

# Synthesis and Properties of Water-soluble Crosswise-disubstituted Phthalocyanines

Salih Dabak<sup>a</sup> and Özer Bekaroğlu<sup>\*b</sup>

<sup>a</sup>TUBİTAK, Marmara Research Centre, Research Institute for Basic Sciences, Department of Chemistry, P.O. Box 21, 41470 Gebze, Kocaeli, Turkey

<sup>b</sup>Department of Chemistry, Technical University of Istanbul, 80626, Maslak, Istanbul, Turkey

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Crosswise-disubstituted metal-free phthalocyanines carrying two 2-(trimethylamino)ethylsulfanyl and two amino groups on peripheral positions have been synthesized by 2:2 condensation of 5-[2-(dimethylamino)ethylsulfanyl]-1,3-diiminoisoindoline and 1,1,3-trichloro-5-nitro-1*H*-isoindole.

The design of novel substituted phthalocyanines (pcs) closely follows the requirements of their intended applications. Since the aim of the present work is to prepare photosensitive materials for photodynamic therapy (PDT),<sup>1,2</sup> the active compounds should have features such as intense absorption on the lower-energy side of visible electromagnetic radiation and solubility in water. Although the synthesis of symmetrical tetra- or octa-substituted pcs by cyclotetramerization of a suitably derived phthalonitrile as the single precursor can be accepted as a relatively straightforward method, unsymmetrical pcs containing different substituents on the benzo groups are extremely difficult to obtain.<sup>3</sup>

Our group has been heavily engaged in the synthesis of novel pcs carrying macrocyclic substituents such as crown ethers,<sup>6,7</sup> monoaza crown ethers<sup>8</sup> and diaza-dioxa,<sup>9</sup> tetraaza-<sup>10</sup> and tetrathia-<sup>11</sup> macrocycles. Some unsymmetrical structures have also been acquired by making use of boron subphthalocyanines.<sup>12,13</sup> The immediate consequences of these peripheral substituents are enhanced solubility in common organic solvents and additional donor sites for alkali or transition metal ions. Pcs with four quaternized aminoethylsulfanyl substituents have been shown to be soluble in aqueous solution over a wide pH range.<sup>14</sup>

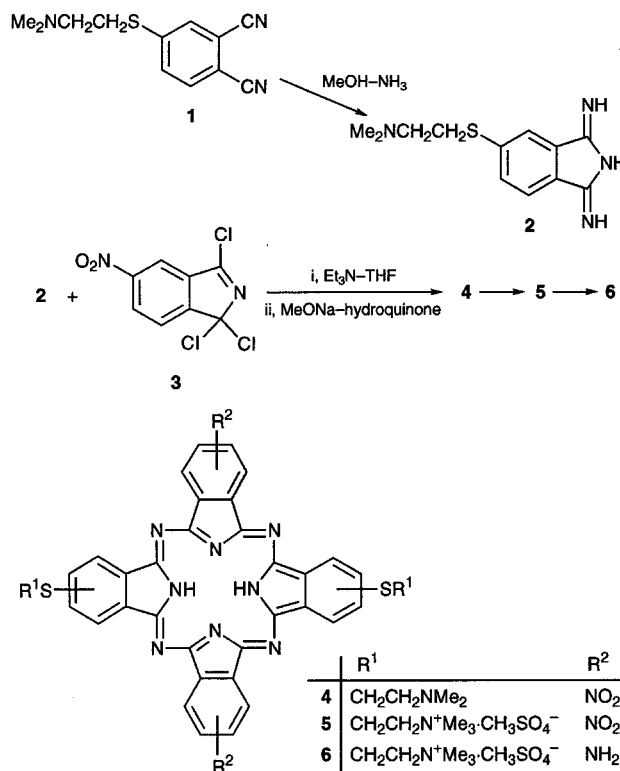
The synthetic procedure based on the crossed condensation of an iminoisoindoline with a 1,1,3-trichloroisoindole derivative was preferred<sup>15,16</sup> and the substituent on the first precursor was chosen to be 2-(dimethylamino)ethylsulfanyl and that on the latter to be nitro. Quaternization of the dimethylamino group and reduction of the nitro into an amine leads to the desired pc which is soluble in water and carries amino functions.

The required precursors to the crosswise-substituted pcs 4–6 are 2 and 3.<sup>15</sup> Starting from 4-nitrophthalonitrile, displacement of the nitro group with the SH function of 2-(dimethylamino)ethanethiol gave the phthalonitrile derivative 1 as reported earlier.<sup>14</sup> This was converted into the iminoisoindole compound 2 by treatment with ammonia in the presence of sodium methoxide. 3 was prepared by chlorination of 4-nitrophthalimide with PCl<sub>5</sub> in *o*-dichlorobenzene as reported in the literature.<sup>15</sup> The crosswise-substituted pc 4 was prepared from the condensation of 2 and 3 in 2:2 ratio in the presence of triethylamine, sodium methoxide and hydroquinone (Scheme).

The desired metallo derivatives of the pcs 4 could not be obtained, either by carrying out the condensation of 2 and 3 in the presence of a metal salt (NiCl<sub>2</sub> or CuCl) or by inserting the metal ion into the metal-free pc 4.

In order to convert 4 into a water-soluble derivative, quaternization with dimethyl sulfate was sufficient. Raney nickel and hydrazine hydrate were used to reduce the nitro substituents into amines.

The critical point in characterizing the new pcs 4–6 is to verify the condensation of the two precursors 2 and 3 in a 2:2 ratio. In addition to the elemental analysis results, mass



Scheme Synthesis of the pcs 4–6

spectra would be definitive. Unfortunately, we could not observe the molecular ion peaks for 4 or 5. However, a molecular ion peak at *m/z* 1003 was found for 6 together with some reasonable fragment ions by the CI technique. Since 6 is the last step among the three phthalocyanines (4–6), it might be accepted as a confirmation of the proposed structures for the first two compounds.

The <sup>1</sup>H NMR spectra of the new phthalocyanines 4–6 in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO gave rather broad peaks, as a consequence of both the aggregation of pc units and the presence of isomers, so it is difficult to differentiate between distinct protons. However, the ratio of aromatic to aliphatic protons appears to show that benzo groups with two different substituents are present in a 2:2 ratio. Also, the broad absorption around 6.6 ppm in 6 can be easily ascribed to NH<sub>2</sub> groups as it disappears on D<sub>2</sub>O exchange. The inner-core protons can be observed only in the case of 4 in CDCl<sub>3</sub>.

The IR spectra of the pcs indicates the presence of nitro groups by stretching vibrations at 1520 and 1340 cm<sup>-1</sup> for 4 and 5 respectively. After reduction, symmetric and asymmetric stretching vibrations of the amino groups in 6 appear at 3420 and 3340 cm<sup>-1</sup>.

The visible absorption spectra of pcs 4–6 differ in some ways from other reported pc derivatives. The split Q band absorption expected for these metal-free derivatives is not present and we have a shoulder at the higher-energy side in

\*To receive any correspondence.

**Table 1** Electrical conductivities of pcs 4–6

Sample	$\sigma_{dc}/\text{S cm}^{-1}$	
	In air	In vacuum
<b>4</b>	$1.03 \times 10^{-8}$	$2.36 \times 10^{-9}$
<b>5</b>	$1.17 \times 10^{-7}$	$6.20 \times 10^{-9}$
<b>6</b>	$5.44 \times 10^{-5}$	$6.38 \times 10^{-11}$

organic solvents (e.g.,  $\text{CHCl}_3$ , DMSO). Especially for the quaternized pcs **5** and **6**, which are also very soluble in water, Q band absorptions are extremely affected by the nature of the solvent. In an aprotic polar solvent (DMSO), the shift of Q bands from **5** to **6** is 24 nm as expected. In water, however, Q bands of both compounds show a blue shift to around 630 nm and the intensities are also lowered. Aggregation of pc units to form dimers, trimers, etc., in water is the main reason for these shifts in the spectra.

The d.c. conductivities as thin films in air and in a vacuum for the crosswise-disubstituted pcs **4–6** are given in the Table. These values correspond with those for semiconductive materials as encountered in a number of substituted pc derivatives.<sup>9,18</sup>

Techniques used:  $^1\text{H}$  NMR, IR, UV–VIS, FAB–MS, electrical conductivity

References: 19

Scheme: 1

Figure: Visible spectra of the quaternized pcs **5** and **6** in DMSO and in water

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