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Facile Purification of *meso*−Tetra(pyridyl)porphyrins and Detection of Unreacted Porphyrin upon Metallation of *meso*−Tetra(aryl)porphyrins

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In this study, different basicity of the pyridyl substituents of meso-tetra(pyridyl)porphyrins and the substituents of the common impurities associated with the synthesis of the porphyrins has been utilized to improve and simplify the purification of these porphyrins. Also, diprotonation of meso-tetraarylporphyrins with weak or strong acids and the associated shifts of the Soret and Q(0,0) bands have been used for the spectrophotometric detection of trace to substantial amounts of unreacted porphyrin upon complexation of porphyrins with iron and manganese.

Keywords: *meso*-Tetra(pyridyl)porphyrins, purification method, metallation of porphyrins, protonation, basicity.

Introduction

Since the first synthesis of *meso*-tetraphenylporphyrin (H_2TPP) by Rothemund in 1936, efforts have been devoted to improve the synthesis and purification of H_2TPP and other porphyrins with different substituents at the *meso*- and *β*-positions.[1-6] The low yield of porphyrin formation by different synthesis methods and the presence of many impurities in the product necessitate the development of new methods of purification in addition to the common traditional methods using column chromatography over silica gel and alumina.[7,8] On the other hand, metallation of porphyrins with metals such as iron or manganese is usually performed using excess amounts of metal salts to ensure the completion of reaction. Also, UV-vis spectroscopy is used to follow the progress of reaction and accordingly the successive addition of metal salt is continued until the disappearance of the Soret band due to the free base porphyrin at *ca*. 418 nm.[9] However, the method cannot be used effectively to monitor the progress and completion of the reaction in the case of iron porphyrins due to the little shifts observed in the Soret band of different porphyrins upon complexation with iron. [10,11] Also, in the UV-vis spectra of Mn porphyrins there are some absorption bands[12-15] around the characteristic Soret band of the free base porphyrin so that the presence of small

amounts of free base porphyrin cannot be detected using the electronic spectra. The presence of undetected porphyrin impurity can lead to the deviation of elemental analysis results from the calculated ones for metalloporphyrins.

Previously we have reported the protonation of *meso*-tetraalkylporphyrins, *meso*-tetraarylporphyrins and *meso*-tetra(4-SO$_3$phenyl)porphyrin with weak and strong protic acids in different solvents.[16,17] The aim of the present work is to show the application of porphyrins protonated species in the development of new purification methods for *meso*-tetra(pyridyl)porphyrins (Figure 1). Also, the UV-vis spectra of partially or fully protonated porphyrins have been shown to be very useful in easy detection of unreacted porphyrin upon the metallation of different porphyrins especially in the case of iron porphyrins due to the nearly superimposed UV-vis spectra of the free base porphyrin and the iron complex in the Soret band region.

Experimental

meso-Tetra(2-pyridyl)porphyrin, $H_2T(2-Py)P$, *meso*-tetra(3-pyridyl)porphyrin, $H_2T(3-Py)P$, *meso*-tetra(4-pyridyl)porphyrin, $H_2T(4-Py)P$, have been prepared according to the literature methods[18,19] with modifications in the purification procedure described in this paper.

In a typical reaction, 3.76 ml (0.04 mol) of 4-pyridylcarboxaldehyde and 2.8 ml (0.04 mol) of freshly distilled pyrrole were added to a flask containing 150 ml of propionic acid under reflux conditions. After *ca*. 30 min, the flask was cooled to room temperature, distilled water (150 ml) was added to the reaction mixture and the product was extracted using 150 ml of dichloromethane (*vide infra*). The p*H* of aqueous solution was in the range of 2.5-3.

^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 MHz spectrometer. The absorption spectra were recorded on a Pharmacia Biotech Ultrospec 4000 UV-vis spectrophotometer.

The spectral data of *meso*-tetrapyridylporphyrins are as follows:

H$_2$T(2-Py)P. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: -2.83 (2H, br, s, NH), 8.20-8.22 (4 *m*-H, adjacent to heteroatom, m), 8.08-8.12
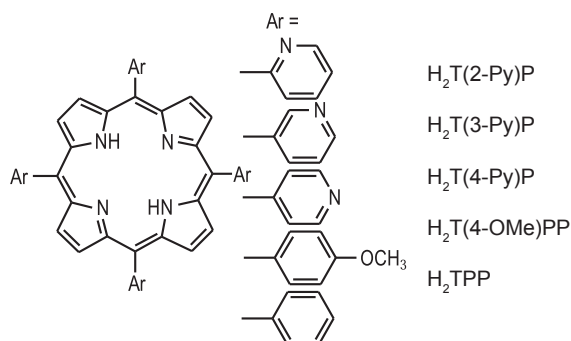

Figure 1. *meso*-Tetraarylporphyrins.

Purification and Metallation of *meso*-Tetra(aryl)porphyrins

(4 *m*-H, m), 9.13-9.15 (4 *o*-H, dd), 7.70-7.74 (4 *p*-H, qn), 8.87 (8H$_\beta$, s). UV-vis (CH$_2$Cl$_2$) λ nm: 417 (Soret), 512, 545, 586, 642.

H$_2$T(3-Py)P. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: -2.83 (2H, br, s, NH), 7.77-7.80 (4H$_m$, dd), 9.46 (4 *o*-H, br, s), 8.52-8.54 (4 *o*-H, br, d), 9.07-9.08 (4 *p*-H, dd), 8.87 (8H$_\beta$, s). UV-vis (CH$_2$Cl$_2$) λ nm: 418 (Soret), 512, 547, 588, 646.

H$_2$T(4-Py)P. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: -2.93 (2H, br, s, NH), 8.15-8.17 (8 *m*-H, dd), 9.06-9.07 (8 *o*-H, dd), 8.87 (8H$_\beta$, s). UV-vis (CH$_2$Cl$_2$) λ nm: 418 (Soret), 512, 547, 588, 646.

H$_2$T(4-OMe)P and H$_2$TPP were prepared according to the literature methods.[6,20]

H$_2$T(4-OMe)P. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: -2.80 (2H, br, s, NH), 4.05 (H$_{methyl}$, s), 7.27-7.31 (4H$_m$ m), 8.21-8.14 (4 *o*-H, m), 8.86 (8H$_\beta$, s). UV-vis (CH$_2$Cl$_2$) λ nm: 417 (Soret), 422, 519, 556, 593, 650.

H$_2$TPP. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: -2.77 (2H, br, s, NH), 7.75-7.77 (12 *m*,*p*-H, m), 8.21-8.24 (4 *o*-H, m), 8.84 (8H$_\beta$, s), UV-vis (CH$_2$Cl$_2$) λ nm: 417 (Soret), 417, 514, 548, 589, 647.

The method of Adler *et al.* has been used to prepare Mn^{III} complexes.[9] The Fe^{III} complexes were prepared using the literature procedure.[10] UV-vis (CH$_2$Cl$_2$) λ nm:

MnTPP(OAc): 382, 406, 477 (λ$_{max}$.), 535, 584, 620.
MnT(4-OMe)PP(OAc): 378, 403, 480 (λ$_{max}$.), 534, 586, 624.
FeTPP(OAc): 371, 414 (λ$_{max}$.), 506, 570, 653, 682.

Results and Discussion

Purification of *meso*-tetra(pyridyl)porphyrins is usually carried out by evaporation of the solvent (acetic- or propionic acid) and washing the solids with a dimethylformamide/ ethanol 1:1 mixture followed by column chromatography over silica gel.[18,19] We have prepared different *meso*-tetra(pyridyl)porphyrins in acetic- or propionic acids under the reflux condition. At the end of reaction, dichloromethane was added to the solution and the reaction mixture was shaken with distilled water. Many impurities were removed from the organic phase and a dark aqueous solution remained. The violet-colored organic phase in the first washing step indicated the selective extraction of *meso*-tetra(pyridyl)porphyrin into dichloromethane which has been checked by UV-vis spectroscopy. While washing with alkaline water (NaOH, 0.05 M) has been used as a step of purification of *meso*-tetraalkylporphyrin by Neya *et al.*,[21] using the alkaline solution in the case of *meso*-tetra(pyridyl) porphyrins, leads to the transfer of most of the impurities into the dichloromethane phase. Common impurities formed in the synthetic steps of porphyrins are porphyrinogens, dipyrromethanes, polypyrromethanes, porphodimethene and chlorins (Figure 2).[7,22,23]

Pyrrole is a very weak base. The pK_a value of protonated pyrrole is 0.4.[24] Accordingly the pyrrole nitrogen is essentially nonbasic. Core protonation of *meso*-tetraalkyl- and *meso*-tetraarylporphyrins with weak and strong protic acids gives the diprotonated species which is completely water insoluble.[16] Also, the porphyrin may be readily released by washing the dichloromethane solution of the dication with neutral or moderately alkaline water. On the other hand, protonation of H$_2$T(4-Py)P with HCl in water leads to the formation of H$_2$T(4-Py)P·6HCl with a saddled porphyrin core which has been revealed by X-ray crystallographic studies.[25] The fully protonated species is completely soluble in water at room temperature and cannot be extracted with dichloromethane from the acidic (pH = 0)
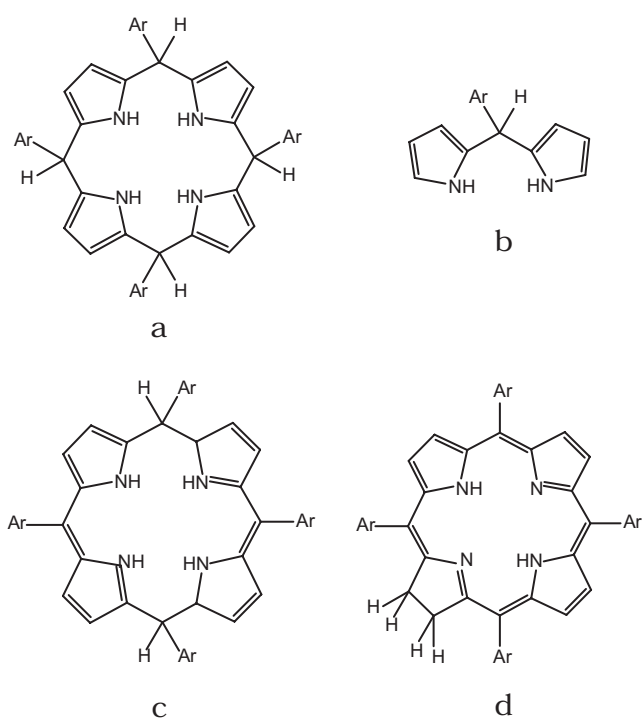
Figure 2. The structure of *meso*-tetraarylporphyrinogen (a), dipyrromethane (b), porphodimethene (c) and tetraarylchlorin (d).

aqueous phase. H$_2$T(4-Py)P has been shown to exist as a free base at pH values larger than 2.5. Pyridine has a pK_a value of 5.25 in aqueous solutions.[14] At pH values smaller than the pK_a most of the pyridine will be in the form of protonated species.[26] Introduction of basic groups such as pyridyl and aminophenyl at the *meso*-positions of porphyrin moiety leads to a decrease in the basicity of the nitrogen atoms of the pyridyl substituents due to the electron-donation from the *meso*-substituents to the porphyrin core.[27,28] Consequently, protonation of the pyridyl groups of *meso*-tetra(pyridyl) porphyrins and formation of hexaprotonated species occur in very acidic solutions *i.e.* at p$H \approx 0$. It should be noted that upon protonation of pyrrolenine nitrogen atoms of *meso*-di-(2,3, or 4-pyridyl)porphyrins using H$_2$SO$_4$ ($\approx 10^{-3}$ to 10^{-5} M), the pyridyl groups remain intact.[27] Also, in a previous work we have shown that the porphyrin core may be protonated with such weak carboxylic acids as acetic or propionic acids. [16,17] The porphodimethene (Figure 2d) impurities are also expected to be removed to less extent with this method.

^{1}H NMR studies have shown that the porphyrinogen and dipyrromethane impurities associated with the synthesis of *meso*-tetra(pyridyl)porphyrins are efficiently removed by washing of the reaction mixture with distilled water. The presence of porphyrinogen and dipyrromethane impurities is easily evident by the appearance of the signal due to the *meso*-protons (Figure 2a) in the regions δ ∼ 5-6 ppm[23] and ∼ 3-6 ppm,[29] respectively. It should be noted that *meso*-tetra(pyridyl)porphyrins show no signal in these regions. [19] Acetic acid (as well as propionic acid) is very soluble in water and, with respect to the pK_a of 4.76[26] for this acid in aqueous solutions, shaking the acetic acid phase with distilled water gives pH of *ca.* 2.4 (*i.e.* ½ pK_a) to the aqueous solution. On the other hand, in porphyrinogen, dipyrromethane and polypyrromethane species resonance interactions between the pyridyl groups and the porphyrinogen core or the pyrrole

rings are prevented by the *sp*[3] hybridization of the *meso*-carbons. Accordingly, the pyridyl groups behave similarly to the free base pyridine and may be protonated at this p*H* conditions. It seems that the solubility of the tetraprotonated *meso*-tetra(pyridyl)porphyrinogen and probable protonation of pyridyl residues of dipyrromethane and polypyrromethane in aqueous solution lead to the efficient removal of these impurities from the organic phase.

Metallation of Porphyrins with Manganese and Iron

Metallation of *meso*-tetraarylporphyrins with manganese is usually performed using the Adler *et al.* method.[9] The UV-vis spectra of *meso*-tetra(4-OCH$_3$phenyl) porphyrin (Figure 1), H$_2$T(4-OMe)P (λ_{max} = 422 and 646 nm for the Soret and *Q*(0,0) bands, respectively) and the Mn^{III} complex (λ_{max} = 480 nm) are demonstrated in Figure 3.

As is observed in Figure 3 there is a large difference between the λ_{max} values of the free base porphyrin and MnT(4-OMe)P(OAc). The metalloporphyrin has absorption bands in the region of *ca*. 400 to 442 nm. On the other hand, the absorption band of H$_2$T(4-OMe)P at 422 nm lies in the same wavelength region. Accordingly, the UV-vis spectrum of the reaction mixture cannot be used to monitor the completeness of the reaction. Protonation of H$_2$T(4-OMe)P with CF$_3$COOH leads to the large shift of the Soret band from 422 nm to 450 nm (Figure 3) and the red shift of the *Q*(0,0) band from 647 to 682 nm. It should be noted that H$_2$T(4-OMe)P has no absorption bands at wavelengths longer than 650 nm. Accordingly, position of the Soret and *Q*(0,0) bands in the spectrum of the diprotonated species may be used to determine the presence of trace to substantial amounts of unreacted porphyrin addition of a dilute solution of CF$_3$COOH in dichloromethane to an aliquot of the reaction mixture and recording the UV-vis spectrum easily shows the presence of unreacted porphyrin. As we have shown previously, different weak and strong carboxylic acids[16,17] may be used to protonate *meso*-tetraaryl and *meso*-tetraalkylporphyrins in addition to the strong inorganic acids. [30,31] In other words, the completeness of the metallation reaction may be monitored by recording the UV-vis spectrum of an aliquot of the reaction mixture in the dichloromethane solution of weak acids such as acetic-, propionic- or formic acid or strong acids such as CF$_3$COOH, HCl and H$_2$SO$_4$.
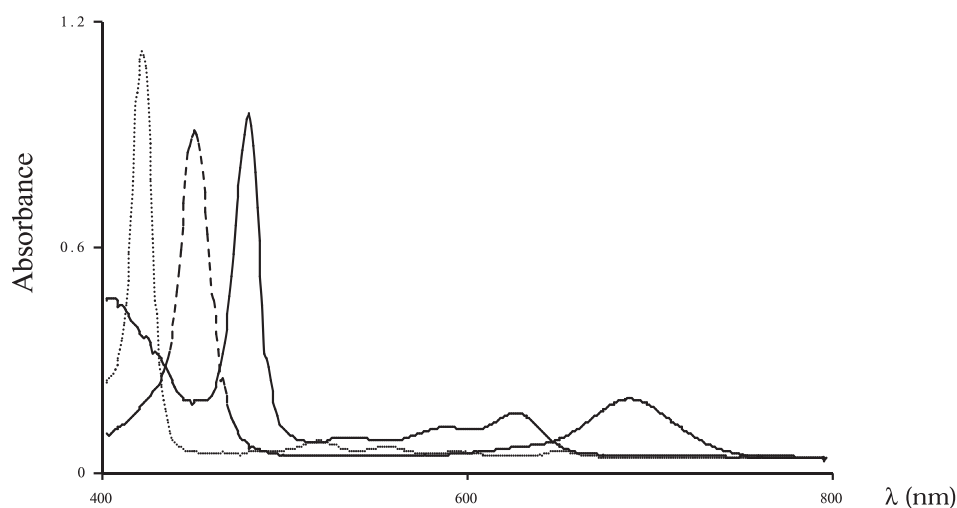

Figure 3. UV-vis spectra of H$_2$T(4-OMe)P (dotted curve), H$_2$T(4-OMe)P(CF$_3$COOH)$_2$ (dashed curve) and MnT(4-OMe)P(OAc) (solid curve) in dichloromethane.
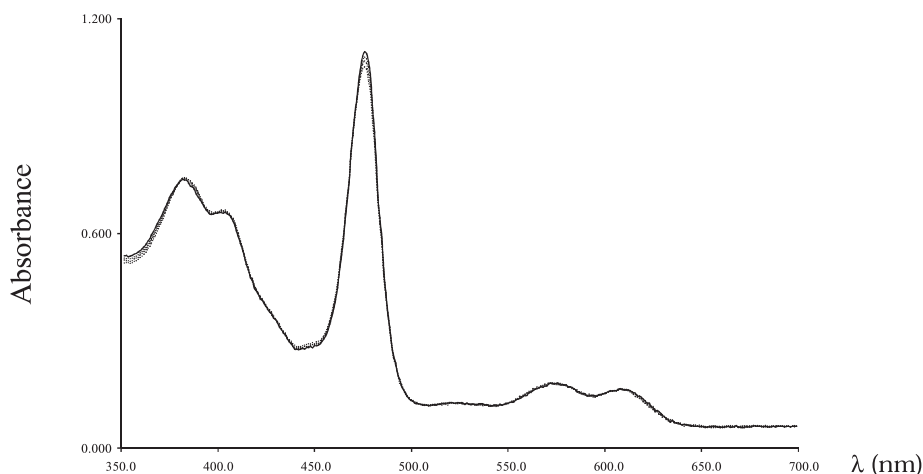

Figure 4. Spectral changes upon successive addition of a solution of CF$_3$COOH in dichloromethane (*ca*. 0.1 M) to the solution of MnTPP(OAc) in CH$_2$Cl$_2$.
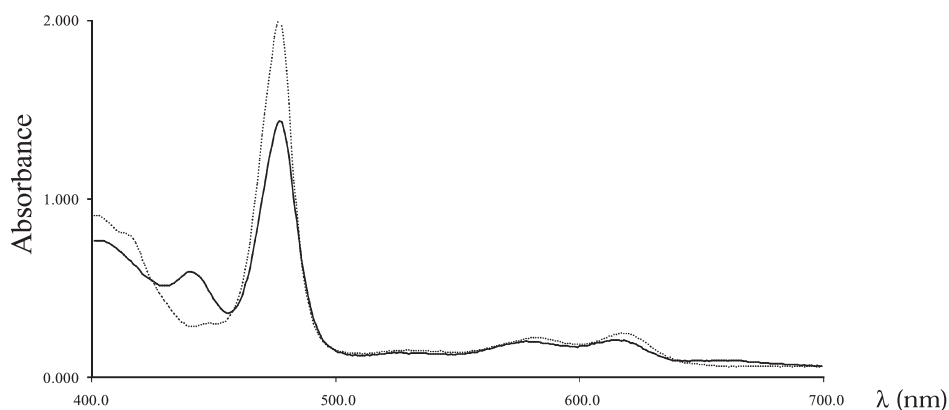
Figure 5. UV-vis spectra of a mixture of MnTPP(OAc) and H_2TPP before (dashed curve) and after the addition of a *ca.* 0.1 M solution of formic acid in dichloromethane.
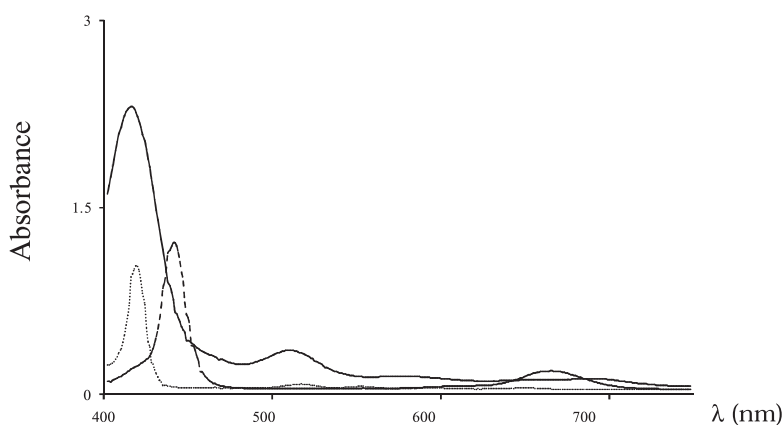

Figure 6. UV-vis spectra of H_2TPP (dotted curve), H_2TPP(CF_3COOH)$_2$ (dashed curve) and FeTPP(OAc) (solid curve) in dichloromethane.

Successive addition of a relatively dilute solution of CF_3COOH in dichloromethane to the solution of MnTPP(OAc) in CH_2Cl_2 led to no detectable change on the position of the bands in UV-vis spectrum (Figure 4). In other words, no ligand release was observed. However, small decreases in the intensity of the Soret band have been observed due to the dilution of the metalloporphyrin.

Figure 5 shows the changes in the UV-vis spectra of a mixture of H_2TPP and MnTPP(OAc) upon the addition of a *ca.* 0.1 M solution of formic acid in dichloromethane formation of H_2TPP(HCOOH)$_2$[16] leads to the appearance of the Soret and $Q(0,0)$ bands at 439 and 660 nm, which are clearly distinguishable from the absorption bands of the metalloporphyrin.

In the case of iron porphyrins, the λ_{max} of the metallated porphyrin usually appears at the same region as the free base porphyrin.[10,12] The UV-vis spectra of FeTPP(OAc) (λ_{max} = 414 nm), H_2TPP (λ_{max} = 418 nm) and H_2TPP(CF_3COOH)$_2$ (λ_{max} = 436 and 648 nm for the Soret and $Q(0,0)$ bands, respectively)[16] are shown in Figure 6. Again the addition of CF_3COOH or weak acids such as formic acid enables us to detect the unreacted porphyrin upon metallation of H_2TPP with iron.

Conclusions

In summary, the decreased basicity of pyridyl residues of *meso*-tetra(pyridyl)porphyrins with respect to those of the impurities such as porphyrinogen, dipyrromethane and porphodimethene has been utilized to improve the purification method of these porphyrins. Most of the impurities associated with the synthesis of *meso*-tetra(pyridyl)porphyrins have been shown to be removed by shaking the reaction mixture with a moderately acidic aqueous solution ($pH \approx 2.5$). This modification significantly reduces the number of purification steps especially the column chromatography ones. Also, the protonation of *meso*-tetraarylporphyrins with weak or strong acids has been shown to be an efficient method for spectrophotometric detection of unreacted porphyrins upon the metallation of porphyrins with manganese and iron.

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