Stereochemistry of the Hydroboration of Alkenes

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Received November 30, 1977

The reactions of (*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ with dialkylboranes (dicyclohexylborane and 9-BBN) produce *threo*- and *erythro*-(1,2-dideuteriohexyl)dialkylboranes, respectively. Further, the reactions of (*E*)- and (*Z*)-1-hexene-*1-d*$_1$ with di(2-deuteriocyclohexyl)borane-*B-d*$_1$ produce *erythro*- and *threo*-(1,2-dideuteriohexyl)di(deuteriocyclohexyl)borane, respectively. These results constitute direct evidence that the hydroboration reaction involves the cis addition of the boron hydrogen moiety to the alkene.

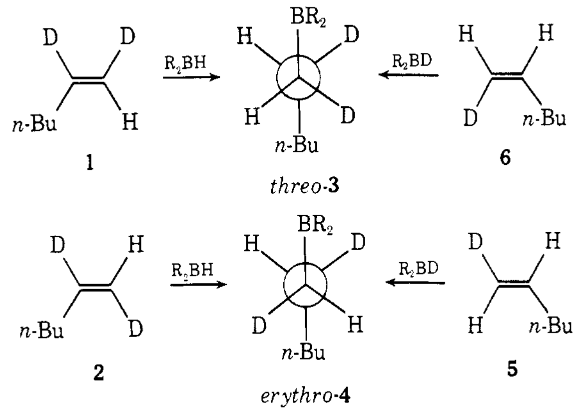
The hydroboration of alkenes has become increasingly important in organic chemistry primarily due to the synthetic versatility of the resultant organoboranes.[2–5] The reaction is generally believed to involve the cis addition of the boron hydrogen moiety to an alkene.[6,7] However, the basis for this belief rests primarily on the fact that hydroboration–oxidation sequences are known to lead to stereospecific cis hydration of alkenes,[8–10] e.g., (*Z*)-2-butene yields *erythro*-2-butanol-*3-d*$_1$ upon deuterioboration (BD_3), oxidation, and saponification. The hydroboration reaction, per se, is of sufficient importance to warrant the unambiguous determination of its stereochemistry.

Nuclear magnetic resonance spectroscopy was chosen as the appropriate analytical method due to its proven utility in stereochemical investigations.[11–14] The NMR analysis of organoboranes is (in the present case) complicated by at least three factors: first, the chemical shifts of the hydrogens on the 1- and 2-carbons are essentially isochronous such that first-order coupling constants are not observable; second, symmetric 1-deuteriotrialkylboranes, i.e., those arising from hydroboration of 1-deuterioalkenes, exist as mixtures of diastereomers giving rise to multiple overlapping resonances in the relevant high-field region of their proton spectra; and, third, the pertinent (1 and 2) resonances in the proton spectra are in a spectral region encumbered by other resonances. These difficulties were circumvented by the utilization of a complexing agent and by employing symmetric hydroborating agents. The use of a simple Lewis base, methylamine, as a complexing agent resulted in a diamagnetic shift of the 1-hydrogen of the product boranes such that vicinal coupling (to the 2-proton) was directly observable in a spectral region unencumbered by other resonances.[15] The use of symmetrical hydroborating agents, e.g., dicyclohexylborane and 9-borabicyclo[3.3.1]nonane (9-BBN), produced enantiomeric rather than diastereomeric products which significantly simplified the NMR analysis.

Results and Discussion

(*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ (**1** and **2**, respectively) were hydroborated with dicyclohexylborane and with 9-BBN. The addition of these (symmetric) dialkylboranes to the diastereomeric hexenes would produce the *threo*- and *erythro*-organoboranes (**3** and **4**, respectively) if the addition of the boron hydride were cis.[16] Trans addition would produce the opposite stereochemical results. In order to present a complete analysis, (*E*)- and (*Z*)-1-hexene-*1-d*$_1$ (**5** and **6**, respectively) were reacted with di(2-deuteriocyclohexyl)borane-*B-d*$_1$ [$(c\text{-}C_6H_{10})_2BD$]. In these reactions, the resultant organoborane products would be the erythro and threo diastereomers, **4** and **3**, respectively, if cis addition were to occur.

The steric bulk of the *n*-butyl and the (complexed) dialkylborane groups ensures that the anti conformer of each product is predominantly populated. The experimental results are summarized in Table I. The magnitudes of the vicinal



($^3J_{HH}$) coupling constants provide compelling evidence[17] for the assigned configurations assuming that the *anti-n*-butyldialkylborane conformation predominates.[18] Thus, the ^{1}H NMR results clearly demonstrate that cis addition occurs, i.e., **1** and **6** both produce the threo diastereomer upon addition of the appropriate dialkylborane while **2** and **5** produce the erythro diastereomer. The high-field regions of the proton NMR spectra of the dicyclohexylborane addition products of (*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ are presented in Figure 1.

Analysis of the hydrogen decoupled deuterium spectra supports the conclusions drawn from the deuterium decoupled proton spectra concerning the stereospecificity of the reaction; only two ^{2}H resonances are observed in the high-field region of the various spectra, one corresponding to the observed 1-H spectrum and the other at the appropriate chemical shift such that computed ^{1}H spectra exhibit the observed relative intensities in the ^{1}H spectrum.

It must be concluded that hydroboration of alkenes proceeds predominantly in a cis manner in accordance with Brown's original proposition.[19]

Experimental Section

All reactions were carried out in flame-dried, nitrogen-flushed glassware. Diglyme (Ansul) was distilled from calcium hydride prior to use. All other solvents were dried over sodium. Borane–methyl sulfide (Aldrich), 9-BBN (Aldrich), 1-hexyne (Farchan), acetic acid-*d*$_1$ (Norell Chemical Co., Inc.), deuterium oxide (Aldrich), and lithium deuteride (Alfa) were used as received.

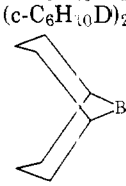
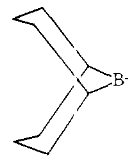
Routine NMR spectra were recorded on Varian T-60 and HA-100 spectrometers; chemical shifts are reported in ppm relative to Me_4Si unless otherwise indicated. ^{2}H decoupled proton and ^{1}H decoupled deuterium NMR spectra were recorded on a Bruker HX-90 spectrometer at 90 and 13.8 MHz, respectively. For proton and ^{2}H spectra the lock signal was benzene. Chemical shifts are referred to benzene and benzene-*d*$_6$, respectively.

1-Hexyne-*1-d*$_1$. 1-Hexyne (300 mmol, 34 mL) was added dropwise to a solution of *n*-butyllithium (350 mmol) in 180 mL of hexane which was contained in a dry, nitrogen-flushed flask cooled to 0 °C. D_2O was added slowly to the lithium salt and the reaction mixture was stirred overnight. Distillation afforded 29 mL (85%) of 1-hexyne-*1-d*$_1$: bp 72 °C; NMR (CCl_4) δ 2.13 (t, 2), 1.46 (m, 4), 0.90 (t, 3).

Di(2-deuteriocyclohexyl)borane-*B-d*$_1$ [$(c\text{-}C_6H_{10}D)_2BD$].

0022-3263/78/1943-1567$01.00/0

Table I. ^{1}H NMR Parameters of *n*-BuCHDCHDBR$_2$[a,b]

Alkene	R_2B–	Registry no.	δ 1-H[c]	δ 2-H[d]	$^3J_{1H\text{-}2H}$[e]
1[f] or 6[h]	$(c\text{-}C_6H_{10}D)_2B$–	65253-12-5	7.00	6.13	3.6
2[g] or 5[i]	$(c\text{-}C_6H_{10}D)_2B$–		6.99	6.12	12.4
1	 B-	65253-14-7	6.74	6.17	3.6
2	 B-	65253-15-8	6.77	6.18	13.3

[a] Deuterium decoupled. [b] Methylamine added as complexing agent (see Experimental Section). [c] Relative to internal benzene. [d] Position determined from ^{2}H derivative relative to internal benzene-d_6. [e] Hz. [f] Registry no. 65253-10-3. [g] Registry no. 65253-11-3. [h] Registry no. 18963-99-0. [i] Registry no. 18963-98-9.

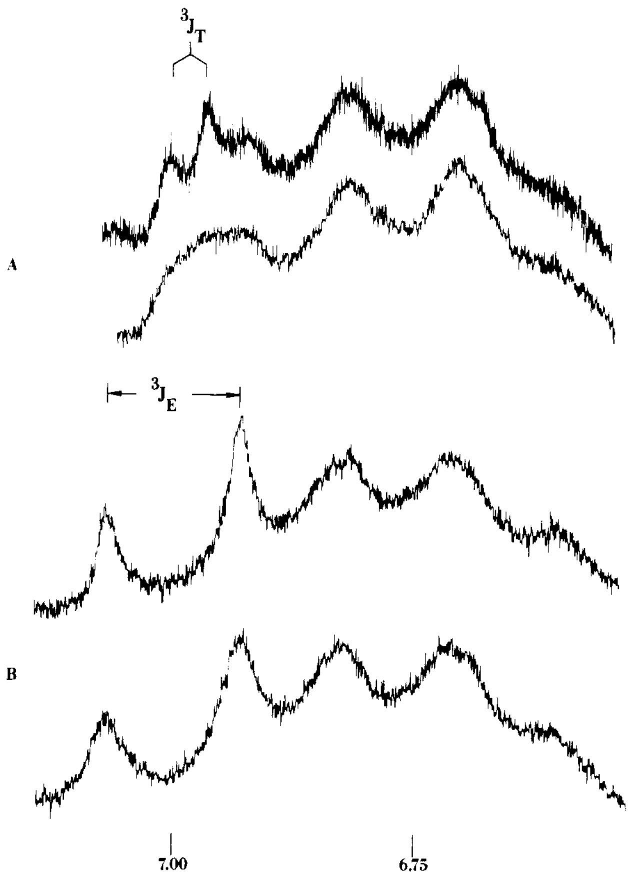


Figure 1. Proton spectra (90 MHz) of 1,2-dideuteriohexyldicyclohexylboranes: (A, upper) ^{2}H decoupled threo diastereomer; (A, lower) normal (undecoupled) spectrum; (B, upper) ^{2}H decoupled erythro diastereomer; (B, lower) normal (undecoupled) spectrum. Chemical shifts relative to benzene; field increasing to left. The low-field resonances arise from the cyclohexyl proton B–CH.

Lithium deuteride (300 mmol, 2.7 g), cyclohexene (200 mmol, 20 mL), and diglyme (100 mL) were placed in a dry, nitrogen-flushed, 250-mL flask equipped with a magnetic stirring bar, reflux condenser, pressure equilizing dropping funnel, and a gas exit tube. A solution of BF_3 in diglyme (400 mmol, 70 mL) was prepared by dissolving BF_3·etherate (400 mmol) in 70 mL of diglyme and distilling the diethyl ether at ambient temperature (20 Torr). This BF_3 solution was added dropwise (1 h) to the reaction mixture which was maintained at 0 °C. Dicyclohexylborane-*B*-d_1 precipitated from the reaction mixture. To ensure complete reaction, the mixture was stirred for 1 h at room temperature and was subsequently utilized for the preparation of deuterated alkenes.

Dicyclohexylborane. Cyclohexene (200 mmol, 20 mL) and 100 mL of diglyme were placed in a dry, nitrogen-flushed, 250-mL flask fitted with a magnetic stirring bar, reflux condenser, septum inlet, and a gas exit tube. The solution was cooled to 0 °C and BH_3·SMe_2 (100 mmol, 9.6 mL) was added via a syringe (10 min). The dicyclohexylborane precipitated during a 1-h period.

(*E*)-1-Hexene-*1,2*-d_2. 1-Hexyne (100 mmol, 11.4 mL) was added to dicyclohexylborane-*B*-d_1 (100 mmol) in diglyme, vide supra. After 1 h, the reaction was complete (the solid dicyclohexylborane dissolves) and the reaction mixture was solvolyzed by addition of acetic acid-d_1 (150 mmol, 7.0 mL). The product (9 mL, 70%) was isolated by fractional distillation: bp 66 °C; NMR (neat) δ 4.90 (broad singlet, 1), 2.00 (t, 2), 1.33 (m, 4), 0.90 (t, 3); mass spectra M$^+$ 86.

(*Z*)-1-Hexene-*1,2*-d_2 was prepared in a manner analogous to the preparation of (*E*)-1-hexene-*1,2*-d_2. 1-Hexyne-d_1 (100 mmol) was reacted with dicyclohexylborane-*B*-d_1 and then protonolyzed with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 66 °C; NMR (neat) δ 4.90 (broadened singlet, 1), 2.00 (t, 2), 1.33 (m, 4), 0.90 (t, 3); M$^+$ 86.

(*E*)-1-Hexene-*1*-d_1. 1-Hexyne (100 mmol, 11.4 mL) was added to dicyclohexylborane (100 mmol) (vide supra) in diglyme at 0 °C. The reaction mixture was stirred for 1 h and dimethyl sulfide was distilled from the mixture (N_2 atmosphere maintained). The mixture was cooled to room temperature and solvolyzed with acetic acid-d_1 (150 mmol, 7.0 mL). The product (9 mL, 70%) was isolated by fractional distillation: bp 65 °C; NMR (CCl_4) δ 5.73 (m, 1), 4.90 (d, 1, $^3J_{HH}$ = 18.0 Hz), 2.00 (m, 2), 1.33 (m, 4), 0.90 (t, 3); mass spectra M$^+$ 85.

(*Z*)-1-Hexene-*1*-d_1 was prepared in a manner analogous to the preparation of **(*E*)-1-hexene-*1*-d_1**. 1-Hexyne-*1*-d_1 was hydroborated with dicyclohexylborane followed by protonolysis with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 65 °C; NMR (neat) δ 5.73 (m, 1), 4.83 (d, 1, $^3J_{HH}$ = 10.0 Hz), 2.00 (m, 2), 1.33 (m, 4), 0.90 (t, 3); M$^+$ 85.

***threo*-1,2-Dideuteriohexyldicyclohexylborane. Method A.** Cyclohexene (4 mmol, 0.4 mL), BH_3·$S(CH_3)_2$ (2 mmol, 0.20 mL), and dioxane (0.5 mL) were added to a nitrogen-flushed, dry NMR tube fitted with a rubber septum. After 30 min, (*E*)-1-hexene-*1,2*-d_2 (2 mmol, 0.20 mL) was added via a syringe and the reaction was allowed to proceed for 1 h at room temperature. (The solid dicyclohexylborane dissolves during this period.) Methylamine (0.50 mL of a 40% aqueous solution) was added and the water layer which formed was removed with a syringe. The ^{2}H decoupled proton spectrum exhibited a doublet (J = 3.6 Hz) centered at 7.00 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibited two broad resonances at 7.00 and 6.13 ppm from internal benzene-d_6. The absence of ^{1}H signals at 6.99 ppm (J = 12.4 Hz) reflects the absence of the erythro diastereomer (vide infra).

Method B. Di(2-deuteriocyclohexyl)borane-*B*-d_1 (2 mmol) (vide supra) in diglyme was added to a nitrogen-flushed, dry NMR tube via syringe. Dioxane (0.5 mL) was added followed by (*Z*)-1-hexene-*1*,d_1 (2 mmol, 0.20 mL). After standing for 1 h at room temperature (the dicyclohexylborane dissolves), methylamine (0.50 mL of a 40% aqueous solution) was added and the water layer was removed with a syringe. The NMR spectrum duplicated that obtained by method A except for the solvent peaks.

***erythro*-1,2-Dideuteriohexyldicyclohexylborane. Method A.** (*Z*)-1-Hexene-*1,2*-d_2 was hydroborated using the procedure outlined for the (*E*) diastereomer, method A. The ^{2}H-decoupled ^{1}H spectrum exhibited a doublet (J = 12.4 Hz) centered at 6.99 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibited two broad resonances at 6.99 and 6.12 ppm relative to internal benzene-d_6. The absence of additional resonances in the ^{1}H spectrum at 7.00 ppm (J = 3.6 Hz) (vide supra) reflects the absence of the threo diastereomer.

Method B. (*E*)-1-Hexene-*1*-d_1 was reacted with di(2-deuteriocyclohexyl)borane-*B*-d_1 using the procedure outlined for the (*Z*) diastereomer, method B. The NMR spectrum duplicated that obtained by method A except for the solvent peaks.

***threo*-1,2-Dideuteriohexyl-9-BBN.** In a nitrogen-flushed glove box, 9-BBN (1.5 mmol, 0.17 g) was placed into an oven-dried NMR tube. Dioxane (0.5 mL) was added followed by (*E*)-1-hexene-*1,2*-d_2 (1.5 mmol, 0.15 mL). After 1 h, methylamine (0.5 mL of a 40% aqueous solution) was added. The water layer was removed with a syringe. The NMR spectrum indicated that the threo diastereomer had formed exclusively. The ^{2}H-decoupled ^{1}H spectrum exhibits a doublet (J = 3.6 Hz) at 6.74 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibits two broad singlets at 6.74 and 6.17 ppm, respectively, from internal benzene-d_6. The absence of additional ^{1}H signals at 6.77 ppm (J = 13.3 Hz) indicates the absence of the erythro diastereomer (vide infra).

***erythro*-1,2-Dideuteriohexyl-9-BBN.** (Z)-1-Hexene-*1,2*-d_2 (1.5 mmol, 0.15 mL) was reacted with 9-BBN (1.5 mmol, 0.17 g) as described for the (E) diastereomer. NMR analysis indicated that only the erythro diastereomer was produced. The ^{2}H-decoupled ^{1}H spectrum exhibits a doublet (J = 13.3 Hz) at 6.77 ppm relative to internal benzene. The ^{1}H-decoupled ^{2}H spectrum consists of two broad singlets at 6.77 and 6.18 ppm relative to internal benzene-d_6. The absence of additional ^{1}H signals at 6.74 ppm (J = 3.6 Hz) indicates the absence of the threo diastereomer (vide supra).

Acknowledgment. The work at Clemson was supported, in part, by the National Institutes of Health (Grant No. 1-R01-GM22788-01) and the National Science Foundation (Grant No. CHE77-07808).

Registry No.—9-BBN, 280-64-8; $BH_3{\cdot}S(CH_3)_2$, 13292-87-0; 1-hexyne, 693-02-7; 1-hexyne-*1*-d_1, 7299-48-1; di(2-deuteriocyclohexyl)borane-*B*-d_1, 65253-16-9; dicyclohexylborane, 1568-65-6; cyclohexene, 110-83-8.

References and Notes

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Synthesis of 9,9-Dimethyl-2-methoxy-5-benzosuberone. An Unexpected Failure of Benzylic Oxidation

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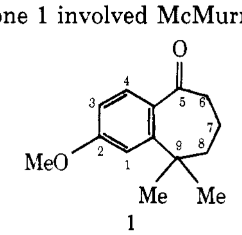
Received July 26, 1977

Attempts to prepare 9,9-dimethyl-2-methoxy-5-benzosuberone (**1**) by benzylic oxidation of 9,9-dimethyl-2-methoxybenzosuberan (**9**) proved unsuccessful. The problems associated with this oxidation are consistent with severe nonbonded interactions associated with the *gem*-dimethyl group in **9** which make formation of an initial benzylic radical difficult. Both nuclear magnetic resonance and ultraviolet data indicate a tendency of an sp^2-hybridized center adjacent to the aromatic nucleus in benzosuberans not to attain planarity with the phenyl ring, in contrast to the corresponding tetralin systems. An efficient synthesis of the ketone **1** from 4,4-dimethyl-6-methoxy-1-tetralone (**3**) is described.

During a study of synthetic approaches to the himachalene class of sesquiterpenes,[1] 9,9-dimethyl-2-methoxy-5-benzosuberone (**1**) was a desired intermediate. Initial attempts to synthesize ketone **1** involved McMurry's ring expansion



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procedure[2] on 4,4-dimethyl-6-methoxy-1-tetralone (**2**) whose straightforward preparation is shown in Scheme I. For future consideration, it should be noted that the benzylic oxidation of tetralin **6** using chromium trioxide–acetic acid–water[3] proceeded in good yield. Treatment of tetralone **2** in dimethyl sulfoxide with methylenetriphenylphosphorane gave a 96% yield of the exocyclic olefin **7** which proved to be very labile.[4] Therefore, the crude exocyclic olefin **7** was subjected to cy-

Scheme I