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Tetrahedron Letters

Tetrahedron Letters 46 (2005) 2365–2368

Novel carboranylporphyrins for application in boron neutron capture therapy (BNCT) of tumors

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Received 8 December 2004; accepted 15 February 2005

Abstract—Condensation of a new carboranylpyrrole **1** with benzaldehydes leads to β-carboranylporphyrins **2** and **3** in good yields. These new porphyrins of high boron content (32–43%) have potential as boron delivery agents for BNCT. The X-ray structures of one β-carboranylporphyrin, of a carboranylpyrrole, and of a side-product are presented.

Boron-containing porphyrins are promising delivery vehicles for the boron neutron capture therapy (BNCT) of cancer, due to their demonstrated selectivity for tumors, usually low systemic toxicity, and their remarkable chemical stability.[1,2] BNCT is a binary therapy for the treatment of cancer, especially of malignant brain tumors, based on the $^{10}B(n,\alpha)^{7}Li$ capture reaction which produces highly cytotoxic particles that cause irreversible damage to tissues.[3,4] Various porphyrin-based agents have been synthesized and shown to selectively deliver therapeutic amounts of boron (>30 μg/g tumor) to animal tumors.[5,6] Most of these compounds contain two or four carborane cages linked to the porphyrin macrocycle via the *meso*-phenyl groups. We report herein the synthesis of novel β-carboranylporphyrins bearing a bis(methylene) linkage between the carborane cages and the β-pyrrolic positions of the porphyrin ring, and containing 32–43% boron by weight. The molecular structure of one of these novel compounds is presented and discussed.

Although several synthetic strategies have been described for the preparation of carboranylbenzaldehydes,[7,8] the precursors to *meso*-(carboranylphenyl)porphyrins, a synthesis of carborane-substituted pyrroles, which are key intermediates to β-carboranylporphyrins, has only recently been reported.[9] Our approach involved an anti-Markovnikov addition of phenylsulfenyl chloride to 1-vinyl- or 1-allyl-*o*-carborane, followed by oxidation, dehydrochlorination, and a Barton–Zard cyclocondensation to afford carboranylpyrroles bearing, respectively, a direct linkage or a methylene group between the carborane cage and the pyrrole ring. However, the tetramerization of these pyrroles led only to low yields of β-carboranylporphyrins, due to both steric and electronic effects caused by the bulky and electron-withdrawing carborane cages.[9] Herein we report the synthesis of a new carboranylpyrrole **1**, bearing a bis(methylene) linkage between the carborane and pyrrole units. We also show that unlike the previously reported carboranylpyrroles, pyrrole **1** can be tetramerized in good yields in the presence of benzaldehydes and an acid catalyst, to afford β-carboranylporphyrins of high boron content.

1-Butenyl-2-methyl-*o*-carborane **4** was obtained in 74% yield from commercially available 1-methyl-*o*-carborane (Scheme 1), upon deprotonation with *n*-butyl lithium followed by alkylation using 4-bromo-1-butene in the presence of LiI.[10] Carborane **4** reacted with in situ-generated phenylsufenyl chloride at −78 °C to regioselectively afford the anti-Markovnikov adduct **5** in 92% yield.[11] The thioether **5** was then oxidized with *m*-chloroperoxybenzoic acid (*m*CPBA) at 0 °C yielding **6**, and dehydrochlorinated in the presence of 1 equiv of DBU to afford sulfone **7**. A slight excess of DBU was found to induce double elimination with formation of conjugated diene **8** as the main product, in 52% yield. The molecular structure of compound **8** was determined[†] and this is shown in Figure 1. Pyrrole **1** was obtained

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Keywords: BNCT; Carborane; Pyrrole; Porphyrin; Carboranylporphyrin.

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[†] Carborane **8**, $C_7H_{18}B_{10}$, monoclinic space group $P2_1/n$, $a = 7.3248(10)$, $b = 21.738(4)$, $c = 8.131(2)$ Å, $\beta = 91.309(7)°$, $V = 1294.3(4)$ Å^3, $Z = 4$, $T = 100$ K, $R = 0.049$ for 4146 unique data with $\theta < 31.5°$ (MoKα). CCDC 253628.

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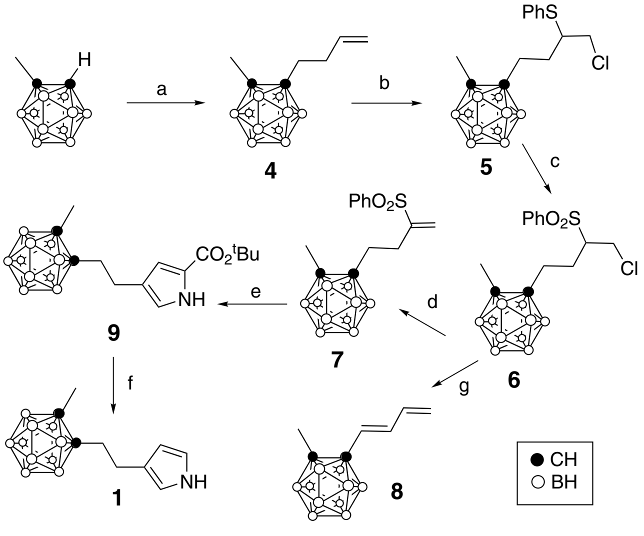
doi:10.1016/j.tetlet.2005.02.077



Scheme 1. Reagents and conditions: (a) *n*-butyl lithium, LiI, 4-bromo-1-butene, THF, −78 °C (74%); (b) PhSCl, CH_2Cl_2, −78 °C (92%); (c) *m*CPBA, CH_2Cl_2, 0 °C (94%); (d) DBU (1 equiv), THF, 0 °C (90%); (e) $CNCH_2CO_2{}^tBu$, NaO^tBu, THF (92%); (f) TFA, CH_2Cl_2 (94%); (g) DBU (2 equiv), THF, room temperature (52%).

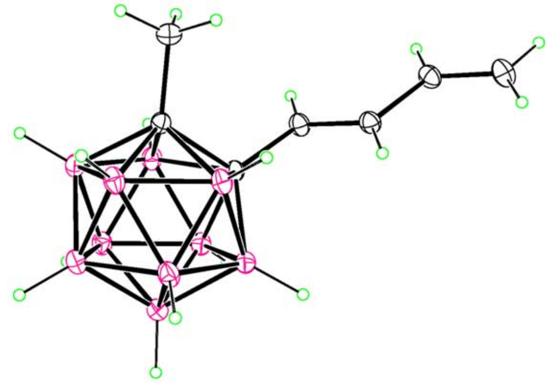


Figure 1. Molecular structure of carborane **8**.

via a Barton–Zard reaction[12] in the presence of sodium *tert*-butoxide and *tert*-butyl isocyanoacetate to produce **9**, followed by cleavage and decarboxylation using trifluoroacetic acid, in 86% overall yield from **7**. The molecular structure of pyrrole **9**[‡] is shown in Figure 2. Pyrrole **1** was characterized by HRMS and by ^1H NMR spectroscopy, which featured the pyrrolic protons at 6.76, 6.61, and 6.09 ppm, and the CH_2 bridge hydrogens centered at 2.77 and 2.44 ppm.[13]

The condensation of carboranylpyrrole **1** with benzaldehyde under Lindsey conditions,[14] using $BF_3{\cdot}Et_2O$ as the catalyst and *p*-chloranil as the oxidant, afforded porphyrins **2** in 49% yield (Scheme 2, R = H). Porphyrins **2** were obtained as a mixture of four type I–IV regioisomers,[15] as shown by the multiplicity of signals in the ^1H NMR spectrum. As expected, the HRMS (MALDI-TOF) of the mixture showed a single peak at *m*/*z* 1353.1622 (calcd 1353.1580) and the UV–vis spectrum featured a characteristic Soret band at 424 nm ($\varepsilon = 352{,}900\ \mathrm{L\,mol^{-1}\,cm^{-1}}$).[16] Insertion of zinc(II) into porphyrins **2**,[17] followed by slow recrystallization of the mixture from toluene uniquely afforded high-quality crystals of the type II isomer of the Zn(II) porphyrin. The molecular structure[§] of this regioisomer is shown in Figure 3. The Zn complex lies on an inversion center, with Zn–N distances 2.043(2) and 2.062(2) Å. The 25-atom porphyrin complex core is nearly planar, with mean deviation 0.034 Å and maximum 0.066 Å. The phenyl groups are roughly perpendicular to this plane, forming dihedral angles of 76.2 and 88.4° with it, and are also approximately perpendicular to each other, forming a dihedral angle of 83.7°. The carboranylethyl substituents are extended, forming torsion angles of 163.0(3) and 178.6(3)° about their central CH_2–CH_2 bonds. Porphyrins **2** were converted into the corresponding *nido*-carborane analogues by base-induced deboronation, as we have previously reported.[17] These four regioisomeric porphyrins, as the tetra-potassium salts, could be separated by HPLC (using a gradient elution of aqueous phosphate buffer/acetonitrile on a C18 column).

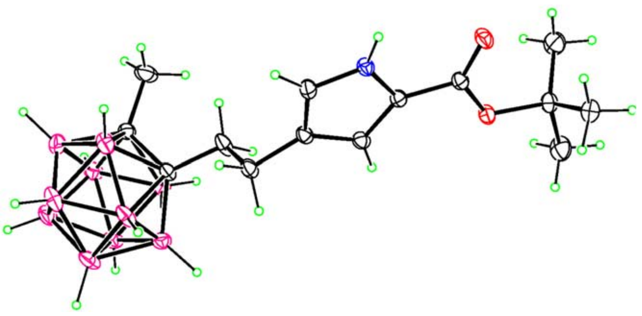
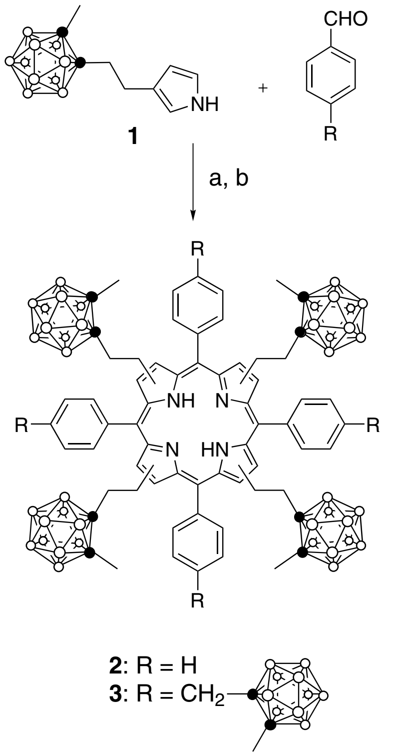


Figure 2. Molecular structure of carboranylpyrrole **9**.

Similarly, condensation of pyrrole **1** with [4-(1-methyl-*o*-carboranyl)methyl]benzaldehyde[8,17] afforded porphyrins **3** as a mixture of regioisomers, in 20% overall yield (Scheme 2, $R = CH_2CC(CH_3)B_{10}H_{10}$). Porphyrins **3** were also characterized by UV–vis, HRMS (MALDI-TOF) and by ^1H NMR spectroscopy.[16] As expected, porphyrins **3** showed a peak in HRMS at *m*/*z* 2033.9923 (calcd 2033.9987), a Soret band in the UV–vis spectrum at 424 nm, and multiple signals for the aromatic protons in the ^1H NMR spectrum. Porphyrins **3** are the first reported boronated porphyrins containing carborane groups linked to both the β-pyrrolic positions and the *meso*-phenyl rings of a porphyrin macrocycle.

[‡] Pyrrole **9**: $C_{14}H_{29}B_{10}NO_2{\cdot}0.5C_7H_8$, monoclinic space group $P2_1/n$, $a = 8.1767(10)$, $b = 24.045(3)$, $c = 11.935(2)$ Å, $\beta = 93.920(5)°$, $V = 2341.0(6)$ Å^3, $Z = 4$, $T = 110$ K, $R = 0.058$ for 8512 unique data with $\theta < 32.6°$ (MoKα). The toluene molecule is disordered about an inversion center. CCDC 257885.

[§] Zn(II)-porphyrin **2** type II isomer, $C_{64}H_{88}B_{40}N_4Zn{\cdot}5C_7H_8$, triclinic space group $P\bar{1}$, $a = 12.480(3)$, $b = 12.710(2)$, $c = 16.746(4)$ Å, $\alpha = 81.854(8)$, $\beta = 82.884(8)$, $\gamma = 89.518(9)°$, $V = 2609.1(10)$ Å^3, $Z = 1$, $T = 105$ K, $R = 0.074$ for 12,856 unique data with $\theta < 28.3°$ (MoKα). One of the three independent toluene molecules is disordered about an inversion center. CCDC 253629.



Scheme 2. Reagents and conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2, room temperature; (b) *p*-chloranil (20–49% from **1**).

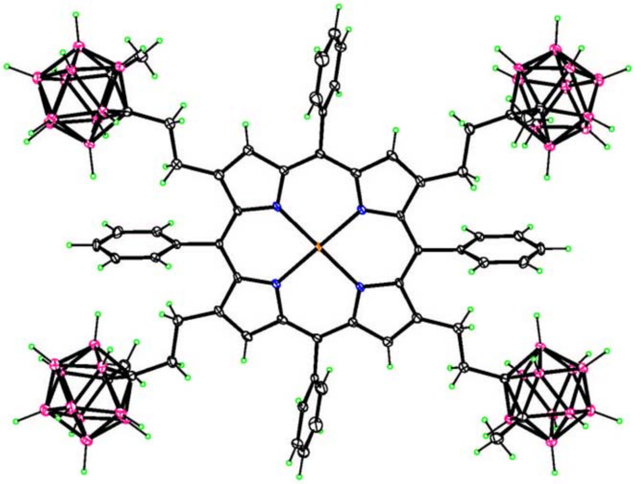


Figure 3. Molecular structure of type II isomer of Zn(II) porphyrin **2**.

In summary, we have synthesized a new carboranylpyrrole (**1**), which can be condensed with benzaldehydes to produce porphyrins in good yields, as mixtures of the four primary type isomers. High boron content porphyrins are obtained using this methodology and these compounds have potential as boron delivery agents for the BNCT treatment of cancer. Our work shows for the first time that multiple boron clusters can be readily incorporated into the same porphyrin macrocycle, linked to both the β-pyrrolic positions and the *meso*-phenyl rings. We also demonstrate that attachment of carborane cages to the porphyrin macrocycle permitted the unusual preferential crystallization of one of the regioisomers in the mixture of primary type isomers. The biological evaluation of porphyrins **2** and **3** and of their water-soluble *nido*-carborane derivatives is currently underway in our laboratories.

Acknowledgements

We thank the National Institutes of Health (R01 CA098902) for support to this work.

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αCH$_2$), 2.70–2.50 (m, 8H, β CH$_2$), 2.41–2.31 (m, 12H, CH$_3$), 2.00–1.92 (m, 12H, CH$_3$), 3.13–0.70 (br m, 80H, BH), −2.81 (br s, 2H, NH).

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