Synthesis and Properties of Three Sulfur-Containing Porphyrins, One Water-Soluble

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Synopsis. Three new porphyrins with sulfur functional groups, one of which is water-soluble, have been prepared. Their UV-visible absorption, fluorescence emission, and ^{1}H NMR spectra as well as their copper(2+) insertion kinetics, pK_3 values and first and second reduction potentials determined. For the water soluble porphyrin, its binding with human serum albumin (HSA) determined.

In recent years several water-soluble synthetic porphyrins and metalloporphyrins have been studied as photosensitizers and radiation modifiers,[1–3] as DNA intercalators,[4–6] as binder with protein macromolecules,[7,8] and as tumor localizers.[9,10] Widely studied among these porphyrins are 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin (4TSPP), 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin (4TCPP), 5,10,15,20-tetrakis(1-methyl-4-pyridinio)porphyrin (4TMPyP) and 5,10,15,20-tetrakis[4-(trimethylammonio)phenyl]porphyrin (4TAPP) and some of their metal complexes. The same porphyrins are also under study as sensitizers in photochemical systems for solar energy conversion.[11,12] In addition to the above, other water soluble porphyrins, namely, 5,10,15,20-tetrakis(2-carboxyphenyl)porphyrin (2TCPP), 5,10,15,20-tetrakis(3-carboxyphenyl)porphyrin (3TCPP), 5,10,15,20-tetrakis(1-methyl-2-pyridinio)porphyrin (2TMPyP) and 5,10,15,20-tetrakis(1-methyl-3-pyridinio)porphyrin (3TMPyP) are known. Some of these are difficult to synthesize and purify. Besides, porphyrins with four negative charges usually remain as dimer in solution.[13] Therefore, it was felt that new water-soluble prophyrins with four positive charges should be prepared for studying the earlier mentioned important biological, biochemical, and photochemical properties. We report here the synthesis of three sulfur containing porphyrins and their physicochemical properties. They are 5,10,15,20-tetrakis[*p*-(methylthio)phenyl]porphyrin (**3**), 5,10,15,20-tetrakis[*p*-(methylsulfonyl)phenyl]porphyrin (**4**), and 5,10,15,20-tetrakis[(*p*-ethylmethylsulfonio)phenyl]porphyrin perchlorate (**5**). Porphyrin **5** is water-soluble.

Experimental

The porphyrin **3** was obtained by refluxing equimolar amounts of pyrrole (**1**) and *p*-(methylthio)benzaldehyde (**2**). Upon reacting **3** with excess *m*-chloroperbenzoic acid in dichloromethane, porphyrin **4** was obtained. Porphyrin **5** was obtained by refluxing **3** with excess triethyloxonium tetrafluoroborate in DMF, followed by removal of DMF, dissolving the residue in water and saturating with solid $NaClO_4$.

UV-visible absorption and fluorescence emission spectra were measured on a SLM/AMINCO DW2C and SLM 4800S

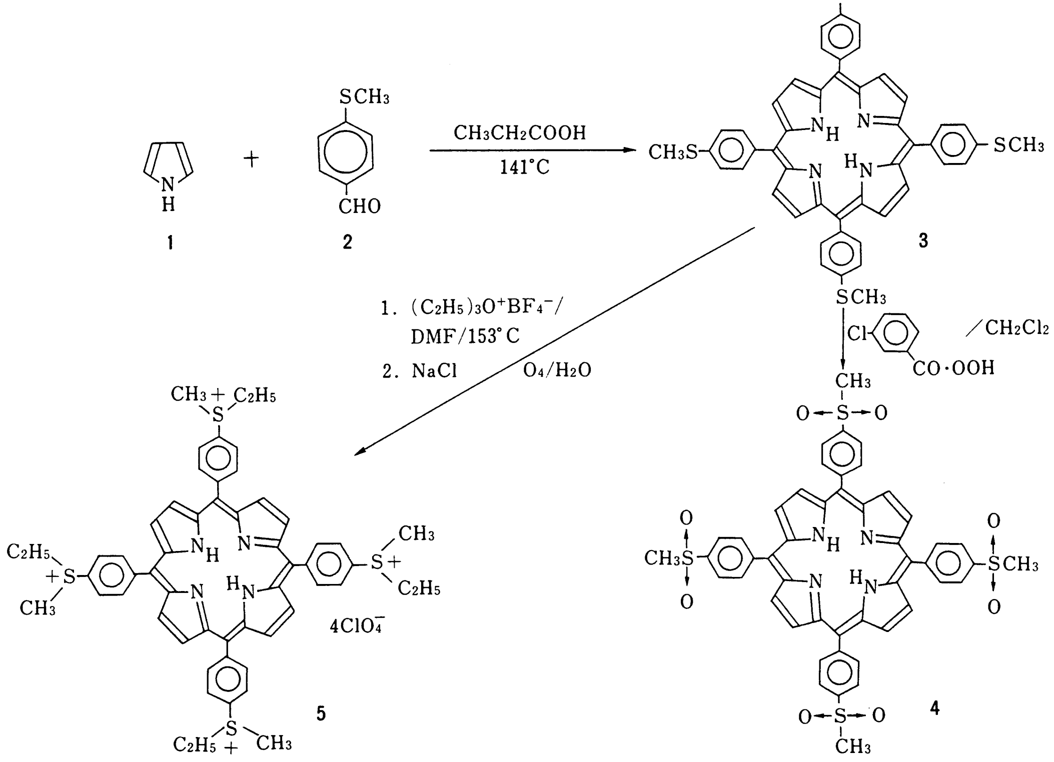

Table 1. UV-Visible Absorption Spectral Data in DMF

Porphyrin	$\lambda_{\max}$/nm ($\varepsilon \times 10^{-3}$)					
3	424(434)	490(9.9)	519(23)	556(18)	594(11)	631(12)
4	424(475)	484(14)	515(32)	549(20)	590(18)	646(13)
5	422(315)	—	516(25)	552(18)	591(16)	646(13)

recording spectrophotometers respectively. ^{1}H NMR spectra were recorded on a Bruker Spectrospin 250 MHz spectrometer. The p$K_3$14) values and kinetics of Cu^{2+} insertion15) are determined by methods described elsewhere. The first and second reduction potentials for the porphyrins were measured by square wave voltammetry (SWV), and verified by cyclic voltammetry. SWV were measured with an EG&G PARC Model 173 Potentiostat/Galvanostat attached to a Model 276 Interface and a Model 178 Electrometer connected to an ACC 178/41 Noise Filter. In addition, an Apple IIe computer with a monitor, an EPSON printer and a software, Model 276 Interface Demonstration Program, Volume II, were used. The Model 276 Interface allowed the potentiostat/galvanostat to be controlled by the Apple IIe computer which incorporates an IEEE-488 Interface. The cyclic voltammograms were measured with an EG&G Model 264A Polarographic Analyzer, an RE 0089 X-Y Recorder and a Model 303A SMDE. A glassy carbon electrode (EG&G PARC Part #G0197) was used as the working electrode throughout. A 10^{-4} M porphyrin solution (1 M=1 mol dm^{-3}) in DMF containing 0.1M TBAP was used for all electrochemical studies. As reference electrode, an aqueous saturated calomel electrode (SCE) was used. The SCE was placed in a bridge tube with vycor tip and was filled with 0.1 M TBAP in DMF. The tip of the bridge tube was placed in the porphyrin solution. A platinum wire was as a counter electrode. Deaeration of the porphyrin solution was achieved by bubbling oxygen-free-argon-saturated with DMF. The binding of porphyrin **5** with HSA was measured by fluorescence quenching of the single tryptophan residue in the protein as it was titrated with the porphyrin solution.16)

Nitrobenzene and DMF were purified by standard methods and distilled under nitrogen before use. TBAP was recrystallized from ethanol and dried in vacuum at room temperature. All other chemicals were used as purchased.

5,10,15,20-Tetrakis[*p*-(methylthio)phenyl]porphyrin (3) was prepared by refluxing equimolar amounts of distilled pyrrole (**1**) and *p*-(methylthio)benzaldehyde (**2**) (0.1 mol each) in propionic acid, (500 ml), for 0.5 h; the solvent was removed under reduced pressure, the residue was dissolved in methanol, cooled and filtered to obtain the porphyrin. Yield: 8—10%. Found: C, 72.31; H, 5.00; N, 7.08%. Calcd for $C_{48}H_{38}N_4S_4$: C, 72.18; H, 4.76; N, 7.02%. ^{1}H NMR ($CDCl_3$): δ=−2.78 (s, 2H from NH), 2.75 (s, 12H from S-CH_3), 7.62 (d, 8H, phenyl protons ortho to porphyrin ring, J=8.23 Hz), 8.11 (d, 8H, phenyl protons meta to porphyrin ring, J=8.25 Hz), 8.85 (s, 8H, pyrrolic).

5,10,15,20-Tetrakis[*p*-(methylsulfonyl)phenyl]porphyrin (4) was prepared by refluxing **3**, (0.01 mol) in dichloromethane (500 ml) solution with *m*-chloroperbenzoic acid (0.16 mol) for 1 h. and subsequent removal of the solvent as well as excess *m*-chloroperbenzoic acid. Yield: 90%. Found: C, 61.80; H, 4.16; N, 5.77; S, 13.69%. Calcd for $C_{48}H_{38}N_4S_4O_8$: C, 62.00; H, 4.10; N, 6.04; S, 13.82%. ^{1}H NMR ($CDCl_3$) δ=2.85 (s, 2H from NH), 3.09 (s, 12H, S-CH_3), 8.09 (d, 8H phenyl protons ortho to porphyrin ring, J=7.26 Hz), 8.44 (d, 8H, phenyl protons meta to porphyrin ring, J=7.94 Hz), 8.85 (s, 8H, pyrrolic).

Table 2. Corrected Fluorescence Emission Spectral Data in DMF

Porphyrin	$\lambda_{\text{ex max}}$ /nm	$\lambda_{\text{em max}}$ /nm	Intensity ratio
3	423	663, 728	10:5.8
4	418	665, 719	10:9.9
5	421	659, 722	10:8.9
TPPa)	420	655, 720	10:8.0

a) TPP is tetraphenylporphyrin. Included for comparison.

5,10,15,20-Tetrakis[*p*-(ethylmethylsulfonio)phenyl]porphyrin Perchlorate (5) was prepared by refluxing **3** (0.01 mol) in DMF (250 ml) with triethyloxonium tetrafluoroborate (0.08 mol) for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in boiling water and solid $NaClO_4$ was added to obtain a precipitate of **5**. It was recrystallized from water and dried. Yield: 85%. Found: C, 51.47; H, 4.64; N, 4.32%. Calcd for $C_{56}H_{58}N_4O_{16}Cl_4S_4$: C, 51.22; H, 4.42; N, 4.27%. ^{1}H NMR (D_2O) δ=−2.79 (s, 2H, from NH), 1.72 (t, 12H, methyl protons of S-CH_2CH_3), 2.06 (q, 8H, methylene protons), 2.76 (S, 12H, S-CH_3), 7.64 (d, 8H, phenyl protons ortho to porphyrin ring, J=6.9 Hz), 8.12 (d, 8H, phenyl protons meta to porphyrin ring J=7.5 Hz), 8.83 (S, 8H, pyrrolic).

Results and Discussion

In the UV-visible absorption spectrum of porphyrin **5**, a shoulder at around 490 nm, observed in **3** and **4**, is missing (see Table 1). Compared to porphyrin **3**, porphyrin **4** and **5** show a blue shift in most of the absorption bands. In 0.05 M NaOH solution, **5** obeyed Beer's law over concentration range of 2×10^{-4} and 2×10^{-7} M. Therefore it does not dimerize or aggregate in aqueous solution, a property observed with 4TMPyP, 3TMPyP, and 2TMPyP. Unlike **3** and TPP, the two corrected emission maxima for porphyrins **4** and **5** are found to be almost equal in intensity (see Table 2). The pK_3 values (see Table 3) show that porphyrin **5** is more acidic than **3** and **4** as well as other water-soluble porphyrins. A good correlation between the rate of Cu^{2+} ion insertion in TPP and porphyrins **3**, **4**, and **5** is observed with their corresponding pK_3 values as well as their first and second reduction potentials (see Table 3). The lower the basicity and the negative first and second reduction potentials of the porphyrin, the

Table 3. pK_3 Values and Kinetics of Cu^{2+} Insertion, and Reduction Potentials

Porphyrin	pK_3±0.01	$\frac{10^{-3} \times k}{\text{min}^{-1}}$	$-E_{1/2}(1)$b)	$-E_{1/2}(2)$e)
TPP	3.99a)	9.7	1.15	1.57
3	3.99a)	9.4	1.06	1.54
4	3.20a)	3.3	0.96	1.44
5	2.81b)	1.2	0.80	1.13

a) In nitrobenzene, b) in water, c) in DMF, d) volts (±0.005) vs. SCE for the reaction $(H_2 \text{ porphyrin})^{\circ} + e^- \rightarrow (H_2 \text{ porphyrin})^-$, e) volts (±0.005) vs. SCE for the reaction $(H_2 \text{ Porphyrin})^- + e^- \rightarrow (H_2 \text{ porphyrin})^{2-}$.

lower is the rate of Cu^{2+} insertion in it.

The binding of the water-soluble porphyrin **5** was studied with HSA in 0.1 M phosphate buffer, pH 7.2, and compared to the results obtained with other monomeric water soluble porphyrins,. Each of these porphyrins bound 1 : 1 with HSA. The dissociation constants for the porphyrin–HSA complex to HSA and the corresponding porphyrins, **5**, 4TMPyP, 3TMPyP, and 2TMPyP are found to 3.26, 2.20, 2.08, and 2.22 M respectively.

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16) Detailed method is described in a forthcoming publication.