Synthesis and Properties of Two New *N*-Alkyl Substituted Phthalocyanines

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The synthesis and properties of tetrakis(1,1-dimethyl-2-phthalimido)ethylphthalocyaninato zinc(II) (**6**) and tetrakis(1,1-dimethyl-2-amino)ethylphthalocyaninato zinc(II) (**7**) are described. *N*-Alkyl substituted phthalonitrile **5** was converted to phthalocyanine **6**, which was deprotected to afford the free amino phthalocyanine **7**.

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Phthalocyanines have been widely studied for many different purposes. Their highly conjugated macrocycle gives these compounds very interesting properties that make them useful materials for both theoretical and applied purposes.

The efficient production of singlet molecular oxygen—when irradiated with visible light—and the capacity of being retained by tumors with some kind of selectivity, are very attractive characteristics that render them potent photosensitizers for the so called photodynamic therapy of cancer [1-3]. Utilization of these dyes as bacteria photoinactivating agents has also become important [4].

Our photochemistry laboratory has been working extensively on the elucidation of different aspects related to the aggregation and photophysical behavior of phthalocyanines in homogeneous [5-6] and micellar [7] media. Common problems to deal with are the low solubility of these dyes in ordinary organic solvents and the synthesis of highly pure, well characterized compounds containing the desired functional groups. The choice of these functional groups defines the chemical properties of the phyhalocyanine and its possibility of linkage to other molecules.

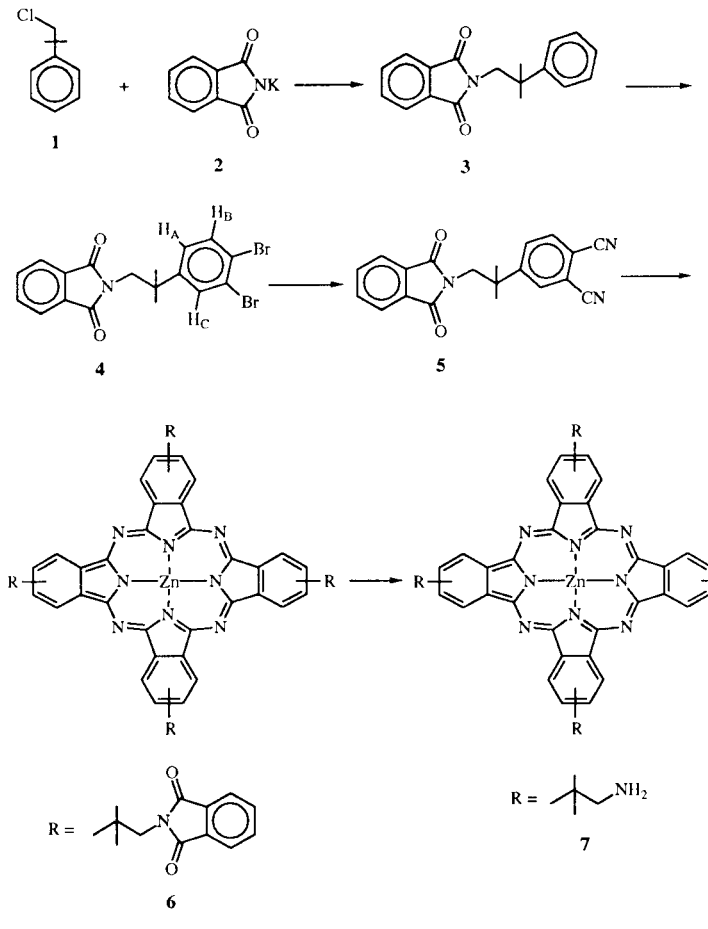
We herein report the synthesis of two new tetra *N*-alkyl substituted phthalocyanines by simple procedures. Taking into account the common problems detailed previously, we decided to introduce a *tert*-butyl group into the molecules that gives the dyes high solubility in almost all organic solvents.

It has been shown that, for better performances in tumor selectivity, the presence of both hydrophobic and hydrophilic groups is required in a single molecule of dye [8]. According to that concept, an amino group seemed to be interesting for its hydrophilic characteristics, or for the possibility of high interaction with proteins or covalent bonding with monoclonal antibodies [9]. Linkage to insoluble polymers could also be carried out for the design of photobactericidal and photodecontaminating materials [10-11].

A phthalimide was chosen as a precursor for the amino group. It shows high thermal stability (condensation of nitriles is performed at more than 200°) and it can be easily converted into an amino group under mild conditions.

As shown in Scheme 1, the sequence begins with the reaction of potassium phthalimide [12] with 1-chloro-2-

Scheme 1



methyl-2-phenylpropane (**1**). No reaction of compound **3** with bromine was observed when the reaction was carried out under reflux with methylene chloride or acetic acid, even in the presence of ferric chloride. Probably, the withdrawing effect of the phthalimido group deactivated the electrophilic substitution in the aromatic ring of **3**, and the reaction had to be performed under stronger conditions. The phthalimide derivative formed, **3**, was then reacted with bromine at its melting point and in the absence of a "halogen carrier". The yield of **4** is high, 74%, and only 6% of *N*-[2-methyl-2-(2,2,5-tribromo)phenyl]propylphthalimide was obtained (see Experimental).

The chromium carbonyl complexes of arenes are useful for activation of the aryl group to nucleophilic attack. Chromium hexacarbonyl reacts poorly with bromobenzene derivatives [13] and bulky substituents [14] retard complex formation. Therefore, nucleophilic substitution of **4** was performed with cuprous cyanide in order to obtain phthalonitrile **5**. *N*-[2-Methyl-(3-bromo-4-cyano)-phenyl]propylphthalimide was obtained as a side product. Attempts to obtain additional amounts of **5** failed when the 3-bromo-4-cyano derivative was reacted in dimethyl sulphoxide with potassium cyanide containing 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) [15].

Reaction of **5** with powdered zinc at 210° yielded the phthalocyaninato zinc(II) **6**. The use of a sealed tube in the above reaction improved the yield and rendered the conversion of the phthalonitrile into the corresponding iminoisoindoline, unnecessary [16-17]. Treatment of **6** with hydrazine in tetrahydrofuran at room temperature [18] gave the phthalocyanine **7**.

The synthesis of tetra-substituted phthalocyanines from the corresponding phthalonitriles, gives a mixture of four possible structural isomers [19]. Just recently, the successful complete separation of all four structural isomers of tetrakis(2-ethyloxy)phthalocyaninato nickel(II) was reported [20]. On the other hand, the reaction of 4-*t*-butylphthalonitrile with powdered zinc was reported to afford a single isomer of tetra-substituted phthalocyanine [21], 2,9,17,24-tetra-*t*-butylphthalocyaninato zinc(II).

However, when *N*-[2-methyl-2-(3,4-dicyano)phenyl]-propylphthalimide (**5**) was reacted with powdered zinc, a mixture of the four possible isomers of **6** was obtained. The isomers of **6** were partially separated by hplc, showing the statistical distribution in a 1:1:2:4 ratio [22]. The resolution could not be improved despite changing both solvent and stationary phase.

A mixture of four isomeric aminophthalocyanines **7** was obtained when **6** was treated with hydrazine. Attempts to separate the isomers by hplc or by tlc (cellulose plaques) did not succeed.

When the mixtures of the isomers of **6** and those of **7** were characterized, each by ^{1}H nmr spectra in deuteriochloroform (10^{-2} *M* solutions), broad signals due to aggregation were obtained. Similar results were obtained for **6** in a 10^{-4} *M* benzene-d_6 solution.

According to our calculations [23], the dimerization constant (in toluene) of phthalocyanine **6** has a value of 2.06 10^4 M^{-1}. This result confirms that **6** exists as a monomer/dimer in a 1:0.8 ratio in 10^{-4} *M* solutions. In order to obtain a real ^{1}H nmr spectrum of the monomer, it would be necessary to work with a more diluted sample, not possible with our nmr spectrometer.

Phthalocyanines **6** and **7** were characterized by their uv-visible spectra. Both compounds **6** and **7** showed the Soret band at λ_{max} 347 nm and the Q band about 675 nm. Both bands are characteristic of the $\pi \rightarrow \pi^*$ transitions of the heteroaromatic electron system of the macromolecule. No additional bands that could be attributed to charge transfer between the phthalimide and phthalocyanine rings were found for compound **6**. The molar absorption coefficients, for the monomeric forms of **6** and **7** are 1.8 10^5 M^{-1} cm^{-1} (toluene, 676 nm) and 1.2 10^5 M^{-1} cm^{-1} (tetrahydrofuran, 674 nm) respectively.

Compounds **6** and **7** present the typical fluorescent emission spectra of zinc phthalocyanines when excited at 610 nm with small Stokes shifts. Absorption and fluorescence spectra are shown in Figure 1.

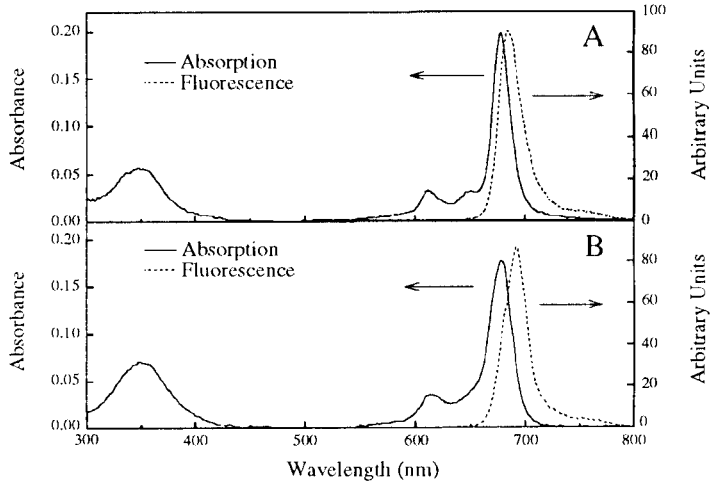


Figure 1. Absorption and fluorescence spectra of **6** (A) 10^{-6} *M* in toluene and **7** (B) 4 10^{-7} *M* in methylene chloride.

With regard to the solubility of the new compounds, whereas tetra-*t*-butylphthalocyaninato zinc(II) is extremely soluble in almost all organic solvents, **6** and **7** show the influence of the *N*-alkyl substituents. Tetrakis(1,1-dimethyl-2-phthalimido)ethylphthalocyaninato zinc(II) (**6**) is soluble in organic solvents such as toluene, methylene chloride, hot propanol, and ethanol; and insoluble in ether or methanol. Tetrakis(1,1-dimethyl-

2-amino)ethylphthalocyaninato zinc(II) (**7**) increases its water solubility and is soluble in hydrochloric acid (0.1 *M*), monobasic potassium phosphate solution (0.01 *M*), and dibasic potassium phosphate solution (0.01 *M*). The phthalocyanine **7** is also soluble in methylene chloride and insoluble in *n*-hexane, ethanol, or ether.

EXPERIMENTAL

Melting points were determined on a Fischer-Jones FBR melting point apparatus and are uncorrected. The ^1H nmr and ^{13}C nmr were recorded in deuteriochloroform on a Bruker AC 200 spectrometer and the ^1H nmr of the phthalocyanines were recorded on a Bruker MSL 300 spectrometer. Mass spectra were obtained with a TRIO 2-2000 (electronic ionization 70 eV) spectrometer. Phthalocyanines FAB-MS were measured using 3-nitrobenzylalcohol as a matrix, with a ZAB SEQ (VG, Fisons) spectrometer. Electronic absorption spectra were determined using a Shimadzu UV-160A spectrophotometer. Fluorescence spectra were recorded on a Perkin Elmer LS-5 spectrofluorometer. Infrared spectra were performed with an FT-IR Nicolet 510P spectrometer. Microanalyses were performed using a Carlo Erba EA 1108 elemental analyzer.

Hplc of phthalocyanines were performed with a Shimadzu LC-6A System, measuring wavelength: 680 nm, Perkin-Elmer columns Silica 100-5 and C18-sil-X-5 (both 25 cm x 4.6 mm). The best separation of **6** was obtained by using the reverse phase column and acetonitrile/methylene chloride (85:15, v/v) as eluent, 1 ml/min. The silica gel used in column chromatography was TLC Kieselgel (Merck). Tlc were performed on precoated silica gel F-254 plaques (Merck, 0.25 mm layer thickness) and cellulose Kodak Chromagram sheets.

Sublimation of **6** and **7**, at 5 10^{-5} mbar and 500°, failed.

N-(2-Methyl-2-phenyl)propylphthalimide (**3**).

A mixture of 27.05 g (0.2 mole) of potassium phthalimide, 33.7 g (0.2 mole) of 1-chloro-2-methyl-2-phenylpropane (**1**), and 100 ml of dimethylformamide was stirred under reflux conditions during 72 hours. The mixture was cooled and 100 ml of water was added. The aqueous phase was extracted with chloroform (3 x 100 ml). The chloroform extractions were washed with 0.3 *N* sodium hydroxide solution (2 x 100 ml), then with water (1 x 100 ml), dried (magnesium sulfate), and evaporated *in vacuo* to eliminate the solvent. The oily residue was steam-distilled to eliminate unreacted **1**. A white water insoluble solid remained after distillation. After cooling, it was filtered, dried, and recrystallized from methanol-water, 23.4 g (42%), mp 108°; ms: m/z 279 (M^+, 11%), 119 (100%), 160 (11.5%); ^1H nmr: δ 7.78 (m, 4H, phthalimide), 7.4 (m, 5H, benzene ring), 3.80 (s, 2H, CH_2), 1.48 (s, 6H, CH_3); ir (potassium bromide): 1773, 1717 (phthalimide CO), 1397, 1383, 1335, 1059, 914, 714, 704 cm^{-1}.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.20; H, 6.15; N, 5.00.

N-[2-Methyl-2-(3,4-dibromophenyl)]propylphthalimide (**4**).

A three-necked flask containing 1.5 g (5 mmoles) of **3**, provided with a reflux condenser with the upper end to an absorption trap containing 0.1 *N* sodium hydroxide with 10% sodium thiosulfate, a magnetic stirrer, and a rubber septum, was immersed in an oil bath at 140°. Bromine (1.5 ml, 0.03 mole) was added during 45 minutes with a syringe and the reaction was continued during 4.5 hours. The reaction mixture was cooled and methylene chloride was added. The organic solution washed with 5% sodium thiosulfate in 5% sodium hydroxide solution (2 x 50 ml) and water (1 x 50 ml). The organic phase was dried (magnesium sulfate) and evaporated to dryness *in vacuo*. The residue was dissolved in a small volume of toluene and filtered through a tlc silica gel column (5 x 30 cm) packed and prewashed with the same solvent. Two bands were eluted using the same solvent under slight pressure; the eluates were evaporated *in vacuo* to dryness. The residue that showed a lower R_f was **4**. It was recrystallized from methanol-water, 1.74 g (74%), mp 103-104°; ms: m/z 437 (M^+, 2.8%), 439 (M^++2, 1.5%), 435 (M^+-2, 1.4%), 160 (100%); ^1H nmr: δ 7.77 (m, 4H, phthalimide), 7.69 (d, 1H, J = 2 Hz, H_C aromatic), 7.57 (d, 1H, J = 8 Hz, H_B aromatic), 7.28 (dd, 1H, J_{AB} = 8 Hz, J_{AC} = 2 Hz, H_A aromatic), 3.78 (s, 2H, CH_2), 1.38 (s, 6H, CH_3); ir (potassium bromide): 1774, 1711 (phthalimide CO), 1400, 1383, 1350, 1335, 1065, 916, 718, 534 cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}NO_2Br_2$: C, 49.46; H, 3.46; N, 3.20. Found: C, 49.30; H, 3.44; N, 3.22.

N-[2-Methyl-2-(2,4,5-tribromophenyl)]propylphthalimide.

The residue with a higher R_f was also recrystallized from methanol-water, 0.166 g (6%), mp 172-173°; ms: m/z 517 (M^++1, 2.5%), 515 (M^+-1, 2.5%), 519 (M^++3, 0.8%), 513 (M^+-3, 0.8%), 160 (100%); ^1H nmr: δ 7.67 (m, 4H, phthalimide), 7.82 (s, 1H, aromatic), 7.45 (s, 1H, aromatic), 4.20 (s, 2H, CH_2), 1.45 (s, 6H, CH_3); ir (potassium bromide): 1775, 1721 (phthalimide CO), 1400, 1383, 1350, 1339, 1063, 1026, 1013, 912, 731, 718 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}NO_2Br_3$: C, 41.89; H, 2.73; N, 2.71. Found: C, 40.76; H, 2.74; N, 2.70.

N-[2-Methyl-2-(3,4-dicyanophenyl)]propylphthalimide (**5**).

A solution of 0.954 g (2.2 mmoles) **4** and 0.4 g cuprous cyanide in dry dimethylformamide (10 ml) was refluxed during 8.5 hours under nitrogen. The solution acquired a green color. After cooling, it was poured into a concentrated ammonia solution (20 ml) and oxygen was bubbled for a few minutes. The solid obtained was filtered, dried, and extracted with ether in a Soxhlet extraction apparatus. The ethereal solution was evaporated to dryness *in vacuo*. The solid residue was washed with hexane so as to eliminate **4** and the monocyano derivative also formed in the reaction. The residue was dissolved in a mixture of toluene-methanol (98:2) and filtered through a tlc silica gel column (4 x 35 cm). After evaporation of the solvent, the solid residue was recrystallized from methanol-water, 0.180 g (25%), mp 147°; ms: m/z 329 (M^+, 4.31%), 160 (100%); ^1H nmr: δ 7.79 (m, 7H, aromatic), 3.83 (s, 2H, CH_2), 1.47 (s, 6H, CH_3); ir (potassium bromide): 2234 (nitrile CN), 1773, 1711 (phthalimide CO), 1402, 1387, 1358, 1337, 1067, 916, 731, 530 cm^{-1}.

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.93; H, 4.59; N, 12.75. Found: C, 72.77; H, 4.57; N, 12.73.

The ^{13}C nmr shows four new signals at δ 115.6, 115.6, 115.4, and 113.7 for the two nitriles and the two adjacent aromatic carbons, instead of the signals at δ 124.7 and 122.6 for the two aromatic carbons adjacent to the bromine groups.

Tetrakis(1,1-dimethyl-2-phthalimido)ethylphthalocyaninato

Zinc(II) (**6**).

A mixture of 0.313 g (0.953 mmole) of **5** and 0.133 g of powdered zinc was heated at 210° in a closed vessel during 5.5 hours. It was cooled; methylene chloride (20 ml) was added and the remaining zinc filtered under suction. The methylene chloride solution was evaporated *in vacuo* and the solid residue washed with ether and air dried. The residue was dissolved in a mixture of toluene-methanol (95:5) and filtered through a tlc silica gel column (4 x 30 cm). After evaporation of the solvent, the deep blue solid was recrystallized from methylene chloride-hexane, 0.183 g (56%); FAB-ms: m/z 1386 $(M+4)^+$; ^1H nmr: δ 8.4 (br, 12H, aromatic phthalocyanine); 7.6 (br, 16H, aromatic phthalimide), 3.9 (br, 8H, CH_2), 1.69 (s, 24H, CH_3); ir (potassium bromide): 1774, 1716 (phthalimide CO), 1384, 1334, 915, 716 cm^{-1}.

Anal. Calcd. for $C_{80}H_{60}N_{12}O_8Zn$: C, 69.49; H, 4.37; N, 12.16. Found: C, 69.61; H, 4.39; N, 12.03.

Tetrakis(1,1-dimethyl-2-amino)ethylphthalocyaninato Zinc(II) (**7**).

A mixture of 0.120 g (0.09 mmole) of **6** and 0.24 ml (7.7 mmoles) of hydrazine [18] in 10 ml of tetrahydrofuran, was stirred during 17 hours at room temperature. The white solid formed was filtered and the green filtrate evaporated *in vacuo*. The residue was dissolved in a 0.1 *N* hydrochloric acid solution and filtered. The solution was then adjusted to *p*H 7 with a 0.1 *N* sodium hydroxide solution. After 24 hours, the fine green powder obtained was filtered, washed twice with cold water, and dried at 40° *in vacuo* to give 67 mg of **7** (90%). Cellulose tlc showed only one band when acetonitrile/0.01 *N* hydrochloric acid (50:50, v/v) was used as the development solvent; FAB-ms: m/z 861 $(M-H)^+$; ^1H nmr: δ 9.43, 9.14, 7.79 (br, 12H, aromatic phthalocyanine), 2.5 (br, 8H, CH_2), 1.45 (s, 24H, CH_3); ir (potassium bromide): 3430, 3377 (NH), 1490, 1088, 918, 749 cm^{-1}.

Anal. Calcd. for $C_{48}H_{52}N_{12}Zn$: C, 66.85; H, 6.08; N, 19.49. Found: C, 67.14; H, 6.09; N, 19.27.

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