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LABILE SYNTHESIS OF PORPHYRIN RING USING 2,6-BIS (OCTYLOXY)BENZALDEHYDE AND DIPYRROMETHANE

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Abstract

Despite the widespread attraction of porphyrins, it has not been utilized to its full extent due to low yield syntheses and poor solubility. In this work, 5,15-bis(2,6-dioctoxyphenyl)porphyrin is synthesized with high yield by using dipyrromethane and 2,6-Bis(octyloxy)benzaldehyde, which has remarkable solubility in organic solvents. 2,6-Bis(octyloxy)benzaldehyde has been synthesized from resorcinol. The synthesis of dipyrromethane has presented a vexing challenge since the reactivity of pyrrole and aldehyde is very high, and it forms dipyrromethane as well as N-confused dipyrromethane and tripyrrane as byproducts. To reduce the formation of by-products, we brought into being the best catalyst and optimized the catalytic quantity to synthesize dipyrromethane with high yield.

Keywords: Porphyrin, 2,6-bis(octyloxy)benzaldehyde, Dipyrromethane, Resorcinol, Solubility

Introduction

Porphyrin($C_{20}H_{14}N_4$) is an aromatic compound, contains 18 π-electrons in its closed ring. When the hydrogen atoms on the large conjugated ring of the porphyrin are partially or totally substituted by other groups, the resulting imitative is porphyrin derivatives whose nitrogen atoms can be combined with metal ions to produce very stable organic complexes and metallo-porphyrins [Mehdi *et al*., 1976].

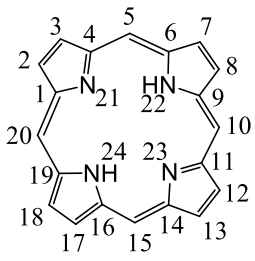

Fig. 1. Structure of porphyrin.

There are many natural porphyrins and their metal complexes, such as chlorophyll, heme, vitamin B-12, cytochrome P-450, catalase, and so on. The most prominent chemical

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activity of the porphyrin system is that it is easy to form a 1:1 complex with metal ions [Mehdi *et al.,* 1976]. Due to the special structure and properties of porphyrin compounds, it has a wide range of uses. Natural porphyrin compounds have many special physiological activities, and many of the functions of life processes are related to metallo-porphyrins [Imahori *et al.,* 2004]. Porphyrins also have many applications, some of which include chemistry, medicine, and biomimetic synthesis [Imahori *et al.,* 2004]. In principle, porphyrins can be used in all of these areas, and their improved synthesis has opened the doors for the potential synthesis of more complex systems with porphyrin building blocks [Uetomo *et al.,* 2011]. Likewise, the nano-world has discovered porphyrin and metallo-porphyrins, a first study investigated their surface structures [Chen *et al.,* 2016]. The true potential of porphyrins and their metal complexes is about growing. The synthesis of new porphyrin with high yield is the major issue now. Although there have been many advances in the synthesis of substituted porphyrins and porphyrin oligomers in recent years, the synthesis of the parent porphyrin, still troublesome for organic chemists [Neya *et al.,* 2006]. Low yields and expense, however, make the synthesis of porphyrin on a large scale impractical. Another challenge that synthetic chemists faced was the high insolubility of porphyrin [Nikiforov *et al.,* 2011]. This somewhat neglected compound should be an attractive target for chemists as its eight *β*-pyrrole and four *meso* positions, both with different reactivity profiles, offer the possibility to further elaborate porphyrins [Vicente *et al.,* 2014]. Lindsey reported the synthesis of porphyrin upon addition of pyrrole in methanol to formaldehyde in methanol and pyridine under a nitrogen atmosphere; however, the yield was very low [Lindsey *et al.,* 1987]. The desire to improve these yields has troubled the chemists over the next couple of years. Steffan Krol improved the yield for the synthesis of porphyrin with a novel one-step synthetic method in which he recovered 5% of the target material [Senge *et al.,* 2010]. This was achieved by treating a dilute solution of 2-hydroxymethylpyrrole with potassium persulfate in glacial acetic acid. The next significant step in the development of a porphyrin synthesis was taken by Longo and Thorne who reported the synthesis of porphyrin again via condensation reaction [Adler *et al.,* 1964]. In general, the yields of porphyrins obtained by such methods are usually low.

In this work, we have synthesized 5,15-bis(2,6-dioctoxyphenyl)porphyrin using dipyrromethane and 2,6-bis(octyloxy)benzaldehyde with high yield which has remarkable solubility in organic solvents. We also found out the best catalyst and optimized the catalytic quantity for the reaction to acquire the remarkable yield. Dipyromethane has also been synthesized using the lowest ratio of pyrrole and paraformaldehyde using acetic acid as solvent as well as catalyst and it reduced the overall expenses of the synthesis.

Materials and Methods

1,3-bis(hydroxy)benzene and other necessary chemicals and reagents were purchased from Sigma-Aldrich and were used without further purification.

The UV-Vis absorption spectra of porphyrin ring were recorded using a Parkin-Elmer Lambda 40 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained from a VARIAN UNITY INOVA 400 instrument. MALDI-TOF Mass analysis was carried out employing an instrument (Voyager DE-STR, Applied Biosystems) in a reflector mode with a matrix of 3,5-dimethyl-4-hydroxytrans-cinnamic acid (sinapinic acid).

Synthesis of 1,3-bis(octyloxy)benzene (1).1,3-bis(hydroxy)benzene (2 g**,** 18.2 mmol) and *n*-bromooctane (10 mL, 60.6 mmol) were successively added to a stirred suspension of KOH (8 g, 142.5 mmol) in 32 mL of DMSO. The reaction was stirred overnight at RT and was then quenched with pouring into 50 mL of water. The product was extracted with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by recrystallization from MeOH/DCM to obtain the product 1 as white crystal (4.1 g, 80%).^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.15 (t, J = 8.4 Hz, 1H, Ar), 6.51 (s, 1H, Ar), 6.48 (d, J = 8.4 Hz, 2H, Ar), 3.95 (t, 4H, J = 6.4 Hz, 2×O-CH_2), 1.76 (m, 4H, 2×CH_2-C$\underline{H_2}$-CH_2), 1.44 (m, 4H, 2×CH_2-CH_2-C$\underline{H_2}$), 1.46-1.29 (m, 16H, 2×CH_2-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_2}$), 0.90 (t, J = 7.6 Hz, 6H, 2×CH_2-C$\underline{H_3}$).

Synthesis of 2,6-bis(octyloxy)benzaldehyde (2). A three neck flask was equipped with an additional funnel and charged with compound **1** (3 g, 10 mmol) and TMEDA (0.39 mL, 4.3 mmol) in 28 mL of THF. The solution was degassed with nitrogen for 15 min and cooled to 0 °C, and then mixed dropwise with 1.6 M *n*-butyllithium in hexane (7.46 mL, 12 mmol) over 20 min., and allowed to stir for 3 h. after warming to RT, DMF (1.46 mL, 20 mmol) was added drop-wise into the reaction mixture, which was stirred for an additional 2 h. The reaction was quenched with pouring into water, and the mixture was extracted with ether (3 × 80 mL), dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The product was recrystallized from hexane to yield a white solid (2.72 g, 75% yield). ^{1}H NMR ($CDCl_3$, 400 MHz):δ_H 10.47 (s, 1H, CHO), 7.31 (t, J = 8.4 Hz, 1H, Ar), 6.47 (d, J = 8.4 Hz, 2H, Ar), 3.95 (t, J = 6.4 Hz, 4H, 2×O-CH_2), 1.77-1.71 (m, 4H, 2×CH_2-C$\underline{H_2}$-CH_2), 1.39 (m, 4H, 2×CH_2-CH_2-C$\underline{H_2}$), 1.25-1.21 (m, 16H, 2×CH_2-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_2}$), 0.81 (t, J = 7.2 Hz, 6H, 2×CH_2-C$\underline{H_3}$).

Synthesis of dipyrromethane (3). Paraformaldehyde (0.6 g, 20 mmol) and pyrrole (15 mL, 500 mmol) were dissolved in a mixture of AcOH (150 mL) and MeOH (50 mL). The solution was stirred for 20 h at 25°C. Then the reaction mixture was washed with water (100 mL × 2) and aqueous KOH solution (0.1 M; 100 mL × 2). The product was purified by flash column chromatography as eluent of DCM to obtain the product 3 as dark green crystal in 35% yield (1.10 g). ^{1}H NMR ($CDCl_3$, 400 MHz):δ_H 7.9 (d, J = 8.4 Hz, 2H, Ar),

6.62 (d, *J* = 8.4 Hz, 2H, Ar), 6.01 (t, *J* = 8.4 Hz, 2H, Ar), 5.95 (d, *J* = 8.4 Hz, 2H, Ar), 3.90 (s, 2H, CH_2).

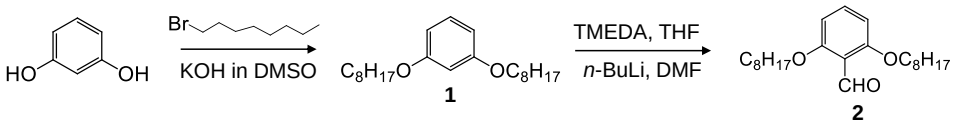
Synthesis of 5,15-bis(2,6-dioctoxyphenyl)porphyrin (4). To a degassed solution of dipyrromethane (0.5 g, 3.43 mmol) and 2,6-bis(octyloxy)benzaldehyde (1.24 g, 3.43 mmol) in DCM (500 ml) was added TFA (1 drop). The solution was stirred under nitrogen atmosphere at RT for 4 h, and charged with DDQ (1.17 g, 5.14 mmol). Then, the mixture was stirred for an additional 1 h. The mixture was basified with Et_3N (0.10 mL) and filtered through silica. After the solvent was removed under reduced pressure, the residue was purified by column chromatography using DCM/hexane (1/2) as eluent. The product was recrystallized from MeOH/DCM to give the product **4** (1.60 g, 50%) as a purple powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 10.13 (s, 2H, Ar), 9.26 (d, *J* = 4.8 Hz, 4H, Ar), 8.96 (d, *J* = 4.8 Hz, 4H, Ar), 7.71 (t, *J* = 8.4 Hz, 2H, Ar), 7.02 (d, *J* = 8.4 Hz, 4H, Ar) 3.83 (t, *J* = 6.4 Hz, 8H, 4×O-CH_2), 1.2 (m, 8H, 4×C$\underline{H_2}$-CH_2), 0.80-0.65 (m, 16H, 4×CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 0.51-0.30 (m, 36H, 4×CH_2-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_2}$-C$\underline{H_3}$), -3.12 (s, 2H, NH). MS (MALDI-TOF): *m/z* 975.89 [M^+]; $C_{64}H_{86}N_4O_4$ (975.39).

Results and Discussion

Fischer reported the first synthesis of porphyrin 1926 and subsequently prepared porphyrin in low yield by adding pyrrole-*α*-aldehyde to boiling formic acid [Vicente *et al.,* 2014]. In 1997 a new synthetic route for the synthesis of porphyrin was developed by Ellis and Langdale which involves acidified water and immiscible organic solvent, and the oxidation was carried out using DDQ, with the yield up to 13.6% [Senge *et al.,* 2010]. It was noted that, if the aqueous phase was eliminated, the yields of porphyrin dropped up to 50%. Evoking all the aforementioned consequences, we choose the long-chain aromatic aldehyde to make the soluble porphyrin to avoid the solubility issue. From the history of porphyrin syntheses, we recognize that pyrrole will not be a good candidate for porphyrin synthesis. We gave more priority to synthesize dipyrromethane, which reduce the cost and increase the yield of the porphyrin materials.

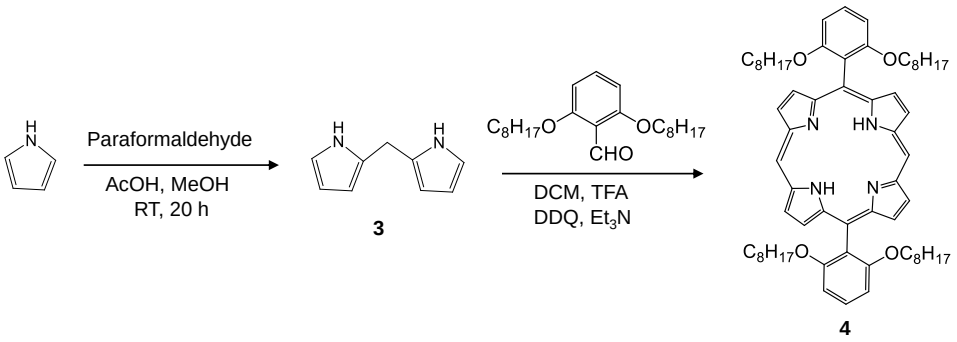
For aldehyde, resorcinol was starting material and performed alkylation reaction to extend the long alkyl chain (octyl) to increase the solubility in organic solvents. This alkylation reaction was performed in basic media with the help of KOH in DMSO solvent with high yield (Scheme 1). The product was purified by recrystallization, and the column chromatography was avoided. This purified alkylated resorcinol was used as a reactant for the next step formylation reaction. *n*-Butyllithium was used to substitute proton and lithiobenzene was produced as intermediate. TMEDA was used to increase the electrophilicity of Li ion. TMEDA has an affinity of lithium ions. When mixed with *n*-butyllithum, TMEDA's nitrogen atoms coordinate to the lithium, forming a cluster of higher reactivity than the tetramer or hexamer that *n*-butyllithium normally adopts. DMF was then added at room temperature to replace the Li ion and produce aldehyde group.

Therefore, the aldehyde precursor was prepared for porphyrin synthesis with long alkyl chain in an aromatic fragment, which is highly soluble in organic solvents (Scheme 1).



Scheme 1. Synthetic route to 2,6-bis(octyloxy)benzaldehyde.

Dipyrromethanes are of wide interest as building blocks in organic synthesis, namely, in the preparation of porphyrins and porphyrin analogues. Usually, pyrrole is used as a solvent of the reaction medium as well as a reactant for the synthesis of dipyrromethane. This excess pyrrole made the synthesis expensive. The yield of this reaction was very low due to poor solubility of paraformaldehyde in neat pyrrole. We tried to avoid to use excess pyrrole and also recovered the pyrrole remaining in the reaction system. Acetic acid and methanol were used as the solvent instead of pyrrole in addition pyrrole, and paraformaldehyde mole ratio was reduced to 25:1 from 40:1. After the completion of the reaction, residual pyrrole was collected by distillation using high vacuum at room temperature and reused for the next reaction. It is reported that TFA usually used as a catalyst for the formation of dipyrromethane. Excess TFA can form polymers/oligomers, which are very difficult to purify and unable to recover remaining pyrrole. It should be maintained to use precise volume of TFA. Even in some cases, it is unidentified to find out the reason for the low yield of the formation of dipyrromethane. However, in acetic acid medium, the synthesis of dipyrromethane is always provided a premeditated amount of product even in large scale reaction (Scheme 2). TFA in large scale reaction is always uncertain about acquiring the premeditated yield.



Scheme 2. Synthetic route to 5,15-bis(2,6-dioctoxyphenyl)porphyrin.

In this reaction, to remove the dissolved oxygen, the solvent was degassed by nitrogen after adding all reagents. Dissolved oxygen can influence the oxidative polymerization of dipyrromethane, which can reduce the yield of macrocyclic porphyrins. Catalytic TFA has an important role in increasing the yield of cyclic porphyrin. Excess TFA will support

to form oligomers among dipyrromethanes. One drop of trifluoroacetic acid is sufficient to run the reaction and acquire the highest yield of porphyrin. After adding the acid, reaction time is very substantial to increase the yield. The reaction should be quenched after 4 hours. Considering all the above conditions, we achieved a 50% yield of cyclic porphyrin, which is the highest ever (Scheme 2). After the formation of the ring, DDQ was added to oxidize the porphyrin ring to improve the conjugation which can absorb visible light from the sources.

To confirm the molecular structure of the porphyrin ring, ^{1}H NMR, MALDI-TOF and UV-Vis spectra were recorded. In NMR spectra, the peak at δ 10.13 is due to the two equivalent methine protons, which are the analogues of the aromatic protons in benzene. However, the porphyrin resonance occurs 2.7 ppm lower in the field than that benzene. The most remarkable feature of the spectrum is the line -3.12 ppm higher in the field than tetramethylsilane. So far as we are aware, no other proton resonance has been reported as such high field for organic compounds. It is assigned this line to the two N-H protons based on its intensity relative to other lines in the spectrum. This resonance line is about 13 ppm higher in the field than the N-H resonance in pyrrole. These unusual chemical shifts for the methine and N-H protons are common to several porphyrins [Lash *et al.,* 1998]. We believe that these shifts are largely attributable to the effect of "ring current" formed by the precession of π electrons about a closed conjugated path in the porphyrin ring.

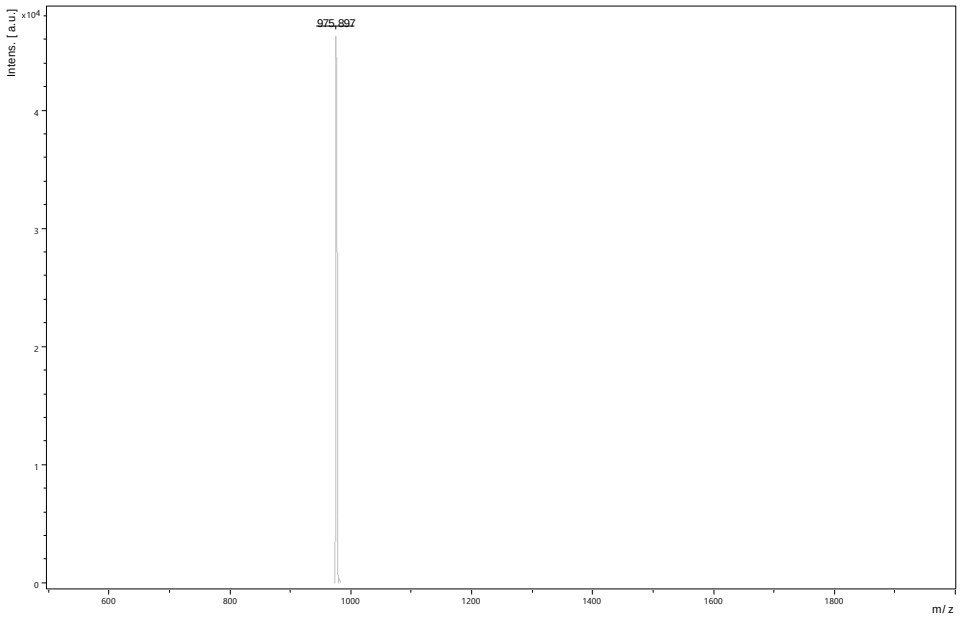


Fig. 2. MALDI-TOF Mass spectra of 5,15-bis(2,6-dioctoxyphenyl)porphyrin.

We also performed positive ion MALDI mass spectra of the porphyrin in the presence of matrix 3,5-dimethoxy-4-hydroxytrans-cinnamic acid (sinapinic acid) (Fig. 2). The studied

porphyrin yielded a peak corresponding to the ionized intact porphyrin. The spectrum is dominated by a single ion species corresponding to the porphyrin radical cation. It is of interest to note that, contributions from protonation of the porphyrin, $[M+H]^+$, appear relatively minor.

The porphyrin macrocycle is a highly conjugated molecule containing 22 π-electrons, but only 18 of them are delocalized according to the Huckel's rule of aromaticity (4n+2 delocalized π-electrons, where n = 4) [Nemykin *et al.*, 2010]. The absorption spectrum of porphyrins has long been understood in terms of the highly successful four-orbital (two highest occupied π orbitals and two lowest unoccupied π* orbitals) model first applied in 1959 by Martin Gouterman [Nemykin *et al.*, 2010].

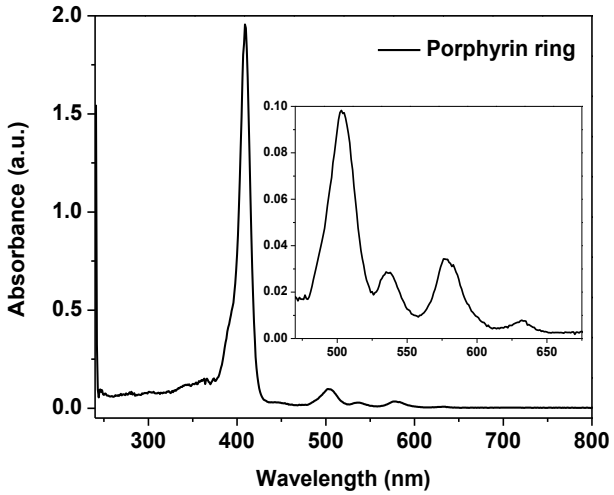


Fig. 3. Optical absorption spectra of 5,15-bis(2,6-dioctoxyphenyl)porphyrin. Inset: Magnification of the high wavelength region

In this spectra, electronic absorption of the porphyrin displays extreme intense bands, the so-called Soret or B-bands in the 370-430 nm range with molar extinction coefficients of 10^5 M^{-1} cm^{-1} (Fig. 3). Moreover, at longer wavelengths, in the 480-650 nm range, their spectra contain a set of weaker, but still considerably intense Q bands with molar extinction coefficients of 10^4 M^{-1} cm^{-1} (Fig. 3). Thus, their absorption bands significantly overlap with the emission spectrum of the solar radiation reaching the biosphere, resulting in efficient tools for conversion of radiation to chemical energy.

In this work, we have synthesized porphyrin molecule with high yield and low cost, which can provide the opportunity to use porphyrin molecules in practical aspects. Solubility was the main issue for porphyrin to make the device in any purpose. This highly soluble porphyrin can solve the difficulties of device fabrication and open the new doors for porphyrin molecules in device applications.

Conclusion

In conclusion, 5,15-bis(2,6-dioctoxyphenyl)porphyrin has been synthesized using dipyrromethane and 2,6-bis(octyloxy)benzaldehyde. The synthesized porphyrin has remarkable solubility in organic solvents. Dipyrromethane has also been synthesized with low cost, which reduces the overall expense of porphyrin synthesis. The final product was identified by ^{1}H NMR and MALDI-TOF mass spectrometry. The most remarkable feature of the spectrum is the line -3.12 ppm higher in the field than tetramethylsilane. The MALDI-TOF mass spectra of porphyrin shown the molecular ion peak at 975.89. The UV-Vis absorption spectra show the identical absorption peaks for the porphyrin molecule.

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