Triazinyl Architecture on Bifunctional Carboranyl Templates for the Production of Potential Neutron Capture Therapy Agents: Synthesis and Characterization of 1,3,5-Triazinylcarborane Derivatives

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Abstract: A method for preparing triazinyl-substituted carboranyl systems using 1,2-, 1,7-, and 1,12-C2B10H12 as cores and [di(alkyl)amino]triazine as substituents is described. A sulfur-containing o-carboranyl cage compound was also incorporated into the 1,3,5-triazine network to generate new types of hybrid compounds having a thio-ether linkage. Within the series of synthesized compounds, one showed increased water solubility arising from the effective camouflaging of the central p-carboranyl unit by the polar functional groups at the periphery. Furthermore, the same compound exhibited high boron uptake in B-16 melanoma cells with low toxicity, showing promise as a BNCT agent.

Key words: carborane scaffold, mono(triazinyl)carborane, bis(triazinyl)carborane, o-carboranylthiolate, triazine architecture, water-solubility, boron neutron capture therapy

As part of our continuing search for new agents suitable for use in boron neutron capture therapy (BNCT), we have utilized an o-carborane framework not only as a boron carrier, but also as a scaffold with which to construct bi-functional biologically active species. Carboranes contain ten boron atoms in a small volume with a 2-dimensional peripheral size similar to that of a benzene molecule. Carborane (C2B10H12) has three isomers, known as ortho-(1,2-C2B10H10), meta-(1,7-C2B10H10), and para-carborane (1,12-C2B10H10), depending on the position of the two carbon atoms in the icosahedral cage framework; derivatives of these carboranes can be produced by replacing the acidic protons of one or both of the C-H units with functional groups.

Water-solubility, high boron uptake, and low toxicity are considered essential characteristics of good BNCT agents. However, since carboranes consist only of C-H and B-H units in the cage, they have lipophilic character. Due to the lipophilic character of the carboranyl unit, introduction of a second functional group into the o-carboranyl triazine that endows the molecule with water-solubility is highly desirable. To meet the requirements for BNCT agents, many attempts have been made in our laboratory to increase the water-solubility of candidate molecules while maintaining high boron uptake and low toxicity. Among many candidates, the 1,3,5-triazine derivatives of the o-carboranyl system seem promising in that they show high boron uptake in cancer cells. Moreover, the water-solubility of these molecules was found to be enhanced by introducing a second functional group such as an alkylamine moiety.

In the search for potential BNCT agents, here we explore a new strategy in which a carborane framework is used as a template for the attachment of functional groups. Since carboranyl systems carry two C-H units in the cage framework, substitution on each unit among the three isomeric carboranes allows the systematic variation of the configuration of functional groups in the periphery, which in turn affects the solubility of the molecule in aqueous media. To address the relationship between the configuration of the peripheral substituents and the biological activity, three isomers of o-, m- and p-carborane have been studied as functionalizable templates. In the context of developing water-soluble BNCT agents, we chose bis(methoxethyl) and bis(hydroxyethyl)amine functional groups for use as peripheral units, as shown in Figure 1.

In addition, as a surrogate of o-carborane, sulfur-containing o-carboranyl cage compounds were incorporated into the 1,3,5-triazine network to generate new types of hybrid compounds as candidate BNCT agents. Therefore, in the present study, mono- and bis(triazinyl) substituted o-, m-, and p-carborane derivatives containing di(methoxethyl) or di(hydroxyethyl) side groups on nitrogen atoms of the 1,3,5-triazine ring were synthesized and tested in vitro. The starting 6-chloro-2,4-bis(di(methoxethyl)amino)1,3,5-triazine (2) was prepared by reacting 2,4,6-trichloro-1,3,5-triazine (1) with the corresponding di(methoxethyl)amine at 0°C for 12 hours in tetrahydrofuran (THF). Compound 2 was then treated with one equivalent of lithiocarborane (3-5) at ~78°C in THF to generate mono(triazinyl) substituted intermediates 6-8 in 71–76% yield (Scheme 1).

The 1H NMR spectra of 6-8 show resonances at around δ = 3.28–3.29 ppm due to the methyl protons in the OCH3 unit and at around δ = 3.51–3.75 ppm due to the ethyl protons in the NCH2CH2O unit (Table 1). The 13C NMR spectra of 6-8 exhibit resonances at around δ = 47.8–47.9
Compounds 6–8 were further treated with four equivalents of BBr₃ to generate the demethylated compounds 9–11 in 75–77% yield (Scheme 1). In the ¹H NMR spectra of 9–11, the signal corresponding to the methyl proton in the OCH₃ unit is not observed, and the resonance due to the ethyl proton in the CH₂CH₂ unit is shifted downfield. Key signals in the ¹³C NMR spectra of 9–11 include resonances at around δ = 51.7–51.9 (CH₂O), 60.2–60.4 (NCH₂) and 164.2–167.2 ppm (triazine ring).

**Figure 1**  o-Carboranyl-substituted 1,3,5-triazine derivatives

**Scheme 1** Synthesis of bis{di(methoxyethyl)amine}- and bis{di(hydroxyethyl)amine}-substituted 1,3,5-triazinyl-carborane derivatives (6–11)
Synthesis and Characterization of 1,3,5-Triazinylcarborane Derivatives

Mercaptoundecahydrododecaborate (B_{12}H_{11}SH^{2−}), known as BSH, is a water-soluble, divalent anionic boron cluster containing an S-H subunit, that exhibits low toxicity. Due to these characteristics, BSH has shown promise as a BNCT agent.\(^{10}\) o-Carboranylthiolate (C_{2}B_{10}H_{11}SH) is similar to BSH in that it has an S-H functional unit in a boron cluster. The thiol functional group can be useful to anchor the o-carboranyl group to the 1,3,5-triazine unit. Prototype reactions have been reported involving a nucleophilic triazine substitution with organic N-, O-, and S-functional groups.\(^{11}\) Therefore, o-carboranylthiolate was employed as a potential nucleophile with which to attack the triazine network to generate o-carboranylthiolate functionalized 1,3,5-triazine derivatives such as 6-(o-carboranylthiolato)-2,4-bis[di(methoxyethyl)amino]-1,3,5-triazine (13). o-Carboranylthiolate was generated in situ by the reaction of o-carborane with an equimolar amount of butyllithium, followed by addition of S\(_8\) in anhydrous THF at −78 °C. Subsequent reaction with chloro-1,3,5-triazines (2) generated the mono-substituted mono(triazinyl)-o-carboranylthiolate (13) in 14% yield (Scheme 2).

In the \(^1\)H NMR spectrum of 13, a signal diagnostic of the methyl protons in the OCH\(_3\) unit at \(\delta = 3.33\) ppm was observed, along with diagnostic signals corresponding to the ethyl protons in the NCH\(_2\)CH\(_2\)O unit at \(\delta = 3.57\) and 3.83 ppm, respectively. Key signals detected in the \(^13\)C NMR spectrum of 13 include those at \(\delta = 48.3\) ppm for the methyl protons, \(\delta = 59.2\) ppm for the ethyl protons, and \(\delta = 67.5\) ppm for the aromatic methyl protons.

Table 1 Summary of Selected Physical and Spectral Properties of the Carboranyl-1,3,5-triazine Derivatives 6–11, 13 and 17–19

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd</th>
<th>Yield (%)(^a)</th>
<th>Mp (°C)(^b)</th>
<th>IR (cm(^{-1}))</th>
<th>(^1)H NMR (δ, ppm)</th>
<th>(^13)C NMR (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>71</td>
<td>45–49</td>
<td>2671</td>
<td>3.28</td>
<td>164.2</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>73</td>
<td>40–45</td>
<td>2604</td>
<td>3.29</td>
<td>164.4</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>76</td>
<td>45–49</td>
<td>2671</td>
<td>3.29</td>
<td>164.4</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>75</td>
<td>74–77</td>
<td>2604</td>
<td>3.73</td>
<td>164.3</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>77</td>
<td>76–79</td>
<td>2606</td>
<td>3.74</td>
<td>164.2</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>77</td>
<td>81–82</td>
<td>2613</td>
<td>3.69</td>
<td>164.5</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>14</td>
<td>94–96</td>
<td>2594</td>
<td>3.33</td>
<td>161.7</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>38</td>
<td>72–75</td>
<td>2571</td>
<td>3.29</td>
<td>164.2</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>51</td>
<td>83–86</td>
<td>2613</td>
<td>3.30</td>
<td>164.5</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>60</td>
<td>92–95</td>
<td>2621</td>
<td>3.28</td>
<td>164.4</td>
</tr>
</tbody>
</table>

\(\delta\) Isolated yields.
\(\pm\) Melting points are uncorrected.

Scheme 2 Preparation of 6-(o-carboranylthiolato)-2,4-bis[di(methoxyethyl)amino]-1,3,5-triazine (13)
The introduction of two triazinyl moieties with polar functional groups into the carboranyl scaffold was expected to increase the water-solubility of the molecule. Thus, the preparation of bis(triazinyl)-o-, -m-, and -p-carboranes 17–19 was attempted by reacting 2 with dilithiocarboranes 14–16 in 2:1 stoichiometry. As outlined in Scheme 3, reaction of 14–16 with two equivalents of 2 at 0 °C in THF yielded bis{4-bis[2,6-di(methoxyethyl)amino]-1,3,5-triazinyl}-o-, -m-, and -p-carborane (17–19), which were then purified by column chromatography (38–60%). Further demethylation was attempted under various reaction conditions with the use of excess BBr₃. However, no identifiable species corresponding to the desired demethylated hydroxyalkyl amine were isolated. In-
stead, extensive self-aggregation was observed after the treatment with BBr₃ in methylene chloride solution.

The ¹H NMR spectra of 17–19 show resonances at around δ = 3.28–3.30 ppm due to the methyl protons in the OCH₃ unit and at around δ = 3.52–3.74 ppm due to the ethylene protons in the NCH₂CH₂O unit (Table 1). Key signals detected in the ¹³C NMR spectra of 17–19 include resonances at around δ = 47.8–47.9 (OCH₃), 57.8–58.0 (CH₂O), 70.4–70.6 (NCH₂) and 164.2–167.8 ppm (triazine ring). Selected physical and spectroscopic properties of 17–19 are listed in Table 1. X-ray crystallographic analysis of 19 confirmed that it contained four di(methoxyethyl)amino groups, effectively camouflaging the central p-carboranyl unit (Figure 3; CCDC No. 655713).

Taking into consideration the three essential requirements for BNCT precursors – water-solubility, high boron uptake, and low cytotoxicity – compounds 6–11, 13 and 17–19, appear to be good candidate molecules (see Table 2). The conversion of the amino functional group on triazine into a more polar substituent with a hydroxyethyl group in the mono-substituted carborane systems 9–11, increased the water-solubility of these molecules to 2.99 × 10⁻⁵ (mol/mL), which is about one order of magnitude higher than the solubilities of the corresponding molecules with methoxyethyl functional groups (6–8). As expected, the bis-substituted carboranes with polar functional bis[di(methoxyethyl)amino]triazinyl groups 17–19, were more soluble in water than were the mono-substituted (triazinyl)carboranes. Furthermore, among the bis(triazinyl)carboranyl series, the p-carboranyl scaffold (19) showed enhanced water-solubility, in accordance with the expectation that the para configuration maximizes the separation between the polar functional bis[di(methoxyethyl)amine] units on the periphery (Table 2).

All ten compounds prepared in the present work (6–11, 13 and 17–19) were found to accumulate in B–16 melanoma cells in considerably higher amounts than BPA (p-boronophenylalanine). Moreover, the ten compounds exhibited low cytotoxicity, with IC₅₀ values (the half maximal inhibitory concentration) in the range of 6.32 × 10⁻⁵ to 6.59 × 10⁻⁴ M. The low cytotoxicities of the ten compounds stand in contrast to the high cytotoxicity of the structurally related compound trimelamol, a triazine derivative with three hydroxyl methyl moieties that is water-soluble and has high anti-tumor activity.¹² The structural modification of 6 to give mono(triazinyl)-o-carboranylthiolate (13) did not alter the characteristics of the compound in terms of water-solubility, boron uptake or cytotoxicity. In fact, the amount of boron taken up varied only slightly among the ten compounds. This may be due to their similar lipophilic characters, even when a polar functional group was introduced in the o-, m-, and p-carboranyl scaffolds. We found no direct correlation between water-solubility and boron uptake in this series.

In summary, a series of mono- and bis(triazinyl)carboranes with polar functional groups such as bis[di(methoxyethyl)amines] and bis[di(hydroxyethyl)amines] were successfully introduced into o-, m-, and p-carboranyl scaffolds. The solubility of the compounds in water was found to depend on the configuration of the triazinyl architecture.

Table 2  Cytotoxicity (IC₅₀) and Boron Uptake for B-16 Melanoma Cancer Cells

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd</th>
<th>IC₅₀ (M)</th>
<th>Boron uptake (µg B/10⁶ cells)</th>
<th>Solubility in H₂O (mol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>7.88 × 10⁻⁵ (± 0.95)</td>
<td>0.78 ± 0.036</td>
<td>1.82 × 10⁻⁶</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>1.86 × 10⁻⁴ (± 0.41)</td>
<td>0.83 ± 0.0031</td>
<td>2.21 × 10⁻⁶</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>1.70 × 10⁻⁴ (± 0.04)</td>
<td>0.74 ± 0.024</td>
<td>3.93 × 10⁻⁶</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>5.93 × 10⁻⁴ (± 0.09)</td>
<td>0.24 ± 0.012</td>
<td>3.51 × 10⁻⁵</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>4.48 × 10⁻⁴ (± 0.29)</td>
<td>0.31 ± 0.081</td>
<td>2.99 × 10⁻⁵</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>3.29 × 10⁻⁴ (± 0.31)</td>
<td>0.42 ± 0.044</td>
<td>4.88 × 10⁻⁵</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>6.32 × 10⁻⁵ (± 0.65)</td>
<td>0.34 ± 0.049</td>
<td>1.87 × 10⁻⁴</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>6.59 × 10⁻⁴ (± 3.3)</td>
<td>0.47 ± 0.1</td>
<td>4.03 × 10⁻⁵</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>2.69 × 10⁻⁴ (± 1.95)</td>
<td>0.47 ± 0.016</td>
<td>2.88 × 10⁻⁵</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>&gt; 100</td>
<td>0.49 ± 0.31</td>
<td>3.16 × 10⁻⁴</td>
</tr>
<tr>
<td>11</td>
<td>BPA</td>
<td>4.49 × 10⁻⁵ (± 0.30)</td>
<td>0.12 ± 0.0028</td>
<td></td>
</tr>
</tbody>
</table>

* Boron uptake by B-16 cells was determined using the ICP-AES method.¹³ See experimental for details.
on the carboranyl scaffold; the highest water-solubility was observed for p-carborane, which has the most effective coverage of the carboranyl core with polar functional groups. An X-ray structural study of 19 confirmed that the p-carboranyl scaffold positions two triazinyl units on opposite sides of the molecule and aligns the second polar functional group in the periphery.

All manipulations were performed under a dry, oxygen-free N 2 or Ar atmosphere using standard Schlenk techniques. THF was distilled under N 2 from Na/benzophenone. CH 2Cl 2 was dried with anhydrous Na 2SO 4 and then concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–MeOH, 1:4; R f = 0.5) to give 9.

Yield: 0.32 g (75%); mp 74–77 °C.

IR (KBr): 3076 (C–H), 2617 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 47.8, 57.9, 61.5, 70.4, 86.5, 164.4, 167.5.

Anal. Calcd for C 20H 28B 10N 6O 4: C, 42.04; H, 8.09; N, 14.42. Found: C, 41.87; H, 8.48; N, 14.10.

Mono[bis(dihydroxyethyl)amino]-1,3,5-triazinyl-o-carborane (9)
To a stirred solution of compound 6 in CH 2Cl 2 (10 mL), at −10 °C, was added BBr 3 (1.5 g, 6.0 mmol) via a syringe. The reaction temperature was maintained at 0 °C for 4 h, then the reaction mixture was quenched with distilled H 2O (30 mL) and extracted with Et 2O (2 × 20 mL). The combined organic layer was washed with distilled H 2O (3 × 30 mL), dried with anhydrous Na 2SO 4 and then concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc–MeOH, 1:4; R f = 0.5) to give 9.

Yield: 0.33 g (77%); mp 76–79 °C.

IR (KBr): 3047 (C–H), 2606 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.07 (s, 4 H), 2.83 (s, 1 H), 3.73 (t, J = 5.5 Hz, 8 H), 3.77 (t, J = 5.0 Hz, 8 H).

13C NMR (acetone-d 6): δ = 51.7, 57.3, 60.3, 75.0, 164.3, 165.4.


10
Yield: 0.33 g (77%); mp 81–82 °C.

IR (KBr): 3047 (C–H), 2606 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.07 (s, 4 H), 3.18 (s, 1 H), 3.74 (t, J = 5.0 Hz, 8 H), 3.79 (t, J = 5.0 Hz, 8 H).

13C NMR (acetone-d 6): δ = 51.9, 55.3, 60.2, 79.4, 164.2, 166.4.


11
Yield: 0.33 g (77%); mp 76–78 °C.

IR (KBr): 3047 (C–H), 2606 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.07 (s, 4 H), 3.41 (s, 1 H), 3.69 (t, J = 4.5 Hz, 8 H), 3.75 (t, J = 5.0 Hz, 8 H).

13C NMR (acetone-d 6): δ = 51.7, 56.8, 60.4, 86.4, 164.5, 167.2.


6-(o-Carboranyliothiolato)-2,4-bis(dii-methoxyethyl)amino)-1,3,5-triazine (13)
To a stirred solution of o-carborane (0.14 g, 1.0 mmol) in THF (20 mL) was added n-BuLi (2.5M, 0.4 mL, 1.0 mmol) via a syringe. A solution of compound 2 (0.38 g, 1.0 mmol) in THF (10 mL) was slowly added to the lithium salt solution at −78 °C. After stirring the reaction mixture at −78 °C for 30 min, after it was slowly warmed to r.t. After stirring for an additional 24 h, the mixture was quenched with distilled H 2O (20 mL) and the crude product was extracted with Et 2O (2 × 20 mL). The organic layer was washed with distilled H 2O (3 × 30 mL), dried with anhydrous Na 2SO 4 and then concentrated in vacuo. The residue was purified by flash column chromatography (CHCl 3–EtOAc, 3:1; R f = 0.4) to give 6.

Yield: 0.35 g (71%); mp 45–49 °C.

IR (KBr): 3076 (C–H), 2617 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.85 (s, 1 H), 3.28 (s, 12 H), 3.54 (t, J = 5.9 Hz, 8 H), 3.77 (t, J = 5.9 Hz, 8 H).

13C NMR (acetone-d 6): δ = 47.9, 57.4, 58.0, 70.6, 75.0, 164.2, 165.6.


7
Yield: 0.36 g (73%); mp 40–45 °C.

IR (KBr): 3047 (C–H), 2604 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.84 (s, 1 H), 3.29 (s, 12 H), 3.55 (t, J = 5.9 Hz, 8 H), 3.75 (t, J = 5.8 Hz, 8 H).

13C NMR (acetone-d 6): δ = 47.9, 55.2, 58.0, 70.1, 70.5, 164.5, 166.9.

Anal. Calcd for C 6H 10B 4N 2O 2: C, 40.42; H, 8.09; N, 14.42. Found: C, 41.71; H, 8.47; N, 14.34.

8
Yield: 0.37 g (76%); mp 45–49 °C.

IR (KBr): 3053 (C–H), 2617 (B–H) cm–1.

1H NMR (acetone-d 6): δ = 2.83 (s, 1 H), 3.29 (s, 12 H), 3.51 (t, J = 5.9 Hz, 8 H), 3.70 (t, J = 5.9 Hz, 8 H).

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Bis{4-bis[2,6-dimethoxyethyl]amino}-1,3,5-triazinyl-α-carborane (17)

The procedure described for the preparation of 6 was implemented using α-carborane (0.14 g, 1.0 mmol), n-BuLi (2.5M, 0.88 mL, 2.2 mmol) and compound 2 (0.76 g, 2.0 mmol). The reaction mixture was refluxed for 3 d to give 17 after workup and flash column chromatography (CHCl$_3$-EtOAc, 1:1, R$_f$ = 0.2).

Yield: 0.31 g (38%); mp 72–75 °C.

1H NMR (acetone-$_d_6$): δ = 5.52 (s, 16 H), 6.19. Found: C, 39.30; H, 7.70; N, 13.56; S, 6.06.

In vitro Boron Incorporation into B-16 Melanoma Cells

B-16 melanoma cells were cultured in Falcon 3025 dishes (150 mm$^2$). When the cell population had increased to fill the dish (8.8 x 10$^6$ cells/dish), the boron compounds (1.0 x 10$^{-4}$ M, 10.8 ppm boron) and BPA (1.0 x 10$^{-3}$ M, 10.8 ppm boron) were added to the dishes. The cells were incubated for 3 h at 37 °C in medium (MEM, 10% FBS; 20 mL). The cells were washed (3 x) with Ca/Mg-free phosphate buffered saline (PBS (-)), collected by rubber policeman, digested with a mixture of 60% HClO$_4$–30% H$_2$O$_2$ (1:2) solution (2 mL), and then decomposed for 1 h at 75 °C. After filtration through a membrane filter (Millipore, 0.22 μm), the boron concentration was determined using ICP-AES (Shimadzu, ICPS–1000–III). Each experiment was performed in triplicate. The average boron concentration of each fraction is indicated in Table 2.

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