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The syntheses of amphiphilic antimony(V)-phthalocyanines and spectral investigation on their aggregation behaviors in aqueous and non-aqueous solutions

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ABSTRACT

Three amphiphilic antimony(V)-phthalocyanines have been synthesized by treating $[Sb(R_4Pc)(OH)_2]^+$ salts in concentrated H_2SO_4 and isolated as zwitter ions, $[Sb(R_4Pc)(SO_4H)(SO_4)]$, where R_4Pc denotes tetra-substituted phthalocyaninate; R_4Pc = pc (R = H), tbpc (R = ^{t}Bu), and tObpc (R = O^{n}Bu). Their solubility (R = tbpc > pc >> tObpc in H_2O (much improved by the presence of surfactant or alcohol) while tbpc > tObpc >> pc in CH_2Cl_2) and aggregation behaviors are highly sensitive to the nature of the peripheral substituents. The pc and tbpc derivatives form well-behaved J-aggregates in aqueous media in the presence of surfactant or alcohol.

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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. 400000 new cases per year and causes significant morbidity and mortality [1,2]. 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]. It seems generally accepted that pentavalent antimonals are prodrugs in which the antimony(V) is reduced to trivalent when they work as drugs [3–6]. We have considered that antimony–phthalocyanine complexes can be promising candidates for new drugs because they are stable, powerful electron acceptors [7–11] and some derivatives undergo facile Sb^V/Sb^{III} conversion under mild conditions [11].

Another interest with respect to the antimony-phthalocyanines in biochemistry is related to photosensitization of singlet oxygen ($^1O_2$) toward photodynamic therapy (PDT) of tumors [12,13] and photodynamic antimicrobial chemotherapy (PACT) [14]. Such photosensitizers are required to have high $^1O_2$ quantum yields as well as stability against the generated $^1O_2$. Antimony(V) phthalocyanine derivatives 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 [15]. Eventually, photophysical properties of antimony(III)-phthalocyanines have been studied [16] and $^1O_2$-photosentizing ability of tetra-tert-butyl-substituted derivative has been exemplified in our earlier work [17]. Another advantage of antimony-phthalocyanines as photosensitizers against conventional phthalocyanines is their intense optical absorption in 700–800 nm [7–11,16,17] where absorption by tissues becomes weaker. Majority of phthalocyanines are known to have their absorption maxima in 650–700 nm region irrespective of their central element [18–20].

From the aforementioned viewpoints, such compounds need to be water-soluble because they must be incorporated into cells. Numbers of water-soluble phthalocyanines have been reported so far [21], but antimony derivatives are unknown. We have attempted to make water-soluble antimony(V)-phthalocyanines by introducing hydroxyl groups into its axial sites and bulky tert-butyl groups (Fig. 1; R = tert-butyl, X = Y = OH^-, n = 1) to enhance hydrophilicity and to improve solubility, respectively [22]. Although this compound is essentially insoluble in water, we have found that it makes hydrophilic colloidal solutions in water–acetone mixed solvent systems. We have been inspired by this finding that introduction of more hydrophilic axial ligands can improve water-solubility of antimony derivatives. As is expected, this working hypothesis has been exemplified in this work as discussed below. Moreover, as they need to be incorporated into tissues via biomembrane, their lipophilicity needs to be taken into consideration [7,8]. Amphiphilicity of compounds may be more favorable than only being water-soluble. In this work, we have undertaken syntheses of such new compounds.

On the other hand, even though sufficiently soluble in water, majority of phthalocyanines are susceptible to molecular aggregation in water [21], which provides an efficient nonradiative relaxation pathway and hence significantly shortens the excited state lifetimes of the phthalocyanines, consequently significantly reducing photochemical activities of

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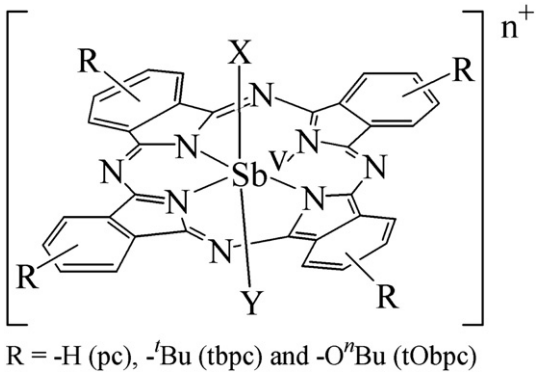

Fig. 1. The antimony(V)-phthalocyanines studied in this work. The X and Y denote axial ligands, and the R represents peripheral substituents; R = H (pc), ^{t}Bu (tbpc) and O^{n}Bu (tObpc). X = −OSO$_3$H, Y = −OSO$_3^-$, and n = 0 for the amphiphilic complexes obtained in this work, and X = Y = OH, and n = 1 for their starting materials.

the macrocycle [23]. Therefore, it is also interesting to study aggregation phenomena in aqueous solutions and compare them with those in non-aqueous media. It is well known that aggregation of phthalocyanines gives rise to significant changes in their optical absorption spectra [18–20,24,25] due to exciton coupling [26] and hence can be monitored by measuring their spectra in solutions. In this work, we report the aggregation-disaggregation phenomena of the new antimony-phthalocyanines under various conditions (concentration, solvent, and/or additives; e.g. surfactant and alcohol).

2. Experimental

2.1. Materials

2.1.1. Starting materials and the other chemicals

Preparation of starting materials, [Sb(pc)(OH)$_2$]I$_3$ [27], [Sb(tbpc)(OH)$_2$]I$_3$ 2H$_2$O [22] and [Sb(tObpc)(OH)$_2$]PF$_6$ [28] (Fig. 1; X = Y = OH$^-$; n = 1) (the latter two are mixtures of four regioisomers based on the positions of their peripheral substituents) is described elsewhere. All the other chemicals were of reagent grade and used without further purification.

2.1.2. Synthesis of (hydrogensulfato)(sulfato)(tetra-tert-butylphthalocyaninato)antimony(V), [Sb(tbpc)(SO$_4$H)(SO$_4$)] 5H$_2$O

The tbpc complex (X = SO_4^{2-}, Y = HSO_4^-; n = 0) has been synthesized by dissolving the starting [Sb(tbpc)(OH)$_2$]I$_3$ into conc. H$_2$SO$_4$ and then by pouring the solution on ice. In a typical experiment, a 100 mg of [Sb(tbpc)(OH)$_2$]I$_3$ 2H$_2$O (0.077 mmol) was dissolved into a 3 ml of ice-cold conc. H$_2$SO$_4$. After filtration, the dark brown solution was dropwise added to ice (ca. 100 g) to precipitate bluish-green solids. The solid was collected by filtration, washed with cold water until the washing turned almost neutral, and then dried over night at 60 °C in vacuo. This was dissolved into a 3 ml of EtOH and the solution was filtered and then a 30 ml of hexane was added to the solution to precipitate the product. The green solid was collected by centrifugation and was recrystallized from CH$_2$Cl$_2$/haxane (1:8). A 47 mg of the desired compound was obtained as [Sb(tbpc)(SO$_4$H)(SO$_4$)] 5H$_2$O (yield 53%). Anal. (found); C; 50.54%, H; 4.93%, N; 9.99%, Calcd. as C$_{48}$H$_{57}$N$_8$O$_{12}$S$_2$Sb; C; 50.49%, H; 5.21%, N; 9.81%. ESI-MS (acetone); m/z = 1051 (^{121}Sb(tbpc)(SO$_4$H)$_2$) and 1053 (^{123}Sb(tbpc)(SO$_4$H)$_2$). IR (/cm^{-1}); 1200–1250 (broad), 1044 (ν (SO$_4$)), 607, 590 (δ (SO$_4$)). UV/VIS; 717 nm ($\log(\varepsilon/M^{-1}*cm^{-1}) = 5.22$ (EtOH).

2.1.3. Synthesis of (hydrogensulfato)(sulfato)(tetra-n-butoxylphthalocyaninato)antimony(V), [Sb(tObpc)(SO$_4$H)(SO$_4$)] 2H$_2$O

The *n*-butoxyl analogue was synthesized in essentially the same way as that for the tbpc derivative: a 150 mg of [Sb(tObpc)(OH)$_2$]PF$_6$ (0.136 mmol) was dissolved into a 12 ml of ice-cold conc. H$_2$SO$_4$. After filtration, the dark brown solution was dropwise added to ice (ca. 100 g) to precipitate bluish-green solids. The solid was collected by filtration, washed with cold water until the washings turned neutral and then dried over night at 80 °C in vacuo (114 mg). This was dissolved into a 10 ml of CH$_2$Cl$_2$ and the solution was filtered and then a 200 ml of benzene was added to the solution to precipitate the product. This procedure was repeated 4 times until the supernatant turned almost colorless. This solid was collected by filtration and dried over night in vacuo (84 mg) and was further recrystallized from CH$_2$Cl$_2$/benzene twice. The desired product has been obtained in this way as dark green crystalline solids of [Sb(tObpc)(SO$_4$)(SO$_4$H)] 2H$_2$O, (yield 48%). Anal. (found); C; 50.54%, H; 4.93%, N; 9.99%, Calcd. as C$_{48}$H$_{57}$N$_8$O$_{12}$S$_2$Sb; C; 50.05%, H; 4.64%, N; 9.73%. ESI-MS (MeOH); m/z = 1115 (^{121}Sb(tObpc)(SO$_4$H)$_2$) and 1117 (the ^{123}Sb counterpart). IR (/cm^{-1}); ca. 1190, 1050 (ν (SO$_4$)), 592, 584 (δ (SO$_4$)). UV/VIS; 735 nm, log ε = 4.87 (CH$_2$Cl$_2$/EtOH = 4:1(v/v) ; this value is tentative because of significant aggregation effects (see below for the details)).

2.1.4. Synthesis of (hydrogensulfato)(sulfato)(phthalocyaninato) antimony(V), [Sb(pc)(SO$_4$)(SO$_4$H)] 4H$_2$O

The unsubstituted analogue has been synthesized in essentially the same way as that for the tbpc derivative: A 61 mg of [Sb(pc)(OH)$_2$]I$_3$ (0.058 mmol) was dissolved into a 100 ml of ice-cold conc. H$_2$SO$_4$. After filtration, the dark brown solution was dropwise added to ice (ca. 100 g) to precipitate bluish-green solids. The solid was collected by filtration, washed with cold acetone and then dried over night at 60 °C in vacuo (39 mg). A portion (30 mg) of this solid was dissolved into a 400 ml of MeOH-H$_2$O (9:1) and the solution was filtered and then a 600 ml of ether was added to the solution to precipitate the product (this procedure was twice repeated). This solid was collected by filtration and dried over night in vacuo (13 mg). The desired product has been obtained in this way as dark green crystalline solids of [Sb(pc)(SO$_4$)(SO$_4$H)] 4H$_2$O (yield 32%). Anal. (found); C; 42.95%, H; 2.74%, N; 12.34%, Calcd. for C$_{32}$H$_{16}$N$_8$O$_{12}$S$_2$Sb; C; 42.73%, H; 2.80%, N; 12.46%. Unlike the other two analogues, the unsubstituted species has not been detected in a protonated form by ESI-MS but detected as sodium and/or potassium salts (CH$_3$CN-H$_2$O (1:1)); m/z = 871 (^{121}Sb(pc)(SO$_4$Na)$_2$) and 873 (the ^{123}Sb counterpart); the complex has also been detected as m/z = 903 (^{121}Sb(pc)(SO$_4$K)$_2$) and 905 (the ^{123}Sb counterpart) upon the addition of an aqueous K$_2$SO$_4$ solution (1.7 mM)) (see ESI-1). IR (/cm^{-1}); ca. 1249, 1045 (ν (SO$_4$)), 601, 588 (δ (SO$_4$)). UV/VIS; 712 nm, log ε = 5.31 (MeOH).

2.2. Measurements

All the measurements of optical absorption spectra were performed with a Shimadzu UV-160A, a Shimadzu UV-1800, or a Hitachi U-3500 spectrophotometer. Emission spectra were recorded on a Hitachi F-2500 fluorescence spectrophotometer. Magnetic circular dichroism (MCD) spectra were recorded on a JASCO J-720 spectropolarimeter equipped with a JASCO MCD-104 electromagnet, which is capable to generate magnetic fields up to 0.8 T. A constant field of a magnitude of 0.65 T was applied to sample solutions during the measurements. ESI-MS spectra were measured with a JEOL-JMS-T100LC mass spectrometer or a Waters Platform LCZ (ZMD) spectrometer both in the positive and negative modes. Fourier-transform IR spectra were recorded on a Perkin-Elmer Spectrum One Spectrometer by a diffuse reflectance method in KBr media. All the measurements were done at room temperature (24 ± 1 °C). Geometry-optimization calculations on the phthalocyaninate ligands (i.e., pc^{2-}, tbpc^{2-}, and tObpc^{2-}) were carried out by using MOPAC (AM1) software.

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