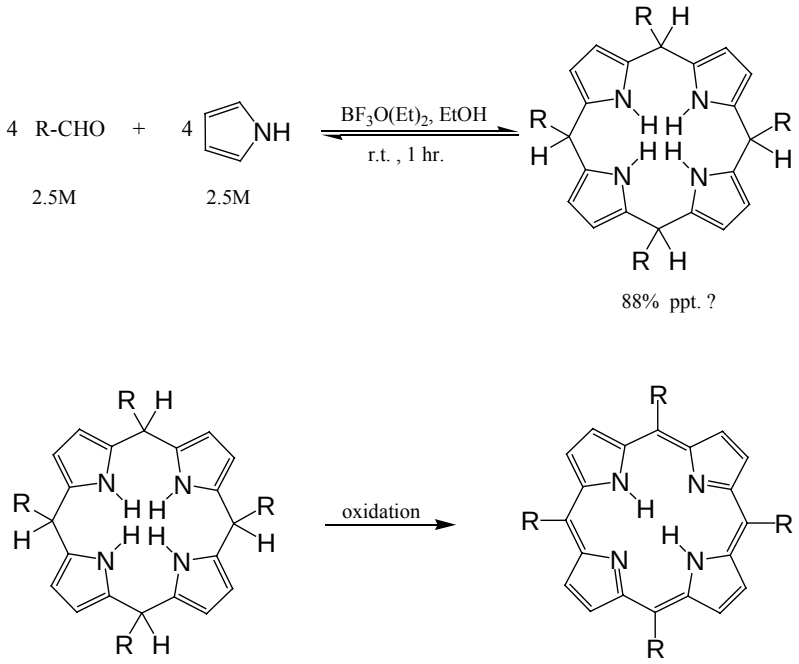
Scheme 3.2 The synthesis of acetone-pyrrole.

Given the low yields in the porphyrin reaction, presumably do to the competition between oligomerization and cyclization, we were anxious to obtain high yields of porphyrinogen that could be further oxidized to porphyrin. If however, the Thorpre-Ingold effect were indeed responsible for the increased yields of porphyrinogen, we would not expect to observe high yields of porphyrinogen when using aldehydes. And although this is the case in both dilute solution and at high concentration in porphyrin reactions using pyridine, propionic acid, $CHCl_3$, toluene and CH_2Cl_2, if there was another reason, solubility for example, for the high yields obtained in the preparation of acetone-pyrrole maybe we could also obtain high yields of the oxidizable porphyrinogen from aldehydes. The advantages of this approach are immediately obvious when one compares the reaction of acetone-pyrrole and benzaldehyde-pyrrole (Table 3.1); high yield, high concentration, and simplified purification.

Table 3.1 A comparison of acetone-pyrrole and benzaldehyde-pyrrole.

	Acetone-Pyrrole	Benzaldehyde-Pyrrole
Solvent	EtOH	$CHCl_3$
Conc.	2.5M	$1x10^{-2}M$
Product	Porphyrinogen	Porphyrin
Yield	88%	30%
Isolation	Filtration	Chromatography

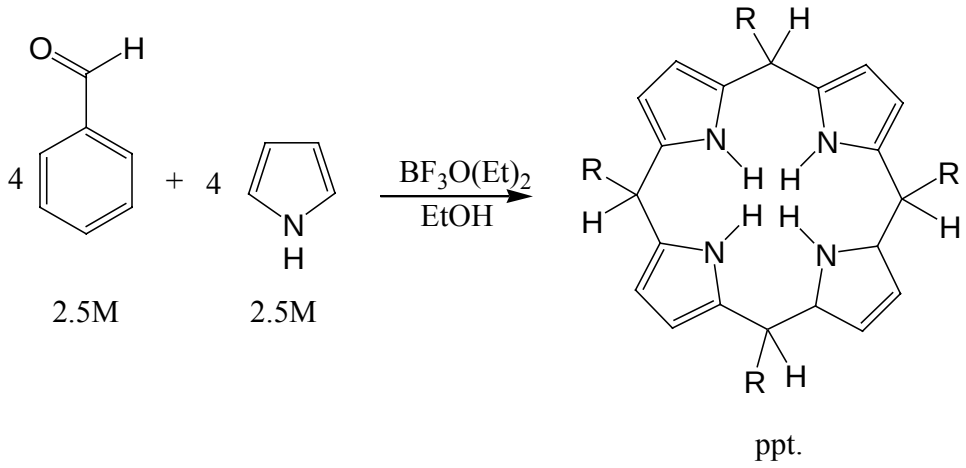
We therefore investigated a new 2-step, 2-pot modification of the porphyrin reaction (Scheme 3.3) using the same conditions for the acid-catalyzed condensation of ketones and pyrrole to see if we could isolate the benzaldehyde porphyrinogen in high yield.



Scheme 3.3 Proposed 2-step, 2-pot synthetic procedure.

Porphyrinogens are known as the precursor to the porphyrin reaction, but since the conjugation of the porphyrin macrocycle is destroyed, porphyrinogens do not have the same planarity, color, or fluorescence as porphyrins. Porphyrinogens occur naturally in small amounts in all living cells, and are often excreted in copious quantities when the porphyrin metabolism is disturbed, as in the diseases of porphyria.

In an attempt to isolate the porphyrinogen, experiments were conducted using benzaldehyde and pyrrole with BF_3 in the presence of ethanol at 0˚C (Scheme 3.4).



Scheme 3.4 Isolation of porphyrinogen.

Low temperatures were used to slow the rate of reaction and also to further decrease the solubility of the porphyrinogen. Indeed, upon addition of BF_3OEt_2 to a pre-cooled and deoxygenated solution containing benzaldehyde (2.5M) and pyrrole (2.5M) a pink precipitate formed immediately. The precipitate was isolated by filtration and washed with saturated sodium bicarbonate. While washing with sodium bicarbonate, the precipitate began turning dark burgundy, which suggested that the precipitate was air

sensitive. Since the identity of the precipitate was not known its solubility was tested with several organic compounds to facilitate characterization (Table 3.2).

Table 3.2 The precipitate's solubility.

SOLVENT	COLOR	SOLUBILITY
Acetone	Black	SS
Acetonitrile	Black	SS
Chloroform	Black	S
Dichloromethane	Black	S
Hexane	Clear	IS
Water	Clear	IS

As a result of doing so, the burgundy precipitate turned dark purple, thus indicating that the unknown precipitate was definitely air sensitive. We also obtained a mass spectrum of the precipitate, (Figure 3.1) and the peak at 621 corresponds to the porphyrinogen. The other peaks represent fragments of the porphyrinogen and higher oligomers, which are presumably trapped when the porphyrinogen precipitates.

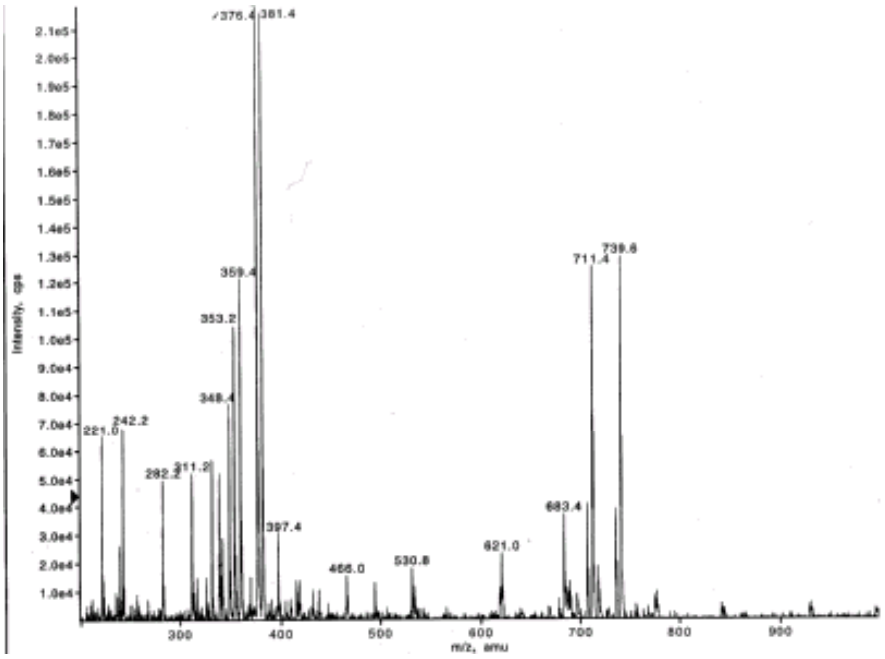
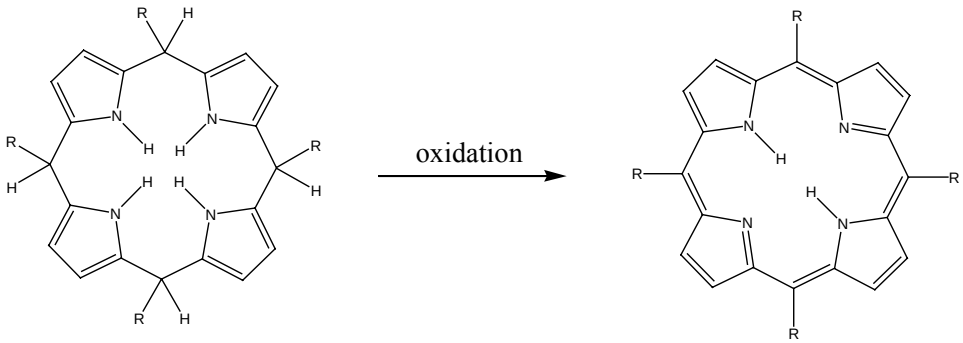


Figure 3.1 The precipitate's mass spectrum.

Final proof was obtained when we converted the "precipitate" to porphyrin using standard oxidation methods (Scheme 3.5). Given the liabilities of using DDQ we are currently investigating a number of other ways to convert porphyrinogen to porphyrin, some of which include: copper salts, zinc acetate, or iodine. High valent transition metals have also been shown to facilitate the oxidation and are also currently being investigated.



Scheme 3.5 The oxidation of porphyrinogen to porphyrin.

The advantages of our 2-step, 2-pot synthesis are that the porphyrin-forming reactions can be performed at higher concentrations whereby porphyrinogen formation is favored over further oligomerization by precipitation from the reaction mixture. This also allows for simple purification by and gives us the opportunity to fine-tune the oxidation conditions in neutral or basic conditions where ring opening will be disfavored.

Conclusion

Contrary to our understanding of the porphyrinogen formation high concentrations can be used to favor the cyclized product, presumably due to the decreased solubility of the porphyrinogen relative to its oligomeric precursors.

Experimental

meso-Tetraphenylporphyrinogen

50mL of cold ethanol, 13.2ml of benzaldehyde, and 8.4ml of distilled pyrrole was purged with argon throughout the reaction in a 250mL, 3 neck-round bottom flask covered with aluminum foil to protect it from the light, while sitting in an ice bath. The solution turned yellow. After 15 minutes of bubbling argon 0.1mL of $BF_3{\cdot}OEt_2$ was added all at once. Upon addition of $BF_3{\cdot}OEt_2$ the solution turned burgundy and a pink precipitate that clumped together formed immediately. The porphyrinogen was collected by filtration, and washed with saturated sodium bicarbonate, m.p. (lit.) 237-238º dec. Found: C, 85.01; H, 5.79; N, 9.20. m/e 621.

References

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CHAPTER 4

CONCLUSION AND FUTURE WORK

Future interest will involve the investigation of several solvents to determine which ones can increase the solubility of the BF_3-complex, which is believe to be the key step in the porphyrin-forming reaction. Also, find solvents in which the porphyrinogen is insoluble. As a result of doing so more porphyrinogen precipitate can be isolated. Finally we will seek optimal conditions for the oxidation of porphyrinogen to porphyrin in high yield. To carry out this task we will be performing reactions at even higher concentrations and lower temperature. We believe the results of these experiments will be success in producing porphyrins in high yield based on what we have observed so far.