Synthesis of carboranyl derivatives of de iteroporphyrin IX

L. I. Zakharkin,[a] V. A. Ol'shevskaya,[a] S. Yu. Panfilova,[a] P. V. Petrovskii,[a] V. N. Luzgina,[b] and R. P. Evstigneeva[b]*

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds, Ru. ian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Fe. eration. Fax: +7 (095) 135 5085. E-mail: olshevsk@in os.ac.ru*

[b]*M. V. Lomonosov Moscow State Academy of Fine Che ical Technology, 86 prosp. Vernadskogo, 117571 Moscow, Russian Federation. Fax: +7 (095) 434 8711. E-mail: evstigneeva@htto. mitht.msk.ru*

Carboranylporphyrins, which can be used in boron neutron-c. oture therapy of cancer, were prepared from natural deuteroporphyrin IX, 3-amino-*o*-carbora e, and 9-hydroxymethyl-*m*-carborane.

Key words: deuteroporphyrin IX, carboranes, acylation, carbor nylporphyrins.

The ability of porphyrins[1] to be selectively accumulated and retained inside malignant tumors over a long period of time has aroused interest in the synthesis of boron derivatives of natural and synthetic analogs of porphyrins with the aim of searching for compounds which satisfy requirements imposed upon specimens for boron neutron-capture therapy. This method shows promise for medical treatment of human malignant tumors, belongs to binary methods for treatment, and involves irradiation of a boron-containing substance, present in a cancer cell and containing the ^{10}B isotope, with thermal neutrons. The nonradioactive ^{10}B isotope undergoes the nuclear reaction $^{10}B(n, \alpha)^7Li$ under the action of neutrons to release a large quantity of energy resulting in destruction of cancer cells.

First carboranylporphyrins were prepared[2] almost 20 years ago. Recently, the syntheses of carboranyl-containing porphyrins for boron neutron-capture therapy have been reported.[3–5] The synthesis of tetracarboranylporphyrins as complexes with Ni, Cu, and Mn was also described.[6] In the compounds studied,[2–6] carboranes are bound to porphyrin through the C atom of the carborane nucleus.

Previously, we have described[7,8] the preparation of carboranyl-containing porphyrins in which carboranes are bound to porphyrin through the B atom of the carborane. As part of continuing studies, we synthesized (Scheme 1) carboranyl-substituted porphyrins containing one amide group (**4**), two amide groups (**5**), or two ester groups (**6**) by the reaction of deuteroporphyrin IX (**1**) with 3-amino-*o*-carborane (**2**) or 9-hydroxymethyl-*m*-carborane (**3**), respectively. In the resulting compounds, deuteroporphyrin IX is bound to the carborane ring through the B atom of the polyhedron.

The reactions with the use of 1.6 molar equiv. of pivaloyl chloride or 2 molar equiv. of ethyl chloroformate afforded amide **4** and diamide **5** in ~30% and 3—5% yields, respectiv y (after column chromatography on SiO_2).

When porph in **1** was activated with di-*tert*-butyl pyrocarbonate (I OC_2O) (in a ratio of 1 : 2), diamide **5** was obtained in 7% yield (Scheme 2).

Ester **6** was p pared from compound **3** and porphyrin **1** in 58% yiel upon activation of the carboxyl groups in compound **1** v th BOC_2O according to Scheme 3.

Compounds **4**–**6** were isolated by column chromatography as dark- ed microcrystals, which are soluble in MeOH, $CHCl_3$, THF, and Me_2CO and are poorly soluble in water, ether, a d nonpolar solvents. The structures of **4**—**6** were confir ed by mass spectra, elemental analysis, and electroni IR, and ^1H NMR spectra.

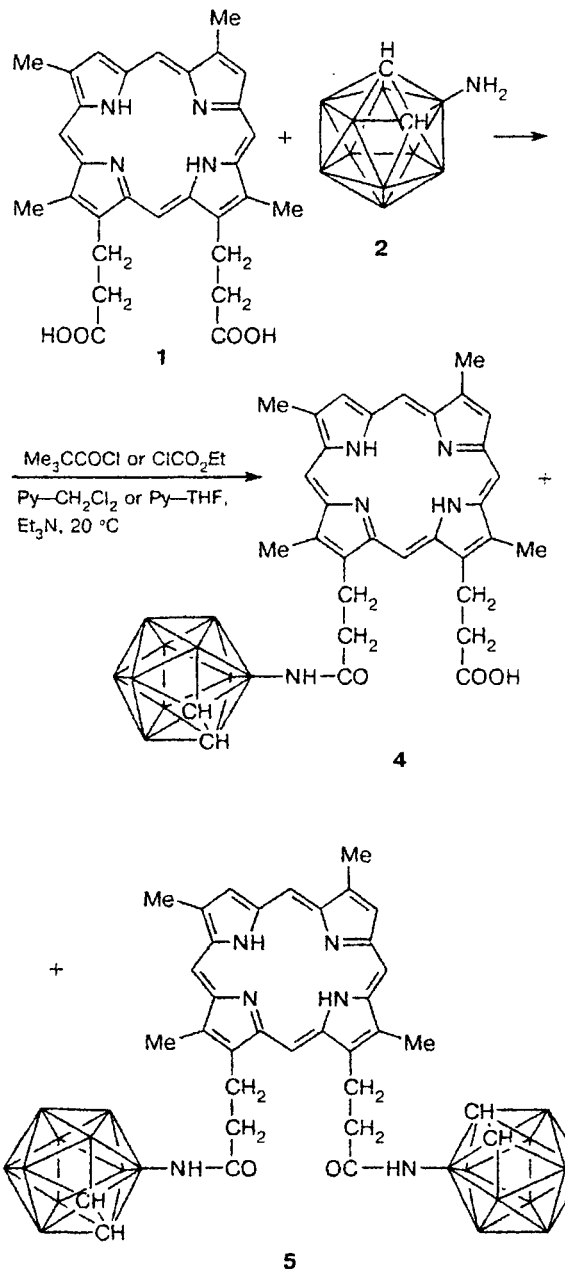
Comparison f the electronic spectra of carboranylporphyrins **4**- **6** with the spectra[9] of dimethyl ester of deuteroporph in IX revealed no changes in the positions of the axima of the absorption bands but showed a decrea in the extinction coefficient. The ^1H NMR spectra data confirmed the structures of the compounds synth sized.

The ^1H NMR spectra of porphyrins **4**—**6** have signals for the *meso*- rotons and signals for the β-protons of the pyrrole rin as well as signals for the NH protons at high field (δ − .42 (**4**), −3.45 (**5**), and −3.82 (**6**)), which confirm the tructure of the porphyrin macrocycle. In addition, the ignals for the CH protons of the carborane nucleus n the ^1H NMR spectra are substantially shifted (δ ~ −3) compared to the corresponding signals of the init l compounds **2** and **3**. The protons attached to the B oms of the carborane polyhedron are observed as a broadened multiplet signal at δ 3.1—1.1 centere at δ 2 with an intensity of 9 H for porphyrin **4** and 18 H for porphyrins **5** and **6**. The signal for the proton of he COOH group of porphyrin **4** is averaged due to e change with H_2O that is present in C_5D_5N.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2337—2339 December, 1999.

1066-5285/99/4812-2312 $22.00 © 2 00 Kluwer Academic/Plenum Publishers

Scheme 1

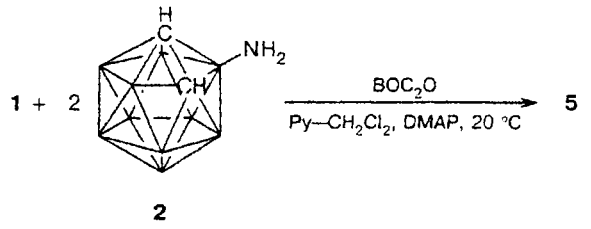


Thus, the mixed anhydride formed from deuteroporphyrin IX and BOC_2O is an efficient acylating agent for the synthesis of carborane derivatives of deuteroporphyrin IX. In the future, we plan to prepare water-soluble forms of these porphyrins.

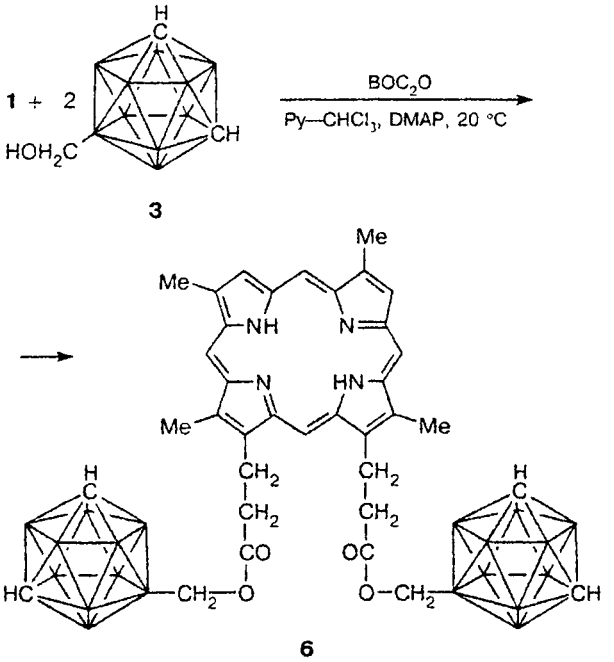
Experimental

The ^1H NMR spectra were recorded on a Bruker AMX-400 instrument in C_5D_5N (for porphyrins **4** and **5**) or

Scheme 2



Scheme 3



$CDCl_3$ (for **6**) as the solvent. The IR spectra were obtained on a UR-20 instrument in KBr pellets. The electronic spectra were recorded on a Hitachi UV-557 instrument. The mass spectra were measured on an MSBKh spectrometer by plasma desorption spectrometry for porphyrins **4** and **5** and on a Varian MAT-731 spectrometer by field desorption for **6**. Compounds **2** [10] and **3** [11] have been prepared previously. The purities of the compounds were checked by TLC on Silufol plates with a 9 : 1 $CHCl_3$—MeOH solvent system. Column chromatography was carried out on L silica gel (40—100 μm) using the same solvent system. The solvents were purified according to standard procedures.

1,3,5,8-Tetramethyl-6(7)-[2-*N*-(*o*-carboran-3-yl)carbamoylethyl]-7(6)-(2-carboxyethyl)porphyrin (4). *A*. Et_3N (46 mg, 0.46 mmol) was added to a solution of porphyrin **1** (100 mg, 0.20 mmol) in a mixture of THF (8 mL) and Py (8 mL) at 0 °C. The reaction mixture was cooled to −15 °C. Then a solution of $ClCO_2Et$ (45 mg, 0.41 mmol) in THF (3 mL) was added dropwise over 30 min and the reaction mixture was kept at this temperature for 30 min. In this case, mixed anhydride was formed (TLC data, a 15 : 1 $CHCl_3$—MeOH mixture). Then amine **2** (62 mg, 0.39 mmol) was added to the reaction mixture at 0 °C, and the mixture was kept for 1.5 h

with a gradual increase in the temperature to 20 °C. After removal of the solvents *in vacuo*, the residue was chromatographed on a column with SiO_2. Amide **4** and diamide **5** were obtained in yields of 38 mg (29%) and 8 mg (5%), respectively. For **4**, found (%): C, 59.21; H, 6.38; N, 10.63. $C_{32}H_{41}B_{10}N_5O_3$. Calculated (%): C, 58.99; H, 6.30; N, 10.75. Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 618 (1.47); 562.2 (3.25); 530.2 (3.75); 496.8 (5.50); 399.6 (64.5). IR, ν/cm^{-1}: 1720 (CO in COOH); 1723 (CO in CONH); 2587 (BH); 3070 (CH of carborane); 3320 (NH). ^1H NMR, δ: 10.52 (s, 1 H, *meso*-H); 10.18 (s, 2 H, *meso*-H); 10.14 (s, 1 H, *meso*-H); 9.25 (s, 1 H, NHCO); 9.11 (s, 1 H, β-pyrrole); 9.08 (s, 1 H, β-pyrrole); 4.40 (m, 2 H, $\underline{CH_2}CH_2CO$); 4.38 (m, 2 H, $\underline{CH_2}CH_2CO$); 3.49 (s, 6 H, 2 Me); 3.44 (s, 6 H, 2 Me); 3.36 (m, 2 H, $CH_2\underline{CH_2}CO$); 3.33 (m, 2 H, $CH_2\underline{CH_2}CO$); 1.12 (br.s, 2 H, CH of carborane); −3.42 (br.s, 2 H, NH of porphyrin). MS, *m/z*: 651.1 $[M]^+$.

B. Et_3N (46 mg, 0.46 mmol) was added to a solution of porphyrin **1** (100 mg, 0.20 mmol) in a mixture of CH_2Cl_2 (8 mL) and Py (8 mL) at 0 °C. The reaction mixture was cooled to −15 °C, a solution of Me_3CCOCl (38 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 0.5 h, and the mixture was kept at this temperature for 0.5 h. Then a solution of amine **2** (42 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at 20 °C for 1 h. Amides **4** and **5** were isolated as described previously in yields of 42 mg (32%) and 5 mg (3%), respectively.

The ^1H NMR, electronic, and IR spectra of both samples of amide **4** are identical.

1,3,5,8-Tetramethyl-6,7-di[2-*N*-(*o*-carboran-3-yl)-carbamoylethyl]porphyrin (5). BOC_2O (100 mg, 0.46 mmol) was added to a solution of porphyrin **1** (100 mg, 0.20 mmol) in a mixture of Py (8 mL) and CH_2Cl_2 (8 mL) at 0 °C and the mixture was stirred for 10 min. Then compound **2** (76 mg, 0.48 mmol) and 4-dimethylaminopyridine (DMAP) (10 mg) were added and the mixture was stirred at 20 °C for 1 h, poured into 2% HCl (400 mL), and extracted with $CHCl_3$. The extract was washed with water and concentrated *in vacuo*. The residue was chromatographed on a column with silica gel and diamide **5** was obtained in a yield of 86 mg (57%). Found (%): C, 51.33; H, 6.71; N, 10.80. $C_{34}H_{52}B_{20}N_6O_2$. Calculated (%): C, 51.51; H, 6.56; N, 10.61. Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619 (1.67); 594 (1.08); 564.8 (3.48); 529.8 (3.79); 496.8 (5.89); 398.4 (69.36). IR, ν/cm^{-1}: 1718 (CO); 2591 (BH); 3060 (CH of carborane); 3305 (NH). ^1H NMR, δ: 10.42 (s, 1 H, *meso*-H); 10.32 (s, 2 H, *meso*-H); 10.28 (s, 1 H, *meso*-H); 9.33 (s, 2 H, NHCO); 9.12 (s, 1 H, β-pyrrole); 9.09 (s, 1 H, β-pyrrole); 4.41 (m, 4 H, $\underline{CH_2}CH_2CO$); 4.66 (s, 12 H, 4 Me); 3.31 (m, 4 H, $CH_2\underline{CH_2}CO$); 2.07 (br.s, 4 H, CH of carborane); −3.45 (br.s, 2 H, NH of porphyrin). MS, *m/z*: 792.7 $[M]^+$.

1,3,5,8-Tetramethyl-6,7-di[2-(*m*-carboran-9-yl)methoxy-carbonylethyl]porphyrin (6). BOC_2O (100 mg, 0.46 mmol) was added to a solution of porphyrin **1** (100 mg, 0.20 mmol) in a mixture of $CHCl_3$ (8 mL) and Py (8 mL) cooled to 0 °C. The reaction mixture was stirred for 10 min and then compound **3** (73 mg, 0.42 mmol) was added. After 5 min, DMAP (10 mg) was added. The reaction mixture was stirred at 20 °C for 1.5 h, poured into 2% HCl (400 mL), and extracted with $CHCl_3$. The chloroform extract was washed with water and the organic layer was separated and concentrated *in vacuo*. An excess of compound **3** was washed off with a 1 : 1 pentane—Et_2O mixture and the residue was chromatographed on a column with silica gel. Porphyrin **6** was obtained as dark-red microcrystals in a yield of 95.4 mg (58%). Found (%): C, 52.30; H, 6.90; N, 6.99. $C_{36}H_{54}B_{20}N_4O_4$. Calculated (%): C, 52.55; H, 6.32; N, 6.81. Electronic spectrum ($CHCl_3$), λ_{max}/nm ($\varepsilon \cdot 10^{-3}$): 619 (2.08); 595 (1.58); 564.4 (4.68); 529.8 (4.87); 496.8 (7.57); 399 (101.53). IR, ν/cm^{-1}: 1726 (CO); 2600 (BH); 3065 (CH of carborane); 3313 (NH). ^1H NMR, δ: 10.13 (s, 2 H, *meso*-H); 10.06 (s, 2 H, *meso*-H); 9.16 (s, 1 H, β-pyrrole); 9.09 (s, 1 H, β-pyrrole); 4.43 (t, 4 H, $\underline{CH_2}CH_2CO$); 4.03 (s, 4 H, B—CH_2); 3.65 (s, 6 H, 2 Me); 3.64 (s, 6 H, 2 Me); 3.43 (t, 4 H, $CH_2\underline{CH_2}CO$); 2.70 (br.s, 4 H, CH of carborane); −3.82 (br.s, 2 H, NH). MS, *m/z*: 822 $[M]^+$.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 97-03-33158a) and INTAS (Grant 96-1114).

References

1. T. J. Dougherty, *Photochem. Photobiol.*, 1983, **38**, 377.
2. R. C. Haushalter, W. M. Butler, and R. W. Rudolph, *J. Am. Chem. Soc.*, 1981, **103**, 2620.
3. S. B. Kahl and M.-S. Koo, *J. Chem. Soc., Chem. Commun.*, 1990, 1769.
4. M. Miura, D. Gabel, G. Oenbrink, and R. G. Fairchild, *Tetrahedron Lett.*, 1990, **103**, 2247.
5. A. S. Phadke and A. R. Morgan, *Tetrahedron Lett.*, 1993, **34**, 1725.
6. M. Miura, D. D. Joel, M. M. Nawrocky, P. L. Micca, C. D. Fisher, J. C. Heinrichs, C. E. Rising, W. Walker, and D. N. Slatkin, in *Advances in Neutron Capture Therapy*, **II**, *Chemistry and Biology*, Eds. B. Larsson, J. Crawford, and R. Weinreich, Elsevier, Amsterdam—Lausanne, 1997, 56.
7. R. P. Evstigneeva, V. N. Luzgina, V. A. Ol'shevskaya, and L. I. Zakharkin, *Dokl. Akad. Nauk*, 1997, **357**, 637 [*Dokl. Chem.*, 1997 (Engl. Transl.)].
8. L. I. Zakharkin, V. A. Ol'shevskaya, R. P. Evstigneeva, V. N. Luzgina, L. E. Vinogradova, and P. V. Petrovskii, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 347 [*Russ. Chem. Bull.*, 1998, **47**, 340 (Engl. Transl.)].
9. J. E. Falk, in *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam—London—New York, 1960, p. 226.
10. L. I. Zakharkin and V. N. Kalinin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 2585 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16** (Engl. Transl.)].
11. L. I. Zakharkin, V. A. Ol'shevskaya, and N. B. Boiko, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 719 [*Russ. Chem. Bull.*, 1996, **45**, 680 (Engl. Transl.)].

Received March 30, 1999