Novel Route to Boron-10 Enriched Pentaborane(9) from Boric Acid and Its Conversion to wV/o-\(^{10}\)Bio\(\text{H}_4\) and anii-\(^{10}\)Bio\(\text{U}_{22}\)- Synthetic Advance in Polyhedral Borane Chemistry and in BNCT Research

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ABSTRACT: Boron-10 enriched boric acid, H\(^3\)\(^{10}\)BO\(_3\), 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-OBu)\(^3\)\(^{10}\)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\(_3\)H\(_5\)I\(_3\)(G\(_8\)O\(_2\)) that reacted further with NiG\(_2\) in benzene at 110°C to produce the corresponding \(^{10}\)B\(_9\)H\(_9\) as the first isolated \(^{10}\)-enriched liquid boron hydride in a laboratory environment. Treatment of this \(^{10}\)B\(_9\)H\(_9\) with NaH or t-BuLi in 2:1 molar ratio underwent a cage expansion reaction to produce the \([M]\)\(^{10}\)B\(_9\)H\(_9\) that undergoes a redox reaction \textit{in situ} with anhydrous NiCl\(_2\) or FeCl\(_3\) in n-hexane, or with bromopentane to yield the corresponding fused cage \(\text{anti-}^{10}\)Bi\(_2\)H\(_{22}\) or \(\text{nido-}^{10}\)Bi\(_2\)H\(_{22}\) as the only solid borane product in good yields thus establishing new synthetic routes for the preparation of \(^{10}\)-enriched polyhedral boranes.

1 INTRODUCTION

One of the greatest factors in promoting the study of the small-cage C\(_2\)B\(_4\) carborane systems was the almost limitless supply of the pentaborane(9) (B\(_5\)H\(_9\)), 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, \textit{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\(_9\)H\(_{14}\)]\(^+\) (Wallbridge, Savory, 1973), [Bn\(_n\)H\(_n\)]\(^+\) (Hosmane, et al., 1987), [Bi\(_n\)H\(_{2n}\)]\(^0\) and other cage expanded borane anions (Middaugh, 1975), and the neutral decaborane, Bio\(_n\)H\(_{12}\) (Toft, 1982). The corresponding \(^{10}\)-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 \(^{10}\)Bio\(_n\)H\(_{12}\) (Natural and \(^{10}\)B-enriched decaborane (Big\(_n\)H\(_{12}\)), and the natural \((\text{iso-}^{10}\text{Bi})\)\(_7\)\(_{22}\) 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 \(^{10}\)-enriched pentaborane(9) has an obvious appeal. It is this incentive that led us to explore alternative routes to \(^{10}\)-enriched polyhedral boranes starting from readily available boric acid, H\(^3\)BO\(_3\). 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 \(\text{anti-}^{10}\)Bi\(_2\)H\(_{22}\) and \(\text{nido-}^{10}\)Bi\(_2\)H\(_{22}\), compounds used as precursors in BNCT research.

Thus, the boron-10-enriched boric acid, H\(^3\)\(^{10}\)BO\(_3\), 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-OBu)\(^3\)\(^{10}\)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\(_3\)H\(_5\)I\(_3\)(G\(_8\)O\(_2\)) that reacted further with NiG\(_2\) in benzene at 110°C to produce the corresponding \(^{10}\)B\(_9\)H\(_9\) as the first isolated \(^{10}\)-enriched liquid boron hydride in a laboratory environment. Treatment of this \(^{10}\)B\(_9\)H\(_9\) with NaH or t-BuLi in 2:1 molar ratio underwent a cage expansion reaction to produce the \([M]\)\(^{10}\)B\(_9\)H\(_9\) that undergoes a redox reaction \textit{in situ} with anhydrous NiCl\(_2\) or FeCl\(_3\) in n-hexane, or with bromopentane to yield the corresponding fused cage \(\text{anti-}^{10}\)Bi\(_2\)H\(_{22}\) or \(\text{nido-}^{10}\)Bi\(_2\)H\(_{22}\) as the only solid borane product in good yields thus establishing new synthetic routes for the preparation of \(^{10}\)-enriched polyhedral boranes.
borohydride, Na\textsubscript{10}BH\textsubscript{4}, in essentially quantitative yields, by using slightly modified literature methods that involve the formation of butyl borate, (-OBu),\textsubscript{3}B, 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).

\begin{equation}
H_3^+B\textsubscript{4}O\textsubscript{3}^- + 3 \text{ n-BuOH} \rightarrow (\text{n-BuO})\textsubscript{3}B + 3 \text{ H}_2O
\tag{1}
\end{equation}

\begin{equation}
4 \text{ NaH} + (\text{n-BuO})\textsubscript{3}B \rightarrow \text{Na}_{10}\text{BH}_{16} + 3 \text{ NaOBu}
\tag{2}
\end{equation}

\begin{equation}
3 \text{ Na}_{10}\text{BH}_{16} + \text{h} \text{ (in diglyme/dioxane)} \rightarrow 2 \text{ H}_2 + 2 \text{ NaH} + \text{Na}[\text{\textsubscript{10}B\textsubscript{3}H\textsubscript{12}(\text{C}_4\text{H}_6\text{O}_2)]}
\tag{3}
\end{equation}

The subsequent oxidation reaction of Na\textsubscript{10}BH\textsubscript{4} with \textit{h} in diglyme, followed by the addition of dioxane during the purification step, gave the dioxane-complexed sodium salt of octahydrotriborate (-1), Na\textsuperscript{10}B\textsubscript{3}H\textsubscript{12}(\text{C}_4\text{H}_6\text{O}_2), in almost quantitative yields [see equation (3)] (Naian, 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 "B-enriched species (Appx. A), there were no ground-breaking additional observations in equations (1) - (3) that are worthy of special comments.

Treatment of Na\textsuperscript{10}H\textsubscript{12} at \text{G(digOa)} with NiCh in anhydrous benzene or heavy mineral oil at 110°C [see equation (4)] gave the corresponding \textsuperscript{10}B\textsubscript{9}H\textsubscript{12} as the first isolated \textsuperscript{10}B-enriched pentaborane(9) in a laboratory environment (Appx. B). Although there have been a number of other methods for the

\begin{equation}
\text{Benzene or Heavy Mineral Oil, 110°C/12h}
\end{equation}

preparation of natural BSH\textsubscript{9} (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 \textsuperscript{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 (C\textsubscript{2}B\textsubscript{4}) 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 \textsuperscript{[B\textsubscript{9}H\textsubscript{17}]^+} ion (Wallbridge, Savory, 1973; Hosmane, et.al., 1987; Middaugh, 1975; Toft, 1982). Therefore, the \textsuperscript{10}B-enriched pentaborane(9) was converted to lithium or sodium salt of the corresponding \textsuperscript{10}B\textsubscript{9}H\textsubscript{17} in \textit{in situ} by the method described elsewhere, and reacted it further with anhydrous NiCh in 2:1 molar ratio to produce the neutral fused borane, \textit{anti}\textsuperscript{\textsuperscript{10}B\textsubscript{9}H\textsubscript{22}}, in 42% yield (see Scheme 1) as a single pure isomer (Appx. C). The natural analogue of this species, along with its \textsuperscript{syn}-isomer as a mixture (Pitochelli, Hawthorne, 1962; Olsen et.al., 1968), has been synthesized by the oxidation reaction of the \textsuperscript{[\textit{c}/\textit{oso-BioH}]}\textsuperscript{10} 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 \textsuperscript{10}B 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 \textsuperscript{B-enriched species} can be

\begin{scheme}
\text{Synthesis of \textit{anti}-\textsuperscript{10}B\textsubscript{9}H\textsubscript{22} from \textsuperscript{\textsuperscript{10}B\textsubscript{9}H\textsubscript{17}}}
\end{scheme}
prepared in sufficient quantities in laboratory settings as a precursor to large-cage bio-boron analogues including those of fused-cage $^{10}$B$_{2}$H$_{2}$ ion (Hosmane et al., 1998). Nonetheless, boron-10 enriched decaborane, $^{10}$BioH$_{10}$, is the key chemical in preparing almost all of the C$_{(CRBC)}$-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 $^{10}$BioH$_{10}$ from $^{10}$B$_{2}$H$_{9}$ that can be prepared as described above. Although the synthetic methodology is identical to that used for anti-$^{10}$B$_{2}$H$_{2}$ 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 $^{10}$BioHu in over 50% yield.

Scheme 2. Synthesis of nido-$^{10}$B$_{10}$H$_{14}$ from $^{10}$B$_{2}$H$_{6}$.

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 metallacarboranes of both the C2B$_{4}$- and C1B$_{6}$-cage systems are currently underway in our laboratories.

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APPENDIX A

Synthesis of Na$^{10}$B$_3$H$_9$3(C4HgO2) from Na$^{10}$BH$_4$.

(A). Synthesis of (n-C4HgO2)B. In a modified literature procedure, a 20 g (327.64 mmol) sample of anhydrous H$_3$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-C4HgOH and 10 mL of toluene were added and the resulting mixture was heated to 130°C over a period of 5h. After attaching 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-C4HgO2)B. (B). Synthesis of Na$^{10}$BH$_4$. In a separate experiment, similar to that described elsewhere, a 200-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 (n-C4HgO2)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 later re-crystallized in dioxane to isolate 8.23 g (25.29 mmol, 94% yield) of pure Na$^{10}$BH$_4$ from anhydrous H$_3$BO$_3$. Synthesis of (n-C4HgO2)B from Na$^{10}$BH$_4$. A 20 mL flask containing 5.92 mmol tert-BuLi (3.48 mL of 1.7 M in n-hexane) and NaH (0.70 g), 12 mL THF, and a magnetic stirring bar. The resulting solution was stirred constantly -78°C for 3h and then warmed to room temperature. 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 $^{10}$BH$_4$ (0.074 g, 1.25 mmol; 40% yield) in the trap held at -94°C. The 0°C trap collected a small quantity of C4HgO2BH3. 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.

APPENDIX B

Synthesis of $^{13}$B$^{13}$H$_4$, from Na$^{13}$B$^{13}$H$_8$ 3(0.0 02): A 500-mL high vacuum flask was charged with 208- g (6.27 mmol) of Na$^{13}$B$^{13}$H$_8$3(C4HgO2) and 0.40 g (3.13 mmol) of anhydrous NiCl$_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 $^{13}$B$^{13}$H$_4$ (0.074 g, 1.25 mmol; 40% yield) in the trap held at -94°C. The 0°C trap collected a small quantity of C4HgO2BH3. 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.

APPENDIX C

Synthesis of n-13B$^{13}$H$_4$2 from $^{13}$BH$_4$: A 1.83 mmol (0.70 g) sample of $^{13}$BH$_4$ was condensed into a 250-mL flask containing 5.92 mmol tert-BuLi (3.48 mL of 1.7 M in n-hexane) and NaH (0.14 g), 12 mL THF, and a magnetic stirring bar. The resulting solution was stirred constantly -78°C for 3h and then at 25°C overnight during which time the mixture 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 n-13B$^{13}$H$_4$. In a procedure, identical to that described above for anti-
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*BiH*₂₅, 15 00 mmol sample of ["BiH"]⁻ was reacted with 15 00 mmol of terf-BuLi to produce the corresponding monothium salt of ["BiH"]⁻ 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 ["BiOH"]⁻, 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-

BigH₂₂