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Synthesis and characterization of a water-soluble porphyrin with a cyclic sulfone

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ABSTRACT

Water-soluble sulfonated tetraarylporphyrins are studied in a wide variety of contexts including as analytical reagents and as possible agents in cancer photodynamic therapy as well as in antiviral and antidiabetic applications. Herein, we report the first synthesis of a pentasulfonated porphyrin bearing an internal cyclic sulfone ring. Treatment of 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin (TPPS4) with fuming H_2SO_4 gave a structure consistent with initial sulfonation followed by dehydration to give a sulfone bridge between an ortho-position of one of the phenyl groups and a β-pyrrole position on the porphine ring (TPPS4Sc). The structure was established by electrospray mass spectrometry and ^1H NMR. The Soret UV–visible absorption is red shifted by about 32 nm compared to that of TPPS4.

Sulfonated tetraphenylporphyrins [e.g., 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin, TPPS4] are increasingly used in a variety of contexts. A wide variety of derivatives are now known, with the large majority having one sulfonic acid per phenyl ring.[1] Sulfonated porphyrins have been shown to inhibit the human immunodeficiency virus.[2–8] Porphyrins with more than four sulfonic acids have been shown to be active, specifically the octasulfonated mesityl porphyrin[6] and mixtures of sulfonated naphthylporphyrins in which many of the components have more than four sulfonic acids per porphyrin.[4] We wished to develop approaches to additional sulfonated tetraphenylporphyrins. Herein we report that reaction of TPPS4 with fuming sulfuric acid gives the first member of a new class of porphyrins in which a sulfone group serves as a bridge between a phenyl ring and a β-pyrrole position.

TPPS4 is commonly made from *meso*-tetraphenylporphyrin (TPP) and concentrated H_2SO_4.[1] In our hands, treatment of TPPS4 with this reagent under dark for 14 d at rt did not result in any further sulfonation of the porphyrin. However, treatment with fuming H_2SO_4 for 2 h at rt (Scheme 1), followed by removal of water and dissolution of the residue in methanol gave a mixture with substantial absorbance at about 440 nm. High performance liquid chromatography (HPLC) of the mixture visualized at 410 nm showed that it was predominantly the starting material TPPS4 (eluting at 14.0 min) with no other peak >5% of this peak. However, when the chromatogram was visualized at 450 nm, a strong new peak eluting at 13.2 min was observed. Under these chromatographic conditions, tri(4-sulfonatophenyl)-monophenyl-porphyrin [TPPS3] elutes at 20.5 min. Thus, the new compound was likely to have a net charge of −4 under the chromatographic conditions. When the reaction time was lengthened to 6 h, the peak at 13.2 min decreased in intensity and a second new peak appeared at 12.4 min when the chromatogram was visualized at 450 nm. When the reaction time was lengthened to 24 h, many small components absorbing at 450 nm were seen. To isolate the first-formed of the new products, the fuming H_2SO_4 treatment was stopped after 2 h to simplify the reaction mixture components. The product eluting at 13.2 min (TPPS4Sc) was isolated.[9]

TPPS4Sc has a Soret band at 444 nm and weak Q bands at 554, 602, and 693 nm (Fig. 1). The bands are red shifted compared to those of TPPS4. In particular, the Soret band of TPPS4Sc is red shifted by about 32 nm. Red shifts of the Soret band are commonly due to protonation of the inner nitrogens (which have a pK_a of about 5.0[1]). However, this long wavelength Soret band was also observed under basic conditions. The red shift of about 32 nm in aqueous solution is too large to be ascribed to sulfonation at the β-pyrrole position; sulfonation at this position results in a bathochromic shift of 3–5 nm per sulfonic acid.[10,11] Another possibility is that the conjugation of the ring has been extended. The most likely structure is one in which initial sulfonation is followed by loss of water to give an intramolecular sulfone.[12,13] This sulfone is expected to have a UV–visible absorbance at longer wavelength as has been observed in the studies of the monocycloketo-porphyrins. The addition of a cyclic keto bridge results in a 37 nm red shift compared to TPP itself (data in CH_2Cl_2).[14,15] The Soret of a cyclic enamine nickel porphyrin is red shifted by 14 nm compared to that of the parent NiTPP (data in CH_2Cl_2).[16,17]

The high resolution mass spectrum of TPPS4Sc gave a molecular formula of $C_{44}H_{27}N_4O_{14}S_5$, consistent with a structure in which SO_2 had been added to the molecule. The negative-ion mode electrospray mass spectrum [(−)ESI-MS] indicated that the parent compound (M, 996) lost one ($M-H^+$, 995), two [($M-2H^+$)/2, 497],

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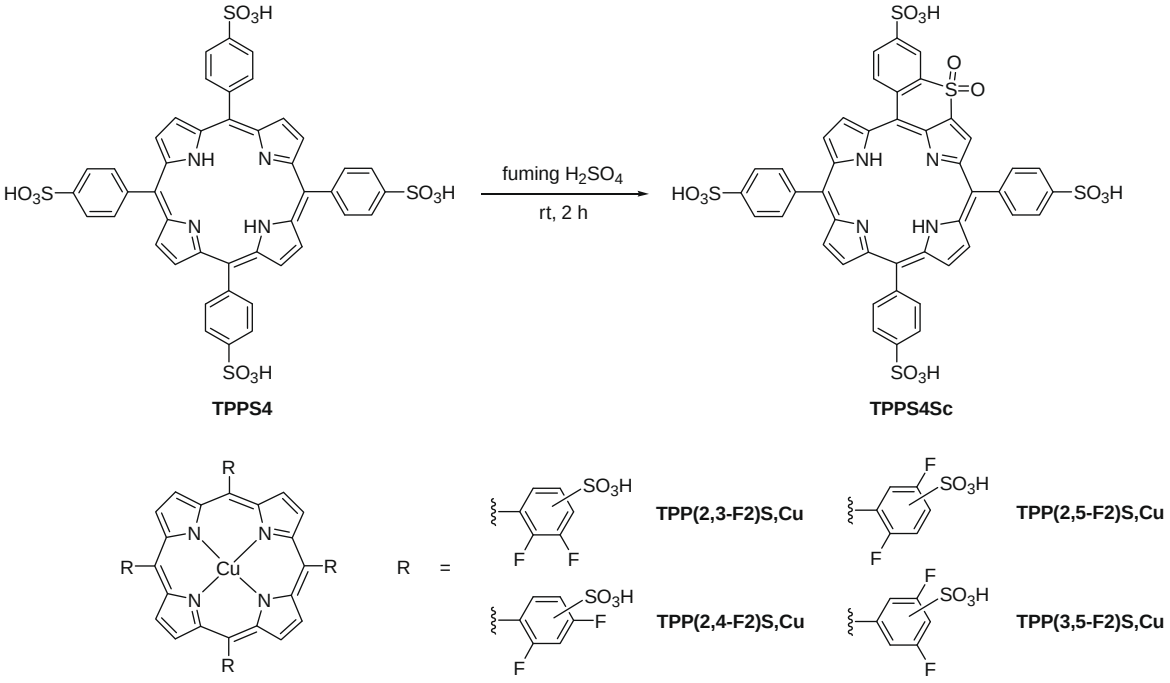

Scheme 1. Conditions for synthesis of TPPS4Sc and structures of TPPS related compounds.

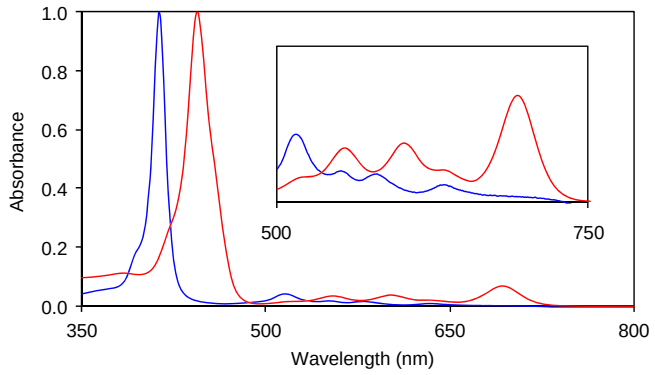

Figure 1. Normalized absorption spectra of TPPS4 (blue) in NH_4OAc aqueous buffer (20 mM, pH 7.7) and TPPS4Sc (red) from the HPLC separation on a ZORBAX Eclipse XDB-C18 (4.6 × 50 mm) column with an elution gradient of 5% MeOH in NH_4OAc buffer (20 mM, pH 7.7) to 38% MeOH over 15 min.

and three [$(M-3H^+)/3$, 331] protons to give net charges of −1, −2, and −3, respectively. The MS/MS spectrum showed a clear pattern of fragmentation. The parent ion ($M-H^+$, 995) lost SO_2 (64) to give peaks at 931 and 867, assigned as $M-SO_2-H^+$ and $M-2SO_2-H^+$. Loss of SO_2 has been observed previously for sulfonated tetrapyrroles.[18] The ^1H NMR showed complicated sets of peaks for the pyrrole and phenyl protons because of the sulfone-induced asymmetry. Integration indicated that one of the phenyl photons shifted downfield by 0.3–0.9 ppm to the pyrrole proton region; this is presumably the proton between the sulfonic acid and the sulfone group. Similar large downfield chemical shifts have been observed for benzene hydrogens between two sulfonic acids.[19]

As outlined above, sulfonation for longer times gave additional species. The component eluting at 12.4 min had a Soret maximum of 452 nm (diode array HPLC). This red shift indicates an additional extension of the conjugation. This species is therefore likely to have a second sulfone bridge (six isomers possible). In the nickel cyclic ketoporphyrin series, a second ketone bridge results in an additional 7–75 nm red shift depending on the isomer formed.[20]

The cyclic sulfone structure also explains the spectra of sulfonated difluoroTPP derivatives studied as anti-HIV therapeutic agents.[3] The spectral characteristics of the Cu chelates of sulfonated difluoroTPP derivatives (Scheme 1) were strongly dependent on the positions of the fluorine substituents (Fig. 2). TPP with fluorines at the 2- and 4-positions gave a product mixture with a λ_{max} at 412 nm, indicating no formation of the cyclic sulfone. This is in line with expected sulfonation patterns; fluoro groups are predominantly *para* (99.1%) and *ortho* (0.9%) directing for sulfonation.[21] Sulfonic acids at the 3- and 5-positions would not be close enough to the pyrrole rings to form an intramolecular sulfone. In contrast, TPP with fluorines at the 3- and 5-positions gave a product mixture with a broad, short band at 448 nm with a slight shoulder at about 490 nm. The 3,5-difluoro substituent pattern would result in sulfonation at the 2-, 4-, and 6-positions; the 2- and 6-sulfonic acids would be able to form cyclic sulfones, thus resulting in a significant red shift of the Soret of the product mixture. The 2,3-difluoro- and 2,5-difluorotetraphenylporphyrins had 445–450 nm spectral bands in addition to the Soret at 415–420 nm. These spectra were

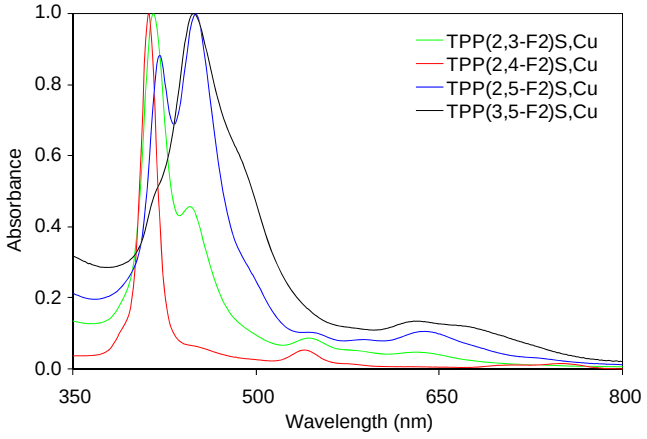

Figure 2. Normalized absorption spectra of the Cu chelates of difluoro derivatives of TPPS4 in NH_4OAc aqueous buffer (20 mM, pH 7.7).

consistent with mixtures of products, with only some components able to cyclize to the sulfone, as expected from the *ortho*, *para* directing nature of the fluorine substituents. The initial position of sulfonation could be either on the phenyl ring or on the porphine ring; sulfonation can occur at the β-pyrrole positions for selected structures.[10,11]

In conclusion, sulfonation of TPPS4 with fuming H_2SO_4 adds one or more additional sulfonic acids to the molecule. The cyclic sulfone form of tetraphenylporphyrin (TPPS4Sc) has been reported for the first time. This cyclic sulfone structure explains previous observations on spectra of difluorotetraphenylporphyrin derivatives and gives a direct synthesis of sulfonated porphyrins with red-shifted spectra, which may be useful in a variety of studies.

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References and notes

1. Hambright, P. Chemistry of Water Soluble Porphyrins. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; pp 129–210.
2. Dixon, D. W.; Marzilli, L. G.; Schinazi, R. F. *Ann. N.Y. Acad. Sci.* **1990**, *616*, 511.
3. Vzorov, A. N.; Dixon, D. W.; Trommel, J. S.; Marzilli, L. G.; Compans, R. W. *Antimicrob. Agents Chemother.* **2002**, *46*, 3917.
4. Dixon, D. W.; Gill, A. F.; Giribabu, L.; Vzorov, A. N.; Alam, A. B.; Compans, R. W. *J. Inorg. Biochem.* **2005**, *99*, 813.
5. Vzorov, A. N.; Bozja, J.; Dixon, D. W.; Marzilli, L. G.; Compans, R. W. *Antiviral Res.* **2007**, *73*, 60.
6. Song, R.; Witvrouw, M.; Schols, D.; Robert, A.; Balzarini, J.; De Clercq, E.; Bernadou, J.; Meunier, B. *Antiviral Chem. Chemother.* **1997**, *8*, 85.
7. Dairou, J.; Vever-Bizet, C.; Brault, D. *Antiviral Res.* **2004**, *61*, 37.
8. Vargas, F.; Rivas, C.; Zoltan, T.; Padron, L.; Izzo, C.; Lopez, V.; Gomez, L.; Pujol, F.; Rangel, H.; Garzaro, D.; Fabbro, R. *Med. Chem.* **2008**, *4*, 138.
9. The reaction mixture was purified via HPLC on an analytical C-18 column (ZORBAX Eclipse XDB-C18, 4.6 × 150 mm) with an elution gradient of 5% MeOH in NH_4OAc buffer (20 mM, pH 7.7) to 60% MeOH over 15 min at 1.0 ml/min to give TPPS4Sc: ^1H NMR (500 MHz, DMSO-d_6) 9.80 (s, 1H, cyclized pyrrole), 8.99–8.56 (7H, 6H from pyrrole and 1H from cyclized phenyl), 8.27–8.05 (m, 14H, phenyl). HRMS (ESI) calcd for $C_{44}H_{27}N_4O_{14}S_5$ ($M-H^+$) 995.0127, found 995.0117.
10. Artaud, I.; Benaziza, K.; Mansuy, D. *J. Org. Chem.* **1993**, *58*, 3373.
11. García-Ortega, H.; Ribó, J. M. *J. Porphyrins Phthalocyanines* **2000**, *4*, 564.
12. Hajipour, A. R.; Zarei, A.; Khazdooz, L.; Pourmousavi, S. A.; Mirjalili, B. B. F.; Ruoho, A. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 2029.
13. Alizadeh, A.; Khodaei, M. M.; Nazari, E. *Tetrahedron Lett.* **2007**, *48*, 6805.
14. Hogan, C. F.; Harris, A. R.; Bond, A. M.; Sly, J.; Crossley, M. J. *Phys. Chem. Chem. Phys.* **2006**, *8*, 2058.
15. Richeter, S.; Jeandon, C.; Gisselbrecht, J. P.; Ruppert, R.; Callot, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 6168.
16. Siri, O.; Smith, K. M. *Tetrahedron Lett.* **2003**, *44*, 6103.
17. Richeter, S.; Jeandon, C.; Gisselbrecht, J. P.; Graff, R.; Ruppert, R.; Callot, H. J. *Inorg. Chem.* **2004**, *43*, 251.
18. Dixon, D. W.; Gill, A. F.; Sook, B. R. *J. Porphyrins Phthalocyanines* **2004**, *8*, 1300.
19. Cerfontain, H.; Zou, Y. S.; Bakker, B. H. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 403.
20. Richeter, S.; Jeandon, C.; Kyritsakas, N.; Ruppert, R.; Callot, H. J. *J. Org. Chem.* **2003**, *68*, 9200.
21. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley: New York, 1992. pp 683–733.