2021

Porphyrins and Porphyrin Applications

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A Thesis Submitted to Fulfill the Requirements of the Honors Program
at Assumption University

Fall 2020

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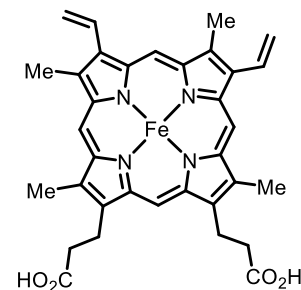
I.   Overview on Porphyrins

Have you ever wondered why blood is red or grass is green? Surprisingly, the colors come from similar sources, each gets its coloration from a special kind of chemical compound called a porphyrin. A porphyrin is a large, continuously connected ring of atoms, known as a macrocycle, that is made up of carbon, nitrogen, and hydrogen. The large outer ring that gives a porphyrin its main structure is composed of four inner pyrrole rings with their nitrogen molecules
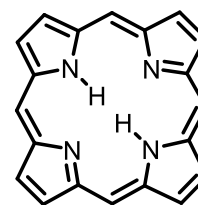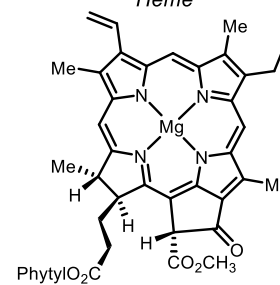
Porphine

oriented to the center of the ring. The study of porphyrins and their chemistry is a vast field that has been in existence for over a century and is still growing to this day[1–3]. Some porphyrins occur in Nature while others are made in the laboratory through chemical synthesis. Naturally occurring porphyrins have been coined as "the pigments of life[4]" because they allow two essential processes of life to occur. These processes are mediated by two naturally occurring porphyrins, the first being a porphyrin within blood. Blood is made of four main parts: platelets, white blood cells, plasma, and red blood cells. Inside these red blood cells are hemoglobin molecules, which contain a natural porphyrin-iron complex, endowing the red blood cell with the ability to bind to oxygen and transport it throughout the body. Hemoglobin is essential to aerobic life since it is central to the transport of oxygen throughout the organism. Plants also contain naturally occurring

Heme

Chlorophyll a

porphyrins within their chlorophyll molecules. Chlorophyll contains a magnesium complex

porphyrin derivative that allows the plant cell to absorb light to create energy, a process called

photosynthesis. These naturally occurring porphyrinoid molecules served as a starting point in

some synthetic porphyrin studies.

Inspired by the natural examples of porphyrins and their significance to life, chemists

have produced many "un-natural" synthetic porphyrins in the laboratory. Synthetic porphyrins

may produce electronic spectra that are different than the naturally occurring porphyrins due to

the structural differences of the porphyrins. This is useful in many different applications because

the optical spectra of porphyrinoid compounds can be fine-tuned by many different synthetic

modifications to macrocycle. This ability to fine tune synthetic porphyrins for specific

applications makes them utilizable in situations where naturally occurring porphyrins would

never be able to be used. Synthetic porphyrins are often created through a stepwise series of

reactions where each step modifies one area of a porphyrin, facilitating future modifications to

achieve the desired electronic effects.

Before diving further into the synthesis of porphyrins, the general structure must first be

understood. A singular porphyrin macrocycle contains four pyrrole molecules attached together

via methine bridges to create a conjugated aromatic ring of eighteen pi (π) electrons.

Cross-Conjugated Pseudo-Olefinic Bonds
Aromatic Macrocycle
Methine Bridges

The stability of porphyinoid molecules can be attributed to the conjugated eighteen π

electron aromatic ring, making it incredibly hard to break apart during subsequent reactions due

to the special stability that aromaticity imparts to compounds. Additionally, porphyrins gain an

innate ability to fluoresce and phosphoresce when irradiated with light due to the conjugation of

the macrocycle. The aromaticity allows the electrons to resonate around the ring, bringing

incredible stability to the planar macrocycle. This imparted stability allows for seemingly

limitless reactions to be done on porphyrins, allowing for a tremendous amount of different

applications for porphyrin compounds[5–9]. A selection of these applications ranging from

potential therapeutic uses to various ion sensors and even catalysts for various types of reactions

will be covered in this review[10–15].

II. Porphyrin Synthesis and Derivatization

A base porphyrin macrocycle is easily synthesized in a condensation reaction using

pyrrole and an aldehyde in refluxing propionic acid[16].This reaction is incredibly reproducible and

reliable, allowing a wide variety of different aldehydes to be used in this reaction. By using aldehydes with different substituents, such as benzaldehyde, a *meso* substituted
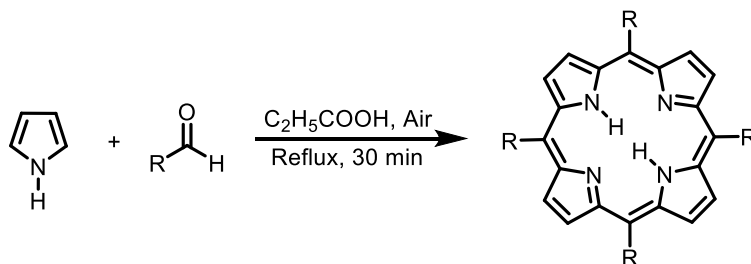
Figure 1. Porphyrin Synthesis Scheme.

porphyrin is synthesized. Aldehydes are commercially available with a very wide variety of

different substituents, which allows for this very versatile reaction to be used to synthesize

countless numbers of different *meso* substituted porphyrins. This is generally the first step in a

stepwise synthesis pathway of a derivatized porphyrin ring. Often the next step in the synthesis

pathway involves the modification, often by oxidation, of the cross conjugated beta-beta (ß-ß)

bonds of the macrocycle.

Reactions imparting modifications on porphyrin macrocycle often occur at the ß-ß bonds of the pyrrolic ring -the pseudo-olefinic cross-conjugated double bonds- because they are easier to reduce than any bond that is a part of the conjugated aromatic ring. The macrocycle of a porphyrin contains 22 total π electrons, but the

ß-ß

Cross-Conjugated Pseudo Olefinic Bonds
Aromatic Macrocycle

ß-ß
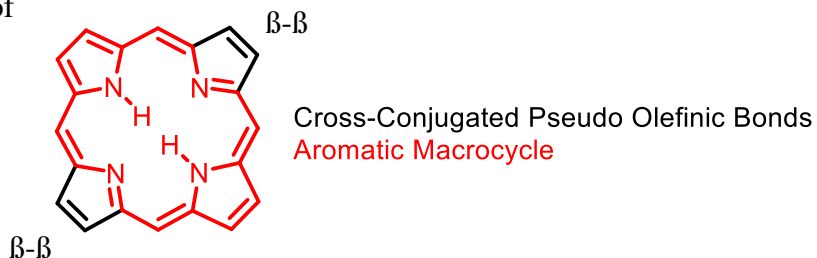
aromaticity, following Hückel's rule of 4n-2, only involves 18 of the π electrons. The remaining four electrons are cross conjugated to the aromatic ring and act as pseudo-olefinic bonds, meaning that they can be more easily oxidized through many different methods. When these bonds are reduced, the naming terminology of the porphyrin changes. When one of the double bonds is reduced the porphyrin becomes a chlorin, but when both double bonds are reduced the porphyrin becomes a bacteriochlorin. Finally, when porphyrins that have their ß-ß double bond modified to a non-pyrrolic heterocycle they are known as pyrrole-modified-porphyrins (PMP's)[1]. Many different synthetic routes can be taken to arrive at a PMP product, however a common reaction pathway to a lactol PMP is an oxidation of the ß-ß bond/bonds to a chlorin/bacteriochlorin product with subsequent derivatization to the lactol/dilactol product[8].

One of the most important oxidation reactions in porphyrin chemistry is the osmium tetroxide mediated dihydroxylation or tetrahydroxylation of one or both ß-ß bonds[17]. During this reaction, the ß-ß bonds are reduced forming chlorin products for the dihydroxylation, and bacteriochlorin products for the tetrahydroxylation.
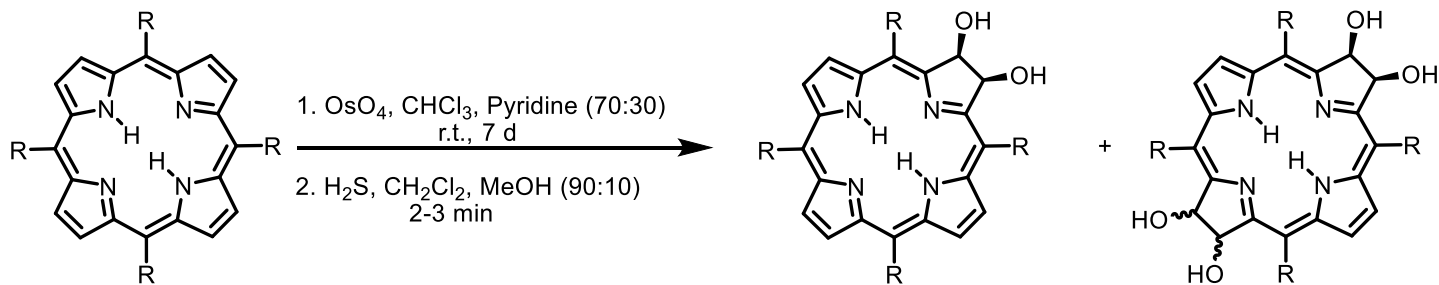
Figure 2. Osmium Tetroxide Mediated Dihydroxy/Tetrahydroxylation.

During the reaction shown in Figure 2, a complex is formed between the osmium tetroxide, pyridine, and the porphyrin being reacted. This osmate ester complex is removed in the subsequent reaction step with hydrogen sulfide gas. In this step the osmate ester is hydrolyzed to form the respective reaction
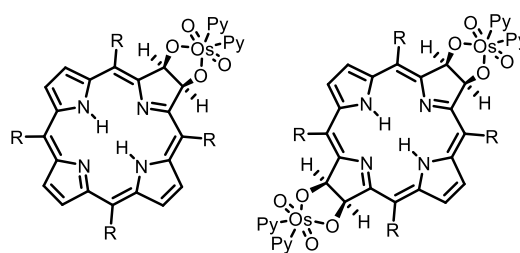
Porphyrin Osmate-Ester Intermediate

products; the dihydroxychlorin and tetrahydroxybacteriochlorin. These products are crucial to the functionalization of the ß-ß bonds. The dihydroxychlorin or tetrahydroxybacteriochlorin product can be reacted with cetyltrimethylammonium permanganate (CTAP) to form the lactone or dilactone PMP, depending on which starting porphyrin was used. This reaction converts the hydroxy groups attached to the ß-ß bonds to lactone moieties within the macrocycle[8]. One downfall to this synthesis pathway is the time it takes to get to the lactone product, taking upwards of two weeks to get to a product making the reaction not very time efficient.

Figure 3. Oxidation of diol to lactone.

Figure 4. Oxidation of tetraol to dilactone.

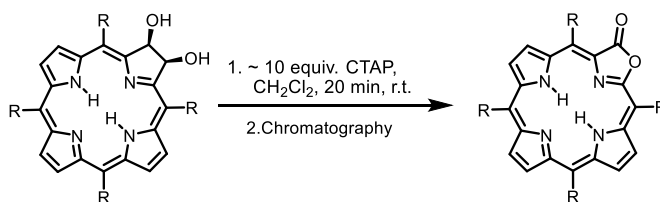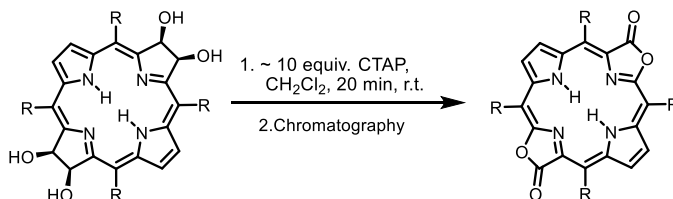Conversely to the stepwise path described above, both lactone products can be created through a direct oxidation of the initial porphyrin macrocycle, if the *meso* substitutions on the macrocycle are very electron withdrawing. Groups such as pentafluorophenyl can be directly oxidized but if the substituents are not very electron withdrawing such as *p*-trifluoromethyl and phenyl, in which case a stepwise synthesis pathway is required, because a direct oxidation reaction on these substituted porphyrins breaks the aromaticity of the macrocycle, effectively destroying the molecule. The first porphyrin to be directly oxidized to its lactone and dilactone derivatives was *meso*-Tetrakis(pentafluorophenyl)porphyrin[8,18]. The substituted porphyrin was reacted with silver acetate in refluxing acetic acid, forming six potential products: the lactone, both dilactone isomers, and three iso-bacteriodilactone isomers. This reaction is incredibly useful
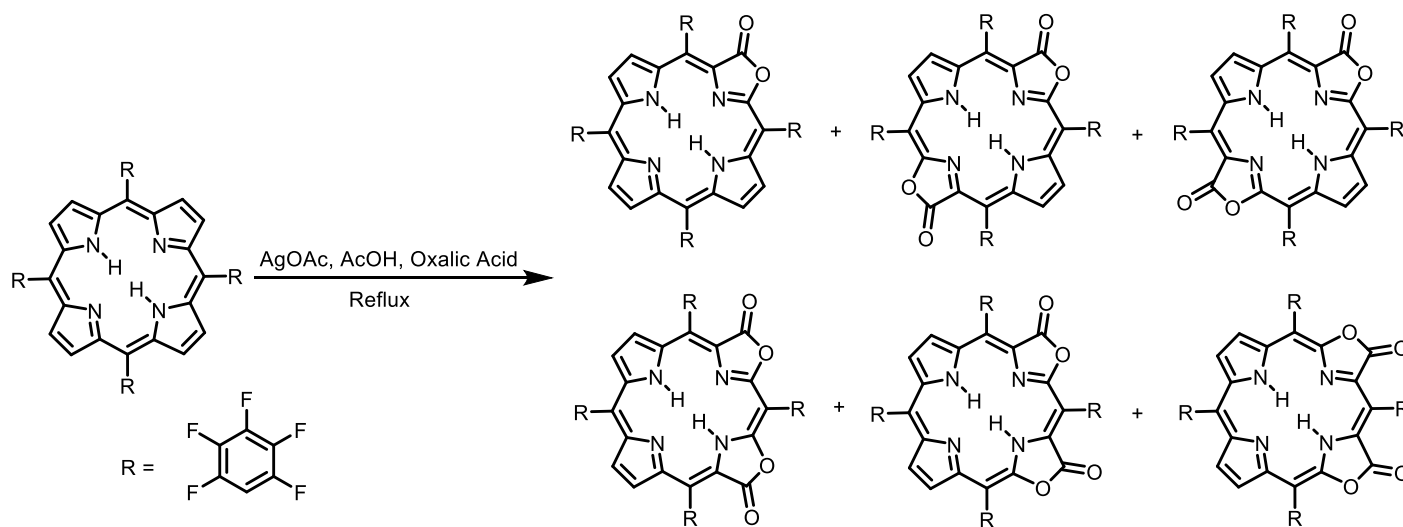
Figure 5. Silver acetate mediated porphyrin direct oxidation.

when the substituents allow it to happen, but the large number of biproducts causes issues with the isolation and purification of the desired product. An improvement was made to this reaction to reduce the number of side products formed, giving only the lactone and both bacteriodilactone isomers as products[14]. The new direct oxidation uses ruthenium chloride, bipyridine, potassium peroxymonosulfate (Oxone), hydroxide, refluxing dichloromethane and water.
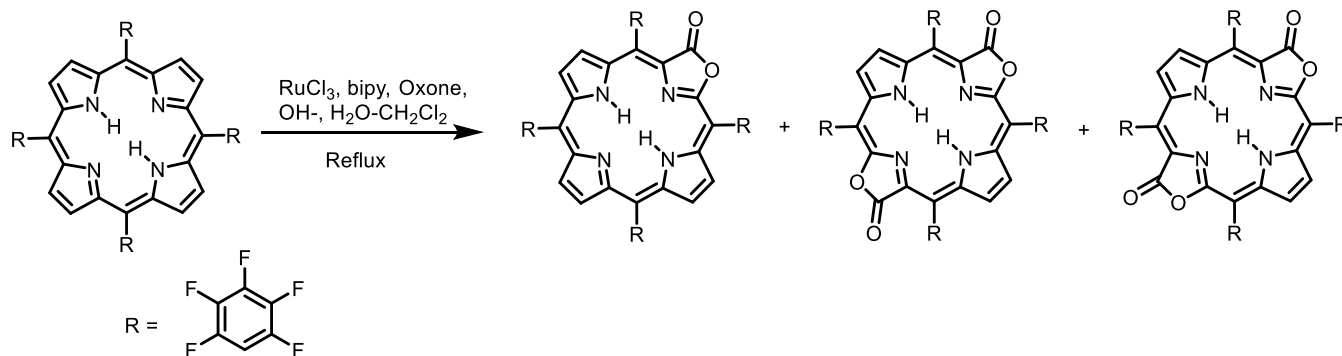
Figure 6. Ruthenium chloride direct oxidation of porphyrins.

Another advantage of this reaction pathway is that the bacteriodilactone isomers were able to be separated after a metal was inserted into the macrocycle[19]. The metal can be removed from the macrocycle after the isomer separation, giving pure isomers of the bacteriodilactone product. This is important because one isomer may have different or undesirable properties compared to the other. These two synthetic pathways give the same final products, whether they are the bacteriodilactone products, or the lactone products, but many other products can be formed through other types of oxidation reactions.

However, the ß-ß bonds are not the only place a porphyrin can be modified. A porphyrin can have its two inner hydrogens removed to form a metal complex, like the naturally occurring heme and chlorophyll complexes. The metalation of a porphyrin macrocycle can generally occur before or after the functionalization of the ß-ß bond. A metal could be inserted into the macrocycle simply to create the metalloporphyrin, or it could be done to assist in the separation of isomers. Zinc is one of the most commonly inserted metals because it is easily inserted and can be removed with a hydrochloric acid solution[19,20].
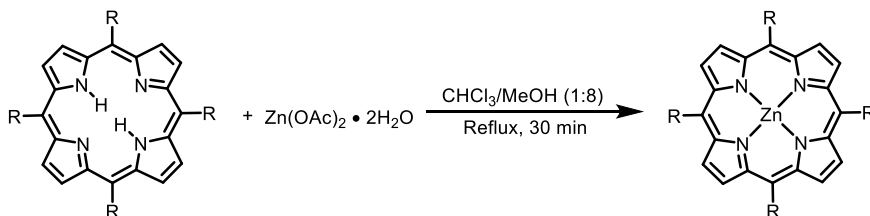
Figure 7. Zinc insertion into porphyrin macrocycle.

Zinc can be inserted into a base porphyrin macrocycle by refluxing a 1:8 mixture of chloroform and methanol with the porphyrin. Zinc acetate is added to the refluxing solution, affording the metalloporphyrin as the product. The same procedure is used to insert zinc into the lactone and bacteriodilactones, but an adjusted solvent system is required along with an elongated reaction time.
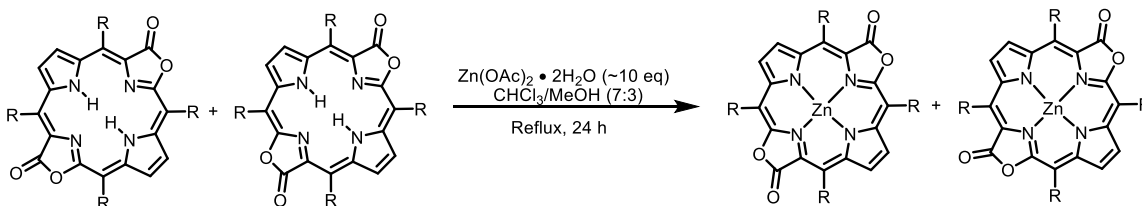
Figure 8. Zinc insertion into bacteriodilactol.

The elongated reaction time is theorized to be due to the electron withdrawing groups at the beta positions of the pyrrolic heterocycles. This is due to the center of the macrocycle obtaining a partial positive charge from the withdrawing groups, making the positive zinc atom harder to insert. In the case of pentafluorophenylporphobacteriodilactone, the addition of zinc allowed previously inseparable isomers to be separated, and the metal could be removed after to afford pure isomers[19].

Finally, porphyrins can be synthesized with *meso* substitutions by using various aldehyde derivatives to form *meso* substituted porphyrins as shown in Figure 1. These porphyrins are synthesized following the Alder-Longo method, simply changing the aldehyde used to create different *meso* substituted porphyrin products[16]. Synthetically created porphyrins have the potential to be useful in a myriad of applications because of the ability for their electronic spectra to be fine-tuned to specific applications.

Porphyrin chemistry expands far and wide beyond the scope of this application review with countless additional synthetic methods on various porphyrin structures. However, these core

syntheses are often the initial steps for the synthesis of the porphyrin derivatives used in the applications discussed below. Being the versatile molecule they are, porphyrins can be modified to fit the needs of a multitude of different applications. This review will cover a select few of these applications ranging from porphyrin derivatives being used as photodynamic light therapy sensitizers, pyrrole modified porphyrins being used as ion sensors, and finally metalloporphyrins being used as catalysts for various reactions.

<u>*2*</u> : Porphyrins and Therapy

Being the versatile molecules that they are, porphyrins have potential as cancer killing drugs if derivatized in specific ways. Objectively, cancer is one of the most widespread and obtrusive diseases on the planet. Nearly all people will say that they have been negatively affected by cancer during their lifetime, even if they have not personally had the disease[21]. Cancer has become so prevalent in society that one in two men and one in three women are now predicted to get cancer during their lifetime[21]. Since there is no outright cure for cancer, painstaking and life altering treatments must be undergone to attempt to eliminate the cancerous cells housed within the body. These treatments range from surgery to remove the malignant tumor to chemo and radiation therapy[22]. One relatively new treatment option is targeted drug therapy where the cancerous tumor is targeted with drugs in an attempt to kill off the cells. This technique can be used in tandem with light therapy to activate the drug inside the malignant tumor. Porphyrins can be synthesized having optical properties that allow activation by specific wavelengths of light. Many porphyrins are activatable by infrared or near-infrared (NIR) light making them ideal candidates for light therapy applications because of infrared lights penetrating ability on the body.

Photodynamic Therapy (PDT) is a technique used to eliminate cancerous tumors using light and a drug that can be activated in vivo. This drug is known as a photosensitizer and when activated by light, a cancer-killing form of oxygen is produced[23]. This cancer-killing oxygen is known as a reactive oxygen species (ROS), which is an unstable oxygen molecule also known as an oxygen radical[24]. To create a ROS, the photosensitizer drug is blasted with light after it is absorbed by the cancerous cells[23]. The light is absorbed, causing the drug to produce ROS that

attack the cancerous cells at the genomic level[23]. It is the genomic level attack that makes PDT a very tantalizing option for the treatment of cancer. One downfall of PDT is that there is potential sensitivity to light after the treatment. This is because while the majority of the photosensitizer will accumulate within the tumor, some will be lost within the bloodstream causing sensitivity to sunlight[23]. This side effect deters the use of PDT, but there are potential ways around this problem.

A potential solution is the use of nanoparticles to encapsulate the photosensitizer. The loaded nanoparticles can then be injected directly into the tumor, allowing much more direct treatment on the malignant growth. This has been tested with a porphyrin photosensitizer on a mouse that was bilaterally injected with prostate carcinoma cells to create tumors visible to the eye[25]. One of the growths was left as a control, while the other was injected with the specially designed nanoparticle. The nanoparticle was created to remain non-phototoxic until cellular internalization, but also to protect the porpholactol from the aqueous cellular environment. When the nanoparticle is injected into the tumor, and internalized within the cell, the nanoparticle releases the porpholactol photosensitizer and becomes phototoxic. Infrared light can be used to activate the porpholactol, causing it to fluoresce and release ROS that attack the cancerous cell's genomic information. In the experiment, the treated tumor was eradicated after 27 days, which shows the potential use of porpholactol derivatives as potential PDT photosensitizers[25].

Porpholactols are chlorin derivatives that are created through oxidative methods. Chlorins

are activatable by infrared light, which makes them potentially ideal

for PDT because infrared light more deeply penetrates the human

body compared to other wavelengths which cannot penetrate on a

level that is effective for therapeutic use. The tested porpholactol,

meso-tetraphenylporpholactol, is a chlorin derivative so it can be

meso-tetraphenylporpholactol
PDT Photosensitizer

activated by infrared light to release ROS. The hydroxide group is radicalized by the infrared

light, and this hydroxide radical attacks the genomic information of the cancerous cell.

PDT is an extremely useful treatment method for tumors close enough to the surface of

the skin for light therapy to be used. However, PDT requires diffused oxygen within the tumor to

be useful and solid tumors often are hypoxic, containing minimal to no oxygen[26]. This generally

inhibits the PDT process because it requires diffuse oxygen to function, making hypoxic tumors

untreatable by this method. This oxygen deficient environment inhibits and complicates many

commonplace cancer treatment methods. However, porphyrin can also be used for photothermal

therapy (PTT), which is an oxygen independent phototherapy that causes the incident light

energy to be absorbed by the porphyrin and dissipated through nonradiative decay[26]. This non-

radiative energy decay causes high heating within the hypoxic tumor, increasing the temperature

to a point where the malignant cells are denatured, effectively causing irreparable damage to the

cancerous cells. This gives porphyrin-based nanostructures the potential to treat hypoxic tumors

as well as non-hypoxic tumors through either PTT or PDT making them a versatile therapeutic

method to subcutaneous malignant tumors.

Porphyrins have a bright future as potential cancer treatment drugs when paired with light

therapies, but their uses are not limited to encapsulation in nanoparticles for targeted cancer

treatment[25]. Porphyrins also have a myriad of uses as diagnostic tools in various forms. Porphyrins and porphyrin derivatives are highly interactive with light, giving them their versatile uses as diagnostic tools. However, porphyrins are poorly water soluble, making them incapable of being injected into the body on their own. Porphyrins must be converted to a nanomedicine form, such as a liposome, micelle, or porphyrin-peptide based nanoparticles[3]. These structures are ideal pairs because of the functions of the nanomedicines, which accumulate in tumors and prevent premature inactivation or clearance by the blood stream, also improving bioavailability in the process[3]. The porphyrin loaded nanomedicines can then be used as both therapeutic agents and diagnostic sensors through various methods such as: magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography(PET), near-infrared fluorescence imaging(NIRFI), photoacoustic imaging (PAI), photodynamic therapy(PDT), photothermal therapy(PTT)[3].

Liposomes are well studied biomolecules that are mainly composed of phospholipids, giving them high biocompatibility inside the body. Liposome nanomedicines for cancer treatment are currently already available, but their efficacy and functionality is limited[3]. Porphyrin derivatives can be used to alleviate the shortcomings of unmodified liposomes, creating porphysomes. Porphysomes are composed of porphyrin-lipid conjugates and liposomes generally composed of phosphatidylcholine and phosphatidylethanolamine forming into bilayer or multilayer structures[3]. The porphysomes exhibit ideal particle sizes for drug delivery, averaging approximately 100 nm length, and the unique properties endowed by the porphyrin core. The porphysome exhibited PAI and NIRFI properties, meaning the porphysome could radiatively decay the incident light to near infrared fluorescence, or transform the incident energy to vibrations allowing detection via sound creating PAI potential[3]. These diagnostic abilities pair

tremendously with the liposomes innate ability to accumulate inside the malignant tumor, giving

highly accurate diagnostic tools for cancerous cells. Once aggregated inside the malignant cells,

the porphysomes can be activated with laser light. This activation causes the porphysomes to

convert the energy to hyperthermia through nonradiative decay, exhibiting a PTT effect, ablating

subcutaneous tumors[3]. Porphysomes are the frontrunner for PTT therapy due to their high

packing density, leading to incredibly high light absorption efficiency, as well as their

biocompatibility and biodegradability[26].

The porphysomes are enzymatically degradable and induce only minimal acute toxicity.

However, due to the porphyrin's innate ability to fluoresce, dissociated porphysomes can give

increased fluorescence values, skewing the readings for the amount of porphysome accumulated

within the tumor[3]. This can be solved however by the doping of the regular porphysome with a

Förster resonance energy transfer (FRET) based porphysome known as a FRETysome[3]. This

allowed for complementary fluorescence readings by having two types of possible readings, one

reading from the combined nanoparticle and one from the porphyrin only when dissociated from

the nanoparticle. If the entire nanoparticle was intact the fluoresce reading given by the

FRETysome would be high, whereas if the nanoparticle was dissociated the fluorescence reading

for the porphyrin dissociated from the nanostructure would be high[3]. This is possible through the

transfer of energy from the porphyrin fluorescence transition within the nanoparticle to the FRET

acceptor that has an electronic excitation energy similar to that of the porphyrin in the

nanoparticle. This energy transfer to the FRET acceptor causes the fluorescence of the acceptor

which is at a different wavelength than the porphyrin. This allows for real time imaging of both

the accumulation of FRETysome within the tumor, but also the structure and dissociation of the

FRETysome within the tumor. The imaging could be measured in real time by the detection of

different fluorescence wavelengths. The improved imaging capabilities paired with the accuracy of the detection of accumulated porphysomes made the FRETysome liposomes highly superior imaging structures compared to porphysomes on their own. The FRETysomes maintain the porphyrins efficacy as a therapeutic agent, making the FRETysome nanoparticles novel treatment for cancers that are easily targetable by laser light.

Micelles are another common nanoparticle that can be formed into a nanomedicine. Micelles are an amphiphilic compound, having both hydrophobic and hydrophilic properties. Micelles are formed in aqueous solutions where the hydrophobic head of the compound faces the core, sticking the chains hydrophilic tail out into the solution. Since the hydrophobic end is pointed away from solution while the hydrophilic end is in solution, the compound forms stable monolayer structures with hydrophobic cores. The stable hydrophobic core gives micelles interesting properties. The hydrophobic core can be loaded with hydrophobic drugs, unlike the liposome which generally are used with hydrophilic drugs[3]. Chemotherapeutic drugs are generally water-insoluble making an *in vivo* delivery difficult. This is where micelles shine because of their intrinsic hydrophobic core. The core can be used as a transporter for these commonly insoluble drugs allowing delivery to the tumor within the body[3]. However, alone micelles face drawbacks because of their small size, allowing for only single drug loading capabilities, along with their difficulty being traced within the body[3].

Porphyrins are naturally hydrophobic molecules making them excellent candidates for construction with micelles. When combined, the therapeutic and diagnostic abilities of porphyrins are imparted into the micelles natural ability to deliver drugs to the cancerous areas of the body. Nanostructures constructed of micelles and porphyrins are known as nanoporphyrins and they acquire the porphyrins ability to fluoresce with NIR light and the micelles ability to

accumulate spontaneously in tumors[3]. This allowed for tumors with a diameter as small as 0.006

mm^2 to be identified by fluorescence[3]. The nanoporphyrin also retains the porphyrinoid ability to

chelate metals. When gadolinium(III) is chelated to the nanoporphyrin it can be used as a

contrasting agent for MRI scans[3]. PET scans can also be performed with this nanoporphyrin

when it is chelated to copper metal-64[3]. MRI-PET tandem imaging can also be performed by

employing a mix of the gadolinium(III) and copper-64 chelated nanoporphyrins[3]. The

nanoporphyrin structures also can be used as therapeutic agents when accumulated within the

tumor. The nanoporphyrins showed effectiveness as PDT and PTT drugs[3]

One of the frontrunning treatments for cancer is the use of a phototherapy alongside a

chemotherapeutic treatment. Nanoporphyrins are one way this symbiotic treatment approach can

be achieved. The nanoporphyrin can be loaded with the chemotherapeutic drug doxorubicin

$(DOX)^3$. The nanoporphyrin will then travel through the body and accumulate within the tumor

using the properties of the micelle building blocks. Then the porphyrin will be activated through

either PDT or PTT to ablate the tumor. The chemotherapeutical drug can therefore be utilized

directly at the malignant source, highly obstructing the tumors capability to reproduce[3]. This

synergy makes the nanoporphyrin therapy approach incredibly effective in stopping cancerous

cells directly at the source.

Peptide chains are another integral part of the human body. Peptide chains are linkages of

amino acids that can change their composition depending on the biological environment it is in.

These changes can cause the function of the peptide to change, or for it to begin being used by

other parts of the body when it shifts to that form. This can be used advantageously in a way to

create self-assembling structures when under certain physiological conditions. Porphyrins can be

conjugated to peptide chains to create cancer-targeting self-assembling porphyrin-peptide-based

nanoparticles(PPK)[3]. When conjugated together, the porphyrin gives a hydrophobic driving force for the structure while the peptide chain presents the hydrophilic driving force that is used for the self-assembly inside the tumor[3]. As expected, the porphyrin provides the nanostructure with NIRF activity for imaging and PDT treatment making the PPK a viable diagnostic tool as well as cancer treatment tool[3]. Interestingly, the peptide chain could be designed to target the mitochondria of the cancerous cells, giving PPK innate cancer apoptosis activities[3]. One drawback of these nanostructures is that the conjugated porphyrins can sometimes become trapped within the nanostructure during the self-assemblies. One way of mediating this issue was to impart a biomimetic approach, using metalloporphyrins coordinated with a small number of peptide chains[3]. This allowed physiological stability as well as excellent nanoparticle circulation through the blood stream, allowing for effective tumor accumulation with exceptionally high PDT responsiveness[3]. Combining the intrinsic properties of each piece of the nanostructure allowed for an effective cancer targeting treatment to be created.

Porphyrins are naturally existing inside both plants and animals, making them great biomimetic options for possible treatments. Porphyrin derivatives have been used in cancer treatment studies on mice and they show highly promising results for the treatment of subcutaneous tumors. Porphyrin therapeutics often have two possible types of therapeutics, PDT and PTT, giving options for treatment path and fine-tuning options. Various nanostructures can be created by combining porphyrin derivatives with naturally occurring structures such as micelles, liposomes, and peptide chains. This allows for much greater bioavailability and biocompatibility. The nanostructures can also be utilized as diagnostic tools to analyze the tumor and then future treatment through PDT, PTT, or drug encapsulation. This allows for a highly

effective tandem diagnostic and treatment tool for subcutaneous tumors to be created out of

porphyrin derivative nanostructures.

3 : Porphyrins as Sensors

I.   Oxygen Sensors

Porphyrins can be modified into thousands of different derivatives to suit a variety of applications, such as medical uses as discussed before, or ion sensing applications to be discussed. The change in the electronic spectra of porphyrins can often be measured by the shift or absence of a previously observed transition. Such changes could be the binding of a desired ion changing the electronic spectra, or the transfer of energy from the porphyrin to another ion giving rise to a different change in electronic spectra. Taking this into account, sensors for various ions can be developed and employed to detect the desired ions. One of the most common porphyrin-based sensor types is the oxygen sensor. This type of sensor can be used in a myriad of applications ranging from oxygen concentration measuring in a reaction or industrial setting to measuring the concentration of dissolved oxygen in waterways to determine the level of pollution. Porphyrins are not limited to sensing for oxygen however, they can also be used as detectors for cyanide or toxic metals in aqueous solutions, and even as lung cancer sensors during breath analysis. These applications are all particularly important for different industry uses, as well as uses in medical treatment and diagnosis fields.

Unless the environment of the site of interest is hermetically sealed with a controlled atmosphere, oxygen will always be a part of what is being monitored. Depending on the site of interest being studied these levels may need to be monitored or controlled. There are many different monitoring techniques but recently sensors based on phosphorescence or the photoexcited state quenching of porphyrin molecules have been in the spotlight[11]. Porphyrins can be used to monitor oxygen levels in various fields, such as chemical applications, deep sea

environments, fluid dynamics, clinical analysis, as well as environmental monitoring[11].

Metalloporphyrins are a commonly used porphyrin that are immobilized onto a solid surface

through a chemical or physical adsorption process, or they are dispersed in an oxygen-permeable

polymer film. These methods allow for four classifications of oxygen sensing systems;

phosphorescence intensity change, phosphorescence lifetime change, change of lifetime of

photoexcited triplet state, intensity change of absorption of photoexcited triplet state. These

newly reported methods could replace some industry standard techniques such as the Winkler

titration and Clark-type electrodes due to their cumbersome nature and time consuming

processes[11]. Oxygen sensing methods based on phosphorescence data have become attractive due

to improved function over fluorescence measurements, as well as the implementation of less

complexed monitors and measuring devices to be used. When the metalloporphyrins, commonly

platinum(II), palladium(II), and zinc(II), are dispersed into the polymer film or immobilized onto

the solid surface the phosphorescence intensity of that organic dye is measured. When the sensor

is in the presence of oxygen, it quenches the phosphorescence of the metalloporphyrin allowing

the concentration of oxygen to be measured. This mechanism is summarized by Figure 9, where

the porphyrin film is excited by the laser from its single zero state, to its single one state. When in the singlet one state the energy will fall to the triplet 1 state, becoming stuck due to the triplet one
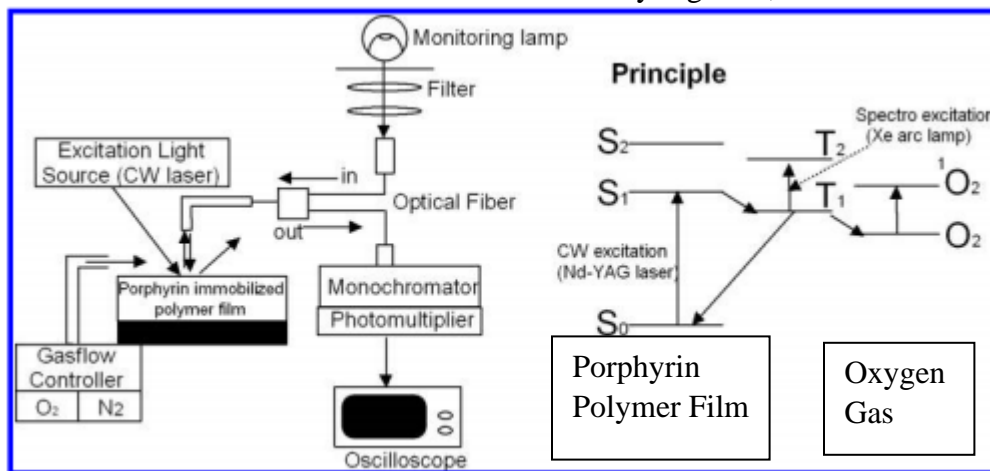

Figure 9: Oxygen sensor apparatus and mechanism of the porphyrin-oxygen energy transfer. Taken from source 17.

to singlet zero energy transfer not being spin allowed, resulting in phosphorescence. While the

porphyrin is stuck in the triplet one state, the oxygen -which has a triplet ground state- takes the

spin allowed energy transfer from the porphyrin, quenching the phosphorescence. These sensors

are highly accurate because they do not consume the oxygen analyte since there is no chemical

reaction between the sensor and analyte, only an energy transfer between the two.

The first oxygen sensor device to be discussed is a metalloporphyrin dispersed in

polymer film. The porphyrins used in this technique are generally platinum, palladium and

ruthenium porphyrins due to their strong phosphorescence at room temperature[11]. Room

temperature phosphorescence capabilities are important because it allows for the sensor to be

used in various natural situations as well as greater ease in measurement because the sensor does

not have to be either cooled or heated to different electronic states in order to achieve adequate

phosphorescence. It is important for the polymer that the metalloporphyrin is dispersed onto to

have high oxygen permeability to facilitate adequate energy transfer. A common oxygen sensor

is platinum octaethylporphyrin (PtOEP) dispersed in polystyrene because of its high oxygen

permeability as well as oxygen selectivity[11,12]. This is a novel oxygen sensor used for measuring

concentration of dissolved oxygen in various systems ranging from, but not limited to, a fish

tank, tap water, and the Songhua River[12]. These three systems provide ideal examples for why

the measurement of dissolved oxygen content is important. In a fish tank the dissolved oxygen

concentration must be high enough for the first to live and grow. While this may seem trivial in a

household fish tank, this could be scaled up to fisheries where juvenile fish are bred and grown

until they are old enough to be released. This measuring technique could be applied to ensure the

fisheries are ethically and properly hatching and growing fish in adequate conditions. The

concentration of dissolved oxygen in tap water is important because it allows the purity of the

water to be determined. Finally, the dissolved oxygen concentration in the Songhua river is important because it allows the determination of how naturally polluted a water source is. This is not only important for the Songhua river, but to all water sources worldwide with quick measurements being able to be made for the oxygen concentrations. However, it is possible for results to be skewed based on the time of measuring during the year because if there are algal blooms and aquatic plant populations are high the results may be either lower than expected or much higher than expected results due to the extra production of oxygen from the plants at different times within the year[12].

Another common sensor system used to determine oxygen concentrations via the luminescence quenching of OEP and PtOEP facilitated by dissolved oxygen is the poly(1-trimethylsilyl-1-propyne) (poly(TMSP)) OEP system[27]. Poly(TMSP) is a porous polymer film with very high gas permeability allowing large amounts of oxygen to diffuse giving great luminescence quenching of gas phase oxygen[11]. The polymer film is tough, generally being 10 μm thick, allowing for enough rigidity to be used in chemical environments as well as environmental analysis systems. The PtOEP poly(TMSP) as well as the PdOEP poly(TMSP) sensor each displayed strong luminescence at room temperature with high quenching via gas phase oxygen, showing that these metalloporphyrins are great sensors for dilute oxygen sensing. The oxygen sensors do not need time to re-equilibrate after quenching luminescence via oxygenation but will actively luminesce in correlation to the oxygen concentration present, making them ideal room temperature oxygen sensors.

II. Ion and Volatile Compound Sensors

Cyanide is a deadly anion that has a colorless gaseous form as well as liquid form. Cyanide is lethal to humans in very small doses, taking only 0.5-3.5 mg of cyanide per kg bodyweight can be lethal[10]. This elevated toxicity to humans is due to cyanides ability to bind to the porphyrin component of human blood, the iron heme group. This permanently inhibits oxygen from binding to the iron in heme, stopping the transfer of oxygen throughout the body. However, despite its toxicity cyanide is a commonly used chemical in industrial applications. This raises concerns for accidental exposure to workers in the facility but also for the accidental leakage into water sources for the general public. Generally, the need for a cyanide sensor is in an aqueous system, such as waterways or industry applications, but commonly known cyanide sensors require organic solvents and the absence of other anions that could cause interference[10]. These interferences cause changes in the optical spectra of the sensors, affecting the measured values of cyanide concentrations.

As stated before, porphyrins are ideal sensors because of their modifiability, chelating ability, and their spectral properties. These criteria make porphyrins a great option for aqueous cyanide sensing. An innate property of the cyanide anion is that it very tightly binds to metal cations as well as oxygen groups. This is a great benefit when designing sensors for the cyanide anion. Porphyrins with metal atoms inserted and oxygen groups become ideal sensors for the cyanide anion because of the innate attraction towards metals and or the nucleophilicity towards the derivatized β-β bonds. However, it has been proven that the bonding of cyanide directly to the metal in the porphyrin exhibits minimal sensing capabilities due to the minor shift in spectra

compared to the nucleophilic attack on the derivatized β-β bond[10]. When the β-β bond is derivatized to a lactone, the cyanide anion can attack the oxygen of the lactone altering the hybridization of the carbonyl carbon giving a large shift in the spectra that makes the lactone derivatized porphyrin a capable sensor for cyanide[10].

The platinum and gallium metalated porpholactones were tested, with the gallium porpholactone being more sensitive to the cyanide anion. Both metaloporpholactones can be PEGylated to allow sensing in the desired pure aqueous solution through the addition of thiol terminated PEG chains to the para position of the meso aromatic groups[10]. To create a reusable aqueous sensor, the gallium PEGylated porpholactone dye can be added to a Nafion® matrix membrane to be used as an aqueous cyanide sensor. The gallium sensor has a higher sensitivity to the cyanide anion, but the platinum sensor has a larger colorimetric response allowing for a more easily viewable change from the naked eye. Figure 10 shows that the freebase sensor exhibits a large color response to the eye, but the spectrophotometric response is less sensitive than the platinum sensor, which has a less obvious color response to the naked eye. However, the platinum sensor has the greatest response to the cyanide anion, shown by the drastic increase at the 703 nm band and decrease of the ~585 nm band. The gallium sensor is the most sensitive, being able to detect concentrations of
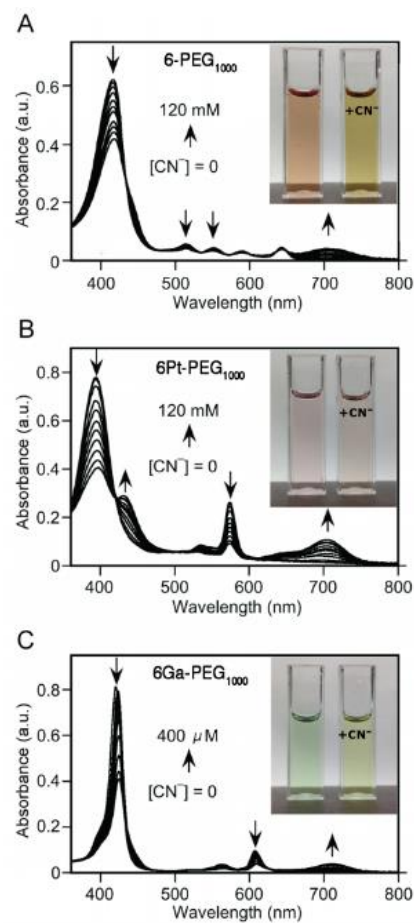

Figure 10: Colorimetric response of the freebase, platinum, and gallium cyanide sensor, taken from source 20.

cyanide 300x lower than the freebase and platinum sensors. The caveat to this is the fact that the spectrophotometric response is less sensitive at the 703 nm wavelength, but the off position of the sensor is more highly selective being around ~603 nm. This reduced gap between the sensor with no cyanide present and cyanide detection increases the selectivity allowing for much lower concentrations of cyanide to be detected[10].

Across the globe, industrial zones containing factories improperly dispose of waste into the environment, often ending up in the surrounding waterways[28]. The waste of these factories varies, but it is commonly transition metals being injected into our waterways. This is particularly hazardous because in the aqueous waterways, the transition metals will complex with the water creating acidic solutions, increasing the acidity, and potentially harming the wildlife that inhabits them. The leeching effects of these contaminated acidic waters pose threats to the buildings surrounding the waterways as well as humans. These detriments to nature and society are compelling reasons for sensors for these metal cations to be created. As stated before, porphyrins have very distinct UV-Visible spectra, often being visibly altered by either a derivatization or sensed molecule. Porphyrins are ideal metal cation sensors due to their ability to interact with the metal cations forming chelation complexes[13]. Complexed porphyrins exhibit a distinctive UV spectrum, but the sensors generally can only chelate one metal cation. This slows the sensing process if every sample must be tested repeatedly with multiple sensors for different metals. Porphyrin sensors have been developed to sense a variety of metals alone, such as mercury, lead, cadmium, iron, and copper, but only few sensors have been developed allowing for multiple cations to be sensed simultaneously[13]. A common issue between all sensors is the inability to be used in purely aqueous solutions, and the inability for particularly heavy metals – cadmium, lead, and mercury- to be sensed simultaneously[13].

An interesting development in porphyrin sensing technology was the synthesis of a water soluble, cationic optical sensor capable of sensing single heavy ions or multiple different heavy ions by UV-Vis absorption[13]. Figure 11 shows a recently developed cationic porphyrin derivative with a freebase core allowing for metal ion chelation, producing different absorption patterns based on which metal was in solution[13]. The porphyrin derivative is able to detect various metals in solution, being a poor sensor for zinc ions and iron ions, but a strong sensor for mercury, cadmium, lead, and copper[13].
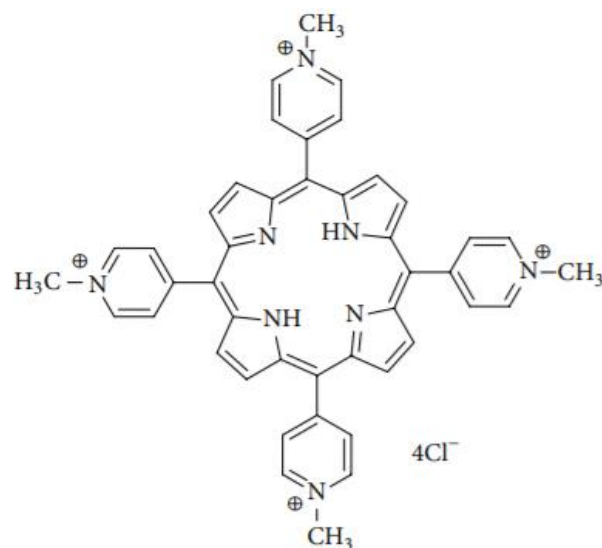

Figure 11: cationic *meso*-tetra(N-methyl-4- pyridyl)porphine tetrachloride sensor molecule, taken from source 21.

Figure 12 shows the free base cationic sensor's UV-Vis absorption spectra with amplified q-band region (~500-~700nm) and the absorption spectra of the cationic sensor with various toxic metal cations.
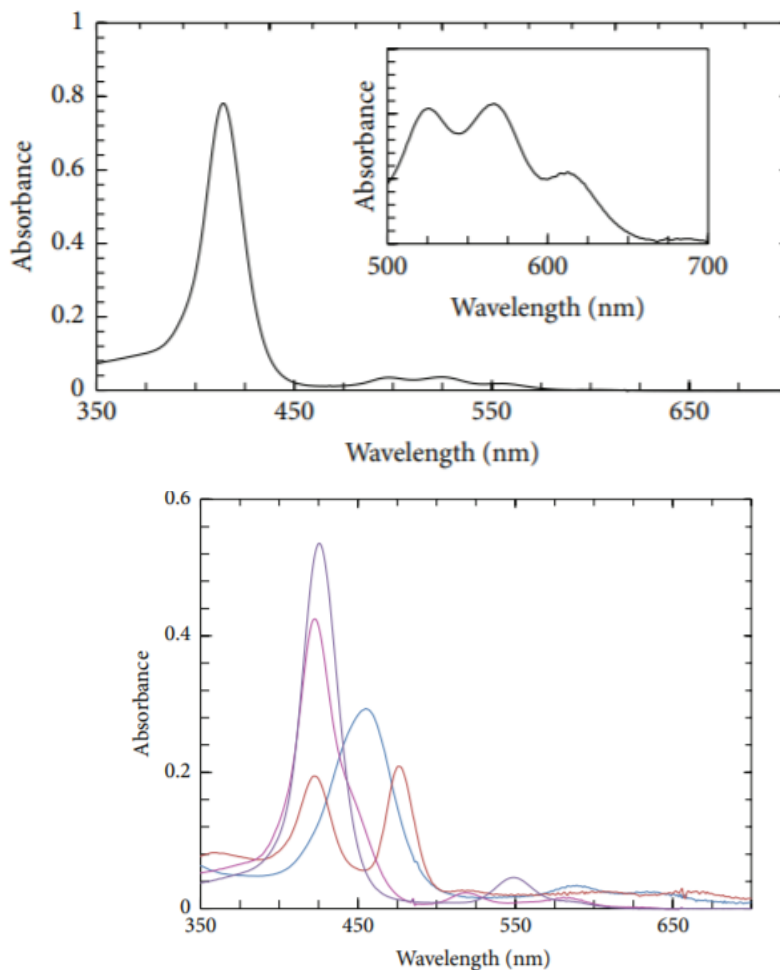

Figure 12: Absorption spectra of freebase cationic porphyrin sensor (Top) with expanded 500-700 nm region and the absorption spectra of the cationic porphyrin sensor with mercury (Blue Curve), lead (Brown Curve), cadmium (Pink Curve), and copper (Purple Curve). Taken from source 21.

The absorption spectra of the cationic sensor with toxic metals greatly changes allowing for single metal detection easily. The cationic sensor can also be used to sense for multiple toxic metals in solution at the same time. Figure 13 shows the increasing amount of cadmium, mercury, and lead being added to the sensor solution, showing increasing absorption of three distinct wavelengths relating to each specific metal cation.
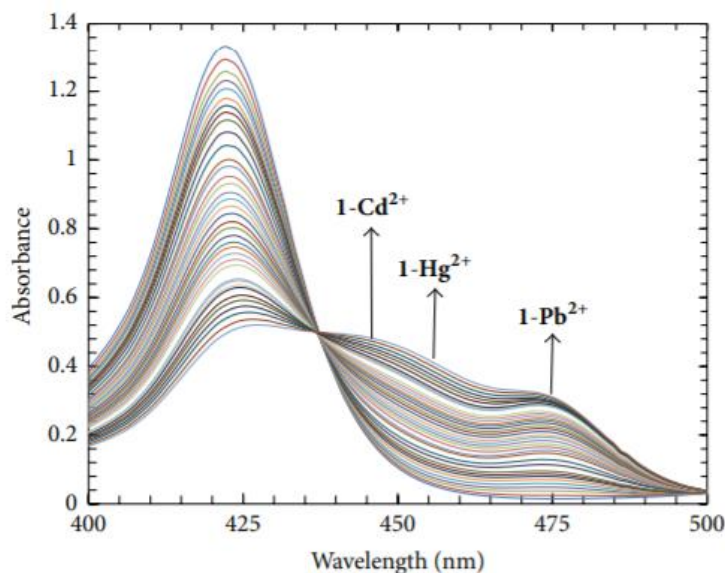
Figure 13: Absorption spectra of increasing amounts of toxic metal cations (cadmium, mercury, and lead) being added to the sensor solution, showing distinctive absorption increases at correlating wavelengths to the toxic metal. Taken from source 21.

This is highly advantageous since a singular molecular sensor can be used to determine if three highly toxic metals are in an aqueous solution. This will greatly reduce the time taken to analyze aqueous samples for multiple heavy metal ions as well as reducing the cost of these techniques because only a single sensor is required.

Sensors are used in a variety of applications such as alcohol analysis to deem if one is fit to drive, or for the analysis of volatile compounds offput by food to measure its freshness[29]. The

breath of human beings is very interesting, often outputting volatile compounds when diseases or infections are present[29]. Solid-state sensors are a non-invasive way of collecting samples from the human body, with the capabilities of screening and diagnosing individuals for pathogens[29]. One striking capability of these sensors is the ability for lung cancer to be identified by a gas sensor with quartz microbalances (QMB) coated with porphyrins[29]. The interaction between volatile compounds from exhaled breath and the porphyrin coating is possible because of the numerous ways of possible analyte binding methods. The porphyrin ring can bind to the analyte through Van der Waals forces, hydrogen bonds, π system interactions, and coordination or chelation to the central metal ion[29]. The QMBs are coated with metalloporphyrin derivatives to mimic natural biologic porphyrins in an attempt to encourage analyte binding. Volatile compounds such as aniline, o-toluidine, and cyclopentane are commonly reported in the breath of lung cancer patients[29]. These compounds are detected with high specificity, allowing for discrimination between cancer patients, healthy individuals, and post operation cancer patients[29]. The porphyrin coated QMB can be placed onto a modified endoscopic probe to retrieve *in situ* air samples, giving evidence to tumor regions emitting volatile chemicals[29]. If unique volatile compounds can be isolated from different types of cancers, there is potential for a cancer specific sensor to be created from porphyrin derivatives.

The electronic spectra of a porphyrin derivatives are often an integral tool for the sensing of ions. The fluorescence and phosphoresce itself can be measured in certain applications, while the quenching of phosphorescence can be used in other applications. The sensing of these ions is often especially important because it can help determine if waste is toxic or containing poisonous anions such as cyanide. UV-Visible spectroscopy is also incredibly important because of the base

porphyrins highly defined spectra. Any change to this highly defined spectrum is easily

identified and interpreted, allowing for highly specific ion sensing.

<u>*4*</u> : Porphyrins as Catalysts

Many chemical reactions often proceed slowly, unless aided by a catalyst or enzyme. Catalysts and enzymes do not affect the products of the reaction, they simply speed up the reaction and are outputted as their initial form. Metalloporphyrins can be used as catalysts in reactions, "tuning" their selectivity for the substrate by derivatizing the substituent groups. The high modularity of the porphyrin macrocycle paired with its high stability makes porphyrins top notch candidates as catalysts for numerous different reactions such as olefin epoxidations, which can be catalyzed by iron chloride complex porphyrins[15]. In addition to this the metalloporphyrin can also be supported on polymers, silica, resins, clays, and polypeptide chains to work as catalysts[15]. These oxidation reactions often require harsh solvents and oxidizers that lead to toxic waste byproducts, imparting additional costs to the total synthesis. Porphyrins offer new and exciting reaction pathways due to their ability to catalyze these reactions, reducing the amount of toxic waste produced due to the generally mild solvents and oxidizers required. Ruthenium metalloporphyrins are widely studied catalysts that have the ability to assist in the oxidation of styrenes, cycloalkenes, steroids, and arenes when covalently supported on soluble supports, or immobilized on insoluble supports[30]. Interestingly, the entire study of metalloporphyrins stems from something much closer to human beings than something in a chemical lab. Inside the liver is a family of hemoproteins known as Cytochrome P450, an enzyme with a hemoprotein core facilitating the detox of foreign drugs within the body[31,32].

Cytochrome P450 is a naturally occurring hemeprotein that is one of the origins of using metalloporphyrins as reaction catalysts[30,31]. Cytochrome P450 exists as a family of enzymes in all organisms, coming in different forms and inhabiting different locations in the body of the

mammal and or plant[31,32]. In humans the enzyme mainly inhabits the liver waiting for foreign compounds to enter[31,32]. These foreign compounds are often drugs and or unknown chemicals that enter the body, and converting them to more water soluble compounds allowing the body to naturally excrete these xenobiotics through waste cycles[31,32]. Cytochrome P450 is known as a monooxygenase and it converts these unknown compounds by adding oxygen to them, which aids in solubilizing these compounds as well as preparing them for other enzymatic pathways[31,32]. This is made possible by the hemeprotein at the core of the enzyme which is an iron metalloprphyrin[30,32]. The core iron atom is able to facilitate and control the oxygen atom transfer and reductases aid in giving the required electrons to facilitate the desired oxidations[33]. Understanding the mechanistic transfer of oxygen by the iron core of the hemoprotein was the basis for using porphyrins and metalloporphyrins as reaction catalysts. This multi-enzymatic system is hard to replicate under non-biological conditions, but it gave a window into the potential of metalloporphyrins following the core structure of cytochrome P450 as oxidative catalysts.

One highly advantageous aspect of using metalloporphyrins as catalysts for oxidative reactions is their high regioselectivity and stereoselectivity for the substrate. Metalloporphyrins can be "tuned" to react with a specific area of the substrate by specific modifications to the porphyrin, such as altering the main porphyrin macrocycles substituents to be "slimmer" or "bulkier" depending on the desired reaction location, or the metalloporphyrin can have various chiral components as ligands furthering the selectivity of the reaction site[34,35]. Generally, the desired reaction site for the oxidation reactions is fairly inert, requiring extremely reactive reagents as well as strong inorganic acids, peroxyacids, and or oxo-metal oxidants, which all are potentially volatile and toxic, to react with the inert hydrocarbon substrate[35]. To compound the

potential toxicity and volatility of the generally required compounds, these reactants produce the desired products in low yields, have little to no chemo, regio, or stereoselectivity, and produce toxic waste as a byproduct which must be properly neutralized and disposed of adding additional cost to the reaction[35]. Many reactions, especially reactions that are used to manufacture pharmaceuticals require specific isomers and chiralities of compounds to get the desired effects of the produced drugs. Therefore, metalloporphyrins have opened a vast number of synthetic pathways offering high regio and stereoselectivity of the products produced. Metalloporphyrins can be derivatized with a vast array of different ligands and substituents, as well as with a variety of useful metals. This derivatization leads to the reactivity and selectivity of the metalloporphyrin catalyst.

Metalloporphyrin catalysts are divided into three categories based on their substituents known as first, second, and third generation catalysts[34]. First generation catalysts are modified at the meso position of the porphyrin macrocycle, second generation catalysts are modified at the meso position as well, but the meso groups are halogenated or derivatized as well[34]. Third generation catalysts have either first generation or second generation derivatization at the meso position as well as halogenated β-β bonds[34]. These derivatizations greatly affect the targeted hydrocarbon bond, but each derivatization is not unique to the derivatization it is designed for. Some metalloporphyrin catalysts can be used for multiple reactions if they are used with that reaction's specific reagents. However, this does change the efficiency of the reaction, with certain metalloporphyrin catalysts being more efficient for specific reactions than others[34]. Metalloporphyrin derivatives have been used as catalysts for many different important industry reactions, such as hydroxylations, aminations, carbenoid insertions, epoxidations, oxidations of alcohols to carbonyls, and oxygenation of sulfides[34,35]. These reactions all use various

generations of metalloporphyrins catalysts, with commonly used metals being iron, manganese, ruthenium and cobalt[34,35]. These metals and the derivatized metalloporphyrins are used for their high stability, ability to be derived to suit a specific reaction, and their selectivity towards the desired location on the substrate[34,35]. Figure 14 summarizes the general reaction scheme with metalloporphyrin catalysis in three reactions commonly used in industry. This is beneficial to the chemical industry because it opens a great deal of reaction pathways that are more efficient to run and
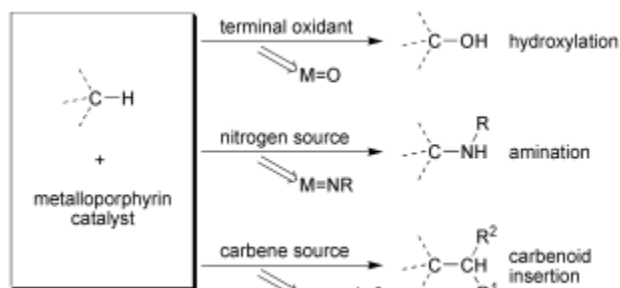

Figure 14: General theory behind common metalloporphyrin catalysis reactions. Figure taken from source 28.

offer significantly less hazardous reaction conditions, leading to less toxic byproduct disposal and fewer total reagents used. These streamlined reaction pathways potentially have the greatest effect on the pharmaceutical industry due to the metalloporphyrin catalyst's ability to improve the efficiency of many reactions that produce pharmacological reagents[34].

Out of all metalloporphyrins, ruthenium metalloporphyrins are generally the most widely used as reaction catalysts. Ruthenium is a desirable metal for metalloporphyrin catalysts because of its close periodic relationship to iron, its ability to form stable high-valent oxo-compounds, and its high catalytic ability for oxidation reactions[30]. The close periodic relationship to iron is important because it mimics the biological molecule cytochrome P450, creating biomimetic metalloporphyrin catalysts out of the ruthenium metal[32]. The stable high-valent oxo-compound intermediates can sometimes be isolated from the reaction mixture, allowing for mechanistic studies to be done, furthering the catalytic knowledge of the ruthenium metalloporphyrin systems[30]. Ruthenium metalloporphyrin derivatives are often used in oxidation systems as

catalysts for the oxidation of a wide variety of organic substrates ranging from styrenes to steroids and benzylic hydrocarbons[30]. However, their use expands far further, efficiently catalyzing epoxidation, hydroxylation, amine dehydration, arene oxidation, alcohol oxidation, phosphine oxidations, and sulfide oxidations[30]. Figure 15 summarizes many of the possible catalysis reactions by ruthenium metalloporphyrins, as well as many other metalloporphyrin catalysts.
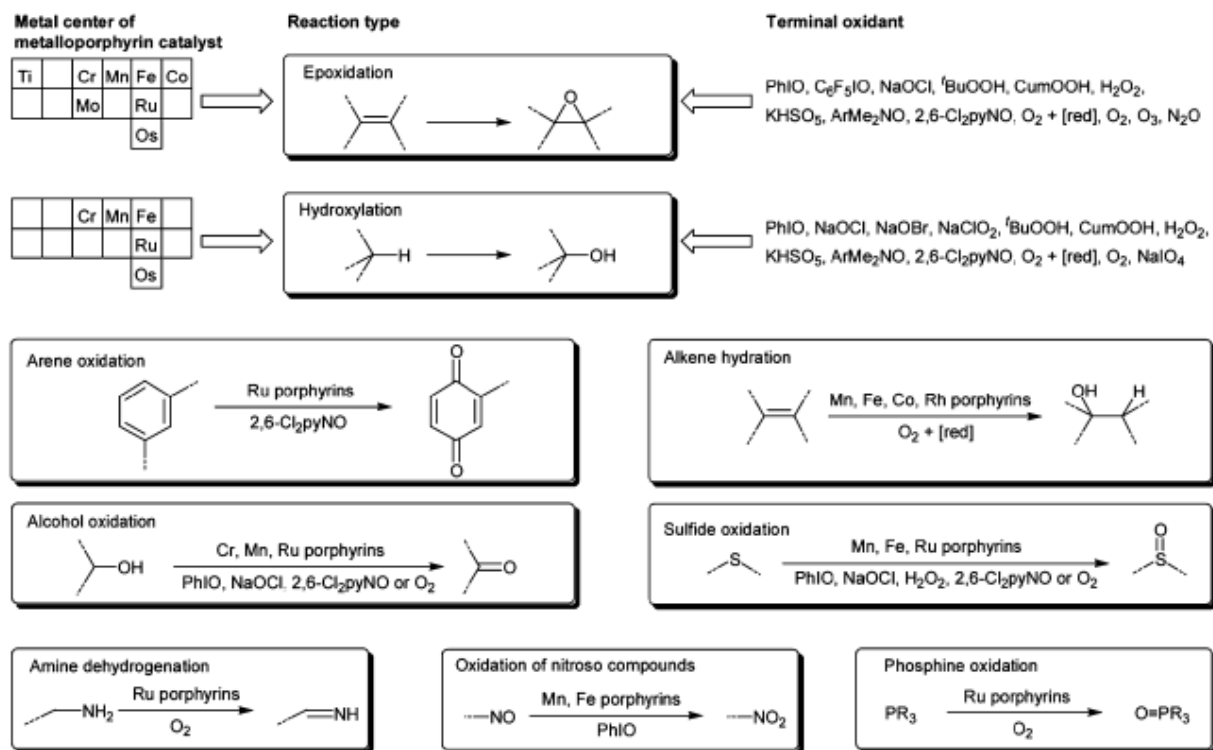

Figure 15: Summary of common ruthenium and other metalloporphyrin catalyst uses. Taken from source 24.

The ruthenium metalloporphyrin catalysts can be attached to various structures to facilitate easier isolation from the reaction mixture, and the ability to recycle the catalyst for purification and reuse[30]. The metalloporphyrin can be grafted onto molecular sieves through coordination bonds, by anchoring the metalloporphyrins to silica gel through coordination bonds or by encapsulation

of the metalloporphyrin into the silica gel matrix, covalently attaching the metalloporphyrin to a peptide resin, and finally by covalently attaching the metalloporphyrin covalently to soluble dendrimer supports[30]. These reactions are great tools for organic syntheses as well as biomimetic studies due to the vast array of substrates usable with a great variety in reagents to facilitate the variety of reactions possible. The ruthenium metalloporphyrin is an efficient biomimetic catalyst that offers a wide selection of catalyzable reactions with high regio, chemo, and stereoselectivity based on the metalloporphyrin substituents[30].

A common reaction in organic synthesis is the olefin epoxidation. However, epoxidation reactions are generally limited by the type of solvent or reagents used, hindering the number of different epoxides that can be synthesized. Porphyrins can be used as useful catalysts for olefin epoxidations due to the large range of useable oxidants, the tunability of the porphyrin macrocycle and its ligands, and finally the diverse range of possible reaction conditions[15]. A typical porphyrin that is used for the epoxidations is iron tetraphenylporphyrin (TPP) because of its stability and reactivity as a catalyst. A more efficient iron porphyrin catalyst is the fluorinated iron tetraphenylporphyrin (FeTFPP) due to its increased stability over FeTPP. These porphyrins can be used in a variety of reaction conditions, and with a variety of hydrocarbons ranging from 1,3-Cyclohexadiene, to cyclooctene and cyclohexene[15]. These reactions use various parameters giving relatively high to high yields (50-95%)[15]. This is a relatively easy synthetic method giving relatively high yields to the desired epoxides.

Cytochrome P450 can be identified as the main starting point of metalloporphyrin catalysis chemistry due to its function within the body. Being replicable in laboratory setting by metalloporphyrin derivatives makes an easily attainable and highly efficient catalyst for a variety of industry standard reactions. The advantages of metalloporphyrin catalysts is the wide variety

of usable reaction systems which are significantly less toxic than common industry reaction systems. There are significant cost benefits to employing such catalysts in organic synthesis which further increases their utility. These factors make metalloporphyrins a tantalizing option to streamline and increase the efficacy of many of these reactions.

<u>*5*</u> : Conclusion

Porphyrins are a fascinating macrocyclic compound that can be modified in a seemingly limitless number of ways. These derivatizations often have noteworthy and unique properties that can be used in a multitude of applications; many derivatizations are outside the scope of this review. Generally, these applications are aimed at improving previously existing processes and treatments. Porphyrins have a longstanding history being used as therapeutic agents for the treatment of cancer. These uses are being developed more every year and porphyrin based diagnostic methods are offering high promises towards improving the accuracies of scanning methods. Porphyrins are also highly utilized as sensors in industrial applications as dissolved oxygen sensors and ion sensors. Porphyrins can be used in applications to test the safety of the waste produced or to test for hazardous waste within the desired product. Furthermore, porphyrins can be used to test for cyanide, toxic metal cations, or to measure the pollution level of waterways through dissolved oxygen concentrations. Volatile compounds can also be sensed by porphyrin derivatives for uses in breath analysis offering sensing applications of lung cancer. Porphyrins can also be used directly in chemical syntheses as reaction catalyst for a variety of important industry reactions. Porphyrin catalyzed reactions are often performed in much more mild reaction conditions producing far less toxic waste than the non-porphyrin catalyzed counterparts. Since porphyrins are so common within living organisms, whether it be heme within the blood or chlorophyll within plants, many of these applications are designed as biomimetic versions to impart similar function. This makes the synthesized porphyrin highly biologically compatible for biological applications as well as highly efficient for industrial applications. Overall, porphyrins are an incredibly interesting, diverse, and versatile class of molecules that expands far and wide beyond the scope of this review.

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