

## A New Synthetic Route to Boron-10 Enriched Pentaborane(9) from Boric Acid and Its Conversion to *anti*-<sup>10</sup>B<sub>18</sub>H<sub>22</sub>

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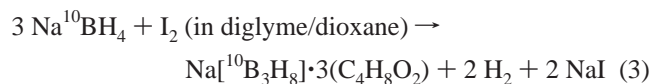
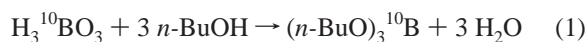
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One of the greatest factors in promoting the study of the small-cage C<sub>2</sub>B<sub>4</sub> carborane systems was the almost limitless supply of the pentaborane(9) (B<sub>5</sub>H<sub>9</sub>), obtained from an extensive U.S.-government surplus, which can then be reacted with a suitable alkyne to form the carborane. At present, that source is no longer available, nor is there a commercial source to take its place.<sup>1</sup> For research to continue in this area, a new, convenient, and safe method of producing the pentaborane(9) must be developed. Ideally, what is desired is a one-pot method of generating pentaborane(9) from a readily available starting material, such as NaBH<sub>4</sub>, which could then further react with the appropriate alkyne to generate, in situ, the corresponding small cage carborane.

Although the pentaborane(9) is a reactive liquid and is potentially explosive when mixed with air,<sup>1</sup> it is an important synthon for a number of higher polyhedral borane cages, including [B<sub>9</sub>H<sub>14</sub>]<sup>-</sup>,<sup>2</sup> [B<sub>11</sub>H<sub>14</sub>]<sup>-</sup>,<sup>3</sup> [B<sub>12</sub>H<sub>12</sub>]<sup>2-</sup> and other cage expanded borane anions,<sup>4</sup> and the neutral decaborane, B<sub>10</sub>H<sub>14</sub>.<sup>5</sup> The corresponding <sup>10</sup>B-enriched species are the precursors for a number of potential boron drugs for use in the clinical trials using boron neutron capture therapy (BNCT). Since there is no commercial source available for any of these species with the exception of the most expensive <sup>10</sup>B<sub>10</sub>H<sub>14</sub>,<sup>6</sup> a convenient synthesis for hitherto unisolated <sup>10</sup>B-enriched pentaborane(9) has an obvious appeal. It is this incentive that led us to explore alternative routes to <sup>10</sup>B-enriched polyhedral boranes starting from readily available boric acid, H<sub>3</sub><sup>10</sup>BO<sub>3</sub>. Herein we report a new synthetic advance in the preparation of boron-10 enriched pentaborane(9) and its one-pot conversion to cage-fused neutral *anti*-<sup>10</sup>B<sub>18</sub>H<sub>22</sub>, a compound envisioned to be a precursor in BNCT research.

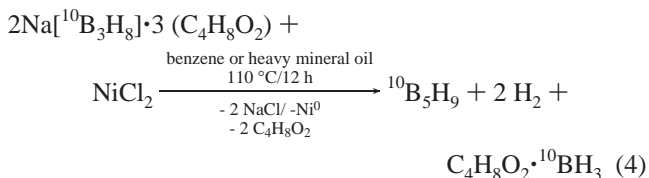
Thus, the boron-10-enriched boric acid, H<sub>3</sub><sup>10</sup>BO<sub>3</sub>, was converted to the corresponding sodium borohydride, Na<sup>10</sup>BH<sub>4</sub>, in essentially quantitative yields, by using slightly modified literature methods that involve the formation of butyl borate, (*n*-OBu)<sub>3</sub><sup>10</sup>B, first and then reacting it with NaH in mineral oil at 250 °C (see eqs 1 and 2).<sup>7,8</sup>



The subsequent oxidation reaction of Na<sup>10</sup>BH<sub>4</sub> with I<sub>2</sub> in diglyme, followed by the addition of dioxane during the purification step, gave the dioxane-complexed sodium salt of octahydrotriborate (-1), Na[<sup>10</sup>B<sub>3</sub>H<sub>8</sub>]·3(C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>), in almost quantitative yields (see eq 3).<sup>9</sup>

Although these synthetic routes were established in the early 1950s and 1970s, they are still the best available methods for these species. The use of hot mineral oil, as in the industrial procedure,<sup>10</sup> prevented the cake formation of the reactant/product mixture in eq 2. With the exception of improvising the routes to a bench-scale preparation of the corresponding <sup>10</sup>B-enriched species,<sup>11</sup> there were no ground-breaking additional observations in eqs 1–3 that are worthy of special comments.

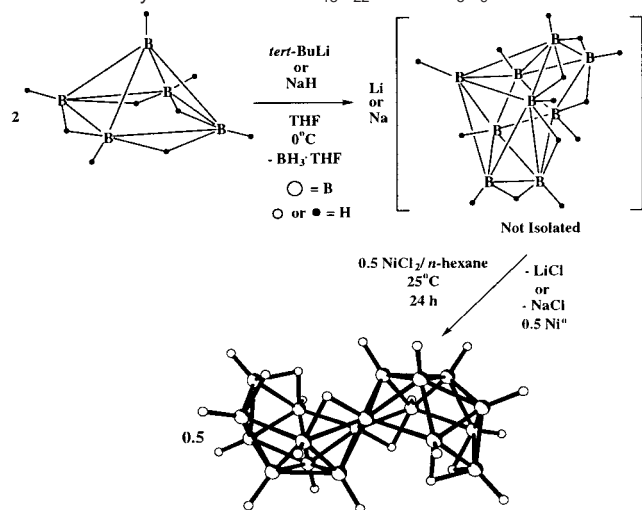
Treatment of Na[<sup>10</sup>B<sub>3</sub>H<sub>8</sub>]·3(C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>) with NiCl<sub>2</sub> in anhydrous benzene or heavy mineral oil at 110 °C (see eq 4) gave the corresponding <sup>10</sup>B<sub>5</sub>H<sub>9</sub> as the first isolated <sup>10</sup>B-enriched pentaborane(9) in a laboratory environment.<sup>12</sup> Although there have been a



number of other methods for the preparation of natural B<sub>5</sub>H<sub>9</sub>,<sup>13–15</sup> the reaction written in eq 4 is by far the most convenient, straightforward, and the safest method of choice to date. Since the <sup>10</sup>B-enriched pentaborane is the only borane product of high volatility, its production, easy isolation, and safe storage in heavy mineral oil make this method most attractive to not only those who work with small-cage (C<sub>2</sub>B<sub>4</sub>) carboranes and metallacarboranes but also to the laboratories that did not have the access to this material previously.

The reaction of natural pentaborane(9) has been profitably exploited for the syntheses of a number of cage-expanded boron hydrides including the [B<sub>9</sub>H<sub>14</sub>]<sup>-</sup> ion.<sup>2–5</sup> Therefore, the <sup>10</sup>B-enriched pentaborane(9) was converted to lithium or sodium salt of the corresponding [<sup>10</sup>B<sub>9</sub>H<sub>14</sub>]<sup>-</sup> in situ by the method described elsewhere<sup>2</sup> and was reacted further with anhydrous NiCl<sub>2</sub> in 2:1 molar ratio to produce the neutral fused borane, *anti*-<sup>10</sup>B<sub>18</sub>H<sub>22</sub>, in 42% yield (see Scheme 1) as a single pure isomer.<sup>16</sup> The natural analogue of this species, along with its *syn*-isomer as a mixture,<sup>17,18</sup> has been synthesized by the oxidation reaction of the [*closo*-B<sub>10</sub>H<sub>10</sub>]<sup>2-</sup> ion, derived from decaborane, and is the most expensive borane reagent on the market.<sup>6</sup> In view of the fact that the biomolecules carrying large-cage borane moieties have the potential to deliver more <sup>10</sup>B atoms to the specific tumor cells for an effective BNCT in cancer treatment,<sup>19</sup> the synthetic route presented in Scheme 1 is of special interest in that its <sup>10</sup>B-enriched species can be prepared in sufficient quantities in laboratory settings as a precursor to large-cage bio-boron analogues including those of the fused-cage [<sup>10</sup>B<sub>22</sub>H<sub>22</sub>]<sup>2-</sup> ion.<sup>20</sup> Nonetheless, this work constitutes the first systematic synthetic approach to pentaborane(9) of both natural and <sup>10</sup>B-enriched analogues and to their cage-expanded neutral and anionic

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**Scheme 1.** Synthesis of *anti*- $^{10}\text{B}_{18}\text{H}_{22}$  from  $^{10}\text{B}_5\text{H}_9$ 

borane species. Detailed investigations on the related boron hydrides, carboranes, and metallacarboranes of both the  $\text{C}_2\text{B}_4$ - and  $\text{C}_2\text{B}_{10}$ -cage systems are currently underway in our laboratories.

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**Note Added after ASAP:** Incorrect nomenclature for the target compound was used in the version posted ASAP June 4, 2002. The corrected version was posted June 6, 2002.

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- Synthesis of  $\text{Na}^{10}\text{B}_3\text{H}_8\cdot 3(\text{C}_4\text{H}_8\text{O}_2)$  from  $\text{H}_3^{10}\text{BO}_3$ .** (A) **Synthesis of  $(n\text{-C}_4\text{H}_9\text{O})_3^{10}\text{B}$ .** In a modified literature procedure,<sup>7</sup> a 20.00 g (327.64 mmol) sample of anhydrous  $\text{H}_3^{10}\text{BO}_3$  was taken in a one-necked 250-mL round-bottom flask to which a Dean–Stark receiver (Aldrich) with a reflux condenser was attached. *n*- $\text{C}_4\text{H}_9\text{OH}$  [97.14 g (1310.57 mmol)] and toluene (50 mL) were added, and the resulting mixture was heated to 130 °C over a period of 5 h. After detaching the Dean–Stark receiver, the product mixture was distilled at 226–228 °C under 1 atm pressure to collect 65.04 g (283.57 mmol, 87% yield) of pure  $(n\text{-C}_4\text{H}_9\text{O})_3^{10}\text{B}$ . (B) **Synthesis of  $\text{Na}^{10}\text{BH}_4$ .** In a separate experiment, similar to that described elsewhere,<sup>8</sup> a 500-mL three-necked flask was charged with 25.00 g of NaH (60% in mineral oil = 625 mmol) in an inert atmosphere and to which a mechanical stirrer, a reflux condenser, and a pressure-equalized dropping funnel that contained 125 mmol (28.67 g) of  $(n\text{-C}_4\text{H}_9\text{O})_3^{10}\text{B}$  were attached. Through the reflux condenser, 150 mL of mineral oil was poured onto the solid NaH, and the resulting mixture was heated to 250–255 °C with constant stirring; then the *n*-butyl borate was added dropwise over a period of 30–35 min. The heating and the mechanical stirring were continued for additional period of 1 h. After the mixture cooled to room temperature, 200 mL of anhydrous pentane was added to the product mixture and filtered through a frit to collect the crude solid product that was washed with several aliquots of dry pentane to remove any residual mineral oil. The washed residue was re-crystallized from anhydrous diglyme to collect 4.05 g (109.31 mmol, 88% yield) of pure  $\text{Na}^{10}\text{BH}_4$ . (C) **Synthesis of  $\text{Na}^{10}\text{B}_3\text{H}_8\cdot 3(\text{C}_4\text{H}_8\text{O}_2)$ .** In a procedure, identical to that described by Ryschkewitsch et al.,<sup>9</sup> a 80.97 mmol (3.00 g) sample of  $\text{Na}^{10}\text{BH}_4$  in 20 mL of diglyme was reacted with 26.99 mmol (6.85 g) of  $\text{I}_2$  in 15 mL of anhydrous diglyme at 95 °C over a period of 2 h. After filtration, the filtrate was concentrated and treated with anhydrous dioxane (~15 mL) to collect the crude solid product that was later recrystallized in dioxane to isolate 8.23 g (25.29 mmol, 94% yield) of pure  $\text{Na}^{10}\text{B}_3\text{H}_8\cdot 3(\text{C}_4\text{H}_8\text{O}_2)$  as a white crystalline solid.
- Synthesis of  $^{10}\text{B}_5\text{H}_9$  from  $\text{Na}^{10}\text{B}_3\text{H}_8\cdot 3(\text{C}_4\text{H}_8\text{O}_2)$ .** A 500-mL high-vacuum flask was charged with 2.04 g (6.27 mmol) of  $\text{Na}^{10}\text{B}_3\text{H}_8\cdot 3(\text{C}_4\text{H}_8\text{O}_2)$  and 0.40 g (3.13 mmol) of anhydrous  $\text{NiCl}_2$  in a drybox and then attached to a vacuum/Schlenk line. After pumping out  $\text{N}_2$  at  $-196$  °C, 1.00 mL of anhydrous  $\text{C}_6\text{H}_6$  was condensed, or 10 mL of anhydrous heavy mineral oil was added to the flask in vacuo and then warmed to 25 °C. The lower half of the flask was immersed in an oil bath and heated to 110 °C during which time the mixture turned dark-brown. The heating was continued overnight, and the flask was removed from the oil bath to cool to 25 °C and then attached to a high-vacuum line. After removing the noncondensable gas at  $-196$  °C, presumably  $\text{H}_2$  (not measured), the volatile products were transferred out of the flask by pumping and then fractionated at room temperature through a series of traps held at 0,  $-45$ ,  $-64$ ,  $-94$ , and  $-196$  °C to collect pure  $^{10}\text{B}_5\text{H}_9$  [0.074 g, 1.25 mmol; 40% yield; vp (25 °C) = 210 mmHg;  $^1\text{H}$  NMR( $\text{C}_6\text{D}_6$ , relative to external TMS)  $\delta$  2.51–(m, br overlapping, 4H,  $J_{\text{BH}} = 55$  Hz), 0.82 (m, br overlapping, 1H,  $J_{\text{BH}} = 59$  Hz),  $-2.63$  (s, v br, 4H<sub>bridge</sub>);  $^{10}\text{B}$  NMR ( $\text{C}_6\text{D}_6$ , relative to external  $\text{BF}_3\cdot\text{OEt}_2$ )  $\delta$   $-13.94$  (d, 4 B,  $J_{\text{BH}} = 54.8$  Hz)  $-53.76$  (d, 1B,  $J_{\text{BH}} = 58.8$  Hz)].<sup>13, 14</sup> in the trap held at  $-94$  °C. The 0 °C trap collected a small quantity of  $\text{C}_4\text{H}_8\text{O}_2\cdot^{10}\text{BH}_3$ . The solvents collected in traps at  $-45$  and  $-64$  °C and the dark residue in the flask containing metallic nickel, NaCl, and boric acid (not measured) were discarded. *Note: The reaction can be scaled up to 20-fold in a single-ended 500-mL stainless steel reactor to synthesize  $^{10}\text{B}_5\text{H}_9$  in multigram quantities and in yields greater than 40%.*
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- Synthesis of *anti*- $^{10}\text{B}_{18}\text{H}_{22}$  from  $^{10}\text{B}_5\text{H}_9$ .** A 11.83 mmol (0.70 g) sample of  $^{10}\text{B}_5\text{H}_9$  was condensed into a 250-mL flask containing 5.92 mmol *tert*-BuLi (3.48 mL of 1.7 M in *n*-hexane) or NaH (0.14 g), 12 mL THF, and a magnetic stirring bar. The resulting solution was stirred constantly at  $-78$  °C for 3 h and then at 25 °C overnight during which time the solution became pale yellow. At this point, the solvents were removed in vacuo, and the resulting solid was dissolved in *n*-hexane and poured into anhydrous  $\text{NiCl}_2$  (0.38 g, 2.96 mmol) at 0 °C, and the resulting heterogeneous mixture was stirred constantly for 24 h. After removal of all the volatiles including the solvent, the remaining residue was heated to 100 °C in vacuo over a period of 6–7 h to collect an off-white crystalline solid, identified as *anti*- $^{10}\text{B}_{18}\text{H}_{22}$  (mp = 127–129 °C).<sup>17, 18</sup> in a detachable U-trap held at 0 °C in 42% yield (0.25 g, 1.23 mmol). The dark residue in the flask, containing metallic nickel, LiCl, and some polymeric solid, was discarded.
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