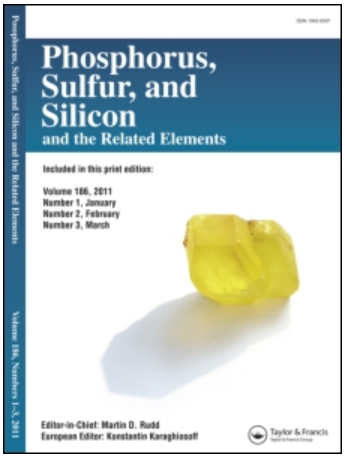

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Synthesis of New Porphyrin-Containing Peptidyl Phosphonates

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Synthesis of New Porphyrin-Containing Peptidyl Phosphonates

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*Synthesis of new, porphyrin-containing peptidyl aminophosphonates is described. The products, derived from 5-(4′-carboxyphenyl)-10,15,20-tri-*p*-tolylporphyrin and some heterocyclic aminophosphonates were obtained in high yield in the reaction of the 5-(4′-carboxyphenyl)-10,15,20-tritolylporphyrin with selected thiophene and pyridine aminophosphonate diphenyl esters by applying a DCC coupling method used in the peptide synthesis. The obtained porphyrin aminophosphonate products were characterized by spectroscopic methods.*

Keywords Aminophosphonate derivatives of 5-(4′-carboxyphenyl)-10,15,20-tri-*p*-tolyl-porphyrin; peptide synthesis; porphyrins; tolylporphyrins

Porphyrins play a very important role both in nature and chemistry, due to their unique properties. The porphyrin structure comprises four pyrrole rings linked by four methine bridges and shows an aromatic character because it obeys the Hückel's rule of aromaticity. The aromatic character of the porphyrins has been shown by some spectroscopic methods (X-ray, NMR etc.).[1]

Existence of pyrrole units in the porphyrin structures causes easy complexation of the most metals by the porphyrins. Such metallic complexes (metalloporphyrins) are well known in nature and exist as the chlorophyll, hemoglobin, and vitamin B_{12}, containing Mg, Fe, and Co, atoms, respectively. Metalloporphyrins are principal species in metabolic processes and in the provision of energy in living

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organisms. They are also used for dehalogenation of polychlorinated hydrocarbons.[2]

In the past two decades, porphyrins have been the subject of many researches due to their biological and spectroscopic properties. Mainly, they are used as so-called Photosensitizers (PS) in the latest-developed method of diagnostic and therapy of cancer Photodynamic therapy (PDT).[3,4] The first photosensitizer, based on a porphyrin (Photofrin), was approved for clinic application in Canada, then in the USA and Japan in 1993. Photofrin is a mixture of about 50 various dimeric derivatives of hematoporphyrins.[3]

We found that some of the amide-type derivatives of tolylporphyrins[5–8] showed also the photosensitizing properties. It was found, that application of the tritolylporphyrin amides[7,8] to human melanoma cells and irradiation with red light (630 nm) causes a 3-fold decrease of the surviving fraction of the human melanoma cells.[9]

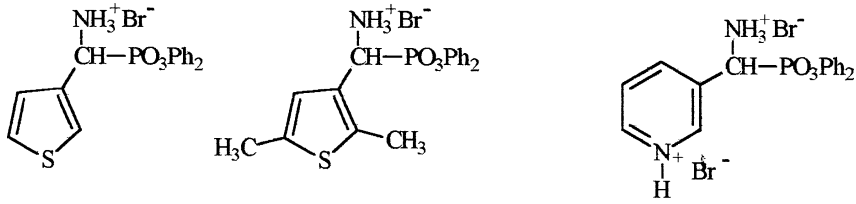
In 2003, synthesis of some aminophosphonic derivatives of porphyrins obtained from the corresponding formylporphyrins of natural origin was described[10] and characterized. The phosphonic moiety was attached directly to the porphyrin core. These compounds were projected as a new kind of photosensitizers.[10]

In this work, we report a first synthesis of some peptidyl, phosphonate derivatives of tolylporphyrin, namely, derivatives of the 5-(4′-carboxyphenyl)-10,15,20-tri-*p*-tolylporphyrin. The porphyrin core is bounded with heterocyclic phosphonate diphenyl ester by a —CO—NH- link, in this case. There is expectancy that some of the obtained porphyrin-phosphonate compounds will show desired biological properties, that is, photosensitive activity.

RESULTS AND DISCUSSION

The 5-(4′-carboxyphenyl)-10,15,20-tri-*p*-tolylporphyrin (**1**) (Scheme 2) needed for synthetic work was prepared by a conventional method of Adler et al.,[11] by condensation of 4-methylbenzaldehyde and 4-carboxybenzaldehyde with pyrrole in boiling propionic acid. The proper product was isolated from the reaction mixture by column chromatography. Amino components, i.e., the thiophene and pyridine diphenyl aminophosphonates **2a–c**, were synthesized according to literature methods[12,13] from the corresponding aldehydes. Structures of the aminophosphonates **2a–c** used for coupling with carboxy-porphyrin **1** are shown in Scheme 1.

Peptidyl aminophosphonic derivatives **3a–c** (Scheme 2) of carboxyporphyrin **1** were obtained in good yield by a typical method used in peptide synthesis. Carboxyporphyrin **1** was coupled



2a **2b** **2c**

SCHEME 1

with aminophosphonate component **2a–c** in the presence of 1,3-dicyclohexylcarbodiimide (DCC), in methylene chloride, at room temperature. 4-(Dimethylamino)pyridine (DMAP) was used as a catalyst to facilitate the coupling reaction. Phosphonic groups in **2a–c** were protected as the phenyl esters. An outline of the reactions carried out is shown in Scheme 2.

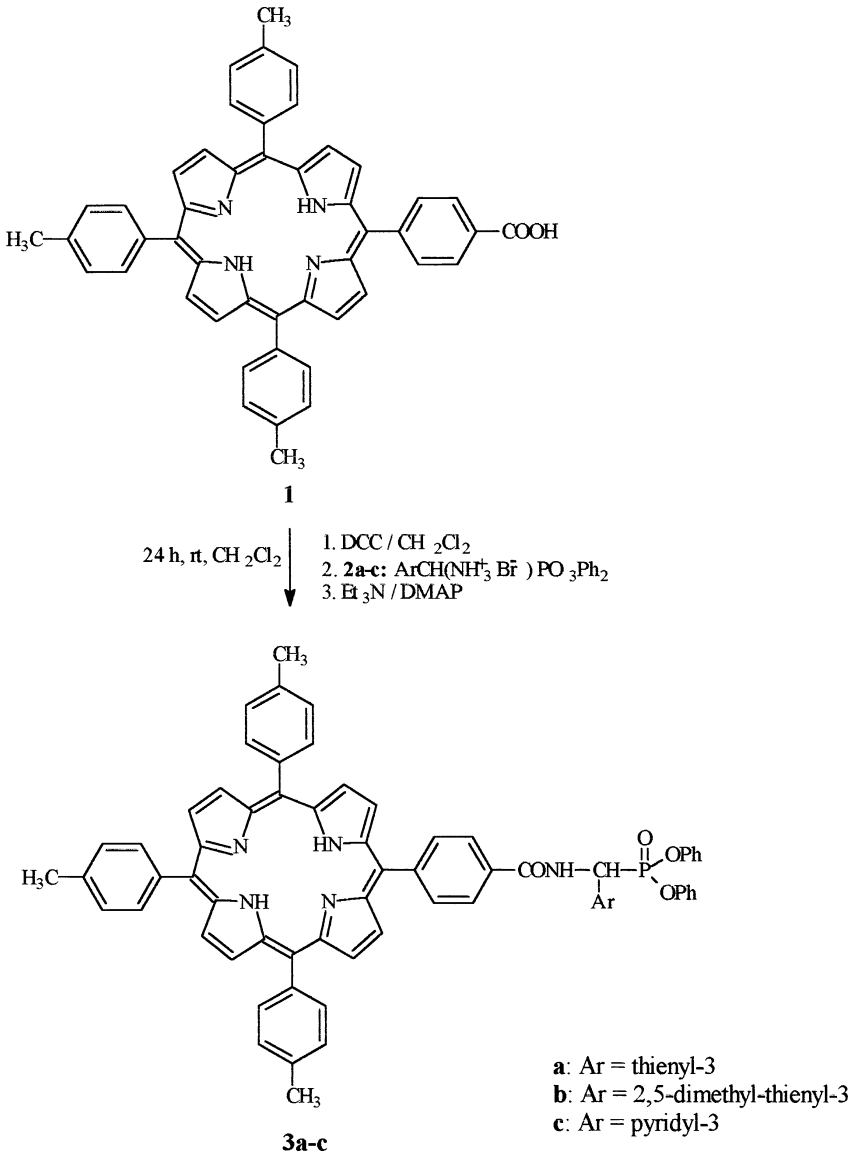
The obtained porphyrin-phosphonopeptides **3a–c** (Scheme 2) were purified by column chromatography and then characterized by means of ^{1}H, ^{31}P NMR, and ESI+Q1MS spectroscopy. ^{31}P signals from NMR were observed in the range of 14.8–15.7 ppm for all the obtained porphyrin-phosphonate products, which is in agreement with the ^{31}P data for other compounds, similar to phosphonopeptides.[13] All of the obtained products **3a–c** were racemic mixtures and no attempts were made to their resolution.

Results of performed biological tests with the obtained products will be given in the near future.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in $CDCl_3$ using 300.13 MHz for ^{1}H NMR and 121.51 MHz for ^{31}P NMR spectra in the Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology. MS analyses were performed on a Finnigan TSQ 700 Instrument (electrospray ionization) on mode ESI+Q1MS at the Department of Chemistry, University of Wroclaw. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200. Elemental analyses were done in the Laboratory of Instrumental Analysis in the Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw. All reagents were purchased from Sigma Aldrich Company.

Diphenyl thiophene-3-methyl(amino)phosphonate (**2a**) and diphenyl 2,5-dimethylthiophene-3-methyl(amino)phosphonate (**2b**) were obtained



SCHEME 2

from thiophene-3-carboxaldehyde and 2,5-dimethylthiophene-3-carboxaldehyde,[14] according to the described method of synthesis of various thiophene aminophosphonates.[12]

2a: Yield: 93%, Mp. 187–189°C, ^{1}H NMR($CDCl_3$), δ, ppm: 9.30 (bs, 3H, NH_3^+), 7.70 (s, 1H, thiophene-2), 7.55 (m, 2H, thiophene-4,5),

7.36–7.09 (m; 10H, Ph), 5.27(d, 1H, CH—P, J = 15.9 Hz). ^{31}P NMR ($CDCl_3$), δ, ppm: 13.88 (s). Elemental Anal. for **2a**: Calc. N, 3.29; P, 7.27; Br, 18.75; Found: N, 3.21; P, 7.25; Br, 18.85.

2b: Yield: 44%. Mp. 141–145°C, ^{1}H NMR ($CDCl_3$), δ, ppm: 9.21 (bs, 3H, NH_3^+), 7.23–6.89 (m, 11H, thiophene-4, Ph), 5.25 (d, 1H, CH—P, J = 16.4 Hz), 2.25 (s, 3H, CH_3), 2.03 (s, 3H, CH_3). ^{31}P NMR ($CDCl_3$), δ, ppm: 10.40 (s). Elemental Anal. for **2b**: Calc. N, 3.08; P, 6.82; Br, 17.59; Found: N, 3.01; P, 6.91; Br, 17.65.

Diphenyl pyridine-3-methyl(amino)phosphonate (**2c**) was prepared as described in the literature.[13]

Procedure for Preparation of 5-(4′-Carboxyphenyl)-10,15,20-tri-*p*-tolylporphyrin (1)

5-(4′-Carboxyphenyl)-10,15,20-tritolylporphyrin was prepared mainly according to the Adler method,[11] with some modifications. The procedure was the following: In a 1 L round-bottom flask, equipped with an efficient mechanical stirrer, were placed 600 mL of propionic acid, 4-tolyladehyde (3.6 g, 30 mmol), and 4-carboxybenzaldehyde (1.5 g, 10 mmol). The mixture was heated to 140–2°C (boiling point) and then pyrrole (6.7 g, 100 mmol) was added during 30 min. Heating was continued for 30 min and cooled. The mixture was left for 24 h, the separated product was filtered off, washed with water several times, and placed with a mixture of water and methanol (v/v: 8:2). Washing was continued until the filtrate become colorless and odorless. The obtained product was dried in air to give a dark solid (the mixture of several porphyrins; 2.1 g, 30%). The mixture of porphyrins was separated by column chromatography (silica gel 60–230 mesh, eluent: chloroform-methanol; v/v 9:1), collecting the second, purple band containing the desired product **1** after evaporation of the solvent. Yield: 400 mg (5%). ^{1}H NMR($CDCl_3$), δ, ppm: 8.90–7.55(m., 24H, Ph's, pyrroles), 2.71(s, 9H, $CH_3 \times 3$), −2.78 (bs, 2H, NH). MS: ESI + Q1MS, 701 (M. + 1).

General Procedure for Preparation of the Aminophosphonate Derivatives of 5-(4′-Carboxyphenyl)-10,15,20-tri-*p*-tolylporphyrin (3a–c)

To a solution of 5-(4′-carboxyphenyl)-10,15,20-tritolylporphyrin (70 mg, 0.1 mmol) in dry methylene chloride (10 mL), was added 1,3-dicyclohexylcarbodiimide (DCC) (21 mg, 0.1 mmol) with stirring. Then a solution of the hydrobromide of aminophosphonate **2a–c** (0.1 mmol) with triethylamine (11 mg) and 4-(dimethylamino)pyridine (DMAP)

(12 mg) in methylene chloride (10 mL) was added and the mixture was stirred for 24 h at room temperature. Then the reaction mixture was evaporated to dryness, treated with ethyl acetate (50 mL), stirred, and filtered. The filtrate was subsequently washed with 0.1 M. aq. HCl (15 mL), 1.0 M. aq. $NaHCO_3$, (2 × 15 mL), and water (3 × 20 mL), dried (anh. Na_2SO_4), filtered, and evaporated to give the crude porphyrin-phosphonate product **3a–c** as a dark-violet solid. The products **3a–c** were additionally purified by column chromatography (silica gel 70–210 mesh, eluent $CHCl_3$-MeOH: 20:1 v/v).

3a: Yield, 75 mg (73%), ^{1}H NMR ($CDCl_3$), δ, ppm: 8.73–6.81 (m., 37H, arom.), 6.52–6.42 (dd, 1H, CH—P, J = 9.78 Hz), 3.33 (bs, 2H), 2.69 (s, 9H, CH_3). ^{31}P NMR ($CDCl_3$), δ, ppm: 15.04 (s). MS: ESI + Q1MS, 1032.0 (M. + 4).

3b: Yield: 68 mg (64%), ^{1}H NMR ($CDCl_3$), δ, ppm: 8.78–7.03 (m., 35H, arom.), 6.06 (d, 1H, CH—P, J = 9.50 Hz), 2.69 (s, 6H, CH_3), 2.63 (m., 3H, CH_3), 2.31 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), −2.84 (bs, 0.2H, NH). ^{31}P NMR ($CDCl_3$), δ, ppm: 15.73 (s). IR (KBr), cm^{-1}: 3324.5 (s), 2928, 2849 (s), 1699 (m.), 1626.3 (s), 1572.9 (s), 1489.5 (m.), 1435.9, 1310.7 (m.), 1261.4 (s), 1088.0 (s), 800.7 (s), 640.5 (m.). MS: ESI + Q1MS, 1058.8 (M. + 2).

3c: Yield: 89 mg (87%), ^{1}H NMR ($CDCl_3$), δ, ppm: 9.08–6.79 (m., 38H, arom.), 5.98–5.88 (dd, 1H, CH—P, J = 9.62 Hz), 4.12 (bs, 2H, NH), 2.69 (s, 6H, CH_3), 2.63 (s, 3H, CH_3), −2.84 (bs, 0.5H, NH). ^{31}P NMR ($CDCl_3$), δ, ppm: 14.80 (s). MS: ESI+Q1MS, 1025.4 (M. + 2).

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