Articles

Synthesis of Core-Modified Porphyrins and Studies of Their Temperature-dependent Tautomerism

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The different core-modified porphyrins 21-thia-23-carba-12-aza-5,10-dimesityl-15,20-diphenylporphyrin (**6**), and their N(12)-methyl derivatives (**8**) were synthesized by acid-catalyzed [3+1] condensation of the corresponding 16-thia-5,10-dimesityltripyrromethanes and 2,4-bis[(α-hydroxy-α–phenyl)methyl]pyrrole. Spectroscopic evidence indicates the existence of two different tautomeric forms at room temperature in porphyrin (**6**). A third form of tautomer was observed when the temperature was lowered to 223 K. The most stable tautomer is one in which the nitrogenic proton resides outside the core of the macrocycle. The ratio of the three different tautomers (outer N-H/ two inner N-H, *i.e.* **6/12/13**) was 1/1/0.5 in the case of (**6**) while the ratio of 1/1/0.3 was observed in the case of (**10**). In the case of 21-oxa-23-carba-12-aza-5,10,15,20-tetraphenylporphyrin (**7**), the only stable tautomeric form observed by ^{1}H NMR was the one that nitrogenic proton resides inside the core on

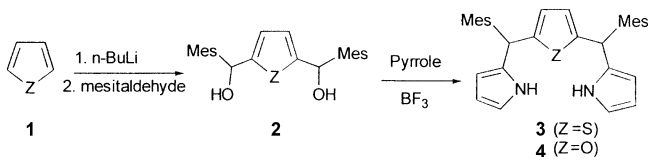
Introduction

Controlled modification of the basic framework of porphyrin-core while keeping aromaticity intact will result in a systematic variation of the spectroscopic properties and electronic energy of the molecules. This is advantageous in building model systems such as molecular devices and light harvesting systems. The systematic construction of such devices requires precise control of energetics and electronic structures of the molecules. The achievement of such control could be accomplished by several different ways. The simplest method would be replacing nitrogen ligands in the core with other heteroatoms and inserting different metal ions in the core. This will change the symmetry of molecule and accordingly change the transition energy between molecular orbitals such as A_{1u} or A_{2u} and p.[1] We have been interested in the development of new synthetic methods for asymmetric porphyrins bearing different core ligands. As a part of these efforts, we have recently reported the synthesis of several core-modified porphyrins.[2~4] We were able to synthesize and characterize the monooxaporphyrin and monothiaporphyrin bearing one inverted pyrrole unit. The synthesis utilized the condensation of a tripyrrane with a disubstituted 5-membered aromatic heterocycles. The tripyrrane derivatives were obtained by acid-catalyzed condensation of 2,5-bis[(α-hydroxy-α-mesityl)methyl]furan or 2,5-bis[(α-hydroxy-α-mesityl)methyl]thiophene with pyrrole. The development of the synthetic methods of core-modified porphyrins prompted us to investigate related methods in synthesizing various core-modified porphyrins with predesignated orientation of the core ligands. Here, we report the stepwise synthesis of core-modified porphyrins bearing one inverted pyrrole and the replacement of the nitrogen with sulfur or oxygen. Modification of the core by the introduction of sufur or oxygen obviously produces a new class of macrocycles. We also observed the existence of different tautomeric forms depending on the composition of core-ligands. The low temperature NMR spectroscopy was performed in order to verify the different tautomeric forms.

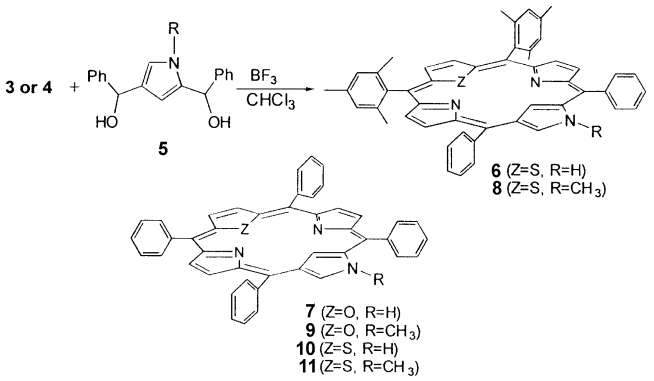
Results and Discussion

Bis-hydroxymethylation of lithiated thiophene is a well-established reaction.[6] The reaction works with bulky aromatic aldehydes such as mesitaldehyde as shown in Scheme 1. Coupling of the 2,5-dilithiofuran with mesitaldehyde gave the corresponding 2,5-bishydroxymethyl (**2)**. 5,10-Dimesityl-16-thia-5,10,15,17-tetrahydrotripyrrin (**3**) and 5,10-dimesityl-16-oxa-5,10,15,17-tetrahydrotripyrrin (**4**) were easily synthesized by condensing 2,5-bis[(α-hydroxy-α-mesityl)methyl] thiophene with pyrrole in the presence of $BF_3{\cdot}O(Et)_2$.[1] Usually, the maximum yields were obtained when two equivanlents of acid was applied as a catalyst. More than 40 equivalents of distilled pyrrole were used as a reactant and solvent. Application of excess pyrrole retards extensive equilibration of the reactants to polypyrrylic compounds.[7]

Condensation of (**3)** with 2,4-bis(α-hydroxy-α-phenylmethyl)pyrrole (**5**) was carried out in chloroform in the presence of $BF_3{\cdot}O(Et)_2$. A bright green colored porphyrin (**6**) was isolated in 26% yield by repeated column chromatography after the oxidative quenching of the reaction mixture



Scheme 1

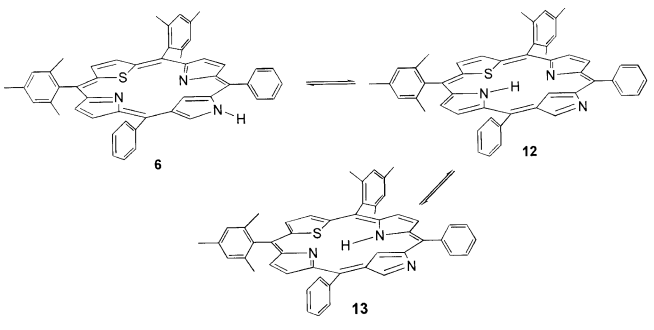


Scheme 2

with DDQ at room temperature. Trace of 5,20-dimesityl-10,15-diphenyl-21-oxaporphyrin which was formed by rearrangement of 2,4-bis(methylene)pyrrole unit during condensation was observed in all attempted reactions.[8]

The same reaction sequence was applied in the synthesis of peripheral N-methyl porphyrin (**8**). Unlike the *meso*-tetraphenyl analogues such as (**10**) and **(11)** that were reported previously,[2~4] the *meso*-mesityl porphyrins (**6**)-(**8**) have good solubility in organic solvents. The separation was quite straightforward and all the porphyrins had a bright green color in solution and on TLC plate. Each individual porphyrin was identified by routine ^{1}H NMR, ^{1}H COSY and mass spectrometry. The existence of different tautomeric forms was easily observed by ^{1}H NMR. The ^{1}H NMR spectrum of free base porphyrin (**6)** was somewhat complex due to the existence of equilibrium of different tautomeric forms as shown in Scheme 3.

The major tautomeric form existing at room temperature in neutral chloroform was porphyrin (**6**) and the minor tautomer (**12**) were observed individually but the inner nitrogenic proton and methine proton were observed as broad signals (Figure 1). The inner methine proton in (**6**) was observed at 2.6 ppm and the outer nitrogenic proton has a signal at 9.64 ppm that was completely disappearing upon adding deuterium oxide. On the other hand, the inner methine proton in (**12**) was observed at -2.97 ppm and inner N-H signal was observed at -1.01 ppm as broad signal. As shown in Figure 1, variable-temperature ^{1}H NMR spectra taken between 296 K and 223 K showed the appearance of the new tautomeric form. The new sets of peaks such as inner methine group at -2.90 ppm and nitrogenic protons at



Scheme 3

-2.28 ppm were clearly seen. The new tautomer is assigned as porphyrin (**13**). This assignment is based on the fact that bond length of C(2)-C(3) (1.382 Å) is shorter than C(3)-C(4) (1.417 Å) in the inverted pyrrole.[9] Thus it must be favorable that proton occupy C(3)-C(4) side instead of C(2)-C(3) side. Further separation of the different tautomeric forms at low temperature clearly indicates that (**12**) is more stable isomer than (**13**). The porphyrin (**6**) is the most stable and predominent isomeric form existing at room temperature (23 °C). The inner methine signal in (**6**) was shifted to 2.16 ppm and the outer N-H signal to 9.88 ppm at 223 K. The sets of signals appeared at -1.01 and -2.28 ppm was completely disappeared upon addition of deuterium oxide.

The ratio of the three tautomeric forms ((**6**)/(**12**)/(**13**)) calculated from the peak area in normalized proton NMR spectra was 2/2/1 at 223 K. The rather complex spectrum of these tautomeric mixture at room temperature goes to the single isomeric form upon addition of trace amount of acid. The proton NMR spectrum of the protonated form was quite simple; the inner methine proton was appeared at -1.09 ppm and N-H proton was completely disappeared. The chemical shifts of other pyrrolic protons were somewhat flexible depending on the amount of acid presence. But the β-pyrrolic resonance of the inverted pyrrole was observed uniquely at 8.58 ppm as singlet.

The ^{1}H NMR spectrum of free base porphyrin (**7)** on the other hand was dramatically different from that of porphyrin (**6)**. Not only single tautomeric form was observed in neutral deuterated chlroform at room temperature but also the inner methine proton was observed at -2.57 ppm that was shifted to -3.31 ppm by addition of trace amount of acid. These results indicate that (**6)** is much more basic and more distorted from planarity than (**7)**. The tautomerization could be prevented by methylation of the outer pyrrole nitrogen.

The porphyrins (**8), (9)** and **(11)** were synthesized by a similar condensation as shown in Scheme 2 and showed similar spectral behaviour to their non-methylated analogues. For example, the inner methine proton show singlet at 2.36 ppm which is shifted to -0.79 ppm on adding acid in porphyrin (**7**) and -3.63 ppm which is shifted to -4.32 ppm by adding acid in porphyrin (**9**). The resonance of inner methine proton is usually shifted upfield due to its exposure to the ring anisotropy. Since the influence of magnetic anisotropy is directly proportional to relative distance from the center of the porphyrin plane, the degree of the chemical shifts of inner methine proton will be good indication of planarity of porphyrins. The inverted pyrrole unit is somewhat tilted away from the porphyrin plane in all cases but the degree of distortion must be different. Judging from the chemical shifts of inner methine proton, (**6**) and (**8**) must be distorted more from the imaginary porphyrin plane than (**7**) and (**9**). These can be explained by which the Van der Waals radii of sulfur is larger than oxygen and accordingly the repulsive force between inner methine proton and sulfur must be greater than that of oxygen. These explanations agree well with the fact that the porphyrin (**8**) has Soret at 451 nm while porphyrin (**9**) has that at 438 nm. These results

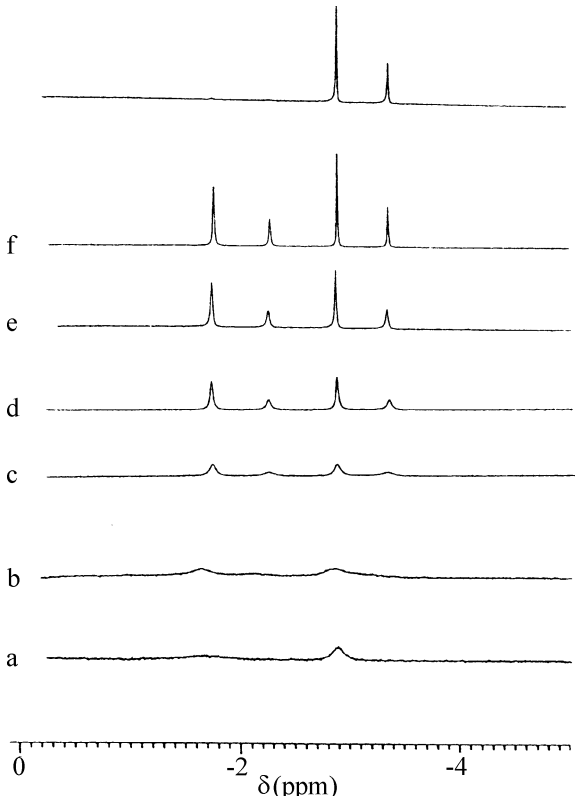


Figure 1. High field region of ^{1}H NMR spectra of porphyrin (**6**) in $CDCl_3$ taken at various temperature. a) 23 °C, b) -10 °C, c) -20 °C, d) -30 °C, e) -40 °C, f) -50 °C. Top trace was taken after adding D_2O.

indicate that the porphyrin (**6**) and (**8**) are more flexible and distorted more from planarity than (**7**) and **(9**). The protonation site of the porphyrin (**8**) and (**9**) could be speculated by analyzing the chemical shifts of the various protons. The chemical shift of the inner methine proton in porphyrin (**9)** is shifted to upfield (-3.63 to -4.35 ppm) and that of N-methyl is almost the same (3.01 to 2.97). The relatively large shift was observed for the β-furanyl protons (8.79 to 9.02) also. The increased positive charge on furanyl oxygen by protonation possibly could be responsible for the change. The furanyl oxygen must move outward direction while methine proton move inward simultaneously and consequently the methine proton is placed under strong influence of diamagnetic ring current. On the other hand, the large upfield shift (2.36 to -0.79 ppm) of the inner methine group in (**8)** was observed and chemical shift of N-methyl group is slightly shifted to downfield (3.36 to 3.58 ppm). The large shift has been observed for the β-thiophenyl protons (8.30 to 9.03 ppm). These observations suggest that protonation on sulfur change the hybridization of sulfur and will be forced out of porphyrin plain and thus inner methine proton efficiently occupy inside the core. The geometric changes accompanying protonation must be more important in both porphyrins. There should be more systematic studies to determine the protonation site unambiguously.

In the case of porphyrin (**7**), only single tautomeric form was observed.[2] The existing tautomer was identified as the one that nitrogenic proton resides inside the core. The evidences are clearly observed in proton nmr spectroscopy. The ^{1}H NMR spectrum of porphyrin (**7**) showed that the inner C-H proton has a doublet at -2.57 ppm, which was shifted to -3.14 ppm upon addition of TFA-d and the inner nitrogenic proton signal shown at -1.04 ppm was completely disappeared.

The same exchange pattern was observed in porphyrin (**10**). Low temperature proton NMR studies performed under the same condition as with (**6**) indicate that three different tautomeric forms also exist at 223 K. The relative ratio of the existing three different isomers (**6**)/(**12**)/(**13**) was 1/1/0.3. These results indicate that substitution of mesityl group instead of phenyl on *meso*-position shift the equilibrium toward (**12**) and (**13**). This is possibly due to enhanced distortion of porphyrin plane by repulsive force between mesityl and β-pyrrolic hydrogens and thus the inverted pyrrole ring is tilted more. It will cause less conjugative effect of *meso*-substituents to the π-systems of porphyrin. Accordingly, the core-size is larger in (**6**) than that of (**10**). Additionally, large size of sulfur and hydrogen attached to the inner methine carbon is already sterically crowded and thus porphyrin (**6**) must be preferred tautomer. Only single tautomeric form is possible in the case of porphyrin (**11**) and signals observed in ^{1}H NMR spectra correspond to the single isomeric form as is expected.

Conclusion

The present synthesis and verification of different tautomeric forms may be useful in the systematic study of core-size dependent tautomerization and deciding the dimension of core size. It will be also advantageous in synthesizing porphyrins having different ligands in the core in the regiospecific manner. The synthetic approaches presented with this article also could be applied to the synthesis of porphyrins bearing inverted pyrroles regiospecifically or other heterocycles. Obviously, replacement of the nitrogen atoms in the core with other heteroatoms produces unique macrocycles with different cavity sizes and complexing abilities. Our demonstration with this report could be applicable for designing various porphyrin-containing model systems. Currently, we are investigating the possibility of synthesizing other core-modified porphyrins using the same analogy.

Experimental Section

Proton NMR spectra (400 MHz, Bruker IFS48), IR spectra (JASCO IR 100), and absorption spectra (Kontron 941 and Hitachi U-3200) were collected routinely. Mass spectra were obtained by low resolution FAB or electron impact. Column chromatography was performed on silica (Merck, 230-400 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. CH_2Cl_2 (Fisher, reagent grade) was used after distillation from K_2CO_3. $CHCl_3$ (Fisher certified A.C.S.) containing 0.75% ethanol was distilled from K_2CO_3. All other reagents were obtained from Aldrich unless noted

otherwise. 2,4-Dibenzoylpyrrole was synthesized by previouly known method.[5] Porphyrin (**10**) and (**11**) were synthesized as reported earlier.[2~4]

2,5-bis[(α-hydroxy-α–mesityl)methyl]thiophene (2). Thiophene (0.16 ml, 2.0 mmol) was added to a 10 mL hexane solution of TMEDA (0.756 mL, 5.0 mmol) and n-butyllithium (2 mL, 5.0 mmol, 2.5 M solution in hexane). The mixture was heated for 1 hr at 90 °C. The reaction mixture was then added dropwise to a solution of mesitaldehyde (0.62 mL, 4.2 mmol) dissolved in THF (10 mL) in an ice bath. The whole mixture was stirred for 30 min at room temperature. The mixture was combined with saturated ammonium chloride (40 mL) and extracted with ether three times. The organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated under reduced pressure and resulting solid was purified by column chromatography (methylene chloride/ethyl acetate=9/1). Yield 0.66 g (87%); ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 4H, Ar-*meta*-H), 6.37-6.34 (m, 2H, thiophene-H), 6.26 (s, 2H, meso-H), 2.83 (bs, 2H, OH), 2.23 (s, 12H, Ar-*ortho*-methyl), 2.21 (s, 6H, Ar-*para*-methyl).

5,10-Dimesityl-16-thiatripyrromethane (3). To a solution of 2,5-bis[(α-hydroxy-α–mesityl)methyl]thiophene (250 mg, 1.71 mmol) and pyrrole (0.91 mL, 34.2 mmol) was added borontrifluoride diethyletherate (85 μL, 1.71 mmol). The mixture was stirred for 30 min. at room temperature then combined with methylene chloride (25 mL) and aqueous sodium hydroxide (1 N, 50 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed *in vaccuo* and the resulting solid was purified by column chromatography (methylene chloride). The two bands were eluted close to each other and the second band was the desired product. Yield 240 mg (75%); ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 2H, pyrrolic N-H), 6.84 (s, 4H, Ar-*m*-H), 6.65 (m, 2H, pyrrolic 5-H), 6.61 (s, 2H, thiophene), 6.16-6.14 (m, 2H, pyrrolic 4-H), 6.02 (bs, 2H, pyrrolic 3-H), 5.99 (s, 2H, *meso*-H), 2.26 (s, 6H, mesityl-*p*-H), 2.11 (s, 12H, mesityl-*o*-H).

5,10-Dimesityl-16-oxatripyrromethane (4). A sample of 2,5-bis[(α-hydroxy-α–mesityl)methyl]furan (500 mg, 1.37 mmol) was treated identically as for (**3**), affording 545 mg (86%) of diastereomeric mixture of products. Unlike (**3**), this reaction gave two diastereomeric mixtures which were not isolated further. The ratio of the two diastereomeric products was 63/37 based on the proton nmr spectra and the mixture was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) for major diastereomer; δ 8.02 (bs, 2H, N-H), 6.86 (s, 4H, Ar-H), 6.62 (m, 2H, pyrrolic-H), 6.12 (m, 2H, pyrrolic-H), 5.90-5.85 (m, 6H, furan, meso and pyrrolic-Hs), 2.28 (s, 6H, Ar-*p*-methyl), 2.10 (s, 12H, Ar-*o*-methyl). For minor isomer; δ 7.99 (bs, 2H, N-H), 6.89 (s, 4H, Ar-H), 6.56 (m, 2H, pyrrolic-H), 6.12 (m, 2H, pyrrolic-H), 5.90-5.85 (m, 6H, furan, *meso* and pyrrolic-Hs), 2.30 (s, 6H, Ar-*p*-methyl), 2.10 (s, 12H, Ar-*o*-methyl).

12-Aza-23-carba-10,15-diphenyl-5,20-dimesityl-21-thiaporphyrin (6). 2,4-bis[(α-hydroxy-α–phenyl)methyl]pyrrole (241 mg, 0.86 mmol) and 5,10-Dimesityl-16-thiatripyrromethane (413 mg, 0.86 mmol) was combined with chloroform (80 mL) then $BF_3{\cdot}O(Et)_2$ (212 μL, 1,73 mmol) was added *via* syrringe. The mixture was stirred for 40 min at room temperature then DDQ (0.78 g, 2 mmol) and triethylamine (3 mL) was added. The whole mixture was stirred for 1 hr and the solvent was removed *in vaccuo*. The resulting black solid was purified by column chromatography on silica (methylene chloride/ethyl acetate, 9 : 1). The impure product eluted as a green band. The pure product was obtained by size exclusion column chromatography (toluene) followed by recrystallization from petroleum ether and methylene chloride. The compound exists as two different tautomeric forms in neutral chloroform, thus the proton NMR spectrum was obtained after adding small amount of TFA-d. Yield 0.16 g (26%); ^{1}H NMR (TFA-d+$CDCl_3$) δ 8.67 and 8.64 (two doublets, 2H, *J*=5.6 Hz, thiophene-H), 8.63 (d, 1H, filpped outer-pyrrolic-H), 8.36 and 7.89 (two doublets, 2H, *J*=4.6 Hz, β-pyrrolic-H), 8.32 and 7.93 (two doublets, 2H, *J*=4.6 Hz, β-pyrrolic-H), 8.16-8.14 (m, 2H, Ar-H), 8.12-8.09 (m, 2H, Ar-H), 7.88-7.76 (m, 6H, Ar-H), 7.22 (s, 4H, Ar(mesityl)-H), 2.52 (s, 6H, Ar(mesityl)-*p*-methyl), 1.92 (d, 12H, Ar(mesityl)-*o*-methyl), -1.05 (d, 1H, inner pyrrolic-H).

12-Aza-23-carba-5,10,15,20-tetraphenyl-21-oxaporphyrin (7). A sample of 2,4-bis[(α-hydroxy-α–phenyl)methyl] pyrrole (0.22 g, 0.793 mmol), 5,10-diphenyl-16-oxatripyrromethane (0.3 g, 0.793 mmol) and $BF_3{\cdot}O(Et)_2$ (195 μL, 2 equiv.) was treated identically as for **6**, affording 70 mg (14%) of desired porphyrins. ^{1}H NMR ($CDCl_3$) δ 8.74 (AA'BB', 2H, furan), 8.71 (s, 1H, α-pyrrolic-H), 8.28-8.23 (m, 2H, Ar-o-H), 8.12-8.08 (m, 4H, Ar-H), 8.09 (m, 2H, Ar-o-H), 7.81-7.70 (m, 12H, Ar-H), 8.55-8.52 (m, 2H, pyrrolic-H), 8.12-8.10 (m, 2H, pyrrolic-H), -2.57 (s, 1H, inner C-H).

12-Aza-23-carba-10,15-diphenyl-5,20-dimesityl-12-methyl-21-thiaporphyin (8). N-Methyl-2,4-bis[(α-hydroxy-α–phenyl)methyl]pyrrole (150 mg, 0.5 mmol) and 5,10-Dimesityl-16-thiatripyrromethane (239 mg, 0.5 mmol) was dissolved in methylene chloride (60 mL) then $BF_3{\cdot}O(Et)_2$ (123 μL, 1 mmol) was added. The mixture was stirred at room temperature for 40 min. The mixture was combined with DDQ (454 mg, 2 mmol) and triethylamine (3 mL) and stirred for an additional 1 hr. The solvent was evaporated in vaccuo and the resulting black solid was purified by column chromatography on silica (methylene chloride/THF, 19 : 1). The fast moving green band was desired product. Further purification was carried out by size exclusion chromatography (toluene). Yield 106 mg (30%); ^{1}H NMR ($CDCl_3$) δ 7.91-7.87 (m, 6H, thiophene and Ar-*o*-H), 7.73 (d, 1H, *J*=4.5 Hz, pyrrolic-H), 7.66 (d, 1H, *J*=4.5 Hz, pyrrolic-H), 7.62-7.58 (m, 6H, Ar-*m*-H), 7.24 (m, 2H, pyrrolic-H), 7.11 (s, 4H, Ar(mesityl)-H), 7.38 (d, 1H, α-pyrrolic-H), 3.36 (s, 3H, N-methyl), 2.48 (s, 6H, mesityl-*p*-methyl), 2.36 (d, 1H, pyrrolic inner C-H), 2.0 (m, 12H, mesityl-*o*-methyl). FAB MS Calcd for $C_{51}H_{43}N_3S$ 729.3178, Found 729.3191.

12-Aza-23-carba-5,10,15,20-tetraphenyl-12-methyl-21-oxaporphyrin (9). A sample of N-methyl-2,4-bis[(α-hydroxy- α–phenyl)methyl]pyrrole (0.116 g, 0.397 mmol), 5,10-diphenyl-16-oxatripyrromethane (0.15 g, 0.397 mmol)

and $BF_3{\cdot}O(Et)_2$ (97.5 μL, 2 equiv.) was treated identically as for **6**, affording 20 mg (8.0%) of the desired porphyrin. ^{1}H NMR ($CDCl_3$/TFA-d) δ 9.07 and 8.97 (two doublets, 2H, *J* =5.0 Hz, furan-H), 8.00 and 8.15 (two doublets, 2H, *J*=4.6 Hz, β-pyrrolic-H), 8.47-8.45 (m, 3H, Ar-*o*-H and α-pyrrolic-H), 8.39-8.37 (m, 2H, Ar-*o*-H), 8.26-8.18 (m, 6H, Ar-*o*-H and β-pyrrolic-H), 7.91-7.78 (m, 12H, Ar-*o*-H), 2.97 (s, 3H, N-methyl), -4.37 (s, 1H, inner C-H) .

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