A NOVEL APPROACH TO THE SYNTHESES OF FUNCTIONALIZED, WATER-SOLUBLE ICOSAHEDRAL CARBORANYL ANIONS. CRYSTAL STRUCTURE OF METHYL *N*-[(TRIMETHYLAMINEBORYL)CARBONYL]-L-TYROSINATE: A SYNTHON FOR NOVEL CARBORANYLPEPTIDES

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Dedicated to Professor Jaromír Plešek on the occasion of his 75th birthday.

New functionalized water-soluble carboranyl anions have been prepared from *ortho*-carborane through lithiation and subsequent derivatization. The reaction of $Li_2[1,2\text{-}C_2B_{10}H_{10}]$ with Me_3NBH_2X produced the carboranylborane dianions, $[1,2\text{-}(BH_2X)\text{-}1,2\text{-}C_2B_{10}H_{10}]^{2-}$ (X = H (**2a**), CN (**2b**), COOMe (**2c**), COOH (**2d**)), while the reaction of $[1\text{-}R\text{-}2\text{-}Li\text{-}C_2B_{10}H_{10}]^-$ with Me_3NBH_2X produced the monoanions $[1\text{-}R\text{-}2\text{-}BH_2X\text{-}C_2B_{10}H_{10}]^-$ (R = C_6H_5, X = H (**2e**), CN (**2f**), COOH (**2h**), $COOCH_3$ (**2g**), $CONHCH(CH_2OH)COOMe$ (**2i**), $CONHCH(CHMe_2)COOMe$ (**2j**), $CONHCH(4\text{-}CH_2C_6H_4OH)\text{-}COOMe$ (**2k**); R = Me, X = H (**2l**), COOH (**2m**)). These water-soluble carboranylboranes have the potential of being effective hydrophilic boron neutron capture therapy (BNCT) agents. The crystal structure of the peptide precursor $Me_3NBH_2CONHCH(4\text{-}CH_2C_6H_4OH)COOMe$ (**3b**) which showed a special promise as a BNCT agent is also described.

Keywords: Carboranes; Boron neutron capture therapy; BNCT; Amino acids; Amineboranes; Peptides.

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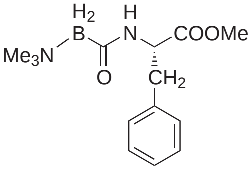
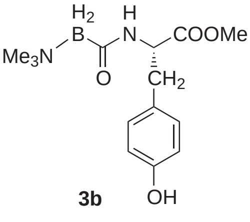
Since their initial descriptions in 1963 [1,2], the icosahedral carboranes in the C_2B_{10} cage system have been the subject of numerous studies[3–5]. Their bonding and structures are intrinsically interesting and their thermal and chemical stabilities make them attractive in both materials chemistry[5] and medicinal chemistry[6]. In the latter area, their high boron content and chemical inertness have resulted in the icosahedral carboranes being extensively investigated for possible use in boron neutron capture therapy (BNCT)[6,7]. One of the problems associated with the use of these compounds is their pronounced hydrophobic character and consequent low solubility in water. Although advantage can be taken of such characteristics[8], much of the research in this area has involved syntheses of derivatives of the carboranes that enhance water solubility. Most of such derivatizations involve replacing the hydrogens on the cage carbons with other groups. This is a well-tested approach, the same report that first described the parent $C_2B_{10}H_{12}$ carborane also described a number of its *C*-substituted derivatives[1,2,9]. Cage-carbon derivatization is usually accomplished by starting with substituted acetylenes in the primary acetylene-decaborane reaction or by removing the cage carbon hydrogens with a strong base, such as butyllithium and reacting the resulting lithiated carboranyl anions with electrophiles. While the use of excess base results in removal of both hydrogens, methods have been developed to remove only one of the hydrogens in the $C_2B_{10}H_{12}$ starting materials[10,11]. Our interest in these compounds stems from our recent observation that the boronated compounds, **3a** and **3b**, showed significant improvement over the BNCT agents 4-boronophenylalanine (BPA) and $Na_2B_{12}H_{11}SH$ (BSH), whose ^{10}B enriched isomers are currently undergoing clinical trials as BNCT agents[12]. It was shown that in a C6 gliosarcoma tumor implanted in a rat brain model, tumor : normal brain (T/N) ratios of *ca* 9 : 1 were found for **3a**, compared to 3 : 1 for BPA. In addition, α-autoradiography showed that **3a** also was incorporated into tumor cells that were infiltrating into normal brain tissue. This is significant since such cells are thought to be a leading cause of tumor recurrence



3a



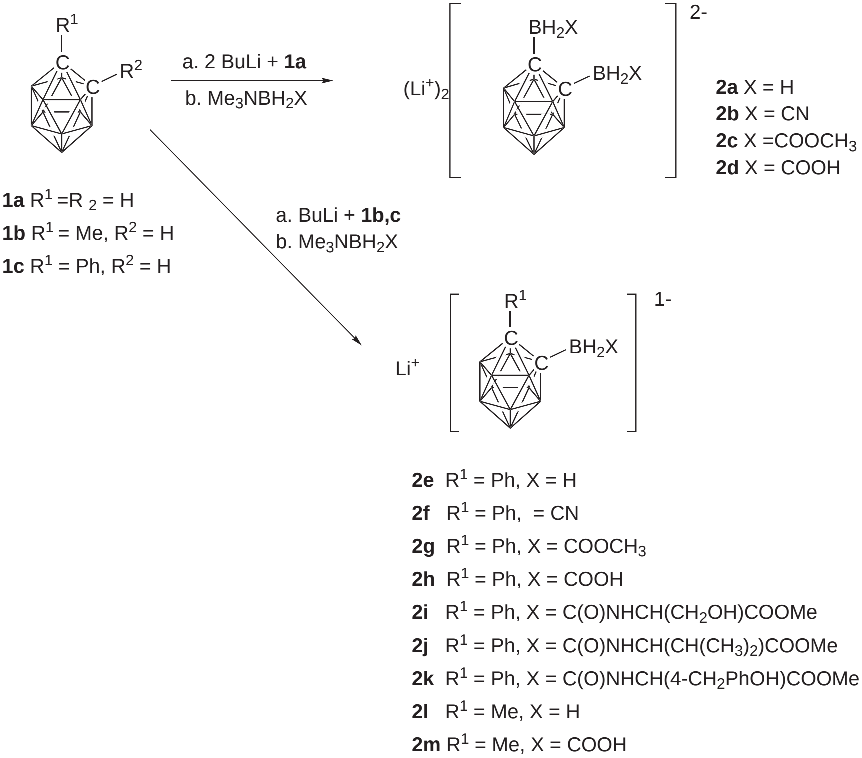
3b

after radiation[13]. These results suggest that the incorporation of C_2B_{10} moieties into boronated peptides might produce a class of compounds that could act as effective BNCT agents. There is precedent for such compounds in that Me_3NBH_2-1,2-$C_2B_{10}H_{11}$ has been synthesized and characterized[14], as well as the series 1-L-BH_2-1,2-$C_2B_{10}H_{11}$ (L = H^-, Me_2S, C_5H_5N, Me_3N and Et_3N)[15]. This report is of the syntheses and characterizations of a series of water-soluble icosahedral carboranylborane anions from the reactions of carboranyl anions or dianions with a series of amine boranes, as outlined in Scheme 1.

EXPERIMENTAL

Materials

The amine boranes of the formula Me_3NBH_2X (X = CONHCH(4-$CH_2C_6H_4OH$)COOMe (**3b**), CN, COOH, $COOCH_3$, CONHCH(CH_2OH)COOMe and CONHCH($CHMe_2$)COOMe) were



SCHEME 1
Preparation of mono- and disubstituted carboranylborane anions

made using the methods described by Spielvogel and co-workers[16,17]. *closo*-1,2-$C_2B_{10}H_{12}$, *closo*-1-Ph-1,2-$C_2B_{10}H_{11}$ and *closo*-1-Me-1,2-$C_2B_{10}H_{11}$ were obtained from KATCHEM and used as received. Cyclohexane, bis(2,2′-dimethoxyethyl) ether (DME) and benzene were dried over sodium metal and benzophenone, and doubly distilled before use. BuLi (2.0 M in cyclohexane) was used as received.

Spectroscopic and Analytical Procedures

^1H, ^{11}B and ^{13}C NMR spectra were recorded on a Brucker Fourier-transform multinuclear NMR spectrometer at 200, 64.2 and 50.3 MHz, respectively. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra (wavenumbers in cm^{-1}) were obtained using a Nicolet Magna 550 FT-IR spectrophotometer. Elemental analyses were obtained using a Perkin Elmer 2400 CHN elemental analyzer.

Synthesis

All experiments were carried out in 250 ml Pyrex glass round-bottom flasks fitted with a nitrogen inlet and containing a magnetic stirring bar. The purity of all known compounds was checked by comparing their IR and NMR spectra and melting points with authentic samples.

General Synthetic Procedure for **2a**–**2m**

All of the carboranyl anions were synthesized using the same general method, as outlined in Scheme 1. Therefore, only a general procedure needs to be described. The specific compound identities are summarized in Scheme 1, while their yields and analytical data are given in Experimental. The dilithium compound of 1,2-$C_2B_{10}H_{12}$ (**1a**) and the monolithium compounds of 1-R^1-1,2-$C_2B_{10}H_{11}$ (R^1 = Ph (**1b**), Me (**1c**)) were prepared by mixing the particular carborane, dissolved in 20 ml of dry distilled DME, with a measured volume of 2.0 M BuLi (cyclohexane solution) to give either a 2 : 1 molar ratio of BuLi : carborane (for **1a**) or a 1 : 1 molar ratio (for **1b** and **1c**). The solution was stirred at room temperature for 0.5 h and then a stoichiometric amount of the selected amine borane, Me_3NBH_2X, dissolved in 20 ml of DME was slowly added and the resulting reaction mixture was refluxed for 48–72 h. The solvents were then removed *in vacuo* and the residue was repeatedly washed with hexane and pentane to remove any unreacted starting materials. The solid was then recrystallized from distilled water to give the particular carboranyl anion as its lithium or dilithium salt. All products were further characterized by recording their ^1H, ^{11}B and ^{13}C NMR spectra and their IR spectra (see below).

Spectroscopic and Analytical Data

Lithium salt of 1,2-(borano)-1,2-dicarbadodecacarborate(2–), $Li_2[1,2\text{-}(BH_3)_2\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2a**). Colorless solid, yield 0.58 g (90%). IR (KBr pellet): 2 575, 2 552 (ν, B–H terminal); 2 289 (ν, as B–H, BH_3 gp); 2 238 (ν, sym B–H, BH_3). ^{13}C NMR (DMSO, relative to Me_4Si): 86.0 (C_{cage}). ^1H NMR (DMSO, relative to Me_4Si): 1.0–1.4 (6 H, q). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ ($J[^{11}B\text{-}^1H]$)): –2.01 (1 H, 146); –9.21 (1 H, 152); –13.01 (2 H, 160); –14.20 (1 H, 174); –19.91 (1 H, unresolved). For $C_2H_{16}B_{12}Li_2$ calculated: 12.90% C, 8.60% H; found: 13.15% C, 8.66% H.

Lithium salt of 1,2-(cyanoborane)-1,2-dicarbadodecacarborate(2–), $Li_2[1,2\text{-}(BH_2CN)_2\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2b**). Colorless solid, yield 0.78 g (95%). IR (KBr pellet): 2 581, 2 561 (ν, B–H terminal); 2 435 (ν, B–H, BH_2CN); 2 205 (ν, CN). ^{13}C NMR (DMSO, relative to Me_4Si): 115.0 (CN), 88.1 (C_{cage}). ^1H NMR (DMSO, relative to Me_4Si): 1.1–1.4 (4 H, t). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –1.89 (1 H, 148); –8.52 (1 H, 155); –12.81 (2 H, 165); –13.98 (1 H, 179); –19.01 (1 H, unresolved). For $C_4H_{14}B_{12}Li_2N_2$ calculated: 20.34% C, 5.93% H, 5.93% N; found: 20.51% C, 6.03% H, 5.88% N.

Lithium salt of 1,2-(methoxycarbonylborane)-1,2-dicarbadodecacarborate(2–), $Li_2[1,2\text{-}(BH_2COOCH_3)_2\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2c**). Colorless solid, yield 0.76 g (73%). IR (KBr pellet): 2 579, 2 556 (ν, B–H terminal); 1 665 (ν, C=O); 2 385 (ν, B–H, BH_2COOMe); 1 375 (δ, CH_3 bend). ^{13}C NMR (DMSO, relative to Me_4Si): 180.0 (C=O), 86.5 (C_{cage}), 54.1 (1 C, OCH_3). ^1H NMR (DMSO, relative to Me_4Si): 1.0–1.3 (4 H, t); 3.8 (3 H, s). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –1.94 (1 H, 147); –9.01 (1 H, 151); –12.97 (2 H, 165); –14.01 (1 H, 176); –19.42 (1 H, unresolved). For $C_6H_{20}B_{12}Li_2O_4$ calculated: 23.40% C, 6.62% H; found: 23.60% C, 6.63% H.

Lithium salt of 1,2-(carboxyborane)-1,2-dicarbadodecacarborate(2–), $Li_2[1,2\text{-}(BH_2COOH)_2\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2d**). Colorless solid, yield 0.66 g (70%). IR (KBr pellet): 3 120 (ν, OH); 2 551(ν, B–H terminal); 2 380 (ν, B–H, BH_2COOH); 1 645 (ν, C=O). ^{13}C NMR (DMSO, relative to Me_4Si): 184.8 (COOH), 88.2 (C_{cage}). ^1H NMR (DMSO, relative to Me_4Si): 0.9–1.3 (4 H, t); ≈8 (2 H, br s). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –1.71 (1 H, 148); –8.41 (1 H, 156); –11.81 (2 H, 169); –13.40 (1 H, 180); –18.89 (1 H, unresolved). For $C_4H_{16}B_{12}Li_2O_4$ calculated: 17.52% C, 5.84% H; found: 18.22% C, 5.77% H.

Lithium salt of 1-phenyl-2-(borano)-1,2-dicarbadodecacarborate(1–), $Li[1\text{-}(C_6H_5)\text{-}2\text{-}(BH_3)\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2e**). Colorless solid, yield 0.47 g (86%). IR (KBr pellet): 2 572, 2 560 (ν, B–H terminal); 2 289 (ν, as B–H, BH_3 gp); 2 238 (ν, sym B–H, BH_3). ^{13}C NMR (DMSO, relative to Me_4Si): 129.0 (Ar); 89.0, 86.2 (C_{cage}). ^1H NMR (DMSO, relative to Me_4Si): 1.0–1.4 (3 H, q); 7.6–7.8 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –3.5 (1 H, 147); –7.91 (1 H, 153); –9.71 (2 H, 157); –9.8 (2 H, 157); –11.01 (2 H, 172); –13.67 (2 H, 156); –20.12 (1 H, unresolved). For $C_8H_{18}B_{11}Li$ calculated: 39.70% C, 7.44% H; found: 40.10% C, 7.40% H.

Lithium salt of 1-phenyl-2-(cyanoborane)-1,2-dicarbadodecacarborate(1–), $Li[1\text{-}(C_6H_5)\text{-}2\text{-}(BH_2CN)\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2f**). Colorless solid, yield 0.54 g (89%). IR (KBr pellet): 2 586, 2 553 (ν, B–H terminal); 2 433 (ν, B–H, BH_2CN); 2 215 (ν, CN); 712, 1 612, 1 489 (ν, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 129.0 (Ar); 89.0, 86.1 (C_{cage}). ^1H NMR (DMSO, relative to Me_4Si): 0.9–1.3 (2 H, t); 7.7–7.9 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –3.2 (1 H, 146); –7.41 (1 H, 154); –9.11 (2 H, 154); –9.21 (2 H, 156); –10.62 (2 H, 174); –13.68 (2 H, 155); –19.12 (1 H, unresolved). For $C_9H_{17}B_{11}LiN$ calculated: 40.50% C, 6.36% H, 5.24% N; found: 40.67% C, 6.66% H, 5.22% N.

Lithium salt of 1-phenyl-2-(methoxycarbonylborane)-1,2-dicarbadodecacarborate(1–), $Li[1\text{-}(C_6H_5)\text{-}2\text{-}(COOCH_3)\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2g**). Colorless solid, yield 0.36 g (53%). IR (KBr pellet): 2 576, 2 562 (ν, B–H terminal); 2 481 (ν, B–H, BH_2COOMe); 1 670 (ν, C=O); 711, 1 602, 1 480 (ν, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 173.5 (C=O); 128.5 (Ar); 89.4, 86.9 (C_{cage}); 55.0 (OCH_3). ^1H NMR (DMSO, relative to Me_4Si): 1.0–1.4 (2 H, t); 3.7 (3 H, s); 7.5–7.8 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3\cdot OEt_2$ (*J*[^{11}B-^1H])): –3.42 (1 H, 146); –7.61 (1 H, 152); –9.59 (2 H, 155); –9.61 (2 H, 156); –10.91 (2 H, 173); –13.61 (2 H, 156); –19.25 (1 H, unresolved). For $C_{10}H_{20}B_{11}LiO_2$ calculated: 40.00% C, 6.67% H; found: 40.72% C, 6.09% H.

Lithium salt of 1-phenyl-2-(carboxyborane)-1,2-dicarbadodecacarborate(1-), $Li[1\text{-}(C_6H_5)\text{-}2\text{-}(BH_2COOH)\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (**2h**). Colorless solid, yield 0.41 g (63%). IR (KBr pellet): 3 112 (ν, OH); 2 588, 2 559 (ν, B–H terminal); 2 383 (ν, B–H, BH_2COOH); 715, 1 611, 1 485 (ν, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 172.4 (COOH); 128.6 (Ar); 89.2, 87.4 (C_{cage}). ^{1}H NMR (DMSO, relative to Me_4Si): 0.8–1.4 (2 H, t); 8.9 (1 H, br s); 7.6–7.9 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3 \cdot OEt_2$ ($J[^{11}B\text{-}^{1}H]$)): –2.98 (1 H, 148); –7.02 (1 H, 153); –8.99 (2 H, 153); –9.01 (2 H, 156); –10.02 (2 H, 174); –13.11 (2 H, 157); –18.99 (1 H, unresolved). For $C_9H_{18}B_{11}LiO_2$ calculated: 37.80% C, 6.30% H; found: 38.20% C, 6.20% H.

Lithium salt of 1-phenyl-2-(methyl N-carbonyl-L-serinatoborane)-1,2-dicarbadodecacarborate(1–), Li[1-(C_6H_5)-2-($BH_2CONHCH(CH_2OH)COOCH_3$)-1,2-$C_2B_{10}H_{10}$] (**2i**). Pale yellow solid, yield 0.42 g (48%). IR (KBr pellet): 3 225 (ν, OH); 3 125 (ν, CH); 2 582, 2 550 (ν, B–H terminal); 2 371 (ν, B–H); 1 700, 1 661 (ν, C=O); 1 375 (δ, CH_3); 1 300–1 400 (δ, OH); 705, 1 621, 1 485 (ν, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 190.0, 184.0 (C=O); 128.4 (Ar); 90.1, 89.2 (C_{cage}); 62.9 (CH_2OH); 54.0 (OCH_3). ^{1}H NMR (DMSO, relative to Me_4Si): 1.0–1.3 (2 H, t); 3.66 (3 H, s); 3.75 (2 H, m); 4.21 (OH, br s); 4.42 (1 H, s); 7.2–7.8 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3 \cdot OEt_2$ ($J[^{11}B\text{-}^{1}H]$)): –4.21 (1 H, 136); –7.69 (1 H, 150); –10.21 (2 H, 158); –11.87 (2 H, 155); –12.01 (2 H, 174); –14.89 (2 H, 157); –17.69 (1 H, unresolved). For $C_{13}H_{25}B_{11}LiNO_4$ calculated: 40.52% C, 6.49% H, 3.64% N; found: 40.49% C, 6.50% H, 3.62% N.

Lithium salt of 1-phenyl-2-(methyl N-carbonyl-L-valinatoborane)-1,2-dicarbadodecacarborate(1–), Li[1-(C_6H_5)-2-($BH_2CONH_2CH(CH(CH_3)_2)$)] (**2j**). Yellow solid, yield 0.38 g (42%). IR (KBr pellet): 3 121 (ν, CH); 2 580, 2 558 (ν, B–H terminal); 2 350 (ν, B–H); 1 739, 1 683 (ν, C=O); 1 389 (δ, CH_3); 711, 1 627, 1 479 (δ, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 188.0, 180.0 (C=O); 127.9 (Ar); 92.1, 88.9 (C_{cage}); 61.0 (NCH); 56.0 (OCH_3); 24.0 (CH); 24.1 (CH_3). ^{1}H NMR (DMSO, relative to Me_4Si): 1.1–1.4 (2 H, t); 0.88 (6 H, d); 2.08 (1 H, m); 3.69 (3 H, s); 4.21 (1 H, d); 7.3–7.7 (5 H, m). ^{11}B NMR (DMSO, relative to $BF_3 \cdot OEt_2$ ($J[^{11}B\text{-}^{1}H]$)): –4.4 (1 H, 148); –8.21 (1 H, 156); –9.18 (2 H, 157); –10.21 (2 H, 158); –15.11 (2 H, 157); –12.16 (2 H, 175); –20.21 (1 H, unresolved). For $C_{15}H_{29}B_{11}LiNO_3$ calculated: 45.11% C, 7.27% H, 3.51% N; found: 45.33% C, 7.23% H, 3.55% N.

Lithium salt of 1-phenyl-2-(methyl N-carbonyl-L-tyrosinatoborane)-1,2-dicarbadodecacarborate(1–), Li[1-(C_6H_5)-2-($BH_2CONHCH(C_6H_4OH)COOCH_3$)-1,2-$C_2B_{10}H_{10}$] (**2k**). White solid, yield 0.52 g (51%). IR (KBr pellet): 3 228 (ν, OH); 3 121 (ν, CH); 2 576, 2 545 (ν, B–H terminal); 2 358 (ν, B–H); 1 701, 1 651 (ν, C=O); 1 372 (δ, CH_3); 1 320–1 430 (δ, OH); 720, 1 637, 1 419 (ν, Ph). ^{13}C NMR (DMSO, relative to Me_4Si): 187.0, 182.0 (C=O); 131.4, 129.2 (Ar); 90.7, 89.1 (C_{cage}); 53.0 (OCH_3); 49.0 (NCH); 32.9 (CH_2Ph). ^{1}H NMR (DMSO, relative to Me_4Si): 0.9–1.3 (2 H, t); 3.77 (3 H, s); 3.01 (2 H, m); 4.98 (1 H, m); 6.8–7.4 (9 H, m); 7.8 (OH, s). ^{11}B NMR (DMSO, relative to $BF_3 \cdot OEt_2$ ($J[^{11}B\text{-}^{1}H]$)): –4.29 (1 H, 146); –7.61 (1 H, 148); –10.12 (2 H, 158); –11.81 (2 H, 154); –14.82 (2 H, 155); –12.34 (2 H, 167); –17.82 (1 H, unresolved). For $C_{19}H_{29}B_{11}LiNO_4$ calculated: 49.50% C, 6.30% H, 3.03% N; found: 49.00% C, 5.99% H, 3.07% N.

Lithium salt of 1-methyl-2-(borano)-1,2-dicarbadodecacarborate(1–), Li[1-(CH_3)-2-(BH_3)-1,2-$C_2B_{10}H_{10}$] (**2l**). Colorless solid, yield 0.40 g (61%). IR (KBr pellet): 2 941 (ν, CH); 2 583, 2 553 (ν, B–H terminal); 2 432 (ν, B–H, BH_2CN); 2 210 (ν, CN); 1 388 (δ, CH_3). ^{13}C NMR (DMSO, relative to Me_4Si): 114.8 (CN); 87.9, 87.0 (C_{cage}); 15.1 (CH_3). ^{1}H NMR (DMSO, relative to Me_4Si): 1.0–1.4 (3 H, q); 3.4 (3 H, s). ^{11}B NMR (DMSO, relative to $BF_3 \cdot OEt_2$ ($J[^{11}B\text{-}^{1}H]$)): –2.73 (1 H, 146); –7,80 (1 H, 151); –10.81 (2 H, 152); –14.02 (2 H, 164); –12.10 (2 H, 167); –12.2 (2 H, 161); –24 (1 H, unresolved). For $C_3H_{16}B_{11}Li$ calculated: 20.23% C, 8.99% H; found: 20.19% C, 8.95% H.

Lithium salt of 1-methyl-2-(carboxyborane)-1,2-dicarbadodecacarborate(1–), Li[1-(CH_3)-2-(BH_2COOH)-1,2-$C_2B_{10}H_{10}$] (**2m**). Colorless solid, yield 0.25 g (36%). IR (KBr pellet): 3 116 (ν, OH); 2 586, 2 548 (ν, B–H terminal); 2 385 (ν, B–H, BH_2COOH); 1 668 (ν, C=O). ^{13}C NMR (DMSO relative to Me_4Si): 174.6 (COOH); 87.8, 87.3 (C_{cage}); 15.3 (CH_3). ^1H NMR (DMSO, relative to Me_4Si): 1.0–1.3 (2 H, t); 3.3 (3 H, s); 9.2 (1 H, br s). ^{11}B NMR (DMSO, relative to $BF_3{\cdot}OEt_2$ ($J[^{11}B\text{-}^1H]$)): –2.33 (1 H, 146); –7.42 (1 H, 153); –10.79 (2 H, 154); –12,12 (2 H, unresolved); –12.28 (2 H, 163); –13.81 (2 H, 165); –22.4 (1 H, unresolved). For $C_4H_{16}B_{11}LiO_2$ calculated: 21.63% C, 7.21% H; found: 22.56% C, 7.06% H.

Crystal Structure Analysis of Methyl *N*-[(Trimethylamineboryl)carbonyl]-L-tyrosinate

Potentially, one of the most promising carboranyl salts is $[1\text{-Ph-2-}(BH_2CONHCH(4\text{-}CH_2C_6H_4OH)COOMe)\text{-1,2-}C_2B_{10}H_{10}]Li$ (**2k**). Its amine borane precursor, $Me_3NBH_2CONHCH(4\text{-}CH_2C_6H_4OH)COOMe$ (**3b**) has been shown to have good BNCT activity[12], and its yield is higher than that of the other carboranyl peptides (see Table I). Therefore, it is imperative that the structures of both **3b** and, if it shows promise, **2k** should be unambiguously determined. As the initial step in this characterization, the structure of **3b** was determined by single-crystal X-ray diffraction analysis.

In a procedure identical to that described elsewhere[17], compound **3b** was synthesized by coupling Me_3NBH_2COOH and the hydrochloride of the amino acid ester, $[NH_3CH(4\text{-}CH_2C_6H_4OH)COOMe]Cl$, using PPh_3, Et_3N and CCl_4. Suitable crystals were obtained by recrystallization of **3b** from a hexane–ethyl acetate (50 : 50) mixture. Several such crystals were indexed on a Siemens SMART CCD diffractometer using 40 frames with an exposure time of 20 s per frame. All of the crystals exhibited the same monoclinic cell. One crystal of good quality was used for data collection at room temperature. A total of 3 536 reflections were collected in the hemisphere of the reciprocal lattice of the monoclinic cell, of which 2 154 were unique with $R_{int} = 0.0663$. An empirical absorption correction using the program SADABS[18] was applied to all observed reflections. The structure was solved by the direct method using the SHELXS and SIR97 programs[18,19]; both programs yielded the same structure. Full-matrix least-square refinement on F^2 was carried out using the SHELXTL program[18]. The final agreement factor values are $R^1 = 0.0666$, $wR^2 = 0.1669$ ($I > 2\sigma$). The unit cell information and refinement details are reported in Table I. CCDC 181586 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

Synthesis and Characterization

A number of carboranylborane mono- and dianions were synthesized by the reaction of either $Li_2[1,2\text{-}C_2B_{10}H_{10}]$ or $Li[1\text{-}R^1\text{-1,2-}C_2B_{10}H_{11}]$ (R^1 = Ph, Me) with different amine boranes of the type Me_3NBH_2X (X = H, CN, COOH, $COOCH_3$, $CONHCH(CH_2OH)COOMe$, $CONHCH(CHMe_2)COOMe$, $CONHCH(4\text{-}CH_2C_6H_4OH)COOMe$ as shown in Scheme 1. When $Li_2[1,2\text{-}C_2B_{10}H_{10}]$ was the carborane precursor, the disubstituted products,

TABLE I
Crystal data and structure refinement for compound **3b**

Empirical formula	$C_{14}H_{23}BN_2O_4$
Formula weight	294.15
Temperature, K	173(2)
Wavelength, Å	0.71073
Crystal system	monoclinic
Space group	$P2_1$
a, Å	6.315(5)
b, Å	11.479(10)
c, Å	11.518(10)
α, °	90
β, °	94.742(18)
γ, °	90
Volume, $Å^3$	832.0(12)
Z	2
Calculated density, Mg m^{-3}	1.174
Absorption coefficient, mm^{-1}	0.084
$F(000)$	316
Crystal size, mm	0.10 × 0.06 × 0.02
θ range for data collection, °	1.77 to 23.36
Index ranges	$-7 \le h \le 7$, $-12 \le k \le 12$, $-9 \le l \le 12$
Reflections collected	3 536
Independent reflections	2 154 (R_{int} = 0.0663)
Completeness, % (to θ = 23.36°)	97.5
Absorption correction	semiempirical from equivalents
Max. and min. transmission	1.000 and 0.562692
Refinement method	full-matrix least-squuares on F^2
Data/restraints/parameters	2 154/1/214
Goodness-of-fit on F^2	0.858
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0666, wR_2 = 0.1669
R indices (all data)	R_1 = 0.1427, wR_2 = 0.2068
Absolute structure parameter	–3(3)
Extinction coefficient	0.006(8)
Largest difference peak and hole, e $Å^{-3}$	0.163 and –0.214

$Li_2[1,2\text{-}R^4\text{-}1,2\text{-}C_2B_{10}H_{10}]$ ($R^4 = BH_3$ (**2a**), BH_2CN (**2b**), BH_2COOMe (**2c**), BH_2COOH (**2d**)) were obtained in yields ranging from 70% (**2d**) to 95% (**2b**). When the carborane monoanions were reacted, the corresponding $Li[1\text{-}R^1\text{-}2\text{-}R^4\text{-}1,2\text{-}C_2B_{10}H_{10}]$ (R^1 = Ph and $R^4 = BH_3$ (**2e**), BH_2CN (**2f**), BH_2COOMe (**2g**), BH_2COOH (**2h**), $BH_2CONHCH(CH_2OH)COOMe$ (**2i**), $BH_2CONHCH(CH(CH_3)_2)COOMe$ (**2j**), $BH_2CONHCH(4\text{-}CH_2C_6H_4OH)$ (**2k**); R^1 = Me and $R^4 = BH_2CN$ (**2l**), BH_2COOH (**2m**)) were obtained in yields ranging from 36% (**2m**) to 86% (**2e**). A review of the spectroscopic and analytical data (see Experimental) shows that, for the same amine borane, the yields decrease in the order $1,2\text{-}C_2B_{10}H_{12}$ > $1\text{-Ph-}1,2\text{-}C_2B_{10}H_{11}$ > $1\text{-Me-}C_2B_{10}H_{11}$, with the former two being quite similar. Therefore, at least as measured by their yields, the dianionic products are formed as readily as the monoanionic ones. The generally lower yields obtained with the boronated derivatives, **2i**–**2k**, could be the result of steric factors. It was found that such factors were of importance in the deprotonation of $1,2\text{-}C_2B_{10}H_{12}$, where the presence of a large solvated counter-ion associated with the monoanion effectively blocked reaction at the second cage carbon[11]. However, the lowest yields were obtained in the reactions of $1\text{-Me-}C_2B_{10}H_{11}$, which is less sterically hindered than the $1\text{-Ph-}C_2B_{10}H_{11}$. Although the CH_3 group is inductively electron-releasing and C_6H_5 is electron-withdrawing[20], it is unlikely that the lower yields of the methyl-substituted monoanions is due to the decreased acidity of the C–H hydrogen in $1\text{-Me-}C_2B_{10}H_{11}$, especially when the yields of the dianions are high. The lower yields for **2l** and **2m** can be traced to loss of product during work-up. The yields reported are for the purified products and there was an unusually large loss of the methyl products on recrystallization from their hot aqueous solutions. In general, the present yields are sufficient to make the method described in Experimental a viable route to the carboranylborane anions that can be tested for use in BNCT.

The compounds were characterized by ^1H, ^{11}B and ^{13}C NMR and IR spectroscopy. The IR spectra of all the products show the expected absorptions for the carborane B–H stretching in the 2 550–2 580 cm^{-1} region, with the exopolyhedral borane bands appearing at slightly lower energies (2 238–2 433 cm^{-1}). The characteristic C–H, C=O, C≡N and O–H stretching absorption bands appear in their proper regions when these groups are present in the compounds. In the same way the ^1H, ^{11}B and ^{13}C NMR spectra show resonances that are consistent with the formulations given in Scheme 1. The ^{13}C NMR spectra all show resonances in the δ 86–92 ppm range due to the cage carbons of the carboranes, with no significant differences being noted between the di- and monoanionic compounds. These cage-carbon chemical shifts are very similar to the value of δ 86.18 ppm found for C(1) in the $[1\text{-}BH_3\text{-}1,2\text{-}C_2B_{10}H_{11}]^-$ anion[21]. The ^{11}B NMR spectra of the products (see Experimental) are also consistent with their formulations. To aid in the interpretation of the data, *ab initio* GIAO molecular orbital calculations have been carried out on selected carboranylborane compounds and the results are summarized in Table II[22]. The assignments in this table are in terms of the standard boron atom numbering system shown in Fig. 1. All of the carboranylborane anions show resonances in the δ –24 to –17 ppm region due to the exopolyhedral borons. These chemical shifts are in agree-

TABLE II
Measured and calculated ^{11}B NMR chemical shifts[a] (δ-scale, ppm) for $[1\text{-}R^1\text{-}2\text{-}R^2\text{-}C_2B_{10}H_{10}]^n$ (refs[1,2])

Compound		*n*	$\delta^{11}B$							Ref.
R^1	R^2		B(3,6)	B(4,5)	B(7,11)	B(8,10)	B(9)	B(12)	B(*exo*)	
H	H	0	–15.80	–14.67	–14.67	–10.25	–3.52	–3.52	–	21
Me	H	0	–11.22	–11.59	–13.66	–10.10	–2.73	7.71	–	21
Me	Me	0	–11.5	–10.6	–10.6	–9.7	–5.1	–5.1	–	24
BH_3	H	–1	–10.31	–9.15	–12.86	–9.15	–3.01	–7.80	–20.43	21
BH_3	H	–1	–12.14	–9.01	–14.73	–9.30	–4.05	–8.93	–23.60	[b]
			–8.83	–6.75	–12.23	–9.15	–0.69	–4.74	–17.83	[c]
CH_3	BH_3	–1	–8.57	–10.08	–9.24	–10.91	–8.88	–5.11	–26.70	[b]
			–5.29	–7.89	–7.10	–9.52	–4.81	–1.36	–19.78	[c]
CH_3	BH_2CN	–1	–8.80	–9.90	–10.35	–10.14	–7.27	–4.51	–29.33	[b]
			–5.57	–7.65	–8.15	–8.99	–3.43	–0.75	–22.28	[c]
Ph	BH_3	–1	–8.50	–10.46	–8.07	–11.39	–7.55	–2.52	–25.70	[b]
			–5.12	–7.98	–6.13	–9.82	–3.57	+1.05	–19.49	[c]
BH_3	BH_3	–2	–5.55	–8.18	–8.18	–13.05	–8.00	–8.00	–25.61	[b]
			–2.55	–6.26	–6.26	–11.12	–3.88	–3.88	–19.24	[c]
BH_2CN	BH_2CN	–2	–5.90	–9.88	–9.88	–11.87	–6.10	–6.10	–29.90	[b]
			–2.95	–7.72	–7.72	–10.29	–2.19	–2.19	–22.88	[c]

[a] Relative to $BF_3{\cdot}Et_2O$. [b] GIOA B3LYP/6-311G**//B3LYP/6-31G*. [c] GIOA RHF/6-311G**//B3LYP/6-31G*.

ment with a value of δ of –20.43 ppm reported by Plešek and co-workers, for the exopolyhedral boron in the $[1\text{-}BH_3\text{-}1,2\text{-}C_2B_{10}H_{11}]^-$ anion[21], as well as those calculated for the equivalent borons (see Table II). It is of interest to note that the exopolyhedral boron resonance for a dianion is essentially the same as found in the monoanion containing the same BH_2X group. Thus, it seems that the negative charge is essentially localized, with very little communication between the two exopolyhedral groups. Depending on the pendant groups on the cage carbons, the carborane cages possess either C_{2v} symmetry (**2a**–**2d**), which should give rise to ^{11}B NMR cage-atom resonances with peak areas ratios of 1 : 1 : 2 : 1 (2 : 2 : 4 : 2), or C_s symmetry (**2e**–**2m**) with a 1 : 1 : 2 : 2 : 2 : 2 peak area ratio pattern. Inspection of the spectral data (Experimental) reveals that this is generally the case. The two downfield resonances, in the spectra of the monoanions, one between δ –1.9 and –4.5 ppm and the other in the δ –8.2 to –7.0 ppm region, are assigned to the boron atoms opposite the two cage carbons. GIAO calculations suggest that the δ –8.2 to –7.0 ppm resonances are due to the borons antipodal to the cage carbons bonded to the exopolyhedral borane group (B(9) in Fig. 1). In general, GIAO calculations on **2e** and **2l** suggest that the order of increasing shielding in the monoanions is B(12) < B(9) < B(3,6) < B(7,11) < B(8,10) < B(4,5) < B(*exo*). Similar calculations on the dianions suggest an order of B(3,6) < B(9,12) < B(4,5,7,11) < B(8,10) < B(*exo*). Since the chemical shifts are more a function of the paramagnetic contribution of the shielding constants[25] and the peaks are quite close together, it is not possible to tell whether these orders hold for the other carboranylboranes given in Scheme 1.

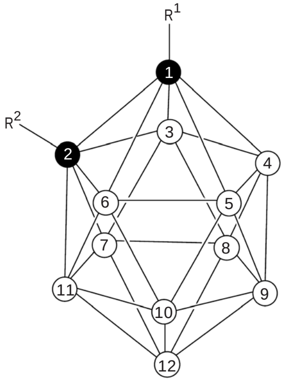


FIG. 1
Atom numbering scheme for 1,2-dicarba-*closo*-dodecaborane(12)

The selection of which carboranylborane could potentially show promise in a BNCT procedure is based in large part on the biological effectiveness of the corresponding amine borane. It is therefore important to assess any structural changes that occur in replacing the amine in the precursor with a carborane group. The most direct way to assess such changes is through a structural investigation of the starting amine boranes and their anion products. As the initial phase of such a study, we present in Fig. 2 the crystal structure of the amine borane **3b**, the precursor of **2k**. The structure shows that a Me_3N group coordinates with the BH_2 unit on the $BH_2CONHCH(4\text{-}CH_2PhOH)COOMe$ group. The synthesis of **2k** involves the replacement of the Me_3N group by a $[1\text{-}Ph\text{-}1,2\text{-}C_2B_{10}H_{10}]^-$ anion. This substitution induces a sizable upfield shift of the BH_2 borane resonance of 6–13 ppm in its ^{11}B NMR spectrum[26]. At this point, it is an open question as to the relative importance of charge and bond polarity changes in causing such spectral changes and whether such spectral changes signal a configuration change in the peptide. A comparison of the structure of **2k** with that of its precursor, shown in Fig. 2, would help in determining the importance of such spectral shifts in selecting likely candidates for further study. Structural studies of **2k** are currently under way in our laboratories.

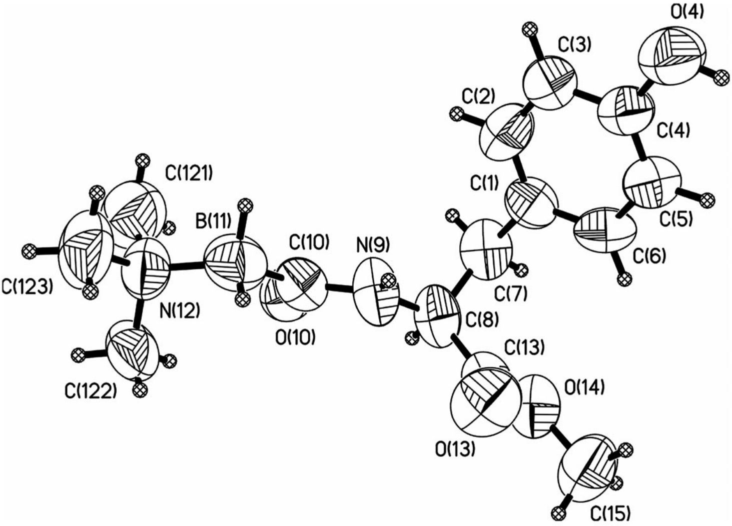


FIG. 2

Crystal structure of methyl *N*-[(trimethylamineboryl)carbonyl]-L-tyrosinate (**3b**) with the thermal ellipsoids drawn at 50% probability level

Applications to BNCT

As pointed out earlier, polyhedral boranes and carboranes are potentially attractive candidates as vehicles for delivering high B-10 concentrations to tumor cells[27,28]. The borane clusters of greatest interest are those containing 9–12 boron atoms. As discussed by Sjöberg[28], such compounds fall into three principal groups: hydrophilic (water-soluble), such as [*closo*-$B_{12}H_{12}$]$^{2-}$ anion, amphiphilic, such as the [*nido*-$C_2B_9H_{12}$]$^{1-}$ anion and the highly lipophilic (fat-soluble), of which *closo*-$C_2B_{10}H_{12}$ is an example. Of the water-soluble clusters, the high symmetry of the $[B_{12}H_{12}]^{2-}$ anion results in multiple attack sites that can give rise to mixtures of polysubstituted products, which complicates directed syntheses. While degradation of the lipophilic *ortho*-carboranes to produce negatively charged [*nido*-$C_2B_9H_{12}$]$^{1-}$ anions will increase water solubility, recent evidence indicates that such changes may increase toxicity[28]. Therefore, alternative candidates must be developed. The compounds shown in Scheme 1 are the first examples of a new class of hydrophilic or amphiphilic compounds of high boron content that might avoid some of the problems that associated with the other boron cluster compounds. It should also be noted that, while the *ortho*-carboranes were used in this report, the synthetic method shown in Scheme 1 is a general one that should work well with *meta*- and *para*-carboranes.

An alternative route to prepare peptides with high boron content by the use of mono- and difunctionalized carboxyborane derivatives is also being explored. These carboxyborane derivatives can be coupled to the amino termini of the amino acids or peptides to give a complimentary set of water-soluble proteins with high boron contents.

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