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Regioselective sulfonation of 2-porphyrinylthiophene under kinetic and thermodynamic control

Yonbon Arai *, Jotaro Nakazaki, Hiroshi Segawa *

Research Center for Advanced Science and Technology, The University of Tokyo, 4-6-1, Komaba, Meguro-ku, 153-8904 Tokyo, Japan

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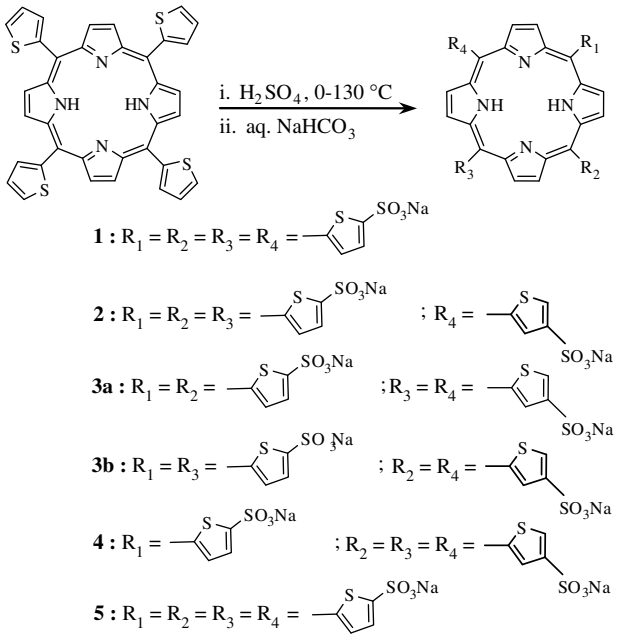
ABSTRACT

Sulfonation of *meso*-tetra(thien-2′-yl)porphyrin with concentrated sulfuric acid was found to produce several tetrasulfonated *meso*-tetra(thien-2′-yl)porphyrin isomers, where sulfonic acid groups were substituted at the 5- or the 4-positions of the thienyl groups, and the tetrasodium salts of the isomers were successfully isolated by reversed-phase HPLC. Temperature dependence of the production ratio of the isomers revealed that sulfonation reactions at the 5- and the 4-positions of 2-porphyrinylthiophene occur under kinetic and thermodynamic control, respectively.

The sulfonation of aromatic compounds is a well-known reversible electrophilic substitution reaction, which leads to regioselective sulfonation under kinetically and thermodynamically controlled conditions. Temperature dependent sulfonation of naphthalene is a typical example of such reactions, which has attracted considerable amount of experimental and theoretical studies.[1] In the case of five-membered aromatic rings, electrophilic substitution occurs at both α- and β-positions depending on their substituents and the reaction condition;[2] however, there has been no report on temperature dependent regioselective sulfonation to the best of our knowledge. Herein, we report that the sulfonation of 2-porphyrinylthiophene with concentrated sulfuric acid shows high positional selectivity at the 5- and the 4-positions depending on temperature. In this study, we first tried to synthesize *meso*-tetrakis(5-sulfothien-2′-yl)porphyrin (T(5-STh)P)[3] aiming to examine its self-assembling behaviour because of its potential *J*-aggregate formation like protonated *meso*-tetrakis(4-sulfonatophenyl)porphyrin *J*-aggregate.[4] In the course of preparing T(5-STh)P according to the reported literature,[3] we found that the sulfonation of *meso*-tetra(thien-2′-yl)porphyrin (TThP) with concentrated sulfuric acid produces unreported sulfonated TThP isomers, whose sulfonic acid groups are substituted at the 4-positions of the thienyl groups (Scheme 1). For gaining insight into the reaction mechanism, the temperature dependence of the sulfonation was examined.

TThP was synthesized through a similar procedure with the reported literature.[5] Sulfonation of TThP was carried out with 96% sulfuric acid at 0–130 °C for 1 h.[6] The neutralized reaction mixture with $NaHCO_3$ was separated by reversed-phase HPLC, and the tetrasodium salts of sulfonated *meso*-tetra(thien-2′-yl)porphyrin isomers of **1**, **2**, **3a** + **3b**, **4** and **5** were successfully isolated (Scheme 1).[7] The compounds **1**–**5** were characterized by UV–vis, ^1H NMR, elemental analyses and mass spectroscopy.[8] ^1H NMR spectra of all the compounds were measured at 80 °C because of the substantial broadening of the signals accompanied with aggregation and/or tautomerism at room temperature (Fig. 1). The ^1H NMR spectra of the isomers only consisted of signals of the pyrrole and the thienyl protons. The two couples of the doublets of the thienyl groups (J_1 = 3.5, J_2 = 1.5 Hz) revealed that the sulfonic acid groups are



Scheme 1.

* Corresponding authors. Tel.: +81 3 5452 5297; fax: +81 3 5452 5299.
E-mail addresses: arai@dsc.rcast.u-tokyo.ac.jp (Y. Arai), csegawa@mail.ecc.u-tokyo.ac.jp (H. Segawa).

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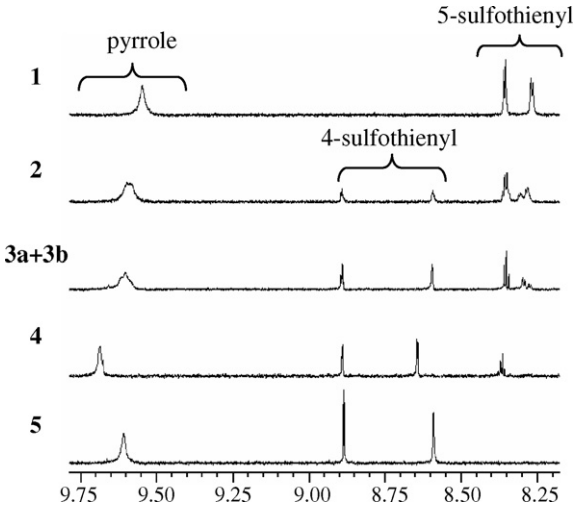


Figure 1. ^{1}H NMR spectra of **1**–**5** in D_2O at 80 °C.

substituted at the 5- and the 4-positions of the thienyl groups. The ratio of the total areas of the signals corresponding to the 5- and the 4-sulfothienyl groups made clear the assignment of each isomer. The slight difference of the peak maxima of UV–vis absorption spectra among the isomers is consistent that the 3-positions of the thienyl groups are not substituted by sulfonic acid groups.[9] It is remarkable that the porphyrin isomers with 5- and 4-sulfothienyl groups could be separated in spite of the seemingly slight structural difference. The successful separation may be due to a considerable difference in their electronic properties,[10] which could differentiate the steric structure such as the rotational angles between the porphyrin core and the thienyl groups.

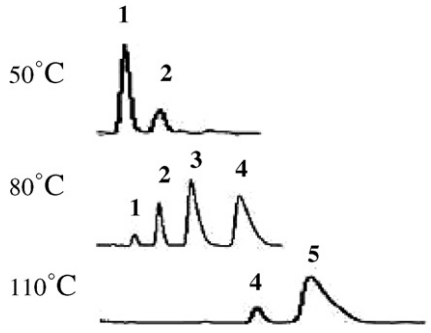


Figure 2. HPLC chromatograms of the reaction products sulfonated at various temperatures.

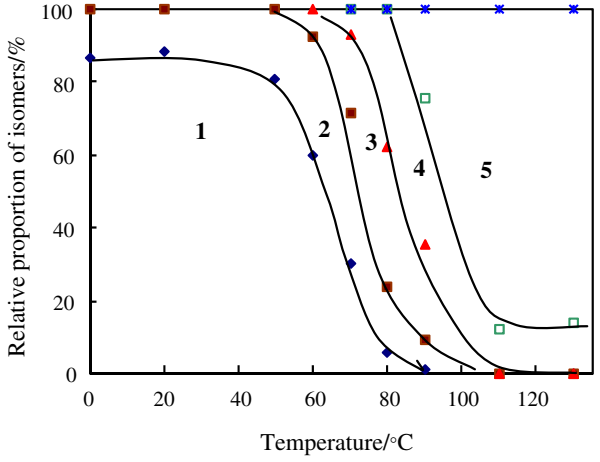
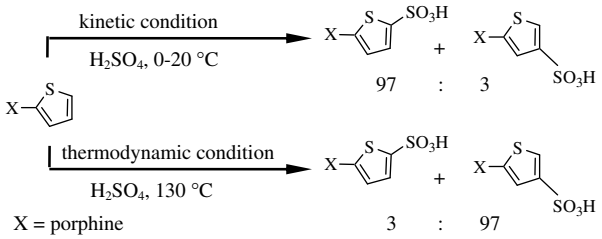


Figure 3. Relative production proportion of **1**–**5** as a function of the sulfonation temperature of TThP.



Scheme 2.

The production yields of the compounds **1**–**5** depended strongly on the reaction temperature, as is shown in HPLC chromatograms of reaction products sulfonated at various temperatures (Fig. 2). Figure 3 shows the diagram depicting the relative production proportion of each isomer to all isomers as a function of the sulfonation temperature of TThP. The diagram demonstrates that a predominant product changes from **1** at lower temperatures to **5** at higher temperatures. This result reveals a high positional selectivity of the sulfonation of 2-porphyrinylthiophene, where the electrophilic substitution reaction at the 5- and the 4-positions occurs under kinetic and thermodynamic control conditions, respectively (Scheme 2).

This finding will lead to further progress of sulfonation reaction of five-membered aromatic compounds and provide important information for the sulfonation of thiophene derivatives.

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References and notes

1. Donaldoson, N. *The Chemistry and Technology Compounds*; Edward Arnold: London, 1958; Nowicki, L.; Zarzycki, R. *J. Chem. Tech. Biotechnol.* **1987**, *39*, 149.
2. Marino, G. *Adv. Heterocycl. Chem.* **1971**, *13*, 235; Belen'kii, I. L.; Kim, G. T.; Suslov, A. I.; Chuvylkin, D. N. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 855; Belen'kii, I. L.; Nesterov, I. D.; Chuvylkin, D. N. *Chem. Heterocycl. Comp.* **2006**, *42*, 1414; Mizuno, A.; Kan, Y.; Fukami, H.; Kamei, T.; Miyazaki, K.; Matsuki, S.; Oyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6609; Arduini, A.; Pochini, A.; Secchia, A.; Ugozzoli, F. *Tetrahedron Lett.* **2003**, *44*, 5755.
3. Igarashi, S.; Saeki, T.; Yotsuyanagi, T. *Bunseki Kagaku* **1983**, *32*, 39.
4. Ohno, O.; Kaizu, Y.; Kobayashi, H. *J. Chem. Phys.* **1993**, *99*, 4128; Pasternack, R. F.; Schaefer, K. F.; Hambright, P. *Inorg. Chem.* **1994**, *33*, 2062; Ribo, J. M.; Crusats, J.; Farrera, J. A.; Valero, M. L. *J. Chem. Soc., Chem. Commun.* **1994**, 681.
5. Adler, A. D.; Losgo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
6. TThP (10 mg) was stirred with 96% sulfuric acid (1 ml) for an hour at several temperatures from 0 to 130 °C. The reaction mixture was put in sufficient amount of acetone to remove unreacted sulfuric acid, and the resulting green precipitate was filtered. The filtered solid was dissolved in distilled water, and the green solution of the porphyrin in the diacid form was changed into its purple freebase form by adding saturated aqueous solution of $NaHCO_3$. The dried solid mixture was extracted with methanol for removing excess salts.
7. Reversed-phase liquid chromatography was performed using a Shimadzu Shim-pack PREP-ODS(H)Kit mounted on a Shimadzu LC-6AD HPLC system. All the experiments were conducted at room temperature. As a mobile phase, methanol/water (typically 54:46, v/v: the composition was changed depending on conditions such as concentration and reaction temperatures) with 0.01 M sodium phosphate buffer (pH 6.8) was used. The reaction mixtures dissolved in distilled water were injected into the sample loop (5 ml). Five fractions with similar absorption spectra were observed, and the area ratio of each fraction (monitored with UV–vis absorption) was found to change systematically depending on the sulfonation temperature. Collected fractions were purified out of salt mixture by utilizing the same HPLC system, where the first eluent of methanol/water (20:80, v/v) extracts majority of inorganic salts and the second

eluent of methanol extracts remaining porphyrins. Compound **1** exited from the column first, and the retention time of other isomers became longer with the increasing number of 4-sulfothienyl group. The total yields of the tetrasodium salts of sulfonated *meso*-tetrakis(thien-2′-yl)porphyrin isomers at each reaction temperature were 54% (20 °C), 49% (50 °C), 50% (80 °C), 51% (110 °C) and 15% (130 °C).

8. For determining the molar absorption coefficients of aqueous solutions of each isomer, porphyrin concentrations were estimated from the concentrations of sulfur measured by ICP-AES.
   Compound **1**: ^{1}H NMR (D_2O, 500 MHz, 80 °C): δ = 8.27 (d, 1 H), 8.36 (d, 1H), 9.55 (s, 2H); ^{13}C NMR (D_2O, 400 MHz, 80 °C): δ = 110.9, 128.7, 131.3, 134.3, 145.3, 148.6, 167.8; Anal. Calcd for $C_{36}H_{18}N_4Na_4O_{12}S_8{\cdot}12H_2O$: C, 34.23; H, 3.35; N, 4.44; Found: C, 34.46; H, 3.53; N, 4.27; ESI-MS (m/z): $[M-3Na]^{3-}$ 325.9, $[M-4Na]^{4-}$ 238.7; UV–vis (H_2O): λ_{max}/nm ($\log\varepsilon$) = 423 (5.55), 523 (4.15), 563 (3.81), 587 (3.85), 648 (3.29).
   Compound **2**: ^{1}H NMR (D_2O, 500 MHz, 80 °C): δ = 8.28 (d, 3H), 8.31 (d, 3H), 8.35 (d, 1H), 8.37 (d, 1H), 9.59–9.60 (m, 8H); ESI-MS (m/z): $[M-3Na]^{3-}$ 325.9, $[M-4Na]^{4-}$ 238.7; UV–vis (H_2O): λ_{max}/nm ($\log\varepsilon$) = 422 (5.52), 522 (4.16), 562 (3.81), 585 (3.85), 646 (3.29).
   Compound **3a** + **3b**: 645.5; ^{1}H NMR (D_2O, 500 MHz, 80 °C): δ = 8.27 (d, 2H), 8.29 (d, 2H), 8.35 (d, 1H), 8.36 (d, 1H), 8.60 (m, 3H), 8.90 (m, 3H), 9.60 (m, 12H); ESI-MS (m/z): $[M-3Na]^{3-}$ 325.9, $[M-4Na]^{4-}$ 238.7; UV–vis (H_2O): λ_{max}/nm ($\log\varepsilon$) = 421 (5.53), 522 (4.16), 562 (3.80), 585 (3.84), 645 (3.25).
   Compound **4**: ^{1}H NMR (D_2O, 500 MHz, 80 °C): δ = 8.36 (d, 1H), 8.37 (d, 1H), 8.64 (m, 3H), 8.89 (m, 3H), 9.69 (s, 8H); ESI-MS (m/z): $[M-3Na]^{3-}$ 325.9, $[M-4Na]^{4-}$ 238.7; UV–vis (H_2O): λ_{max}/nm ($\log\varepsilon$) = 421(5.54), 522 (4.17), 562 (3.79), 584 (3.85), 646 (3.28).
   Compound **5**: ^{1}H NMR (D_2O, 500 MHz, 80 °C): δ = 8.59 (d, 1 H), 8.89 (d, 1H), 9.61 (s, 2H); ^{13}C NMR (D_2O, 400 MHz, 80 °C): δ = 111.2, 130.2, 131.6, 132.7, 143.4, 143.7, 164.8; Anal. Calcd for $C_{36}H_{18}N_4Na_4O_{12}S_8{\cdot}10H_2O$: C, 35.23; H, 3.12; N, 4.57; Found: C, 36.01; H, 3.20; N, 4.52; ESI-MS (m/z): $[M-3Na]^{3-}$ 325.9, $[M-4Na]^{4-}$ 238.7; UV–vis (H_2O): λ_{max}/nm ($\log\varepsilon$) = 421 (5.55), 522 (4.17), 562 (3.79), 587 (3.84), 646 (3.31).
9. Bruckner, C.; Foss, P. C. D.; Sullivan, J. O.; Pelto, R.; Zeller, M.; Birgea, R. R.; Crundwell, G. *Phys. Chem. Chem. Phys.* **2006**, *8*, 2402.
10. The pK_{a_1}s of **1** and **5** were measured as 5.3 and 6.7, respectively. The large difference in pK_{a_1} means that the electronic properties of 5- and 4-sulfothienyl groups differ in a considerable extent.