Synthesis and spectroscopic properties of new water-soluble phthalocyanines containing pyridinium hydrochloride fragments

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New 2,9,16,23-tetra[*o*-(hydroxymethyl)benzyloxy]-substituted phthalocyanines were synthesized. Their reaction with 4-bromopyridine afforded 2,9,16,23-tetra[*o*-(4-pyridyloxymethyl)benzyloxy]-substituted analogs, treatment of which with HCl led to water-soluble pyridinium salts. Spectroscopic properties of the phthalocyanines obtained were studied and a hypsochromic shift of the Q-band of the hydrochloride as compared with the corresponding pyridinium analogs was observed.

Key words: phthalocyanines, nucleophilic substitution, synthesis, electronic absorption spectra.

In the last decade, water-soluble phthalocyanines attract enormous attention. Numerous investigations show their high activity in photodynamic cancer therapy.[1,2] In addition, water-soluble phthalocyanines with regular structure can be also used for the construction of supramolecular structures.[3]

In the present work, the synthesis of new phthalocyanine ligands and complexes, containing pyridine and pyridinium hydrochloride fragments in the peripheral substituents, is proposed.

It is known[4] that it is virtually impossible to synthesize phthalocyanines containing hydroxy- or amino groups by the self-cyclization of the corresponding phthalogenes. In our opinion, this is caused by high reactivity of those groups in the complex-forming reactions. In fact, attempted tetramerization of phthalodinitrile **1**, the synthesis of which was described by us earlier,[5] in the presence of zinc acetate both in various solvents and by fusion of the reagents, unfortunately, did not lead to phthalocyanine complex **2**. However, the introduction of trimethylsilyl protecting group into phthalodinitrile **1** enabled us to easily accomplish the complex-forming reaction by the reflux of the corresponding reagents in *N*,*N*-dimethylaminoethanol (DMAE) (Scheme 1).

The removal of the protecting group occurred during quenching of the reaction mixture, resulting in the isolation of the target zinc complex **2** in 32% yield.

The synthesis of the ligand-phthalocyanine starting from phthalodinitrile **1** was of no less interest. Thus, the fusion of **1** with lithium methoxide within wide range of temperatures (150—300 °C) led to the target ligand **3** in trace amount irrespective of the phthalodinitrile : base ratio. We succeeded in obtaining of phthalocyanine **3** in 39% yield only by the reflux of the reagents in isoamyl alcohol. It is of interest to note that, in contrast to complex **2**, the yield of ligand **3** does not virtually depend on the intermediate introduction of trimethylsilyl group into phthalodinitrile **1** molecule.

Attempted synthesis of complex **2** starting from ligand **3** by its reaction with zinc acetate or acetylacetonate failed, the yield of the target complex **2** did not exceed 10%, while a phthalocyanine polymer, insoluble in most organic solvents, was the main reaction product. Formation of the polymer can be explained by a side process of intermolecular dehydration in the presence of zinc acetate. This suggestion was confirmed by almost complete polymerization of phthalocyanine **3** after a significant increase of the salt amount as compared with the stoichiometric quantity. In this case, the formation of complex **2** was not observed.

The presence of four equivalent hydroxy groups in phthalocyanine **2** and its ligand **3** allowed us to modify their structure to obtain compounds **4** and **5** containing pyridine fragments in high yield. Earlier,[6] we found the optimal reaction conditions for the nucleophilic substitution of the nitro group in phthalocyanine macrocycle and in 4-nitrophthalodinitrile, which gave the target products in almost quantitative yield. The method developed

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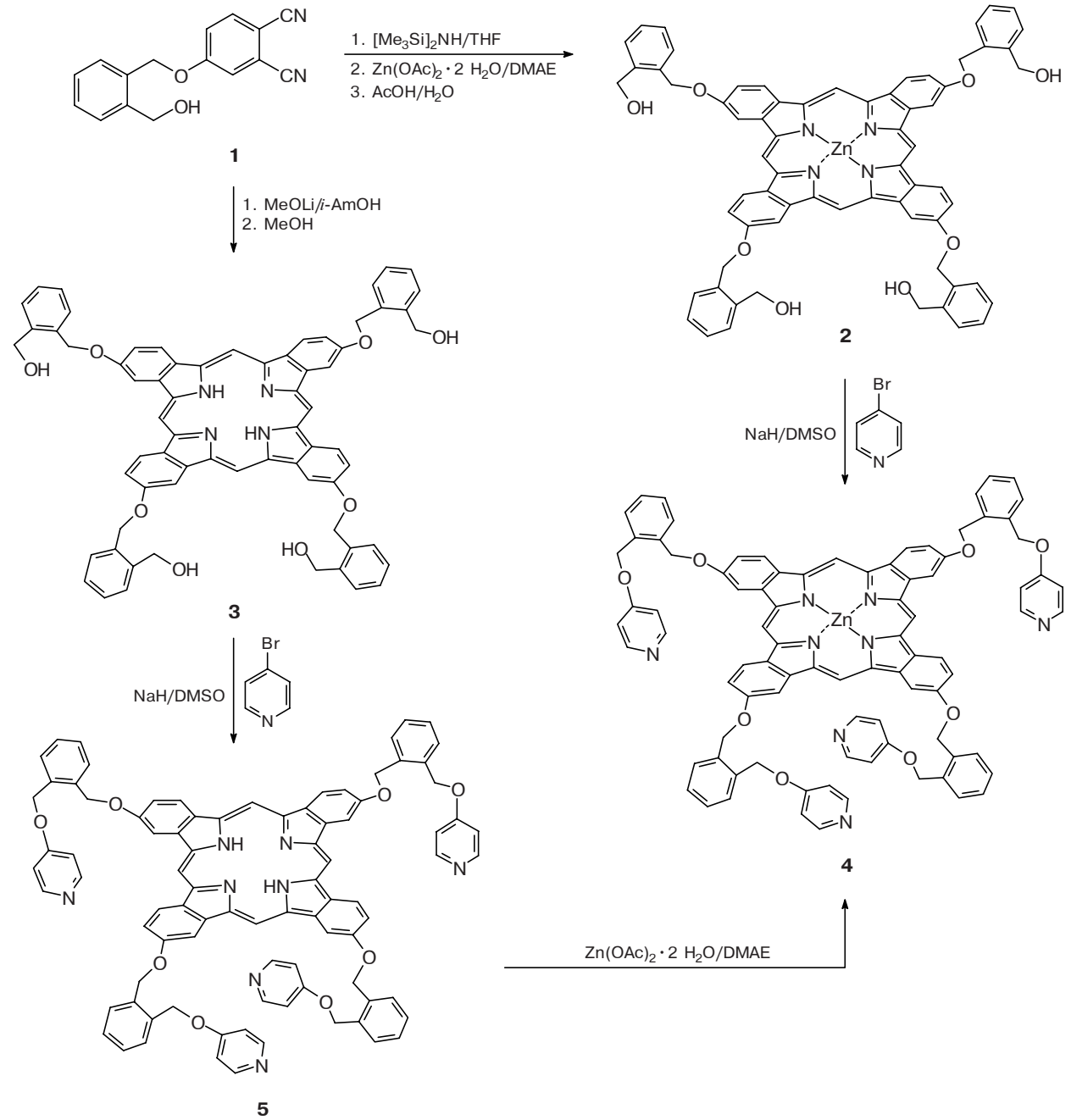
Scheme 1



allowed us to carry out the nucleophilic substitution of bromine in 4-bromopyridine by the reaction with phthalocyanines **2** and **3**. It is important to note that, in contrast to ligand **3**, phthalocyanine **5**, having no free OH groups, readily undergoes metallation to give compound **4** in 79% yield.

The structures of phthalocyanines **2—5** synthesized were confirmed by IR and NMR spectroscopy, as well as by mass spectrometry. In the IR spectra of phthalocyanines **2** and **3**, an absorption band characteristic of the O—H bond vibrations was observed at 3400 cm^{-1}. In the ^1H NMR spectra of compounds **2—5**, signals of the benzyl protons, which resonate as two singlets due to their magnetic non-equivalency, were found in the region δ 4.95—5.70 (16 H); signals of the aromatic protons of the phthalocyanine macrocycle are downfield shifted by ~1.3 ppm as compared with signals of the peripheral substituents. The nucleophilic substitution, as well as the incorporation of the metal into the macrocycle allowed us to find out a number of interesting properties in the

^{1}H NMR spectra. Thus, a replacement of H atom by 4-pyridyl group (**2** → **4** and **3** → **5**) leads to a slight downfield shift of all the signals of the aromatic protons (~0.2 ppm), leaving signals of the benzyl protons in methylene fragment bound to the OH (**2** and **3**) or pyridyloxy groups (**4** and **5**) almost unchanged, in contrast to the benzyl protons in the alternative CH_2 fragments, for which a downfield shift by ~0.5 ppm is observed. In its turn, the incorporation of the metal (**3** → **2** and **5** → **4**) mainly leads to a downfield shift of signals of the protons of the phthalocyanine ring (~1 ppm) and here again, strictly opposite regularities are observed for the methylene protons of different types.

In the mass spectra (MALDI-TOF) of phthalocyanines **2**—**5**, peaks of the molecular ions and the corresponding fragment ions with characteristic isotope splitting were observed. In case of compounds **2** and **3**, the fragmentation is mainly reduced to the sequential elimination of the peripheral substituents, leaving as the radicals. As a result of such a cleavage of the molecular ions, peaks with *m/z* 639 and 576 are observed in the mass spectra, which correspond to tetrahydroxy-substituted phthalocyanines, *viz.*, metal complex and ligand, respectively. When 2,5-dihydroxybenzoic acid (DHB) is used as the matrix, the protonated ions $[M + H]^+$ are exclusively registered instead of molecular ions. For phthalocyanines **4** and **5**, the fragmentation of the molecular ions is exclusively observed in the presence of the matrix. In the absence of DHB, peaks of the molecular ions and characteristic fragment ions are observed. Fragmentation of phthalocyanines **4** and **5** proceeds as the sequential elimination of $C_5H_4NO^{\bullet}$ radicals rather than the whole peripheral substituent, as it is in cases of compounds **2** and **3**. The isotopic picture of peaks of all the ions strictly corresponds to the theoretically calculated one.

Phthalocyanines **2**—**5** obtained are also characterized by the electronic absorption spectra (EAS, Table 1).

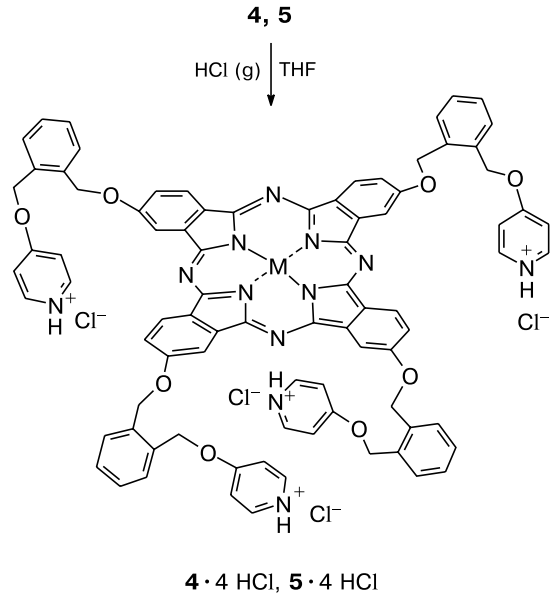
As it could be seen from the data in Table 1, the introduction of the pyridyl substituent both into the molecule of the free ligand **3** and its zinc metal complex **2** virtually has no effect on the positions of the main absorption bands in the EAS.

The corresponding water-soluble hydrochlorides **4**·4 HCl and **5**·4 HCl were obtained by the reaction of phthalocyanines **4** and **5** with HCl (Scheme 2).

Table 1. Electronic absorption spectra of phthalocyanines **2**—**5** (THF)

Compound	λ/nm		
	Soret-band	Wiggle satellite	Q-Band
2	350	612	677
3	342	—	666, 703
4	352	611	676
5	344	—	667, 703

Scheme 2



4·4 HCl, **5**·4 HCl

g — gas.
M = Zn (**4**), H_2 (**5**)

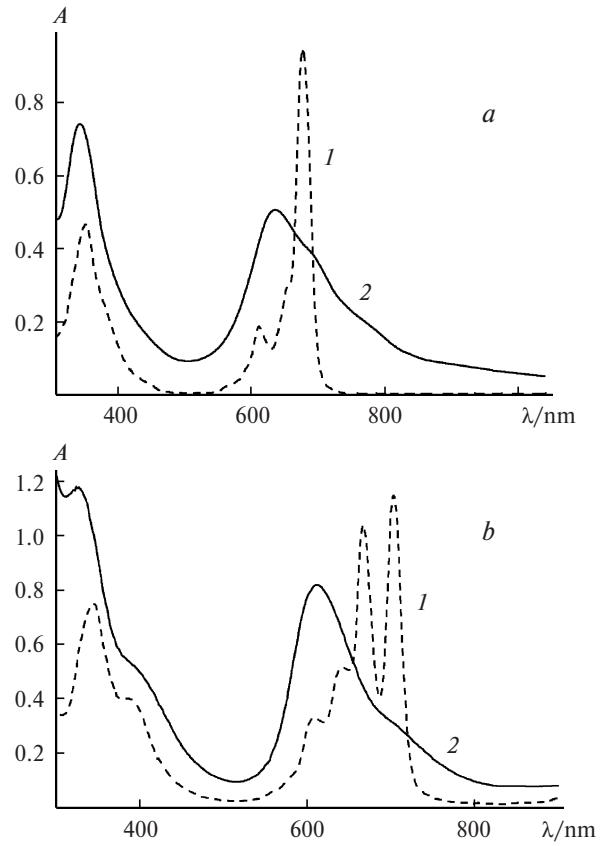


Fig. 1. Electronic absorption spectra of phthalocyanines **4** and **5** (THF) (*1*) and their hydrochlorides **4**·4 HCl and **5**·4 HCl (H_2O) (*2*): metal complexes **4** and **4**·4 HCl (*a*) and ligands **5** and **5**·4 HCl (*b*).

Table 2. Electronic absorption spectra of hydrochlorides **4**·4 HCl and **5**·4 HCl (H_2O

Compound	λ/nm	
	Soret-band	Q-Band
4·4 HCl	343	636
5·4 HCl	324	611

It is important to point out a significant changes in the character of the EAS of water solutions of the salts in comparison with the starting phthalocyanines containing pyridine fragment, which apparently, is caused by a specific dipole-dipole interactions in water solutions (Fig. 1).

A strong hypsochromic shift of the absorption maximums of hydrochlorides **4**·4 HCl and **5**·4 HCl (Table 2) relatively to the ones of the corresponding starting phthalocyanines also indicates the specific intermolecular interaction of the macrocycles in water solutions.

The character of the EAS of hydrochlorides **4**·4 HCl and **5**·4 HCl remains virtually unchanged in a wide range of concentrations (10^{-3}—10^{-6} mol L^{-1}).

Experimental

^{1}H NMR spectra were recorded on a Brucker AM-300 spectrometer (300.13 MHz), electronic absorption spectra were recorded on a Helios-α spectrophotometer in quartz cuvettes 0.5 cm thick in THF, DMF, and H_2O. Mass spectra were recorded on a Autoflex II instrument (MALDI-TOF), IR spectra were recorded on a Nicolet Nexus IR-Fourier spectrometer in KBr pellets. Column chromatography was performed on silica gel 60 (40×63 μm) (Merck). All the solvents were purified according to the standard procedures just before use. Samples of $Zn(OAc)_2 \cdot 2H_2O$ were kept in vacuum drying oven at 100 °C for 4 h before synthesis. Phthalodinitrile **1** was obtained by the procedure described earlier.[5] Commercially available 4-bromopyridine (Aldrich) was used without additional purification.

Zinc 2,9,16,23-tetra[*o*-(hydroxymethyl)benzyloxy]phthalocyanine (2). Hexamethyldisilazane (0.2 mL, 0.96 mmol) was added to a solution of dinitrile **1** (235 mg, 0.89 mmol) in THF (2 mL), the mixture was refluxed for 0.5 h, then, the solvent was evaporated on a rotary evaporator. The reaction mixture was dissolved in DMAE (10 mL), $Zn(OAc)_2 \cdot 2H_2O$ (97 mg, 0.44 mmol) was added to the solution, and the mixture was refluxed for 2.5 h. After the reaction was over, the reaction mixture was quenched with aqueous AcOH (5%, 200 mL). The precipitate formed was filtered off and sequentially washed with water (2×50 mL) and hot methanol (5×50 mL). The product was first purified by recrystallization from DMF, then, by chromatography on silica gel (eluent, $CHCl_3$—THF, 1 : 1) to obtain complex **2** (80 mg, 32%). IR, ν/cm^{-1}: 3411 (OH). MS (MALDI-TOF, DHB), *m/z* (I_{rel} (%)): 1120 $[M + H]^+$ (49), 1001 $[M - C_8H_9O]^+$ (95), 879 $[M - 2\ C_8H_9O]^+$ (62), 759 $[M - 3\ C_8H_9O]^+$ (38), 639 $[M - 4\ C_8H_9O]^+$ (45). ^{1}H NMR (THF-d_8), δ: 5.00 (s, 4 H, OH); 5.50 (s, 8 H, CH_2); 5.65 (s, 8 H, $C\underline{H}_2OH$); 7.30—7.70 (m, 16 H, Ar); 8.50—9.00 (m, 12 H, Ar). EAS (THF), λ_{max}/nm (logε): 350 (3.18), 612 (1.45), 677 (4.93).

2,9,16,23-Tetra[*o*-(hydroxymethyl)benzyloxy]phthalocyanine (3). Freshly prepared MeOLi (72 mg, 1.89 mmol) was added to a solution of dinitrile **1** (500 mg, 1.89 mmol) in 3-methylbutanol (10 mL) and the mixture was refluxed for 2.5 h. Then, the reaction mixture was concentrated, methanol (100 mL) was added to the oily residue, and the mixture was refluxed for 30 min. The target product was filtered off and recrystallized from DMF to obtain ligand **3** (194 mg, 39 %). IR, ν/cm^{-1}: 3400 (OH). MS (MALDI-TOF), *m/z* (I_{rel} (%)): 1058 $[M]^+$ (33), 937 $[M - C_8H_9O]^+$ (62), 817 $[M - 2\ C_8H_9O]^+$ (48), 697 $[M - 3\ C_8H_9O]^+$ (29), 576 $[M - 4\ C_8H_9O]^+$ (97). ^{1}H NMR (THF-d_8), δ: –4.50 (br.s, 2 H, NH); 4.95 (s, 8 H, CH_2); 5.45 (s, 8 H, $C\underline{H}_2OH$); 7.10—7.40 (m, 16 H, Ar); 7.50—7.80 (m, 12 H, Ar). EAS (THF), λ_{max}/nm (logε): 342 (3.82), 666 (4.71), 703 (4.89).

Zinc 2,9,16,23-tetra[*o*-(4-pyridyloxymethyl)benzyloxy]phthalocyanine (4). Method ***A***. Sodium hydride (8 mg, 0.333 mmol) was added to a solution of compound **2** (20 mg, 0.017 mmol) in DMSO (4 mL). After the evolution of hydrogen ceased, 4-bromopyridine (12 mg, 0.076 mmol) was added to the reaction mixture, and it was kept at 30 °C for 25 min. The reaction mixture was quenched with water, the precipitate formed was filtered off and sequentially washed with water (2×50 mL) and hot methanol (5×50 mL). The product was subjected to chromatography on silica gel (eluent, $CHCl_3$—THF, 5 : 1) to obtain complex **4** (22 mg, 88%).

Method ***B***. Zinc acetate dihydrate (10 mg, 0.053 mmol) was added to a solution of phthalocyanine **5** (50 mg, 0.035 mmol) in DMAE (10 mL). The mixture was refluxed for 45 min. After the reaction was over, the reaction mixture was quenched with water, the product formed was filtered off and purified similarly to the procedure described in method ***A*** to obtain complex **4** (40 mg, 79%).

MS (MALDI-TOF), *m/z* (I_{rel} (%)): 2865 $[2\ M]^+$ (9), 2773 $[2\ M - PyO]^+$ (4), 2958 $[2\ M + PyO]^+$ (10), 3050 $[2\ M + 2\ PyO]^+$ (3), 639 $[M - 4\ C_{13}H_{12}NO]^+$ (96). ^{1}H NMR (THF-d_8), δ: 5.00, 5.70 (both s, 8 H each, CH_2); 7.30—7.45 (m, 32 H, Py); 7.52—7.81 (m, 32 H, Ar); 8.75—9.10 (m, 24 H, Ar). EAS (THF), λ_{max}/nm (logε): 352 (2.45), 611 (1.22), 676 (4.92).

2,9,16,23-Tetra[*o*-(4-pyridyloxymethyl)benzyloxy]phthalocyanine (5). Ligand **5** (98 mg, 91%) was obtained starting from phthalocyanine **3** (80 mg, 0.075 mmol) and 4-bromopyridine (53 mg, 0.338 mmol) similarly to the synthesis of compound **4** (see above, method ***A***) from compound **2**. MS (MALDI-TOF), *m/z* (I_{rel} (%)): 1365 $[M]^+$ (12), 1273 $[M - PyO]^+$ (18), 1180 $[M - 2\ PyO]^+$ (15), 576 $[M - 4\ C_{13}H_{12}NO]^+$ (98). ^{1}H NMR (THF-d_8), δ: 5.50, 4.83 (both s, 8 H each, CH_2); 7.10—7.25 (m, 32 H, Py); 7.70—7.85 (m, 32 H, Ar); 7.10—7.25 (m, 24 H, Ar). EAS (THF), λ_{max}/nm (logε): 344 (2.97), 667 (4.35), 703 (4.91).

Zinc 2,9,16,23-tetra[*o*-(4-pyridyloxymethyl)benzyloxy]phthalocyanine tetrahydrochloride (4·4 HCl). A solution of compound **4** (10 mg, 0.007 mmol) in THF (4 mL) was saturated with gaseous HCl until a precipitate began to form. After the reaction mixture was kept for 15 min, the precipitate was filtered off and dried at reduced pressure to obtain compound **4**·4 HCl (10 mg, 95%). Hydrochloride **4**·4 HCl is soluble in water. EAS (water), λ_{max}/nm: 343, 636.

2,9,16,23-Tetra[*o*-(4-pyridyloxymethyl)benzyloxy]phthalocyanine tetrahydrochloride (5·4 HCl). Hydrochloride **5**·4 HCl (11 mg, 96%) was obtained starting from phthalocyanine **4**

(10 mg, 0.007 mmol) similarly to the synthesis of compound **4**·4 HCl. EAS (water), λ_{max}/nm: 324, 611.

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