

T.C.

**GEBZE INSTITUTE OF TECHNOLOGY
INSTITUTE OF ENGINEERING AND NATURAL
SCIENCES**

**AMPHIPHILIC AND WATER SOLUBLE
PHTHALOCYANINES**

Mahmut Ali ERMEYDAN

MASTER THESIS

DEPARTMENT OF CHEMISTRY

GEBZE

2008

T.C.

**GEBZE INSTITUTE OF TECHNOLOGY
INSTITUTE OF ENGINEERING AND NATURAL
SCIENCES**

**AMPHIPHILIC AND WATER SOLUBLE
PHTHALOCYANINES**

Mahmut Ali ERMEYDAN

MASTER THESIS

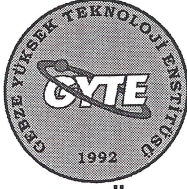
DEPARTMENT OF CHEMISTRY

SUPERVISOR

Dr. Fabienne DUMOULIN

GEBZE

2008



GEBZE YÜKSEK
TEKNOLOJİ
ENSTİTÜSÜ

MÜHENDİSLİK VE FEN BİLİMLERİ ENSTİTÜSÜ
JÜRİ ONAY FORMU

JÜRİ

ÜYE (TEZ DANIŞMANI): Yrd. Doç. Dr. Fabienne DUMOULIN

ÜYE : Prof. Dr. Vefa AHSEN

ÜYE : Prof. Dr. Yıldırım ERBİL

Gebze Yüksek Teknoloji Enstitüsü Mühendislik ve Fen Bilimleri Enstitüsü Yönetim Kurulu'nun 22/06/2008 tarih ve 2008/22 sayılı kararı ile yukarıdaki öğretim elemanlarından oluşmuş jüri tarafından düzenlenen 27/06/2008 tarihli Tez Savunma Tutanağı neticesinde Yüksek Lisans / Doktora öğrencisi Mahmut Ali ERNEVDAN'ın çalışması GYTE Mühendislik ve Fen Bilimleri Yönetim Kurulu/...../..... tarih ve/....../..... sayılı kararıyla KİMYA.....Anabilim Dalında Yüksek Lisans / Doktora tezi olarak onaylanmıştır.

İMZA/MÜHÜR

ÖZET

TEZİN BAŞLIĞI: Amfifilik ve Suda Çözünen Ftalosiyeninler

YAZAR ADI: Mahmut Ali ERMEYDAN

Ftalosiyeninler (Pc) 1927'den beri bilinen bileşikler olup pigment, boya ve katalizör olarak çok miktarda tüketilmekte ve sahip oldukları müstesna fiziksel ve kimyasal kararlılıkları ve ilginç makrosiklik yapıları nedeniyle çok değişik alanlarda araştırmalara konu olmaktadır. Farklı süstitüentlere sahip birçok Pc türevleri sentezlenmiştir. Ancak karbonhidrat süstitüentli Pclerin literatürde çok az olduğu farkedilmiştir.

Bu yüksek lisans tezinde, ftalosiyenin bileşikleri üzerine bir monosakkarit olan galactoz şekeri süstitüe edilmiştir. Bu yeni Pc türevleri simetrik (A4 tipi) ya da asimetrik (AB3 tipi) yapıdadırlar. Böylece amfifilik özellik gösteren, suda çözünebilen ve kendikendilerine düzenlenebilen bileşikler elde edilmiştir.

Bu tezin ileri çalışmalarında uygulama açısından suda-çözünen simetrik Pc bazı kanser türlerinin tedavisinde kullanılan Fotodinamik Terapi yöntemiyle test edilmek üzere hazırlanmıştır. Asimetrik Pc ise LB metodu kullanılarak piroelektrik özelliklerinin incelenmesi için hazırlanmıştır.

SUMMARY

TITLE of the THESIS: Amphiphilic and Water Soluble Phthalocyanines

NAME of the AUTHOR: Mahmut Ali ERMEYDAN

Phthalocyanines (Pc) are known since 1927 to be used as dyes, pigments and catalysts in large amounts. Because of their excellent physical and chemical stability and interesting macrocyclic structures they have taken place in various research areas. Many derivatives with different substituents were prepared to give them different properties. However, it was realized that a few research have been made on Pcs which have carbohydrates substituents.

In this thesis, a monosaccharide (galactose) was grafted to phthalocyanine compounds by glycosylation reactions. These phthalocyanine derivatives are symmetric (A4 type) and asymmetric (AB3 type). Thus, compounds which have water-solubility and self-assembly property were obtained.

In terms of application as further research of this thesis, water-soluble symmetric phthalocyanines were prepared to be tested with Photodynamic Therapy which is a treatment for some types of cancer. The amphiphilic phthalocyanine was prepared to investigate pyroelectrical properties from their films prepared using LB method.

ACKNOWLEDGMENTS

I would like to acknowledge the support, teaching, encouragement, and patience of Dr. Fabienne Dumoulin, without whom I would not have succeeded, and Prof. Dr. Vefa Ahsen who welcomed me among his team. I would also like to acknowledge the entire Department of Chemistry as a great environment for young chemists to gain knowledge, deep understanding, and priceless mentoring and I would like to thank to Dr. Dominique Lafont who accepted me in his lab in Université Claude Bernard for three months. Finally, I would like to thank to my family for their moral support.

TÜBİTAK is gratefully acknowledged for its financial support.

INDEX

	Page
SUMMARY	iv
ÖZET	v
ACKNOWLEDGEMENTS	vi
INDEX	vii
SYMBOLS AND ABBREVIATIONS	x
LIST OF FIGURES	xi
LIST OF SCHEMES	xii
1. INTRODUCTION	1
2. THEORY	3
2.1. Phthalocyanines	3
2.1.1. General Synthesis Pathways of Phthalocyanines	4
2.1.1.1. Metal-Free Phthalocyanines	4
2.1.1.2. Metal Phthalocyanine Complexes	6
2.1.1.3. Synthesis of Asymmetric Phthalocyanines (AB3)	11
2.1.2. Applications of Phthalocyanines	15
2.1.2.1. General Applications	15
2.1.2.2. Photodynamic Therapy	15
2.1.2.3. Self Assemblies: Liquid Crystals and Monolayers	18
2.2. Glycosylation	23

2.2.1. Glycosyl Donors	23
2.2.2. Stereochemistry Control	24
3. PURPOSE AND THE COVER OF THE THESIS	26
3.1. Existing Carbohydrated Phthalocyanines	26
3.2. Water Soluble Phthalocyanines for PDT	31
3.3. Amphiphilic Phthalocyanines for Self-Assemblies	33
3.4. Presentation of Target Molecules	36
4. DISCUSSION	38
4.1. Synthesis of the galactose substituted water soluble ZnPc	38
4.1.1. Synthesis of the nitrile 9	38
4.1.2. Synthesis of the Pc 11 , purification, analyses	40
4.2. Synthesis of the Amphiphilic NiPc 14	44
4.2.1. When to proceed to the glycosylation?	44
4.2.2. Starting nitriles	45
4.2.3. Pc formation and glycosylation	45
5. CONCLUSION	48
6. EXPERIMENTAL	49
6.1 Reagents and equipments	49
6.2. Synthesis of Precursors (1-7)	51
6.2.1. 4-nitrophthalimid (1)	51
6.2.2. 4-nitrophthalamid (2)	52
6.2.3. 4-nitrophthalonitril (3)	53

6.2.4. 1,2,3,4,6-pentha-O-benzoylgalactopyranose (4)	54
6.2.5. 2,3,4,6-tetra-O-benzoylgalactopyranose (5)	55
6.2.6. 4,5-dichlorophthalonitrile (6)	56
6.2.7. 4,5-bis(hexylthio)phthalonitrile (7)	57
6.3. Synthesis of New Compounds (8-13)	58
6.3.1. 4-[2,3,4,6-tetra-O-benzoylgalactopyranosyloxy]phthalonitrile(8)	58
6.3.2. 4-(galactopyranosyloxy)phthalonitrile(9)	59
6.3.3. 4-(2 {2[2(2-hydroxyethoxy)ethoxy]ethoxy} ethoxy)phthalonitrile (10)	60
6.3.4. [2(3),9(10),16(17),23(24)-Tetrakis(α/β -D-galactopyranosyloxy) phthalocyaninato] zinc (11)	61
6.3.5. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-(2 {2[2(2-hydroxy ethoxy)ethoxy]ethoxy} ethoxy)) phthalocyaninato nickel(II) (12)	62
6.3.6. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4- {2[2(2 {2[(2,3,4,6-tetra-O-benzoylgalactopyranosyl)oxy]ethoxy} ethoxy)ethoxy]ethoxy}) phthalocyaninato nickel(II) (13)	64
6.3.7. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-[2-(2-{2-[2-(galactopyranosyloxy)ethoxy]ethoxy} ethoxy)ethoxy]) phthalocyaninato nickel(II)(14)	66
7. STRUCTURES AND SPECTRA OF THE PRODUCTS (Annex)	67
7.1. Structures Of All Products	67
7.2. Spectra Of All Products	69
REFERENCES	77
CURRICULUM VITAE	81

SYMBOLS AND ABBRAVIATIONS

Pc	Phthalocyanine
Pc H ₂	Metal-Free Phthalocyanine
MPc	Metallo Phthalocyanine
DMF	Dimethyl formamide
UV/Vis	Ultra Violet/Visible
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene(1,5-5)
FT-IR	Fourier Transform Infrared
NMR	Nuclear Magnetic Resonance
ES	Electron Spray
FAB	Fast Atomic Bombardment
TLC	Thin Layer Chromatography
MALDI	Matrix-Assisted Laser Desorption/Ionization
Å	Angstrom
ICI	International Chemical Imperial
PDT	Photodynamic Therapy
APT	Attach Proton Test
DEPT	Distortionless Enhancement by Polarization Transfer
DSC	Differential Scanning Calorimetry
HPLC	High Pressure Liquid Chromatography
MW	Microwave

LIST OF FIGURES

<u>Figure</u>	<u>Page</u>
2.1: A family of four tetrapyrrolic macrocycles	3
2.2:	8
2.3:	9
2.4: Mechanisms (types I and II) of ROS (reactive oxygen species) generation by combination of light, photosensitizer (P), and ground-state oxygen ($^3\text{O}_2$). Ground-state photosensitizer (S_0) is irradiated with visible light generating excited singlet state photosensitizer (S_1). S_1 can relax back to excited state photosensitizer (T_1) generating superoxide radical ($^3\text{O}_2^{\cdot-}$) (mechanism type I) and/or singlet oxygen ($^1\text{O}_2$) (mechanism type II)	17
2.5: A schematic illustration showing a spread monolayer at the air/water interface	19
2.6: A schematic illustration showing the components of an amphiphile (left), and the orientation of an amphiphile adopted at an interface (right).	20
2.7: Schematic illustration of a Langmuir film balance with a Wilhelmy plate electrobalance measuring the surface pressure, and barriers for reducing the available surface area.	21
2.8:	25
3.1:	32
3.2:	32
3.3:	35
3.4: Surface pressure-area isotherm.	35
3.5: Structure of 11	36
3.6: Structure of amphiphilic Pc 14	37
4.1: HPLC chromatogram of ZnPc 11 with a retention time of 23 min. Mobile phase: water 88 %, acetonitrile 12%.	41
4.2: UV-Vis spectrum of ZnPc 11 in water	42
4.3: UV-Vis Spectrum of Pc 13 in Toluene	42
4.4: UV-Vis Spectrum of Pc 13 in CHCl_3	42
4.5: UV-Vis Spectrum of Pc 14 in CHCl_3	42

LIST OF SCHEMES

Schemes	Page
2.1:	5
2.2:	5
2.3:	6
2.4:	7
2.5: Synthesis of chloro[subphthalocyaninato]boron (III)	9
2.6: The Synthesis of Superphthalocyanines from Phthalonitrile	10
2.7: Asymmetrical preparation of phthalocyanine using succinimide	12
2.8: Asymmetrical preparation of phthalocyanine using diisoiminoindoline	12
2.9:	13
2.10:	23
2.11:	24
2.12, 2.13:	25
3.1: First carbohydrated phthalocyanine	27
3.2: Reagents and conditions: (i) DMF, K ₂ CO ₃ , rt; (ii) DMAE, ZnCl ₂ , reflux.	28
3.3: Reagents and conditions: (i) NaH, toluene, N ₂ , 70°C; (ii) ZnCl ₂ , DMAE, N ₂ , reflux; (iii) TFA/H ₂ O (9:1), rt.	28
3.4: Preparation of galactose-containing Si(IV)Pcs	29
3.5:	30
3.6:	30
3.7:	31
3.8: Synthesis of water soluble Pc	33
3.9:	34
4.1: Synthesis of galactose substituted water soluble ZnPc (11)	38
4.2: Synthesis of asymmetric Pc 14	44

1. INTRODUCTION

Sugars- or saccharides- are the most abundant bio-molecule on the planet. They are important in a number of biological roles. Most obviously they are known as a major component of your diet. Insoluble sugars also function as structural material in the cell walls of plants and bacteria and in the connective tissue and cell coats of animals. Sugar polymers serve to lubricate skeletal joints. Small sugars (one or two carbohydrates units) are highly water-soluble. Sugars can be attached to proteins (in glycoproteins) and lipids (in glycolipids) and these *glycosylated* compounds serve (i) as antigenic sites; (ii) provide signals that determine the cellular localization of proteins and (iii) function as signals that allow cells to recognize each other and adhere in the formation of tissues and organs.

With this biological background, the *O*-glycosylation, which is an important organic synthetic pathway to attach a sugar to other sugar moieties or other molecules, is again becoming more important. From a synthetic point of view, the efficiency of the *O*-glycosylation reaction generally involves high chemical yields as well as regio- and stereoselectivity. Among them, high regioselectivity is easily realized by the selective protection of the hydroxyl groups of the glycosyl acceptor. Although great achievements in the development of versatile and efficient glycosylation and building block strategies have been made during the last years, there is still the need for more efficient procedures to prepare glycoconjugates.

Phthalocyanines (Pcs) have been known for more than seventy years. These compounds have been widely investigated as advanced materials for diverse applications, including photobiological and medical applications. Phthalocyanines have characteristic absorption spectra, with a Soret band at approximately 350 nm and a usually narrow but very strong Q band around 675 nm. In addition to being red shifted compared to porphyrins, light absorption of phthalocyanines is approximately two orders of magnitude stronger than the highest Q band absorption of a porphyrin. These spectral characteristics make Pcs being considered as photosensitizers of the second generation, and they are now widely used as Photodynamic Therapy (PDT)

agents. The photophysical properties of the phthalocyanine dyes are strongly influenced by the presence and nature of the coordinated central metal. Closed shell, diamagnetic ions (such as Zn^{2+} , Al^{3+} and Ga^{3+}), confer to Pcs complexes excellent generation of singlet oxygen capabilities. Their low dark toxicity is another key point to be used as photosensitizers. The overall photosensitizing properties of a Pc complexe can be tailored by the nature of its substituents, especially on a solubility point of view, and by the choice of the center metal.

Pcs are known as well to exhibit self-assembling properties. Depending on their substitution pattern, it is possible to obtain organized supramolecular edifices, such as liquid crystals or monolayers at the air-water-interface. Amphiphilicity (often resulting of asymmetric substitution pattern) of the Pcs allows to obtain easily such monolayers.

Phthalocyanine–carbohydrate conjugates are uncommon. We decide to develop the synthesis of carbohydrated Pcs, to obtain potential photosensitizers on a first part, and amphiphilic Pcs in which the carbohydrate will be the hydrophilic part. The monolayers at the air-water interface of this later Pc will be studied in further works.

2. THEORY

2.1 Phthalocyanines

Phthalocyanines were first synthesized as byproducts of industrial chemical reactions in the early twentieth century. The first academic reports on phthalocyanines were published by Linstead and coworkers in 1934 [1]. The dyes which are usually blue or green in color have been widely used as colorants. Their electro-optic behavior has led to their use in xerography (photocopying and laser printing) [2]. Phthalocyanines have also potential use in a variety of other applications, including nonlinear optical generation and limiting [3], photodynamic therapy [4], photovoltaics [5], sensors [6], electrochromic displays [7], and information storage [8]. Phthalocyanines are a member of the class of compounds known as tetrapyrrolic macrocycles. Other members of this class (Figure 2.1) include porphyrins and tetraazaporphyrins (i.e. porphyrazines). Phthalocyanines might be called tetrabenzotetraazaporphyrin as well. Phthalocyanines have a strong optical absorbance in the red and near-IR portions of the electromagnetic spectrum, and are stable under a wide range of thermal and electrochemical conditions.

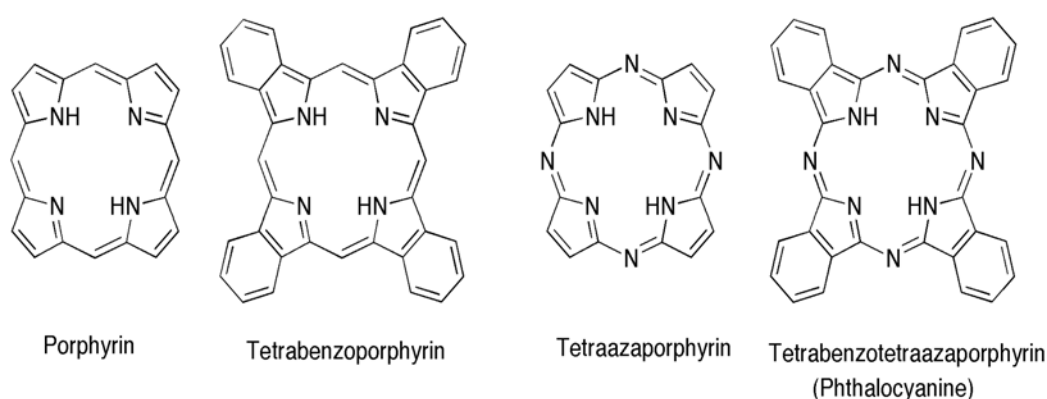


Figure 2.1: A family of four tetrapyrrolic macrocycles

2.1.1. General Synthesis Pathways of Phthalocyanines

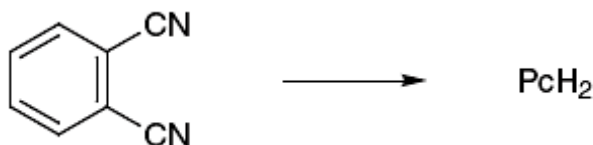
2.1.1.1. Metal-Free Phthalocyanines

Most syntheses of phthalocyanine ($M = 2H^+$) use either phthalonitrile or isoindolinediimine (diiminoisoindoline) as the starting material. Great care must be taken during its preparation and purification to avoid unintentional incorporation of metal ions. Commercially available phthalocyanine is often heavily contaminated with a range of metal containing derivatives such as copper(II) phthalocyanine. It has been shown that even a small amount of metal phthalocyanine impurity can have a profound effect on the electronic properties of the material [10]. Metal-containing phthalocyanines cannot be removed during purification by sublimation, therefore, the use of starting materials and solvent of high purity and Teflon or quartz reaction vessels is recommended for the preparation of ultra-pure metal-free phthalocyanine for electronic studies. In addition to the methods listed below, phthalocyanine has been prepared by the dehydrogenation of tetracyclohexenotetraza porphyrin by heating (300–320°C) or by the action of a strong oxidant (e.g., DDQ) [11]. It is also possible to prepare phthalocyanine from 2-cyanobenzamide by heating (260°C) with powdered antimony metal in naphthalene [12].

From Phthalonitrile:

As noted, the direct cyclotetramerization of phthalonitrile to give phthalocyanine (Scheme 2.1) requires a two-electron reduction and the donation of two protons from a co-reactant or solvent. Reagents such as hydroquinone and 1,2,3,6-tetrahydropyridine are particularly effective, and a good yield of phthalocyanine can be achieved from the incorporation of these reducing agents into cyclotetramerizations carried out in the melt at elevated temperatures (~275°C) [13], or in protic solvents [14]. The addition of a catalytic amount of a non-nucleophilic base, such as 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), is beneficial to the yield of the cyclotetramerization product, when the reaction is carried out in a protic solvent such as pentanol or 2-(dimethylamino)ethanol [15]. High-pressure, electrochemical

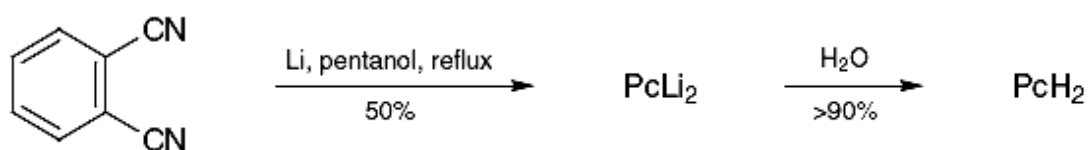
reduction, sodium benzenetellurolate, and light also assist phthalocyanine formation in protic solvents.



Scheme 2.1

From Generation and Demetalation of a Labile Metal Complex:

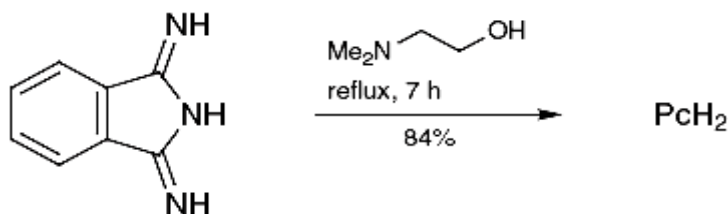
A number of metal-containing phthalocyanines are readily demetalated by the action of acid; these include the complexes with lithium(I), sodium(I), potassium(I), magnesium(II), beryllium(II), silver(II), cadmium(II), mercury(II), lead(II), and antimony(III) ions [16]. The in situ demetalation of a phthalocyanine complex during an acid workup provides a convenient synthesis from phthalonitrile (Scheme 2.2). Template macrocyclization of phthalonitriles in the presence of lithium salt in pentanol or another high-boiling alcohol under reflux (particular synthetic value is the '*Linstead method*') leads to the PcLi_2 [17]. Metal-free phthalocyanine is obtained as a crystalline precipitate by the addition of dilute aqueous acid, acetic acid, or water to the resulting solution.



Scheme 2.2

From Isoindolinediimine: Isoindolinediimine (often referred to as 1,3-diiminoisoindoline), an addition product of ammonia and phthalonitrile, is a useful starting material for phthalocyanine synthesis. It can be prepared by the reaction of phthalonitrile with ammonia in methanol, isolated and then used for cyclotetramerization reactions in a higher-boiling protic solvent [e.g., 2-

(dimethylamino)ethanol]. Alternatively, isoindolinediimine can be prepared *in situ* by passing a stream of ammonia through a solution of the phthalonitrile in 2-(dimethylamino) ethanol at reflux [18].



Scheme 2.3

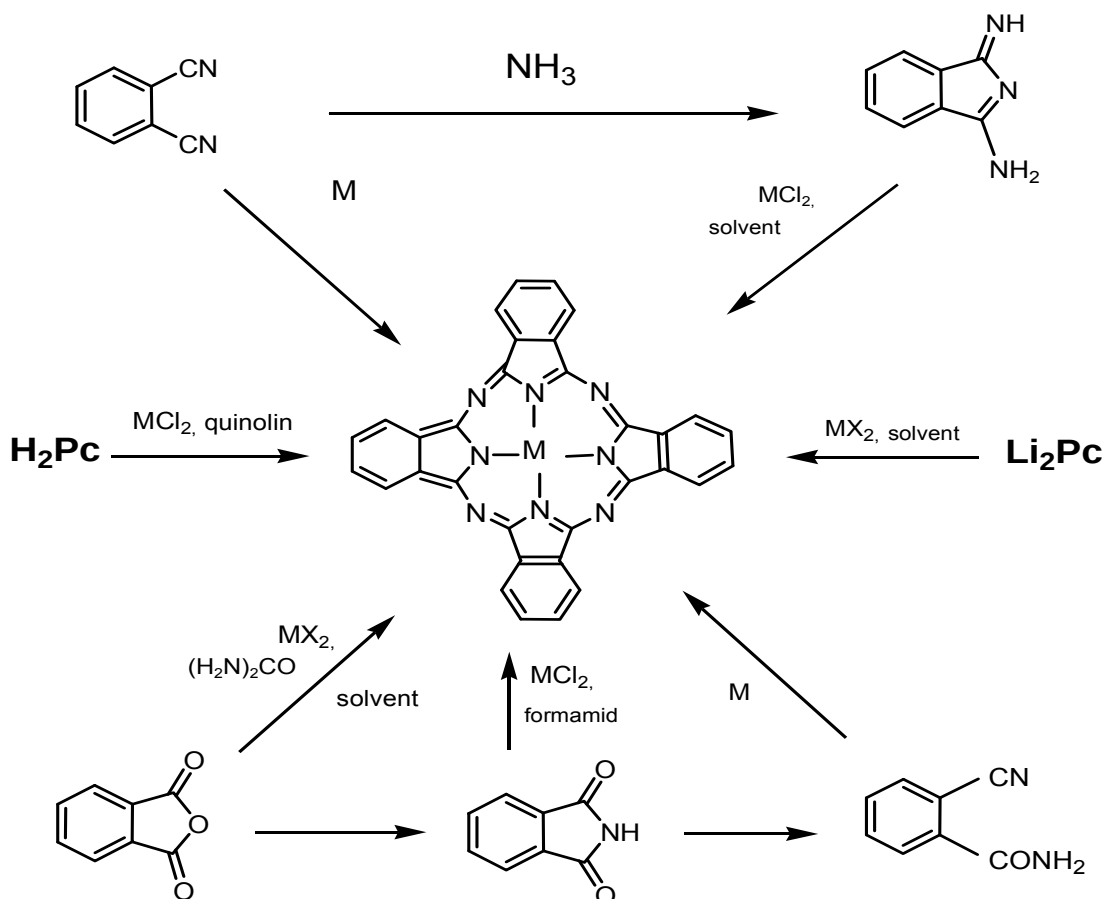
2.1.1.2. Metal Phthalocyanine Complexes

There are several pathways to prepare metallophthalocyanines. The differences of these ways are both related to metal, reaction environment and phthalocyanine precursors. At least seventy different metals have been used to synthesis phthalocyanines. Pc macrocycle generally stay as dianion (Pc²⁻) and can oxidize or reduce between different oxidation states. Many ions (such as Cu²⁺, Co²⁺, Fe²⁺) bears strongly and they could not be removed easily. Actually, some synthetic pathways have advantage toward stability of metallo-phthalocyanines, and provide *template effect* while the formation of macrocycle (Scheme 2.4).

To achieve high yields of macrocycles at high concentrations, a way to orient the reactive sites such that they readily undergo cyclization was needed. Transition metals, with their ability to gather and dispose of ligands in a given predictable geometry, can induce a “*template effect*.” By binding to the linear molecule, to influence its geometry, a metal “*template*” can accelerate either the intramolecular or the intermolecular reaction. Thus the judicious choice of a metal ion and the relative locations of donor atoms would allow a metal to control the cyclization process.

The *template effect* can be divided into two slightly more specific effects: The **kinetic template effect** describes the directive influence of the metal ion controls the

steric course of a sequence of stepwise reactions. In cases where the **thermodynamic template effect** operates, the metal ion perturbs an existing equilibrium in an organic system and the required product is produced often in high yield as a metal complex. In most cases, the kinetic template effect is operative; however an assignment cannot be made in all cases [19].



Phthalocyanines can act as a ligand to most, if not all, metal and metalloid elements, although complexes with some metals such as the more active actinides have not been reported to date. Phthalocyanine has proved itself a versatile macrocycle, which adapts to the requirements of each metal species (M) to form a complex of an appropriate structure (Figure 2.2), sometimes with the involvement of additional ligands (L) (Figure 2.3). The normal oxidation state of the phthalocyanine macrocycle is -2 . Therefore, if M represents a metal ion with a charge of $+2$ there is

no need for additional ligands to retain neutrality, although neutral ligands such as pyridine or water are often incorporated.

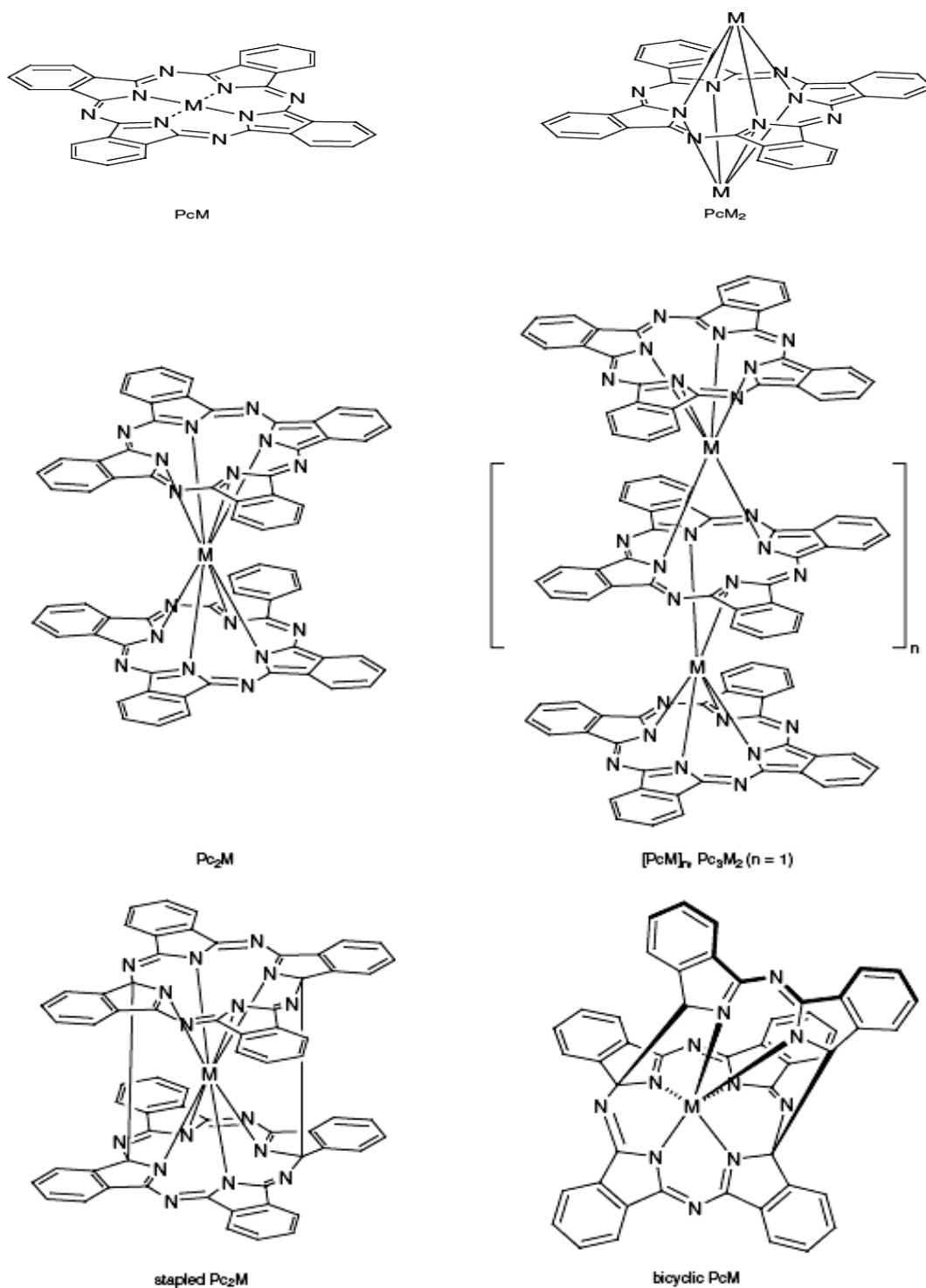


Figure 2.2

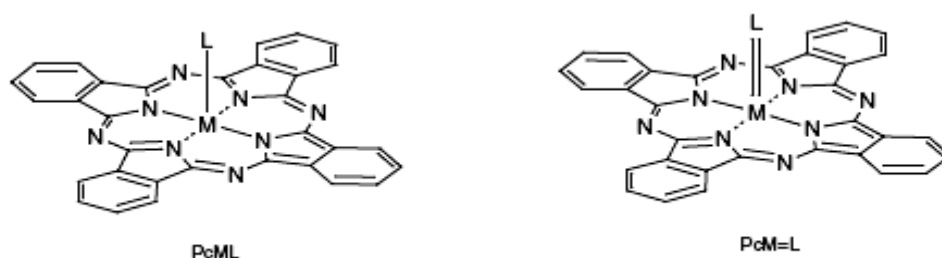
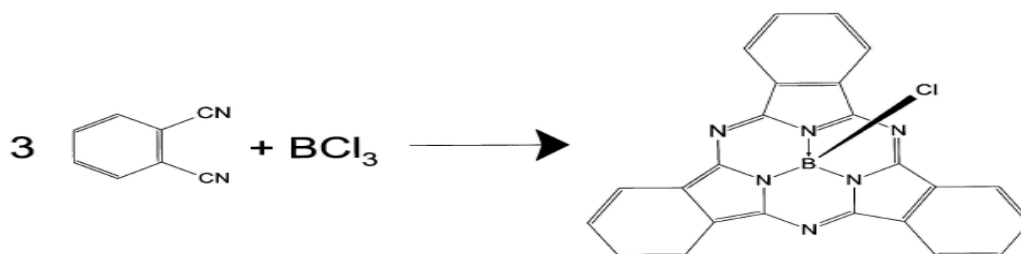


Figure 2.3

Subphthalocyanines

The first subphthalocyanine (SubPc) was reported by Meller and Ossko when it was accidentally synthesized in 1972 [20]. The group was trying to prepare derivatives of phthalocyanines (Pc) that contained boron (unique for subPcs) as the central metal by reacting phthalonitrile with haloboranes (Scheme 2.5). The subphthalocyanine, chloro[subphthalocyaninato]boron(III), was reported by them, and a crystal structure for the compound was reported in 1974. Not until 1990 were these compounds reported again when the bromo-derivative of the t-butyl substituted macrocycle was reported by Kobayashi et al [21].



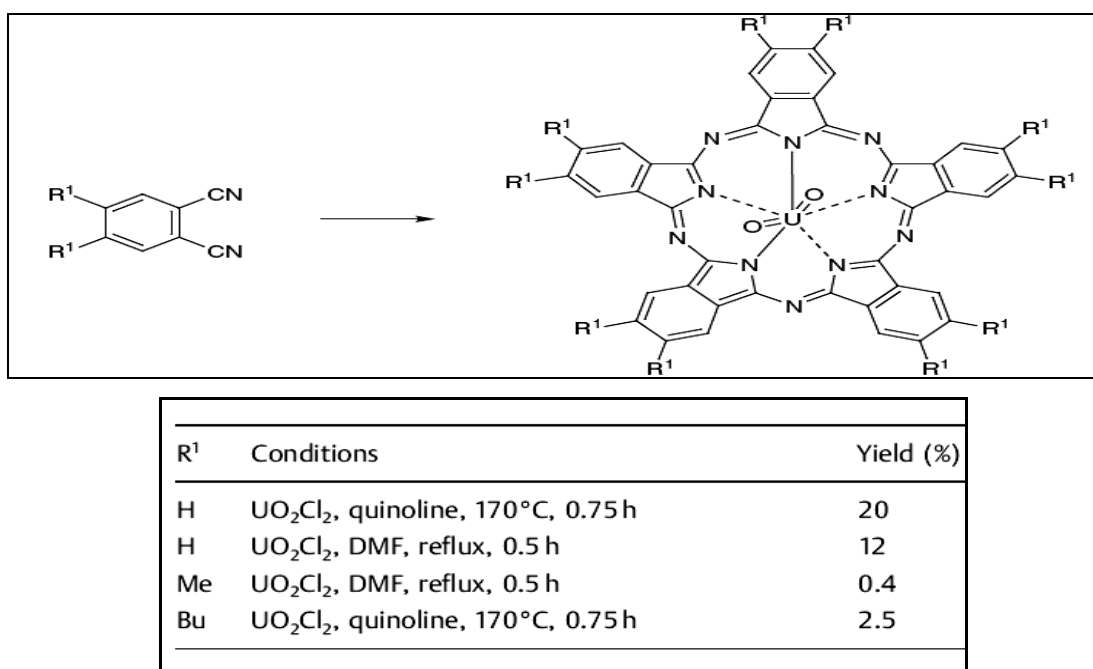
Scheme 2.5: Synthesis of chloro[subphthalocyaninato]boron (III).

As a class of compounds, subphthalocyanines remained relatively unexplored for a long time because of, in part, the troublesome processes required for their purification. When research on them finally began in the early 1990s, it was not for their own properties as much as it was for a study into the properties of the phthalocyanines, the larger homologues to the subphthalocyanines. It was found that

asymmetrical phthalocyanines (hemiazaporphyrins), which are difficult to synthesize otherwise, can be synthesized by a ring enlargement of subphthalocyanines.

Superphthalocyanines

Superphthalocyanine is a macrocycle composed of five isoindoline units surrounding a dioxouranyl cation. It displays a broadened, red-shifted Q-band (~920 nm) relative to that of phthalocyanine and is unstable at high temperatures; giving phthalocyanine as a decomposition product. Uranium appears unique in its ability to form superphthalocyanines.



Schema 2.6: The Synthesis of Superphthalocyanines from Phthalonitrile [22,23,24]

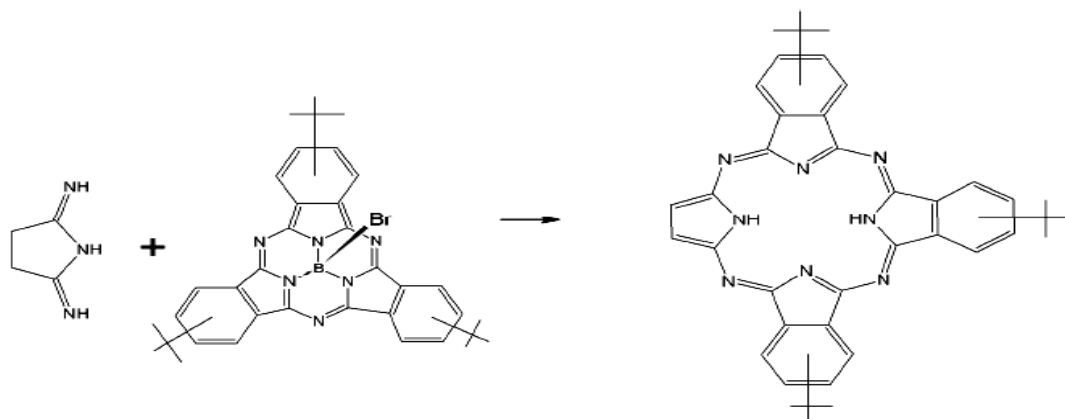
2.1.1.3. Synthesis of Asymmetric Phthalocyanines (AB3)

Phthalocyanines with an AAB₂B substitution pattern (also termed *cis*-A₂B₂) have been prepared via reactive intermediates called “half-phthalocyanines”. Some examples of *cis*-A₂B₂ phthalocyanines have also been prepared by the macrocyclization of linked phthalonitriles. Lastly, a direct approach to ABAB phthalocyanines (also termed *trans*-A₂B₂) is available via the “crossed-condensation” method.

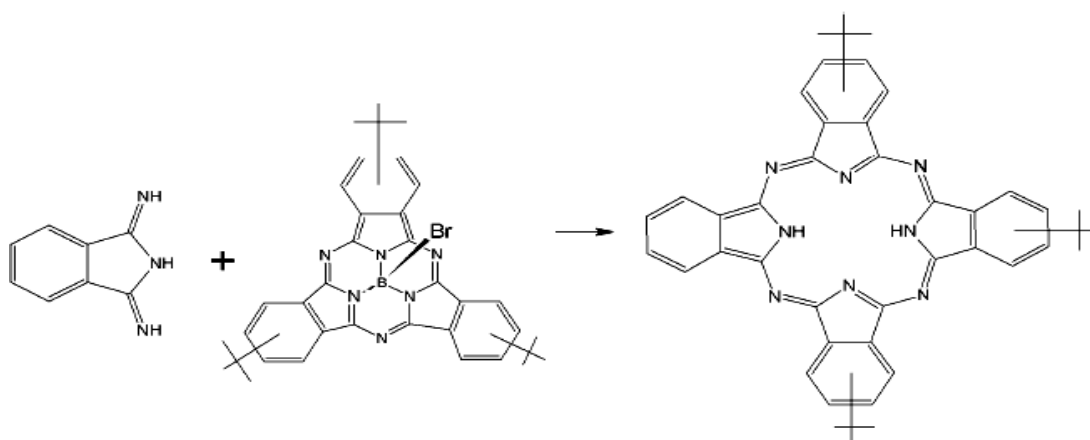
There are also asymmetric phthalocyanines (A₃B type) which are generally used for making LB films or liquid crystals. **Statistical condensation** and use of **subphthalocyanines** are two methods of preparing asymmetric Pcs.

Use of subphthalocyanines: selective method

In 1990, it was discovered that an asymmetrical phthalocyanine could be made by treating a subphthalocyanine with succinimide (Scheme 2.7) or a diisoiminoindoline analog (Scheme 2.8). Phthalocyanines were considered more stable than the subphthalocyanines, so it was believed the subphthalocyanines would be open to accepting an isoindole group and would become a monosubstituted form of the phthalocyanine to relieve ring strain. In the ring enlargement reaction, the central metal atom and the axial ligand are lost from the ring structure and remain in the reaction solvent [25]. The early investigations, which used general aromatic solvents such as toluene, benzene, or chloronaphthalene, did not result in the synthesis of ring-enlarged phthalocyanines. Later, it was found that in mixed solvents containing DMSO and aromatic solvents, the ring enlargement did take place. Since this discovery, many other investigations into the ring enlargement of the subphthalocyanine to the substituted phthalocyanine have taken place [26]. Importance of this method is its selectivity because the ring-enlargement process leads to only one type of phthalocyanine, AB₃.



Scheme 2.7: Asymmetrical preparation of phthalocyanine using succinimide.

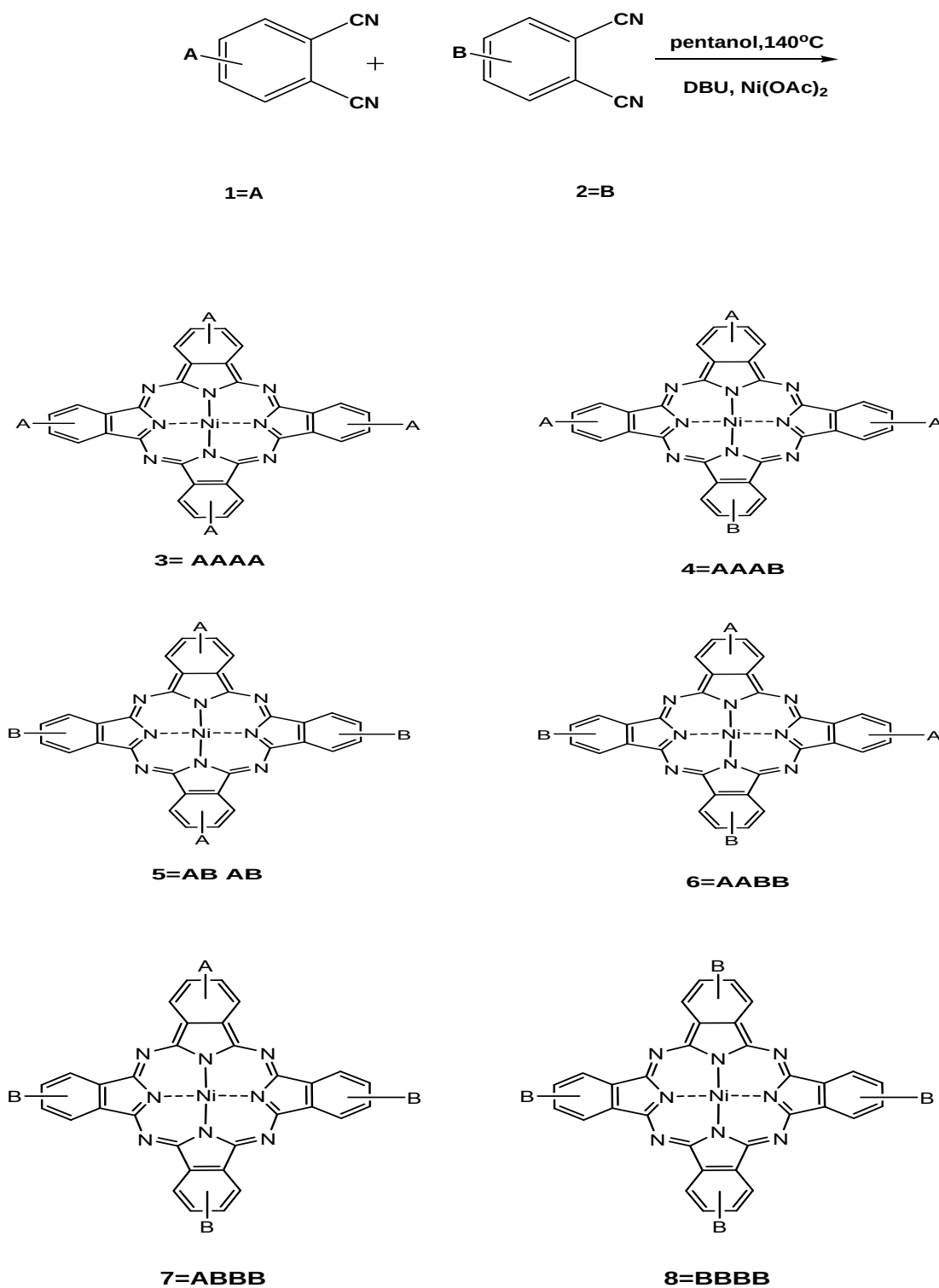


Scheme 2.8: Asymmetrical preparation of phthalocyanine using diisoiminoindoline.

Statistical Condensation Method for the synthesis of Asymmetric Pcs

It is possible to synthesize high functionalized phthalocyanines the combination of two different phthalonitriles. By using phthalonitrile A and B, six different phthalocyanines can be prepared statistically.

The reaction of **1** and **2** yields six different isomers (Scheme 2.9).



Scheme 2.9

With this statistical method, the amount of each isomer can be changed by changing the ratio of phthalonitrile **1** and **2**. Thus, the desired isomer will be prepared in increased yield.

The following table presents the ration of possible phthalocyanines from the nitriles **1** and **2**, assuming the nitriles have same kinetic under different stoichiometry.

If the ratio between A and B is 1:1 (50%), the possibility of getting AA, AB and BA is about $(0.5)^2 = 0.25$. Also AB and BA is assumed to have same contribution because A and B have two permutations. Besides the possibility of six Pcs (3-8) is $(0.5)^4 = 0.0625$. This number should be multiplied with the permutation. In this simple model, template, steric and electronic effect and the change in the ratio of nitriles during the reaction has not been considered.

The given example on Table 2.1, the permutations and the guessed stoichiometric ratios of different reactions are used as given in the Cook model. The guessed ratios calculated by statistical method are definitely presented in the table. It is possible to get different ratios of isomers by changing concentrations of A and B. For example; if the ratio of A:B is 3:1, the isomer AAAB has a yield about 42%.

A:B	3(AAAA)	4(AAAB)	5(ABAB)	6(AABB)	7(ABBB)	8(BBBB)
1:1	6.25	25	12.5	25	25	6.25
3:1	31.6	42.2	7.0	14.1	4.7	0.4
9:1	65.6	29.2	1.6	3.2	0.4	0.01
Per	1	4	2	4	4	1

Table 2.1: The ratio of possible products with the statistical method.

2.1.2. Application of Phthalocyanines

2.1.2.1. General Applications

Their resulting strong color, coupled with renowned chemical and thermal stability, explains the ubiquitous use of phthalocyanines as highly stable blue (or green) pigments and dyes. In addition to their long established use as colorants, phthalocyanines are exploited commercially for optical data storage, catalysis, and as photoconductors in xerography. They are also of interest as materials for non-linear optics, liquid crystals, ordered thin films, photodynamic cancer therapy, molecular semiconductors, components of highly conducting charge-transfer salts, and polymers, photovoltaic devices, electrochromic devices, fuel cells, and sensors. The synthesis of phthalocyanine and its substituted derivatives is often driven by the desire to exploit and improve performance in one of these technological or therapeutic arenas.

Because of the content and the aim of this research focus on the photodynamic therapy and self-assembly properties of phthalocyanines, these two topics are going to be detailed.

2.1.2.2. Photodynamic Therapy

Photodynamic therapy involves administration of a tumor-localizing photosensitizing agent, which may require metabolic synthesis (i.e., a prodrug), followed by activation of the agent by light of a specific wavelength. This therapy results in a sequence of photochemical and photobiologic processes that cause irreversible photodamage to tumor tissues. Results from preclinical and clinical studies conducted worldwide over a 25-year period have established photodynamic therapy as a useful treatment approach for some cancers. Since 1993, regulatory approval for photodynamic therapy involving use of a partially purified, commercially available hematoporphyrin derivative compound (Photofrin) in patients with early and advanced stage cancer of the lung, digestive tract, and genitourinary tract has been obtained in Canada, The Netherlands, France, Germany, Japan, and the United States. We have attempted to conduct and present a

comprehensive review of this rapidly expanding field. Mechanisms of subcellular and tumor localization of photosensitizing agents, as well as of molecular, cellular, and tumor responses associated with photodynamic therapy, are discussed. Technical issues regarding light dosimetry are also considered. [*J. Natl. Cancer Inst.* 1998;90:889–905]

Photochemotherapy of cancer is often called “photodynamic therapy (PDT).” The term “photodynamic action” [27] is used to distinguish photosensitized reactions in biology from the physicochemical processes occurring in the emulsions of photographic films. Blum [28] suggested that this definition should be applied only to photochemical reactions in which oxygen was consumed. Such reactions are also called photosensitized processes of type I and type II depending on the nature of the primary steps, namely, the initial involvement of radical intermediates that are subsequently scavenged by oxygen or the generation of the highly cytotoxic singlet oxygen ($^1\text{O}_2$) (Figure 2.4) by energy transfer from the photoexcited sensitizer. $^1\text{O}_2$ has a short lifetime in biologic systems (<0.04 microsecond) and, therefore, was also shown to have a short radius of action (<0.02 mm) [29].

The current era of PDT began with studies by R. L. Lipson and S. Schwartz at the Mayo Clinic in 1960 who observed that injection of crude preparations of hematoporphyrin led to fluorescence of neoplastic lesions visualized during surgery. To gain an optimal tumor localizing preparation, Schwartz treated hematoporphyrin with acetic acid and sulfuric acid and obtained a porphyrin mixture that he termed “hematoporphyrin derivative” (HPD), which was used by Lipson et al. [30] for tumor detection. HPD contains several porphyrins, monomers as well as dimers and oligomers [31]. HPD has been partially purified, with the less-active porphyrins’ monomers removed, to form Photofrin®, the most widely used photosensitizer in clinical PDT. Because of the long-lasting skin phototoxicity of Photofrin, several new photosensitizers have recently been introduced in clinical trials [32,33]. Photofrin absorbs light only up to about 640 nm; light at longer wavelengths penetrates farther into tissue, and most of the new sensitizers have stronger absorbance at 650–850 nm.

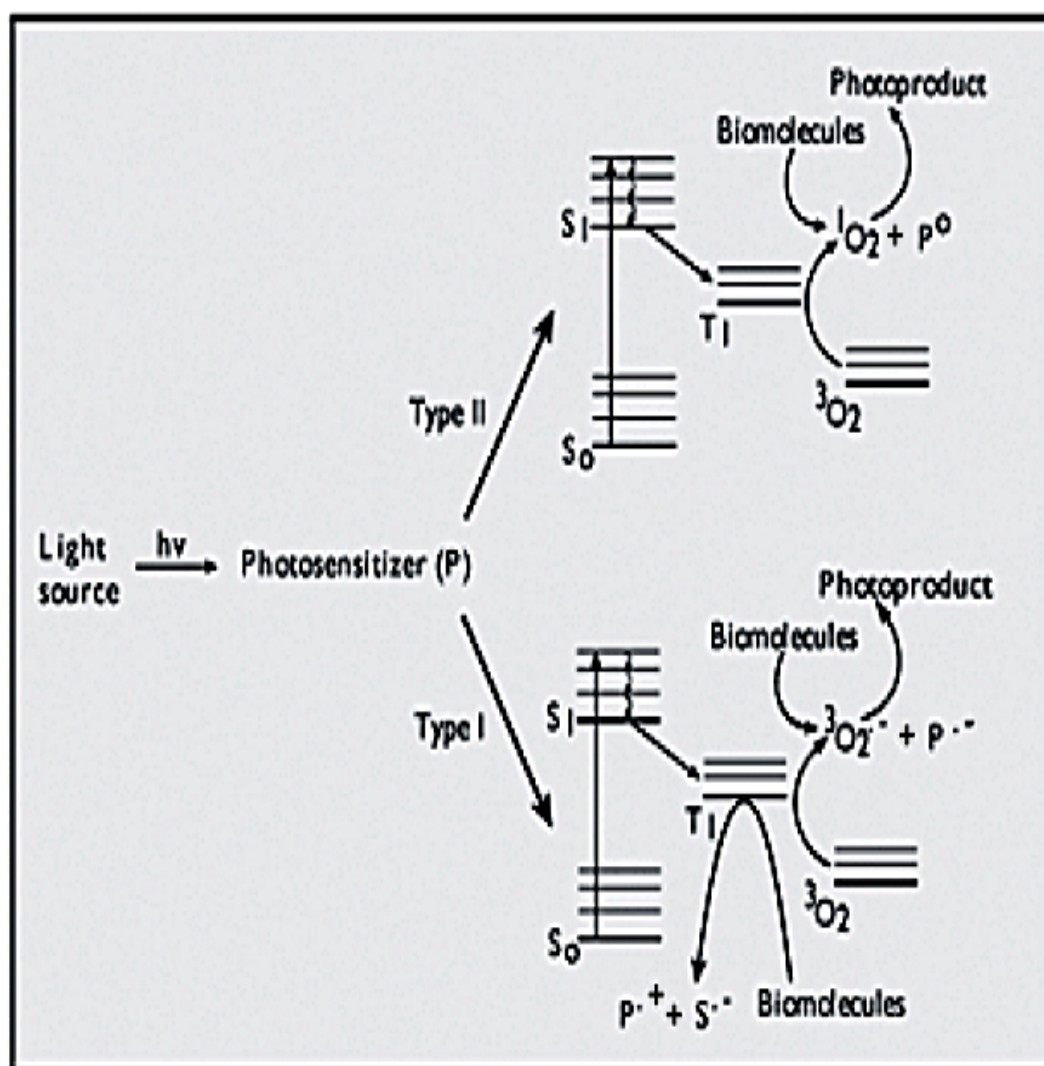


Figure 2.4: Mechanisms (types I and II) of ROS (reactive oxygen species) generation by combination of light, photosensitizer (P), and ground-state oxygen ($^3O_2$). Ground-state photosensitizer (S_0) is irradiated with visible light generating excited singlet state photosensitizer (S_1). S_1 can relax back to excited state photosensitizer (T_1) generating superoxide radical ($^3O_2^{\cdot-}$) (mechanism type I) and/or singlet oxygen ($^1O_2$) (mechanism type II)

2.1.2.3. Self-Assemblies: Liquid Crystals and Monolayers

Liquid Crystals:

Liquid Crystals (LCs) are state of matter intermediate between that of a crystalline and an isotropic liquid. They possess many of the mechanical properties of liquid, *e.g.*, high fluidity, formation, and coalescence of droplets. At the same time they are similar to crystals in that they exhibit anisotropy in their optical, mechanical, electrical, and magnetic properties.

The characteristic feature of LCs is the presence of long-range *orientational* order in the arrangement of constituent molecules, and sometimes one- or two-dimensional quasi long-range *translational* or *positional order*. LCs exhibit a great variety of phases, which differ one from another by their structure and physical properties.

Although LCs, or mesophases, combine the properties of a solid and an isotropic liquid, they exhibit very specific electrooptical phenomena, which have no corresponding analogues in solids or in isotropic liquids.

Monolayers at the air-water interface:

Insoluble monolayers: Many of the amphiphilic substances insoluble in water can with the help of a volatile and water insoluble solvent easily be spread on a water surface to form an insoluble monolayer at the air/water interface. These monolayers, also called Langmuir (L) films, represent the extreme case when considering adsorption to interfaces because all molecules are concentrated in a one molecule thick layer at the interface. The amphiphilic nature of the surfactants dictates the orientation of the molecules at the interface (air/water or oil/water) in such a way that the polar head group is immersed in the water and that the long hydrocarbon chain is pointing towards air, gas or oil (Figure 2.5)

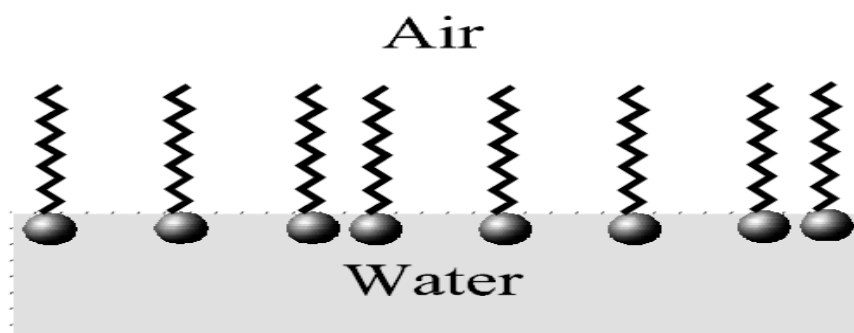


Figure 2.5: A schematic illustration showing a spread monolayer at the air/water interface

The hydrocarbon chain of the substance used for monolayer studies has to be long enough in order to be able to form a insoluble monolayer. A rule of thumb is that there should be more than 12 hydrocarbons or groups in the chain ($(\text{CH}_2)_n$, $n > 12$). If the chain is shorter, though still insoluble in water, the amphiphile on the water surface tend to form micelles. These micelles are water soluble, which prevents the build-up of a monolayer at the interface. On the other hand if the length of the chain is too long the amphiphile tends to crystallize on the water surface and consequently does not form a monolayer. It is difficult to determine the optimal length for the hydrocarbon chain because its film forming ability also depends on the

polar part of the amphiphile. Furthermore, the amphiphile has to be soluble in some organic solvent which is highly volatile and water insoluble (chloroform or hexane is commonly used).

Surface tension: Surface tension can be said to be a measurement of the cohesive energy present at an interface. The common units for surface tension are dynes/cm or mN/m. Polar liquids, such as water, have strong intermolecular interactions and thus high surface tensions. Any factor which decreases the strength of this interaction will lower surface tension. Thus an increase in the temperature of this system will lower surface tension. Any contamination, especially by surfactants, will lower surface tension. Therefore researchers should be very cautious about the issue of contamination.

Surfactants: Surface active agents (surfactants) are a larger class of molecules which have a significant technological and biological importance. Generally these molecules consist of a hydrophilic (water soluble) and a hydrophobic (water insoluble) part. This amphiphilic nature of surfactants is responsible for their association behaviour in solution (micelles, bilayers, vesicles, etc.) and their accumulation at interfaces (air/water or oil/water). The hydrophobic part usually consists of hydrocarbon or fluorocarbon chains, while the hydrophilic part consists of a polar group (-OH, -COOH, -NH₃⁺, -PO₄⁻(CH₂)₂NH₃⁺ etc.).

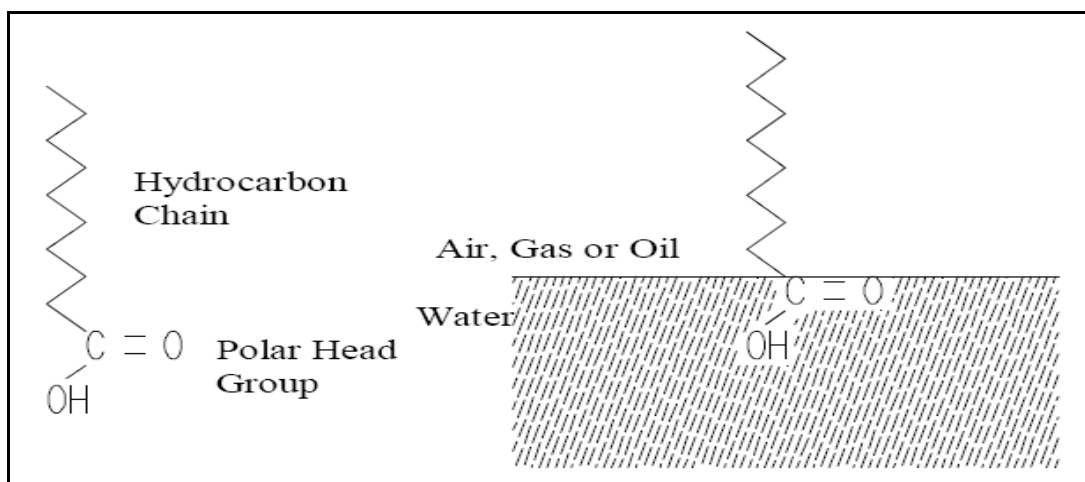


Figure 2.6: A schematic illustration showing the components of an amphiphile (left), and the orientation of an amphiphile adopted at an interface (right).

Surface Pressure: As earlier was mentioned the air/water interface possesses an excess free energy originating from the difference in environment between the surface molecules and those in the bulk. This interfacial free energy is accessible by measurements of the surface tension, γ . The surface tension of water is around 73 mN/m at 20°C, which is an exceptionally high value compared to other liquids and consequently makes water a very good subphase for monolayer studies (Figure 2.7).

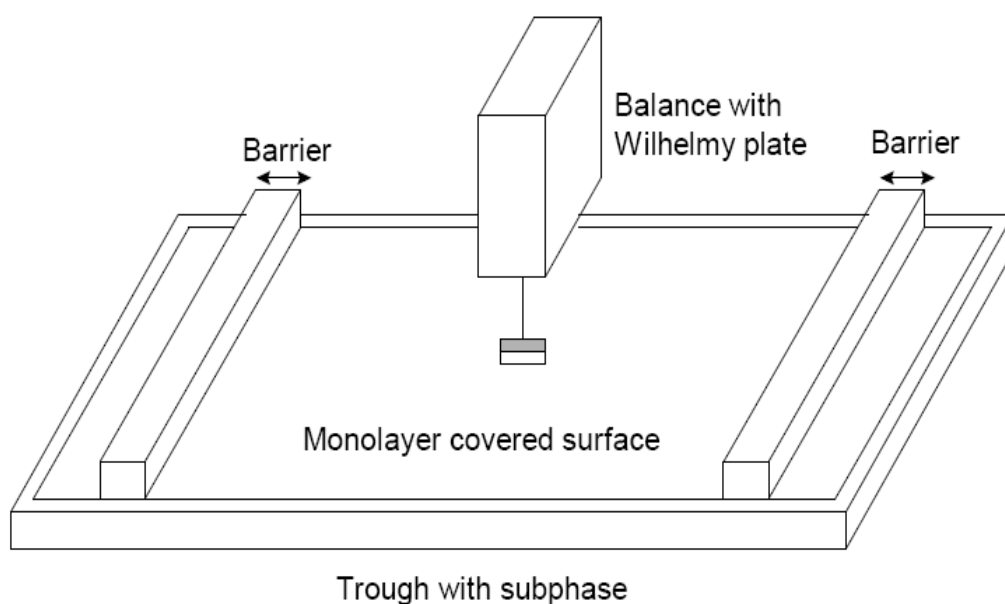


Figure 2.7: Schematic illustration of a Langmuir film balance with a Wilhelmy plate electrobalance measuring the surface pressure, and barriers for reducing the available surface area.

Thin organic films of a thickness of a few nanometers (a monolayer) are the source of high expectations as being useful components in many practical and commercial applications such as sensors, detectors, displays and electronic circuit components [35,36,37]. The possibility to synthesize organic molecules, almost without limitations, with desired structure and functionality in conjunction with a sophisticated thin film deposition technology enables the production of electrically, optically and biologically active components on a nanometer scale. An organic thin film can be deposited on a solid substrate by various techniques such as thermal evaporation, sputtering, electro-deposition, molecular beam epitaxy, adsorption from

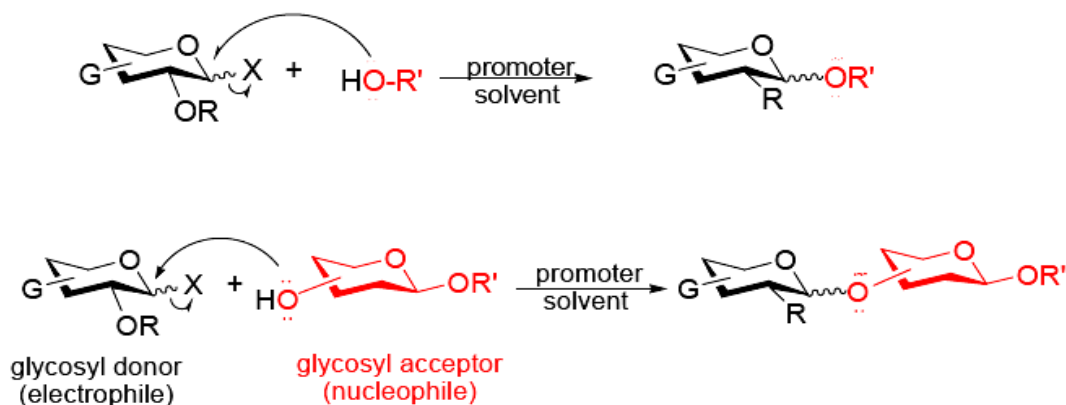
solution, Langmuir-Blodgett (LB) technique, self-assembly, etc..[38] The LB-technique is one of the most promising techniques for preparing such thin films as it enables (i) the precise control of the monolayer thickness, (ii) homogeneous deposition of the monolayer over large areas and (iii) the possibility to make multilayer structures with varying layer composition. An additional advantage of the LB technique is that monolayers can be deposited on almost any kind of solid substrate.

Today, we are in a situation where the production of ultrathin organic films with the LB-technique has slowly started to find possible practical applications in many fields. However, even though the ideas for practical applications are growing the L and LB films are still mostly used as model systems for example for biomembrane research and multilayer coatings.

In order to understand how the properties of floating monolayers (L films) are being measured, it is useful to introduce some common knowledge of surface chemistry. Surface tension, surfactants, insoluble monolayers, surface pressure, LB film balance, Surface Pressure- Area isotherms, Deposition LB films are main terms for LB film technique.

2.2. Glycosylation

General scheme:



Scheme 2.10

The basics of glycosylation focuses either formation of the glycosidic bond through classical Koenigs–Knorr type reactions where the anomeric oxygen originates from the aglycon or through retention of the anomeric oxygen via anomeric O-arylation or O-alkylation reactions. The latter methodology is based on deprotonation of the anomeric hydroxyl of sugars, thus, generating an anomeric oxide. The O-arylation or O-alkylation leads to the glycoside bond. This method turned out to be extremely important for the synthesis of a variety of glycosides.

To make a glycosylation reaction, a donor and an acceptor, which needs to have one hydroxyl group, are required. The glycosyl donors should be activated by a reliable promotor (TMSOTf, NIS).

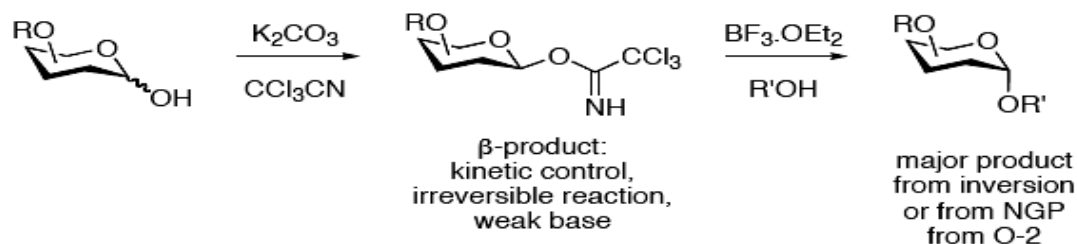
2.2.1. Glycosyl Donors

To prepare donors, there are several ways and several groups are used to make a leaving group. These are the common leaving groups:

SR – thioglycosides, SeR – selenoglycosides, S(O)R – glycosyl sulfoxides, O(CH₂)₃CH=CH₂ – n-pentenyl glycosides, OAc – glycosyl acetates, Cl, Br –

glycosyl chlorides and bromides, F – glycosyl fluorides, $\text{OC}(\text{NH})\text{CCl}_3$ – glycosyl trichloroacetimidates. Only glycosyl trichloroacetimidate will be presented here.

Glycosyl trichloroacetimidates are unstable to protecting group manipulations, and so are introduced directly before glycosylation. Require selective deprotection of OH-1 selective deacetylation, hydrolysis of allyl-, n-pentenyl or thioglycoside etc.

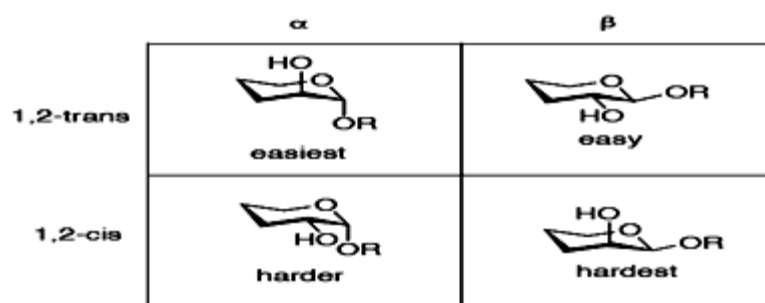


Scheme 2.11

Depending on the base used, either the α or β trichloroacetimidate may be selectively formed. Useful as glycosylation (with catalytic Lewis acid) will often go with inversion of configuration as the major pathway in the absence of a participating protecting group at the 2-position.

2.2.2. Stereochemistry Control

There are 4 classes of glycosidic bonds formation.



The anomeric effect may not be invoked to account for α -selectivity in glycosylation reactions as it refers to the increased stability of the glycosylation products, and glycosylation reactions are generally under kinetic control. However, the transition-state leading to the β -anomer is often less stable than that leading to the α -anomer of product, and this kinetic effect may be used to explain the selectivity.

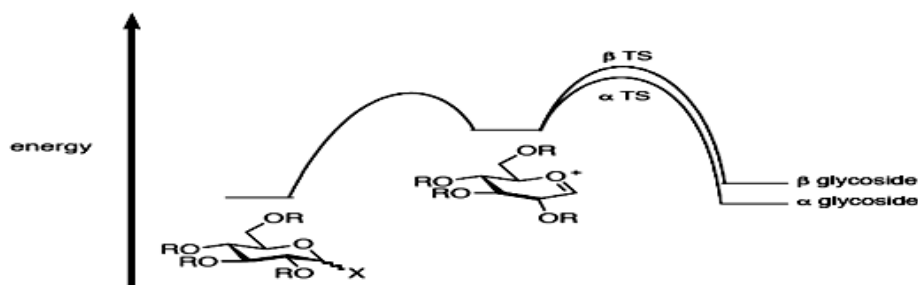
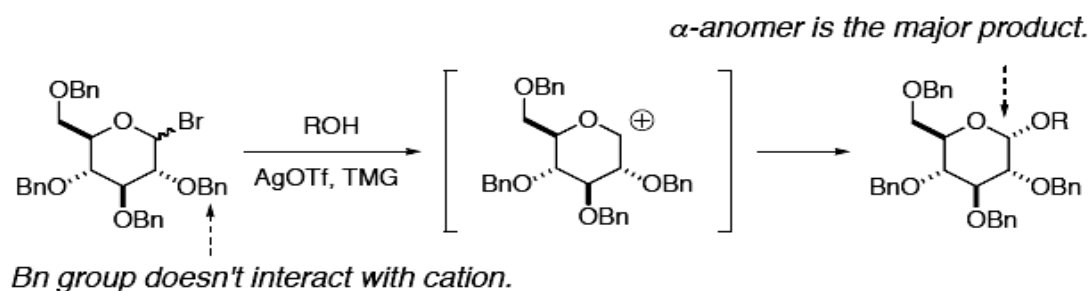


Figure 2.8

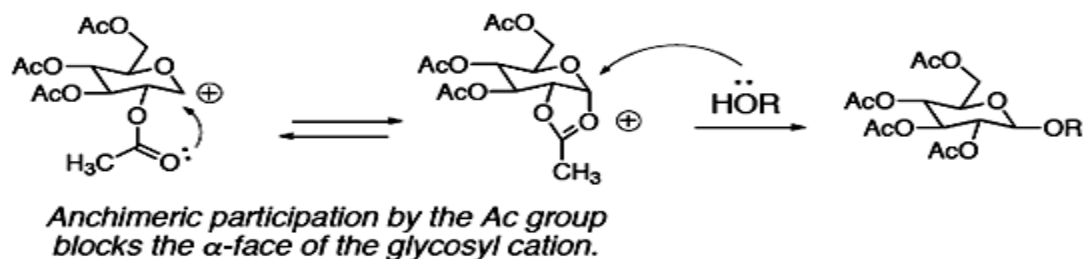
Anchimeric Assistance:

The nature of the protecting group at C2 can dictate the stereochemical outcome of glycosylation reactions. When the protecting group at C2 does not interact with the glycosyl cation intermediate, the α -glycoside is the kinetic product of glycosylation.



Scheme 2.12

Protecting groups that can interact with the glycosyl cation protect the α -face, leading to β -glycosylation.



Scheme 2.13

3. PURPOSE and the COVER of the THESIS

Hydrophilicity of sugars can be exploited to produce either hydrophilic Pcs, eventually water soluble, or amphiphilic molecules when associated with hydrophobic moiety on asymmetric Pcs.

Photo Dynamic Therapy is the main application for water-soluble Pcs. The non toxicity of both the Pc macrocycle and the carbohydrates offers good biocompatibility. The self-assembled edifices of amphiphilic Pcs are used to obtain monolayers and liquid crystals, looking forward to various applications: sensors, bio-sensors...

We will first of all have an overview of all the existing carbohydrate substituted Pcs. Then, the reported works on water-soluble Pcs then on amphiphilic ones will be mentioned. Hereafter we will present the molecules we designed and synthesized during this thesis in order to enlarge the knowledge on carbohydrate Pcs.

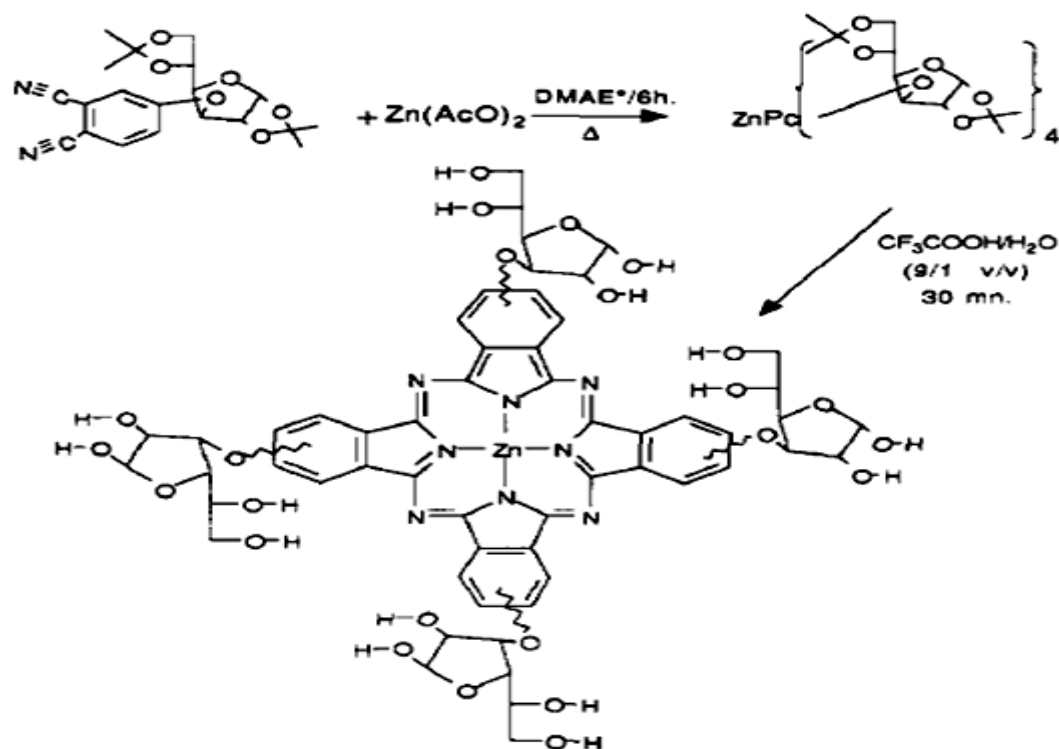
3.1. Existing Carbohydrated Phthalocyanines

There are a few carbohydrate phthalocyanines reported so far: less than 10 papers since the first one published twenty years ago. Carbohydrates are usually used as water solubilising substituent to produce potential photosensitizers with both symmetric and asymmetric substitution pattern.

The first one, published in 1989, was a tetra α -D-glucofuranose substituted ZnPc highly soluble in water [41]. The protected phthalocyanine was prepared (61% yield) in the presence of zinc acetate, from the protected sugar substituted phthalonitrile. This phthalonitrile was obtained by the quantitative condensation of 4-nitrophthalonitrile and 1,2:5,6-diisopropylidene-D-glucofuranose. Treatment of protected ZnPc with trifluoroacetic acid/water gives the unprotected phthalocyanine (Scheme 3.1).

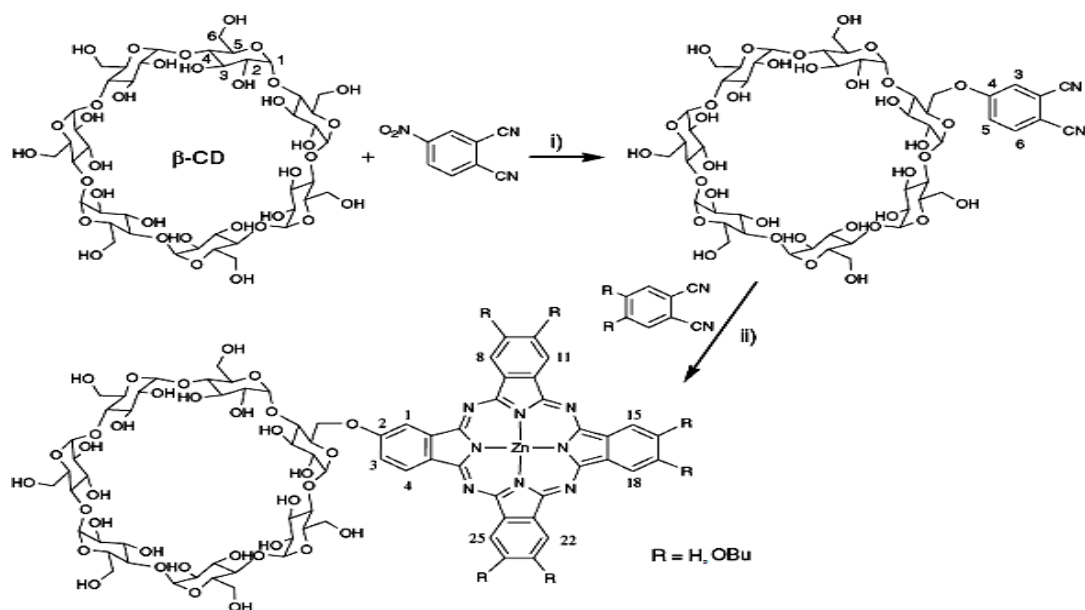
The authors observed that in organic solvents, a tetra α -D-glucofuranose substituted ZnPc shows a spectrum typical of monomeric metallated phthalocyanine,

with a Soret band and Q band. The optical spectra of the Pc are characteristic of a dimer in water and of a monomer in DMSO. This new class of phthalocyanines on which glucofuranoses were linked present an increase of their steric hindrance in the vicinity of the metal site and of their solubility in water.



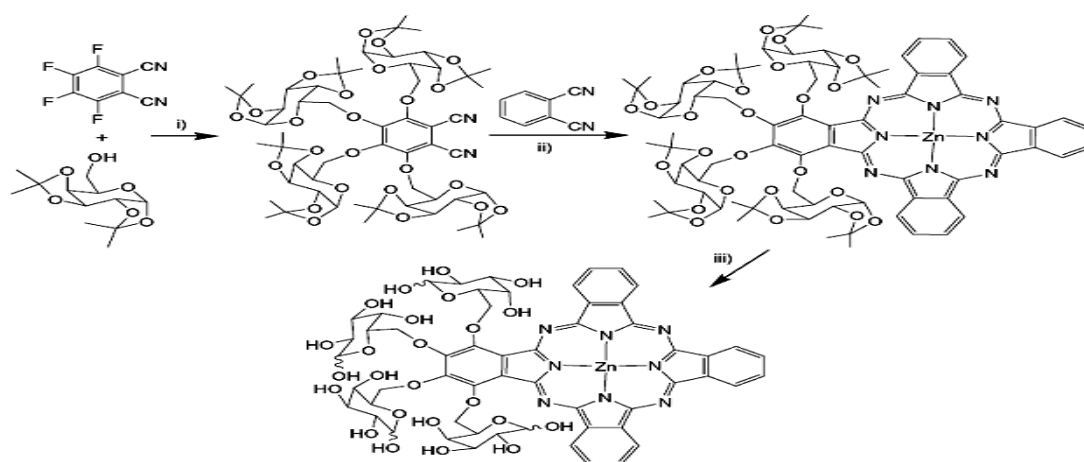
Scheme 3.1: First carbohydrated phthalocyanine

Then other non-axially carbohydrate substituted phthalocyanine is an asymmetric and water-soluble phthalocyanine- β -cyclodextrin dyads which were prepared via a statistical cross condensation of a 4-(β -cyclodextrin) phthalonitrile with unsubstituted phthalonitriles [42] (Scheme 3.2).



Scheme 3.2: Reagents and conditions: (i) DMF, K_2CO_3 , rt; (ii) DMAE, ZnCl_2 , reflux.

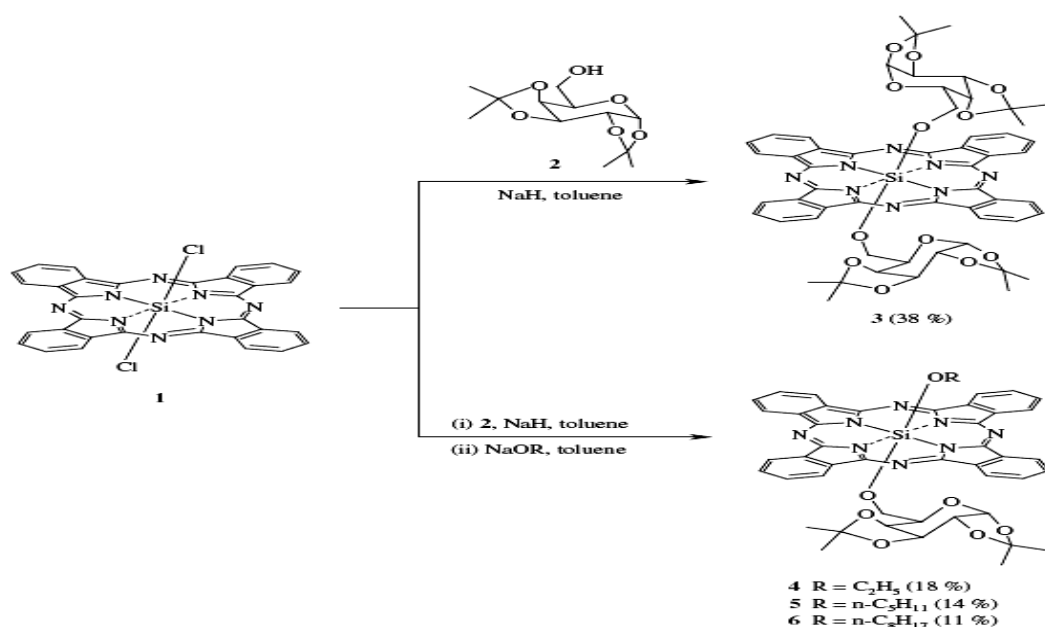
Asymmetric carbohydrate water-soluble Pc was reported, prepared via a statistical cross-condensation of Tetrakis (1,2:3,4-di-O-isopropylidene- α -D-galactopyranos-6-yl) phthalonitrile with phthalonitrile [43]. The new Pc, with amphiphilic character, thought to be useful as a selective photosensitizer in photodynamic therapy, as well as for constructing phthalocyanine-based supramolecular systems (Scheme 3.3).



Scheme 3.3: Reagents and conditions: (i) NaH, toluene, N_2 , 70°C ; (ii) ZnCl_2 , DMAE, N_2 , reflux; (iii) TFA/ H_2O (9:1), rt.

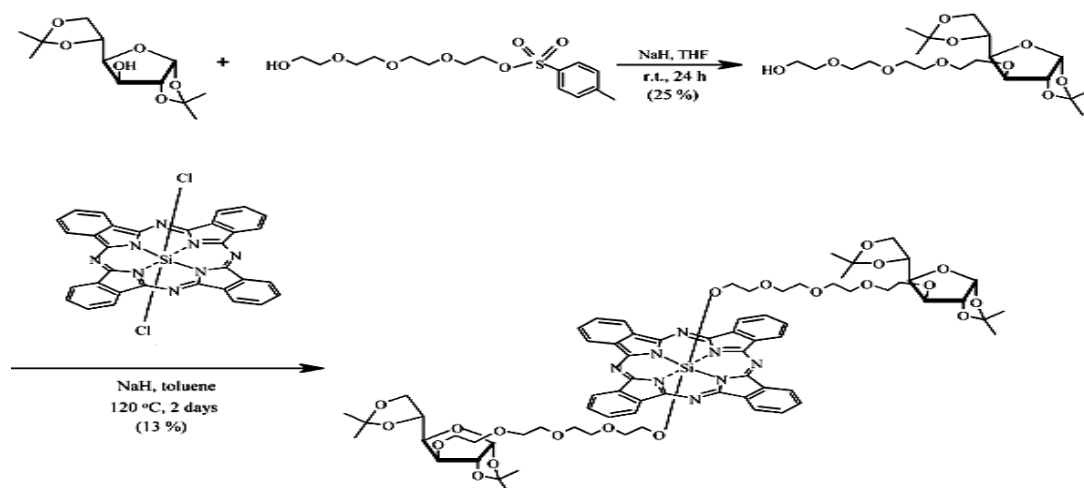
Pcs bearing carbohydrates in axial position have been reported as well.

Another research group in 2005 treated non-substituted Si(IV)Pc dichloride with 1,2:3,4-di-O-isopropylidene- α -D-galactopyranose in the presence of NaH in toluene to obtain the axially disubstituted product SiPc in 38% yield [44] (Scheme 3.4). The reaction was the nucleophilic substitution of chlorides on the central Silicon atom, by the unprotonated primary hydroxyl of the galactose. Water solubility of the product was increased enough to make PDT test even with protected groups. The amphiphilicity was then modulated by asymmetric axial substitution pattern: carbohydrate on one side and alkyl chain on the other side.



Scheme 3.4: Preparation of galactose-containing Si(IV)Pcs

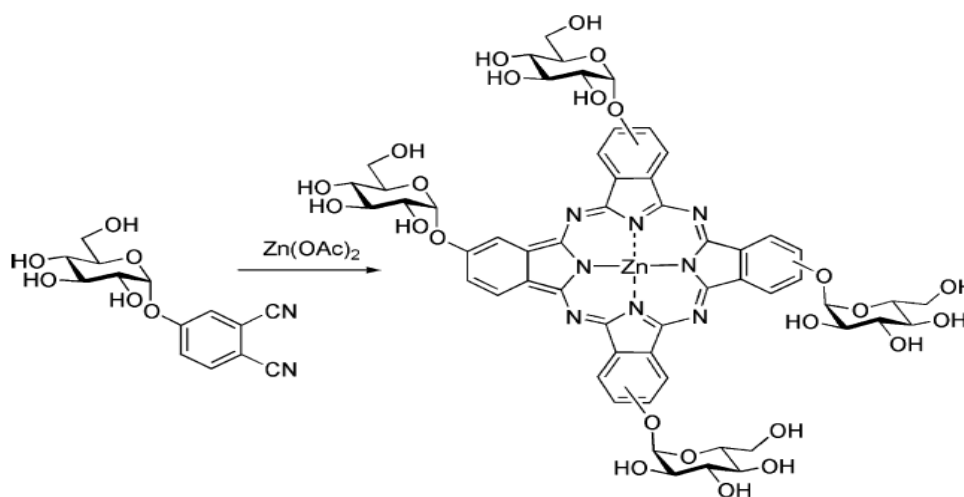
The last reported literature in 2007, which discussed two novel glucoconjugated silicon(IV) phthalocyanines [45] have been prepared and examined for their photophysical and biological properties. With two axial 1,2:5,6-di-O-isopropylidene-RD-glucofuranose substituents linked to the silicon center through the tetraethylene glycol chain, both compounds are highly soluble and remain non-aggregated in *N,N*-dimethylformamide (Scheme 3.5).



Scheme 3.5

Previously presented Pcs had no glycosidic bond between the carbohydrates and corresponding phthalocyanines. Now, the first glycosidic linkage and subsequent expeditious Pc synthesis will be presented here.

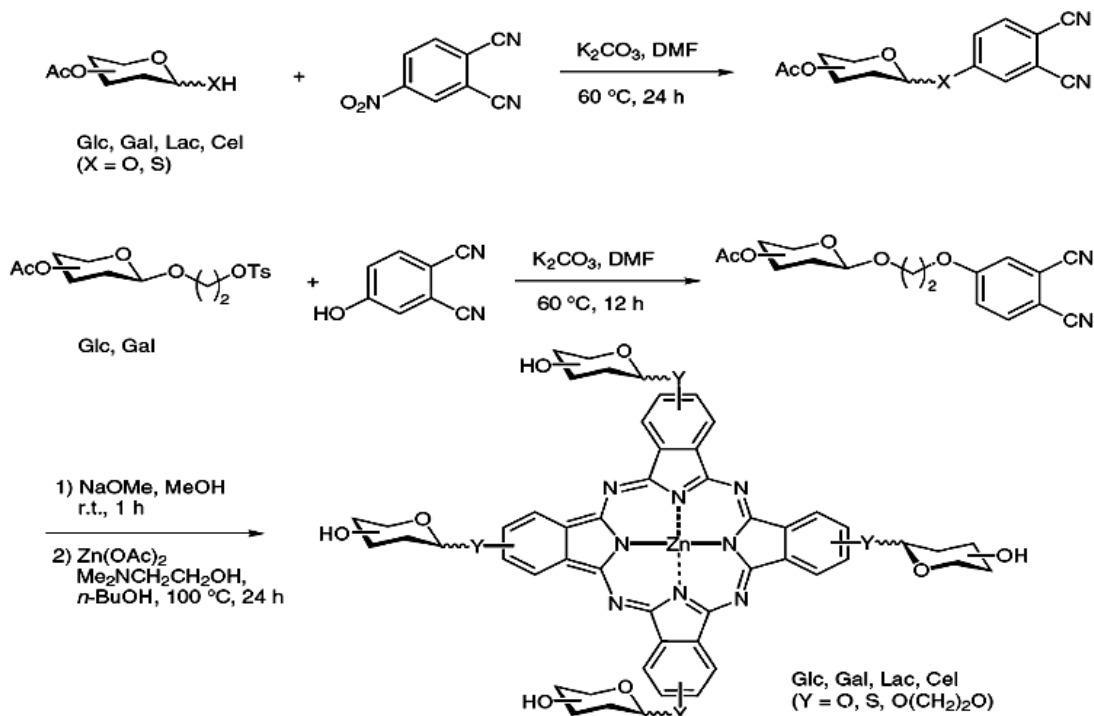
There is only one literature reported newly about the preparation of phthalocyanine-glycoconjugates over a *glycosidic* bond formation [46]. Synthesized ZnPcs have quite good water solubility, thus they are assumed to lead to considerable results on biochemical tests (Scheme 3.6).



Scheme 3.6

As the expeditious work to the literature above, Hanack and Ziegler reported the synthesis of several novel phthalocyanine glycoconjugates linked anomERICALLY to

the glycoses, for which classical phthalocyanine template chemistry with the corresponding unprotected phthalonitrile glycosides was used [47] (Scheme 3.7).



Scheme 3.7

3.2. Water Soluble Phthalocyanines for PDT

Due to their high tendency of aggregation, the solubility of Pcs has been a challenge since the first works lead on these molecules. Many efforts focus now on the water solubility, and many strategies have been developed: ionic substituents, axial hydrophilic substitution, and various hydroxylated substituents.

Except carbohydrate conjugated Pcs, there are many water soluble phthalocyanines reported so far by grafting ionic groups either on axial, peripheral or non-peripheral position of the macrocycle. Most common are SO_3^{2-} for the anionic ones, the cationic ones resulting of the quaternarization of amino or pyridine [48] group. The presence of polyoxoethylene group [49] or hydroxyls [50] helps as well to water-solubilize a Pc. Here some examples of water soluble Pcs will be given.

First example is about obtaining water-soluble phthalocyanine by quaternarization of pyridino groups. This paper is abstracted on a spectroscopic investigation of the binding of the non-aggregated water-soluble GaPc derivatives [48]. (Figure 3.1)

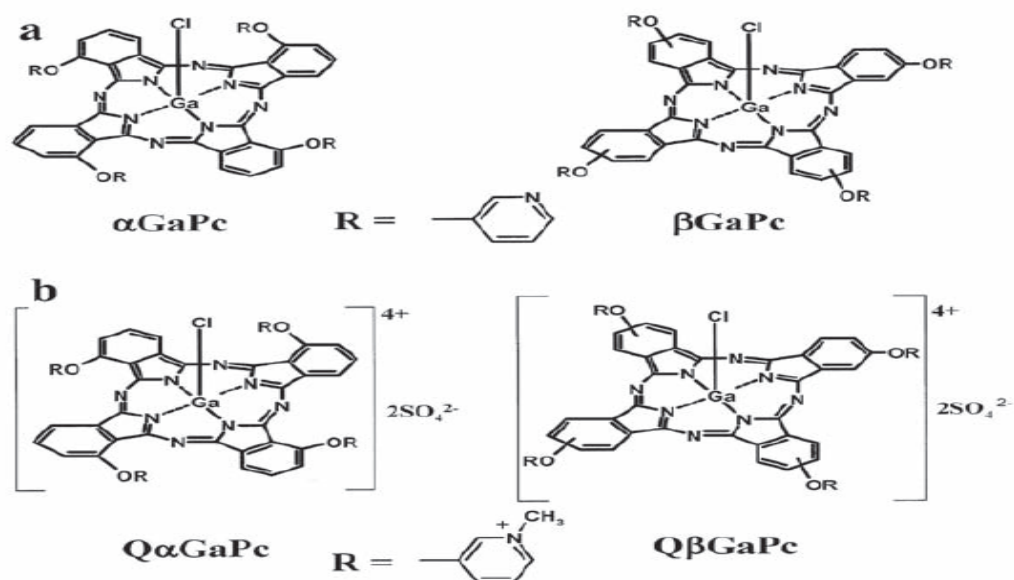


Figure 3.1

In another paper, novel derivatives of Pcs which are soluble in water as well as in most polar solvents have been prepared. For this purpose, Pcs carrying linear oligoethyleneoxy chains of two different chain lengths with -OH end groups were designed [49]. (Figure 3.2)

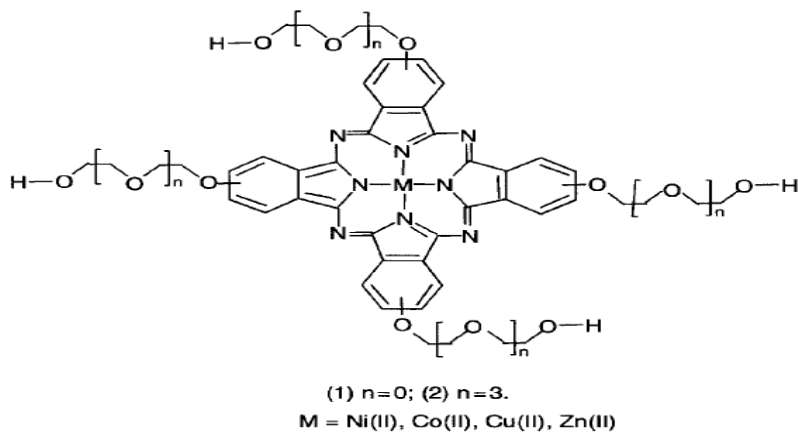
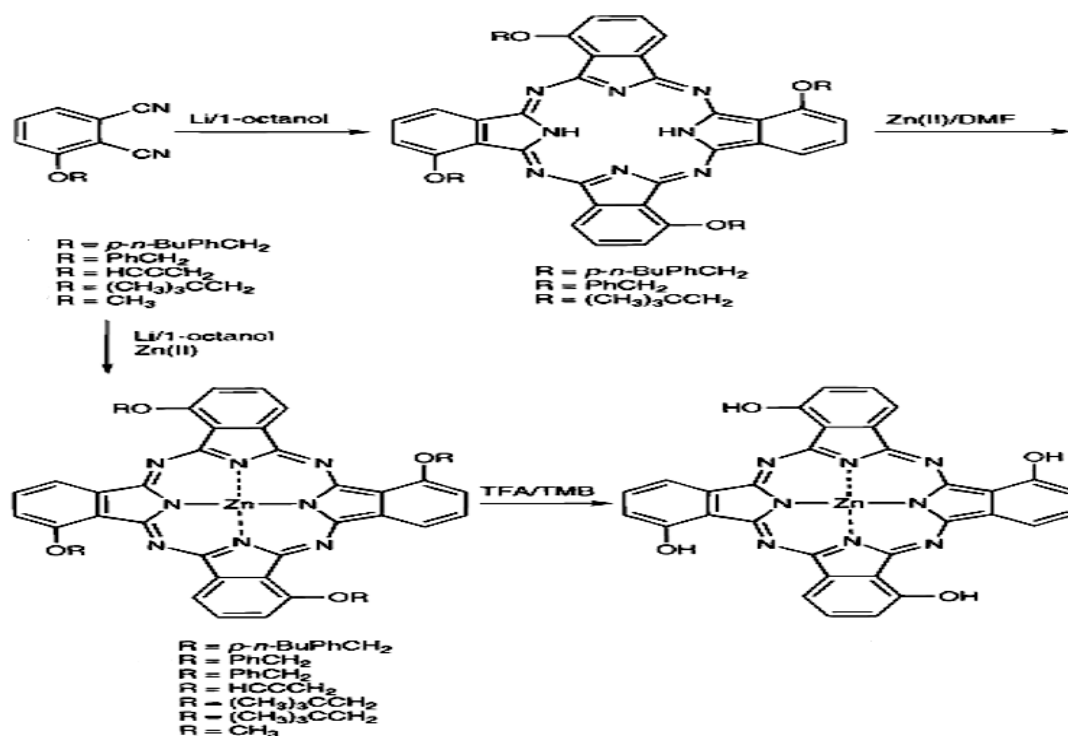


Figure 3.2

This literature is again an example of water soluble phthalocyanine with non-peripherally substituted hydroxyl groups [50]. (Scheme 3.8)



Scheme 3.8: Synthesis of water soluble Pc

3.3. Amphiphilic Phthalocyanines for Self-Assemblies

Amphiphilic phthalocyanines are synthesized for different purposes; PDT, electrical conductivity, electronic properties, gas sensing properties through making Langmuir-Blodgett films and properties of LB films which is the only application interests us for our purpose.

In 1996, the synthesis and thin film characterization of four octasubstituted phthalocyanines (Pcs) were reported. [2,3,9,10,16,17,23,24-octakis(dodecylcarboxylato) phthalocyaninato]copper, [2,3,9,10,16,17,- 23,24-octakis(*N*-dodecylamide)phthalocyaninato] copper, and [2,3,9,10,16,17,23,24-octakis(2-(benzyloxy)-ethoxy)phthalocyaninato]copper [51], and the corresponding zinc phthalocyanine analog, were prepared and their aggregation properties characterized



Another research was published in 1999 [52]. A series of asymmetrically substituted amphiphilic phthalocyanines were synthesized and deposited as Langmuir-Blodgett films onto glass and/or glass substrates bearing aluminum

interdigitated electrode patterns. It is reported that the films showed fast response to NO_2 with almost complete recovery at room temperature and it was indicated that layer ordering and molecular packing within the LB films are important factors determined the gas-sensing properties. (Figure 3.3)

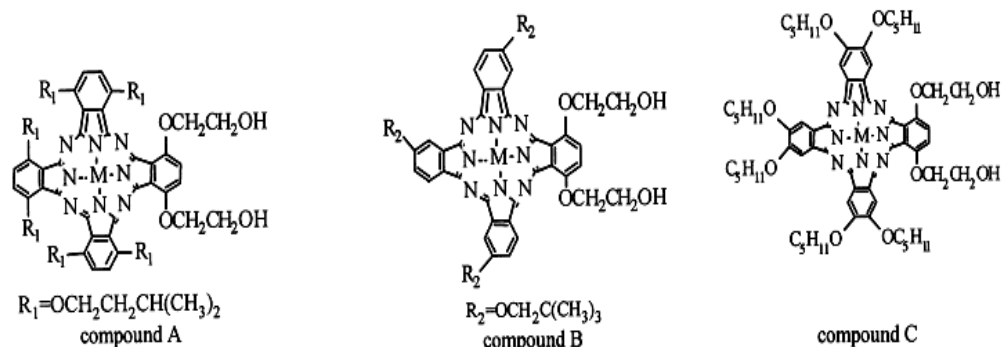
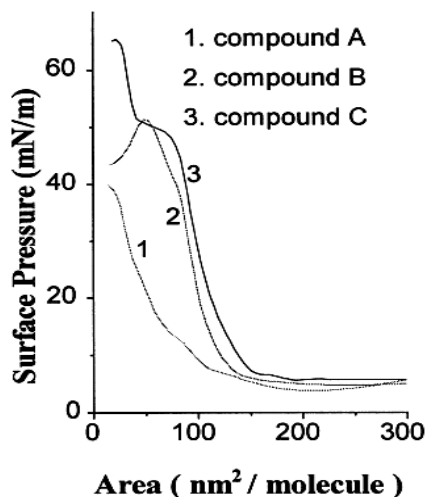


Figure 3.3

Figure 3.4 indicates the isotherms of the corresponding molecules, **A**, **B** and **C**. In the π -A isotherm of compound **C** (curve 3) there is distinct phase transition and two abrupt increases in slope and exhibiting a plateau, indicating that two kinds of

Figure 3.4: Surface pressure-area isotherm



well-condensed monolayers had been formed.

The lower pressure region corresponds to monolayer and the higher pressure region corresponds to bilayer. Compound **B** gives slightly different π -A isotherm (curve 2) without a plateau. Compound **A** shows somewhat expanded π -A isotherm (curve 1) and it can be seen that the monolayer collapses at a relatively low pressure compared with curves 2 and 3, suggesting that the monolayer is less stable [52]. (Figure 3.4)

3.4. Presentation of Target Molecules

In this thesis, two carbohydrate substituted Pcs have been synthesized and characterized. One of them is a water soluble zinc phthalocyanine for further PDT investigations, and the other is an amphiphilic phthalocyanine to further study its self-assembling properties.

Water soluble Phthalocyanine

Some metallophthalocyanines are good photosensitizers according to the type of metal chosen. The metals such as Zn, Al, Si... have the property to convert, when irradiated by correct wavelengths, triplet oxygen to singlet oxygen, which is a toxic molecule able to kill cancer cells. This is the well-known principle on which type-II photosensitizers have been developed. Another requirement is then necessary to be a good photosensitizer: high water-solubility to be biocompatible. So, we considered to make a water-soluble and biocompatible phthalocyanine. To achieve this goal, use of carbohydrates was a bright idea.

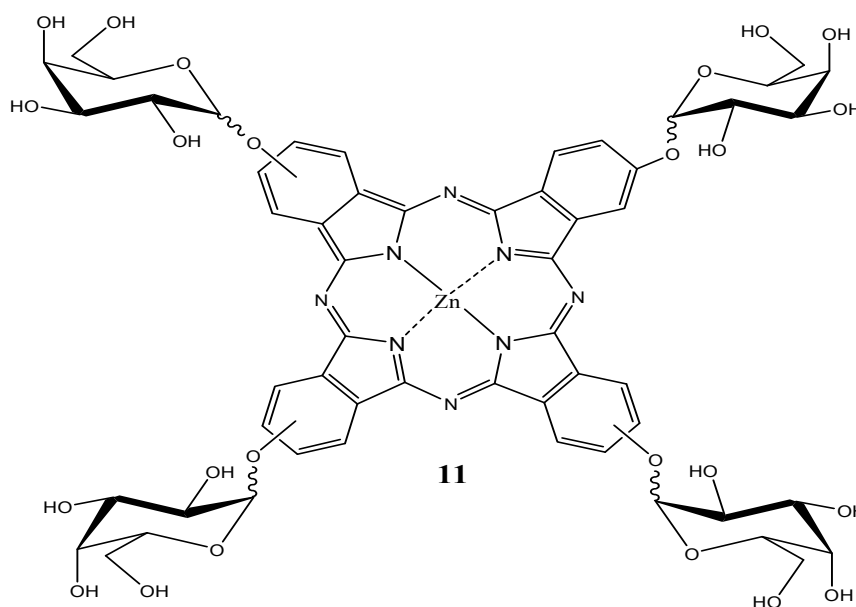


Figure 3.5: Structure of **11**.

Choice of the metal: Zinc is known to be one of the best metal on a $^1\text{O}_2$ generation point of view and is the most commonly used for preliminary investigations of potential photosensitizers efficiency.

Galactose was chosen for the glycosylation reactions because it has not been reported in the literature [47] which is presented in the first part of this section “Existing Carbohydrated Phthalocyanines”. It is in addition expected to be largely absorbed by cancerous cells that constant multiplication requires elevated metabolism.

Thus:

We prepared the tetrasubstituted ZnPc bearing galactose with glycosidic bond on the macrocycle in peripheral position.

Amphiphilic Phthalocyanine

The other molecule has been prepared to investigate self-assembly properties. This is an AB3 type asymmetric phthalocyanine which is synthesized in three steps. First one is the synthesis of asymmetric Pc with tetra-ethylene glycol and six membered alkyl chains by statistical condensation method, second step is the glycosylation reaction with the trichloroacetimidate derivative of galactose, and the third step is deprotection of galactose.

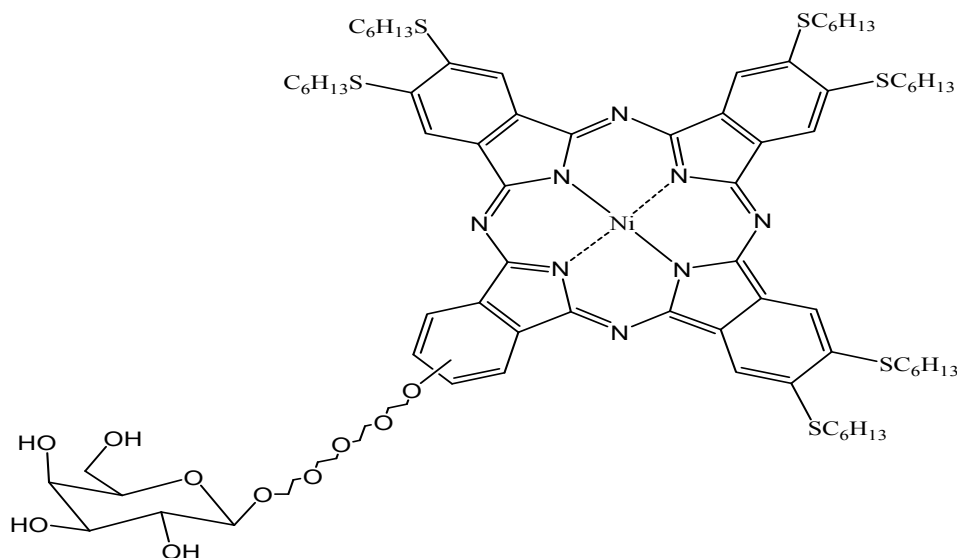
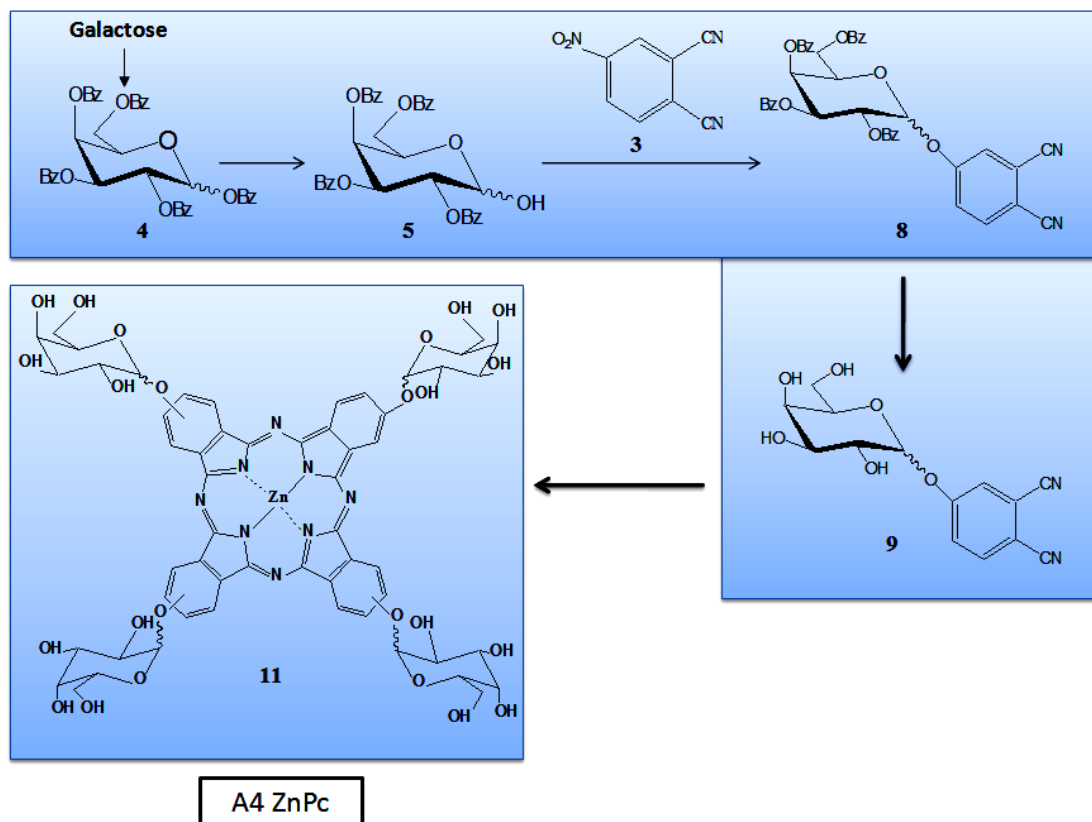


Figure 3.6: Structure of Amphiphilic Pc 14

4. DISCUSSION

4.1. Synthesis of the galactose substituted water soluble ZnPc (11)



Scheme 4.1: Synthesis of galactose substituted water soluble ZnPc (11)

4.1.1. Synthesis of the nitrile 9

Nitrile **9** is made from 4-nitrophthalonitrile (**3**) and tetrabenzoylated galactose (**5**).

4-nitrophthalonitrile (**3**) and precursors (**4** and **5**) were prepared as reported [53,54]. Starting from Phthalimide, **3** was synthesized in three steps: nitro addition to the Phthalimide, 4-Nitrophthalimide to 4-Nitrophthalamide, the last step was the synthesis of 4-Nitrophthalonitrile (**3**) in DMF at 0°C.

4 was synthesized from α/β mixture of commercial galactose in pyridine and benzoyl chloride. The reaction was run at 0°C to avoid the formation of furanose instead of the desired pyranose. Selective deprotection of C-1 (anomeric carbon) of pentabenzoylated galactose (**4**) was carried out with hydrazine acetate in DMF to get **5**.

Benzoylated nitrile **8** was prepared with the coupling of **3** and **5**, using DMF as a solvent, potassium carbonate as base. Quantitative yield was obtained as well as high α -selectivity. The bond formed between **3** and **5** is a glycosidic bond obtained through nucleophilic nitrite displacement of nitrobenzenes by anomeric glycosyl oxides (O-arylation of galactose). [56]

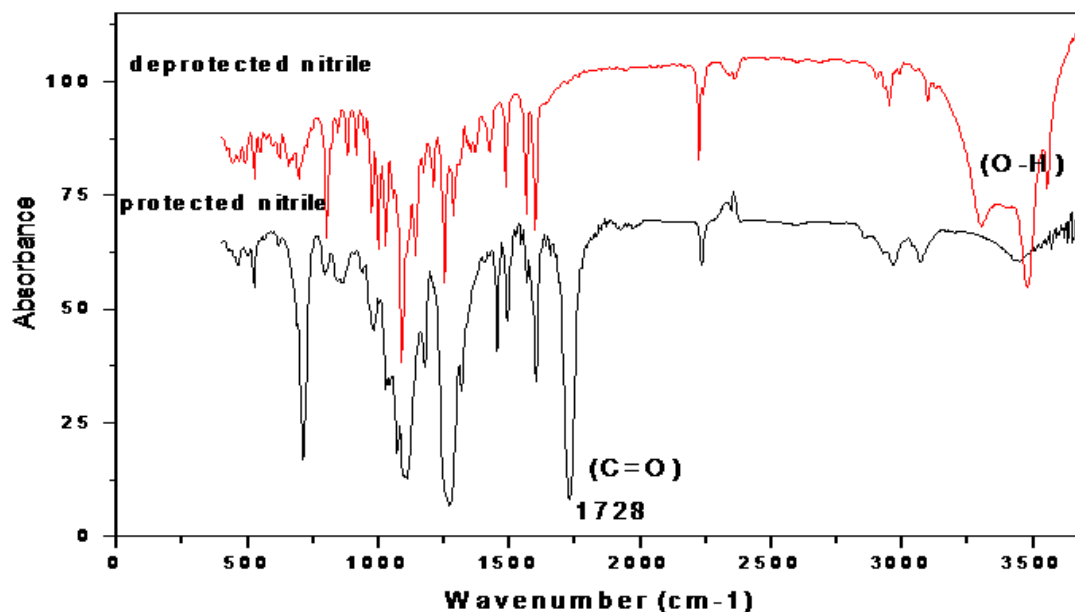
9 was unprotected under Zemplén conditions [55] (cat. sodium methoxide, dry methanol) from **8**. This process is a transesterification which is the process of exchanging the alkoxy group of an ester compound with another alcohol. These reactions are often catalyzed by the addition of an acid or base.

^1H NMR, ^{13}C NMR, Mass Spectrometry were used to characterize the nitriles **8** and **9** [Spectra 7.1, 7.2, 7.3, 7.4, 7.5, 7.6].

The mass spectra shows the molecular weight plus sodium peaks at 745.2 for nitrile **8** and at 329.1 for nitrile **9** [Spectra 7.1, 7.4]. On ^1H -NMR spectrum the characteristic proton peaks of protected galactose (**8**) are observed at 4.4-6.2 ppm. At 7.0-8.2 ppm the aromatic proton peaks of benzoyl groups and benzene ring are observed [Spectrum 7.2]. After deprotection, no benzoyl protons are observed any more on the ^1H -NMR spectrum of nitrile **9**. Benzene protons are at 7.3-7.8 ppm region. The characteristic H-1 proton of galactose is a doublet at 5.6 ppm with a coupling of 3.68 Hz. The other protons' shifts are between 3.4-4 ppm. The integral values are very good and show the all 10 protons except the -OH protons. The shift at 4.33 ppm is from DOH [Spectrum 7.5].

Interpretation of ^{13}C -NMR spectra of both nitriles **8** and **9** shows that the galactoses on the galactosylated nitriles are mainly in α -form which can be

understood from ^{13}C -NMR shifts. The α -form has a characteristic anomeric C-1 shift at 95 ppm where β -form has C-1 at 100 ppm [Spectra 7.3, 7.6].



The comparison of IR spectrums of both nitriles (benzoylated **8** and unprotected **9**) proves that carbonyl groups of benzoyl disappear with the formation of deprotected nitrile **9**.

4.1.2. Synthesis of the Pc **11**, purification, analyses

The tetragalactose substituted zinc phthalocyanine (**11**) was synthesized using the classic phthalocyanine template reaction with deprotected nitrile **9** (the Pc are synthesized starting from the α/β mixture). It was reported that the debenzoylation after the synthesis of Pc from benzoylated nitriles was an incomplete process that is why deprotection takes place before the tetramerization⁴. A solvent mixture of DMAE 2:1 n-butanol was used for the reaction for a better yield because when the reaction was carried out either in DMAE or in n-butanol alone, yields were low [56]. Reaction was performed at 110°C for 24h under argon atmosphere. For purification, reaction mixture was dissolved in a minimum amount of water, and then precipitated in acetone, recovered with centrifugation. For further purification, **11** was washed with ethanol and ethyl acetate and recovered again with centrifugation. Finally **11** was completely purified with preparative HPLC.

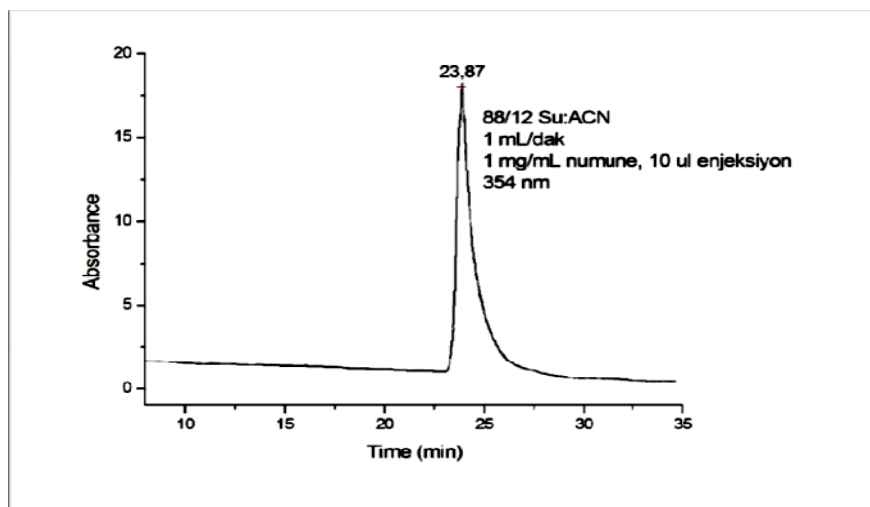


Figure 4.1: HPLC chromatogram of ZnPc **11** with a retention time of 23 min. Mobile phase: water 88 %, acetonitrile 12%.

The chromatogram is the proof of purification.

The yield of the compound **11** is not considerable enough. The possible reasons of this result are fragility of galactose derivatives under reaction condition and not having the perfect reaction condition for this synthesis. Also the purification process was very difficult and some of the product has been lost at this step to get pure compound.

^1H NMR, ^{13}C NMR, Mass Spectrometry were used to characterize **11**. UV spectrum was recorded to use for further purpose, PDT.

The mass spectrum of **11** shows molecular weight plus hydrogen peak at 1290.4 [Spectrum 7.10]. ^1H -NMR spectrum shows the characteristic H-1 of β -deprotected galactose as a doublet at 6.05 ppm and three broad singlet of phthalocyanine ring around 7-8 ppm [Spectrum 7.11]. The ^{13}C -NMR spectrum shows all carbon shifts of galactose carbons. The C-1 shifts at 99 ppm and other carbon shifts of galactose are around 60-70 ppm. The carbon shifts of phthalocyanine ring are between 120-160 ppm.

Prepared Pc **11** is soluble in water so UV-vis spectrum was recorded in water.

According to the Beer Lambert Law, it is observed that there is a linear correlation between absorbance and the concentration (Graph 1. and 2.). There are two bands on the spectrum. Both of them are typical bands for phthalocyanines. One is B-band at 335 nm and the other is Q-band at 634 nm. According to the sharpness of the peaks, it is said that there is a small aggregation.

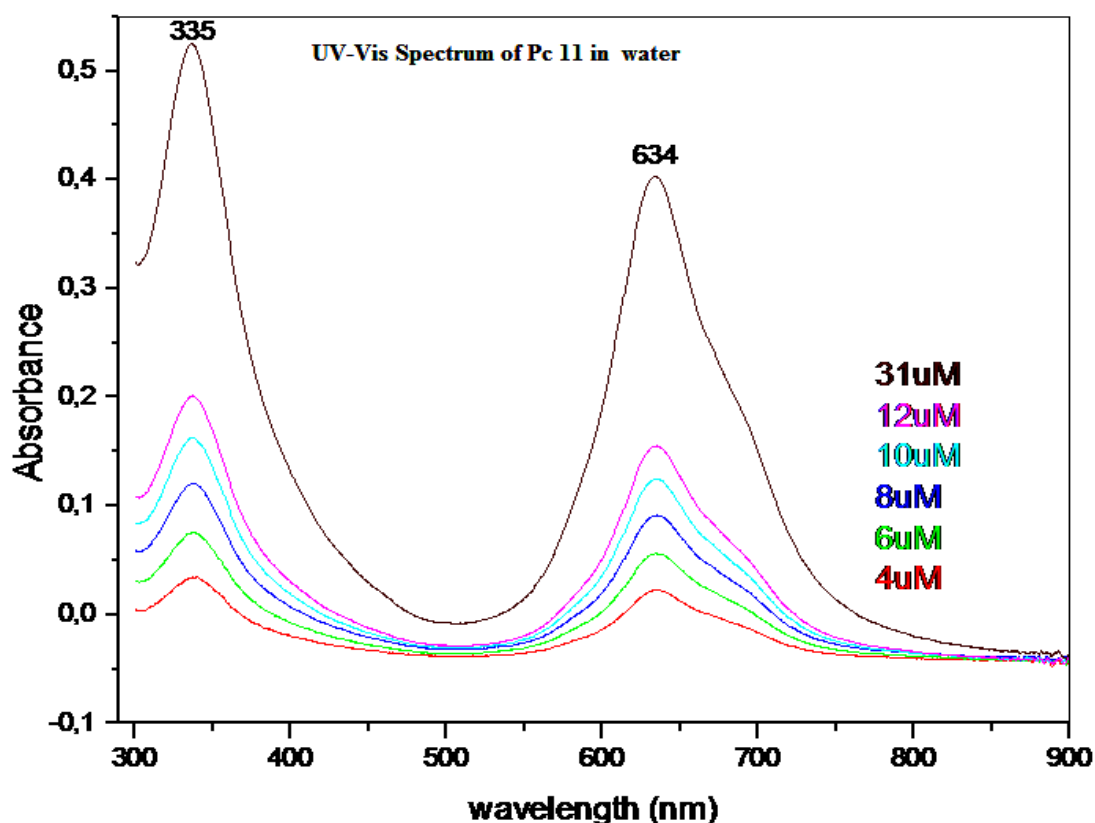


Figure 4.2: UV-Vis spectrum of ZnPc **11** in water

Extinction coefficient of the product at $\lambda_{\text{max}2}$: 634 nm (Q band) is $1,13 \times 10^4$ calculated from the equation $A = \epsilon c l$. To investigate coherence of concentration and absorbance 3 different concentrations in μM level were prepared; absorbance values and coefficient values are on the Table 4.1. The linear line indicated at Graph 4.1 shows the Beer-Lambert linearity.

Molarity	Absorbance	ϵ [l mol ⁻¹ cm ⁻¹)x10 ⁴]
8 μ M	0,0913	1,14
10 μ M	0,1246	1,12
12 μ M	0,155	1,13

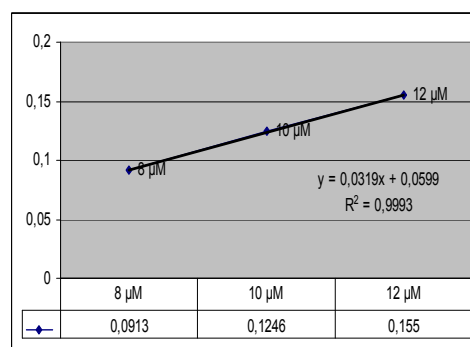


Table 4.1: Extinction coef. is accepted as $1,13 \times 10^4$ for 634 nm.

Graph 4.1: Beer-Lambert linearity

Extinction coefficient of the product at $\lambda_{\max 1}$: 335 nm (B band) is $1,16 \times 10^4$ calculated from the equation $A = \epsilon c l$. To investigate coherence of concentration and absorbance 3 different concentrations in μ M level were prepared; absorbance values and coefficient values are on the Table 4.2. The linear line indicated at Graph 4.2 shows the Beer-Lambert linearity.

Molarity	Absorbance	ϵ [l mol ⁻¹ cm ⁻¹)x10 ⁴]
8 μ M	0,1195	1,15
10 μ M	0,1615	1,16
12 μ M	0,1996	1,165

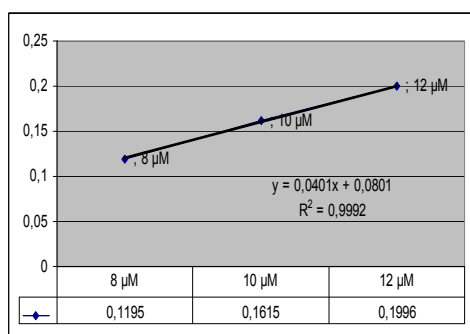
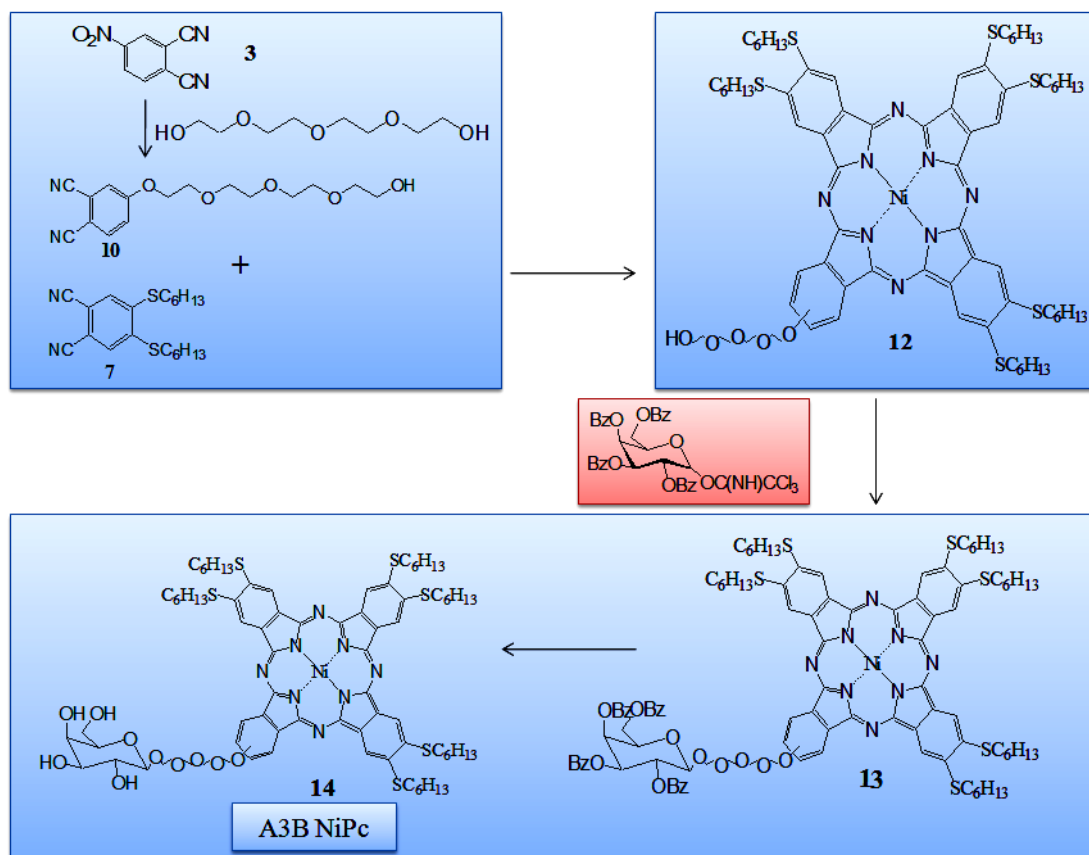


Table 4.2: Extinction coef. is accepted as $1,16 \times 10^4$ for 335 nm.

Graph 4.2: Beer-Lambert linearity

4.2. Synthesis of the Amphiphilic NiPc 14



Scheme 4.2: Synthesis of asymmetric Pc 14

4.2.1. When to proceed to the glycosylation?

Our first preoccupation was to choose when to proceed to the glycosylation step. To avoid the likely degradation of benzoylated galactose during the Pc ring formation, the glycosylation is achieved on the previously formed NiPc 12. AB3 type new galactosylated Pc 14 was prepared in two steps after the synthesis of 12, used as the acceptor.

In each step solubility of Pcs differs according to the substituent. Dichloromethane dissolves both Pc 12 and 13, however more polar final product 14 dissolves only in chloroform. This result is convenient to the further research on LB-films which is generally applied by using chloroform as the solvent.

4.2.2. Starting nitriles

The starting nitrile dihexylthio **7** was synthesized as reported [57].

The nitrile **10** was prepared with a coupling between 4-nitrophthalonitrile (**3**) and tetraethyleneglycol. The formation is optimized by portionwise addition of potassium carbonate and the excess use of tetraethyleneglycol (5 equivalents of tetraethyleneglycol for 1 equivalent of 4-nitrophthalonitrile). Yield of the product is 50% which is quite good for such synthesis.

The nitrile **10** has been characterized with ¹H NMR, ¹³C NMR and Mass Spectrometry [Spectra 7.7, 7.8, 7.9].

The mass spectrum shows molecular weight plus sodium peak at 343.2 [Spectrum 7.7]. The ¹H-NMR spectrum of nitrile **10** shows the benzene peaks between 7-8 ppm and protons of tetraethylenglycol at 3.5-4.3 ppm. The integrals prove only mono-substituted phthalonitrile has been prepared [Spectrum 7.8]. The ¹³C-NMR spectrum is also well resolved. Quarternar carbon on benzene ring shifts at 162 ppm and other carbons of benzene ring shifts between 105-135 ppm. The carbons of tetraethyleneglycol shifts between 60-75 ppm [Spectrum 7.9].

4.2.3. Pc formation and glycosylation, purification

Pc **12** was synthesized by the statistical condensation of nitriles **7** and **10**. Reaction was carried out at 150°C in pentanol, using DBU and nickel chloride. Eight equivalents of **7** and one equivalent of **10** were reacted to give only the AB3 Pc **12** and the B4 octa-substituted NiPc from the nitrile **7**.

Because the reaction was started with big quantity of nitriles, a pre-purification with Soxhlet was needed. Impurities after concentration of reaction mixture were eliminated with ethanol and dichloromethane was used to recover product from Soxhlet. Purification was achieved on silicagel column chromatography. Dichloromethane was the first eluent to eliminate the symmetric NiPc resulting from the cyclotetramerization of the nitrile **7**. Ethanol 1: 20 dichloromethane was then used to take product from the column. Some fluorescent impurities were still present

in the products: they were removed by a second column: elution by ethyl acetate and acetone were used to eliminate traces of impurities, the Pc remaining on the top of the column. Yield of the Pc **12** was 20% which is a great success for AB3 type synthesis by statistical condensation.

Pc **13** was obtained by the galactosylation of **12** (acceptor), using trichloroacetimidate of galactose as the donor and TMSOTf as the promoter. The hydroxyl group of the Pc **12** selectively replaces the living group on the C-1 (anomeric carbon) of the galactose. Only the β -glyside has been obtained. Reaction takes place at 0°C in strongly anhydrous medium. Yield of the galactosylation step was 95%.

Pc **14** was prepared by deprotection of Pc **13**. The condition for deprotection is the use of sodium methoxide as catalyst in dry methanol (Zemplen condition). After deprotection, the methyl benzoate (transesterification) formed as byproduct which was removed by washing the reaction mixture with hexane.

¹H NMR, Mass Spectrometry were used to characterize products **13** and **14** [Spectra 7.14, 7.15, 7.16, 7.17, 7.18].

Mass spectrum of **13** and **14** shows molecular weight plus hydrogen peaks at respectively 2039.0 and 1622.7 [Spectra 7.14, 7.17]. ¹H-NMR of the benzoylated galactosylated Pc **13** shows methyl shifts and protons of alkyl chain between 0.9-2 ppm. Tetraethylenglycol protons shift are between 3-4.2 ppm. The aromatic protons of both phthalocyanine and benzoyl groups are between 7.1-8.1 ppm [Spectrum 7.15]. The characteristic shifts of galactose are observed between 4.3- 6 ppm [Spectrum 7.16]. After debenzoylation of Pc **13**, all benzoyl protons disappeared and carbohydrate protons shifted to 4-5 ppm region [Spectrum 7.18].

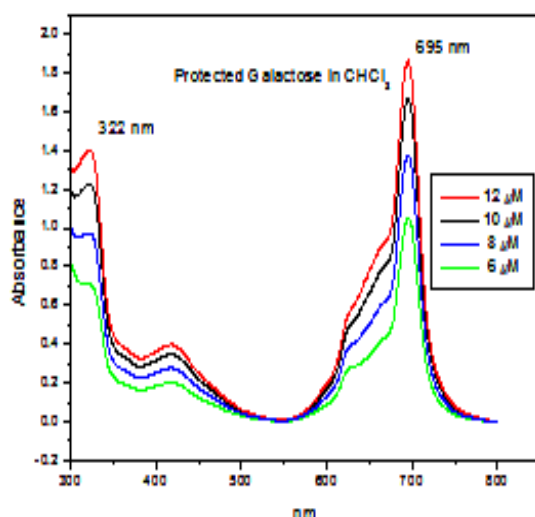


Figure 4.4: UV-Vis Spectrum of Pc **13** in Toluene

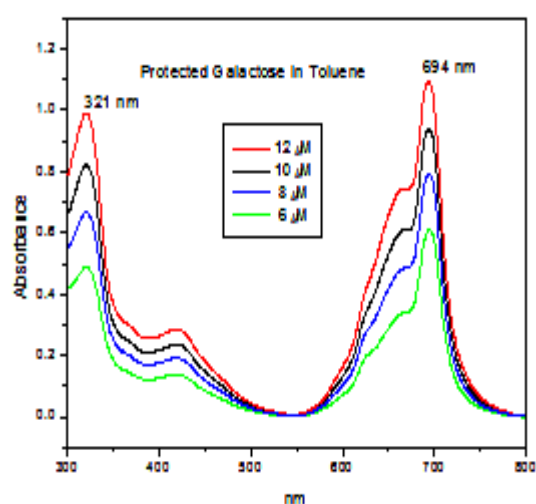


Figure 4.3: UV-Vis Spectrum of Pc **13** in CHCl_3

UV-Vis Spectrum of both benzoylated and debenzoylated Pcs **13** and **14** have been recorded at different concentrations. Benzoylated Pc **13** has an absorbance in the Q-band region at 694-695 nm in chloroform and toluene and has an absorbance in the Soret-band region at 322-321 nm. The debenzoylated Pc **14** has an absorbance in the Q-band region at 695 nm and at Soret-band at 320 nm. Pc **13** and Pc **14** have typical phthalocyanine absorbance at Q-band and both Pcs' absorbance spectrums indicate Beer Lambert linearity. The comparison of UV-Vis spectrums of benzoylated (**13**) and debenzoylated (**14**) compounds shows that deprotection does not affect absorbance of the compound.

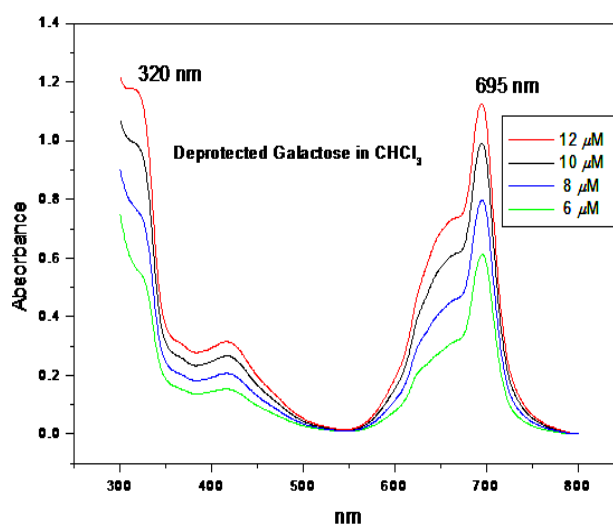


Figure 4.5: UV-Vis Spectrum of Pc **14** in CHCl_3

5. CONCLUSION

2 new carbohydrate Pcs have been obtained during this thesis and fully characterized: a symmetric one and an asymmetric one.

One of these phthalocyanines bears four galactose derivatives (**11**). The product has been synthesized by classic tetramerization of galactosylated phthalonitrile **9**. The symmetric ZnPc **11** has been designed as a photosensitizer for a further purpose: The Photodynamic Therapy Test. Its water solubility allows further tests as potential photosensitizer.

The AB3 type amphiphilic nickel phthalocyanine **14** has been prepared through several steps. Starting from two types of nitriles (**7** and **10**), first of all the asymmetric nickel phthalocyanine **12** has been prepared. Then the glycosylation reaction between phthalocyanine **12** (acceptor) and trichloroacetimidate derivative of galactose (donor) has been achieved in very good yield. It is the first time a phthalocyanine is used as an acceptor for a glycosylation reaction. Finally the protected compound **13** has been deprotected under Zemplén conditions to form Pc **14**.

The amphiphilic NiPc **14** has been designed to investigate its monolayer behavior. Further work lead on the asymmetric phthalocyanine prepared during this thesis will consist in the preparation of monolayer at the air-water interface to study the basic parameters of such self-assembly.

The thesis includes basically synthesis and characterization of two new final compounds. These compounds are prepared for different applications. They will be valorized during the investigations whose will be reported later on.

6. EXPERIMENTAL

6.1. Reagents and Equipments

Tablo 6.1. Reagents used for the thesis

<i>Name of the Reagent</i>	<i>Company</i>	<i>Catalog No</i>	<i>Property</i>
Phthalimide	Merck	8.07303	For synthesis
Galactose 99%	Acros	150615000	For synthesis
DMF	Merck	1.03053	Pure
Thionyl Chloride	Fluka	88952	Pure
Benzoyl Chloride	Merck	8.01804	Pure
NaHCO ₃	Fluka	71630	Pure
NaOH	Merck	1.06462	Pure pellets
DMSO	Merck	8.02912	For synthesis
Potassium Carbonate			Anhydrous
2-(dimethylamino)etanol	Merck	8.03237	For synthesis
%98'lik H ₂ SO ₄	Merck	1.00748	For synthesis
%65'lik HNO ₃	Merck	1.00443	Pure
THF	Merck	1.08114	Pure
Zn(OAc) ₂	Merck	1.08800	Pure
Sodium Acetate	Riedel-de Haen	25060	Pure
1,8-diazabisiklo [5,4,0] undec-7-ene (DBU)	Fluka	33481	Pure
NiCl ₂ .6H ₂ O	Fluka	72247	Pure
Acetic Acid	Riedel-de Haen	27225	Pure

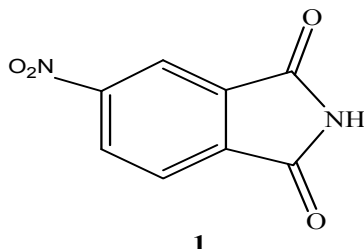
Hydrochloric Acid	Technique		
Sodium Sulfate	Merck	1.06645	Anhydrous
Silicagel 60	Merck	1.07734	0.043-0.063 mm
n-pentanol	Merck	8.04393	For synthesis
Ethanol	Technique		
Methanol	Technique		
Chloroform	Technique		
Dichloromethane	Technique		
Pyridine	Riedel-de Haen	16037	Pure

Table 6.2. Equipments used for characterization

Name	Model	Place
Melting Point	Büchi 535	GYTE
FT-Infrared Spectrometry	Bio-Rad FTS 175C	GYTE
NMR Spectrometry	Varian 500 MHz	GYTE
Mass Spectrometry	Bruker LC-ESI-MS	GYTE
Elemental Analysis		TÜBİTAK-MAM
UV/Vis. Spectrometry	Schimadzu 2001 UVPc	GYTE

6.2. Synthesis of precursors (1-9)

6.2.1. 4-nitrophthalimid (1)



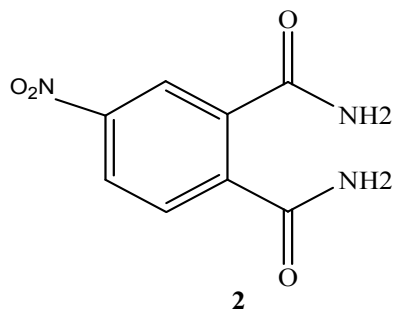
Concentrated sulfuric acid (200 mL) and fuming nitric acid (50 mL) were mixed in a beaker and cooled to 15°C in an ice bath. **Phthalimide** (40 g, 0.27 moles) was added by portions within 1 hour. Solution was stirred 30 minutes more. After complete dissolution, the yellow solution is allowed to reach room temperature. Then reaction mixture was cooled 0°C and poured into ice (1 kg). Yellow precipitates were filtered, washed with cold distilled water and crystallized in ethanol (500 mL). Crystals were dried under vacuum.

39.2 g Yield 75%.

m. p. 195-199°C, litt 195-199 °C [53].

C₈H₄N₂O₄, MW: 192.13 g/mol

6.2.2. 4-nitrophthalamid (2)



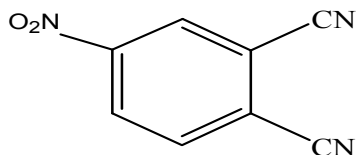
1 (20 g, 0.104 moles) was stirred in 25% ammonia solution (140 mL) in a beaker at room temperature one night. Reaction was checked with TLC (10 Dichloromethane/1 Methanol) and finished by filtration. **2** was washed with cold water. White precipitates were dried under vacuum.

17.4 g Yield 80%.

Melting point 197°C. litt. 197-199 [53]

$C_8H_7N_3O_4$, MW: 209.16 g/mol

6.2.3. 4-nitrophthalonitril (**3**)



3

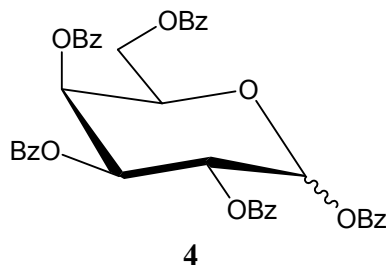
DMF (75 mL, technique) was put into a reaction balloon and cooled to 0°C. Thionyl Chloride (7.5 mL) was added to reaction mixture drop by drop. White vapor was observed. Solution was stirred 10 min at 0°C. **2** (10 g, 0.048 mole) was added to the reaction balloon by portions. After addition of **2**, ice bath removed, reaction mixture was stirred two hours more at room temperature, and then poured into ice (500 g). Precipitates were filtered, washed with Sodium bicarbonate (5%) and cold water. **3** was dried under vacuum.

6.95 g Yield 84%.

Melting point 140°C. litt. 141 °C [53].

C₈H₃N₃O₁, MW: 173.13 g/mol

6.2.4. 1,2,3,4,6-penta-*O*-benzoylhexopyranose (4)



Galactose (15 g, 0.083 moles) and pyridine (500 mL) were put into 1L balloon, cooled with ice bath. Benzoyl chloride (50 mL) was added to reaction mixture drop by drop. Yellow solution, white precipitates were observed. After one night 10 mL of water was added to reaction mixture. When solid dissolved, reaction mixture was poured into ice. Precipitates were filtered, washed with water and hydrochloric acid (conc.), dried under vacuum.

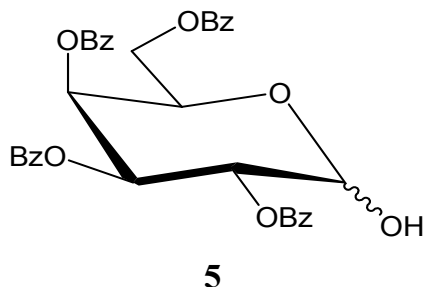
53.6 g Yield 95%.

Melting point 140°C. litt. 141 °C [54].

C₄₁H₃₂O₁₁, MW: 700.69 g/mol

¹H NMR: (CDCl₃): δ 8.22-7.25 (m, aromatic H,), 6.96 (d, 1H, $J_{1,2}$ 3.65 Hz, H-1), 6.20 (dd, 1H, $J_{3,4}$ 3.24, $J_{4,5}$ 1.00 Hz, H-4), 6.14 (dd, 1H, $J_{3,2}$ 10.72, $J_{3,4}$ 3.31 Hz, H-3), 6.04 (dd, 1H, $J_{2,3}$ 10.71, $J_{2,1}$ 3.67 Hz, H-2), 4.85 (t, 1H, $J_{5,6b}$ 6.96 Hz, H-5), 4.64 (dd, 1H $J_{6a,6b}$ 11.35, $J_{6a,5}$ 6.44 Hz, H-6a), 4.44 (dd, 1H, $J_{6b,6a}$ 11.36, $J_{6b,5}$ 6.95 Hz, H-6b)

6.2.5. 2,3,4,6-tetra-*O*-benzoylhexopyranose (**5**)

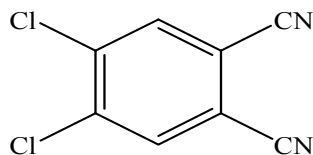


4 (6 g, 8.6 mmol) and Hydrazine Acetate (1.5g, 15mmol) were put into DMF (50 mL, technique) in a balloon, stirred all night at room temperature. Orange color was observed. Product was poured into ethyl acetate (300 mL), extracted with brine, (5%) sodium bicarbonate, and dried by using sodium sulfate. **5** was purified with Column Chromatography (2 ethyl acetate/3 hexane).

4.4 g Yield %80 [54].

C₃₄H₂₈O₁₀, MW: 596.58 g/mol

6.2.6. 4,5-dichlorophthalonitrile (**6**)



6

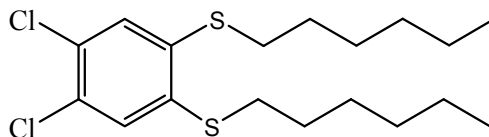
DMF (330 mL, technique) was put into a reaction balloon and cooled to 0°C. Thionyl chloride (230 mL) was added to reaction mixture drop by drop. White vapor observed. Solution was stirred 10 min at 0°C. **4,5-Dichlorophthalamide** (66 g, 0.28 mole) was added to the reaction balloon by portions. After addition, ice bath removed, reaction mixture was stirred two hours more at room temperature, and then poured into ice (1 kg). Precipitates were filtered, washed with sodium bicarbonate (5%) and cold water. **6** was dried under vacuum.

51 g. Yield 93%.

Melting point was 183°C. litt. 182-184 °C [58].

C₈H₂Cl₂N₂, MW: 197.02 g/mol

6.2.7. 4,5-bis(hexylthio)phthalonitrile (7)



7

Hexanethiol (42.8 mL) was dissolved in absolute dimethyl sulfoxide (175 mL) under argon and **6** (30 g, 0.15 mole) was added. After stirring for a while, anhydrous potassium carbonate (36.5 g, 0.26 mole) was added portionwise in 2h with continuous stirring. Reaction mixture was stirred under argon at room temperature for 24h. Then water (250mL) was added and the aqueous phase extracted with dichloromethane (3 x 250 mL). Combined organic phase was treated first with sodium carbonate solution (5%), then with water and dried over anhydrous sodium sulfate. Solvent was evaporated; product was crystallized in ethanol and dried under vacuum.

18.1 g Yield 66%

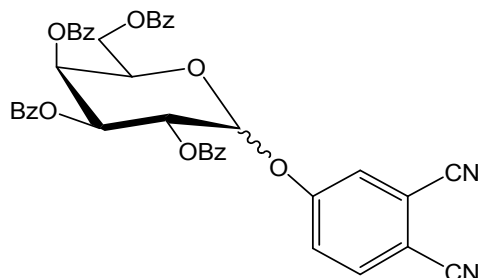
Melting Point 69°C. lit. 70 °C [57].

C₁₈H₂₈Cl₂S₂, MW: 379.45 g/mol

6.3. Synthesis of New Compounds (8-14)

6.3.1. 4-[(2,3,4,6-tetra-O-benzoylgalactopyranosyl)oxy]phthalonitrile

(8)



8

3 (0.87 g, 5 mmol) and **5** (3 g, 5 mmol) put into DMF. While stirring, potassium carbonate (4.2g, 30 mmol) was added to reaction mixture by portionwise. 12 h later reaction mixture was poured into ethyl acetate (300mL), extracted with Sodium bicarbonate (%5) and water. Ethyl acetate phase was dried with sodium sulfate and distilled. Product was purified with Column Chromatography (Ethyl acetate 2:3 Hexane).

2.94 g. Yield 81%.

Melting Point 152-155°C.

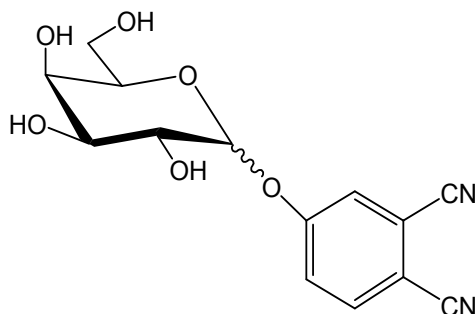
C₄₂H₃₀N₂O₁₀, MW: 722.70 g/mol.

Mass Spectrum (ESI-MS) m/z: At 723.2 [M+H]⁺, 745.2 [M+Na]⁺

¹H NMR : (CDCl₃) δ 8.15-7.25 (m, 23H, aromatics), 6.25 (dd, 1H, *J*_{3,4} 3.11, *J*_{4,5} <0.5 Hz, H-4), 6.2 (dd, 1H, *J*_{3,2} 10.70, *J*_{3,4} 3.18, Hz, H-3), 6.09 (d, 1H, *J*_{1,2} 3.24 Hz, H-1), 5.88 (dd, 1H, *J*_{2,3} 10.70, *J*_{2,1} 3.54 Hz, H-2), 4.64 (t, 1H, H-5), 4.55 (dd, 1H *J*_{6a,6b} 11.53, *J*_{6a,5} 5.64 Hz, H-6a), 4.46 (dd, 1H, *J*_{6b,6a} 11.71, *J*_{6b,5} 4.73 Hz, H-6b).

¹³C NMR: (CDCl₃) 165.64, 165.69, 165.80, 166.01 [C=O], 133.65, 133.82, 133.98, 134.04 (C^{IV}, aromatics), 121.42, 121.73, 135.43 (C-6', C-2', C-5'), 128.56, 128.73, 128.76, 128.95, 129.00, 129.24, 129.58, 129.83, 129.97, 130.11 (CH, aromatics), 115.46, 115.05 (C-CN), 109.49, 117.55, 158.94 (C^{IV}, C-4', C-3', C-1'), 95.27 (C-1), 69.32(C-3), 69.06 (C-2), 68.53 (C-5), 68.34 (C-4), 62.87 (C-6).

6.3.2. 4-(galactopyranosyloxy)phthalonitrile (**9**)



9

An α/β mixture (10:1) of **8** (1.0g, 2.0 mmol) was suspended in anhydrous MeOH (25 mL). NaOMe (20%, 100 mmol) was added and the solution was stirred for 1 h. Dowex 50WX8-400 ion-exchange resin was added to neutralize the reaction mixture. The resin was filtered off and the solvent distilled under vacuum.

0.27 g Yield 65%

Melting Point 220-222°C.

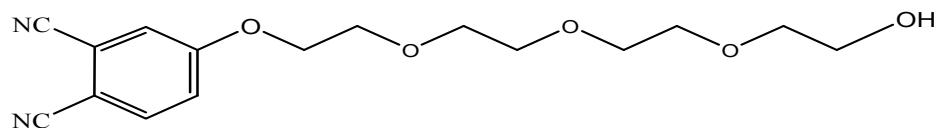
C₁₄H₁₄N₂O₆, MW: 306.27 g/mol.

Mass Spectrum (ESI-MS) m/z : 329.1 [M+Na]⁺

¹H NMR: (D₂O) δ d 7.79 (H-3'Ar, $J_{3',2'}$ 8.83 Hz, 1H), d 7.63 (H-1'Ar, $J_{1',2'}$ 2.49 Hz, 1H), dd 7.49 (H-2'Ar, 1H), 5.62 (H-1, $J_{1,2}$ 3.68 Hz, 1H), 3.91 (H-2, $J_{2,1}$ 3.68, $J_{2,3}$ 9.61 Hz, 1H), m 3.87-3.83 (H-4, H-3, 2H), m 3.70 (H-5, 1H), dd 3.62 (H-6a, $J_{6a,6b}$ 11.60, $J_{6a,5}$ 7.01 Hz, 1H), dd 3.57 (H-6b, $J_{6b,6a}$ 11.59, $J_{6b,5}$ 4.94 Hz, 1H)

¹³C NMR: (D₂O) δ 160.77 (C-1'), 135.43 (C-5'), 121.91 (C-2'), 121.90 (C-5'), 117.04 (C-3'), 115.63 (C-4'CN), 115.27 (C-3'CN), 108.23 (C-4'), 98.75 (C-1), 73.21 (C-5), 69.93 (C-3), 69.51 (C-2), 69.31 (C-4), 61.38 (C-6).

**6.3.3.4-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethoxy)
phthalonitrile (10)**



10

3 (3g, 17.3mmol) and tetra ethylene glycol (15mL, 86.5mmol) were dissolved in DMSO (75mL). Anhydrous potassium carbonate (104mmol) was added to reaction solution by portionwise. 24h later reaction mixture was poured into ethyl acetate (250mL) and extracted with water. Organic phase was dried using sodium sulfate and ethyl acetate was distilled under vacuum. Column Chromatography was used for purification (eluent: Ethyl acetate).

2.7 g Yield 50%.

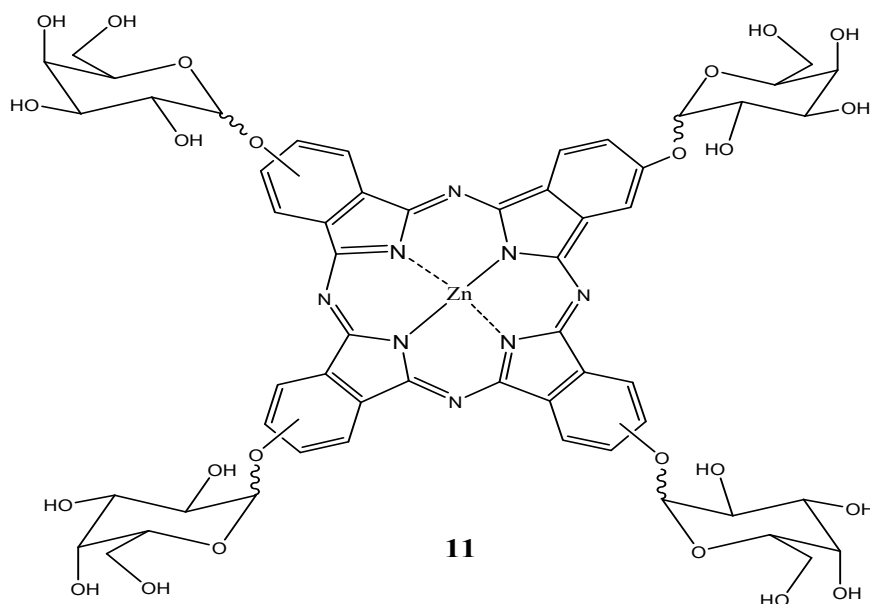
C₁₆H₂₀N₂O₅, MW: 320.34 g/mol.

Mass Spectrum (ESI-MS) m/z: 743.2 [M+Na]⁺

¹H NMR: (CDCl₃) δ d 7.72 (H-2 Ar, J_{3,2} 8.77 Hz, 1H), d 7.34 (H-1 Ar, J_{1,2} 2.57 Hz, 1H), dd 7.25 (H-3 Ar, 1H), m 4.25 (H-4, H-5, 2H), m 3.89 (H-6, H-7, 2H), m 3.73-3.61 (12H), s 2.27 (O-H)

¹³C NMR: (CDCl₃) δ 162.21 (C-7), 135.39 (C-5), 120.06 (C-6), 119.88 (C-8), 117.60 (C-2), 115.89 (C-4 CN), 115.49 (C-2 CN), 107.67 (C-4), 72.71-61.91 (C-9,10,11,12,13,14,15,16).

6.3.4.[2(3),9(10),16(17),23(24)-Tetrakis(α/β -D-galactopyranosyl-oxy) phthalocyaninato] zinc (11**)**



9 (0.325 g, 1.06 mmol) was dissolved in a mixture of 2-(dimethylamino)ethanol (1 mL) and BuOH (0.5 mL), and Zn(OAc)₂ (183mg, 1mmol) was added. The mixture was stirred under argon for 24 h at 100 °C. After cooling, the residue was dissolved in a minimal amount of H₂O and crude **11** was precipitated in acetone. The solid was filtered off, redissolved in a minimal amount of H₂O, precipitated again in acetone, and collected by filtration. Purification was achieved by preparative RP-HPLC chromatography (H₂O/MeCN, 10:1) to afford **11** as a green solid.

140 mg Yield 10%.

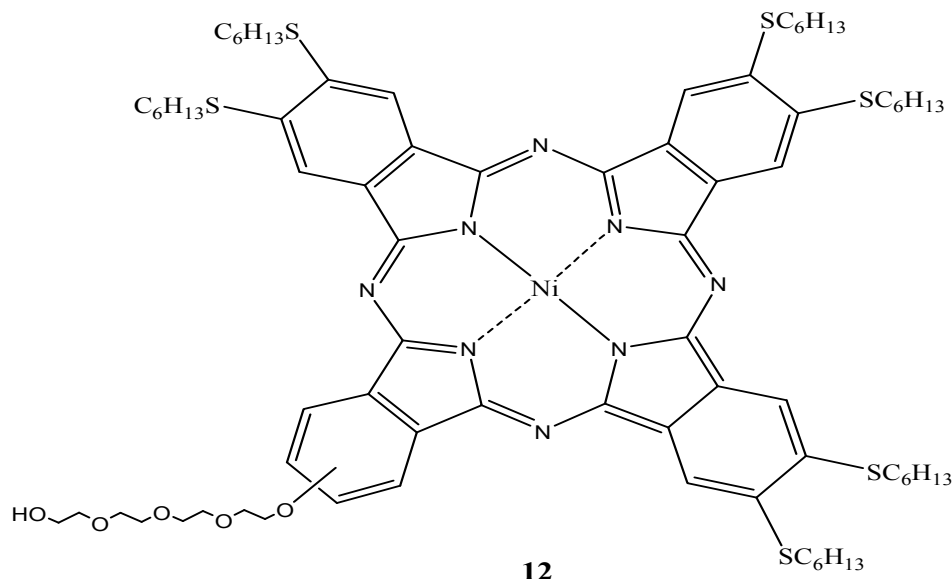
C₅₆H₅₆N₈O₂₄Zn, MW: 1290.47 g/mol.

Mass Spectrum (ESI-MS) m/z: 1290.4 [M+H]⁺

¹H NMR: (DMSO-*d*₆) δ 9.35 (bs, 4 H, H-5'), 9.08 (bs, 4 H, H-3'), 7.95 (bs, 4H, H-6'), 6.05 (bd, 4 H, H-1).

¹³C NMR: (DMSO-*d*₆) δ 163.20 (C-1'8'), 155.20 (C-4'), 137.64 (C-2'), 135.33 (C-7'), 124.40 (C-6'), 123.20 (C-5'), 120.53 (C-3'), 99.52 (C-1), 73.39 (C-2), 70.20 (C-4), 69.26 (C-3), 68.82 (C-5), 61.00 (C-6).

6.3.5. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-(2-{2-[2-(2-hydroxyethoxy) ethoxy] ethoxy}ethoxy)phthalonitrile) phthalocyaninato nickel(II) (12)



7 (13.5g, 37.5mmol, 8eq), **10** (1.5g, 4.7mmol) and NiCl₂ (5.5g, 42.2mmol) dissolved in anhydrous n-pentanol (30mL), 1 pipette of DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) was added to the reaction solution. The mixture was stirred 24h at 150°C. After cooling, reaction mixture was precipitated in water, and filtered off. Soxhlet was used for pre-purification: Ethanol was used first to eliminate soluble impurities and Dichloromethane to get product. And for further purification Column Chromatography was used.

Column chromatography on silicagel using a elution gradient (dichloromethane then progressive increase of the polarity to dichloromethane 20 – ethanol 1) gives pure **12**. Dark green solid.

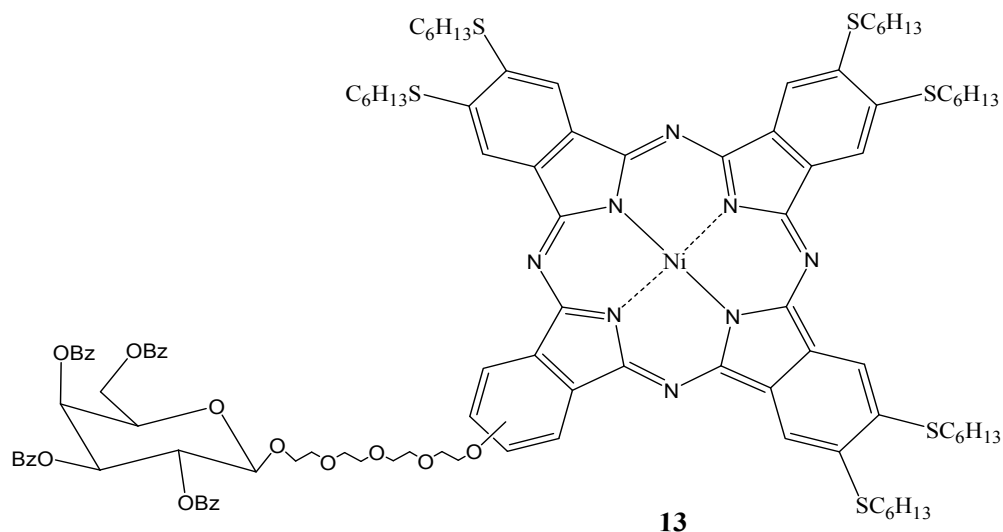
1.6 g Yield 20%.

C₇₆H₁₀₄N₈NiO₅S₆, MW: 1460.77 g/mol.

Mass Spectrum (ESI-MS) m/z: 1460.7 [M+H]⁺

¹H NMR: (C₆D₆) δ 8.56-7.20 (m, aromatic H), 4.25 (m, 2H, OCH₂), 4.04 (ddd, 1H, C-1OCH), 3.86 (t, 1H, OCH₂), 3.75 (ddd, 1H, C-1OCH), 3.75-3.50 (m, 8H, 4OCH₂), 3.33-3.14 (m, 12H, 6SCH₂), 2.14-1.96 (m, 12H, 6SCH₂CH₂), 1.82-1.68 (m, 12H, 6SCH₂CH₂CH₂), 1.54-1.29 (m, 24H, 12CH₂ alkyl chains), 1.06-0.95 (m, 18H, 6 CH₃ alkyl chains)

6.3.6. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-{2-[2-(2-{2-[(2,3,4,6-tetra-*O*-benzoyl galactopyranosyl)oxy]ethoxy}ethoxy)ethoxy] ethoxy}) phthalocyaninato nickel(II) (13)



An anhydrous condition was essential for the reaction so pre-heated molecular sieve pellets and dry dichloromethane were used. 2,3,4,6-tetra-*O*-benzoyl-1-*O*-(2,2,2-trichloroethanimidoyl) galactopyranose (0.23g, 0.315mmol, 2eq) and **12** (0.23g, 0.157mmol) were dissolved in dichloromethane (10mL). Solution was cooled to 0°C and TMSOTf (250μL) was added under argon. Mixture was stirred 5-6 hours at 0°C. Molecular sieve was filtered off using dichloromethane. Organic phase extracted with sodium bicarbonate (conc.) and water. Organic phase was dried with sodium sulfate and concentrated. Product was purified with Column Chromatography (eluent: CH₂Cl₂/EtOH, 100:1).

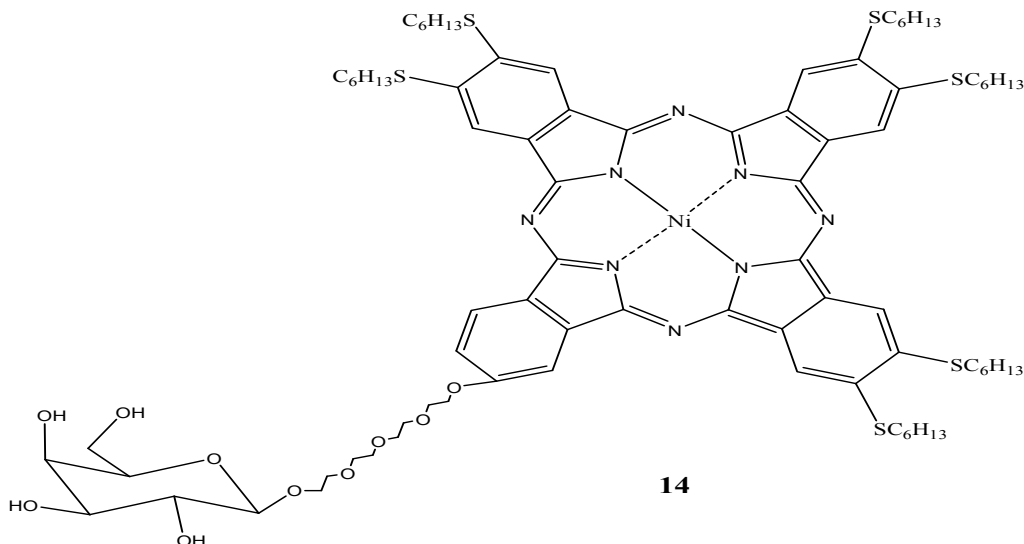
290 mg Yield 90%.

C₁₁₀H₁₃₀N₈NiO₁₄S₆, MW: 2039.34 g/mol.

Mass Spectrum (ESI-MS) *m/z*: 2039.0 [M+H]⁺

¹H NMR: (CDCl₃) δ 8.56-7.20 (m, aromatic H), 5.97 (dd, 1H, $J_{3,4}$ 3.3, $J_{4,5}$ < 0.5 Hz, H-4), 5.80 (dd, 1H, $J_{1,2}$ 8.1, $J_{2,3}$ 10.3 Hz, H-2), 5.60 (dd, 1H, H-3), 4.67 (m, 2H, CH₂OC₆H₃), 4.64 (dd, 1H, $J_{5,6a}$ 6.4, $J_{6a,6b}$ 11.2 Hz, H-6a), 4.38 (dd, 1H, $J_{5,6b}$ 6.6 Hz, H-6b), 4.24 (m, 2H, OCH₂), 4.29 (m, 1H, H-5), 4.04 (ddd, 1H, C-1OCH), 3.93 (t, 1H, OCH₂), 3.87 (ddd, 1H, C-1OCH), 3.80-3.56 (m, 8H, 4OCH₂), 3.42-3.25 (m, 12H, 6SCH₂), 2.10-1.96 (m, 12H, 6SCH₂CH₂), 1.84-1.68 (m, 12H, 6SCH₂CH₂CH₂), 1.60-1.40 (m, 24H, 12CH₂ alkyl chains), 1.08-0.95 (m, 18H, 6 CH₃ alkyl chains)

6.3.7. 2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-[2-(2-{2-(galactopyranosyloxy) ethoxy} ethoxy)ethoxy]ethoxy)ethoxy)) phthalocyaninato nickel(II) (14)



13 (100 mg, 0.05 mmol) was suspended in anhydrous MeOH (25 mL). NaOMe (%20, 100 mmol) was added and the solution was stirred for 24 h. Reaction solution was concentrated. Product was washed with hexane (3x25ml) and dissolved with chloroform (50). Organic phase was extracted with water (2x35ml), dried with sodium sulfate and concentrated.

70 mg Yield 88%.

C₈₂H₁₁₄N₈NiO₁₀S₆, MW: 1622.91 g/mol.

Mass Spectrum (ESI-MS) m/z: 1622.7 [M+H]⁺

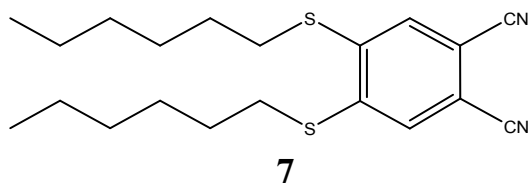
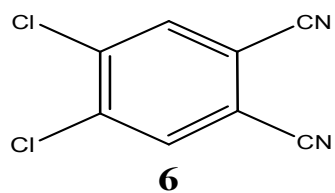
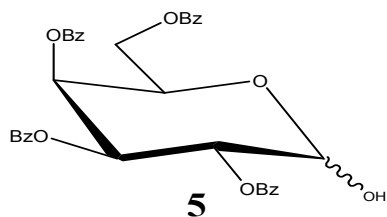
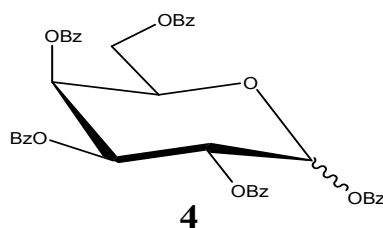
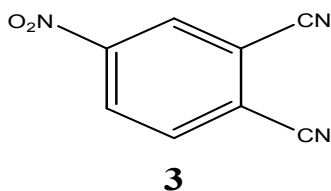
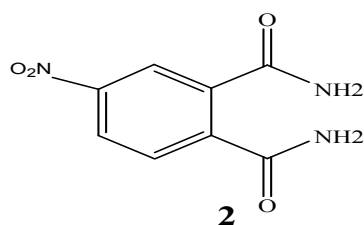
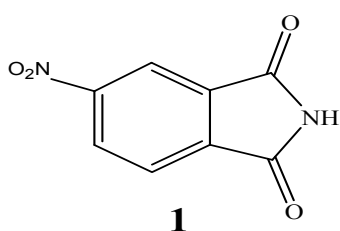
¹H NMR: (CDCl₃+CD₃OD 4:1): δ 8.01-6.97 (m, 9H, Aromatic H), 4.88 (d, 1H, H-1), 4.26-2.81 (m, 34H, H-2, H-3, H-4, H-5, H-6a, H-6a, 8OCH₂, 6SCH₂), 2.03-1.92 (m, 12H, 6SCH₂CH₂), 1.88-1.67 (m, 12H, 6SCH₂CH₂CH₂), 1.55-1.35 (m, 24H, 12CH₂ alkyl chains), 1.05-0.90 (m, 18H, 6 CH₃ alkyl chains).

7. STRUCTURES AND SPECTRA OF THE PRODUCTS (Annex)

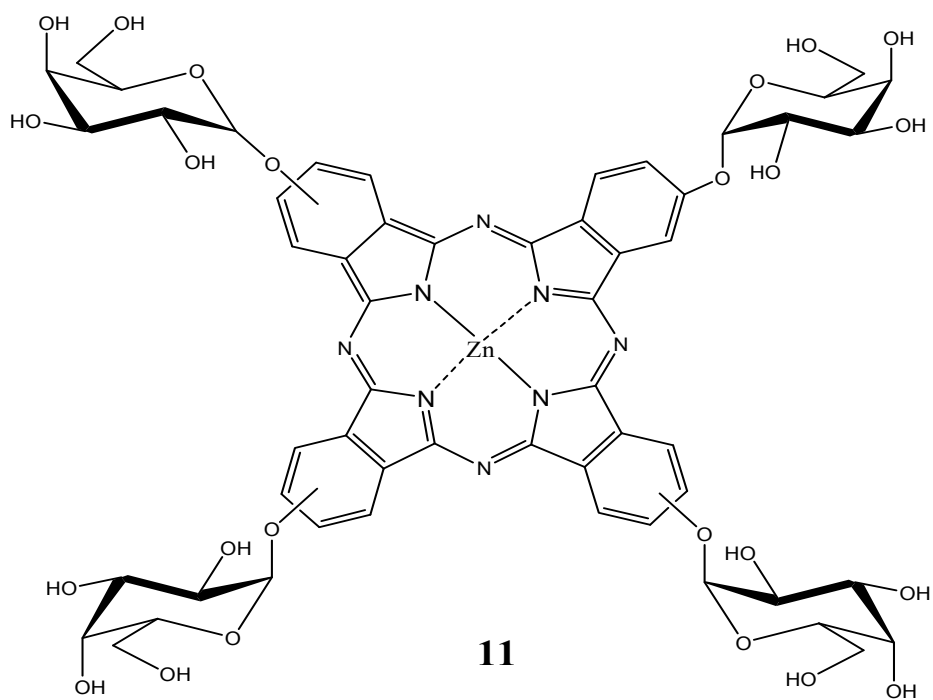
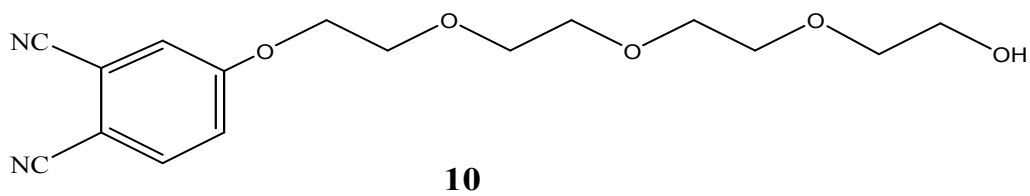
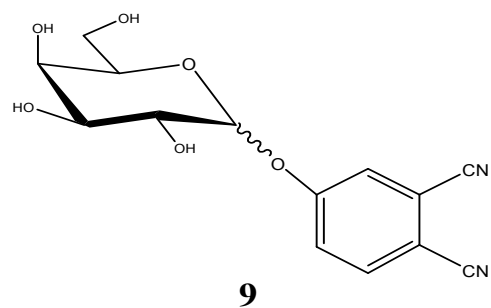
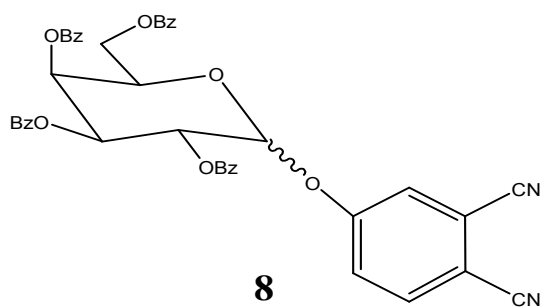
7.1. Structures Of All Products

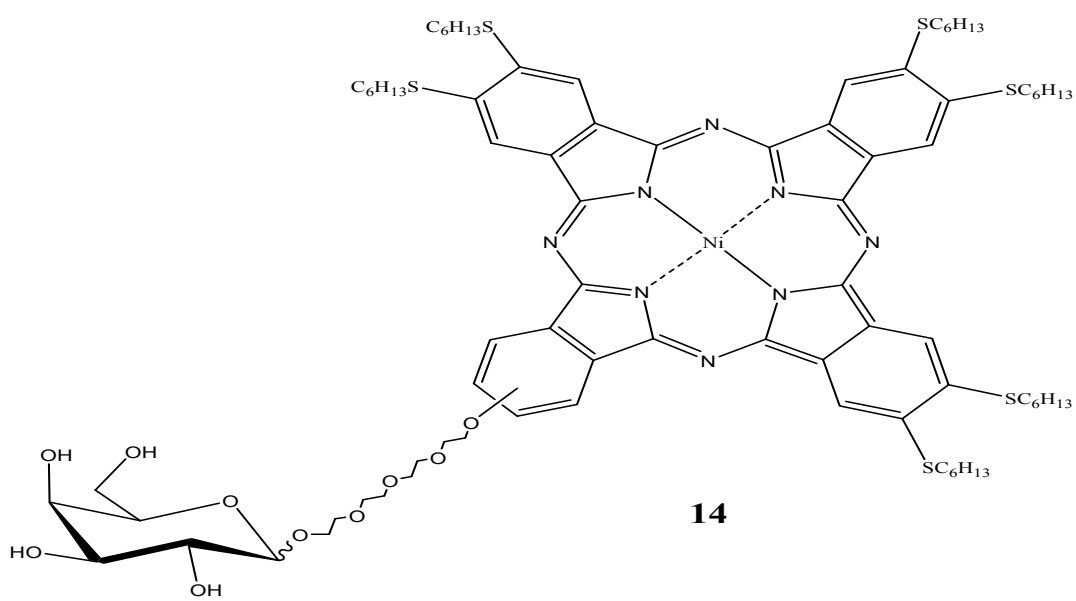
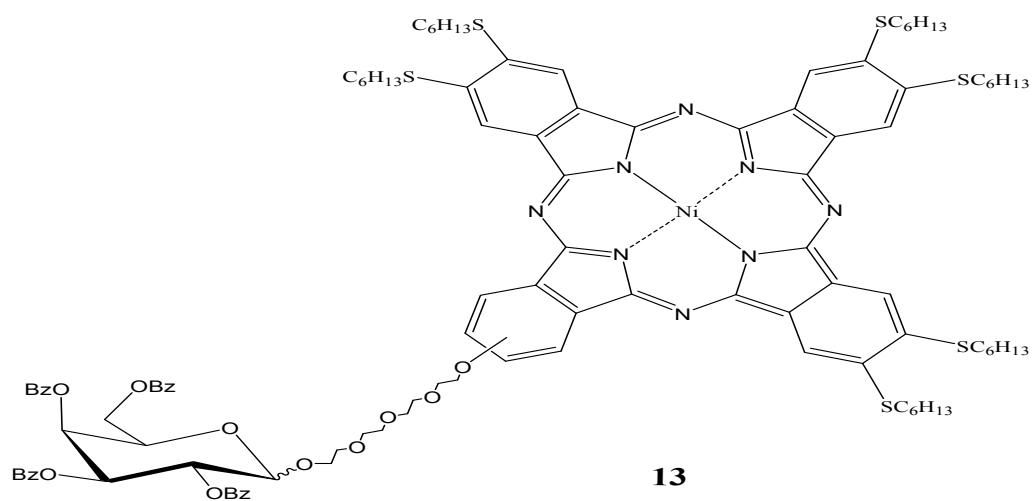
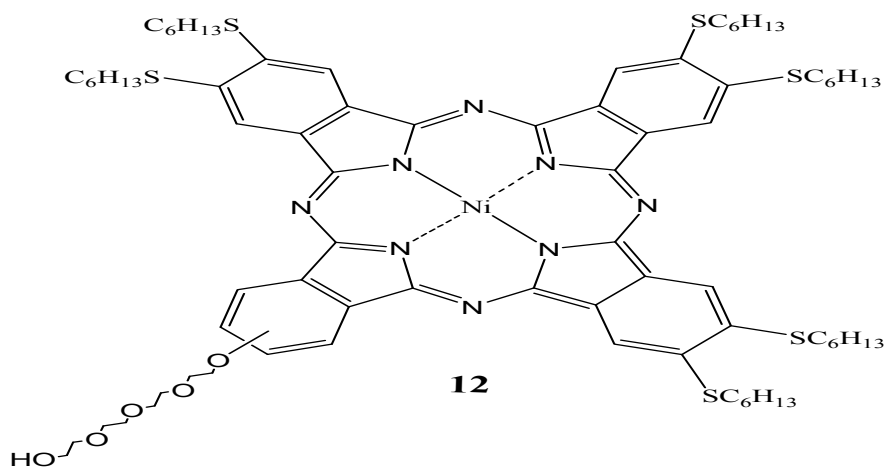
Presentation of all the prepared molecules during this Master Thesis.

Known compounds



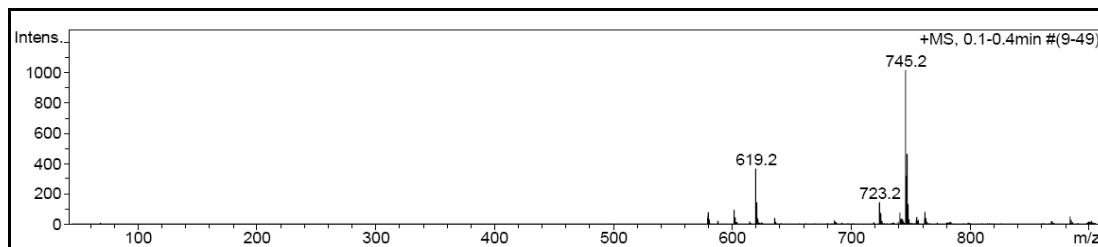
New compounds



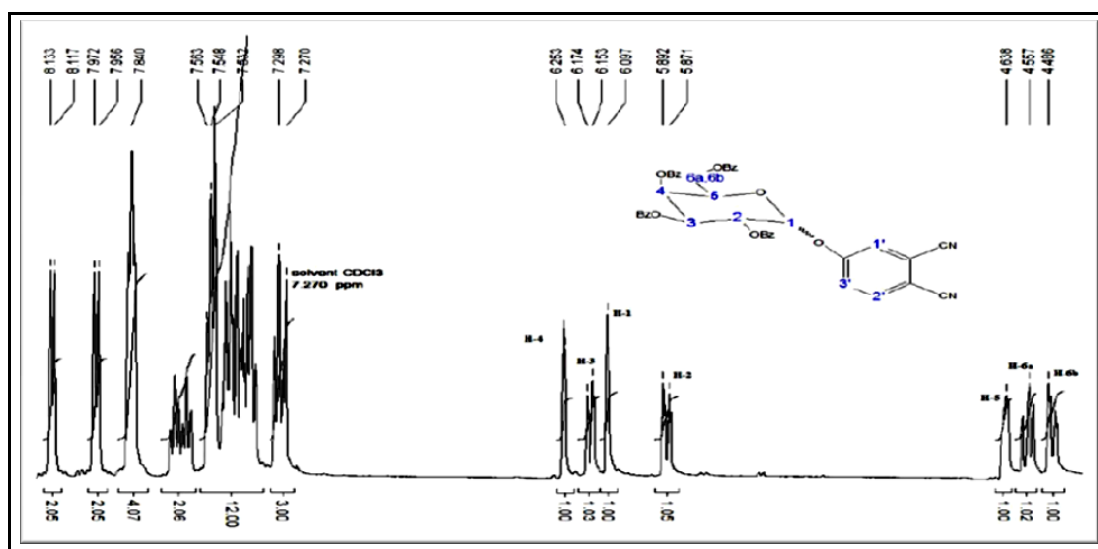


7.2. Spectra Of All Products

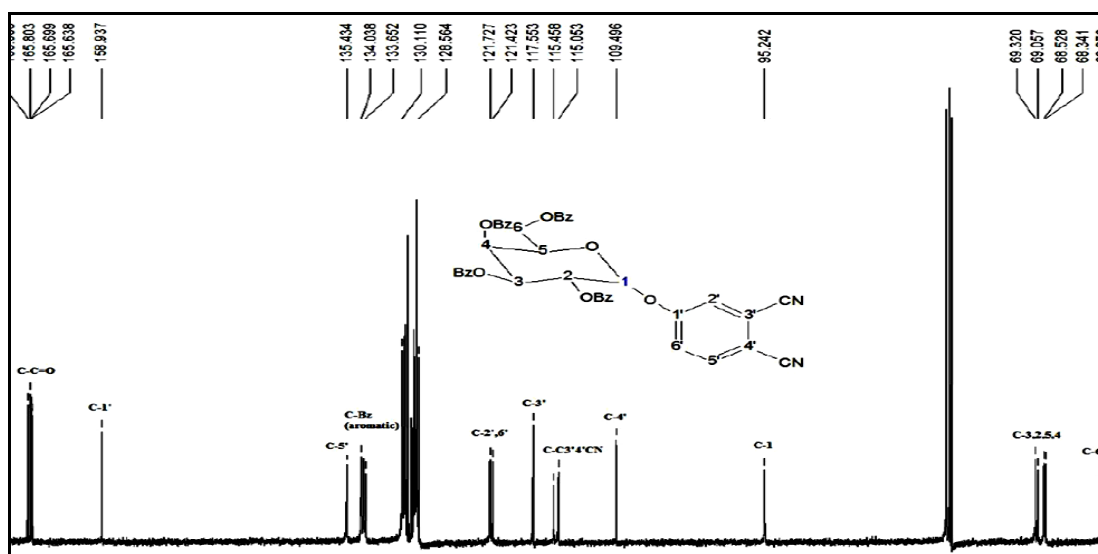
4-[(2,3,4,6-tetra-O-benzoylgalactopyranosyl)oxy]phthalonitrile (8)



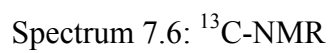
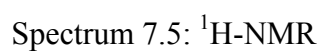
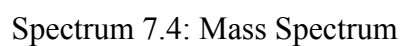
Spectrum 7.1: Mass Spectrum



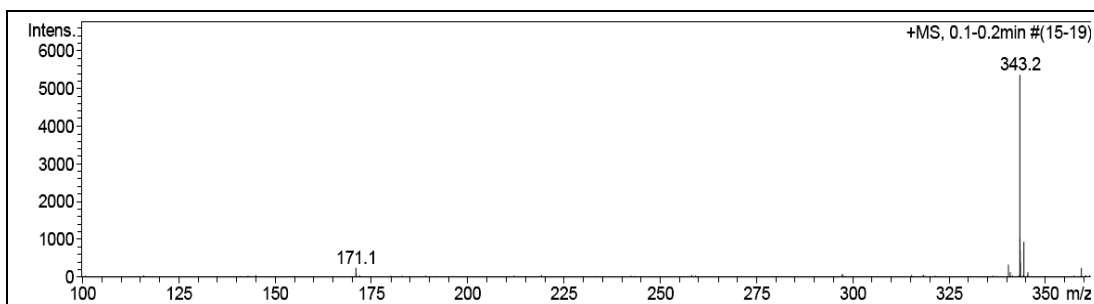
Spectrum 7.2: ¹H-NMR



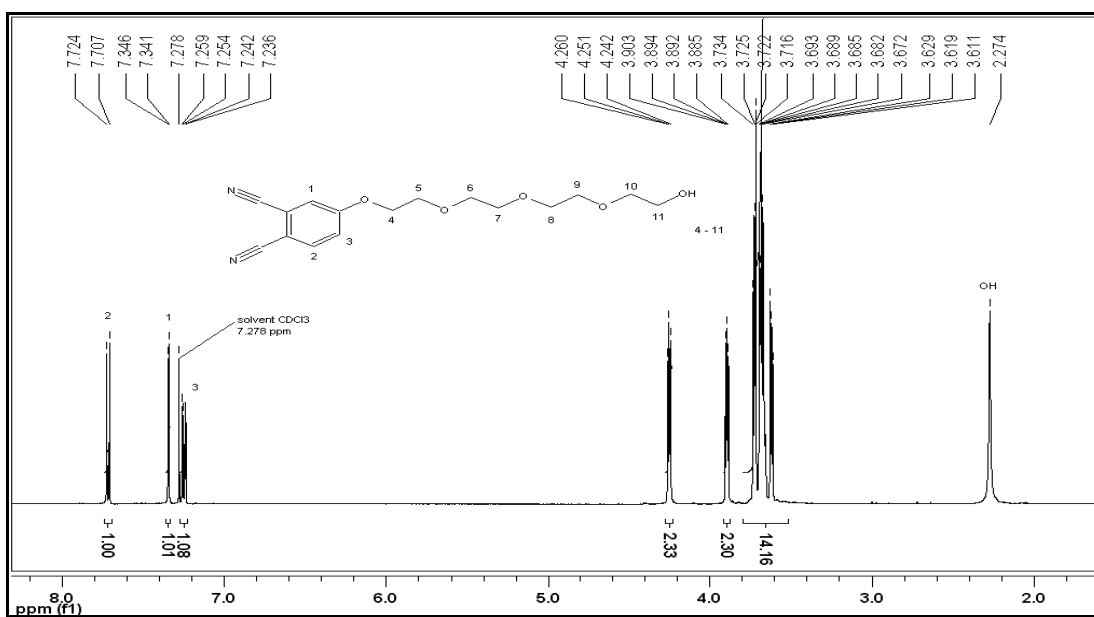
Spectrum 7.3: ¹³C-NMR



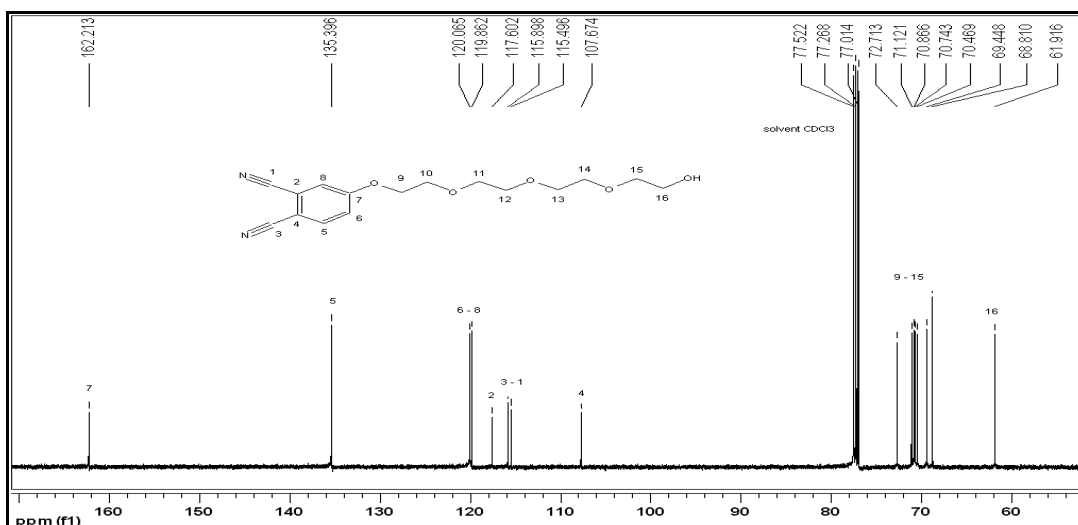
4-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethoxy)phthalonitrile (10)



Spectrum 7.7: Mass Spectrum

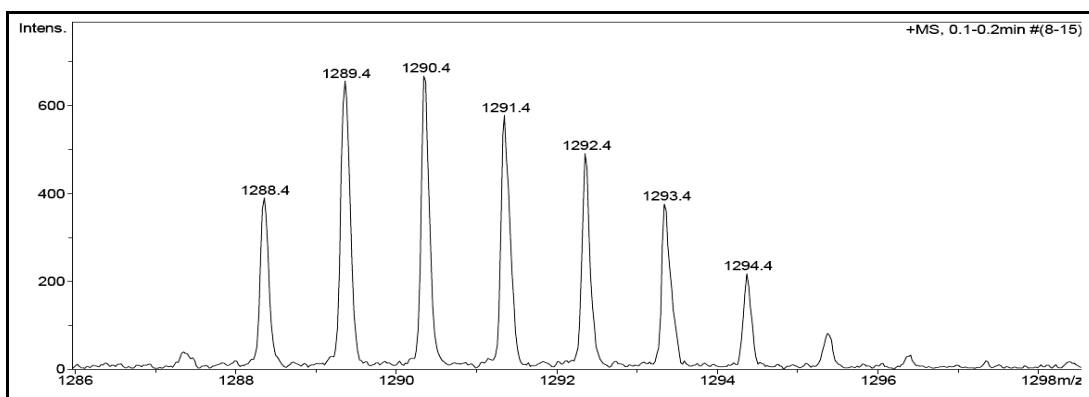


Spectrum 7.8: ¹H-NMR

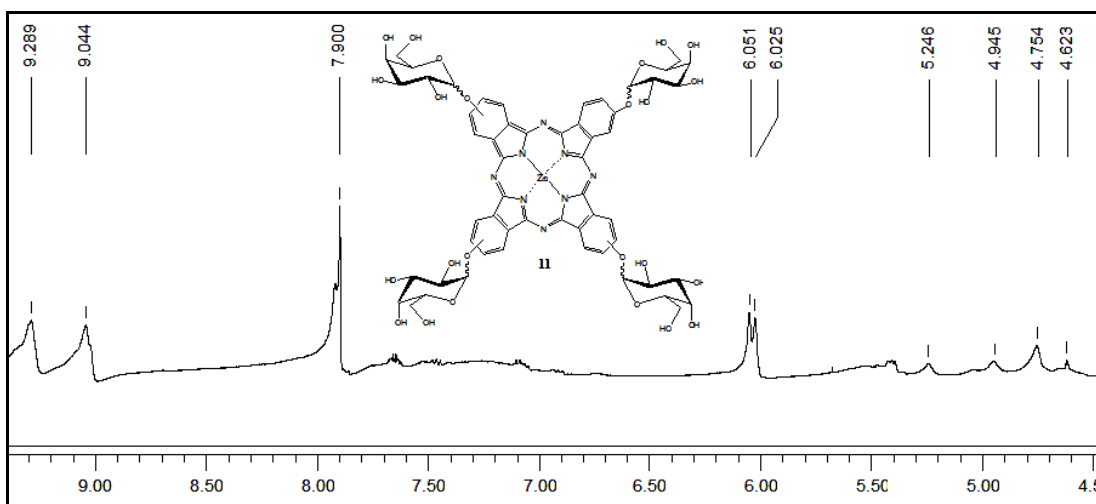


Spectrum 7.9: ¹³C-NMR

**[2(3),9(10),16(17),23(24)-Tetrakis(α/β -D-galactopyranosyl-oxy)
phthalocyaninato] zinc (11)**

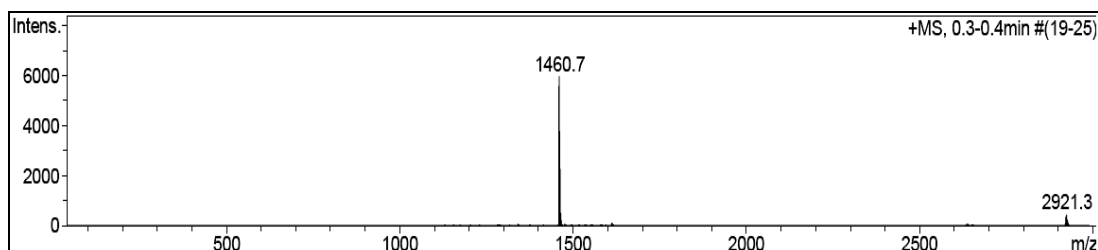


Spectrum 7.10: Mass Spectrum

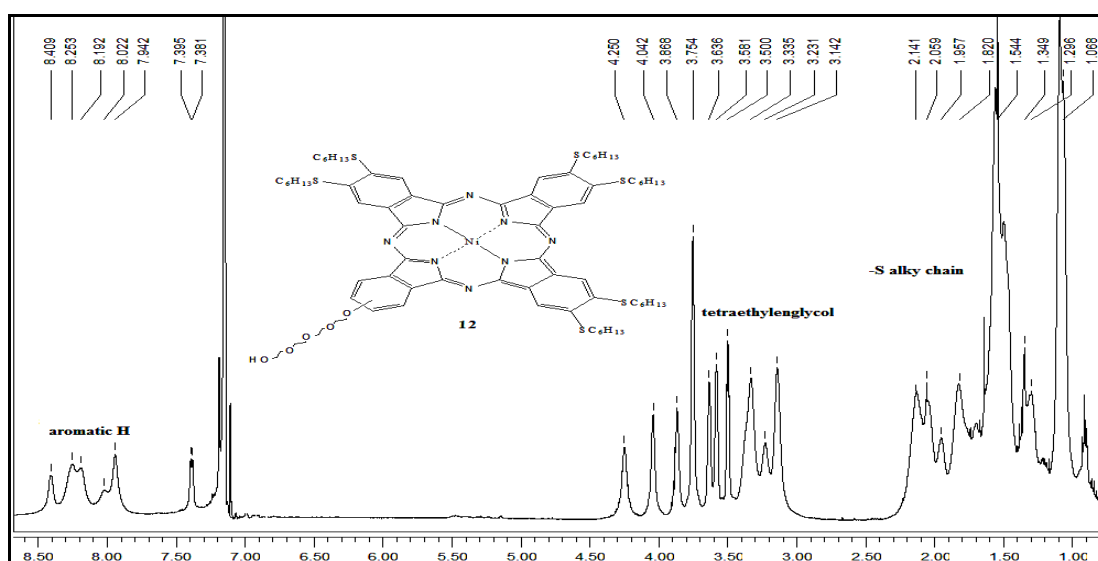


Spectrum 7.11: ^1H -NMR

2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethoxy)phthalonitrile) phthalocyaninato nickel(II) (12)

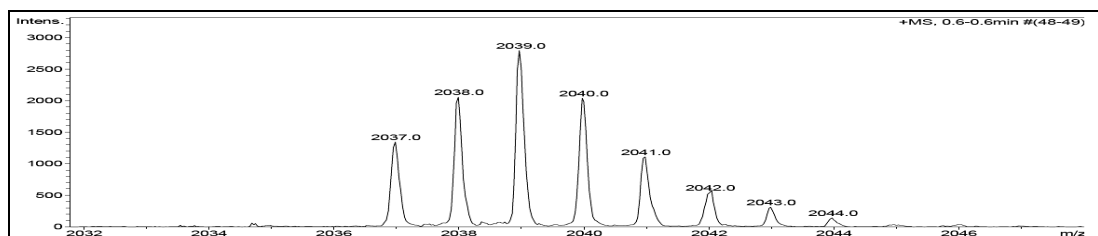


Spectrum 7.12: Mass Spectrum

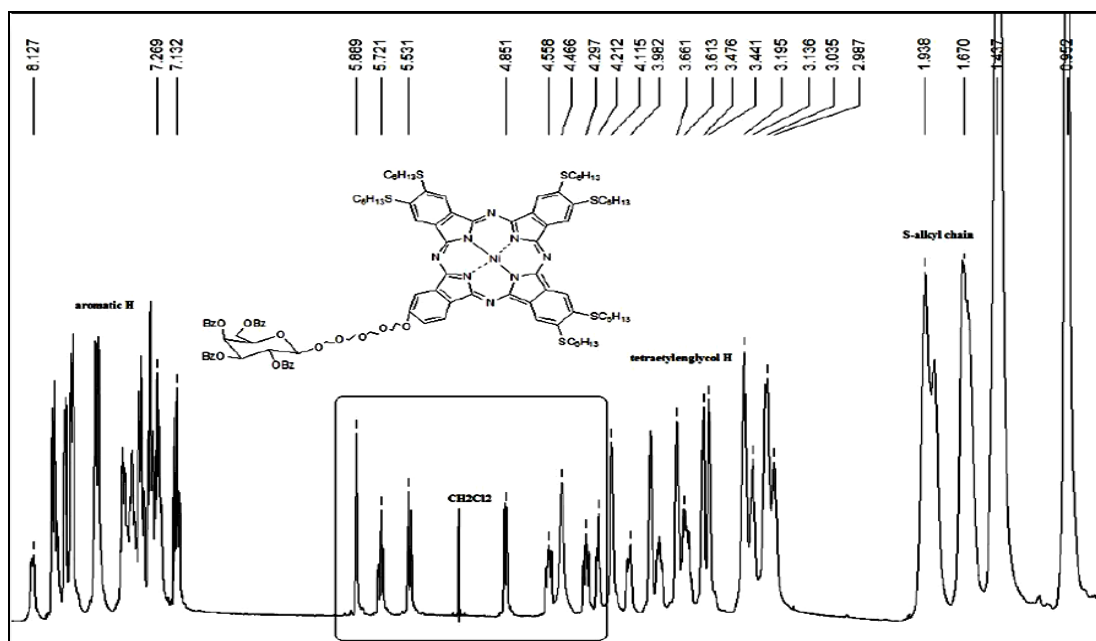


Spectrum 7.13: $^1\text{H-NMR}$

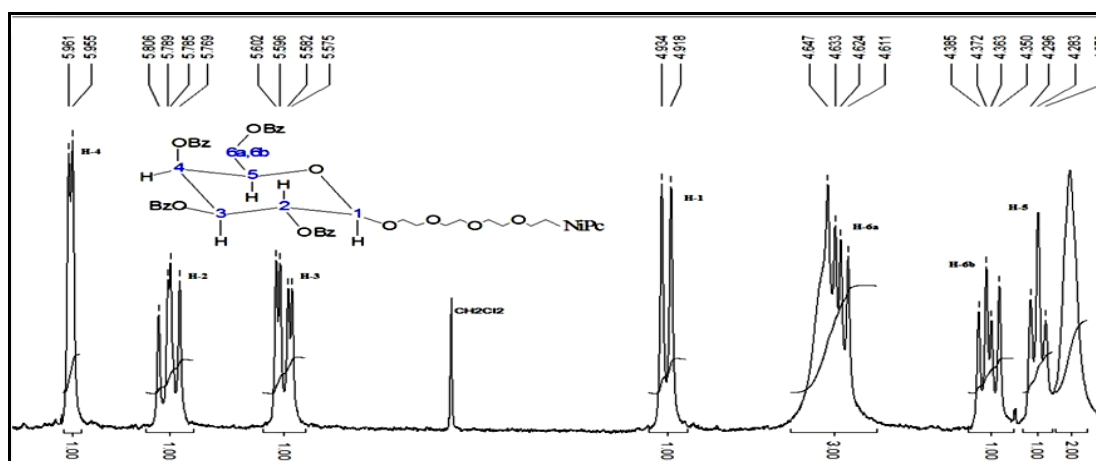
2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-{2-[2-(2-{2-[(2,3,4,6-tetra-O-benzoyl galactopyranosyl)oxy]ethoxy}ethoxy)ethoxy]ethoxy})phthalocyaninato nickel(II) (13)



Spectrum 7.14: Mass Spectrum

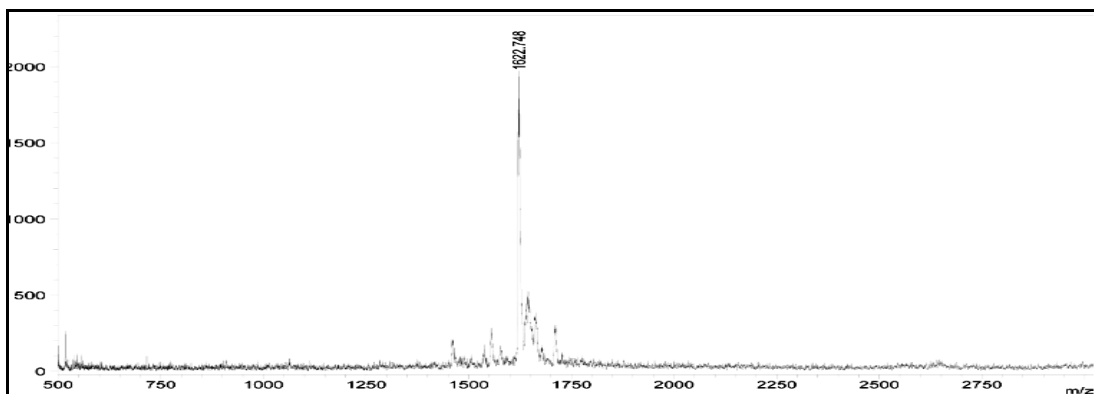


Spectrum 7.15: ¹H-NMR Spectrum

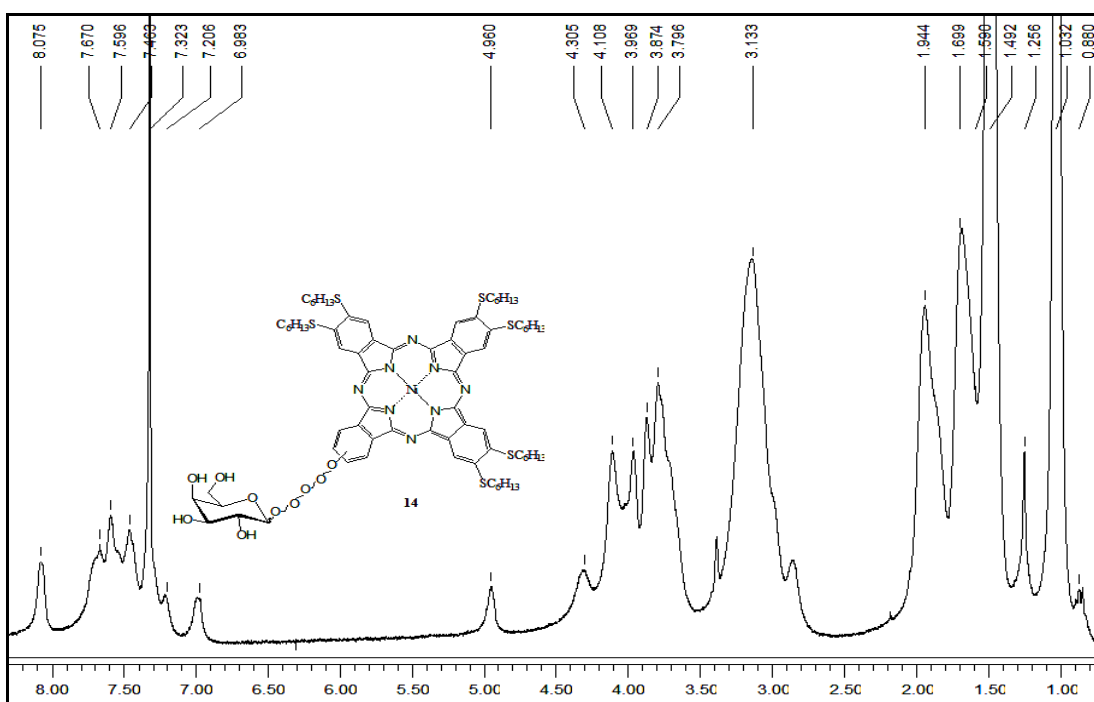


Spectrum 7.16: ¹H-NMR Spectrum 2.5-6 ppm

2,3,9,10,16,17-Hexakis(hexylthio)-23(24)-(4-[2-(2-{2-[2-(galactopyranosyloxy)ethoxy]ethoxy}ethoxy)ethoxy]) phthalocyaninato nickel(II) (14)



Spectrum 7.17: Mass Spectrum



Spectrum 7.18: ¹H-NMR

REFERENCES

1. (a) Linstead, R. P. *J. Chem. Soc.* 1934, 1016–1017; (b) Byrne, G. T.; Linstead, R. P.; Lowe, A. R. *J. Chem. Soc.* 1934, 1017–1022; (c) Linstead, R. P.; Lowe, A. R. *J. Chem. Soc.* 1934, 1022–1027; (d) Dent, C. E.; Linstead, R. P. *J. Chem. Soc.* 1934, 1027–1031; (e) Linstead, R. P.; Lowe, A. R. *J. Chem. Soc.* 1934, 1031–1033; (f) Dent, C. E.; Linstead, R. P.; Lowe, A. R. *J. Chem. Soc.* 1934, 1033–1039.
2. Christie, R. M. *Colour Chemistry*, Royal Society of Chemistry: Cambridge, UK, 2001.
3. Law, K.-Y. *Chem. Rev.* 1993, 93, 449–486.
4. Calvete M.; Yang G. Y.; Hanack M. *Synth. Met.* 2004, 141, 231–243.
5. Allen C. M.; Sharman W. M.; Van Lier J. E. *J. Porphyrins Phthalocyanines* 2001, 5, 161–169.
6. Petritsch K.; Friend R. H.; Lux A.; Rozenberg G.; Moratti S. C.; Holmes A. B. *Synth. Met.* 1999, 102, 1776–1777.
7. Zhou R.; Josse F.; Gopel W.; Ozturk Z. Z.; Bekaroglu O. *Appl. Organomet. Chem.* 1996, 10, 557–577.
8. Jiang J.; Kasuga K.; Arnold D. P. In *Supramolecular Photosensitive and Electroactive Materials*, Nalwa, H. S. Ed., Academic Press: San Diego, CA, 2001, 188–189.
9. (a) Li J.; Gryko D.; Dabke R. B.; Diers J. R.; Bocian D. F.; Kuhr W. G.; Lindsey J. S. *J. Org. Chem.* 2000, 65, 7379–7390; (b) Gryko D.; Li J.; Diers J. R.; Roth K. M.; Bocian D. F.; Kuhr W. G.; Lindsey, J. S. *J. Mater. Chem.* 2001, 11, 1162–1180; (c) Gross T.; Chevalier F.; Lindsey J. S. *Inorg. Chem.* 2001, 40, 4762–4774; (d) Schweikart K.-H.; Malinovskii V. L.; Diers, J. R.; Yasseri A. A.; Bocian D. F.; Kuhr W. G.; Lindsey J. S. *J. Mater. Chem.* 2002, 12, 808–828; (e) Schweikart K.-H.; Malinovskii V. L.; Yasseri A. A.; Li J.; Lysenko A. B.; Bocian D. F.; Lindsey J. S. *Inorg. Chem.* 2003, 42, 7431–7446; (f) Wei L.; Padmaja K.; Youngblood W. J.; Lysenko A. B.; Lindsey J. S.; Bocian D. F. *J. Org. Chem.* 2004, 69, 1461–1469.
10. Thompson J. A.; Murata K.; Durcharne R.; Poirier M.; Hoffman B. M., *Phys. Rev. B: Condens. Matter, Mater. Phys.*, (1999) 60, 523.
11. Ficken G. E.; Linstead, R. P., *J. Chem. Soc.*, (1952), 4846.

12. Byrne G. T.; Linstead R. P.; Lowe A. R., *J. Chem. Soc.*, (1934), 1017.
13. Thompson J. A.; Murata K.; Miller D. C.; Stanton J. L.; Broderick W. E.; Hoffman B. M.; Ibers J.A., *Inorg. Chem.*, (1993) 32, 3546.
14. Edmondson S. J.; Hill J. S.; Isaacs N. S.; Mitchell P. C. H., *J. Chem. Soc., Dalton Trans.*, (1990), 1115.
15. Tomoda H.; Yoshioka K.; Orita, S.; Saito S.; Shiraishi S., *Heterocycles*, (1983) 20, 117.
16. Lever A. B. P., *Adv. Inorg. Radiochem.*, (1965) 27, 27.
17. Barrett P. A.; Frye D. A.; Linstead R. P., *J. Chem. Soc.*, (1938), 1157.
18. Brach P. J.; Grammatica S. J.; Ossanna O. A.; Weinberger L., *J. Heterocycl. Chem.*, 1970; 7, 1403.
19. Melson G.A., *Coordination Chemistry of Macrocyclic Compounds*. New York: Plenum Press Ed. (1979).
20. Zyskowski C. D.; Kennedy V. O. *J. Porphyrins Phthalocyanines* 2000, 4, 649-654.
21. Kobayashi N.; Kondo R.; Nakajima S.; Osa, T. *J. Am. Chem. Soc.* 1990, 112, 9641-9643.
22. Cuellar E. A.; Marks T. J., *Inorg. Chem.*, (1981) 20, 3766.
23. Cuellar E. A.; Stojakovic D. R.; Marks T. J.; Adler A. D.; Giordano R. S., *Inorg. Synth.*, (1980) 20,97.
24. Marks T. J.; Stojakovic D. R., *J. Am. Chem. Soc.*, (1978) 100, 1695.
25. Weitmeyer A.; Kliesch H.; Wöhrle D. *J. Org Chem.* 1995, 60, 4900-4904.
26. Kobayashi N.; Ishizaki T.; Ishii K.; Konami H. *J. Am. Chem. Soc.* 1999, 121, 9096-9110.
27. Von Tappeiner H, Jodlbauer A. Über die Wirkung der photodynamischen (fluoreszierenden) Stoffe auf Protozoen und Enzyme. *Deutsches Arch Klin Med* 1904;39:427–87.
28. Blum HF. New York: Reinhold, 1941. Reprinted. New York: Hafner, 1964.
29. Moan J, Berg K. *Photochem Photobiol* 1991;53: 549–53.
30. Dougherty TJ, Henderson B. Historical perspective: Schwartz S, Winkelman JW, Lipson RL. In: Henderson BW, Dougherty TJ, editors. Photodynamic therapy. New York: *Marcel Dekker Inc.*, 1992:1–15.
31. Moan J. *Photochem Photobiol.* 1986;43:681–90.

32. Dougherty TJ. *J Clin Laser Med.* 1996;14:219–21.
33. Gomer CJ. *Photochem Photobiol.* 1991;54: 1093–107.
34. Pass HI. *J. Natl. Cancer Inst.* 1993;85:443–56.
35. Roberts, G., Ed. *Langmuir-Blodgett Films*, Plenum Press, New York (1990).
36. Swalen J.D.; Allara D.L.; Andrade J.D.; Chandross E.A.; Garoff S.; Israelachvili J.; McCarthy T.J.; Murray R.; Pease R.F.; Rabolt J.F.; Wynne K.J.; Yu H. *Langmuir*, 3 (1987) 932.
37. Breton M. *J. Macromol. Sci. – Rev. Macromol. Chem.*, C21 (1981) 61.
38. Petty M.C. *Thin Solid Films*, 210/211 (1992) 417.
39. N. McKeown I. Chambrier M. Cook *J. Chem. Soc. Perkin Trans.*, 1990, 1, 1169
40. R. Jung, PhD Thesis, Univ. Tübingen, Germany 2000
41. Maillard P., Guerquin-Kern J.-L. and Momenteau M., *J. Am. Chem. Soc.*, 1989, 111(25), 9125-9127
42. Anderson O. Ribeiro, João P.C. Tomé, Maria G. P.M.S. Neves, Augusto C. Tomé, José A.S. Cavaleiro, Osvaldo A. Serra and Tomás Torres, *Tetrahedron Lett.*, 2006, 47(34), 6129–6132.
43. Anderson O. Ribeiro, João P.C. Tomé, Maria G.P.M.S. Neves, Augusto C. Tomé, José A.S. Cavaleiro, Yassuko Iamamoto and Tomás Torres, *Tetrahedron Lett.*, 2006, 47(52), 9177-9180.
44. Lee P. P. S., Lo P.-C., E. Y. M. Chan, W.-P. Fong, W.-H. Koc and D. K. P. Ng, *Tetrahedron Lett.*, 2005, 46(9), 1551-1554
45. Pui-Chi Lo, Crystal M. H. Chan, Jian-Yong Liu, Wing-Ping Fong, Dennis K. P. Ng, *J. Med. Chem.* 2007, 50, 2100-2107
46. X. Alvarez-Mico, M. J. F. Calvete M., Hanack and T. Ziegler, *Tetrahedron Lett.*, 2006, 47, 3283–3286
47. X. Alvarez-Mico, M. J. F. Calvete M., Hanack and T. Ziegler, *Synthesis*, 2007, 14, 2186–2192
48. Durmuş M, Nyokong T, Ogunsipe A. *J. Phorphyrins Phthalocyanines* 2007;11: 635-644.
49. Karabörk S, Serin S., *Synth. React. Inorg. Met-Org. Chem.*, 2002 ;32(9) :1635-1647.

50. Mougang Hu, Nicole Brasseur, S. Zeki Yildiz, Johan E. van Lier and Clifford C. Leznoff *J. Med. Chem.* 1998, 41, 1789-1802.
51. Armstrong N. R., Chau L.-K., Chen S.-Y., Collins N., O'Brien D. F., Osburn E.
52. Ding X., Shen S., Xu H. Zhou Q. *Dyes and Pigments* 1999;40: 187-191
53. Young J.G. and Onyebuagu W. *J. Org. Chem.*, 1990; 55: 2155
54. B. D'accorso Norma and Thiel Inge M.E. *J. Carbohydrate Chem.*, 1989, 8(5), 743-751
55. Hartman, M; Coward, J. *J. Am. Chem. Soc.* 2002, 124, 10036.
56. X. Alvarez-Mico, M. J. F. Calvete, M. Hanack and T. Ziegler, *Carbohydr. Res.*, 2006, 324, 440–447.
57. A. Gürek, Ö. Bekaroğlu, *J. Chem. Soc., Dalton Trans.*, 1994, 1419.
58. D. Wöhrle, M. Eskes, K. Shigehara and A. Yamada, *Synthesis*, 1993, 194–196.

CURRICULUM VITAE

Mahmut Ali Ermeydan

Gebze Institute of Technology

Department of Chemistry

Education:

1998- 2001: Aydın Anatolian High School

2001- 2006: Grad.Bilkent University, Faculty of Science, Department of Chemistry

2006- 2008: Ms. Degree, Gebze Institute of Technology, Department of Chemistry

Achievements:

- ▶ Full scholarship awarded by Bilkent University

Congress:

- ▶ ICPP-5, International Conference of Porphyrins and Phthalocyanines, Moskow, Russia, 5-12 July, 2008

- ▶ International Congress of Organic Chemistry, Erzurum, Turkey, 5-9 June, 2007

Research Experiences:

- ▶ **L'Université Claude Bernard, Lyon 1:** I made a 3 months Internship in L'Université Claude Bernard **Lyon 1** on glycosylation and first application of “click” chemistry on phthalocyanines under the supervisory of Dr. Dominique Lafont who is an expert on carbohydrates and “click” chemistry. (Spring 2008)

- ▶ **TUBITAK Project:** 2 years experience on phthalocyanines and carbohydrate chemistry with the synthesis and characterization of water soluble and amphiphilic phthalocyanines. (2006-2008 season)

- ▶ **Senior Project:** Synthesis and Characterization of WO_x/ZrO_2 using W(VI) precursors under Supervisorship of Asoc. Prof. Kantcheva. (DRUV-vis, Photo-

spectrometry, Raman, XRD, FT-IR in situ, EPR for Chemical Analyses) (Fall 2005-Spring 2006)

► **ÜLKER Food Industry & Trade Inc.** I made summer practice on chocolate production and quality analysis; which includes: ingredients and constituent chemicals, chemical and physical composition of cocoa beans and products, physical properties and effects of processing. (Summer 2003-2004)

► **MN Pharmaceuticals** I made summer training on solubility and retention time of drugs, also instrumental analysis with GC/MS Gas Chromatography/Mass Spectrometry (GC/MS).(Summer 2003-2004)