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Further insight into aryl nitration of tetraphenylporphyrin

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ABSTRACT

We report an in-depth study on *meso*-aryl nitration of tetraphenylporphyrin. In contrast to previous studies, new evidence reveals that tetrakis(*p*-nitrophenyl) derivative can be obtained as a major product. Successful isolation of the barely soluble product toward a remarkable yield of nearly 90% has been reached by means of a solid phase extraction technique. Distribution of different nitro-porphyrin components is reassessed with respect to varying acid content in the reactions. An *ortho*-effect model is proposed to describe the formation mechanism.

1. Introduction

Porphyrin functionalization has long been of great interest in the chemistry community because of the vast potentials and demands for porphyrin derivatives in diverse fields, such as materials,[1] supramolecular chemistry,[2] and biomimetic models.[3] Particularly, aryl nitration of *meso*-tetraphenylporphyrin (abbreviated as **H_2TPP**) has been attractive since **H_2TPP** is commercially available and the diversity of nitro-group substitution consents to a great synthetic scaffold for sophisticated porphyrin arrays.[4] In comparison with the Rothemund synthesis and its cross-condensation modifications,[5,6] the nitration route often brings about superior yields of the targeted porphyrin products.

As early as more than 20 years ago, Kruper and co-workers realized a simple process to afford a series of highly substituted derivatives based upon electrophilic aromatic substitution of **H_2TPP** using red fuming nitric acid (Scheme 1).[7] This approach was found valid for mono-, di-, and tri-substituted species (**1**–**4**), but none of the anticipated tetra-derivative (**5**) was observed even at larger excesses of nitrating agent being used. Meng et al. later studied the effect of time on the similar nitration reactions and revealed that a trace quantity of **5** (~2% yield with impurities) can be obtained while the reaction time was extended to 2 days.[8] However, further prolonging the reaction time ended up with failure only. The absence or a very low level of **5** observed in the reactions was usually understood as a result of macrocyclic degradation.[4a,7–9] Recently, a modified process having an improved yield of **2** was described by Ostrowski and Lopuszynska using yellow fuming nitric acid, but still no **5** can be detected.[4a] Is it the truth that the nitration reactions of **H_2TPP** using nitric acid restrict the formations to **1**–**4** only? In this paper, we report an in-depth study aimed at providing more information on the nitration process as well as on the characterization of **5**. New evidence shows that **5** can be formed readily during the reactions. Under proper control of the reactions, critical degradation can be avoided and a remarkable product yield of nearly 90% can be achieved by means of a solid phase extraction technique. Distribution of different nitro-porphyrin components is consequently reassessed with respect to varying acid content in the reactions.

2. Results and discussion

To gain an insight into the case, we simulated a similar nitration experiment on **H_2TPP** according to the above reference.[7] We successfully isolated pure **1**–**4** from the crude products by using column chromatography following standard procedures. However, when adding a large quantity of fuming nitric acid to the reaction, the overall yield of the isolated products went down dramatically.

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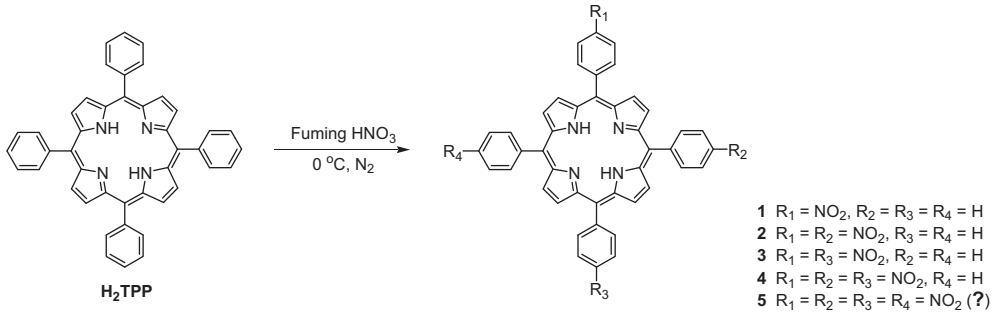

Scheme 1. *meso*-Aryl nitration of **H_2TPP**.

A large amount of dark red insoluble matter was found on the top of the column instead. Is it really caused by the macrocyclic degradation? In order to clear the obscurity, we endeavored to purify and characterize the unknown compound in detail. Through repetitive elution, a poorly soluble product can be finally extracted and purified. Our initial attempt of characterization was made on using FAB-mass spectrometry, but unfortunately, there were no obvious identifiable peaks in its spectrum (Fig. S1 in Supplementary data). Although FAB-mass spectrometry was unable to identify the compound, its mass characterization can be realized with the assistance by MALDI-TOF high resolution mass spectrometry. Surprisingly, as shown in Fig. 1, a $[M+H]^+$ ion peak at m/z 795.463 is observed in its spectrum, being a good indicator for the presence of **5** or its isomers (NO_2 group(s) located at the porphyrin β-pyrrolic position(s)) when compared to the calculated value (m/z 794.1868) of the M^+ ion ($C_{44}H_{26}N_8O_8$). Metallo-**H_2TPP**s under minimal effect of relatively electroneutral metal ions would be nitrated specifically on the *meso*-position instead of on the β-position.[10] It is therefore highly foreseeable that metal-free **H_2TPP** holds a similar feature that the predominant *meso*-nitration would afford the corresponding nitro-product, **5**, solely. In an attempt to collect more Supplementary data, the compound was subjected to ^{1}H NMR measurement after dissolved in deuterochloroform. Since the compound was just sparingly soluble, we failed to receive any characteristic resonance signals from a normal dissolution sample (only solvent peaks can be identified from the spectrum). However, by bringing the solution to saturation with mild warming, a resolved ^{1}H NMR spectrum can be successfully granted. As shown in Fig. 2A, although the still very low concentration solution gives rise to a strong carbon satellite effect, all the peaks in concern in the spectrum can be nicely

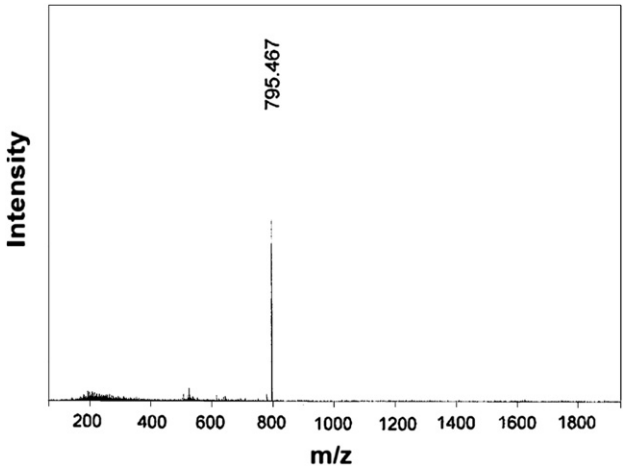

Fig. 1. HRMS spectrum of the insolubles (**5**) prepared from nitration of **H_2TPP**.

assigned in accord with the theoretical chemical shift values of **5**. For example, the protons on the pyrrole rings resonates at 8.83 ppm; the presence of NO_2 group attached to the phenyl ring contributes strongly to deshielding effect of the proton nuclei, resulting in resonating at higher δ values, namely ~8.4 and ~8.7 ppm (protons *meta* and *ortho* to NO_2 group, respectively). Integrating the areas of the resonance peaks also suggests a correct macrocyclic structure of **5** that their peak ratios are in agreement with the molecular structure of its each component. The characterization information unambiguously allows us to identify the compound clearer. In addition to the commonplaces for its structural determination, its UV–vis and fluorescence spectra were measured as well for supplementary reference (Figs. S2 and S3 in Supplementary data). The results seem to provide the first evidence that a significant yield of **5** may be harvested from the fundamental nitration reaction of **H_2TPP** using red fuming nitric acid.

For assuring the validity of our results, we had a comparison of the characterization data with the reported information, e.g., the NMR records, available from the condensation mode. Unexpectedly, the NMR readings in this study were found only agreeable partially with the published data.[11] What is wrong? Did our characterization get into mistakes due to the poor solubility of the compound? To further make it clear, an additional investigation was carried out. We synthesized **5** through a typical condensation method[12] and compared it side-by-side with the nitrated compound. From its NMR spectrum (saturated in $CDCl_3$) shown in Fig. 2B, we are able to identify the same structural features as those observed in the nitration case. When doing an A and B comparison, a duplicate spectrum is revealed with all the chemical shift data in line with each other. We can see that the two products originating from the different routes appear the same as each other, which is also evidenced by the MALDI-TOF MS analysis done (Fig. S4 in Supplementary data). A second characterization support toward **5** can be established by converting the NO_2 groups, if there exist, to NH_2 groups. Herein, under standard $SnCl_2$/HCl conditions,[13] we successfully received the expected corresponding aminoporphyrin, tetra(aminophenyl)porphyrin (**H_2TAPP**). As revealed in Fig. 3, the reduced compounds come up with completely resolved ^{1}H NMR spectra in deutero DMSO, which both look indistinguishable to each other. The resonance peaks consent to the molecular structure of **H_2TAPP**, e.g., the protons of its amine (NH_2) and aromatic groups at δ ~5.6, ~7.0, ~7.9, and ~8.9 ppm, respectively. Furthermore, FAB-mass characterization (Fig. S5 in Supplementary data) divulged an equivalent protonated molecular ion peak ($[M+H]^+$) at m/z ~675.0 in each of the spectra, signifying probably the presence of **H_2TAPP** (calcd M^+ of **H_2TAPP**=m/z 674.3) in each sample. Such data offer consistent evidence in support of the characteristics of **5** seen in our preceding work.

It becomes clear that product **5** is present observably in the nitration process of **H_2TPP**, however to what extent of the nitration occurs? What is the product yield? Due to the poor solubility of **5**,

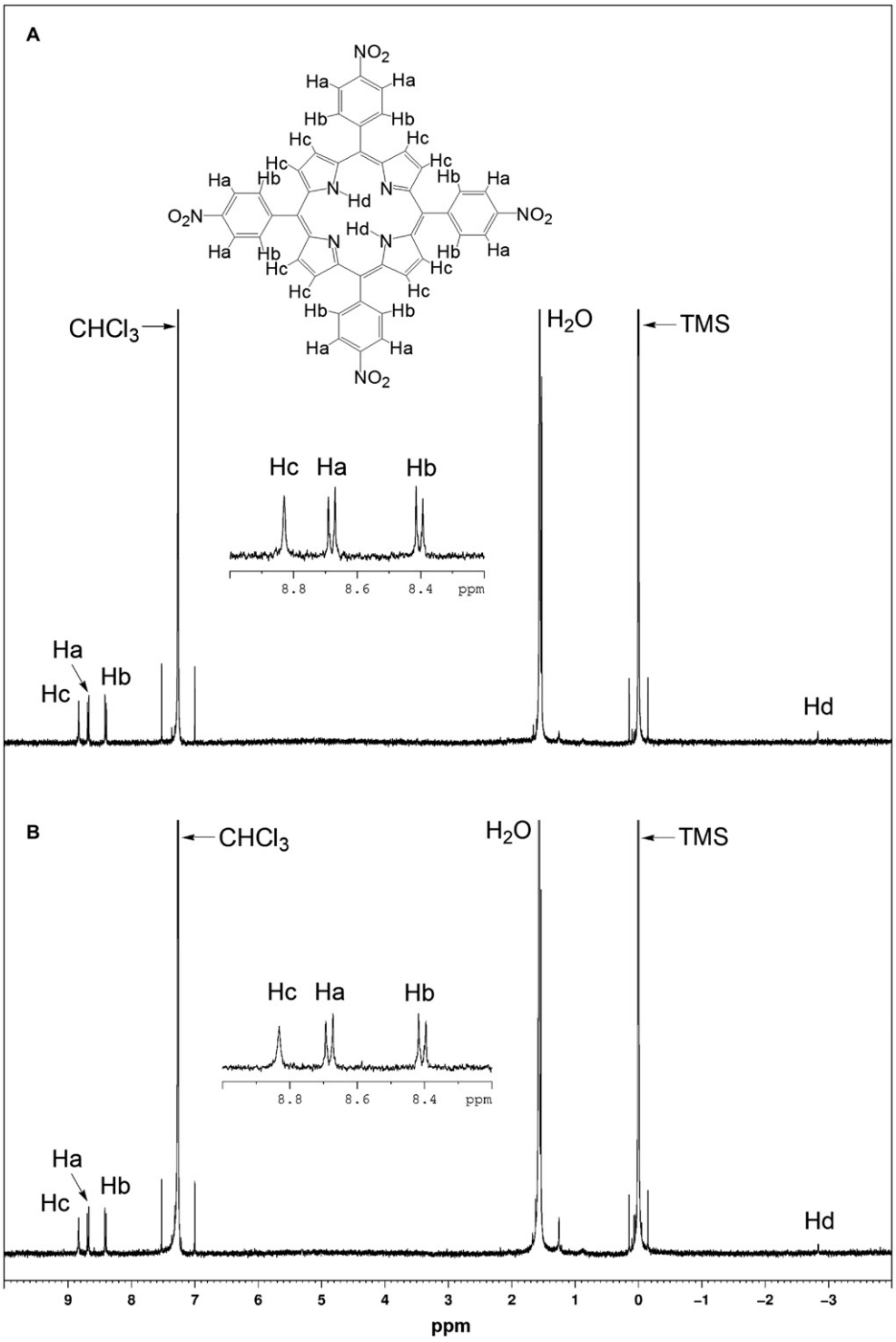

Fig. 2. ^{1}H NMR spectrum of **5** prepared via (A) a nitration reaction and (B) a condensation reaction, respectively, in $CDCl_3$. Chemical shifts δ ~7.0 and ~7.5 were attributed to $CHCl_3$ carbon satellite. The shifts near 0 were due to TMS carbon satellite.

our prior purification procedure requires tedious chromatographic elution that makes its large scale synthesis almost unfeasible. The traditional method by means of Soxhlet apparatus or recrystallization seems not effective too.[13,14] We thus adopted a special method to realize a large-scale synthesis, in which silica gel was employed as a substrate to retain the product upon a chromatographic separation and subsequently removed to release the pure product back (see Experimental section for detail). Through this efficient method, high yield and high purity product can be realized along with low solvent consumption. We did a series of studies concerning the effect of varying the acid content and found that the yield of **5** can be as high as 88% in the reaction. The detailed results are given in Table 1.

Studies on the distribution of different nitro-porphyrin components show us more interesting results (Table 1). When less fuming nitric acid is added to the **H_2TPP** solution, mono-substitution is always dominant. However, when acid content increases, there is a shift from mono- to tetra-nitrated product except

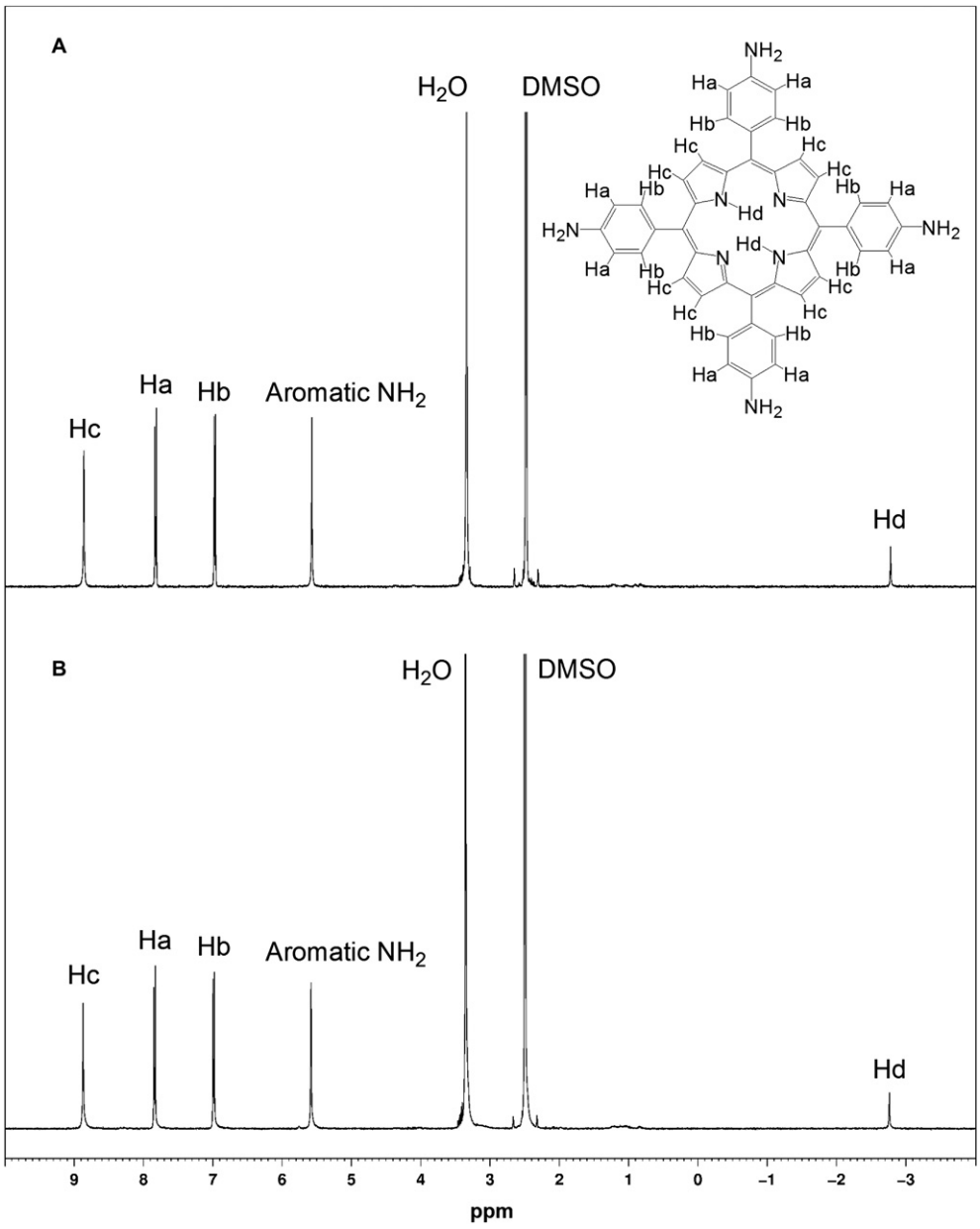

Fig. 3. ^{1}H NMR spectra of the reduced products originating from (A) condensation and (B) nitration, respectively, in DMSO-d_6.

Table 1
A series of ratios (acid to **H_2TPP**) was experienced

Equiv of fuming nitric acid	Yield[a] (%)			
	1	**2** & **3**[b]	**4**	**5**
17	53	5	0	Trace
22	50	8	3	Trace
29	0	28	7	60
35	0	2	2	87
40	0	0	Trace	88

[a] Percentage isolatable yield after silica gel chromatography.
[b] Di-nitrated part contains both the cis and trans isomers, and the cis isomer dominates in all the cases.

4 being hard to be formed all the time. After adding a large amount of acid, tetra-substitution does prevail in the process. The stepwise nitration reaction seems to be following some rules. When **H_2TPP** is mono-nitrated, further nitration does not occur fairly on other phenyl groups until the acid content is high enough. The neighboring phenyl rings would be more susceptible to electrophilic nitration than the opposite one, leading to more cis isomer available. It is believed that the *ortho*-effect plays an important role in the reaction mechanism, thus determining the formation of each species. When the di-nitro species (either cis or trans) is further reacted, this effect aids strongly toward a tetra-substituted product. It is then supportive to explain why the tri-nitrated product is always noble under all the reaction conditions and how the major products could be formed. A diagram about the proposed mechanism is illustrated in Fig. 4. The dashed arrows indicate relatively difficult routes to proceed.

Without question, porphyrin degradation is always of a concern in any porphyrin synthesis, although the relevant studies were seldom reported so far.[15] The overall yield of the nitration reaction could not reach 100% and it might be truly due to this problem especially in consideration of the greater reactivity of porphyrin macrocycle compared with phenyl.[16] In the above experiment, TLC analysis on certain raw products showed some other colored spots,

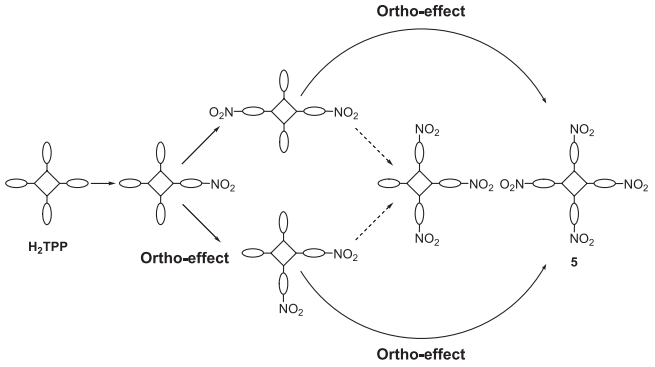

Fig. 4. Proposed reaction mechanism.

which may stand for such impurities from oxidative degradation. Because of this, we have probed the change of the reaction with relation to some extreme conditions. For example, we added a bit largely excess of fuming nitric acid to a chloroform solution of **H_2TPP** at room temperature and observed that the dark red solution gradually turned into clearly light red. Its UV–vis spectrum exhibited no typical Soret band absorption at all, suggesting a result of degradation of the porphyrin macrocycle. It was realized that only in an ice-bath under an inert atmosphere was the aryl nitration of **H_2TPP** largely controlled.

3. Conclusion

Synthetic approaches to functionalized porphyrins based on condensation (e.g., Rothemund and Lindsey's) are usually multi-step processes.[5,6,12] On the contrary, nitration of tetra-arylporphyrins leading to highly substituted derivatives is of great importance particularly in view of its simplicity, yield, and well regiospecific control. In this paper, we have made a further insight into a very important nitration process of **H_2TPP** toward a series of useful nitroporphyrin compounds. We confirmed that the tetra-substituted derivative is in fact a major product rather than being degraded in the process. The porphyrin product can be isolated with a remarkable yield of nearly 90% based on an unusual separation technique (practical for its large scale production). Because of its low solubility, previous characterizations were usually vague. In this work, a substantial characterization of both the nitration and condensation products was presented and evaluated. The proposed *ortho*-effect model can be used to interpret the progress of the nitration reaction reasonably. More detailed mechanism study is now underway.

4. Experimental section

4.1. General

Chloroform was pre-washed with water to remove trace amount of ethanol stabilizer, dried with magnesium sulfate and then distilled over calcium hydride. Pyrrole was freshly distilled from calcium hydride before use. Tetraphenylporphyrin (**H_2TPP**) was prepared according to standard procedures. Other starting materials were used as received. ^{1}H NMR spectra were recorded on a Bruker Avance DRX-400 NMR spectrometer in deuterated solvents. Tetramethylsilane (TMS) and the protic residues of the solvents were used as internal references for the NMR analyses. Low-resolution mass spectra (LR-MS) were recorded on a Finnigan MAT SSQ-710 mass spectrometer, in positive-ion mode, where *m*-nitrobenzyl alcohol was chosen as the matrix. High-resolution mass spectra (HR-MS) were recorded on a Bruker Biflex III matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer, in *m*/*z*. UV–vis Spectra were recorded on a OLIS Cary 300 spectrophotometer. Fluorescence spectra were recorded on a Jasco FP-6300 spectrometer.

4.2. Synthetic procedures and analytical data

*4.2.1. Synthesis of 5,10,15,20-tetrakis(4-nitrophenyl)-21H,23H-porphyrin (**5**).*

4.2.1.1. Via nitration method. A typical experimental procedure (e.g., **H_2TPP**/fuming nitric acid=1:35) is given below. Under an argon atmosphere, red fuming HNO_3 (2.4 mL, 56.7 mmol,) was added dropwise over a period of 20 min at 0 °C to a 150 mL chloroform solution of **H_2TPP** (1.0 g, 1.62 mmol). The reaction was kept for 30 min and then quenched with an aqueous ammonia solution slowly. The organic layer was extracted and evaporated to dryness under reduced pressure. The residual brown powder was washed with boiling water and then subjected to a column separation process. In the process, the powder was first absorbed onto silica gel followed by an elution with ethyl acetate. The remained dark red band was collected and added into a KOH solution (5% w/v, molar ratio of KOH to silica gel is 2) to remove silica gel. Centrifugation along with repetitive washing with D. I. water afforded the pure product in 87% yield (1.12 g). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.83 (s, 8H, pyrrole alkene protons), 8.68 (d, J=8.0 Hz, 8H, protons *ortho* to NO_2), 8.40 (d, J=8.0 Hz, 8H, protons *meta* to NO_2), −2.83 (s, 2H, protons inside porphyrin macrocycle). LR-MS (FAB, *m*/*z*): calcd M^+: 794.2; found: no obvious identifiable peak. MALDI-TOF (*m*/*z*): calcd M^+: 794.1868; found $[M+H]^+$: 795.467. UV–vis ($CHCl_3$, at saturated concentration, λ_{max}, nm): 424, 517, 552, 591, 647. Fluorescence ($CHCl_3$, at saturated concentration, nm): λ_{ex} 424, λ_{em} 652.

4.2.1.2. Via condensation of 4-nitrobenzaldehyde and pyrrole. The synthesis was based on the condensation of nitrobenzaldehyde with pyrrole according to the method described in the literature.[12] The product yield was ~4%. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.83 (s, 8H, pyrrole alkene protons), 8.68 (d, J=8.0 Hz, 8H, protons *ortho* to NO_2), 8.41(d, J=8.0 Hz, 8H, protons *meta* to NO_2), −2.84 (s, 2H, protons inside porphyrin macrocycle). LR-MS (FAB, *m*/*z*): calcd M^+ 794.2; found: no identifiable peak. MALDI-TOF (*m*/*z*): calcd M^+: 794.1868; found $[M+H]^+$: 795.1970. UV–vis ($CHCl_3$, at saturated concentration, λ_{max}, nm): 425, 518, 552, 593, 648. Fluorescence ($CHCl_3$, at saturated concentration, nm): λ_{ex} 424, λ_{em} 651.

*4.2.2. Synthesis of 5,10,15,20-tetrakis(4-aminophenyl)-21H,23H-porphyrin (H_2TAPP) via reduction of **5**.* The synthesis followed published procedures.[13] Here, we report its ^{1}H NMR and FAB-mass characterization data only.

4.2.2.1. From nitration method. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 8.88(s, 8H, pyrrole alkene protons), 7.84(d, 8H, J=5.1 Hz, protons *ortho* to NH_2 groups), 7.00(d, 8H, J=5.1 Hz, protons *meta* to NH_2 groups), 5.56 (s, 8H, anilinic protons), −2.74(s, 2H, protons inside porphyrin macrocycle). LR-MS (FAB, *m*-nitrobenzyl alcohol, *m*/*z*): calcd M^+: 674.3; found $[M+H]^+$: 675.0.

4.2.2.2. From condensation method. ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 8.88 (s, 8H, pyrrole alkene protons), 7.85 (d, 8H, J=5.1 Hz, protons *ortho* to NH_2 groups), 7.00 (d, 8H, J=5.1 Hz, protons *meta* to NH_2 groups), 5.56 (s, 8H, anilinic protons), −2.74(s, 2H, protons inside porphyrin macrocycle). LR-MS (FAB, *m*-nitrobenzyl alcohol, *m*/*z*): calcd M^+: 674.3; found $[M+H]^+$: 675.1.

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Supplementary data

Copies of other mass spectra of compound **5** obtained from typical nitration and condensation methods and its reduced products are available. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.06.031.

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