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Synthesis of Carborane Derivatives of 2-(2-Carboxyvinyl)-25,10,15,20-tetraphenylporphine

R. P. Evstigneeva[1], V. N. Luzgina[1], A. Yu. Gorshkov[1], P. V. Petrovskii[2], V. A. Ol'shevskaya[2], and L. I. Zakharkin[2†]

[1] *Lomonosov Moscow Academy of Fine Chemical Technology, pr. Vernadskogo 86, Moscow, 119571 Russia*

[2] *Nesmeyanov Institute of Organometallic Compounds, Russian Academy of Sciences, Moscow, Russia*

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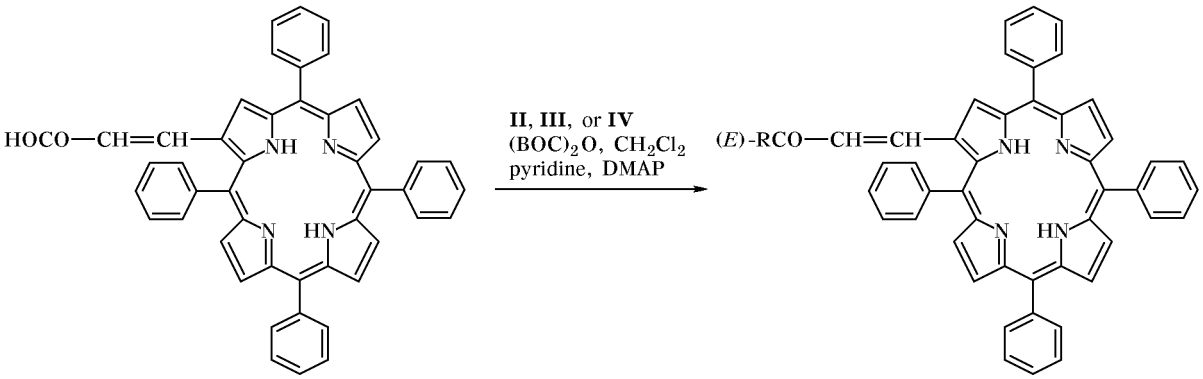
Abstract—New carboranyl-containing porphyrins were synthesized from 2-(2-carboxyvinyl)-5,10,15,20-tetraphenylporphine and 9-hydroxymethyl-*m*-carborane, 1-hydroxymethyl-*o*-carborane, and 3-amino-*o*-carborane. Physical properties of the products were studied.

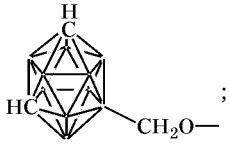
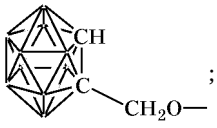
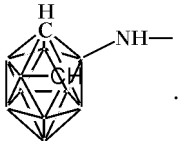
The development of boron neutron capture therapy of brain tumors [1] has aroused interest in the synthesis of new carborane-containing porphyrins as potential subjects for medical studies. The available experimental data of chemical and medical studies indicate exclusive efficiency and significance of this line. The results of investigations in the field of synthesis and physicochemical properties of carboranyl-containing porphyrins considerably extend fundamental knowledge on this unique class of compounds.

Due to accessibility of the parent porphyrin, tetraphenylporphine derivatives are widely used in various chemical synthesis, including preparation of carboranylporphyrins [2–4]. With the goal of obtaining carborane-containing porphyrins we used as starting compound 2-(2-carboxyvinyl)-5,10,15,20-tetraphenylporphine (**I**) which was synthesized by the procedure developed previously in [5]. Porphyrin **I** was brought into condensations with various compounds to obtain new molecular structures with versatile properties

Scheme 1.



I **V–VII**

V, R =  ; **VI**, R =  ; **VII**, R =  .

† Deceased.

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[6–8]. As boron-containing components we selected 9-hydroxymethyl-*m*-carborane (**II**), 1-hydroxymethyl-*o*-carborane (**III**), and 3-amino-*o*-carborane (**IV**) [9].

Compounds **V**–**VII** were synthesized following the mixed anhydride technique with the use of di-*tert*-butyl pyrocarbonate as dehydrating agent. This procedure was successfully applied by us previously in the the preparation of other carboranyl porphyrin derivatives [10, 11]. Covalent bonds between porphyrin **I** and carboranes **II** and **III** having hydroxymethyl groups on B^9 (**II**) or a carbon atom (**III**) were formed with participation of the carboxy group in **I** (via ester bond). Carborane **IV** added through amide bond. The structure of the products was proved by electron absorption, IR, ^{1}H NMR, and mass spectra, and their purity was checked by TLC.

Carborane-containing porphyrins **V** and **VII** are unstable on storage. After 2–3 days, initial porphyrin **I** was detected by chromatography in their originally pure samples. The mass spectra of **V** and **VII** contain ion peaks corresponding to the molecular weight minus boron atom. No decomposition of **VI** was observed. These findings may be explained in terms of specific structure of porphyrins **V**–**VII** where the carborane moieties occur in conjugation with the exocyclic double bond in the acrylic acid moiety of **I**.

Carborane systems are characterized by an appreciable influence of substituent in the polyhedron on the electronic properties of carboranyl groups [12, 13]. In the series of compounds **II**–**IV**, the strongest electron-donor effect was found for 9-*m*-carboranyl group, σ_I = –0.16 [12]. By contrast, 1-*o*-carboranyl group exhibits a strong negative inductive effect, σ_I = 0.38 [13], while 3-*o*-carboranyl group is a weak electron-acceptor, σ_I = 0.11 [13]. Therefore, the stability of of compound **VI** on storage and under electron impact may be explained by stabilizing effect of conjugation between the porphyrin system in **I** and 1-*o*-carboranyl polyhedron (**III**).

While examining the electron absorption spectra of **V**–**VII**, we observed reduction in the intensity of bands of pophyrins **V** and **VI** relative to those of initial compound **I**, especially in the intensity of the Soret band. The latter was displaced by 4–5 nm to the short-wave region, and insignificant shift of bands in the visible region was revealed. Compound **VI** is characterized by reduction of the molar absorption coefficient of the Soret band, while the other parameters of bands in the visible region of the spectra of **VI** and **I** are identical. The IR spectra of freshly prepared samples of **V**–**VII** contained B–H vibration band at 2576 (**V**), 2590 (**VI**), and 2590 cm^{-1} (**VII**). Such a band is typical of *closo*-carboranes.

In the ^{1}H NMR spectra of **V**–**VII**, coupling constants for the vinyl protons were 18.2, 16.4, and 14.8 Hz, respectively, indicating *trans* configuration of the double bond. The corresponding coupling constant in the spectrum of **I** is J = 15.5 Hz [5]. Protons attached to boron atoms in the carborane polyhedron give a multiplet signal in the region δ 3.0–1.1 ppm with its center at δ 2.2 ppm; its intensity corresponds to 9H in the spectra of **V** and **VII** and to 10H in the spectrum of **VI**. The ^{1}H NMR spectra of **V**–**VII** also contained signals from protons of the phenyl groups and β-protons of the pyrrole rings.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer using pyridine-d_5 as solvent. The IR spectra were measured on a UR-20 instrument from samples pelleted with KBr. The electron spectra were recorded on a Jasco 7800 spectrophotometer. The mass spectra were run on a Vision-2000 mass spectrometer (MALDI technique). The purity of the products was checked by thin-layer chromatography on Silufol plates using chloroform–methanol (9:1, A) and chloroform–hexane (9:1, B) as eluent. Column chromatography was performed on silica gel (0.040–0.063 mm, Merck). The solvents were purified by standard methods.

2-[2′-(*m*-Carboran-9-ylmethoxycarbonyl)vinyl]-5,10,15,20-tetraphenylporphine (V). To a solution of 60 mg (0.0876 mmol) of porphyrin **I** in a mixture of 3.5 ml of methylene chloride and 3.5 ml of pyridine we added at 0°C 60 mg (0.275 mmol) of di-*tert*-butyl pyrocarbonate, and the mixture was stirred for 10 min. Carborane **II**, 40.5 mg (0.23 mmol), and 4-dimethylaminopyridine (DMAP), 15 mg, were added, and the mixture was stirred for 3 h at 20°C and poured into 300 ml of 2% hydrochloric acid. The product was extracted into chloroform, the extract was dried over sodium sulfate and evaporated, and the residue was ground with hexane–ether (1:2). The precipitate was separated and purified by column chromatography on silica gel using chloroform–methanol (9:1) as eluent. The solvent was removed from the eluate, and the residue was subjected to additional purification by thin-layer chromatography (solvent system A). Yield 47.2 mg (64%), R_f 0.27 (A). Electron spectrum ($CHCl_3$–0.5% CH_3OH), λ_{max}, nm ($\varepsilon \times 10^{-3}$): 656 (2.34), 601 (4.16), 563 (5.69), 523.2 (9.98), 430 (101.3). IR spectrum, ν, cm^{-1}: 3350 (NH),

2850 (CH), 2576 (BH), 1730 (CO, ester). ^{1}H NMR spectrum, δ, ppm: 9.00 s (1H, β-H), 9.03 s (4H, β-H), 8.98 s (2H, β-H), 7.88–7.82 m (20H, H_{arom}), 7.25 d (1H, C**H**=CHCO, J = 18.2 Hz), 6.90 d (1H, CH=C**H**CO, J = 18.2 Hz), 4,45 s (2H, BCH_2), 2.07 br.s (2H, CH, carborane), –2.28 s (2H, NH). Mass spectrum, m/z: 829.4 $[M-BH]^+$.

2-[2′-(*o*-Carboran-1-ylmethoxycarbonyl)vinyl]-5,10,15,20-tetraphenylporphine (VI) was obtained by the above procedure from porphyrin **I** and 1-hydroxymethyl-*o*-carborane (**III**). Yield 43 mg (70%). R_f 0.53 (B). Electron spectrum ($CHCl_3$–0.5% MeOH), λ_{max}, nm ($\varepsilon \times 10^{-3}$): 661.2 (3.57), 603 (6.09), 565 (7.79), 525 (15.99), 434 (122.31). IR spectrum, ν, cm^{-1}: 3320 (NH), 2891 (CH), 2590 (BH), 1720 (CO, ester). ^{1}H NMR spectrum, δ, ppm: 9.31 s (1H, β-H), 9.01 s (4H, β-H), 8.94 s (2H, β-H), 8.24–7.85 m (20H, H_{arom}), 7.20 d (1H, C**H**=CHCO, J = 16.4 Hz), 6.97 d (1H, CH=C**H**CO, J = 16.4 Hz), 4.35 s (2H, OCH_2), 2.44 br.s (1H, CH, carborane), –2.29 s (2H, NH). Mass spectrum, m/z: 842 $[M+1]^+$.

2-{2′-[*N*-(*o*-Carboran-3-yl)carbamoyl]vinyl}-5,10,15,20-tetraphenylporphine (VII) was prepared as described above for porphyrin **V** from compound **I** and 3-amino-*o*-carborane (**IV**). Yield 47.3 mg (78.4%). R_f 0.3 (A). Electron spectrum (CH_2Cl_2), λ_{max}, nm ($\varepsilon \times 10^{-3}$): 672 (1.81), 620 (0.76), 557.8 (1.22), 522.0 (2.42), 429 (34.12). IR spectrum, ν, cm^{-1}: 3400 (NH), 2950 (CH), 2590 (BH), 1650 (amide I), 1560 (amide II). ^{1}H NMR spectrum, δ, ppm: 9.03 m (4H, β-H), 8.97 s (1H, β-H), 8.81 s (2H, β-H), 8.58–7.85 m (20H, H_{arom}), 7.67 d (1H, C**H**=CHCO, J = 14.8 Hz), 7.41 d (1H, CH=C**H**CO, J = 14.8 Hz), 2.3 br.s (2H, CH, carborane), –2.3 s (2H, NH, porphine). Mass spectrum, m/z: 815 $[M-B]^+$.

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