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The synthesis and spectral investigation of a novel highly water-soluble, aggregation-free antimony(V)-phthalocyanine absorbing light in optical therapeutical window

Hiroaki Isago [a,*], Harumi Fujita [a], Tamotsu Sugimori [b]

[a] National Institute for Materials Science, 1-2-1, Sengen, Tsukuba, Ibaraki, 305 0047, Japan
[b] Graduate School of Medicine and Pharmaceutical Sciences, Univ. of Toyama, 2630, Sugitani, Toyama, 930 0194, Japan

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ABSTRACT

A novel antimony–phthalocyanine, $[Sb(H_3tsppc)(OH)_2]$, where H_3tsppc denotes monodeprotonated tetrakis {(2′,6′-dimethyl-4′-sulfonic acid)phenoxyl}phthalocyaninate, has been synthesized through sulfonation of $[Sb(tppc)(OH)_2]^+$ (tppc denotes tetrakis{(2',6'-dimethyl)phenoxyl}phthalocyaninate) in concentrated sulfuric acid. This compound is highly soluble in water (ca. 4×10^{-2} M) without surfactant or alcohol. Moreover, it has been found free from aggregation in water up to almost 10^{-4} M, unlike its copper and metal-free analogues, and show an intense optical absorption and emission band in optical therapeutical window (700–800 nm). The axial hydroxyl groups play a crucial role in disaggregation of the antimony derivative in water.

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1. Introduction

Organic pentavalent antimonals have been first-line drugs for chemotherapy of *Leishmaniasis*, which is endemic in 88 countries in tropical and subtropical region with ca. 400,000 new cases per year and causes significant morbidity and mortality [1–3]. However, as problems of clinical resistance to the existing antimonals in use have become aggravated, new antimonals need to be developed before the resistance spreads worldwide [1–3]. Pentavalent antimonals are known to be prodrugs in which the antimony(V) is reduced to antimony(III) when they work as drugs [1,4–7]. Antimony–phthalocyanine complexes can be promising candidates for new drugs because they are stable, powerful electron acceptors [8–12] and some derivatives undergo facile Sb^V/Sb^{III} conversion under mild conditions [11]. Furthermore, some of the antimony compounds used for the treatment of *Leishmaniasis* have also been investigated for potential antitumor activity [13].

Another interest with respect to antimony–phthalocyanines (hereafter phthalocyanine will be referred to Pc) in biochemistry is related to photosensitization of singlet oxygen ($^1O_2$) toward photodynamic therapy (PDT) of tumors [14,15] and photodynamic antimicrobial chemotherapy (PACT) [16]. Such photosensitizers are required to have high $^1O_2$ quantum yields as well as stability against the generated $^1O_2$. Antimony(V) Pcs are considered to be an excellent photosensitizer because of the presence of heavy atom (antimony), which would facilitate singlet-triplet intersystem crossing in their π system due to a metal-induced strong spin-orbit coupling [17]. Eventually, photophysical properties of antimony(III)-Pcs have been studied by Nyokong's group [18] and $^1O_2$-photosentizing ability of tetra-tert-butyl-substituted derivative has been exemplified in our earlier work [19]. Another advantage to employ antimony–Pcs as photosensitizers against conventional Pcs is their intense optical absorption in 700–800 nm [8–12,18–21] where absorption by tissues becomes weaker. Majority of Pcs are known to have their absorption maxima in 650–700 nm irrespective of their central element [22–24].

From the aforementioned viewpoints, such antimony compounds need to be sufficiently soluble in water because they must be incorporated into cells. We have quite recently reported a few amphiphilic antimony(V)–Pc derivatives bearing sulfates at their axial sites, but their solubility in water was insufficient and they needed aids of surfactant or alcohol to be sufficiently solubilized [20]. Solubility in water has to be improved because disuse of chemicals like surfactant or alcohol makes the patients less stressful. Another problem is that majority of water-soluble Pcs (numbers of papers have been published so far) undergo molecular aggregation to a considerable extent in water even though highly soluble [25]. Aggregation phenomena are common in chemistry of Pcs and are known to give rise to significant changes in their physical properties [20,26–29] and hence are an intriguing subject from a viewpoint of supramolecular chemistry [30]. However, it causes a serious problem in the aforementioned applications because it considerably reduces photochemical activities of the macrocycles [31].

* Corresponding author. Tel.: +81 29 859 2734; fax: +81 29 859 2701.
E-mail address: ISAGO.Hiroaki@nims.go.jp (H. Isago).

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We have undertaken synthesis of more water-soluble antimony–Pcs that are free from aggregation. In our previous work, we have found that presence of bulky peripheral substituents (tert-butyl) is capable to more effectively disaggregate antimony(V)–Pc in water than that of less bulky groups (hydrogen or n-butyl) [20]. Therefore, more bulky groups may more effectively achieve disaggregation. In this work, we have chosen 2′,6′-dimethylphenoxyl group as the peripheral substituent in the starting materials (i.e. tppc derivatives in Fig. 1) because it is not only bulky but also is readily sulfonated so that totally six highly hydrophilic groups (two axial sulfates and four peripheral sulfonates) can be introduced into one molecule. Contrary to our expectation, the axial hydroxyl groups were not replaced by sulfate, nevertheless, the obtained product ([$Sb(H_3tsppc)(OH)_2$]) has been found sufficiently soluble and free from aggregation in water. We report herein spectral study on the title compound as well as its copper ([$Cu(H_4tsppc)$]) and metal-free (H_6tsppc) analogues (Fig. 1) for comparison.

2. Experimental

2.1. Materials

2.1.1. Starting materials and the other chemicals

Preparation of the starting materials, [$Sb(tppc)(OH)_2]I_3$, (R= 2′,6′-dimethyl-phenoxyl, M = antimony(V); X = Y = OH^- in Fig. 1), [$Sb(tppc)Cl_2]SbCl_4$ (M = antimony(V); X = Y = Cl^-), [Cu(tppc)] (M = copper(II); X = Y = null) and H_2tppc (M = H_2; X = Y = null) (as mixtures of four regioisomers based on the positions of the peripheral substituents) is described in our earlier work [32]. All the other chemicals were of reagent grade and used without further purification.

2.1.2. Synthesis of $[Sb(H_3tsppc)(OH)_2]\ 11H_2O$

A 200 mg of [$Sb(tppc)(OH)_2]I_3$ (0.13 mmol) was dissolved to ice-cold conc. H_2SO_4 (16 ml). After filtration, the dark brown solution was dropwise added to ice (ca. 80 g) to precipitate solids, which were collected by filtration. It was dissolved into water (60 ml) and the solution, to which was added MeOH (6 ml), was concentrated into tar below 45 °C (it should be noted that without the addition of alcohol the solution vigorously bubbled during the evaporation). This was dissolved into MeOH (8 ml) and then ether (40 ml) was added to the solution to precipitate fine yellow-green powder, which turned tarry during the succeeding centrifugation process. This procedure was repeated 3 times until the product solidified. The solid was collected by centrifugation, dried over night at 40 °C under vacuum and then recrystallized 3 times from 50 ml of EtOH/hexane (8:42) until the mother liquid turned clear (79 mg, yield 37%). The same compound was obtained when [$Sb(tppc)(OH)_2]PF_6$ was used as the starting material. Anal (%), Found: C, 46.30; H, 4.06; N, 6.85; Calcd (for $C_{64}H_{71}N_8O_{29}S_4Sb$): C, 46.13; H, 4.29; N, 6.72. SIMS (Secondary Ion Mass Spectrometry; solid); m/z = 1467 ($^{121}Sb(H_3tsppc)(OH)_2$) and 1469 (its ^{123}Sb counterpart) as shown in Fig. 2a. IR (/cm^{-1}); 1189 s and 1106 s (ν(S = O)), 700 m (ν(CS)), 644 m and 589 m (δ(OSO)). UV/visible (UV/VIS); 724 nm, log ($\varepsilon/M^{-1}\times cm^{-1}$) = 5.16, 663 nm, 4.73, 427 nm, 4.51, 344 nm, 4.87 and 307 nm, 4.73 (EtOH).

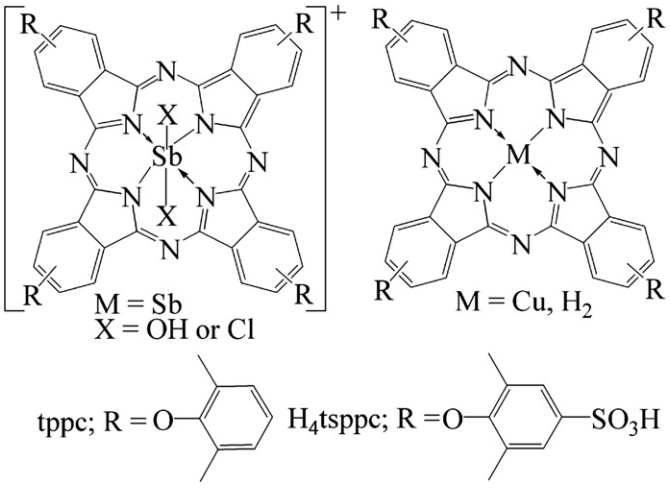

Fig. 1. Structures of the Pcs studied in this work (as mixtures of four regioisomers based on the positions of peripheral substituents).

2.1.3. Synthesis of $[Cu(H_4tsppc)]\ 5H_2O$

[Cu(tppc)] (50 mg; 0.047 mmol) was dissolved to ice-cold conc. H_2SO_4 (10 ml). After filtration, the dark brown solution was dropwise added to ice (ca. 50 g) and precipitated solids were collected by filtration and dissolved into water (150 ml) and again filtered. After MeOH (10 ml) was added, the filtrate was concentrated into tar below 50 °C. This was dissolved into MeOH (10 ml) and then ether (40 ml) was added to precipitate fine blue powder, which was collected by centrifugation (the powder turned tarry during the centrifugation); this procedure was repeated 6 times until the product solidified. This was dried over night at 40 °C under vacuum and then recrystallized 3 times from 10 ml of EtOH/hexane (1:3) until the mother liquid turned clear and dried over night at 80 °C under vacuum (56 mg, yield 81%). Anal (%), Found: C, 53.04; H, 4.36; N, 7.34. Calcd (for $C_{64}H_{58}N_8O_{21}S_4Cu$): C, 52.40; H, 3.99; N, 7.64. SIMS (solid); m/z = 1376 ($Cu(H_4tsppc)+H^+$). IR (/cm^{-1}); 1153 s and 1004 s (ν(S = O)), 700 m (ν (CS)), 638 m and 586 (δ(OSO)). UV/VIS; 677 nm, log ($\varepsilon/M^{-1}\times cm^{-1}$) = 5.30, 610 nm, 4.65, 342 nm, 4.91 and 276 nm, 4.80 (EtOH).

2.1.4. Synthesis of $H_6tsppc\ 6H_2O$

H_2tppc (107 mg; 0.11 mmol) was dissolved to ice-cold conc. H_2SO_4 (16 ml). After filtration, the dark brown solution was dropwise added to ice (ca. 50 g) and precipitated solids were collected by filtration and dissolved into water (50 ml) and again filtered. After MeOH (90 ml) was added, the filtrate was concentrated into tar below 50 °C. This was dissolved into MeOH (2 ml) and then acetone (48 ml) was added to precipitate fine blue powder, which was collected by centrifugation (the powder turned tarry during the centrifugation); this procedure was repeated 4 times until the product solidified. This was dried over night at 40 °C under vacuum and then recrystallized 3 times from 10 ml of EtOH/hexane (1:3) until the mother liquid turned clear and dried over night at 40 °C under vacuum (71 mg, yield 45%). $H_6tsppc\ 6H_2O$; Anal (%), Found: C, 53.83; H, 4.64; N, 7.87; Calcd. (for $C_{64}H_{62}N_8O_{22}S_4$): C, 54.00; H, 4.39; N, 7.87. MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization-Time-of-Flight Mass spectrometry; matrix-free); m/z = 1314 (H_6tsppc). IR (/cm^{-1}); ca. 1120–1180 s and 1000–1050 s (ν(S = O)), ca. 680–720 m (ν(CS)), ca. 620–680 m and ca. 530–580 m (δ(OSO)). UV/VIS (EtOH); 701 nm, log ($\varepsilon/M^{-1}\times cm^{-1}$) = 5.25, 664 nm, 5.17, 637 nm, 4.77, 603 nm, 4.55, 342 nm, 4.95 and 286 nm, 4.87.

2.1.5. Synthesis of $[Sb(H_3tsppc)Cl_2]$

[$Sb(tppc)Cl_2]SbCl_4$ (41 mg; 0.03 mmol) was dissolved to ice-cold conc. H_2SO_4 (2.5 ml). After filtration, the dark brown solution was dropwise added to ice (ca. 72 g) and precipitated solids were collected by filtration and washed with water (20 ml) until the washing turned neutral. After MeOH (10 ml) was added, the filtrate was concentrated into tar below 50 °C. This was dissolved into EtOH (4 ml) and then ether (40 ml) was added to make the product tarry. This procedure was repeated 3 times until solid was obtained (it should be noted the color of the solution gradually turned greenish in EtOH, MeOH, and CH_3CN). The solid was collected by centrifugation

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