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# Synthesis and simple separation of β-pyrrole sulfonated porphycenes

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**Abstract**—New water-soluble porphycenes having sulfonic acid groups at the β-pyrrolic positions were synthesized and characterized by UV–vis, NMR, IR, and mass spectroscopy as well as elemental analyses. The series of mono- to tri-sulfonato derivatives were simply separated by the extraction method.


Water-soluble porphyrins and their metal complexes have been attracting much attention because of their versatile utility as photosensitizer in photodynamic therapy (PDT),[1] DNA cleavage catalyst[2,3] as well as biomimetic oxidation catalyst in aqueous solutions.[4] Water solubility of these compounds is enhanced by the peripheral substitution of the porphyrin ring with polar or ionic groups. Among them, sulfonated porphyrins are one of the most studied derivatives from the viewpoint of synthetic facility, high water solubility, and unique aggregation properties in water.[5] In contrast, it is known that porphycene, the structural isomer of porphyrin first prepared by Vogel et al.,[6] opened the door to a new direction of research in the quest for PDT photosensitizers due to its interesting physicochemical properties.[7–10] Therefore, a modified porphycene having a sulfonic acid group ($SO_3H$) at the peripheral β-pyrrolic position will attract considerable interest as a highly water-soluble porphycene, although there is no report describing the preparation of $SO_3H$-containing porphycene. And there is no example for synthesis of porphycene exhibiting high water solubility.[11] In this study, the synthesis and characterization of new water-soluble porphycenes, which have sulfonic acid moieties at the β-pyrrolic positions, are reported.

2,7,12,17-Tetra-*n*-propylporphycene ($H_2$TPrPc) was synthesized by the reported method.[6] Sulfonation of the pyrrole rings of $H_2$TPrPc was carried out in the presence of 25% fuming sulfuric acid as shown in Scheme 1. Typical sulfonation reaction is described as follows: $H_2$TPrPc (30 mg, 0.063 mmol) was dissolved in 0.9 mL of 25% fuming sulfuric acid and 0.1 mL of $CH_2Cl_2$ as co-solvent at room temperature. After the solution was stirred vigorously for 25 min, the color of the solution changed from deep blue to green. Mono-, di-, and tri-sulfonated porphycenes at the β-pyrrolic positions were obtained in moderate yields. It is noted that fuming sulfuric acid is a good sulfonation reagent for $H_2$TPrPc compared to concentrated sulfuric acid. When we used 96% sulfuric acid as a sulfonation reagent, no sulfonated product was obtained even at 373 K, and unreacted $H_2$TPrPc was recovered after stirring for 1 day.

Sulfonated porphycenes were separated by following simple procedures as shown in Scheme 2. After stirring with fuming sulfuric acid, the reaction mixture was poured into cold water and the solution was neutralized with saturated $NaHCO_3$ aqueous solution, and the unreacted $H_2$TPrPc was recovered by extraction with $CCl_4$. To the resultant $H_2O$ layer was added ethyl acetate and the mono-sulfonated product **1** was extracted into the organic layer. Then subsequent extraction of the residue ($H_2O$ layer) with *n*-$C_4H_9OH$ afforded di-sulfonated products **2a** and **2b**. Finally, tri-sulfonated product **3** was extracted with *i*-$C_3H_7OH$ from the residue. All the extracted products were easily characterized by UV–vis and NMR spectroscopy. In this way, each sulfonated product was separated by only the extraction method without column chromatography.

*Keywords*: Water-soluble porphycene; Sulfonation of macrocycle; Separation with extraction.
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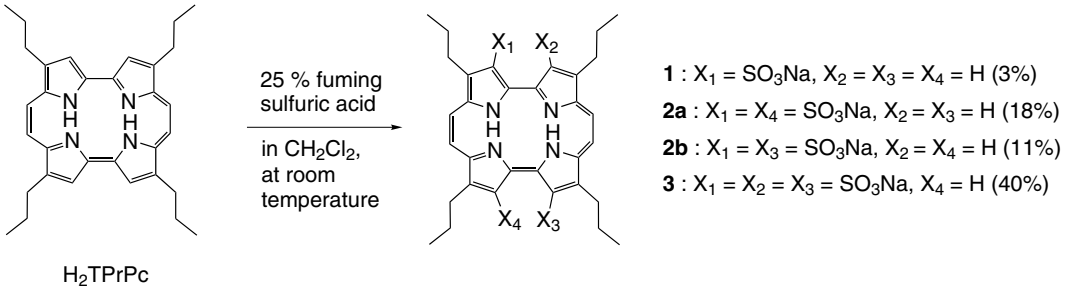
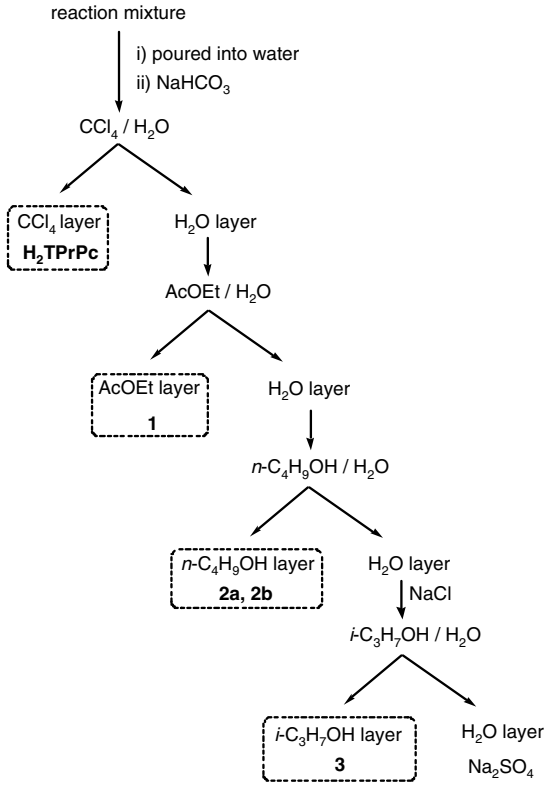



**Scheme 1.**

Compounds **1**,[†] **2a**,[‡] **2b**,[‡] and **3**[§] were characterized by UV–vis, NMR, IR, and mass spectroscopy as well as elemental analyses.[¶] The sulfonated products were isolated as sodium salt confirmed by mass and IR spectroscopic analyses. The $^1$H NMR spectra of **1**, **2a**, **2b**, and **3** are shown in Figure 1. The $^1$H NMR spectrum of **1** reveals three singlets assigned to three pyrrole protons at $\delta$ 9.15, 9.30, and 10.60, respectively. The methine-bridge protons appear as a couple of AB-pattern quartets at $\delta$ 9.61–9.84. The remaining one pyrrole proton of tri-sulfonated compound **3** appeared as a singlet at $\delta$ 10.36 and its methine-bridge protons also appeared as a couple of AB-pattern quartets at $\delta$ 9.26/9.61 and $\delta$ 9.42/9.55, respectively. Unfortunately, we could not find the conditions to separate the di-sulfonated isomers **2a** (*cis*) and **2b** (*trans*) completely. Each of the pyrrole and methine-bridge protons of the two isomers is assigned by 2D NMR (COSY) as shown in Figure 1. Methine-bridge protons of **2a** isomer appeared as two-singlet signals at $\delta$ 9.77 and 9.87, respectively. In contrast, those of **2b** isomer appeared at $\delta$ 9.79–9.93 as quartet signals. The ratio of isomers (**2a** and **2b**) was determined by peak integration of the $^1$H NMR spectrum as 1.8 to 1 for **2a** and **2b**, and the preference of *cis* isomer **2a** is observed.




**Scheme 2.**

[†] **1**: Yield, 3%; $^1$H NMR ($CD_3OD$, 500 MHz): $\delta = 1.28$ [m, 6H, –C*H*$_3$], 1.34 [m, 6H, –C*H*$_3$], 2.34 [m, 6H, β-C*H*$_2$–], 2.42 [m, 2H, β-C*H*$_2$–], 3.85 [t, 2H, α-C*H*$_2$–], 3.91 [t, 2H, α-C*H*$_2$–], 4.03 [t, 2H, α-C*H*$_2$–], 4.39 [t, 2H, α-C*H*$_2$–], 9.15 [s, 1H, pyrrole], 9.30 [s, 1H, pyrrole], 9.61 [d, 1H, methine], 9.65 [d, 1H, methine], 9.71 [d, 1H, methine], 9.84 [d, 1H, methine], 10.6 [s, 1H, pyrrole]; $^{13}$C NMR ($CD_3OD$, 125 MHz): $\delta = 14.7$, 14.8, 14.9, 15.3 (–*C*H$_3$), 26.3, 26.4, 26.6, 28.9 (β-*C*H$_2$–), 29.9, 30.7, 31.0, 31.3 (α-*C*H$_2$–), 109.4, 110.4, 113.3, 114.1 (methine), 122.7, 125.2, 128.1, 131.4, 136.3, 139.0, 139.6, 140.2, 140.4, 143.4, 143.9, 146.5, 148.6, 149.4, 151.0, 151.2 (pyrrole); UV–vis (in $CH_3OH$): [$\lambda_{max}$/nm], 369, 380, 567, 608, 643; IR, $\nu$/cm$^{-1}$: 1040 (S=O str.), 1194 (S=O str.); MALDI-TOF-MS (dithranol matrix, $m/z$): [M]$^+$, 580.6, [M−Na]$^+$, 558.6.

[‡] A mixture of isomers **2a** and **2b** was totally obtained in 29% yield. The following analyses were carried out as a mixture. UV–vis (in $H_2O$): [$\lambda_{max}$/nm], 374, 383, 572, 612, 646; UV–vis (in $CH_3OH$): [$\lambda_{max}$/nm], 375, 381, 573, 616, 653; IR, $\nu$/cm$^{-1}$: 1046 (S=O str.), 1203 (S=O str.); MALDI-TOF-MS (dithranol matrix, $m/z$): [M]$^+$ 682.1, [M−Na]$^+$ 660.2, [M−2Na]$^+$, 638.4; Anal. Calcd for $C_{32}H_{36}N_4Na_2O_6S_2{\cdot}H_2O$: C, 54.85; H, 5.47; N, 7.99. Found: C, 54.59; H, 5.20; N, 7.79.

[§] **3**: After the extraction with *i*-$C_3H_7OH$, the product was purified by gel-filtration chromatography with Sephadex LH-20 with $CH_3OH$ elute to remove a trace amount of $Na_2SO_4$. The tri-sulfonated product exhibits high solubility toward water. Yield, 40%; $^1$H NMR ($CD_3OD$, 500 MHz): $\delta = 1.34$ [m, 12H, –C*H*$_3$], 2.14 [m, 1H, β-C*H*$_2$–], 2.24 [m, 5H, β-C*H*$_2$–], 2.36 [m, 2H, β-C*H*$_2$–], 3.88 [t, 2H, α-C*H*$_2$–], 3.93 [m, 2H, α-C*H*$_2$–], 4.06 [m, 2H, α-C*H*$_2$–], 4.21 [m, 2H, α-C*H*$_2$–], 9.26 [d, 1H, methine], 9.42 [d, 1H, methine], 9.55 [d, 1H, methine], 9.61 [d, 1H, methine], 10.36 [s, 1H, pyrrole]; $^{13}$C NMR ($CD_3OD$, 125 MHz): $\delta = 14.8$, 15.3, 15.5, 15.6 (–*C*H$_3$), 26.0, 28.0, 28.1, 28.4 (β-*C*H$_2$–), 29.7, 30.4, 30.7, 31.1 (α-*C*H$_2$–), 107.9, 112.8, 115.2, 120.5 (methine), 129.0, 130.7, 135.2, 135.5, 135.6, 137.1, 138.2, 141.2, 141.5, 141.9, 145.3, 148.3, 149.3, 149.5, 151.2, 151.3 (pyrrole); UV–vis (in $H_2O$): [$\lambda_{max}$/nm], 371, 387, 603, 643, 686; UV–vis (in $CH_3OH$): [$\lambda_{max}$/nm], 372, 385$_{sh}$, 604, 650, 688; IR, $\nu$/cm$^{-1}$: 1044 (S=O str.), 1183 (S=O str.); MALDI-TOF-MS (dithranol matrix, $m/z$): [M−Na]$^+$ 762.1, [M−3Na]$^+$ 718.2; ESI-TOF-MS ($m/z$): [M]$^+$ 784.4, [M−2Na]$^+$ 740.3; Anal. Calcd for $C_{32}H_{35}N_4\ Na_3O_9S_3{\cdot}2H_2O$: C, 46.72; H, 4.30; N, 6.55. Found: C, 46.82; H, 4.50; N, 6.55.

[¶] When the reaction was carried out in 0.6 mL of 25% fuming sulfuric acid and 0.4 mL of $CH_2Cl_2$ as co-solvent at room temperature, there was no difference in product distribution compared to that for the present reaction conditions. On the other hand, when the reaction was carried out in 0.1 mL of 25% fuming sulfuric acid and 0.9 mL of $CH_2Cl_2$ at room temperature for 25 min, di-sulfonated compound was obtained as a major product; **2a** and **2b**, 57%; **3**, 10%.

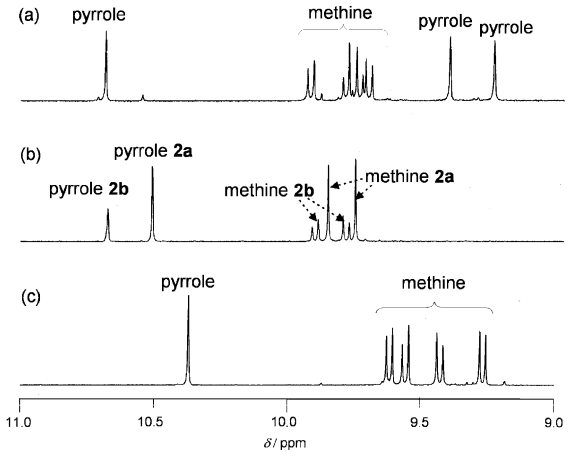



**Figure 1.** $^1$H NMR spectra of (a) **1**, (b) **2a** and **2b**, (c) **3** in $CD_3OD$ at 298 K.

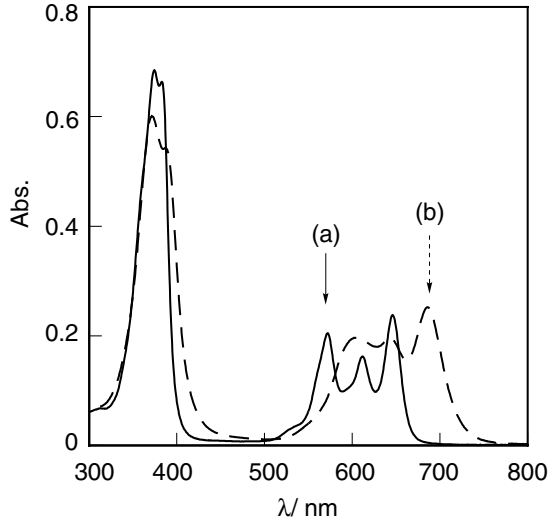



**Figure 2.** Electronic spectra of (a) **2a** and **2b**, $0.92\times10^{-5}$ M, (b) **3**, $0.95\times10^{-5}$ M in $H_2O$ at 298 K.

The sulfonated derivatives **2a**, **2b**, and **3** exhibit solubility toward water at neutral pH. Electronic spectra of sulfonated products in $H_2O$ are shown in Figure 2.[‖] The Q-bands at the visible region for the sulfonated compounds are all red-shifted with increase in the number of $SO_3H$ groups on the porphycene ring.

In summary, new water-soluble porphycenes having sulfonic acid groups as substituent at the β-pyrrolic positions were successfully synthesized. Direct modification of the porphycene ring is presumably an efficient procedure for functionalization of porphycenes.[12,13] Application toward PDT study and metalation to catalysis is expected by using sulfonated porphycenes and their metal complexes.

[‖] Mono-sulfonated product (**1**) exhibits low solubility toward neutral water.

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