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Syntheses and Evaluation of Phthalocyanine Derivatives for Applications in Photodynamic and Boron Neutron Capture Therapies for Cancer

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SYNTHESES AND EVALUATION OF PHTHALOCYANINE DERIVATIVES FOR APPLICATIONS IN PHOTODYNAMIC AND BORON NEUTRON CAPTURE THERAPIES FOR CANCER

A Dissertation

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M.S., Nankai University, 2004
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DEDICATION

To my parents: Mingzhen Tang and Baiwen Li. Thank you for being wonderful parents; for giving me life, unconditional love, support, education, guidance, most importantly the freedom to make my own decisions. You have always been my source of strength and inspiration. I can never thank you enough for what you have done in my life.

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LIST OF ABBREVIATIONS

δ	Chemical shift
λex	Excitation wavelength
br	Broad
BBr_3	Boron tribromide
$BBr_3{\cdot}SMe_2$	Boron tribromide dimethyl sulfide
n-BuLi	N-butyl lithium
$BF_3.OEt_2$	Boron trifluoride etherate
BOC	Tert-butyl carbamate
BPA	L-4-dihydroxyborylphenylalanine
BSH	Disodium mercapto-closo-dodecaborate
ºC	Degrees Celsius
d	Doublet
DPBF	Diphenylisobenzofuran
$CHCl_3$	Chloroform
CH_3OH	Methanol
^{13}C NMR	Carbon 13 nuclear magnetic resonance
BNCT	Boron neutron capture therapy
D_2O	Deuterated water
DBU	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1, 5-Diazabicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
DMAE	N, N-dimethylamino-ethanol

DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
ESI	Electrospray ionization
FAB	Fast atom bombardment
FDA	United States Food and Drug Administration
FT-IR	Ffourier transform infrared
h	Hours
H_2Pc	Metal-free phthalocyanine
HpD	Haematoporphyrin derivatives
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IC_{50}	Inhibitory concentration 50%
IR	Infrared
J/cm^2	Joule per square centimeters
LET	Linear energy transfer
MALDI	Matrix assisted laser desorption/ionization
MeI	Methyl iodide
MeOH	Methanol
MS	Mass spectrometry
m/z	Mass to charge ratio
nm	Nanometer
nM	Nanomolar

NA	Not available
NMP	N-methylpyrrolidone
NMR	Nuclear magnetic resonance
OH	Hydroxy
ppm	Parts per million
Pc	Phthalocyanine
PcH_2	Free base phthalocyanine
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PS	Photosensitizer
Py.HCl	Pyridine hydrochloride
q	Quartet
rt	Room temperature
RES	Reticulo-endothelial-system
ROS	Reactive oxygen species
s	Singlet
SiPc	Silicon phthalocyanine
t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropiperine
TLC	Thin layer chromatography
TMSBr	Trimethylsilyl bromide

TMSI	Trimethylsilyl iodide
µM	Micromolar
UV-Vis	Ultraviolet visible
ZnPc	Zinc phthalocyanine

ABSTRACT

Chapter I introduced the background of phthalocyanines including its physical properties and various synthetic methods of free-base and metallo-phthalocyanines. The background of PDT and BNCT was introduced and the objective of ideal sensitizers was described.

Chapter II described the synthesis and characterization of a series of pyridiloxy-substituted zinc phthalocyanines with different length of alkyl groups. Pyridiloxy-substituted silica phthalocyanines bearing different associated axial ligands, were alkylated with methyl or PEG chains. Biological study was performed on these cationic pyridiloxy-substituted zinc phthalocyanines.

Chapter III introduced the synthesis and photophysical properties of A_3B-type zinc phthalocyanines conjugated with one or two cobalta-carborane cages. They are highly soluble in polar solvents such as methanol, acetone, DMF and DMSO. Their absorption and emission properties are solvent-dependent, and had ~0.1 fluorescence quantum yields. These Pcs may have potential application as dual sensitizers in the PDT and BNCT treatment of tumors.

Chapter IV introduced the synthesis and characterization of octa, tetra and dihdroxy-substituted phthalocyanines using different synthetic strategies.

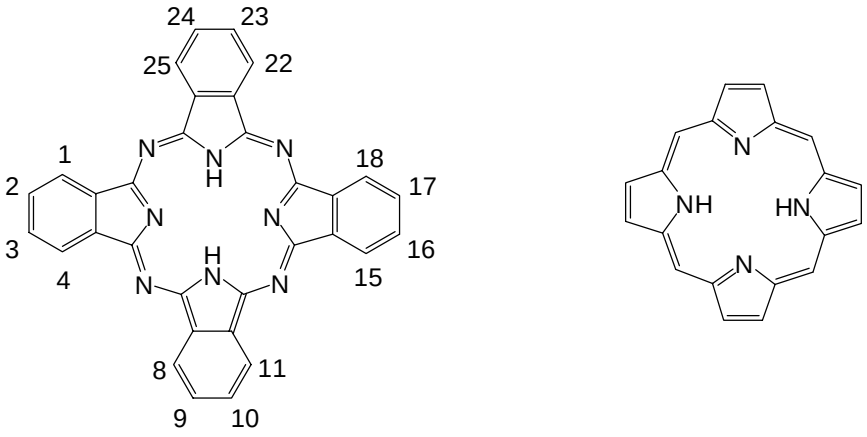
Chapter V introduced the synthesis and characterization of octaphosphonate-substituted zinc phthalocyanine.

CHAPTER 1

INTRODUCTION

1.1 Overview of Phthalocyanines

Phthalocyanine (Pc), known as an azoporphyrin derivative, is a class of synthetic tetrapyrrolic compound which is closely related to the naturally occurring porphyrin.[1, 2] Structure difference between Pc and porphyrin is that Pc has four extended benzo subunits and four nitrogen atoms at the *meso* positions on the macrocycle (Figure 1.1). Pc consists of a symmetrical macrocycle containing four isoindole units with a central cavity of appropriate size to fit more than 70 metal ions. Pc is an aromatic ring system due to its planar conjugated array of 18 π-electrons.



(a) **(b)**

Figure 1.1. **(a)** Metal-free phthalocyanine; **(b)** metal-free porphyrin.

Pc was firstly reported as a dark blue insoluble byproduct during the preparation of ortho-cyanobenzamide from phthalimide and acetic acid by Braun and Tcherniac in 1907.[1] Twenty years later, de Diesbach and von der Weid of Fribourg University observed an unexpected stable blue material in the reactions of ortho-dibromobenzene with copper cyanide in refluxing pyridine.[1] The mystery of the new compound wasn't

resolved until Linstead et al. succeeded in determining its structure using several methods in the early 1930s.[3-9] Pc is finally elucidated as a symmetrical, aromatic macrocycle of 18 π-electrons, which is composed of four identical isoindole units.

Monomeric metallo-Pcs have characteristic absorption spectra including a Soret band in the visible region at approximately 350 nm, and a major strong Q band at around 670 nm with a molar extinction coefficient in the range of 10^5 $M^{-1}cm^{-1}$ (Figure 1.2).[10]

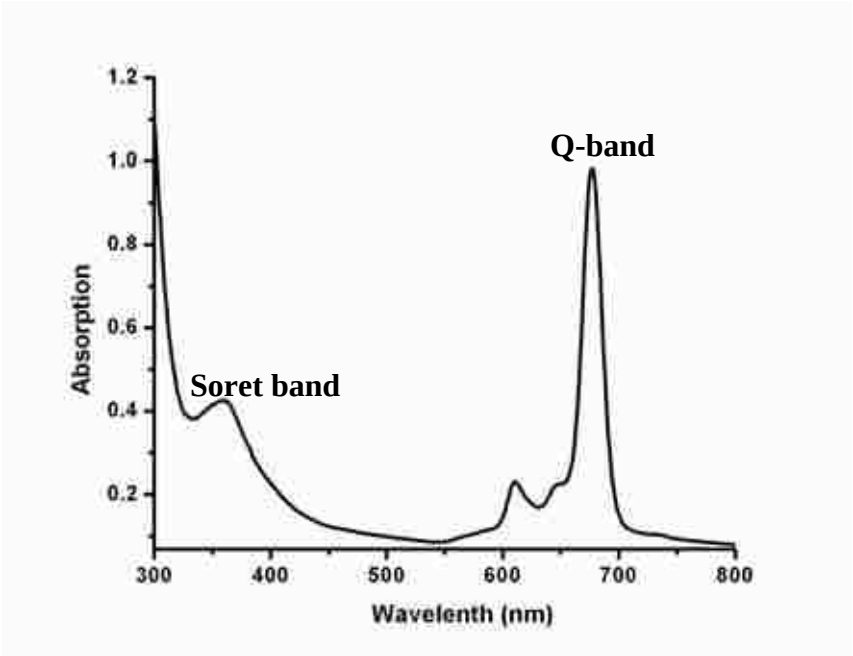


Figure 1.2. Typical absorption spectrum of a metallo-Pc in DMSO.

Pc normally has high thermal and chemical stabilities. It is also well known that the largest disadvantage of this kind of material is its extreme insolubility in most solvents due to its intrinsic nature. The planarity of the aromatic core and its extreme hydrophobicity leads to a pronounced tendency for aggregation. Unsubstituted Pc is poorly soluble in most organic solvents and water. In order to increase the solubility, Pcs' backbone can be modified by attaching various substituent at the macrocycle periphery or centrally chelated metal ions which typically have oxidation states of +2 or greater.

1.2 Synthetic Strategies for Phthalocyanines

1.2.1 General Aspects of Phthalocyanine Synthesis

The precursors of Pcs include phthalic acid, phthalonitrile, phthalic anhydride, phthalimide, diiminoisoindoline, o-cyanobenzamide, cyclohex-1-ene-1,2- dicarboxylic

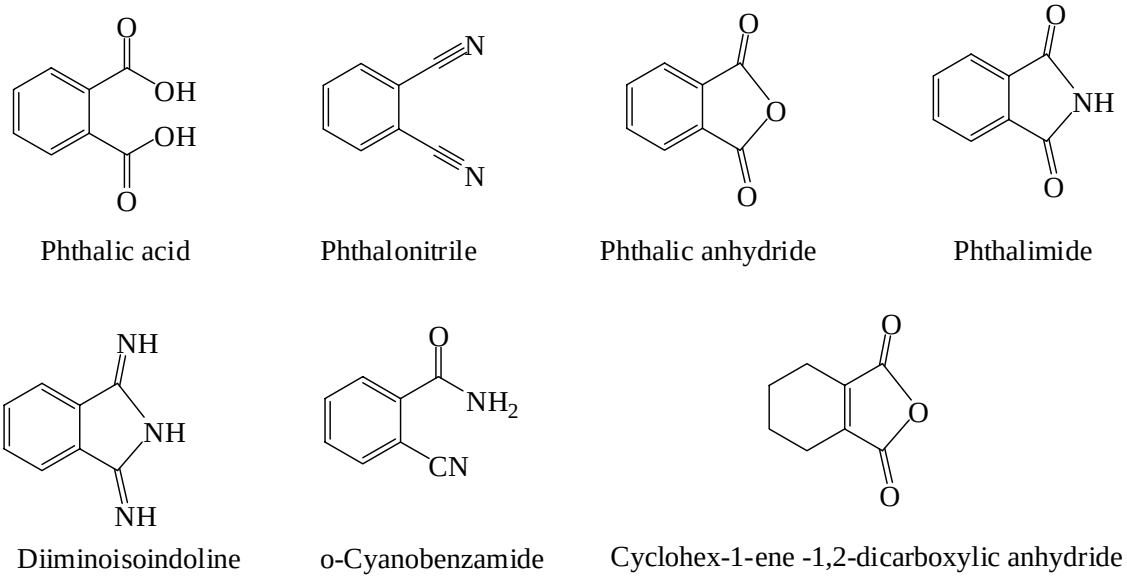
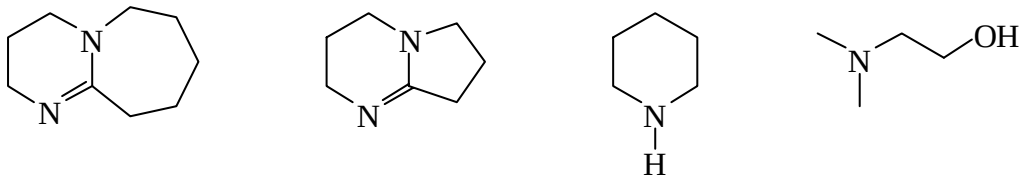


Figure 1.3. Basic Pc precursors.

anhydride (Figure 1.3). Among these, phthalonitrile is the most useful precursor in the synthesis of Pc. Phthalonitrile is generally used in a reaction involving heating with a metal template in a high boiling point solvent, such as chlorobenzene, quinoline or 1-chloronaphthalene.

In the early 1980s,[11, 12] Tomoda *et. al.* published a simple method to synthesize Pc by heating 1,2-dicyanobenzene with a catalytic amount of DBU or DBN in an alcoholic solvent. High yields of 70% for metal-free and 80% for metal-containing Pc were achieved. Since the organic bases DBU and DBN were first employed in Pc synthesis by Tomoda, this method and the related preparation of metal-containing Pcs are referred to as “Tomoda method”. Common organic bases used in the synthesis of Pc are DBU, DBN, piperidine and DMAE (Figure 1.4). Wohrle and Knothe found in 1991 that the presence

of an organic base such as DBU and DBN is important in the synthesis of Pc.[13] These organic bases can generally lead to high yield in Pc formation and more purity when various substituted dinitriles are used as the precursors. It was also reported that the use of weaker bases such as TEA, pyridine and THP failed to promote Pc formation while stronger bases than DBU and DBN did not improve the reaction.



DBU DBN Piperidine DMAE

Figure 1.4. Structures of common organic bases used in the syntheses of Pcs.

The symmetry of the resulting Pc largely depends on the structure of the precursors used in the reaction. Unsubstituted or symmetrically substituted precursors can lead to symmetric Pcs. For example, 4,5 - or 3,6 - disubstituted phthalonitriles can only lead to symmetric octasubstituted Pcs.

Unsymmetrically substituted precursors may lead to complicated mixtures of Pcs containing several constitutional isomers. For example, a 4 - substituted phthalonitrile can lead to four constitutional isomers: C_{4h}, C_{2v}, C_s, D_{2h} (Figure 1.5). The modification of the properties of the substituent on the phthalonitrile and optimization of the reaction condition can improve the formation of one or two major isomers. However, in most cases, the separation of constitutional isomers is troublesome and difficult. The yields of products are poor due to tedious chromatography purification procedures.

1.2.2 Mechanisms of Phthalocyanines' Formation

The formation of Pcs using phthalonitrile as precursor usually requires the presence of a high boiling point alcohol such as pentanol or butanol as the solvent and a

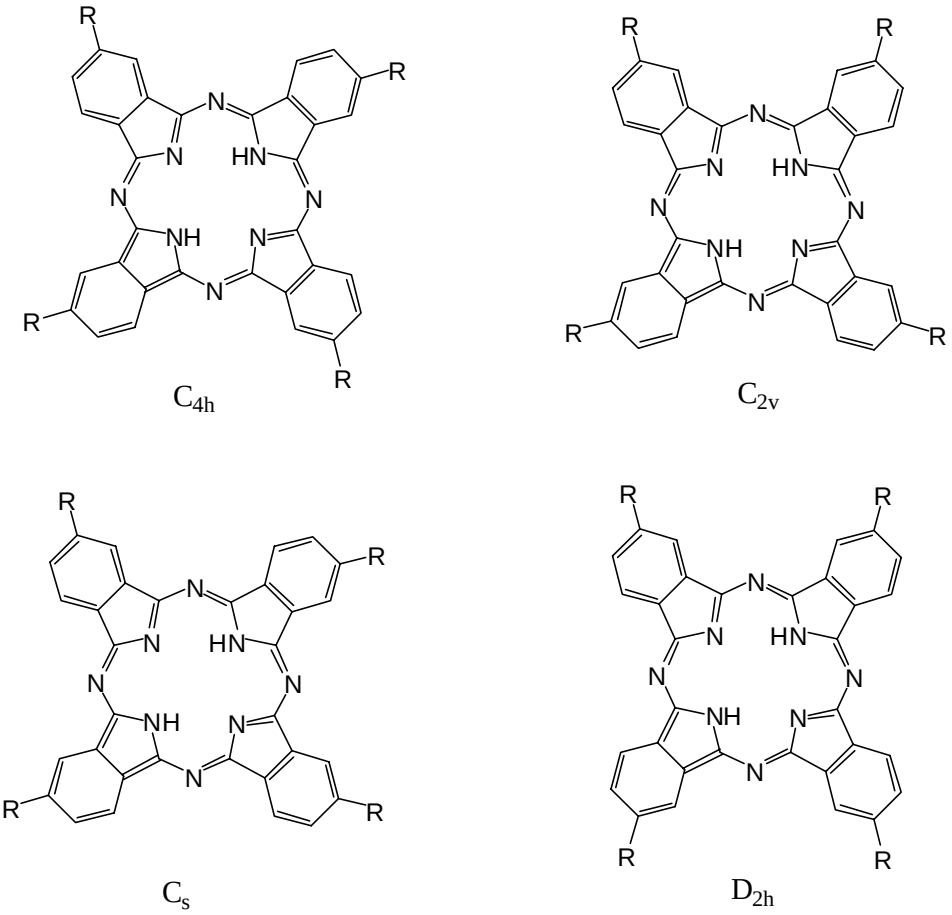
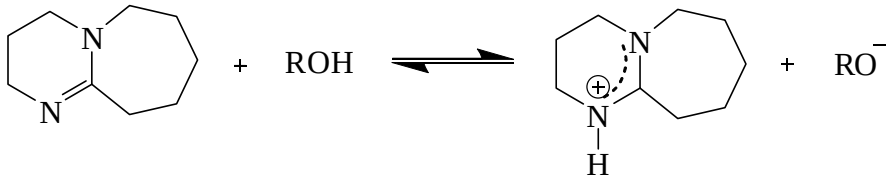


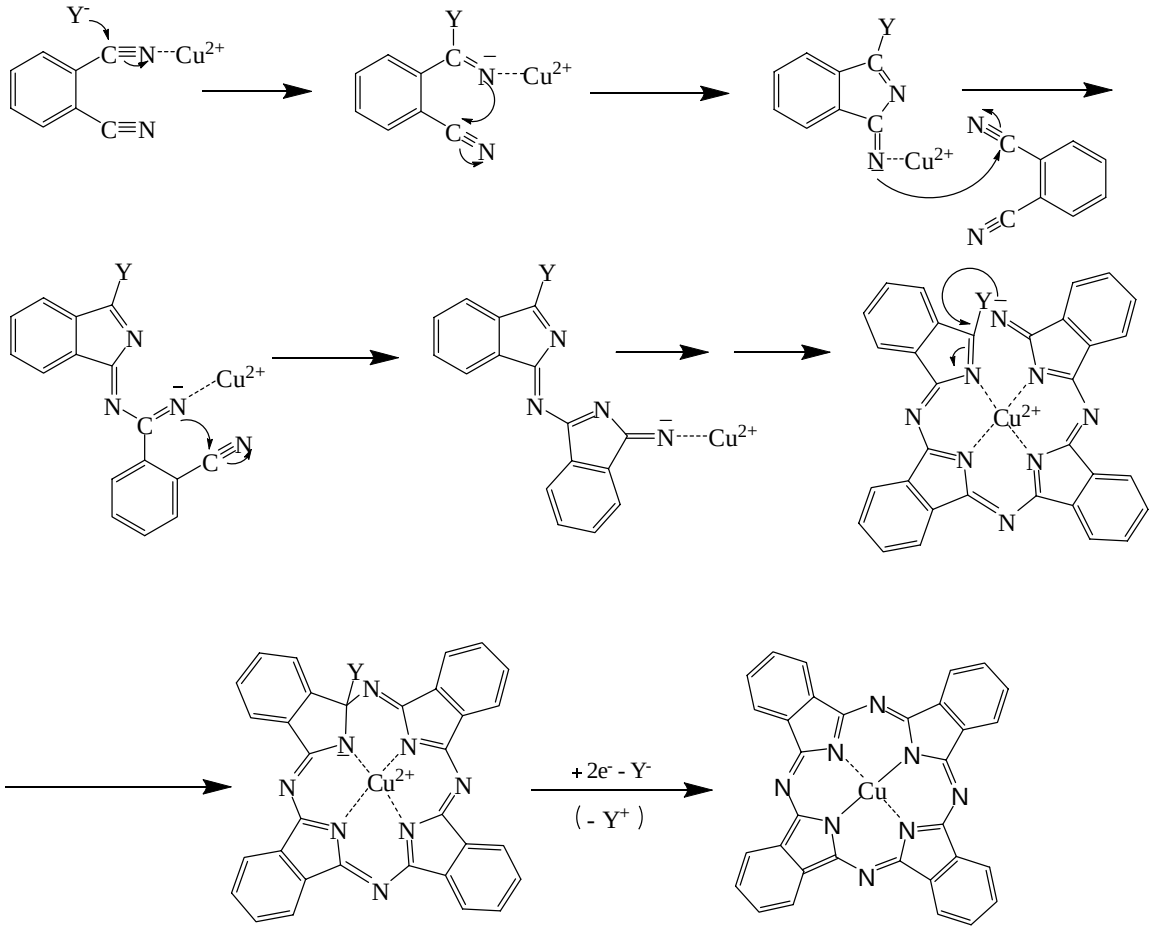
Figure 1.5. Structures and symmetries of different Pc constitutional isomers.

strong base such as DBU or DBN. Tomada *et. al.*[11] proposed the role of the strong base as being an electron acceptor (Scheme 1.1). As a result, alkoxide anion (RO^-) is both the



Scheme 1.1. Mechanism of formation of RO^- (Y^-)[11] in Pc synthesis.

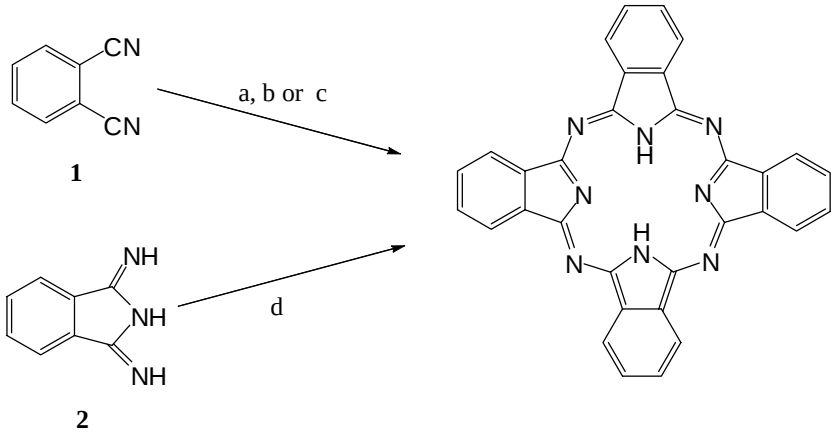
nuleophile and reducing agent that reacts with a cyano group of a phthalonitrile to form an alkoxyisoindolenine intermediate as shown in Scheme 1.2.[14] The dimeric intermediate reacts further with two molecules of the precursor to get the metal complex.



Scheme 1.2. Mechanisms of formation of a metallo-Pc.[14]

1.2.3 Synthesis of Symmetrical Phthalocyanine

The strategies to synthesize metal-free symmetrical Pcs are summarized in Scheme 1.3.[15] Phthalonitrile **1** and diiminoisoindoline **2** can both be used as precursors to obtain metal-free Pc. Lithium alkoxide formed in situ by the addition of lithium to a primary alcohol is normally used, when phthalonitrile is the precursor. The lithium ion can be easily removed by acidic or aqueous work-up after the macrocyclization. Metallo-free Pc (H_2Pc) can also be synthesized by using a suitable organic reducing agent such as a hydroquinone. The "Tomoda method"[11] involves heating of a phthalonitrile with a base (e.g. DBU, DBN) in a high boiling point solvent (e.g. n-pentanol) or in a basic solvent such as DMAE to afford H_2Pc in high yields (70%).



Scheme 1.3 (a) Lithium, pentanol, followed by aqueous hydrolysis; (b) fusion with hydroquinone; (c) heat with a base (e.g. DBU, DBN); (d) refluxing in a high boiling point alcohol (e.g. n-pentanol).[15]

Metallo-Pc can be prepared in several ways.[1] They can be formed from phthalonitrile or diiminoisoindoline in the presence of the metal ion as a template for the cyclotetramerization. The direct metallation of H_2Pc is another clean and high-yielding synthetic approach. Phthalic anhydride and phthalimide can also be used as the precursors in the presence of metal salts to produce metallo-Pc in good yields.

The high stability of unsubstituted Pc allows its purification by sublimation at 600 ºC in vacuo.[16-18] This method is useful to obtain ultra-pure materials. Another method of purification that relies on the stability of Pc is recrystallization from concentrated sulfuric acid and water. This method is particularly suitable to copper (II)-Pc which has no solubility in any organic solvent and is stable in sulfuric acid solution.[5] Traditional purification methods such as column chromatography on alumina and silica gel, recrystallization and extraction can be applied to soluble Pcs. However, Pcs' strong tendency for aggregation in solution may hinder its clean separation using these techniques.

1.2.4 Synthesis of Non-Centrosymmetric Phthalocyanine

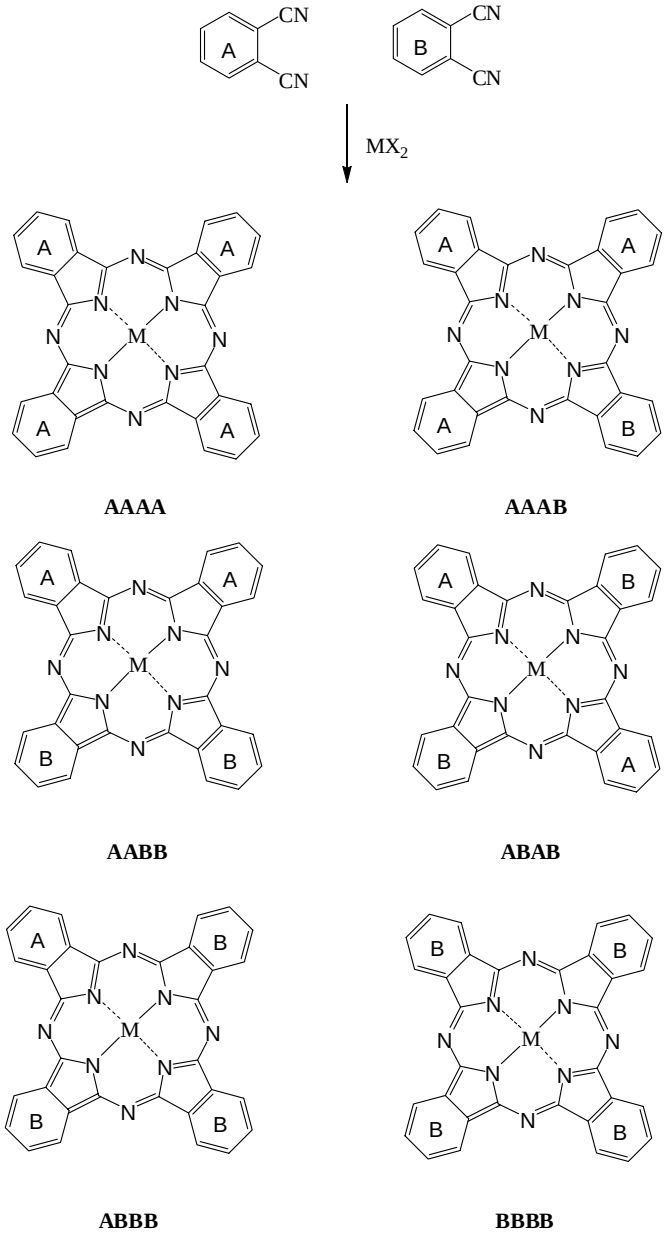
Non-centrosymmetric Pc can be obtained by mixed condensation of two different phthalonitriles. It can lead to asymmetric Pc when unsymmetrically substituted precursors are used. In this case, different constitutional isomers are obtained as a mixture. Because of Pc's low solubility and tendency for aggregation, it is difficult to separate and characterize the different isomers.[19] Only a few examples in the literature show the successful separation of isomers by Hanack and co-workers, using an especially designed HPLC column.[20, 21] The selective synthesis of unsymmetrically substituted Pcs is a big challenge for Pc chemists. In the past years, several approaches have been investigated for the synthesis of unsymmetrically substituted A_3B-type Pcs (subunits: A and B). The synthetic methods to A_3B-type Pcs can be summarized as: 1) statistical condensation; 2) ring expansion; and 3) polymer support synthesis (see below).

1.2.4.1 Statistical Condensation

Statistical condensation method is the traditional method to synthesize the A_3B-type Pc containing three identical and one different isoindole subunits. It is based on the reaction of two differently substituted phthalonitrile or diiminoisoindoline A and B. The reaction affords a mixture of six constitutional isomers (Scheme 1.4). The drawback of this method is the difficult purification procedure. Chromatography is generally used to do the tedious separation of the mixed products. The yield is normally low and contamination of the different isomers may occur.

One of the solutions is to modify one of the phthalonitriles with bulky or rigid substituents which can provide different solubility features to the macrocycles, and as a result, makes the separation easier. Especially when a phthalonitrile with rigid groups at

the 3 and 6 positions reacts with another phthalonitrile, fewer isomers are obtained.[22, 23] Varying the stoichiometry is another way to control the ratio of isomers produced in the



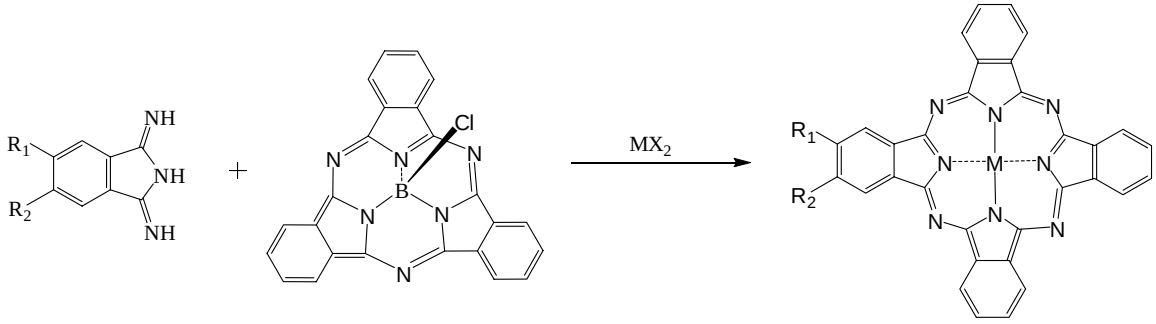
Scheme 1.4. Statistical condensation of two phthalonitriles **A** and **B**.

statistical condensation. Cook and *et. al.* reported that condensation of a phthalonitrile bearing long chain groups at the 3,6-positions and another differently substituted phthalonitrile in a 9:1 ratio can lead to simpler mixtures and separations in the purification step.[24-28] In summary, the electronic properties, the position of the

substituents on the phthalonitrile precursors and their ratio can be the factors that determine the ratio of the Pc isomers produced.

1.2.4.2 Ring Expansion

In the late 1980s, Kobayashi and his coworkers developed a new method to synthesize A_3B-type Pc.[29] This method involves the ring expansion reaction of a subphthalocyanine in the presence of succinimide or diiminoisoindoline derivatives as the reactants (Scheme 1.5).



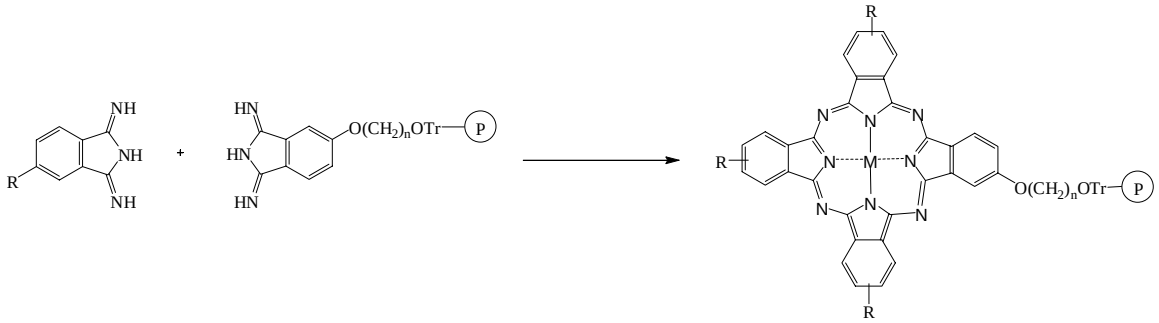
Scheme 1.5. Selective synthesis of A_3B-type Pc.[29]

The selectivity of this ring expansion reaction is highly dependent on the reactants' properties and the reaction conditions. It was reported that the best yield of the unsymmetrically substituted Pc could be achieved by using a metal template and by selectively choosing the substituents on the two reactants.[30] The best yields were achieved in the case of reactions between subphthalocyanines bearing either no substituents or electron-withdrawing groups, and diiminoisoindoline derivatives bearing electron-donating groups.[30] Van Lier and Sharman reported the synthesis of A_3B-type fluorinated Pcs by the ring expansion method in 2005.[31] Dodecafluorinated subphthalocyanine and diiminoisoindoline in 1:5 ratio reacted in DMSO at room temperature. The yield to obtain the dodecafluorinated Pc was up to 60%. Although in some cases the subphthalocyanine approach can be an efficient method to synthesize

unsymmetrically substituted Pcs, in many cases it may lead to a mixture of statistical Pc products. This may be caused by the partial or total fragmentation of the subphthalocyanine ring followed by statistical ring closure of the fragmentation products, and as a result leading to a mixture of all possible Pcs.[32, 33]

1.2.4.3 Polymer Support

The method of using a polymeric support to synthesize A_3B-type Pcs was developed by Leznoff and coworkers in 1982.[34-36] It requires that a mono-functionalized phthlaonitrile or diiminoisoindoline can be bounded to the solid phase. The insoluble polymer bounded precursor (B) can react with another free precursor (A) to afford the A_3B-type polymer bounded Pc (Scheme 1.6). The A_3B-type Pc can be purified by



Scheme 1.6. Synthesis of A_3B-type Pc on a polymer support.[34-36]

washing away the soluble A_4-type byproduct and the resulting desired Pc can be cleaved from the solid-phase under mild conditions. Recently, Dr. Hammer Robert reported the solid-phase synthesis of A_3B-type Pc using a PEG-based support with Wang linker.[99] However, it requires the easy-on and off properties of the precursors to the solid-phase, which limits its application in the universal method of synthesis of A_3B-type Pcs.

1.3 Applications of Phthalocyanine

Pcs have been widely used as colorants or dyes,[37-39] photoconducting materials,[40] chemical sensors,[41-43] semiconductors,[44, 45] industrial catalysts[46-48] and non-linear optical

materials.[49, 50] The Pcs' potential applications in various areas are due to their intense blue-green color, high photostability, high degree of aromaticity and unique electronic spectra. Pcs as near-IR dyes can also be used as fluorescent probes for application in the area of bioconjugations and labeling of biomolecules. La Jolla Blue (Figure 1.6) is the first commercially available Pc dye bearing two water-soluble axial polyethylene glycol moieties and two free carboxylic acid groups available for bioconjugation. Different

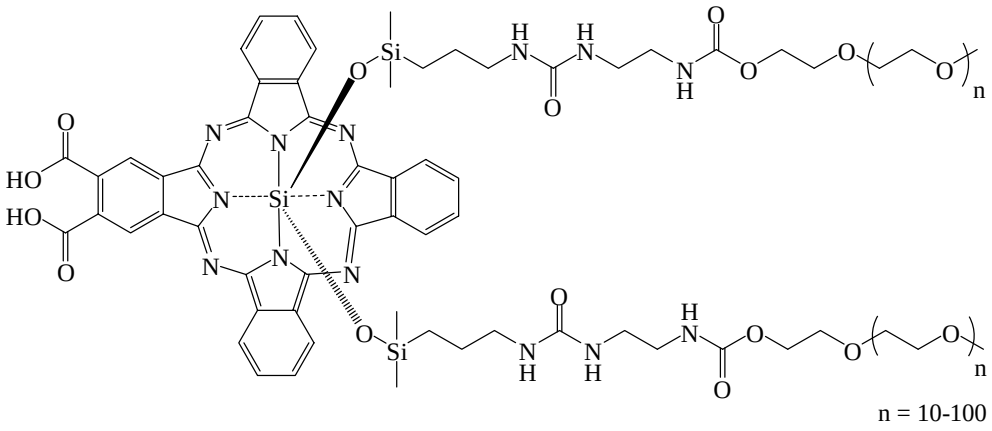


Figure 1.6. Structure of La Jolla Blue dye™.[51]

types of biomolecules such as nucleobases,[52] oligonucleotides,[51, 53-55] peptides,[56] and proteins[57-59] have been reported to bind with Pc dyes. These bioconjugates have potential applications in bioimaging and bioanalytical areas.

1.3.1 Applications in Photodynamic Therapy (PDT) of Cancer

Pc, as a second-generation photosensitizer, has been widely used in PDT.[10, 60] Photodynamic action was first reported by Raab in 1900.[1] He observed that Paramecia (unicellular organisms) were killed when exposed to light in the presence of acridine and eosin dyes.[61] Since then, photodynamic therapy (PDT) was developed as a promising modality utilizing a photosensitizer, visible or near-infrared radiation and O_2 to destroy unwanted cells. This technique has been accepted in the clinic as a curative or palliative therapy for cancer. In 1995, the FDA approved the first photosensitizing agent called

Photofrin® (a purified form of HpD, haematoporphyrin derivative) which has full approval in several countries for clinical use. However, Photofrin® has some drawbacks such as difficult reproducibility in synthesis, long half-life in patients, far from optimal spectral properties and low selectivity for tumors at 2 mg/kg.[62, 63] As a consequence, benzoporphyrin derivatives, chlorines, purpurins, phthalocyanines have emerged as second-generation photosensitizers.

Among these, Pcs have promising applications in the PDT treatment of cancer.[64, 65] Since Pcs contain four iminoisoindoline units, they have more extended π-conjugates than porphyrins and stronger absorptions in the far-red region of the optical spectrum. They typically have a major Q absorption band around 670 nm with high molar extinction coefficient, in the range of 10^5 $M^{-1}cm^{-1}$, while the longest λ absorbing band of Photofrin® has only 3000 $M^{-1}cm^{-1}$ at 630 nm.[66] In general, Pcs allow deeper penetration of light through tissue since longer wavelengths of light penetrate tissue more efficiently than shorter ones. Furthermore, cheaper diode lasers can be used in the near-IR range.

Several Pc derivatives such as ZnPc (CGP55847), $AlPcS_4$ (Photosense®) and Pc 4 have been in clinical trials to evaluate their photoefficiency in PDT.[63, 67, 68] Pc 4 bearing one siloxy axial ligand and one hydroxyl group has been in Phase I trial for cancer treatment (Figure 1.7).[69, 70]

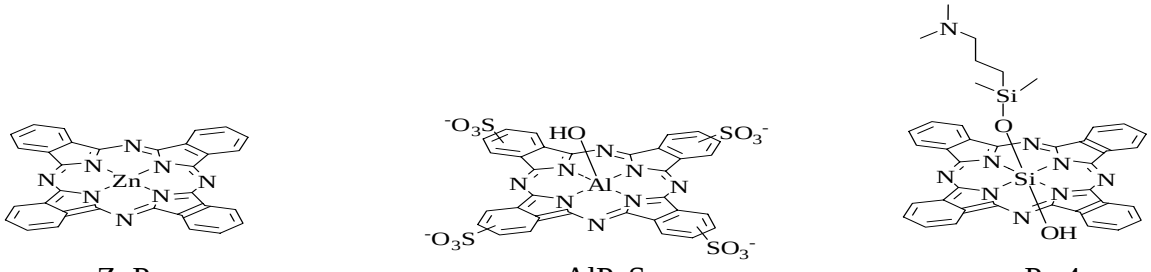


Figure 1.7. Structure of Pcs currently under clinical investigation for PDT.[63, 67, 68]

1.3.1.1 Mechanisms of PDT

Figure 1.8 shows the basic steps involved in the treatment of cancer patients with PDT. In the PDT treatment, a photosensitive drug is injected into the cancer patient. After

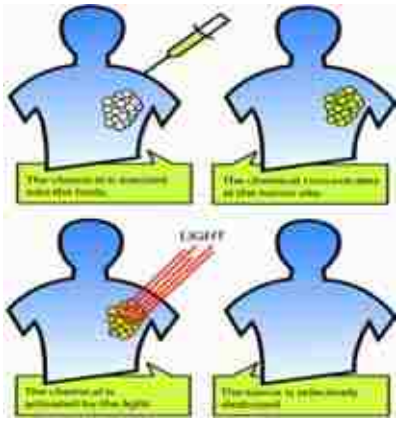


Figure 1.8. Treatment of a cancer patient with PDT.[71]

selective localization in the malignant cells, the drug is activated by appropriate wavelength of light to produce reactive cytotoxic oxygen species that induce tumor death, while normal cells remain intact.[72]

$$\text{sensitizer} + h\nu \longrightarrow {}^1\text{sensitizer}^*$$

$${}^1\text{sensitizer}^* \xrightarrow{\text{ISC}} {}^3\text{sensitizer}^*$$

(a)

$${}^3\text{sensitizer}^* + {}^3\text{sensitizer}^* \longrightarrow \text{sensitizer}^{+\bullet} + \text{sensitizer}^{-\bullet}$$

$${}^3\text{sensitizer}^* + \text{substrate} \longrightarrow \text{substrate}^{+\bullet} + \text{sensitizer}^{-\bullet}$$

$$\text{sensitizer}^{-\bullet} + {}^3O_2 \longrightarrow \text{sensitizer} + O_2^{-\bullet}$$

$$\text{substrate}^{+\bullet} + {}^3O_2 \longrightarrow \text{oxidative damage}$$

$$\text{substrate} + O_2^{-\bullet} \longrightarrow \text{oxidative damage}$$

(b)

$${}^3\text{sensitizer}^* + {}^3O_2 \longrightarrow \text{sensitizer} + {}^1O_2$$

$${}^1O_2 + \text{substrate} \longrightarrow \text{oxidative damage}$$

Scheme 1.7. PDT (a) Type I mechanism; (b) Type II mechanism.[72]

During the application of PDT, the photosensitizer being activated by light will undergo two different processes to produce cytotoxic species. Scheme 1.7 shows the Type I and Type II mechanisms of these processes. The photosensitizer is first excited from the ground state (S_0) to its first excited singlet state (S_1). It is then converted to the triplet state (T_1) through an intersystem crossing (ISC). In Type I mechanism, the exited state of the photosensitizer (T_1) will react with a substrate to produce radical ions. These highly reactive species will interact with ground state molecular oxygen to yield superoxide and other anions which cause oxidative damage. In Type II mechanism, the exited state of photosensitizer (T_1) reacts with molecular oxygen to yield highly toxic singlet oxygen species that induces oxidative damage. Both of these two types of processes can cause irreparable biological damage within the target tissues.[72]

1.3.1.2 Ideal Photosensitizers for Application in PDT

An ideal photosensitizer for PDT should meet the following criteria:[63, 64, 72, 73] 1) it should be chemically pure and maintain a constant composition throughout treatment; 2) it should have minimal dark toxicity; 3) it should accumulate preferentially in tumor tissue; 4) it should target sensitive or vulnerable tumor cell sites; 5) it should have high photochemical reactivity; 6) it should have a large absorption coefficient within the wavelength range 600-800 nm; 7) it should be rapidly cleared from normal tissues after the treatment. Although it is difficult for a photosensitizer to fulfill all the above parameters, we make an effort to synthesize water-soluble Pcs as promising second-generation photosensitizers.

A potential photosensitizing drug should be amphiphilic for crossing cellular membranes.[60] Pc and porphyrin macrocycles are intrinsically hydrophobic. Various hydrophilic functional groups such as sulfonic acid,[74-76] phosphonic acid,[77-80] carboxylic

acid,[81, 82] hydroxy[83] and quaternary ammonium salts[84, 85] have been used as peripheral substituents or axial ligands to make these macrocycles amphiphilic. Recently, our group has reported the synthesis and biological evaluation of cell targeted peptide conjugated zinc Pcs.[56] These conjugates show high phototoxicity toward human carcinoma HEp2 cells and preferentially localized in the lysosomes.

Wohrle and Durantini reported the synthesis of positively charged Zn (II)-pyridiloxy-substituted Pcs.[84, 85] However, they only beared four positive charges and consisted of a mixture of constitutional isomers. In Chapter II, we report our design and synthesis of positively charged zinc and silicon pyridiloxy-substitute Pcs bearing eight positive charges and different side chains and associated axial ligands. Van Lier and Leznoff reported the synthesis of a series of hydroxy-substituted Zn-Pcs and their biological investigation.[83] In Chapter IV, we report our design and synthesis of soluble octa-, tetra- and di-hydroxy-substituted Pcs.

1.3.2 Applications in Boron Neutron Capture Therapy (BNCT) of Cancer

Boron neutron capture therapy (BNCT) is a binary cancer treatment that involves the activation of a tumor-localized sensitizer containing boron-10 (^{10}B) nuclei with low energy neutrons.[86, 87] The resulting excited and highly cytotoxic species $^{4}He^{2+}$ and $^{7}Li^{3+}$

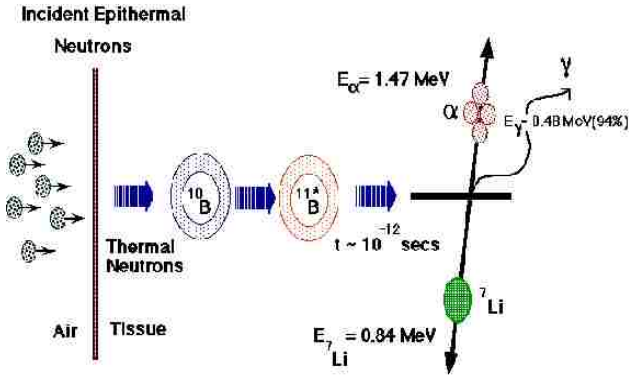
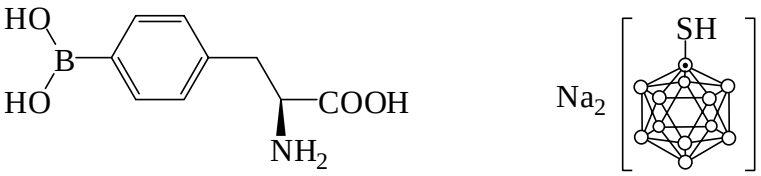


Figure 1.9. Schematic of boron-10 neutron interaction.[88]

are released and have short travel distances in tissues (up to 10 μm). The concept of BNCT is sketched in Figure 1.9.

Two compounds currently in clinical trials are disodium mercapto-closo-dodecaborate $Na_2B_{12}H_{11}SH$ (BSH) and L-4-dihydroxyborylphenylalanine (BPA) (Figure 1.10).[89-93] However, these early-investigated BNCT agents do not show much selectivity



BPA BSH

Figure 1.10. Structures of BPA and BSH.

for tumor cells and no long retention times in tumors. For effective BNCT, the ^{10}B-containing agent has to fulfill the following requirements: 1) tumor concentration of ^{10}B/g in the range 15–30 μg; 2) localize preferentially within or in close proximity to the tumor cell nuclei; 3) low persistence in blood and normal tissues; 4) selectivity of tumor/normal tissue greater than 5; 5) low toxicity; 6) persistence in tumor during all the irradiation treatment.[94] Boronated-porphyrin has shown higher tumor-targeting selectivity and longer retention time in tumors.[94, 95] Recently, our group has reported the synthesis and biological evaluation of a series of porphyrin conjugated with cobaltacarborane cages.[96-98] In Chapter II, we report our design and synthesis of a series of soluble A_3B-type cobaltacarborane conjugated Pcs.

1.4 References

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CHAPTER 2

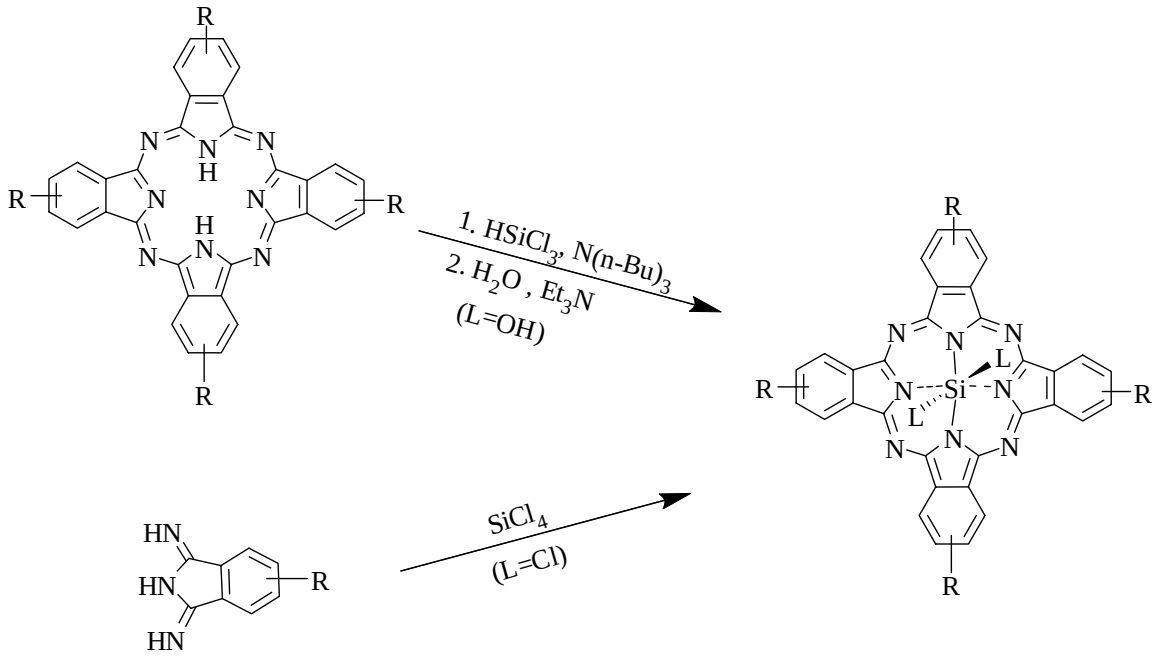
SYNTHESES AND PROPERTIES OF CATIONIC OCTAPYRIDILOXY-SUBSTITUTED PHTHALOCYANINES*

2.1 Background

Cationic photosensitizers are promising PDT drug candidates in the study of PDT since they were reported to potentially target highly vulnerable intracellular sites and lead to effective DNA photodamage.[1-3] A series of positively charged pyridiloxy-substituted zinc Pcs have shown higher photodynamic activity than FDA-approved Photofrin® which is the first approved drug for PDT, and their biological efficacy can be adjusted by the introduction of alkyl groups of different length.[4-6] In this Chapter, eight cationic pyridiloxy-substituted zinc or silicon Pcs were synthesized and their spectroscopic properties were evaluated. The biological properties of this series of Pc were also investigated and summarized later in this Chapter.

Silicon Pcs can be synthesized in two ways as summarized in Scheme 2.1. In 1965, Lowery reported a simple synthesis of silicon-dichlorophthalocyanine.[7] 1,3-Diiminoisoindoline was used as the starting material. It reacted with silicon tetrachloride in quinoline to give 71% yield of the Pc, while the reaction of o-cyanobenzamide with silicon tetrachloride only gave 35% yield of the Pc. Another method is by direct metallation of the metal-free Pc using trichlorosilane in the presence of tri-n-butylamine.[8,9] The second method is similar to the synthesis of silicon porphyrins. The dilithioporphyrin reacts with trichlorosilane to give nearly quantitative yield of the metallated silicon porphyrin.[10] Rodgers et. al. reported that Si-octahexylphthalocyanine

* Parts of this Chapter have appeared in the *Journal of Medicinal Chemistry*.[11]



Scheme 2.1. Methods to synthesize silicon-Pcs.

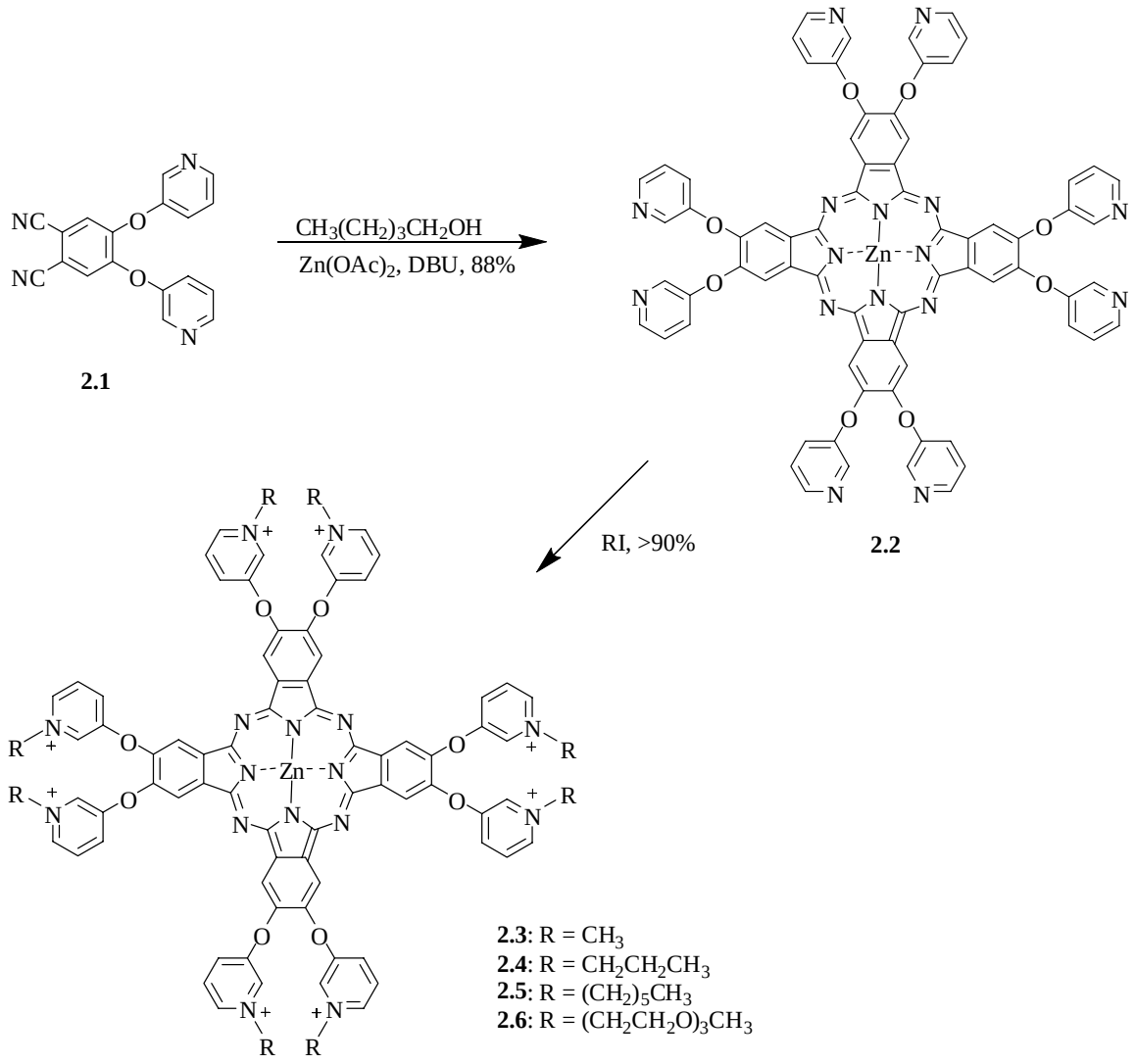
dichloride could be synthesized from the metal-free Pc and trichlorosilane in 47% yield.[8] Silicon-octahexylphthalocyanine dihydroxide was synthesized by reacting metal-free octahexylphthalocyanine and tri-n-butylamine with trichlorosilane in dichloromethane at room temperature.[3] The reaction was complete in 4 hours and the subsequent hydroxylation with water and triethylamine afforded 84% overall yield of the silicon-Pc dihydroxide.[3]

In this Chapter, a series of cationic silicon-Pcs were synthesized from a diiminoisoindoline derivative and silicon tetrachloride. Efforts to make silicon-octapyridiloxyphthalocyanine dihydroxide by the direct metallation reaction did not succeed because of the poor solubility of the metal-free precursor in most organic solvents. When the method of direct metallation was applied to the synthesis of the silicon Pc, attention must be taken to select appropriate substituents at the periphery of the macrocycle in order to solubilize the free-base Pc. In general, the first method, when

1,3-diiminoisoindoline is used as the precursor, can be widely applied to the synthesis of silicon-Pcs.

2.2 Synthesis of Octapyridiloxy-Substituted Zinc Phthalocyanines

Octapyridiloxy-substituted zinc Pcs **2.3**-**2.6** were synthesized in two steps shown in Scheme 2.2. The synthesis of octapyridiloxy-substituted zinc Pc was accomplished via the direct and convenient method of cyclotetramerization catalyzed by DBU in n-pentanol using phthalonitrile **2.1** as the starting material.



Scheme 2.2. Synthesis of zinc Pcs.

According to the procedure of Wöhrle,[12] **2.1** was synthesized in 86% yield from commercially available 4,5-dichlorophthalonitrile and 3-hydroxypyridine. The nucleophilic aromatic displacement reaction was catalyzed by finely grained potassium carbonate as a mild base. The first trial toward the synthesis of 4,5-(4-pyridiloxy)phthalonitrile was not successful, probably due to the lower nucleophilicity of the hydroxyl group at the 4-position of the pyridine ring. The X-ray crystal structure of the key intermediate **2.1** is shown in Figure 2.1. One of the pyridine rings is disordered by 2-fold rotation and the other one appears to be ordered. The two OPy groups are oriented differently with respect to the phthalonitrile, with tortion angles -59.8(2)º about C1-O1 and -7.0(2) º about C2-O2. The colorless crystal was grown from slow evaporation of dichloromethane.

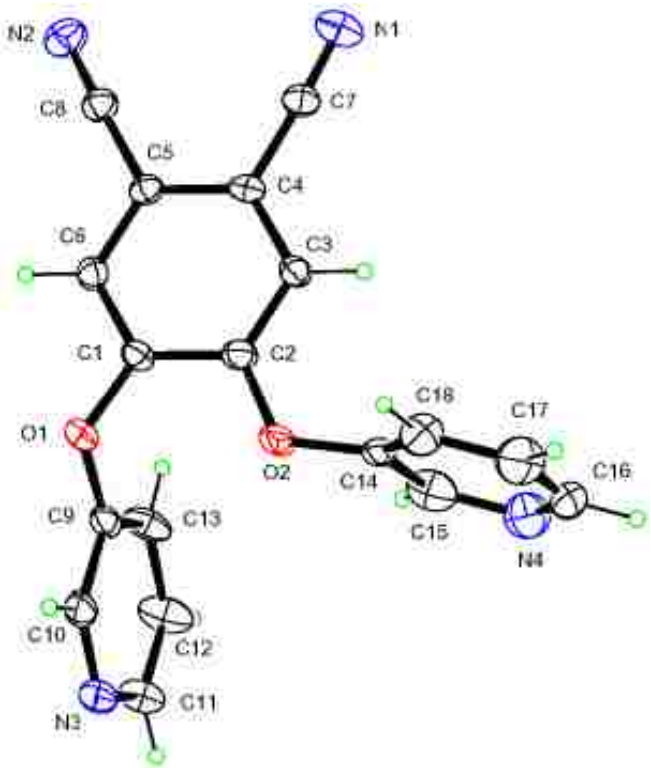


Figure 2.1. Single crystal X-ray structure of **2.1**.

The cyclotetramerization reaction used zinc acetate as the metal source. The reaction solution was refluxed in dry n-pentanol using a small amount of DBU as the catalyst. The crude product was washed successively and repeatedly (3 times) with dichloromethane, acetone and cold methanol. Pc **2.2** was obtained as a dark green solid in an improved yield of 88% compared with the lithium method.[4]

However, Pc **2.2** has limited solubility in most common organic solvents, including DCM, THF, ethyl acetate, methanol and DMSO. The addition of pyridine did not induce disaggregation in solution. Nevertheless this compound is very soluble in TFA, probably due to the protonation of the pyridine groups. In addition, TFA did not induce demetalation of Pc **2.2** in a short time period, as observed by MALDI-TOF mass

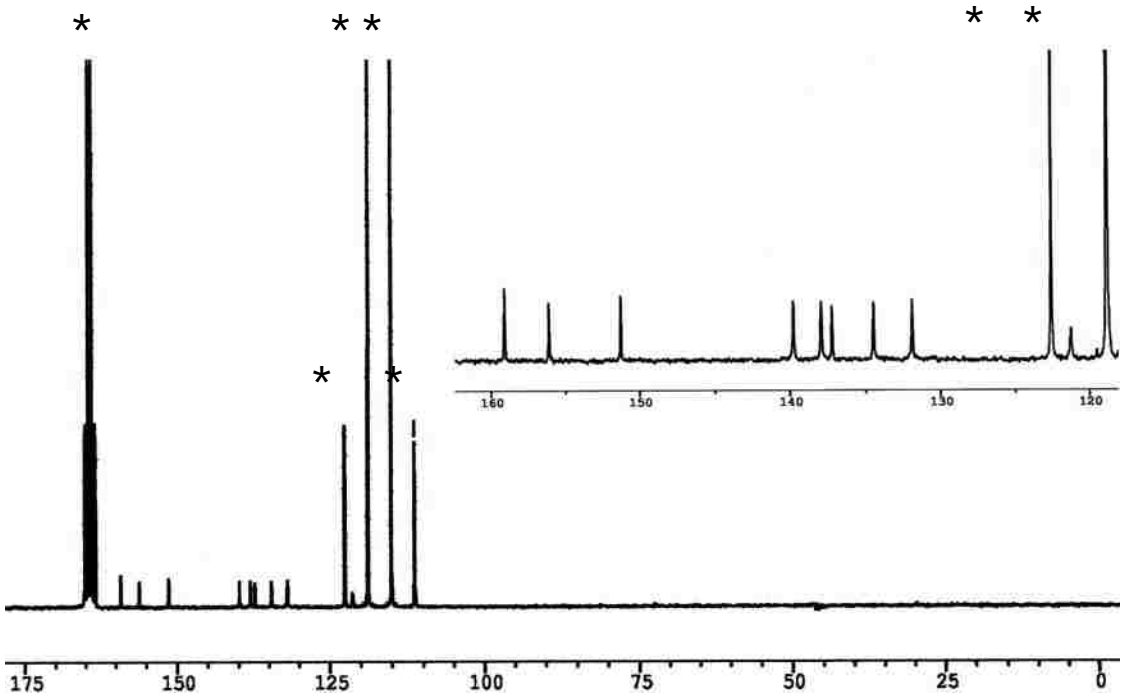


Figure 2.2. ^{13}C NMR spectrum of Pc **2.2** in d-TFA at 300 MHz. * solvent signals.

spectrometry and UV-Vis spectrophotometry. Therefore it was possible to obtain ^{1}H NMR and ^{13}C NMR spectra of Pc **2.2** in deuterated TFA. Figure 2.2 shows the ^{13}C NMR

spectrum of Pc **2.2** in pure deuterated TFA. As expected for symmetrically substituted Pc **2.2,** nine peaks were observed in the downfield region of the ^{13}C NMR spectrum.

Pc **2.2** was then alkylated with three alkyl iodides of different length (methyl, propyl and hexyl) as shown in Scheme 2.2. The appropriate alkyl iodide was used not only as the reagent but also as the solvent. After heating the reaction at 40 ºC for one day, methyl iodide can be removed by evaporation under reduced pressure to obtain pure Pc **2.3**. Since propyl and hexyl iodides have high boiling points, the blue solids were filtered under vacuum after the reaction and washed with acetone repeatedly. The alkylated zwitterionic salts **2.3**-**2.5** were obtained in quantitative yield. The cationic alkylated Pcs **2.3**-**2.5** have better solubility in organic solvents than neutral Pc **2.2**, due to the presence of the alkyl groups and positive charges that induce disaggregation. Pc **2.3** alkylated with methyl groups has better solubility in water than Pcs **2.4** and **2.5** with propyl and hexyl groups respectively, because of the shorter aliphatic and less hydrophobic alkyl chains. All three cationic Pcs **2.3**-**2.5** have high solubility in DMSO

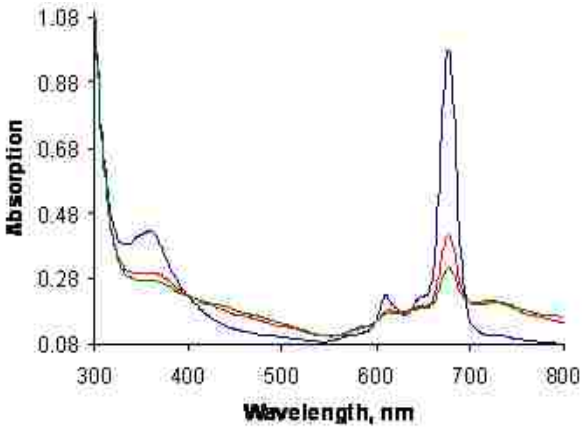


Figure 2.3. Absorption spectra of Pcs **2.3** (blue)**, 2.4** (red)**, 2.5** (green) in DMSO at 5 µM.

and have a major Q absorption band at 677 nm. In particular, Pc **2.3** shows the largest extinction coefficient for the Q band of these cationic Pcs, as shown in Figure 2.3.

Furthermore the extinction coefficient decreased with the increasing length of the alkyl chain.

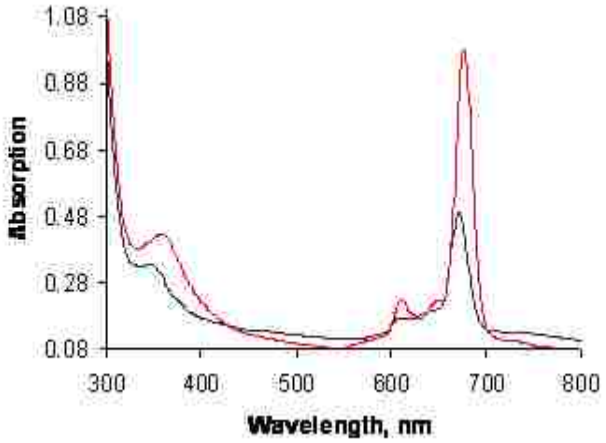


Figure 2.4. Absorption spectra of Pc **2.3** in DMSO (red) and water (black) at 5 μM.

The absorption spectra of Pc **2.3** in DMSO and in water are shown in Figure 2.4. It was observed that the Q band of Pc **2.3** had a 5 nm red shift from water to DMSO and was less intense in water compared with that in DMSO due to its higher tendency for aggregation in water.

From the fluorescence spectra (Figure 2.5), Pc **2.3** also has higher fluorescence intensity in DMSO than in water. This is due to its better solubility and less aggregation in DMSO (see also Table 2.1 below).

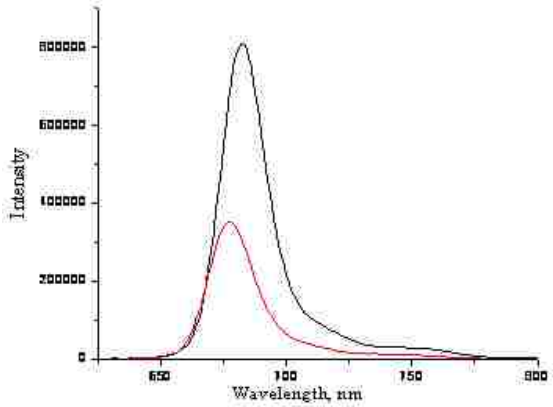
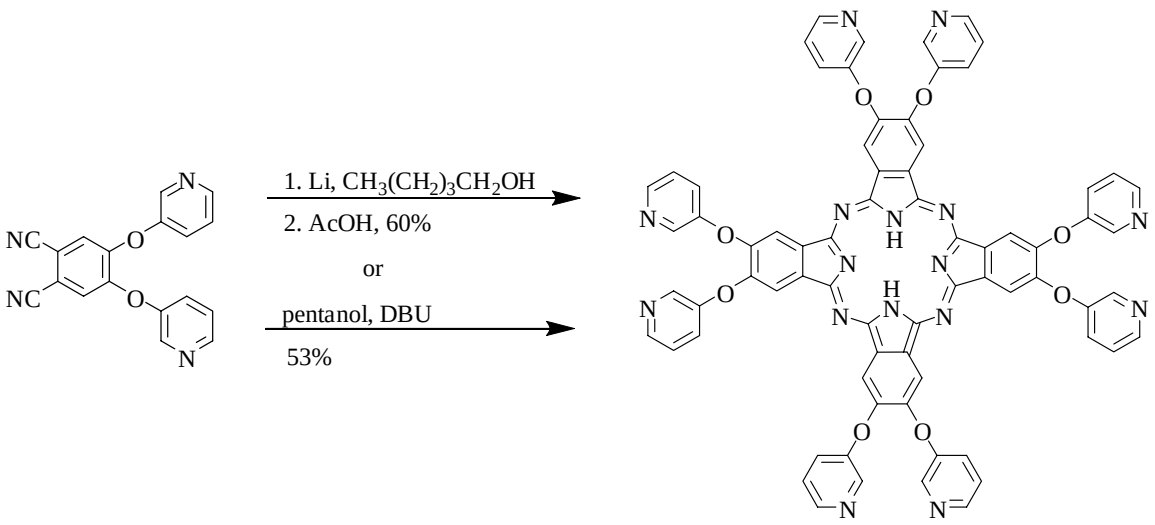


Figure 2.5. Emission spectra of Pc **2.3** in DMSO (black) and water (red) at 400-600 nM, excitation at 610 nm.



2.1 **2.7**

Scheme 2.3. Synthesis of metal-free Pc **2.7**.

The free-base pyridiloxy-substituted Pc was synthesized through the lithium method in pentanol, followed by quenching using acetic acid (Scheme 2.3). The overall yield to achieve the free-base Pc is 60%. The synthesis of **2.7** was also accomplished by heating **2.1** in pentanol in the presence of a small amount of DBU as the catalyst. Pc **2.7** as a dark blue solid was obtained in 53% yield after washing with different solvents.

Pegylated zinc and free-base Pcs **2.6** and **2.8** are shown in Figure 2.6. Conjugation of Pcs **2.2** and **2.7** with triethylene glycol iodide was accomplished by heating in a sealed tube at 70 ºC for 6 days. ZnPc **2.6** was isolated from the reaction solution by centrifugation and washed with acetone and dichloromethane. The crude product was purified on a Sephadex LH-20 column using methanol for elution. The free-base Pc **2.8** was purified using a similar procedure to Pc **2.6**. The two pegylated Pcs were obtained as dark green solids in 90% yield. We are collaborating with Dr. Jayne Garno of the LSU Chemistry Department to study the different aggregation behavior of these two pegylated Pcs in aqueous solution. The main observations of this study show that the Zn-Pc **2.6**

aggregates to a higher extent than the free-base Pc **2.8**. Pc **2.6** forms leaves-like large aggregates. On the other hand, Pc **2.8** forms microcrystals of smaller sizes.

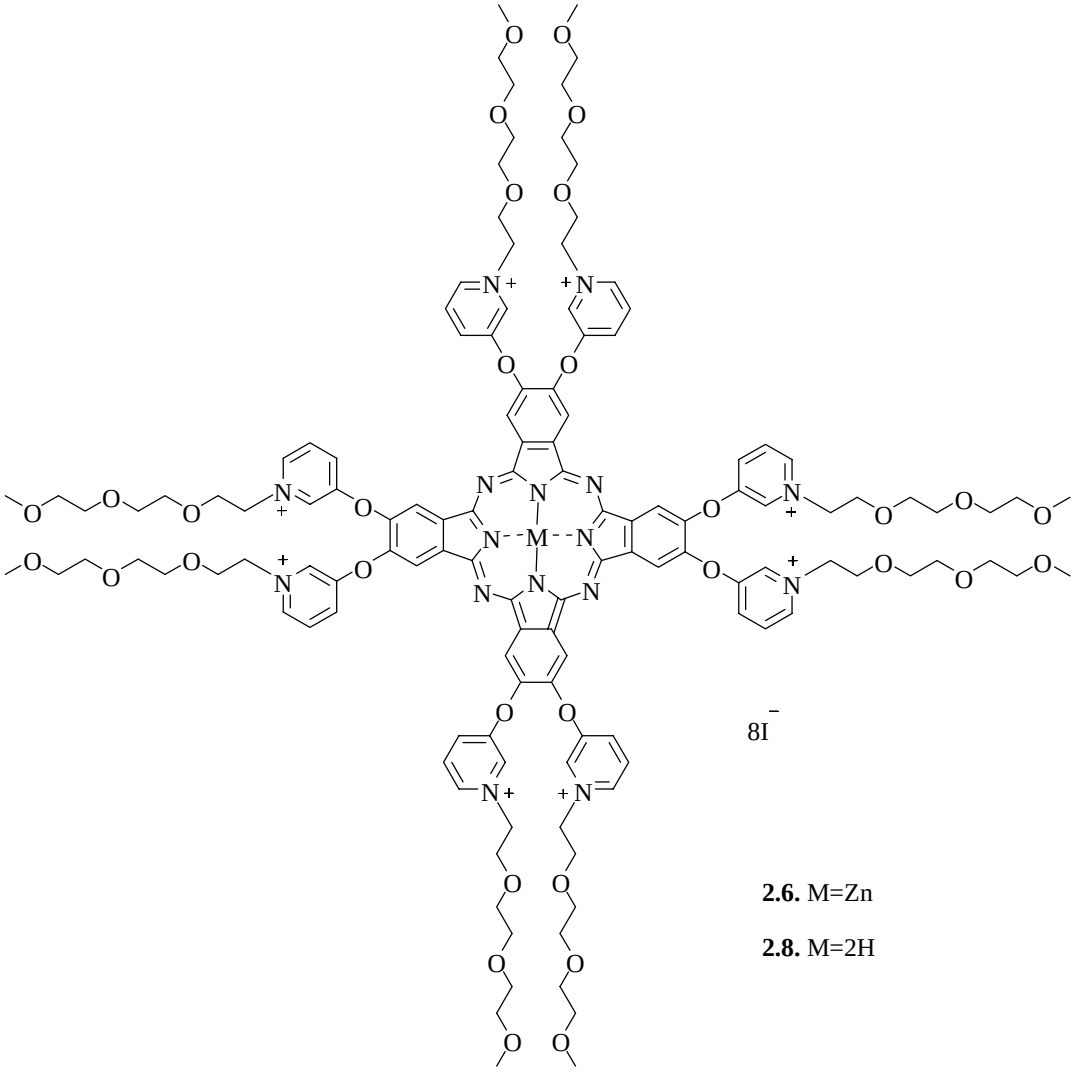


Figure 2.6. Target zinc and free-base Pcs.

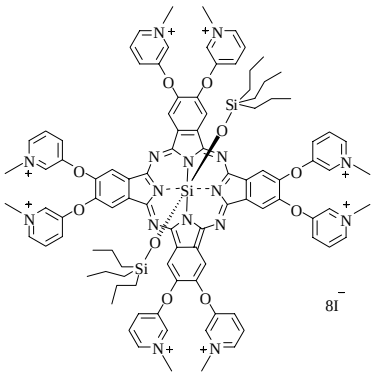
2.3 Synthesis of Octapyridiloxy-Substituted Silicon Phthalocyanines

Pcs are notorious for their strong tendancy to aggregate in solution,[13, 14] which can significantly decrease their photosensitizing ability through self-quenching.[15] In order to decrease Pc aggregation and to increase their photodynamic activity, various hydrophilic and amphiphilic groups (e.g. carboxylates, sulfonates, phosphonates, PEGs)[16-21] and bulky axial ligands [e.g. $OSiMe_2(CH_2)_3NMe_2$ and $OCH(CH_2NMe_2)_2$][18, 22-

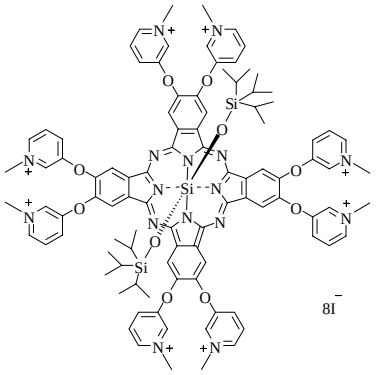
[25] have been introduced at the macrocycle periphery and the center metal with III or higher oxidation state (e.g. Si, Al, Ge and Sn), respectively. In our study, we found that the pyridinium moieties at the periphery of Pc can not prevent its serious aggregation in solution. Even long aliphatic chains up to six carbons were found not to efficiently prevent the Pc's aggregation in solution. Therefore, we hypothesized that bulky and hydrophobic axial ligands attached to the center silicon could more effectively prevent Pcs' aggregation and improve its solubility in solution. Recently, two glucosylated Si(IV)-Pcs were shown to have high phototoxicity toward human carcinoma HT29 and HepG2 cells,[26] and a Si(IV)-Pc bearing two solketal axial substituents was found to be highly phototoxic to both 14C and B16F10 cell lines.[27] Since ZnPcs show limited solubility in water, in our investigation of new water-soluble and effective PDT sensitizers, we decided to combine, in a single macrocycle, peripheral cationic pyridyloxy groups and two bulky axial ligands on centrally chelated Si(IV) ions. Therefore, we synthesized a series of cationic pyridiloxy-substituted Pcs (Figure 2.7) bearing either a methyl or a short PEG chain on the pyridyl groups and Si(IV) coordinating metals, with two large axial ligands on the silicon complexes. The properties of this series of water-soluble Pcs are compared and discussed in later in this Chapter.

Pyridiloxy-substituted phthalonitrile **2.1** was converted to the corresponding diiminoisoindoline **2.9** by heating the reaction solution with ammonia gas in the presence of sodium methoxide in methanol for five hours. The diiminoisoindoline **2.9** was obtained in 91% yield. As shown in Scheme 2.4, the cyclotetramerization reaction takes place with the mixture of **2.9** and silicon tetrachloride in freshly distilled quinoline under the protection of argon. After silicon tetrachloride was added dropwise to the reaction solution, the mixture was heated up to 220 ºC. The solution was cooled down after 1

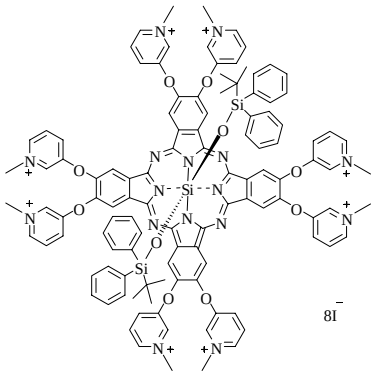
hour. The solid was filtered and washed repeatedly (3 times) with water, methanol and acetone giving dark blue Si(IV)-Pc dichloride **2.10** in 98% yield. The ^{1}H NMR spectrum



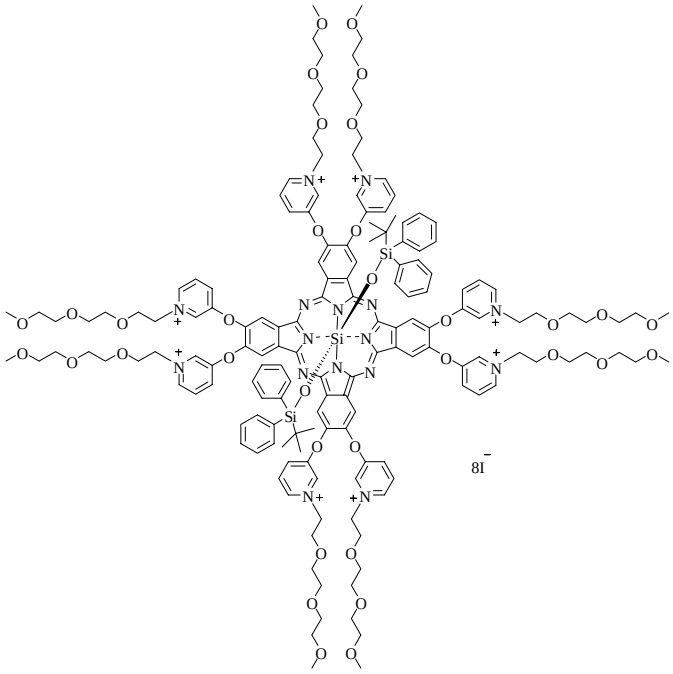
2.15



2.16

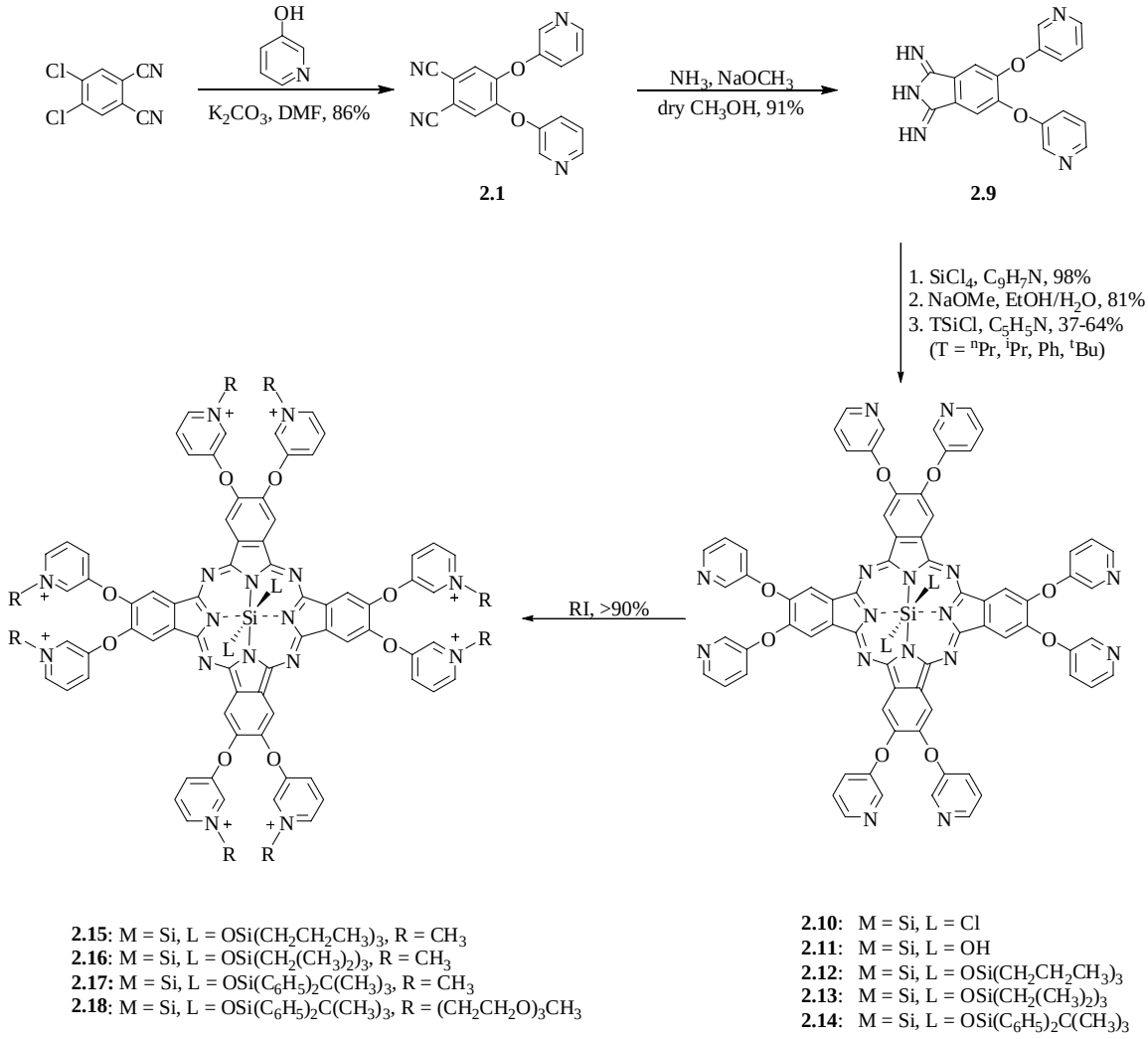


2.17



2.18

Figure 2.7. Target silicon Pcs.



Scheme 2.4. Synthesis of silicon Pcs.

can be interpreted clearly with one peak from the Pc core and four peaks from the peripheral pyridinium moieties in the upfield region. The dihydroxylation of Pc **2.10** was accomplished with sodium methoxide in ethanol/water. The presence of the OH groups in Pc **2.11** was confirmed by FT-IR, which shows a broad peak at 3382.3 cm^{-1} (O-H) and a sharp peak at 844.6 cm^{-1} (Si-O). Pc **2.11** was obtained in 81% yield. The MALDI-TOF spectra of Pc **2.10** and Pc **2.11** show the same pattern of ion cleavage of one axial ligand, as it is often observed for this type of compound.[e.g.28]

Pcs **2.15-2.18** were obtained by reacting Pc **2.11** with a large excess of the corresponding alkylchlorosilane in dry pyridine, at 115 °C under argon atmosphere. The excess silane reagent was washed out with pentane and Pcs **2.12-2.14** were purified by column chromatography on silica gel, using THF for elution. The ^{1}H NMR spectra of **2.12-2.14** in either deuterated THF or DMF characteristically shows the Pc macrocycle protons in the downfield region at > 9 ppm, the pyridyl protons between 8-9 ppm, the aliphatic protons on the axial ligands significantly upfield shifted below 0 ppm, and the axial ligand aromatic protons below 7 ppm. The MALDI-TOF MS spectra of Pcs **2.12-2.14** all show the base peak corresponding to the cleavage of one axial ligand. They show high solubility in polar organic solvents, such as chloroform, DMF, THF and DMSO, and slight solubility in acetone and hexane.

Alkylation of Si(IV)-Pcs **2.12-2.14** gave the corresponding octa-cationic derivatives **2.15-2.17** in yields higher than 90% by reaction with the corresponding methyl iodide at 40 ºC. The spectrum of ^{1}H NMR in deuterated THF or DMF testify the exact structure of the desired compounds according to the integration and chemical shifts of the Pc core and peripheral pyridinium parts. The Pc core proton was in the downfield region at above 9 ppm, and all of the pyridinium peaks show in the upfield in the region at 8-9 ppm. The aliphatic protons of the axial ligands have significantly upfield shift to below 0 ppm, and the aromatic protons in the axial ligands shifted to below 7 ppm. The sharp peaks in the ^{1}H NMR show the monomeric states for these Pcs existing in the solvents. The MALDI-TOF spectra of the target cationic methylated compounds are more complicated than those for their corresponding neutral Pc precursors, since seven or eight alkylated groups can be cleaved, in combination with the loss of one axial ligand. The ESI spectra show the loss of several iodines and one of the axial ligands. All cationic

Si(IV)-Pcs were also characterized by NMR, MS, UV-vis and fluorescence spectroscopy, and are highly soluble in protic solvents such as methanol and water.

Cationic Pc **2.18** with eight triethoxy ligands was synthesized using a similar method, with PEGI in place of CH_3I. PEGI was synthesized in 98% yield from the corresponding tosylate PEGTs, which was prepared according to Schultz's procedure[42] in 88% yield. The pegylation reaction proceeded for 6 days to get the pure octapegylated Pcs. The reaction was followed by ^1H NMR. The products were purified by washing with dichloromethane and acetone followed by chromatography in a gel permeation column LH-20 in methanol.

2.4 Photophysical Studies of Octapyridiloxy-Substituted Zinc and Silicon Phthalocyanines

The spectral properties of zinc Pcs **2.3**, **2.6**, **2.15-2.18** in DMSO, methanol, DMF, acetonitrile and water different pH values are summarized in Table 2.1. The absorption and emission properties of this series of Pcs depend significantly on the solvent used and the solution pH. Both the nature of the N-pyridyl group (methyl vs. triethylene glycol) and the centrally chelated metal and associated axial ligands affect the photophysical properties of the Pc macrocycles. The Si(IV)-Pcs bearing two bulky axial ligands show significantly higher fluorescent quantum yields than the Zn(II)-Pcs, in all solvents studied. Among the Si(IV)-Pcs, Pc **2.15** bearing two flexible tri(*n*-propyl)siloxy axial groups has the highest fluorescence quantum yield in aqueous media at all pH values investigated (5.0. 6.0, 7.0, 7.4 and 8.0), whereas Pc **2.16** bearing two tri(isopropyl)siloxy axial groups, the most hydrophobic of the Si(IV)-Pcs synthesized, has the highest quantum yield in organic solvents (DMSO and methanol).

The neutral Si(IV)-Pcs **2.12-2.14** also showed high fluorescence quantum yields

Table 2.1. Spectral properties of Pcs **2.3, 2.6, 2.15-2.18** in different media*.

media (pH)	**2.3**	**2.6**	**2.15**	**2.16**	**2.17**	**2.18**
DMSO						
abs.	360, 611, 677	356, 611, 677	360, 608, 676	360, 610, 678	359, 612, 681	359, 612, 680
em.	682	682	679	681	684	683
S.S.	5	5	3	3	3	3
Q.Y.	0.0614	0.0692	0.0518	0.0763	0.0361	0.0670
DMF						
abs.	358, 610, 676	354, 610, 676	360, 607, 675	360, 609, 677	358, 611, 679	357, 611, 679
em.	679	680	678	679	682	681
S.S.	3	4	3	2	3	2
Q.Y.	0.0685	0.0759	0.0434	0.0921	0.0557	0.0973
Acetonitrile						
abs.	351, 671	350, 608, 672	358, 604, 671	358, 606, 673	356, 608, 676	357, 608, 676
em.	675	674	672	675	678	678
S.S.	4	2	1	2	2	2
Q.Y.	0.0328	0.0455	0.0343	0.0572	0.0688	0.0664
MeOH						
abs.	349, 670	351, 607, 671	359, 603, 670	358, 606, 672	355, 607, 675	356, 608, 675
em.	674	675	671	674	677	677
S.S.	4	4	1	2	2	2
Q.Y.	0.0394	0.0546	0.0958	0.1146	0.0748	0.0987
Aqueous(5.0)						
abs.	346, 631, 674	352, 675	357, 608, 675	357, 606, 673	352, 612, 680	353, 611, 678
em.	681	679	677	680	683	681
S.S.	7	4	2	7	3	3
Q.Y.	0.0041	0.0388	0.1136	0.0645	0.0658	0.0615
Aqueous(6.0)						
abs.	346, 632, 667	351, 675	357, 608, 674	356, 610, 677	353, 612, 680	353, 611, 678
em.	678	680	677	680	683	681
S.S.	11	5	3	3	3	3
Q.Y.	0.0032	0.0368	0.0839	0.0495	0.0449	0.0495
Aqueous(7.0)						
abs.	346, 632, 667	350, 676	357, 608, 674	356, 610, 677	353, 612, 680	353, 611, 678
em.	679	680	677	680	682	681
S.S.	12	4	3	3	2	3
Q.Y.	0.0038	0.0350	0.0732	0.0455	0.0566	0.0594
Aqueous(7.4)						
abs.	347, 632, 668	351, 676	356, 608, 674	357, 610, 677	352, 612, 680	352, 611, 678
em.	679	680	677	679	682	681
S.S.	11	4	3	2	2	3
Q.Y.	0.0034	0.0384	0.0740	0.0445	0.0613	0.0519
Aqueous(8.0)						
abs.	347, 632, 668	352, 676	357, 608, 674	357, 610, 677	352, 612, 680	353, 611, 678
em.	679	680	677	680	682	681
S.S.	11	4	3	3	2	3
Q.Y.	0.0033	0.0309	0.0756	0.0452	0.0604	0.0469

*abs: absorption maxima (nm); em: emission maxima (nm); S.S.: Stokes shift (nm); Q.Y.: quantum yield.

in organic solutions (see Table 2.2). The fluorescent quantum yields of Pcs **2.3, 2.6, 2.15-2.18** in aqueous media were found to generally decrease with the pH, being the largest at pH 5.0 as previously observed.[29] The cationic Pcs bearing triethylene glycol chains on the pyridyloxy groups showed higher fluorescence quantum yields in organic solvents than

the corresponding methylated Pcs, although in aqueous media similar values were observed (Table 2.1).

In DMSO all Pcs show strong absorption and emission bands at ~ 677 and 681 nm, respectively, and Stokes shifts of 3 and 5 nm for the Si(IV) and Zn(II) complexes, respectively, as it is typical for this type of compound (Figure 2.8).[29-32] Although the Zn(II)-Pcs show aggregation in protic solvents (methanol and water), as evidenced by the splitting and/or broadening of their Q absorption bands, and significant decrease in the intensity of their emission bands and quantum yields, the Si(IV)-Pcs show intense and sharp Q bands and the highest fluorescence quantum yields in methanol solution.

Table 2.2. Spectral properties of Pcs **2.12**-**2.14** in organic solvents[a].

media	**2.12**	**2.13**	**2.14**
DMSO			
abs.	361, 611, 679	361, 612, 680	364, 614, 683
em.	681	682	685
S.S.	2	2	2
Q.Y.	0.1861	0.1194	0.1677
DMF			
abs.	360, 608, 676	360, 610, 678	363, 612, 681
em.	678	680	683
S.S.	2	2	2
Q.Y.	0.1786	0.1819	0.1709
MeOH			
abs.	359, 606, 672	358, 607, 674	361, 609, 677
em.	675	676	679
S.S.	3	2	2
Q.Y.	0.1668	0.1433	0.1318
Acetonitrile			
abs.	359, 609, 674	359, 676	363, 615, 679
em.	676*	677*	681
S.S.	2	1	2
Q.Y.	0.0983*	0.0342*	0.0610*

a: abs: absorption maxima (nm); em: emission maxima (nm); S.S.: Stokes Shift (nm); Q.Y.: quantum yield (nm). *: apparently, N.A.: not available

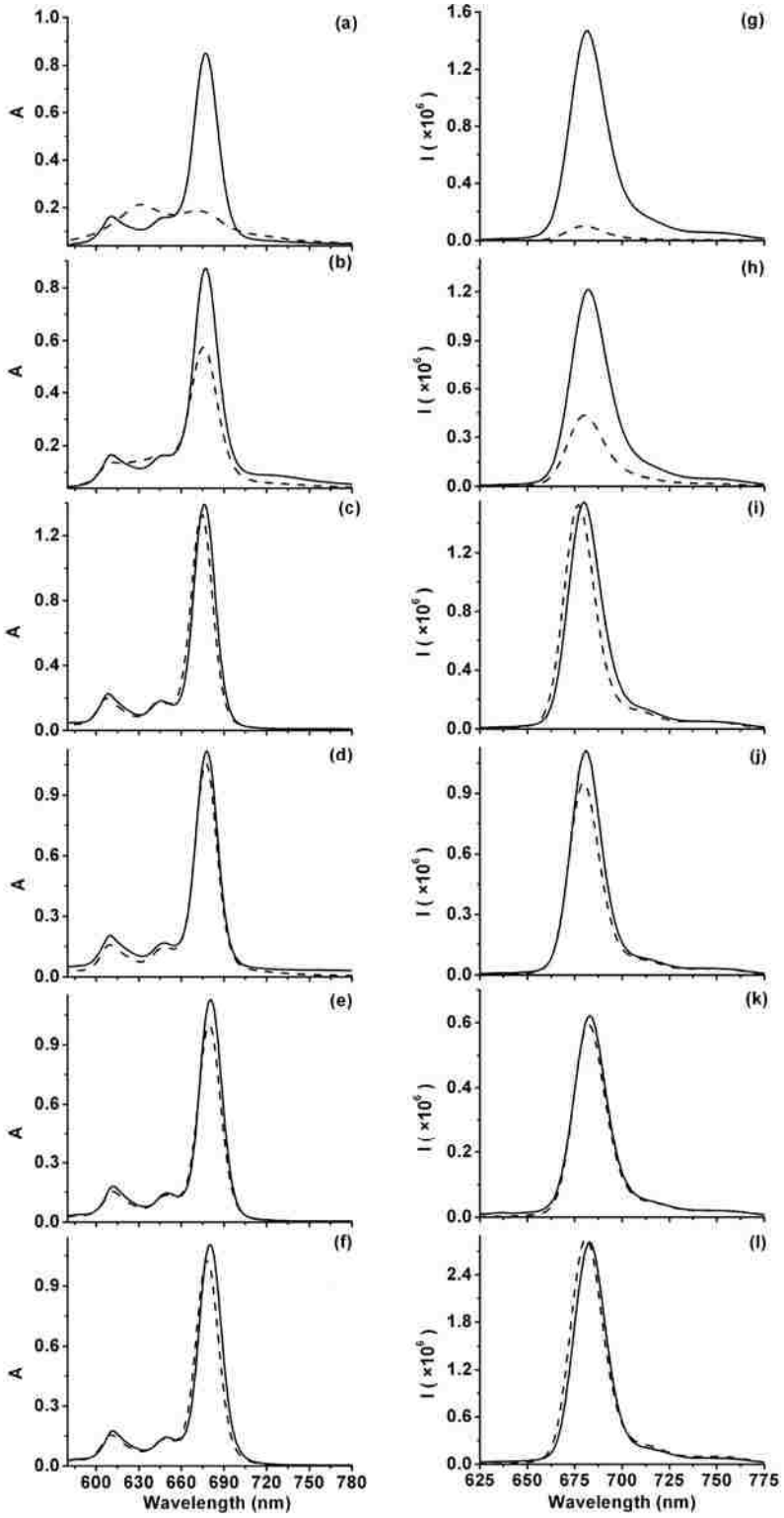


Figure 2.8. (a-f) Absorption spectra of Pcs **2.3**, **2.6**, **2.15-2.18** at 5 µM in DMSO (solid line) and in phosphate buffer (100 mM, pH 7.4) (dashed line); (g-l) Emission spectra of Pcs **2.3**, **2.6**, **2.15-2.18** at 80 nM in DMSO (solid line) and in phosphate buffer (100 mM, pH 7.4) (dashed line).

Pc aggregation in solution often results in broadening of the Q band absorptions, and bathochromic and hypsochromic shifts.[33, 34] Whereas only a few examples of J-type aggregates have been documented, for example protonation of a tetrasulfonated Zn(II)-Pc in aqueous acetonitrile caused a bathochromic shift of the Q band,[35] most of the aggregates are believed to be H-type, causing blue shifts and fluorescence quenching.[34, 36-38] Although the octa-cationic Zn(II)-Pcs **2.3** and **2.6** exist in their monomeric forms in DMSO, showing sharp Q absorption bands at 677 nm (Figure 2.8.a,b) and emission bands at 682 nm (Figure 2.8.g,h), in aqueous media they both form H-type aggregates as seen by the broadening and pronounced reduction in the intensity of their absorption and emission bands, along with reduction of their fluorescence quantum yields. Among all the Pcs evaluated in this study, Zn(II)-Pc **2.3** has the strongest tendency for aggregation in aqueous media and as a result it shows fluorescence quantum yields in water about one order of magnitude lower than all other cationic Pcs **2.6**, **2.15-2.18**.

The presence of the eight tri(ethylene glycol) chains on Zn(II)-Pc **2.6** significantly decreases its tendency for aggregation in aqueous media compared with Zn(II)-Pc **2.3** bearing eight methyl groups, and as a result Pc's **2.6** Q absorption band follows the Lambert Beer's law (see Figure 2.9. (a)). However, the most efficient structural feature for minimizing aggregation of these cationic macrocycles is the presence of a centrally chelated silicon ion and associated bulky axial ligands. All Si(IV)-Pcs **2.15-2.18** were found to exist mainly as monomers in both DMSO and aqueous solutions, showing similar intense and sharp Q band absorptions (Figure 2.8. c-f) that strictly follow the Lambert Beer's law (see Figure 2.9. (b)-(e)) and similarly intense emission bands (Figure 2.8.i-l) in both media.

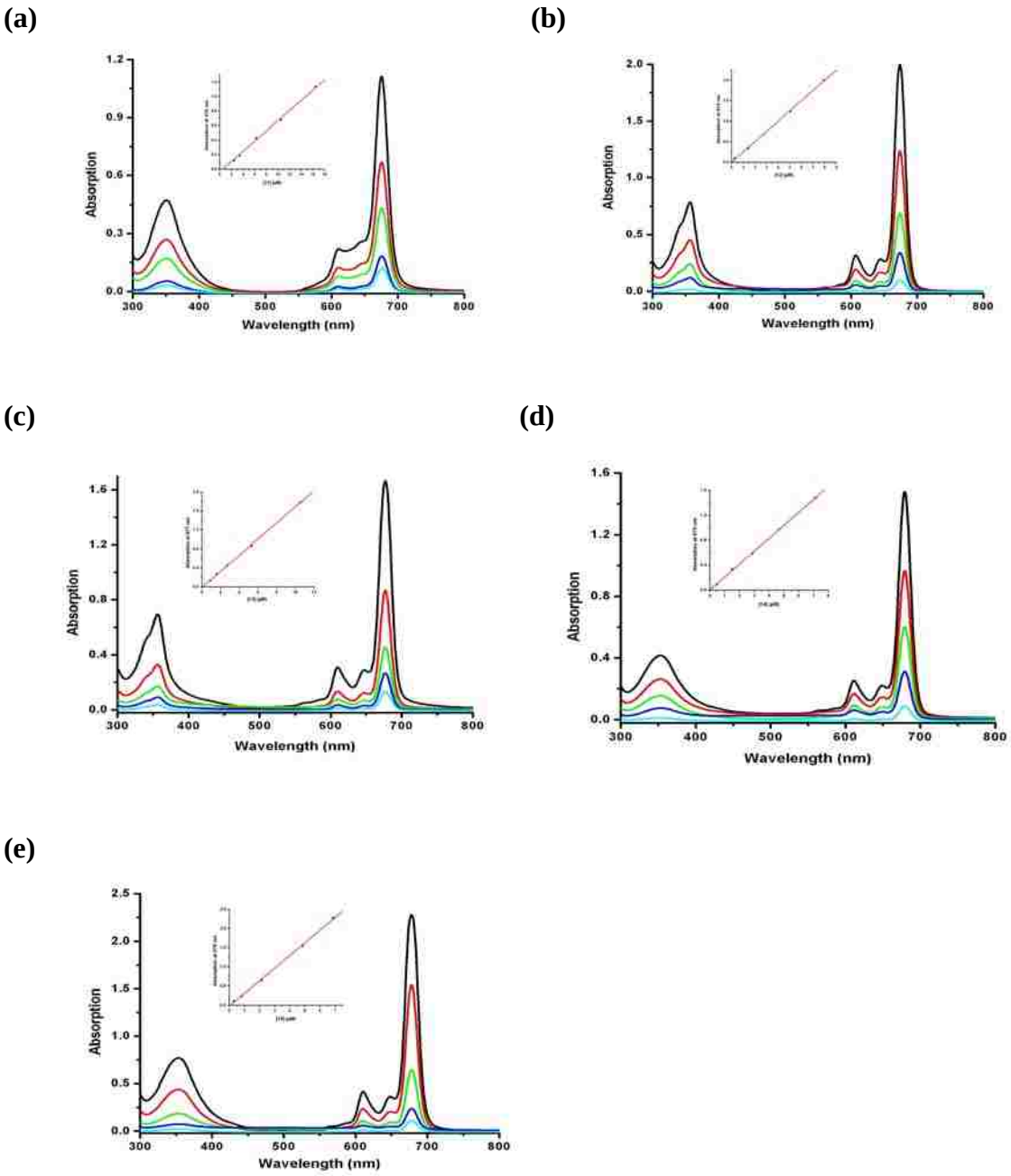


Figure 2.9. (a) Absorption spectra of Pc **2.6** in 10 mM phosphate buffer pH 7.4 at 16.4 µM (black), 10.9 µM (red), 6.2 µM (green), 3.5 µM (blue), and 2.5 µM (light blue) concentrations; (b) absorption spectra of Pc **2.15** in 10 mM phosphate buffer pH 7.4 at 7.9 µM (black), 5.1 µM (red), 2.8 µM (green), 1.4 µM (blue), and 0.2 µM (light blue) concentrations; (c) absorption spectra of Pc **2.16** in 10 mM phosphate buffer pH 7.4 at 10.5 µM (black), 5.3 µM (red), 2.7 µM (green), 1.6 µM (blue), and 0.9 µM (light blue) concentrations; (d) absorption spectra of Pc **2.17** in 10 mM phosphate buffer pH 7.4 at 7.1 µM (black), 4.7 µM (red), 2.9 µM (green), 1.5 µM (blue), and 0.5 µM (light blue) concentrations; (e) absorption spectra of Pc **2.18** in 10 mM phosphate buffer pH 7.4 at 6.9 µM (black), 4.9 µM (red), 2.1 µM (green), 0.8 µM (blue), and 0.3 µM (light blue) concentrations.

The singlet oxygen quantum yields for Pcs **2.6**, **2.15-2.18** were determined in DMSO as previously reported,[39] and were found to be in the range 0.09-0.15, as shown in Table 2.3. These values are characteristic for this type of Pc;[26, 39] Si(IV)-Pc **2.16** was found to have the highest singlet oxygen quantum yield whereas Si(IV)-Pc **2.18** bearing eight short PEG chains had the lowest. It is possible that the singlet oxygen is inactivated by the PEG chains, as it has been previously observed.[40, 41] Pc **2.16**, the most hydrophobic of all the Si(IV)-Pcs synthesized, shows the highest quantum yield in DMSO.

Table 2.3. Singlet-oxygen quantum yields in DMSO.

Pc	Φ_Δ
Pc 2.6	0.115
Pc 2.15	0.134
Pc 2.16	0.150
Pc 2.17	0.110
Pc 2.18	0.094

2.5 Summary of Biological Evaluation

The experiments using human carcinoma HEp2 cells of this series of cationic silicon and zinc Pcs were conducted in our laboratory by Mr. Timothy J. Jensen. The details of these investigations can be found in our published paper.[11] As a brief summary, the study shows that all water-soluble Pcs were readily taken up by human HEp2 cells and the extent of their accumulation within cells depends on their hydrophobic character and increased in the order **2.18** < **2.15** < **2.17** < **2.16** < **2.6**. Intracellularly, all Pcs localized preferentially within the cell lysosomes. The dark-toxicity of Pcs **2.6**, **2.15**-**2.18** was evaluated in human HEp2 cells exposed to increasing concentrations of each Pc up to 100 μM. Only Zn(II)-Pc **2.6**, the most accumulated within cells, showed measurable dark toxicity with an estimated IC_{50} ~ 85 μM. All Si(IV)-Pcs were found to be non-toxic to HEp2 cells in the dark up to 100 μM concentrations. Upon exposure to a low light dose

(1 J/cm^2) all Pcs were highly toxic to HEp2 cells. The Zn(II)-Pc **2.6** and Si(IV)-Pcs **2.15** and **2.17** were the most phototoxic (IC_{50} = 2.2 μM at 1 J/cm^2 light dose), probably as a result of their ability to generate singlet oxygen and low tendency for aggregation. We are collaborating with Dr. Kwang-Poo Chang of the Chicago Medical School to study the effects of this series of zinc- and silicon-Pcs **2.6**, **2.15**-**2.18** on *Leishmania*-infected and non-infected J774 cells of murine tumor macrophages. The preliminary study indicates that Pc **2.18** appears to be most promising to have selective activity against phogolysosomal *Leishmania*, leaving macrophages unharmed as the host cells.

2.6 Conclusion

In this Chapter, a series of new cationic pyrilydoxyPcs (**2.6**, **2.15**-**2.18**) bearing either Zn(II) or Si(IV) coordinated metal ions and methyl, propyl, hexyl or short PEG groups on the pyridyls, was successfully synthesized. The Si(IV)-Pcs bearing two bulky axial ligands exist mainly as monomers in both organic and aqueous solutions, and show higher fluorescence quantum yields in solution than the Zn(II)-Pcs. The only water-soluble Zn(II)-Pc is Pc **2.6**. Both these Pcs form aggregates in aqueous media, in particular Pc **2.3** bearing eight N-methyl groups; the presence of eight short PEGs increases the solubility of the Pc macrocycle in protic solvents but a centrally chelated silicon ion and associated bulky axial ligands is more efficient in minimizing Pc aggregation. This series of water-soluble Pcs exhibited singlet oxygen quantum yields in DMSO in the range 0.09-0.15 and their *in vitro* properties depended on both their tendency for aggregation and hydrophobic character. The most hydrophobic Pc **2.6** tested accumulated the most within HEp2 cells and was highly phototoxic (IC_{50} = 2.2 μM at 1 J/cm^2 light dose). Among the Si(IV)-Pcs, those with the lowest tendency for aggregation in aqueous media (**2.15** and **2.17**) and high ability for producing ROS were also highly

phototoxic (IC_{50} = 2.2 μM at 1 J/cm^2 light dose). All Pcs localized subcellularly preferentially within the lysosomes. Of all this series of water-soluble Pcs, Si(IV)-Pc **2.18** appears to be most promising to have selective activity against phogolysosomal *Leishmania*, leaving macrophages unharmed as the host cells.

2.7 Experimental

2.7.1 Synthesis

All air and moisture sensitive reactions were performed under an argon atmosphere. All solvents and reagents were purchased from commercial sources, unless otherwise stated. Dry solvents excluding methanol were purified using a Braun solvent purification system. Dry methanol was obtained by re-distillation after refluxing over calcium hydride for 5 h. Silica gel 60 (230×400 mesh, Sorbent Technologies) was used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using polyester backed TLC plates 254 (precoated, 200 μm) from Sorbent Technologies. NMR spectra were recorded on a DPX-250 or ARX-300 Bruker, or a Varian Inova-500 spectrometers (250 MHz, 300 MHz or 500 MHz for ^{1}H, 63 MHz, 75 MHz or 125 MHz for ^{13}C). The chemical shifts are reported in δ ppm using the following deuterated solvents as internal references: CD_2Cl_2 5.32 ppm (^{1}H), 53.8 ppm (^{13}C); d-TFA 11.5 ppm (^{1}H), 164.2 ppm (^{13}C); d-DMSO 2.49 ppm (^{1}H), 39.5 ppm (^{13}C); d-THF 3.58 ppm (^{1}H), 1.73 ppm (^{13}C); d-CH_3OH 4.78 ppm (^{1}H), 49.0 ppm (^{13}C); d-DMF 8.01 ppm (^{1}H), 162.7 ppm (^{13}C); CD_3CN 1.93 ppm (^{1}H), 118.2 ppm (^{13}C); D_2O 4.63 ppm (^{1}H). Electronic absorption spectra were measured on a Perkin-Elmer Lambda 35 UV-vis spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrophotometer. Mass spectra were obtained on either a Bruker ProFlex III MALDI-TOF mass spectrometer using α-cyano-4-hydroxycinnamic acid or dithranol as the matrix, or an Applied Biosystems QSTAR

XL quadrupole TOF MS for ESI. Elemental analyses were performed on a Thermo Finnigan Flash 1112 CHN elemental analyzer. Melting points were measured on a Fisher-Johns apparatus.

Phthalonitrile 2.1. 4, 5-Dichlorophthalonitrile (1.0 g, 5.0 mmol) and 3-hydroxypyridine (2.2 g, 23.1 mmol) were dissolved in 15 mL of dry DMF at 80 °C under argon. Potassium carbonate (4.5 g, 32.6 mmol) was added to the reaction solution in 8 portions every 5 min. The reaction solution was heated for 3 h, then cooled to room temperature and poured into 100 mL of ice water. After filtration under vacuum, the crude product was purified by column chromatography on neutral alumina using methanol/dichloromethane 1:50 for elution. The title compound (1.37 g) was obtained as a pale white solid in 86% yield. ^{1}H NMR (CD_2Cl_2): δ 8.53 – 8.51 (m, 2H, Py-H), 8.42 (s, 2H, Py-H), 7.42 – 7.41 (m, 4H, Py-H), 7.31 (s, 2H, Ar-H). ^{13}C NMR (CD_2Cl_2): δ 151.53, 147.46, 142.19, 127.18, 125.24, 123.67 (Ar-C, Py-C), 115.21 (CN), 112.19 (Ar-C). FTIR (solid): 2236.8 (CN), 1211.3 (C-O) cm^{-1}. MS (MALDI-TOF) *m/z* 315.31 $[M+H]^+$, calcd. for $C_{18}H_{11}N_4O_2$ 315.09. Anal. calcd. for $C_{18}H_{10}N_4O_2$: C 68.79, H 3.21, N 17.83; Found: C 68.58, H 3.33, N 17.78.

Crystal data for **2.1**: Colorless, $C_{18}H_{10}N_4O_2$, M_r=314.3, monoclinic space group C2/c, a=24.573(3), b= 9.417(2), c= 16.076(3) Å, β=128.21(2)˚, V=2923.0(12) $Å^3$, Z=8, ρ_{calcd}=1.428 gcm^{-3}, MoKα radiation (λ=0.71073 Å; μ=0.098 mm^{-1}), T=110K, 32427 data by Nonius KappaCCD, R=0.057 (3531 with $F^2>2\sigma$), Rw=0.149 (all F^2) for 5539 unique data having θ<33.1˚ and 217 refined parameters, CCDC 652076. Crystals were grown by slow evaporation of dichloromethane.

Triethylene glycol iodide. Compound $CH_3(OCH_2CH_2)_3I$ was synthesized from the corresponding tosylate $CH_3(OCH_2CH_2)_3Ts$, which was prepared according to

Schultz's procedure[42] in 88% yield. For triethylene glycol tosylate $CH_3(OCH_2CH_2)_3Ts$: ^1H NMR (CD_2Cl_2): δ 7.78 (d, J = 8.3 Hz, 2H, Ar-H), 7.37 (d, J = 8.3 Hz, 2H, Ar-H), 4.12 (t, J = 4.5 Hz, 2H, OCH_2), 3.64 (t, J = 4.5 Hz, 2H, OCH_2), 3.53 (s, 6H, OCH_2), 3.49 (t, J = 1.6 Hz, 2H, OCH_2), 3.32 (s, 3H, OCH_3), 2.44 (s, 3H, Ar-CH_3). ^{13}C NMR (CD_2Cl_2): δ 145.44, 133.24, 130.22, 128.21 (Ar-C), 72.22 (OCH_2), 71.01, 70.77, 70.72, 69.84, 68.92 (OCH_2), 58.95 (OCH_3), 21.72 (Ar-CH_3). MS (ESI) *m/z* 319.12 $[M+H]^+$, 320.13 $[M+2H]^+$, 336.15 $[M+H_2O]^+$, 341.10 $[M+Na]^+$, calcd. for $C_{14}H_{23}O_6S$ 319.12, $C_{14}H_{24}O_6S$ 320.13, $C_{14}H_{24}O_7S$ 336.12, $C_{14}H_{22}NaO_6S$ 341.10. To a solution of this compound (10 g, 0.031 mol) in 80 mL of dry acetone was added NaI (9.9 g, 0.062 mol) and the reaction was refluxed for 20 h. After cooling to room temperature, the solution was filtered under vacuum and washed with acetone. The filtrate was collected and concentrated. The residue was dissolved in 100 mL of dichloromethane, washed successively with 1 N sodium thiosulfate solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the product was obtained as light yellow liquid (8.5 g) in 98% yield. ^1H NMR (CD_2Cl_2): δ 3.73 (t, J = 6.8 Hz, 2H, OCH_2), 3.64 – 3.56 (m, 6H, OCH_2), 3.52 – 3.48 (m, 2H, OCH_2), 3.33 (s, 3H, OCH_3), 3.27 (t, J = 6.8 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$): δ 77.42, 77.00, 76.58, 71.77, 70.42, 70.03 (OCH_2), 58.85 (OCH_3). MS (ESI) *m/z* 275.01 $[M+H]^+$, 292.04 $[M+H_2O]^+$, calcd. for $C_7H_{16}IO_3$ 275.01, $C_7H_{17}IO_4$ 292.02.

ZnPc 2.2. Phthalonitrile **2.1** (0.4 g, 1.27 mmol) and zinc acetate dihydrate (0.1 g, 0.45 mmol) were mixed and heated at 80 °C in 15 mL of dry pentanol. After adding a few drops of DBU, the temperature was raised to 140 °C. The mixture was heated overnight and then concentrated under reduced pressure. The crude product was washed three times successively with dichloromethane, acetone and cold methanol. The title product was

obtained as a dark blue solid (0.37 g) in 88% yield; mp > 250 °C. UV-vis (DMSO): λ_{max} (log ε) 678 (4.08) nm. ^{1}H NMR (d-TFA): δ 9.60 (s, 8H, Ar-H), 9.00 (s, 8H, Py-H), 8.81 (br, 8H, Py-H), 8.62 (br, 8H, Py-H), 8.29 (br, 8H, Py-H). ^{13}C NMR (d-TFA): δ 159.07, 156.10, 151.27, 139.77, 137.94, 137.23, 134.47, 131.88, 121.24 (Ar-C, Py-C). MS (MALDI-TOF) *m/z* 1320.78 [M^{+}], calcd. for $C_{72}H_{40}N_{16}O_8Zn$ 1320.25.

ZnPc 2.3. Pc **2.2** (0.2 g, 0.15 mmol) and 25 mL of CH_3I were stirred at 40 °C and the reaction was followed by ^{1}H NMR. After 1 day, methyl iodide was removed under reduced pressure. The crude product was washed with acetone to yield the title compound as a dark greenish blue solid (0.35 g) in 96% yield; mp > 250 °C. UV-vis (DMSO): λ_{max} (log ε) 677 (4.84), 611 (4.21), 359 (4.48) nm. ^{1}H NMR (D_2O): δ 9.16 (s, 8H, Ar-H), 9.00 (s, 8H, Py-H), 8.56 (d, J = 6.1 Hz, 8H, Py-H), 8.48 (d, J = 8.4 Hz, 8H, Py-H), 8.00 – 8.04 (m, 1H, Py-H), 4.32 (s, 24H, CH_3). ^{13}C NMR (D_2O): δ 157.24, 151.70, 147.57, 142.07, 137.20, 136.06, 134.66, 130.380, 117.26 (Ar-C, Py-C), 50.00 (CH_3). MS (MALDI-TOF) *m/z* 1320.48 [M-8I-8CH_3]$^{+}$, 1335.43 [M-8I-7CH_3]$^{+}$, calcd. for $C_{72}H_{40}N_{16}O_8Zn$ 1320.25, $C_{73}H_{43}N_{16}O_8Zn$ 1335.27.

ZnPc 2.4. Pc **2.2** (0.2 g, 0.15 mmol) and 25 ml iodopropane was stirred at 40 ºC for 2 days. The crude product can be filtered under vacuum and washed by acetone to get dark blue solid quantitatively. MS (MALDI-TOF) *m/z* 1320.588 (PyPcZn, M-8I-8C_3H_7), 1364.566 (PyPcZn+C_3H_7, M-8I-7C_3H_7) (calculated for $C_{72}H_{40}N_{16}O_8Zn$ 1320.251, $C_{75}H_{47}N_{16}O_8Zn$ 1364.314); UV-vis (DMSO): λ_{max} (log ε): 612.49 (4.106), 677.29 (4.450) nm.

ZnPc 2.5. Pc **2.2** (0.2 g, 0.15 mmol) and 25 ml iodohexane was stirred at 65 ºC for 2 days. The crude product can be filtered under vacuum and washed by acetone to get dark blue solid quantitatively. MS (MALDI-TOF) *m/z* 1320.397 (PyPcZn, M-8I-8C_6H_{13}),

1405.616 (PyPcZn+C_6H_{13}, M-8I-7C_6H_{13}) (calculated for $C_{72}H_{40}N_{16}O_8Zn$ 1320.251, $C_{78}H_{53}N_{16}O_8Zn$ 1405.353); UV-vis (DMSO):λ_{max} (log ε): 677.52 (4.323) nm.

ZnPc 2.6. Pc **2.2** (0.02 g, 0.015mmol) and $CH_3(OCH_2CH_2)_3I$ (1.5g, 5.5 mmol) were heated to 70 °C in a sealed 10 mL thick-wall tube for 6 days. The product was isolated from the reaction solution by centrifugation and washed twice with acetone and twice with dichloromethane. The crude product was purified on a Sephadex LH-20 column using methanol for elution. The product was vacuum dried at 30 °C for 2 days to afford the title compound as a dark blue solid (56 mg) in 92% yield; mp 173 – 175 °C. UV-vis (DMF): λ_{max} (log ε) 675 (4.74), 609 (4.10), 354 (4.36) nm. UV-vis (H_2O):λ_{max} (log ε) 674 (4.56), 611 (3.94), 351 (4.27). ^{1}H NMR (d-DMF): δ 9.69 (s, 8H, Ar-H), 9.60 (s, 8H, Py-H), 9.21 (d, J = 5.3 Hz, 8H, Py-H), 8.88 (d, J = 7.6 Hz, 8H, Py-H), 8.48 – 8.42 (m, 8H, Py-H), 5.12 (br, 16H, OCH_2), 4.16 (br, 16H, OCH_2), 3.72 (br, 16H, OCH_2), 3.57 – 3.44 (m, 48H, OCH_2), 3.26 (s, 24H, OCH_3). ^{13}C NMR (d-DMF): δ 157.24, 153.86, 147.70, 142.12, 137.98, 136.65, 134.73, 129.97, 117.57 (Ar-C, Py-C), 72.34, 70.81, 70.66, 69.63, 62.21, 58.70 (OCH_2), 21.41 (OCH_3). MS (MALDI-TOF) *m/z* 1320.60 [M-8PEG]$^+$, 1467.04 [M-7PEG]$^+$, 1613.94 [M-6PEG]$^+$, 1762.01 [M-5PEG]$^+$, calcd. for $C_{72}H_{40}N_{16}O_8Zn$ 1320.25, $C_{79}H_{55}N_{16}O_{11}Zn$ 1467.35, $C_{86}H_{70}N_{16}O_{14}Zn$ 1614.46, $C_{93}H_{85}N_{16}O_{17}Zn$ 1761.56. HRMS-ESI *m/z* 549.9806 [M-6I-H]$^{5+}$, 575.5675 [M-5I]$^{5+}$, 751.9363 [M-4I]$^{4+}$, 1044.5473 [M-3I]$^{3+}$, calcd. for $[C_{128}H_{159}I_2N_{16}O_{32}Zn]^{5+}$ 549.9737, $[C_{128}H_{160}I_3N_{16}O_{32}Zn]^{5+}$ 575.5562, $[C_{128}H_{160}I_4N_{16}O_{32}Zn]^{4+}$ 751.9437, $[C_{128}H_{160}I_5N_{16}O_{32}Zn]^{3+}$ 1043.8633.

H_2Pc 2.7. Method A. Phthalonitrile **2.1** (2 g, 6.4 mmol) was put in 100 three-neck round bottom flask, the flask was evacuated and refill with argon for three times. Pentanol (40 mL) was added through syringe and the reaction was heated to 90 °C. Small

pieces of lithium (0.2 g, 28.57 mmol) were added to the reaction solution with cautious. The temperature was increased to 135 °C and remained for 24 hour. After reaction, the solution was cooled down to room temperature. Acetic acid (glacial, 9 ml) was added. The reaction was stirred for 15 min under room temperature. The reaction solution was poured to a mixture of 450 mL ice water and 50 mL methanol and green solid precipitated out. The solid was filtered and washed with water, ethyl acetate, dichloromethane and methanol to get dark green solid (1.2 g) in 60% yield. **Method B.** Phthalonitrile **2.1** (0.75 g, 2.39 mmol) was heated at 80 °C in 20 mL of dry pentanol. After adding DBU (0.36 mL, 2.39 mmol), the temperature was raised to 140 ºC. The mixture was heated for 24 hours and then concentrated under reduced pressure. The crude product was washed three times successively with water, dichloromethane, acetone and cold methanol. The title product was obtained as a dark blue solid (0.4 g) in 53% yield; mp > 250 °C. ^{1}H NMR (d-TFA, 400 MHz): δ 8.89 (s, 8H, Ar-H), 8.69 (d, 8H, J = 5.4 Hz, Py-H), 8.52 (d, 8H, J = 5.4 Hz, Py-H), 8.19 – 8.15 (m, 8H, Py-H). ^{13}C NMR (d-TFA, 100 MHz): δ 159.51, 151.39, 139.87, 138.22, 134.53, 132.07 (Ar-C, Py-C). MS (MALDI-TOF) *m/z* 1258.94 $[M]^{+}$, calcd. for $C_{72}H_{42}N_{16}O_8$ 1258.34.

H_2Pc 2.8. Pc **2.7** (59 mg, 0.045 mmol) and $CH_3(OCH_2CH_2)_3I$ (3 g, 11 mmol) were heated at 70 ºC in a sealed 10 mL thick-wall tube for 6 days. The product was isolated from the reaction solution by centrifugation and washed twice with acetone and twice with mixed solvents of hexane/acetone (1/1). The crude product was purified on a Sephadex LH-20 column using methanol for elution. The product was vacuum dried at 30 ºC for 2 days to afford the title compound as a dark blue solid (110 mg) in 72% yield; UV-vis (DMF): λ_{max} (log ε) nm. UV-vis (H_2O): λ_{max} (log ε). ^{1}HNMR (d-DMF): δ 9.71 (br, 16H, Ar-H, Py-H), 9.19 (br, 16H, Py-H), 8.44 (br, 8H, Py-H), 5.13 (br, 16H,

OCH_2CH_2O), 4.18 (br, 16H, OCH_2CH_2O), 3.73 (br, 16H, OCH_2CH_2O), 3.51 – 3.43 (m, 48H, OCH_2CH_2O), 3.24 (s, 24H, CH_3O).). ^{13}C NMR (d-DMF): δ 157.09, 156.90, 148.87, 142.24, 137.09, 135.48, 134.78, 130.02, 118.04 (Ar-C, Py-C), 72.23, 70.71, 70.55, 69.35, 62.05 (OCH_2), 58.69 (OCH_3). ESI *m/z* 512.7199 $[M-7I-2H]^{5+}$, 538.3411 $[M-6I-H]^{5+}$, 563.9609 $[M-5I]^{5+}$, 736.7974 $[M-4I]^{4+}$, 1024.8740 $[M-3I]^{3+}$, calcd. for $[C_{128}H_{160}IN_{16}O_{32}]^{5+}$ 512.0086, $[C_{128}H_{161}I_2N_{16}O_{32}]^{5+}$ 537.4158, $[C_{128}H_{162}I_3N_{16}O_{32}]^{5+}$ 563.1735, $[C_{128}H_{162}I_4N_{16}O_{32}]^{4+}$ 735.6930, $[C_{128}H_{163}I_5N_{16}O_{32}]^{3+}$ 1023.2255.

Bis(pyridine-3-yloxy)diiminoisoindoline 2.9. Phthalonitrile **2.1** (2 g, 6.4 mmol) and sodium methoxide (0.5 g, 9.3 mmol) were dissolved in 100 mL of freshly distilled methanol. Ammonia gas was bubbled into the solution for 50 min at room temperature. The solution was then heated to 65 °C and refluxed under a slow stream of ammonia gas for 5 h. The solvent was removed under reduced pressure. Water (150 mL) was added to the concentrated residue to precipitate the product. The product was filtered and washed thoroughly with water to afford light green crystals of the title compound (1.9 g) in 91% yield; mp 122 – 124 °C. ^1H NMR (d-DMSO): δ 8.52 (br, 1H), 8.39 – 8.34 (m, 6H), 7.62 (br, 2H), 7.51 – 7.47 (m, 2H), 7.42 – 7.38 (m, 2H). ^{13}C NMR (d-DMSO): δ 152.97, 148.32, 144.85, 140.13, 124.95, 124.71, 113.63 (Ar-C, Py-C). FTIR (solid): 3036.73, 2963.08, 1667.2 (CN), 1213.2 (CO) cm^{-1}. MS (MALDI-TOF) *m/z* 332.20 $[M+H]^+$, 354.14 $[M+Na]^+$, calcd. for $C_{18}H_{14}N_5O_2$ 332.11, $C_{18}H_{13}N_5O_2Na$ 354.10.

SiPc 2.10. Dry diiminoisoindoline **2.9** (0.5 g, 1.5 mmol) was added to 5 mL of freshly redistilled quinoline. The reaction solution was stirred under argon for 10 min and then silicon tetrachloride (0.5 mL, 2.2 mmol) was added dropwise to the solution. The temperature was raised to 220 °C and maintained for 1 h. The solution was cooled to room temperature. The solid was filtered under vacuum and washed successively with

water, methanol and acetone. The title compound was obtained as a dark blue solid (0.5 g) in 98% yield; mp > 250 °C. UV-vis (DMSO): λ_{max} (log ε) 677 (3.83) nm. ^{1}H NMR (d-TFA): δ 9.66 (br, 8H, Ar-H), 8.98 (br, 8H, Py-H), 8.73 (br, 8H, Py-H), 8.58 (br, 8H, Py-H), 8.21 (br, 8H, Py-H). ^{13}C NMR (d-TFA): δ 158.95, 152.09, 151.43, 139.324, 137.64, 136.40, 134.08, 131.48, 120.53 (Ar-C, Py-C). MS (MALDI-TOF) *m/z* 1319.82 $[M-Cl]^+$, calcd. for $C_{72}H_{40}ClN_{16}O_8Si$ 1319.27.

SiPc 2.11. A mixture of Pc **2.10** (0.45 g, 0.33 mmol) and sodium methoxide (1.5 g, 27 mmol) in 60 mL of water/ethanol (5:1) was heated to reflux for 5 h. The solvent was removed under reduced pressure and the product was isolated by precipitation upon addition of 10 mL of water. The slurry solid was filtered and washed thoroughly with water. The final product was dried under vacuum at 40 °C for 2 days to afford the title compound as a dark blue solid (0.35 g) in 81% yield; mp > 250 °C. UV-vis (DMSO): λ_{max} (log ε) 677 (4.11), 609 (3.64), 364 (3.94) nm. ^{1}H NMR (d-TFA): δ 9.72 (br, 8H, Ar-H), 9.03 (br, 8H, Py-H), 9.81 (br, 8H, Py-H), 8.65 (br, 8H, Py-H), 8.63 (br, 8H, Py-H), 8.29 (br, 8H, Py-H). ^{13}C NMR (d-TFA): δ 159.11, 152.24, 151.58, 139.46, 137.78, 136.55, 134.20, 131.61, 120.67 (Ar-C, Py-C). FTIR (solid): 3382.3 (O-H), 1209.5 (C-O), 844.6 (Si-O) cm^{-1}. MS (MALDI-TOF) *m/z* 1301.81 $[M-OH]^+$, 1318.63 $[M]^+$, calcd. for $C_{72}H_{41}N_{16}O_9Si$ 1301.30, $C_{72}H_{42}N_{16}O_{10}Si$ 1318.30.

SiPc 2.12. Pc **2.11** (0.17 g, 0.125 mmol) was dissolved in 10 mL of dry pyridine at 115 °C under an argon atmosphere. Chlorotripropylsilane (0.7 mL, 3.2 mmol) was added to the reaction solution dropwise via syringe. After 8 h another portion of chlorotripropylsilane (0.5 mL, 2.2 mmol) was added. The reaction solution was refluxed for another 9 h. The solvent was evaporated to dryness, and 10 mL of pentane were added. After sonication for 5 min, the crude product was obtained by centrifugation. The

solid was further purified using a short silica column and THF for elution. The title compound was dried under vacuum at 40 °C and obtained as a dark greenish blue solid (0.11 g, 52%); mp > 250 °C. UV-vis (CH_2Cl_2): λ_{max} (log ε) 674 (5.34), 644 (4.54), 607 (4.60), 360 (4.92) nm. ^{1}H NMR (d-THF): δ 9.30 (s, 8H, Ar-H), 8.58 (d, J = 2.7 Hz, 8H, Py-H), 8.46 (dd, J = 1.0, 4.5 Hz, 8H, Py-H), 7.63 – 7.59 (m, 8H, Py-H), 7.45 – 7.41 (q, 8H, Py-H), -0.15 (t, J = 7.2 Hz, 18H, CH_3), -0.99 – -1.07 (m, 12H, CH_2), -2.29 – -2.34 (m, 12H, CH_2). ^{13}C NMR (d-THF): δ 154.75, 151.75, 149.04, 146.15, 141.46, 133.91, 125.48, 125.09, 116.40 (Ar-C, Py-C), 17.84, 16.42, 15.87 ($CH_2CH_2CH_3$). MS (MALDI-TOF) *m/z* 1457.88 $[M\text{-}OSi(C_3H_7)_3]^+$, calcd. for $C_{81}H_{61}N_{16}O_9Si_2$ 1457.44).

SiPc 2.13. Pc **2.11** (0.12 g, 0.088 mmol) and chlorotriisopropylsilane (0.4 mL, 1.8 mmol) reacted as described above for Pc **2.12** and the title compound was obtained as a dark greenish blue solid (94 mg, 64%); mp > 250 °C. UV-vis (CH_2Cl_2): λ_{max} (log ε) 677 (5.13), 646 (4.21), 609 (4.28), 359 (4.63) nm. ^{1}H NMR (d-DMF): δ 9.43 (s, 8H, Ar-H), 8.68 (s, 8H, Py-H), 8.57 (d, J = 4.4 Hz, 8H, Py-H), 7.84 (d, J = 8.4 Hz, 8H, Py-H), 7.64 – 7.59 (m, 8H, Py-H), -1.06 (d, J = 8.0 Hz, 36H, CH_3), -1.94 – -2.01 (m, 6H, CH). ^{13}C NMR (d-DMF): δ 154.36, 151.52, 148.90, 146.18, 141.22, 133.22, 126.15, 125.68, 116.01(Ar-C, Py-C), 16.11, 11.42 ($CH(CH_3)_2$). MS (MALDI-TOF) *m/z* 1631.23 $[M+H]^+$, 1457.42 $[M\text{-}OSi(C_3H_7)_3]^+$, calcd. for $C_{90}H_{83}N_{16}O_{10}Si_3$ 1631.58, $C_{81}H_{61}N_{16}O_9Si_2$ 1457.43.

SiPc 2.14. Pc **2.11** (0.2 g, 0.15 mmol) and tert-butyldiphenylchlorosilane (0.8 mL, 3.0 mmol) reacted as described above for Pc **2.12** and the title compound was obtained as a dark greenish blue solid (99 mg, 37%); mp 185-187 °C. UV-vis (DMF): λ_{max} (log ε) 680 (5.09), 650 (4.29), 612 (4.36), 363 (4.59) nm. ^{1}H NMR (d-DMF): δ 9.19 (s, 8H, Ar-H), 8.75 (d, J = 2.6 Hz, 8H, Py-H), 8.60 (d, J = 4.5 Hz, 8H, Py-H), 8.01 (s, 8H, Py-H), 7.92 –

7.90 (m, 8H, Py-H), 7.70 – 7.66 (m, 8H, Py-H), 6.99 (t, J = 7.3 Hz, 4H, Ar-H), 6.57 (t, J = 7.4 Hz, 8H, Ar-H), 4.91 (d, J = 7.1 Hz, 8H, Ar-H), -1.22 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (d-DMF): δ 154.44, 151.27, 148.62, 146.13, 141.19, 133.79, 133.30, 133.21, 128.94, 126.94, 126.39, 125.78, 115.95 (Ar-C, Py-C), 24.99, 17.00 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 1794.37 M^+, 1539.26 $[M-(OSiPh_2{}^tBu)]^+$, calcd for $C_{104}H_{78}N_{16}O_{10}Si_3$ 1794.54, $C_{88}H_{59}N_{16}O_9Si_2$ 1539.42.

SiPc 2.15. Pc **2.12** (20 mg, 0.01 mmol) and CH_3I (7 mL) reacted as described above for Pc **2.3** and the title compound was obtained as a greenish blue solid (27 mg, 95%); mp > 250 °C. UV-vis (H_2O): λ_{max} (log ε) 674 (5.03), 644 (4.31), 607 (4.35), 356 (4.68) nm. ^1H NMR (d-CH_3OH): δ 9.95 (s, 8H, Ar-H), 9.21 (s, 8H, Py-H), 8.77 (d, J = 6.0 Hz, 8H, Py-H), 8.48 (d, J = 9.0, 8H, Py-H), 8.17 – 8.11 (q, 8H, Py-H), 4.48 (s, 24H, N-CH_3), -0.20 (t, J = 7.2 Hz, 18H, CH_3), -1.07 – -1.16 (m, 12H, CH_2), -2.41 – -2.48 (m, 12H, CH_2). MS (MALDI-TOF) *m/z* 1644.87 $[M-7CH_3-8I]^+$, 1456.46 $[M-OSi(C_3H_7)_3-8CH_3-8I]^+$, calcd. for $C_{91}H_{85}N_{16}O_{10}Si_3$ 1645.59, $C_{81}H_{61}N_{16}O_9Si_2$ 1457.44. HRMS-ESI *m/z* 795.1072 $[M-3I]^{3+}$, 564.8538 $[M-4I]^{4+}$, 532.6256 $[M-5I-H]^{4+}$, 525.8209 $[M-5I-(CH_3)_2+H]^{4+}$, calcd. for $[C_{98}H_{106}I_5N_{16}O_{10}Si_3]^{3+}$ 795.0936, $[C_{98}H_{106}I_4N_{16}O_{10}Si_3]^{4+}$ 564.9740, $[C_{98}H_{105}I_3N_{16}O_{10}Si_3]^{3+}$ 532.6161, $[C_{96}H_{101}I_3N_{16}O_{10}Si_3]^{3+}$ 525.9824.

SiPc 2.16. Pc **2.13** (35 mg, 0.02 mmol) and CH_3I (8 mL) reacted as described above for Pc **2.3** and the title compound was obtained as a greenish blue solid (28 mg, 96%); mp > 250 °C. UV-vis (H_2O): λ_{max} (log ε) 677 (4.84), 648 (4.05), 610 (4.07), 356 (4.45) nm. ^1H NMR (d-DMF): δ 9.97 (s, 8H, Ar-H), 9.67 (s, 8H, Py-H), 9.21 (d, J = 5.8 Hz, 8H, Py-H), 8.86 (d, J = 8.8 Hz, 8H, Py-H), 8.46 – 8.45 (m, 8H, Py-H), 4.72 (s, 24H, N-CH_3), -1.08 (d, J = 7.5 Hz, 36H, CH_3), -1.98 – -2.10 (m, 6H, CH). MS (MALDI-TOF) *m/z* 1457.69 $[M-8MeI-OSi(C_3H_7)_3]^+$, 1472.70 $[M-7MeI-OSi(C_3H_7)_3]^+$, 1630.80 [M-

8MeI]$^{+}$, 1645.82 [M-7MeI]$^{+}$, calcd. for $C_{81}H_{61}N_{16}O_9Si_2$ 1457.44, $C_{82}H_{64}N_{16}O_9Si_2$ 1472.46, $C_{90}H_{82}N_{16}O_{10}Si_3$ 1630.57, $C_{91}H_{85}N_{16}O_{10}Si_3$ 1645.59. HRMS-ESI *m/z* 795.4410 [M-3I]$^{3+}$, 752.8038 [M-4I-H]$^{3+}$, 564.6037 [M-4I]$^{4+}$, 532.6259 [M-5I-H]$^{4+}$, calcd. for $[C_{98}H_{106}I_5N_{16}O_{10}Si_3]^{3+}$ 795.6001, $[C_{98}H_{105}I_4N_{16}O_{10}Si_3]^{3+}$ 752.8038, $[C_{98}H_{106}I_4N_{16}O_{10}Si_3]^{3+}$ 564.5941, $[C_{98}H_{105}I_3N_{16}O_{10}Si_3]^{3+}$ 532.6161.

SiPc 2.17. Pc **2.14** (20 mg, 0.01 mmol) and CH_3I (4 mL) reacted as described above for Pc **2.3** and the title compound was obtained as a greenish blue solid (29 mg, 91%); mp 217-219 °C. UV-vis (H_2O): λ_{max} (log ε) 679 (4.81), 649 (3.96), 612 (4.01), 352 (4.29) nm. ^{1}H NMR (d-DMF): δ 9.79 (s, 8H, Ar-H), 9.71 (s, 8H, Py-H), 9.25 (d, J = 5.3 Hz, 8H, Py-H), 8.88 (d, J = 7.8 Hz, 8H, Py-H), 8.57 – 8.54 (m, 8H, Py-H), 7.04 (t, J = 7.3 Hz, 4H, Ar-H), 6.68 (t, J = 7.4 Hz, 8H, Ar-H), 4.89 (d, J = 7.0 Hz, 8H, Ar-H), 4.76 (s, 24H, N-CH_3), -1.24 (s, 18H, C(CH_3)$_3$). ^{13}C NMR (d-DMF): δ 156.47, 149.87, 148.76, 143.06, 138.95, 135.06, 134.24, 133.70, 133.05, 130.17, 129.32, 127.36, 117.61 (Ar-C, Py-C), 49.61 (N-CH_3), 25.24, 17.04 (C(CH_3)$_3$). MS (MALDI-TOF) *m/z* 1810.95 [M-7MeI-I+H]$^{+}$, calcd. for $C_{105}H_{82}N_{16}O_{10}Si_3$ 1810.57. HRMS-ESI *m/z* 850.0984 [M-(OSiPh$_2$^{t}Bu)-I+2H]$^{3+}$, 606.0964 [M-(OSiPh$_2$^{t}Bu)-2I+2H]$^{4+}$, 573.6194 [M-(OSiPh$_2$^{t}Bu)-3I+H]$^{4+}$, 541.6409 [M-(OSiPh$_2$^{t}Bu)-4I]$^{4+}$, calcd. for $[C_{96}H_{85}I_7N_{16}O_9Si_2]^{3+}$ 849.9846, $[C_{98}H_{85}I_6N_{16}O_9Si_2]^{3+}$ 606.1078, $[C_{96}H_{84}I_5N_{16}O_9Si_2]^{4+}$ 573.7842, $[C_{96}H_{83}I_4N_{16}O_9Si_2]^{3+}$ 541.8062).

SiPc 2.18. Pc **2.14** (45 mg, 0.025mmol) and $CH_3(OCH_2CH_2)_3I$ (2.2 g, 8.2 mmol) reacted as described above for Pc **2.6** and the title compound was obtained as a dark blue solid (94 mg, 94%); mp 82-84 °C. UV-vis (H_2O): λ_{max} (log ε) 678 (4.76), 649 (3.90), 610 (3.96), 353 (4.25) nm. ^{1}H NMR (CD_3CN): δ 9.58 (s, 8H, Ar-H), 9.43 (s, 8H, Py-H), 8.97 (d, J = 5.3 Hz, 8H, Py-H), 8.63 (d, J = 7.7 Hz, 8H, Py-H), 8.29 (t, J = 7.6 Hz, 8H, Py-H),

6.98 (t, J = 7.3 Hz, 4H, Ar-H), 6.57 (t, J = 7.3 Hz, 8H, Ar-H), 5.02 (br, 16H, OCH_2), 4.84 (d, J = 7.1 Hz, 8H, Ar-H), 4.14 (br, 16H, OCH_2), 3.70 (br, 16H, OCH_2), 3.55 – 3.47 (m, 48H, OCH_2), 3.28 (s, 24H, OCH_3), -1.26 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_3CN): δ 156.50, 149.97, 148.87, 142.63, 138.42, 136.02, 134.40, 133.96, 133.15, 130.39, 129.55, 127.50, 117.49 (Ar-C, Py-C), 72.48, 71.16, 70.88, 70.79, 69.38, 62.73, 59.01 (OCH_2), 25.37 (OCH_3), 17.20, 4.81 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 3985.42 $[M-H]^+$, 3603.91 $[M-OSiPh_2{}^tBu-I-H]^+$, 3476.98 $[M-OSiPh_2{}^tBu-2I-H]^+$, 3348.09 $[M-OSiPh_2{}^tBu-3I-2H]^+$, 3221.20 $[M-OSiPh_2{}^tBu-4I-2H]^+$, calcd. for $C_{160}H_{197}I_8N_{16}O_{34}Si_3$ 3985.58, $C_{144}H_{178}I_7N_{16}O_{33}Si_2$ 3603.56, $C_{144}H_{178}I_6N_{16}O_{33}Si_2$ 3476.66, $C_{144}H_{177}I_5N_{16}O_{33}Si_2$ 3348.74, $C_{144}H_{177}I_4N_{16}O_{33}Si_2$ 3221.84). HRMS-ESI *m/z* 1202.3092 $[M-(OSiPh_2{}^tBu)-I+2H]^{3+}$, 870.0024 $[M-(OSiPh_2{}^tBu)-2I+2H]^{4+}$, 670.6225 $[M-(OSiPh_2{}^tBu)-3I+2H]^{5+}$, 645.2429 $[M-(OSiPh_2{}^tBu)-4I+H]^{5+}$, calcd. for $[C_{144}H_{181}I_7N_{16}O_{33}Si_2]^{3+}$ 1202.1943, $[C_{144}H_{181}I_6N_{16}O_{33}Si_2]^{4+}$ 869.9196, $[C_{141}H_{181}I_5N_{16}O_{33}Si_2]^{4+}$ 670.5548, $[C_{144}H_{180}I_4N_{16}O_{33}Si_2]^{3+}$ 645.3780.

2.7.2 Photophysical Study

All absorption spectra were measured on a Perkin-Elmer Lambda 35 UV-vis spectrometer with 10 mm path length quartz cuvettes. Emission spectra were obtained on a Fluorolog 3 spectrofluorimeter. Pure solvents were used as reference solutions. All solvents were either ACS spectrophotometric or HPLC grade. Sodium phosphate dibasic was purchased from EMD. Milli-Q water (resistance 18 MΩ) was prepared in-house. The phosphate buffer solutions were prepared by dissolving 1.43 g anhydrous sodium phosphate dibasic in 100 ml water followed by pH adjustment with concentrated hydrochloride or sodium hydroxide solution using a Thermo Orion Model 410 pH meter. Stock solutions (10 mM DMSO) of all Pcs were prepared. All dilutions were prepared by

spiking 0.2-2 µL of the corresponding DMSO stock solutions into 1 mL of each solvent. The optical densities of the solutions used for the emission studies were between 0.04-0.05 at the excitation wavelength (610 nm) to eliminate inner filter effects. All the measurements were performed within 3 h of solution preparation.

Fluorescent quantum yields were calculated using a secondary standard method.[43] Methylene blue, a dye with excitation/emission wavelengths similar to Pcs, was used as the reference. The equation ($Q = Q_R \frac{I}{I_R}\frac{OD_R}{OD}\frac{n^2}{n_R^2}$) was applied to calculate the quantum yield of the Pcs. In this equation, the fluorescence intensities of the analyte (I) and standard (I_R), optical densities of the analyte (OD) and standard (OD_R), and the refractive indexes of the analyte solvent (n) and standard solvent (n_R) are incorporated, in addition to Q_R, the quantum yield of the reference standard (0.03 for methylene blue).[44, 45]

Singlet oxygen quantum yields were obtained in DMSO at room temperature, using ZnPc (Φ_Δ = 0.67) as reference and 1,3-diphenylisobenzofuran (DPBF) as scavenger, according to the procedure previously described.[39] The DPBF absorption decay was followed at 417 nm. The singlet oxygen quantum yields were determined with an accuracy of about 10%.

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CHAPTER 3

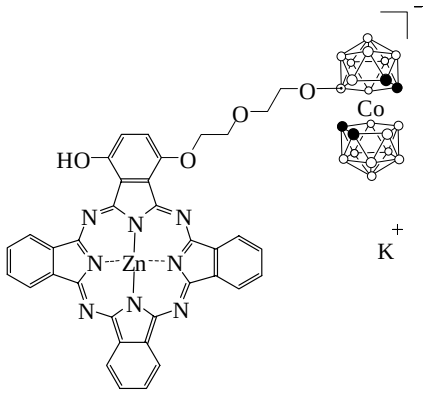
SYNTHESES AND PROPERTIES OF CARBORANYL CONJUGATED PHTHALOCYANINES*

3.1 Background

Boron-containing Pcs have potential applications in the boron neutron capture therapy (BNCT) and photodynamic therapy (PDT) of cancer. BNCT and PDT are both bimodal techniques for cancer treatment. BNCT agents rich in boron-10 nuclides and with selective localization in malignant cells, have the ability of capturing low energy neutrons by boron-10 nuclei to produce high linear energy transfer (high-LET) α-particles and recoiling lithium-7 nuclei while releasing about 2.4 MeV of kinetic energy.[1-3] The highly toxic LET particles have limited pathlengths in tissue (< 10 μm).[1-3] Two clinically-approved boron containing compounds, mercapto-*closo*-dodecaborate (BSH) and 4-hydroxyborylphenylalanine (BPA), are currently used in the clinical trials in the USA, Japan and Europe.[1] PDT is a binary modality using a photosensitizer (PS) and visible light to produce reactive oxygen species which can selectively destroy malignant cells.[4] Pc has an advantage as a PDT photosensitizers, because it generally has a strong absorption within the "therapeutic window" (600-800 nm) for optimal light penetration deep through tissue, and high singlet oxygen quantum yields which are crucial for PDT treatment.[5, 6] Various boronated porphyrins and derivatives have been synthesized and evaluated in vitro or in vivo studies as BNCT anti-cancer agents.[7] Recently, our group has reported the syntheses of a series of porphyrin-cobaltacarborane conjugates and their biological evaluations.[8-11] The dual applications of carboranylchlorin and tetrabenzoporphyrin for the PDT and BNCT have also been reported by our group.[12-14]

* Parts of this Chapter have appeared in the *Tetrahedron Letters*.[35]

Pcs' well-known disadvantage is their high tendency to aggregate in most organic solvents and aqueous media due to the hydrophobic and planar nature of the Pc macrocycle. For these reasons Pcs' applications in the both areas of PDT and BNCT have been retarded. Only a few examples of Pc-boron conjugates have been reported to date.[15-18] In this Chapter, we report the syntheses and photophysical study of a series of A_3B-type zinc Pcs containing one or two cobaltacarborane clusters (Figure 3.1). Pcs **3.7-3.10** are conjugated to one or two cobaltacarborane clusters via one short polyethylene glycol chain. PEG-conjugated anti-cancer drugs are known to increase the serum lifetime, to reduce the uptake from the reticulo-endothelialsystem (RES) and to enhance the phototoxicity and vascular permeability in tumor tissues.[19-23]



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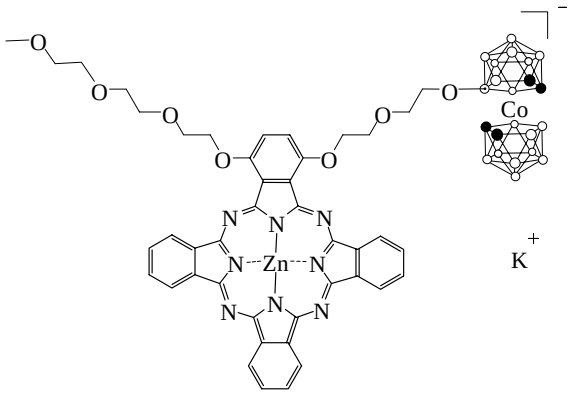

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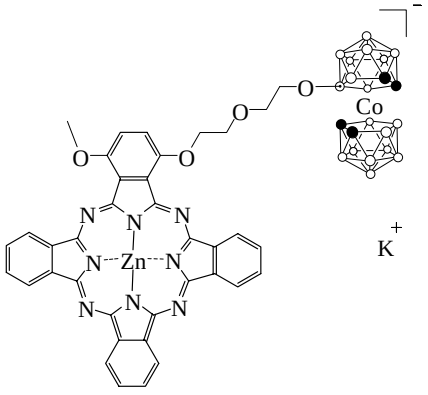

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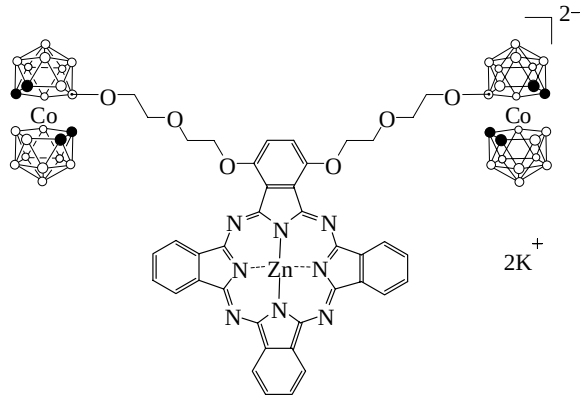
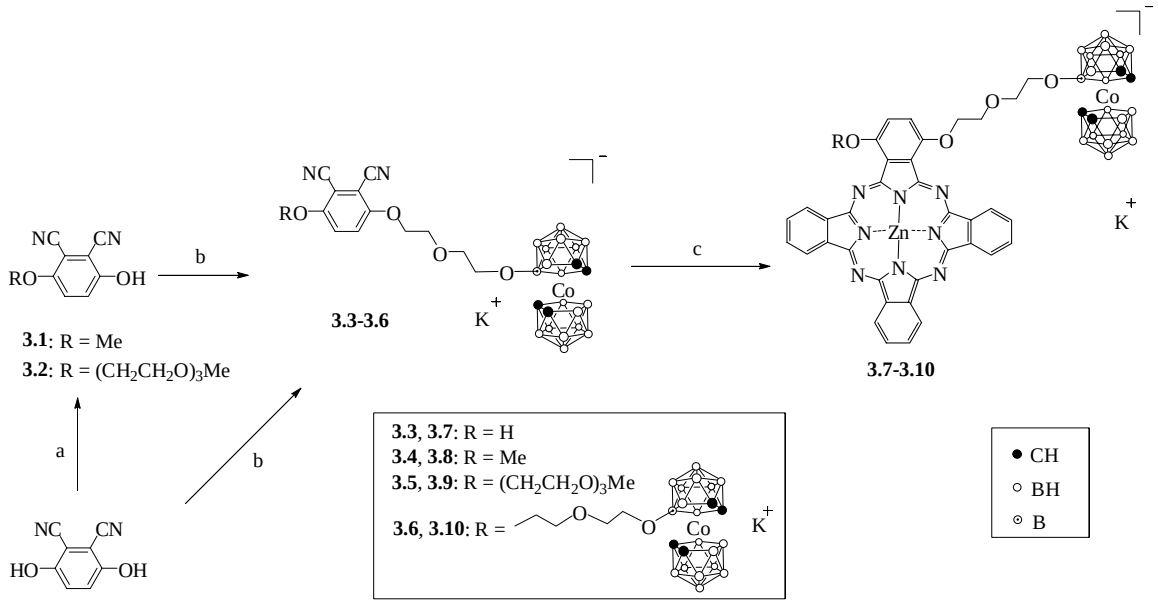


3.10

Figure 3.1. Structures of target Pc conjugates.

3.2 Synthesis of Carboranyl Conjugated Phthalocyanines



Scheme 3.1. Synthesis of ZnPc-Cobaltacarborane conjugates **3.7-3.10**. Reagent and conditions: (a) RI, K_2CO_3, DMF, 24 h (16-50%); (b) 3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$), K_2CO_3, 60 °C, 24 h (>92%); (c) phthalonitrile, $Zn(OAc)_2$, quinoline, 220 °C, 1 h (8 - 17%).

The synthetic routes to conjugates **3.7-3.10** are shown in Scheme 3.1. Zinc Pcs **3.7-3.10** were synthesized from the corresponding conjugated phthalonitrile and excess unsubstituted phthalonitrile using zinc as the template in 8–17% yields. Zwitterionic 3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$) was synthesized from Cs[3,3′-Co(1,2-$C_2B_9H_{10}$)$_2$] in dry dioxane in 93% yield, according to the literature.[24, 25] I was able to obtain an improved result of X-ray structure analysis, which is shown in Figure 3.2.[25] 2,6-Dihydroxyphthalonitrile reacted with 3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$) after activation with anhydrous potassium carbonate in acetone. Conjugated phthalonitrile **3.6** containing two cobaltacarborane clusters was obtained in 96% yield. 2,6-Dihydroxyphthalonitrile was monosubstituted using one equivalent of methyl iodide or triethylene glycol iodide[26] to produce the monohydroxy-containing phthlaonitriles **3.1**

and **3.2** in 50% and 16% yields, respectively. The crystal structure of **3.1** is shown in Figure 3.3.

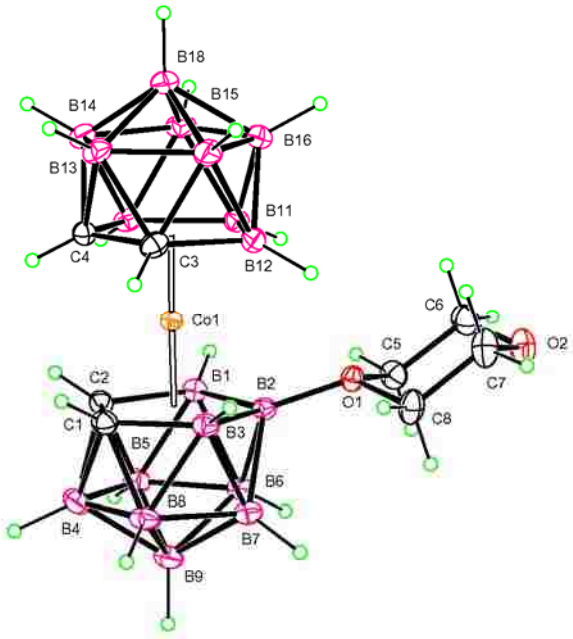


Figure 3.2. Single crystal X-ray structure of 3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$).

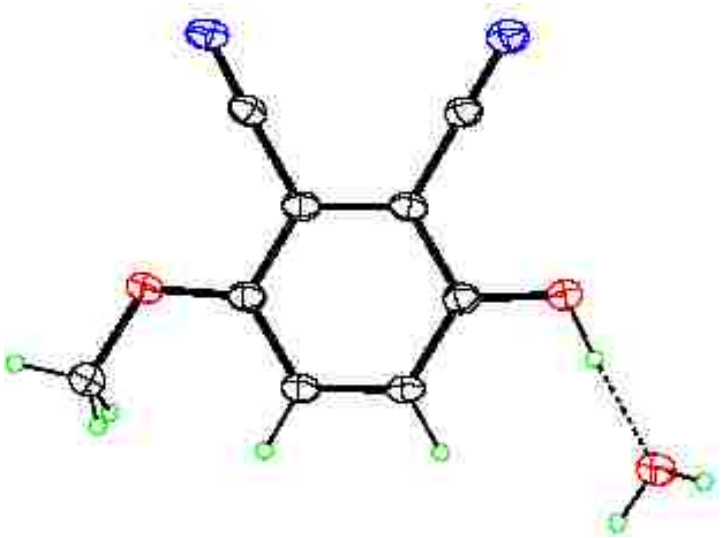


Figure 3.3. Single crystal X-ray structure of phthalonitrile **3.1**.

After activation with anhydrous potassium carbonate in acetone or acetone/chloroform mixed solvents, monohydroxy-containing phthalonitriles **3.1** or **3.2** reacted with 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$) to produce conjugated phthalonitriles **3.4** or **3.5**, each containing one cobaltacarborane cluster. An excess amount of reagent 2,6-dihydroxyphthalonitrile reacted with 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$) (1′,2′-$C_2B_9H_{10}$) to produce the mono-cobaltacarborane conjugated phthalonitrile **3.3**. All the dioxane ring-opening reactions afforded the phthalonitrile conjugates in yields above 92%. The presence of the dicarbollide cages and the attached ethylene glycol chains makes phthalonitrile conjugates **3.3**–**3.6** very soluble in polar organic solvents, such as acetone, methanol and acetonitrile.

A_3B-type Pcs are generally synthesized by three methods: 1) statistical condensation, 2) ring expansion, and 3) polymer support.[27] We applied the traditional method of statistical condensation to synthesize the zinc Pcs **3.7**-**3.10** in 8-17% yields. The macrocyclization reactions took place by heating in quinoline at 220 °C for one hour in the presence of zinc acetate. Cobaltacarborane cages were found to survive these reaction conditions of quinoline at high temperature. Some bases such as Li and DBU generally used in the Pc formation reactions didn't produce any expected product, which may be due to the incompatability of the carborane moiety with these bases. Solid state synthesis is widely used in the synthesis of borane conjugated Pcs.[15, 18] Unfortunately, it also did not succeed in this case.

We found that using excess amount of reagent phthalonitrile (A) over carborane-conjugated phthalonitrile (B) (molar ratio 30:1) produced only one A_3B-type Pc, besides the A_4-type Pc. The production of only one type of Pc except for the A_4-type Pc is due to the large molar ratio of the two phthalonitrile precursors and the steric hindrance of the

cobaltacarborane cages linked via diethylene glycol chains at the 1,4-positions on the Pc periphery. By taking advantage of the large difference in solubility of the two resulting Pcs, the purification was simplified. After the reaction, the A_4-type Pc was easily removed from the desired product by filtration since the A_4-type Pc is not soluble in most solvents. The crude product containing the A_3B-type Pc was further purified by Sephadex LH-20 column in acetone, followed by HPLC on a C_{18} column using multiple gradient methods with elution of mixed solvents of water and acetonitrile (see Experimental section). Dark bluish green solids of the target Pcs **3.7**-**3.10** were obtained in 8–17% yields. These low yields may be due to the impurities produced during the high temperature reactions, and/or the purification methods such as HPLC which may have removed some aggregates formed in the solvents used.

The idea of attaching cobaltacarborane cages to the Pc's periphery in the last step, in order to increase the product yield, was not realistic, because the limited solubility of the Pc precursor prevents its further modification. A trial to synthesize free base Pc conjugated with cobaltacarborane moiety was not successful. The zinc acetate used as the template in this reaction was found to play an important role in this macrocyclisation step.

The dicobaltacarborane conjugated Pc **3.10** is very soluble in polar organic solvents such as acetone, methanol, DMSO, DMF and THF. Figure 3.4 shows the molecular structure of **3.10**. The Zn-O bond indicated that the metal inside the macrocycle is in five coordination state and the axial ligand probably comes from the solvent (i.e. water). The DEPT spectrum of **3.10** in Figure 3.5 clearly shows that the dicarbollide CH carbons are characteristic at 54.15 and 47.24 ppm and the aliphatic CH_2 carbons in the range of 69-73 ppm in deuterated DMF. The ^{13}C NMR spectrum of **3.10**

has the expected six peaks in the upfield region at 72.98, 71.27, 70.49, 69.34, 54.15 and 47.24 ppm. Pcs **3.7-3.10** have the same pattern of peaks in this region, and the OCH_3 carbon in Pc **3.8** appears at 57.49 ppm.

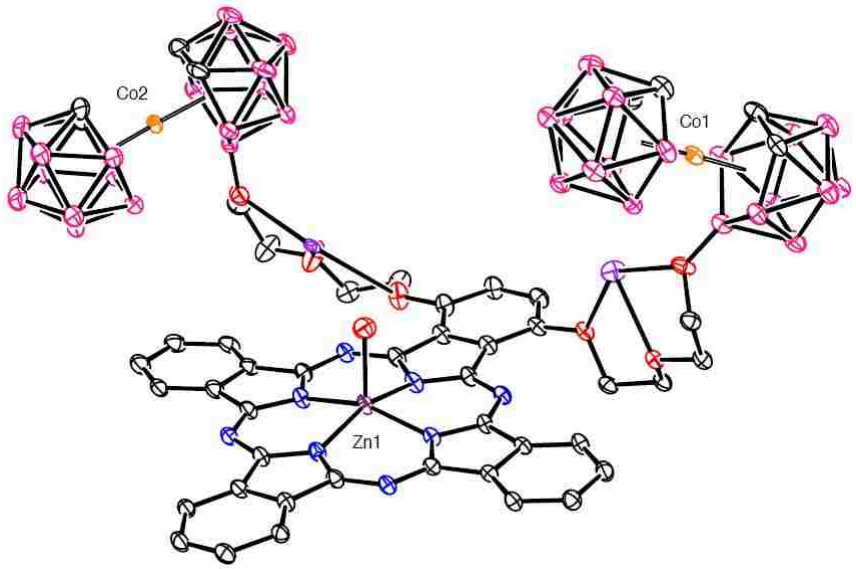


Figure 3.4. Single crystal X-ray structure of Pc **3.10**.

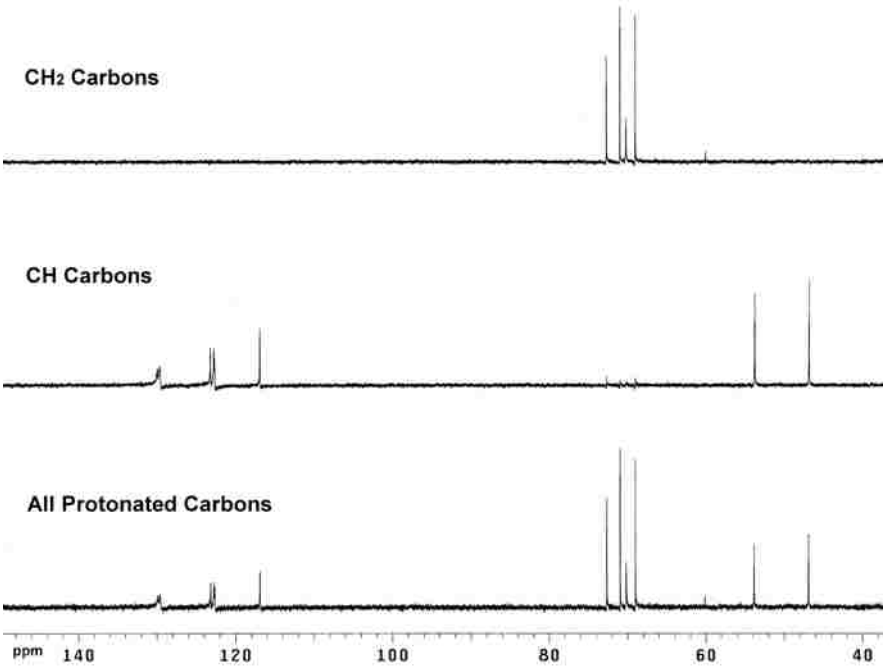


Figure 3.5. DEPT spectrum of Pc **3.10** in d-DMF (solvent: 34.9, 29.7 ppm).

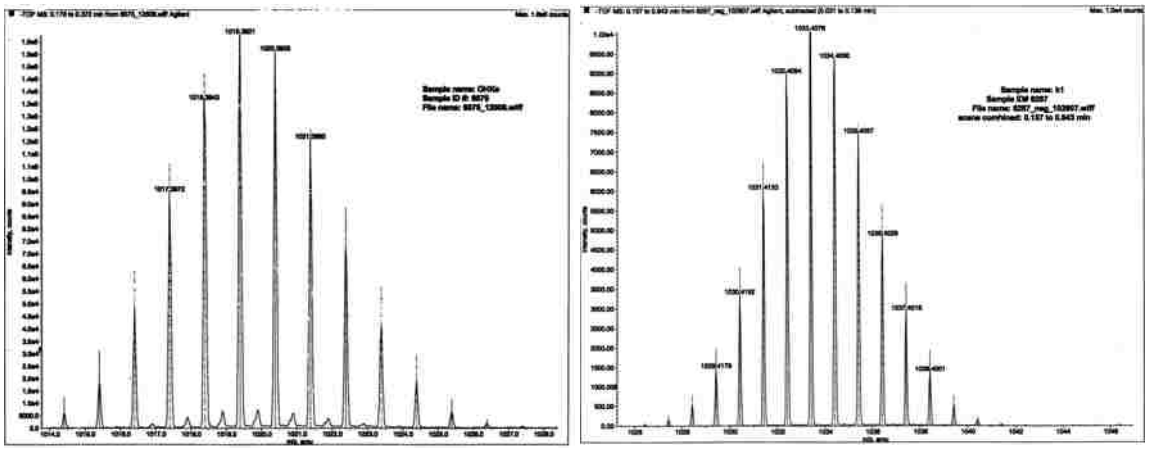
All target Pcs in d-DMF show the characteristic macrocycle protons of the three identical isoindole subunits in the range of 8–10 ppm. The two protons of the cobaltacarborane-substituted isoindole unit are in the range of 7–8 ppm and they have almost the same chemical shifts as the two aromatic protons of their corresponding phthalonitrile conjugates. The ^{1}H NMR spectra show that the conjugated phthalonitriles in d-acetone have the dicarbollide CH protons overlapping as one sharp peak at 3.6 ppm and two sets of CH_2 protons of the diethylene glycol chain overlapping as a broad peak at 4.2 ppm. It is interesting to observe that the dicarbollide CH protons of the corresponding conjugated Pcs in d-DMF shifted downfield to about 4.3 ppm and split into two peaks resembling two kinds of protons contained in the cobaltacarborane cages, while the CH_2 protons of the diethylene glycol chain show four sets of peaks in the range of 5.0–3.9 ppm.

All Pcs investigated show similar MS (ESI) negative ion pattern as $[M-K]^-$, except for Pc **3.10** containing two cobaltacarborane cages showing the pattern as $[M-2K+H]^-$ at 1430.7214 *m/z*. The mononegative molecular ions of all Pcs (**3.7** at 1019.3921; **3.8** at 1033.4076; **3.9** at 1165.4859 and **3.10** at 1430.7214 *m/z*, Figure 3.6) show the same characteristic isotopic patterns which are due to the existence of large number of boron atoms.

Trace amount of demethylated byproduct in the high temperature macrocyclisation reaction of Pc **3.8** was observed in the ESI-MS spectrum at 1019 *m/z*. The separation of Pc **3.7** from Pc **3.8** is difficult by HPLC. Remethylation with excess methyl iodide was performed after the macrocyclisation reaction in order to convert all of Pc **3.7** to Pc **3.8**. The reaction was followed by ESI-MS until the disappearance of the peak at 1019 *m/z*. The pure Pc **3.8** was obtained by reverse phase HPLC using water (A)

and acetonitrile (B) as the mobile phase with a multi-step gradient method from 70% B to 100% B.

(a) **(b)**



(c) **(d)**

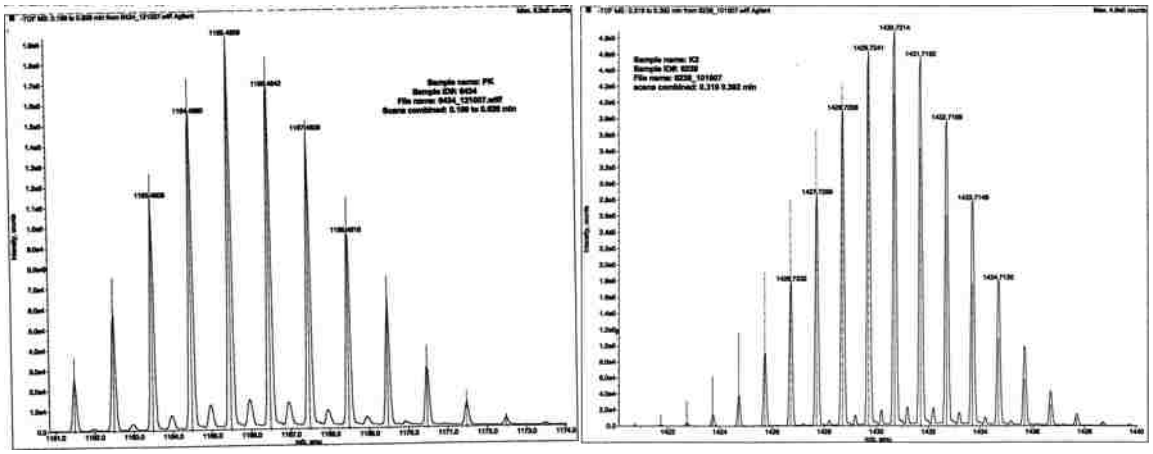


Figure 3.6. HRMS-ESI spectra for Pcs (a) **3.7,** (b) **3.8**, (c) **3.9**, (d) **3.10**.

3.3 Spectroscopic Properties of Cobaltacarboranyl-Phthalocyanines

Pcs **3.7**-**3.10** are soluble in polar organic solvents such as acetone, methanol, DMF and DMSO. Pc **3.8**-**3.10** were found to exist mainly as monomers in acetone showing strong and sharp Q band absorptions that strictly follow the Lambert Beer's law (see Figure 3.7). It is observed that these A_3B-type Pcs containing 1,4-substituents have

(a) **(b)**

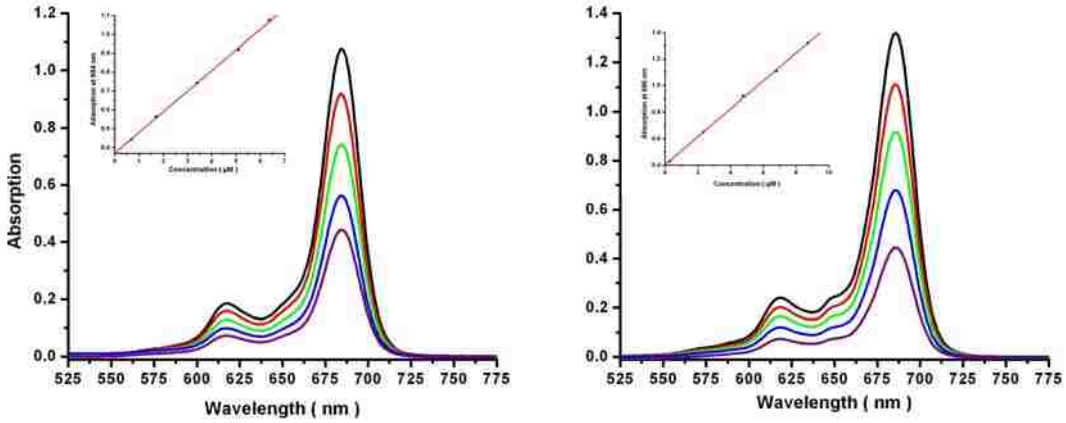


Figure 3.7. (a) Absorption spectra of Pc **3.8** in acetone at 6.4 µM (black), 5.1 µM (red), 3.4 µM (green), 1.7 µM (blue), and 0.7 µM (purple) concentrations; (b) Absorption spectra of Pc **3.10** in acetone at 8.7 µM (black), 6.8 µM (red), 4.8 µM (green), 2.3 µM (blue), and 0.3 µM (purple) concentrations.

longer wavelength for the maximum absorption than those having 2,3-substituents due to their special geometry.[26] Figure 3.8 (a) shows that Pc **3.10** has a maximum absorption wavelength at 684 nm in acetone, 695 nm in DMF and 696 nm in DMSO. Figure 3.8 (b) shows that Pc **3.10** has a maximum emission peak at 691 nm in acetone, and 6-11 nm red shift can be found in DMF and DMSO. Pcs **3.8** and **3.10** have the same patterns of

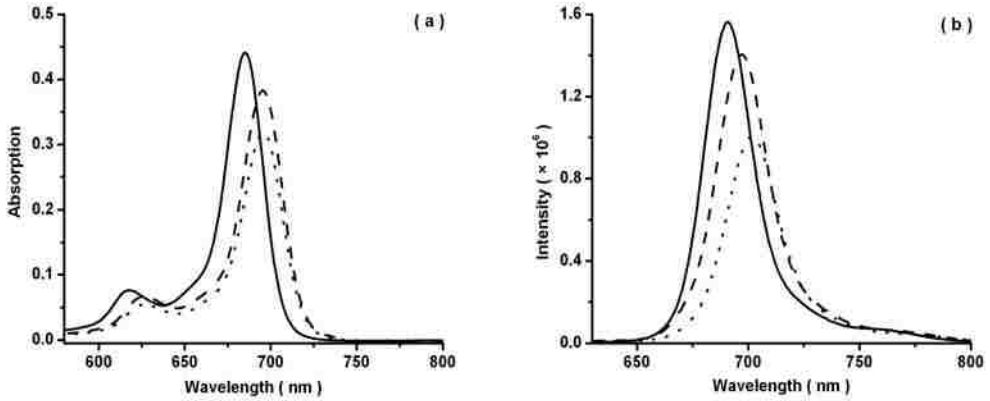


Figure 3.8. (a) Absorption spectra of Pc **3.10** at 2.8 µM in acetone (solid line), DMF (dash line) and DMSO (dot line); (b) Emission spectra of Pc **3.10** at 300 nM in acetone (solid line), DMF (dash line) and DMSO (dot line), excited at 620 nm.

absorption and emission spectra in acetone, DMF and DMSO. Pc **3.8** has the maximum absorption wavelengths at 695 nm in DMSO and DMF and 9 nm of blue shift in acetone. Both Pcs **3.8** and **3.10** have relatively large Stokes shift of 6-8 nm in methanol, acetone and DMSO, while only 2 nm in DMF. Pc **3.9** bearing one triethylene glycol chain has the maximum absorption wavelength at 689 nm and relatively large Stokes shift of 7 nm in DMF. The phenomena of solvatochromism shift of these anionic carborane containing Pcs is consistent with those reported by Teixidor.[28]

All the zinc-Pc conjugates, except for Pc **3.7**, are soluble in polar organic solvents. Pc **3.7** containing one free hydroxyl group may form aggregates through hydrogen bonding explaining its lower solubility in solution.[29] The absorption and emission spectra of all Pcs in DMSO are shown in Figure 3.9. Pcs **3.9** and **3.10** have the same absorption peaks at 695 nm in DMSO, and Pc **3.8** containing one methoxy group has a red shift of 1 nm, at 696 nm. All Pcs **3.8**–**3.10** have the same emission peak at 702 nm in DMSO. Pc **3.7** containing one hydroxyl group has a red shift of 13 nm compared

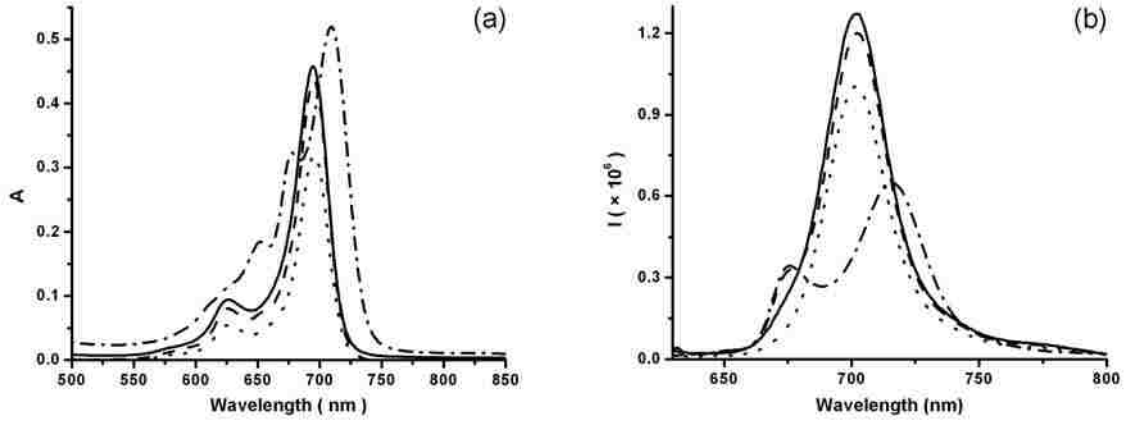


Figure 3.9. (a) Absorption spectra of Pc **3.7** (dash dotted line) at 4.2 µM, Pc **3.8** (dotted line) at 2.0 µM, Pc **3.9** (solid line) at 3.0 µM, Pc **3.10** (dashed line) at 3.3 µM in DMSO; (b) Emission spectra of Pc **3.7** (dash dotted line) at 0.42 µM, Pc **3.8** (dotted line) at 0.20 µM, Pc **3.9** (solid line) at 0.30 µM, Pc **3.10** (dashed line) at 0.33 nM in DMSO, excited at 620 nm.

with Pc **3.8**. It has a hypsochromic shift shown as a shoulder in the absorption spectra, which is probably due to the formation of a dimer species. In the emission spectra, Pc **3.7** has a significant decrease of the intensity, and the production of a minor peak at 676 nm, maybe due to the formation of dimer species.

The spectroscopic data observed for Pcs **3.7**–**3.10** in different organic solvents and aqueous solution (pH = 7.4) are summarized in Table 3.1. Pc **3.9** containing one PEG chain and one cobaltacarborane cage has the highest fluorescent quantum yield among all Pcs in DMF, methanol and acetone. Pc **3.7** containing one hydroxyl group has the lowest fluorescent yields among all Pcs in all the solvents tested, which is probably due to its strong tendency for aggregation in the solvent. As a result, the aggregation in solution largely decreases its fluorescent and singlet oxygen quantum yields.[30] These A_3B- type Pcs have relatively large Stokes shift in the range of 5-10 nm. Nevertheless, Pc

Table 3.1. Spectral properties of Pc **3.7**-**3.10** in different media*.

Pc		DMSO	DMF	MeOH	Acetone	Buffer[d]
3.7	abs	709[b]	705[b]	696[b]	700[b]	659[c]
	em	715[b], 676	712[b], 673	706[b], 670	707[b], 669	680[c]
	SS	6	7	10	7	NA
	QY	0.0682	0.0671	0.0273	0.0554	NA
3.8	abs	696, 627	695, 627	687, 620	684, 618	652[c]
	em	702	697	694	691	683[c]
	SS	6	2	7	7	NA
	QY	0.1354	0.1445	0.1034	0.1035	NA
3.9	abs	695, 626	689, 622	686, 621	685, 618	654[c]
	em	702	696	694	690	683[c]
	SS	7	7	8	5	NA
	QY	0.1311	0.1550	0.1192	0.1532	NA
3.10	abs	695, 626	695, 626	687, 620	686, 618	659[c]
	em	702	697	695	692	681[c]
	SS	7	2	8	6	NA
	QY	0.1220	0.125	0.0897	0.1103	NA

*abs: absorption maxima (nm); em: emission maxima (nm); S.S.: Stokes Shift (nm); Q.Y.: quantum yield (nm). [b] major peak. [c] broad. [d]100 mM phosphate buffer , pH = 7.4.

3.8 and **3.10** have the lowest Stokes shift of 2 nm in DMF. All Pcs show the highest Stokes shift in methanol among all the solvents tested. The spectroscopic properties of these carboranyl-functionalized Pcs depend on both the carborane moieties and solvent environment.[28]

3.4 Synthesis of Carboranyl Conjugated Phthalonitriles and Future Work

Zwitterionic 3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$) can undergo dioxane ring-opening reaction in the presence of various of nucleophilic reagents, such as halides (fluoride, chloride), hydroxide,[31] cyanide, amines,[32] phenolates[33] and pyrrolyl ligands.[34] A series of carboranyl-substituted phthalonitriles were designed (Figure 3.10) and phthalonitriles **3.12**, **3.13** and **3.16** have been synthesized in 85-94% yields (Schemes 3.2-3.4). The carboranyl conjugated phthalonitriles **3.12**, **3.13** and **3.16** were synthesized from the corresponding substituted phthalonitrile containing pyridyl or hydroxyl groups.

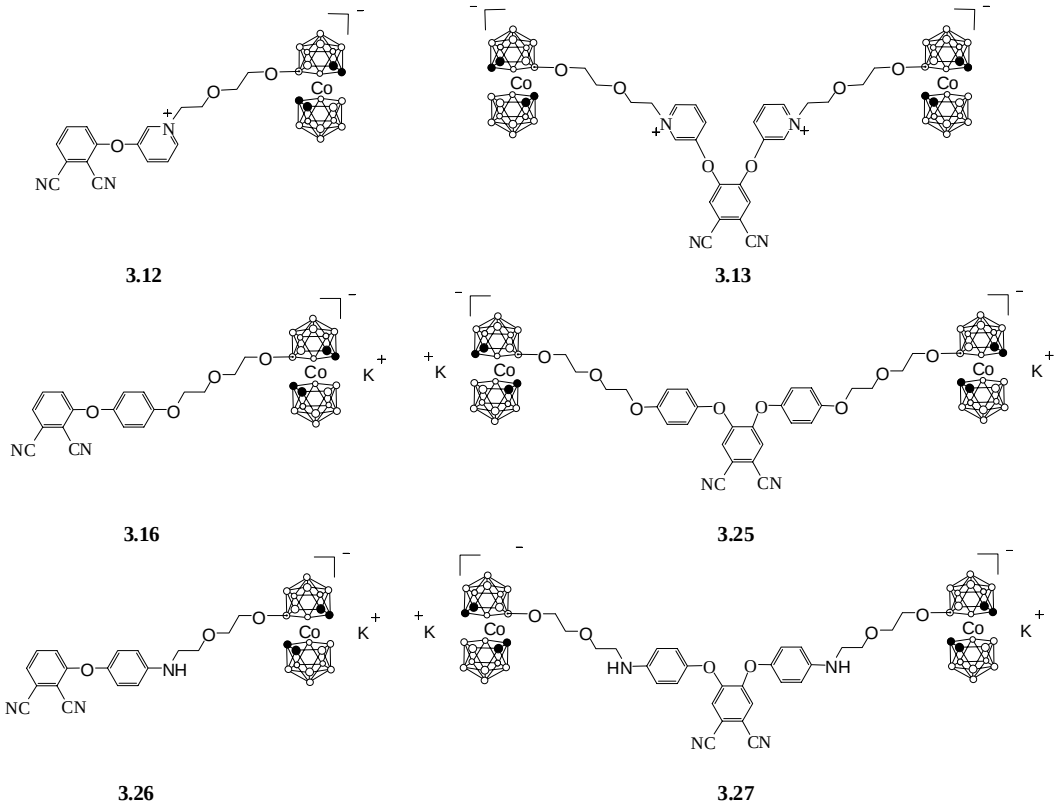
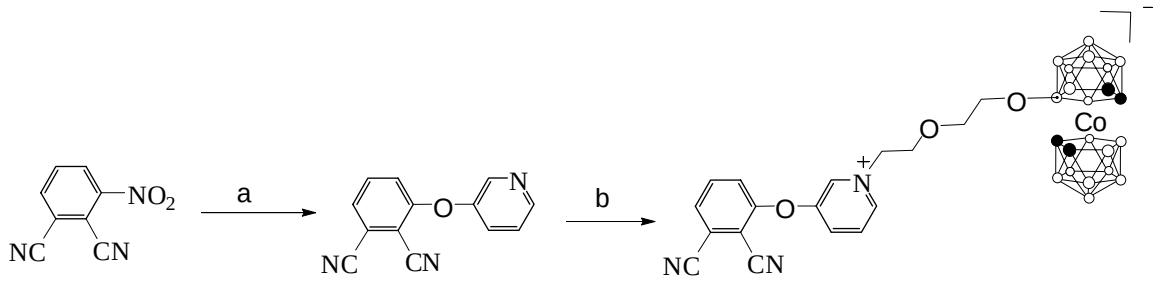
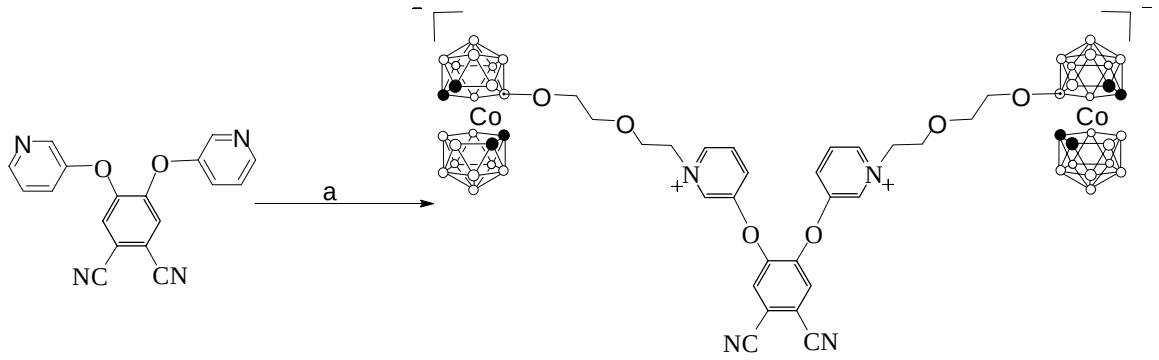


Figure 3.10. Target phthalonitrile conjugates.



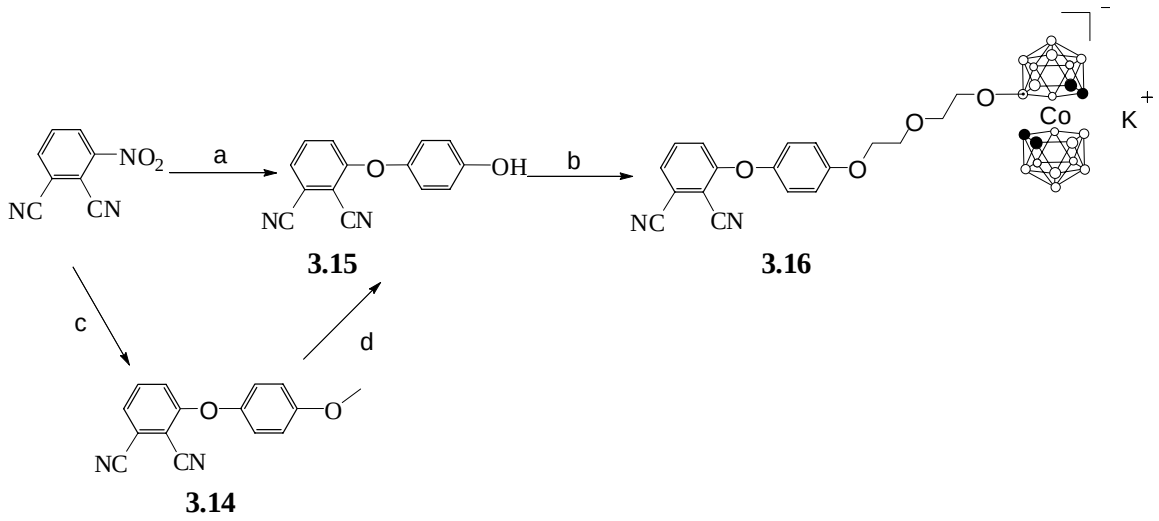
3.11 **3.12**

Scheme 3.2. Syntheses of phthalonitrile conjugate **3.12**. Reagents and conditions: (a). 3-hydroxypyridine, K_2CO_3, 90 °C (74%); (b). 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$), 50 °C (94%).



3.13

Scheme 3.3. Syntheses of phthalonitrile conjugate **3.13**. Reagents and conditions: (a). 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$), 50 °C (85%).

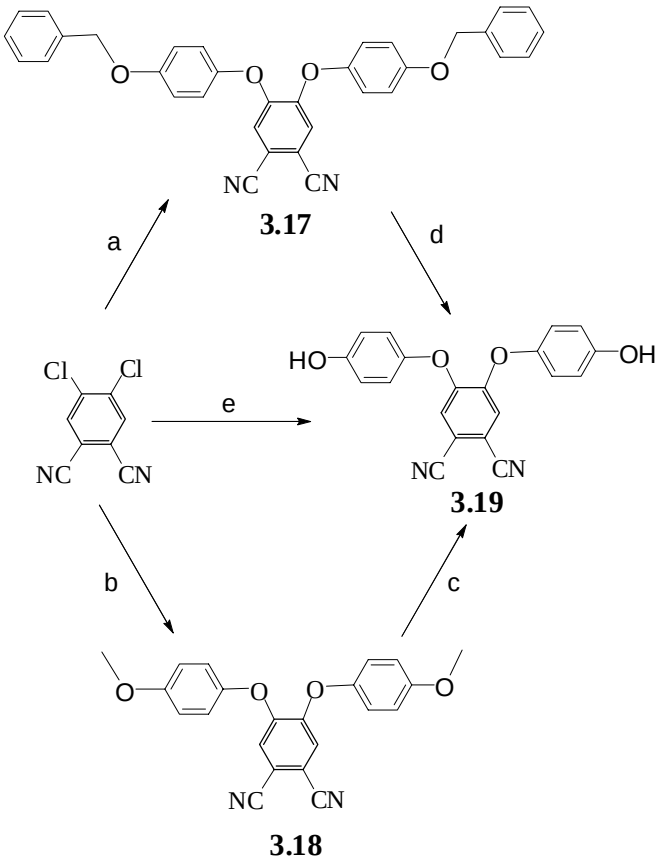


3.15 **3.16**

3.14

Scheme 3.4. Syntheses of phthalonitrile conjugate **3.16**. Reagents and conditions: (a). hydroquinone, K_2CO_3, 50 °C to r.t. (22%); (b). 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$), K_2CO_3, 50 °C (94%); (c). 4-methoxyphenol, K_2CO_3, 90 °C (83%); (d). BBr_3, -80 °C (40%).

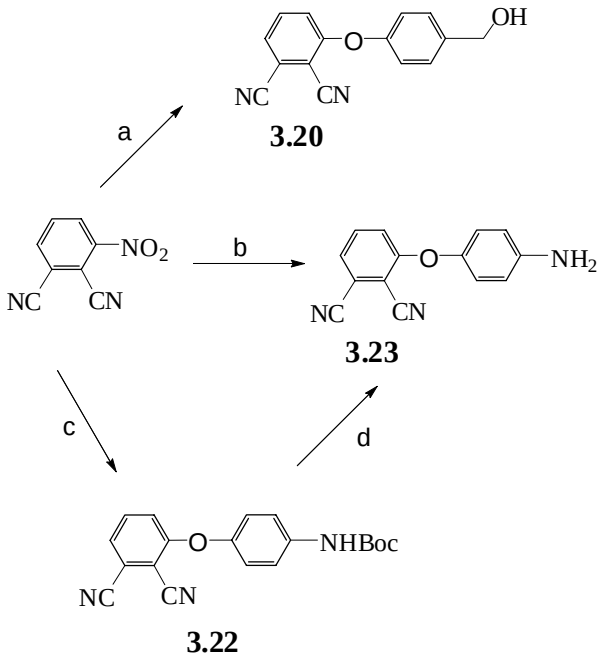
I have also synthesized other mono and di-amino or hydroxyl-substituted phthalonitriles as shown in Scheme 3.5-3.8. Phthalonitrile **3.19** containing two free hydroxyl groups was synthesized in three different routes. 4,5-Dichlorophthalonitrile reacted with hydroquinone in the presence potassium carbonate to get phthalonitrile **3.19**. Phthalonitrile **3.17** containing benzyloxy groups proceeded hydrogenation reaction with 10% Pd/C to obtain the desired phthalonitrile **3.19** in 22% overall yield. Phthalontrile **3.18** containing methoxyl groups reacted with boron tribromide to afford phthalonitrile



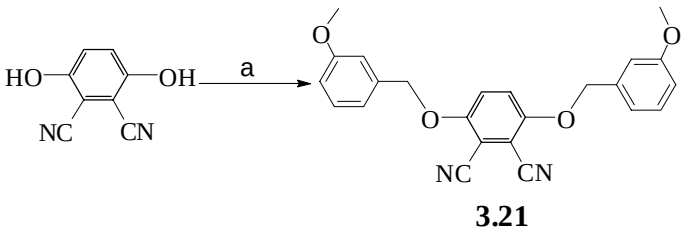
Scheme 3.5. Syntheses of phthalonitrile **3.19**. Reagents and conditions: (a). 4-benzyloxyphenol, K_2CO_3, 80 °C (48%); (b). 4-methoxyphenol, K_2CO_3, 80 °C (58%); (c). BBr_3, -80 °C (29%); (d). Pd/C (10%), r.t., (46%).

3.19 in 17% overall yield. Phthalonitrile **3.23** containing one free amino group was synthesized from 3-nitrophthalonitrile and 4-aminophenol in 75% yield. It was also

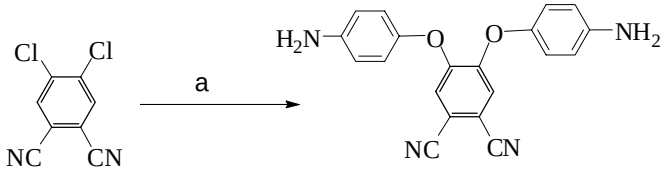
synthesized from phthalonitrile **3.22** containing Boc group by deprotection reaction with TFA at room temperature in 72% overall yield. Molecular structures of phthalonitriles **3.11**, **3.15**, **3.17**, **3.19**, **3.21** and **3.24** are shown in Figure 3.11. Further modification of these phthalonitriles with 3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$) will lead to carboranyl-functionalized phthalonitriles. The statistical condensation method will be applied to these conjugated phthalonitriles to afford A_3B-type Pcs.



Scheme 3.6. Syntheses of phthalonitriles **3.20** and **3.23**. Reagents and conditions: (a). 4-hydroxy-benzyl alcohol, K_2CO_3, r.t., (28%); (b). 4-aminophenol, K_2CO_3, 60 °C (75%); (c). N-Boc-4-aminophenol, K_2CO_3, 80 °C (80%); (d). TFA, DCM, r.t. (90%).

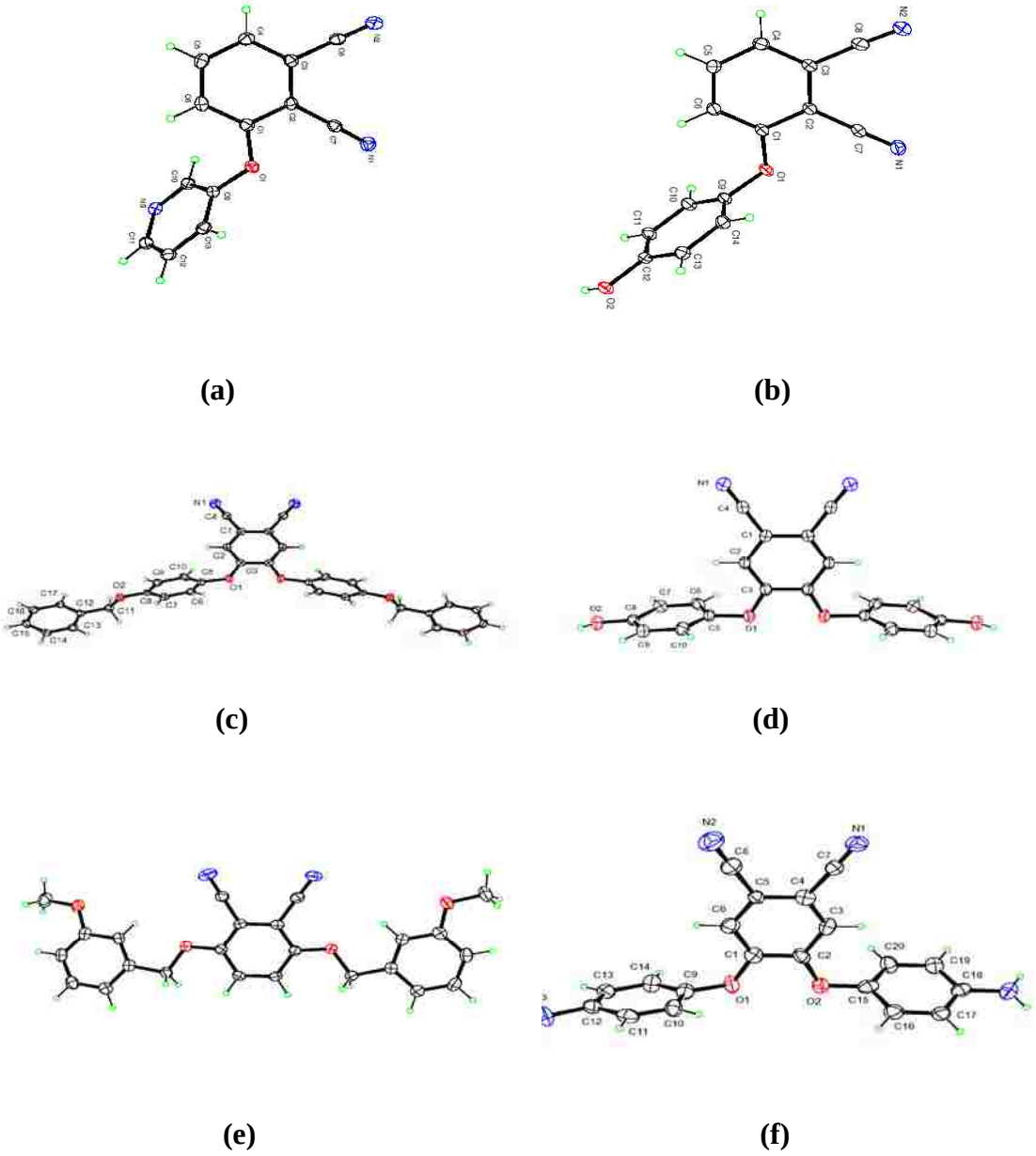


Scheme 3.7. Syntheses of phthalonitrile **3.21**. Reagents and conditions: (a). 1-(bromomethyl)-3-methoxybenzene, 60 °C (98%).



3.24

Scheme 3.8. Syntheses of phthalonitrile **3.24**. Reagents and conditions: (a). 4-aminophenol, K_2CO_3, 60 °C (66%).



(a) **(b)**

(c) **(d)**

(e) **(f)**

Figure 3.11. Single crystal X-ray structures of **3.11** (a), **3.15** (b), **3.17** (c), **3.19** (d), **3.21** (e), **3.24** (f).

3.5 Conclusion

Four novel carboranyl-conjugated A_3B-type Pcs were successfully synthesized in 8-17% yields. These Pcs are highly soluble in polar solvents such as methanol, acetone, DMF and DMSO, their absorption and emission properties are solvent-dependent, and have ~0.1 fluorescence quantum yields. Several new phthalonitriles have been synthesized which can also be converted into A_3B-type carboranyl-conjugated Pcs. The X-ray structures of several of these new compounds were obtained. These Pcs may have potential application as dual sensitizers in the PDT and BNCT treatment of tumors.

3.6 Experimental

All chemicals were purchased from commercial sources and used directly without further purification. Silica gel 60 (230×400 mesh, Sorbent Technologies) and alumina gel (50 – 200 μm, neutral, standard activity I, Sorbent Technologies) were used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using polyester backed TLC plates 254 (precoated, 200 μm) from Sorbent Technologies. NMR spectra were recorded on a DPX-250 or AV-400 Bruker spectrometers (250 MHz or 400 MHz for ^{1}H, 63 MHz or 100 MHz for ^{13}C). The chemical shifts are reported in δ ppm using the following deuterated solvents as internal references: CD_3COCD_3 2.04 ppm (^{1}H), 29.92 ppm (^{13}C); d-DMF 2.92 ppm (^{1}H), 34.89 ppm (^{13}C). Electronic absorption spectra were measured on a Perkin-Elmer Lambda 35 UV-vis spectrometer. High resolution ESI mass spectra were obtained on an Agilent Technologies 6210 Time-of-Flight LC/MS. HPLC separation and analyses were carried out on a Dionex system equipped with a P680 pump and a UVD340U detector. Semi-preparative column was Luna C_{18} 100 Å, 5 μm, 10 × 250 mm from Phenomenex, USA. Analytical HPLC was carried out on a Delta Pak C_{18} 300 Å, 5 μm, 3.9 × 150 mm (Waters, USA) column; flow

rate 1.0 mL/min; injected volume 20 µL; wavelength detection 350 nm; solvent A H_2O, solvent B acetonitrile. Multi-step gradient elution method was used. Condition a: time 0 min, 70% B; 10 min, 80% B; 20 min, 90% B; 37 min, 100%; condition b: time 0 min, 75% B; 10 min, 85% B; 20 min, 100% B; 37 min, 100%; condition c: time 0 min, 85% B; 10 min, 95% B; 20 min, 100% B; 37 min, 100%

Zwitterionic [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)].[24] 0.5 g Cs[3,3′-Co(1,2-$C_2B_9H_{10}$)$_2$] was dissolved in 50 mL anhydrous 1, 4-dioxane. Boron trifluoride diethyl etherate (1.1 mL, 8.8 mmol) was added dropwise to the solution. The reaction was refluxed under an atmosphere of argon for 5 h. After the solution was cooled down to room temperature, the solvent was evaporated. The crude product was obtained by chromatography on alumina gel using DCM : hexane (4:1) as the eluent to afford orange solid 0.56 g (93%).^{1}H NMR (acetone-d_6, 400 MHz): δ 4.69 (t, J = 4.1 Hz, 4H, OCH_2), 4.40 (s, 2H, CH), 4.05 (t, J = 4.1 Hz, 4H, OCH_2), 4.02 (s, 2H, CH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.54 (t, J = 4.2 Hz, 4H, OCH_2), 4.03 (t, J = 4.2 Hz, 4H, OCH_2), 3.77 (s, 2H, CH), 3.33 (s, 2H, CH). ^{13}C NMR (acetone-d_6, 400 MHz): δ 83.98, 66.24 (OCH_2), 55.17, 48.87 (CH).

Phthalonitrile 3.1. 2, 6-Dihydroxyphthalonitrile (1 g, 6.27 mmol) was dissolved in 90 mL DMF with argon flow. Potassium carbonate (0.85 g, 6.27 mmol) was added in three portions. After adding methyl iodide (0.38 mL, 6.27 mmol) dropwise into the solution in four portions, the solution was stirred at room temperature in the sealed system for 1 day. After the reaction, the solution was quenched with 90 mL 1 N HCl solution. The precipitate was filtered under vacuum. The crude product was purified by column chromatography on neutral alumina using methanol/dichloromethane 1:20 for elution. The title compound (0.4 g) was obtained as a white crystal in 50% yield. ^{1}H

NMR (acetone-d_6, 250 MHz): δ 7.47-7.36 (m, 2H, Ar-H), 3.96 (s, 3H, OCH_3). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.31, 155.39, 123.68, 119.83, 114.30, 114.19, 103.56, 102.57 (Ar-C, CN), 57.38 (OCH_3). HRMS-ESI: *m/z* 173.0355 $[M-H]^-$, calcd. for $[C_9H_5N_2O_2]^-$ 173.0356.

Phthalonitrile 3.2. 2, 6-Dihydroxyphthalonitrile (1 g, 6.3 mmol) was dissolved in 90 mL DMF with argon flow. Potassium carbonate (0.85 g, 6.3 mmol) was added in three portions. After adding triethylene glycol iodide (1.65 mL, 6.3 mmol) dropwise into the solution in four portions, the solution was stirred at room temperature in the sealed system for 1 day. After the solution was cooled down to room temperature, the precipitate was removed from the solution by filtration. The solution was concentrated and added with 10 mL acetone, the precipitate was filtered again. The solvent was evaporated to get viscous liquid. The crude product was purified with aluminum column with ethanol / dichloromethane 5 / 95 for elution to get pale white solid 0.3 g in 16% yield. ^1H NMR (acetone-d_6, 250 MHz): δ 7.49 (d, J = 9.4 Hz, 1H, Ar-H), 7.36 (d, J = 9.4 Hz, 1H, Ar-H), 4.30 (t, J = 4.5 Hz, 2H, OCH_2), 3.84 (t, J = 4.5 Hz, 2H, OCH_2), 3.67 – 3.63 (m, 2H, OCH_2), 3.59 – 3.54 (m, 4H, OCH_2), 3.46 – 3.43 (m, 2H, OCH_2), 3.26 (s, 3H, OCH_3). ^{13}C NMR (acetone-d_6, 63 MHz): δ 155.80, 155.75, 123.66, 121.65, 114.37, 114.28, 104.30, 102.42 (Ar-C, CN), 72.53, 71.46, 71.14, 70.96, 70.81, 70.07 (OCH_2), 58.70 (OCH_3). HRMS-ESI: *m/z* 305.1140 $[M-H]^-$, 306.1169 $[M]^-$, calcd. for $[C_{15}H_{17}N_2O_5]^-$ 305.1142, $[C_{15}H_{18}N_2O_5]^-$ 306.1216.

Phthalonitrile Conjugate 3.3. A mixture of 2, 6-Dihydroxyphthalonitrile (0.38 g, 2.4 mmol) and potassium carbonate (0.066 g, 0.48 mmol) in acetone were refluxed at 60 °C under argon. After 20 min, [3,3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.20g, 0.48 mmol) was added to the reaction solution in 3 portions. The reaction solution was

heated for 24 h, then cooled to room temperature and evaporate the solvent out. The crude product was purified by silica gel chromatography using methanol/dichloromethane 5: 95 for elution to get the title compound (0.27 g) as an orange solid in 93% yield. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.52 (d, J = 9.4 Hz, 1H, Ar-H), 7.37 (d, J = 9.4 Hz, 1H, Ar-H), 4.31 – 4.29 (m, 2H, OCH_2), 4.23 (br, 4H, OCH_2), 3.84 – 3.82 (m, 2H, OCH_2), 3.57 (s, 4H, CH), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (acetone-d_6, 100 MHz): δ 156.01, 155.62, 123.62, 121.95, 114.35, 114.26, 104.37, 102.40 (Ar-C, CN), 73.05, 71.00, 70.14, 69.31 (OCH_2), 55.09, 47.24 (CH). HRMS-ESI: *m/z* 570.3495 $[M-K]^-$, calcd. for $[C_{16}H_{32}B_{18}CoN_2O_4]^-$ 570.3495.

Phthalonitrile Conjugate 3.4. A mixture of **3.1** (0.08 g, 0.46 mmol) and potassium carbonate (0.066 g, 0.48 mmol) in mixed solvents of acetone and chloroform (5:1) were refluxed at 60 °C under argon. After 20 min, [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.20g, 0.48 mmol) was added to the reaction solution in 3 portions. The reaction solution was heated for 16 h, then cooled to room temperature and evaporate the solvent out. It was dissolved in 50 mL ethyl acetate and washed with 10 mL water for 3 times. The crude product in the organic layer was purified by silica gel chromatography using methanol/dichloromethane 1:10 for elution to get the title compound (0.95 g) as an orange solid in 92% yield. ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.68 (d, J = 9.5 Hz, 1H, Ar-H), 7.56 (d, J = 9.5 Hz, 1H, Ar-H), 4.34 (t, J = 4.7 Hz, 2H, OCH_2), 4.24 (br, 4H, OCH_2), 3.99 (s, 3H, OCH_3), 3.84 (t, J =4.7 Hz, 2H, OCH_2), 3.57 (s, 4H, CH), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.84, 156.34, 121.69, 119.49, 114.03, 105.33, 104.40 (Ar-C, CN), 73.10, 71.06, 70.21, 69.35 (OCH_2), 57.45 (OCH_3), 55.06, 47.26 (CH). HRMS-ESI: *m/z* 584.3677 $[M-K]^-$, calcd. for $[C_{17}H_{34}B_{18}CoN_2O_4]^-$ 584.3653.

Phthalonitrile Conjugate 3.5. A mixture of **3.2** (0.15 g, 0.49 mmol) and potassium carbonate (0.066 g, 0.48 mmol) in acetone were refluxed at 60 °C under argon. After 20 min, [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.21g, 0.51 mmol) was added to the reaction solution in 3 portions. The reaction solution was heated for 24 h, then cooled to room temperature and evaporate to dry. The crude product was purified by silica gel chromatography using methanol/dichloromethane 5: 95 for elution to get the title compound (0.34 g) as an orange solid in 92% yield. ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.66–7.56 (m, 2H, Ar-H), 4.37 – 4.32 (m, 4H, OCH_2), 4.21 (br, 4H, OCH_2), 3.90 – 3.83 (m, 4H, OCH_2), 3.71 – 3.68 (m, 2H, OCH_2), 3.62 – 3.57 (m, 8H, OCH_2, CH), 3.50 – 3.46 (m, 2H, OCH_2), 3.28 (s, 3H, OCH_3), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.08, 155.79, 121.13, 120.77, 113.93, 113.78, 104.63, 104.56 (Ar-C, CN), 72.76, 71.91, 70.94, 70.69, 70.42, 70.23, 69.78, 69.64, 69.08 (OCH_2), 58.74 (OCH_3), 54.36, 47.00 (CH). HRMS-ESI: *m/z* 716.4434 $[M\text{-}K]^-$, calcd. for $[C_{23}H_{46}B_{18}CoN_2O_7]^-$ 716.4444.

Phthalonitrile Conjugate 3.6. A mixture of 2, 6-dihydroxyphthalonitrile (0.15 g, 0.94 mmol) and [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.82g, 1.97 mmol) in 40 mL acetone (phenol-free) were refluxed at 60 °C under argon. Potassium carbonate (0.27 g, 1.97 mmol) was added to the reaction solution in 3 portions every 5 min. The reaction solution was heated for 24 h, then cooled to room temperature and evaporate the solvent out. It was dissolved in 100 mL of ethyl acetate and washed with 20 mL of water for 3 times. The crude product in the organic layer was purified by silica gel chromatography using methanol/dichloromethane 1:40 for elution to get the title compound (0.95 g) as an orange solid in 96% yield. ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.62 (s, 2H, Ar-H), 4.34 (t, J = 5.0 Hz, 4H, OCH_2), 4.22 (br, 8H, OCH_2), 3.86 (t, J = 5.0

Hz, 4H, OCH_2), 3.59 (s, 8H, CH), 3.00 – 1.50 (br, 34H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 156.31, 121.20, 114.04, 105.00 (Ar-C, CN), 72.99, 70.84, 69.98, 69.27 (OCH_2), 54.91, 47.20 (CH). HRMS-ESI: *m/z* 489.8393 $[M-2K]^{2-}$, calcd. for $[C_{24}H_{60}B_{36}Co_2N_2O_6]^{2-}$ 489.8374.

Pc Conjugate 3.7. Phthalonitrile (1.52 g, 12.0 mmol), anhydrous zinc acetate (0.36 g, 2.0 mmol) and conjugated phthalonitrile **3.3** (60 mg, 0.1 mmol) were added into a 10 mL thick-wall Schlenk tube. The tube was dried by purge-and-refill with argon for three times. Then 1.0 mL of freshly distilled quinoline was added and the solution was heated to 220 °C. After 1 hour, the reaction residue was cooled down to room temperature. The solid in the solution was filtered and washed completely with acetone and methanol. The dark green filtrate was concentrated to dryness. The crude product was purified with a Sephadex LH-20 column using acetone for elution. The pure conjugated phthalocyanine **3.7** was obtained by reverse phase HPLC on a Luna C_{18} semi-preparative column using water / acetonitrile as the mobile phase with a multi-step gradient method (condition c). The pure product was collected and vacuum dried at 30 °C for 2 days to afford a dark bluish green solid (8.0 mg) in 8% yield based on the amount of **3.3** used. ^1H NMR (d-DMF, 400 MHz): δ 9.37 – 9.03 (m, 8H, Ar-H), 8.34 – 8.12 (m, 6H, Ar-H), 4.52 – 4.37 (m, 8H, OCH_2, CH), 4.11 – 4.05 (m, 2H, OCH_2), 3.97 -3.96 (m, 2H, OCH_2), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (d-DMF, 100 MHz): δ 153.36, 152.59, 139.35, 138.80, 134.75, 134.50, 130.31, 130.15, 129.96, 129.76, 123.33, 122.96 (Ar-C), 73.08, 71.17, 70.06, 69.44 (OCH_2), 54.34, 47.28 (CH). HRMS-ESI: *m/z* 1019.3921 $[M-K]^-$, calcd. for $[C_{40}H_{44}B_{18}CoN_8O_4Zn]^-$ 1019.3914. HPLC: t_R = 5.873 min. UV-vis (DMSO): λ_{max} (log ε) 706 (5.09).

Pc Conjugate 3.8. Phthalonitrile (0.76 g, 6.0 mmol), anhydrous zinc acetate (90 g, 0.5 mmol) and conjugated phthalonitrile **3.4** (30 mg, 0.05 mmol) were added into a 10 mL thick-wall Schlenk tube. The tube was dried by purge-and-refill with argon for three times. Then 0.5 mL freshly distilled quinoline was added and the solution was heated to 220 °C. After 1 hour, the reaction residue was cooled down to room temperature. The solid in the solution was filtered and washed completely with acetone and methanol. The dark green filtrate was concentrated to dryness. The crude product was purified with a Sephadex LH-20 column using acetone for elution. The crude product and potassium carbonate (22 mg, 0.16 mmol) was dissolved in 10 mL of acetone with argon flow. After 10 min, methyl iodide (0.01 mL, 0.16 mmol) was added dropwise into the solution. The solution was stirred at room temperature in the sealed system. The reaction was followed by ESI-MS until the disappearance of the peak of the demethylation byproduct. One day later, the solvent was evaporated out and another Sephadex LH-20 column was applied to get the crude product with the elution of acetone. The pure conjugated Pc **3.8** was obtained by reverse phase HPLC on a Luna C_{18} semi-preparative column using water / acetonitrile as the mobile phase with a multi-step gradient method (condition a). The pure product was collected and vacuum dried at 30 °C for 2 days to afford a dark bluish green solid (6.5 mg) in 12% yield based on the amount of **3.4** used. ^{1}H NMR (d-DMF, 400 MHz): δ 9.35 (br, 6H, Ar-H), 8.23-8.22 (m, 6H, Ar-H), 7.61 (br, 2H, Ar-H), 4.96 (br, 2H, OCH_2), 4.60 (s, 3H, OCH_3), 4.49 (t, J = 4.7 Hz, 2H, OCH_2), 4.41 (s, 2H, CH), 4.37 (s, 2H, CH), 4.06 (t, J = 5.4 Hz, 2H, OCH_2), 3.97 (t, J = 5.4 Hz, 2H, OCH_2), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (d-DMF, 100 MHz): δ 154.08, 153.78, 153.65, 152.26, 151.07, 139.25, 139.05, 130.11, 129.90, 129.77, 123.37, 122.95, 117.09, 115.21 (Ar-C), 72.98, 71.21, 70.42, 69.39 (OCH_2), 57.49 (OCH_3), 54.27, 47.27 (CH). HRMS-ESI: *m/z*

1033.4076 $[M-K]^-$, calcd. for $[C_{41}H_{46}B_{18}CoN_8O_4Zn]^-$ 1033.4071. HPLC: t_R = 4.693 min. UV-vis (acetone): λ_{max} (log ε) 684 (5.26), 618 (4.49); UV-vis (DMSO): λ_{max} (log ε) 695 (5.20), 627 (4.50).

Pc Conjugate 3.9. Phthalonitrile (0.76 g, 6.0 mmol), anhydrous zinc acetate (90 mg, 0.5 mmol) and conjugated phthalonitrile **3.5** (38 mg, 0.05 mmol) were added into a 10 mL thick-wall Schlenk tube. The tube was dried by purge-and-refill with argon for three times. Then 0.5 mL freshly distilled quinoline was added and the solution was heated to 220 °C. After 1 hour, the reaction residue was cooled down to room temperature. The solid in the solution was filtered and washed completely with acetone and methanol. The dark green filtrate was concentrated to dryness. The crude product was purified on a Sephadex LH-20 column using acetone for elution. The pure conjugated Pc **3.9** was obtained by reverse phase HPLC on a Luna C_{18} semi-preparative column using water / acetonitrile as the mobile phase with a multi-step gradient method (condition c). The pure product was collected and vacuum dried at 30 °C for 2 days to afford a dark bluish green solid (10.0 mg) in 17% yield based on the amount of **3.5** used. ^{1}H NMR (d-DMF, 400 MHz): δ 9.44 (br, 6H, Ar-H), 8.25 (br, 6H, Ar-H), 7.76 (br, 2H, Ar-H), 5.00 (br, 4H, OCH_2), 4.51 – 4.47 (m, 4H, OCH_2), 4.38 (s, 2H, CH), 4.35 (s, 2H, CH), 4.11 (t, J = 5.0 Hz, 2H, OCH_2), 4.06 (t, J = 5.1 Hz, 2H, OCH_2), 3.96 (t, J = 5.3 Hz, 2H, OCH_2), 3.82 (t, J = 4.9 Hz, 2H, OCH_2), 3.65 (t, J = 4.8 Hz, 2H, OCH_2), 3.57 (br, 2H, OCH_2), 3.22 (s, 3H, OCH_3), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (d-DMF, 100 MHz): δ 154.32, 154.10, 153.95, 153.68, 153.65, 151.66, 151.55, 139.52, 139.14, 130.25, 129.98, 129.90, 128.15, 127.91, 127.74, 123.54, 123.11, 123.01, 117.35 (Ar-C), 73.02, 72.40, 71.54, 71.25, 71.20, 70.92, 70.86, 70.60, 69.40(OCH_2), 58.58 (OCH_3), 54.24, 47.26

(CH). HRMS-ESI: *m/z* 1165.4859 $[M-K]^-$, calcd. for $[C_{47}H_{58}B_{18}CoN_8O_7Zn]^-$ 1165.4862. HPLC: t_R = 4.523 min. UV-vis (DMSO): λ_{max} (log ε) 695 (5.19), 626 (4.47).

Pc Conjugate 3.10. Phthalonitrile (0.76 g, 6.0 mmol), anhydrous zinc acetate (90 mg, 0.5 mmol) and conjugated phthalonitrile **3.6** (50 mg, 0.05 mmol) were added into a 10 mL thick-wall Schlenk tube. The tube was dried by purge-and-refill with argon for three times. Then 0.5 mL freshly distilled quinoline was added and the solution was heated to 220 °C. After 1 hour, the reaction residue was cooled down to room temperature. The solid in the solution was filtered and washed completely with acetone and methanol. The dark green filtrate was concentrated to dryness. The crude product was purified on a Sephadex LH-20 column using acetone for elution. The pure conjugated phthalocyanine **3.10** was obtained by reverse phase HPLC on a Luna C_{18} semi-preparative column using water / acetonitrile as the mobile phase with a multi-step gradient method (condition c). The pure product was collected and vacuum dried at 30 °C for 2 days to afford a dark bluish green solid (11.3 mg) in 15% yield based on the amount of **3.6** used. ^{1}H NMR (d-DMF, 250 MHz): δ 9.55-9.45 (m, 6H, Ar-H), 8.34-8.26 (m, 6H, Ar-H), 7.81 (br, 2H, Ar-H), 5.03-4.99 (m, 4H, OCH_2), 4.54-4.50 (m, 4H, OCH_2), 4.39 (s, 4H, CH), 4.36 (s, 4H, CH), 4.08 (t, J = 5.2 Hz, 4H, OCH_2), 3.98 (t, J = 5.2 Hz, 4H, OCH_2), 3.00 – 1.50 (br, 34H, BH). ^{13}C NMR (d-DMF, 63 MHz): δ 154.26, 154.12, 153.98, 153.77, 151.57, 139.67, 139.21, 130.13, 129.79, 123.46, 123.03, 122.93, 117.12 (Ar-C), 72.98, 71.27, 70.49, 69.34 (OCH_2), 54.15, 47.24 (CH). HRMS-ESI: *m/z* 1430.7214 $[M-2K+H]^-$, calcd. for $[C_{48}H_{73}B_{36}Co_2N_8O_6Zn]^-$ 1430.7214. HPLC: t_R = 6.040 min. UV-vis (acetone): λ_{max} (log ε) 686 (5.36), 618 (4.62); UV-vis (DMSO): λ_{max} (log ε) 695 (5.12), 626 (4.41).

Phthalonitrile 3.11. 3-Nitrophthalonitrile (1.5 g, 8.7 mmol) and 3-hydroxypyridine (1.5 g, 15.8 mmol) were dissolved in dry DMF (30 mL). Potassium carbonate (20 g, 14.5 mmol) was added to the solution in five portions. The reaction was heated at 90 °C for 4 hours. After the reaction, the solution was cooled down to room temperature and poured to ice water (500 mL) to get precipitate. The crude product was further purified by alumina column with elution of methanol/DCM (5/95) to afford earth pink solid (1.4 g, 74%). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 8.54 – 8.48 (m, 2H, Ar-H), 7.70 – 7.44 (m, 4H, Ar-H), 7.15 – 7.12 (m, 1H, Ar-H). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 160.16, 151.10, 147.58, 142.71, 135.29, 128.30, 127.86, 125.10, 121.16, 117.67, 115.43, 112.91, 106.84 (Ar-C, CN). MS (MALDI-TOF) *m/z* 221.946 M^+, calcd. for $C_{13}H_7N_3O$ 221.059.

Phthalonitrile Conjugate 3.12. A mixture of phthalonitrile **3.11** (0.1 g, 0.45 mmol) in acetone (50 mL) were refluxed at 50 °C under argon. [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.2 g, 0.48 mmol) was added to the reaction solution in 3 portions. The reaction solution was heated for 1 day, then cooled to room temperature and evaporated to dry. The crude product was purified by silica gel chromatography using methanol/DCM 5: 95 for elution to get the title compound as a yellow solid (0.3 g, 94%). ^{1}H NMR (acetone-d_6, 250 MHz): δ 9.34 – 9.28 (m, 2H, Ar-H), 8.69 – 8.66 (m, 1H, Ar-H), 8.35 – 8.29 (m, 1H, Ar-H), 8.05 – 7.96 (m, 2H, Ar-H), 7.83 – 7.79 (m, 1H, Ar-H), 5.01 (t, J = 4.4 Hz, OCH_2), 4.13 – 4.06 (m, 4H, OCH_2), 3.94 (br, 2H, OCH_2), 3.64 (s, 4H, CH), 3.00 – 1.50 (br, 17H, BH). ^{13}C NMR (acetone-d_6, 63 MHz): δ 158.15, 155.06, 143.84, 138.80, 137.03, 131.24, 130.21, 124.39, 118.17, 115.76, 113.03, 108.84 (Ar-C, CN), 73.32, 69.75, 69.70, 63.08, 52.73, 47.35 (OCH_2, CH). HRMS-ESI: *m/z* 631.3981 $[M-H]^-$, calcd. for $[C_{21}H_{36}B_{18}CoN_3O_3]^-$ 631.3815.

Phthalonitrile Conjugate 3.13. A mixture of 4,5-bis(pyridin-3-yloxy)phthalonitrile **2.1** (0.1 g, 0.3 mmol) in acetone (50 mL) were refluxed at 50 °C under argon. [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.27g, 0.65 mmol) was added to the reaction solution in 3 portions. The reaction solution was followed by TLC and heated for 3 days, then cooled to room temperature and evaporate to dry. The crude product was purified by silica gel chromatography using methanol/ethyl acetate 5: 95 for elution to get a yellow solid (0.3 g, 85%). ^{1}H NMR (acetone-d_6, 300 MHz): δ 9.38 (s, 2H, Ar-H), 9.27 (d, J = 4.8 Hz, 2H, Ar-H), 8.63 – 8.59 (m, 2H, Ar-H), 8.32 – 8.27 (m, 2H, Ar-H), 8.21 (s, 2H, Ar-H), 4.99 (br, 4H, OCH_2), 4.10 (br, 4H, OCH_2), 4.04 (br, 4H, OCH_2), 3.92 (br, 4H, OCH_2), 3.66 (s, 8H, CH), 3.00 – 1.50 (br, 34H, BH). ^{13}C NMR (acetone-d_6, 75 MHz): δ 154.80, 149.91, 143.54, 138.39, 136.36, 130.21, 127.07, 115.09, 114.71 (Ar-C, CN), 73.35, 69.72, 69.63, 62.88, 52.51, 47.32 (OCH_2, CH). HRMS-ESI: *m/z* 1134.7528 $[M-2K+H]^-$, calcd. for 1134.7353 $[C_{34}H_{67}B_{36}Co_2N_4O_6]^-$.

Phthalonitrile 3.14. 3-Nitrophthalonitrile (1.5 g, 8.7 mmol) and 4-methoxyphenol (1.6 g, 12.9 mmol) were dissolved in dry DMF (30 mL). Potassium carbonate (20 g, 14.5 mmol) was added to the solution in five portions. The reaction was heated at 90 °C for 2 hours. After the reaction, the solution was cooled down to room temperature and poured to ice water (500 mL) to get precipitate. The crude product was further purified by alumina column with elution of DCM to afford white solid (1.8 g, 83%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.54 (t, J = 8.2 Hz, 1H, Ar-H), 7.39 (d, J = 7.6 Hz 1H, Ar-H), 7.02 – 6.90 (m, 5H, Ar-H), 3.80 (s, 3H, Ar-H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 161.53, 157.51, 146.70, 134.43, 126.47, 121.60, 119.69, 116.86, 115.34, 115.13, 112.78, 105.11 (Ar-C, CN), 55.59 (OCH_3). MS (MALDI-TOF) *m/z* 250.934 M^+, calcd. for $C_{15}H_{10}N_2O_2$ 250.074.

Phthalonitrile 3.15. Method A. Hydroquinone (1.0 g, 9 mmol) and potassium carbonate (1.6 g, 11.6 mmol) were dissolved in anhydrous DMF (30 mL) under argon flow. The solution was heated to 50 ºC. 3-Nitrophthalonitrile (1 g, 5.8 mmol) was dissolved in DMF (2 mL) and the solution was injected into the solution through syringe. The reaction solution was remained at 50 ºC for two hours and stirred at room temperature for two days. After the reaction the solvent was evaporated to dry. 1 N hydrochloride solution (30 mL) was added to the residue and the precipitate was filtered and washed with water. It was dissolved in acetone (50 mL) and dried over anhydrous sodium sulfate. The crude product was purified by chromatography on silica column with elution of DCM/methanol (95/5) to afford white solid (0.3 g, 22%). **Method B**. Procedure was silimar to that described as method B for **3.19**, 40% yield was obtained. ^{1}H NMR (acetone-d_6, 250 MHz): δ 8.75 (br, 1H, OH), 7.79 (t, J = 4.3 Hz, 1H, Ar-H), 7.68 – 7.65 (m, 1H, Ar-H), 7.20 – 7.16 (m, 1H, Ar-H), 7.10 – 7.07 (m, 2H, Ar-H), 6.96 – 6.92 (m, 2H, Ar-H). ^{13}C NMR (acetone-d_6, 63 MHz): δ 162.59, 156.44, 147.18, 136.16, 127.83, 122.64, 121.14, 117.60, 117.38, 116.22, 113.87, 105.63 (Ar-C, CN). HRMS-ESI: *m/z* 237.0655 $[M+H]^+$, calcd. for $[C_{14}H_9N_2O_2]^+$ 237.0658.

Phthalonitrile Conjugate 3.16. A mixture of phthalonitrile **3.15** (0.1 g, 0.41 mmol) and potassium carbonate (61.5 mg, 0.46 mmol) in acetone (50 mL) were refluxed at 50 °C under argon. After 20 min, [3, 3′-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1′,2′-$C_2B_9H_{10}$)] (0.18 g, 0.43 mmol) was added to the reaction solution in 3 portions. The reaction solution was heated for 1 day, then cooled to room temperature and evaporated to dry. The crude product was purified by silica gel chromatography using methanol/DCM 5: 95 for elution to get a yellow solid (0.24 g, 94%). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.81 – 7.77 (m, 1H, Ar-H), 7.68 – 7.66 (m, 1H, Ar-H), 7.22 – 7.16 (m, 3H, Ar-H), 7.09 – 7.07

(m, 2H, Ar-H), 4.25 (br, 4H, OCH_2), 4.16 (t, J = 4.8 Hz, 2H, OCH_2), 3.82 (t, J = 4.8 Hz, 2H, OCH_2), 3.59 (s, 4H, CH), 3.00 – 1.50 (br, 34H, BH). ^{13}C NMR (acetone-d_6, 100 MHz): δ 162.39, 157.97, 148.14, 136.21, 127.94, 122.49, 121.36, 117.34, 117.13, 116.20, 113.83, 105.72 (Ar-C, CN), 72.85, 70.12, 69.27, 68.98 (OCH_2), 55.15, 47.22 (CH). HRMS-ESI: *m/z* 646.3819 $[M-K]^-$, calcd. for 646.3812 $[C_{22}H_{36}B_{18}CoN_2O_4]^-$.

Phthalonitrile 3.17. 3, 6-Dihydroxyphthalonitrile (0.5 g, 2.5 mmol) and 4-benzyloxyphenol (1.1 g, 5.5 mmol) were dissolved in DMF (15 mL). Potassium carbonate (4.8 g, 34.8 mmol) was added into the solution in five portions and the reaction solution was heated to 80 °C. After 3 hours, the reaction solution was cooled to room temperature and the solution was poured into ice water and the solid was filtered. The crude product was purified with silica column eluted with DCM/hexane (4/1) to afford the white solid (0.65 g, 48%). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 7.46 – 7.40 (m, 10H, Ar-H), 7.13 (s, 2H, Ar-H), 7.08 (br, 8H, Ar-H), 5.11 (s, 4H, OCH_2). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 157.14, 152.80, 147.81, 137.20, 128.97, 128.48, 127.97, 121.82, 121.17, 116.90, 115.74, 110.17 (Ar-C, CN), 70.95 (OCH_2). MS (MALDI-TOF) *m/z* 525.697 $[M+H]^+$, calcd. for $C_{34}H_{25}N_2O_4$ 525.181.

Phthalonitrile 3.18. 4,5–Dichlorophthalonitrile (1 g, 5.1 mmol) and 4-methoxyphenol (2.5 g, 20.1 mmol) were dissolved in dry DMF (30 mL). The reaction solution was heated to 80 °C. Potassium carbonate (7.4 g, 53.6 mmol) was added into the solution in six portions every five minutes. After three hours, the reaction solution was cooled to room temperature and the solution was poured into ice water (500 mL) and the solid was filtered. The crude product was purified with alumina column eluted with DCM/hexane (3/1) to afford the white floppy solid (1.1 g, 58%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.03 – 6.97 (m, 10H, Ar-H), 3.82 (s, 6H, OCH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ

157.99, 152.84, 147.50, 121.82, 120.96, 115.89, 115.75, 110.04 (Ar-C, CN), 56.07 (OCH_3). MS (MALDI-TOF) *m/z* 371.967 M^+, calcd. for $C_{22}H_{16}N_2O_4$ 372.110.

Phthalonitrile 3.19. Method A. Phthalonitrile **3.17** (0.2 g, 0.38 mmol) and 10% palladium on charcoal (0.02 g) was put in a 100 mL three-neck Schlenk flask and the flask was degassed for three times. DCM (25 mL) was injected into the flask and the hydrogen filled balloon was connected to the flask. The reaction solution was stirred at room temperature for 2 days. After the reaction, the solution was filtered through a celite cake under vacuum. The solution was evaporated to dry and purified by chromatography with silica gel eluted with DCM/methanol (95/5) to afford white solid (0.06 g, 46%). **Method B.** Phthalonitrile **3.18** (1.5 g, 4 mmol) was dissolved in freshly distilled DCM (50 mL). The reaction solution was stirred at -80 °C. Boron tribromide (0.8 mL, 8.5 mmol) in DCM (20 mL) was added dropwise in 10 min through an additional funnel. The reaction solution was kept at -80 °C for one hour and continued to stir at room temperature for 24 hours. The reaction solution was poured into 200 mL ice water slowly. The precipitate was dissolved in 300 mL ethyl acetate and extracted with 100 mL 2N sodium hydroxide solution. It is neutralized with 1 N hydrochloride solution and extracted with 300 mL ether. The organic layer was dried over anhydrous sodium sulfate. The crude product was purified by chromatography on silica column with elution of methanol/DCM (10/90) to afford yellow solid (0.4 g, 29%). **Method C**. Procedure was silimar to that described as method A for **3.15**, 15% yield was obtained. ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.13 (s, 2H, Ar-H), 7.02 (d, J = 8.9 Hz, 4H, Ar-H), 6.91 (d, J = 8.9 Hz, 4H, Ar-H). ^{13}C NMR (acetone-d_6, 63 MHz): δ 168.59, 155.50, 154.57, 148.69, 128.37, 121.75, 117.34, 112.29 (Ar-C, CN).

Phthalonitrile 3.20. 3 - Nitrophthalonitrile (1 g, 5.8 mmol) was dissolved in DMF (15 mL). 4-Hydroxy-benzyl alcohol (1.1 mg, 8.9 mmol) and potassium carbonate (5 g, 36 mmol) were added into the solution. The reaction solution stirred at room temperature for 15 hours. The reaction solution was concentrated. The residue was poured into mild acidic hydrochloric solution (pH = 5, 300 mL). The solid was filtered and washed with water. The crude product was purified with alumina column eluted with ethyl acetate/hexane (10/1) to afford the white floppy solid (0.4 g, 28%).^{1}H NMR (d-acetone, 400 MHz): δ 7.85 – 7.81 (m, 1H, Ar-H), 7.73 – 7.71 (m, 1H, Ar-H), 7.50 (d, 2H, J = 8.6 Hz, Ar-H), 7.27 – 7.24 (m, 1H, Ar-H), 7.20 (d, 2H, J = 8.6 Hz, Ar-H), 4.67 (s, 2H, CH_2), 4.33 (br, 1H, OH). ^{13}C NMR (d-acetone, 100 MHz): δ 161.67, 154.04, 141.33, 136.24, 129.46, 128.47, 122.21, 120.80, 117.60, 116.17, 113.76, 106.61 (Ar-C, CN), 63.92 (CH_2). HRMS-ESI: *m/z* 233.0708 $[M\text{-}OH]^+$, 273.0634 $[M+Na]^+$, calcd. for $C_{15}H_9N_2O$ 233.0709, $C_{15}H_{10}N_2O_2Na$ 273.0634.

Phthalonitrile 3.21. 3, 6-Dihydroxyphthalonitrile (2 g, 12.5 mmol) and 1-(bromomethyl)-3-methoxybenzene (5.2 mL, 36 mmol) were dissolved in DMF (60 mL). Potassium carbonate (7 g, 51 mmol) was added into the solution in five portions and the reaction solution was heated to 60 °C. After ten hours, the reaction solution was cooled to room temperature and the solution was poured into ice water and the solid was filtered. The crude product was purified with alumina column eluted with DCM/hexane (3/2) to afford the white floppy solid (4.78 g, 98%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.34 – 7.29 (m, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 7.01 – 6.98 (m, 2H, Ar-H), 6.90 – 6.87 (m, 1H, Ar-H), 5.17 (s, 2H, OCH_2), 3.81 (s, 3H, OCH_3). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 160.44, 155.25, 137.11, 130.24, 119.65, 114.31, 113.49, 113.00, 106.03 (Ar-C, CN), 72.00 (OCH_2), 55.62 (OCH_3).

Phthalonitrile 3.22. 3-nitrophthalonitrile (2 g, 11.6 mmol) and N-Boc-4-aminophenol (3.6 g, 17 mmol) were dissolved in DMF (30 mL). Potassium carbonate (25 g, 0.18 mol) was added into the solution in five portions and the reaction solution was heated to 80 °C. After 2 hours, the reaction solution was cooled to room temperature and the solution was poured into ice water and the solid was filtered. The crude product was purified with alumina column eluted with DCM to afford the white solid (3.1 g, 80%).^{1}H NMR (acetone-d_6, 250 MHz): δ 8.58 (br, 1H, NH), 7.80 (t, J = 8.2 Hz, 1H, Ar-H), 7.70 - 7.66 (m, 3H, Ar-H), 7.25 – 7.14 (m, 3H, Ar-H), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (acetone-d_6, 63 MHz): δ 162.06, 153.67, 149.42, 138.63, 136.15, 128.07, 121.68, 121.52, 120.68, 117.39, 116.15, 113.77, 105.94 (Ar-C, CN), 80.21, 28.42 ($C(CH_3)_3$). HRMS-ESI: *m/z* 336.1340 $[M+H]^+$, calcd. for $[C_{19}H_{18}N_3O_3]^+$ 336.1342; 353.1604 $[M+H_2O]^+$, calcd. for $[C_{19}H_{19}N_3O_4]^+$ 353.1376; 358.1163 $[M+Na]^+$, calcd. for $[C_{19}H_{17}N_3O_3Na]^+$ 358.1168.

Phthalonitrile 3.23. Method A. Phthalonitrile **3.22** (2 g, 6.0 mmol) was dissolved in mixed solvents of DCM (50 mL) and TFA (10 mL). The reaction solution was stirred at room temperature for three hours. After the reaction the solvent was evaporated to dry. 1 N sodium hydroxide solution (30 mL) was added to the residue and white precipitate was out. The solid was filtered and dissolved in ethyl acetate (200 mL). The organic solution was washed with 1 N sodium hydroxide solution (20 mL, × 1) and brine (20 mL, × 2) and dried over anhydrous sodium sulfate. The crude product was purified by chromatography on alumina column with elution of DCM/methanol (98/2) to afford white solid (1.3 g, 90%). **Method B**. Procedure was silimar to that described as for **3.24**, 75% yield was obtained. ^{1}H NMR (acetone-d_6, 250 MHz): δ 7.78 (t, J = 8.2 Hz, 1H, Ar-H), 7.63 (d, J = 7.6 Hz, 1H, Ar-H), 7.16 (d, J = 8.6 Hz, 1H, Ar-H), 6.94 (d, J = 8.8 Hz, 2H, Ar-H), 6.76 (d, J = 8.8 Hz, 2H, Ar-H), 4.81 (br, 2H, NH_2). ^{13}C NMR (acetone-d_6,

63 MHz): δ 163.08, 147.86, 145.09, 136.08, 127.50, 122.26, 120.90, 117.28, 116.28, 116.20, 114.00, 105.26 (Ar-C, CN). HRMS-ESI: *m/z* 236.0813 $[M+H]^+$, calcd. for $[C_{14}H_{10}N_3O]^+$ 236.0818.

Phthalonitrile 3.24. 4,5–Dichlorophthalonitrile (0.5 g, 2.5 mmol) and 4-aminophenol (0.56 g, 5.1 mmol) were dissolved in anhydrous DMF (10 mL) and heated to 60 °C. Potassium carbonate (2.3 g, 16.7 mmol) was added into the solution in six portions every five minutes. After one day, the reaction solution was cooled to room temperature and the solution was poured into ice water (500 mL) and the solid was filtered. The crude product was purified with alumina column eluted with DCM/hexane (5/1) and methanol/DCM (2/98) to afford the yellow solid (0.57 g, 66%). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 7.08 (s, 2H, Ar-H), 6.92 (d, J = 8.8 Hz, 4H, Ar-H), 6.74 (d, J = 8.8 Hz, 4H, Ar-H), 3.83 (br, 4H, NH_2). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 153.19, 145.65, 145.53, 121.91, 120.44, 116.62, 116.02, 109.58 (Ar-C, CN). HRMS-ESI: *m/z* 343.1189 $[M+H]^+$, calcd. for $[C_{20}H_{15}N_4O_2]^+$ 343.1189.

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CHAPTER 4

SYNTHESES OF A SERIES OF HYDROXY-SUBSTITUTED ZINC PHTHALOCYANINES

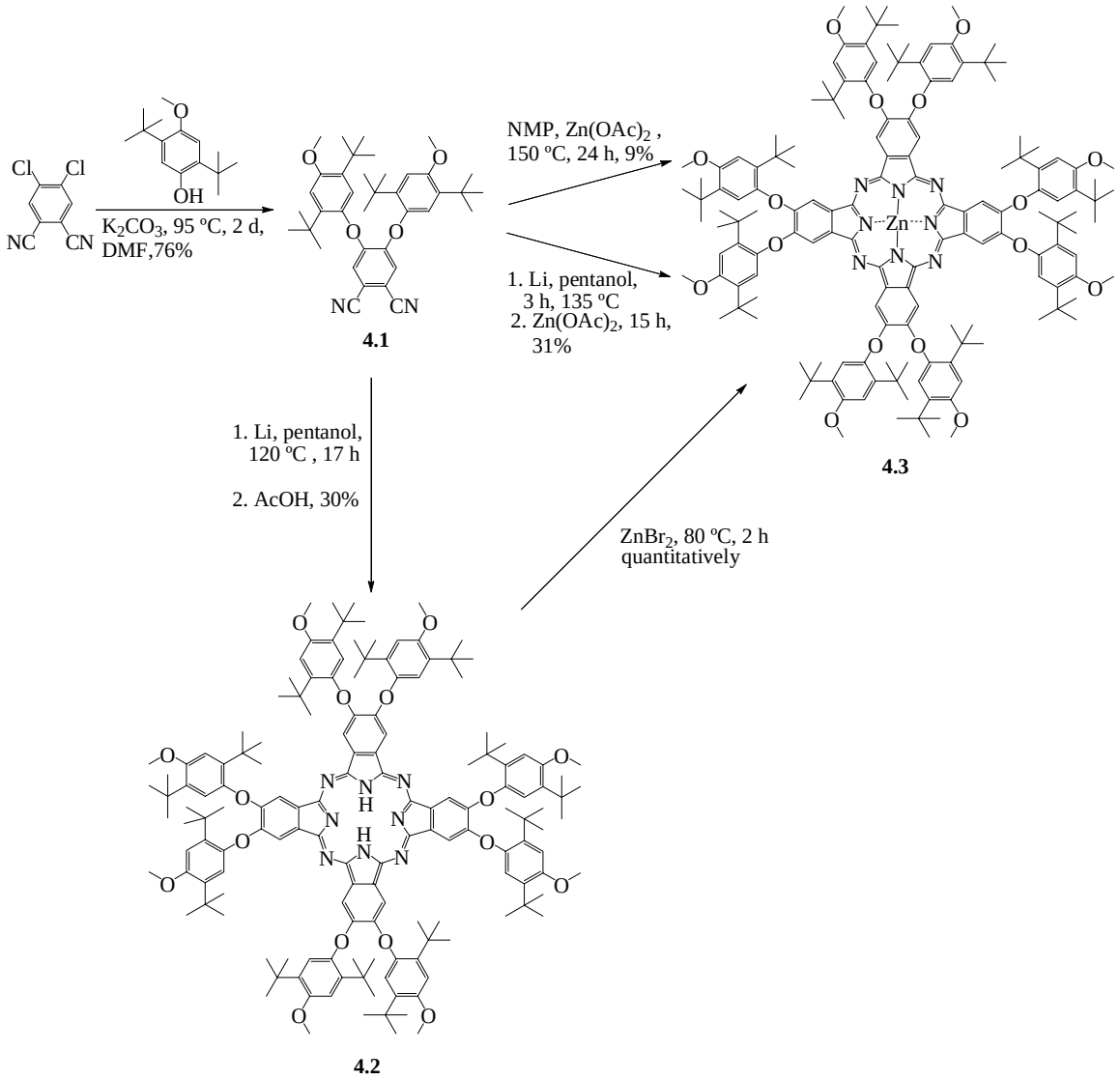
4.1 Background

Pcs are well-known of their high tendency for aggregation in organic solvents and aqueous solution. As a result, they can be modified by appropriate substituents[1, 2] in order to diminish their tendency for aggregation in solution. Some hydrophilic groups such as sulfonic acid, carboxylic acid and hydroxyl groups[3-7] have been introduced to the Pc macrocycles in order to increase the amphiphilicity of Pc and promote the permeability of cell membranes. Meso-tetrahydroxyphenyl chlorin (mTHPC) is a second-generation PDT photosensitizer which shows higher photosensitizing efficiency than Photofrin®, an FDA-approved PDT photosensitizer. mTHPC has been applied in the treatment of early prostate cancer and is currently undergoing Phase II trials.[2, 8-11] Leznoff and van Lier reported that hydroxyl-substituted Pcs were also potential PDT agents in 1998.[12] In this Chapter, we report the syntheses and characterization of octa, tetra and dihydroxy-substituted zinc Pcs.

4.2 Synthesis of Octahydroxy-substituted Zinc Phthalocyanines

Octahydroxy-substituted zinc Pc can be synthesized using two strategies. The first synthetic strategy is shown in Scheme 4.1. 4,5-Di-(2,5-di-tert-butyl-4-methoxy)-phthalonitrile **4.1** was synthesized using a previously published procedure[13] involving heating 4,5-dichlorophthalonitrile and 2,5-di-tert-butyl-4-methoxyphenol in dry DMF in the presence of potassium carbonate, but using a longer reaction time 40 h instead of 3 h. The reaction was followed by ^{1}H NMR until complete disappearance of the mono-

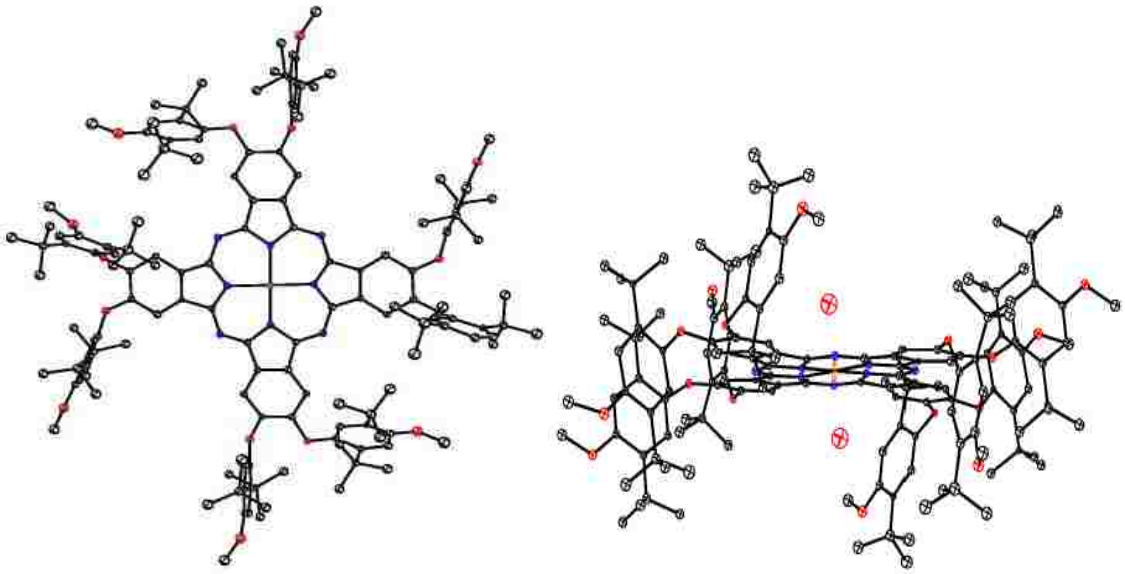
substituted phthalonitrile which is indicated by the missing of its characteristic chemical shift at 7.899 ppm.



Scheme 4.1. Synthesis of octa(4-methoxyphenyl)-substituted Pcs.

Two different methods were investigated for the cyclotetramerization reaction of phthalonitrile **4.1** (Scheme 4.1). The method using NMP as a solvent was investigated first.[13, 14] The precursor **4.1** was dissolved in dry NMP, excess of anhydrous zinc acetate was added and the reaction solution was heated to 150 ºC under argon for 1 day. The solid was filtered and purified by chromatography on silica gel column affording Pc **4.3**

in 9% yield. In the second method, precursor **4.1** was treated with lithium in dry pentanol at 135 ºC. It was refluxed for 3 hours, then zinc acetate was added to the solution and it was refluxed for another 15 hours. The solid was washed with mixed solvents of methanol and water 3 times after the removal of pentanol. Then it was extracted with hexane and further purified by silica gel column chromatography, using hexane/DCM (2:1) for elution. The yield of this reaction was increased to 31% after purification. The free-base Pc **4.2** was isolated in 30% yield by work up with acetic acid after the cyclotetramerization with lithium in dry pentanol and the zinc complex **4.3** was obtained in quantitative yield upon metallation of Pc **4.2** using $ZnBr_2$ in DMF.

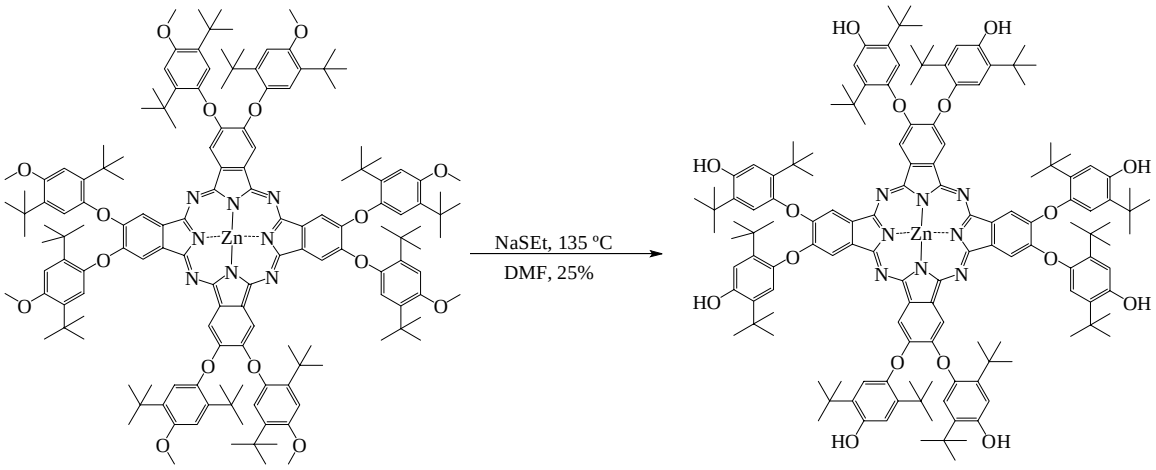


(a) **(b)**

Figure 4.1. (a) Top view of single crystal structure of Pc **4.3**; (b) side view of single crystal structure of Pc **4.3**.

The zinc complex **4.3** is very soluble in many organic solvents such as DCM, acetone, THF, hexane while slightly soluble in methanol. A suitable crystal for X-ray analysis was obtained by slow diffusion of methanol into chloroform. Figure 4.1 shows

the structure of Pc **4.3**. From the top view, we can observe that the peripheral phenyl rings are perpendicular to the plane of the Pc macrocycle to minimize steric hindrance. From the side view, we can observe that the macrocycle core is planar with zinc metal occupying the inner core of the Pc. The zinc metal may coordinate with one water molecule, which may come from the solvents used for purification. The bulky tert-butyl groups might minimize the aggregation of this compound in solution which probably explains the large extinction coefficient of 3.0×10^5 ($L.mol^{-1}.cm^{-1}$) observed for this Pc at 678.45 nm in acetone.

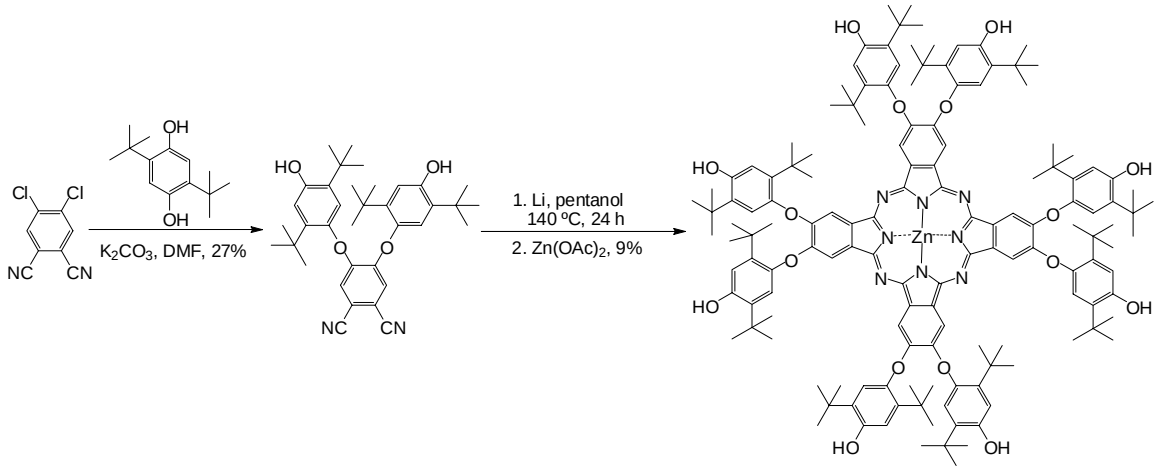


4.3 **4.5**

Scheme 4.2. Synthesis of octahydroxy-substituted zinc Pc.

Various methods including BBr_3,[15, 16] $BBr_3 \cdot SMe_2$,[17] $Py \cdot HCl$[18] and TMSI[19, 20] were investigated for the demethylation reaction. Unfortunately, none of these methods led to the desired product, Pc **4.5**, in reasonable yield. Boron tribromide as a Lewis acid was investigated for the deprotection of the methoxyl groups in dry DCM at -78 ºC in an argon atmosphere.[15, 16] The butyl groups at the phenyl rings were found to be cleaved under these acidic conditions, as indicated by the MALDI-TOF mass spectrum. Although the product could be isolated by column chromatography followed by preparative TLC,

only about 1% yield was obtained. Boron tribromide dimethylsulfide complex[17] was also tried under the same condition used with boron tribromide, but no desired product was observed, as indicated by MALDI-TOF mass spectrometry after 2 days. Other methods, using pyridine hydrochloride[18] and iodotrimethylsilane[19, 20] for the deprotection of the methoxyl groups didn't work here either. Finally, sodium ethanethiolate was used to do the demethylation,[21, 22] as shown in Scheme 4.2. A mixture of Pc **4.3** and excess sodium ethanethiolate was heated in dry DMF at 135 ºC for 1 day under an argon atmosphere. The reaction was followed by MALDI-TOF mass spectrometry. After the reaction, the solution was poured into water and extracted with ethyl acetate to obtain the crude Pc **4.5** product. Pure Pc **4.5** was obtained after purification with Sephadex LH-20 and HPLC using methanol as the isocratic solvent system. However, the yield was only 25% and partial debenzylation as a side reaction was observed to occur under these conditions.

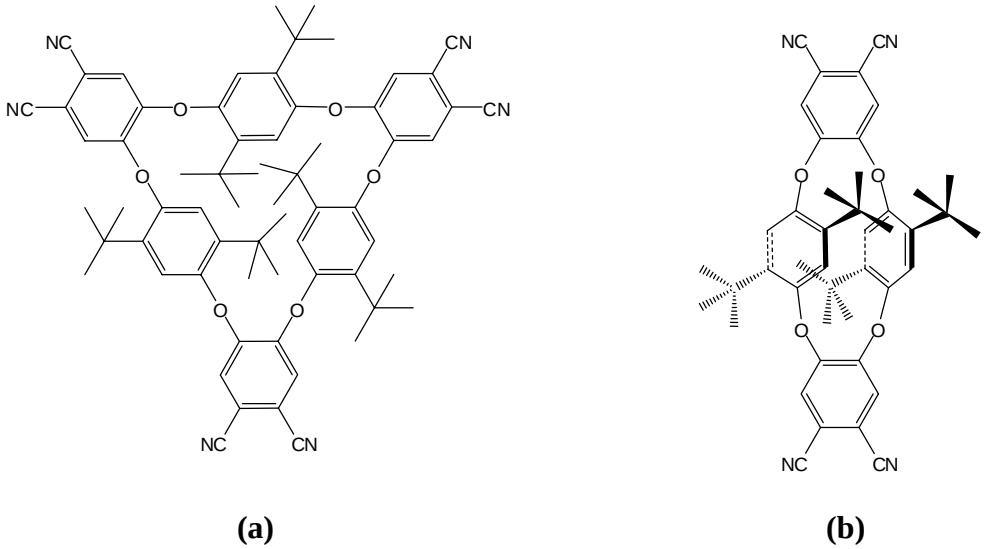


4.4 **4.5**

Scheme 4.3. Synthesis of octahydroxy-substituted zinc Pc.

Therefore, the first strategy to synthesize octahydroxy-substituted zinc Pc involved three steps and afforded the target product in 5% overall yield. In order to avoid

the troublesome demethylation step, I investigated another methodology, as shown in Scheme 4.3. The synthesis started with the reaction of 2,5-di-tert-butyl-hydroquinone and 4, 5-dichlorophthalonitrile (Scheme 4.3). 4,5-Bis (2,5-di-tert-butyl-4-hydroxyphenoxy)-phthalonitrile **4.4** was obtained in 27% yield. In this reaction, no side products of trimer or dimer were observed (Figure 4.2). It is probably due to the large steric hindrance of the two butyl groups at the hydroquinone moiety. The following macrocyclization reation using lithium metal afforded the target Pc **4.5** in 9% yield. This two-step synthesis has an overall yield of 2% which is similar to that of the first strategy investigated, but involves one less step and can be completed in a shorter time period.



(a) **(b)**

Figure 4.2. Possible side products of phthalonitrile **4.4**: (a) trimer and (b) dimer.

The octahydroxy-substituted zinc Pc **4.5** is soluble in polar solvents such as acetone, methanol, acetonitrile, DMF and DMSO. It is also soluble in some nonpolar solvents such as DCM and THF because of the presence of sixteen hydrophobic tert-butyl groups at the Pc's periphery. Figure 4.3 shows the ^{1}H NMR of Pc **4.5** in d-acetone at 250 MHz. The peak (singlet) at 8.8 ppm is due to the protons at the Pc's backbone and the

peaks (doublet) at 7.06 ppm and 7.03 ppm are due to the protons on the phenyl rings at the periphery of the Pc.

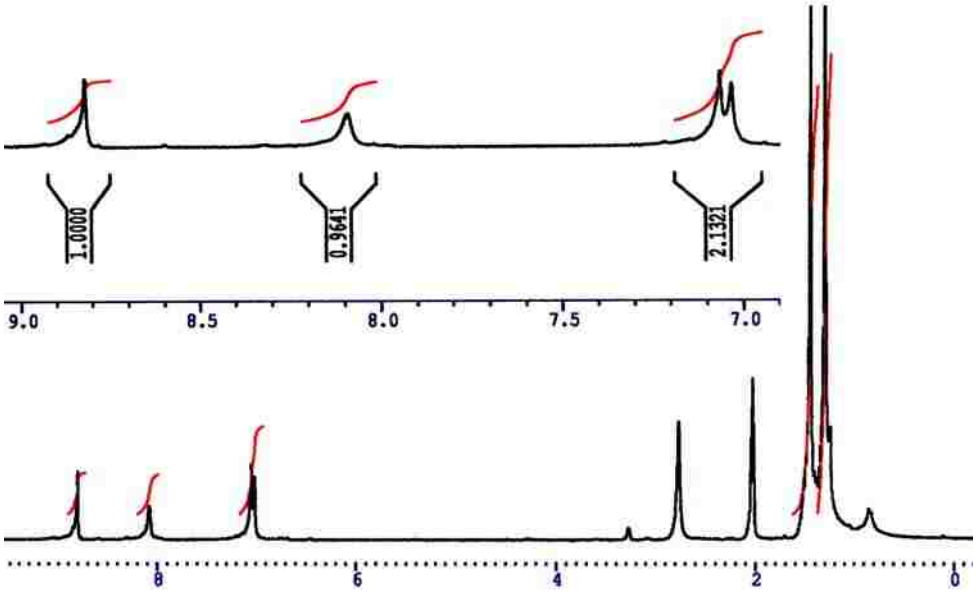


Figure 4.3. ^{1}H NMR of Pc **4.5** in d-acetone at 250 MHz.

The broad peak at 8.1 ppm is due to the hydroxyl groups on the phenyl rings. The upfield peaks at 1.5 ppm and 1.3 ppm are due to two sets of butyl groups attached to the phenyl rings. Pc **4.5** has a strong Q absorption peak in its UV-vis spectrum with an extinction coefficient of 1.1×10^{5} (L.mol^{-1}.cm^{-1}) at 678.7 nm in acetone (Figure 4.4).

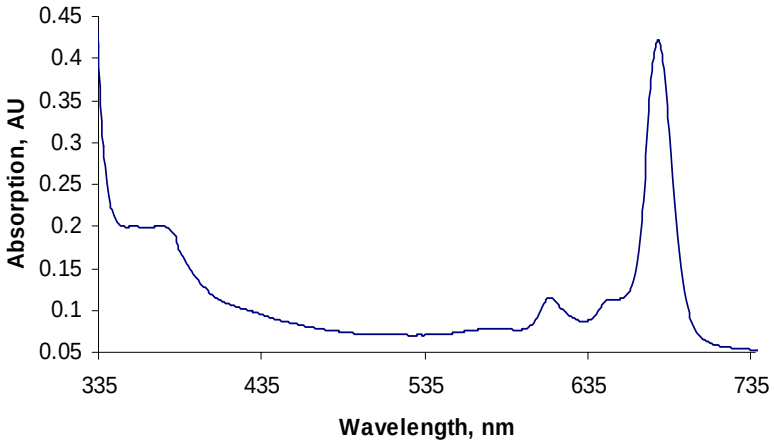
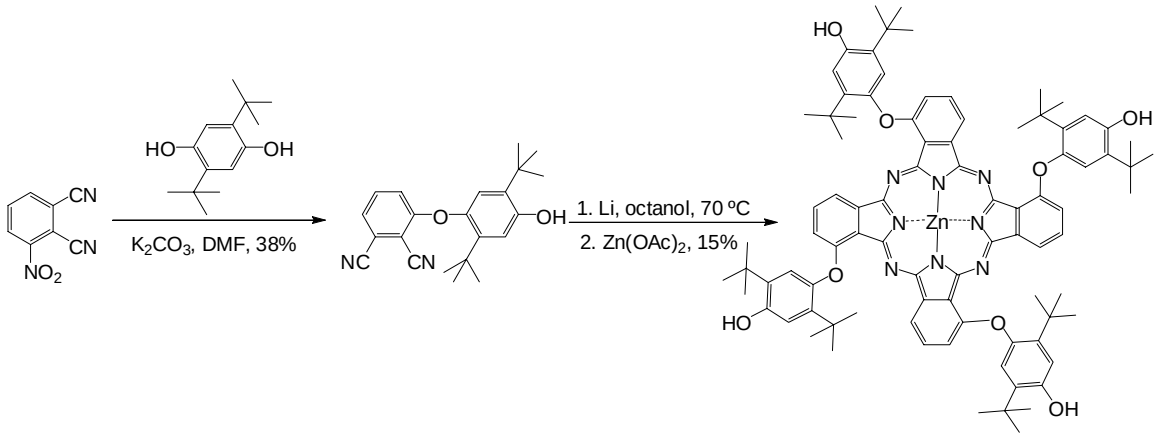


Figure 4.4. Absorption spectrum of Pc **4.5** in acetone at 2 μM.

4.3 Synthesis of Tetrahydroxy-Substituted Zinc Phthalocyanines

3-Substituted phthalonitrile **4.6** was synthesized from 3-nitrophthalonitrile and 2,5-di-ertbutylhydroquinone in the presence of potassium carbonate in 38% yield (Scheme 4.7). The single crystal structure of phthalonitrile **4.6** is shown in Figure 4.7. The yield is unexpectedly low because of a side reaction leading to the dimer species **4.7**



4.6 **4.8**

Scheme 4.7. Synthesis of Pc **4.8**.

(Figure 4.8) in 46% yield. Figure 4.9 shows the two independent molecules in the crystal structure. This dimeric side product is a good starting material to synthesize Pc-dimer species.

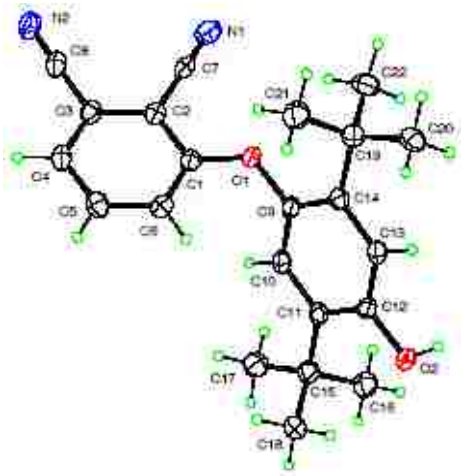


Figure 4.7. Single crystal X-ray structure of phthalonitrile **4.6**.

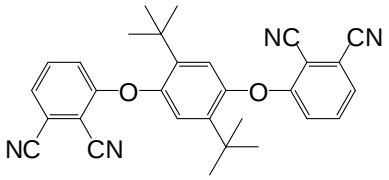


Figure 4.8. Molecular structure of dimer **4.7**

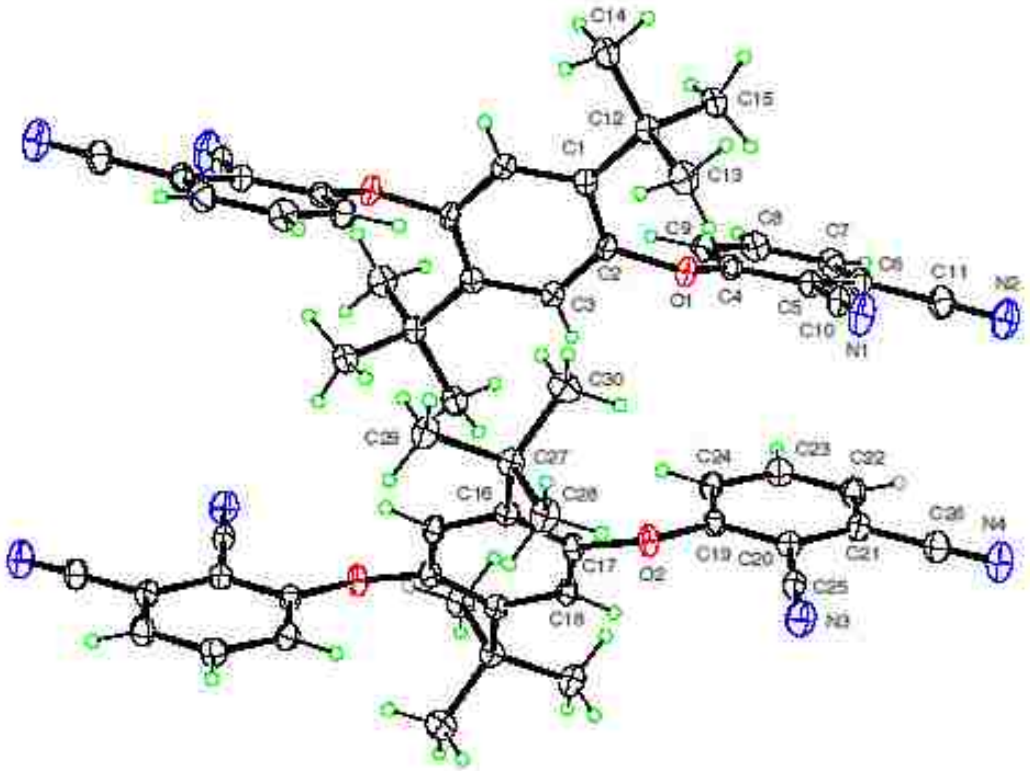
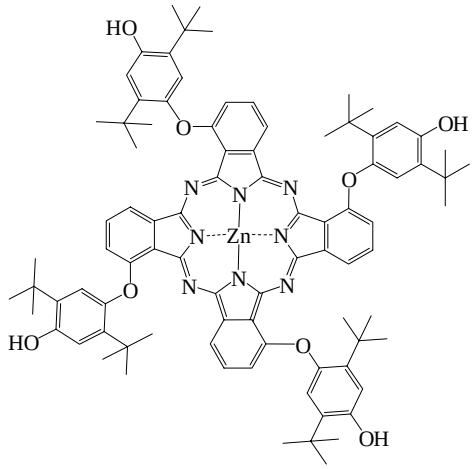
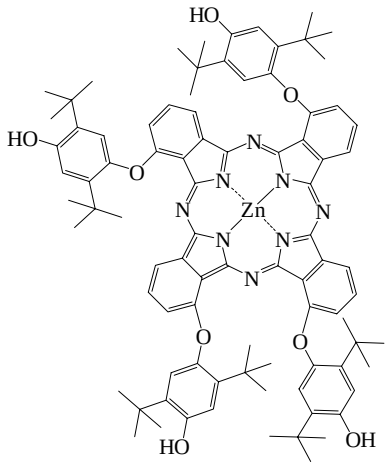


Figure 4.9. Single crystal X-ray structure of dimer **4.7**.

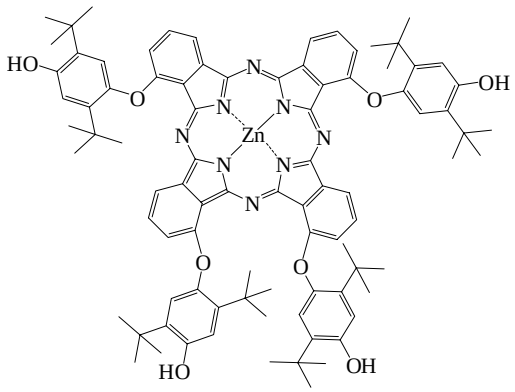
Macrocyclization of monosubstituted phthalonitrile can result in a mixture of four constitutional isomers with C_{4h}, C_s, C_{2v}, D_{2h} molecular symmetry (Figure 4.10). The separation has been done by Hanack and his coworker using high pressure liquid chromatography.[23, 24] They stated that the isomer distribution of tetra-α-substituted metal Pc depends on the nature of the substituent, reaction condition and metal center.[25] The first trial using lithium in pentanol at 140 ºC leads to all possible isomers. However, only C_{4h} as the major isomer can be collected after chromatography purification. The method



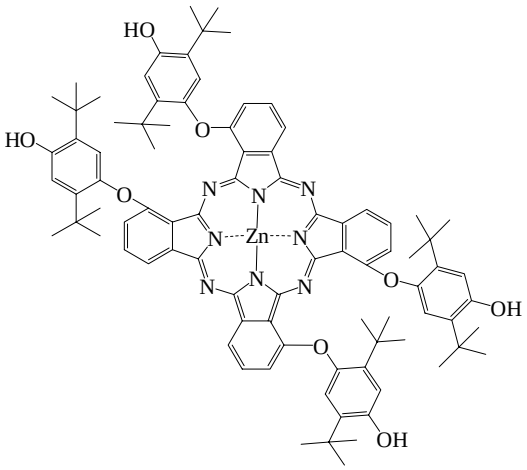
C_{4h}



Cs



C_{2v}



D_{2h}

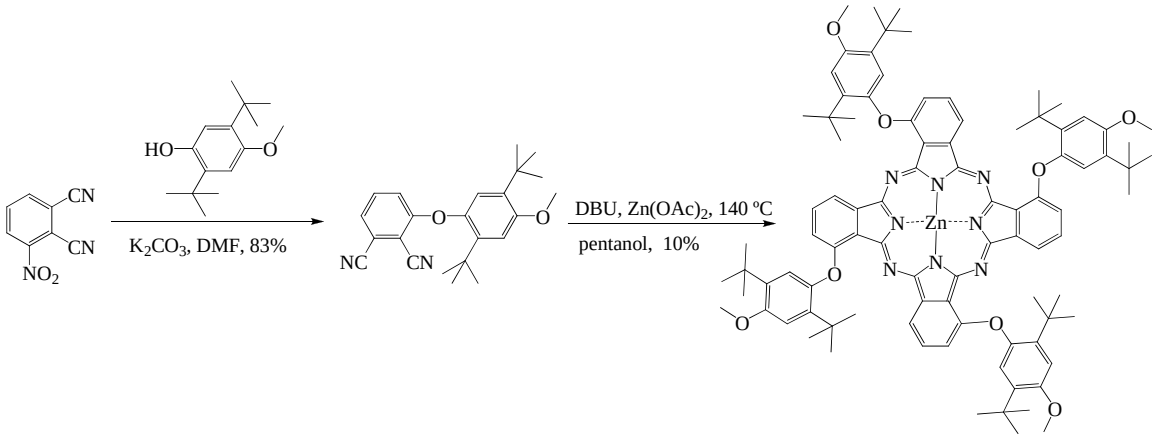
Figure 4.10. Four possible constitutional isomers for tetrahydroxy-substituted Pc.

to decrease the reaction temperature and increase the reaction time can favor the production of C_{4h} isomer when the bulky substituent is at the α position.[26] The second trial using lithium in octanol at 70 ºC for 24 hours led to cleaner products and less isomers. Two green bands were observed on the preparative alumina TLC plate, but only the more polar band as the major product was able to be collected and characterized.

From the spectrum of ^{1}H NMR in deuterated DMF, Pc **4.8** with C_{4h} symmetry has the same splitting pattern of the Pc core protons in the range of 7–9 ppm as what has been

reported for a different C_{4h} Pc.[2, 27] The broad peak downfield at 9.6 ppm is attributed to the hydroxyl group, which is consistent with the chemical shifts of the hydroxyl groups in Pc **4.13**. The peak at 7.3 ppm is due to the aromatic protons on the substituted phenyl group.

Tetrasubstituted Pc **4.10** containing four MeO groups was synthesized using the same strategy (Scheme 4.8). The macrocyclization reaction took place at 140 ºC in pentanol producing mixed isomers. The isomer with C_{4h} symmetry was isolated. The same pattern on the ^{1}H NMR spectrum in the range of 7–9 ppm in deuterated DCM was observed, except that the disappearance of the OH peak at 9.6 ppm and the overlapping of one proton of the substituted phenyl ring and one proton on the macrocycle core at 7.40 ppm.

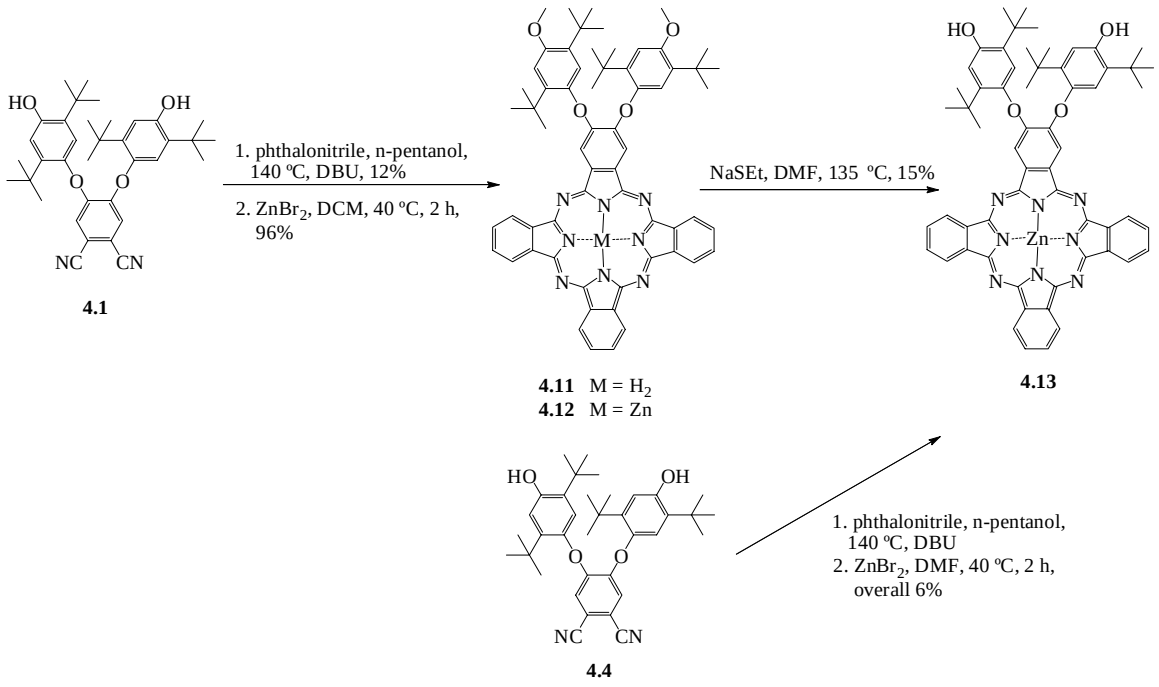


4.9 **4.10**

Scheme 4.8. Synthesis of Pc **4.10**.

4.4 Synthesis of Dihydroxy-Substituted Zinc Phthalocyanines

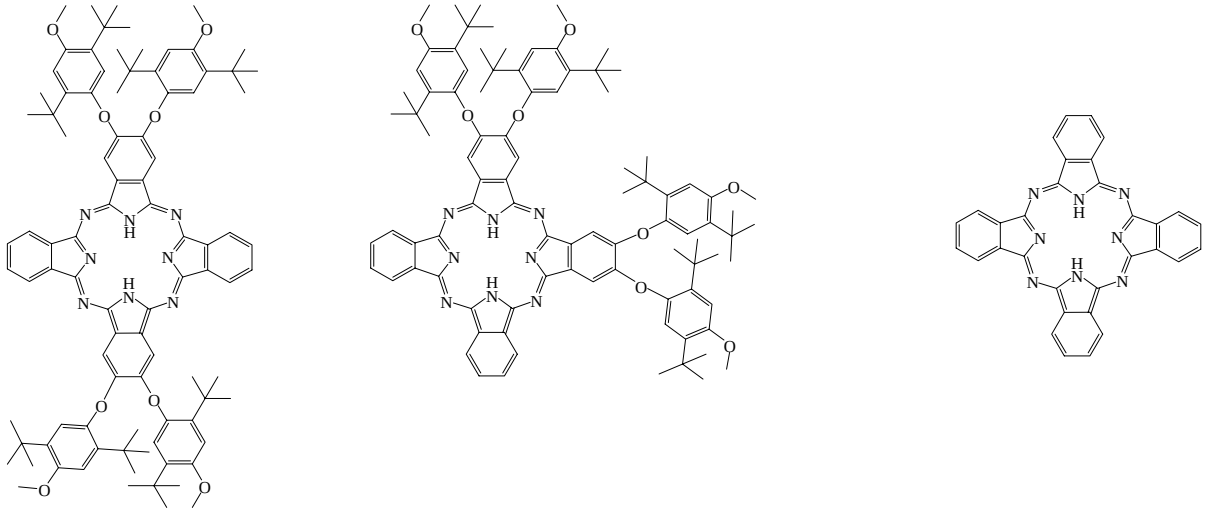
The A_3B-type (A phthalonitrile; B **4.1**) free-base Pc **4.11** was synthesized by the method of statistical condensation using a small amount of DBU as the catalyst in dry n-pentanol (Scheme 4.4). With the phthalonitrile ratio of 20:1 (A/B), the formation of A_4,



Scheme 4.4. Synthesis of dihydroxy-substituted zinc Pc.

A_3B and A_2B_2 Pcs (Figure 4.5) were observed after the reaction. No AB_3 isomer was produced from the analysis of the MALDI-TOF mass spectrum of the reaction mixture. Since A_4-type Pc is not soluble in any solvent, it can be easily removed by filtration after the reaction. The A_3B-type Pc as the major product was isolated by chromatography on a short silica gel column. Figure 4.6 (a) shows that A_3B (982) and A_2B_2 (1450) Pcs were both formed when the phthalonitrile ratio was 20:1 (A:B) in the cyclotetramerization reaction. When the phthalonitrile ratio was increased to 40:1 (A:B), the A_2B_2-type Pc was not produced, as indicated by MALDI-TOF mass spectrometry, as shown in Figure 4.6 (b). Under these conditions, Pc **4.11** was isolated in 12% yield.

The free-base Pc **4.11** was soluble in $CHCl_3$, CH_2Cl_2 and THF, while not soluble in polar solvents such as acetone. The following step of insertion of zinc metal into the Pc



A_2B_2 A_4

Figure 4.5. Structures of A_2B_2- and A_4- type Pcs.

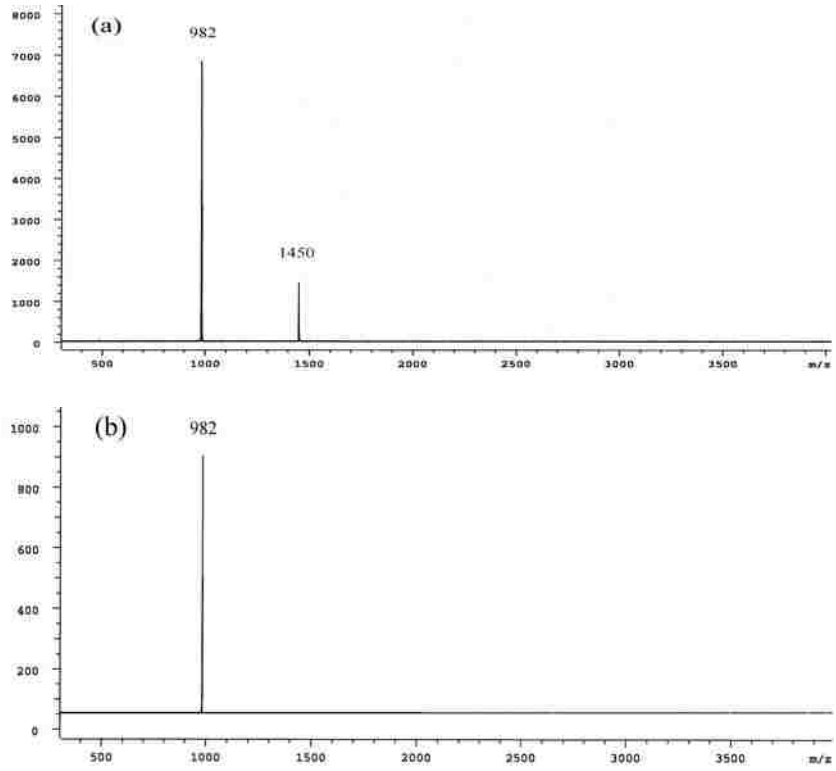
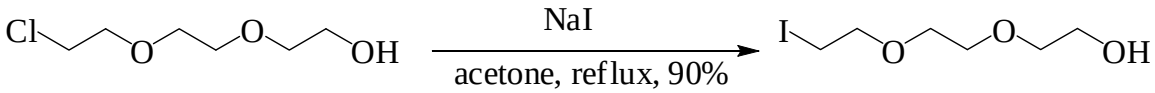


Figure 4.6. Mass spectra of the crude product **4.11** with different phthalonitrile ratios (a) A/B=20, (b) A/B=40.

macrocycle using dry DMF as solvent was not successful probably due to the insolubility of the free base Pc in DMF. Changing the solvent to DCM made the reaction proceed in

quantitative yield. The deprotection of the methoxyl groups of Pc **4.12** with sodium ethanethiolate produced both free-base and zinc Pcs. Therefore, the demethylation reaction of free-base Pc **4.11** was accomplished first, before the metallation reaction. However, the yield was low and the target Pc **4.13** was synthesized by zinc insertion with zinc bromide in dry DMF.

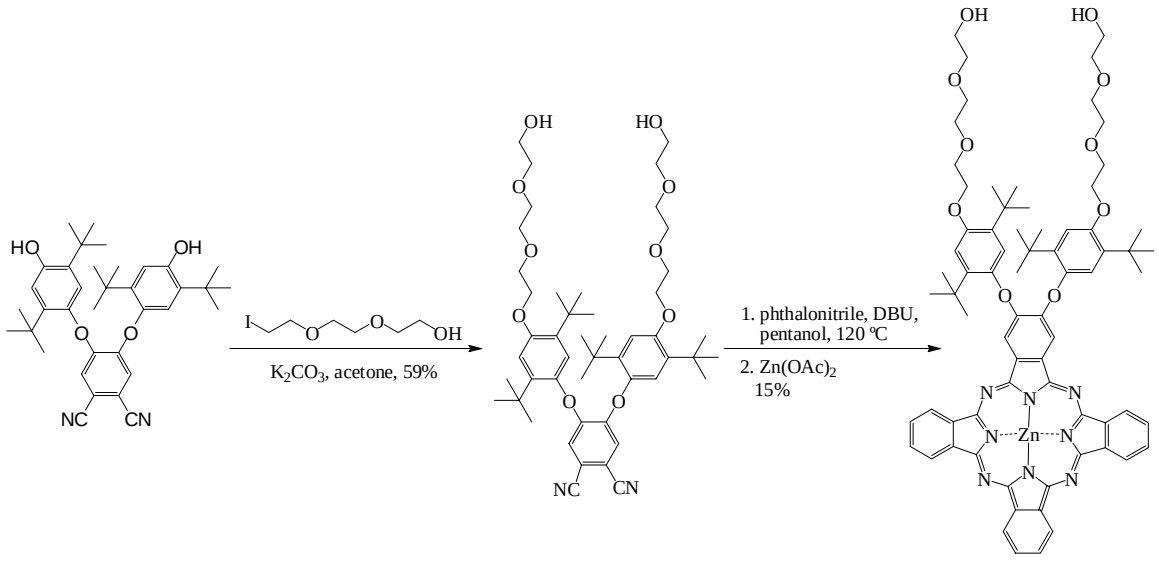
We tried a second strategy to synthesize Pc **4.13**. Phthalonitrile **4.4** and 4,5-dichlorophthalonitrile was macrocyclized by heating at 140 ºC in dry pentanol and in the presence of a catalytic amount of DBU. The free-base Pc was identified by a peak at 954.90 (*m/z*) by MALDI-TOF mass spectrometry. The following metallation reaction took place by heating the reaction solution in DMF at 40 ºC. The macrocyclization reaction has a yield of 6% using zinc template. Pc **4.13** containing two hydroxyl groups shows good solubility in DMF, however, it shows tendency for aggregation in DCM, acetone and methanol.



4.14

Scheme 4.5. Synthesis of PEG precursor.

In order to improve the solubility of the A_3B-type zinc Pc, two short PEG chains containing two free hydroxyl groups were conjugated to the Pc. 2-[2-(2-Iodoethoxy)ethoxy]ethanol[28] was synthesized from 2-[2-(2-chloroethoxy)ethoxy]ethanol and sodium iodide in 90% yield (Scheme 4.5).



4.4 **4.15** **4.16**

Scheme 4.6. Synthesis of PEG-conjugated Pc **4.16**.

Scheme 4.6 shows the synthesis of Pc **4.16**. Phthalonitrile **4.4** reacted with 2-[2-(2-iodoethoxy)ethoxy]ethanol at 50 ºC for two days to produce phthalonitrile **4.15** containing two short PEG chains in 59% yield. Using the method of statistical condensation, a large excess of phthalonitrile reacted with **4.15** in the presence of a small amount of DBU to give the A_3B-type zinc Pc **4.16** in 15% yield. Because of the presence of the amphiphilic PEG chains and the hydrophobic tert-butyl groups, Pc **4.16** is highly soluble in various solvents such as acetone, methanol, DCM and DMF.

4.5 Conclusion

In this Chapter, octa, tetra and dihydroxyl-substituted Pcs were synthesized in pure form using different synthetic strategies. All Pcs are highly soluble in polar organic solvents. Photophysical studies are being conducted and will be soon reported.

4.6 Experimental

All chemicals were purchased from commercial sources and used directly without further purification. Silica gel 60 (230×400 mesh, Sorbent Technologies) and alumina gel

(50–200 μm, neutral, standard activity I, Sorbent Technologies) were used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using polyester backed TLC plates 254 (precoated, 200 μm) from Sorbent Technologies. Prep alumina and silica TLC plates were purchased from Sorbent Technologies Inc. (w / UV 254, 1000 μm) NMR spectra were recorded on a DPX-250 or AV-400 Bruker spectrometers (250 MHz or 400 MHz for ^{1}H, 63 MHz or 100 MHz for ^{13}C). The chemical shifts are reported in δ ppm using the following deuterated solvents as internal references: CD_3COCD_3 2.04 ppm (^{1}H), 29.92 ppm (^{13}C); d-DMF 2.92 ppm (^{1}H), 34.89 ppm (^{13}C). Electronic absorption spectra were measured on a Perkin-Elmer Lambda 35 UV-vis spectrometer. High resolution ESI mass spectra were obtained on an Agilent Technologies 6210 Time-of-Flight LC/MS. HPLC separation and analyses were carried out on a Dionex system equipped with a P680 pump and a UVD340U detector. Semi-preparative column was Luna C_{18} 100 Å, 5 μm, 10 × 250 mm from Phenomenex, USA. Analytical HPLC was carried out on a Delta Pak C_{18} 300 Å, 5 μm, 3.9 × 150 mm (Waters, USA) column; flow rate 1.0 mL/min; injected volume 20 μL; wavelength detection 350 nm.

Phthalonitrile 4.1. 4, 5-Dichlorophthalonitrile (1 g, 5 mmol) and 2, 5-di-tert-butyl-4-methoxyphenol (4 g, 16.4 mmol) were dissolved in 30mL dry DMF at 95 ºC under argon's flow. Potassium carbonate (4.5 g, 32.8 mmol) was added to the reaction solution in 8 portions every 5 min. After 1 day, another portion (2 g, 14.5 mmol) of 2, 5-di-tert-butyl-4-methoxyphenol was added to the reaction solution. The reaction was followed by ^{1}H NMR with the missing of mono-substituted phthalonitrile. After 24 hours the reaction solution was cooled to room temperature and poured into 250 mL ice water. After filtration under vacuum, the cruder product was purified through a silica column

with mixed elution hexane/DCM (4/1). The product was recrystallized with hexane to get pure white solid (2.3 g, 77%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.18 (s, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 6.95 (s, 2H, Ar-H), 3.95 (s, 6H, OCH_3), 1.42 (s, 18H, $C(CH_3)_3$), 1.40 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 156.27, 153.31, 145.56, 140.40, 138.61, 120.88, 120.63, 116.00, 111.76, 109.68 (Ar-C, CN), 55.80 (OCH_3), 35.06, 34.96, 30.62, 29.85 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 596.87 $[M]^+$, calcd. for $[C_{38}H_{48}N_2O_4]^+$ 596.36.

H_2Pc 4.2. Phthalonitrile **4.1** (0.5 g, 0.84 mmol) was put in a 25 mL three-neck flask and the flask was evacuated and refill with argon for three times. Pentanol (5 mL) was added in through syringe and the reaction solution was heated to 120 ºC. Lithium (0.048 g, 6.8 mmol) was added in small pieces. The reaction was kept for 17 hours. The reaction solution was cooled down to room temperature. Acetic acid (15 mL) was added to the solution and it stirred for half an hour. The solution was poured to 200 mL solution of ice water/methanol (10/1). The mixed the solution was stirred vigorously for one hour. The product was filtered and then dissolved in 100 mL of hexane. The impurity was removed by filtration. The product solution was dried over anhydrous sodium sulfate overnight. The solvent was evaporated out and the residue was washed with methanol until the filtrate was colorless. The product was dried under vacuum at 70 ºC to get fresh green solid (0.15 g, 30%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.90 (s, 8H, Ar-H), 7.09 (s, 8H, Ar-H), 7.07 (s, 8H, Ar-H), 3.97 (s, 24H, OCH_3), 1.52 (s, 72H, $C(CH_3)_3$), 1.27 (s, 72H, $C(CH_3)_3$), -0.35 (s, 2H, NH). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 154.66, 152.21, 149.30, 138.72, 137.55, 132.83, 118.29, 113.36, 111.91 (Ar-C), 56.01 (OCH_3), 35.10, 34.81, 30.39, 29.85 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 2388.37 $[M]^+$, calcd. for $C_{152}H_{194}N_8O_{16}$ 2388.46.

ZnPc 4.3. Phthalonitrile (0.38 g, 0.64 mmol) was dissolved in 3 mL dry pentanol at 135 ºC. With the protection of argon, metal lithium (0.1 g, 14 mmol) was added carefully to the reaction solution in small pieces. After two minutes, the reaction solution turns to green. It was heated for 3 hours. Then 400mg of anhydrous zinc acetate was added. It was refluxed for another 3 hours. The solvent was removed under reduced pressure. The dry residue was washed with methanol: H_2O (1:1) for three times and extracted with 100 ml hexane. The crude product was purified by going through a silica column with the elution of hexane/DCM (2/1) to obtain pure green solid (0.12 g, 31%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.89 (s, 8H, Ar-H), 7.06 (s, 8H, Ar-H), 7.05 (s, 8H, Ar-H), 3.95 (s, 24H, OCH_3), 1.50 (s, 72H, $C(CH_3)_3$), 1.25 (s, 72H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 154.50, 153.37, 151.57, 149.49, 138.57, 137.43, 134.39, 118.12, 113.38, 111.87 (Ar-C), 56.00 (OCH_3), 35.06, 34.76, 30.34, 29.81 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 2451.80 $[M]^+$, calcd. for $C_{152}H_{192}N_8O_{16}Zn$ 2451.38.

Phthalonitrile 4.4. 2, 5-Di-tert-butyl-hydroquinone (2.3 g, 10.3 mmol) was dissolved in 30 mL of DMF. The reaction flask was charged with nitrogen and potassium carbonate (0.7 g, 5.1 mmol) was added into the reaction solution in five portions. The solution was heated to 50 ºC. 4, 5-dichlorophthalonitrile (0.5 g, 2.6 mmol) was dissolved in 10 mL of DMF as solution A and added to the reaction solution through additional funnel dropwise in 30 minutes. After addition of solution A, the temperature was raised to 100 ºC and heated for three days. After the solution was cooled down, it was concentrated to 10 mL and poured to 100 mL of ice water, the solution was neutralized by 1 N HCl solution until pH = 5. The precipitates were filtered and further purified by chromatography on silica gel with hexane/DCM (1/1) and MeOH/DCM (2/98) to get white solid (0.4 g, 27%). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.09 (s, 2H, Ar-H), 6.84 (s, 2H,

Ar-H), 6.79 (s, 2H, Ar-H), 5.01 (s, 2H, OH), 1.37 (s, 18H, $C(CH_3)_3$), 1.31 (s, 18H, $C(CH_3)_3$). ^{1}H NMR (d-acetone, 400 MHz): δ 8.66 (s, 2H, OH), 7.27 (s, 2H, Ar-H), 6.99 (s, 2H, Ar-H), 6.85 (s, 2H, Ar-H), 1.34 (s, 18H, $C(CH_3)_3$), 1.31 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 153.03, 144.75, 139.71, 135.39, 120.80, 120.05, 115.54, 115.41, 109.11 (Ar-C, CN), 34.18, 34.01, 29.88, 28.89 ($C(CH_3)_3$). HRMS-ESI: *m/z* 567.3219 $[M-H]^-$, 568.3245 $[M]^-$, 1135.6526 $[2M-H]^-$, calcd. for $[C_{36}H_{43}N_2O_4]^-$ 567.3228, $[C_{36}H_{44}N_2O_4]^-$ 568.3261, $[C_{72}H_{87}N_4O_8]^-$ 1135.6524. FTIR (solid): 3463.7 (br, OH), 2236.0 (CN) cm^{-1}.

ZnPc 4.5. Method A. ZnPc **4.3** (60 mg, 0.024 mmol) and sodium ethanethiolate (900 mg, 9.6 mmol) were dissolved in 35 ml dry DMF. The reaction was refluxing at 135 ºC for 24 hours under argon protection. The reaction was followed by MALDI-TOF mass spectroscopy. After one day, the reaction solution was poured into 150 mL H_2O. It was extracted with ethyl acetate (50 mL, ×3) and then dried over anhydrous sodium sulfate. The crude product was purified by Sephadex LH-20 with methanol. After chromatography with HPLC using methanol as the mobile phase, green solid was obtained (15 mg, 25%). **Method B.** Phthalonitrile **4.4** (0.08 g, 0.14 mmol) was dissolved in 3 mL of pentanol in 25 mL three neck flask. The solution was heated at 135 ºC. Lithium (30 mg, 4.3 mmol) was added into the solution in small portions and the reaction solution was heated for 10 hours. The solution was cool down to room temperature, and zinc acetate (0.1 g, 0.55 mmol) was added. The solution was refluxed at 135 ºC for two hours and then evaporated to dry and dissolved in 100 mL water. The suspension stayed in the refrigerator for three hours. The green precipitate was filtered under vacuum and washed with water. The crude product was purified by chromatography on alumina column with elution of methanol/DCM (2/98). The final product was purified by HPLC

with methanol as the mobile phase, green solid was obtained (7 mg, 9%). ^{1}HNMR (d-acetone, 250 MHz): δ 8.818 (s, 8H, Ar-H), 8.088 (br, 8H, OH), 7.061 (s, Ar-H, 8H), 7.029 (s, Ar-H, 8H), 1.462 (s, 9H, $C(CH_3)_3$), 1.311 (s, 9H, $C(CH_3)_3$). ^{13}CNMR (d-methanol, 63 MHz): δ 154.542, 153.015, 152.833, 149.049, 139.927, 135.914, 134.645, 119.631, 116.406, 113.237 (Ar-C), 35.373, 35.344, 31.002, 30.116 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 2338.71 $[M]^+$, calcd. for $C_{144}H_{176}N_8O_{16}Zn$ 2339.25. HRMS-ESI: *m/z* 1168.6159 $[M-2H]^{2-}$, calcd. for $[C_{144}H_{174}N_8O_{16}Zn]^{2-}$ 1168.6194. t_R = 11.23 min (MeOH). UV-vis (acetone): λ_{max} (log ε) 678.66 (5.04) nm.

Phthalonitrile 4.6. 2, 5-Di-tert-butylhydroquinone (3.2 g, 14 mmol) was dissolved in 100 mL DMF. The reaction flask was charged with nitrogen and potassium carbonate (2 g, 14 mmol) was added into the reaction solution in five portions. The solution was heated to 50 ºC. 3-Nitrophthalonitrile (2 g, 11 mmol) was dissolved in 40 mL of DMF as solution A and added to the reaction solution through additional funnel dropwise in 30 minutes. After addition of solution A, the temperature was raised to 100 ºC and kept for 20 hours. After the solution was cooled down, it was concentrated to 20 mL and poured to 100 mL water, the precipitates were filtered and recrystallized with acetone to get dimeric phthalonitrile **4.7** as white solid and the solution was evaporated to dry and further purified by chromatography on silica gel with MeOH/DCM (2/98) to get light yellow solid (1.5 g, 38%). ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.58 – 7.54 (m, 1H, Ar-H), 7.43 – 7.41 (m, 1H, Ar-H), 7.04 – 7.02 (m, 1H, Ar-H), 6.84 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 1.34 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 162.31, 152.55, 145.13, 140.86, 136.15, 134.89, 126.65, 120.88, 120.26, 117.44, 116.41, 115.86, 113.65, 105.59 (Ar-C, CN), 34.68, 34.49, 30.45, 29.49 ($C(CH_3)_3$). HRMS-ESI: *m/z* 347.1766 $[M-H]^-$, 348.1791 $[M]^-$, 695.3580 $[2M-H]^-$, calcd. for

$[C_{22}H_{23}N_2O_2]^-$ 347.1766, $[C_{22}H_{24}N_2O_2]^-$ 348.1838, $[C_{44}H_{47}N_4O_4]^-$ 695.3597. FTIR (solid): 3440.9 (br, OH), 2243.0 (CN) cm^{-1}. **Dimer 4.7** (1.2 g, 46%). ^1H NMR (CD_2Cl_2, 400 MHz): δ 7.66 – 7.62 (m, 2H, Ar-H), 7.52 – 7.50 (m, 2H, Ar-H), 7.52 – 7.50 (m, 2H, Ar-H), 7.13 – 7.11 (m, 2H, Ar-H), 7.00 (s, 2H, Ar-H), 1.30 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 160.73, 149.51, 141.97, 134.67, 127.04, 121.10, 120.34, 117.39, 115.19, 112.87, 105.92 (Ar-C, CN), 34.50, 29.78 ($C(CH_3)_3$).

ZnPc 4.8. **Method A.** Phthalonitrile **4.6** (80 mg, 0.23 mmol) was dissolved in 3 mL pentanol. The solution was protected by argon and heated to 130 ºC. Lithium (15 mg, 2.2 mmol) was added into the solution in small pieces. After heating for 4 hours, zinc acetate (50 mg, 0.27 mmol) was added into the solution and continued to heat for 2 hours. The solvent was evaporated out and dissolved in mixed solvents of methanol/water (1/1). The green solid was filtered and washed with dichloromethane. The crude product was further purified by chromatography on alumina column with the elution of methanol/DCM (5/95) and followed by a preparative alumina TLC with the elution of methanol/DCM (2/98) to afford a green solid as the major product (7 mg, 8%). The crude product was further purified by HPLC. **Method B**. Lithium (0.033 g, 4.6 mmol) was dissolved in octanol (5 mL) and heated to 170 ºC for 1 hour to get a homogeneous solution. Then the solution was cooled down to room temperature and phthalonitrile **4.6** (50 mg, 0.14 mmol) in DCM (1 mL) was added into the reaction solution through syringe. After four hours, anhydrous zinc acetate (40 g, 0.2 mmol) was added into the solution. The reaction solution was heated to 70 ºC for 24 hours. The solution was loaded to a silica column directly to get one fraction with elution of methanol/DCM (2/98). Ethanol (10 mL) was added to the solution and the solution was concentrated by azeotropic distillation. Hexane (5 mL) was added to the residue (1 mL) and the

suspension was centrifuged to get crude solid product. The crude product was eluted with acetone on a short Sephdex LH-20 column to remove any insoluble impurities. Then the product was loaded on silica preparative TLC plate and developed with hexane/DCM (1/4) and DCM/methanol (98/2). Two major green bands were collected. The two isomers were purified separately on alumina preparative TLC plate with developing solvents of hexane/DCM (1/4) and DCM/methanol (98/2). The crude product was obtained as dark green solid (8 mg, 15%). Further purification was done by HPLC. ^{1}H NMR (d-DMF, 400 MHz): δ 9.60 (br, 4H, OH), 9.08 (d, J = 7.4 Hz, 4H, Ar-H), 8.10 (t, J = 7.5 Hz, 4H, Ar-H), 7.45 (d, J = 7.4 Hz, 4H, Ar-H), 7.30 (s, 8H, Ar-H), 1.71 (s, 36H, $C(CH_3)_3$), 1.41 (s, 36H, $C(CH_3)_3$). HRMS-ESI: *m/z* 1459.6721 $[M+H]^+$, calcd. for $[C_{88}H_{97}N_8O_8Zn]^+$ 1459.6730.

Phthalonitrile 4.9. 3-Nitrophthalonitrile (0.4 g, 2.3 mmol) and 2, 5-di-tert-butyl-4-methoxyphenol (0.6 g, 2.8 mmol) were dissolved in 20 mL DMF and heated to 90 ºC. Potassium carbonate (4.2 g, 30.4 mmol) was added into the solution in five portions. The reaction solution was heated for 4 hours. After the solution was cooled down to room temperature, the solution was poured into 450 mL ice water and white solid precipitated out. The solid was filtered under vacuum. The solid was dissolved in 100 mL DCM and dried over sodium sulfate. The crude product was purified by chromatography on alumina gel with elution of DCM/hexane (4/1) to afford white solid (1.0 g, 83%). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 7.58 – 7.52 (m, 1H, Ar-H), 7.44 – 7.40 (m, 1H, Ar-H), 7.02 – 6.95 (m, 2H, Ar-H), 6.78 (s, 1H, Ar-H), 3.88 (s, 3H, OCH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 162.19, 156.34, 144.98, 140.47, 138.40, 134.87, 126.62, 120.55, 120.19, 117.38, 115.87, 113.67, 111.60, 105.54 (Ar-C,

CN), 55.73 (OCH_3), 34.88, 34.83, 30.44, 29.60 ($C(CH_3)_3$). MS (MALDI-TOF) *m/z* 362.25 $[M]^+$, calcd. for $C_{23}H_{26}N_2O_2$ 362.20.

ZnPc 4.10. Phthalonitrile **4.9** (0.1 g, 0.28 mmol) and zinc acetate (0.05 g, 0.27 mmol) were put in a 25 ml schlenk flask and it was evacuated and refilled with argon for three times. Pentanol (3 mL) was added into the flask and the solution was heated to 140 ºC. Small amount of DBU (13 µL) was added through syringe. The reaction was followed by TLC until the disappearance of the starting material. After heating for 4 hours, the solution was cooled down to room temperature. The solvent was evaporated to dry and the crude product was purified by chromatography with silica gel eluted with ethyl acetate/hexane (1/10). A second silica column was applied with elution of ethyl acetate/DCM/hexane (3/10/1) to get the major fraction. The major fraction was further purified by preparative silica TLC with elution of DCM/hexane (5/1) to afford bluish green solid (11 mg, 10%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 9.07 (d, 4H, Ar-H), 7.93 (t, 4H, Ar-H), 7.40 (t, 4H, Ar-H), 7.21 (s, 4H, Ar-H), 4.02 (s, 12H, OCH_3), 1.75 (s, 36H, $C(CH_3)_3$), 1.40 (s, 36H, $C(CH_3)_3$). MS (MALDI-TOF) *m/z* 1514.54 $[M]^+$, calcd. for $C_{92}H_{104}N_8O_8Zn$ 1514.73.

H_2Pc 4.11. Phthalonitrile **4.1** (0.3 g, 0.5 mmol) and phthalonitile (7.6 g, 59.3 mmol) was mixed together in 50 mL dry pentanol at 140 ºC. With the protection of argon, 0.6 mL DBU was added dropwise to the reaction solution. After refluxing for 9 hours, the reaction solution was cooled to room temperature. Pour the solution to 200 mL methanol and filter under vacuum. The insoluble solid was washed with methanol and DCM. The filtrate was concentrated and the residue was loaded on a short silica column using DCM as the elution. The product was dried under vacuum to get the blue solid (0.06 g, 12%). ^{1}H NMR ($CDCl_3$ with one drop of d-TFA, 300 MHz): δ 7.98 – 7.87 (m,

18H, Ar-H), 4.11 (s, 6H, OCH_3), 1.72 (s, 18H, $C(CH_3)_3$), 1.46 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF) *m/z* 982.81 $[M]^+$, calcd. for $C_{62}H_{62}N_8O_4$ 982.49.

ZnPc 4.12. H_2Pc **4.11** (0.07 g, 0.7 mmol) and zinc bromide (0.16 g, 0.7 mmol) was dissolved in 20 mL DCM and refluxed for 2 hours. After the reaction solution was cooled down to room temperature, it was filtered to remove excess amount of salt. The residue was purified by chromatography on silica column with the elution of DCM/THF (20/1) to yield the bluish green solid (0.067 g, 96%). ^{1}H NMR (d-THF, 250 MHz): δ 9.32 – 9.27 (m, 4H, Ar-H), 9.22 – 9.19 (m, 2H, Ar-H), 9.04 (s, 2H, Ar-H), 8.11 – 8.08 (m, 4H, Ar-H), 8.05 – 8.02 (m, 2H, Ar-H), 7.31 (s, 2H, Ar-H), 7.17 (s, 2H, Ar-H), 4.01 (m, 6H, Ar-H), 1.61 (s, 18H, $C(CH_3)_3$), 1.38 (s, 18H, $C(CH_3)_3$). MS (MALDI-TOF) *m/z* 1044.84 $[M]^+$, calcd. for $C_{62}H_{60}N_8O_4Zn$ 1044.40.

ZnPc 4.13. Phthalonitrile **4.4** (0.1 g, 0.176 mmol) and phthalonitrile (1.9 g, 15 mmol) were mixed together in 50 mL dry pentanol at 140 ºC. With the charging of argon, DBU (0.2 mL) was added into the solution. The reaction proceeded for 24 hours. After the reaction, the solvent was evaporated to dry. The residue was dissolved in acetone and the byproduct zinc Pc was removed by filtration. The crude product was purified by chromatography with alumina column eluted with methanol/DCM (5/95) to get the free base. MS (MALDI-TOF) *m/z* 954.90 $[M]^+$, calcd. for $C_{60}H_{58}N_8O_4$ 954.46. The free-base Pc was dissolved in 20 mL DMF and heated to 40 ºC for two days. Then the solvent was evaporated to dry. The crude product was purified by alumina column with MeOH/DCM (2/98) and the following alumina preparative TLC afforded the product as greenish blue product (10 mg, 6%). ^{1}H NMR (d-DMF, 400 MHz): δ 9.61 (br, 2H, OH), 9.35 – 9.17 (m, 6H, Ar-H), 8.95 (s, 2H, Ar-H), 8.23 – 8.13 (m, 6H, Ar-H), 7.32 (s, 2H, Ar-H), 7.28 (s, 2H, Ar-H), 1.60 (s, 18H, $C(CH_3)_3$), 1.46 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (d-DMF, 100

MHz): δ 162.90, 154.10, 153.95, 153.87, 153.80, 153.20, 152.29, 147.88, 139.79, 139.11, 139.03, 138.93, 135.30, 134.24, 123.15, 122.94, 122.80, 119.97, 116.15, 111.68 (Ar-C), 29.77 ($C(CH_3)_3$, other carbon signals shielded by d-DMF). LR-MS (MALDI-TOF) *m/z* 1016.25 $[M]^+$, calcd. for $C_{60}H_{56}N_8O_4Zn$ 1016.37.

2-[2-(2-Iodoethoxy)ethoxy]ethanol 4.14. 2-[2-(2-Chloroethoxy)ethoxy]ethanol (10 g, 59.2 mmol) and sodium iodide (55 g, 0.37 mol) were dissolved in acetone (100 mL) and the refluxed for 24 h. The solution was filtered to remove the salt and the acetone was evaporated to dry. Water (15 mL) was added to dissolve the slurry. Ether (100 mL) was used to extract the product for three times. The combined organic solution was dried over sodium sulfate and the solvent was evaporated to dry. It was dried at 40 ºC under vacuum for 24 h to afford the reddish yellow viscous liquid (14 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.61 (t, J = 6.8 Hz, 2H, OCH_2), 3.57 (t, J = 4.6 Hz, 2H, OCH_2), 3.52 (s, 4H, CH_2), 3.45 (t, J = 4.6 Hz, 2H, OCH_2), 3.14 - 3.10 (m, 3H, OCH_2, OH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 72.20, 71.43, 69.88, 69.74, 61.18, 2.67. HRMS-ESI: *m/z* 260.9975 $[M+H]^+$, 282.9796 $[M+Na]^+$, calcd. for $[C_6H_{14}O_3I]^+$ 260.9982, $[C_6H_{13}O_3INa]^+$ 282.9807.

Phthalonitrile 4.15. Phthalonitrile **4.4** (0.2 g, 0.35 mmol) and potassium carbonate (0.24 g, 1.7 mmol) were dissolved in acetone (20 mL). The flask was charged with argon and the reaction solution was heated to 50 ºC. 2-[2-(2-Chloroethoxy)ethoxy]ethanol (0.28 g, 1.1 mmol) was added into the reaction solution by syringe. Another portion of 2-[2-(2-chloroethoxy)ethoxy]ethanol (0.14 g, 0.5 mmol) and potassium carbonate (0.12 g, 0.9 mmol) was added into the reaction solution. The reaction was followed by TLC and another two days later the reaction went to complete. The reaction solution was cooled down to room temperature and the inorganic salt was

removed by filtration under vacuum. The solution was concentrated and loaded on a silica column. The product was eluted with DCM/methanol (98/2) and dried to afford slight yellow viscous liquid (0.18 g, 59%). ^{1}H NMR (d-acetone, 250 MHz): δ 7.32 (s, 2H, Ar-H), 7.06 (s, 2H, Ar-H), 6.91 (s, 2H, Ar-H), 4.23 (t, J = 4.4 Hz, 4H, OCH_2), 3.92 (t, J = 4.4 Hz, 4H, OCH_2), 3.70 – 3.51 (m, 18H, OCH_2, OH), 1.37 (s, 18H, $C(CH_3)_3$), 1.35 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (d-acetone, 63 MHz): δ 155.67, 153.54, 146.33, 140.36, 138.51, 121.97, 120.61, 116.12, 112.72, 110.15 (Ar-C, CN), 73.45, 71.21, 71.14, 70.50, 68.53, 61.89 (OCH_2), 35.22, 35.14, 30.60, 29.94 ($C(CH_3)_3$). HRMS-ESI: *m/z* 833.4947 $[M+H]^+$, calcd. for $[C_{48}H_{69}N_2O_{10}]^+$ 833.4946.

ZnPc 4.16. Phthalonitrile **4.4** (0.2 g, 0.24 mmol) and phthalonitrile (1.8 g, 14 mmol) were dissolved in pentanol (20 mL). The flask was charged with argon. The reaction solution was heated to 140 ºC and DBU (0.1 mL, 0.66 mmol) was added. After three hours, zinc acetate (0.8 g, 4.4 mmol) was added to the reaction solution. The temperature was decreased to 100 ºC and kept for eight hours. After the reaction, the solution was cooled down to room temperature and filtered under vacuum. The solid was washed with acetone and methanol. The filtrate was evaporated to dry. The residue was loaded on a silica column and the crude product was eluted with ethyl acetate/methanol (98/2) to afford dark green solid (60 mg, 15%). HRMS-ESI: *m/z* 1283.5362 $[M+H]^+$, calcd. for $[C_{72}H_{81}N_8O_{10}Zn]^+$ 1283.5367.

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CHAPTER 5

SYNTHESES OF PHOSPHONATE-SUBSTITUTED PHTHALOCYANINES

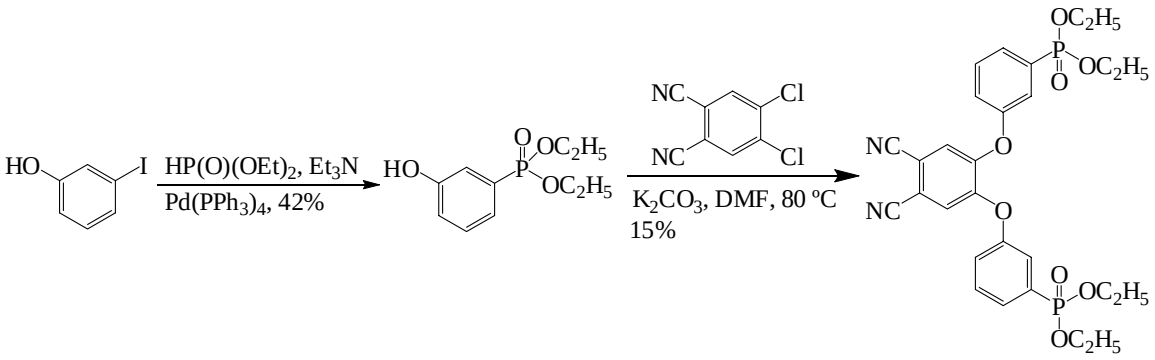
5.1 Background

Phosphonic acid containing dyes, for example porphyrins,[1-3] Pcs,[4-6] chlorins[7] and small molecule dyes such as cyanine and squaraine dyes,[8] have been synthesized and applied in biological and material sciences, such as fluorescent labels and as organic photovoltaic devices. Some examples of bisphosphates[9, 10] were shown to have good activity in inhibiting the growth of human cell lines (MCF-7, NCI-H460, SF-268).

Only a few papers to date have reported the synthesis of Pcs bearing phosphonate substituents.[4-6, 11] In this Chapter, one symmetric Pc containing eight phosphonate groups was synthesized.

5.2 Synthesis of Octaphosphonate-Substituted Zinc Phthalocyanine

Two methods of phosphonation were investigated in our synthetic strategy. The Pd (0)–catalyzed carbon-phosphorus bond formation is a classical method to synthesize the aryl phosphonic acids. Dialkylarylphosphonates can be synthesized from aryl bromides or iodides with dialkyl phosphite in the presence of triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium.[12, 13] A precursor containing a phosphonate ester group was synthesized through the Pd (0)–catalyzed reaction in 41% yield (Scheme 5.1). 3-Iodophenol was coupled with diethylphosphite using 10% tetrakis(triphenylphosphine)-palladium as the catalyst, in the presence of freshly redistilled triethylamine without any solvent. The reaction proceeded in an inert gas environment for 5 hours to afford the product **5.1** as colorless viscous liquid in 41% yield. 4-Iodophenol was tried as the starting material in the Pd (0) coupling reaction, but



5.1 **5.2**

Scheme 5.1. Synthesis of phosphonate conjugated phthalonitrile.

It was not successful. The reaction of 3-phosphonate-substituted phenol **5.1** and 4,5-dichlorophthalonitrile led to diphosphonate-substituted phthalonitrile **5.2** in 15% yield. Therefore, the overall yield to synthesize the precursor of diphosphonate-substituted phthalonitrile is only 6%. We also investigated the Pd (0)-catalyzed phosphonation reaction on the octaiodo-substituted zinc Pc **5.4** (Figure 5.1), but this reaction was not successful either.

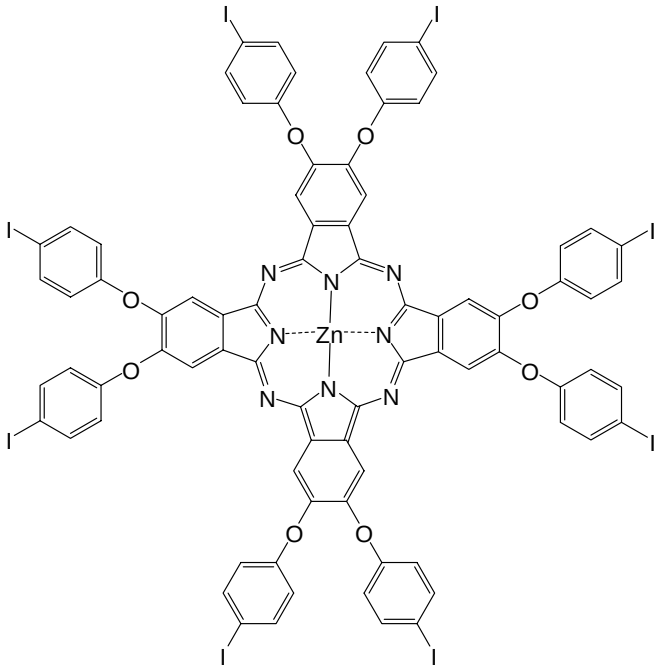
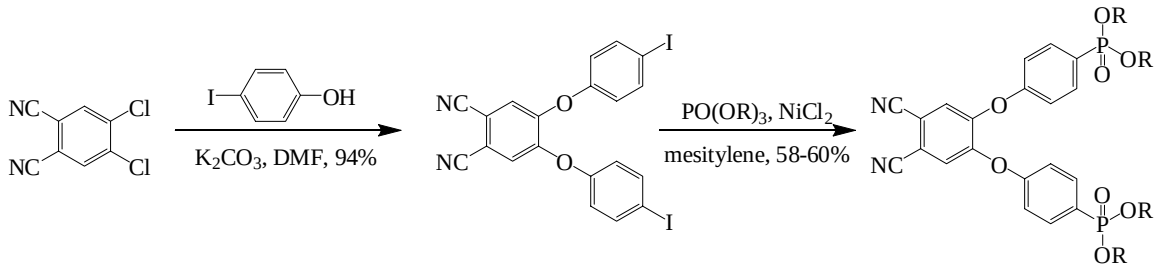


Figure 5.1. Structure of Octaiodo-substituted Pc **5.4**.

Since the yield of diphosphonate-substituted phthalonitrile **5.2** was not favorable, we decided to investigate another phosphonation method: the Michaelis-Arbuzov reaction. Aryl iodides or bromides reacted with trialkyl phosphites in the presence of a catalytic amount of anhydrous nickel dichloride.[14, 15] The diiodo-substituted phthalonitrile **5.3** was synthesized from 4-iodophenol and 4, 5-dichlorophthalonitrile in 94% yield as shown in Scheme 5.2. Figure 5.2 shows the single crystal structure of **5.3**. The following phosphonation reaction took place from phthalonitrile **5.3** and tributylphosphite or triethylphosphite catalyzed by a small amount of nickel dichloride in mesitylene (Scheme 5.2). These two reactions gave similar yields of 60% to afford the diphosphonate-substituted phthalonitriles **5.5** and **5.6**. The overall yield to synthesize the phosphonate-substituted phthalonitrile **5.5** and **5.6** is 58-60%, which is much higher than that obtained from Pd (0)-catalyzed reaction.

The lithium method was applied in the macrocyclization reaction (Scheme 5.3). The first trial to use DBU as the catalyst didn't lead to any desired product. The idea of using **5.5** as the precursor to synthesize a soluble octaphosphonate-substituted zinc Pc bearing sixteen butoxyl groups was not realistic, since some unexpected de-esterification



5.3

5.5: $R_1 = C_4H_9$
5.6: $R_2 = C_2H_5$

Scheme 5.2. Synthesis of phosphonate conjugated phthalonitriles.

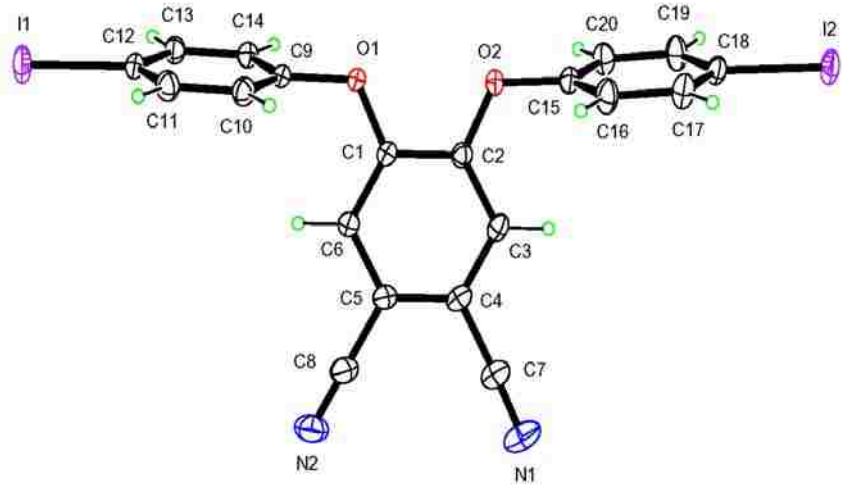
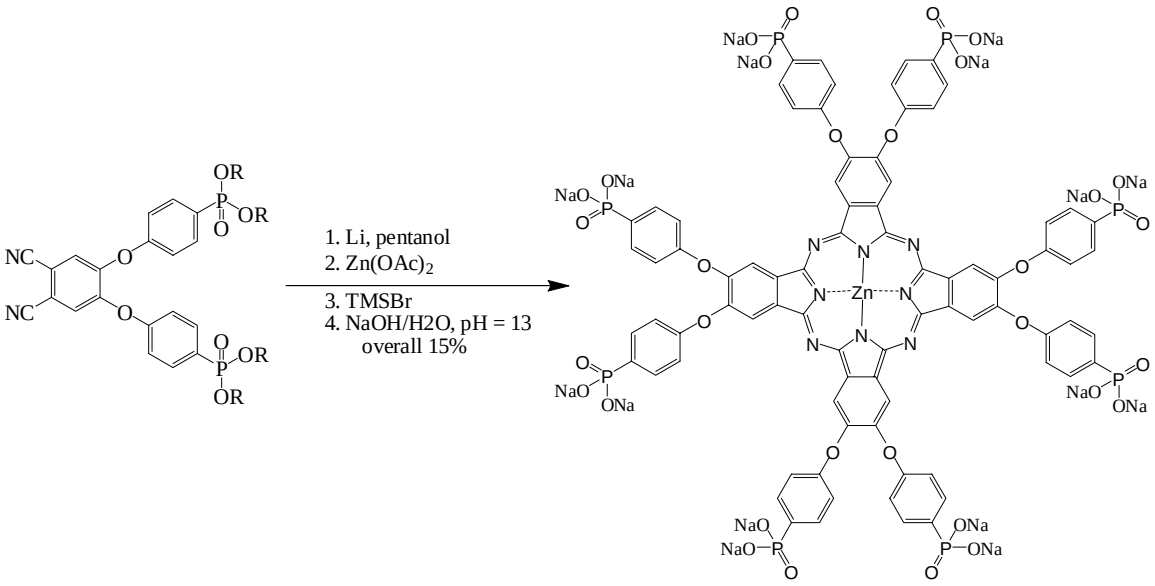


Figure 5.2. X-ray crystal structure of phthalonitrile **5.3**.

was observed under the strong basic conditions. The de-esterification of the phosphonate groups from the crude intermediate was complete by reacting with bromotrimethylsilane[16] at 100 ºC in a sealed tube for four days followed by ^{1}H NMR. The octaphosphonic acid-substituted Pc was not soluble in most common solvents, while it is soluble under basic aqueous solution when it is in the partial or fully ionic forms.



5.5: $R_1 = C_4H_9$ **5.7**
5.6: $R_2 = C_2H_5$

Scheme 5.3. Synthesis of octaphosphonic acid-substituted Pc **5.7**.

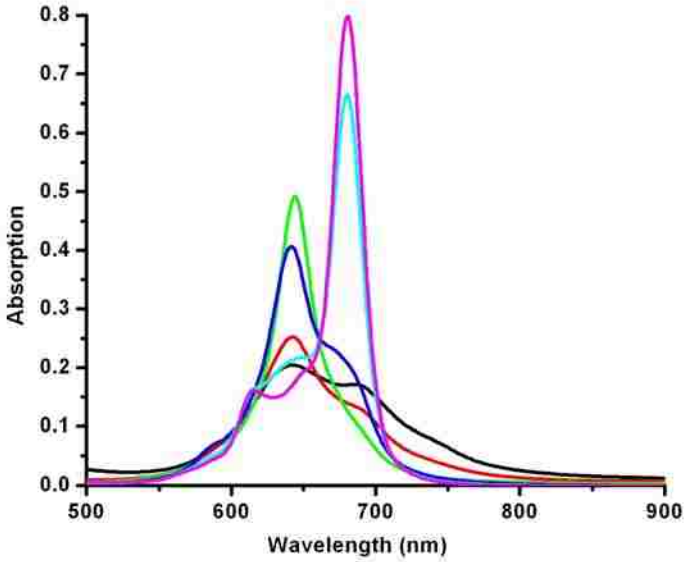


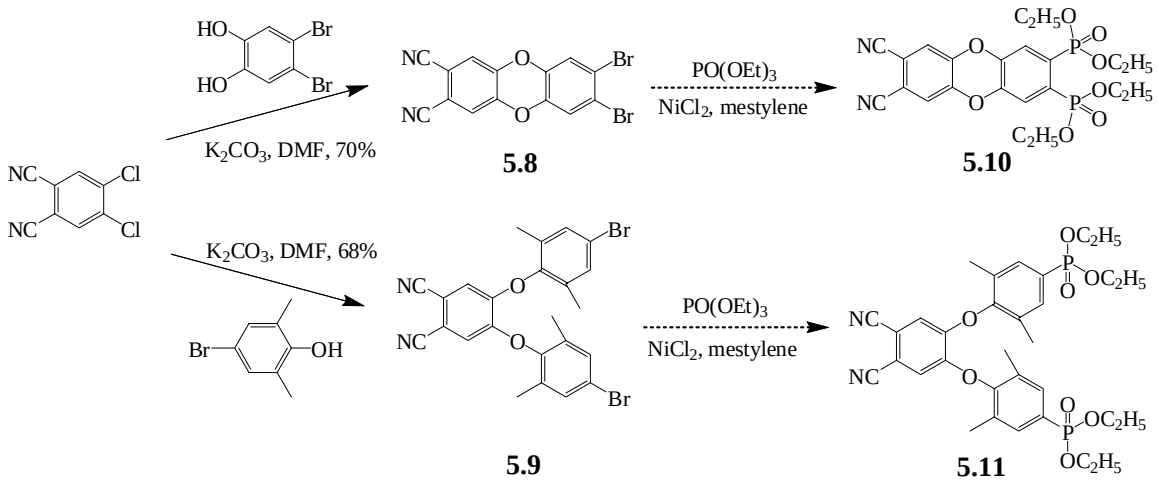
Figure 5.3. Absorption spectra of Pc **5.7** in 100 mM phosphate buffer at pH 11.0 (magenta), pH 9.0 (cyan), pH 8.0 (blue), pH 5.0 (green), pH 3.0 (red), pH 2.0 (black) at 5 µM.

Figure 5.3 shows the UV/Vis spectra of Pc **5.7** at pH 11.0, 9.0, 8.0, 5.0, 3.0 and 2.0. The absorption spectra at higher pH values (~ 9.0-12.0) show a strong Q band at 681 nm. With the decreasing pH values, the Q band has a blue shift to 644 nm, and the intensity of the peak at 681 nm decreases while the intensity of the peak at 644 nm increases to the highest until the pH value reaches to ~ 5.0. At lower pH values (~ 1.0-3.0), broadening of the peak and decreasing intensity were observed due to the aggregation of the neutral form of the Pc **5.7**.

5.3 Synthesis of Precursors

Two phthalonitriles **5.8** and **5.9** containing Br groups were synthesized in good yields from 4,5-dichlorophthalonitrile as shown in Scheme 5.4. The reaction to synthesize substituted dibenzo-p-dioxine **5.8** took 15 min to be completed. After purification, the yield is 70%. Phthalonitrile **5.9** was synthesized in 68% yield. Figure 5.4 shows the single crystal structure of this precursor. Future work will involve the synthesis of phosphonate-

substituted phthalonitriles **5.10**-**5.11** and macrocyclization of **5.8**-**5.11** to obtain the corresponding Pcs.



Scheme 5.4. Syntheses of phthalonitrile precursors.

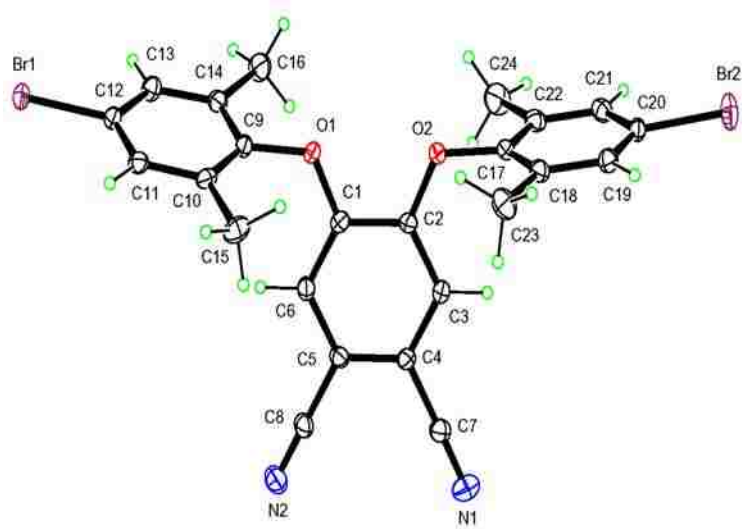


Figure 5.4. Single crystal X-ray structure of phthalonitrile **5.9**.

5.4 Conclusion

In this Chapter, one zinc Pc containing eight phosphonic acid groups was synthesized and characterized. The photophysical study of this Pc is currently underway.

Two phthalonitriles containing Br groups were also synthesized and can be further modified by phophonation reaction as precursors of phosphonate-substituted Pcs.

5.5 Experimental

Phenol 5.1. 3-Iodophenol (0.41 g, 2 mmol) and tetrakis(triphenylphosphine)-palladium (0.2 g, 0.2 mmol) were put in the Schlenk tube. It was degassed and refilled with argon for three times. Dry diethylphosphite (2.9 mL, 21.8 mmol) and triethylamine (3.1 mL, 22 mmol) which were deoxygenated were injected through plastic syringe. The reaction was heated at 100 ºC for 5 hours. After heating, the reaction residue was diluted with DCM and washed with 1 M hydrochloride solution for twice, and then washed with sodium bicarbonate solution and water twice respectively. The solution was dried over anhydrous sodium sulfate. The crude product was purified by chromatography with silica gel eluted by mixed solvents of DCM : methanol (95/5) to afford colorless viscous liquid (0.17 g, 42%). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 8.82 (br, 1H, OH), 7.69 – 7.63 (m, 1H, Ar-H), 7.37 - 7.31 (m, 1H, Ar-H), 7.26 - 7.18 (m, 1H, Ar-H), 7.13 – 7.09 (m, 1H, Ar-H), 4.17 - 4.08 (m, 4H, OCH_2CH_3), 1.33 (t, J = 4.9 Hz, OCH_2CH_3, 6H). ^{13}C-NMR (CD_2Cl_2, 63 MHz): δ158.84 (d), 130.79 (d), 127.32, 122.63 (d), 121.06 (d), 119.69 (d, Ar-C), 63.41 (d, OCH_2CH_3), 16.83 (d, OCH_2CH_3). ^{31}P NMR (CD_2Cl_2, 101 MHz): δ 20.61.

Phthalonitrile 5.2. 4, 5 – Dichlorophthalonitrile (0.047 g, 0.24 mmol) and phenol **5.1** (0.144 g, 0.63 mmol) were dissolved in 10 mL of anhydrous DMF. The flask was charged with argon and heated to 80 ºC. Potassium carbonate (0.2 g, 1.5 mmol) was added into the solution in three portions. The reaction solution was heated for three hours. After the reaction solution was cooled down to room temperature the solution was poured into 50 mL of cold water. DCM (100 mL × 2) was used to extract the product. The crude product was purified with silica column using solvent system of methanol/DCM (5/95) to

get the colorless viscous liquid (0.02 g, 15%). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.61 (s, 2H, Ar-H), 7.57 – 7.49 (m, 4H, Ar-H), 7.34 - 7.28 (m, 2H, Ar-H), 7.24-7.21 (m, 2H, Ar-H), 4.06 - 4.00 (m, 8H, OCH_2CH_3), 1.23 (t, J = 7.1 Hz, 12H). ^{13}C NMR (CD_3OD, 75 MHz): δ 156.76 (d), 152.24, 132.24 (d), 129.06 (d), 126.76, 123.99, 122.31 (d), 115.90, 113.56 (Ar-C, CN), 64.14 (d), 16.62 (d). ^{31}P NMR (CD_2Cl_2, 121 MHz): δ 24.58.

Phthalonitrile 5.3. 4, 5-Dichlorophthalonitrile (2g, 10.1 mmol) and 4-iodophenol (17.9 g, 81.2 mmol) were dissolved in 25 mL of DMSO. The reaction solution was heated at 80 ºC under argon. Potassium carbonate (4 g, × 7) was added every 5 minutes. After the addition of potassium carbonate, the reaction was proceeded for another 1.5 hours. After the reaction solution was cooled down to room temperature, the reaction solution was poured into 400 mL of ice water. The solution was filtered under vacuum and yellow solid paste was obtained. The solid was dissolved in 100 mL of DCM and dried over anhydrous sodium sulfate. The crude product was purified by silica gel with the elution of hexane/ DCM (1/4) to afford white solid (5.4 g, 94 %). ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 7.73 (d, J = 7.1 Hz, 4H, Ar-H), 7.24 (s, 2H, Ar-H), 6.79 (d, J = 7.1 Hz, 4H, Ar-H). ^{13}C NMR (CD_2Cl_2, 63 MHz): δ 154.83, 151.79, 140.60, 126.57, 122.25, 115.55, 111.35, 89.65 (Ar-C).

Pc 5.4. Phthalonitrile **5.3** (0.5 g, 0.9 mmol) and zinc acetate dihydrate (0.073 g, 0.3 mmol) were dissolved in anhydrous n-pentanol (20 mL). The reaction solution was heated to 140 ºC and catalytic amount of DBU (0.5 mL) was added through syringe. The turbid solution was remained at 140 ºC overnight. After the reaction, the solution was cooled down to room temperature and filtered under vacuum. The green solid was purified by chromatography on silica gel with THF (0.2 g, 40%). ^{1}H NMR (d-THF, 250

MHz): δ 9.02 (s, 8H, Ar-H), 7.72 (d, J = 8.7 Hz, 16H, Ar-H), 6.04 (d, J = 7.1 Hz, 16H, Ar-H).

Phthalonitrile 5.5. Phthalonitrile **5.3** (0.5 g, 0.9 mmol) and anhydrous nickel dichloride (27 mg, 0.2 mmol) were put in a 50 mL of two-neck round bottom flask. The flask was vacuum-refill with argon for three times and anhydrous mestylene (25 mL) was added through syringe and the solution was heated to 160 ºC. Tributyl phosphite (0.8 mL, 2.9 mmol) in 10 mL mestylene was added into the reaction solution dropwise through additional funnel in 30 min. The reaction solution was heated for 16 hours. The green solution was dissolved in 20 mL DCM and filtered through vacuum to remove any inorganic salts and then fractionally distilled to remove any high boiling point reagent and byproduct. The residue was purified with alumna column eluted by methanol/DCM (5/95) to afford clear viscous liquid (0.36 g, 58%). ^{1}H NMR (d-acetone, 400 MHz): δ 7.90 (s, 2H, Ar-H), 7.82 – 7.77 (m, 4H, Ar-H), 7.26 – 7.23 (m, 4H, Ar-H), 4.05 – 3.95 (m, 8H, $O(CH_2)_3CH_3$), 1.65 – 1.58 (m, 8H, $O(CH_2)_3CH_3$), 1.42 – 1.32 (m, 8H, $O(CH_2)_3CH_3$), 0.88 (t, J = 7.4 Hz, 12H, $O(CH_2)_3CH_3$). ^{13}C NMR (d-acetone, 100 MHz): δ 158.60 (d), 150.76, 134.06 (d), 126.35, 124.41, 118.20 (d), 114.80, 112.50 (Ar-C, CN), 65.39 (d, $O(CH_2)_3CH_3$), 32.28 (d, $O(CH_2)_3CH_3$), 18.50 ($O(CH_2)_3CH_3$), 12.92 ($O(CH_2)_3CH_3$). ^{31}P NMR (d-acetone, 162 MHz): δ 17.03. HRMS-ESI: *m/z* 697.2802 $[M+H]^+$, calcd. for $[C_{36}H_{47}N_2O_8P_2]^+$ 697.2802. FTIR (solid): 2233.8 (CN), 1207.6 (C-O), 1167.2 - 1104.2 (P=O) cm^{-1}.

Phthalonitrile 5.6. Phthalonitrile **5.3** (1 g, 1.8 mmol) and anhydrous nickel dichloride (55 mg, 0.4 mmol) were put in a 50 mL of two-neck round bottom flask. The flask was vacuum-refill with argon for three times and anhydrous mestylene (35 mL) was added through syringe and the solution was heated to 160 ºC. Triethyl phosphite (0.9 mL,

5.2 mmol) in 10 mL mestylene was added into the reaction solution dropwise through additional funnel in 30 min. The reaction solution was heated for 16 hours. The green solution was fractionally distilled to remove any high boiling point reagent and byproduct. The residue was purified with alumna column eluted by methanol/DCM (2/98) to afford clear viscous liquid (0.6 g, 60%). ^{1}H NMR (d-acetone, 400 MHz): δ 7.93 (s, 2H, Ar-H), 7.82 – 7.76 (m, 4H, Ar-H), 7.26 – 7.23 (m, 4H, Ar-H), 4.10 – 3.99 (m, 8H, OCH_2CH_3), 1.25 (t, J = 7.1 Hz, 12H, OCH_2CH_3). ^{13}C NMR (d-acetone, 100 MHz): δ 159.36 (d), 151.46, 134.77 (d), 127.22, 125.08, 118.90 (d), 115.58, 113.23 (Ar-C, CN), 62.53 (d, OCH_2CH_3), 16.52 (d, OCH_2CH_3). ^{31}P NMR (d-acetone, 162 MHz): δ 17.05. HRMS-ESI: *m/z* 585.1550 $[M+H]^+$, calcd. for $[C_{28}H_{31}N_2O_8P_2]^+$ 585.1550. FTIR (solid): 2232.5 (CN), 1211.7 (C-O), 1163.1 (P=O), 957.0 (C-O-P) cm^{-1}.

Pc 5.7. Phthalonitrile **5.6** (0.5 g, 0.86 mmol) was dissolved in anhydrous pentanol (15 mL). The flask was charged with argon and heated to 140 ºC. Lithium (0.05 g, 7.1 mmol) was added in small pieces carefully. The reaction solution was heated for 48 hours. After the temperature dropped to 120 ºC, anhydrous zinc acetate (0.4 g, 2.2 mmol) was added. The reaction solution was heated for ten hours. After the reaction solution cooled down to room temperature, the solution was filtered under vacuum and the solid was washed with DCM and acetone for three times. The solid was dissolved in 1N NaOH solution (10 mL) and 1N HCl solution was added to the green solution to get the precipitate out. Green solid was obtained after centrifugation. The solid was washed with water for two times and dried at 80 ºC under vacuum for 24 hours. The intermediate was put in a thick-wall tube. The tube was evacuated and refilled with argon repeatedly for three times and bromotrimethylsilane (3 mL, 22.7 mmoL) was added through plastic syringe. The sealed tube was heated to 100 ºC and remained at this temperature for four

days followed by H NMR. After the reaction, the reagent was evaporated out under vacuum. The solid was dissolved in 1N NaOH solution (10 mL) and 1N HCl solution was added to the green solution to get the precipitate out. The solid was washed with water, acetone/methanol (1/1) for two times. Then the solid was dissolve in 1N NaOH solution (2 mL) and filtered. The solution was added dropwise into the 1N HCl solution (10 mL) and ethanol (5 mL) was added. The mixed suspension was centrifuged and the product was dried under 80 ºC under vacuum for 24 hours to afford dark green shinning solid (0.06 g, 15%). ^{1}H NMR (D_2O, pH = 14, 400 MHz): δ 8.50 (s, 8H, Ar-H), 7.50 (t, 16H, Ar-H), 8.12 (d, J = 8.1 Hz, 16H, Ar-H). ^{31}P NMR (D_2O, pH = 14, 162 MHz): δ 12.04.

Phthalonitrile 5.8. 4, 5-Dichlorophthalonitrile (0.5 g, 2.5 mmol) and 4, 5-dibromobenzene-1, 2-diol (0.7 g, 2.6 mmol) were dissolved in 10 mL DMSO. The reaction solution was heated at 90 ºC under argon. Potassium carbonate (5.5 g, 40 mmol) was added in 6 portions every 5 minutes. After the addition of potassium carbonate, the reaction was proceeded for another 0.5 hours. After the reaction solution was cooled down to room temperature, the reaction solution was poured into 100 mL ice water. The solution was filtered under vacuum and brown solid was obtained. The solid was dissolved in 100 mL DCM and dried over anhydrous sodium sulfate. The crude product was purified by silica gel with the elution of hexane/ DCM (1/4) to afford earth white solid (0.8 g, 70 %). ^{1}H NMR (d-DMSO, 250 MHz): δ 7.85 (s, 2H, Ar-H), 7.52 (s, 2H, Ar-H).

Phthalonitrile 5.9. 4, 5-Dichlorophthalonitrile (0.5 g, 2.5 mmol) and 4-bromo-2, 6-dimethylphenol (1.5 g, 7.5 mmol) were dissolved in 25 mL DMSO. The reaction solution was heated at 80 ºC under argon. Potassium carbonate (1 g, × 7) was added every 5 minutes. After the addition of potassium carbonate, the reaction was proceeded

for another 3 hours. After the reaction solution was cooled down to room temperature, the reaction solution was poured into 500 mL of ice water. The solution was filtered under vacuum and yellow solid paste was obtained. The solid was dissolved in 100 mL of DCM and dried over anhydrous sodium sulfate. The crude product was purified by silica gel with the elution of hexane/ DCM (1/4) to afford white solid (0.9 g, 68%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.38 (s, 4H, Ar-H), 6.82 (s, 4H, Ar-H), 2.17 (s, 12H, Ar-H). ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 150.29, 149.24, 133.52, 133.04, 120.04, 118.47, 115.80, 110.68 (Ar-C), 16.20 (CH_3).

5.6 References

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APPENDIX A: CHARACTERIZATION DATA FOR COMPOUNDS IN CHAPTER 2

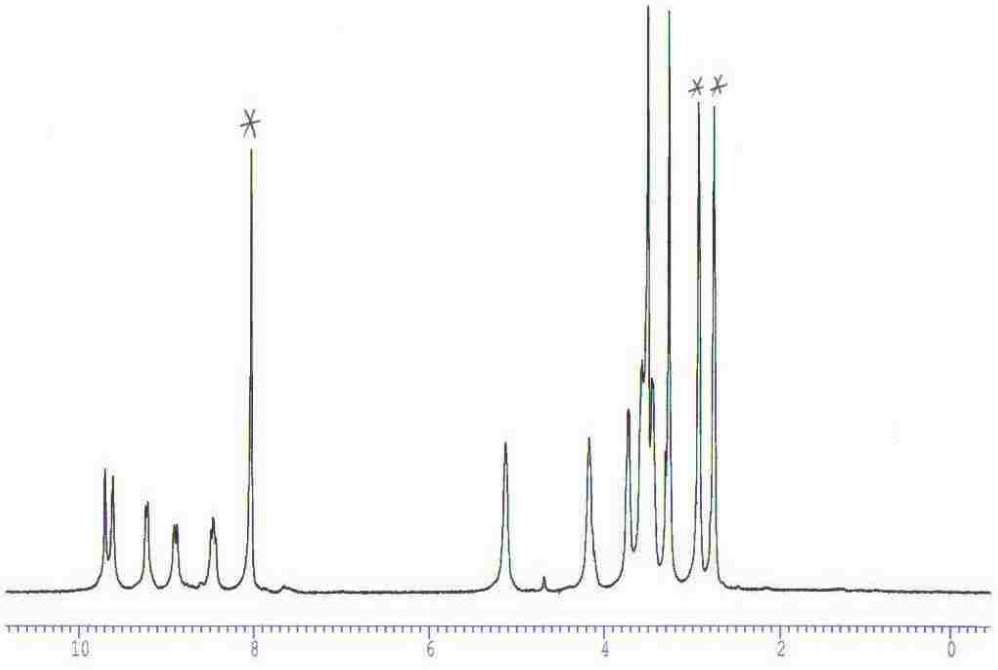

Figure A.1. ^{1}H NMR of Pc **2.6** in d-DMF (*denotes solvents).

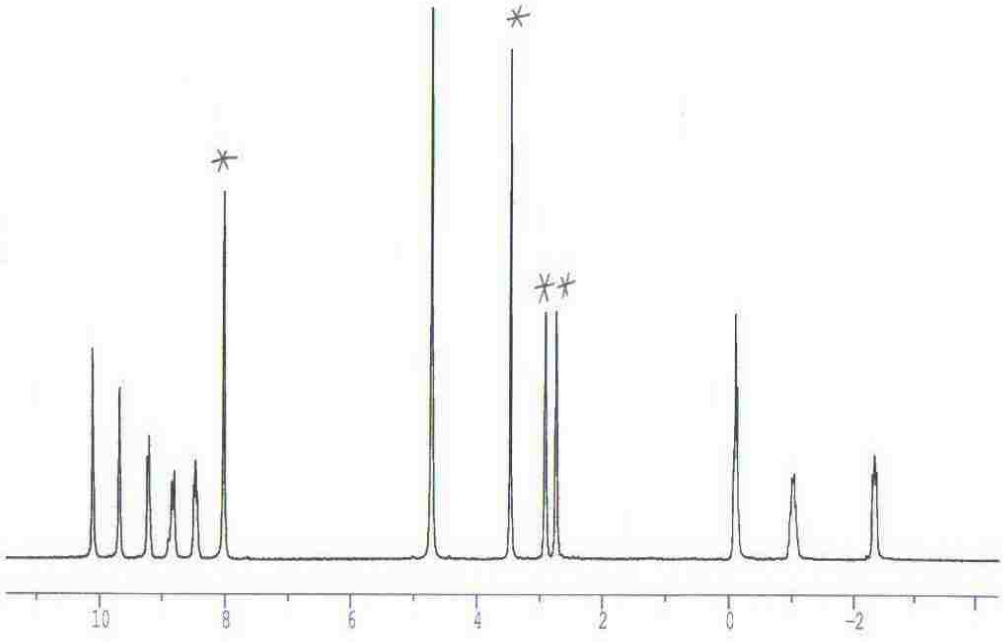

Figure A.2. ^{1}H NMR of Pc **2.15** in d-DMF (*denotes solvents).

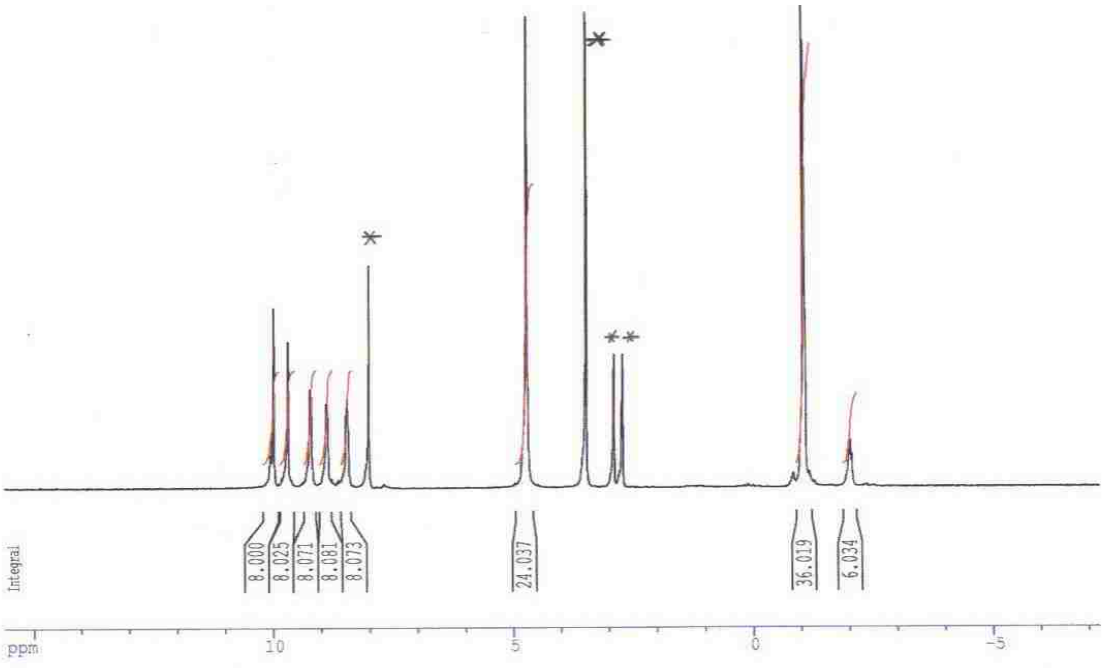

Figure A.3. [1]H NMR of Pc **2.16** in d-DMF (*denotes solvents).

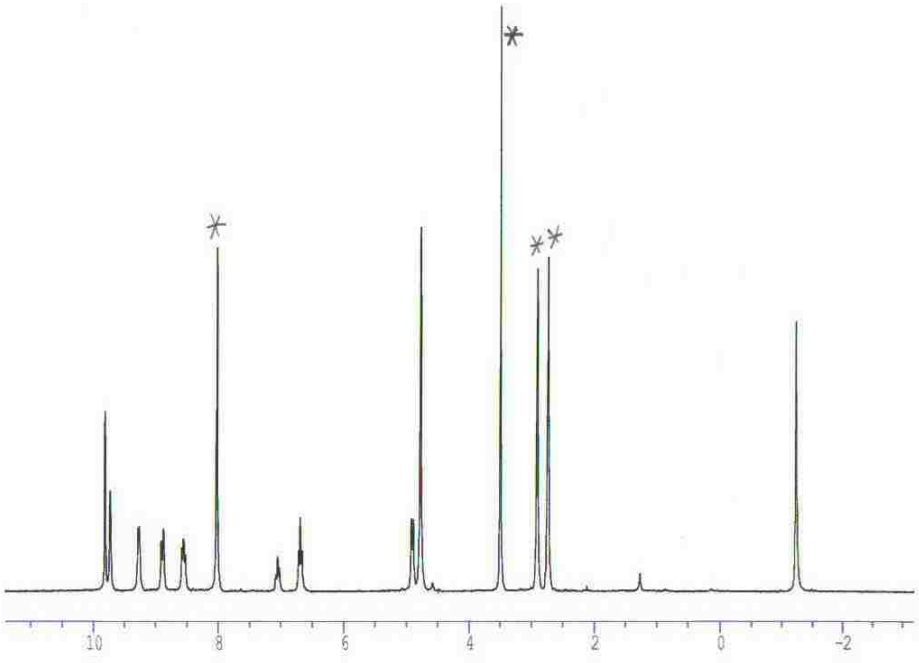

Figure A.4. [1]H NMR of Pc **2.17** in d-DMF (*denotes solvents).

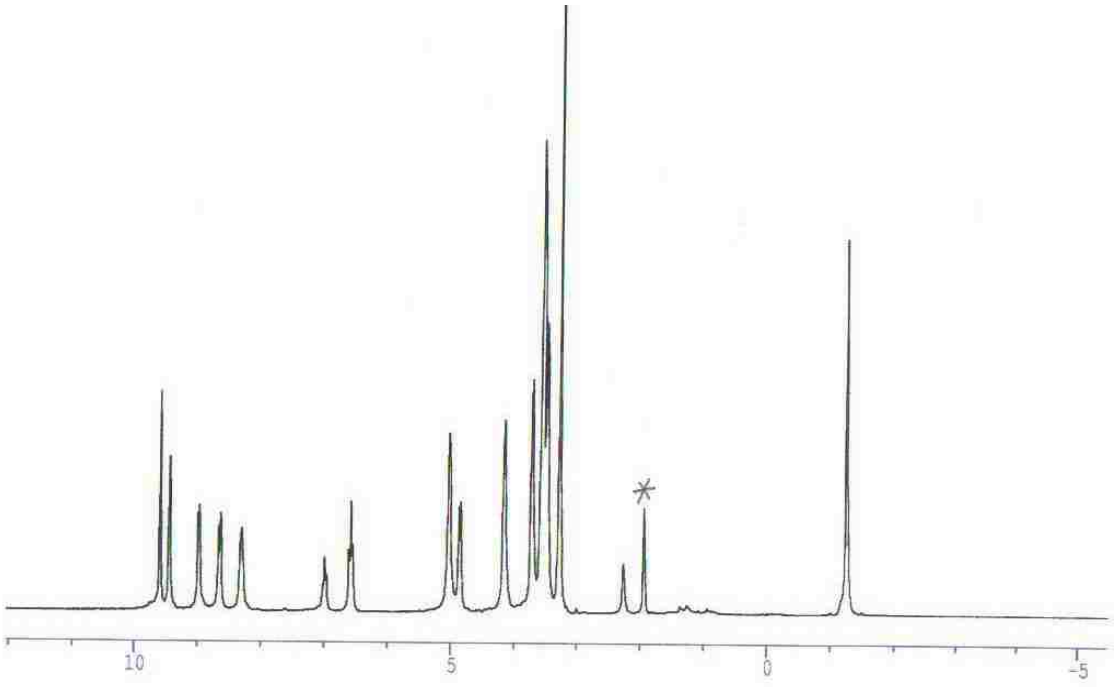

Figure A.5. ^{1}H NMR of Pc **2.18** in d-DMF (*denotes solvents).

APPENDIX B: CHARACTERIZATION DATA FOR COMPOUNDS IN CHAPTER 3

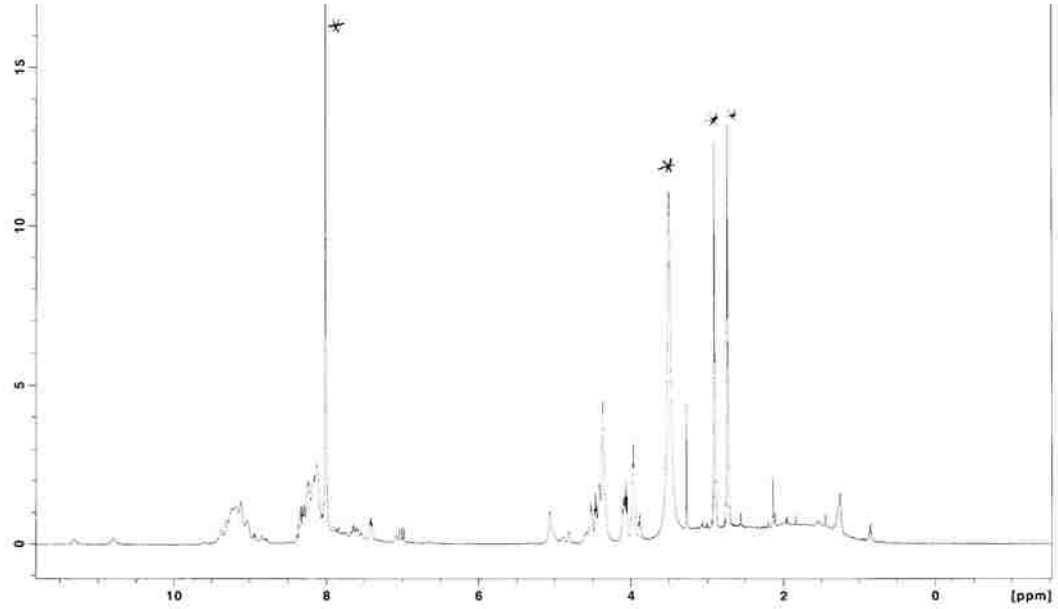

Figure B.1. ^{1}H NMR spectrum of conjugated Pc **3.7** in d-DMF (*denotes solvents).

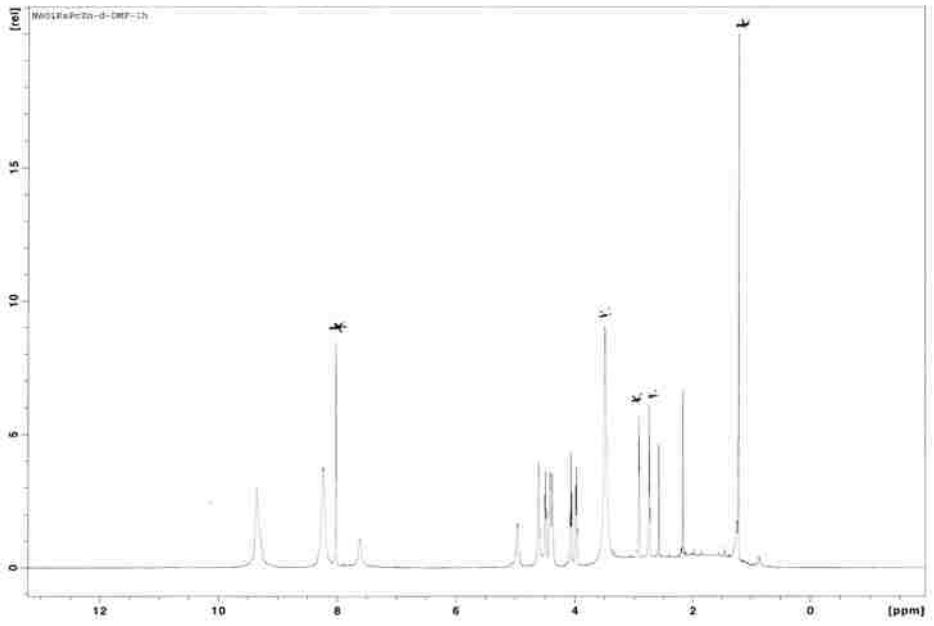

Figure B.2. ^{1}H NMR spectrum of conjugated Pc **3.8** in d-DMF (*denotes solvents).

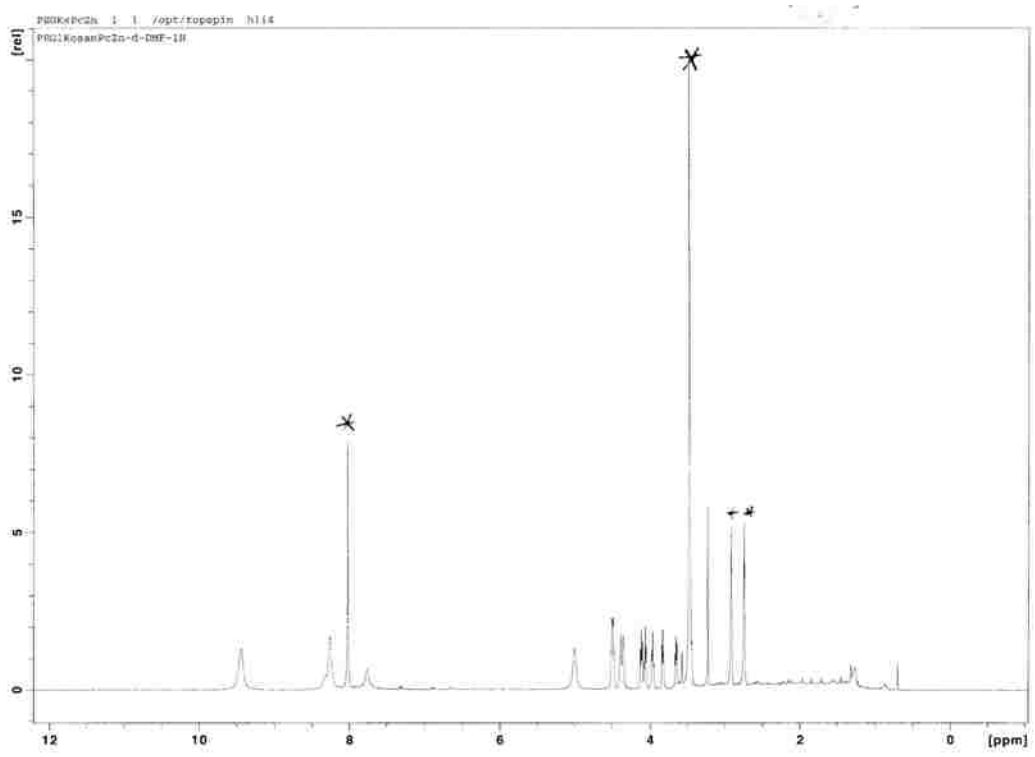

Figure B.3. ^{1}H NMR spectrum of conjugated Pc **3.9** in d-DMF (*denotes solvents).

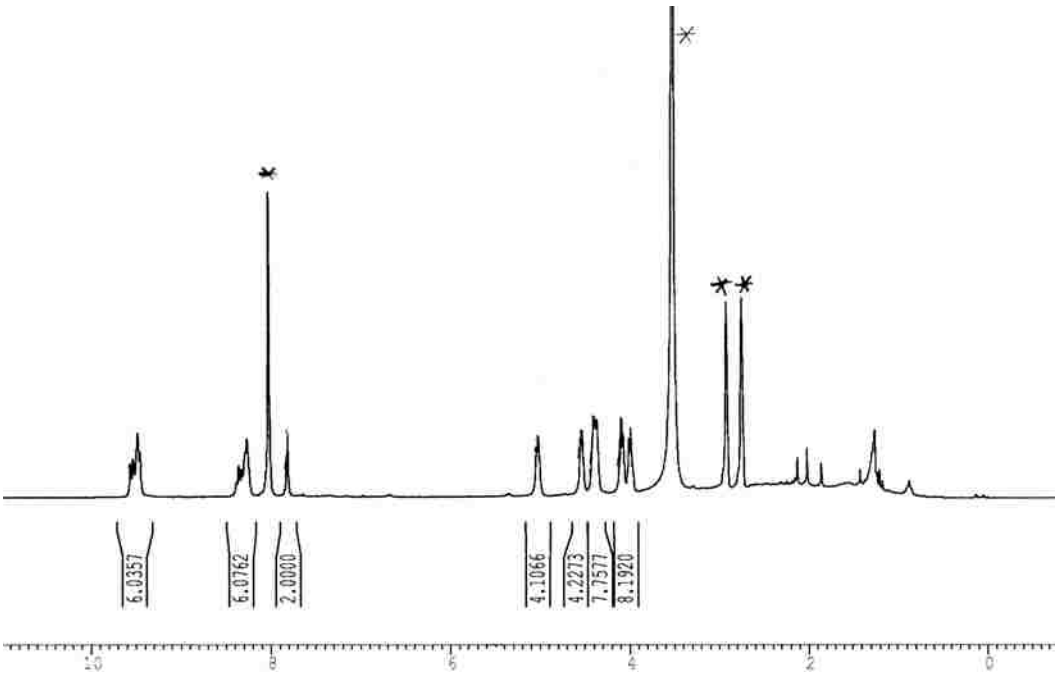

Figure B.4. ^{1}H NMR spectrum of conjugated Pc **3.10** in d-DMF (*denotes solvents).

APPENDIX C: CHARACTERIZATION DATA FOR COMPOUNDS IN CHAPTER 4

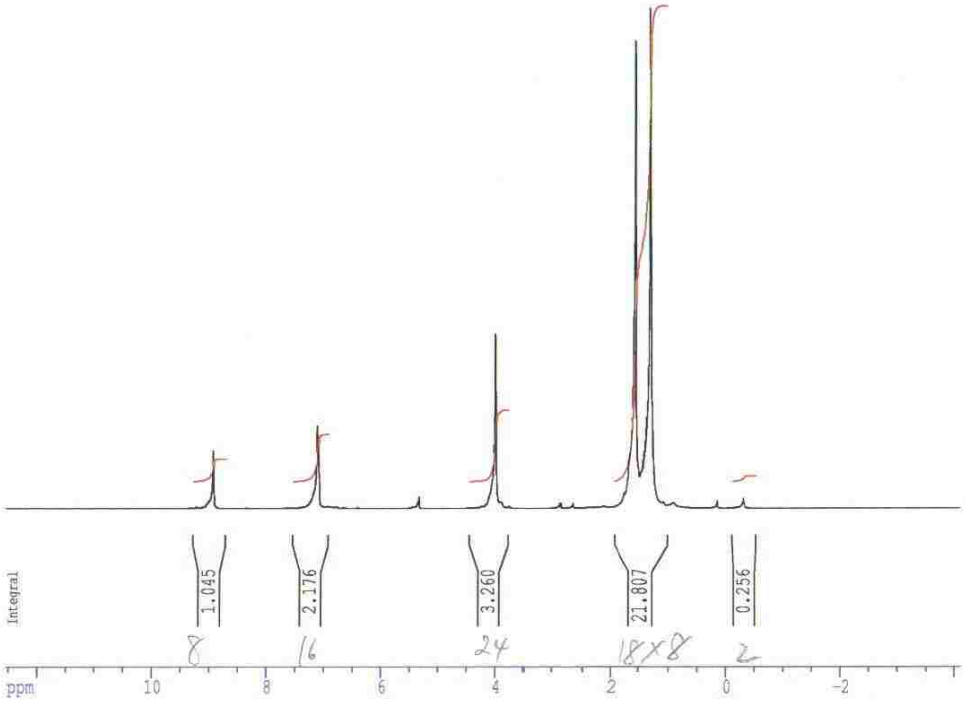

Figure C.1. ^{1}H NMR spectrum of Pc **4.2** in d-DCM (*denotes solvents).

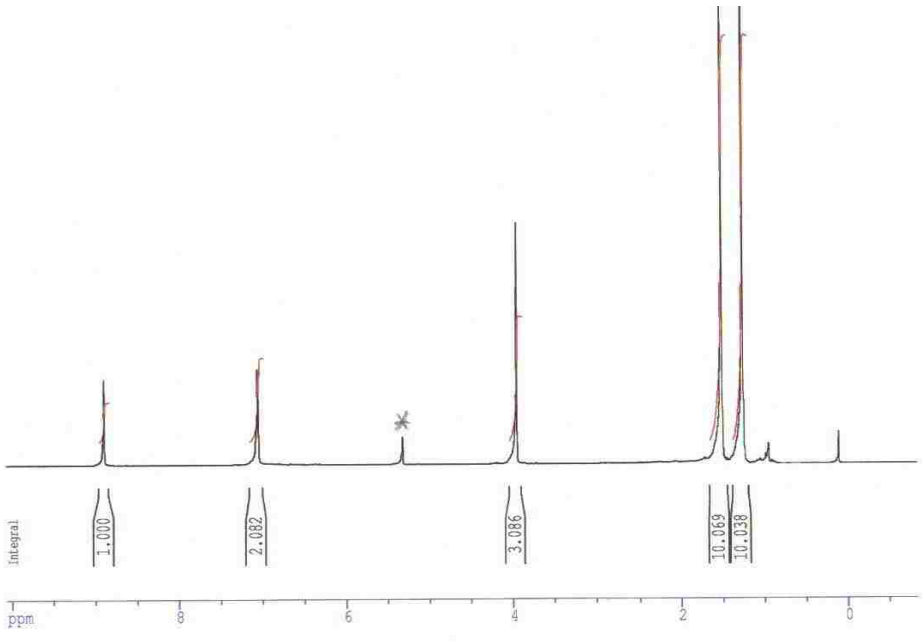

Figure C.2. ^{1}H NMR spectrum of Pc **4.3** in d-DCM (*denotes solvents).

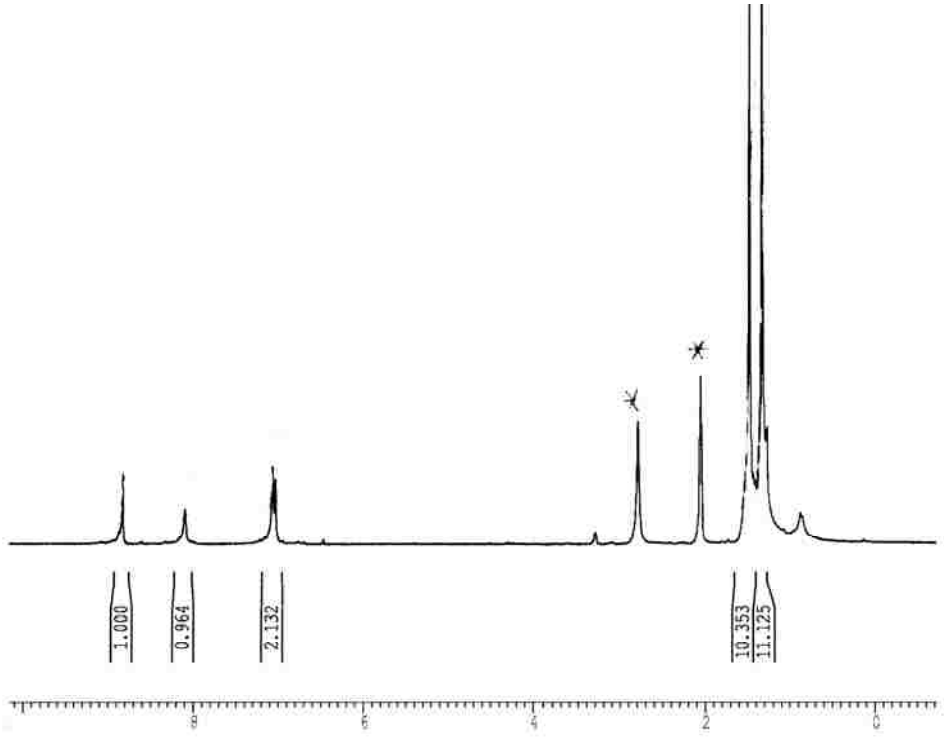

Figure C.3. [1]H NMR spectrum of Pc **4.5** in d-acetone (*denotes solvents).

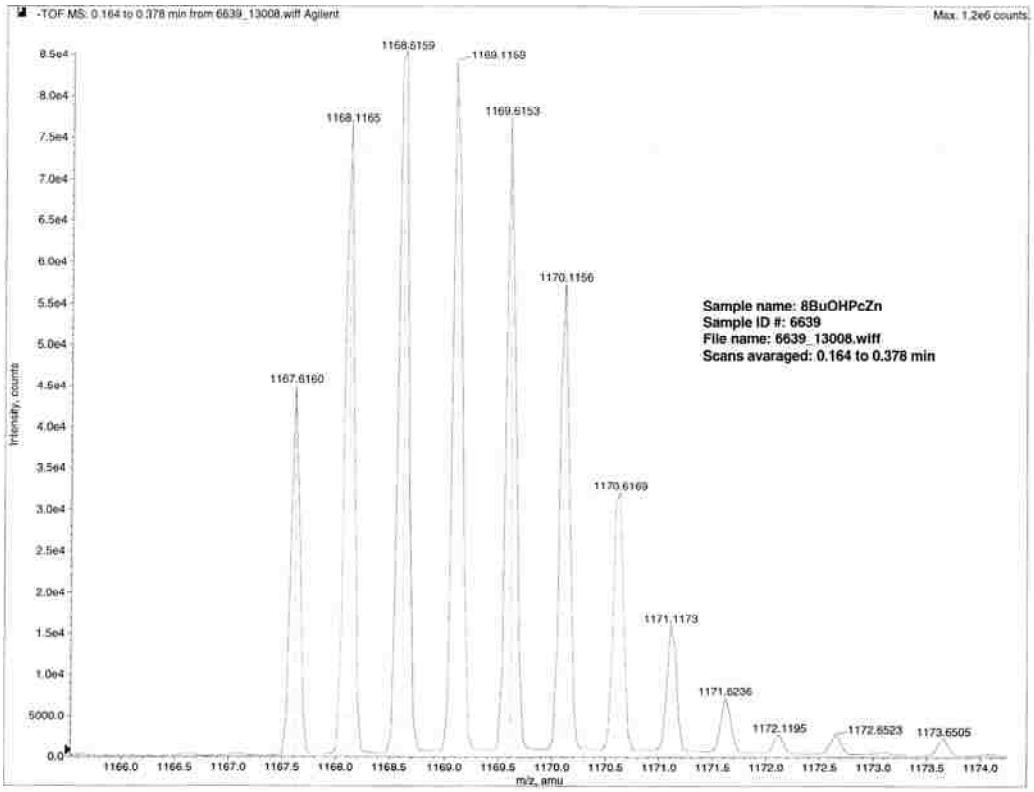

Figure C.4. HRMS-ESI spectra of Pc **4.5**.

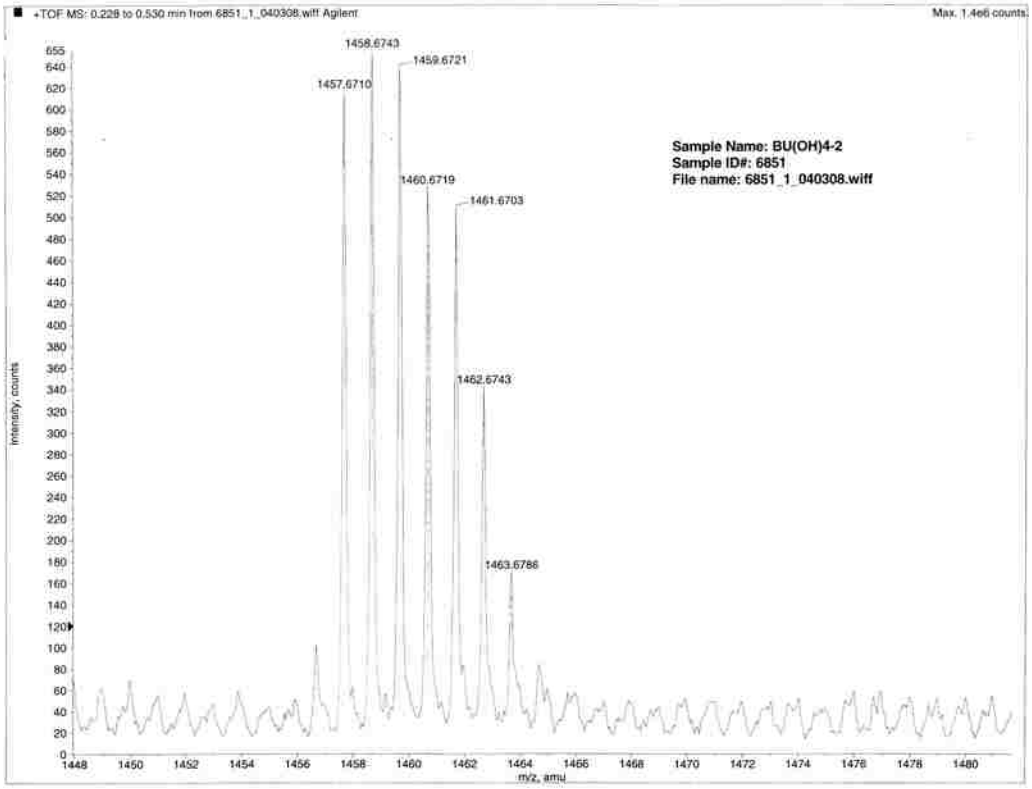

Figure C.5. HRMS-ESI spectra of Pc **4.8**.

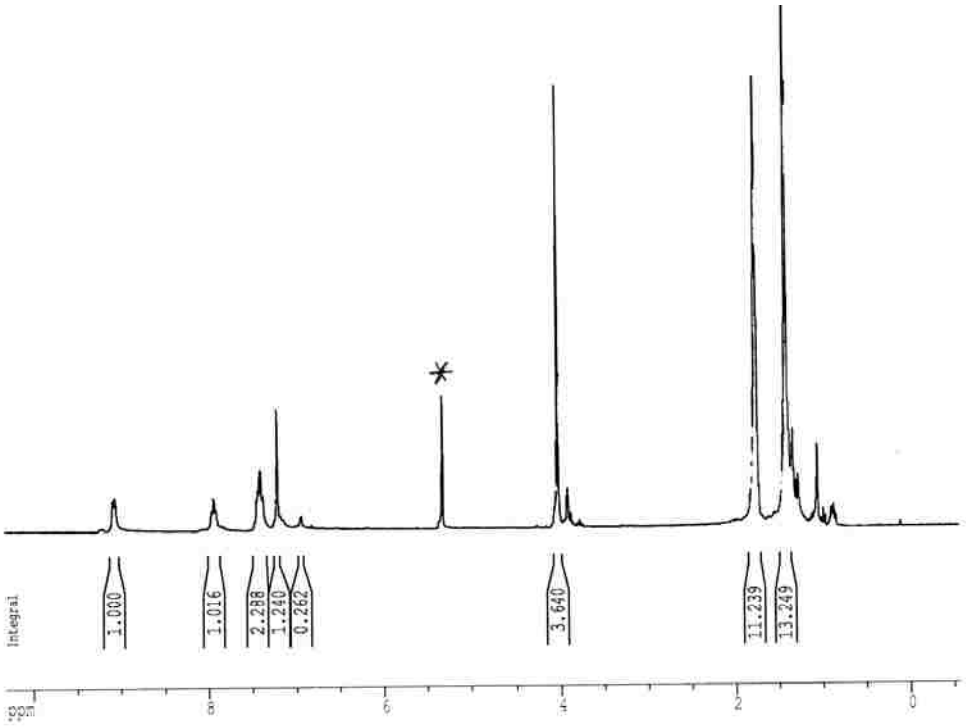

Figure C.6. ^{1}H NMR spectrum of Pc **4.10** in d-DCM (*denotes solvents).

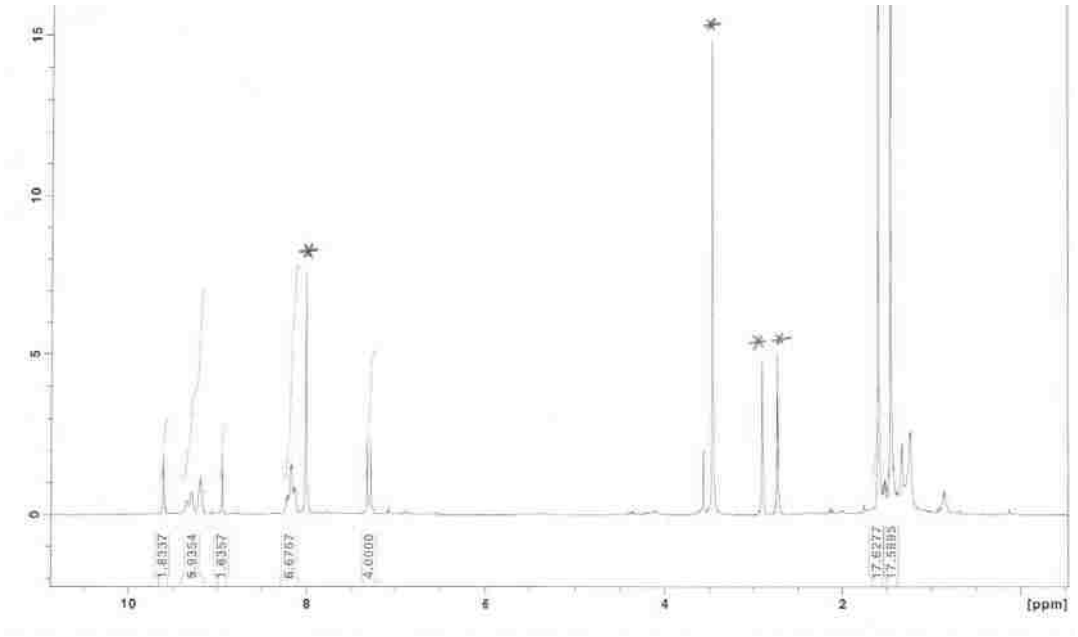

Figure C.7. [1]H NMR spectrum of Pc **4.13** in d-DMF (*denotes solvents).

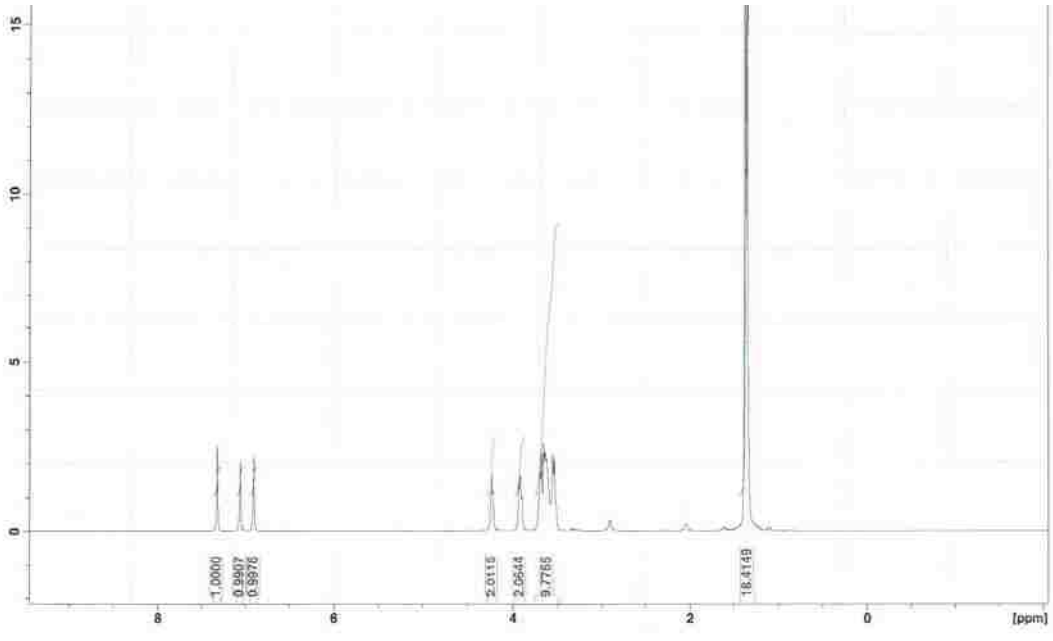

Figure C.8. [1]H NMR spectrum of phthalonitrile **4.15** in d-acetone (*denotes solvents).

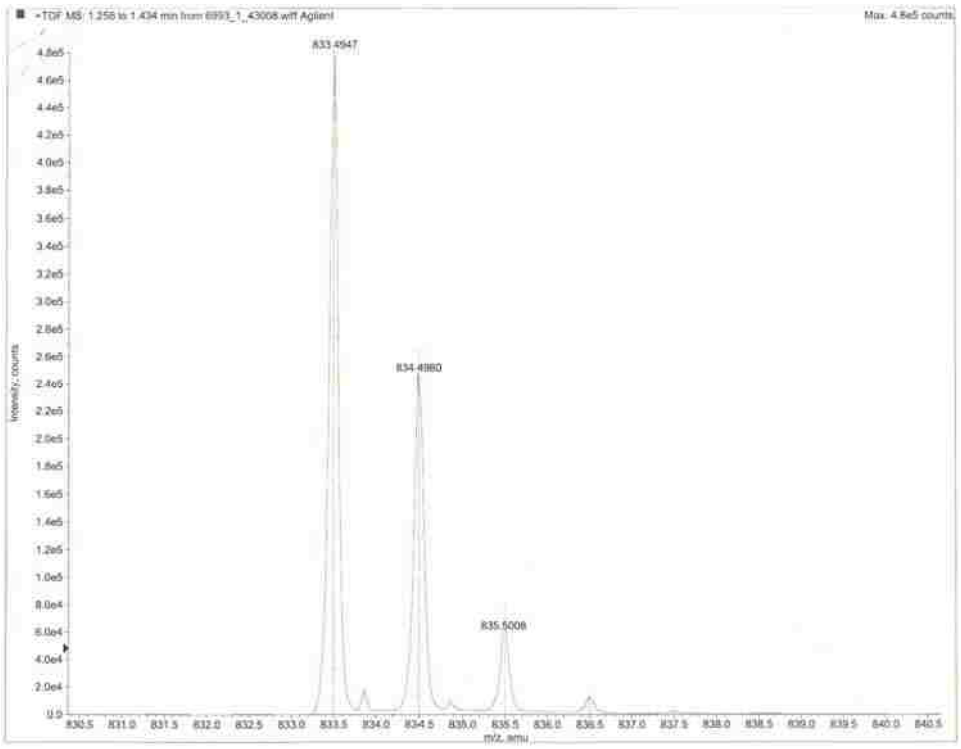

Figure C.9. HRMS-ESI spectra of phthalonitrile **4.15**.

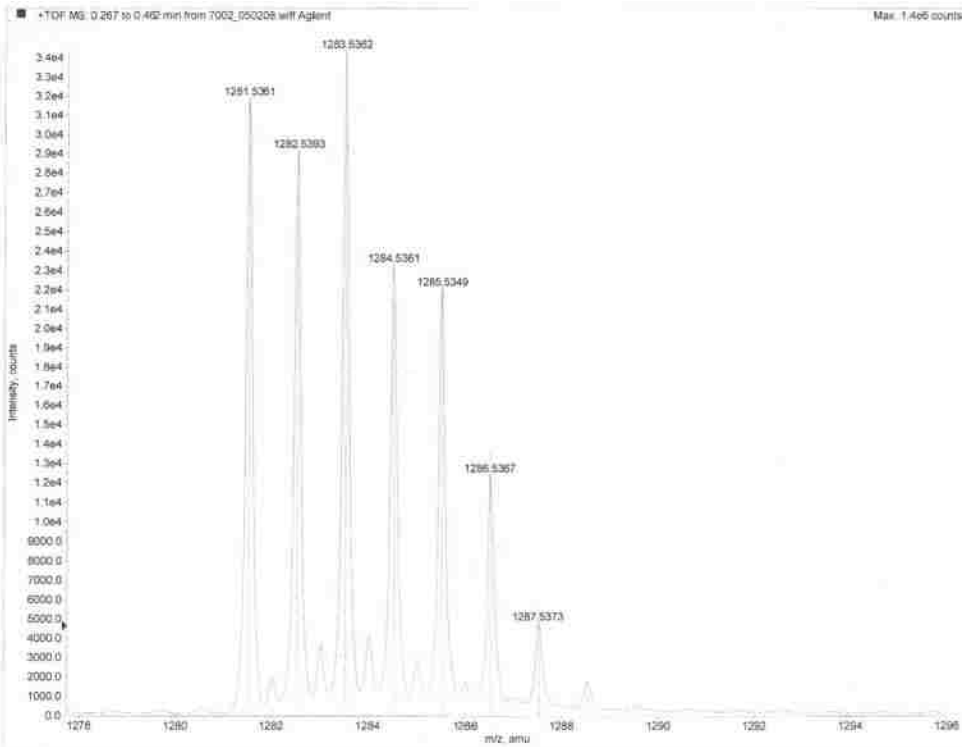

Figure C.10. HRMS-ESI spectra of Pc **4.16**.

APPENDIX D: CHARACTERIZATION DATA FOR COMPOUNDS IN CHAPTER 5

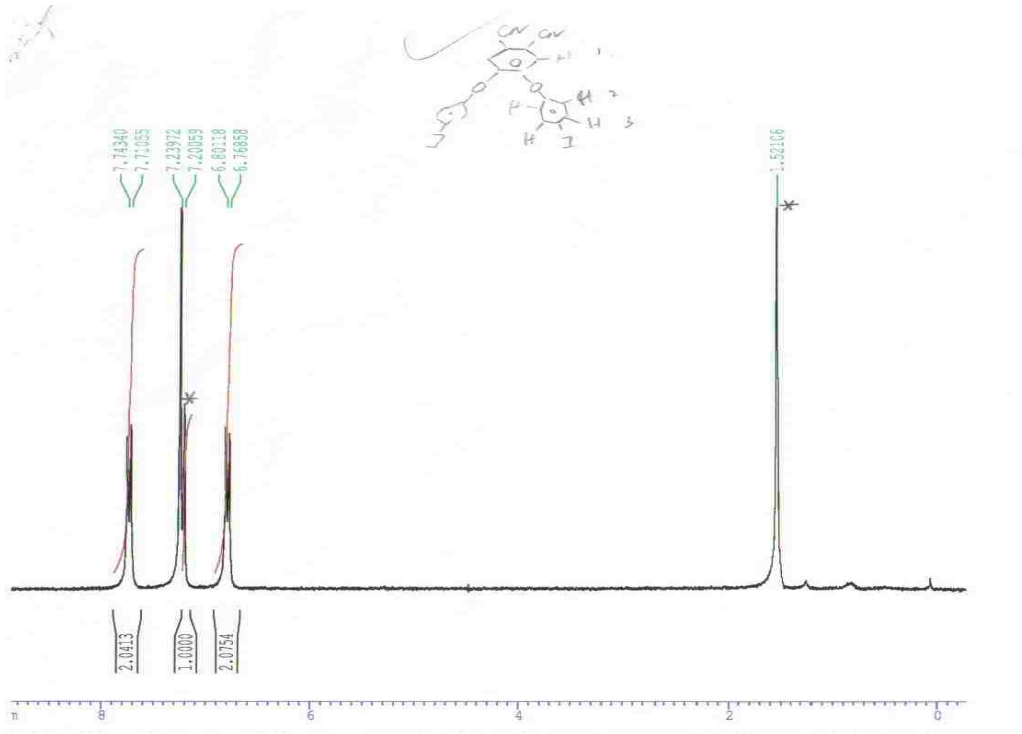

Figure D.1. ^{1}H NMR spectrum of phthalonitrile **5.3** in d-DCM (*denotes solvents).

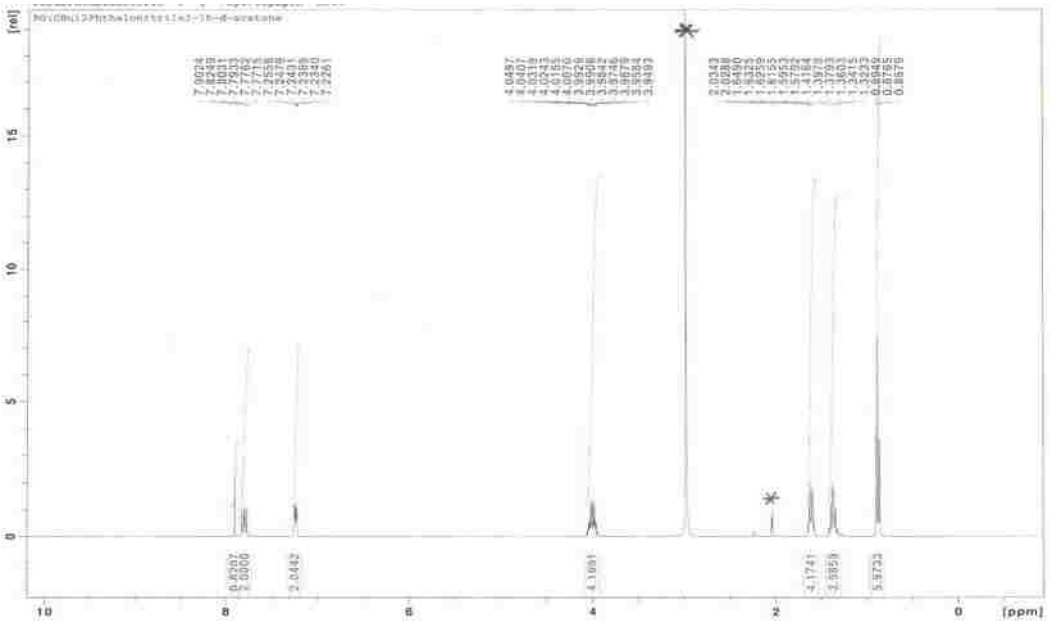

Figure D.2. ^{1}H NMR spectrum of phthalonitrile **5.5** in d-acetone (*denotes solvents).

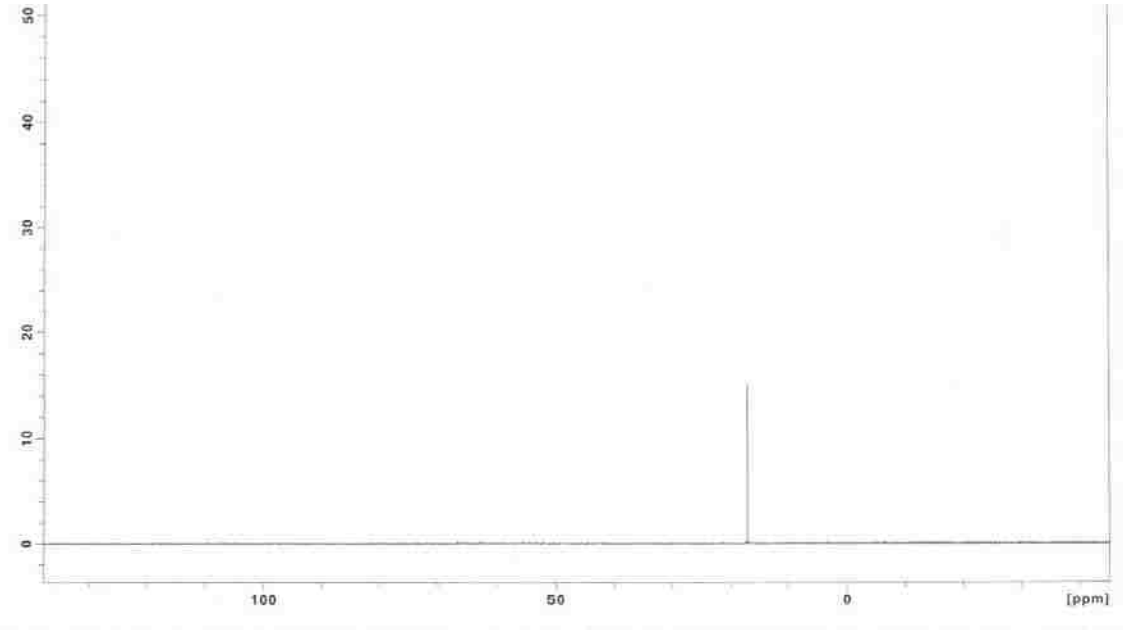

Figure D.3. ^{31}P NMR spectrum of phthalonitrile **5.5** in d-acetone.

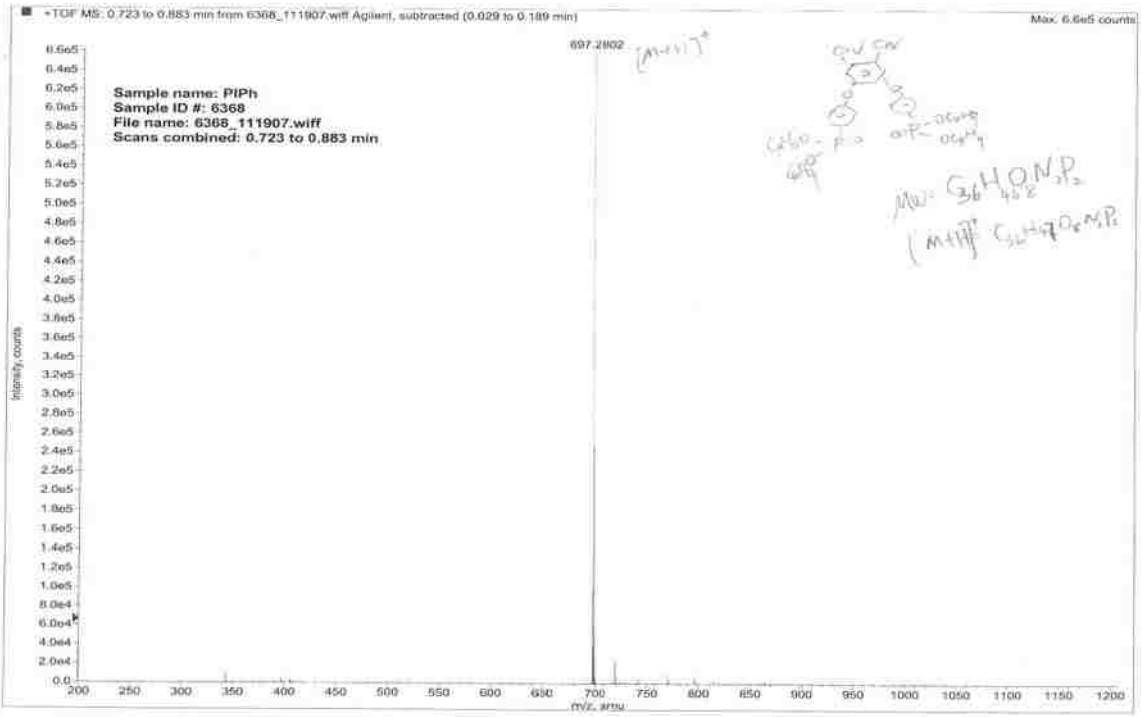

Figure D.4. HRMS-ESI spectra of phthalonitrile **5.5**.

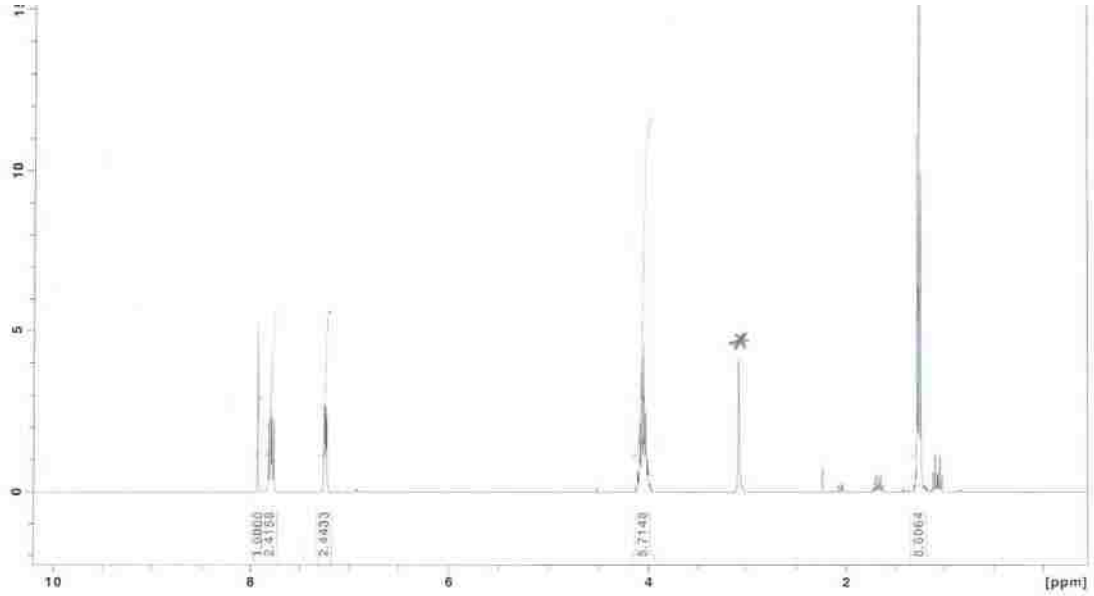

Figure D.5. [1]H NMR spectrum of phthalonitrile **5.6** in d-acetone (*denotes solvents).

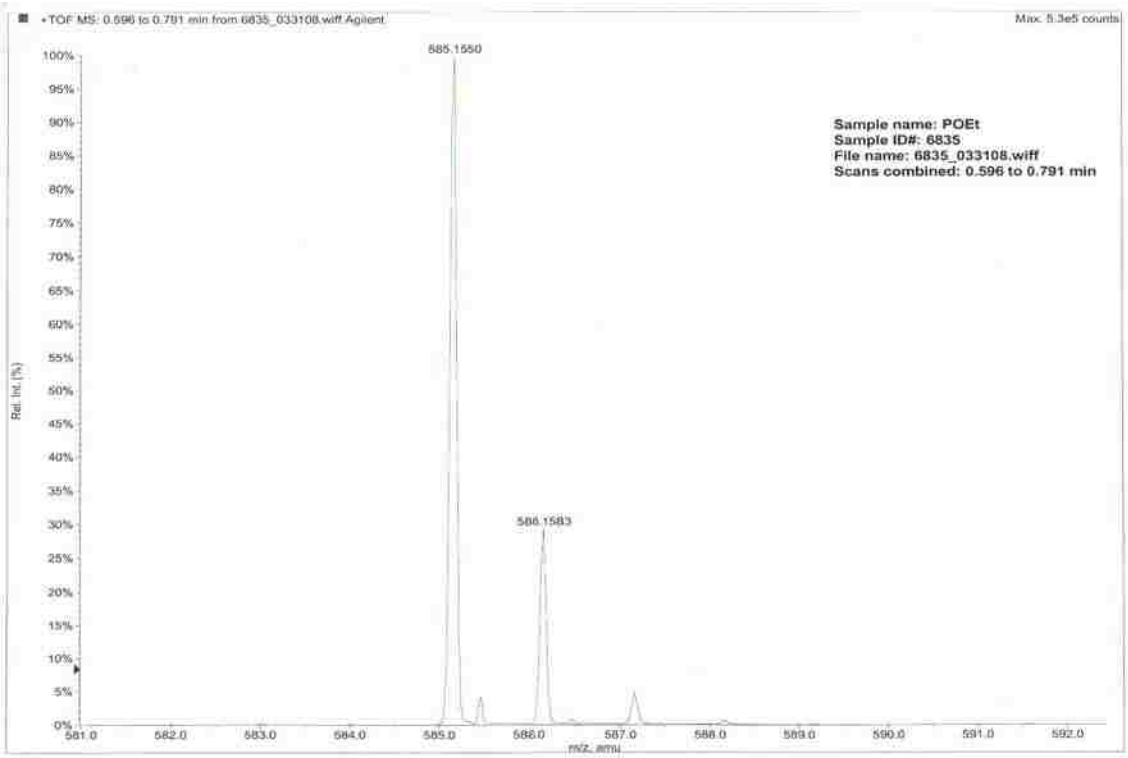

Figure D.6. HRMS-ESI spectra of phthalonitrile **5.6**.

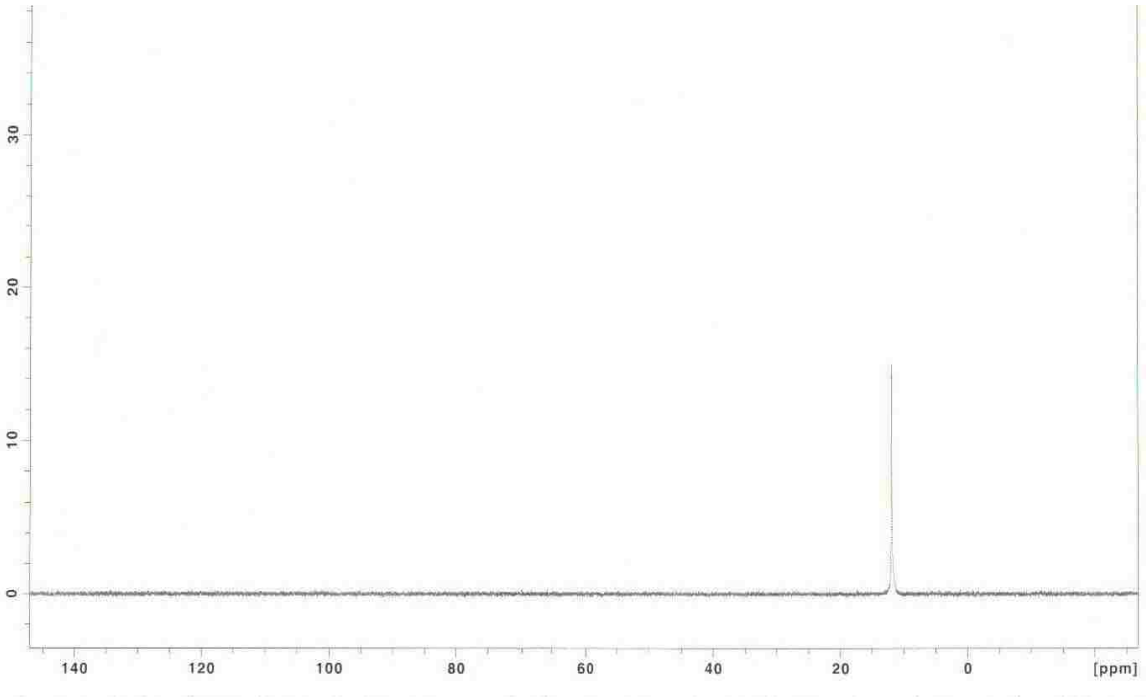

Figure D.7. ^{31}P NMR spectrum of Pc **5.7** in D_2O (pH=13).

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The author, Hairong Li, was born in November, 1978, in Tianjin, China. She grew up and spent all her time at her hometown. She graduated from Nankai University in her hometown with bachelor degree of science in chemistry in 2001. After graduation, she stayed in the same University to finish her master degree of science in organic chemistry in 2004. In the August of 2004, she came to Louisiana State University and joined Dr. Vicente's group. She designed and synthesized three series of phthalocyanine derivatives for applications in PDT and BNCT for cancer under the guidance of Dr.Vicente. She will receive her doctoral degree on Dec. 19th, 2008.