Novel, Water-Soluble Carboranyl Derivatives of Anthraquinones, Flourenones, and Sulfones: A Synthetic Investigation

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New functionalized, water-soluble, carboranyl derivatives of anthraquinones, flourenones, and sulfones are reported. Monolithiation of *o*-carborane, methyl-*o*-carborane, or phenyl-*o*-carborane and their subsequent reaction with the appropriate chloroamides (**1**, **2**, **9**, or **13**) of anthracene, flourenone, and sulfone produced 1,5(or 2,6)-bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}anthracene-9,10-dione [R = H, CH_3, C_6H_5] (**3**−**8**), 2,7-bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}-9-flourenone [R = H, CH_3, C_6H_5] (**10**−**12**), and bis{4-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]}phenyl sulfone [R = H, CH_3, C_6H_5] (**14**−**16**) in 49−78% yields as new carborane derivatives of anthraquinones, flourenones, and sulfones. The decapitation reaction of the *closo*-carborane species (**3**−**8**, **10**−**12**, **14**−**16**) with KOH in refluxing ethanol (C_2H_5OH) produced the corresponding open cage (*nido*) compounds (**3a**−**8a**, **10a**−**12a**, **14a**−**16a**) that are robust and water-soluble species, a requirement to impart lower toxicity for an effective cancer drug. All of these compounds were characterized by infrared spectroscopy, ^1H, ^{13}C, and ^{11}B NMR spectroscopy, and other physical property measurements.

Introduction

Boron neutron capture therapy (BNCT) is a potentially powerful form of radiotherapy involving the preferential incorporation of boron-10-containing compounds into tumor cells, followed by irradiation of the tumor by thermal neutrons.[1] On absorption of a neutron, the B_5^{10} atom undergoes a fission reaction to produce high linear energy transfer (LET) He_2^4 and Li_3^7 particles that are confined to a radius comparable to the dimensions of a cell. Thus, irradiation will result in the destruction of the tumor cell in which the particles are generated, with little damage to the surrounding tissue. Several requirements must be met in order for this therapy to be effective: (i) a concentration of 25−30 μg B_5^{10} atoms/g of tumor must be achieved; (ii) a tumor:normal tissue (T:N) ratio of the boron delivery agent greater than 1 is necessary; and (iii) the agent should be of low toxicity.[2] A large number of compounds have been studied as BNCT agents, e.g., nucleic acid precursors,[3] amino acids,[4] peptides,[5] phospholipids,[6] carbohydrates,[7] lipoproteins,[8] porphyrins,[9] DNA alkylators,[10] DNA intercalators,[11] DNA groove binders,[12] polyamines,[13] oligonucleotides,[14] monoclonal-bispecific antibodies,[15] and hormones.[16] There has been a special interest in the development of boron compounds that

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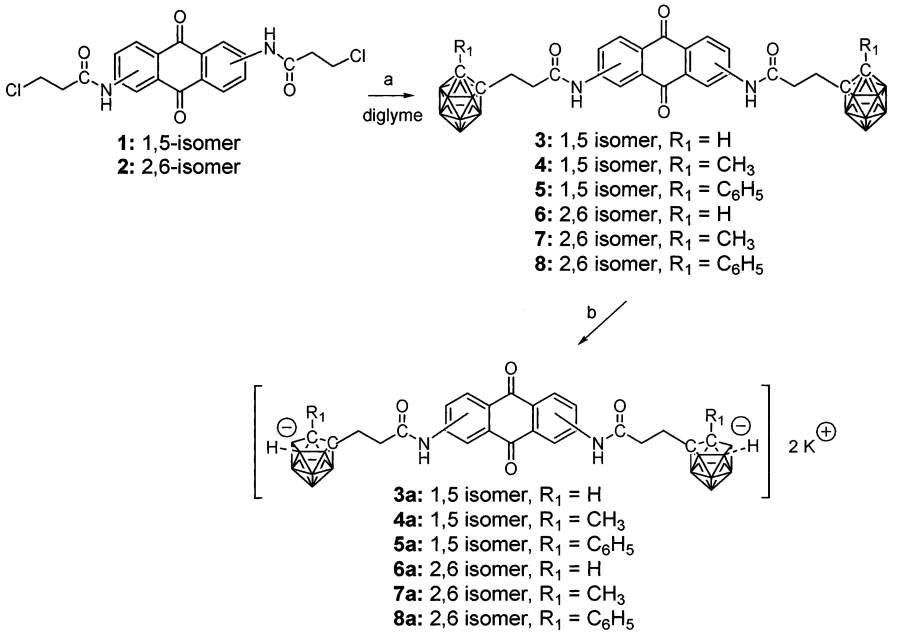
Scheme 1. Synthetic Scheme for the Preparation of 1,5(or 2,6)-Bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}anthracene-9,10-dione [R = H, CH_3, C_6H_5] and 1,5(or 2,6)-Bis{3-[8-(7-R-7,8-dicarba-*nido*-undecaboranyl)]propionamido}anthracene-9,10-dione [R = H, CH_3, C_6H_5]



a: 2 eq. 1-R-1,2-$C_2B_{10}H_{11}$[R = H, CH_3, C_6H_5] + 2 eq. *n*-BuLi in cyclohexane
b: KOH/Ethanol

Table 1. Yields and Melting Points of the Compounds in Schemes 1−3

reactants (g, mmol)	compd	products (g, mmol)	yield (%)	mp (°C)
1[a] (1.07, 2.56); Cb[b] (0.74, 5.12)	**3**	0.88, 1.39	54.3	102
1[a] (1.07, 2.56); Cb[c] (0.82, 5.12)	**4**	1.23, 1.84	72.1	115
1[a] (1.07, 2.56); Cb[d] (1.13, 5.12)	**5**	1.34, 1.69	66.3	123
2[e] (1.07, 2.56); Cb[b] (0.74, 5.12)	**6**	1.05, 1.64	64.2	100
2[e] (1.07, 2.56); Cb[c] (0.82, 5.12)	**7**	1.31, 1.97	77.1	113
2[e] (1.07, 2.56); Cb[d] (1.13, 5.12)	**8**	1.26, 1.60	62.5	121
3 (1.00, 1.57)	**3a**	1.08, 1.56	99.4	>350
4 (1.00, 1.50)	**4a**	1.06, 1.47	98.0	>350
5 (1.00, 1.27)	**5a**	1.05, 1.25	98.4	>350
6 (1.00, 1.57)	**6a**	1.07, 1.55	98.7	>350
7 (1.00, 1.50)	**7a**	1.04, 1.44	96.0	>350
8 (1.00, 1.27)	**8a**	1.07, 1.26	99.2	>350
9[f] (1.00, 2.56); Cb[b] (0.74, 5.12)	**10**	0.90, 1.48	58.0	82
9[f] (1.00, 2.56); Cb[c] (0.82, 5.12)	**11**	1.12, 1.76	68.8	89
9[f] (1.00, 2.56); Cb[d] (1.13, 5.12)	**12**	1.41, 1.85	72.1	98
10 (1.00, 1.64)	**10a**	1.08, 1.62	98.8	>350
11 (1.00, 1.57)	**11a**	1.08, 1.56	99.4	>350
12 (1.00, 1.31)	**12a**	1.04, 1.27	96.9	>350
13[g] (1.50, 5.22); Cb[b] (1.51, 10.44)	**14**	1.47, 2.91	55.8	78
13[g] (1.50, 5.22); Cb[c] (1.65, 10.44)	**15**	1.87, 3.50	67.2	82
13[g] (1.50, 5.22); Cb[d] (2.30, 10.44)	**16**	1.70, 2.58	49.4	85
14 (1.00, 1.98)	**14a**	1.08, 1.93	97.5	>350
15 (1.00, 1.87)	**15a**	1.10, 1.87	99.9	>350
16 (1.00, 1.52)	**16a**	1.06, 1.49	98.0	>350

[a] **1** = 1,5-bis(3-chloropropionamido)anthracene-9,10 dione. [b] Cb = 1,2-dicarba-*closo*-dodecaborane (**12**). [c] Cb = 1-methyl-1,2-dicarba-*closo*-dodecaborane (**12**). [d] Cb = 1-phenyl-1,2-dicarba-*closo*-dodecaborane (**12**). [e] **2** = 2,6-bis(3-chloropropionamido)anthracene-9,10 dione. [f] **9** = 2,7-bis(3-chloropropionamido)-9-flourenone. [g] **13** = 4-chlorophenyl sulfone.

could be concentrated at or near the cell's DNA, and a number of boron-containing DNA intercalators have been evaluated as potential BNCT agents.[11] Neidle and co-workers[17] have recently shown that substituted flourenones and anthraquinones act as telomerase inhibitors. Since the telomerase enzyme is a reverse transcriptase that elongates the 3′ ends of the telomerase DNA,[18] it occurred to us that the carborane-substituted flourenone, anthracene-9,10-dione, and sulfone compounds could prove to be potential precursors for DNA-interactive, BNCT drugs. In fact, the use of large cage polyhedral boranes, such as $B_{10}H_{10}^{2-}$ and $B_{12}H_{12}^{2-}$, and carboranes, such as the *o*-carborane, as efficient boron transfer agents in BNCT has been the subject of a number of studies.[19,20] Such compounds have the advantage of being able to deliver high boron

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concentrations in compact molecular forms. We have attempted to take advantage of the DNA affinity of the flourenones and anthraquinones and the high boron content of the polyhedral boron cages by synthesizing a series of structurally related anthracene-9,10-diones (**3**−**8**), flourenones (**10**−**12**), and phenyl sulfones (**14**−**16**), along with the corresponding open cage *nido* derivatives (**3a**−**8a**, **10a**−**12a**, **14a**−**16a**), as potential BNCT agents that could bind to DNA. This report is a description of the synthetic pathways used for the preparation of these compounds, along with their characterizations. If further studies on these compounds demonstrate promise as tumor-targeting agents, the particular compounds will further be screened and extensive toxicological studies will be performed.

Experimental Section

Materials. 1,2-Dicarba-*closo*-dodecaborane (12) and 1-methyl- or phenyl-1,2-dicarba-*closo*-dodecaborane (12) were purchased from KATCHEM, Ltd., Czech Republic, and sublimed before use. Dimethoxyethane (DME) was distilled using sodium and benzophenone, while *n*-BuLi (2.0 M solution in cyclohexane, Aldrich) and 4-chlorophenyl sulfone (**13**) (Aldrich) were used as received. All other solvents and reagents were either degassed or saturated with argon until used.

Table 2. Analytical Data for the Compounds

compd	formula	analysis
3	$C_{24}H_{38}B_{20}N_2O_4$	theoretical C: 45.14; H: 5.96; N: 4.39 found C: 45.64; H: 5.83; N: 4.40
4	$C_{26}H_{42}B_{20}N_2O_4$	theoretical C: 46.85; H: 6.30; N: 4.20 found C: 46.99; H: 6.35; N: 4.22
5	$C_{36}H_{46}B_{20}N_2O_4$	theoretical C: 54.68; H: 5.82; N: 3.54 found C: 54.72; H: 5.85; N: 3.59
6	$C_{24}H_{38}B_{20}N_2O_4$	theoretical C: 45.14; H: 5.96; N: 4.39 found C: 45.55; H: 6.03; N: 4.48
7	$C_{26}H_{42}B_{20}N_2O_4$	theoretical C: 46.85; H: 6.30; N: 4.20 found C: 46.98; H: 6.32; N: 4.55
8	$C_{36}H_{46}B_{20}N_2O_4$	theoretical C: 54.68; H: 5.82; N: 3.54 found C: 54.87; H: 5.93; N: 3.62
3a	$C_{24}H_{38}B_{18}N_2O_4K_2$	theoretical C: 41.50; H: 5.48; N: 4.03 found C: 42.01; H: 5.66; N: 4.07
4a	$C_{26}H_{42}B_{18}N_2O_4K_2$	theoretical C: 43.21; H: 5.82; N: 3.88 found C: 43.28; H: 5.76; N: 3.77
5a	$C_{36}H_{46}B_{18}N_2O_4K_2$	theoretical C: 51.06; H: 5.44; N: 3.31 found C: 50.95; H: 5.46; N: 3.49
6a	$C_{24}H_{38}B_{18}N_2O_4K_2$	theoretical C: 41.50; H: 5.48; N: 4.03 found C: 42.12; H: 5.53; N: 4.19
7a	$C_{26}H_{42}B_{18}N_2O_4K_2$	theoretical C: 43.21; H: 5.82; N: 3.88 found C: 43.39; H: 5.61; N: 3.84
8a	$C_{36}H_{46}B_{18}N_2O_4K_2$	theoretical C: 51.06; H: 5.44; N: 3.31 found C: 51.19; H: 5.44; N: 3.51
10	$C_{23}H_{38}B_{20}N_2O_3$	theoretical C: 45.20; H: 6.23; N: 4.50 found C: 45.23; H: 5.97; N: 4.55
11	$C_{25}H_{42}B_{20}N_2O_3$	theoretical C: 47.02; H: 6.58; N: 4.39 found C: 47.56; H: 6.60; N: 4.44
12	$C_{35}H_{46}B_{20}N_2O_3$	theoretical C: 55.11; H: 6.04; N: 3.67 found C: 55.19; H: 5.92; N: 3.77
10a	$C_{23}H_{38}B_{18}N_2O_3K_2$	theoretical C: 41.44; H: 5.70; N: 4.20 found C: 41.48; H: 5.74; N: 4.21
11a	$C_{25}H_{42}B_{18}N_2O_3K_2$	theoretical C: 43.23; H: 6.05; N: 4.03 found C: 43.26; H: 6.04; N: 4.11
12a	$C_{35}H_{46}B_{18}N_2O_3K_2$	theoretical C: 51.34; H: 5.62; N: 3.42 found C: 51.39; H: 5.64; N: 3.44
14	$C_{16}H_{30}B_{20}SO_2$	theoretical C: 37.90; H: 59.21 found C: 37.99; H: 59.23
15	$C_{18}H_{34}B_{20}SO_2$	theoretical C: 40.46; H: 63.72 found C: 40.60; H: 63.88
16	$C_{28}H_{38}B_{20}SO_2$	theoretical C: 51.00; H: 57.88 found C: 51.09; H: 57.85
14a	$C_{16}H_{30}B_{18}SO_2K_2$	theoretical C: 34.22; H: 53.30 found C: 34.32; H: 53.41
15a	$C_{18}H_{34}B_{18}SO_2K_2$	theoretical C: 36.66; H: 57.71 found C: 36.70; H: 57.88
16a	$C_{28}H_{38}B_{18}SO_2K_2$	theoretical C: 47.02; H: 53.20 found C: 47.42; H: 53.55

Spectroscopic and Analytical Procedures. Proton, boron-11, and carbon-13 pulse Fourier transform NMR spectra were recorded on a Varian multinuclear NMR spectrometer at 200, 64.2, and 50.3 MHz, respectively. Infrared spectra were recorded using a Nicolet Magna 550 FT-IR spectrophotometer equipped with OMNIC software. Solid samples were prepared as KBr pellets. Elemental analyses were obtained using an in-house Perkin-Elmer 2400 CHN elemental analyzer. Melting points were measured on a Meltemp apparatus and are uncorrected.

Synthetic Procedures. All experiments were carried out in a Pyrex glass round-bottom two-necked flask of 250 mL capacity, containing a magnetic stirring bar and nitrogen inlet. All known compounds were identified by comparing their IR and/or NMR spectra with those of authentic samples. 1,5-Bis-(3-chloropropionamido)anthracene-9,10-dione (**1**), 2,6-bis(3-chloropropionamido)anthracene-9,10-dione (**2**), and 2,7-bis(3-chloropropionamido)-9-flourenone (**9**) were prepared using the literature methods.[17,18]

Preparation of 1,5(or 2,6)-Bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}anthracene-9,10-dione [R = H, CH_3, C_6H_5]. The general methods,

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Table 3. ^{1}H NMR Spectral Data[a]

compd	δ, ppm
3	0.60−1.48 (br, B−H), 2.82 (4H, t, CH_2), 3.65 (2H, s, CH), 3.41 (4H, t, CH_2), 7.76, 8.03, 9.10 (6H, d, aromatic)
4	0.50−1.42 (br, B−H), 2.84 (4H, t, CH_2), 1.00 (6H, s, CH_3), 3.36 (4H, t, CH_2), 7.73, 8.46, 8.92 (6H, d, aromatic)
5	0.60−1.42 (br, B−H), 2.83 (4H, t, CH_2), 3.26 (4H, t, CH_2), 7.98, 8.35, 8.79 (6H, d, aromatic), 8.80−9.01 (10H, m, phenyl)
6	0.50−1.52 (br, B−H), 2.81 (4H, t, CH_2), 3.67 (2H, s, CH), 3.38 (4H, t, CH_2), 8.05, 8.21, 8.48 (6H, d, aromatic)
7	0.40−1.5 (br, B−H), 2.90 (4H, t, CH_2), 1.02 (6H, s, CH_3), 3.40 (4H, t, CH_2), 7.98, 8.19, 8.44 (6H, d, aromatic)
8	0.50−1.20 (br, B−H), 2.85 (4H, t, CH_2), 3.30 (4H, t, CH_2), 8.02, 8.18, 8.51 (6H, d, aromatic), 8.50−8.90 (10H, m, phenyl)
3a	−2.28 (br, B−H−B), 2.76 (4H, t, CH_2), 3.48 (4H, t, CH_2), 3.63 (2H, s, CH), 7.82, 8.54, 8.82 (6H, d, aromatic)
4a	−2.21 (br, B−H−B), 2.58 (4H, t, CH_2), 1.19 (6H, s, CH_3), 3.50 (4H, t, CH_2), 7.62, 8.42, 8.82 (6H, d, aromatic)
5a	−1.96 (br, B−H−B), 2.82 (4H, t, CH_2), 3.32 (4H, t, CH_2), 7.62, 8.52, 8.92 (6H, d, aromatic), 8.60−9.10 (10H, m, phenyl)
6a	−2.21 (br, B−H−B), 2.60 (4H, t, CH_2), 3.41 (4H, t, CH_2), 3.62 (2H, s, CH), 8.06, 8.24, 8.41 (6H, d, aromatic)
7a	−2.18 (br, B−H−B), 2.62 (4H, t, CH_2), 1.12 (6H, s, CH_3), 3.52 (4H, t, CH_2), 7.82, 8.16, 8.39 (6H, d, aromatic)
8a	−1.98 (br, B−H−B), 2.80 (4H, t, CH_2), 3.35 (4H, t, CH_2), 7.95, 8.22, 8.53 (6H, d, aromatic), 8.50−8.82 (10H, m, phenyl)
10	0.50−1.30 (br, B−H), 2.80 (4H, t, CH_2), 3.38 (4H, t, CH_2), 3.62 (2H, s, CH) 7.62, 7.70, 7.92 (6H, d, aromatic)
11	0.50−1.35 (br, B−H), 2.82 (4H, t, CH_2), 3.37 (4H, t, CH_2), 1.03 (6H, s, CH_3) 7.68, 7.72, 7.94 (6H, d, aromatic)
12	0.60−1.40 (br, B−H), 2.79 (4H, t, CH_2), 3.24 (4H, t, CH_2), 7.69, 7.81, 7.95 (6H, d, aromatic), 8.40−8.70 (10H, m, phenyl)
10a	−2.18 (br, B−H−B), 2.74 (4H, t, CH_2), 3.44 (4H, t, CH_2), 3.65 (2H, s, CH), 7.70, 7.85, 7.98 (6H, d, aromatic)
11a	−2.24 (br, B−H−B), 2.56 (4H, t, CH_2), 1.18 (6H, s, CH_3), 3.48 (4H, t, CH_2), 7.68, 7.84, 7.96 (6H, d, aromatic)
12a	−1.98 (br, B−H−B), 2.81 (4H, t, CH_2), 3.35 (4H, t, CH_2), 7.64, 7.81, 8.02 (6H, d, aromatic), 8.10−8.78 (10H, m, phenyl)
14	0.50−1.50 (br, B−H), 3.68 (2H, s, CH), 7.50, 7.82, 7.93 (8H, d, aromatic)
15	0.48−1.43 (br, B−H), 1.12 (6H, s, CH_3), 7.48, 7.79, 7.99 (8H, d, aromatic)
16	0.50−1.50 (br, B−H), 7.50, 7.84, 7.98 (8H, d, aromatic) 8.05−8.40 (10H, d, phenyl)
14a	−2.41 (br, B−H−B), 7.56, 7.85, 7.96 (8H, d, aromatic)
15a	−2.52 (br, B−H−B), 7.46, 7.83, 7.92 (8H, d, aromatic)
16a	−2.21 (br, B−H−B), 7.43, 7.86, 7.98 (8H, d, aromatic)

[a] Solvent is DMSO-d_6.

solvents, and reaction times used for the preparation of **3**−**8** were the same and are outlined in Scheme 1. Therefore, only a general synthetic procedure will be described. In the preparation of compounds **3**, **4**, and **5**, a 1:1 molar reactant ratio was obtained by adding a measured volume of 2.00 M *n*-BuLi (in cyclohexane) to a solution of 1-R-1,2-$C_2B_{10}H_{11}$ [R = H, CH_3, C_6H_5] dissolved in dimethoxyethane (DME) solvent at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then was allowed to warm to room temperature and stirred at that temperature for an additional 30 min. At this point, the appropriate amount of the particular chloroamide (**1** or **2**), dissolved in DME, was added into the reaction flask with a pipet to give a 0.5:1 molar ratio of amide to carborane. After complete addition, the reaction mixture was stirred for 3 days at room temperature. The solution was then evaporated to dryness, and 25 mL of distilled water was added to the resulting residue. The solution was stirred at room temperature for 5 h, resulting in the formation of a precipitate that was filtered off. The collected solid was washed with 10 mL of pentane and 10 mL of hexane, air-dried, and then recrystallized in DMF/methanol (9:1). Subsequent analysis on the crystalline sample showed it to be *x*,*y*-bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}anthracene-9,10-dione [x = 1, y = 5, R = H (**3**), CH_3 (**4**), C_6H_5 (**5**); x = 2, y = 6, R = H (**6**), CH_3 (**7**), C_6H_5 (**8**)]. The quantitative information on the reactants and the products including the yields and melting points is listed in Table 1, and analytical data are shown in Table 2. The compounds were characterized by their ^{1}H (Table 3), ^{11}B (Table 4), and ^{13}C (Table 5) NMR spectra, as well as by infrared spectroscopy (Table 6).

Preparation of 1,5(or 2,6)-Bis{3-[8-(7-R-7,8-dicarba-*nido*-undecaboranyl)]propionamido}anthracene-9,10-dione [R = H, CH_3, C_6H_5]. The conversions of the *closo*-carborane compounds, **3**−**8**, to their corresponding *nido* products, **3a**−**8a**, were accomplished using similar reaction times and conditions. Therefore, only a general procedure will be described. Excess powdered KOH was added to a one-necked round-bottom flask of 250 mL capacity. Argon was allowed to flow into the system for about 10 min, after which 95% ethanol was added, and the mixture was stirred for 20 min until the KOH dissolved. The particular *closo*-carboranyl compound (**3**−**8**) was then added, causing the solution to turn reddish brown in color. The resulting solution was stirred for 6 h and refluxed for an additional 12 h. At this point, the solution was cooled to room temperature and then CO_2 gas was bubbled into the solution for 30 min until the formation of white precipitate ceased. The precipitate was removed by filtration, the solvent from the filtrate was then removed under reduced pressure, and the resulting solid residue obtained was recrystallized in 50% ethanol solution to isolate the corresponding *nido*-carborane dianions {*x*,*y*-bis{3-[8-(7-R-7,8-dicarba-*nido*-undecaboranyl)]propionamido}anthracene-9,10-dione}$^{2-}$ [x = 1, y = 5, R = H (**3a**), CH_3 (**4a**), C_6H_5 (**5a**); x = 2, y = 6, R = H (**6a**), CH_3 (**7a**), C_6H_5 (**8a**)] as their potassium salts. The yields were all quantitative, based on the starting *closo*-carborane (**3**−**8**) (see Table 1); analytical data are given in Table 2. As

Table 4. ^{11}B NMR Spectral Data[a,b]

compd	δ, ppm (J[^{11}B−^{1}H], Hz)[c]
3	−7.38 (B, 130.3), −9.41 (B, 134.82), −11.51 (2B, 141.24), −13.71 (2B, unresolved), −15.89 (4B, unresolved)
4	−7.71 (B, 135.4), −9.82 (B, 142.5), −12.04 (2B, 146.3), −14.32 (2B, unresolved), −16.01 (4B, unresolved)
5	−7.21 (B, 130.9), −9.25 (B, 134.1), −11.34 (2B, 141.24), −13.54 (2B, unresolved), −15.77 (4B, unresolved)
6	−7.31 (B, 130.2), −9.34 (B, 134.8), −11.44 (2B, 138), −13.45 (2B, unresolved), −15.82 (4B, not found)
7	−7.01 (B, 139.3), −9.78 (B, 137.3), −11.92 (2B, 147), −14.21 (2B, unresolved), −15.80 (4B, unresolved)
8	−7.11 (B, 128.4), −9.11 (B, 139.3), −11.28 (2B, 148.3), −13.51 (2B, not found), −15.91 (4B, unresolved)
3a	−7.01 (B, 71.2), −8.12 (B, 78.3), −9.34 (B, 156.6), −11.78 (2B, 141.8), −13.99 (B, 122.6), −15.90 (B, unresolved), −32.40 (B, 123.2), −34.32 (B, 141.8)
4a	−7.21 (2B, 77.04), −8.41 (B), −12.90 (B), −15.21 (3B, 121.3), −35.30 (B, 141.2), −37.50 (B, 146.9)
5a	−6.89 (2B, 84.7), −8.21 (B), −12.39 (B), −14.58 (3B, 114), −31.80 (B, 141.2), −34.00 (B, 145.9)
6a	−7.06 (B, 77.6), −8.27 (B, 78.9), −9.50 (B, 157.9), −11.96 (2B, 143.8), −14.20 (B, 129), −16.21 (B, unresolved), −31.90 (B, 121.9), −33.8 (B, 140)
7a	−7.16 (2B, 83), −8.46 (B), −13.10 (B), −15.40 (3B, 120), −35.10 (B, 141.2), −37.30 (B, 143.2)
8a	−6.81 (2B, 86.7), −8.16 (B), −12.36 (B), −14.62 (3B, 115), −33.00 (B, 141.2), −35.20 (B, 143.1)
10	−9.10 (B, 139.6), −11.28 (B, 141.3), −13.48 (2B, 146.3), −15.82 (2B, unresolved), −18.01 (4B, unresolved)
11	−10.70 (B, 136.4), −12.98 (B, 140.2), −15.01 (2B, 145.3), −17.40 (2B unresolved), −19.50 (4B, unresolved)
12	−8.60 (2B, 135), −11.21 (2B, 140.0), −13.54 (2B, 149), −16.10 (2B, unresolved), −18.21 (2B, unresolved)
10a	−8.68 (B, 77.04), −9.88 (B, 84.1), −11.19 (B, 159.8), −13.68 (2B, 138.7), −15.84 (B, 132.3), −17.90 (B, unresolved), −33.70 (B, 139.3), −35.87 (B, 148.4)
11a	−9.82 (2B, 74.4), −10.95 (B), −15.45 (B), −18.02 (3B, 128.4), −34.20 (B, 147.7), −36.50 (B, 151.4)
12a	−8.42 (2B, 87.9), −9.79 (B), −13.98 (B), −16.24 (3B, 121), −32.80 (B, 138.7), −34.96 (B, 148.4)
14	−5.80 (B, 147.6), −8.10 (B, 154), −10.50 (2B, 147.5), −12.80 (2B, 160.5), −15.60 (4B, unresolved)
15	−6.20 (B, 154), −8.60 (B, 145.1), −10.80 (2B, 147), −13.10 (2B, 166.9), −15.80 (4B, unresolved)
16	−5.10 (B, 141.2), −7.30 (B, 136.1), −9.42 (2B, 146.3), −11.70 (2B, 154.1), −14.10 (4B, unresolved)
14a	−4.90 (B, 121.9), −6.80 (B, 128.4), −8.80 (B, 154), −11.20 (2B, 122), −13.10 (B, 141.2), −15.30 (B, unresolved), −34.10 (B, 147.6), −36.40 (B, 151)
15a	−5.90 (2B, 121.9), −7.80 (B), −10.30 (B), −13.50 (3B, 126.4), −33.90 (B, 147.6), −36.20 (B, 152.4)
16a	−4.80 (2B, 128.4), −6.80 (B), −8.30 (B), −11.23 (3B, 125), −32.60 (B, 147.6), −34.80 (B, 142)

[a] Relative to $BF_3{\cdot}Et_2O$. [b] Solvent is DMSO-d_6. [c] Relative intensities in parentheses.

was their *closo* precursors, the *nido* compounds were characterized by their ^{1}H (Table 3), ^{11}B (Table 4), and ^{13}C (Table 5) NMR spectra, as well as by infrared spectroscopy (Table 6).

Preparation of 2,7-Bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}-9-flourenone [R = H (10), CH_3 (11), C_6H_5 (12)] and Their Conversion to Their *nido* Derivatives (10a−12a). The preparation of compounds **10**, **11**, and **12** was accomplished by the reaction of 2,7-bis(3-chloropropionamido)-9 flourenone (**9**) with the *closo*-carboranes 1-R-1,2-$C_2B_{10}H_{11}$ [R = H, CH_3, C_6H_5] in a 1:2 molar ratio of flourenone to carborane, using the same general procedures, solvents, and reaction time as described above in the preparation of compounds **3**−**8**. The quantitative information of the reactants and the products including the yields and melting points is given in Table 1 and their analytical data are shown in Table 2. The conversion of **10**−**12** to their corresponding *nido*-carborane anions, **10a**−**12a**, followed the same procedure described earlier in the preparation of **3a**−**8a** and need not be repeated here. Analytical and spectroscopic data for **10a**−**12a** are listed in Tables 2−6.

Preparation of 4-Bis{4-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]}phenyl Sulfone [R = H(14), CH_3(15), C_6H_5(16)] and Conversion to Their Corresponding *nido*-Carborane Dianions (14a−16a). As shown in Scheme 3, the preparation of the 4-bis{4-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]}phenyl sulfone [R = H (**14**), CH_3 (**15**), C_6H_5 (**16**)] was accomplished by the reaction of 4-chlorophenyl sulfone (**13**) with 1-R-1,2-$C_2B_{10}H_{11}$ [R = H, CH_3, C_6H_5] in a 1:2 molar ratio of sulfone to carborane, using the same reaction conditions, times, and solvents as used in the preparation of **3**−**8** (see Table 1 for the quantitative information on the reactants and the products including the yields and melting points). The potassium salts of their corresponding *nido*-carborane dianions, K_2{4-bis([8-(7-R-7,8-dicarba-*nido*-undecaboranyl)]phenyl sulfone} [R = H (**14a**), CH_3 (**15a**), C_6H_5 (**16a**)] were prepared by the reaction of the corresponding *closo*-carborane precursors, **14**−**16**, with ethanolic KOH using the same reaction conditions and procedures described above for the preparation of **3a**−**8a**. Analytical and spectroscopic data for the carborane-sulfone derivatives are given in Tables 2−6.

Results and Discussion

The carboranyl-substituted anthraquinones (**3**−**8**), flourenones (**10**−**12**), and sulfones (**14**−**16**) were produced in moderate yields (49 to 77%) from the reaction

Table 5. ^{13}C NMR Data for the Compounds[a]

compd	δ, ppm
3	22.30, 30.00 (CH_2), 167.90, 172.00 (C═O), 128.20 (aromatic), 71.80 (carborane C, carboranyl CH not observed)
4	20.00 (CH_3), 25.00, 33.50 (CH_2), 167.20, 170.60 (C═O), 127.20−128.50 (aromatic), 70.80, 61.90 (carborane C)
5	23.30, 31.70 (CH_2), 168.50, 175.00 (C═O), 127.00−129.50 (aromatic), 70.50, 61.20 (carborane C)
6	22.50, 30.40 (CH_2), 168.40, 171.90 (C═O), 127.50−129.00 (aromatic), 72.40 (carborane C, carboranyl CH not observed)
7	18.00 (CH_3), 23.00, 31.60 (CH_2), 168.50, 172.40 (C═O), 127.00−129.50 (aromatic), 71.10, 61.30 (carborane C)
8	24.00, 32.50 (CH_2), 168.20, 171.50 (C═O), 128.00−130.00 (aromatic), 69.40, 58.50 (carborane C)
3a	21.60, 32.10 (CH_2), 169.20, 171.60 (C═O), 128.00−129.30 (aromatic), 59.20 (carborane C, carboranyl CH not observed)
4a	24.00, 33.10 (CH_2), 20.50 (CH_3), 168.20, 176.00 (C═O), 127.10−129.00 (aromatic), 60.50, 58.20 (carborane C)
5a	23.60, 31.80 (CH_2), 167.40, 171.00 (C═O), 128.00−129.60 (aromatic), 60.60, 59.80 (carborane C)
6a	22.20, 30.80 (CH_2), 168.00, 173.10 (C═O), 127.30−129.00 (aromatic), 60.10 (carborane C, carboranyl CH not observed)
7a	23.00, 30.20 (CH_2), 22.00 (CH_3), 167.80, 175.40 (C═O), 127.50−129.50 (aromatic), 62.40, 56.40 (carborane C)
8a	25.00, 33.10 (CH_2), 167.90, 170.20 (C═O), 127.60−129.00 (aromatic), 61.20, 56.30 (carborane C)
10	23.10, 31.60 (CH_2), 167.50, 172.40 (C═O), 127.30−129.20 (aromatic), 70.60, (carborane C, carboranyl CH not observed)
11	22.00 (CH_3), 24.20, 32.80 (CH_2), 168.20, 175.30 (C═O), 128.00−129.40 (aromatic), 73.20, 60.40 (carborane C)
12	25.00, 31.60 (CH_2), 167.10, 173.30 (C═O), 128.00−131.00 (aromatic), 70.10, 62.40 (carborane C)
10a	21.60, 29.60 (CH_2), 167.90, 172.30 (C═O), 127.80−129.50 (aromatic), 60.10 (carborane C, carboranyl CH not observed)
11a	20.80, 32.10 (CH_2), 24.00 (CH_3), 166.10, 174.80 (C═O), 128.00−129.00 (aromatic), 61.20, 59.60 (carborane C)
12a	23.20, 34.20 (CH_2), 168.20, 171.40 (C═O), 128.00−129.10 (aromatic), 61.30, 58.40 (carborane C)
14	127.20−128.50 (aromatic), 71.40 (carborane C, carboranyl CH not observed)
15	127.50−129.00 (aromatic), 73.20, 61.40 (carborane C)
16	127.90−129.20 (aromatic), 72.60, 60.80 (carborane C)
14a	128.00−129.50 (aromatic), 59.80 (carborane C, carboranyl CH not observed)
15a	127.10−129.20 (aromatic), 62.00, 58.60 (carborane C), 28.00 (CH_3)
16a	127.90−129.80 (aromatic), 62.40, 60.10 (carborane C)

[a] Solvent is DMSO-d_6.

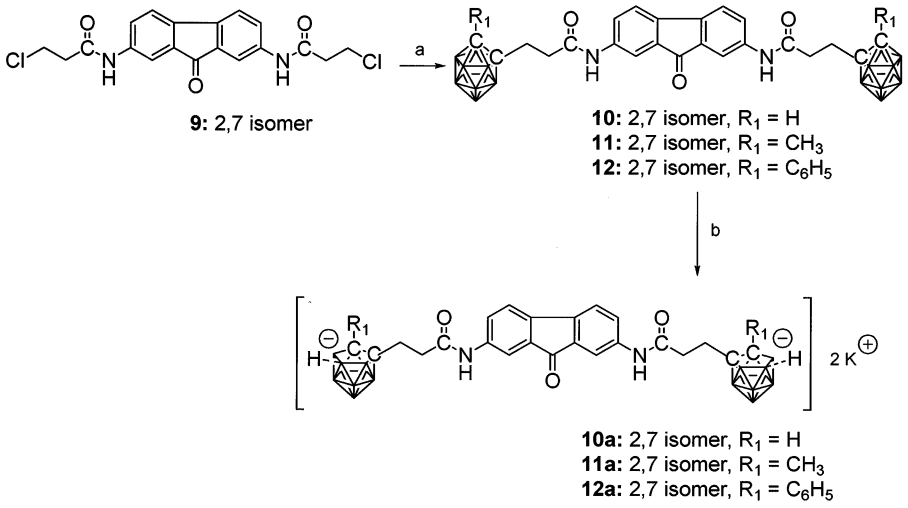
Table 6. Infrared Absorption Data

compd	δ, ppm
3	1521, 1681 (ν, C═O), 2583 (ν, B−H)
4	1519, 1681 (ν, C═O), 2580 (ν, B−H), 1339 (ν, CH_3)
5	1522, 1684 (ν, C═O), 2574 (ν, B−H)
6	1524, 1683 (ν, C═O), 2581 (ν, B−H)
7	1523, 1689 (ν, C═O), 2585 (ν, B−H), 1343 (ν, CH_3)
8	1521, 1685 (ν, C═O), 2579 (ν, B−H)
3a	1524, 1690 (ν, C═O), 2517 (ν, B−H)
4a	1521, 1676 ν, C═O), 2519 (ν, B−H), 1337 (ν, CH_3)
5a	1523, 1678 (ν, C═O), 2516 (ν, B−H)
6a	1526, 1684 (ν, C═O), 2512 (ν, B−H)
7a	1518, 1672 (ν, C═O), 2517 (ν, B−H), 1338 (ν, CH_3)
8a	1520, 1682 (ν, C═O), 2510 (ν, B−H)
10	1520, 1675 (ν, C═O), 2576 (ν, B−H)
11	1528, 1676 (ν, C═O), 2590 (ν, B−H), 1335 (ν, CH_3)
12	1526, 1679 (ν, C═O), 2572 (ν, B−H)
10a	1521, 1679 (ν, C═O), 2509 (ν, B−H)
11a	1516, 1680 (ν, C═O), 2512 (ν, B−H), 1340 (ν, CH_3)
12a	1524, 1689 (ν, C═O), 2520 (ν, B−H)
14	2576 (ν, B−H)
15	2583 (ν, B−H), 1331 (ν, CH_3)
16	2572 (ν, B−H)
14a	2510 (ν, B−H)
15a	2516 (ν, B−H), 1346 (ν, CH_3)
16a	2522 (ν, B−H)

of the monolithiated [1-(R)-$C_2B_{10}H_{10}$]$^-$ anion (R = H, CH_3, C_6H_5) and the particular bis(3-chloropropionamido) reagents, **1**, **2**, **9**, or **13**, in a 2:1 molar ratio of the reactants. Lithiation of the carborane was carried out in dimethoxyethane (DME), as described elsewhere.[21,22] Use of the DME solvent is especially critical in the reaction of the *o*-carboranes since the presence of the bulky Li(DME) group effectively blocks lithiation at the neighboring cage carbon. For the 1-CH_3- and 1-C_6H_5-substituted carboranes, diethyl ether would have sufficed. Even with the use of DME, the percent yields of the *o*-carboranyl derivatives are generally lower than those obtained from the phenyl- and methyl-substituted ones. It was found that, in the presence of DME, dihalides, such as $Br(CH_2)_3Br$, favored the formation of dilithiated intermediates even when a 1:1 molar ratio of *o*-carborane to *n*-BuLi was used.[21] It was speculated that the formation of stable cyclic compounds overcomes the blocking ability of the Li(DME) unit. In the reactions shown in Schemes 1−3, the anthraquinone (**1**, **2**), flourenone (**9**), and sulfone (**13**) reagents were all dihalides and the lower yields for the *o*-carborane precursors could be due in part to a competing reaction favoring the formation of cyclic products. It should be pointed out that no independent evidence can be found

(21) Viñas, C.; Benakki, R.; Teixidor, F.; Casabo, J. *Inorg. Chem.* **1995**, *34*, 3844.
(22) Teixidor, F.; Viñas, C.; Benakki, R.; Kivekäs, R.; Sillampää, R. *Inorg. Chem.* **1997**, *36*, 1719.

Scheme 2. Synthetic Scheme for the Preparation of 2,7-Bis{3-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]propionamido}-9-flourenone [R = H, CH_3, C_6H_5] and Their Corresponding *nido* Derivatives



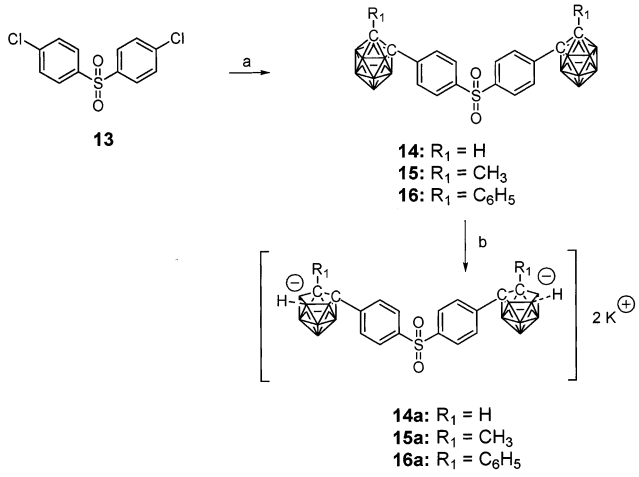
9: 2,7 isomer

10: 2,7 isomer, R_1 = H
11: 2,7 isomer, R_1 = CH_3
12: 2,7 isomer, R_1 = C_6H_5

10a: 2,7 isomer, R_1 = H
11a: 2,7 isomer, R_1 = CH_3
12a: 2,7 isomer, R_1 = C_6H_5

a: 2 eq. 1-R-1,2-$C_2B_{10}H_{11}$[R = H, CH_3, C_6H_5] + 2 eq. *n*-BuLi in cyclohexane
b: KOH/Ethanol

Scheme 3. Synthetic Scheme for the Preparation of 4-Bis{4-[2-(1-R-1,2-dicarba-*closo*-dodecaboranyl)]}phenyl Sulfone [R = H, CH_3, C_6H_5] and Their *nido* Derivatives



13

14: R_1 = H
15: R_1 = CH_3
16: R_1 = C_6H_5

14a: R_1 = H
15a: R_1 = CH_3
16a: R_1 = C_6H_5

a: 2 eq. 1-R-1,2-$C_2B_{10}H_{11}$[R = H, CH_3, C_6H_5] + 2 eq. *n*-BuLi in cyclohexane
b: KOH/Ethanol

for the presence of such cyclic compounds in the final reaction mixtures. In addition, the number of intervening atoms between the halides would argue against the formation of such cyclic product. Nonetheless, the possibility of the formation of such compounds cannot be ruled out completely. The initial production of the lithium salt of the 1-R-$C_2B_{10}H_{10}$ (R = H, Me, Ph) anion was done at −78 °C, followed by room-temperature addition of the halogenated species. Since it has been observed that high temperature lowers the yield and produces several side products, the two-stage temperature change during the reaction was found to overcome these problems.

Since one of the major requirements for an effective BNCT drug is water solubility, the *closo*-carborane species were converted to anionic, water-soluble *nido* derivatives by the decapitation reaction in ethanolic KOH. The yields in these reactions were essentially quantitative in all cases, indicating that the presence of the large organic moieties on the carboranes do not inhibit their tendency to undergo controlled hydrolysis.

All of the *closo*-carborane derivatives (**3**−**8**, **10**−**12**, and **14**−**16**) were characterized by IR and NMR spectroscopic techniques, melting points, and elemental analyses (see Tables 2−6). The melting points of the *closo*-carborane species, listed in Table 1, show a consistent increase with increased substitution on the carborane unit. In the case of the anthraquinone derivatives (**3**−**8**), the spectral and physical characterization parameters of the 1,5- and 2,6-isomers are essentially the same. The differentiation between the 1,5- and 2,6-isomers of the products is based on the knowledge of the structures of the precursors, **1** and **2**, coupled with the assumption that isomerization does not occur during the course of the reactions. Given the nature of the reactions outlined in Scheme 1, that is a fairly safe assumption. The ^{1}H, ^{13}C, and ^{11}B NMR spectra show peaks consistent with the formulations given in Schemes 1−3 but offer no unique insights into their structures. However, they do confirm the bonding between the carborane and bis(3-chloropropionamido) compounds. The ^{1}H NMR spectra of the products show peaks in the range 0.4−1.5 ppm for the B−H's (Table 3), the ^{11}B NMR spectra, given in Table 4, are consistent with the presence of *closo*-C_2B_{10} cages, and the ^{13}C NMR spectra show resonances for both the carborane cage as well as other peaks as expected from the compounds (Table 5). In addition, the IR spectra showed the typical ν(B−H) absorption at frequencies above 2550 cm^{-1}, characteristic of *closo*-1-R-2-R′-1,2-$C_2B_{10}H_{10}$ derivatives (Table 6).

The spectral and analytical data also confirm that the reactions of the *closo*-carborane derivatives **3**−**8**, **10**−**12**, and **14**−**16** with KOH removed a BH vertex adjacent to the cage carbons with the addition of a

bridge hydrogen to form the corresponding *nido* species, **3a**−**8a**, **10a**−**12a**, and **14a**−**16a**. The ^{1}H NMR spectra of the open cage compounds showed peaks in the range −1.9 and −2.3 ppm, which can be assigned to B−H−B hydrogen (see Table 3). Strong absorption due to B−H bonds near 2520 cm^{-1} that are consistent with the *nido* species (see Table 6) were observed in the IR spectrum.[23] An inspection of Table 4 shows that one of the most apparent changes in the ^{11}B NMR spectra on going from the *closo*-carborane species **3**−**8** and **14**−**16** to their respective *nido* products is the appearance of two upfield resonances in the $\delta = -31$ to −38 ppm range. Ab initio GIAO[24] chemical shift calculations show that when *closo*-$C_2B_{10}H_{12}$ loses a boron vertex to form [*nido*-$C_2B_9H_{12}]^-$, there is an upfield shift of the ^{11}B NMR resonances of the unique and apical borons of the latter compound to $\delta = -41.9$ ppm and −38.1 ppm, respectively, from their original value of $\delta = -9.1$ ppm.[25] Therefore, the major changes seen in Table 4 are compatible with the formulations given in Scheme 1.

Conclusions

We have demonstrated that the synthesis of carboranyl derivatives of anthraquinones, flourenones, and sulfones can be achieved in a simple and efficient synthetic route that can be of general interest in BNCT research. Although extensive biological testing needs to be done, these compounds have the potential to serve as the basis for important boron delivery agents in the treatment of cancer via BNCT technology. The work on such carborane species and their related chemistry is currently underway in our laboratories.

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