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Syntheses of carbon–carbon linked carboranylated porphyrins for boron neutron capture therapy of cancer

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Abstract

Total syntheses of six carboranyl-containing porphyrins bearing 33–44% boron by weight for potential application in boron neutron capture therapy of tumors, are described; these novel compounds feature carbon–carbon linkages between the carboranyl groups and the *meso*-phenyl substituents. © 2000 Published by Elsevier Science Ltd.

Boron neutron capture therapy (BNCT)[1] is a modality for cancer treatment that involves the irradiation of ^{10}B-rich tumors with low-energy neutrons. Subsequent production of high linear energy transfer particles, $^{4}He^{2+}$ (α-particle) and $^{7}Li^{3+}$, cause severe damage to tumor cells through ionization processes. Because the cytotoxic ions produced in the nuclear reaction have limited path distances in tissue (approximately one cell diameter), the success of this localized form of cancer therapy depends upon the selective uptake of boron within tumor cells. BNCT is a particularly attractive modality for the treatment of patients with high-grade gliomas and metastatic brain tumors whose life expectancy is generally less than one year, despite aggressive treatments using surgery, and radio- and chemotherapy. In recent years several research groups have developed a variety of new ^{10}B carriers with improved tumor selectivity over the two boron neutron capture agents currently undergoing clinical trials in the US, Europe and Japan (disodium mercapto-*closo*-dodecaborate (BSH)[2] and L-4-dihydroxyborylphenylalanine (BPA)[3]). Of the new boron-delivery agents, porphyrins appear to be particularly promising tumor-selective compounds[4–8] because of their demonstrated tendency to accumulate in neoplastic tissue.[9] We report herein the synthesis of a series of novel carboranylated porphyrins containing 33–44% boron by weight, and featuring carbon–carbon linkages between the porphyrin macrocycle and the carboranyl groups. Our synthetic routes to the new carboranylporphyrins (Schemes 1–3)

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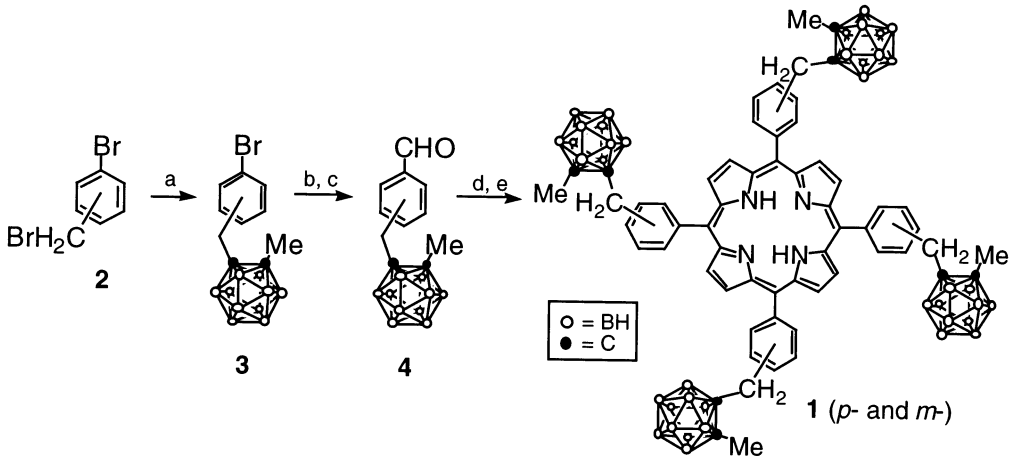
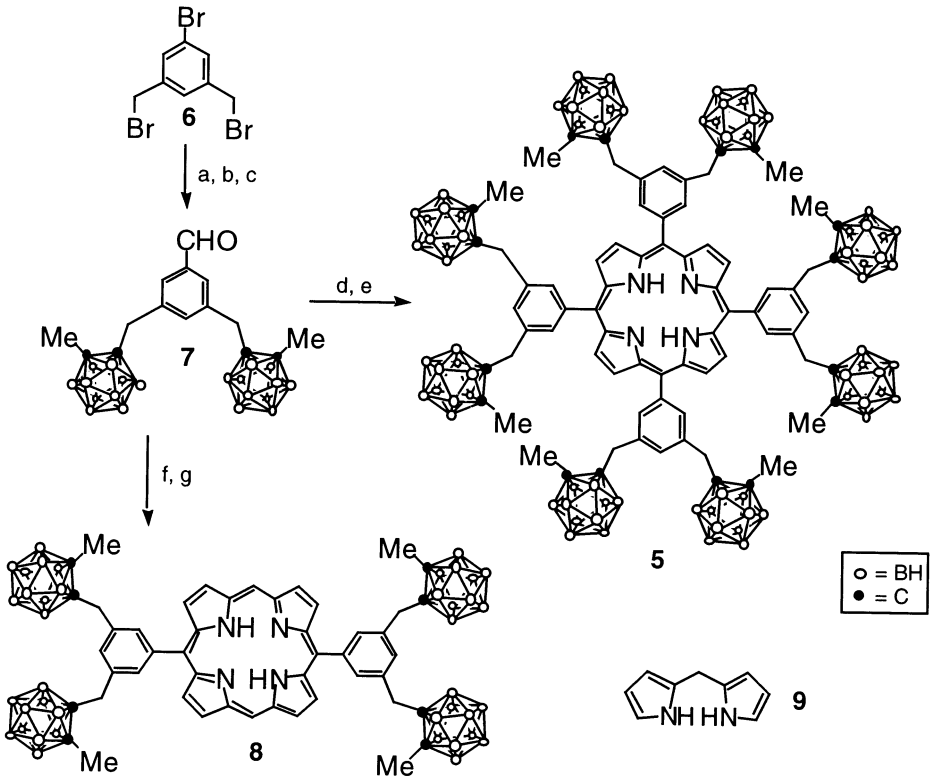
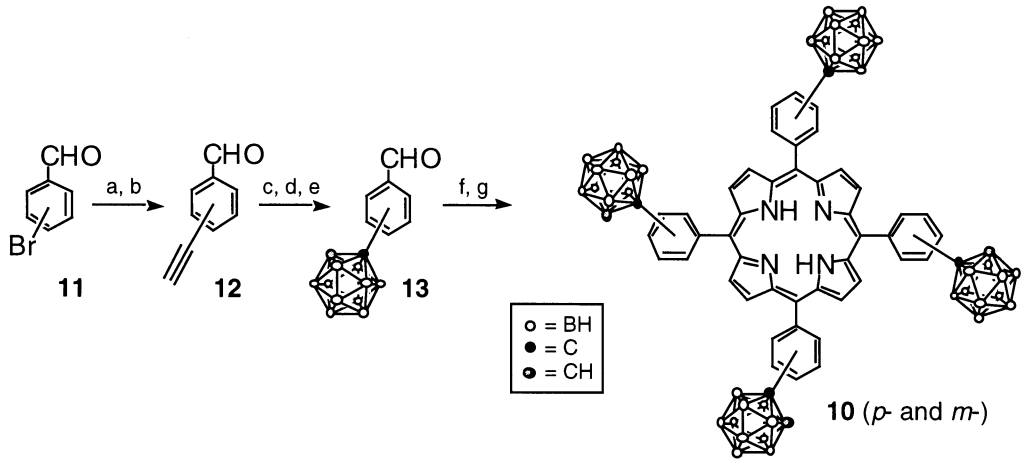
utilize *meso*-arylporphyrin platforms because these offer opportunities for incorporation of multiple carborane units about the porphyrin skeleton; the routes also have the advantage of being expeditious, highly reproducible and high yielding.



Scheme 1. (a) 1-Lithium-2-methyl-*o*-carborane, 1,2-dimethoxyethane, reflux 10 h; (b) *n*-BuLi, THF, –78°C, then DMF; (c) 5% HCl; (d) pyrrole, TFA, in CH_2Cl_2; (e) *p*-chloranil



Scheme 2. (a) 1-Lithium-2-methyl-*o*-carborane, THF, LiI, room temperature 20 h; (b) *n*-BuLi, THF, –78°C, then DMF; (c) 5% HCl; (d) pyrrole, TFA, in CH_2Cl_2; (e) DDQ; (f) **9**, TFA, in CH_2Cl_2; (g) *p*-chloranil



Scheme 3. (a) $Pd(OAc)_2$, PPh_3, NEt_3 ethynyltrimethylsilane; (b) K_2CO_3, MeOH; (c) 1,2-ethanedithiol, $BF_3{\cdot}OEt_2$; (d) $B_{10}H_{14}$, Et_2S, toluene, 80°C, 3 days; (e) $Hg(ClO_4)_2{\cdot}3H_2O$/THF; (f) pyrrole, TFA, in CH_2Cl_2; (g) *p*-chloranil

Porphyrins **1** (*para*- and *meta*-substituted) were prepared in four steps and in 16–18% *overall* yield from the corresponding bromomethylbromobenzenes **2** (Scheme 1). Reaction of the lithium anion[10] of 1-methyl-*o*-carborane with 3- and 4-(bromomethyl)bromobenzenes, produced **3** in respectively 75% (*para*) and 65% (*meta*) yields. Benzaldehydes **4** were prepared in 62–79% yield, by lithium bromide exchange, followed by addition of DMF.[11] Condensation of benzaldehydes **4** with pyrrole under Lindsey-type conditions (using 10^{-2} M of reagents and 5×10^{-3} M TFA)[12] afforded porphyrins **1** in 32% (*para*) and 33% (*meta*) yields.

Using the same synthetic methodology, porphyrin **5** (containing 80 atoms of boron) and 5,15-disubstituted porphyrin **8**, were synthesized as shown in Scheme 2. Di(bromomethyl)bromobenzene **6** was obtained in 33% yield from 3,5-dimethylbromobenzene.[13] Reaction of **6** with 1-lithium-2-methyl-*o*-caborane, followed by conversion of the bromo substituent into formyl, produced di-carboranylbenzaldehyde **7** in 45% overall yield. Condensation of **7** with pyrrole under Lindsey-type conditions afforded porphyrin **5** in 15% yield. 5,15-Disubstituted porphyrin **8** was prepared in 34% yield by reaction of **7** with dipyrromethane **9**[14] (Scheme 2).

The structurally related carboranylporphyrins **10**, bearing the carborane cages on the *para*- and *meta*-positions and directly linked to the *meso*-phenyl groups, were synthesized according to Scheme 3. Ethynylbenzaldehydes **12** were prepared from 3- and 4-bromobenzaldehydes **11** in 78–82% yield by a palladium-mediated coupling reaction with ethynyltrimethylsilane, followed by basic cleavage of the trimethylsilyl group.[15] The preparation of the *o*-carborane cages from the terminal acetylene groups of **12** was accomplished using decaborane and ethylsulfide, in 52–67% yield;[16] the success of this reaction is dependent upon the initial protection of the formyl group with 1,2-ethanedithiol in the presence of $BF_3{\cdot}OEt_2$, followed by the *o*-carborane preparation step, and deprotection with $Hg(ClO_4)_2$ in aqueous THF.[17] Benzaldehydes **13** were condensed with pyrrole under the same conditions as above, producing porphyrins **10** in 33% (*para*) and 34% (*meta*) yields.

In order to achieve water-solubility, the tetra(*nido*-carboranyl) derivatives of porphyrins **1**, **8** and **10** were prepared by basic degradation of the *o*-carboranyl cage using pyridine and piperidine in a 3:1 ratio,[18] followed by ion-exchange using a Dowex 50WX2-100 resin in the

potassium form,[4] in 90–98% overall yield. The biological properties of the hydrophobic *o*-carboranylporphyrins and the amphiphilic *nido*-carboranylporphyrins are under investigation.

All new compounds synthesized possessed spectroscopic data in accord with the assigned structures.[19] Preliminary X-ray structures of porphyrins **5** (as the dication) and the Zn(II) complexes of **1** and **10** (*para*-substituted) have also been secured. Porphyrins **1**, **5**, **8** and **10** show intense Soret bands (ε=400,000–500,000) in chloroform at 417 nm (406 for di-*meso*-substituted **8**) and etio-type absorption spectra. The water-soluble *nido*-carboranylporphyrins show intense Soret bands in acetone (ε=350,000–450,000) and less intense, broader bands in water (ε= 100,000–200,000). In the ^{1}H NMR spectra the *o*-carborane B*H* protons consistently appear between 1.5 and 3.4 ppm, and the methyl-carborane group typically shows as a sharp singlet at 2.3 ppm. The C*H*-carborane proton of porphyrins **10** absorbs at about 4.3 ppm as a broad singlet. The N*H* protons typically appear as singlets at −2.8 ppm and the β-pyrrolic hydrogens as singlets at about 8.8 ppm (for **1**, dication of **5** and **10**), and as doublets at 9.0 and 9.6 (for **8**); porphyrin **8** also displays a single *meso*-proton signal at 11.0 ppm. The ^{1}H NMR spectra of the *nido*-carboranyl-porphyrins, in d_6-acetone, typically show the B*H* protons on the open face of the *nido*-carboranes between −2.5 and −1.9 ppm and the remaining B*H*s at 0.9–2.4 ppm. The CH_3- and C*H*-carborane protons, adjacent to the open face, appear upfield shifted at 1.6 and 2.6 ppm, respectively. The porphyrin N*H*, β-, and *meso*-protons remain essentially unchanged ($\Delta\delta$ less than 0.5 ppm). The spectra in D_2O show broad bands characteristic of porphyrin aggregation.[20]

Acknowledgements

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19. Selected spectroscopic data for new compounds: Porphyrin **1** (*p*-substituted), MS (MALDI) m/z 1296.0 [M^+]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): −2.80 (br, 2H), 1.6–3.1 (br, 40H), 2.34 (s, 12H), 3.81 (s, 8H), 7.59 (d, $J=8.0$ Hz, 8H), 8.20 (d, $J=8.0$ Hz, 8H), 8.85 (s, 8H); ^{1}H NMR (d-TFA/$CDCl_3$, 400 MHz, δ ppm): −1.08 (br, 4H), 1.6–3.0 (br, 40H), 2.38 (s, 12H), 3.89 (s, 8H), 7.87 (d, $J=7.8$ Hz, 8H), 8.54 (d, $J=7.8$ Hz, 8H), 8.73 (s, 8H); UV–vis ($CHCl_3$) λ_{max}: 417 nm (ε 444,700), 514 (15,400), 548 (7200), 588 (5100), 644 (3800). Porphyrin **1** (*m*-substituted), MS (MALDI) m/z 1295.7 [M^+]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): −2.84 (br, 2H), 1.5–3.0 (br, 40H), 2.20 (s, 12H), 3.74 (s, 8H), 7.62 (m, 4H), 7.74 (m, 4H), 8.05 (m, 4H), 8.18 (m, 4H), 8.84 (s, 8H); UV–vis ($CHCl_3$) λ_{max}: 417 nm (ε 497,500), 514 (19,100), 549 (8800), 588 (6100), 645 (4700). Compound **3** (*p*-substituted), MS (EI) m/z 327.1 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.3–3.0 (br, 10H), 2.15 (s, 3H), 3.41 (s, 2H), 7.06 (d, $J=8.1$ Hz, 2H), 7.48 (d, $J=8.1$ Hz, 2H). Compound **3** (*m*-substituted), MS (EI) m/z 327.1 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.3–3.1 (br, 10H), 2.16 (s, 3H), 3.42 (s, 2H), 7.13 (d, $J=7.8$ Hz, 1H), 7.23 (t, $J=7.8$ Hz, 1H), 7.33 (s, 1H), 7.47 (d, $J=7.8$ Hz, 1H). Compound **4** (*p*-substituted), MS (EI) m/z 276.2 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.5–3.0 (br, 10H), 2.19 (s, 3H), 3.54 (s, 2H), 7.38 (d, $J=8.0$ Hz, 2H), 7.89 (d, $J=8.0$ Hz, 2H), 10.04 (s, 1H). Compound **4** (*m*-substituted), MS (EI) m/z 276.2 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.4–3.1 (br, 10H), 2.19 (s, 3H), 3.55 (s, 2H), 7.48 (d, $J=7.8$ Hz, 1H), 7.56 (t, $J=7.8$ Hz, 1H), 7.70 (s, 1H), 7.85 (d, $J=7.8$ Hz, 1H), 10.04 (s, 1H). Porphyrin **5**, MS (MALDI) m/z 1977.3 [M^+]; ^{1}H NMR (d-TFA/$CDCl_3$, 400 MHz, δ ppm): −0.80 (br, NH), 1.5–3.1 (br, 80H), 2.31 (s, 24H), 3.91 (s, 16H), 7.72 (s, 4H), 8.33 (s, 8H), 8.74 (s, 8H); UV–vis ($CHCl_3$) λ_{max}: 414 nm (ε 497,300), 509 (20,300), 543 (8300), 588 (6200), 642 (4300). Compound **7**, MS (EI) m/z 446.4 [M^+]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.5–3.0 (br, 20H), 2.20 (s, 6H), 3.55 (s, 4H), 7.30 (d, $J=1.6$ Hz, 1H), 7.67 (d, $J=1.6$ Hz, 2H), 10.03 (s, 1H). Porphyrin **8**, MS (MALDI) m/z 1144.0 [M^+]; ^{1}H NMR (d-TFA/$CDCl_3$, 400 MHz, δ ppm): −1.92 (br, NH), 1.4–3.2 (br, 40H), 2.30 (s, 12H), 3.89 (s, 8H), 7.71 (s, 2H), 8.34 (s, 4H), 9.03 (d, $J=4.5$ Hz, 4H), 9.61 (d, $J=4.5$ Hz, 4H), 10.98 (s, 2H); UV–vis ($CHCl_3$) λ_{max}: 406 nm (ε 398,800), 499 (17,700), 534 (5400), 572 (5700), 627 (1600). Porphyrin **10** (*p*-substituted), MS (MALDI) m/z 1184.5 [M+1]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): −2.89 (br, 2H), 1.7–3.4 (br, 40H), 4.28 (br, 4H), 7.90 (d, $J=8.0$ Hz, 8H), 8.18 (d, $J=8.0$ Hz, 8H), 8.78 (s, 8H); ^{1}H NMR (d-TFA/$CDCl_3$, 400 MHz, δ ppm): −0.97 (br, 4H), 1.8–3.4 (br, 40H), 4.31 (br, 4H), 8.13 (d, $J=8.0$ Hz, 8H), 8.51 (d, $J=8.0$ Hz, 8H), 8.68 (s, 8H); UV–vis ($CHCl_3$) λ_{max}: 418 nm (ε 469,000), 514 (18,200), 550 (8600), 590 (6200), 646 (4900). Porphyrin **10** (*m*-substituted), MS (MALDI) m/z 1183.4 [M^+]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): −2.88 (br, 2H), 1.6–3.5 (br, 40H), 4.19 (br s, 4H), 7.78 (m, 4H), 7.94 (m, 4H), 8.27 (m, 4H), 8.33 (m, 4H), 8.80 (s, 8H); UV–vis ($CHCl_3$) λ_{max}: 418 nm (ε 479,000), 514 (17,100), 549 (8400), 588 (6100), 644 (4300). Compound **13** (*p*-substituted), MS (EI) m/z 248.2 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.6–3.2 (br, 10H), 4.03 (br, 1H), 7.65 (d, $J=8.4$ Hz, 2H), 7.86 (d, $J=8.4$ Hz, 2H), 10.04 (s, 1H). Compound **13** (*m*-substituted), MS (EI) m/z 248.2 [M^+]; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.5–3.3 (br, 10H), 4.04 (br, 1H), 7.56 (t, $J=7.8$ Hz, 1H), 7.79 (d, $J=7.8$ Hz, 1H), 7.91 (d, $J=7.8$ Hz, 1H), 7.96 (s, 1H), 10.02 (s, 1H).
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