

Novel Route to Boron-10 Enriched Pentaborane(9) from Boric Acid and Its Conversion to w/o - $^{10}\text{B}i\text{O}H_4$ and $anti$ - $^{10}\text{B}is\text{C}_2\text{H}_2$ - Synthetic Advance in Polyhedral Borane Chemistry and in BNCT Research

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ABSTRACT: Boron-10 enriched boric acid, $H_3^{10}B\text{O}_3$, was converted to the corresponding sodium borohydride, $Na^{10}BH_4$, in essentially quantitative yields, by using slightly modified literature methods involving the formation of butyl borate, $(n\text{-OBu})^{10}B$, first and then reacting it with NaH in mineral oil. The oxidation reaction of $Na^{10}BH_4$ with I_2 in diglyme and subsequent addition/purification in dioxane gave $Na^{10}B_3H_7 \cdot 3(G/H_8O_2)$ that reacted further with $NiCl_2$ in benzene at 110°C to produce the corresponding $^{10}B_5H_9$ as the first isolated ^{10}B -enriched liquid boron hydride in a laboratory environment. Treatment of this $^{10}B_5H_9$ with NaH or $t\text{-BuLi}$ in 2:1 molar ratio underwent a cage expansion reaction to produce the $[M]^{10}B_6H_6$ that undergoes a redox reaction *in situ* with anhydrous $NiCl_2$ or $FeCl_3$ in n -hexane, or with bromopentane to yield the corresponding fused cage $anti$ - $^{10}BiH_2$ or $nido$ - $^{10}Bn\}Hu$ as the only solid borane product in good yields thus establishing new synthetic routes for the preparation of ^{10}B -enriched polyhedral boranes.

1 INTRODUCTION

One of the greatest factors in promoting the study of the small-cage C_2B_4 carborane systems was the almost limitless supply of the pentaborane(9) (B_5H_9), obtained from an extensive US-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 (Edwards Air Force Base, 1999). In order 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 $NaBH_4$, which could then further react with the appropriate alkyne to generate, *in situ*, the corresponding small cage carborane.

Pentaborane(9) has already been proven to be an important synthon for a number of higher polyhedral borane cages, including $[B_9H_{14}]^+$ (Wallbridge, Savory, 1973), $[B_nH_n]^+$ (Hosmane, et.al., 1987), $[B_{10}H_{12}]^{2+}$ and other cage expanded borane

anions, (Middaugh, 1975), and the neutral decaborane, $B_{10}H_{12}$ (Toft, 1982). The corresponding ^{10}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 $^{10}B_{10}H_{12}$ (Natural and ^{10}B -enriched decaborane ($B_{10}H_{12}$), and the natural *iso*- $B_{10}H_{12}$ are commercially available by KATCHEM LTD., Czech Republic, for the price of \$15, \$150, and \$140, respectively, for a gram sample of each) a convenient synthesis for hitherto unisolated ^{10}B -enriched pentaborane(9) has an obvious appeal. It is this incentive that led us to explore alternative routes to ^{10}B -enriched polyhedral boranes starting from readily available boric acid, $H_3^{10}B\text{O}_3$. 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 $anti$ - $^{10}BiH_2$ and $nido$ - $^{10}Bn\}Hu$, compounds used as precursors in BNCT research.

Thus, the boron-10-enriched boric acid, $H_3^{10}B\text{O}_3$, was converted to the corresponding sodium

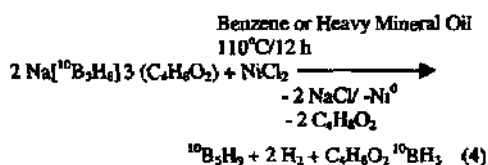
borohydride, Na¹⁰BH₄, in essentially quantitative yields, by using slightly modified literature methods that involve the formation of butyl borate, (←-OBU)₃¹⁰B, first and then reacting it with NaH in mineral oil at 250°C [see equations (1) and (2)] (Schlesinger et.al, 1953, Schlesinger, Brown, Finholt., 1953).



The subsequent oxidation reaction of Na¹⁰BH₄ with *h* in diglyme, followed by the addition of dioxane during the purification step, gave the dioxane-complexed sodium salt of octahydrotriborate (-1), Na¹⁰[B₃H₆]₃(C₄H₈O₂), in almost quantitative yields [see equation (3)] (Nainan, Ryschkewitsch, 1974).

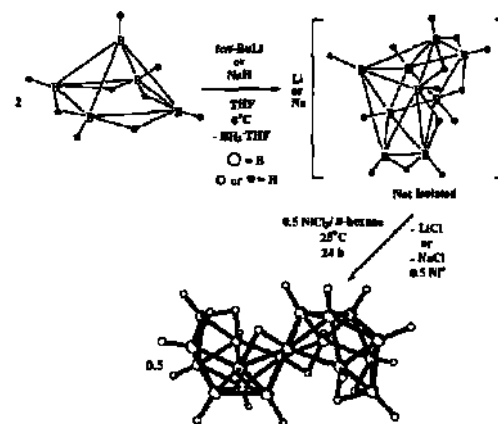
Although these synthetic routes have been established in early 1950's and 1970's, they are still the best available methods for these species. The use of hot mineral oil, as in the industrial procedure ((Serrard, 1961), prevented the cake formation of the reactant/product mixture in equation (2). With the exception of improvising the routes to a bench-scale preparation of the corresponding ¹⁰B-enriched species (Appx. A), there were no ground-breaking additional observations in equations (1) - (3) that are worthy of special comments.

Treatment of Na¹⁰BH₄ with NiCh in anhydrous benzene or heavy mineral oil at 110°C [see equation (4)] gave the corresponding ¹⁰B₅H₉ as the first isolated ¹⁰B-enriched pentaborane(9) in a laboratory environment (Appx. B). Although there have been a number of other methods for the



preparation of natural B₅H₉ (McCarty, Di Giorgio, 1951 ; Ryschkewitsch, Miller, 1975; Davis, 2000) the reaction written in equation (4) is by far the most convenient and straightforward method of choice to

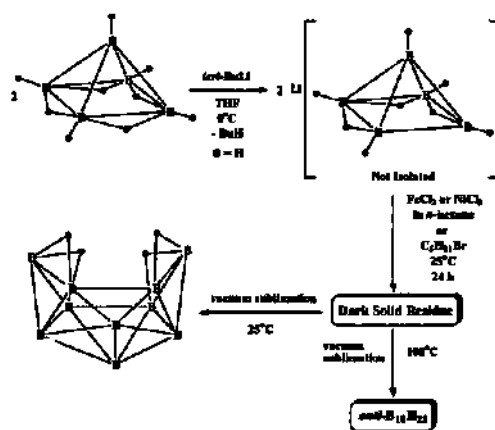
date. Since the B-enriched pentaborane is the only borane product of high volatility, its safe production, easy isolation and storage in heavy mineral oil make this method most attractive to not only those who work with small-cage (C₂B₄) carboranes and metallocarboranes, but also to the laboratories that did not have the access to this material previously.



Scheme 1. Synthesis of anrt-¹⁰B₅H₉ from ¹⁰B₅H₉

The reaction of natural pentaborane(9) has been profitably exploited for the syntheses of a number of cage expanded boron hydrides including the [B₉H₉]ⁿ ion (Wallbridge, Savory, 1973; Hosmane, et.al., 1987; Middaugh, 1975; Toft, 1982). Therefore, the ¹⁰B-enriched pentaborane(9) was converted to lithium or sodium salt of the corresponding ("BQH₉") *in situ* by the method described elsewhere,² and reacted it further with anhydrous NiCh in 2:1 molar ratio to produce the neutral fused borane, *anti*-¹⁰B₁₀H₂₂, in 42% yield (see Scheme 1) as a single pure isomer (Appx. C). The natural analogue of this species, along with its *syn*-isomer as a mixture (Pitochelli, Hawthorne, 1962; OlsenetaJ., 1968), has been synthesized by the oxidation reaction of the [c/oso-BioHio]²⁻ ion, derived from decaborane, and is the most expensive borane reagent on the market. In view of the fact that the bio-molecules carrying large-cage borane moieties have the potential to deliver more ¹⁰B atoms to the specific tumor cells for an effective BNCT in cancer treatment (Soloway et.al, 1998), the synthetic route presented in Scheme 1 is of special interest in that its ¹⁰B-enriched species can be

prepared in sufficient quantities in laboratory settings as a precursor to large-cage bio-boron analogues including those of fused-cage [$^{10}\text{B}_{10}\text{H}_{12}$] $^{2-}$ ion (Hosmane et al., 1998). Nonetheless, boron-10 enriched decaborane, $^{10}\text{B}_{10}\text{H}_{14}$, is the key chemical in preparing almost all of the $\text{C}_{(\text{CRBC})}$ -substituted bio-boron molecules that are being investigated as boron drugs for BNCT clinical trials in the US and the world (Soloway, 1998). This incentive led us to investigate an alternative route for the synthesis of $^{10}\text{B}_{10}\text{H}_{14}$ from $^{10}\text{B}_5\text{H}_9$ that can be prepared as described above. Although the synthetic methodology is identical to that used for *anti*- $^{10}\text{B}_{10}\text{H}_{12}$ except for the oxidizing agent (Scheme 2), the room-temperature high-vacuum sublimation of the product, instead of heating it to 100°C, produced pure $^{10}\text{B}_{10}\text{H}_{14}$ in over 50% yield.



Scheme 2. Synthesis of nido- $^{10}\text{B}_{10}\text{H}_{14}$ from $^{10}\text{B}_5\text{H}_9$

Thus, this work constitutes the first systematic synthetic approach to pentaborane(9) of both natural and ^{10}B -enriched analogues and to their cage expanded neutral and anionic borane species. Detailed investigations on the related boron hydrides, carboranes and metallocarboranes of both the C2B4- and C1Bw-cage systems are currently underway in our laboratories.

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APPENDIX A

Synthesis of $\text{Na}^{10}\text{B}_3\text{H}_8 \cdot 3(\text{C}_4\text{H}_8\text{O}_2)$ from H^{10}BO_2 :
(A). *Synthesis of (n-C₄H₉OH)₃B*. In a modified literature procedure, a 20 g (327.64 mmol) sample of anhydrous H^{10}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. To which 97.14 g (1310.57 mmol) of *n*-C₄H₉OH and 50 mL of toluene were added and the resulting mixture was heated to 130°C over a period of 5h. 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 $\{n\text{-C}_4\text{H}_9\text{O}\}_3\text{B}$. (B). *Synthesis of Na¹⁰BH₄*. In a separate experiment, similar to that described elsewhere,⁸ a 500-mL three-necked flask was charged with 25 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 $(i\text{-C}_4\text{H}_9\text{O})_3\text{B}$ 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 and then the *n*-butyl borate was added drop-wise over a period of 30-35 minutes. The heating and the mechanical stirring were continued for additional period of 1h. After cooling to room temperature, 200 mL 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 Na[¹⁰B₃H₈]·3(C₄H₈O₂)*. In a procedure, identical to that described by Ryschkewitsch, *et al.*,⁹ 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 I_2 in 15 mL 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 re-crystallized 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.

APPENDIX B

Synthesis of $^{10}\text{B}_3\text{H}_8$ 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 NiCl_2 in a dry-box and then attached to a vacuum/Schlenk line. After pumping out the nitrogen at -196°C, 10.0 mL anhydrous benzene was condensed into the flask and then warmed to room temperature. The lower half of the flask was immersed in an oil bath maintained at 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 non-condensable gas, presumably hydrogen (not measured), at -196°C, the volatile products were fractionated at room temperature through a series of traps held at 0, -45, -64, -94, and -196°C to collect pure $^{10}\text{B}_3\text{H}_8$ (0.074 g, 1.25 mmol; 40% yield)^{13,14} in the trap held at -94°C. The 0°C trap collected a small quantity of $\text{C}_4\text{H}_8\text{O}_2 \cdot \text{B}_3\text{H}_8$. 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 twentyfold in a single-ended 500-mL stainless-steel reactor to synthesize ¹⁰B₃H₈ in multigram quantities and in yields greater than 40%.*

APPENDIX C

Synthesis of B_3H_8 from $^{10}\text{B}_3\text{H}_8$: A 11.83 mmol (0.70 g) sample of $^{10}\text{B}_3\text{H}_8$ 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 onto anhydrous 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 B_3H_8 ,^{17,18} 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 or NaCl, and some polymeric solid, was discarded. Synthesis of B_3H_8 from $^{10}\text{B}_3\text{H}_8$: In a procedure, identical to that described above for *anti*-

¹⁰Bi₈H₂a, 15.00 mmol sample of ¹⁰B₈H₉ was reacted with 15.00 mmol of *tert*-BuLi to produce the corresponding monothium salt of [¹⁰B₈H₉]⁻ ion in THF and was reacted, without isolation, immediately with 7.50 mmol of bromopentane, anhydrous FeCl₃, or anhydrous NiCl₂ to produce 7.45 mmol (50% yield) of ¹⁰B₁₀H₁₁, obtained as a colorless crystalline solid by room-temperature sublimation of the residue *in vacuo* over a period of 10-12 hours. The continued vacuum sublimation of this residue at 100°C gave 1.25 mmol of *anti*-B₁₀H₁₂.