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Synthesis and characterization of 5,10,15,20-tetra[(3,4-dimethoxy-6-nitro)phenyl] porphyrinatocopper(II)

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ABSTRACT

The new porphyrin, 5,10,15,20-tetra[3,4-dimethoxy-6-nitro phenyl] porphyrin, has been synthesized and characterized using FAB-mass spectroscopy, ^{1}*HNMR,* ^{13}*CNMR and UV-Vis spectrophotometry. The NMR confirmed the structure of the compound and the mass spectrum was in agreement with the proposed molecular formula. The UV-Vis absorption spectrum of synthesized compound shows characteristic spectral patterns similar to proposed structure with a Soret band at 419 nm and four Q bands at 515, 550, 590, and 648 nm. Protonation of the porphyrin with TFA resulted in the expected red shift of the Soret band. Excitation at 419nm gave an emission at 650nm. Metal complex of the newly synthesized porphyrin ligand 5,10,15,20-tetra[3,4-dimethoxy-6-nitro phenyl] porphyrinatocopper(II) was synthesized and characterized by various analytical techniques.*

Keywords: Porphyrin; Spectral analyses; Metal complex; TGA-DTA analyses.

INTRODUCTION

Porphyrin-type compounds constitute a major class of pharmacological agents under investigation for application in the early diagnosis and treatment of cancer by photodynamic therapy and a variety of other diseases. Two porphyrins derivatives, purified Hematoporphyrin derivative and Verteporfin, are FDA-approved for the photodynamic therapy treatment of melanoma, early and advanced stage cancer of the lung, digestive track, genitourinary track, and the wet form of age-related muscular degeneration, respectively. Both of these drugs are mixtures of compounds with limited specificity for tumor tissue. Although both drugs have been successfully used to treat several thousand of passions worldwide, skin photosensitivity is often and undesirable side effect in purified hemetoporphyrin derivative photodynamic therapy due to prolonged retention of this drugs in patient's skin. This unwanted side effects has been minimized or illuminated with the use of second-generation photodynamic therapy photo sensitizers, currently undergoing clinical investigation. Prostate cancer is the most common internal malignancy in the word. Most cases are organ confined and are presently treated by either surgery, external beam radiation or branchytherapies. Unit recently, photodynamic therapy was not a viable alternative for prostate cancer treatment due to the limited tissue penetration

ability of the laser wavelengths, normally used in photodynamic therapy and the poor tumor selectivity of the currently available photosensitizes. However, the development of drugs photo activated in the infrared region coupled with the use of optical fibers inserted transperineally into the prostate have allowed efficient interstitial light delivery. These optical fibers allow laser exposure of the entire gland.

On the basis of these advances, a limited number of clinical trials using photodynamic therapy against human prostate cancer have been performed. Three have involved the use of photodynamic therapy against diseases in men who had local recurrence following external beam radiation. Traditional treatment options for these men include prostatectomy, ctyosurgery, ot further radiation. In these studies, photodynamic therapy was successfully delivered, produced little or no lasting incontinence or erectile dysfunction, induced necrosis in the tumors sites, and reduced PSA levels. In addition, at least one trail utilized photodynamic therapy as the initial treatment of organ-confined prostate cancer, in this trial, mTHPC was used, and it also induced necrosis, decreased PSA levels, and left patients with little incontinence and erectile dysfunction. Thus photodynamic therapy is a developing option for patients who choose a minimally invasive procedure. However, a major drawback of mTHPC as well as other currently known photo sensitizers is there poor selectivity for prostate tumor. Therefore a major goal for prostate cancer photodynamic therapy is to develop photosensitizing agents with tumor selectivity and more favorable tumor to non tumor tissue biodistribution.

Since photosensitize specific delivery, transport, and special distribution within tumor tissues are all affected by multiple physicochemical and biological factors, the development of strategies that allow active tumor targeting are essential for improving their biological efficacy. Several strategies have been investigated aimed at improving the selective delivery of Porphyrin sensitizers to tumor tissues; most of these involve the conjugation of photo sensitizers to carrier proteins, oligonuletides, monoclonal antibodies, and peptide sequences directed against antigens or ligands that are over expressed on cancer cells.

MATERIALS AND METHODS

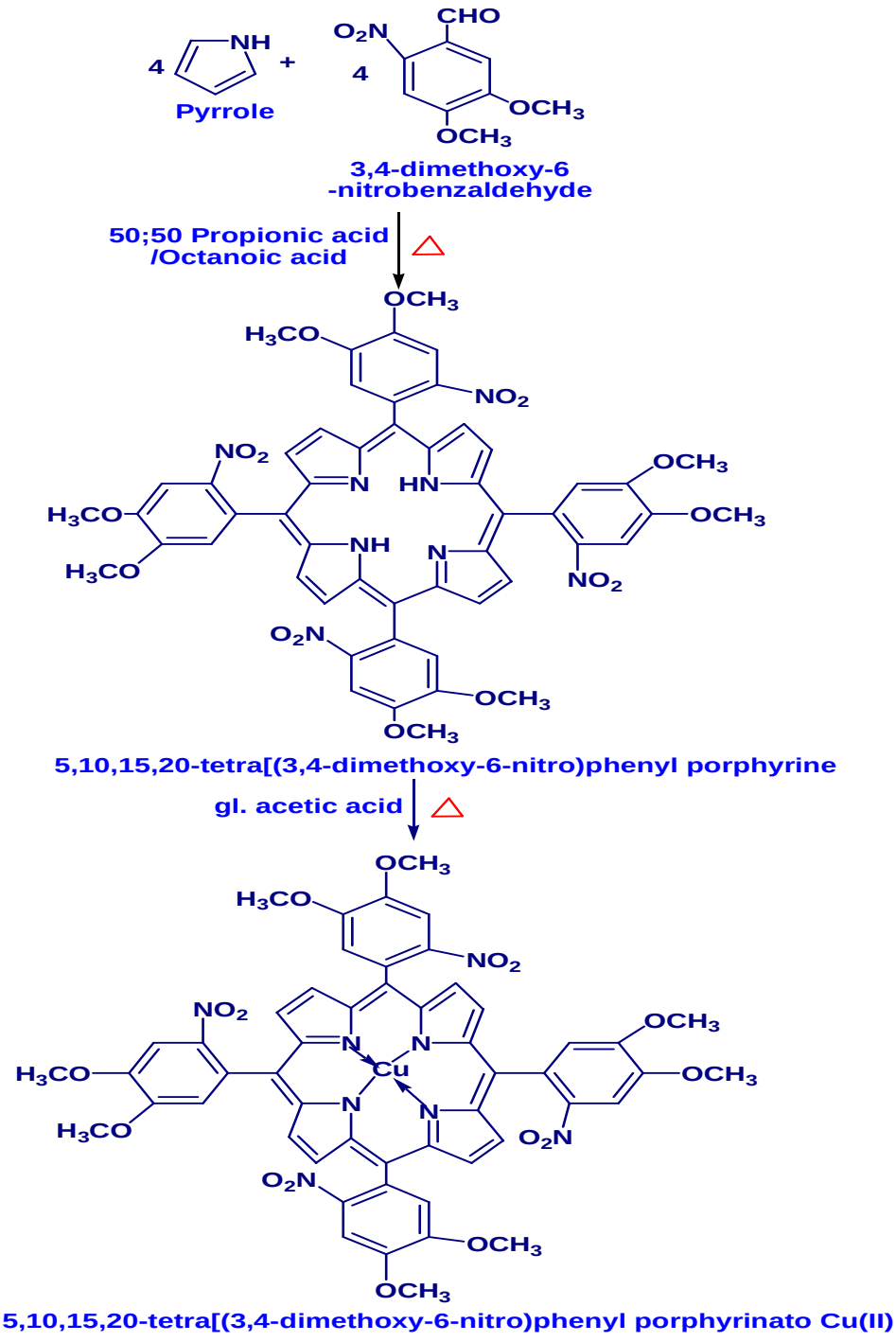
Pyrrole, cupric chloride, propionic acid, octanoic acid, used in the synthesis of 5,10,15,20-tetra[3,4-dimethoxy-6-nitrophenyl] porphyrin were purchased from Merck and used as received. 5,10,15,20-tetra[3,4-dimethoxy-6-nitrobenzaldehyde was prepared from literature method. Solvents used for synthesis were of AR grade. The spectroscopic grade chloroform was obtained from Aldrich Chemical Company and was used for electronic absorption ultraviolet UV-Vis absorption spectra for the base ligand was recorded on a (V –Pharmaspec1700, Shimadzu) UV-Vis absorption spectra for the metallated ligand complexes was recorded on a Jasco V-530.NMR spectra for the ligand was recorded on a Bruker AM360 or Bruker AM500 spectrometer at approximately 298K. The Nuclear Overhauser Effect(NOE) experiments were carried out at 313K on the Bruker AM500 spectrometer with $CDCl_3$ as the solvent. The chemical shifts are reported in parts per million (δ) with respect to an internal reference peak of residual unadulterated solvent (that is, 7.24 ppm for $CHCl_3$ in $CDCl_3$) or TMS.

Synthesis of 5,10,15,20-tetra[3,4-dimethoxy-6-nitrophenyl] porphyrin

A double necked 250 ml round bottomed flask fitted with a reflux condenser and a stirrer, was charged with octanoic acid(60ml) and propionic acid(60ml), to these solvent mixture, 5,10,15,20-tetra[3,4-dimethoxy-6-nitrobenzaldehyde(2.11gm , 0.01M) was added. This mixture was heated at 180°C with stirring when the 3,4-hydroxy-6-nitro benzaldehyde was dissolved the solution was slight yellow. To this solution, pyrrole(0.7Ml 0.01M) was added giving an amber

colored solution. This was brought to reflux, and kept at this temperature for 6 Hours. The reaction process was monitored by TLC. This solution was allowed to cool for 1 Hour and the electronic absorption spectrum was measured. After cooling, the solution was added to a 500 ml separatory funnel followed by chloroform (120 mL) and 1M $NaHCO_3$ (120 ml). The mixture was thoroughly sacked until the acids were neutralized. The solution was then left in the funnel overnight to allow complete separation of the two layers. The bottom layer containing the crude porphyrin was collected, evaporated to dryness and purified using column chromatography (dry silicagel, 70-230 mesh, eluent: 8:2 mixture of chloroform and methanol) to give 0.18 gm. The overall reaction yield was 9%. Spectral characterization data were shown in table.

Reaction Scheme (Graphical Presentation of Ligand-Metal complex)



Synthesis of 5,10,15,20- tetra [3,4-hydroxy-6-nitro phenyl]porphyrinato-copper(II)
A boiling mixture of 5,10,15,20-[(3,4-hydroxy-6-nitro)phenyl porphyrin (10.34gm, 0.01M) and hydrated cupric chloride (1.70gm, 0.01M)in 50 ml glacial acetic acid was refluxed for one hour. The solution was then transferred to separator funnel with chloroform. Water was then added to the separator funnel and the resulting chloroform layer was washed several times with water to completely remove the reaction solvents and inorganic salts. The chloroform layer was then dried over anhydrous sodium sulphate and after that it was evaporated to yield the final product which was dried in a vacuum desiccator.

RESULTS AND DISCUSSION

5,10,15,20-tetra[3,4-dimethoxy-6-nitro phenyl] porphyrin was prepared from pyrrole, 3,4-dimethoxy-6-nitro benzaldehyde and using a 50:50 mixture of propionic and octanoic acids as the solvent (Scheme 1). This solvent system was found by Lindsey and coworkers to work better than the normal acetic acid method used by Adler and many others in preparation of porphyrins[1,2]. Porphyrins are usually produced in low yields and our porphyrin was no exception. The overall yield of the reaction was 9%. The composition was verified by obtaining the exact mass using mass spectrometry. The measured mass, 1034.83 a.m.u., was in excellent agreement with the calculated value of newly prepared porphyrin was further characterized by ^{1}H-^{13}C-NMR and UV-Vis spectroscopy.

Nuclear Magnetic Resonance Spectroscopy
The sample was analyzed using ^{1}H-^{13}C-NMR. A ^{1}H-^{13}C-NMR correlation was done using a heteronuclear chemical shift correlation experiment In addition, a heteronuclear multiple bond correlation was done to locate the quaternary carbons of the compound. Nuclear Overhauser Effect (NOE) results were consistent with the proposed structure. ^{1}H-NMR studies of porphyrin reveal the aromatic nature of the porphyrin macrocycle. A diamagnetic ring current deshields protons outside the macrocycle from the external magnetic field. β-pyrrole and *meso* protons are included in this category of protons. The macrocycle is made up of two pyrrole units and two pyrrolenine units. The pyrrole units have an aromatic sextet of electrons. The pyrrolenine units have only five π electrons. To compensate for this shortage of π electrons in the pyrrolenine, an electron is pulled from the meso carbons. So, *meso* carbons have a tendency to be electron deficient and thus the meso protons are shifted further downfield than the β-protons. The same diamagnetic ring current that deshields the protons on the outside of the macrocycle shields the protons on the inside of the macrocycle from the external magnetic field. Thus, the N-H protons are shifted up field, even farther than the tetramethylsilane (TMS) peak[3].

The diamagnetic ring current of this porphyrin deshields the β-pyrrole protons of this porphyrin, thus, we expect to find the signal for this proton downfield of most of the other protons. Also, it is expected that it will appear as a singlet with integral of eight protons. Three singlets appear in the spectrum downfield: H_2 at 9.01 ppm. The integration of this peak gives 8-proton This assignments is consistent with the NOE data. The remaining singlet is at -2.75 ppm. Due to the shielding experienced by the N-H proton, H_1, it was expected that it would be shifted far upfield and thus it was assigned to this peak. The integration of this peak is two protons, which is consistent with this assignment. A summary of the ^{1}H-NMR for the chemical shift and multiplicities are given in table ^{13}C-NMR peaks were assigned from the corresponding spectrum, from data obtained in the ^{13}C-^{1}H correlation and from data of a heteronuclear multiple bond correlation. The ^{13}C assignments are given in Table 2.

Electronic absorption spectra of 5,10,15,20-tetra[3,4-dimethoxy-6-nitro phenyl] porphyrin.
The electronic absorption spectrum for synthesized porphyrin is similar to that of all porphyrins. There is an intense absorption at 419 nm the Soret band and Q bands are observed at 515, 550, 590, and 648 nm. A series of solutions were prepared of varying concentrations of porphyrin in $CHCl_3$. The concentrations ranged from 2.7 x 10^{-5} to 1.6 x 10^{-6}M. UV-vis spectra were taken for each of the solutions. The purpose of these experiments was to elucidate the extinction coefficient of the Soret band for the porphyrin as well as the different Q bands and to determine if Beer's Law was obeyed. This porphyrin displays an extinction coefficient of 3 x 10^5 $cm^{-1}M^{-1}$ for the Soret band at 419 nm. Four Q bands are observed at 515, 550, 590, and 648 nm with extinction coefficients given as 1 x 10^4 $cm^{-1}M^{-1}$, 6 x 10^3 $cm^{-1}M^{-1}$, 5 x 10^3 $cm^{-1}M^{-1}$, and 7 x 10^3 $cm^{-1}M^{-1}$, respectively.

FT-IR
In IR spectrum of [3,4-hydroxy-6-nitro phenyl]porphyrin, the IR bands at 3317.8 cm^{-1} and 968.3 cm^{-1} of ligand are due to the NH-stretching and banding vibration of the porphyrin core. But they disappear in the complex because the hydrogen atom in the NH-bonding is replaced by a cupric metal ion[4].

Molar conductivity of ligand and metal complexes were recorded using 1×10^{-3} M solution of DMF on Equiptronics Conductivity Meter EQ660A.The molar conductance measurements of the complex in DMF is 9.1 $\Omega^{-1}cm^2mol^{-1}$, indicating their non-ionic nature. The observed magnetic moments for the Cu(II) complex with ligand was 1.91 B.M., the value for one unpaired electron is theoretically 1.73 B.M. indicate distorted square-planer geometry. Ligand-Metal complex ratio is calculated by ESI mass, spectrophotometric analysis, and found to be identical as shown in scheme.

Table 1. Chemical shifts and multiplicities of protons on 5,10,15,20-tetra[3,4-dimethoxy-6-nitro phenyl] porphyrin in chloroform-*d*

Chloroform-d		
	Multiplicity	Chemical Shift (δppm)
H_1	s	-2.71
H_2	s	9.01
H_3	s	6.49
H_4	d	5.00
H_5	t	3.73
H_6	d	6.45
H_7	s	3.62

Table 2. Summary of ^{13}C-NMR assignments

Carbon	Peak(ppm)main data used in assigning peak
C-H_2	130.15 (^{13}C at318K)
meso-c	119.13
c-meso-c	144.05 (^{13}C)
C-H_3	124.71(^{13}C - ^{1}H Correlation)
C-H_4	130.81(^{13}C - ^{1}H Correlation)
C-H_5	126.28(^{13}C - ^{1}H Correlation)
C-H_6	120.12(^{13}C - ^{1}H Correlation)
C-H_7	114.12(^{13}C - ^{1}H Correlation)

CONCLUSION

In summary, we present the first report of the synthesis and characterization of [3,4-dimethoxy-6-nitro phenyl] porphyrin and it's metal complex with cupric ion. The result of the spectrophotometric analysis was in agreement with the proposed formulation. This ligand and it's metal complex are being studied further for usefulness in applications involving electron transfer.

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