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Polyester-Based Carborane-Containing Dendrons

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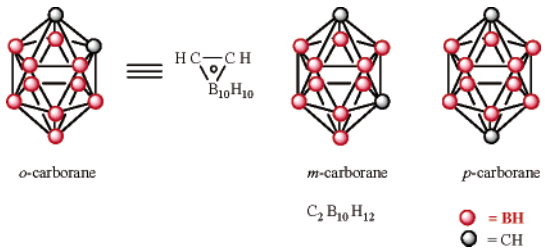
New carborane-containing dendrons based on a 2,2-bis(hydroxymethyl)propanoic acid scaffold have been prepared for applications in boron neutron capture therapy. A generation-2 carborane-containing dendron carrying 40 boron atoms was the highest generation synthetically available due to the steric crowding. The structure of this dendron has been simulated by molecular dynamics. A 10-carbon linker carrying a carboxylic group has been installed at the focal point of the dendron to distance the attachment point from the sterically hindered core.

Introduction

Boron neutron capture therapy (BNCT) is a binary form of cancer treatment in which two nontoxic species, a boron-containing compound and thermal neutrons, interact to cause a cytotoxic event in or near cancer cells. Boron-10 nuclides capture slow-moving neutrons and undergo a fission reaction, producing lethal high linear energy transfer $^{4}He^{2+}$ and $^{7}Li^{3+}$ particles[1−4] with a penetration range of approximately the diameter of one cell (9−10 μm).[5] Several factors define the choice of agents suitable for BNCT. Bringing a sufficient number of boron atoms to cancer cells ($\geq 10^{9}$ ^{10}B atoms/cell $\approx$ 20−35 μg ^{10}B/cell) is critical.[6,7] In this respect, carboranyl clusters, such as *o*-, *m*-, and *p*-carborane (Chart 1) have received much attention[6−19] due to their high kinetic stability, high boron content, and ease of derivitization.[7,20] Among the carboranyl clusters shown in Chart 1, *o*-carborane is particularly attractive due to its ease of preparation from decaborane.[21]

Chart 1



Carboranyl clusters have been incorporated into biologically relevant molecules such as nucleic acid bases, epidermal growth factor, liposomes, intercalators, and antibodies for use in BNCT.[7] In addition, carbon nanotubes have been functionalized with carboranes for BNCT applications.[22] Several strategies have been used to increase the boron content of BNCT agents, such as attachment of multiple carboranes to a porphyrin framework[7,23] and incorporation of carboranes into macromolecules. The use of macromol-

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ecules in drug delivery[24−27] has been shown to enhance the targeting and efficiency of the treatment.[28−30] Dendrimers, albeit harder to prepare than linear polymers, are characterized by a low polydispersity index (∼1.0) and thus show very reproducible pharmacokinetic behavior,[31−33] making them ideal candidates for model studies. Dendritic polymers allow control of solubility, molecular weight, and most importantly, multiplicity of therapeutic agents via modification of their periphery.[34] Previously, dendrimers carrying multiple carboranes have been prepared for use in BNCT[35−42] but demonstrated low water solubility and cytotoxicity.[43] More recently, biocompatible polyester dendrimers have been elegantly prepared with as many as 16 *p*-carboranes in their interior, and water solubility has been achieved by modification of their periphery, making them good candidates for use in BNCT.[44]

One drawback when using dendrimers for drug delivery is their uniform exterior functionality. Although the outer shell of dendrimers can be used to control their solubility and targeted delivery, introducing a combination of different functional groups at the periphery of a given dendrimer remains challenging. Thus, we decided to explore the possibility of synthesizing *functional dendrons* (i.e., dendritic wedges) for use in BNCT, in which carborane moieties would be attached to the exterior of the dendron, while a targeting functionality would be found at the focal point. Alternatively, the focal point could be used to combine a carborane-containing dendron with other dendrons carrying targeting moieties and/or solubilizing groups, thus producing a modular macromolecular BNCT agent. Herein, we describe the synthesis and properties of *o*-carborane-containing dendrons.

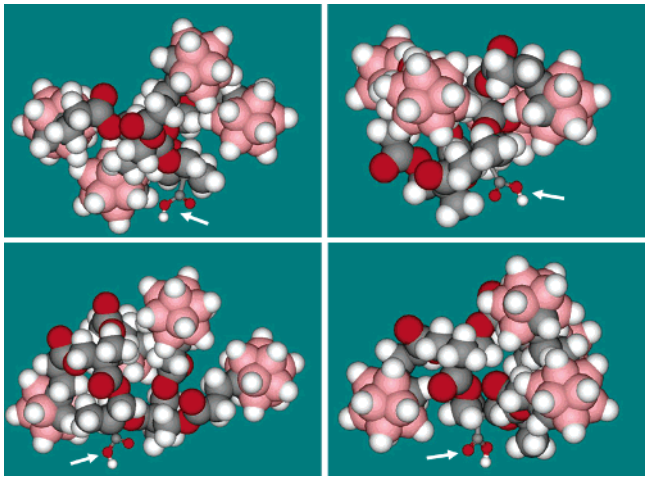

Figure 1. Representative structures of **BCD-2A** obtained by MD simulations (boron atoms, pink; carbon atoms, gray; hydrogen atoms, white; oxygen atoms, red). Carboxyl groups are marked with white arrows.

Experimental Section

General. All reagent-grade solvents were used without further purification except for dichloromethane and toluene, which were dried over calcium hydride. Decaborane and 1-*n*-butyl-3-methylimidazolium chloride were purchased from Alfa Aesar. 4-Pentynoic acid (98%) and dicyclohexylcarbodiimide (99%) were purchased from Lancaster Synthesis, Inc. Zinc dust was purchased from Fisher Scientific. 2,2,2-Trichloroethanol and 10-hydroxydecanoic acid were purchased from Aldrich. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was purchased from Advanced ChemTech. 4-Dimethylaminopyridinium 4-toluenesulfonate was prepared as previously reported.[45]

TLC: Merck silica gel 60 F_{254} plates (Al support, 0.2 mm thickness); detection of carborane compounds by $KMnO_4$ stain. IR spectra: Perkin-Elmer-FT-1600-IR spectrometer; in cm^{-1}. NMR Spectra: Varian VXL-300 or Varian Unity-300 at 300 MHz for ^1H, 160 MHz for ^{11}B, and 75 MHz for ^{13}C; Bruker DRX at 600 MHz for ^1H and 150 MHz for ^{13}C. Mass spectra were obtained using Finnigan MAT95, ThermoFinnigan LCQ and Micromass Quattro II. Molecular dynamics simulations were performed using Cerius^2, v4.5 (Accelrys, Inc.). For simulated annealing, a Dreiding force field was used. Each structure shown in Figure 1 has been obtained after five annealing cycles from 300 to 500 K in a total of 220 ps and by choosing the lowest-energy structure of each cycle.

Synthesis of 2,2,2-Trichloroethyl-4-pentynoate (3). 4-Pentynoic acid (**2**, 4.35 g, 44.31 mmol) and 2,2,2-trichloroethanol (5.0 mL, 52.00 mmol) were dissolved in dry dichloromethane (83 mL). 4-(Dimethylamino)pyridiunium *p*-toluenesulfonate (DPTS, 2.71 g, 9.21 mmol) was added followed by DCC (10.22 g, 49.53 mmol). The reaction mixture was stirred at room temperature under nitrogen overnight. The DCU was then filtered off and the filtrate was evaporated. The byproducts were precipitated in cold hexanes and filtered through a glass funnel. The filtrate was concentrated and purified by flash chromatography on silica gel, eluting with hexanes and gradually increasing the polarity to 70:30 hexanes/EtOAc to give **3** as a yellow oil (9.60 g, 93%). TLC (silica) R_f = 0.82

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(hexanes/EtOAc: 70:30). IR (neat, cm^{-1}): 3298, 2994, 2945, 2918, 2120, 1756, 1433, 1143. ^1H NMR ($CDCl_3$): δ 4.77 (s, 2H, CH_2CCl_3), 2.73 (td, $J = 7.2$, 1.4 Hz, 2H, CH_2), 2.58 (tdd, $J = 7.2$, 2.7, 0.9 Hz, 2H, CH_2), 2.01 (t, $J = 2.7$ Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 170.38, 94.94, 82.03, 74.26, 69.68, 33.28, 14.46. MS (CI): m/z 229 $[M + H]^+$.

Synthesis of Trichloroethyl 3-(1′,2′-Dicarbo-*closo*-dodecaborane-1′-yl)propanoate (4). 2,2,2-Trichloroethyl-4-pentynoate (**3**, 9.40 g, 41.22 mmol) and decaborane (7.62 g, 62.21 mmol) were dissolved in a biphasic system of toluene (153 mL) and 1-butyl-3-methylimidazolium chloride (6.18 g, 35.36 mmol). The reaction mixture was vigorously stirred to form an emulsion and heated to 120 °C under nitrogen. After 1 h, the reaction mixture was cooled to room temperature, diluted with toluene (100 mL), and transferred to a separatory funnel. The organic layer was washed with 1 M NaOH (3 × 100 mL) and brine (3 × 100 mL), dried over sodium sulfate, and filtered, and the solvent was removed in vacuo to give a yellow oil. This crude material was purified by liquid chromatography on silica gel, eluting with hexanes and gradually increasing the polarity to 60:40 hexanes/ethyl acetate, affording **4** as a white solid (6.60 g, 46%). TLC (silica) $R_f = 0.76$ (hexanes/EtOAc, 70:30). IR (neat, cm^{-1}): 3070, 3000, 2951, 2921, 2581, 1742, 1172. ^1H NMR ($CDCl_3$): δ 4.77 (s, 2H, CH_2CCl_3), 3.73 (bs, 1H, CH), 2.69 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$): δ 170.19, 94.13, 83.50, 74.53, 61.75, 33.33, 32.58. ^{11}B NMR ($CDCl_3$): δ −2.74, −6.18, −10.03. −12.46, −13.55. MS (CI): m/z 348 $[M + H]^+$.

Synthesis of 3-(1′,2′-Dicarbo-*closo*-dodecaborane-1′yl)propanoic Acid (1). Carborane trichlorester **4** (5.0 g, 12.37 mmol) was dissolved in 90% acetic acid (113 mL), followed by the addition of zinc dust (11.1 g, 169.77 mmol). The reaction mixture was stirred at room temperature under nitrogen for 3 h, after which TLC revealed the disappearance of the starting material,. The zinc was filtered off and washed with deionized water (2 × 70 mL) then dichloromethane (2 × 70 mL). Using a separatory funnel, the aqueous phase was washed with dichloromethane (2 × 70 mL). The organic layers were combined, washed with water (3 × 50 mL) and brine (3 × 50 mL), and then dried over sodium sulfate. The solvent was removed in vacuo, giving **1** as a white solid (2.8 g, 90%). ^1H NMR ($CDCl_3$): δ 3.67 (bs, 1H, CH), 2.65−2.54 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$): δ 171.1, 73.7, 61.7, 33.3, 32.5. ^{11}B NMR ($CDCl_3$): δ −2.51, −5.96, −11.93, −12.57, −13.31, in agreement with published data.[46]

Synthesis of Generation-1 Boron-Containing Dendron (BCD-1). The acid **1** (186 mg, 0.852 mmol), gen-1 dendron (75.4 mg, 0.337 mmol), and EDC (197 mg, 1.030 mmol) were dissolved in dry dichloromethane (3 mL). 4-Dimethylaminopyridine (DMAP, 14.4 mg, 0.118 mmol) was then added to the reaction flask. The reaction mixture was stirred under nitrogen for 24 h. Upon completion, dichloromethane was added (25 mL). Using a separatory funnel, the organic layer was washed with water (3 × 20 mL), 10% sodium bicarbonate (3 × 20 mL), and brine (3 × 20 mL) then dried over sodium sulfate. The solvent was removed in vacuo, giving a white foam that was purified by liquid chromatography on silica gel, eluting with hexanes and gradually increasing the polarity to 70:30 hexanes/ethyl acetate to give **BCD-1** as a white solid (179 mg, 86%). TLC (silica) $R_f = 0.83$ (hexanes/EtOAc, 60:40). IR (neat, cm^{-1}): 3062, 2938, 2577, 1737, 1164, 1132. ^1H NMR ($CDCl_3$): δ 7.36 (m, 5H, Ar), 5.18 (s, 2H, CH_2Ar), 4.24 (q, $J =$ 12, 6 Hz, 4H, CH_2O), 3.68 (bs, 2H, CH), 2.48 (m, 8H, CH_2), 1.28 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 172.28, 171.04, 135.54, 128.84, 128.78, 128.46, 73.90, 67.18, 66.02, 61.76, 46.37, 33.21, 32.54, 17.99. ^{11}B NMR ($CDCl_3$): δ −2.83, −6.26, −10.11, −12.54, −13.27. MS (CI): m/z 622 $[M + H]^+$.

Synthesis of Generation-2 Boron-Containing Dendron (BCD-2). The acid **1** (235 mg, 1.090 mmol), gen-2 dendron (985 mg, 0.216 mmol) and EDC (248 mg, 1.300 mmol) were dissolved in dry dichloromethane (4 mL). DMAP (8.5 mg, 0.070 mmol) was then added to the reaction flask. The reaction mixture was stirred under nitrogen for 48 h. Upon completion, dichloromethane was added (25 mL). Using a separatory funnel, the organic layer was washed with water (3 × 20 mL), 10% sodium bicarbonate (3 × 20 mL), and brine (3 × 20 mL) then dried over sodium sulfate. The solvent was removed in vacuo, giving a white foam that was purified by liquid chromatography on silica gel, eluting with hexanes and gradually increasing the polarity to 70:30 hexanes/ethyl acetate to give **BCD-2** as a white solid (203 mg, 75%). TLC (silica) $R_f =$ 0.53 (hexanes/EtOAc, 60:40). IR (neat): υ 3056, 2954, 2582, 1733, 1167, 1134. ^1H NMR ($CDCl_3$): δ 7.37 (m, 5H, Ar), 5.17 (s, 2H, CH_2Ar), 4.25 (q, $J = 12.6$ Hz, 4H, CH_2O), 4.16 (m, 8H, CH_2), 3.74 (bs, 4H, CH), 2.56 (bs, 16H, CH_2), 1.31 (s, 3H, CH_3), 1.19 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): δ 174.75, 171.84, 171.12, 135.39, 129.01, 128.93, 128.53,73.65, 66.55, 65.81, 61.79, 46.94, 33.30, 32.63, 17.96. ^{11}B NMR ($CDCl_3$): δ −2.74, −6.01, −10.03, −12.46. MS (CI): m/z 1248 $[M + H]^+$.

Synthesis of Generation-2 Boron containing dendron acid (BCD-2A). The dendron **BCD-2** (183 mg, 0.147 mmol) was dissolved in methanol (60 mL). Palladium (10% on carbon, 210 mg) was then added under nitrogen to the Parr hydrogenation bomb. The reaction mixture was stirred at room temperature under 45 psi of H_2 atmosphere for 19 h. The bomb was then depressurized; the reaction mixture was filtered over a pad of Celite and washed with methanol (2 × 30 mL). The solvent was removed in vacuo, giving the off-white solid **BCD-2A** (143 mg, 84%). TLC (silica) $R_f =$ 0.88 (EtOAc/MeOH, 80:20). IR (neat, cm^{-1}): 3359, 3057, 2577, 1734, 1234, 1167, 1132. ^1H NMR ($CDCl_3$): δ 4.24 (m, 12H, CH_2), 3.76 (bs, 4H, CH), 2.58 (bs, 16H, CH_2), 1.32 (s, 3H, CH_3), 1.28 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): δ 180.55, 172.00, 171.20, 73.22, 68.73, 65.93, 61.85, 46.83, 33.36, 32.63, 18.06. ^{11}B NMR ($CDCl_3$): δ −2.57, −5.84, −9.78, −12.46. MS (ESI+): m/z 1178 $[M + Na]^+$.

Synthesis of Acetonide Generation-2 Dendron with Benzyl 10-Hydroxydecanoic Acid Linker (AGen-2L). The acetonide-protected gen-2 acid dendron (147 mg, 0.329 mmol), benzyl-10-hydroxydecanoate (57 mg, 0.205 mmol), and EDC (58 mg, 0.302 mmol) were dissolved in dry dichloromethane (3 mL). DMAP (10.8 mg, 0.088 mmol) was then added to the reaction flask. The reaction mixture was stirred under nitrogen for 48 h. Upon completion, dichloromethane was added (20 mL). Using a separatory funnel, the organic layer was washed with water (3 × 20 mL), 10% sodium bicarbonate (3 × 20 mL), and brine (3 × 20 mL) then dried over sodium sulfate. The solvent was removed in vacuo, giving a white foam that was purified by liquid chromatography on silica gel, eluting with 90:10 hexanes/ethyl acetate and gradually increasing the polarity to 70:30 hexanes/ethyl acetate to give **AGen-2L** as a colorless oil (27 mg, 18%). TLC (silica) $R_f = 0.55$ (hexanes/EtOAc, 60:40). IR (neat, cm^{-1}): 2921, 2851, 1738, 1218, 1154, 1082. ^1H NMR ($CDCl_3$): δ 7.36 (m, 5H, Ar), 5.12 (s, 2H, CH_2Ar), 4.33 (s, 4H, CH_2), 4.15 (d, $J = 12$ Hz, 4H, CH_2), 4.11 (t, $J = 12$ Hz, 2H, CH_2), 3.62 (d, $J = 12$ Hz, 4H, CH_2), 2.36 (t, $J = 12$ Hz, 2H, CH_2), 1.63 (m, 4H, CH_2), 1.42 (s, 6H, CH_3), 1.37 (s, 6H, CH_3), 1.29 (bs, 10H, CH_2), 1.26 (s, 3H, CH_3), 1.68 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): δ 173.62, 173.52, 172.60, 135.90, 128.53, 128.15, 66.05, 65.94, 65.43, 61.79, 46.71, 42.02, 34.29, 29.27, 29.16, 29.14, 29.07,

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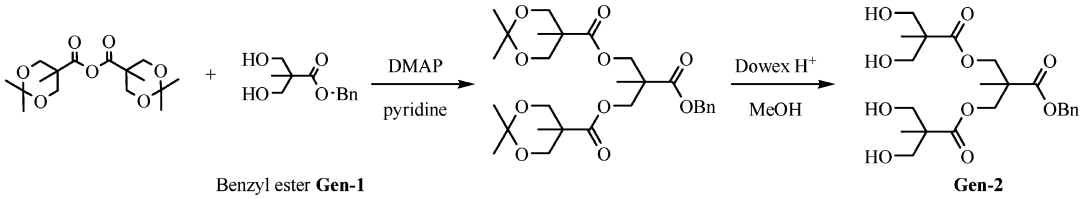
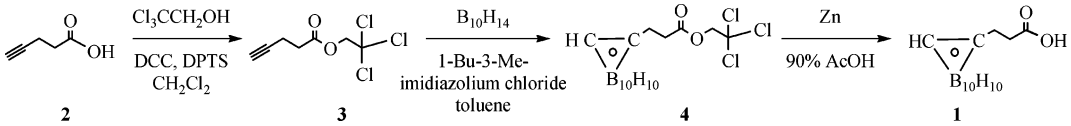
Scheme 1



Scheme 2



28.50, 25.84, 24.91, 24.80, 22.42, 20.63, 18.60, 17.71. MS (CI): *m*/*z* 707 $[M + H]^+$.

Synthesis of Generation-2 $(OH)_4$ Dendron with Benzyl-10-hydroxydecanoic Acid Linker (Gen-2L). AGen-2L (26 mg, 0.0367 mmol) was dissolved in methanol (3 mL). Dowex H^+ (72 mg) was then added to the reaction flask under nitrogen. The reaction mixture was stirred at room temperature for 3 h, after which the resin was then filtered off and washed with methanol (2 × 10 mL). The solvent was removed in vacuo, giving the colorless solid **Gen-2L** (23 mg, 99%). TLC (silica) $R_f = 0.58$ (EtOAc/Acetone, 80:20). IR (neat, cm^{-1}): 3245, 2931, 2855, 1728, 1461, 1219, 1135, 1042. ^1H NMR ($CDCl_3$): δ 7.35 (m, 5H, Ar), 5.11 (s, 2H, CH_2-Ar), 4.43 (d, $J = 10.9$ Hz, 2H, CH_2), 4.24 (d, $J = 10.9$ Hz, 2H, CH_2), 4.21 (t, $J = 6$ Hz, 2H, CH_2), 3.68 (m, 8H, CH_2), 2.35 (t, $J = 6$ Hz, 2H, CH_2), 1.63 (m, 4H, CH_2), 1.09 (s, 3H, CH_3), 1.06 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$): δ 178.29, 175.24, 173.24, 131.80, 128.71, 128.34, 126.31, 67.45 66.29, 65.01, 62.69, 49.90, 46.46, 34.46, 29.26, 28.63, 25.96, 25.05, 18.35, 17.30. MS (CI): *m*/*z* 627 $[M + H]^+$.

Synthesis of Generation-2 Boron-Containing Dendron with Benzyl-10-hydroxydecanoic Acid Linker (BCD-2L). Gen-2L (22 mg, 0.352 mmol), carborane acid **1** (39 mg, 0.181 mmol) and EDC (50 mg, 0.262 mmol) were dissolved in dry dichloromethane (2 mL). DMAP (3.1 mg, 0.0254 mmol) was then added to the reaction flask. The reaction mixture was stirred under nitrogen for 48 h. Upon completion, dichloromethane was added (20 mL). Using a separatory funnel, the organic layer was washed with water (3 × 20 mL), 10% sodium bicarbonate (3 × 20 mL), and brine (3 × 20 mL) then dried over sodium sulfate. The solvent was removed in vacuo, giving a white foam that was purified by liquid chromatography on silica gel, eluting with 70:30 hexanes/ethyl acetate and gradually increasing the polarity to 100% ethyl acetate to give **BCD-2L** as a white solid (6.5 mg, 13%). TLC (silica) $R_f = 0.77$ (hexanes/EtOAc, 60:40). IR (neat, cm^{-1}): 3061, 2920, 2850, 2591, 1738, 1730, 1241, 1169. ^1H NMR ($CDCl_3$): δ 7.36 (m, 5H, Ar), 5.12 (s, 2H, CH_2Ar), 4.23 (m, 12H, CH_2), 4.12 (t, $J = 6$ Hz, 2H, CH_2), 3.76 (bs, 4H, CH), 2.58 (bs, 16H, CH_2), 2.36 (t, $J = 6$ Hz, H2H, CH_2), 1.66 (m, 2H, CH_2), 1.31 (s, 3H, CH_3), 1.29 (s, 6H, CH_3), 1.26 (bs, 10H, CH_2). ^{13}C NMR ($CDCl_3$): δ 173.57, 171.96, 171.70, 170.83, 136.08, 128.52, 128.16, 128.12, 73.22, 69.36, 66.81, 65.62, 61.60, 55.57, 41.88, 46.50, 34.29, 32.50, 29.72, 29.30, 29.17, 29.09, 28.90, 28.54, 26.20, 24.91, 17.87, 17.73, 17.07. ^{11}B NMR ($CDCl_3$): δ −2.35, −3.81, −3.96, −9.52, −11.16, −13.20. MS (CI): *m*/*z* 1420 $[M + H]^+$.

Results and Discussion

Our choice of the dendritic scaffold was dictated by general requirements for BNCT agents.[20] Thus, to construct the dendrons, we selected a polyester backbone[47,48] based on 2,2-bis(hydroxymethyl)propanoic acid (bis-MPA) that has been shown to be biodegradable, nonimmunogenic, water-soluble, and nontoxic to cells in vivo.[49] The polyester bis-MPA-based dendrons were synthesized using the reported[47,48] divergent approach shown in Scheme 1.

Esterification suggested itself as the preferred method to attach a carboranyl moiety to the polyhydroxyl outer shell of the dendrons. However, we and others[44] have found that the esterification of carboranyl acids in which the carboxylic group is directly attached to the boron cluster is impaired by the steric bulk of the boron cluster. Thus, direct attachment of such acids to bis-MPA proved impossible, and it became apparent that a spacer, such as a propanoic acid derivative,[46] was necessary to reduce the steric hindrance around the carboxylic group. To avoid the deprotonation/protection/deprotection sequence required for the preparation of bifunctional *p*-carboranes,[44] we relied on the hydroboration reaction of alkynes with decaborane which yields *o*-carboranyl derivatives.[10,50−52] The synthesis of *o*-carboranyl acid **1** is shown in Scheme 2. 4-Pentynoic acid **2** was first protected as the trichloroester **3** since acids (and alcohols) are known to degrade the polyhedral borane cage ($B_{10}H_{14}$) involved in the insertion reaction.[10,50−52] Previously, *o*-carboranes have been synthesized via a base-promoted two-step process.[10,50−52] This reaction involves formation of an activated $B_{10}H_{12}L_2$ adduct (where L is typically acetonitrile) followed by alkyne insertion to yield the *o*-carborane product. Applied to the preparation of **1**, this procedure required 4 days with yields of ca. 50%. Thus, a more efficient route was sought. The use of ionic liquids (IL) in the hydroboration of alkenes and alkynes has been recently reported.[21] This reaction involves a refluxing biphasic system of toluene and an ionic liquid (1-butyl-3-methylimidazolium chloride,

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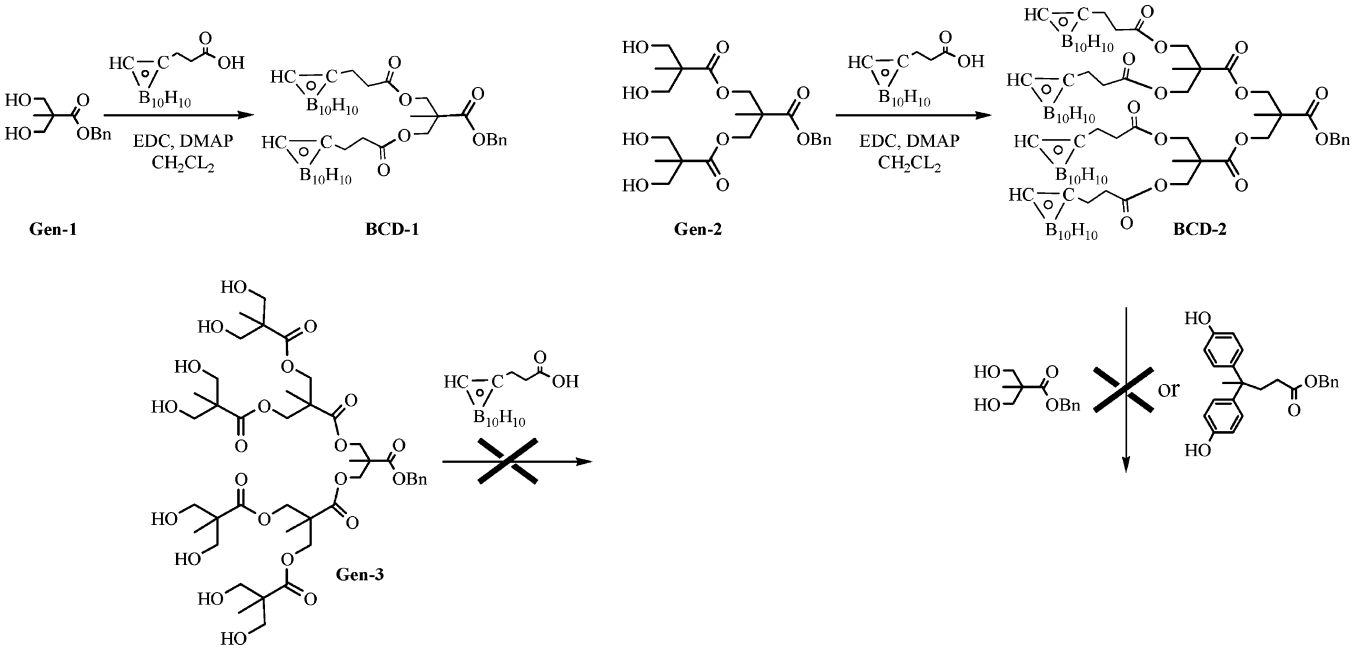
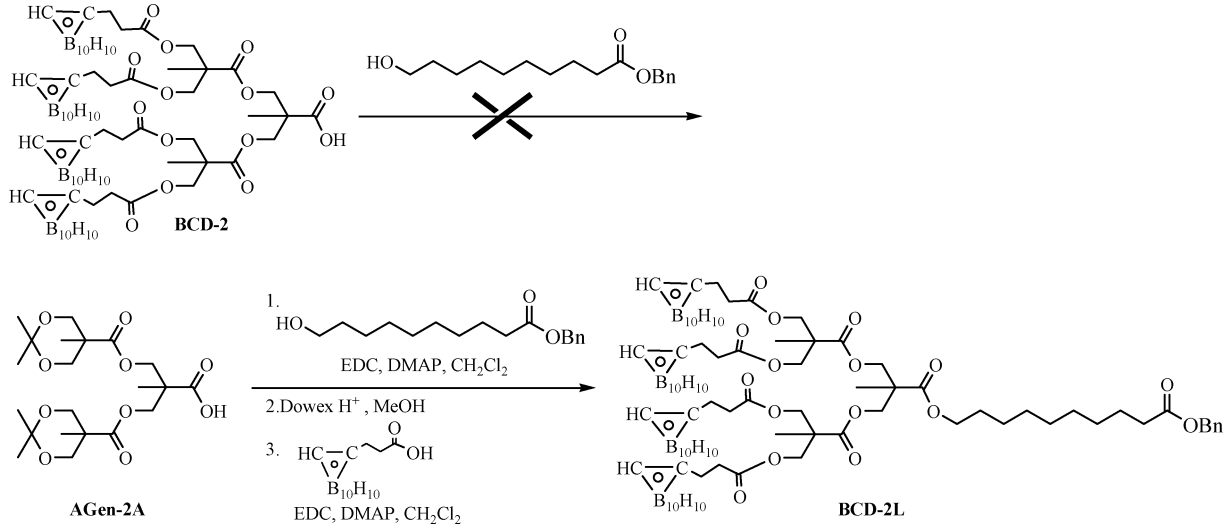
Scheme 3



Scheme 4



(bmim)Cl) that allows the hydroboration to proceed in a matter of hours. Indeed, when this procedure was applied to the preparation of **3** (Scheme 2), the reaction time was reduced from 4 days to 1 hour. The yield remained reasonably high, and the ionic liquid could be easily removed by flash chromatography. The trichloroester **3** was then cleaved[53] to yield the *o*-carboranyl acid **1**.

In the consequent step, **1** was coupled to the benzyl ester of bis-MPA using conditions similar to those reported earlier,[44] providing generation-1 boron-containing dendron **BCD-1** (Scheme 3). However, further coupling of **BCD-1** to the benzyl ester of bis-MPA to prepare a higher-generation boron-containing dendron in a convergent fashion could not be achieved (Scheme 3). Using a divergent approach, we were able to couple *o*-carboranyl acid **1** to generation-2 bis-MPA-based dendron (Scheme 3) to obtain generation-2 carborane-containing dendron **BCD-2** (with four boron clusters). Unfortunately, this procedure failed to provide the next-generation dendron **BCD-3** (with eight boron clusters) upon coupling of **1** to the generation-3 bis-MPA-based dendron (Scheme 3). Equally unsuccessful were our attempts to synthesize **BCD-3** through the coupling of **BCD-2** to the benzyl ester of bis-MPA (Scheme 3). In an attempt to alleviate the steric strain associated with the 1,3-diol of bis-MPA, we investigated the benzyl ester of 4,4-bis-(4-hydroxyphenyl)pentanoic acid.[54] However, the increased spatial separation between the hydroxyl groups of this new core did not improve the reactivity, and higher-generation boron-containing dendrons could not be accessed.

On the basis of the above observations, it appears that, with four carborane cages, the **BCD-2** dendron is extremely

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(54) Al-Azemi, T. F.; Bisht, K. S. *Polymer* **2002**, *43*, 2161−2167.

sterically hindered. This was confirmed by molecular dynamics simulations of its three-dimensional structure (representative structures are shown in Figure 1). The calculated dendron possesses a globular structure with a hindered carboxylic focal point. This explains its lack of reactivity toward the benzyl ester of bis-MPA and suggests that higher-generation boron-containing dendrons are unattainable through coupling of **1** to higher generations of bis-MPA-based dendrons.

To further explore the reactivity of the carboxylic group at the focal point and to enable the attachment of **BCD-2** to other moieties, we first considered adding a 10-carbon alkyl linker to the focal point of **BCD-2** using 10-hydroxybenzyldecanate,[55] easily prepared from the corresponding acid.[56] However, the esterification at the focal point of **BCD-2** with this primary alcohol failed (Scheme 4), presumably for the same steric reasons. An alternative route was chosen to install the linker, and it proved to be successful. The acetonide-protected generation-2 dendritic acid (**AGen-2A**, Scheme 4) was prepared by hydrogenation of its benzyl ester as previously reported;[47,48] the linker was attached to the focal point first followed by the attachment of the carboranyl acid **1** to yield **BCD-2L** (Scheme 4). Installing this linker shifts the carboxylic group outside the sterically hindered dendron and should allow its incorporation into BNCT macromolecular agents.

(55) Holt, D. A.; Luengo, J. I.; Yamashita, D. S.; Oh, H.-J.; Konialian, A. L.; Yen, H. K.; Rozamus, L. W.; Brandt, M.; Bossard, M. J.; Levy, M. A.; Eggleston, D. S.; Liang, J.; Schultz, L. W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 9925−9938.

(56) We consistently obtained yields higher (e.g., 81% vs 54%) than previously reported.

Conclusions

We prepared new carborane-containing dendrons based on a 2,2-bis(hydroxymethyl)propanoic acid (bis-MPA) scaffold and showed that they are highly sterically congested. A generation-2 carborane-containing dendron carrying 40 boron atoms was the highest generation synthetically available. The structure of this dendron has been simulated by molecular dynamics. A 10-carbon linker carrying a carboxylic group has been installed at the focal point of the dendron to distance the attachment point from the sterically hindered core. We are presently working on the attachment of these dendrons to targeting moieties for use in BNCT.

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