Syntheses of Trisulfonated Phthalocyanines and Their Derivatives Using Boron(III) Subphthalocyanines as Intermediates

Svetlana V. Kudrevich, Sandra Gilbert, and Johan E. van Lier*

MRC Group in the Radiation Sciences, Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Québec J1H 5N4, Canada

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Phthalocyanines (Pc) and their symmetrically substituted derivatives have received extensive attention over the last decades due to their distinct properties (e.g., electrical conductivity,[1] electrochromism,[2] mesophase formation,[3] and aggregation into monolayers of Langmuir−Blodgett type),[4] which make them unique substrates for new materials.[5] Much less is known about the unsymmetrical derivatives of Pc, which are of particular interest in the development of materials for nonlinear optics[6] as well as for medical applications.[7,8]

The limited use of the latter type of compounds can be attributed to the difficulties encountered in isolating the desired products derived from the conventional synthetic approach involving condensation of two or more different phthalonitrile (diiminoisoindoline) derivatives. The complex statistically defined mixture obtained in this procedure requires time-consuming chromatographical separations, and the yields of desired products usually are very low.[9] Thus, efficient synthetic routes to each isomer are required. In this context three methods for the preparation of mono- and disubstituted lipophilic Pcs and their analogs are noteworthy: condensation of an iminoisoindoline derivatives with either 1,3,3-trichloroisoindoline,[10] a sterically crowded diiminoisoindoline,[11] or a 1,3-bis((3′-imino-1′-isoindolinydene)amino)-1,2,4-triazole (or its metal complex).[12] None of these methods have, however, been applied to the synthesis of Pcs featuring hydrophilic substituents, such as sulfo groups, on the benzo rings. The design of synthetic routes to water-soluble and amphiphilic Pcs carrying well-selected substituents remains a challenge. Due to water solubility and ease of formulation these compounds are particularly sought after as photosensitizers for medical application. Some amphiphilic Pcs, envisioned for this application, such as zinc mono(*tert*-butyl)trisulfoPc, could not be obtained using the conventional condensation of two different precursors. Recently, we reported a method for preparing monosulfonated Pcs and their derivatives *via* the Meerwein reaction, a procedure that affords selected positional isomers without chromatographical separation of polysulfonated mixtures.[13] However, di- and trisulfonated Pcs cannot be obtained *via* this route.

On account of this, we evaluated an alternative procedure for the preparation of unsymmetrical Pcs with identical substituents on three of the benzo rings. Preorganization of three phthalonitrile units as a subphthalocyanine (SubPc) of boron(III)[14,15] and subsequent conversion into a Pc macrocycle *via* reaction with various substituted diiminoisoindolines has proven to be an efficient procedure to obtain unsymmetrical Pcs featuring different lipophilic substituents, such as alkyl-, alkoxy-, (alkylthio)-, nitro-, and crown ester groups.[16] This kind of stepwise reaction is highly dependent on the reactants (SubPc and diiminoisoindoline) and often leads to a low yield of the expected Pcs due to the formation of other products originating from cleavage of the SubPc.[16f,g] This template reaction, employing SubPcs, has not previously been applied to the preparation of water-soluble Pcs, and SubPcs substituted with hydrophilic moieties attached to the benzo rings have, to our knowledge, not previously been reported.

Compared to Pcs, SubPcs, i.e., the lower homologues of Pc composed of three diiminoisoindoline units, have been much less studied. This is mainly due to difficulties encountered with their purification.[14,16be,17] To synthesize tris(4-chlorosulfonyl)SubPcB(Br) (**2**) from 4-(chlorosulfonyl)phthalonitrile (**1**),[18] we used a commercially available 1 M solution of BBr_3 in dichloromethane (Scheme 1). The reaction was conducted in 1-chlorobenzene, which has a lower boiling point as compared to 1-chloronaphthalene, i.e., the solvent previously used for such cyclotrimerization. In contrast to the unsubstituted analog, which was synthesized at much higher temperatures (e.g., at the reflux temperature of 1-chloronaphthalene),[14] the reaction leading to **2** started readily at room temperature and was completed in 1 h at 40 °C. 1-Chlorobenzene was evaporated at reduced pressure, leaving product **2** as a dark purple solid. Compound **2** was obtained in high yield (>60%), and the assigned structure was confirmed

* To whom correspondence should be addressed. Tel.: (819) 563-5555, ext. 4603. Fax: (819) 564-5442. E-mail: jvanlier@courrier.usherb.ca.

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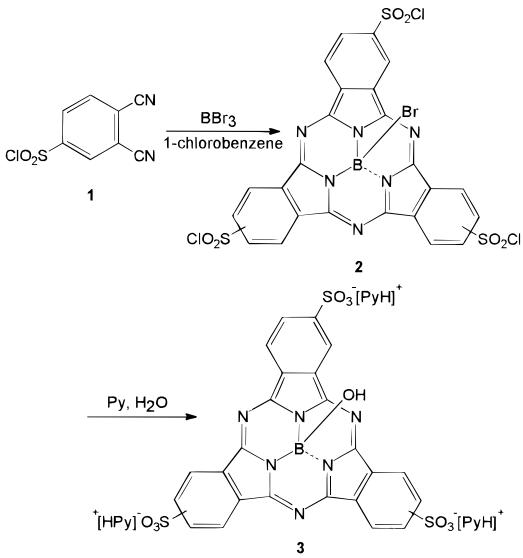
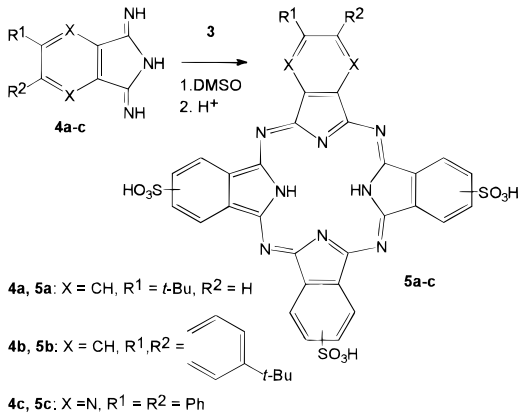
Scheme 1



Scheme 2



by FAB-MS, UV−vis, NMR, and IR spectroscopic data. No peaks corresponding to tris(chlorosulfonyl)SubPcBBr derivatives brominated on the benzo rings showed up in the mass spectra of **2**. Compound **2** is soluble in organic solvents (i.e., chloroform, toluene, methanol). The chlorosulfonyl groups of **2** are susceptible to rapid hydrolysis accompanied by destruction of the macrocycle, and the compound should be protected from atmospheric air. TLC of **2** on silica gel or alumina plates using chloroform as eluant revealed two spots corresponding to the C_1- and C_3-type isomers.[19] Unfortunately, we also detected rapid destruction of the compound on the adsorbent. Due to this unstability, we did not attempt chromatographical purification and used the material directly in the next step of the reaction sequence. Without modification, compound **2** cannot be used as precursor to prepare unsymmetrical Pcs since the chlorosulfonyl moieties may react with the imino groups of diiminoisoindolines. Thus, the sulfonyl chloride **2** was first converted to the sulfo acid derivative. Attempts to hydrolyze **2** in concd or diluted HCl, diluted aqueous solution of NaOH, or ammonia led to destruction of the boron SubPc macrocycle. Compound **2** was found to be stable in a mixture of water/pyridine (2:1). The solution was stirred for 12 h at room temperature, the solvent was evaporated under reduced pressure, and the residue was reprecipitated from acetone to afford the pyridinium salt **3** as golden purple crystals in 60% yield. Compound **3** was characterized by combustion analysis and spectroscopic data. Compound **3** is soluble in water, DMF, DMSO, and methanol. The UV−vis spectrum of **3** in water features a sharp absorption maximum at 569 nm, which is characteristic for SubPcs. HPLC analysis of an aqueous solution of the salt **3** revealed a single peak with t_R 12 min, which is similar to the t_R of tetrasulfonated PcM in this systems.[20]

The reactions of **3** with diiminoisoindoline derivatives **4a**−**c**[21] were all accomplished in dry DMSO (yield of Pc up to 31%), at temperatures lower than those required for similar ring expansion reactions reported earlier.[16] For example, compound **3** reacts with **4a** at room temperature (Scheme 2). Our attempts to perform this reaction with precursors other than 1,3-diiminoisoindolines, including *o*-dinitriles and 1-imino-3-thioisoindoline,[22] failed. The maximum temperature used for the preparation of the unsymmetrical Pcs **5a**−**c** from **3** was 70 °C. Excess diiminoisoindoline in the reaction mixture did not result in formation of the corresponding symmetrical metal-free Pc derivatives. Progress of the ring expansion reaction was followed spectrophotometrically: the intensity of the absorption bands, characteristic for the metal-free Pc **5a**, benzonaphthoporphyrazine **5b**, and azaphthalocyanine **5c** (around 650−700 nm), gradually increase during the course of the reaction, whereas the peak of the boron SubPc (around 570 nm) gradually disappears. The sulfoPc tripyridinium salts **5a**−**c** were precipitated from DMSO upon the addition of methanol and/or chloroform and isolated by filtration to yield almost pure products. Multiple redissolvation of the pyridinium salts in water, followed by reprecipitation with HCl, gave analytical samples of the corresponding sulfo acids. HPLC analysis[20] of the latter compounds showed the presence of a single fraction ($t_R \sim 20$ min), in each case consisting of three poorly resolved peaks of the type isomers, corresponding to the trisulfonated Pcs. No tetrasulfoPc, which might originate from the cleavage of boron trisulfoSubPc (as in the case of lipophilic SubPcs with electron-donating substituents[16f,g]), was found in the reaction mixtures for compounds **5a,c**, and only traces of tetrasulfoPc were formed in the case of **5b**. It is likely that the electron-withdrawing sulfo substituents and lower reaction temperatures are responsible for this clean reaction.

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Supporting Information Available: Experimental procedures, elemental analyses data for compounds **3** and **5a**−**c**, ^{1}H NMR and ^{13}C NMR spectra for compound **2**, MS data and UV−vis spectra for compounds **2, 3,** and **5a**−**c**, IR spectra for compounds **2** and **3**, HPLC analytical data, and retention times for all water-soluble compounds (4 pages).

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(21) 1,3-Diiminoisoindoline derivatives **4a**−**c** were obtained by treatment of the corresponding dinitriles with sodium methylate and ammonia in methanol. **4a** was obtained from 4-*tert*-butylphthalonitrile (commercially available from TCI America), **4b** from 6-*tert*-butyl-2,3-dicyanonaphthalene (Kovshev, E. I.; Puchnova, V. A.; Luk'yanets, E. A. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 364), and **4c** from 5,6-diphenyl-2,3-dicyanopyrazine (Rothkopff, H. W.; Wöhrle, D.; Müller, R.; Kossmell, G. *Chem. Ber.* **1975**, *108*, 875−886).

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