To the Graduate Council:

I am submitting herewith a dissertation written by Ray Jackson Newton, Jr. entitled "Part I. Stereochemistry and Mechanism of the Hydroboration of Olefins and of the Subsequent Protonolysis of Organoboranes; Part II. A New Oxidation Procedure for Organoaluminum Compounds." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

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Vice Chancellor
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PART I. STEREOCHEMISTRY AND MECHANISM OF THE HYDROBORATION OF OLEFINS AND OF THE SUBSEQUENT PROTONOLYSIS OF ORGANOBORANES; PART II. A NEW OXIDATION PROCEDURE FOR ORGANOALUMINUM COMPOUNDS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Ray Jackson Newton, Jr.

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1366198

DEDICATION

The author wishes to dedicate this work to his wife, Pamela Kay Parson Newton, whose love, companionship, support, and encouragement were unfailing during his entire academic career.

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The author wishes to express his sincere gratitude and deepest appreciation to Dr. George W. Kabalka for his guidance, advice, and encouragement during the course of this work.

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The author humbly expresses his gratitude to God the Father, God the Son, and God the Holy Spirit for a life of health, happiness, and spiritual and material blessings.

The inspiration to see this work to its completion is expressed in Philippians 4:13, "I can do all things through Christ which strengtheneth me."

ABSTRACT

Part I

The hydroboration reaction is generally believed to involve the cis addition of the boron and hydrogen atoms across the carbon-carbon double bond of an alkene. The basis for this belief rests primarily on the fact that the hydroboration-oxidation sequence is known to lead to stereospecific cis hydration of alkenes and on the assumption that the oxidation step has supposedly been shown to proceed with retention of configuration at the carbon originally attached to boron. In order to unambiguously determine the stereochemistry of the hydroboration reaction, (E)- and (Z)-1-hexene-1,2-d_2 were hydroborated with dialkylboranes (dicyclohexylborane and 9-BBN). Following complexation with methylamine, ^{2}H-decoupled, ^{1}H NMR analysis of the organoboranes revealed formation of 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 produced erythro- and threo-(1,2-dideuteriohexyl)-di(2-deuteriocyclohexyl)borane, respectively. These results constitute the first direct evidence that the hydroboration reaction does indeed involve the cis addition of the boron and hydrogen atoms across the carbon-carbon double bond of an olefin.

With the stereochemistry of the hydroboration reaction firmly established, the synthesis of organoboranes of known stereochemistry is possible. These organoboranes can be utilized to investigate the stereochemistry of organoborane, transformation reactions. A study of the stereochemistry of the protonolysis of organoboranes was undertaken because the hydroboration-protonolysis sequence is known to be an

attractive alternate to metal-catalyzed hydrogen reduction of olefins. Accordingly, (Z)- and (E)-1-phenyl-3,3-dimethyl-1-butene-1,2-d_2 were hydroborated to give erythro- and threo-organoboranes, respectively. ^{2}H-decoupled, ^{1}H NMR analysis of the subsequent protonolysis products derived from these organoboranes indicated formation of erythro- and threo-1-phenyl-3,3-dimethylbutane-1,2-d_2, respectively. These results clearly demonstrate that the protonolysis of organoboranes via carboxylic acids proceeds with retention of configuration at the carbon originally attached to boron and that the hydroboration-protonolysis sequence provides for the overall cis hydrogenation of an alkene.

Part II

Recently it was demonstrated that trimethylamine N-oxide and its corresponding dihydrate were convenient oxidizing agents for organoboranes. In light of the sometimes inefficient autoxidation of organoaluminum compounds by molecular oxygen, a study was conducted to investigate the utility of trimethylamine N-oxide as an oxidizing reagent for organoaluminum compounds. The major findings show that this reagent is effective in the oxidation of trialkyl- and triarylaluminum compounds in hydrocarbon solvent at elevated temperatures. The rate of oxidation is temperature dependent. However, vinyl groups attached to aluminum are not oxidized by the reagent, and alkylaluminum halides react to produce only tars under the conditions utilized.

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PART I.

STEREOCHEMISTRY AND MECHANISM OF THE HYDROBORATION OF OLEFINS AND OF THE SUBSEQUENT PROTONOLYSIS OF ORGANOBORANES

CHAPTER I

INTRODUCTION TO ORGANOBORANE CHEMISTRY

A. General Introduction

In the twenty-two years since the appearance of the first reports by H. C. Brown and B. C. S. Rao that olefins could be easily converted to organoboranes via the hydroboration reaction, the chemistry of boron compounds has undergone rapid development.[1,2] A compendium of their synthetic utility includes conversion to various classes of organic compounds including alcohols, aldehydes and ketones, carboxylic acids and derivatives, nitriles, alkyl halides, amines, alkenes and dienes, thioethers, and alkanes. Recently organoboranes have gained prominence as alkylating agents, adding carbon-carbon bond formation to the already long list of synthetic transformation.[3]

Historically, it was the discovery of the rapid reaction between olefins and diborane in ether solvents which provided the impetus for exploration of the hydroboration reaction and, subsequently, the chemistry of the resultant organoboranes. With the abundance of synthetic opportunities available from organoborane intermediates, it is of particular importance that the hydroboration reaction be thoroughly studied and characterized. Many investigations have been conducted to provide information on the factors which govern the scope, mechanism, stereochemistry, and regiochemistry of the reaction. For the most part, the study summarized in this dissertation concludes an investigation of the hydroboration

reaction.

B. Preparation and Structural Features of Diborane

Diborane, B_2H_6, the simplest isolated boron hydride, can be prepared by several methods. The most common method is the reaction, in ethereal solvents, of LiH, NaH, $LiAlH_4$, or $NaBH_4$ with a boron trihalide.[4] This method also provides a convenient preparation of diborane-d_6, B_2D_6, by substituting a metal deuteride for the metal hydride.

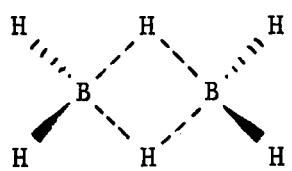
$$6\ LiH + 8\ BCl_3 \longrightarrow B_2H_6 + 6\ LiBCl_4$$

$$3\ NaBH_4 + 4\ BF_3 \longrightarrow 2\ B_2H_6 + 3\ NaBF_4$$

$$6\ LiD + 8\ BF_3 \longrightarrow B_2D_6 + 6\ LiBF_4$$

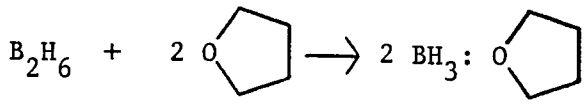
$$3\ LiAlD_4 + 4BF_3 \longrightarrow 2\ B_2D_6 + 3\ LiAlF_4$$

Diborane is a dimer of borane, BH_3, possessing bridging hydrogen atoms which result from two two-electron, three-center bonds.[5] In the B_2H_6 molecule, there are fourteen bonding orbitals available



and only twelve electrons to fill them. The excess of atomic orbitals over electrons causes the three-coordinate boron to be electron deficient.

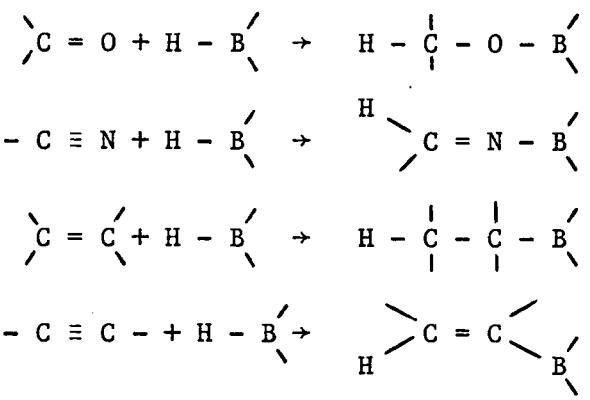
Diborane in tetrahydrofuran, or other Lewis-base solvents, dissociates to form the borane-ether complex.[6] The reaction of diborane with olefins in the gas phase, or in non-Lewis-base solvents, is



extremely slow even at high temperatures and long reaction times.[7] However, catalytic amounts of weak Lewis bases cause a nearly instantaneous reaction to occur at temperatures as low as 0°C. This suggests that the actual hydroborating agent is the borane-ether complex rather than diborane itself. Fortunately, several borane-ether complexes are now commercially available including borane-tetrahydrofuran and borane-methyl sulfide.

C. The Hydroboration Reaction

The addition of boron hydride to multiple bonds between carbon-carbon, carbon-nitrogen, and carbon-oxygen appears to be a general reaction. The term hydroboration is usually applied to

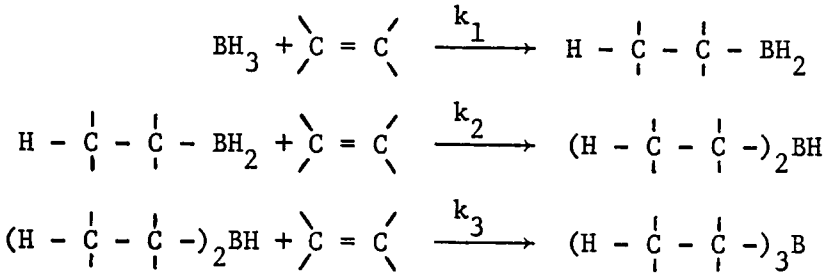


reactions involving the addition of boron hydride to carbon-carbon multiple bonds.[8]

1. Hydroboration of Alkenes

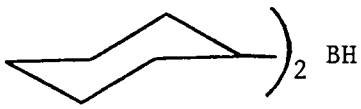
In general alkenes undergo the hydroboration reaction with

borane-ether solutions to afford a trialkylborane. In some reactions involving highly substituted alkenes, the degree of steric interaction around the central boron atom may be such that the reaction proceeds only to the dialkyl- or monoalkylborane stage.[9] Mono-

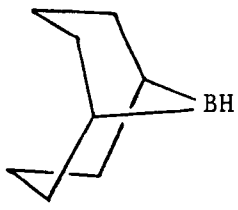


and disubstituted ethylenes generally form trialkylboranes, while tri- and tetrasubstituted ethylenes form the di- and monoalkylboranes, respectively. Cyclic olefins, with the exception of cyclopentene, react with borane to form dialkylboranes.

These partially alkylated boranes can be used as selective hydroborating agents when control of regioselectivity or reactivity is desired.[10,11] Of those used in this manner, dicyclohexylborane (DCHB) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two of the more effective hydroborating agents.



DCHB



9-BBN

The stoichiometry of the reaction with hindered alkenes clearly illustrates the importance of steric effects in controlling the

extent of the hydroboration reaction. Such effects are also indicated by the preference of boron for the less substituted carbon of an alkene[12] and by the increased regiospecificity shown in hydroborations utilizing the bulky borane derivatives.[10] While steric factors predominate in determining the degree of regiospecificity in the placement of the boron atom, electronic factors cannot be ignored.

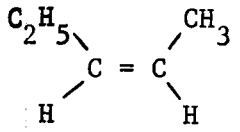
Monosubstituted terminal olefins, $RCH = CH_2$, react with BH_3 to give mainly the 1-boraalkanes along with approximately 6% of the 2-boraalkanes. The length or degree of branching of the alkyl group has little effect on isomer distribution.

$$\underline{n}\text{-}C_7H_9\text{-}\underset{6\%}{CH} = \underset{94\%}{CH_2} \qquad C_2H_5\text{-}\underset{7\%}{CH_2} = \underset{93\%}{CH_2} \qquad (CH_3)_3C\text{-}\underset{6\%}{CH} = \underset{94\%}{CH_2}$$

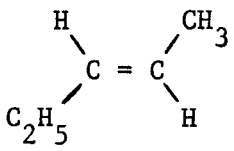
In the case of disubstituted terminal alkenes, $RR'C = CH_2$, there is a nearly quantitative addition of boron to the terminal carbon atom.

$$CH_3CH_2\overset{\overset{CH_3}{|}}{\underset{1\%}{C}} = \underset{99\%}{CH_2} \qquad \text{Ø}\text{-}\overset{\overset{CH_3}{|}}{\underset{tr}{C}} = \underset{100\%}{CH_2}$$

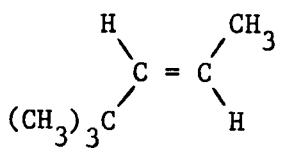
Disubstituted internal olefins, $RCH = CHR'$, undergo approximately equal distribution of the boron atom to each carbon atom of the double bond. There is little difference in distribution in hydroboration of <u>cis-trans</u> isomers. A slight preference for the less hindered carbon of the double bond is noticed when one of the alkyl groups is highly branched.



45% 55%

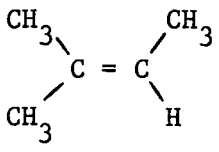


49% 51%

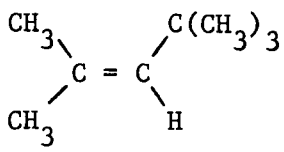


42% 58%

Trisubstituted olefins, RR'C = CHR", show great preference for formation of the less substituted derivative, even branching of the alkyl group on the less hindered carbon has no effect on distribution.



2% 98%

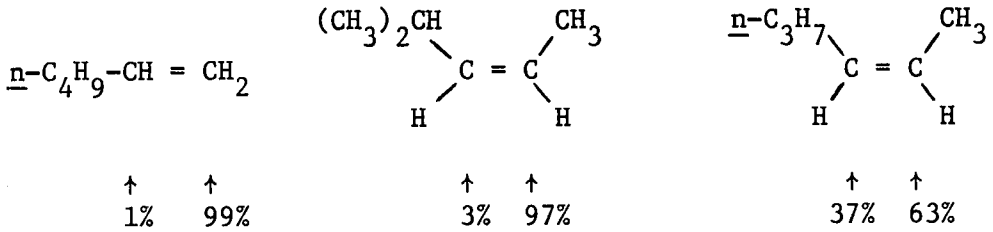


2% 98%

Tetrasubstituted alkenes, RR'C = CR"R'", react with borane to give approximately equal mixtures of the two possible isomers.

The extent of hydroboration depends on the steric interactions between the alkene and the alkylborane. In the case of hindered olefins such as 2-methyl-2-butene and 2,3-dimethyl-2-butene, the hydroboration reaction stops at the di- and monoalkylborane stages giving disiamylborane and thexylborane respectively.[13]

The mono- and dialkylboranes can react with relatively unhindered olefins to form trialkylboranes. These bulky organoboranes are useful hydroborating agents because they are sensitive to the steric environment of double bonds. In most cases, hydroboration with these reagents results in an overwhelming preference of boron for the less hindered carbon. Distributions with disiamylborane (Sia_2BH) are:[14]



↑ 1% ↑ 99% ↑ 3% ↑ 97% ↑ 37% ↑ 63%

Other dialkylboranes such as dicyclohexylborane and 9-borabicyclo-[3.3.1]nonane react similarly.[15]

One of the outstanding features of the hydroboration reaction is its ability to accommodate various functional substituents. The reaction of borane with carbon-carbon multiple bonds is much faster than its reaction with many common functional groups. The exceptions are the easily reducible groups such as aldehydes and ketones as well as groups containing acidic hydrogens which react to liberate hydrogen gas. The presence of halogens, ethers and acetoxy groups does not affect the hydroboration reaction. However, the placement of these groups adjacent to the boron atom can lead to undesirable reactions in the resulting organoborane.[16]

The presence of substituents in olefinic molecules can affect the regiochemistry (the placement of the boron atom) by exhibiting pronounced electronic effects. The following example is illustrative:[16]

$CH_2 = CHCH_2 - X$

↑	↑	X
0	100%	Cl
5%	95%	OAc
16%	84%	OEt
94%	6%	H

The amount of the isomer with boron at the position beta to

the substituent decreases with decreasing electronegativity of the substituent.

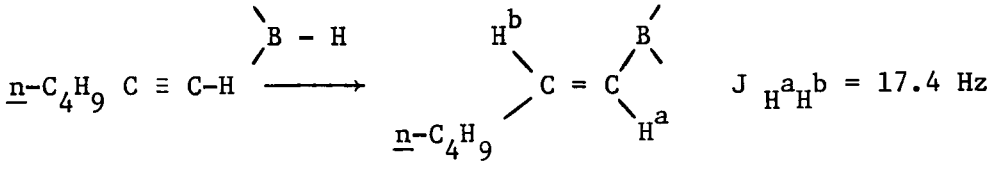
Steric effects dominate electronic effects in determining regiochemistry in the organoborane. Hydroboration with the bulky disiamylborane, demonstrates this clearly.[17]

	$ClCH_2CH_2CH=CH_2$	
	↑	↑
(BH_3)	18%	82%
(Sia_2BH)	1%	99%

To summarize, the regiochemistry of the boron atom placement in an alkene is determined by both steric and electronic factors with steric factors dominating when the two oppose each other in a given reaction.

2. Hydroboration of Alkynes

Alkynes are readily hydroborated to form either vinylboranes or diboraalkane derivatives depending upon the stoichiometry of the reaction, the type of alkyne used, and the hydroborating reagent. It has been shown that the initial step in the reaction is formation of a trans vinylborane; the result of a cis addition of the boron-hydride across the carbon-carbon triple bond. Conclusive proof lies in the fact that, in the hydroboration of 1-hexyne, a large coupling between the vinyl hydrogens is observed in the ^1H NMR.[18]



If the alkyne is disubstituted, the acetylene is more reactive than the intermediate vinylborane and the reaction proceeds predominately to the trivinylborane stage. With terminal alkynes, the initially formed monovinylborane is more reactive than the unreacted alkyne and preferential dihydroboration occurs to form the 1,1-dibora derivative, $RCH_2CH(BR'_2)_2$. The utilization of a hindered hydroborating agent in a 1:1 stoichiometry prevents formation of dihydroboration products and produces the monovinyldialkylboranes.[19]

In unsymmetrical dialkylalkynes, and terminal alkynes, there is a preference for attachment of boron at the less hindered position of the triple bond. This is especially true when a dialkylborane is used as the hydroborating agent.[20] Thus in the hydroboration of 1-hexyne with dicyclohexylborane, the boron atom is placed at the terminal carbon exclusively.[21]

This clearly demonstrates the parallelism of steric effects in the hydroboration of alkynes and alkenes. Furthermore, a recent study of electronic effects in the hydroboration of isomeric methoxy-2-hexynes reveals results analogous to those observed for substituted alkenes.[22]

D. Selected Reactions of Organoboranes

Organoboranes possess such extensive synthetic possibilities that it is beyond the scope of this dissertation to discuss all of the reactions that have been reported. Certain reactions will be reviewed because studies concerning their stereochemistry shed

light upon the stereochemistry of the hydroboration reaction.

1. Oxidation

One of the first reactions to be discovered was the oxidation of organoboranes to the corresponding alcohols. The uniqueness of this reaction lies in the fact that the hydroboration-oxidation sequence transforms an alkene into an alcohol of predominant anti-Markovnikov orientation. Hydroboration and oxidation of terminal and internal alkynes yields aldehydes and ketones, respectively.[8]

a. Elemental Oxygen. There are several means by which organoboranes can be oxidized. One of the simplest methods involves the direct reaction of organoboranes with oxygen. This exothermic reaction proceeds quite rapidly. The resulting alkoxyboranes are readily converted to the desired alcohols via hydrolysis. The mechanism of the oxidation of alkylboranes by oxygen has been shown to be a complex multi-step process involving free radicals.[23]

b. Alkaline Hydrogen Peroxide. One of the most convenient and widely studied oxidation methods is affected by alkaline hydrogen peroxide.

$$R_3B + 3H_2O_2 + NaOH \longrightarrow 3ROH + NaB(OH)_4$$

Various aspects of this reaction have been studied in detail, revealing that: (1) oxidation of boronic acids, $RB(OH)_2$, is second order overall, being first order in boronic acid and first order in hydrogen peroxide;[24,25,26] and (2) oxidation of

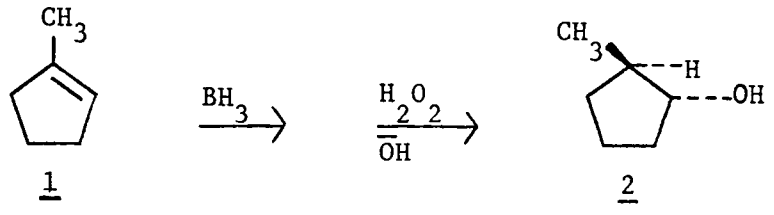
benzene-[^{18}O]-boronic acid with isotopically normal hydrogen peroxide in [^{18}O] water produces isotopically normal phenol.[27] These facts have led to the following proposed mechanism for the reaction:

$$H_2O_2 + OH^- \rightleftarrows HOO^- + H_2O$$

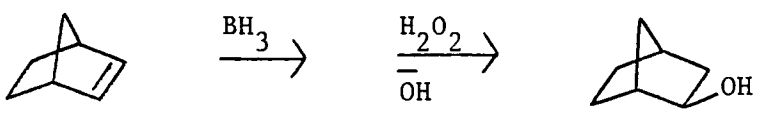
$$RB(OH)_2 + HOO^- \rightleftarrows [HO - \underset{\displaystyle OH}{\overset{\displaystyle R}{\overset{|}{\underset{|}{B}}}} - O - OH]^- \rightarrow$$

$$HO\text{-}\underset{\displaystyle OH}{\overset{\displaystyle |}{\underset{|}{B}}}\text{-}OR + OH^- \xrightarrow{H_2O} ROH + B(OH)_3$$

One of the most valuable synthetic aspects of the hydroboration-oxidation sequence via alkaline hydrogen peroxide is that an overall cis hydration of a carbon-carbon double bond is achieved. Thus the hydroboration of 1-methylcyclopentene(1) followed by oxidation, yields the pure (>99%) trans-2-methylcyclopentanol(2). Similarly, norbornene(3) yields exo-norbornanol(4) (99.5%).[28]



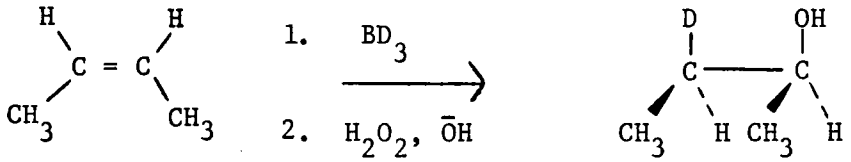
1 2



3 4

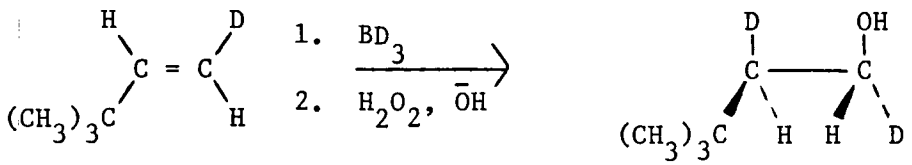
First shown for cyclic alkenes the hydroboration-oxidation

sequence has been shown to produce cis hydration of an internal acyclic alkene. Thus (Z)-2-butene(5) yields erythro-2-butanol-3-d_1(6), upon deuterioboration (BD_3), oxidation and protonation.[29]



5 6

More recently, the conversion of (E)-3,3-dimethylbutene-1-d_1(7), to erythro-3,3-dimethylbutan-1-ol-1,2-d_2(8) has been achieved by deuterioboration-oxidation.[30]

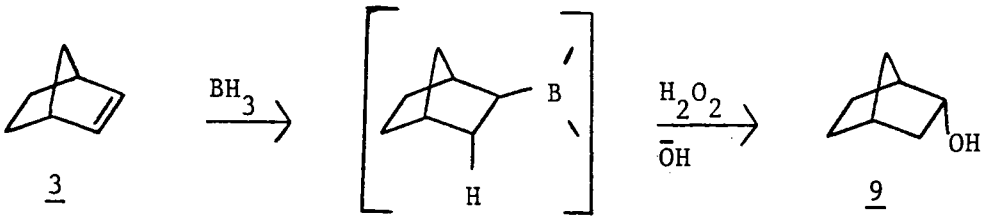


7 8

Although the hydration sequence corresponds to a clean cis hydration of the double bond, it is not possible, from these results alone, to draw conclusions as to the stereochemical characteristics of each step in the reaction. Thus the results are consistent with either a cis addition of the boron and hydrogen which is followed by oxidation occurring with retention of configuration, or a trans addition of the boron and hydrogen which is followed by oxidation occurring with inversion of configuration.

Brown and Zweifel, in considering the possible trans hydroboration of norbornene(3), anticipated that the boron atom should prefer the less hindered exo position. Oxidation with inversion

of configuration would then produce endo-norbornanol(9).



3 9

Since only the exo-norbornanol was formed, they concluded retention of configuration occurs during oxidation and, consequently, a cis addition occurs during the hydroboration step.[31]

While this observation is indeed interesting it is not at all conclusive in light of the widely known preference for exo attack in reactions involving the norbornyl system.[32] It is, at best, a rationalization of product formation.

Unfortunately this tenuous conclusion, derived from results utilizing norbornene, has been cited repeatedly in the literature as the "proof" that the oxidation of organoboranes occurs with retention of configuration. Furthermore, extrapolations have been made to other olefins in the assignment of hydroboration products of "known" stereochemistry.

The most relevant study concerned with the stereochemistry of the oxidation step reveals that alkaline hydrogen peroxide oxidation of chiral 1-phenylethylboronic acid produces chiral 1-phenylethanol.[33] Since the absolute configuration of the chiral 1-phenylethylboronic acid was not determined, no definitive statement as to whether the reaction proceeds with retention or inversion at the chiral carbon can be made. The only conclusion demanded is that oxidation takes place in a stereospecific manner.

c. Trimethylamine N-oxide. Recently, it has been reported that the commercially available trimethylamine N-oxide dihydrate is an efficient reagent for organoborane oxidations.[34] This reagent offers a significant improvement in the oxidation of sensitive, functionally substituted organoboranes since it avoids the alkaline condition necessary for hydrogen peroxide oxidation. The resulting alcohols have been shown to possess the same stereochemistry as those obtained via alkaline hydrogen peroxide oxidation.[35,36]

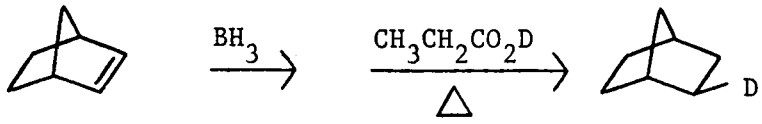
2. Protonolysis

Unlike their alkylaluminum counterparts, trialkylboranes are remarkably stable to water at room temperature. Treatment with concentrated mineral acids facilitates the protonolysis reaction; however, heating under reflux with such acids is necessary to bring about the loss of just one alkyl group.[37]

Somewhat unexpectedly, the organoboranes have proved to be quite susceptible to protonolysis by carboxylic acids. It has been observed that triethylborane can be quantitatively converted to ethane by refluxing in excess propionic acid for 2-3 hours.[38]

$$(CH_3CH_2)_3B \xrightarrow[\Delta]{CH_3CH_2CO_2H} 3CH_3CH_3$$

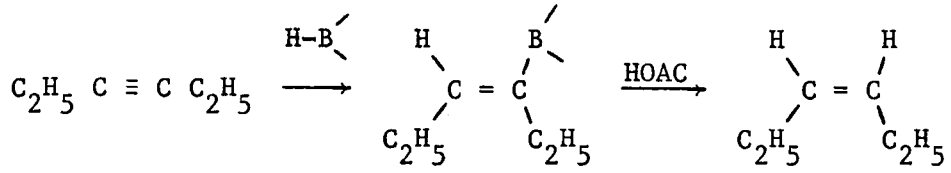
The reaction appears to be stereospecific. The hydroboration of norbornene(3) followed by deuteriolysis yields exo-deuterionorbornane(10).[39]



3 10

While the stereochemistry observed has been described as retention of configuration during the protonolysis step, it is based on the "assumed" exo-norbornylborane intermediate, as postulated by Brown and Zweifel (vide supra).

Organoboranes of the vinyl type, readily obtained by the hydroboration of acetylenes, undergo protonolysis readily. The compounds are completely protonolysed by acetic acid at 0°C. The reaction proceeds with retention of configuration at the carbon attached to boron, converting acetylenes into cis olefins of high purity.[40]

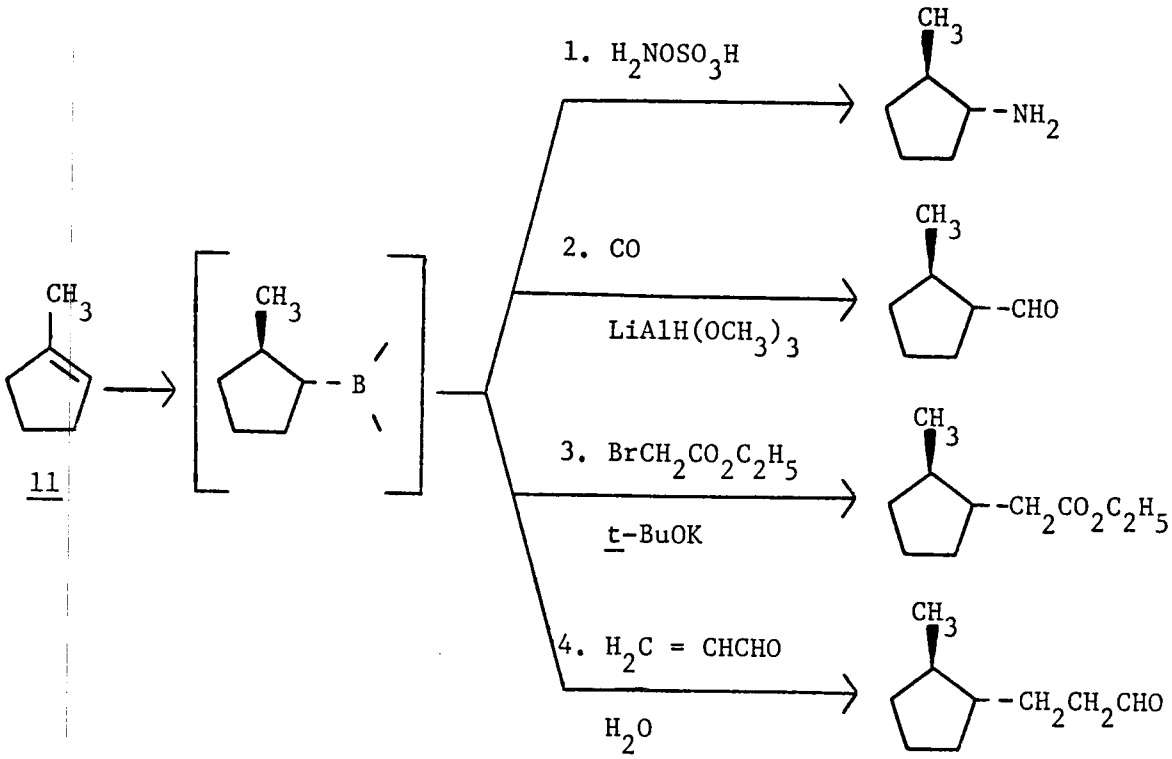


3. Additional Reactions

Other synthetic transformations involving organoboranes which proceed in a highly stereospecific manner include: (1) amination with hydroxylamine-O-sulphonic acid;[41] (2) carbonylation with carbon monoxide;[42] (3) carboxymethylation with ethyl bromoacetate;[42] (4) γ-propanalation with acrolein;[42] (5) base-induced halogenation;[43,44] and (6) mercuration with mercury(II) acetate.[45]

All but the last two were reported to proceed with stereospecific retention of configuration at the carbon originally

attached to boron. For example the hydroboration product of 1-methylcyclopentane(11) is converted into the respective trans products.[42] However, assignment of the trans stereochemistry to



the organoborane intermediate was based on the assumption that the stereochemistry of the oxidation step had been shown to occur with retention of configuration (vide supra).[31] Thus it was assumed that the respective trans products were formed via mechanisms involving retention of configuration at the carbon attached to boron.

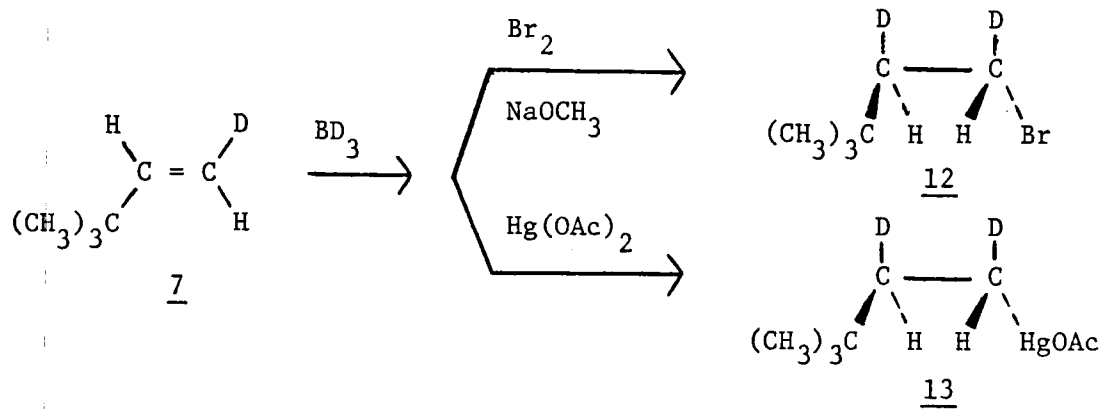
Discounting the assumption that the oxidation proceeds with retention of configuration, a stereospecific inversion transformation from a cis organoborane precursor serves equally well to explain the observed trans products.

The γ-propanalation with acrolein reveals one of the dangers

in overstating a stereochemical assignment. Brown, et al., have described the reaction as stereospecific, proceeding with retention at the carbon atom undergoing substitution. Actually two products were isolated and identified, the trans product (91%) and the cis product (9%).[46] With the formation of such a large percentage of cis product, the term "stereoselective" rather than "stereospecific" best describes this reaction as both retention and inversion are involved in product formation. Furthermore, the γ-propanalation with acrolein has been shown to proceed via free radical intermediates.[47] A free radical process cannot be described as being stereospecific. Thus the large amount of trans product reflects its thermodynamic stability rather than a stereospecific reaction mechanism. Thermodynamic factors can also be postulated to be controlling the product distributions in the other reactions involving cyclic organoboranes.

In contrast to the other transformations, the base-induced halogenation and mercuration (of primary alkylboranes) reactions produce products of opposite configuration from those of the other stereospecific reactions.

The deuterioboration of (E)-3,3-dimethylbutene-1-d_1 (7), followed by sodium methoxide assisted bromination or mercuration with mercury(II) acetate, produces threo-1-bromo-3,3-dimethylbutane-1,2-d_2 (12) or threo-3,3-dimethyl-1-butyl-1,2-d_2 mercuric acetate (13), respectively. [Deuterioboration-oxidation of (E)-3,3-dimethylbutene-1-d_1, gives erythro-3,3-dimethylbutan-1-ol-1,2-d_2, see page 13.]



These transformations have been described as proceeding with greater than 95% inversion of configuration.[44,45] Again, the stereochemical assignment of inversion was based upon the fact that the products exhibited the opposite configuration from the alcohol obtained via oxidation of the intermediate organoboranes. [The oxidation, as noted earlier, was assumed to occur with retention of configuration.]

It is quite evident from this review that the stereochemical assignment of each organoborane transformation has been based directly, or indirectly, upon the assumption that oxidation occurs with retention of configuration. We contend that the original assignment of oxidation of trinorbornylborane proceeding with retention of configuration as proposed by Brown and Zweifel is, at best, circumstantial and that such an assignment is yet to be conclusively made.

E. Mechanism of the Hydroboration Reaction

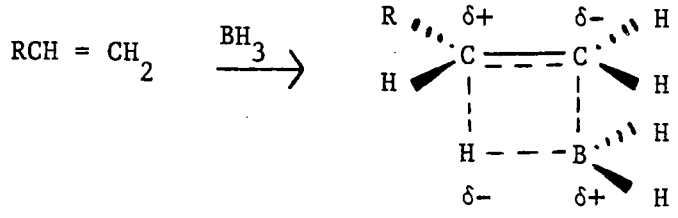
Considering its increasing use in organic chemistry in the twenty-two years since its discovery, it is indeed surprising that the mechanism of the hydroboration of alkenes has not been more firmly established.

The pathway from initial reactants to final products involves three consecutive addition reactions, five monomer-dimer equilibria, complex formation-dissociation, and three redistribution and elimination reactions.[48] This intricate interplay of reactions adds to the elusiveness of a description of the mechanism of hydroboration.

Several facts which shed light upon the hydroboration reaction mechanism are: (1) the hydroboration is a very facile addition, usually being complete within a few minutes at 0°C[1]; (2) the hydroboration of tetramethylethylene with borane in tetrahydrofuran exhibits both a hydrogen-deuterium and a boron(10)-boron(11) kinetic isotope effect;[49] (3) the direction of addition is strongly influenced by steric effects, resulting in boron addition to the least hindered carbon of the olefin (however, electronic effects can occasionally overcome the steric requirements of the addition with electron-withdrawing groups on the olefin favoring substitution alpha to the electronegative substituent);[16] (4) there is no significant buildup of hydridic character on the boron's hydrogens as confirmed by the absence of reduction of the silicon-chlorine bonds during the addition of borane in tetrahydrofuran to methylchlorosilylalkenes.[50]

Herbert C. Brown was the first to propose a mechanism for the

hydroboration reaction. He concluded that the hydroboration of an alkene involves a simple, four-center transition state with the direction of addition controlled primarily by the polarization of the boron-hydrogen bond, $\overset{\delta+}{B}\!\!-\!\!\overset{\delta-}{H}$.[8] The net result is an addition of



the boron hydrogen bond across the carbon-carbon double bond. The regiochemistry of boron-placement is determined by an interplay of electronic factors which stabilize the incipient carbonium ion in the alkene and steric interaction between the substituents on the alkene and those attached to boron.

Two very important implications that arise from Brown's proposed mechanism are the cis stereochemistry in the placement of the boron and hydrogen atoms across the carbon-carbon double bond and the concertedness of the four-center transition state.

1. Stereochemical Implication of Hydroboration

Despite a widely held belief to the contrary, the hydroboration of alkenes has never been shown to occur via cis addition of borane to olefin. This misconception is the result of a fundamental misunderstanding of the facts. What is known is that the hydroboration of an alkene followed by oxidation with alkaline hydrogen peroxide gives an overall cis hydration of a double bond, see page 12.

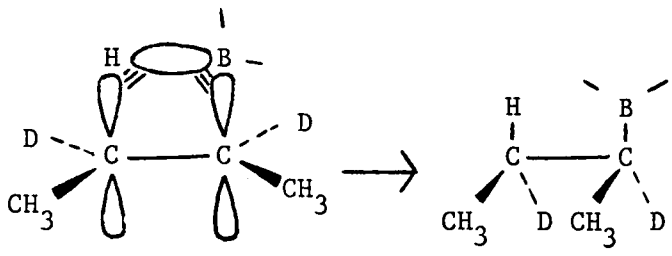
The data do not resolve the fundamental question as to the stereochemistry of each step in the hydroboration-oxidation sequence. Although the majority of the scientific community believes that hydroboration is "known" to occur in a cis fashion, their faith is based on the assumption that the oxidation step has been "shown" to occur with complete retention of configuration at the migrating carbon. However, a thorough review of the literature (vide supra) reveals no conclusive evidence for assignment of stereospecific retention of configuration during oxidation.

Therefore, the stereochemistry of the hydroboration step remains in question and has not been established by Brown and Zweifel to occur via a cis addition of the boron and hydrogen atoms across the carbon-carbon double bond.

2. Concertedness Implication of Hydroboration

The observation of both a hydrogen-deuterium and a boron(10)-boron(11) kinetic isotope effect can be accounted for only if both the hydrogen and the boron atom are involved in either bond breaking or formation during the rate-determining step of the hydroboration reaction. This clearly implies that the hydroboration reaction involves a concerted rate-determining step. The observation that there is no significant buildup of hydridic character on boron's hydrogens during the hydroboration reaction also serves to confirm the concerted nature of the reaction. Consequently, any mechanism proposed for the hydroboration reaction must account for its concertedness; moreover, it must do so under the thermal conditions observed for rapid hydroboration at 0°C.

In considering Brown's originally proposed mechanism, the four-center transition state fulfills the requirement of a concerted rate-determining step. As drawn, it also implies a cis stereochemistry in placement of boron and hydrogen atoms across the carbon-carbon double bond. A cis, four-center transition state has significant symmetry barriers for a thermal reaction. It involves a perpendicular approach of the sigma boron-hydrogen bond to the π orbital of the carbon-carbon double bond. Thus the hydroboration of (Z)-2-butene-2,3-d_2 (14) would presumably yield the cis hydroboration



14 15

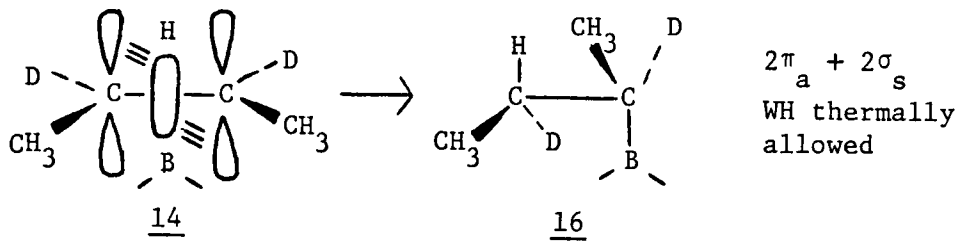
$2\pi_s + 2\sigma_s$

WH thermally forbidden

product 15 which results from bond formation when the sigma bond and π orbital overlap in a suprafacial direction. However, the overlap between two electrons in a sigma bond and two electrons in a π orbital occurring in a suprafacial direction is said to be a thermally forbidden process according to rules of symmetry established by Woodward and Hoffmann.[51] While Brown's cis, four-center transition state accounts for a concerted mechanism, it cannot do so under the thermal conditions observed for the hydroboration reaction.

One possible alternate mechanism is a trans, four-center transition state in which the sigma boron-hydrogen bond approaches

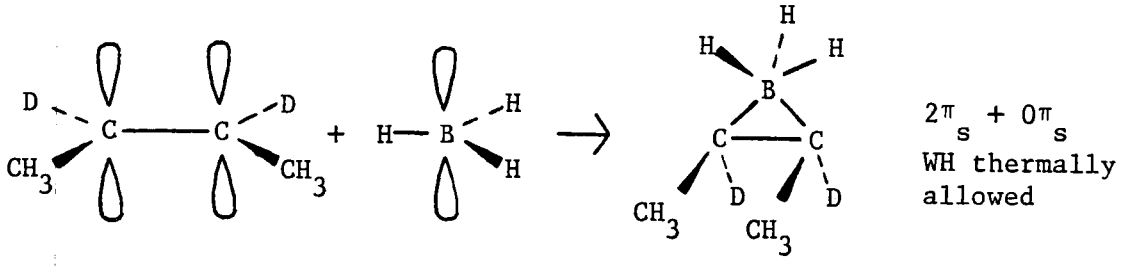
the π orbital in a parallel manner. The hydroboration of compound 14 via this mechanism would give the trans hydroboration product 16



14 16

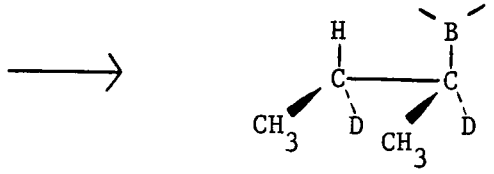
This transition state involves a two-electron π orbital in antarafacial overlap with a two-electron sigma bond in suprafacial overlap. Such a process is symmetry allowed under thermal conditions.[51]

Recently, Jones suggested a two-step mechanism for the hydroboration reaction. He postulated an equilibrium between borane and olefin involving interaction between the vacant p orbital of boron and occupied π orbital of the olefin which results in the production of a three-center, two-electron π complex intermediate. The formation of the π complex intermediate is a thermally allowed, 2πs + 0πs, process. The second step involves a rate-determining, concerted conversion of the intermediate to the cis hydroboration product 15. This is illustrated for compound 14 as follows:



14

π complex



15

Jones argues that, when the symmetry of the orbitals involved in the π complex is considered, such a complex can convert to products in a thermal, symmetry-allowed, concerted process.[52]

It appears that both a trans, four-center transition state and one involving a π complex account equally well for a thermal, concerted hydroboration mechanism. However the expected hydroboration products are different in each case. A trans hydroboration product is expected from a trans, four-center state, while a cis hydroboration product is predicted for a transition state involving a π complex. Therefore until the stereochemistry of the hydroboration products are known, it will be impossible to make a definitive statement concerning the mechanism of the hydroboration of alkenes.

Furthermore, until it is clearly demonstrated that either the

hydroboration reaction proceeds in a cis manner or the oxidation of organoboranes occurs with retention of configuration, the stereochemical assignments of the other transformations, as they now appear in the literature, are in jeopardy.

CHAPTER II

STEREOCHEMISTRY AND MECHANISM OF THE HYDROBORATION OF ALKENES

A. Statement of the Problem

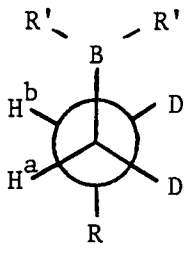
It is now clear that, even though the majority of the scientific community believes the hydroboration of an alkene involves the cis addition of the boron and hydrogen atoms across the carbon-carbon double bond, their belief is unsubstantiated. The hydroboration reaction is of sufficient importance to warrant the unambiguous determination of its stereochemistry. We initiated a study to determine the stereochemistry of the hydroboration of alkenes by characterizing the hydroboration products themselves, rather than attempt a proof of retention or inversion during subsequent transformation steps.

B. Synthetic Approach

Nuclear magnetic resonance spectroscopy, hereafter referred to as NMR, was chosen as the appropriate analytical method due to its proven utility in stereochemical investigations.[53,54,55] Karplus has established the relationship between the dihedral angle and the coupling constant for protons on vicinal carbons.[56] In general when the vicinal hydrogens form a dihedral angle of 40°-60° a small coupling constant (less than 5 Hz) is observed, while a dihedral angle of 160°-180° produces a large value (often greater than 10 Hz).

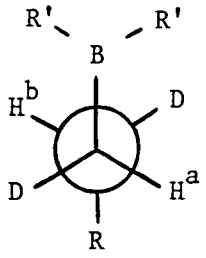
We proposed to synthesize the following threo- and

erythro-diastereomers (drawn in their most populated conformations):



threo

$J_{H^aH^b}$ = small value



erythro

$J_{H^aH^b}$ = large value

By measuring the coupling constant between the vicinal hydrogens ($J_{H^aH^b}$), the assignment of threo or erythro can be made to each diastereomer. Since the stereochemistry of each alkene precursor would be known, a definitive statement as to cis or trans placement of the boron and hydrogen atoms would be possible.

The ^1H NMR analysis of threo- or erythro-organoboranes is complicated by several factors. First, interfering resonances are possible if the boron atom is not placed exclusively at the terminal carbon of the alkene. Second, 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. Third, if the anti conformer of each organoborane is not highly populated, only time-averaged coupling constants will be observed instead of the desired coupling constants. Fourth, the chemical shifts of the hydrogens on the carbons alpha and beta to boron are essentially isochronous such that hydrogens on these carbons do not couple in first order fashion. Fifth, deuterium-hydrogen coupling broadens

the resonance lines in the ^1H NMR spectra of hydrogens coupled to deuteriums. These factors cause serious difficulties in the measurement of the small hydrogen-hydrogen coupling value for the threo hydroboration product.

The first three of these difficulties were easily circumvented by the utilization of sterically demanding, symmetrical, hydroborating agents such as dicyclohexylborane (DCHB) and 9-borabicyclo[3.3.1]nonane(9-BBN), see page 5. The steric bulk of these hydroborating agents directed placement of the boron atom to the terminal carbon of the alkene, see page 8. In addition, the steric interactions between the alkyl groups on boron and the alkyl portion of the olefin assured that the anti conformer of the organoboranes was thermodynamically favored. Furthermore, the use of a dialkylhydroborating agent precluded the formation of diastereomers because only one chiral carbon, alpha to boron, was formed in each organoborane molecule (i.e., hydroboration produced only the enantiomeric pair).

The fourth difficulty was alleviated by using a simple Lewis base, methylamine, as a complexing agent. The formation of the organoborane-amine complex induced an upfield shift in the ^1H NMR spectra of the hydrogens alpha and beta to boron. This is illustrated for triethylborane as follows:

$$\underset{\substack{\text{b} \quad \text{a} \\ \delta 1.19 \quad \delta 0.95}}{CH_3\text{-}CH_2\text{-})_3B} \xrightarrow{NH_2Me} \underset{\substack{\text{b} \quad \text{a} \\ \delta 0.78 \quad \delta 0.32}}{CH_3\text{-}CH_2\text{-})_3B\cdot NH_2Me}$$

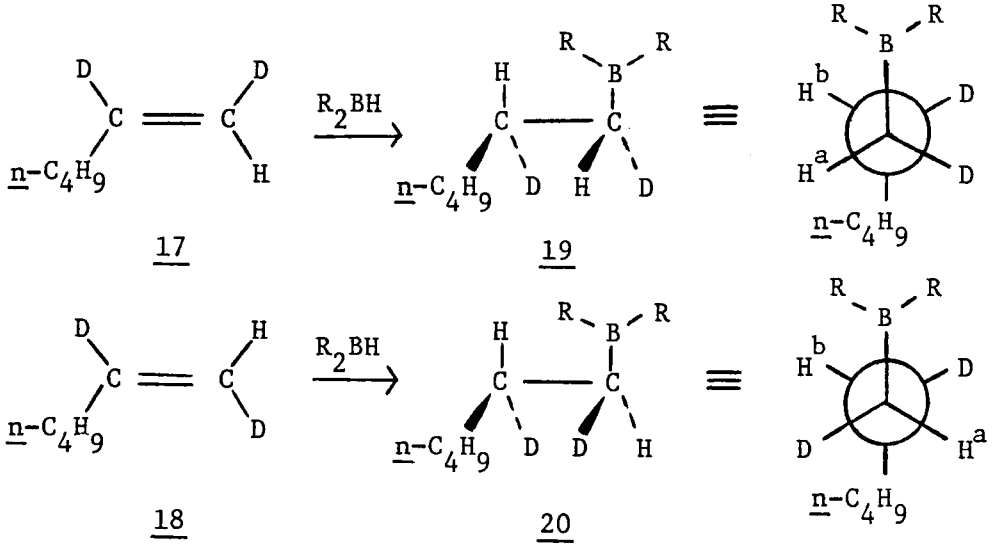
The resultant difference in the chemical shifts for the hydrogens

alpha and beta to boron is great enough to insure first order coupling.[57]

The last complication was overcome by using a NMR spectrometer equipped with a deuterium decoupler to obtain the ^{1}H NMR spectra. This double-resonance technique (deuterium decoupling) removed the line-broadening caused by deuterium-hydrogen coupling without affecting the hydrogen-hydrogen coupling.

The proposed threo- and erythro-organoboranes can be synthesized by two independent routes as illustrated in Schemes I and II. Scheme I outlines the hydroboration of (E)- and (Z)-1-hexene-1,2-d_2, (17) and (18) respectively. The addition of a dialkylborane to these hexenes produce the threo- and erythro-organoboranes, (19) and (20) respectively, if the addition of the boron and hydrogen atoms to these alkenes occurs in the assumed cis manner.

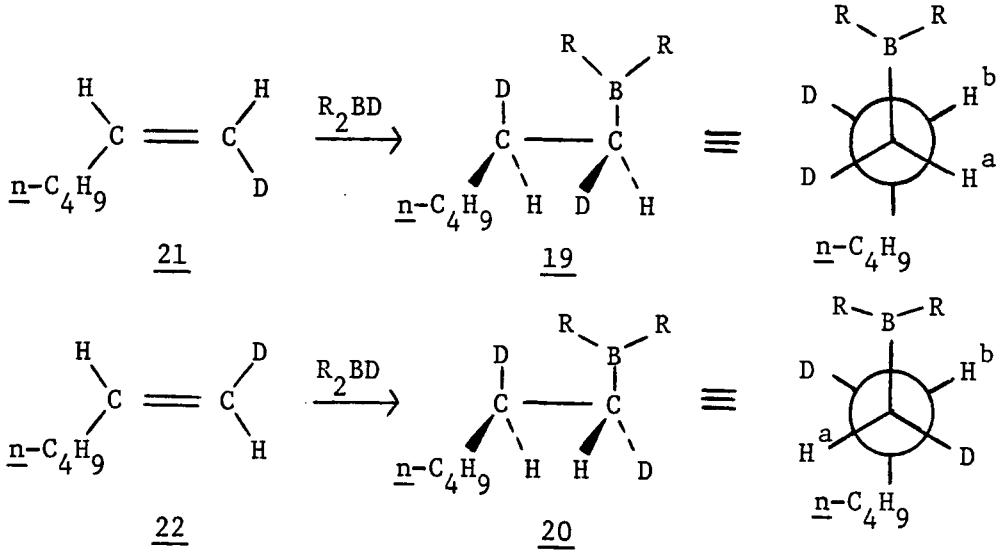
Scheme I



Trans addition would give the opposite stereochemical results such that alkenes 17 and 18 would yield, upon hydroboration, the erythro- and threo-organoboranes, (20) and (19) respectively. Thus, once the stereochemistry of the organoboranes has been determined experimentally, the occurrance of either cis or trans addition can be unambiguously identified.

Scheme II shows the deuterioboration of (Z)- and (E)-1-hexene-1-d_1, (21 and 22) to give the threo- and erythro-organoboranes, (19) and (20) respectively, assuming cis addition. A trans addition

Scheme II



would produce the opposite stereochemical results.

In order to present a complete stereochemical analysis for hydroboration and deuterioboration, we synthesized the threo- and erythro- diastereomers via both of the procedures outlined in Schemes I and II.

C. Results and Conclusions

1. Results

As outlined in Scheme I, (E)-1-hexene-1,2-d_2 (17) was hydroborated with dicyclohexylborane (DCHB). After treatment with methylamine, the resultant complex exhibited a ^{1}H NMR spectrum in which the peak at the highest field was assigned to the hydrogen which was on the carbon (in the hexyl group) alpha to the boron. Upon deuterium decoupling, this peak revealed a vicinal ($J_{H^aH^b}$) coupling constant of 3.6 Hz, indicating formation of threo-1,2-dideuteriohexyl—DCHB, Figure 1.

Furthermore, the hydroboration of (Z)-1-hexene-1,2-d_2 (18) with DCHB gave a product which, after complexation, exhibited a ^{2}H-decoupled, ^{1}H NMR spectrum in which the hydrogen on the carbon (in the hexyl group) alpha to the boron atom showed a vicinal ($J_{H^aH^b}$) coupling constant of 12.4 Hz. This large value indicated the formation of erythro-1,2-dideuteriohexyl—DCHB, Figure 2.

Corroborating results were obtained utilizing 9-borabicyclo[3.3.1]nonane (9-BBN) as the hydroborating agent. Alkenes 17 and 18 reacted with 9-BBN to give threo-1,2-dideuteriohexyl—9-BBN ($J_{H^aH^b}$ = 3.6 Hz), (Figure 3) and erythro-1,2-dideuteriohexyl—9-BBN ($J_{H^aH^b}$ = 13.3 Hz), (Figure 4), respectively.

Not surprisingly, the results obtained from the deuterioboration products achieved via Scheme II supported the initial experiments. The deuterioboration of (Z)- and (E)-1-hexene-1-d_1 (21 and 22) with di(2-deuteriocyclohexyl)borane-B-d_1 (DCHB-D) gave threo- and erythro-1,2-dideuteriohexyl—DCHB-D, respectively. The

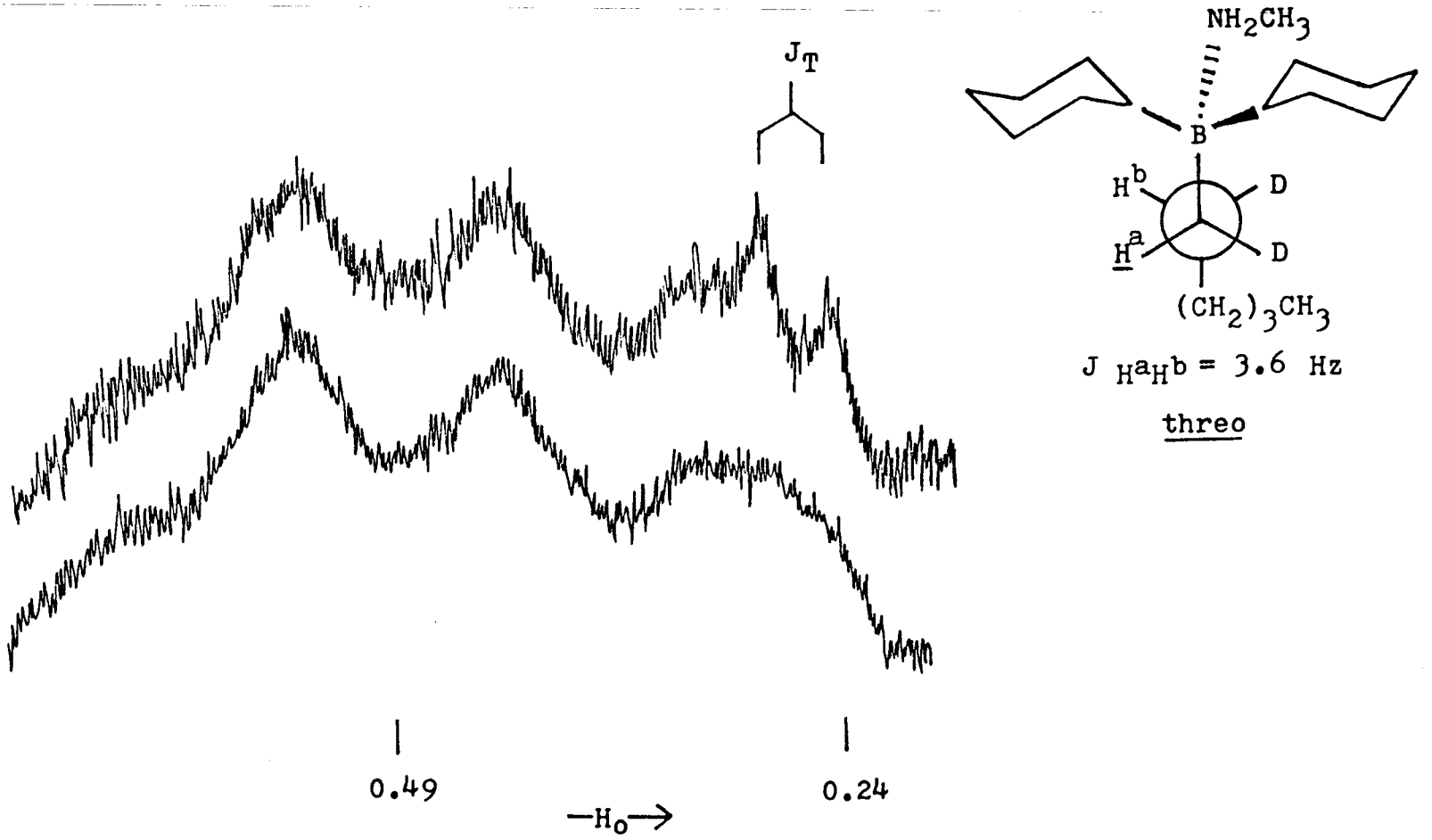


Figure 1. ^1H NMR spectrum (90 MHz) of threo-1,2-dideuteriohexyl-DCHB. Upper portion is ^2H-decoupled; lower portion is normal (undecoupled) spectrum.

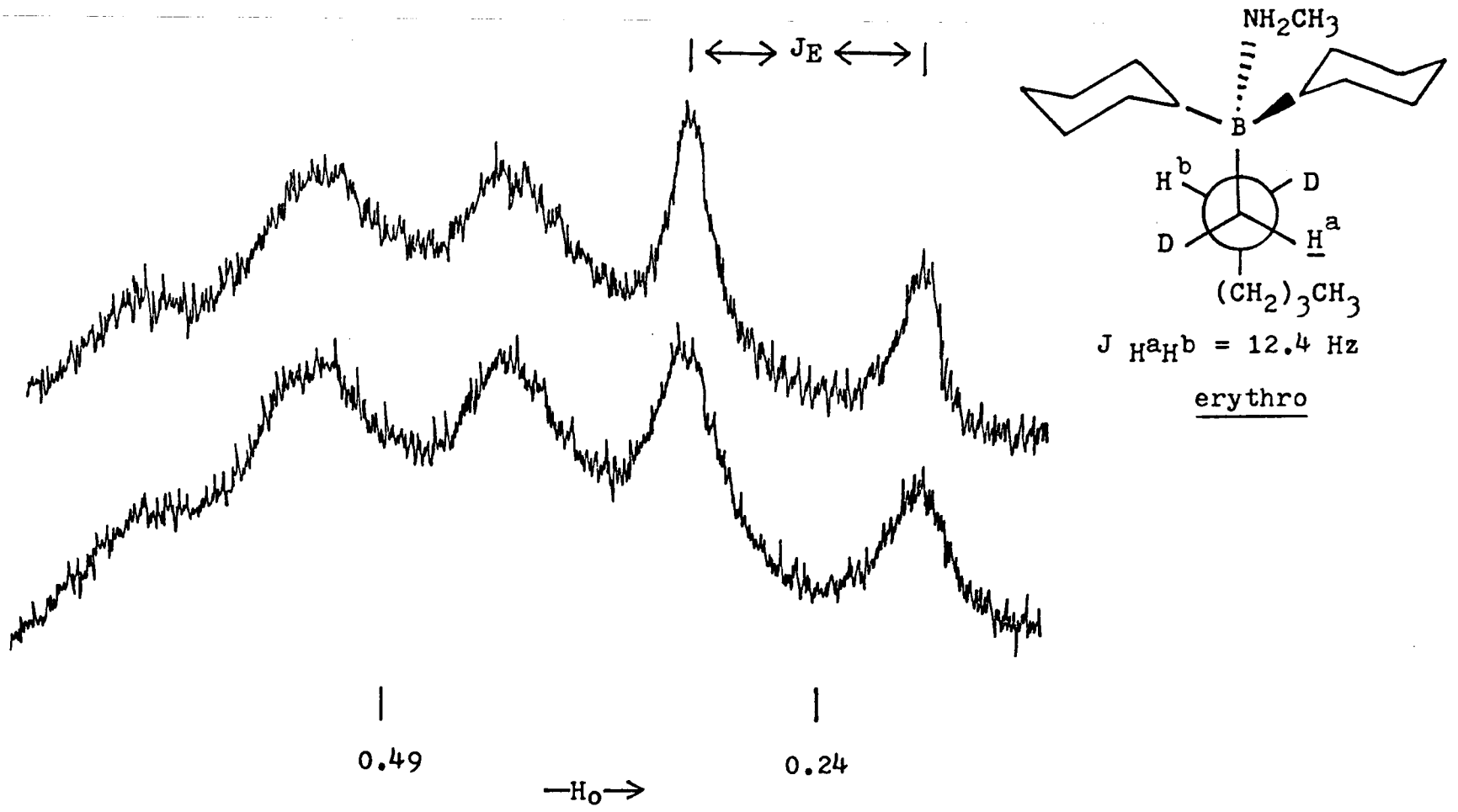


Figure 2. ^{1}H NMR spectrum (90 MHz) of erythro-1,2-dideuteriohexyl-DCHB. Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.

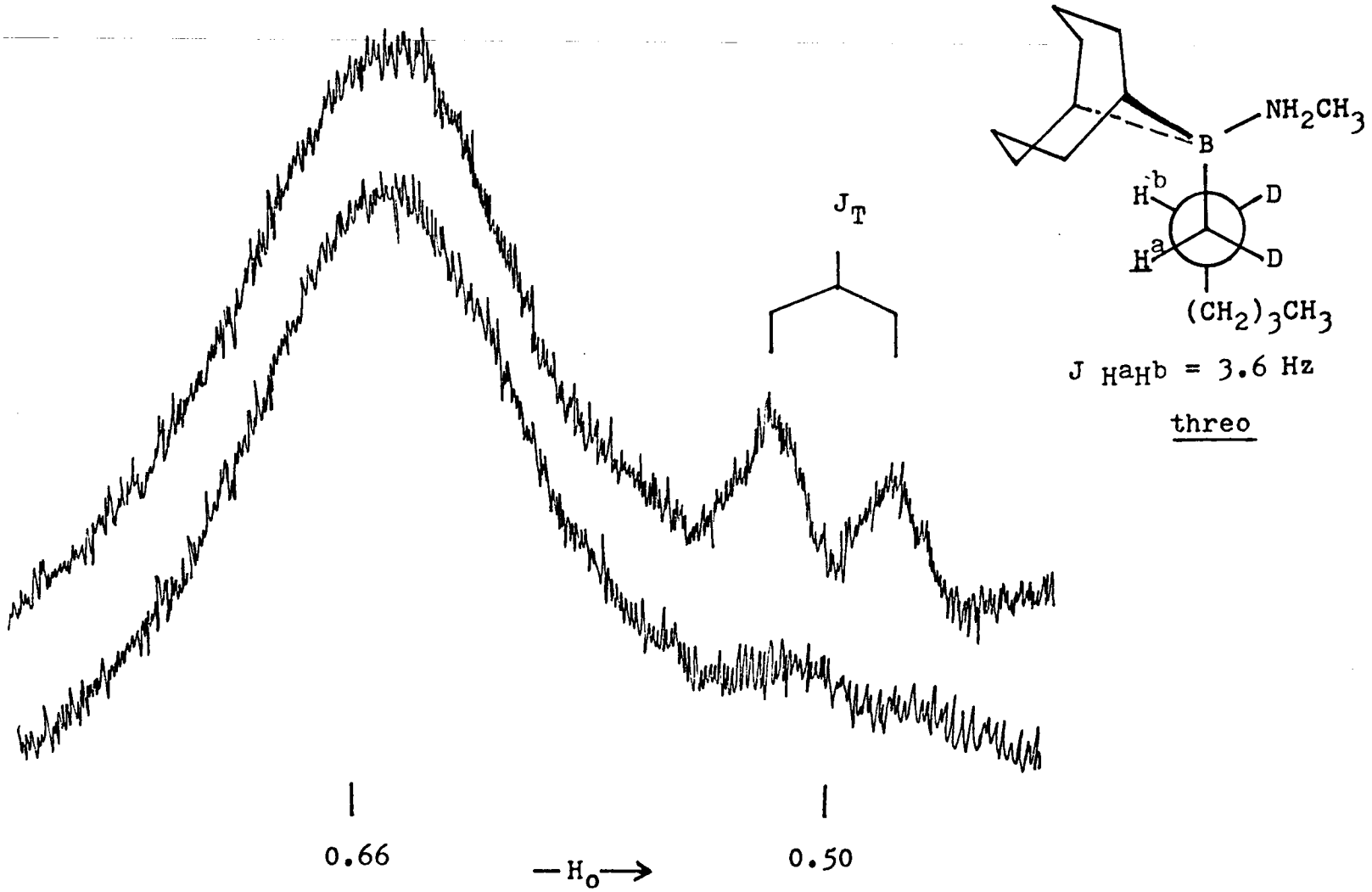


Figure 3. ^{1}H NMR spectrum (90 MHz) of threo-1,2-dideuteriohexyl-9-BBN.

Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.

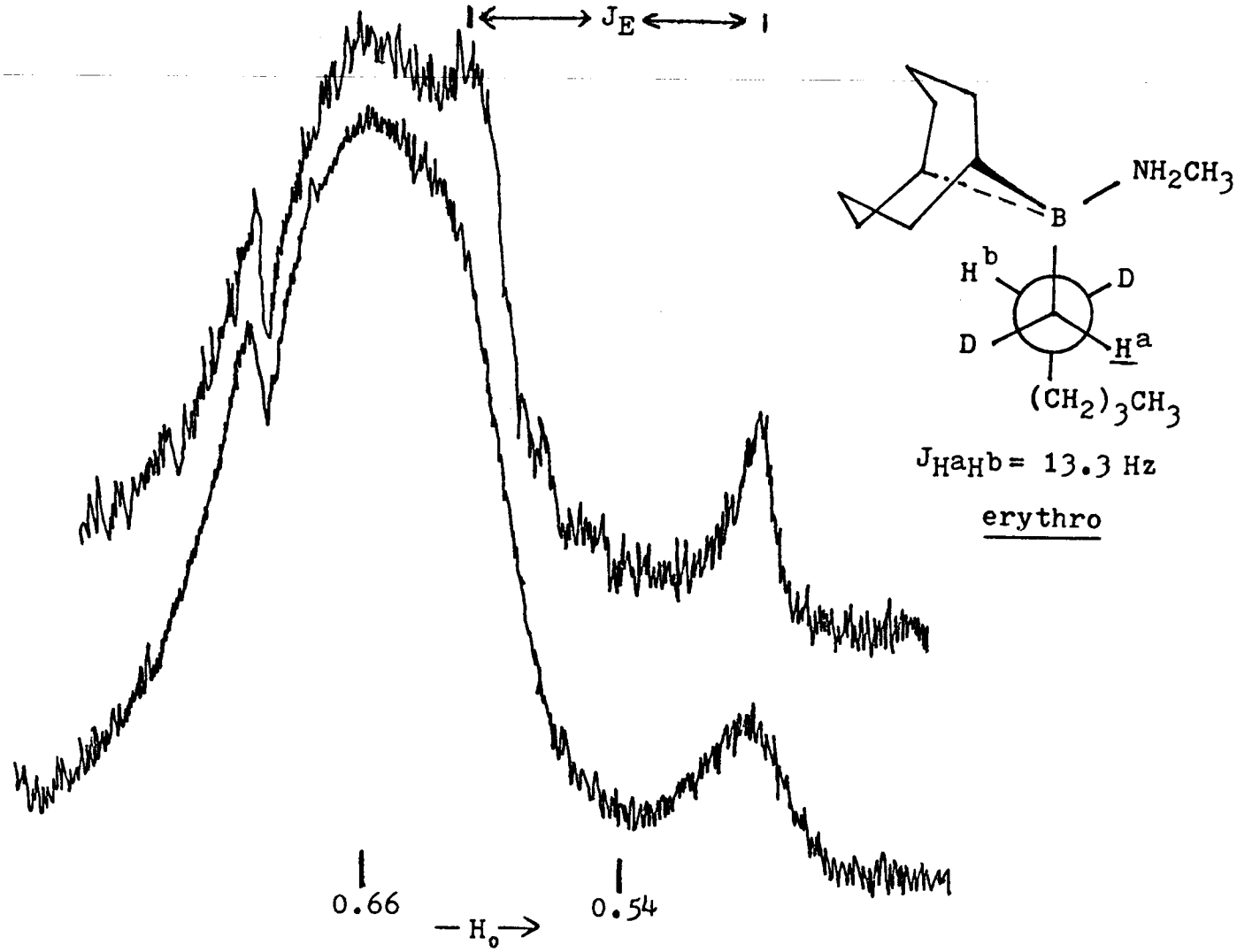


Figure 4. ^{1}H NMR spectrum (90 MHz) of erythro-1,2-dideuteriohexyl-9-BBN. Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.

high-field regions of the ^{1}H NMR spectra of these threo- and erythro-diastereomers duplicated those obtained in Scheme I with dicyclohexylborane as the hydroborating agent, Figures 1 (p 33) and 2 (p 34), respectively.

2. Conclusions

These results prove conclusively that, in the hydroboration of alkenes, the boron and hydrogen atoms add in a cis manner to the carbon-carbon double bond.[58]

The stereospecific cis hydroboration products are in accordance with both Brown's cis, four-center transition state and Jones' three-center, π complex intermediate. Assuming the hydroboration reaction does not violate Woodward's and Hoffmann's rules of symmetry, Jones' π complex intermediate best describes the mechanism of the hydroboration of alkenes.[52] However, until evidence for the intermediacy of a π complex (i.e., infrared or Raman spectra shifts) during hydroboration is presented, Brown's cis, four-center transition state cannot be ruled out.

With the cis stereochemistry of the hydroboration reaction now firmly established, the alkaline hydrogen peroxide oxidation reaction in the hydroboration-oxidation sequence (which has been proven to yield the cis hydration product) can be described unambiguously as occurring with stereospecific retention of configuration. As a result, the stereochemical assignments of the other transformations, based previously on the assumption that oxidation occurred with retention of configuration are, indeed, correct. Accordingly, amination, carbonylation, and

carboxymethylation, do occur with retention of configuration, while base-induced halogenation and mercuration of a primary alkylborane proceed with inversion of configuration. [Mercuration of tri-exo-norbornylborane has been determined to proceed with at least 93% retention of configuration.[59]]

D. Experimental

1. General Techniques

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), deuterium oxide (Aldrich), lithium deuteride (Alfa), cyclohexene (Eastman), methylamine as a 40% aqueous solution (Fisher) were used as received.

Routine ^{1}H NMR spectra were recorded on Varian T-60 and HA-100 spectrometers; chemical shifts are reported in ppm relative to internal Me_4Si(TMS). ^{2}H-decoupled, hydrogen and ^{1}H-decoupled, deuterium NMR spectra were recorded on a Bruker HX-90 spectrometer at 90 and 13.8 MHz, respectively (for hydrogen and deuterium spectra, the lock signal was benzene). Chemical shifts, which were assigned relative to internal benzene and benzene-d_6, respectively, are normalized to TMS using δ TMS = δ7.20 - δ benzene (benzene-d_6).

2. Synthesis of Reagents

a. Di(2-deuteriocyclohexyl)borane-B-D_1[$(c\text{-}C_6H_{10}D)_2BD$]

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-equalizing, 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 ethyl 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. Di(2-deuteriocyclohexyl)borane-B-D_1(DCHB-D) precipitated from the reaction mixture. To ensure complete reaction, the mixture was stirred for 1 h at room temperature and was immediately utilized for deuterioboration.

b. Dicyclohexylborane.[60] 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 $BH_3 \cdot SMe_2$ (100 mmol, 9.6 mL) was added via a syringe (10 min). The dicyclohexyborane(DCHB) precipitated during a 1-h period.

c. 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 resultant lithium acetylide and the reaction mixture was stirred overnight. Distillation afforded 29 mL (85%) of 1-hexyne-1-d_1: bp 72°C; ^1H NMR (CCl_4) δ 2.13 (t,2), 1.46 (m,4) 0.90 (t,3). The isotopic purity of this

compound was determined by the absence of an acetylenic hydrogen in the ^{1}H NMR.

3. Synthesis of Deuterated Alkenes

a. (E)-1-Hexene-1,2-d_2(17). 1-Hexyne (100 mmol, 11.4 mL) was deuterioborated with DCHB-D (100 mmol) in diglyme, (vide supra). After 1 h the reaction was complete (the solid DCHB-D dissolves), 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; ^{1}H NMR (neat) δ 4.90 (broad singlet, 1), 2.00 (t,2), 1.33 (m,4), 0.90 (t,3); mass spectra, M^+ 86.

b. (Z)-1-Hexene-1,2-d_2(18). This isomer was prepared in a manner analogous to the preparation of (E)-1-hexene-1,2-d_2. 1-Hexyne-1-d_1 (100 mmol) was reacted with DCHB-D and then protonolyzed with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 66°C; ^{1}H NMR (neat) δ 4.90 (slightly broadened singlet, 1), 2.00 (t,2), 1.33 (m,4), 0.90 (t,3); M^+ 86.

c. (E)-1-Hexene-1-d_1(22). 1-Hexyne (100 mmol, 11.4 mL) was hydroborated with DCHB (100 mmol) in diglyme at 0°C (vide supra). The reaction mixture was stirred for 1 h and the dimethyl sulfide (BH_3 solvent used to prepare DCHB) was distilled from the mixture (nitrogen 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; ^{1}H NMR (CCl_4) δ 5.73 (m,1), 4.90 (d, 1, J_{HH} = 18.0 Hz),

200 (m,2), 1.33 (m,4), 0.90 (t,3); mass spectra M^+ 85. The vinyl coupling constant of 18.0 Hz agreed with that of (E)-3.3-dimethylbutene-1-d_1 reported in Reference 30.

d. (Z)-1-Hexene-1-d_1 (21). This isomer was prepared in a manner analogous to the preparation of (E)-1-hexene-1-d_1. 1-Hexyne-1-d_1 was added to DCHB followed by protonolysis with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 65°C; ^{1}H NMR (neat) δ 5.73 (m,1), 4.83 (d, 1, J_{HH} = 10.0 Hz), 2.00 (m,2), 1.33 (m,4), 0.90 (t,3); M^+ 85. The vinyl coupling constant of 10.0 Hz agreed with that of (Z)-1-butene-1-d_1 reported in Reference 61.

4. Preparation of the threo- and erythro-Diastereomers[15]

a. threo-1,2-Dideuteriohexyl—DCHB. Cyclohexene (4 mmol, 0.4 mL), $BH_3 \cdot SMe_2$ (2 mmol, 0.2 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, 0.2 mL) was added via a syringe and the reaction was allowed to proceed for 1 h at room temperature. (The solid DCHB dissolves during this period.) Methylamine (0.5 mL of a 40% aqueous solution) was added and the water layer which formed was removed with a syringe. The ^{2}H-decoupled, ^{1}H-spectrum exhibited a doublet ($J_{H^aH^b}$ = 3.6 Hz) centered at δ 0.20. The ^{1}H-decoupled, ^{2}H-spectrum exhibited two broad resonances at δ 1.07 and 0.20. The absence of ^{1}H signals at δ 0.21 ($J_{H^aH^b}$ = 12.4 Hz) indicates the absence of the erythro-diastereomer (vide infra).

b. erythro-1,2-Dideuteriohexyl—DCHB. (Z)-1-Hexene-1,2-d_2 was hydroborated using the procedure outlined for the E-diastereomer. The ^{2}H-decoupled, ^{1}H-spectrum exhibited a doublet ($J_{H^aH^b}$ = 12.4 Hz) centered at δ 0.21. The ^{1}H-decoupled, ^{2}H-spectrum exhibited two broad resonances at δ 1.08 and 0.21. The absence of additional resonances in the ^{1}H NMR spectrum at δ 0.20 ($J_{H^aH^b}$ = 3.6 Hz) (vide supra) indicates the absence of the threo-diastereomer.

c. 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 exhibited a doublet ($J_{H^aH^b}$ = 3.6 Hz) at δ 0.46. The ^{1}H-decoupled, ^{2}H-spectrum exhibited two broad singlets at δ 1.03 and 0.46. The absence of additional ^{1}H signals at δ 0.43 ($J_{H^aH^b}$ = 13.3 Hz) indicated the absence of the erythro-diastereomer (vide infra).

d. 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 its E-diastereomer. NMR analysis indicated that only the erythro-diastereomer was produced. The ^{2}H-decoupled, ^{1}H-spectrum exhibited a doublet ($J_{H^aH^b}$ = 13.3 Hz) at δ 0.43. The ^{1}H-decoupled, ^{2}H-spectrum consisted of two broad singlets at δ 1.02 and 0.43. The absence of additional ^{1}H signals at δ 0.46 ($J_{H^aH^b}$ = 3.6 Hz)

indicated the absence of the threo-diastereomer (vide supra).

e. threo-1,2-Dideuteriohexyl—DCHB-D. Di(2-deuteriocyclohexyl)borane-B-d_1 (2 mmol) (vide supra) in diglyme was added to a nitrogen-flushed, dry NMR tube via a syringe. Dioxane (0.5 mL) was added, followed by (Z)-1-hexene-1-d_1 (2 mmol, 0.2 mL). After standing for 1 h at room temperature (the DCHB-D dissolves), methylamine (0.50 mL of a 40% aqueous solution) was added and the water layer was removed with a syringe. Except for the solvent peaks, the NMR spectrum duplicated that obtained for threo-1,2-dideuteriohexyl—DCHB.

f. erythro-1,2-Dideuteriohexyl—DCHB-D. (E)-1-Hexene-1-d_1 was deuterioborated with DCHB-D using the procedure outlined for its Z-diastereomer. Except for the solvent peaks, the NMR spectrum duplicated that obtained for erythro-1,2-dideuteriohexyl—DCHB.

CHAPTER III

STEREOCHEMISTRY AND MECHANISM OF THE PROTONOLYSIS OF ORGANOBORANES

A. Mechanisms of Synthetic Transformations

As described in Chapters I and II, organoboranes are readily formed by the regioselective and stereospecific hydroboration reaction. Once synthesized, organoboranes can undergo transformation reactions via several mechanistic pathways.

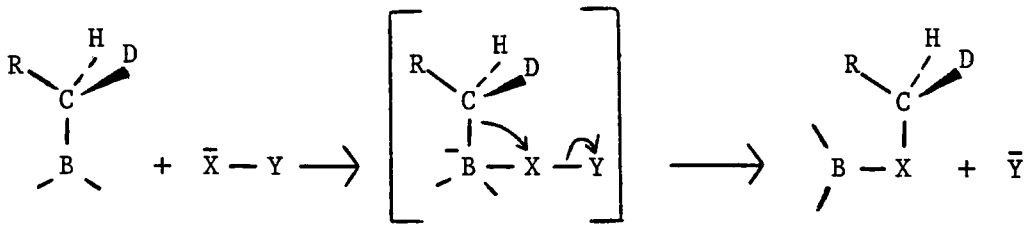
1. Free Radical Chain Reactions

Several organoborane reactions are believed to occur by free radical mechanisms.[62,63] Even though the free radical reactions are both synthetically and mechanistically important, product formation via free radicals is never stereospecific making a comprehensive discussion of their chemistries inappropriate.

2. Intramolecular Anionotropic Rearrangements

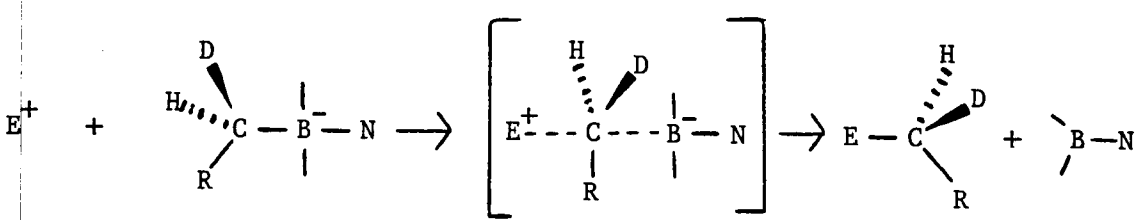
The most common mechanism by which organoboranes react is that of the intramolecular anionotropic rearrangement,[64] hereafter referred to as IAR. The IAR mechanism is also called the ate-complex mechanism, being derived from the nomenclature of four-coordinate boron compounds. Transformations which proceed via the IAR mechanism are believed to occur by a 1,2-alkyl migration similar to that proposed for the alkaline hydrogen peroxide oxidation, see page 12. It can now be stated that the products of an IAR mechanism are formed stereospecifically with retention of configuration

at the migrating carbon. The IAR mechanism is shown for a general case as follows:

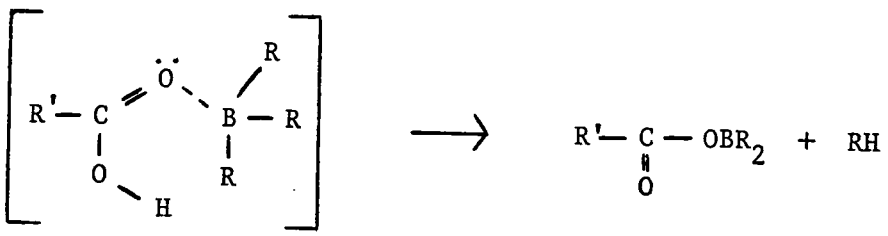


3. Electrophilic Substitutions

Electrophilic substitution is a reaction of widespread importance in organometallic chemistry. At present only four reactions--base-induced bromination,[43,44] base-induced iodination,[65] mercuration of a primary alkylborane,[44] and protonolysis with carboxylic acids[39]--have been described as organoborane transformations which proceed via electrophilic substitution. The first three reactions are of interest because an inversion of configuration occurs at the carbon attached to boron. This stereochemical result is best explained by a reaction mechanism involving back-side attack of the electrophile at the carbon-boron bond through a transition state, illustrated as follows:



Normally, electrophilic substitution reactions occur either with retention or racemization of the products,[66,67,68] rather than inversion. Indeed, Brown has described the protonolysis of organoboranes with carboxylic acids as one which proceeds via electrophilic substitution giving retention of configuration,[39] see page 15. He attributes the effectiveness of carboxylic acids in organoborane protonolysis to their ability to coordinate with the organoborane forming a closed six-membered transition state having the boron-carbon bond in position for an intramolecular attack by the proton.[8]



This mechanism is supported by a kinetic study which showed that the protonolysis of an organoborane is second order overall (being first order in organoborane and first order in carboxylic acid) and that a primary hydrogen-deuterium isotope effect is observed during the electrophilic attack.[69]

As mentioned in Chapter I, the stereochemical assignment of retention of configuration during organoborane protonlysis is based on the exo-deuterionorbornane product obtained by deuteriolysis of an "assumed" tri-exo-norbornylborane intermediate. Even if the stereochemical assignment of retention of configuration were correct

in this case, Brown recognized that it was not possible to generalize rigorously from this single result with the norbornane system to all other organoboranes.

The difficulty with such generalizations becomes clearly apparent when one considers the mercuration of organoboranes. Brown and Larock reported that mercuration with mercuric benzoate of tri-exo-norbornylborane gave at least 93% of exo-norbornylmercuric benzoate. They concluded that the mercuration of trialkylboranes most likely proceeded with complete retention of configuration at the carbon attached to boron analogous to the protonolysis reaction.[59] Their conclusion contrasts dramatically with that of Gielen and Fosty who reported that mercuration with mercuric acetate of tri(erythro-3,3-dimethyl-1-butyl-1,2-d_2) borane proceeded with greater than 95% inversion of configuration,[45] see page 18.

Davies and Roberts have attempted to extend the hypothesis that protonolysis occurs with retention of configuration to an acyclic organoborane. They reacted chiral dibutyl-1-phenylethylboronate with deuteriooctanoic acid which produced chiral deuterioethylbenzene. However, their assignment of retention of configuration at the carbon originally attached to boron is only speculation since no attempt was made to determine the absolute configuration of either the reactant or product.[33]

B. Statement of the Problem

While the protonolysis of tri-exo-norbornylborane appears to proceed with retention of configuration, the stereochemistry of

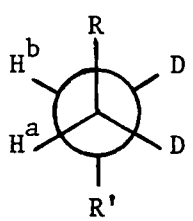
the protonolysis of other cyclic and acyclic organoborane intermediates has yet to be established.

We proposed to determine the stereochemistry of the protonolysis of acyclic organoboranes of known configuration by analyzing the protonolysis products. In so doing, we would also determine whether the hydroboration-protonolysis sequence provides for the cis hydrogenation (as demonstrated for alkynes, see page 16) or trans hydrogenation of acyclic alkenes.

C. Synthetic Approach

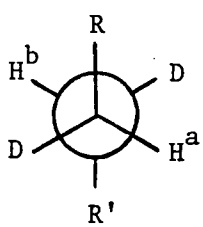
For reasons cited in Chapter II, NMR spectroscopy was chosen as the analytical method taking advantage of the Karplus relationship between the dihedral angle and the coupling constant for hydrogens or vicinal carbons.

We intended to employ the hydroboration-protonolysis sequence to synthesize the following threo- and erythro-diastereomers.



threo

$J_{H^aH^b}$ = small value



erythro

$J_{H^aH^b}$ = large value

The measurement of the coupling constant between the vicinal hydrogens would allow the assignment of threo or erythro to each diastereomer. Since the stereochemistry of each alkene precursor

and its organoborane intermediate would be known, the stereochemistry of the protonolysis reaction could be determined. Additionally, the hydroboration-protonolysis sequence could be defined as proceeding to give either cis or trans hydrogenation of acyclic alkenes.

In order to measure the coupling constant between the vicinal hydrogens in the ^{1}H NMR spectrum of each threo- and erythro-diastereomer, several criteria must be met. First, although vicinal hydrogens which have the same chemical shift do spin-spin couple, splitting is not observed. The chemical shift difference in Hz ($\Delta\nu$) between the vicinal hydrogens must be sufficiently greater than the spin-spin coupling constant (J) in order to observe a first order splitting pattern ($\Delta\nu/J$ greater than 10).[70] Second, the anti conformer of each diastereomer must be highly populated in order to observe the desired coupling constants instead of time-averaged coupling constants.

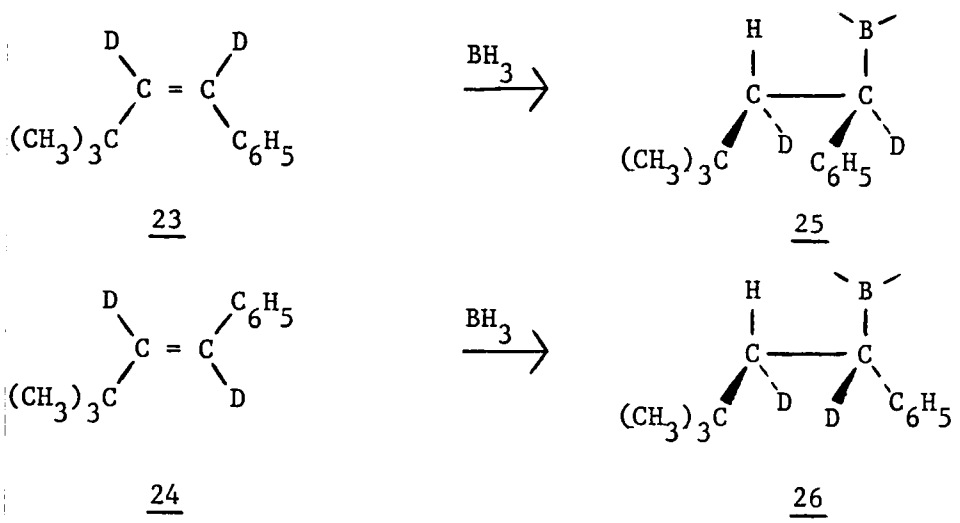
These criteria would be met if the R and R' substituents on the vicinal methine carbons of the threo- and erythro-diastereomers (see page 48) were phenyl and t-butyl. When these groups are present, the chemical shift difference of the vicinal methine carbons is calculated to be $\Delta\delta = 1.30$.[71] If the ^{1}H NMR spectra were recorded on a 90 MHz spectrometer, the chemical shift difference would be 117 Hz (1.30 x 90 MHz). Of the two diastereomers, the erythro-diastereomer would be expected to exhibit the larger coupling constant with a value of approximately 12.4 Hz, see Figure 2 (page 34). The splitting pattern would approach first order ($\Delta\nu/J$ = 117 Hz/12.4 Hz = 9.44) for the erythro-diastereomer and even more so for the

threo-diastereomer with its smaller coupling constant. The steric interactions between the phenyl and the bulky t-butyl substituents should assure that the anti conformer of each diastereomer would be thermodynamically favored over the syn and gauche conformers.

One additional complication which was expected in the measurement of the vicinal coupling constants was line broadening in the ^1H NMR spectra of the diastereomers due to deuterium-hydrogen coupling. As discussed in Chapter II, this difficulty can be overcome by using a NMR spectrometer equipped with a deuterium decoupler to obtain the ^1H NMR spectra.

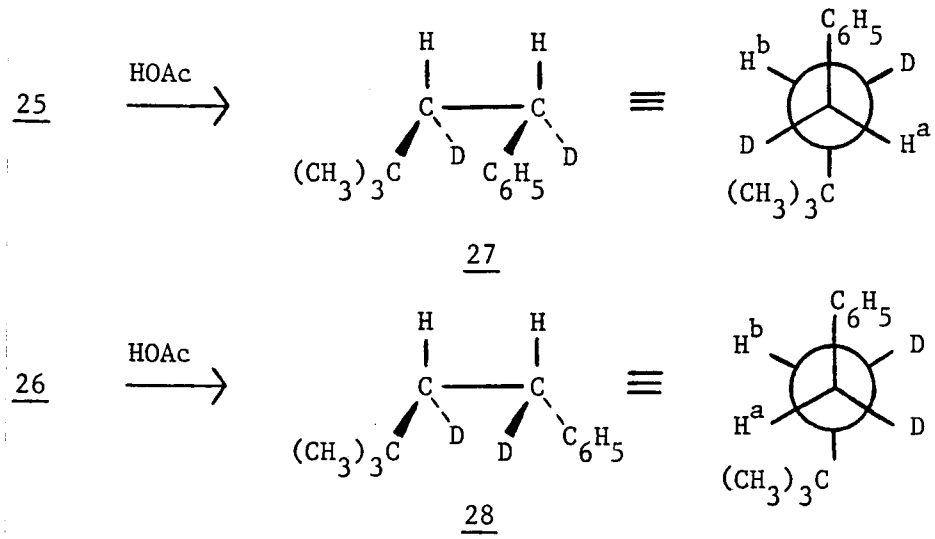
With these considerations in mind, we synthesized (Z)- and (E)-1-phenyl-3,3-dimethyl-1-butene-1,2-d_2, (23) and (24) respectively. The stereospecific cis hydroboration of alkenes 23 and 24 (Scheme III) would give organoboranes 25 and 26 respectively.

Scheme III



A subsequent protonolysis of organoboranes 25 and 26 (Scheme IV) would yield erythro- and threo-1-phenyl-3,3-dimethylbutane-1,2-d_2, (27) and (28) respectively, if protonolysis occurs with retention of configuration at the carbon originally attached to boron.

Scheme IV



An inversion of configuration would produce the opposite stereochemical results such that organoboranes 25 and 26 would yield, upon protonolysis, diastereomers 28 and 27, respectively. Thus, once the stereochemistry of the protonolysis products had been determined, the occurrence of either retention or inversion of configuration would be ascertained.

In order to provide diastereomers of known stereochemistry, the original alkenes 23 and 24 were cis hydrogenated over palladium on carbon to yield diastereomers 27 and 28, respectively.[72]

D. Results and Conclusions

1. Results

As presented in Scheme III, (Z)-1-phenyl-3,3-dimethyl-1-butene-1,2-d_2(23) was hydroborated with borane-tetrahydrofuran (BH_3•THF) to give organoborane 25. After treatment with acetic acid (Scheme IV), a product was isolated whose ^{2}H-decoupled, ^{1}H NMR spectrum showed that the hydrogen on the carbon adjacent to the phenyl substituent (H^a) exhibited a vicinal ($J_{H^aH^b}$) coupling constant of 12.4 Hz indicating formation of erytho-1-phenyl-3,3-dimethylbutane-1,2-d_2(27), Figure 5. An identical coupling constant value was observed when alkene 23 was hydrogenated over palladium on carbon which indicated formation of alkane 27, Figure 6.

Furthermore, the hydroboration of (E)-1-phenyl-3,3-dimethyl-1-butene-1,2-d_2(24) with BH_3•THF gave organoborane 26. Following protonolysis, organoborane 26 yielded a product whose ^{2}H-decoupled, ^{1}H NMR spectrum showed that the hydrogen on the carbon adjacent to the phenyl substituent (H^a) exhibited a vicinal ($J_{H^aH^b}$) coupling constant of 5.0 Hz indicating formation of threo-1-phenyl-3,3-dimethylbutane-1,2-d_2(28), Figure 7. An identical coupling constant value was observed when alkene 24 was hydrogenated over palladium on carbon which indicated formation of alkane 28, Figure 8.

2. Conclusions

These results clearly demonstrate that the protonolysis of acyclic organoboranes via carboxylic acid does occur in a stereospecific fashion with retention of configuration at the carbon

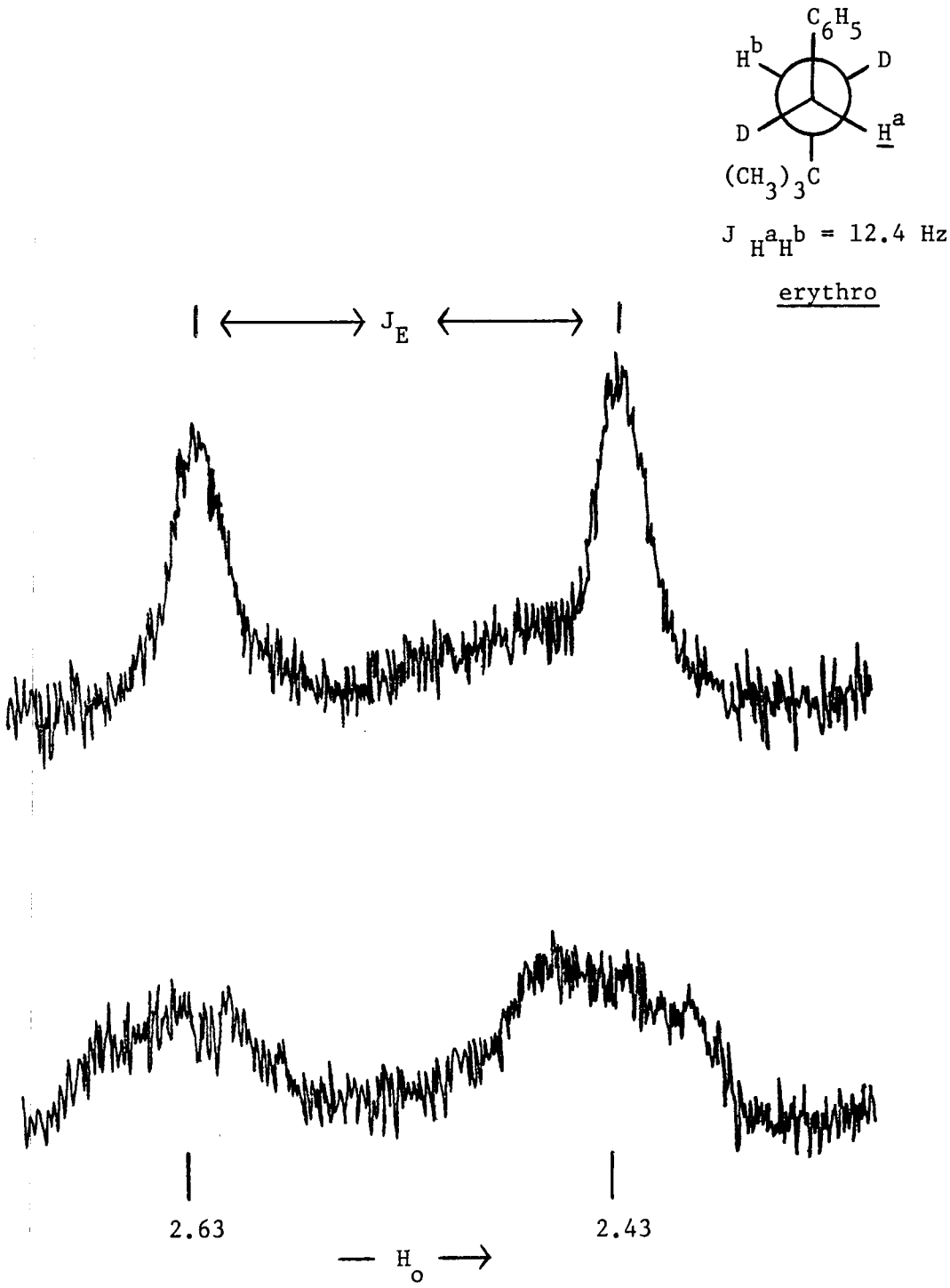
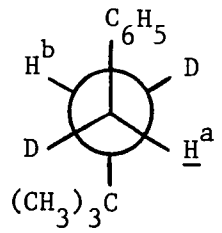


Figure 5. ^{1}H NMR spectrum of erythro-1-phenyl-3,3-dimethylbutane-1,2-d_2 obtained via hydroboration-protonolysis.

Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.



$J_{H^aH^b}$ = 12.4 Hz

erythro

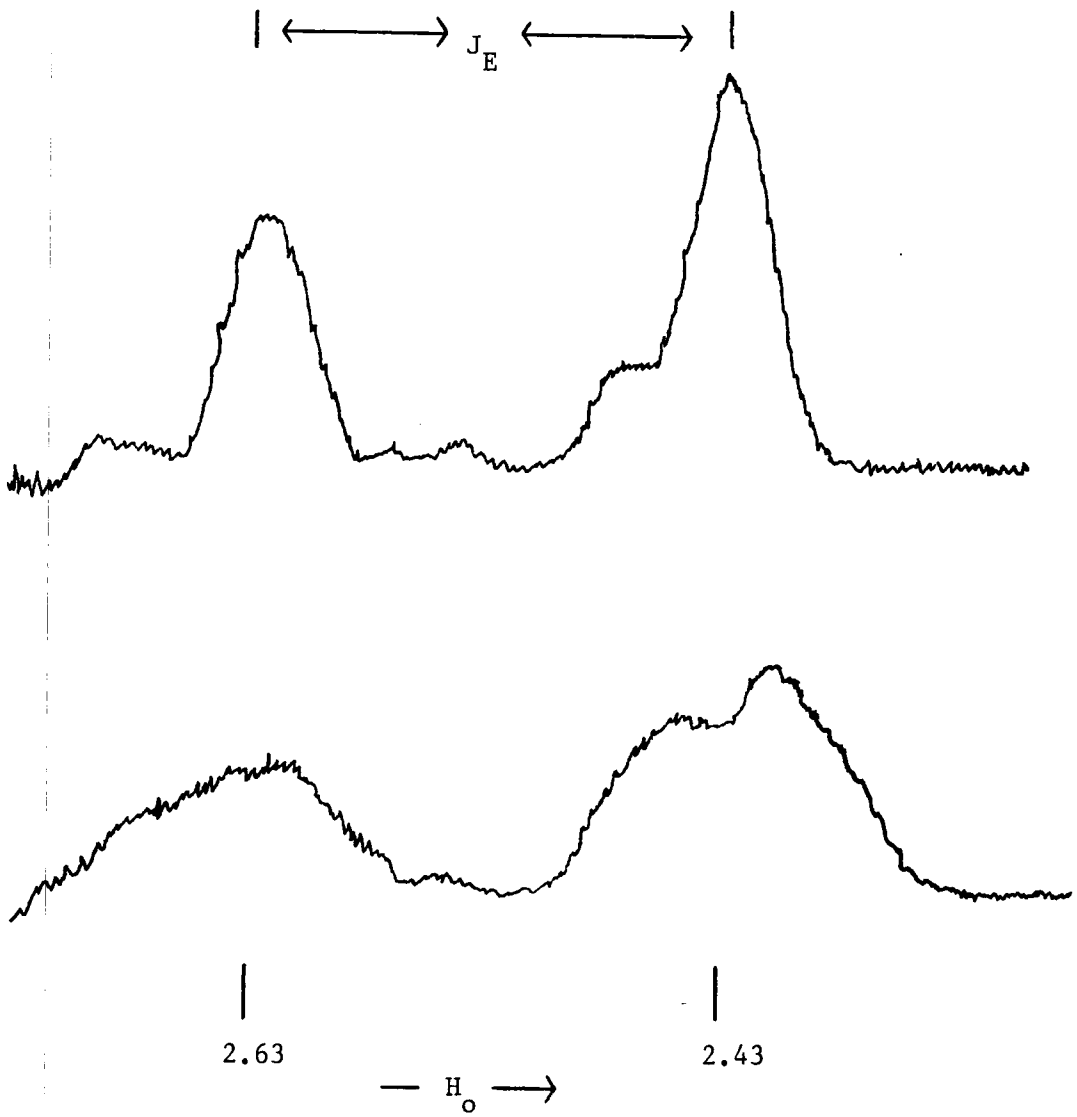


Figure 6. ^{1}H NMR spectrum of erythro-1-phenyl-3,3-dimethylbutane-1,2-d_2 obtained via hydrogenation over palladium on carbon.

Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.

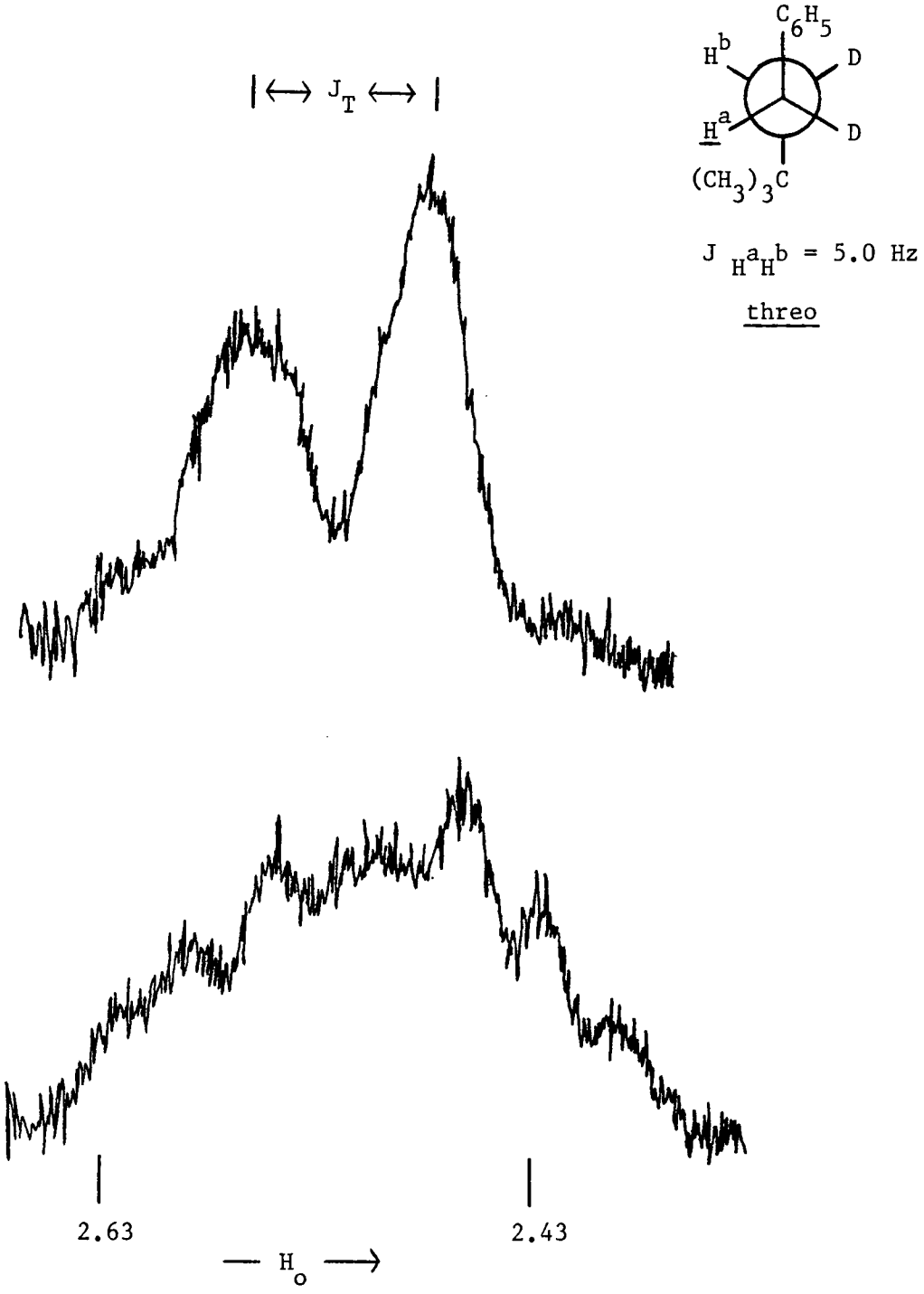


Figure 7. ^1H NMR spectrum of threo-1-phenyl-3,3-dimethylbutane-1,2-d_2 obtained via hydroboration-protonolysis.

Upper portion is ^2H-decoupled; lower portion is normal (undecoupled) spectrum.

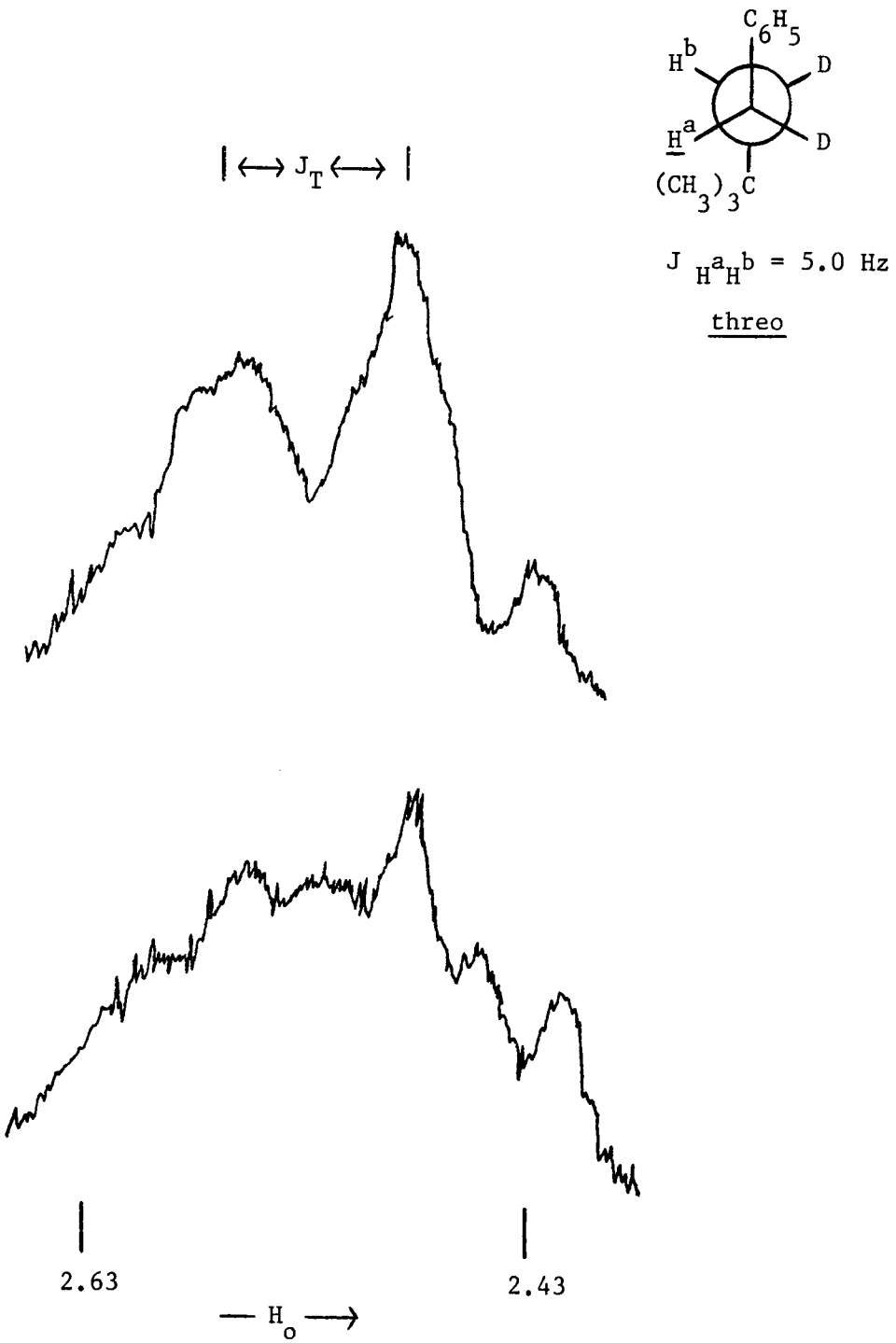


Figure 8. ^{1}H NMR spectrum of threo-1-phenyl-3,3-dimethylbutane-1,2-d_2 obtained via hydrogenation over palladium on carbon.

Upper portion is ^{2}H-decoupled; lower portion is normal (undecoupled) spectrum.

originally attached to boron. In addition, the hydroboration-protonolysis sequence can now be described to give cis hydrogenation for acyclic as well as cyclic alkenes.

E. Experimental

1. General Techniques

The hydroboration reactions were carried out in flame-dried, nitrogen-flushed glassware. Diglyme (Ansul) was distilled from calcium hydride prior to use. All other solvents were used as received. Bromine (Fisher), 3,3-dimethylbutene (Aldrich), potassium t-butoxide (Aldrich), magnesium turnings (Fisher), ethyl bromide (Fisher), copper(I)chloride (Alfa), iodobenzene (Aldrich), lithium aluminum deuteride (Merck, Sharp, and Dohme), cyclohexene (Eastman), acetic acid-d_4 (Aldrich), 9,10-dibromoanthracene (Eastman), iodine (Fisher) and palladium on carbon (Fisher) were used as received.

Routine ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer. ^{2}H-decoupled hydrogen and ^{1}H-decoupled deuterium NMR spectra were recorded on a Bruker HX-90 spectrometer at 90 and 13.8 MHz, respectively. Chemical shifts for the ^{1}H NMR spectra are reported in ppm relative to internal TMS. Chemical shifts for the ^{2}H NMR spectra, which were assigned relative to internal benzene-d_6, are normalized to TMS.

2. Synthesis of Reagents

a. 3,3-Dimethyl-1-butyne. This compound was prepared from

1,2-dibromo-3,3-dimethylbutane (840 mmol, 130.0 mL) (synthesized from 3,3-dimethyl-1-butene and bromine) and potassium t-butoxide (1.84 mole, 206.4 g) as outlined in Reference 73. The product was isolated by fractional distillation through a 6-inch Vigreux column: bp 36-38°C; ^{1}H NMR (neat) δ 1.91 (s,1), 1.21 (s,9). These values agree with those reported in Reference 73.

b. 1-Phenyl-3,3-dimethyl-1-butyne. With a few modifications, the procedure described in Reference 74 was followed in the synthesis of this compound. An ethylmagnesium bromide (510 mmol, 67.5 g) in ethyl ether was prepared in a dry, three-necked flask equipped with a pressure equalizing dropping funnel, reflux condenser and magnetic stirring bar. 3,3-Dimethyl-1-butyne was placed in the dropping funnel and added over a 2-h period into the Grignard solution cooled to 0°C (ice bath). The mixture was left to stir overnight to ensure complete conversion to the acetylide salt. The ethyl ether solvent was then removed by distillation through a simple still head, leaving a gray, powdery solid. Pyridine (400 mL) was added as solvent, followed by copper(I) chloride (500 mmol, 50.0 g) and iodobenzene (500 mmol, 56.0 mL). The reaction flask was heated (oil bath) to reflux pyridine and left overnight.

The contents of the reaction flask were poured into a 1-L separatory funnel containing 300 mL of water. This mixture was extracted with four 100-mL portions of ether. The combined ether layers were washed with four 100-mL portions of 2N aqueous HCl, and then two 100-mL portions of aqueous $NaHCO_3$(saturated). The ether layer was separated and dried over anhydrous magnesium sulfate.

The ether was removed on a rotovac leaving a dark brown oil which was distilled through a 6-inch Vigreux column to give the product: bp 68°C/7.2 mm (lit.[75] bp 84°C/10 mm); ^{1}H NMR (CCl_4) δ 7.26 (m,5), 1.36 (s,9); ir (CCl_4) 3100 cm^{-1} (vs), 2900 (vs), 2260 (m).

c. Di(2-deuteriocyclohexyl)borane-B-d_1 (DCHB-D). This hydroborating agent was prepared as described in Chapter II (page 38), except lithium aluminum deuteride ($LiAlD_4$) was used as the deuterium source and ethyl ether was used as the solvent.[76]

d. Borane-tetrahydrofuran (BH_3·THF). A 1.77 M BH_3·THF solution was prepared and standardized as described in Reference 77.

3. Synthesis of Deuterated Alkenes

a. (Z)-1-Phenyl-3,3-dimethyl-1-butene-1,2-d_2 (23). DCHB-D (65 mmol) (vide supra) was prepared in a dry, nitrogen-flushed, 250-mL, three-necked flask equipped with a pressure equalizing dropping funnel, reflux condenser, magnetic stirring bar, and a gas exit tube. 1-Phenyl-3,3-dimethyl-1-butyne (60 mmol, 9.48 g) was placed in the dropping funnel and added over a 1-h period. The reaction mixture was heated (oil bath) to reflux for 3 h to ensure complete hydroboration. Acetic acid-d_4 (200 mmol, 12.1 mL) was placed into the emptied dropping funnel and added (1 h). Heating was continued overnite. The contents of the reaction flask were transferred into a 500-mL separatory funnel. The ether layer was extracted with four 100-mL portions of water, then with 100 mL of saturated aqueous $NaHCO_3$ and dried over anhydrous magnesium sulfate.

After filtration of the magnesium salts and removal of the ether layer, a yellow oil was obtained. Fractional distillation of this yellow oil through a 6-inch Vigreux gave a clear product: bp 46-48°C/1 mm; ^{1}H NMR (neat) δ 7.1 (s,5), 0.95 (s,9). These ^{1}H NMR values for the phenyl and t-butyl hydrogens correspond exactly to those reported for (Z)-1-phenyl-3,3-dimethyl-1-butene.[78] The absence of ^{1}H signals at δ 6.46 to 5.4 reflects the absence of vinylic hydrogens and indicates the isotopic purity of 23. The ^{1}H-decoupled, ^{2}H NMR spectrum exhibited two signals at δ 6.29 (broad singlet, 1) and 5.49 (broad singlet, 1). These values for vinylic deuteriums correspond to those reported for the vinylic hydrogens in the nondeuteriated compound.[78]

b. (E)-1-Phenyl-3,3-dimethyl-1-butene-1,2-d_2 (24). G. S. Hammond, et al., had shown that photolysis of (Z)-stilbene, in the presence of a low-energy sensitizer, 9,10-dibromoanthracene, affected establishment of a photostationary state that was almost pure (E)-stilbene.[79] With this in mind, an attempt was made to photoisomerize the Z-isomer (23) to the E-isomer (24). The degree of isomerization was followed by integration of the ^{1}H NMR signals at δ 1.09 (hydrogens in the t-butyl group of the E-isomer) and δ 0.95 (hydrogens in the t-butyl group of the Z-isomer).

Into a clean, dry 8-inch pyrex test tube was placed the Z-isomer (23) (42 mmol, 8.0 mL), 9,10-dibromoanthracene (0.84 mmol, 0.28 g) and dioxane (30 mL). After heating on a steam bath for 5 min to effect solution, the mixture was degassed by bubbling nitrogen through it for 10 min and then sealed with a rubber septum.

The test tube was irradiated with a 700-watt Hanovia high pressure mercury lamp. Samples were taken over an 80-h period and analyzed to determine the degree of isomerization. After irradiating for 80 h, a photostationary state was reached which contained the Z- and E-isomers in a 15:85 ratio, respectively. To increase the percentage of the E-isomer a thermal isomerization was attempted.[80] The dioxane solution was cooled below room temperature, whereupon the photosensitizer precipitated and was removed by filtration. The filtrate was placed into a 50-mL flask equipped with a reflux condenser and magnetic stirring bar. Iodine (6.3 mmol, 0.8 g) was added, and the mixture was heated (oil bath) to reflux. After a 48-h period, ^{1}H NMR analysis showed at least 97% of the E-isomer (24) in the final mixture. The product was recovered by fractional distillation through a 6-inch Vigreux column: bp 52-54°C/1 mm; ^{1}H NMR (CCl_4) δ 7.17 (m,5), 1.09 (s,9). These values for the phenyl and t-butyl hydrogens correspond exactly to those reported for (E)-1-phenyl-3,3-dimethyl-1-butene.[78] The absence of a ^{1}H signal at δ 6.17 reflects the absence of vinylic hydrogens and indicates the isotopic purity of 24. The ^{1}H-decoupled, ^{2}H NMR spectrum exhibited one signal at δ 6.15 (broad singlet, 2). This value for the vinylic deuteriums corresponds to that reported for the vinylic hydrogens in the nondeuteriated compound.[78]

4. Synthesis of erythro- and threo-Diastereomers

a. erythro-1-Phenyl-3,3-dimethylbutane-1,2-d_2 (27). Method A. Diglyme (10 mL) and the Z-alkene 23 (4.2 mmol, 0.8 mL) were placed

in a dry, nitrogen-flushed, 50-mL flask fitted with a septum inlet, reflux condenser, magnetic stirring bar, and a gas exit tube. The solution was cooled to 0°C (ice bath) and BH_3·THF (2.1 mmol, 1.19 mL) was added via a syringe (10 min). The reaction mixture was allowed to warm to room temperature and then heated (oil bath) to 50°C for 1 h to ensure complete hydroboration. Acetic acid (20 mmol, 2.0 mL) was added in one portion and the temperature maintained at 110°C for 3 days. The reaction flask was cooled to ambient temperature and its contents transferred to a 250-mL separatory funnel. The flask was washed with two 25-mL portions of pentane, and these washings were added to the separatory funnel. The organic layer was extracted with four 50-mL portions of cold water then with 50 mL of aqueous $NaHCO_3$ (saturated). The pentane layer was separated and dried over anhydrous magnesium sulfate. The product was isolated by fractional distillation through a 6-inch Vigreux column: bp 44-46°C/1 mm; ^{2}H-decoupled, ^{1}H NMR (neat) δ 7.07 (s,5), 2.53 (d, 1, $J_{H^aH^b}$ = 12.4 Hz), 1.53 (d, 1, $J_{H^aH^b}$ = 12.4 Hz), 0.93 (s,9).

Method B. The Z-alkene 23, (5.2 mmol, 1.0 mL), pentane (5 mL), and a palladium on charcoal catalyst (0.1 g) were hydrogenated at 30 psi for 5 h. The catalyst was removed by filtration, and the pentane evaporated to give the product. The ^{2}H-decoupled, ^{1}H NMR spectrum duplicated that obtained by Method A.

b. threo-1-Phenyl-3,3-dimethylbutane-1,2-d_2 (28). Method A. The E-alkene 24 was hydroborated and protonolyzed using the procedure outlined for the Z-alkene. The alkane product was isolated by distillation: bp 52-54°C/1 mm; ^{2}H-decoupled, ^{1}H NMR (neat) δ 7.07

(s,5), 2.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz) 1.53 (d, 1, $J_{H^aH^b}$ = 5.0 Hz), 0.93 (s,9).

Method B. The E-alkene 24 was hydrogenated over palladium on charcoal using the procedure outlined for the Z-alkene. The ^2H-decoupled, ^1H NMR spectrum duplicated that obtained by Method A.

PART II

A NEW OXIDATION PROCEDURE FOR ORGANOALUMINUM COMPOUNDS

CHAPTER IV

TRIMETHYLAMINE N-OXIDE OXIDATION OF ORGANOALUMINUM COMPOUNDS

A. Introduction

1. A Brief Survey of Organoaluminum Chemistry

Organoaluminum compounds, although known for a hundred years, remained mere laboratory curiosities until the discoveries of K. Ziegler and H. G. Gellert.[81] The first of these discoveries was the direct synthesis of trialkylaluminum compounds from aluminum metal, olefins, and hydrogen. The second was the formation of carbon-carbon bonds by the addition of alkylaluminum compounds to olefins.

These compounds are used mainly as components of the Ziegler-Natta catalysts for the polymerization of olefins, although their use in the manufacture of primary alcohols is of growing importance.[81,82]

2. Synthetic Routes to Organoaluminum Compounds

While of major industrial importance, the direct synthesis of organoaluminum compounds from aluminum metal, olefin, and hydrogen is of little value in the laboratory. Furthermore, in contrast to borane, alane does not reduce carbon-carbon double bonds to give the corresponding trialkylaluminum.[83]

$$AlH_3 + 3 \quad \backslash C = C / \quad \longrightarrow \quad H - \overset{|}{\underset{|}{C}} - \overset{|}{\underset{|}{C}} -)_3 Al$$

Fortunately, dialkylaluminum hydrides will add to the

carbon-carbon multiple bonds of terminal alkenes,[84] and internal or terminal alkynes.[85]

$$RR'C = CH_2 + HAlR''_2 \longrightarrow RR'CHCH_2AlR''_2$$

$$RC \equiv CR' + HAlR''_2 \longrightarrow RHC = CR'AlR''_2$$

One of the most convenient laboratory synthesis of trialkylaluminum compounds takes advantage of the fact that isoalkylaluminums undergo a facile displacement reaction. At temperatures above 60°C, triisobutylaluminum dissociates with elimination of isobutene and formation of diisobutylaluminum hydride which reacts with added terminal alkenes.[86] Thus, tri-n-octylaluminum can be prepared, by heating (110°C) three equivalents of 1-octene with one equivalent of the commercially available diisobutylaluminum hydride, according to the following equation:

$$(i\text{-}C_4H_9)AlH + 3\ H_2C = CH(CH_2)_5CH_3 \longrightarrow CH_3(CH_2)_7\text{-})_3Al + 2\ i\text{-}C_4H_8$$

Other important laboratory preparations of trialkylaluminum compounds involve transmetalation, between Grignard[87] or organolithium[88] reagents and aluminum chloride, and transalkylations between trialkylboranes and trialkylaluminums.[89]

3. Properties and Chemical Reactivity of Trialkylaluminum Compounds

Like the organoboranes, most of the chemistry of organoaluminum compounds is readily understood in terms of the Lewis acidity of the organoaluminum monomers which is directly related to the electronegativity of the aluminum atom. Organoaluminum

compounds are markedly stronger Lewis acids than the organoboranes. As neat liquids, trialkylaluminums exist as dimers having electron-deficient bonding very similar to diborane, see page 3. The lower molecular weight trialkylaluminums, e.g., trimethylaluminum, tend to be dimeric in hydrocarbon solutions.[90]

Chemically, the organoaluminum reagents are similar to the Grignard reagents. Like the Grignard reagents, trimethyl- and triethylaluminum will alkylate aldehydes and ketones to give, following workup, the corresponding secondary and tertiary alcohols.[91,92] However, other trialkylaluminum compounds tend to reduce rather than alkylate carbonyl groups.[93] Organoaluminum compounds and Grignard reagents both react with protic solvents to form the alkanes and metal hydroxides.[94]

Several reactions of trialkylaluminum compounds, including oxidation,[95] halogenation,[84] and carbonylation[96], are analogous to reactions involving organoboranes.

Additionally, the trialkylaluminum compounds react with olefins by addition of the carbon-aluminum bond to the carbon-carbon double bond of an olefin. Indeed, it is this single reaction which has made them the most widely used, on an industrial scale, of all the organometallic reagents.[97]

B. Statement of the Problem

Historically, organoaluminum compounds have been converted to their corresponding alcohols by an autoxidation with molecular oxygen followed by hydrolysis of the aluminate intermediate. Product

yields from this reaction are reported to approach 100%,[98] but are

$$R_3Al \xrightarrow{O_2} (RO)_3Al \xrightarrow{H_3O^+} 3\ ROH$$

often in the 70-90% range.[95] These oxidations presumably proceed via a free radical chain process with the accompanying byproducts of peroxides, hydrocarbons, and hydrogen.[99]

Recently, it was demonstrated that trimethylamine N-oxide and its dihydrate are convenient oxidizing agents for organoboranes.[34,100,101] The yields of the alcohols (in the 90-100% range) are at least as good as those obtained in the alkaline hydrogen peroxide oxidation of organoboranes.

We decided to investigate the utility of trimethylamine N-oxide as an oxidizing reagent for organoaluminum compounds.

C. Results and Conclusions

1. Results

The reaction of trimethylamine N-oxide with organoaluminum reagents was first reported by Köster.[102] The reaction produces a 1:1 addition complex which is stable at room temperature. We have found that this complex decomposes readily at higher temperatures in hydrocarbon solvent to yield the corresponding alkoxy derivative. Further reaction produces the totally oxidized derivative which yields the alcohol upon hydrolysis.

$$R_3Al \xrightarrow{(CH_3)_3NO} R_3\bar{A}l\text{-}O\text{-}\overset{+}{N}(CH_3)_3 \xrightarrow{\Delta} R_2Al\text{-}OR$$

$$R_2AlOR \xrightarrow[\Delta]{2(CH_3)_3NO} (RO)_3Al \xrightarrow{H_3^+O} 3\ ROH$$

The oxidation is temperature dependent. The rate increases with increasing temperature. The results for tri-n-propylaluminum are representative and are shown in Figure 9.

The oxidation of a variety of primary trialkylaluminum compounds proceed at nearly the same rate under comparable conditions. The only exception is trimethylaluminum which is oxidized rather slowly. The dimeric nature of this compound, even at elevated temperatures, presumably retards formation of the necessary trimethylamine N-oxide complex.[103] The results are summarized in Figure 10.

Products and yields of the oxidation reaction of several organoaluminum compounds with $(CH_3)_3NO$ are shown in Table I.

Not surprisingly, oxidation of mixed tri-n-alkylaluminums proceeds in a statistical fashion. Thus the oxidation of diisobutyl-n-decylaluminum with one equivalent of trimethylamine N-oxide produces an equivalent of alcohols in a 2:1 ratio (isobutanol: n-decanol).

The trimethylamine N-oxide procedure is unique in that triphenylaluminum is oxidized rapidly to generate phenol. Oxidation of arylaluminum compounds utilizing molecular oxygen is reported to be slow and inefficient.[104]

$$Ph_3Al \xrightarrow[\Delta]{3(CH_3)_3NO} \xrightarrow{H_3O^+} 3\ PhOH$$

Vinyl groups are not oxidized by the reagent. Reaction of vinyldialkylaluminum compounds with trimethylamine N-oxide affords oxidation of only the alkyl portion of the compound, as only

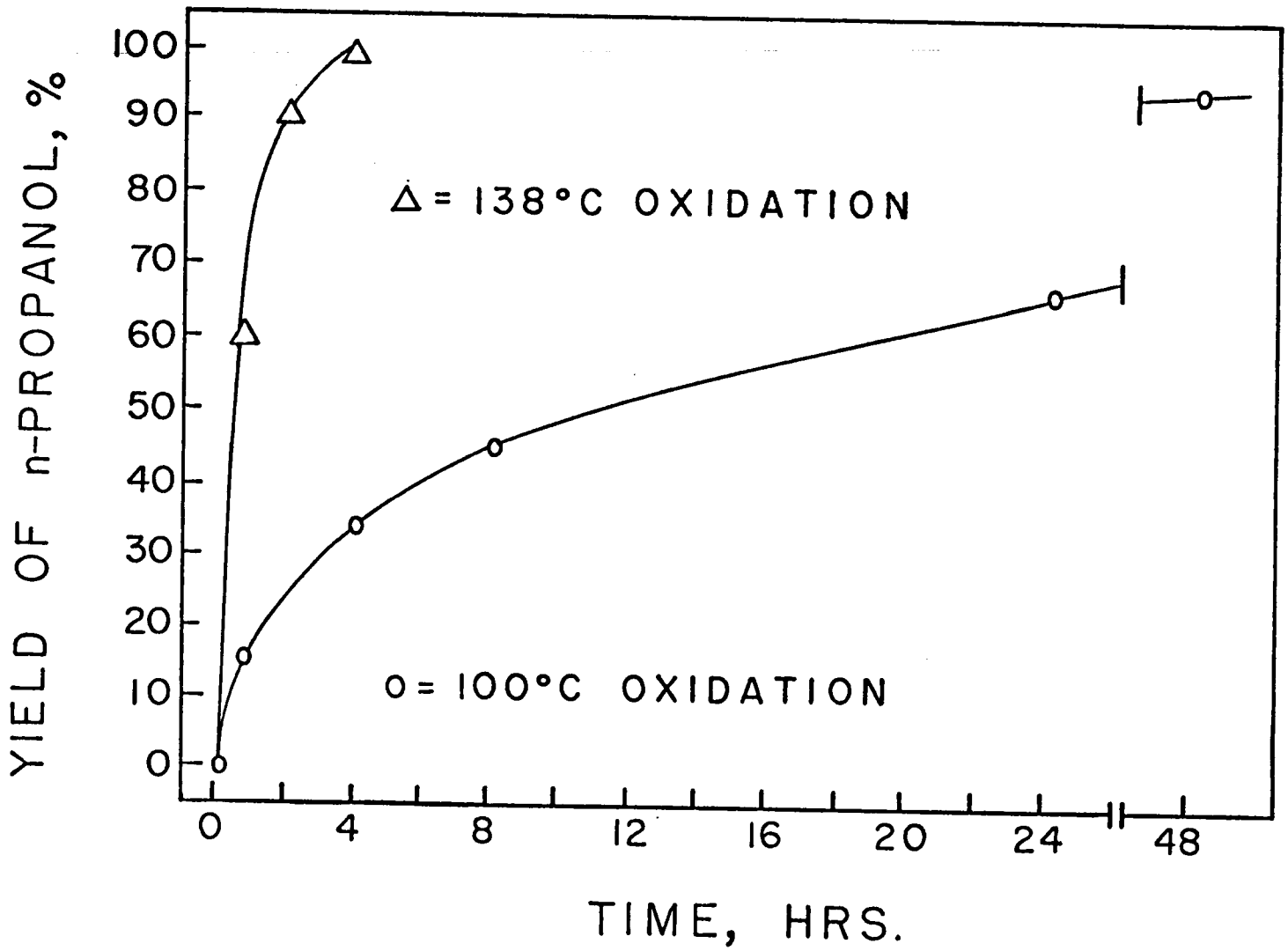


Figure 9. Temperature effects on the oxidation of tri-n-propylaluminum.

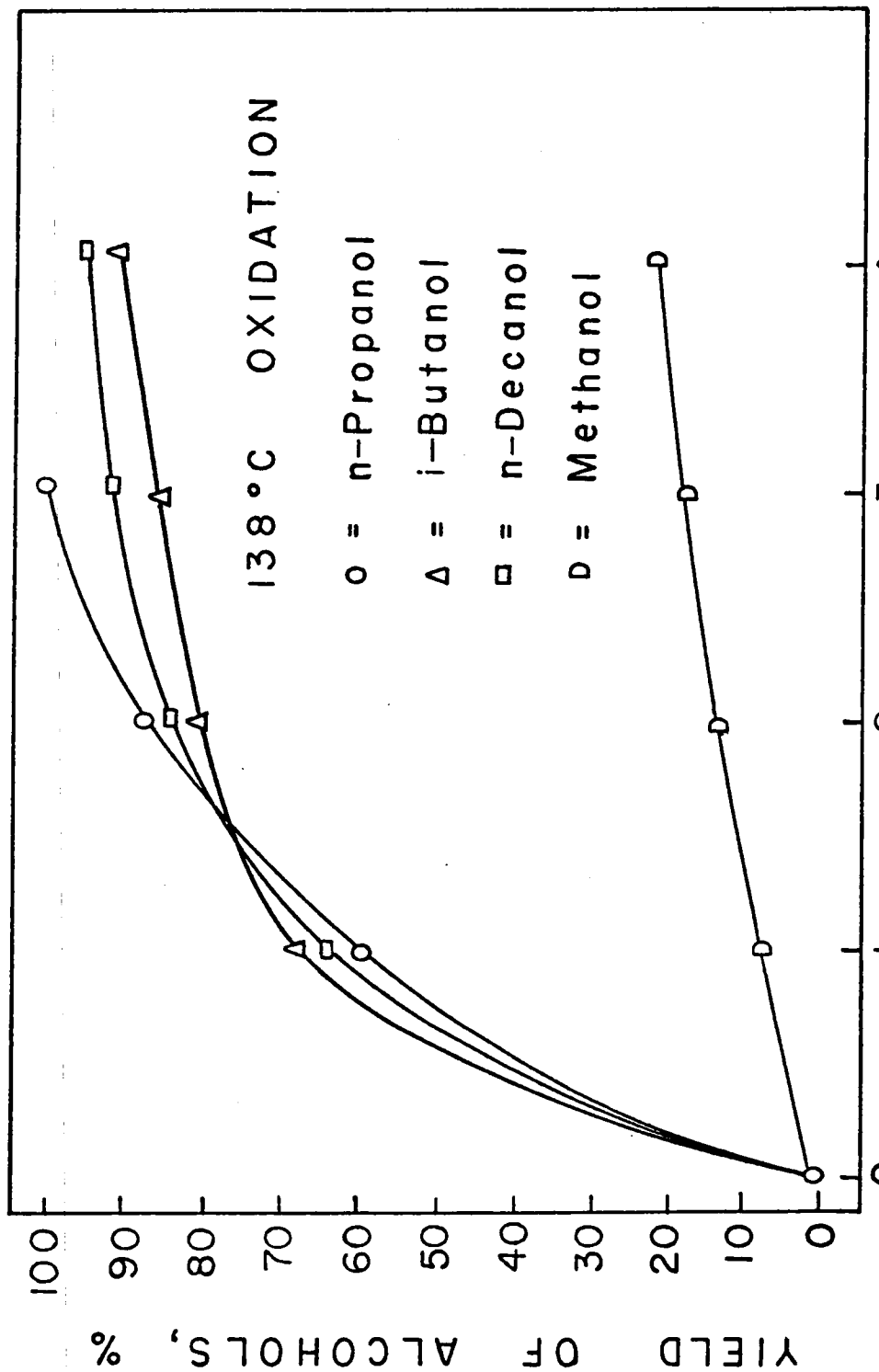


Figure 10. Relative rates of oxidation of various trialkylaluminum compounds.

TABLE I

OXIDATION OF ORGANOALUMINUM COMPOUNDS WITH $(CH_3)_3NO$

Compound	Product	Yield (%)[a]
Trimethylaluminum	methanol	21
Tri-n-propylaluminum	n-propanol	100
Tri-i-butylaluminum	i-butanol	94
Tri-n-octylaluminum	n-octanol	94
Tri-n-decylaluminum	n-decanol	94
Triphenylaluminum	phenol	97[b]
Di-i-butyl(2-phenylethenyl)aluminum	i-butanol	100[c]
Di-i-butyl(1-hexenyl)aluminum	i-butanol	100
Diethylaluminum chloride	ethanol	0
Ethylaluminum dichloride	ethanol	0

[a]Yields determined by ^1H NMR after four hours at 138 C.

[b]Yield determined by GLPC after one hour at 138 C.

[c]Yield determined by ^1H NMR after three days at 80 C.

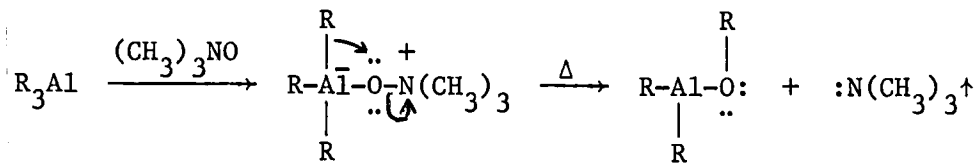
diisobutanol (and no hexanol) is observed during the oxidation of diisobutyl(1-hexenyl)aluminum.

Reactions of alkylaluminum dihalides and dialkylaluminum halides with trimethylamine N-oxide produce only tars under the conditions utilized.

2. Conclusions

These results demonstrate that trimethylamine N-oxide is an effective oxidizing agent for trialkyl- and triarylaluminum compounds. Furthermore, in laboratory oxidations of these compounds, trimethylamine N-oxide should be considered as a viable alternative to the molecular oxidation procedure, as no oxidation byproducts have been observed and product yields are significantly improved with this new procedure.

The mechanism of this oxidation reaction most likely parallels that of the intramolecular anionotropic rearrangement proposed for the organoboranes.[35]



D. Experimental

1. General Techniques

All oxidation reactions were carried out in flame-dried, nitrogen-flushed glassware. Routine ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer. The yields for the oxidation of the aliphatic organoaluminum compounds were determined via NMR by

integration of the ^1H NMR signals at δ 0.33 ($-CH_2-Al$) and 3.66 ($-CH_2-O-Al$). Gas chromatographic analyses (GLPC) were performed on a Varian Aerograph 90-P equipped with a 1.5m x 7mm column packed with 15% SE-30 on Chromosorb P 60-80. The yield of phenol was determined by GLPC.

Trimethylamine N-oxide was prepared by subliming the commercially available (Aldrich) trimethylamine N-oxide dihydrate. The trimethylamine N-oxide was transferred in a dry glove bag and stored under dry argon until used. Triisobutylaluminum was used as received from Texas Alkyls. Trimethylaluminum, tri-n-propylaluminum, diethylaluminum chloride and ethylaluminum dichloride were used as received from Ventron Corporation. Diisobutylaluminum hydride was used as the neat liquid which was obtained by distillation of the pentane from a pentane solution (Ventron). 1-Hexyne was used as received from Farchan. 1-Octene, 1-decene, phenylacetylene, and triphenylborane were used as received from Aldrich. m-Xylene was dried over molecular sieves prior to use.

2. Preparation of Organoaluminum Compounds

a. Tri-n-octylaluminum. 1-Octene (30 mmol, 4.69 mL) and diisobutylaluminum hydride (10 mmol, 1.42 g) were added to a dry, nitrogen-flushed, 50-mL flask fitted with a sidearm, reflux condenser, magnetic stirring bar, and gas exit tube. The reaction mixture was heated to 110°C (oil bath) and stirred at this temperature for two days to ensure complete conversion to tri-n-octylaluminum.

b. Tri-n-decylaluminum. Tri-n-decylaluminum was prepared in a manner analogous to tri-n-octylaluminum. 1-Decene (30 mmol, 5.66 mL) was used and the reaction mixture was heated to 140°C for two days.

c. Diisobutyl(1-hexenyl)aluminum. m-Xylene (15 mL) and 1-hexyne (10 mmol, 1.15 mL) were added to the described apparatus (vide supra). The flask was cooled to 0°C and diisobutylaluminum hydride (10 mmol, 1.42 g) was added. The reaction mixture was allowed to warm to room temperature while stirring overnight.

d. Diisobutyl(2-phenylethenyl)aluminum. This reagent was prepared in a fashion analogous to diisobutyl(1-hexenyl)aluminum utilizing phenylacetylene (5 mmol, 0.55 mL) and diisobutylaluminum hydride (5 mmol, 0.71 g).

e. Triphenylaluminum. Triphenylaluminum was prepared from triphenylborane (10 mmol, 2.42 g) and trimethylaluminum (10 mmol, 0.72 g) according to a procedure outlined in Reference 106.

3. Oxidation of the Organoaluminum Compounds

The oxidation of tri-n-propylaluminum is representative. The tri-n-propylaluminum (10 mmol, 1.56 g) and m-xylene (15 mL) were added via syringe to a dry, nitrogen-flushed, 50-mL flask fitted with a sidearm, reflux condenser, magnetic stirring bar, and gas exit tube. While flushing the flask with nitrogen, the reflux condenser was removed and anhydrous trimethylamine N-oxide (30 mmol, 2.25 g) was added in one portion. With the reflux condenser

attached, the reaction flask was placed in a oil bath (140°C). The reaction mixture was gently refluxed with efficient stirring for 4 h. Aliquots were removed at 1-h intervals and analyzed by ^{1}H NMR to determine the extent of oxidation.

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VITA

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He entered the University of Tennessee-Knoxville Graduate School in January, 1975, where he held a teaching assistantship for three-and-a-half years. During his graduate years he fulfilled a lifelong dream by obtaining his private pilot's license. A special graduation present was received from his wife when she gave birth to their first child, Melissa Kay Newton, on May 30, 1978. He will graduate in August, 1978 and begin a professional career with the Tennessee Eastman Company in Kingsport, Tennessee.

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