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SYNTHESES OF PORPHYCENE
AND N,N'-BRIDGED PORPHYCENES

presented by

Irene M. Morrison

has been accepted towards fulfillment
of the requirements for

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Chris K. Chang
Major professor

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SYNTHESES OF PORPHYCENE AND N,N'-BRIDGED PORPHYCENES

By

Irene M. Morrison

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ABSTRACT

SYNTHESES OF PORPHYCENE AND N,N'-BRIDGED PORPHYCENES

By

Irene M. Morrison

The formation of a one-carbon bridge between pyrrolic nitrogen atoms of porphycene, forming a seven-membered ring in a bicyclic compound, was achieved by using DMF/$POCl_3$ in Vilsmeier-type reaction conditions. N,N'-Bridging was also accomplished by using N-methylformanilide in 1,2-dichloroethane/$POCl_3$, and 3-(dimethylamino)-acrolein in 1,2-dichloroethane/$POCl_3$ affording N,N'-((N,N-dimethyl-amino)methylene)-2,7,12,17-tetrapropylporphycene, N,N'-((N-methyl-aniline)methylene)-2,7,12,17-tetrapropylporphycene, and N,N'-(C-C=C-NMe_2)-2,7,12,17-tetrapropylporphycene, respectively. N,N'-((N-methyl-amino)methylene)-2,7,12,17-tetrapropylporphycene was characterized by NMR and x-ray crystallography. Synythesis of 2,7,12,17-tetrapropyl-porphycene was also optimized to provide a higher yield of this rather difficult-to-obtain macrocycle.

This is dedicated to the memory of Tom Morrison, who was my inspiration for this work.

ACKNOWLEDGEMENTS

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Finally I would like to express my thanks to my family and dear friends for their understanding, encouragement and love.

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LIST OF ABBREVIATIONS

DCI	Desorption chemical ionization
FAB	Fast atom bombardment
OEP	Octaethylporphyrin
PDT	Photodynamic therapy
R_f	Retardation factor
RT	Room temperature
TEBA	Triethylbenzylammonium chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TPP	Tetraphenylporphyrin
TPPc	Tetrapropylporphycene

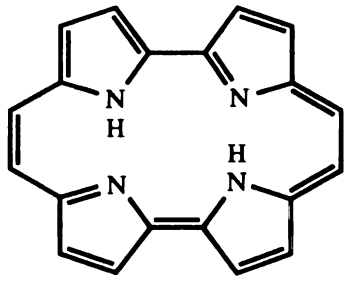
INTRODUCTION

Although the concept of a light-activated sensitizer resulting in cell death was first used to treat cancer in 1903,[1] it is only recently that photodynamic therapy (PDT) has been investigated on a large scale. The exact mechanisms of action for effective PDT in cancer treatment are not known. Studies with animal models have indicated that generation of singlet oxygen is the main mechanism for PDT cytotoxicity producing vascular damage to the blood vessels of the tumor resulting in tumor hypoxia and cytotoxicity.[2,3]

PDT is an oxygen-dependent photochemical oxidative process which requires three simultaneously present components for cytotoxicity: a sensitizer, light and oxygen. The sensitizer must localize in tumors and have photodynamic properties that, when activated by light, lead to cytotoxicity. The most widely used sensitizers in clinical studies have been porphyrin-based photosensitizers, which are preferentially absorbed and retained by cancerous tissues. Why the sensitizer is retained to a greater extent in tumors than in normal tissues is unknown, however, the distribution of different porphyrin-based sensitizers is determined by the individual chemical properties, including lipophilicity or hydrophilicity, polarity, pH, anionic or cationic charge, and aggregate size.[4] Since porphyrins in general have weak absorption at 630 nm, the wavelength usually used for treatment, it is desirable to develop photosensitizers with

strong absorption at longer wavelengths. The absorption at longer wavelengths allows greater tissue penetration by low energy light and prevents the problems associated with light absorbance by naturally present biologic chromophores such as hemoglobin.[5]

A compound currently under study as a photosensitizer with strong absorption at longer wavelengths is porphycene **1**. Since 1990 Vogel has been granted two U.S. patents and applied for two international patents[6] for porphycene-based compounds useful in PDT.



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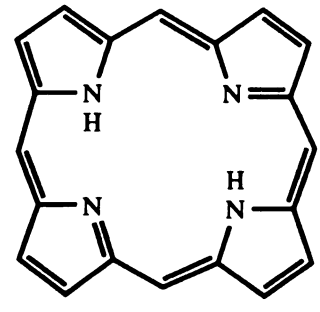

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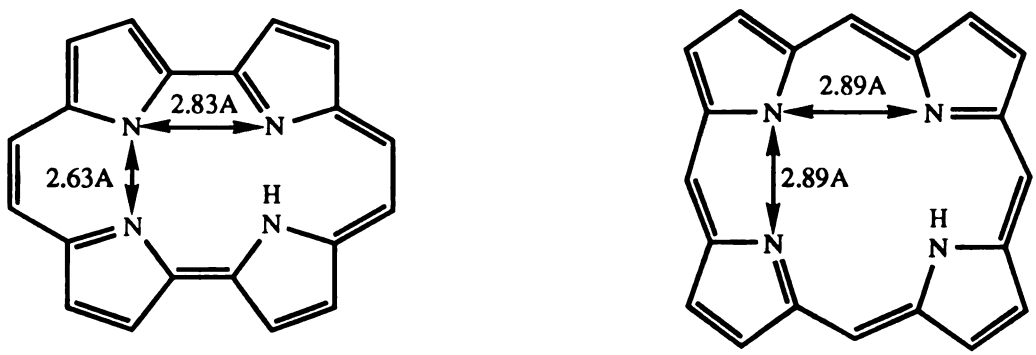
Porphycene is an aromatic tetrapyrrolic macrocycle resembling porphyrin **2** in chemical, structural and spectral respects. This structural isomer of porphyrin is derived by merely shuffling the pyrrole and methine moieties.

Porphycene was first synthesized[7] and characterized in 1986 by Vogel. It is stable in air, crystallizes in the form of violet needles, and is soluble in organic solvents to give blue solutions showing red-violet fluorescence. The name "porphycene" was suggested for **1** because the compound possesses structural features of both porphyrins and acenes.

The spectra[7] of the compound provide convincing evidence as to its structure and aromaticity. The simplicity of the ^{1}H and ^{13}C NMR spectra

as reported by Vogel indicate the equivalence of the four pyrrole rings which is readily explained by assuming that porphycene, like many porphyrins, is subject to NH tautomerism that is rapid on the NMR timescale. The NH signal of porphycene (δ 3.15) is significantly less shifted to high field, relative to that of pyrrole (δ 7.70), than is that of porphyrin (δ -3.76). This is suggestive of strong intramolecular N-H···N hydrogen bonding in porphycene, which is expected if the molecule is planar. The mass spectrum also confirms the structure with the molecular ion, m/e 310, as the base peak. An x-ray crystallographic analysis showed the molecule to be virtually planar, with a maximum distance of C and N atoms from the mean plane: ± 0.04 Å. It also showed that the cavity between the pyrrole rings in porphycene is smaller that that in porphyrin. In porphycene the four nitrogen atoms form a rectangle, the sides of which



porphycene porphyrin

Figure 1. N-N' Distances in porphycene and porphyrin.

are 2.83 Å (N_1N_2) and 2.63 Å ($N_1N_{1'}$) long compared to porphyrin's NN' distance of 2.89 Å (Figure 1). This finding further supports the strong

hydrogen bonding evidenced by the NMR spectrum. The uv/visible spectrum of porphycene consists of a double band at λ = 358/370 nm, which is a Soret band, and three longer wavelength bands at λ = 558, 596, and 630 nm, which are the Q-bands. This finding supports the porphyrin-like nature of the compound, however, porphycene shows higher absorption for the Q-bands. It is this finding along with porphycene's stability toward photooxidation, high quantum yield of fluorescence and singlet oxygen sensitization,[8] that suggest that this novel porphyrinoid and its alkyl derivatives are potential agents for PDT.

N,N' One-carbon bridged porphyrins were first synthesized by Johnson *et al.*[9] in 1975 by the condensation of ethyl diazoacetate with cobalt porphyrins giving a salt, which by the action of acid under oxidative conditions, was converted to 21,22-ethoxycarbonylmethyleneoctaethyl-porphyrin with removal of the metal. When synthesized from Co(II) octaethylporphyrin (OEP), rather stable N,N' bridged porphyrins were formed with a yield of 51.9% from the intermediate salt. When synthesized from tetraphenylporphyrin (TPP), the reaction was slower with a much lower yield (3%), and the bridged compounds were less stable probably due to steric interaction between the *meso*-phenyl and the ethoxycarbonylmethylene fragment. Hot solvents easily decomposed the TPP-bridged compounds back to TPP.

A series of N,N'-bridged porphyrins were synthesized in 1982 by Callot *et al.*[10] using TPP with chloroform and base under phase transfer conditions (NaOH, H_2O, ROH, TEBA), giving yields ranging from 16-25%. Under the same conditions, OEP gave a low yield (5.5%) of bridged porphyrin, which is a reversal of Johnson's studies using OEP and TPP.

The purpose of this study was to improve the synthesis of a soluble and symmetric porphycene, 2,7,12,17-tetrapropylporphycene (TPPc), and to use it as the parent compound to further synthesize other N-alkylated porphycenes, in an attempt to develop new sensitizers useful for PDT.

N-Alkyl porphycenes, by their similarity to N-alkyl porphyrins, should be compatible with living systems. N-Alkylated porphyrins are synthesized in nature by cytochrome P-450,[11] and N-substituted porphyrins are produced by hemoglobin and myoglobin from the interaction with hydrazines *in vivo* and *in vitro*.[12] And in the early 1980s it was discovered that a metabolite of certain drugs was N-methylprotoporphyrin IX.[13]

Synthetically, N-alkylation of most non-*meso*-substituted and *meso*-tetraaryl porphyrins, except where noted, can be effected by a number of methods: 1) direct alkylation with a stoichiometric amount of the highly reactive triflouromethanesulfonate in refluxing methylene chloride;[14] 2) direct alkylation with a 100-fold excess of alkyl iodide with acetic acid in refluxing xylene;[15] 3) direct alkylation with dimethylsulfate in refluxing 1,2-dichlorobenzene;[16] 4) formation of an acetoxy complex of zinc(II) by heating with ethyldiazoacetate in chlorobenzene, followed by migration of the acetoxy from the zinc atom to a nitrogen atom, acidic elimination of the zinc atom, alkaline hydrolysis of the ester, and photochemical decarboxylation by exposure to sunlight;[17] and 5) decomposition of an N,N'-bridged porphyrin intermediate by treatment with an alkyl iodide followed by *p*-toluenesulfonic acid (acceptable yields are only obtained for *meso*-tetraarylporphyrins).[10]

Our attempts to alkylate the porphycene by the CH_3I method, however, was unsuccessful, presumably owing to the low basicity of the

nitrogen of porphycene (pK_a=1.3) as compared with a typical porphyrin (pK_a=5.5).

When Cu(II) TPPc was treated with the Vilsmeier reagent ($DMF/POCl_3$) instead of the expected formylation product(s), we obtained a N,N'-bridged porphycene whose structure, as will be discussed later in this thesis, was determined by NMR and x-ray crystallography. N,N'-Dialkylporphyrins are rare; N,N'-bridged compounds are even more unusual. Some of the alkoxymethylene-bridged porphyrins of Callot *et al.*[10] were reported being not very stable and have a tendency to cleave one or both N-C bonds. Our N,N'-bridged porphycenes are very stable presumably because of the closer N-N' distance.

This thesis presents first an improved synthesis of the 2,7,12,17-tetrapropylporphycene, and then the synthesis and characterization of two N,N'-bridged macrocycles derived from this porphycene.

RESULTS AND DISCUSSION

The synthesis of the parent porphycene is shown in Figures 2 and 3. In the first step a saturated aqueous solution of sodium nitrite was added dropwise to a cold solution of ethyl butyrylacetate in acetic acid, followed by stirring for 2 hours at RT, resulting in the formation of oxime **4**.

The condensation of pyrrole **6** was achieved by dropwise addition of oxime **4** along with small portions of zinc powder to a well-stirred solution of ethyl acetoacetate **5** in acetic acid, maintaining the reaction temperature below 75° C. The reaction mixture was then heated to 90° C with stirring for another hour, then poured over ice water to precipitate the fine light yellow powdery product.

The α-methyl of pyrrole **6** was oxidized to α-carboxylic acid by dropwise addition of bromine, under nitrogen, to a cooled solution of pyrrole **6** dissolved in formic acid, glacial acetic acid and acetic anhydride, followed by dropwise addition of sulfuryl chloride with vigorous stirring, maintaining the reaction temperature below 10° C. Hydrolysis was accomplished by slow addition of water followed by treatment with sodium bicarbonate in ethanol and acidic workup yielding light yellow-green crystals, pyrrole **7**.

Decarboxylation was accomplished by dissolving pyrrole **7** and sodium bicarbonate in water and 1,2-dichloroethane and heating the mixture. To the reaction mixture was added dropwise an aqueous solution

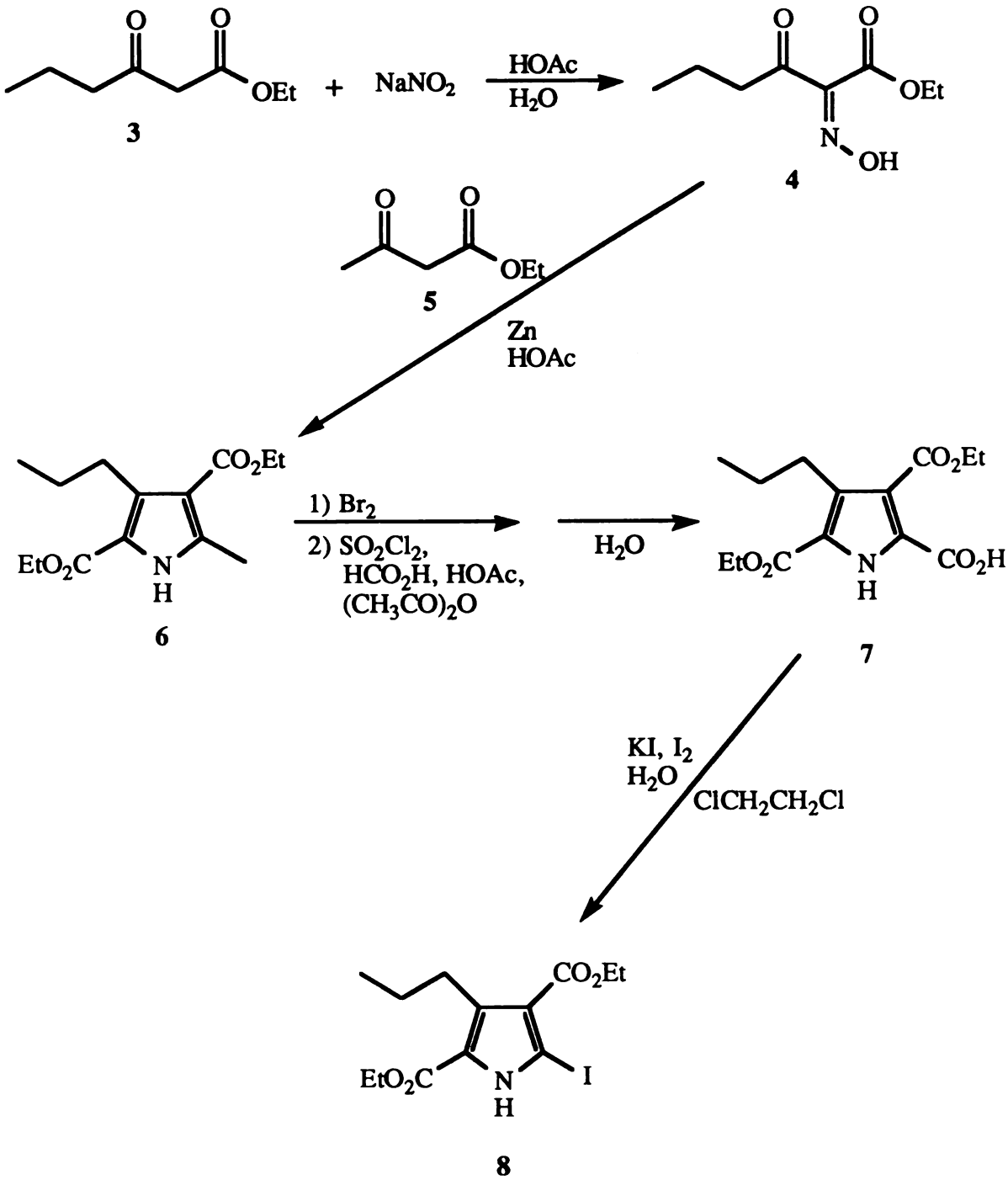


Figure 2. Synthesis of iodopyrrole **8**.

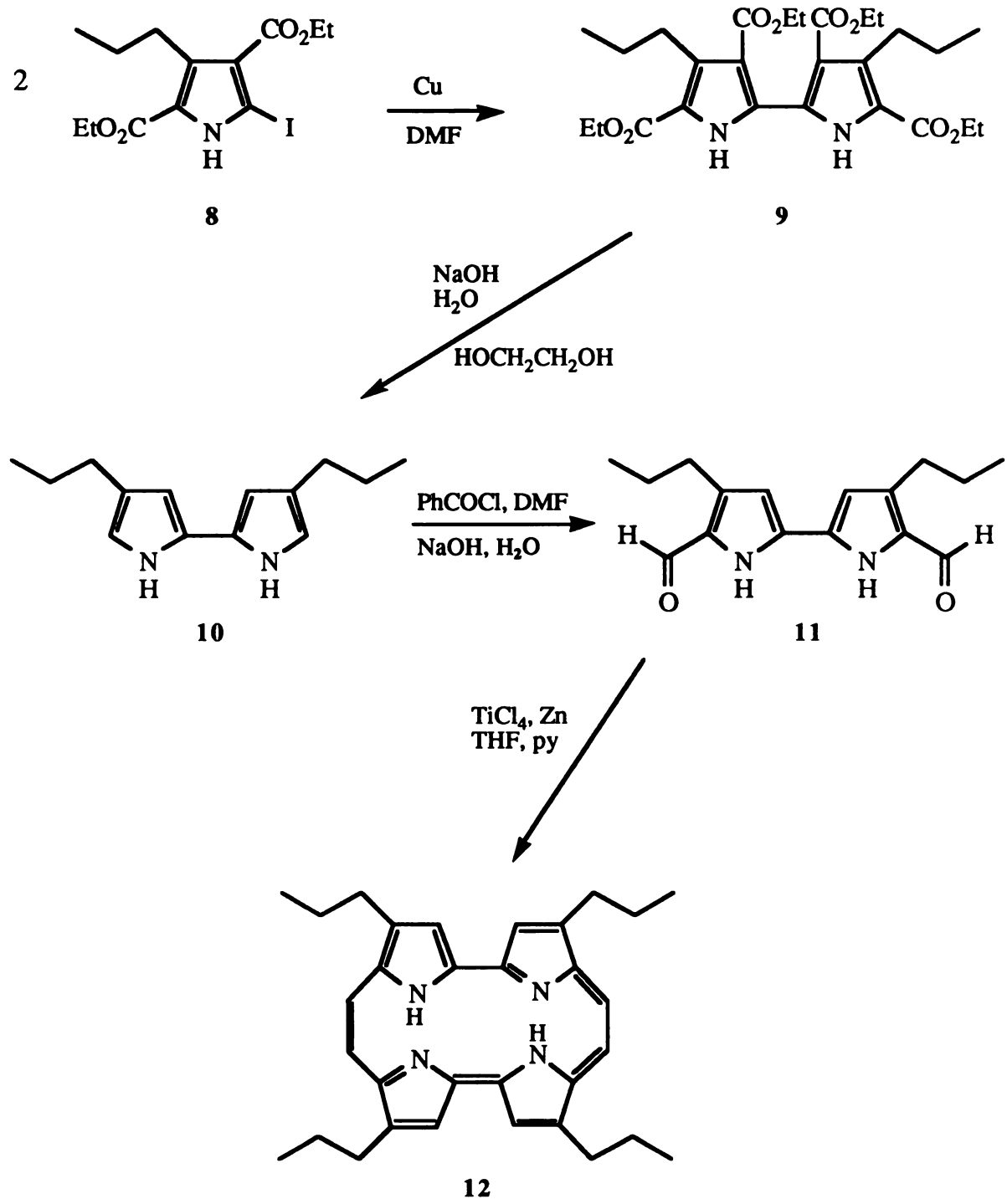


Figure 3. Synthesis of 2,7,12,17-tetrapropylporphycene **12**.

of iodine and potassium iodide, followed by refluxing for one hour, forming the iodopyrrole **8**, as creamy white needles.

Using an Ullmann type reaction, coupling of iodopyrrole **8**, dissolved in N,N-dimethylformamide at RT to which freshly ground copper bronze was added, afforded white needle-like crystals, bipyrrole **9**. It was found that activating the copper and freshly grinding it immediately before use gave more consistent results and a slightly higher yield.

Hydrolysis and decarboxylation of bipyrrole **9** was accomplished in one step by dissolving bipyrrole **9** in a solution of ethylene glycol, sodium hydroxide and water and refluxing the reaction mixture for 24 hours under nitrogen. The solution was cooled and poured into water forming bipyrrole **10** as a fine bluish gray powder which precipitated out and was filtered, washed and dried. This was an improvement over Vogel's 2-step procedure[18] in which hydrolysis occured in aqueous sodium hydroxide/ ethanol solution, then decarboxylation was accomplished by sublimation at 160° C in small batches, under reduced pressure. These two steps, under best conditions, gave an overall yield of 77%. By using a higher boiling point solvent (ethylene glycol), the one-step procedure gave a greatly improved yield of 96%.

Using Vilsmeier type reaction conditions, bipyrrole **10** was dissolved in warm, dry N,N-dimethylformamide under nitrogen and cooled. Benzoyl chloride was added dropwise to the cooled solution with stirring. The reaction mixture was heated at 100° C for 18 hours under nitrogen, then cooled and poured into cold water. With stirring, 10% aqueous sodium hydroxide solution was slowly added until gold precipitate formed and the smell of amine was apparent and persistent. The precipitate was collected on celite, washed with water, rinsed with a small amount of

methanol and dried. Bipyrrole **11** was extracted from the celite with hot chloroform, and the filtrate was evaporated in vacuo. The product was recrystallized as a greenish gold powder in methylene chloride/methanol (2%). The Vilsmeier reaction typically uses phosphorous oxychloride to generate a highly reactive $POCl_3$/DMF reagent for the electrophilic aromatic substitution. We assumed that because the bipyrrole **10** was very electron-rich, the high reactivity of the reagent was not required. By substituting benzoyl chloride, a milder reagent, we were able to reduce the amount of dark tarry by-products typical of Vilsmeier reactions and increase the yield by 5%.

The final step, the cyclization of bipyrrole **11** to 2,7,12,17-tetrapropylporphycene **12**, was accomplished by reductive coupling using a modification of the McMurry coupling reaction. Under a nitrogen atmosphere freshly activated zinc dust was suspended in dry THF with stirring, and titanium tetrachloride was added dropwise. After the exothermic addition was complete, the reaction mixture was heated to reflux and refluxed for 15-20 minutes. Bipyrrole **11** was dissolved in dry THF and pyridine and added dropwise to the gently refluxing titanium mixture. The reaction mixture was refluxed for another hour, cooled, quenched with an aqueous solution of potassium carbonate, and allowed to sit for 36 hours at RT. That liquid which could not be decanted off was gravity filtered through cotton. The solution was evaporated in vacuo to minimal volume, and the crude product was extracted with methylene chloride and evaporated in vacuo. The residue was dissolved in methylene chloride/hexane (3:1) and chromatographed on a silica gel column with methylene chloride/hexane (3:1). 2,7,12,17-Tetrapropylporphycene **12** was the only nonpolymeric product obtained. Recrystallization from

methylene chloride/methanol (1:1) afforded fine violet needles. As was true with the copper bronze in a previous step, freshly activating the zinc and grinding it immediately before use improved the yield of this cyclization step from a previous 18% to a much higher yield of 26%.

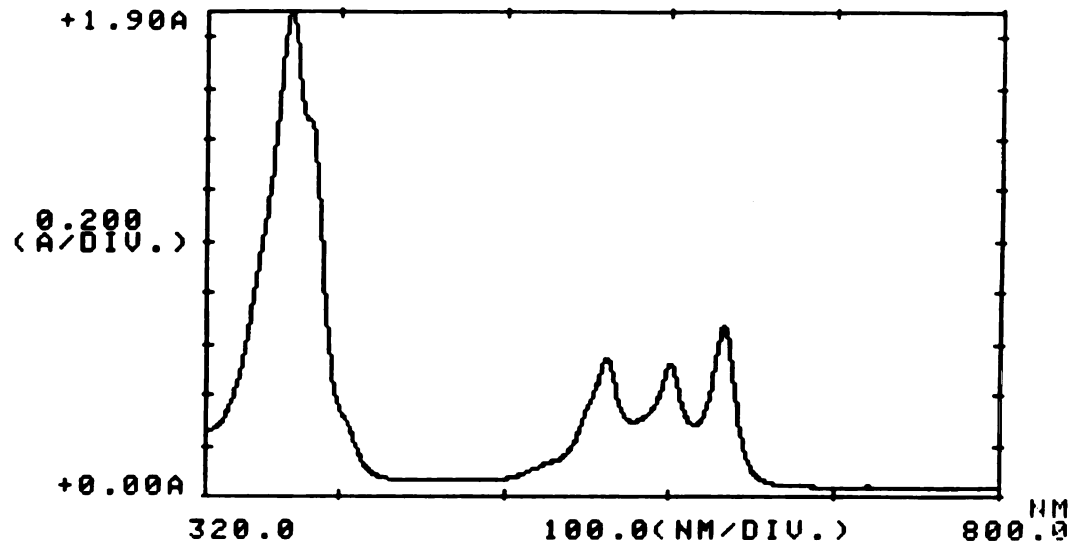


Figure 4. UV/Visible spectrum of 2.7,12,17-tetrapropylporphycene **12**.

The uv/visible spectrum of TPPc **12** (Figure 4) shows a large Soret band indicating high absorbance in the ultraviolet region. In the visible region there are three Q-bands of lower intensity, the greatest of which is at 633 nm, which makes it a candidate for use in PDT. Porphycene's intensity near 635 nm in the visible region is greater than that of porphyrin.

^{15}N-2,7,12,17-Tetrapropylporphycene **17** was synthesized on a much smaller scale using the same procedure as for non-labeled porphycene

except for the incorporation of the labeled nitrogen. Instead of using solid sodium nitrite as the source of the pyrrole-N, an aqueous labeled sodium nitrite solution was generated. Labeled nitric oxide, $^{15}N^{18}O$, was mixed (4:1) with dioxygen, both in small portions, above an aqueous sodium hydroxide solution protected from the atmosphere. After mixing of the gases was complete the labeled sodium nitrite solution was stirred for 30 minutes, then used in the next step. Spectral data confirmed the structure. ^{1}H NMR was identical to that of non-labeled TPPc **12**; the mass spectrum molecular ion m/e was 482; and ^{15}N NMR gave only one sharp singlet at δ 189.0 at 30° C and 188.7 at 0° C (Figure 5), which disagrees with the literature value[19] of 161 ppm. The ^{15}N-TPPc and its Ni(II) and Cu(II) complexes are being characterized by resonance Raman spectroscopy.

A portion of the TPPc **12** was converted to the copper(II) derivative for use in the synthesis of bridged compounds. This was accomplished by dissolving TPPc **12** in glacial acetic acid under argon with stirring. Copper(II) acetate and sodium acetate were added, and the reaction mixture was then refluxed for 19 hours. After cooling to RT the product was extracted with methylene chloride, washed with water and evaporated in vacuo to dryness. Recrystallization from methylene chloride/methanol afforded a quantitative yield of violet crystals.

Each bridged compound resulted from a one-pot synthesis. N,N'-((N,N-Dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13** was synthesized from both TPPc **12** and Cu(II) TPPc in separate reactions (Figure 6). Under an atmosphere of argon the porphycene was dissolved in N,N-dimethylformamide with gentle warming. The solution was then

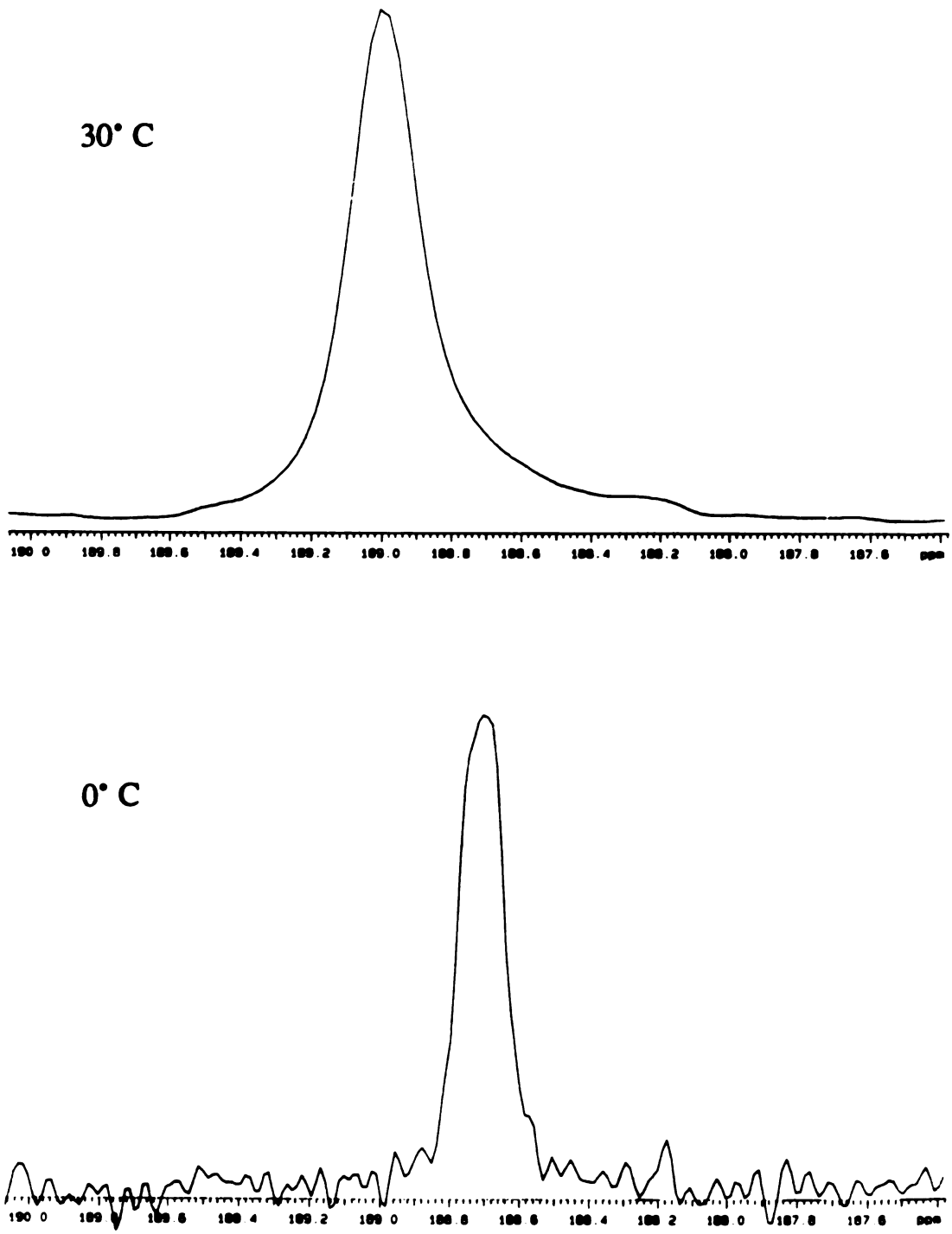
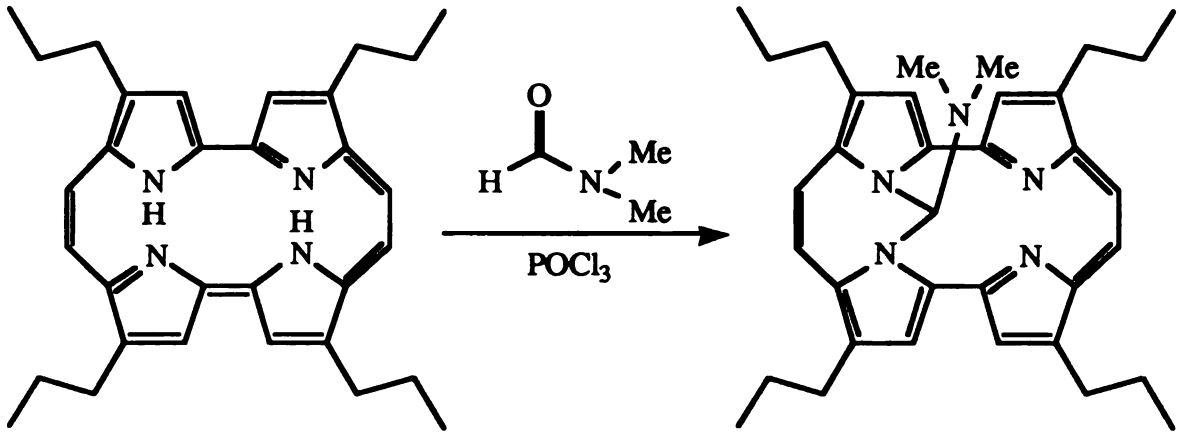


Figure 5. ^{15}N NMR of ^{15}N-2,7,12,17-tetrapropylporphycene at 30° C and 0° C.



12 13

Figure 6. Synthesis of N,N'-((N,N-dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13**.

cooled to 20° C and phosphorous oxychloride was added dropwise with stirring, maintaining the temperature at 20° C throughout the addition. The reaction mixture was allowed to warm to RT, and was stirred under argon for 20 hours, monitored frequently by uv/visible spectra and TLC to assess progress of the reaction by the shape of the uv/visible sepctrum and the amount of unreacted starting material present on TLC. The solution was poured over ice and with stirring a 10% aqueous sodium hydroxide solution was slowly added until the mixture was neutral. The crude product was extracted with methylene chloride, washed with water and evaporated in vacuo to near dryness. The residue was dissolved in methylene chloride/methanol (10%). TLC showed two spots present and the crude product was separated by preparative TLC with methylene chloride/methanol (10%). Two major blue bands appeared and were removed from the plate and the products isolated. However, on TLC the product from each band separated into two spots with similar R_f values,

appearing to be the same compound. The crude products from the two bands were combined, dissolved in methylene chloride and chromatographed on a silica gel column with methylene chloride/ triethylamine (3 drops). The bridged product was isolated as a single fraction and evaporated in vauco to dryness. Again, the TLC of this product showed two spots which eventually converged into one spot when left in the eluent for a longer period of time. Each blue band from the plate and later the chromatographed product behaved in a similar manner producing the same TLC Rf values. The conclusion drawn from this behavior was the two bands or spots on TLC are a phenomenon caused by the silical gel and they represent the N-protonated and nonprotonated forms of the same compound.

Spectral data confirms the structure of N,N'-((N,N-dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13**. In the ^1H NMR (Figure 7) the peak at δ 6.08 (1H, s, NH) indicates the proton is in a benzylic-like position. The protons of the amino methyls and the proton on the methylene bridge are quite shielded by the aromatic ring current and appear at δ -1.78 and -5.06 respectively. The uv/visible spectrum (Figure 8) is of the shape which has been characteristic of all the bridged compounds, the three Q-bands merge into one peak around 618 nm (with absorbance about half that of the Soret band) with a broad shoulder peak around 583 nm, and a broadened Soret band. The structure is also supported by the mass spectrum, which shows the M+1 peak at m/e 534. This product, as with all of the bridged compounds, resisted attempts to recrystallize it; upon drying, a film coated the flask but no crystals formed. The amorphous solid was dark blue upon drying.

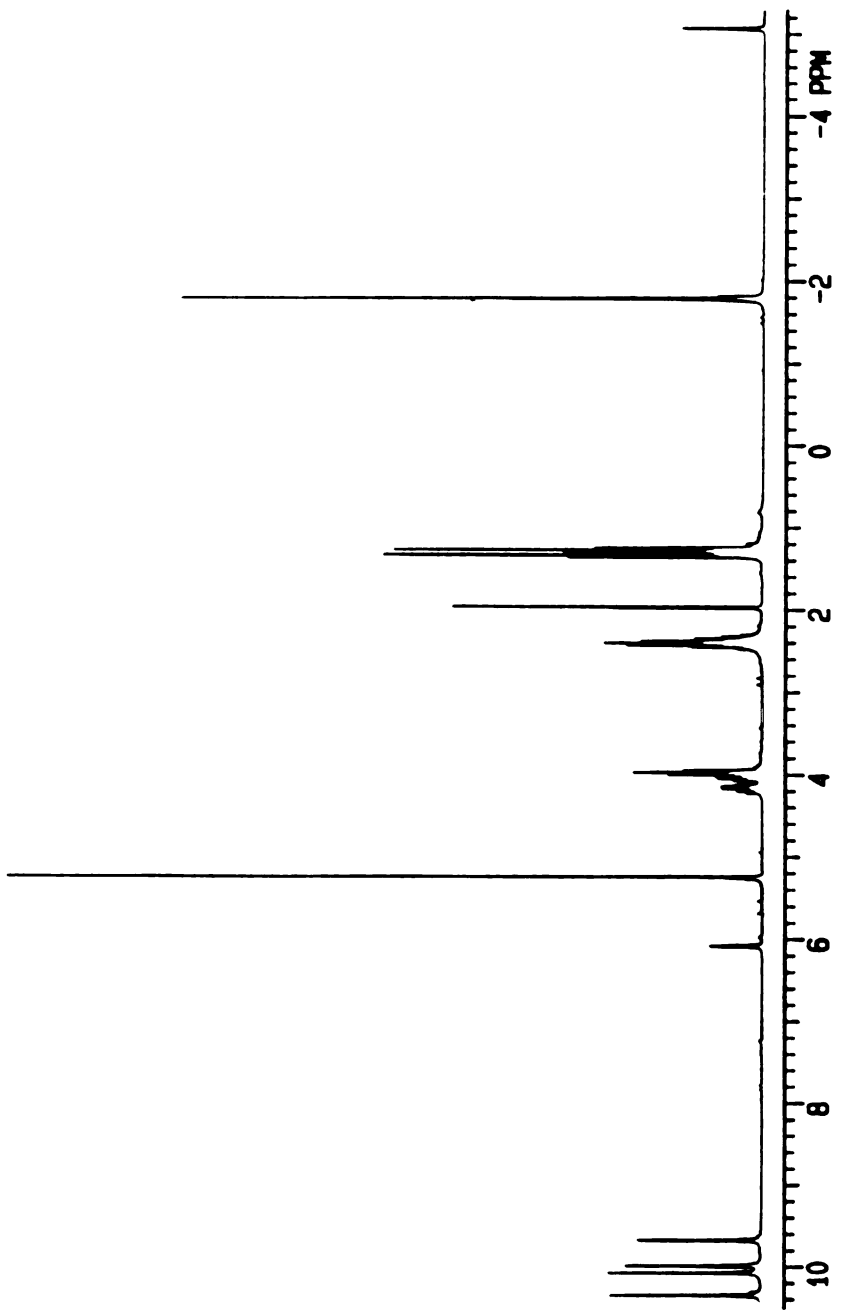


Figure 7. ^{1}H NMR spectrum of N,N'-((N,N-dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13**.

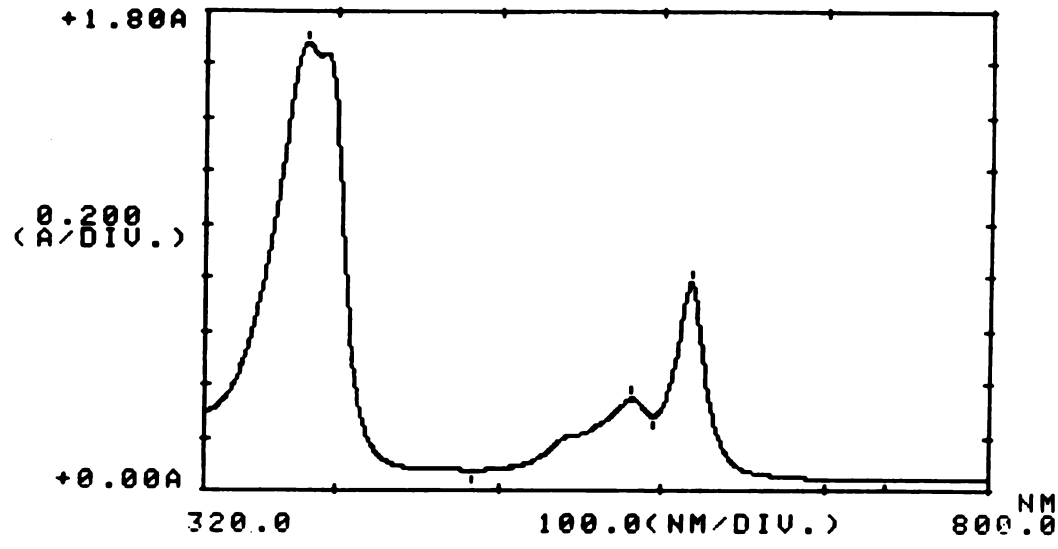


Figure 8. UV/Visible spectrum of N,N'-((N,N-dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13**.

The product was sent to Professor S.-M. Peng's laboratory at National Taiwan University for crystallization and x-ray crystallography. In order to improve crystallinity, they attempted to prepare the Cu(II) complex of this compound by heating it with $Cu(ClO_4)_2$ in CH_3CN. The product finally crystallized to reveal an x-ray structure as shown in Figure 9. This structure confirms the N,N'-bridged positions, but showed a monomethylamine on the bridging methylene, N,N'-((N-methylamino) methylene)-2,7,12,17-tetrapropylporphycene **14**. A review of all of our data confirmed that the product sent to them was indeed a dimethylamine. An as yet unknown process caused the loss of one methyl during crystallization. This finding caused us to attempt crystallization in the manner used by the outside laboratory that would duplicate their findings,

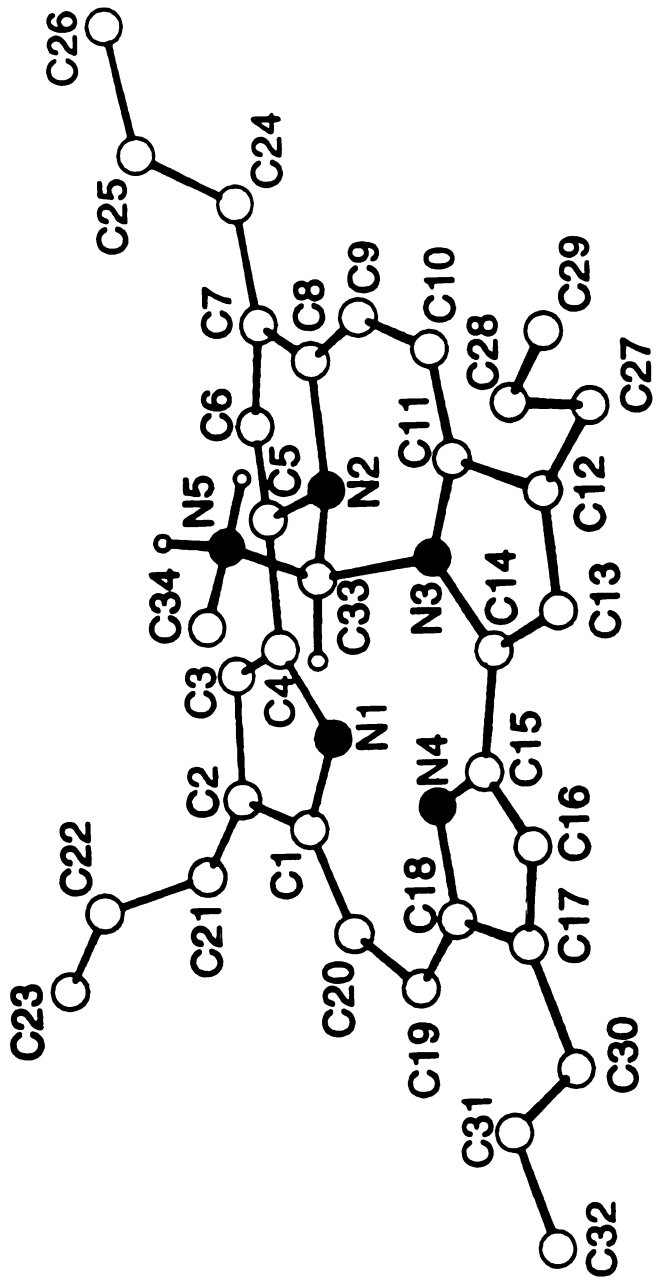
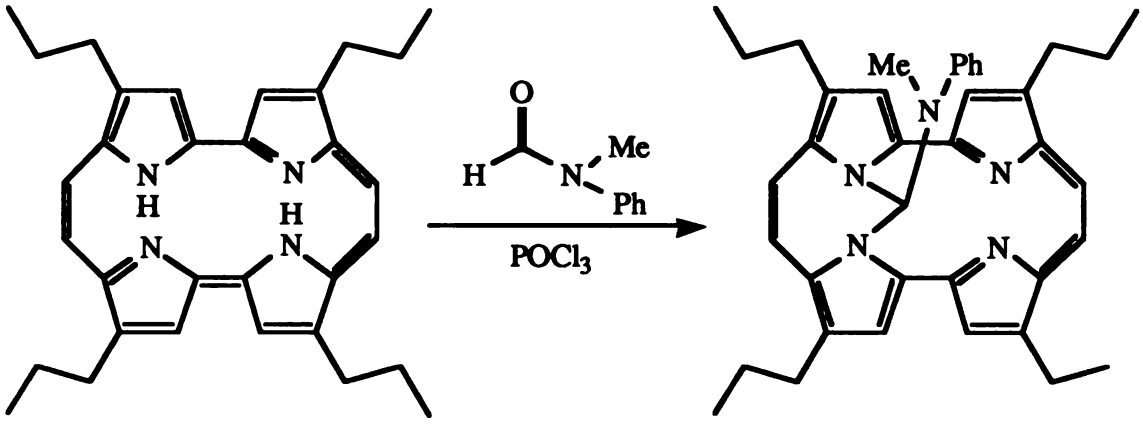


Figure 9. X-Ray crystallographic structure of N,N'-((N-methylamino)-methylene)-2,7,12,17-tetrapropylporphycene **14**.

producing the monomethylamine product. N,N'-((Dimethylamino) methylene)-2,7,12,17-tetrapropylporphycene **13** was dissolved in acetonitrile and a small amount of copper(II) perchlorate was added. The mixture was heated to reflux and refluxed to dryness. Although recrystallization attempts were unsuccessful, the mass spectrum supports the monomethylamine structure with the molecular ion peak at m/e 519.

Several attempts were made to incorporate a methyl (instead of the methine proton) on the methylene bridge using acetamide as the reagent. In monitoring the progress of the reaction, no hint of a product was ever apparent on uv/visible spectra or by TLC. The substituent on the methylene bridge lies very nearly in the plane of the porphycene ring and steric constraints appear to restrict this substituent to a proton only. The molecular model of this compound shows very little available space for the substituent.

N,N'-((N-Methylaniline)methylene)-2,7,12,17-tetrapropyl-porphycene **15** was synthesized (Figure 10) by dissolving TPPc **12** in 1,2-dichloroethane under argon with gentle heating. The solution was cooled and N-methylformanilide was added, followed by the dropwise addition of phosphorous oxychloride. The reaction mixture was allowed to come to RT and was stirred under argon with monitoring for 4 days, when it was poured over ice. 10% Aqueous sodium hydroxide was added slowly with stirring until the solution was neutral. The product was extracted with methylene chloride, washed with water and evaporated in vacuo to near dryness. The residue was dissolved in methylene chloride and chromatographed on a silica gel column with methylene chloride. Polarity



12 15

Figure 10. Synthesis of N,N'-((N-methylaniline)methylene)-2,7,12,17-tetrapropylporphycene **15**.

of the eluent was increased by adding methanol (to 10%) to remove the blue product, which was evaporated in vacuo to dryness. Again, attempts to recrystallize the product were unsuccessful. The uv/visible spectrum (Figure 11) was characteristic of the bridged products. The mass spectrum gave M+1 as m/e 596.

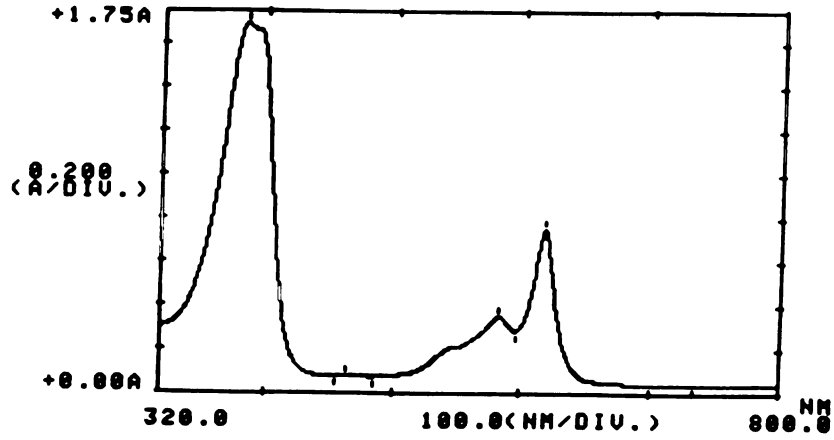
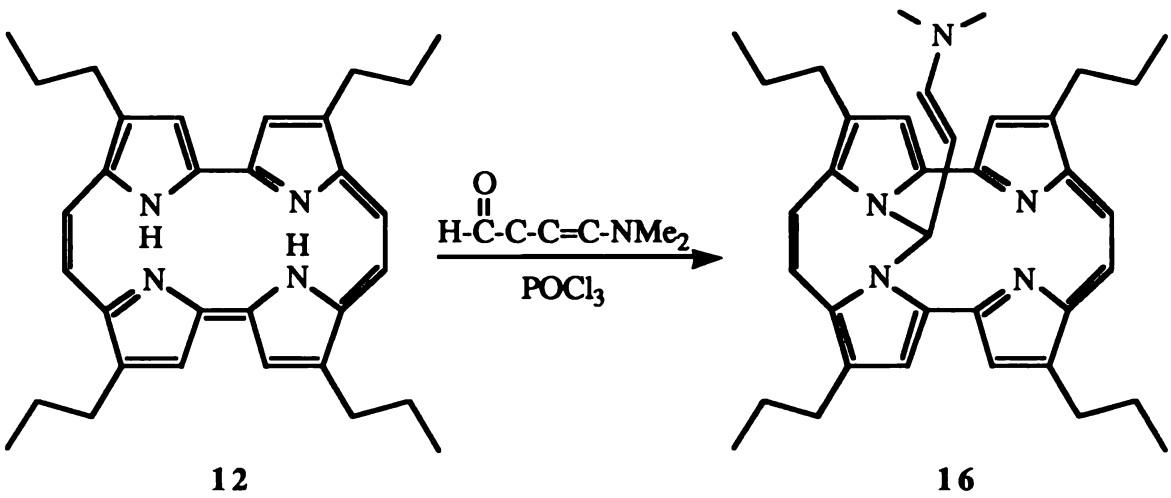


Figure 11. UV/Visible spectrum of N,N'-((N-methylaniline)methylene)-2,7,12,17-tetrapropylporphycene.

Proton NMR (Figure 12, next page) confirmed the structure. The protons on the phenyl ring are shifted upfield due to the shielding by the ring current and appear at δ 6.41 (para), 5.92 (meta) and 3.07 (ortho). The amino methyl protons appear at δ -2.11 and the methylene bridge proton appears at δ -5.99.

N,N'-(C-C=C-NMe_2)-2,7,12,17-tetrapropylporphycene **16** was synthesized in a procedure similar to the previous bridged compounds (Figure 13).



12 16

Figure 13. Synthesis of N,N'-(C-C=C-NMe_2)-2,7,12,17-tetrapropylporphycene **16.**

To prevent polymerization of the reagent, 3-(dimethylamino)-acrolein was dissolved in cold 1,2-dichloroethane before adding it to the cold porphycene solution. The reaction was again monitored by uv/visible spectra and TLC. At 3 days the reaction mixture showed no remaining starting material, was poured over ice and 10% aqueous sodium hydroxide

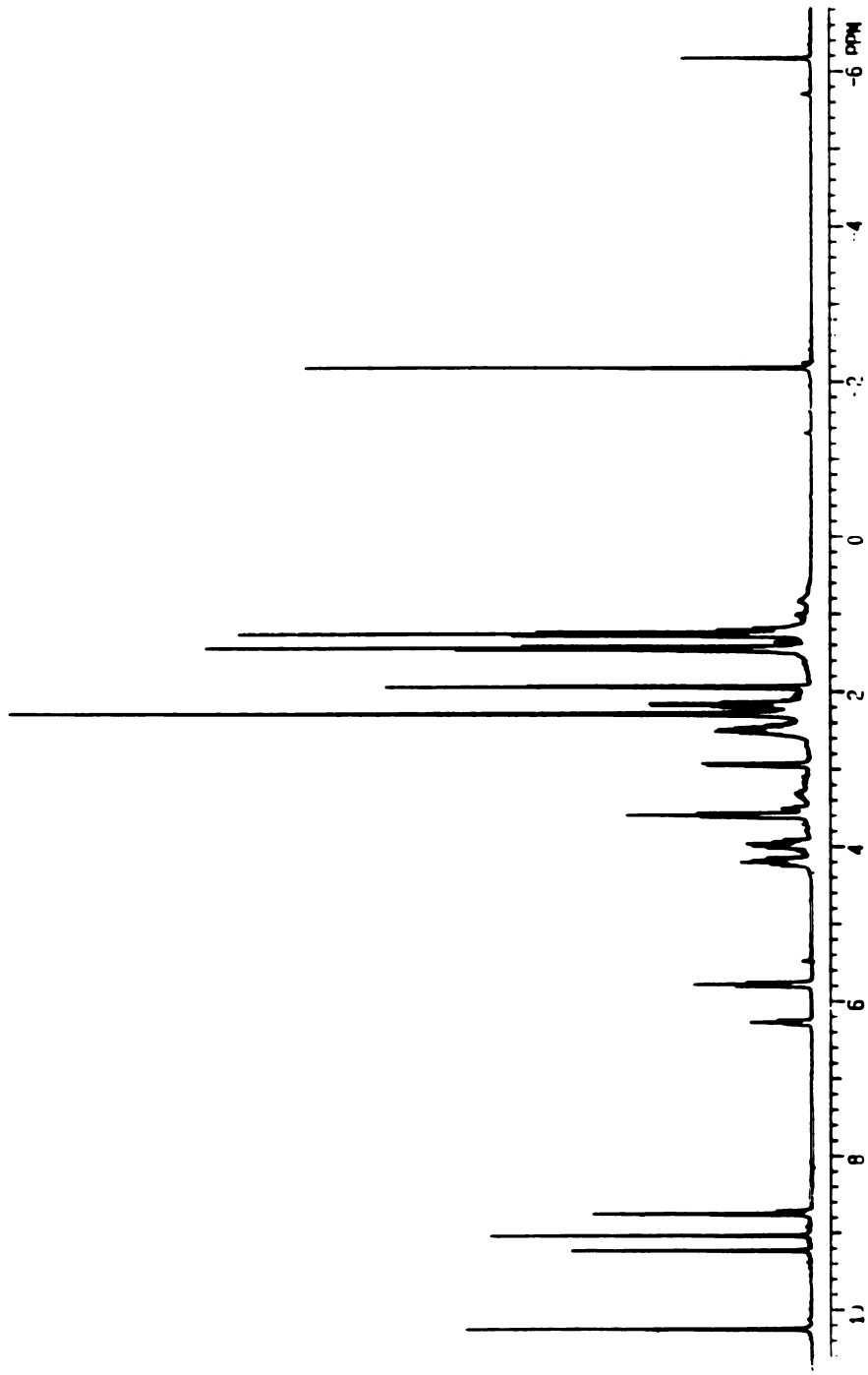


Figure 12. ^{1}H NMR spectrum of N,N'-((N-methylaniline)methylene-2,7,12,17-tetrapropylporphycene **15**.

was slowly added until the solution was neutral. The organic layer was separated, washed with water and evaporated in vacuo to near dryness. The crude product was chromatographed on a silica gel column. In the first attempt at purification of this product the polarity of the solvent was changed with methanol (10%) which instantly decomposed the product to starting material. In subsequent attempts acetonitrile was used to successfully remove the product from the column. Attempts to recrystallize this product were unsuccessful. UV/visible spectra consistently gave evidence that a bridged product was formed (Figure 14),

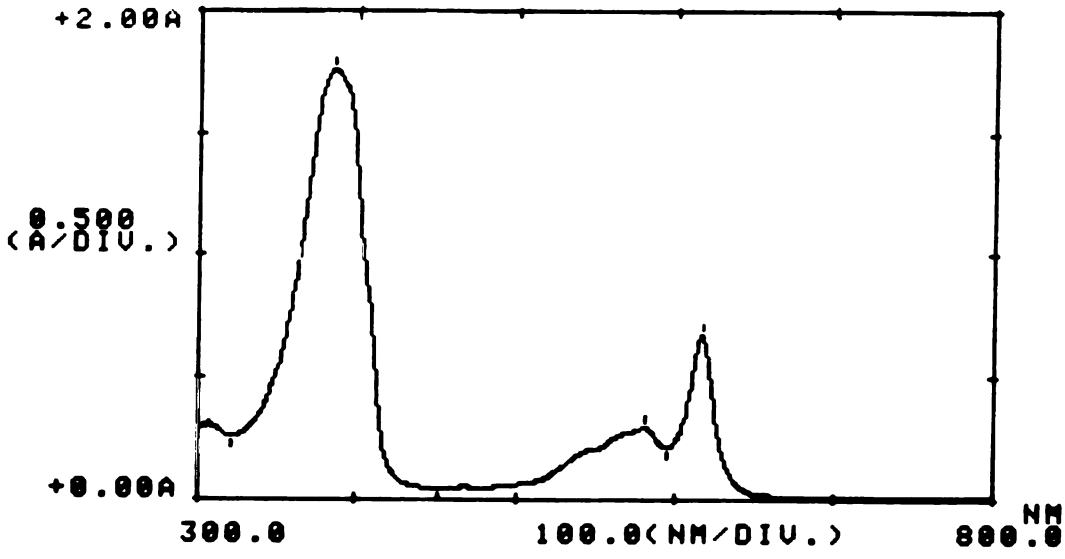


Figure 14. UV/Visible spectrum of N,N'-(C-C=C-NMe_2)-2,7,12,17-tetrapropylporphycene **16**.

however, it is a very labile product and did not withstand direct electron impact, DCI, nor FAB mass spectra attempts. NMR results were inconclusive due to lack of purification.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were obtained on a Varian Gemini 300 FT NMR spectrometer. All chemical shifts were recorded in parts per million (ppm) relative to tetramethylsilane. ^{15}N Nuclear magnetic resonance spectra were obtained on a VXR 500 NMR spectrometer using a saturated aqueous sodium nitrite solution with the peak at 228.9 ppm as the internal standard. Melting points were obtained with an electrothermal melting point apparatus and are uncorrected. UV/visible spectra were obtained on a Shimatzu UV-160 spectrophotometer. Preparative thin layer chromatography plates from Analtech were used (silica gel GF, 1000 or 1500 μm), and in column chromatography 200-400 mesh silica gel was used. Mass spectral determinations were made on a Fisons TRIO-1 GC-MS mass spectrometer purchased under an NIH Shared Instrumentation Grant (S10RR06506-01).

2,4-Diethoxycarbonyl-5-methyl-3-propyl pyrrole **6**

Ethyl butyrylacetate (98%) **3** (100 g, 0.62 mol) was dissolved in glacial acetic acid (125 mL), and a saturated aqueous solution of sodium nitrite (43.5 g, 0.63 mol) was added dropwise with stirring. The reaction mixture was kept under 20° C with an ice water bath. After addition was complete the reaction mixture was stirred for an additional 2 hours, forming oxime **4**.

Ethyl acetoacetate **5** (79.4 g, 0.61 mol) was dissolved in glacial acetic acid (250 mL). With stirring, zinc powder (30 g) was added, then the above oxime solution **4** was dropped in slowly. Additional zinc powder (150 g) was added in small portions until the oxime addition was finished. The reaction temperature was maintained below 75° C. After the addition was complete, the reaction mixture was heated to 80° C and stirred for 1 hour. The reaction mixture was cooled to 60° C and poured into ice water (2 L). The crude product, pyrrole **6,** was precipitated as a yellow solid which was collected by filtration, washed with water and dried in air. Recrystallization from methanol gave yellowish white plates (101 g, 62%), m.p.: 100-102° C. ^{1}H NMR ($CDCl_3$): δ 9.70 (1H, s, br, NH), 4.28 (4H, m $CO_2C\underline{H}_2CH_3$), 3.00 (2H, dd, $C\underline{H}_2CH_2CH_3$), 2.49 (3H, s, CH_3), 1.53 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.34, 1.32 (3H each, t, $CO_2CH_2C\underline{H}_3$), 0.92 (3H, t, $CH_2CH_2C\underline{H}_3$).

2,4-Diethoxycarbonyl-3-propyl-5-carboxylic acid pyrrole **7**

2,4-Diethoxycarbonyl-5-methyl-3-propyl pyrrole **6** (150 g, 0.562 mol) was dissolved in a mixture of formic acid (405 mL), glacial acetic acid (405 mL) and acetic anhydride (90 mL) by warming on a steam bath. The hot solution was stirred, cooled in an ice bath and put under nitrogen. Bromine (97.5 g, 31.5 mL, 0.6 mol) was added dropwise over a 15-minute period with stirring. Sulfuryl chloride (273.3 g, 165 mL, 2.0 mol) was added dropwise with vigorous stirring over a 3 hour period, during which time the reaction temperature was kept below 10° C.

The reaction mixture was kept at 0-5° C overnight, without stirring, fitting the flask with a drying tube. Water was slowly added to the solution with swirling until the bubbling (with addition of water)

stopped. The solution was poured into water (2 L) causing the crude product to precipitate as a peach solid suspended on the top as a thick layer. After standing for 30 minutes, the solid was filtered, well washed with water and suction dried. The crude product was dissolved in a minimal volume of ethanol (550-600 mL) while heating on a steam bath, and treated with sodium bicarbonate (87.5 g) in small portions with swirling. The reaction mixture was then diluted with water (1250 mL). After standing for 30 minutes the insoluble byproduct was removed by gravity filtration through cotton. The filtrate was cautiously acidified with concentrated hydrochloric acid (40 mL) with stirring. The precipitated product, pyrrole **57** was filtered, washed with water to neutral, and dried in air as a very light yellow-green powder (129.98 g, 77.9%), m.p.: 136-137° C. ^{1}H NMR ($CDCl_3$): δ 14.82 (1H, s, CO_2H), 10.34 (1H, s, br, NH), 4.49, 4.39 (2H each, q, $CO_2C\underline{H}_2CH_3$), 3.08 (2H, dd, $C\underline{H}_2CH_2CH_3$), 1.57 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.48, 1.41 (3H each, t, $CO_2CH_2C\underline{H}_3$), 0.96 (3H, t, $CH_2CH_2C\underline{H}_3$).

2,4-Diethoxycarbonyl-5-iodo-3-propyl pyrrole **8**

2,4-Diethoyxcarbonyl-3-propyl-5-carboxylic acid pyrrole **7** (60 g, 0.2 mol) was dissolved in 1,2-dichloroethane (300 mL). Sodium bicarbonate (67.2 g, 0.8 mol) and water (500 mL) were added, and the reaction mixture was heated on the steam bath. Upon warming, the starting material dissolved with effervesence. To this mixture a solution of iodine (55.8 g, 0.22 mol) and potassium iodide (99.6 g, 0.6 mol) in water (300 mL) was added dropwise over a 10-minute period, with stirring. The solution was refluxed for 1 hour, and the excess iodine was destroyed with a solution of sodium bisulfite (10 g) in water (20 mL). The reaction

mixture was cooled in an ice bath and methylene chloride (400 mL) was added. The organic phase was separated, washed with water, heated on the steam bath and evaporated to minimal volume (200 mL). Ethanol (250 mL) was added, and the reaction mixture was heated to boiling and removed from the heat. The product was recrystallized by adding water (20 mL). White needle and powder crystals formed which were collected by filtration, washed with cold ethanol/water (30%) and air dried. More pyrrole **8** was recovered from the mother liquor (66.08 g, 83.6%), m.p.: 153-155° C. ^{1}H NMR ($CDCl_3$): δ 9.98 (1H, s, br, NH), 4.38 (4H, m, $CO_2C\underline{H}_2CH_3$), 3.06 (2H, dd, $C\underline{H}_2CH_2CH_3$), 1.57 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.40, 1.39 (3H each, t, $CO_2CH_2C\underline{H}_3$), 0.95 (3H, t, $CH_2CH_2C\underline{H}_3$).

3,3',5,5'-Tetraethoxycarbonyl-4,4'-dipropyl-2,2'-bipyrrole **9**

The procedure previously used by Grigg[20] was followed. 2,4-Diethoxycarbonyl-5-iodo-3-propyl pyrrole **8** (80 g, 0.211 mol) was dissolved in N,N-dimethylformamide (400 mL), and freshly ground copper bronze (80 g) was added. The mixture was stirred at RT for 20 hours. The copper was then filtered and washed with hot chloroform (200 mL X2). The filtrate and washings were combined and washed with 1N hydrochloric acid (400 mL X2) and water (400 mL X2). The solvent was evaporated in vacuo, and the crude product was recrystallized from methylene chloride/methanol (1:1) to give long white needles which were filtered, rinsed with methanol and allowed to air dry (34.47 g, 64.8%), m.p.: 156-158° C. ^{1}H NMR ($CDCl_3$): δ 14.18 (2H, s, br NH), 4.40 (8H, m, $CO_2C\underline{H}_2CH_3$), 3.08 (4H, dd, $C\underline{H}_2CH_2CH_3$), 1.58 (4H, m, $CH_2C\underline{H}_2CH_3$), 1.43 (12H, t, $CO_2CH_2C\underline{H}_3$), 0.98 (6H, t, $CH_2CH_2C\underline{H}_3$).

4,4'-Dipropyl-2,2'-bipyrrole **10**

3,3',5,5'-Tetraethoxycarbonyl-4,4'-dipropyl-2,2'-bipyrrole **9** (53 g, 0.105 mol) was added to ethylene glycol (1800 mL) with stirring, under nitrogen. A solution of sodium hydroxide (45.18 g) in water (300 mL) was added. The reaction mixture was gently refluxed for 24 hours. The heat was removed and the solution was allowed to cool to below 100° C. The solution was poured into ice water (6 L), forming a fine bluish gray precipitate throughout. After sitting 1 hour, the product was filtered, washed with water to neutral and allowed to air dry to gray powder (22.11 g, 97.1%), m.p.: 139-140° C (dec). ^{1}H NMR (DMSO-d_6): δ 10.46 (2H, s, br, NH), 6.52, 6.07 (2H each, s, br, pyrrole-Hα), 2.44 (4H, t, $C\underline{H}_2CH_2CH_3$), 1.62 (4H, sext, $CH_2C\underline{H}_2CH_3$), 0.96 (6H, t, $CH_2CH_2C\underline{H}_3$).

4,4'-Dipropyl-5,5'-dicarbaldehyde-2,2'-bipyrrole **11**

4,4'-Dipropyl-2,2'-bipyrrole **10** (36.45 g, 0.169 mol) was dissolved in warm, dry N,N-dimethylformamide (1170 mL) under a nitrogen atmosphere. The solution was cooled to 20° C in an ice bath. Benzoyl chloride (128.85 g, 106.4 mL, 0.917 mol) was added dropwise with stirring, keeping the temperature at 20° C. The cold water bath was removed and the solution was allowed to sit for 5 minutes at RT, then it was heated to 100° C where it was kept for 18 hours under nitrogen.

The reaction mixture was cooled to RT and poured into cold water (1800 mL). 10% Aqueous sodium hydroxide solution (60 mL) was added slowly with stirring until precipitate formed and the smell of amine was apparent and persistent.

The precipitate was collected on celite, washed with water, rinsed with methanol and dried. The crude product was extracted from the

celite with hot chloroform (1800 mL) and the solvent was evaporated in vacuo. The residue was recrystallized in a minimal volume of methylene chloride/methanol (2%). The gold powdery crystals were filtered and allowed to air dry (28.0 g, 61.0%), m.p.: 232-234° C (dec). ^{1}H NMR ($CDCl_3$): δ 12.25 (2H, s, br, NH), 9.62 (2H, s, CHO), 6.46 (2H, s, pyrrole-Hβ), 2.73 (4H, t, $C\underline{H}_2CH_2CH_3$), 1.70 (4H, sext, $CH_2C\underline{H}_2CH_3$), 0.98 (6H, t, $CH_2CH_2C\underline{H}_3$).

2,7,12,17-Tetrapropylporphycene **12**

Freshly activated zinc dust (28.99 g, 0.443 mol) was suspended in dry THF (800 mL) under an atmosphere of nitrogen with stirring. Titanium tetrachloride (42.2 g, 24.4 mL, 0.223 mol) was added dropwise to the stirring reaction mixture. The solution was heated to reflux and refluxed for 15-20 minutes.

4,4'-Dipropyl-5,5'-dicarbaldehyde-2,2'-bipyrrole **11** (6.0 g, 0.022 mol) was dissolved in dry THF (500 mL) and pyridine (29 mL) and added fast dropwise to the gently refluxing titanium reaction mixture. After addition the reaction mixture was refluxed another 1 hour. The heat was removed and the reaction flask was cooled to RT in cold water. An aqueous solution of potassium carbonate (41.7 g, 125 mL H_2O) was added slowly and the reaction mixture was allowed to sit for 36 hours. Most of the liquid was decanted off, the rest of the mixture was gravity filtered through cotton. The filtrate was evaporated in vacuo to minimal volume, dissolved in methylene chloride and separated. The organic layer was evaporated in vacuo, and the resulting solid was dissolved in a minimal volume of methylene chloride/hexane (3:1) and chromatographed on a silica gel column with methylene chloride/hexane (3:1). Recrystallization

from methylene chloride/methanol (1:1) afforded fine violet needles (1.35 g, 25.6%), m.p.: 192-194° C. ^{1}H NMR ($CDCl_3$): δ 9.70 (4H, s, bridge H), 9.28 (4H, s, pyrrole Hβ), 4.01 (8H, t, $C\underline{H}_2CH_2CH_3$), 3.25 (2H s, br, NH), 2.41 (8H, sext, $CH_2C\underline{H}_2CH_3$), 1.34 (12H, t, $CH_2CH_2C\underline{H}_3$); mass spectrum, m/e 478.

^{15}N-2,7,12,17-Tetrapropylporphycene **17**

Labeled nitric oxide, $^{15}N^{18}O$, (2.39 g, 1629 mL, 0.072 mol) was mixed with dioxygen (0.67 g, 470 mL, 0.021 mol), both in small portions by a gas syringe, above an aqueous solution of sodium hydroxide (4.0 g, 0.10 mol, 20 mL H_2O), protected from the atmosphere. The solution was stirred for an additional 30 minutes after mixing of the gases was complete.

This step involving the incorporation of labeled nitrogen into the aqueous sodium nitrite solution was the only step which was different from the synthesis of nonlabeled 2,7,12,17-tetrapropylporphycene; all subsequent steps were the same as above. ^{15}N NMR (CD_2Cl_2): δ 189.0 (s) at 30° C and 188.7 (s) at 0° C; mass spectrum, m/e 482.

Cu(II)-2,7,12,17-tetrapropylporphycene

2,7,12,17-Tetrapropylporphycene **12** (0.050 g, 0.105 mmol) was dissolved in glacial acetic acid (37.5 mL) under argon. Copper(II) acetate (0.0125 g, 0.626 mmol) and sodium acetate (0.008 g) were added with stirring. The reaction mixture was heated under argon to reflux and refluxed for 19 hours, then allowed to cool to RT. The reaction mixture was partitioned in methylene chloride (250 mL) and water (250 mL). The organic layer was separated, washed with water (250 mL) and evaporated

to dryness. Recrystallization from methylene chloride/methanol gave a quantitative yield of violet crystals.

N,N'-((N,N-Dimethylamino)methylene)-2,7,12,17-tetrapropylporphycene **13**

2,7,12,17-Tetrapropylporphycene **12**, or Cu(II)-2,7,12,17-tetrapropylporphycene (0.50 g, 0.105 mmol) was dissolved in N,N-dimethylformamide (75 mL) under an atmosphere of argon with gentle warming. The solution was cooled to 20° C and phosphorous oxychloride (8.23 g, 5 mL, 0.054 mol) was added dropwise with stirring, maintaining the temperature at 20° C during the addition. The reaction mixture was allowed to warm to RT, and stirring under argon was continued for 20 hours. The solution was poured over ice (50 g) and 10% aqueous sodium hydroxide (100 mL) was added slowly with stirring. The product was extracted with methylene chloride (500 mL) and washed with water (200 mL). The organic layer was evaporated in vacuo to near dryness. The residue was dissolved in methylene chloride/methanol (10%) and separated by preparative TLC. The crude product was dissolved in dichloromethane and chromatographed on a silica gel column (2 x 18 cm) with methylene chloride/triethylamine (3 drops). The bridged product was evaporated in vacuo to dryness. ^{1}H NMR ($CDCl_3$): δ 10.34, 10.07 (2H each, s, bridge H), 9.98, 9.67 (2H each, s, pyrrole Hβ), 6.08 (1H, s, NH), 4.15, 3.98 (8H, m, $C\underline{H}_2CH_2CH_3$), 2.40 (8H, m, $CH_2C\underline{H}_2CH_3$), 1.29 (12H, dt, $CH_2CH_2C\underline{H}_3$), -1.78 (6H, s, N-$C\underline{H}_3$), -5.06 (1H, s, $C\underline{H}$); mass spectrum, m/e 534 (M + 1).

N,N'-((N-Methylamino)methylene)-2,7,12,17-tetrapropylporphycene **14**

N,N'-((N,N-Dimethylamino)methylene)-2,7,12,17-tetrapropyl-porphycene **13** (0.040 g, 0.075 mmol) was dissolved in acetonitrile (30 mL) and a small amount of copper (II) perchlorate (10-15 mg) was added. This mixture was brought to reflux on the steam bath and was refluxed to dryness. Mass spectrum, m/e 519.

N,N'-((N-Methylaniline)methylene)-2,7,12,17-tetrapropylporphycene **15**

2,7,12,17-Tetrapropylporphycene **12** (0.050 g, 0.105 mmol) was dissolved in 1,2-dichloroethane (75 mL) under argon with gentle heating. The reaction mixture was cooled to 5° C and N-methylformanilide (0.142 g, 0.13 mL, 1.05 mmol) was added under argon with stirring. Phosphorous oxychloride (8.23 g, 5 mL, 0.054 mol) was added dropwise over 5 minutes with stirring. The solution was allowed to come to RT and stirring under argon was continued for 4 days. The reaction mixture was poured over ice (50 g) and 10% aqueous sodium hydroxide (100 mL) was added slowly with stirring. The product was extracted with methylene chloride (500 mL) and washed with water (200 mL). The organic layer was evaporated in vacuo to near dryness. The residue was dissolved in methylene chloride and chromatographed on a silica gel column (1.5 x 15 cm). The product was evaporated in vacuo to dryness. ^{1}H NMR (CD_3CN): δ 10.30, 9.29 (2H each, s, bridge H), 9.12, 8.82 (2H each, s pyrrole Hβ), 6.41 (1H, t, *p*-Ph-H), 5.92 (2H, t, *m*-Ph-H), 4.30, 4.07, 3.64 (2H, m, 2H, m, 4H, m,$C\underline{H}_2CH_2CH_3$), 3.07 (2H,d, *o*-Ph-H),2.33, 2.21 (4H each, m, m, $CH_2C\underline{H}_2CH_3$), 1.45, 1.28 (6H each, t, t, $CH_2CH_2C\underline{H}_3$), -2.11 (3H, s, N-CH_3), -5.99 (1H, s, C-H); mass spectrum, m/e 596 (M + 1).

N,N'-(C-C=C-NMe2)-2,7,12,17-Tetrapropylporphycene **16**

2,7,12,17-Tetrapropylporphycene **12** (0.050 g, 0.105 mmol) was dissolved in 1,2-dichloroethane (75 mL) under argon with stirring and gentle warming. The solution was cooled to 5° C. 3-(Dimethylamino)-acrolein (0.104 g, 0.105 mL, 1.05 mmol) was dissolved in cold (5° C) 1,2-dichloroethane (15 mL) and added to the reaction mixture, followed by the dropwise addition of phosphorous oxychloride (8.23 g, 5 mL, 0.054 mol) over a 5 minute period. The reaction mixture was allowed to warm to RT, and stirring under argon was continued for 3 days. The reaction mixture was poured over ice (50 g), and 10% aqueous sodium hydroxide (50 mL) was added slowly with stirring. The organic layer was separated and washed with water (100 mL), then evaporated in vacuo to near dryness. The crude product was dissolved in methylene chloride/acetonitrile and chromatographed on a silica gel column (1.5 x 14 cm) prepared with methylene chloride. The product was evaporated in vacuo to dryness. Attempts to recrystallize the product were unsuccessful.

Attempts to prepare:

N-Methyl-2,7,12,17-tetrapropylporphycene

2,7,12,17-Tetrapropylporphycene **12** (0.050 g, 0.105 mmol) was dissolved in a soultion of *m*-xylene (85 mL), glacial acetic acid (5 mL) and iodomethane (10 mL) under argon. The solution was refluxed for 27 hours. No trace of N-methylporphycene was indicated by uv/visible spectrum nor TLC.

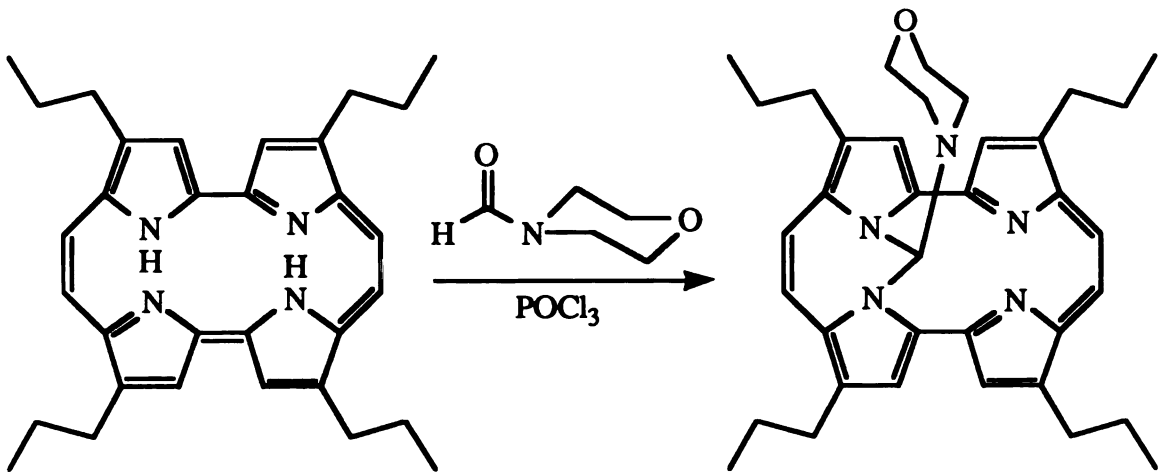
Trichloroacetic acid (5.15 g) was dissolved in a solution of *m*-xylene (15 mL) and iodomethane (10 mL) and was added to the reaction mixture. Refluxing was continued for another 3 days. The uv/visible

spectrum is indicative of an N-substituted TPPc as it is of the same shape as the bridged porphycenes, and unlike the shape of TPPc, however, N-methylporphycene has not been isolated.

FUTURE WORK

Because of the great stability of the N,N'-bridged porphycenes, they may provide interesting ways to build suprastructures on the macrocycle.

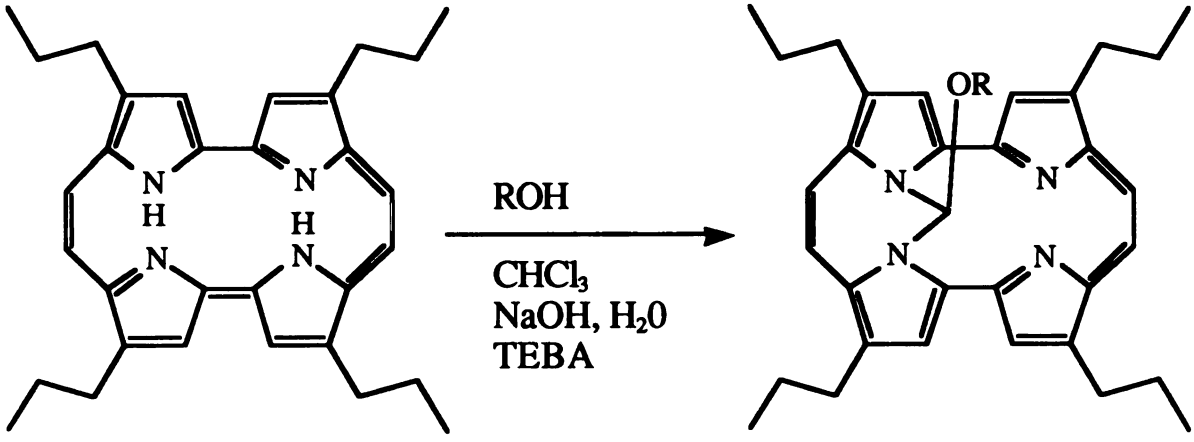
Work in the series of N,N'-bridged porphycenes will continue. Planned first is the synthesis of N,N'-((morpholine)methylene)-2,7,12,17-tetrapropylporphycene **17** (Figure 15), following a procedure similar to that used previously. A 5-fold excess of 4-formylmorpholine will be used and the reaction mixture will be heated to 50° C and kept there as the progress of the reaction is monitored by uv/visible spectra and TLC. Workup will be accomplished in the same manner as before.



12 **17**

Figure 15. Synthesis of N,N'-((morpholine)methylene)-2,7,12,17-tetrapropylporphycene **17**.

The synthesis of other N-substituted porphycenes will be attempted. The first reaction attempted will be the addition of carbenes generated by $CHCl_3$ and NaOH in various alcohols to produce alkoxy-substituted methylene-bridged porphycenes (Figure 16).



12 18

Figure 16. Synthesis of N-alkoxy-2,7,12,17-tetrapropylporphycene **18**.

Also planned is to connect two 2,7,12,17-tetrapropylporphycenes with methylene bridges using piperazine as the connector (Figure 17). The reagent that will be used to accomplish this is 1,4-piperazine-dicarboxaldehyde. It is hoped that this compound may be of value as a PDT agent, much like porphyrin dimers.

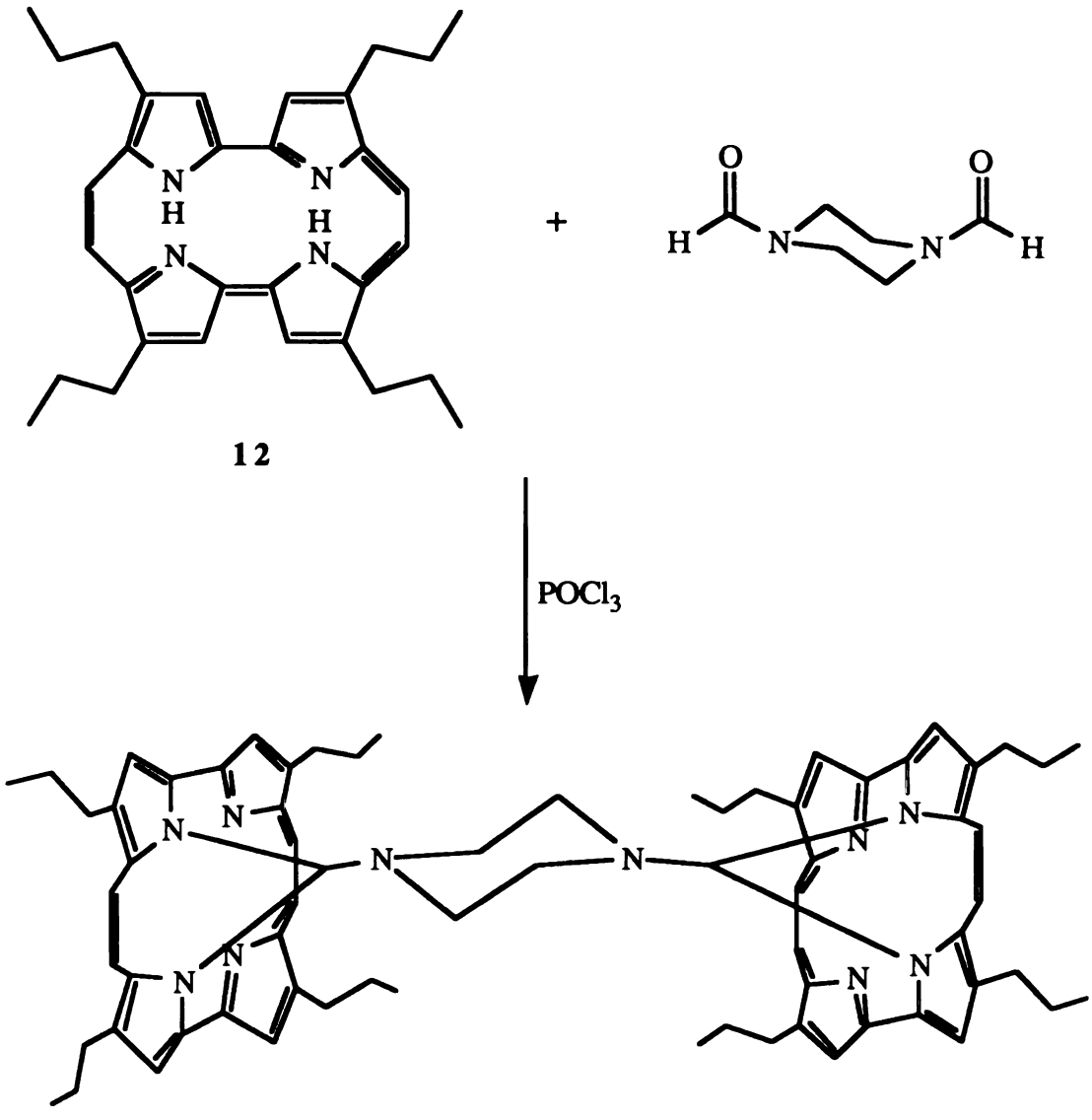


Figure 17. Synthesis of 2,7,12,17-tetrapropylporphycene dimer with piperazine connector.

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