



Novel Water-Soluble Phthalocyanines Substituted with Phosphonate Moieties on the Benzo Rings

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Abstract: The synthesis and characterization of a series of phthalocyanine derivatives bearing phosphonate substituents directly bound to the aromatic rings of the phthalocyanine is described. These novel water-soluble phthalocyanine tetraphosphonates are of interest for different applications, particularly as photosensitizers in photodynamic therapy. Furthermore, this synthetic approach allows for more versatility in the preparation of hydrophilic macrocycles. Copyright © 1996 Elsevier Science Ltd

In addition to their traditional uses as dyes and photoconducting agents in photocopying devices, the importance of phthalocyanines (Pcs) is rapidly growing in many other fields. These include chemical sensors,¹ electrochromism,² molecular metals, photochemical etching, and liquid crystals.³ The water-soluble phthalocyanines are among the more effective photosensitizers used for the photodynamic therapy of cancer⁴ and the photoinactivation of viruses in stored blood products.^{5,6}

Among the water-soluble phthalocyanines, the sulfonated derivatives have received the most attention due to their accessibility. Conventional synthetic methods for preparing sulfonated phthalocyanines involve harsh acidic reaction conditions resulting in complex isomeric mixtures. New applications of water-soluble and amphiphilic phthalocyanines call for synthetic methods with greater control of regioselectivity and accessibility to diverse types of hydrophilic substituents. New procedures for preparing single isomers or well-defined constitutional isomeric mixtures of phthalocyanines and their aza-analogs, substituted with sulfo-, carboxy- and phosphonoalkyl groups, have been developed in our laboratory.⁷⁻¹⁰ As an extension of this work, we now report on the synthesis of phthalocyanines bearing phosphonate substituents directly bound to the aromatic rings of the macrocycle.

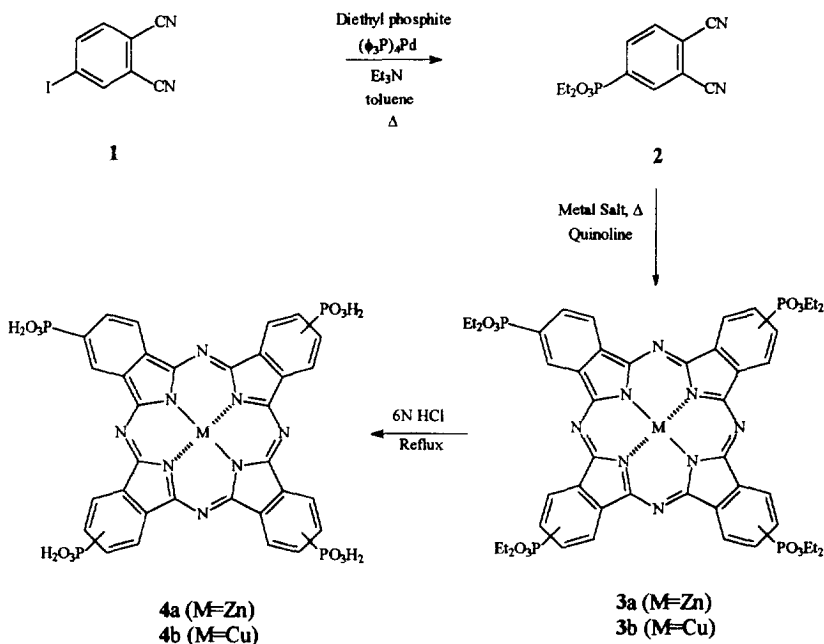
4-Diethoxyphosphinyl phthalonitrile **2** was prepared by phosphorylation of 4-iodophthalonitrile **1**¹¹ with diethyl phosphite in the presence of Pd⁰ catalyst and triethylamine in an inert atmosphere.¹² Column chromatography on silica gel using 40% methanol in toluene as eluant ($R_f = 0.32$) afforded compound **2** in 60% yield with the assigned structure being supported by elemental analysis and spectroscopic data.¹³

Complexation of the dinitrile **2** with different metal salts failed in the absence of solvent (probably due to the high melting point of this compound, decomp. > 220 °C) or when non-basic, high boiling solvents such as 2,4,6-trichlorobenzene, 1-chloronaphthalene, tetrahydronaphthalene, sulpholane etc. were used. The use of urea, which normally facilitates complexation of dinitriles, was not appropriate because of its possible interaction with the phosphonate moiety. Therefore, we conducted the reaction in basic solvents, such as quinoline or imidazole, providing an acceptor for the evolving acid while sparing the phosphonate ester bond.

Condensation of the dinitrile **1** with metal salts (zinc acetate dihydrate, copper (I) chloride, nickel chloride hexahydrate, cobalt (II) chloride hexahydrate) followed by extensive washing with methanol, hot water and acetone afforded the corresponding metal complexes **3a,b** in satisfactory yields (30-60%).¹⁴

Diethoxyphosphinyl substituted phthalocyanines are insoluble in most common organic solvents. They are, however, soluble in quinoline at spectral concentrations (10^{-6} M), exhibiting a $\lambda_{\text{max}} \sim 690$ nm depending on the nature of the central atom. The IR spectrum of zinc tetra(4-diethoxyphosphinyl)phthalocyanine **3a** features strong bands between $1163\text{-}1112\text{ cm}^{-1}$ (P=O stretch), and at 950 cm^{-1} (P-O-C aliph.).

Hydrolysis of the diethylphosphinyl group was accomplished by heating the complexes **3a-d** in 6N HCl (reflux, 20 h). Products **4a,b** were collected by filtration, washed with 1N HCl and methanol, then purified by reprecipitation from the slightly basic solution via the addition of conc. HCl.¹⁵ The resulting phthalocyanine tetraphosphonates are soluble in water. IR spectra are characteristic for the phosphonates, e.g. the spectrum of the Zn complex **4a** features bands at $1151, 1120\text{ cm}^{-1}$ (P=O) and 2900 (broad), $951\text{-}943\text{ cm}^{-1}$ (P-O-H). HPLC analysis of the complexes **4a,b**¹⁶ revealed a single peak for the phthalocyanine tetraphosphonate with a retention time (t_R) around 11 minutes for each compound (formation of four constitutional isomers postulated).



Of particular interest are the aggregation properties of these novel phthalocyanines. In 0.1N NaOH (pH >12), their solutions are green, giving a UV-visible spectrum corresponding to that of monomeric Pc with a strong absorption at ~ 680 nm with an ϵ of $225\ 000\ \text{M}^{-1}\ \text{cm}^{-1}$. In the meanwhile, in pH 5 buffer, these Pc give a blue solution and are highly aggregated judging from their UV-visible spectrum which is characterized by a weaker absorption with an ϵ of only $40\ 000\ \text{M}^{-1}\ \text{cm}^{-1}$ at ~ 615 nm. This is most likely due to the acidity of

the phosphonate moieties. At higher pH, they are completely ionized, leading to a large amount of negative charge on the Pc periphery which would prevent aggregation. At lower pH, the phosphonate groups are most likely only partially ionized and therefore, there is less negative charge to prevent aggregation. Furthermore, intermolecular hydrogen bonds can potentially form between the ionized portion of one phosphonate group and the protonated portion of another. This could enhance aggregation by pulling the Pc together, leading to the large observed increase in aggregation between pH 5 and pH 12.

Novel water-soluble phthalocyanine tetrakisphosphonates are of interest for different applications, particularly as photosensitizers in photodynamic therapy. Furthermore, this synthetic approach allowed for more versatility in the preparation of hydrophilic macrocycles.

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- Compound 2: *Selected spectroscopic data*: HRMS (EI) Theor. 264.0664 Exp. 264.0660. IR ν/cm^{-1} (KBr) 3096, 3066, 3035 (arom. C-H), 2974, 2934, 2895 (aliph. C-H), 2235 (C \equiv N), 1232 (phosphate ester P=O), and 1093-1049 (P-O-C). 300 MHz ^1H NMR δ (DMSO- d_6) 8.0-8.2 (3H, m, aromatic), 3.3

- (4H, b, CH₂ ester) and 0.9-1.0 (6H, t, CH₃). 300 MHz ¹³C NMR δ (DMSO-d₆) 136.2 (arom. C), 133.6 (arom. C), 132.9 (arom. C), 130.25 (arom. C), 115.9 (C≡N), 114.4 (arom. C), 113.4 (arom. C), 59.5 (CH₂ ester), 16.5 (CH₃). UV-visible, λ, nm (ε) [in DMSO]: 299 (1970), 289 (1940), 260 (4790).
14. Due to the insolubility of the compounds **3a,b** in organic solvents, it was impossible to obtain satisfactory results for the microanalysis. The same reason did not allow for the acquisition of FAB mass spectra. *Selected spectroscopic data.* IR, compounds **3a,b** both feature the following bands: ν/cm⁻¹ (KBr) 3050 (arom. C-H), 2965-2840 (aliph. C-H), 1163-1112 (phosphate ester P=O) and 990 (P-O-C). UV-visible, λ_{max}, nm: compound **3a**, 689 [in DMSO], 685 [in triphenylphosphite], compound **3b**: 687 [in DMSO].
15. Satisfactory elemental analyses were obtained for compounds **4a,b**. *Selected spectroscopic data:* IR, compounds **4a,b** both feature the following bands: ν/cm⁻¹ (KBr) 2900 (P-O-H), 1152-1120 (P=O) and 951-943 (P-O-H). UV-visible, λ, nm (log ε) [in 0.01N NaOH], **4a**: 679 (5.35), 616 (4.51), 339 (4.82); **4b**: 683 (5.33), 614 (4.54), 345 (4.86). UV-visible, λ, nm (log ε) [in pH 5 phosphate buffer], **4a**: 616 (4.76). HPLC analysis conducted on a 0.94 x 25 cm column packed with ODS-2, C-18 reversed phase particles, CSC Montreal, and operated with a linear gradient from 100% aqueous sodium phosphate buffer, pH 5.5, to 100% methanol over a period of 30 minutes at a flow rate of 1.5 ml/min and with the UV-visible detector set at 680 nm: compound **4a** gave a single peak at 11 minutes and compound **4b** gave a single peak at 10.75 minutes.
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