Synthetic and Structural Studies of *meso*-Tetraphenyltrithiasapphyrin: X-ray Crystal Structure of S-Inverted *meso*-Tetraphenyltrithiasapphyrin

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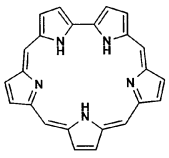
In recent years, large porphyrin-like macrocycles, the so-called expanded porphyrins, have attracted great attention due to their large application in the field of 1) photosensitizer for photodynamic therapy 2) magnetic resonance imaging contrast agent 3) chelating receptors for anions and cations 4) solar energy conversion device 5) RNA hydroysis catalysts 6) recognition of neutral substrates like water and methanol.[1]

Amough a number of expanded porphyrins, a pentapyrrolic macrocyclic compound, sapphyrin **1**, is one of the most studied expanded porphyrin.[2] For the first time, Latos-Grazynski and co-workers reported synthesis of *meso*-tetraphenylsapphyrin in 1995.[3] It was found that the acid-catalyzed, oxidative reaction of benzaldehyde with pyrrole in a 1 : 3 molar ratio gave *meso*-tetraphenylporphyrin as the main product. However, carful examination of the minor fraction revealed that a side-product of this reaction was the *meso*-tetraphenylsapphyrin with a yield of 1.1%. Surpringly, the *meso*-tetraphenylsapphyrin had a N-inverted structure, as evidenced by ^{1}H NMR spectroscopic analysis.

Heterosapphyrins in which a furan, thiophene, or selenophene moiety serves to replace one or more of the pyrrole rings are reported.[4] Recently, *meso*-tetraphenyltrithiasapphyrins **2** were also postulated to have S-inverted structures without X-ray crystal structures.[5] Very recently, we synthesized and determined the X-ray crystal structure of *meso*-diphenyloxadithiasapphyrin.[6] The crystal structure revealed that the *meso*-diphenyloxadithiasapphyrin has an O-inverted structure. Here we report a crystal structure and a reactivity of the S-inverted *meso*-tetraphenyltrithiasapphyrin **2**, and a synthesis of normal *meso*-tetraphenyltrithiasapphyrins **3**.



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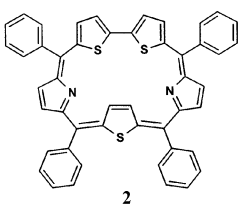

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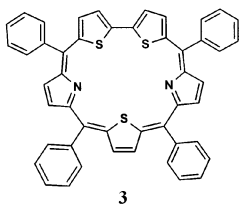

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Experimental Section

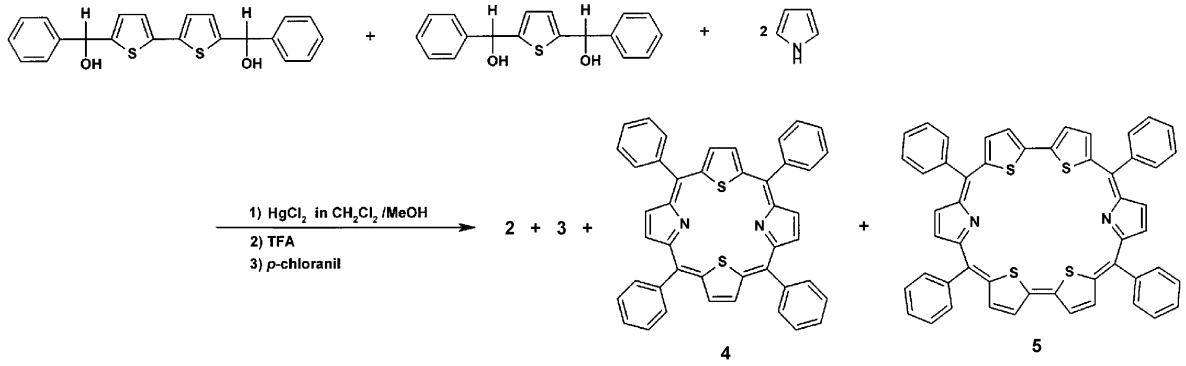
Materials and Instrumentation. Thiophene, pyrrole, benzaldehyde and tetramethylethylenediamine were purchased from Aldrich and distilled under N_2 just before use. $BF_3 \cdot$ etherate (Aldrich), and *n*-BuLi (10 M in hexane, Aldrich) bithiophene (Aldrich) were used as received.

^{1}H NMR spectra were recorded on a Bruker AC-200F NMR spectrometer operating at 200 MHz. Electronic absorption and FT-IR spectra were recorded on a Hewlett Packard 8453 and a Bio-Rad FTS 165 spectrophotometer, respectively. High resolution FAB-MS spectra were obtained on a JSM-HX 110A-HX 110A.

S-Inverted *meso*-tetraphenyltrithiasapphyrin 2 was synthesized according to a modified procedure.[5] 2,5-Bis(phenylhydroxymethyl)thiophene (1.0 g, 2.65 mmol), 2,5-bis(phenylhydroxymethyl)-2,2′-bithiophene (0.78 g, 2.65 mmol) and pure pyrrole (0.36 mL, 5.3 mmol) in $CHCl_3$ was stirred for 10 min under Ar atmosphere. $BF_3 \cdot OEt_2$ (0.1 mL, 2.65 mmol) was added to the above solution and the solution was stirred for 1 hr. *p*-Chloranil (0.66 g, 2.65 mmol) was added and the mixture was refluxed for another 1 hr. The solvent was evaporated and the mixture of products was chromatographed on flash silica gel with $CHCl_3$/*n*-hexane (v/v = 60/40) as eluant for **2** (yield = 12.8%). Anal calcd for $C_{48}H_{30}N_2S_3$: C, 78.89%; H, 4.14%; N, 3.84% Found: C, 78.61%; H, 4.41%; N, 3.92%.

***meso*-Tetraphenyltrithiasapphyrin 3**. $HgCl_2$ (1.0 g, 3.96 mmol) was added to a CH_2Cl_2 (100 mL) solution of 2,5-bis(phenylhydroxymethyl)thiophene (0.39 g, 1.32 mmol), 2,5-bis(phenylhydroxymethyl)-2,2′-bithiophene (0.5 g, 1.32 mmol) in Ar atmosphere. Pyrrole (0.18 mL, 2.65 mmol) was titrated to the above solution and the reaction mixture was stirred at room temperature for 10 min. A metal-templated condensation reaction was conducted with addition of trifluoroacetic acid (0.1 mL, 1.32 mmol). After stirring the solution for one hour *p*-chloranil (1 g, 3.96 mmol) was added for oxidation. Solvents were removed and the residual solution was purified by flash silica gel chromatography with CH_2Cl_2/*n*-hexane (v/v = 60/40) as eluant for **3** (yield=1%). UV-vis (λ_{max}, nm, $CHCl_3$), 471, 582, 621, 736, 821. ^{1}H NMR (toluene-d_8) δ 9.80 (q, 4H, bithiophene), 9.63 (d, 2H, pyrrole), 9.20 (d, 2H, pyrrole), 8.90 (2H, thiophene), 8.20 (m, 8H, *o*-phenyl), 7.59 (m, 12H, *m,p*-phenyl), HR FAB-MS ($M+H^+$): *m/z* 731.1666 (calcd for $C_{48}H_{30}N_2S_3+H^+$ 731.1643).

Tricarbonylrhenium(I) complex of 2, 2 · Re(CO)$_3$. The compound **2** (100 mg, 1.37×10^{-4} mol) and $Re_2(CO)_{10}$ (0.27 g, 4.1×10^{-4} mol) was refluxed in decanaphthalene (30 mL) for 1 hr under Ar atmosphere. The resulting solution was concentrated and was subjected to flash silica gel chromatography with benzene/*n*-hexane (v/v = 40/60). UV-vis (λ_{max},



Scheme 1

nm, $CHCl_3$), 515, 670, 730, 824, 931. ^{1}H NMR ($CDCl_3$) δ 11.07 (d, 1H, bithiophene), 10.60 (d, 1H, bithiophene), 10.38 (d, 1H, bithiophene), 10.12 (d, 1H, bithiophene), 8.81 (s, 2H, pyrrole), 8.52 (m, 4H, *o*-phenyl), 8.34 (d, 1H, pyrrole), 8.25 (d, 1H, pyrrole), 7.89 (m, 12H, *m,p*-phenyl) -1.20 (s, 1H, thiophene), FAB-MS ($M+H^+$): *m/z* 999.09 (68.4%), 1001.10 (100%) [(calcd for $C_{51}H_{29}N_2O_3S_3Re+H^+$ 999.1505 (natural abundance of ^{185}Re 37.07%) 1001.1505 (natural abundance of ^{187}Re 62.93%)].

X-ray crystallography. A crystal having dimension 0.3 × 0.35 × 0.4 mm was mounted on a fiber. X-ray data were collected on a CAD 4 Mach 3 diffractometer equipped with graphite-monochromated Mo-Kα (λ = 0.71074 Å) radiation at room temperature. The unit cell was determined to be monoclinic, $P2_1/n$ (No. 14) on the basis of 25 reflections. The data were collected by using the ω-2θ scan technique in the range $2.09 \leq \theta \leq 24.97^\circ$. Lorentz and polarization corrections were applied to the intensity data. No absorption correction was applied. The structure was solved by direct method and refined by full-matrix least-squares calculation with SHELXL-97.[7] Anisotropic thermal parameters were used for all non-hydrogen atoms. Crystal and intensity data are given in Table 1.

Table 1. Crystal data for 5,10,15,20-tetraphenyl-25,27,29-trithiasapphyrin

Formula	$C_{49}H_{31}Cl_3N_2S_3$
Formula weight	850.29
Temperature	293(2) K
Wavelength	0.71074 Å
Space group	P21/*n* (No. 14)
a	17.922(2) Å
b	11.024(2) Å
c	21.849(3) Å
β	107.91(3)°
Volume	4107.5(10) A^3
Z, Calculated density	4, 1.375 g/cm^3
Absorption coefficient	0.414 mm^{-1}
Crystal size	0.3 × 0.35 × 0.4 mm
θ range for data collection	2.09 to 24.97°
Index ranges	$0 \leq h \leq 21$, $0 \leq k \leq 13$, $-25 \leq l \leq 24$
Reflections collected / unique	7444 / 7200 [R(int) = 0.0194]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7200 / 0 / 658
Goodness-of-fit on F^2	1.043
Final R indices [I>2σ(I)]	R = 0.0505, Rw = 0.1286
R indices (all data)	R = 0.0889, Rw = 0.1521
Largest diff. peak	0.492

$R = \Sigma \, ||Fo|-|Fc|| / \Sigma |Fo|$. $Rw = [\Sigma\omega (||Fo|-|Fc||)^2 / \Sigma\omega |Fo|^2]^{1/2}$. $\omega = 1/\sigma^2(|Fo|)$. Goodness-of-fit = $[\Sigma\omega (Fo^2-Fc^2)^2/(Nreflections-Nparams)]^{1/2}$

Results and Discussion

The one-spot condensation of 5,5'-bis(phenylhydroxymethyl)-2,2'-bithiophene with 1 mol of 2,5-bis(phenylhydroxymethyl)thiophene and 2 mol of pyrrole in the presence of $BF_3 \cdot OEt_2$ conducted over 1hr, followed by oxidation with *p*-chloranil, produced a mixture of three products. The three products in flash silica gel chromatography eluted to give dithiaporphyrin[8] **4**, trithiasapphyrin **2** and tetrathiarubyrin[9] **5**,

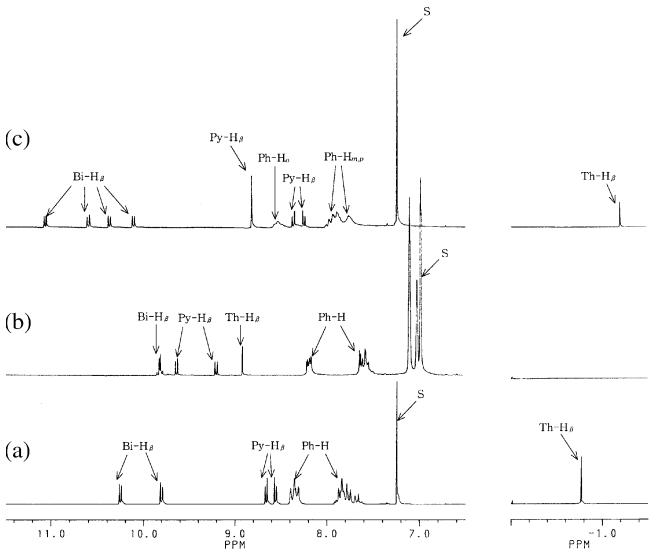


Figure 1. ^{1}H NMR spectra of (a) compound **2** in $CDCl_3$, (b) compound **3** in toluene-d_8, (c) complex **2** · Re(I)$(CO)_3$ in $CDCl_3$. Bi-H$_\beta$ = β-protons of bithiophene, Py-H$_\beta$ = β-protons of pyrrole, Th-H$_\beta$ = β-protons of thiophene, Ph-H = protons of phenyl, Ph-H$_o$ = *ortho*-protons of phenyl, Ph-H$_{m,p}$ = *meta*- and *para*-protons of phenyl, S = solvent. Regions from 0-6.5 ppm are omitted for the expansion of the spectrum.

succesively. The 2nd fraction contained S-inverted *meso*-tetraphenyltrithiasapphyrin.

As shown in Figure 1-a), the β-bithiophene protons and the β-pyrrole protons of **2** appeared at 8.5-10.2 ppm in the ^{1}H NMR spectrum while β-protons of thiophene opposite to the bithiophene located at -0.78 ppm. One general trend in the aromatic macrocycles is that the external ring protons showed large downfield shift and the internal protons showed large upfield shift due to the diamagnetic ring current. This result suggests that **2** has a S-inverted structure. Such a conclusion was only based on the ^{1}H NMR data without the crystal structure.

Further evidence for the structural assignment came from a single crystal X-ray diffraction analysis. X-ray quality single crystals of **2** were obtained by layering **2** in dichloromethane with *n*-hexane. As illustrated in Figure 2, the sulfur atom of the thiophene was evidently located outside of the core of the macrocycle. The crystal structure revealed a nearly planar macrocyclic conformation except the inverted thiophene. As illustrated in Figure 3, the thiophene was tilted with respect to the average mean plane by 25.13°. The average mean plane refers to a plane containing C(1), C(4), C(5), C(6), C(9), C(10), C(15), C(16), C(19), C(20), C(21), and C(24) with a standard deviation of 0.0778 Å. Compared with the core size of sapphyrin, separation for N(1)---N(2) was 6.391 Å, which was larger that the core size of the sapphyrin (5.0 Å). The C---C separation for C(1)---C(4), C(11)---C(14) and C(21)---C(24) was 2.495, 2.538, and 2.499 Å, respectively, while the C---C distance for C(6)---C(9) and C(16)---C(19) was 2.179 and 2.174 Å, respectively. The average C_α---C_α distance for the thiophene (2.538 Å) was considerably greater than the average value (2.179 Å) for the pyrrole. This large separation of the C_α---C_α distance increases the core size and hence may induce a ring strain to invert the thiophene ring.

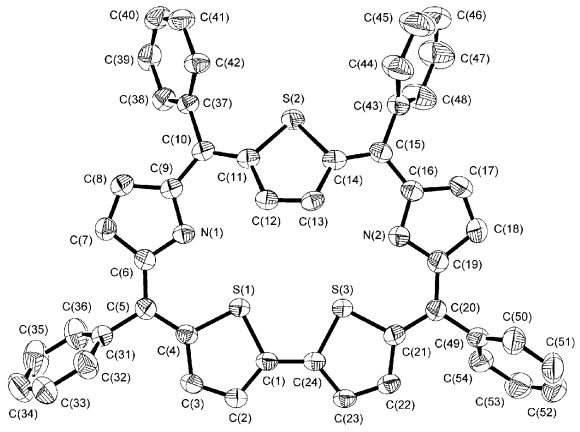


Figure 2. Top View of 5,10,15,20-Tetraphenyl-25, 27, 29-triphenylsapphyrin **2** (ORTEP, 30% probability). All hydrogens and solvent atoms are excluded for clarity.

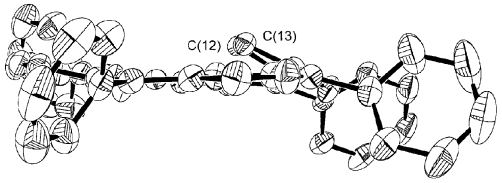


Figure 3. Side View of 5,10,15,20-Tetraphenyl-25, 27, 29-triphenylsapphyrin **2** (ORTEP, 30% probability). All hydrogens and solvent atoms are excluded for clarity.

The important feature of the structure was the presence of hydrogen-bonding interactions in the cavity between C(12)-H(12)---N(1) [H(12)---N(1) 2.31(3) Å, 115°], C(12)-H(12)---S(1) [H(12)---S(1) 2.80(3) Å, 121°], C(13)-H(13)---N(2) [H(13)---N(2) 2.36(3) Å, 117°], C(13)-H(13)---S(3) [H(13)---S(3) 2.89(3) Å, 120°]. To the best of our knowledge, the intramolecular hydrogen bonding interactions between C-H---N and C-H---S in the porphyrin derivatives have not been reported yet, but intermolecular hydrogen bonding interactions have been reported in the dimeric structure of dithiasapphyrins.[10]

The four phenyl groups were tilted by 69.63, 55.39, 65.60, and 62.72° relative to the average mean macrocyclic plane. Distance for C(5)-C(31), C(10)-C(37), C(15)-C(43), and C(20)-C(49) are equal to 1.487(4), 1.487(4), 1.483(4), and 1.486(4) Å, respectively.

Compound **2** reacts with $Re_2(CO)_{10}$ in refluxing decaline

Table 2. Selected bond lengths [Å] and angles [°] for **2**

S(1)-C(1)	1.726(3)	S(1)-C(4)	1.735(3)
S(2)-C(14)	1.749(3)	S(2)-C(11)	1.756(3)
S(3)-C(24)	1.728(3)	S(3)-C(21)	1.731(3)
N(1)-C(9)	1.346(4)	N(1)-C(6)	1.362(4)
N(1)--N(2)	6.391(3)	N(2)-C(16)	1.347(4)
N(2)-C(19)	1.365(4)	C(1)-C(2)	1.388(4)
C(1)-C(24)	1.423(4)	C(2)-C(3)	1.374(5)
C(3)-C(4)	1.403(4)	C(4)-C(5)	1.414(4)
C(5)-C(6)	1.401(4)	C(5)-C(31)	1.487(4)
C(6)-C(7)	1.446(4)	C(7)-C(8)	1.341(4)
C(8)-C(9)	1.459(4)	C(9)-C(10)	1.428(4)
C(10)-C(11)	1.398(4)	C(10)-C(37)	1.487(4)
C(11)-C(12)	1.417(4)	C(12)-C(13)	1.337(4)
C(13)-C(14)	1.417(4)	C(14)-C(15)	1.400(4)
C(15)-C(16)	1.430(4)	C(15)-C(43)	1.483(4)
C(16)-C(17)	1.441(4)	C(17)-C(18)	1.337(5)
C(18)-C(19)	1.440(4)	C(19)-C(20)	1.403(4)
C(20)-C(21)	1.419(4)	C(20)-C(49)	1.486(4)
C(21)-C(22)	1.407(4)	C(22)-C(23)	1.370(4)
C(23)-C(24)	1.391(4)		
C(1)-S(1)-C(4)	92.22(14)	C(14)-S(2)-C(11)	92.80(14)
C(24)-S(3)-C(21)	92.52(14)	C(9)-N(1)-C(6)	107.2(2)
C(16)-N(2)-C(19)	106.6(2)	C(2)-C(1)-C(2)	130.6(3)
C(2)-C(1)-S(1)	111.0(2)	C(24)-C(1)-S(1)	118.3(2)
C(6)-C(5)-C(4)	122.3(3)	N(1)-C(6)-C(5)	121.5(3)
N(1)-C(9)-C(8)	109.5(3)	C(11)-C(10)-C(9)	121.3(3)
C(10)-C(11)-S(2)	124.4(2)	C(15)-C(14)-S(2)	123.5(2)
N(2)-C(16)-C(15)	123.7(3)	N(2)-C(19)-C(20)	120.7(3)
C(19)-C(20)-C(21)	121.5(3)	C(20)-C(21)-S(3)	124.0(2)

Symmetry transformations used to generate equivalent atoms:

solution to produce a tricarbonylrhenium(I) complex. The presence of the molecular weight peak at 999.09 and 1001.10 with an approximately 2 : 3 intensity ratio in the FAB-MS spectrum confirms the formation of the mononuclear complex, **2** · $Re(CO)_3$. As shown in Figure 1-c), a resonance of one β-H of the thiophene in the ^{1}H NMR spectrum was observed at -1.20 ppm with a intensity of one proton, which indicates the formation of a bonding between the rhenium(I) metal and the β-carbon of the thiophene. β-Protons of the bithiophene appeared as four doublets, showing a lack of symmetry. In the FT-IR spectrum, carbonyl stretching peaks were observed at 2000.2 and 1899.9 cm^{-1}. The reaction of **2** with excess $Re_2(CO)_{10}$ did not produce a bis[tricarbonylrhenium(I)] complex, **2** · $[Re(CO)_5]_2$ probably because of the steric hindrance of the tricarbonyl group.

The *meso*-tetraphenyltrithiasapphyrin **3** in which the sulfur atom of thiophene lays inside of the cavity was synthesized by metal templated synthesis. Metal templated reaction of 5,5'-bis(phenylhydroxymethyl)-2,2'-bithiophene, 2,5-bis-(phenylhydroxymethyl)-thiophene, and pyrrole in the presence of $HgCl_2$ resulted in a mixture of four products. The products are dithiaporphyrin **4**, **2** as the major products, and a trace amount of **3** as well as tetrathiarubyrin **5**. The 3rd fraction contained **3**. According to the mass spectrum, the molecular weight of **3** is identical with that of **2**. However, the ^{1}H NMR spectrum and the UV-vis spectrum of **3** are quite different from those of **2**.

In the ^{1}H NMR spectrum for **3** (Figure 1-b), the β-H of the thiophene appeared as a singlet at 8.90 ppm instead of -0.78 ppm, thereby implying that the sulfur atom of thiophene faces the center of the cavity.

The electronic absorbance of **3** showed a Soret band at 471 nm and Q-type transitions at 621, 670, 736, and 821 nm, while **2** had a Soret band at 507 nm and Q-type transitions at 622, 678, 777, and 875 nm. Typically, the electronic spectra of the sapphyrins and their heterologs are dominated by an intense Soret band in the 435-470 nm regions for the free base and less intense 2-5 Q bands in the 600-800 nm spectral region.[2] Further studies of **3** cannot be performed due to the limited availability.

In conclusion, *meso*-tetraphenyltrithiasapphyrin **2** has the S-inverted structure due to the large ring strain and the hydrogen bonding interaction in the cavity. However, the metal-templated reaction affords the formation of the normal *meso*-tetraphenyltrithiasapphyrins **3**. The β-proton of inverted thiophene in **2** is acidic enough to react with $Re_2(CO)_{10}$ in refluxing decaline solution to produce the tricarbonylrhenium(I) complex of **2**.

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