A One Step Synthesis of Boronated *meso*–Tetraphenylporphyrins

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5,10,15,20-Tetrakis(4-aminophenyl)porphyrin and their metal complexes were used for a one stage synthesis of boronated porphyrins with elevated boron content (~30-35%). The reaction of amino groups in para position of porphyrin phenyl rings with carborane triflates, epoxides and isocyanates smoothly led to carboranylsubstituted secondary amines, amino alcohols and amides potentially applicable in anticancer boron neutron capture therapy (BNCT). 5-(4-Aminophenyl)-10,15,20-triphenylporphyrin was used as a model compound in reactions with above mentioned functionally substituted carboranes.

Keywords: Porphyrins, carboranylmethyl triflates, carboranylepoxides, carboranylisocyantes, carboranylporphyrins, boron neutron capture therapy (BNCT).

Introduction

The boronated derivatives of porphyrins and chlorins are under an extensive investigation as clinically applicable drugs for binary anticancer strategy called boron neutron capture therapy (BNCT).[1-3] In this method the tetrapyrrole macrocycle plays a vector-like role in preferential delivery of the conjugate to the tumor cells whereas ^{10}B isotope serves for generating a local radioactive reaction upon tumor irradiation with thermal neutrons. Moreover, low-to-null dark toxicity and fluorescent characteristics of boronated tetrapyrrole containing agents allow for visual control of intratumoral drug accumulation. Second generation drugs such as disodium salt of mercapto-*closo*-dodecaborate (BSH) and L-4-dihydroxyboryl phenylalanine (BPA) are currently used in clinical protocols.[4] Unfortunately, for these agents the ratio tumor:extratumoral milieu is limited. Furthermore, BSH is chemically unstable and is oxidized by air oxygen.[5-6] The boron content in BPA is relatively low (~ 5 %) which requires dose escalation for efficient therapy. These drawbacks make necessary the search for novel compounds with optimized characteristics.

Recently the *meso*-tetraphenylporphyrin-based boronated porphyrins with elevated (20%) boron content have been reported.[1] These compounds have ester, amide and ether bonds between the boron polyhedra and the porphyrin macrocycle. In this study we developed a one stage synthesis of boronated porphyrins with hydrolytically resistant spacer groups using the available amino derivatives of *meso*-tetraphenylporphyrin, namely, (5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1**)[7] and 5,10,15,20-tetrakis(4-aminophenyl)porphyrin (**2**)[8]), and functionally substituted carboranes (such as triflates, epoxides or isocyanates). The aminoporphyrin **1** that contains one amino group in the macrocycle was used as a model compound for optimization of synthesis of tetrasubstituted carboranylporphyrins from aminoporphyrin **2**.

Experimental

The ^1H NMR spectra were recorded on Bruker Avance-400 spectrometer. The IR spectra were registered on Specord M-82 of Carl Zeiss spectrometer in KBr tablets or in hexachloro-1,3-butadiene. The UV-vis spectra were measured on a spectrophotometer Jasco UV 7800 series in $CHCl_3$. The mass spectra were obtained using VISION 2000 (MALDI) mass spectrometer, the most intense peaks were given for each compound. The identities of new compounds were verified on TLC 60 F_{254} plates (Merck). Merck silica gel L 0.04-0.08 mesh was used for column chromatography. The solvents were purified according to standard procedures.

*General procedure of synthesis of carboranylporphyrins **5, 6**.*

To the solution of 0.035 mmol of porphyrin **1** in 10 ml of THF 0.35 mmol of sodium acetate and 0.07 mmol of carborane **3** or **4** were added, and the mixture was refluxed for 12 h. Then the reaction mixture was poured into water (20 ml) and extracted with $CHCl_3$ (3x5 ml). The organic solution was washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed on a SiO_2 column (1x15 cm) using $CHCl_3$ as an eluent.

*5-[4-(o-Carboran-1-yl)methyl]aminophenyl-10,15,20-triphenyl porphyrin, **5***. Yield 26 mg (73%). Found: C 71.10, H 5.56, B 14.08, N 9.26 %. $C_{47}H_{43}B_{10}N_5$ requires C 71.82, H 5.51, B 13.75, N 8.91 %. *m/z* (MALDI): 786 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3442 (NH), 2595 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 418 (4.05), 515 (3.57), 550 (3.18), 647 (2.81). ^1H NMR ($CDCl_3$) δ ppm: 8.84 (8H, s, *pyrrole*-H), 7.74 - 8.20 (19H, m, Ph), 4.32 (1H, br.s, NH), 3.76 (1H, br.s, *carborane*-CH), 1.82 (2H, s, CH_2), -2.78 (2H, s, *pyrrole*-NH).

*{5-[4-(1-Carba-closo-dodecaboran-1-yl) methylaminophenyl]-10,15,20-triphenyl porphyrin}cesium, **6***. Yield 31 mg (74%). Found: C 60.73, H 4.86, B 12.24, N 7.92 %. $C_{46}H_{43}B_{11}CsN_5$ requires C 60.20, H 4.72, B 12.96, N 7.63 %. *m/z* (MALDI): 785 [M-Cs^+]. IR (KBr) ν_{max} cm^{-1}: 3448 (NH), 2531 (BH). UV-vis λ_{max} ($CHCl_3$) nm (lg ε): 421 (4.11), 516 (3.36), 553 (3.15), 649 (2.85). ^1H NMR ($CDCl_3$) δ ppm: 8.83 (8H, s, *pyrrole*-H), 7.76 - 8.20 (19H, m, Ph), 4.35 (1H, br.s, NH), 1.81 (2H, s, CH_2), -2.80 (2H, s, *pyrrole*-NH).

*General procedure of synthesis of carboranylporphyrins **7, 8**.*

To the solution of 0.035 mmol of porphyrin **2** in 20 ml of acetonitrile 0.35 mmol of sodium acetate and 0.24 mmol carborane

3 or **4** were added, and the mixture was refluxed for 10-15 h. Then the reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (3x7 ml). The organic solution was dried over Na_2SO_4, and evaporated in vacuo. The residue was washed with hexane (2x5 ml) and chromatographed on a SiO_2 column (1x20 cm) using $CHCl_3$:CH_3OH (8:1 v/v) as an eluent.

5,10,15,20-Tetrakis[4-(o-carboran-1-yl)methyl] aminophenylporphyrin, 7. Yield 32 mg (67%). Found: C 52.08, H 6.39, B 32.79, N 8.74 %. $C_{56}H_{82}B_{40}N_8$ requires C 51.75, H 6.36, B 33.27, N 8.62 %. *m/z* (MALDI): 1299 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3389 (NH), 2595 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 421(4.17), 515(3.48), 550(3.15), 650(3.09). ^{1}H NMR ($CDCl_3$) δ ppm: 8.81 (8H, s, *pyrrole*-H), 7.75 - 8.29 (16H, m, Ph), 4.33 (4H, br.s, NH), 3.60 (4H, br.s, *carborane*-CH), 1.81 (8H, s, CH_2), -2.78 (2H, s, *pyrrole*-NH).

{5,10,15,20-Tetrakis[4-(1-carba-closo-dodecaboran-1-yl) methyl]aminophenylporphyrin} cesium, 8. Yield 48 mg (72%). Found: C 34.65, H 4.61, B 25.53, N 6.24 %. $C_{52}H_{82}B_{44}Cs_4N_8$ requires C 34.19, H 4.52, B 26.04, N, 6.13 %. *m/z* (MALDI): 1295 [M-4Cs^+]. IR (KBr) ν_{max} cm^{-1}: 3335 (NH), 2534 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 427(4.23), 522(2.34), 561(2.30), 657(2.15). ^{1}H NMR ($CDCl_3$) δ ppm: 8.90 (8H, s, *pyrrole*-H), 7.80 - 8.42 (16H, m, Ph), 3.61 (4H, br.s, NH), 1.81 (8H, s, CH_2), -2.72 (2H, s, *pyrrole*-NH).

General procedure of synthesis of carboranylporphyrins ***15***–***18***.

To the solution of 0.07 mmol of porphyrins **11** or **12** in 10 ml of acetonitrile 0.22 mmol of carboranes **9** or **10** and a catalytic amount (1 mg, 0.007 mmol) of $ZnCl_2$ were added. The reaction mixture was refluxed for 15 h and monitored by thin-layer chromatography in $CHCl_3$:hexane (3:1 v/v). Then acetonitrile was evaporated in vacuo. The residue was dissolved in 10 ml of $CHCl_3$, washed with water (2x10 ml), dried over Na_2SO_4. $CHCl_3$ was evaporated and residue was purified on a SiO_2 column (1x20 cm) using $CHCl_3$ as an eluent, affording carboranylporphyrins **15–18**.

Zn complex of 5,10,15-triphenyl-20-[p-(1'-o-carboranyl-phenyl-2'-hydroxypropyl)aminophenyl]porphyrin, ***15***. Yield 50 mg (71.4%). Found: C 68.74, H 5.15, B 10.78, N 7.29 %. $C_{55}H_{49}B_{10}N_5OZn$ requires C 68.14, H 5.09, B 11.15, N 7.22 %. *m/z* (MALDI): 970 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3383 (OH, NH), 2586 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 424 (4.95), 556 (4.08), 599 (3.75). ^{1}H NMR ($CDCl_3$) δ ppm: 8.96 (2H, s, *pyrrole*-H), 8.86 (6H, s, *pyrrole*-H), 8.12 (1H, s, NH), 7.05 - 7.95 (24H, m, Ph), 3.78 – 3.83 (1H, m, CH), 2.45 (1H, br.s, OH), 2.18 (1H, dd, C*H*H-N, $^2J_{нн}$ = 14.2 Hz, $^3J_{нн}$ = 4.0 Hz), 1.90 (1H, dd, CH*H*-N, $^2J_{нн}$ = 14.2 Hz, $^3J_{нн}$ = 12.1 Hz), 1.85 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.4 Hz, $^3J_{нн}$ = 7.5 Hz), 1.64 (1H, dd, CH*H*-carborane, $^2J_{нн}$ = 16.4 Hz, $^3J_{нн}$ = 3.8 Hz).

Zn complex of 5,10,15-triphenyl-20-[p-(1'-o-carboranyl-2'-hydroxypropyl)aminophenyl]porphyrin, ***16***. Yield 50 mg (83.3%). Found: C 65.21, H 5.13, B 12.54, N 7.96 %. $C_{49}H_{45}B_{10}N_5OZn$ requires C 65.87, H 5.08, B 12.10, N 7.84 %. *m/z* (MALDI): 893 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3496 (OH, NH), 2591 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 425 (4.97), 555 (4.11), 595 (3.83). ^{1}H NMR ($CDCl_3$) δ ppm: 8.99 (2H, s, *pyrrole*-H), 8.85 (6H, s, *pyrrole*-H), 8.19 (1H, s, NH), 7.12 - 8.02 (19H, m, Ph), 4.08 (1H, br.s, *carborane*-H), 3.77 - 3.83 (1H, m, CH), 2.42 (1H, br.s, OH), 2.22 (1H, dd, C*H*H-N, $^2J_{нн}$ = 15,2 Hz, $^3J_{нн}$ = 5,1 Hz), 2.13 (1H, dd, CH*H*-N, $^2J_{нн}$ = 15,2 Hz, $^3J_{нн}$ = 13,0 Hz), 1.97 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16,2 Hz, $^3J_{нн}$ = 8,1 Hz), 1.71 (1H, dd, CH*H*-carborane, $^2J_{нн}$ = 16,2 Hz, $^3J_{нн}$ = 4,5 Hz).

Pd complex of 5,10,15-triphenyl-20-[p-(1'-o-carboranyl-phenyl-2'-hydroxypropyl)aminophenyl]porphyrin, ***17***. Yield 50 mg (78.5%). Found: C 65.91, H 4.92, B 10.61, N 7.01 %. $C_{55}H_{49}B_{10}N_5OPd$ requires C 65.37, H 4.89, B 10.02, N 6.93 %. *m/z* (MALDI): 1011 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3321 (OH, NH), 2586 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 424 (4.93), 558 (4.04), 595 (3.69). ^{1}H NMR ($CDCl_3$) δ ppm: 9.01 (2H, s, *pyrrole*-H), 8.92 (6H, s, *pyrrole*-H), 8.21 (1H, s, NH), 7.15 - 7.88 (24H, m, Ph), 3.78 - 3.85 (1H, m, CH), 2.40 (1H, br.s, OH), 2.25 (1H, dd, C*H*H-N, $^2J_{нн}$ = 14.2 Hz, $^3J_{нн}$ = 4.0 Hz), 2.00 (1H, dd, CH*H*-N, $^2J_{нн}$ = 13.9 Hz, $^3J_{нн}$ = 12.6 Hz), 1.91 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 14.8 Hz, $^3J_{нн}$ = 7.6 Hz), 1.71 (1H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 14.8 Hz, $^3J_{нн}$ = 3.5 Hz).

Pd complex of 5,10,15-triphenyl-20-[p-(1'-o-carboranyl-2'-hydroxypropyl)aminophenyl]porphyrin, ***18***. Yield 60 mg (82.7%). Found: C 63.56, H 4.91, B 10.91, N 7.55 %. $C_{49}H_{45}B_{10}N_5OPd$ requires C 62.98, H 4.85, B 11.57, N 7.49 %. *m/z* (MALDI): 934 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3319 (OH, NH), 2585 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 423 (4.97), 555 (4.10), 595 (3.78). ^{1}H NMR ($CDCl_3$) δ ppm: 9.02 (2H, s, *pyrrole*-H), 8.87 (6H, s, *pyrrole*-H), 8.23 (1H, s, NH), 7.20 - 8.14 (19H, m, Ph), 4.13 (1H, br.s, *carborane*-H), 3.82 - 3.91 (1H, m, CH), 2.50 (1H, br.s, OH), 2.22 (1H, dd, C*H*H-N, $^2J_{нн}$ = 15,2 Hz, $^3J_{нн}$ = 5,1 Hz), 2.06 (1H, dd, CH*H*-N, $^2J_{нн}$ = 11.9 Hz, $^3J_{нн}$ = 10.2 Hz), 1.98 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 15.3 Hz, $^3J_{нн}$ = 8.0 Hz), 1.69 (1H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 15.3 Hz, $^3J_{нн}$ = 4.8 Hz).

General procedure of synthesis of carboranylporphyrins ***19–22.***

To the solution of 0.07 mmol of porphyrins **13** or **14** in 15 ml of THF 0.72 mmol of carboranes **9** or **10** and a catalytic amount (2 mg, 0.014 mmol) of $ZnCl_2$ were added. The reaction mixture was refluxed for 18 h and monitored by thin-layer chromatography in $CHCl_3$:hexane (5:1 v/v). THF was evaporated in vacuo. The residue was dissolved in 10 ml of $CHCl_3$, washed with water (2x10 ml), dried over Na_2SO_4. The solvent was evaporated and the residue was purified on a SiO_2 column (1x20 cm) using the mixture of $CHCl_3$:CH_3OH (15:1 v/v) as eluent, affording carboranylporphyrins **19–22**.

Zn complex of 5,10,15,20-tetra[p-2-hydroxy-3-(1'-o-phenyl-carboran-2'-yl)propyl]aminophenylporphyrin, ***19***. Yield 90 mg (75.0%). Found: C 57.81, H 6.22, B 22.89, N 6.17 %. $C_{88}H_{112}B_{40}N_8O_4Zn$ requires C 57.33, H 6.12, B 23.45, N 6.08 %. *m/z* (MALDI): 1842 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3417 (OH, NH), 2585 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 437 (4.91), 560 (3.80), 607 (3.38). ^{1}H NMR ($CDCl_3$) δ ppm: 9.67 (8H, s, *pyrrole*-H), 8.89 (4H, s, NH), 7.23 - 8.61 (36H, m, Ph), 3.64 – 3.76 (4H, m, CH), 2.60 (4H, br.s, OH), 2.42 (4H, dd, C*H*H-N, $^2J_{нн}$ = 14.1 Hz, $^3J_{нн}$ = 3.9 Hz), 2.26 (4H, dd, CH*H*-N, $^2J_{нн}$ = 14.1 Hz, $^3J_{нн}$ = 12.7 Hz), 2.03 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.3 Hz, $^3J_{нн}$ = 7.6 Hz), 1.58 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 16.3 Hz, $^3J_{нн}$ = 3.3 Hz).

Zn complex of 5,10,15,20-tetra[p-2-hydroxy-3-(1'-o-carboran-2'-yl)propyl]aminophenylporphyrin, ***20***. Yield 80 mg (83.0%). Found: C 50.37, H 6.21, B 27.78, N 7.35 %. $C_{64}H_{96}B_{40}N_8O_4Zn$ requires C 49.94, H 6.29, B 28.09, N 7.28 %. *m/z* (MALDI): 1539 [M^+]. ν_{max} (hexachloro-1,3-butadiene)/cm^{-1} 3410 (OH, NH), 2590 (BH). UV-vis λ_{max} ($CHCl_3$) nm (lg ε): 436 (4.91), 561 (3.90), 607 (3.53). ^{1}H NMR ($CDCl_3$) δ ppm: 9.66 (8H, s, *pyrrole*-H), 8.79 (4H, s, NH), 7.20 - 8.60 (16H, m, Ph), 3.62 – 3.73 (4H, m, CH), 3.20 (4H, br.s, *carborane*-H), 2.65 (4H, br.s, O*H*), 2.40 (4H, dd, C*H*H-N, $^2J_{нн}$ = 14.3 Hz, $^3J_{нн}$ = 4.0 Hz), 2.24 (4H, dd, CH*H*-N, $^2J_{нн}$ = 14.0 Hz, $^3J_{нн}$ = 12.5 Hz), 2.00 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.0 Hz, $^3J_{нн}$ = 7.9 Hz), 1.50 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 16.1 Hz, $^3J_{нн}$ = 3.5 Hz).

Pd complex of 5,10,15,20-tetra[p-2-hydroxy-3-(1'-o-phenylcarboran-2'-yl)propyl]aminophenylporphyrin, ***21***. Yield 130 mg (84.5%). Found: C 56.71, H 5.87, B 22.45, N 6.05 %. $C_{88}H_{112}B_{40}N_8O_4Pd$ requires C 56.08, H 5.99, B 22.94, N 5.95 %. *m/z* (MALDI): 1886 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3338 (OH, NH), 2585 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 428 (4.90), 535 (3.76), 610 (3.30). ^{1}H NMR ($CDCl_3$) δ ppm: 9.48 (8H, s, *pyrrole*-H), 8.67 (4H, s, NH), 7.17 - 8.55 (36H, m, Ph), 3.64 – 3.79 (4H, m, CH), 2.55 (4H, br.s, OH), 2.31 (4H, dd, C*H*H-N, $^2J_{нн}$ = 13.5 Hz, $^3J_{нн}$ = 3.9 Hz), 2.16 (4H, dd, CH*H*-N, $^2J_{нн}$ = 13.5 Hz, $^3J_{нн}$ = 11.4 Hz), 2.11 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 14.6 Hz, $^3J_{нн}$ = 6.9 Hz), 1.63 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 14.6 Hz, $^3J_{нн}$ = 4.0 Hz).

Pd complex of 5,10,15,20-tetra[p-2-hydroxy-3-(1'-o-carboran-2'-yl)propyl]aminophenylporphyrin, ***22***. Yield 85 mg (77.0 %). Found: C, 48.21; H, 6.07; B, 27.64; N, 7.18 %. $C_{64}H_{96}B_{40}N_8O_4Pd$ requires C, 48.64; H, 6.12; B, 27.36; N, 7.09 %. *m/z* (MALDI): 1580 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3340 (OH, NH), 2592 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 435 (4.89), 561 (3.87), 610 (3.45). ^{1}H NMR ($CDCl_3$) δ ppm: 9.40 (8H, s, *pyrrole*-H), 8.68 (4H, s, NH), 7.10 - 8.50 (16H, m, Ph), 3.60 – 3.69 (4H, m, CH), 3.15 (4H, br.s, *carborane*-H), 2.50 (4H, br.s, OH), 2.30 (4H, dd, C*H*H-N, $^2J_{нн}$ = 13.7 Hz, $^3J_{нн}$ = 3.8 Hz), 2.10 (4H, dd, CH*H*-N, $^2J_{нн}$ = 13.6 Hz, $^3J_{нн}$ = 11.0 Hz), 2.05 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 14.8 Hz, $^3J_{нн}$ = 6.6 Hz), 1.60 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 14.8 Hz, $^3J_{нн}$ = 4.1 Hz).

General procedure of synthesis of carboranylporphyrins ***23*** *and* ***24***.

To the solution of 0.05 mmol of **15** or **16** in 10 ml of $CHCl_3$ 0.1 ml of trifluoroacetic acid was added and the reaction mixture was kept at 20^0 C with stirring for 2 h. The solvent was evaporated in vacuo. The residue was purified on a SiO_2 (column 1x20 cm) using $CHCl_3$ as eluent.

5,10,15-Triphenyl-20-[p-(1'-o-carboranylphenyl-2'-hydroxypropyl)aminophenylporphyrin, ***23***. Yield 40 mg (94.8%). Found: C 73.32, H 5.58, B 11.59, N 7.89 %. $C_{55}H_{51}B_{10}N_5O$ requires C 72.90, H 5.67, B 11.93, N 7.73 %. *m/z* (MALDI): 904 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3379 (OH, NH), 3061 (Ph), 2585 (BH). UV-vis 85 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 15.8 Hz, $^3J_{нн}$ = 7.3 Hz), 1.67 (1H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 15.8 Hz λ_{max} ($CHCl_3$) nm (lg ε): 421 (4.96), 553 (4.10), 597 (3.78). ^{1}H NMR ($CDCl_3$) δ ppm: 8.89 (2H, s, *pyrrole*-H), 8.77 (6H, s, *pyrrole*-H), 8.02 (1H, s, NH), 6.96 - 7.93 (24H, m, Ph), 3.70 – 3.80 (1H, m, CH), 2.46 (1H, br.s, OH), 2.20 (1H, dd, C*H*H-N, $^2J_{нн}$ = 13.9 Hz, $^3J_{нн}$ = 4.0 Hz), 1.93 (1H, dd, CH*H*-N, $^2J_{нн}$ = 13.9 Hz, $^3J_{нн}$ = 12.4 Hz), 1., $^3J_{нн}$ = 3.8 Hz), -2.68 (2H, br.s, pyrrole-NH).

5,10,15-Triphenyl-20-[p-(1'-o-carboranyl-2'-hydroxypropyl)aminophenylporphyrin, ***24***. Yield 0.40 mg (93.5%). Found: C 70.58, H 5.78, B 13.36, N 8.61 %. $C_{49}H_{47}B_{10}N_5O$ requires C 70.90, H 5.71, B 13.02, N 8.44 %. *m/z* (MALDI): 828 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3403 (OH, NH), 3059 (Ph), 2585 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 422 (4.98), 555 (4.15), 596 (3.86). ^{1}H NMR ($CDCl_3$) δ ppm: 9.01 (2H, s, *pyrrole*-H), 8.94 (6H, s, *pyrrole*-H), 8.66 (1H, s, NH), 6.93 - 7.87 (19H, m, Ph), 4.12 (1H, br.s, *carborane*-H), 3.63 – 3.77 (1H, m, CH), 2.75 (1H, dd, C*H*H-N, $^2J_{нн}$ = 13.2 Hz, $^3J_{нн}$ = 3.5 Hz), 2.43 (1H, dd, CH*H*-N, $^2J_{нн}$ = 13.2 Hz, $^3J_{нн}$ =12.7 Hz), 2.42 (1H, br.s, OH), 1.96 (1H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.7 Hz, $^3J_{нн}$ = 6.9 Hz), 1.58 (1H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 16.7 Hz, $^3J_{нн}$ = 3.8 Hz), -2.75 (2H, br.s, pyrrole-NH),

General procedure of synthesis of carboranylporphyrins ***25, 26***.

To the solution of 0.03 mmol of **19** or **20** in 10 ml of $CHCl_3$ 0.1 ml of trifluoroacetic acid was added and reaction mixture was kept at 20^0 C with stirring for 2 h. The solvent was evaporated in vacuo. The residue was purified on a SiO_2 (column 1x20 cm) using $CHCl_3$:CH_3OH (14:1 v/v) as eluent.

5,10,15,20-Tetra[p-2-hydroxy-3-(1'-o-phenylcarboran-2'-yl) propyl]aminophenylporphyrin, ***25***. Yield 50 mg (95.0%). Found: C 59.04, H 6.37, B 24.57, N 6.38 %. $C_{88}H_{114}B_{40}N_8O_4$ requires C 59.37, H 6.45, B 24.29, N 6.29 %. *m/z* (MALDI): 1780 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3416 (OH, NH), 2586 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 423 (4.92), 553 (3.83), 599 (3.43). ^{1}H NMR ($CDCl_3$) δ ppm: 9.65 (8H, s, *pyrrole*-H). 8.93 (4H, s, NH), 7.36 - 8.65 (36H, m, Ph), 3.71 - 3.82 (4H, m, CH), 2.60 (4H, br.s, OH), 2.35 (4H, dd, C*H*H-N, $^2J_{нн}$ = 13.9 Hz, $^3J_{нн}$ = 3.9 Hz), 2.18 (4H, dd, CH*H*-N, $^2J_{нн}$ = 13.9 Hz, $^3J_{нн}$ = 12.3 Hz), 2.08 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.2 Hz, $^3J_{нн}$ = 6.9 Hz), 1.64 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 16.2 Hz, $^3J_{нн}$ = 3.9 Hz), -2.63 (2H, br.s, *pyrrole*-NH).

5,10,15,20-Tetra[p-2-hydroxy-3-(1'-o-carboran-2'-yl) propyl]aminophenylporphyrin, ***26***. Yield 42 mg (93.5%). Found: C 52.39, H 6.72, B 29.03, N 7.46 %. $C_{64}H_{98}B_{40}N_8O_4$ requires C, 52.08; H, 6.69; B, 29.30; N, 7.59 %. *m/z* (MALDI): 1477 [M^+]. IR (hexachloro-1,3-butadiene) ν_{max} cm^{-1}: 3410 (OH, NH), 2602 (BH). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 433 (4.93), 563 (3.95), 612 (3.62). ^{1}H NMR ($CDCl_3$) δ ppm: 9.60 (8H, s, *pyrrole-H*), 8.90 (4H, s, NH), 7.40 - 8.70 (16H, m, Ph), 3.70 – 3.87 (4H, m, C*H*), 3.25 (4H, br.s, *carborane*-H), 2.58 (4H, br.s, OH), 2.30 (4H, dd, C*H*H-N, $^2J_{нн}$ = 14.0 Hz, $^3J_{нн}$ = 4.0 Hz), 2.20 (4H, dd, CH*H*-N, $^2J_{нн}$ = 13.6 Hz, $^3J_{нн}$ = 12.0 Hz), 2.04 (4H, dd, C*H*H-C-carborane, $^2J_{нн}$ = 16.0 Hz, $^3J_{нн}$ = 7.0 Hz), 1.60 (4H, dd, CH*H*-C-carborane, $^2J_{нн}$ = 16.0 Hz, $^3J_{нн}$ = 3.8 Hz), -2.60 (2H, br.s, *pyrrole*-NH).

General procedure of synthesis of carboranylporphyrins ***30–32.***

To the solution of porphyrin **1** (0.08 mmol) in 10 ml of toluene 0.16 mmol of corresponding isocyanato carborane (**27**, **28** or **29**) was added, and the reaction mixture was refluxed for 8–48 h. The toluene was evaporated in vacuo, and the residue was purified on SiO_2 (column 1x20 cm) using CH_2Cl_2-hexane mixture (7:2 v/v) as eluent.

5-[4-(o-Carboran-1-yl)aminocarbonylaminophenyl]-10,15,20-triphenylporphyrin, ***30***. Yield 57 mg (87.7%). Found: C 68.79, H 5.22, B 13.54, N 10.43 %. $C_{47}H_{42}B_{10}N_6O$ requires C 69.27, H 5.19, B 13.27, N 10.31 %. *m/z* (MALDI): 816 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3411 (NH), 2598 (BH), 1628 (C=O). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 418 (4.94), 522 (4.07), 555 (3.79), 646 (3.08). ^{1}H NMR ($CDCl_3$) δ ppm: 8.89 (8H, s, *pyrrole*-H), 7.35 - 8.20 (19H, m, Ph), 5.23 (2H, s, NH), 3.64 (1H, br.s, *carborane*-H), -2.14 (2H, br.s, *pyrrole*-NH).

5-[4-(o-Carboran-9-yl)aminocarbonylaminophenyl]-10,15,20-triphenylporphyrin, ***31***. Yield 38 mg (58.5%). Found: C 68.92, H 5.16, B 13.41, N 10.36 %. $C_{47}H_{42}B_{10}N_6O$ requires C 69.27, H 5.19, B 13.27, N 10.31 %. *m/z* (MALDI): 816 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3389 (NH), 2593 (BH), 1631 (C=O). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 420 (4.92), 522 (4.03), 552 (3.78), 647 (3.04). ^{1}H NMR ($CDCl_3$) δ ppm: 8.76 (8H, s, *pyrrole*-H), 7.20 - 8.10 (19H, m, Ph), 5.12 (2H, s, NH), 3.44 (1H, br.s, *carborane*-H), -2.20 (2H, br.s, *pyrrole*-NH).

5-[4-(m-Carboran-9-yl)aminocarbonylaminophenyl]-10,15, 20-triphenylporphyrin, ***32***. Yield 43 mg (66.2%). Found: C 68.92, H 5.14, B 13.44, N 10.40 %. $C_{47}H_{42}B_{10}N_6O$ requires C 69.27, H 5.19, B 13.27, N 10.31 %. m/z (MALDI): 816 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3387 (NH), 2596 (BH), 1629 (C=O). UV-vis ($CHCl_3$) λ_{max} nm (lg ε): 425 (4.93), 525 (4.02), 560 (3.78), 649 (3.00). ^{1}H NMR ($CDCl_3$) δ ppm: 8.89 (8H, s, *pyrrole*-H), 7.45 - 8.32 (19H, m, Ph), 5.27 (2H, s, NH), 3.61 (1H, br.s, *carborane*-H), -2.03 (2H, br.s, *pyrrole*-NH).

General method of synthesis of carboranylporphyrins ***33–35.***

To the solution of **2** (0.075 mmol) in the mixture of 10 ml of toluene and 10 ml of acetonitrile 0.6 mmol of the corresponding isocyanato carborane (**27**, **28** or **29**) was added, and the reaction mixture was refluxed for 8-48 h. The solvents were evaporated in vacuo, and the product was isolated by column chromatography (column 1x20 cm) with CH_2Cl_2-CH_3OH mixture (10:1 v/v) as eluent.

5,10,15,20-Tetra[4-(o-carboran-1-yl)aminocarbonylaminophenyl] porphyrin, ***33***. Yield 95 mg (90.5%). Found: C 47.88, H 5.43, B 30.07, N 11.96 %. $C_{56}H_{78}B_{40}N_{12}O_4$ requires C 47.51, H 5.55, B 30.55, N 11.87 %. m/z (MALDI): 1418 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3416 (NH), 2605 (BH), 1627 (C=O). UV-vis (CH_3CN) λ_{max} nm (lg ε): 419 (4.95), 520 (4.10), 557 (3.84), 647 (3.11). ^{1}H NMR (CD_3CN) δ ppm: 8.82 (8H, s, *pyrrole*-H), 7.40 - 8.33 (16H, m, Ph), 5.40 (8H, s, NH), 3.76 (4H, br.s, *carborane*-H), -2.05 (2H, br.s, *pyrrole*-NH).

5,10,15,20-Tetra[4-(o-carboran-9-yl)aminocarbonylaminophenyl]porphyrin, ***34***. Yield 68 mg (64.8%). Found: C 47.93, H 5.50, B 29.98, N 11.89 %. $C_{56}H_{78}B_{40}N_{12}O_4$ requires C 47.51, H 5.55,

B 30.55, N 11.87 %. m/z (MALDI): 1418 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3385 (NH), 2586 (BH), 1630 (C=O). UV-vis (CH_3CN) λ_{max} nm (lg ε): 420 (4.94), 517 (4.13), 560 (3.87), 645 (3.08). ^1H NMR (CD_3CN) δ ppm: 8.85 (8H, s, *pyrrole*-H), 7.30 - 8.30 (16H, m, Ph), 5.61 (8H, s, NH), 3.70 (4H, br.s, *carborane*-H), -2.10 (2H, br.s, *pyrrole*-NH).

5,10,15,20-Tetra[4-(m-carboran-9-yl)aminocarbonylamino-phenyl]porphyrin, ***35***. Yield 74 mg (70.5%). Found: C 47.94, H 5.66, B 30.12, N 12.04 %. $C_{56}H_{78}B_{40}N_{12}O_4$ requires C 47.51, H 5.55, B 30.55, N 11.87 %. m/z (MALDI): 1418 [M^+]. IR (KBr) ν_{max} cm^{-1}: 3390 (NH), 2592 (BH), 1628 (C=O). UV-vis (CH_3CN) λ_{max} nm (lgε): 420 (4.94), 517 (4.12), 560 (3.87), 645 (3.07). ^1H NMR (CD_3CN) δ ppm: 8.96 (8H, s, *pyrrole*-H), 7.35 - 8.18 (16H, m, Ph), 5.54 (8H, s, NH), 3.67 (4H, br.s, *carborane*-H), -2.18 (2H, br.s, *pyrrole*-NH).

Results and Discussion

*Carboranylmethylation of Porphyrins **1** and **2** with Carboranylmethyl Triflates*

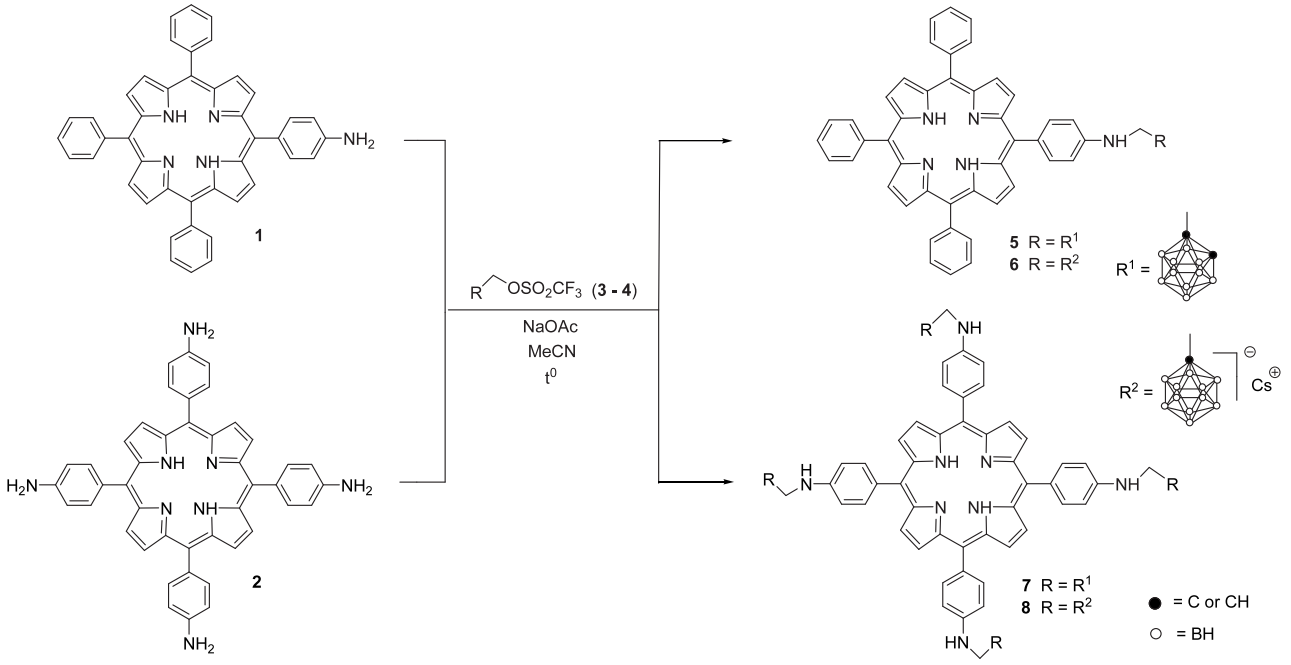
Previously we have synthesized 1-trifluoromethane sulfonylmethyl-*o*-carborane (**3**)[9] and 1-trifluoromethane sulfonylmethyl-1-carba-*closo*-dodecaborate cesium (**4**).[10] These compounds were efficient in the reactions of alkylation of aminoethyl group in chlorophyll *a* derivatives.[3,10-11] In contrast to aryl- and vinyl triflates widely used in chemical modifications of aromatic compounds,[12] the reactions of carboranyltriflates **3** and **4** with nucleophiles remain poorly investigated. We took advantage of the fact that triflates **3** and **4** are highly reactive with *N*-nucleophiles and conjugated the carborane polyhedra with porphyrins **1** and **2** (Scheme 1).

Alkylation of amino groups in **1** and **2** with carboranyltriflates **3** and **4** in the presence of sodium acetate in acetonitrile produced mono- and tetracarborane substituted porphyrins (**5–8**) with quantitative yields (Scheme 1). Importantly, **6** and **8** that contain anionic *closo*-monocarbadodecaboranyl group were soluble in water, making these compounds perspective for practical use.

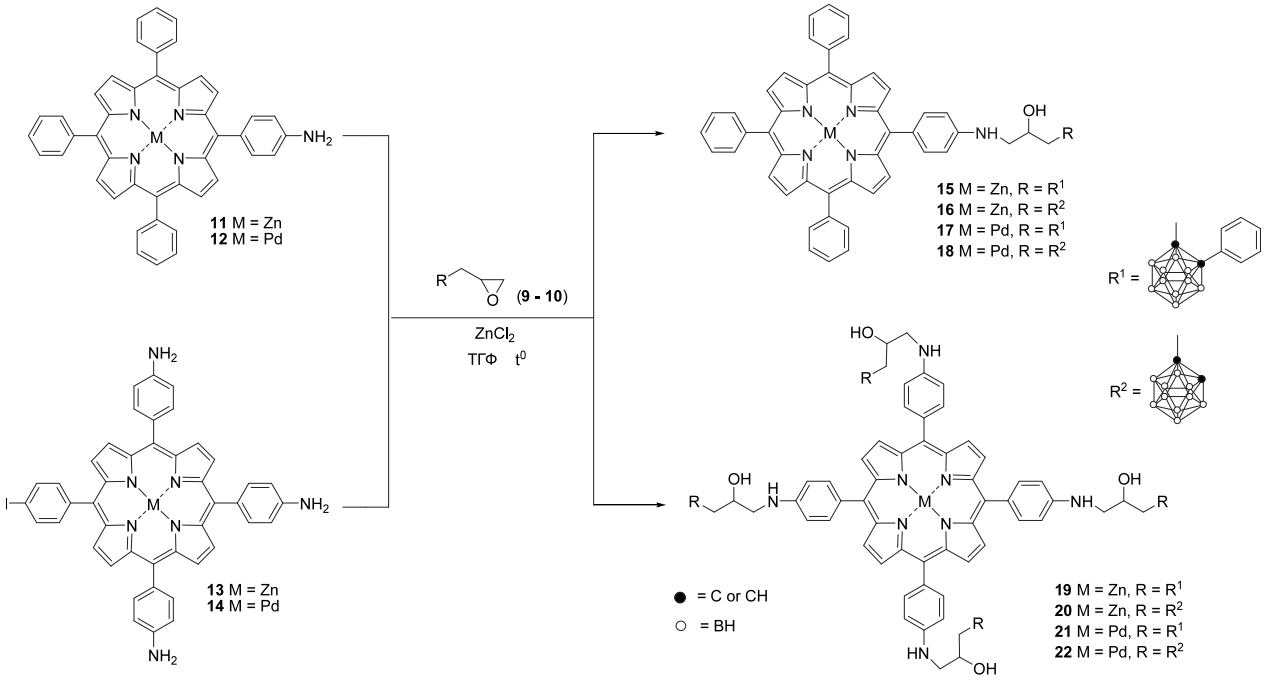
A structurally close compound in which three *o*-carborane polyhedra were linked to the porphyrin macrocycle through the aminomethylene group[13] has been synthesized by sequential transformations of 5,10,15-tris(4-nitrophenyl)-20-phenylporphyrin into the respective amino derivative after reduction in $SnCl_2$-HCl. Then the amino derivative reacted with 1-formyl-*o*-carborane and ultimately the prepared imino derivative was reduced with $NaBH_4$ to produce 5,10,15-tris[(carboranylaminomethyl)phenyl]-20-phenylporphyrin. In our method structurally similar compounds can be synthesized in one step with high yields.

*Aminolysis of Carboranylepoxides with Aminoporphyrins **1** and **2***

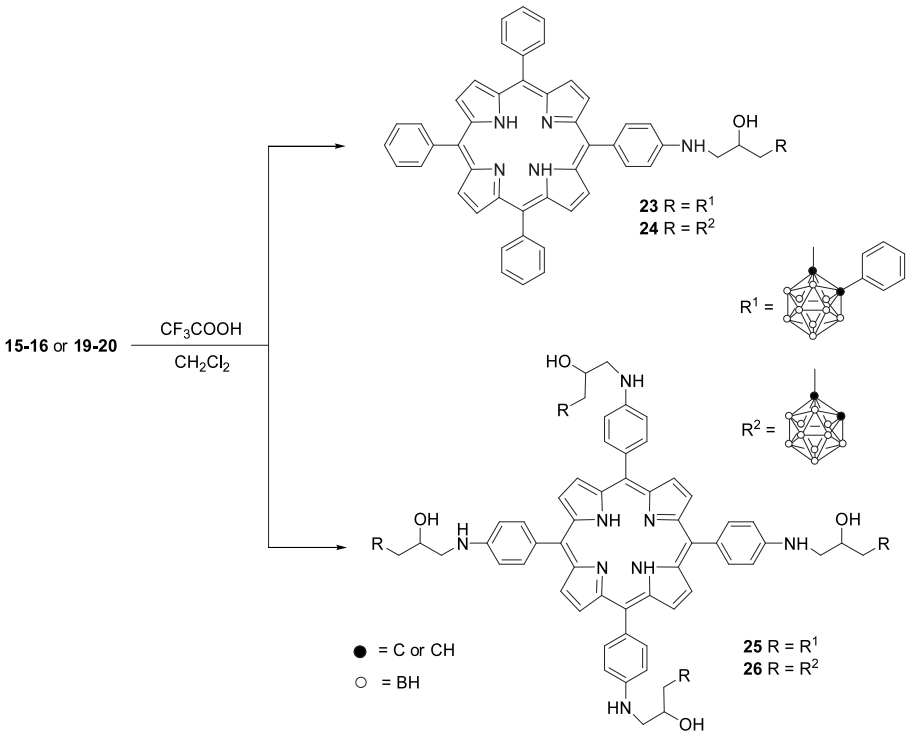
Another approach for direct introduction of boron polyhedra into aminoporphyrins **1** and **2** is based on the reaction of aminolysis of 1,2-carboranylepoxides.[14-15] Aminolysis of epoxides is efficient for preparation of β-aminoalcohols, the important intermediates in the synthetic procedures to obtain biologically active compounds. However, it remained unknown whether aminoporphyrins **1** and **2** react with organic epoxides. To functionalize the amino groups in **1** and **2** with carborane epoxides **9-10**[16] we used the catalytic activity of zinc chloride in the opening of the epoxide ring with nucleophiles.[17] However, zinc chloride might react with porphyrins to form metal complexes. Therefore, we first obtained Zn (**11, 13**) and Pd (**12, 14**) complexes of **1** и **2,**[18-19] and these metal complexes were put into the reactions with carborane epoxides. We found that the catalytic opening of the epoxide ring in carboranes **9–10** by amino groups of metal containing porphyrins (**11–14**) easily occurred in boiling acetonitrile or THF in the presence of 1-3 mol% $ZnCl_2$. These reactions resulted in boronated metal porphyrins **15-22** in which the aminoalcohol spacer linked the carborane polyhedron with the porphyrin macrocycle (Scheme 2). All compounds were obtained in high yields.



Scheme 1.



Scheme 2.



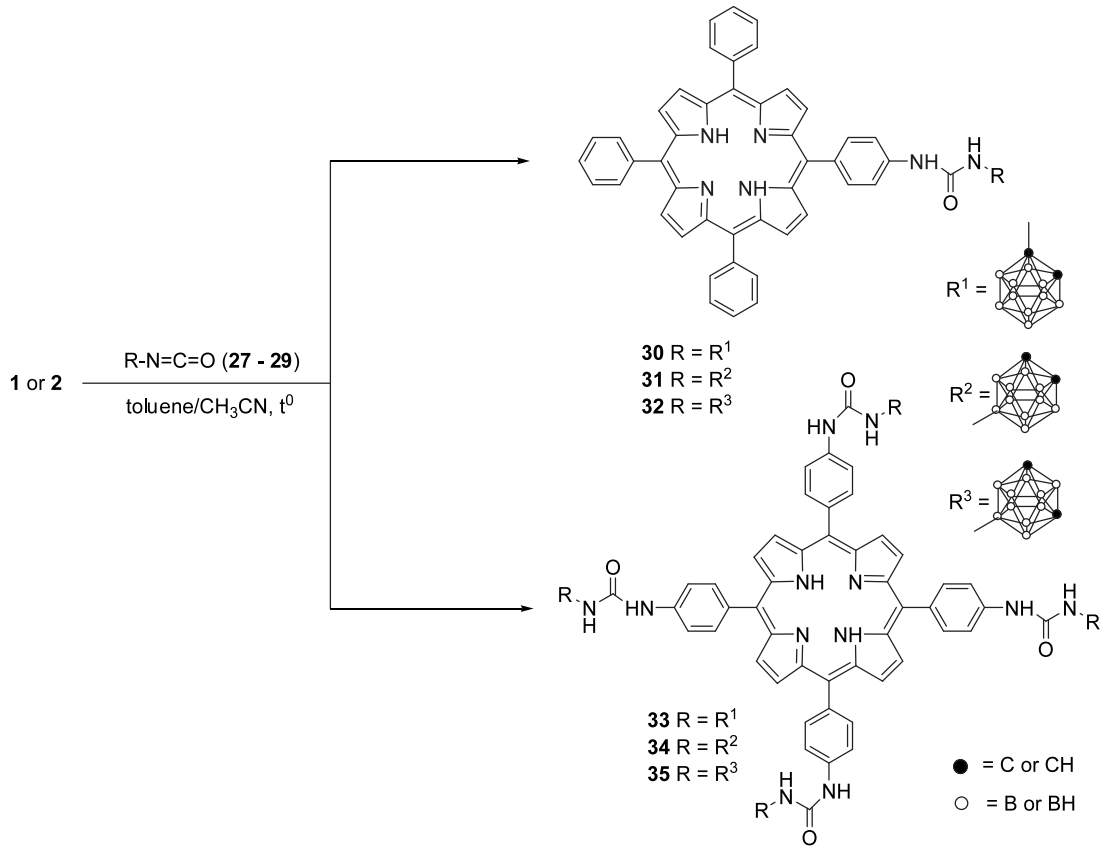
Scheme 3.

Demetallation of the products of aminolysis of **15–16** and **19–20** with trifluoroacetic acid in methylene chloride[20] allowed us to obtain boronated β-aminoalcohol derivatives of porphyrins **23–26** in good yields (Scheme 3).

Interestingly, only one regioisomer was formed in this reaction. It seems likely that the attack by amine nucleophile takes place exclusively at the less hindered position, namely at the methylene group of epoxyde ring. Compounds **15–26** possess the asymmetric carbon atom, and presumably two enantiomeres can be formed. The reactions of carboranylepoxides **9, 10** with free base porphyrins **1** and **2** generated very low yields (<3%) of resulting products, probably, because of the deficit of the catalyst due to preferential formation of metal porphyrin complexes.

*Amidation of Porphyrins **1** and **2** with Carboranylisocynates*

To introduce the carborane polyhedra into **1** and **2** we used 1-isocyanato-*o*-carborane (**27**),[21] 9-isocyanato-*o*- and 9-isocyanato-*m*-carboranes (**28, 29**)[22] in which the isocyanate group is hydrolytically stable and can react with



Scheme 4.

primary and secondary amines. The reactions of **1** and **2** with isocyanates **27–29** in boiling toluene smoothly produced stable boron containing conjugates **30-35** (Scheme 4).

The position of the isocyanate group in the carborane significantly influenced the rate of the reaction and the yields of carboranylporphyrins **30-35**. As expected, the ability of isocyanate **27** to react with amino groups in **1** and **2** was higher than that of isocyanates **28, 29**. This difference can be explained by a nonuniform distribution of electron density on skeletal atoms of carborane polyhedra[23] that gives rise to various electronic effects of carboranyl groups as substituents. Therefore, the same functional groups linked to the skeletal atoms would show differential activity. In compound **27** the N=C=O group is linked to the electron-withdrawing 1-*o*-carboranyl group (σ_i = + 0.38)[24-25] whereas in compounds **28** and **29** the N=C=O groups are located at electron-donating 9-*o*- (σ_i = -0.23) and 9-*m*- (σ_i = -0.12)[24-25] carboranyl groups, thereby making the nucleophilic conjugation of aminoporphyrins **1** and **2** more difficult. In the resulting carboranylporphyrins **30–35** the carboranes are linked to the porphyrin macrocycle via stable amide bonds. One may anticipate that **30-35** will fit the requirements for BNCT since the conjugation of boron polyhedra to dendrimers via the amide bonds of a similar nature has been shown to produce efficient agents.[26-27]

The spectral data (UV-, IR-, ^{1}H NMR- and mass-spectra) confirmed the structure of compounds **5–8**, **15–26** and **30–35**. IR spectra of novel boronated porphyrins exhibit intense bands at 2585-2600 cm^{-1} (**6**, **9**, **15–26**, **30–35)** and 2530-2534 cm^{-1} (**5, 7**) corresponding to the stretching vibrational modes of BH groups of neutral and anionic *closo*-carborane polyhedra, respectively. In all IR spectra of novel carboranylporphyrins there are bands at 3400 cm^{-1} assigned to the vibrational modes of NH groups. It is worth-noting that in compounds **15–26** the bands of NH groups overlap with those of OH groups of amino alcohol spacer lying in the spectral region of 3200–3600 cm^{-1}. In **30 – 35** the bands at about 1630 cm^{-1} are attributed to amide C=O groups.

In the NMR ^{1}H spectra of **5–8**, **15–26**, **30–35** the singlet signals at δ = 4.30–5.40 ppm corresponded to the protons of spacer's amino groups. In **5–8** the singlet signals at δ = 1.80 ppm reflected the protons in methylene groups, thereby confirming the conjugation of carborane polyhedra with porphyrin macrocycles. According to ^{1}H NMR spectra the protons of methylene groups in **15–26** are magnetically non-equivalent and manifested themselves as the doublets of doublets signals.

Conclusions

In summary, we developed a simple and efficient synthetic approaches to carboranyl substituted amino-porphyrin derivatives based on the one stage reactions of amino derivatives of 5,10,15,20-tetraphenylporphyrins with carboranylmethyl triflates or carboranyl isocyanates. We found that the $ZnCl_2$-catalyzed aminolysis of carborane epoxides with aminophenylporphyrins were of importance only in a case of metal complexes of tetrapyrrole macrocycles. These reactions were highly regioselective. Demetallation of zinc complexes produced free base boronated porphyrin amino alcohols in high yields.

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