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Preparation and Characterization of (E)-1-Alkenylboranes and(E)-1-Alkenylboronates an Investigation of Borane/Nitrone Reactions

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Preparation and characterization of
(E)-1-Alkenylboranes and (E)-1-Alkenylboronates
And
An Investigation of Borane/Nitrone Reactions

A Thesis

Presented to

The Faculty of the Department of Chemistry

The College of William and Mary in Virginia

In Partial Fulfillment

Of the Requirements for the Degree of

Masters of Arts

by

Philip L. Smith

1991

APPROVAL SHEET

This thesis is submitted in partial fulfillment of

the requirements for the degree of

Masters of Arts

Philip L. Smith

Philip L. Smith

Approved, September 1991

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Christopher J. Abelt

Christopher J. Abelt, Ph.D.

DEDICATION

For George and Herminia, my parents, Stella and Kimberly, my sisters, and Christain, my brother.

ACKNOWLEDGMENTS

I wish to express my sincere appreciation to Dr. Hollis, under whose professional guidance this investigation was undertaken, and to thank him for all the assistance, advice, constructive criticism, and patience throughout this year. I also wish to thank Dr. Christopher Abelt and Dr. Brenda Wojciechowski for all the help and advice I received from them. I am also grateful to Mike and Bonnie Glasgow who graciously allowed me to live in their home while I wrote the majority of my thesis. And of course, a word of thanks goes to all my friends for keeping me on-track and motivated.

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ABSTRACT

The primary objective in this research was to prepare and study the reactive properties of α,β-unsaturated boron compounds. A series of (E)-1-alkenyl boranes, boronic acids, anhydrides, and boronates were prepared and characterized via NMR and GC/MS. A comparison of the chemical shifts of the vinyl protons of the prepared alkenyl boron compounds with analogous carbonyl compounds reveals similar trends in double bond polarization. Numerous attempts were made to prepare carboxylate and thiolate esters of alkenyl boronic acids but none were successful.

The reactions of nitrones with these types of boron compounds were also studied. Prior to this work, reactions of this type were undocumented in the literature.

The reaction of triethylborane with diphenylnitrone followed by hydrolysis produced N-(1-phenylpropyl)-N-phenylhydroxylamine via a rearrangement type reaction centered at boron. This product, which was characterized based on proton NMR, carbon-13 NMR, and mass spectral data, appears to be a novel compound. This reaction is synthetically important because one new carbon-carbon bond is formed along with the creation of a new chiral center during product formation.

PREPARATION AND CHARACTERIZATION OF

(E)-1-ALKENYLBORANES AND (E)-1-ALKENYLBORONATES

And

AN INVESTIGATION OF BORANE/NITRONE REACTIONS

CHAPTER ONE

MOLECULAR MECHANICS
AND VARIABLE TEMPERATURE NMR

OVERVIEW:

Molecular Mechanics

A large portion of research dealing with molecular geometries and molecular energies involves using quantum mechanical calculations. But another, somewhat newer approach to structural analysis that has become a very important tool in the chemistry laboratory is that of force field calculations called molecular mechanics. In this method, a molecule is represented by a "model" wherein its structure is described mathematically. Potential functions of the structural features such as bond lengths, bond angles, nonbonded interactions, and torsion are combined to construct a force field. The sum of the energy contributions from the potential functions gives the energy, E, called the steric energy.[1]

The force field calculations are designed to minimize the potential energy of the hypothetical structure relative to the true or ideal value. The accuracy of the method is then dependent upon how closely the hypothetical model resembles the true molecule. In order to do this, parameters such as estimated bond lengths, natural bond angles, dipole moments, etc. are input and the force field is constructed. The initial steric energy is calculated and then minimized to give an optimum geometry. This optimized geometry, which will hopefully correspond with the actual structure of the molecule, can then be used to calculate other useful physical properties such as heat of formation, crystal packing arrangement, conformational energies, or transition state structure.[1,2]

MMX, the molecular mechanics program used in this investigation, is a modified version of the original MM1 program written by Norman Allinger in 1973.[1] Packaged with the program is a parameters list containing reusable information such as standard bond lengths and bond angles, common atomic orbital hybridizations, and torsional constants. Standardization of data allows the program to recognize certain atoms and arrangements and associate predetermined properties with them. It is therefore convenient to list these common atoms and groups in a parameters table along with their characteristics so that these data need not be entered by the programmer upon each use. The program enters the assigned values based on the parameters. The included parameters by no means limit the user. Additional parameters may be entered by way of a parameter input file. These new parameters are read by the main program and utilized in the construction of the force field.

In order to use MMX, a starting geometry must be input to the program. The starting geometry of the molecule/model is entered as three dimensional Cartesian coordinates which also contain information defining each atom type and the types of bonds connecting them. The program takes the starting geometry and calculates the initial interatomic distances, bond angles, and torsional angles. From this, the initial steric energy is calculated. The program then "moves" the atoms and recalculates the steric energy. This is repeated until the minimum energy is found.

The structure corresponding to this energy minimum is reported as the optimized geometry. Once this has been determined, "experiments" can be performed and physical properties can be calculated. This ease of use, coupled with the high speed and minimal cost, is the most appealing aspect of using molecular mechanics.

OVERVIEW:

Determination of Internal Rotational Barriers Using Variable Temperature NMR

The use of NMR techniques in studying molecular conformational dynamics has increased with the advent of more powerful spectroscopic and analytical instrumentation. One relatively new method is the use of variable temperature NMR to calculate internal rotational barriers.[3] A typical high resolution NMR spectrum contains information of three types: chemical shifts, spin-spin coupling, and absorption intensity. The former two are based upon the magnetic environment of each nucleus; the latter is observed in a one to one ratio with the number of nuclei giving rise to the signal.[3,4]

If internal rotation within a molecule gives rise to energetically different rotamers, then the nuclei of those rotamers will also experience different magnetic environments. This difference in magnetic environment causes each rotamer to give rise to distinct NMR signals with different chemical shifts and coupling constants. The ability to observe these different signals, though, depends upon the rotamer lifetimes and their populations. In order to see each species, interconversion must be relatively slow (i.e. rotational barrier is reasonably high). Lifetimes must be on the order of 1/10th second or longer, corresponding to an activation energy of 4.5 kcal/mole or larger.[3] This means that rotation must be reasonably hindered by steric interactions or the torsional axis must contain some double bond character.

Raising or lowering the temperature changes both the population and rate of interconversion. At a given temperature, the typical NMR spectrum will often fall within two extreme cases. The observed spectrum may simply be a statistical average of the signals arising from the different rotamers. In this case, the rate of interconversion is fast relative to the NMR time scale. At the opposite extreme, the spectrum will consist of the superimposed spectra of the "frozen-out" rotamers. Here, the interconversion rate is very slow relative to the NMR time scale. Between these extremes lies a region where variable temperature NMR may be used to determine the magnitudes of the rotational barriers[3,4]

For example, one can consider a molecule with two low energy rotational isomers in which each is distinct. At some low temperature, the rate of interconversion will be slow and the spectrum will appear as the superimposed spectra of the two rotamers. Raising the temperature increases the rate of interconversion and causes the lines to appear blurred as the resonances coalesce. As the temperature is further raised, the rate of interconversion between the two rotamers increases. Under these conditions, the spectrum appears with sharp resonances. The rapidly interconverting nuclei "feel" an effective averaged magnetic field. Analysis of the change in lineshapes during this variable temperature process may be used to determine the magnitude of the rotational barrier.

LITERATURE REVIEW:

The Nature of the Carbon-Boron Bond in α,β-Unsaturated Boron Compounds

Numerous investigations dealing with the nature of the boron-carbon bond in various vinyl boranes have been performed using a variety of techniques. Much evidence supporting π-type interactions between boron's empty p-orbital and the neighboring π-bond has been presented as well as evidence refuting it.

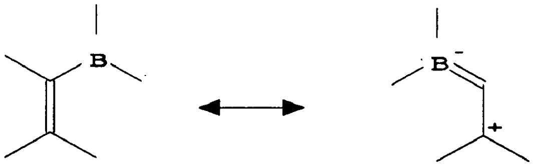


Figure 1

The nature of this interaction is a direct indication of the extent to which boron acts as an electron withdrawing species. The mesomeric forms of alkenylboranes (Figure 1) could thus be used to depict the delocalization of electron density within these types of molecules.

Investigations studying ^{13}C chemical shifts of alkenylboranes and alkenylboronates[6,7] show dramatic changes in β-carbon chemical shifts which are

Table 1

Compound	Vinyl Substituent	δ C_β relative to ethylene (ppm)
$B(CH=CH_2)_3$	$B(CH=CH_2)_2$	+15.2
$FB(CH=CH_2)_2$	$FB(CH=CH_2)$	+18.1
$ClB(CH=CH_2)_2$	$ClB(CH=CH_2)$	+18.7
$BrB(CH=CH_2)_2$	$BrB(CH=CH_2)$	+20.3
$F_2B(CH=CH_2)$	F_2B	+20.9
$Cl_2B(CH=CH_2)$	Cl_2B	+21.7
$Br_2B(CH=CH_2)$	Br_2B	+23.5
$(n\text{-}BuO)_2B(CH=CH_2)$	$(n\text{-}BuO)_2B$	+11.3

believed to result from π-type interactions between boron's empty p-orbital and the π-bond. A comparison of chemical shifts between boron substituted alkenes and unsubstituted alkenes show the that boron's presence causes marked downfield shifts of the β-carbon resonances[7a] (see Table 1[8b] and Figure 2[8a]).

The deshielding of the β-carbon is also observed in the β-proton chemical shifts. These shifts are are analogous to that seen in α,β-unsaturated carbonyl compounds. Although the downfield shifts are not as dramatic, boron substituted alkenes do display similar polarizations of the boron-vinyl π system resulting in downfield shifting of the β-proton resonances (see Figure 2).

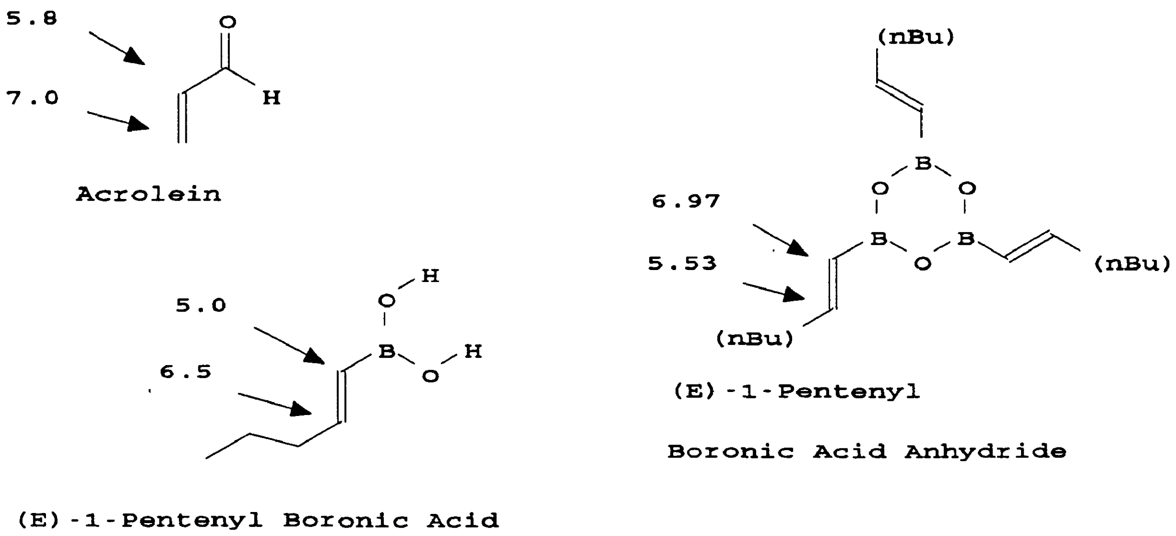


Figure 2

A variable temperature ^{1}H NMR investigation of (dimethylamino-methylvinyl borane revealed significant π-type interaction within the molecule (Figure 3).

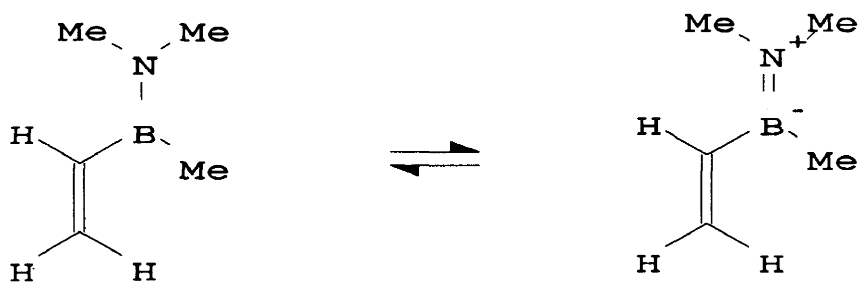
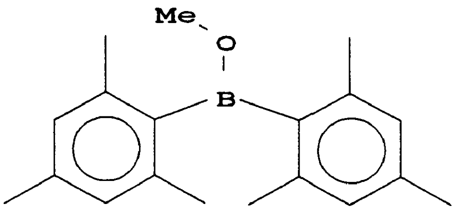


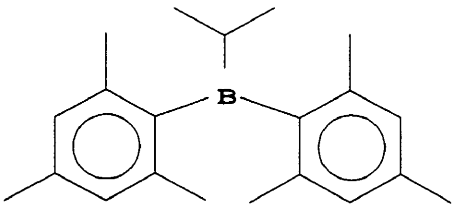
Figure 3

Two distinct methyl resonances for the amino methyl groups appear over a range of temperatures without merging or broadening. This indicates restricted rotation about the nitrogen-boron bond. The appearance of only two signals for the amine methyls also indicates simultaneous restriction about the boron-carbon bond. Rotation about the this bond would produce *cis* - and *trans* - isomers, each with a distinct NMR spectrum. The vinyl proton resonances also do not merge or broaden. These findings are consistent with hindered rotation about the boron-nitrogen and boron carbon bonds due to conjugation throughout the molecule.[8a]

Mislow and coworkers performed a variable temperature NMR investigation of various diarylborinates and diarylboranes (see Figure 3).[9] They determined that



Dimesityl
Methyl Borinate



Dimesityl
Isopropyl Borane

Table 2

Compound	Aryl Group Rotation ΔG_T	T°C	Alkoxy Group Flip ΔG_T	T°C
B,B-dimesityl-methylborinate	11.8	-35	13.2	-35
B,B-dimesityl-*i*-propylborane	9.3	-98		

the rotational barrier about the boron-aryl bonds in the borinates were larger than those observed in the boranes. The conjugation of boron's empty p-orbital and the adjacent oxygen in the borinates appears to enhance the boron-aryl π-interaction. Rotational barriers for comparison are listed in Table 2.

Williams and coworkers[10] calculated the rotational barrier about the boron-phenyl bond in dichlorophenylborane using *ab initio* techniques and also concluded that significant π-type interaction existed between boron and the phenyl group. The interaction was viewed as a definite factor in governing the geometry of the molecule. The calculations were performed on the two most probable conformations: 1) planar, in which the plane of the phenyl and the plane formed by the BCl_2 group coincide; and 2) the phenyl plane and the BCl_2 group are twisted 90 degrees relative to each other. The planar conformation was found to be energetically more favorable with barrier to rotation of 8.8 kcal/mole.

A semi-empirical study[11] investigating the π-electronic structure of difluorovinylboranes and fluorodivinylboranes suggests that considerable π-electron density is contributed through back bonding to boron's p-orbital from the halogen atoms and not from the vinyl group. The magnitude of the back donation from the halogens in vinyl-BX_2 systems is observed in inverse relation to the halogen electronegativity:

$$B{-}Br \quad > \quad B{-}Cl \quad > \quad B{-}F$$

Armstrong and Perkins[12] propose that electron density may even be donated from the halogens to the vinyl group through boron. In a semi-empirical study performed on vinyl-BX_2 and $(vinyl)_2B$-X systems where X = hydrogen or alkyl (so that X does not interact with the π-system), multiple bond orders between boron and carbon (sp^2) reportedly ranged from 1.19 to 1.21.

A study of the vibrational spectrum of dichlorophenylborane[13] revealed that considerable π-type character exists between the boron and the phenyl group. The vibrational frequencies were utilized to calculate a rotational barrier about the boron-carbon bond of 45 kcal/mole.

Infrared and Raman[14] investigations of difluorovinylborane revealed that the rotational barrier about the carbon-boron bond in these molecules was only very small. The authors conclude that the relatively small barrier of 4.17 kcal/mole simply reflected a two-fold barrier and was not indicative of π-interaction between boron and carbon. In addition, Holliday et al.[15] concluded from a photoelectron spectrum of trivinylborane that only limited conjugation exists in the molecule, again suggesting only insignificant π-interaction between boron and the sp^2 carbon. Others[16] suggest that the reason only a small interaction between boron and carbon was being observed was due to the back-bonding that was occurring in the boron-halogen bonds. Groups attached to boron which do not possess nonbonded electrons would allow boron to more fully interact with the neighboring π-bond.

Ab initio investigations[17,18] on borinic acid esters (H_2B-OR) show strong π-type interactions between boron and oxygen. Reported rotational barriers about the boron-oxygen bond range from 12.6 to 16.4 kcal/mole, much higher than most reported barriers for boron-carbon(sp^2) bonds. Molecules of the type H_2B-X where X = Me, F, phenyl, OH, or NH_2 all possess bond orders greater than one for the B-X bond (listed in increasing order). Previously reported data from the infrared spectrum of trimethylborate esters[19] also indicate strong electronic interaction between boron and oxygen. Assessment of the bond orders yielded values around 1.4.

The nature of the boron-carbon bond in alkenyl and phenyl boron compounds has been extensively studied. The abundance of information addressing the topic has led to numerous speculations regarding the electron withdrawing power of trigonal boron. The nature of this interaction is important in understanding and predicting reactive properties of organoboron compounds.

RESULTS:

Molecular Mechanics

The existing structural data from literature sources were compiled in an attempt to build an MMX input card describing an (E)-1-alkenyl boronic acid or (E)-1-alkenyl boronate ester (see Appendix A). The main parameters needed to perform an MMX calculation are stretching, bending, torsional, and dipole constants. These parameters, once refined, could be used to perform future molecular mechanics calculations on vinyl boronic acids, anhydrides, or esters.

The various parameters compiled originated from a variety of sources. Bond lengths and bond angles for boron compounds were taken directly from reference books[8,20]; pertinent parameters, such as B-O bond dipole moment and B-O stretching constants, used by Kahn et al.[14] in their MM study of boron enolates, provided some of the needed information as well as the B-O-C-C torsional parameter. The exhaustive compilation of molecular mechanics parameters from the literature yielded less than half of those needed to fully define an alkyl or an alkenyl boronate ester for the MMX program.

The parameters still needed for the MMX input card, which included eleven torsional parameters and six bending parameters were drawn directly from the MMX default parameters listing for the carbocation. These would later be modified for use as boron parameters.

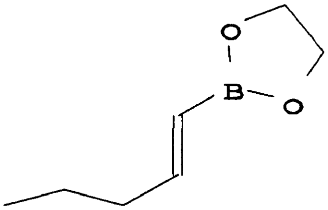


Figure 5

The Alchemy molecular drawing program provided the means to build and edit the models of the cyclic boronates to be studied in this investigation (please see Appendix B). The simplicity of Alchemy allowed for quick entry of atoms, atom types, and connectivity data which were all displayed in graphical (as opposed to numerical) format. The molecule depicted in Figure 5, (E)-1-pentenyl-1,3-dioxaborolane, was used as the model compound. Within Alchemy, a picture of the molecule was simply drawn onto the screen. Options within the program allowed for model refinement: bond angles and lengths as well as torsional angles were set to what was thought to be the most likely minimum energy conformation: coplanar and π-bond bond.

Once the geometry of the molecule was entered into Alchemy, an output file was written in Sybil format by the program. This output file contained the atom types, connectivity listings, and spatial arrangement of each atom in the model/molecule. The Sybil file was then read into PC-Model where an MMX parameter file was appended to the atom connectivity data. This new set of data was written to an MMX input file.

MMX then reads the input file, performs its calculations, and writes the results to an output file containing the newly optimized geometry for the molecule. The intended plan was to input an already minimized structure to MMX. If MMX changed the geometry during the minimization, then the parameters would be modified until it no longer found a different energy minimum. The use of angle fixing and bond length fixing would allow for modification of a small number of parameters instead of attempting to modify them all at once. Appendix B gives examples of MMX input files. Since a complete set of parameters was not compiled, output files from MMX do not contain significant results.

RESULTS:

Variable Temperature NMR

(E)-1-Pentenyl-1,3-dioxa-4-methylborolane was used as the model compound in the variable temperature NMR study due to the asymmetric nature of the borolane ring. If the minimum energy conformations of the molecule are taken to be those in which the π-bond and borolane are coplanar, then they will interconvert via rotation about the carbon-boron bond. Partial double bond character between the boron and carbon would hinder rotation. Analysis of the spectra obtained over a range of temperatures should yield a quantitative value for the rotational barrier. This, in turn, may be used to determine a torsional parameter for use in MMX calculations.

Proton spectra were taken every 10°C decrease in temperature down to -90°C, the lowest temperature attainable using acetone-d_6 as solvent. Even at -90°C the spectra showed little change, only slight broadening of the peaks which was probably due to freezing of the solvent.

DISCUSSION

The magnitude of the rotational barrier about the boron-carbon bond was to be determined. However, variable temperature ^{1}H NMR did not yield the expected results. No significant line broadening was observed to indicate that the dioxaborolane ring rotation was slowing, even at -90°C. Another possible reason that coalescence was not observed may be inherent in the molecule chosen. The rotamers of the 4-methyldioxaborolane may not have been different enough to result in distinct spectra arising from each rotamer.

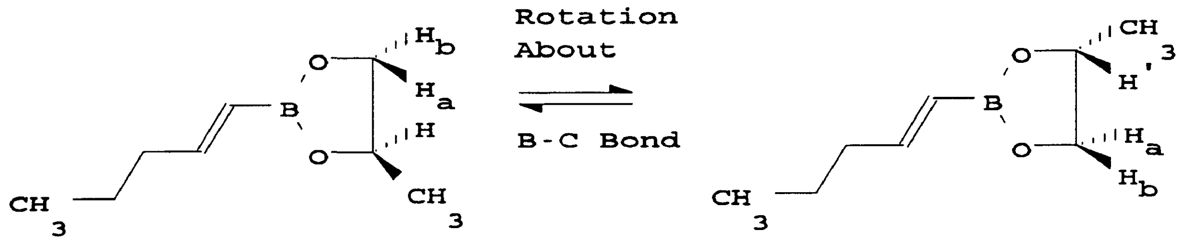


Figure 6

If this were the case, ring rotation may have been slowed but would not have been observed.

Since the rotational barrier about the boron-carbon bond could not be ascertained from the NMR study, the MMX torsional parameters were also not determined. In addition to trying to determine the rotational barrier from NMR data, use of the FIXTOR option in MMX was attempted. FIXTOR allows the user to define a torsional angle which is to remain fixed during minimization. The dihedral angle between the π-bond and the borolane ring was to be programmed in increments from 0° to 90°. The resulting steric energy at each conformation could then be used to estimate a rotational barrier and circuitously derive the MMX torsional parameter. In the end, though, the lack of the necessary parameters prohibited the use of the technique.

Even though a numerical value was not determined for the rotational barrier, insight was gained as to the nature of electron withdrawing power of boron. The review of work performed by others on the topic and NMR spectra of the vinyl boronates and anhydrides that are routinely prepared in our laboratory show definite effects on the shifts of the vinyl protons due to the boron moiety. Conjugation through boron's p-orbital is obvious within these types of molecules and undoubtedly plays a large role in shaping the molecule's minimum energy geometry and reactivity.

Appendix A

The following tables list the MMX parameters defining boron and some of its physical properties. This listing is a compilation of those values found in the literature for boron enolates and trimethyl borate. Also included are unmodified parameters for the carbocation from the master parameters listing of MMX. The atom identification numbers have been changed so that MMX will treat these values as properties of boron and not the carbocation.

The first row of numbers listed directly below tells MMX the number and type of parameters that are to be read from the input card. The numbers as well as their position in the card tell MMX that 20 torsional, six stretching, one van der Waals, and 13 bending parameters are to be input.

Torsional Constants:

Column 1: Special torsional term for cyclobutane, all others set this to zero.

Columns 2-5: Atom types of the dihedral angle. Atom 26 is trigonal boron, atom 6 is oxygen, atom 2 is sp^2 carbon.

Columns 6-8: Rotational barrier constants V1, V2, and V3 respectively. A value of 15 is approximately 60 kcal/mole and corresponds to the carbon-carbon rotational barrier in ethylene.

Stretching Parameters and Dipole Moment:

Columns 1-2: Atom types.

Column 3: Bond stretching constant in mdynes/angstrom.

Columns 4: Minimum energy, natural bond length.

Column 5: If either atom has one or less hydrogens attached, then this value for bond length is entered. If set to zero, then the value in column four is used.

Column 6: Bond dipole moment entered if atoms are different. If this value is greater than zero, then the atom listed in Column 1 is the more electronegative atom.

Columns 7-8: Special assignment for π-type atoms. Not entered.

Van der Waals Parameter:

Column 1: Atom type.

Column 2: "Hardness" of the atom in kcal/mole.

Column 3: Van der Waals radius in angstroms.

Bending Constants:

Columns 1-3: Atom types.

Column 4: Bending constant.

Column 5: Natural, minimum potential energy bond angle.

Definition of Boron:
A set of Parameters for MMX Optimization

20	6	1	13	0	0	0

20 Torsional Parameters

0	26	06	02	02	-.939	1.641	-.253
0	26	06	01	01	1.263	1.956	0.196
0	01	26	06	01	0.000	4.500	0.000
0	05	1	26	01	0.000	0.000	-.080
0	05	1	26	01	0.000	0.000	0.080
0	5	1	01	26	0.000	0.000	0.750
0	1	1	26	06	0.063	0.974	0.465
0	01	01	26	01	0.000	0.000	0.000
0	01	01	01	26	2.398	-1.44	3.525
0	02	02	02	26	0.000	15.00	1.000
0	01	02	02	26	-2.70	15.00	0.000
0	02	26	06	20	0.000	0.000	0.000
0	02	26	06	01	1.000	2.300	0.000
0	05	02	26	06	0.000	16.25	0.000
0	06	26	06	20	0.000	0.000	0.000
0	01	06	26	06	0.000	0.000	0.000
0	26	02	02	05	0.000	15.00	0.000
0	05	26	02	05	0.000	15.00	0.000
0	05	26	02	02	0.000	15.00	0.000

6 Stretching Parameters and Bond Dipole Moment

26	5	3.240	1.187	0.000	0.43
6	26	6.260	1.373	0.000	0.72
2	26	4.23	1.520	0.000	0.00
1	26	4.09	1.578	0.000	0.00
3	26	4.25	1.515	0.000	0.00

1 Van der Waals Parameter

26	0.034	1.980

13 Bending Parameters

6	26	1	1.2427	116.688	0
5	1	26	0.4540	111.588	0
1	26	1	0.6095	122.070	0
26	6	2	1.3247	127.808	0
1	2	26	0.4900	115.524	0
5	26	5	1.1572	122.310	0
5	26	6	0.7290	118.850	0
2	2	26	0.4300	120.000	0
26	2	5	0.3600	120.000	0
2	26	6	0.7000	124.300	0
26	6	1	0.7700	118.000	0
26	6	20	0.1000	120.000	0
6	26	6	0.7000	120.000	0

Listed below is an example of an MMX input card. This particular card defines boronic acid, $HB(OH)_2$. The card consists of three dimensional coordinates of each atom in the molecule and an attached atom list with bond orders. The additional parameters needed to define boron, listed on the preceding pages, have not been included here but would have been needed for an actual running of MMX.

MMX input card for boronic acid:

```
 BoronicAcid                                  70 0001 10.
FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF0F
000000
  10   1.5  8  1  5  0  0  0  0  4  0  1     1  0
  1  2  0  0  0  0  0  0  0  0  0  0  0  0  0  0
  2  3  1  4  1  5  2  6  2  7
 00.00000  0.00000  0.00000  26   0 -1.02430  -.18640  -.32290  06   0
 -1.63700  0.43830  0.16120  21   0 00.34210  0.69520  0.79500  05   0
 00.92800  -.46410  -.39460  05   0 -1.16750  -.71980  -.08840  20   0
 -1.04950  0.01510  -.88750  20   0 00.00000  0.00000  0.00000  00   0
```

Appendix B

The support files for Alchemy were modified in order to include boron within the listing of the available atoms. The original program package did not include boron so structural characteristics such as boron's hybridization and standard bond lengths were appended into the files necessary to perform input and output operations only. Data necessary to perform minimization operations within Alchemy were not entered because MMX, a more powerful minimization program was to be used. The following tables are partial listings of the support files that were modified. Shown are only the newly entered data regarding boron compounds. The Alchemy manual outlines briefly the process of updating support files. These directions were followed during these modifications.

Table 3 is a partial listing of the ATOMDEF.TAB file. The columns from left to right give the atom label, atomic number, atom geometry, designated color,

Table 3

LABEL	ATN	GEOM	COLOR	ELN	VDWRA	SYBIL TYPE
C3	6	TH	light_grey	2.5	1.52	1
B	5	TG	yellow	0.0	1.25	26
O3	8	BI4	red	3.5	1.36	8
N3	7	PYR	sky_blue	3.0	1.45	5
H	1	L1	dark_cyan	2.1	1.08	13

electronegativity, Van der Waals radius, and the Sybil atom type. Sybil is also a molecular modeling software package. This number is included so that Alchemy can write data in a format readable by Sybil or other compatible programs.

Table 4

B	B	1598	1
B	Br	1880	1
B	Cl	1715	1
B	H	1210	1
B	O2	1205	2
B	O3	1362	1
Br	Al	2340	1

Table 4 is a partial listing of the modified BONDINFO.TAB file. The first and second columns tell which atoms are bonded together. The third column gives the bond distance in nanometers. The fourth column gives the bond order.

APPENDIX C

The following values are taken directly from literature sources from:

References 21a: Parameters for H_2BO-Vinyl

	Atom Types	MM Parameter(s)
Bond Lengths		
	26-6 (B-O)	$r_o = 1.3728$
	26-5 (B-H)	$r_o = 1.1867$
Standard Bond Angles	5-26-6 (H-B-O)	$\theta = 118.85$
	26-6-2 (B-O-C)	$\theta = 130.11$
	5-26-5 (H-B-H)	$\theta = 122.31$
Dipole Moment		
	26-6 (B-O)	$\mu = 0.72$
	25-5 (B-H)	$\mu = 0.43$
Bond Stretch		
	26-6 (B-O)	$K_s = 6.2601$
	26-5 (B-H)	$K_s = 3.2396$
Angle Bends		
	5-26-6 (H-B-O)	$K_B = 0.7290$
	26-6-2 (B-O-C)	$K_B = 0.3733$
	5-26-5 (H-B-H)	$K_B = 1.1572$
Torstional Barriers	26-6-2-2 (B-O-C=C)	0.0, 1.5, 1.5
	26-6-2-1 (B-O-C-C)	-1.15, 1.5, 0.58
	5-26-6-2 (H-B-O-C)	0.0, 10, 0.0

References 21b: Parameters for L_2BO-Vinyl

Bond Length And Stretch	B-C (26-6)	$K_r = 4.0268$ $r_o = 1.5771$
	B-O (26-6)	$K_r = 6.2081$ $r_o = 1.3865$

Bond Angles And Bends	O-B-C (6-26-1)	$\theta = 116.688$
		$K_B = 1.2427$
	H-C-B (5-1-26)	$\theta = 111.588$
		$K_B = 0.4540$
	C-B-C (1-26-1)	$\theta = 122.070$
		$K_B = 0.6\text{-}95$
	B-O-C (26-6-2)	$\theta = 127.808$
		$K_B = 1.3247$
	C-C-B (1-1-26)	$\theta = 115.524$
		$K_B = 0.4900$

Torsion

Atoms	V1	V2	V3
B-O-C=C (26-6-2-2)	-0.9390	1.6410	-0.2529
B-O-C-C (26-6-1-1)	1.2630	1.9561	0.1957
C-B-O-C (1-26-6-2)	0.0000	4.5000	0.0000
H-C-B-O (5-1-26-6)	0.0000	0.0000	-0.0800
H-C-B-C (5-1-26-1)	0.0000	0.0000	0.0800
C-C-B-O (1-1-26-6)	0.0631	0.9738	0.4647
C-C-B-C (1-1-26-1)	0.0000	0.0000	0.0000*
C-C-C-B (1-1-1-26)	2.3980	-1.4400	3.5240

Van der Waals

B (26) $r_{vdw} = 1.9800$ $\epsilon = 0.0340$

Notes:

* The combined potential for the C-C-B-O and C-C-B-C terms are listed as that for the C-C-B-O torsion. The values listed for the C-C-B-C term are thus set to zero.[21b]

Bond lengths are in Angstroms.

Bond stretching constants are in mdynes/Angstrom.

Bond angle bending constants are in mdynes/rad_2.

Bond angles are tabulated in degrees.

Torsional terms are in kcal/mole.

Also see Reference 31 for additional MM information regarding boron enolates.

CHAPTER TWO

PREPARATIONS OF ORGANOBORON COMPOUNDS

OVERVIEW

Over the past three decades, advances in organoboron chemistry have yielded numerous powerful techniques employable in synthetic work. The development of highly selective hydroborating reagents as well numerous borohydride reducing reagents has increased the versatility and applicability of organoboron intermediates in the synthesis of natural products and other organic compounds. Research efforts of Brown, Matteson and others have demonstrated the wide applicability of organoboron chemistry. Stereodefined organoboron compounds have been utilized in the synthesis sugars[23b], insect pheromones[23,24], chiral alcohols[22,23], (E)- and (Z)-vinyl bromides[24], alkene carboxylic esters[22], and numerous types of conjugated dienes[25].

Frankland[22] first reported the synthesis of organoborane compounds in 1859.

$$3(C_2H_5)_2Zn \quad + \quad 2(C_2H_5O)_3B \quad \text{------>} \quad 2(C_2H_5)_3B \quad + \quad 3Zn(OC_2H_5)_2$$

He discovered that the reaction of an organometallic compound with alkoxy or haloboranes yielded trialkylboranes.

In 1939, it was observed that diborane reacts with aldehydes and ketones at 0°C

$$2RCHO + \frac{1}{2}(BH_3)_2 \text{ ---- > } (RCH_2O)_2BH \text{ ---- > } 2RCH_2OH + (HO)_3B$$

forming alkoxyboranes. Hydrolysis of the products yielded the corresponding alcohols.

Prior to World War II, only two laboratories in the world synthesized organoboron compounds, one in Germany and one in the United States. Interest in boron chemistry was therefore virtually nonexistent simply due to the scarcity of materials. Interest in boron chemistry gained momentum as new preparative methods were devised that allowed for convenient synthesis of organoboron reagents. The work performed under the direction of H. I. Schlesinger and H. C. Brown dramatically underscored the importance of this new and powerful tool for organic synthesis. Over the following decades, the use and applicability of organoboron reagents in preparative work has continuously intensified. Today numerous laboratories are involved with studying the chemistry and utility of organoboron reagents.

LITERATURE REVIEW OF SYNTHETIC METHODS

Hydroboration:

The hydroboration reaction[22] serves as a primary route to the synthesis of organoboron compounds. The addition of a B-H bond across a carbon-carbon multiple bonds is termed a hydroboration. The reaction normally proceeds with placement of boron on the less hindered carbon with subsequent addition of hydride to the more substituted carbon.

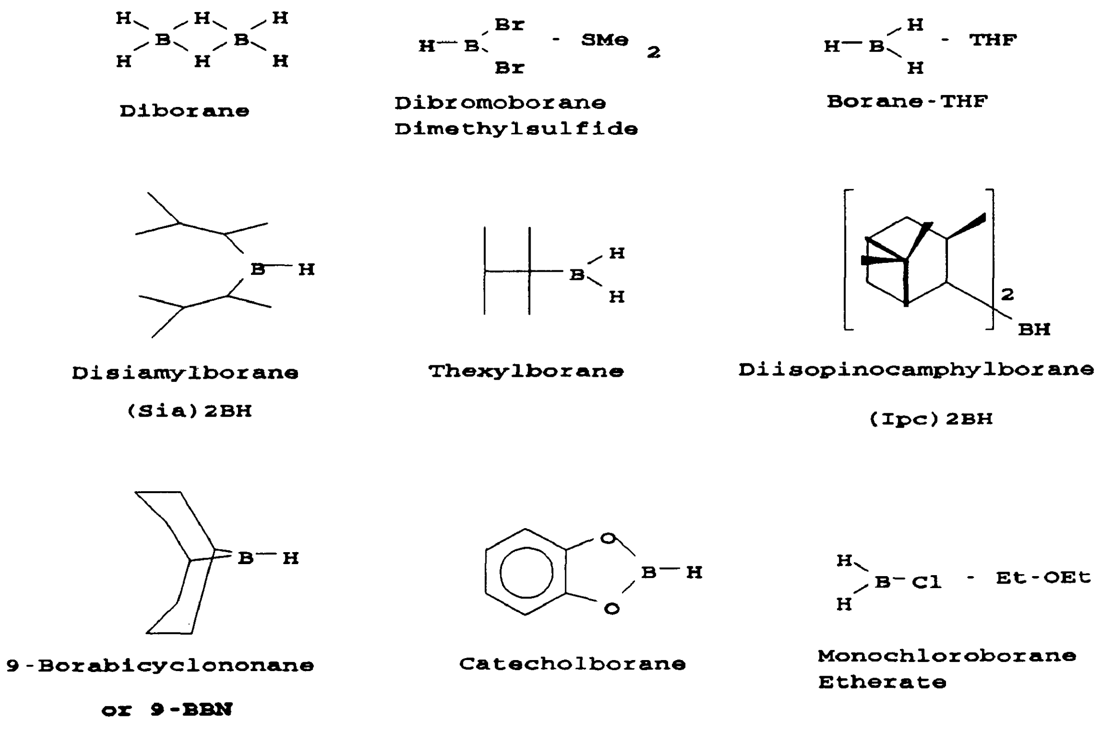


Figure 7

Diborane in ethyl ether, or simply borane-etherate, was the only hydroborating reagent available in the early days of organoboron chemistry. Today numerous hydroborating reagents are commercially available in a variety of solvents. A few common ones are shown in Figure 7.[22] All hydroborating reagents show similar regio- and stereoselective properties but not all with the same magnitude of selectivity. In general, the more hindered the boron atom in the reagent, the more selective the addition (see Table 5)[22].

Table 5

	Site of Addition (%):			
	1-Hexene		2-hexene	
	$\underline{C}_2$	$\underline{C}_1$	$\underline{C}_3$	$\underline{C}_2$
BH_3-THF	6	94	43	57
$(Sia)_2BH$	1	99	3	97
9-BBN	0.1	99.9	0.2	99.8

The addition of borane, commercially available as borane-THF, to three equivalents of alkene produces the trialkylborane. The reaction occurs with sequential production of monoalkylborane, dialkylborane, and finally trialkylborane as the three B-H bonds each add to an alkene. The isolation of mono- and dialkylboranes can be accomplished by controlling the reaction conditions so that the second or third B-H bond does not react. Typically, the use of hindered olefins slows or obstructs sequential addition before the second or third hydroboration depending upon the reagents used. Once prepared, mono- or dialkylboranes may be use as hydroboration reagents themselves for the preparation of mixed alkylboranes.[22]

Hydroboration of alkenes in which the two faces of the double bond are sterically dissimilar occurs preferentially at the less hindered face.[22] For example, the hydroboration of α-pinene occurs with very high facial and regioselectivity. Each borane adds to two molecules of α-pinene forming diisopinocamphylborane (Ipc_2-BH, see Figure 7) which may be used as a chiral hydroborating reagent. The hydroboration of norbornene or of (Z)-2-butene, for example, with Ipc_2-BH followed by oxidation results in the production of enantiomerically pure or enriched alcohols (see Figure 8).[22]

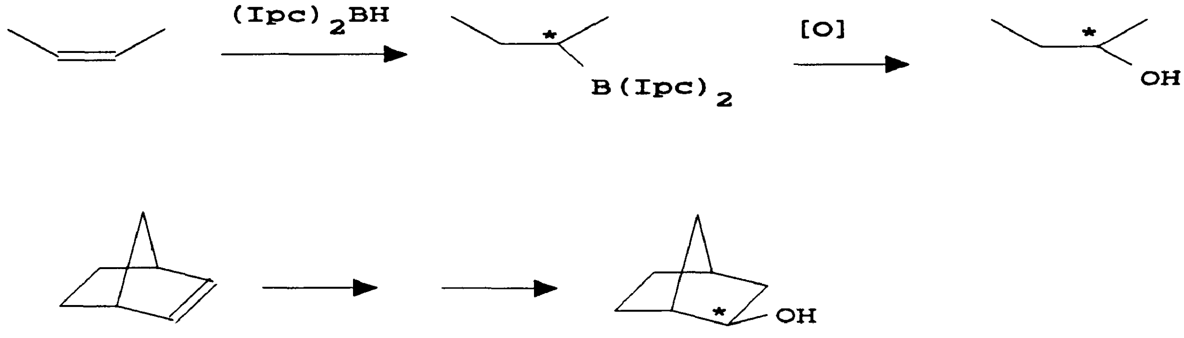


Figure 8

Another common hydroborating reagent which is synthesized from the reaction of borane-THF and 1,5-cyclooctadiene is 9-borabicyclononane or 9-BBN (see Figure 7). The hindered environment of the boron in 9-BBN enhances the regioselectivity in hydroboration reactions relative to borane-THF (see Table 5). This makes 9-BBN a very useful reagent for the production of high purity stereodefined organoboranes.

For example, the hydroboration of 1-decene with 9-BBN yields 99.9% terminal borane. The use of 9-BBN to hydroborate cyclic alkenes also results in high yields of stereodefined product (see Figure 9).

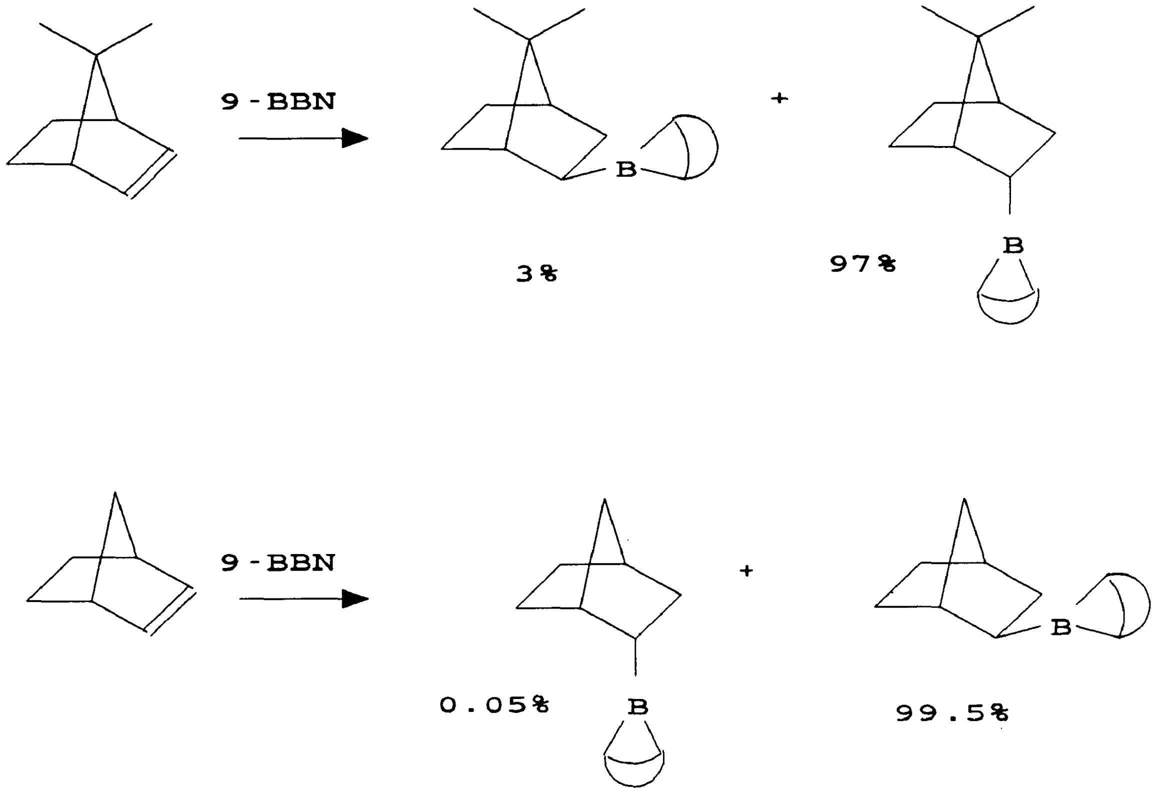


Figure 9

Dihaloborane-dimethylsulfide complexes such as dichloroborane-dimethylsulfide ($HBCl_2$-DMS) or dibromoborane-dimethylsulfide ($HBBr_2$-DMS) may be used in the preparation of alkyldihaloboranes. Stereo- and regioselectivity of hydroborations using these reagents are about the same as with 9-BBN.[22] The easy removal of the halogens after hydroboration by hydrolysis is a quick method utilized for preparing boronic acids.

The hydroboration of alkynes proceeds in a fashion similar to the corresponding alkenes.[22] The regioselectivity of the hydroboration is once again very high, yielding anti-Markovnikov (E)-alkenyl boranes or dihydroborated alkanes. For example, the hydroboration 1-pentyne gives rise to (E)-1-pentenyl dibromoborane which may be converted to the corresponding acid upon hydrolysis (see Figure 10).

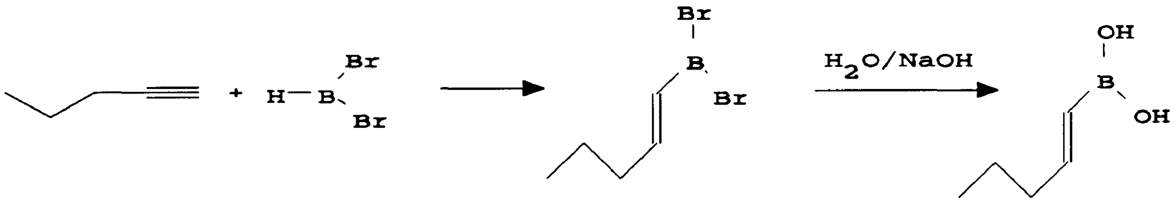


Figure 10

The dihydroboration product will be formed if borane (BH_3) is used as the hydroborating reagent, even if the reagents are combined in the proper stiochiometric ratio. The use of other reagents such as catecholborane or a dihaloborane will produce the (E)-alkenes in high yields with very little of the dihydroboration product.

Oxidation of Organoboranes

The preparation of alcohols, phenols, aldehydes, and ketones from organoboranes is accomplished through oxidative cleavage of the carbon-boron bonds. The stability of organoboranes toward oxidation increases with steric hinderance of the boron atom. The presence of atoms possessing available nonbonding electrons that are attached directly to boron also interferes with oxidation. In general, though, most organoboranes can be oxidized under the proper conditions.

Upon oxidation, alkylboranes give rise to alcohols; arylboranes are oxidized to phenols; alkenylboranes generally give rise to aldehydes or ketones.[22] The use of alkaline hydrogen peroxide is the most widely used method of oxidizing organoboranes (see Figure 11).[22]

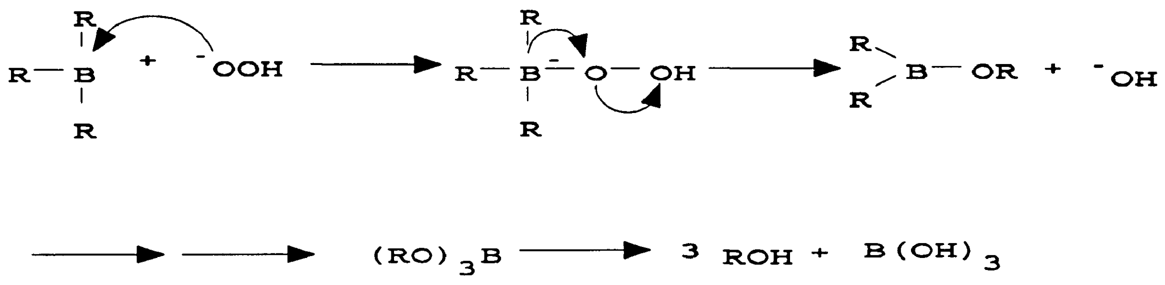


Figure 11

The reaction is thought to proceed as follows: the hydroperoxide anion attacks boron forming a quaternary intermediate. Through a rearrangement process, an alkyl group migrates with retention of configuration forming an alkoxyborane and displacing hydroxide ion. With water present, the boron-alkoxy bond is hydrolyzed forming the alcohol. Each alkyl group is sequentially converted to alcohol upon hydrolysis forming three moles of alcohol per mole or trialkylborane. The reaction proceeds essentially quantitatively.

Protonolysis of Organoboranes

Carboxylic acids are employed in the removal of boron from organoboron compounds with subsequent addition of hydrogen. Treatment of trialkylborane with excess anhydrous carboxylic acid at room temperature quickly produces two equivalents of alkane. The third alkyl, being more difficult to dislodge, may be removed by heating the mixture at reflux for a few hours giving an overall yield of three moles of alkane per mole of organoborane.[22]

As with oxidation, the stereochemistry of the alkyl groups is preserved upon protonolysis. The synthesis of alkanes from alkenes is often accomplished via hydroboration-protonolysis type reactions. The preparation of (E)-alkenes may also be accomplished through the hydroboration-protonolysis of internal alkynes. Typically, protonolysis of alkenylboranes is easier than the protonolysis of alkylboranes and, thus, the reactions may be performed at lower temperatures.[22]

Reduction of Functional Groups with Boron Hydrides

Borohydrides are often employed to reduce organic functional groups. In general, the ease of reduction with borohydrides follows the pattern: acid chloride > aldehyde > ketone > ester > amide > alkyl halide. Table 6 lists some common types of functionalities along with the type of borohydride often employed in their reduction.

Table 6

Reactivity in decreasing order	Typical solvent	Example
$LiBH_4$	ether	aldehydes, ketones, esters, lactones
$NaBH_4$	water, alcohol	aldehydes, ketones, imines, epoxides (slow)
$Zn(BH_4)_2$		base-sensitive compounds, aldehydes, ketones, imines, epoxides
$Cd(BH_4)_2$	ether	acid chlorides

RESULTS AND DISCUSSION

The main objectives in this research were to investigate the reactive properties of α,β-unsaturated organoboron compounds. Previously reported evidence indicates that the boron will act to withdraw π-electron density from electron rich substituents. The ability of boron to draw electron density from an adjacent π-bond and from attached species with nonbonded electrons has been documented (see Chapter One).

The primary focus was to synthesize and study the reactive properties of (E)-1-alkenylboronates and (E)-1-alkenylboranes. Interest in these types of compounds arose due to their relatively easy preparation and the lack of previously reported work on the topic. These types of compounds are also of specific interest due to their potential use as dienophiles in Diels-Alder reactions or as dipolarophiles in 1,3-dipolar cycloadditions.

One possible starting point for the synthesis of these compounds would be to use the easily prepared alkenyl boronic acids and then modify them. The preparation of (E)-1-alkenyl boronic acids, which has become routine in our laboratory, involves the hydroboration of 1-alkynes in methylene chloride using dibromoborane-DMS as a hydroborating reagent. The reaction, performed at room temperature, produces the (E)-1-alkenyl dibromoborane-DMS. This is subsequently converted to the corresponding boronic acid by treatment with aqueous sodium hydroxide (2.2N).

The aqueous base serves to quench the evolved hydrogen bromide (HBr) as it is formed upon hydrolysis of the borane. Hydrogen bromide could conceivably add to the double bond thereby diminishing the product yield.

The boronic acid is recovered from the product mixture by extraction with 5:1 ether-methylene chloride. Removal of the solvent under reduced pressure yields a white semi-solid which is a mixture of the acid and the anhydride forms. Through the use of ^{1}H NMR, the ratio of the acid to the anhydride can be calculated and the reaction yield determined. Typical yields range from 50-85%.

The use of boronic acids in reactions is complicated by the uncertainty in the amount of anhydride that is present. The ratio of acid to anhydride must be determined just prior to each use because the it changes with variation in atmospheric moisture. This is done by integrating the vinyl proton NMR resonances arising from each form and calculating their molar ratio.

Alkenyl boronic acids may be stored for lengthy periods of time under nitrogen without any noticeable degradation. The acid also appears to be relatively stable to air oxidation and to hydrolytic cleavage of the boron-carbon bond. Proton NMR clearly shows a well-defined doublet arrising from the α-vinyl proton and a doublet-triplet from the β-vinyl proton.

The ^{1}H NMR spectra of alkenyl boronic acids and α,β-unsaturated carboxylic acids show similar trends in vinyl proton chemical shifts. The α-proton of pentenyl boronic acid appears at 5.4 ppm whereas the α-proton of crotonic acid appears at 5.8. The β-protons appear at 6.5 and 7.0 for the boronic acid and carboxylic acid respectively. This downfield shift of the β-protons can be explained by invoking the resonance forms shown below both types of acids (see Figure 8).

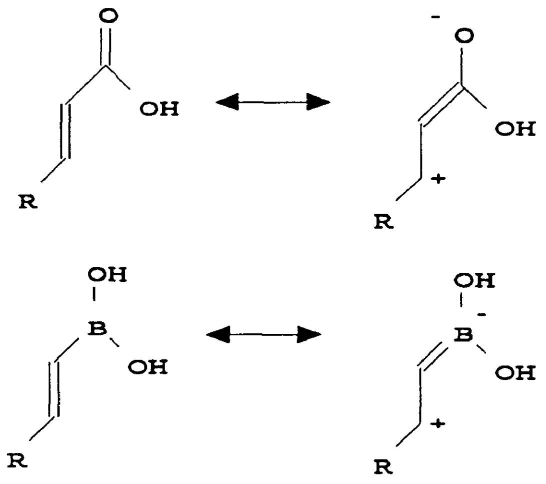


Figure 12

Delocalization of electron density gives the β proton a partial positive charge. This is consistent with the downfield shifts observed in the ^{1}H NMR for the β-protons relative to the α-protons. The smaller downfield shift associated with vinyl protons of the boronic acid relative to the those in the carboxylic acid may by interpreted as a less effective resonance withdrawing of electron density by the boron.

Conversion of boronic acids to the corresponding anhydrides simply involves driving off water. The conversion can be done simply by leaving the acid in a dessicator for a few weeks or by azeotropic removal of water using a Dean-Stark distillation apparatus. The latter technique was the preferred method, taking only a few hours for complete conversion. The anhydride is a clear or light yellow oil in contrast to the semi-solid acid.

Table 7

	α-vinyl proton		β-vinyl proton	
	Chemical Shift	Coupling	Chemical Constant	Coupling Shift
Constant				
Pentenyl-				
Acid	5.4	17.9	6.5	17.9, 6.4
4-Methylborolane	5.4	17.9	6.6	17.9, 6.4
Anhydride	5.6	17.9	6.9	17.9, 6.8
Hexenyl-				
Acid	5.4	17.6	6.5	17.6, 6.6
di(*l*-menthol)ester	5.2	17.9	6.5	17.9, 6.4
Anhydride	5.5	17.2	7.0	17.2, 5.8
Octenyl-				
Acid	5.4	17.2	6.5	17.2, 6.4
Anhydride	5.5	17.1	7.0	17.1, 5.9
Crotonic Acid	5.8		7.1	

Chemical shifts are in ppm relative to TMS.
Coupling constants are in Hertz.

Proton NMR of boronic anhydrides shows a much greater downfield shift of the vinyl protons relative to those of the corresponding acids. The ability of boron to withdraw electron density from the adjacent π-bond now approaches that of analogous carboxylic acids. This more pronounced polarization of the double bonds of the anhydride relative to the acids may be explained by simply noting the ratio of oxygen to boron in each form. In the acid (or the ester), the ratio is two oxygens per boron. In the anhydride, the ratio is one to one. This reduces the amount of electron density donated to boron by oxygen allowing boron to withdraw more electron density from the π-bond.

Either the anhydride or the acid may serve as starting material in the preparation of the (E)-1-alkenyl boronate esters. Preparation of esters employs the same technique as making the anhydride from the acid. Two equivalents of monofunctional alcohol or one equivalent of diol is added to the boronic acid. The ratio increases to three to one for diols with anhydrides or six to one for monofunctional alcohols with the anhydride. The evolved water is driven off by azeotropic distillation. Removal of the remaining solvent is done under vacuum and the crude product may be purified by Kugelrohr distillation. The ethylene glycol ester of hexenyl boronic acid, for example, distills between 25° and 60°C at 0.2 torr. Yields range from 60-90% with the higher yields being more typical.

The pentenyl, hexenyl, and octenyl ethylene glycol esters were used most frequently due to their ease of preparation and identification. These esters are reasonably stable to hydrolysis from atmospheric moisture but should still be kept under inert conditions for extended storage. Like the anhydride, the ester is a clear or pale yellow oil.

Synthesis of boronic acid thiolate esters was attempted by substituting thiol or dithiol compounds in place of alcohols in the previously outlined preparation of boronates. The thiol derivatives should display downfield shifts of the vinyl protons similar to that observed with the anhydride but perhaps not as great. The orbitals of sulfur and boron do not match as well in energy as do those of boron and oxygen. Hence, the π-type interaction between boron and sulfur is expected to the be reduced. This would manifest itself in increased electron delocalization from the π-bond to boron's empty p-orbital. The vinyl protons of the boronic acid thiolate esters should show a greater downfield shift than the corresponding acids.

The sulfur compounds were added to the alkenyl boronic acids in 2:1 stoichiometry for monofunctional thiols and 1:1 for dithiols. Analysis of the crude product mixtures using ^{1}H NMR revealed that no reaction had taken place. The boronic acid, though, had been converted to the anhydride form.

A new approach to synthesizing the thiolate esters involved using the dihaloborane form instead of the acid form. Hydroboration of 1-pentyne with dibromoborane would yielded (E)-1-pentenyl dibromoborane. In a separate reaction vessel, propane dithiol and sodium hydride were combined to produce the sodium thiolate (see Figure 13). The mixtures were then combined by cannulating the borane into the second reaction flask. The mixture was allowed to react over a period of several hours. Analysis of the crude product mixture with NMR and GC/MS revealed that this reaction had not proceeded as desired.

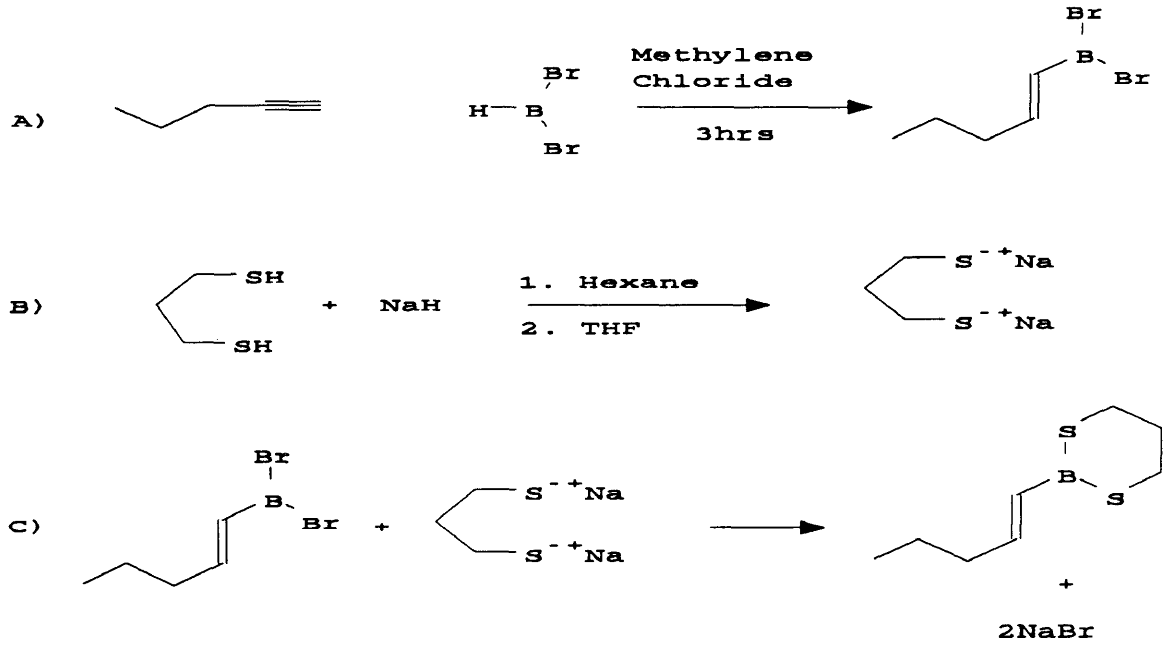


Figure 13

The preparation of boronic acid/carboxylic acid anhydrides was also attempted. It was hoped that the carboxylic acids would add to the boronic acid to produce the mixed anhydride. The addition of a carbonyl group opposite the ester linked oxygen should enhance the electron withdrawing power of boron. The effect, once again, would be to further polarize the the double bond.

The first strategy followed was to combine the two acids together in benzene and azeotropically remove the water produced in the reaction. This is the standard method of preparing the boronic esters. This procedure was followed with a variety of carboxylic acids (and one sulfonic acid): o-phthalic acid, 3-chlorobenzoic acid, benzilic acid, p-nitrobenzioc acid, benzoic acid, and p-toluenesulfonic acid. None of these attempts were successful.

A second strategy was devised in which (E)-1-alkenyl dibromoborane was used in lieu of boronic acid. The carboxylic acid was added directly to the borane and nitrogen was bubbled through the solvent to remove the evolved HBr gas. The nature of the evolved gas was tested with a wet piece of Alkacid paper confirming its acidic nature. Once again, the desired products were not found in the reaction mixture.

In some instances, the vinyl peaks of the starting alkenyl boronic acids or alkenyl dibromoboranes did not move indicating that no reaction had taken place. In most cases, though, the vinyl resonances disappeared. In these cases, the reaction formed an uncharacterizable mixture of products. The disappearance of the vinyl peaks may have been due to a reaction of the carboxylic acid with the double bond. Alternatively, the carboxylic acids may also have reacted with the boron in a

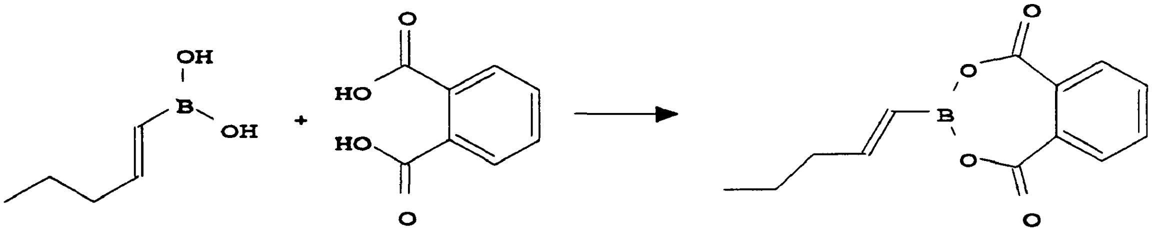
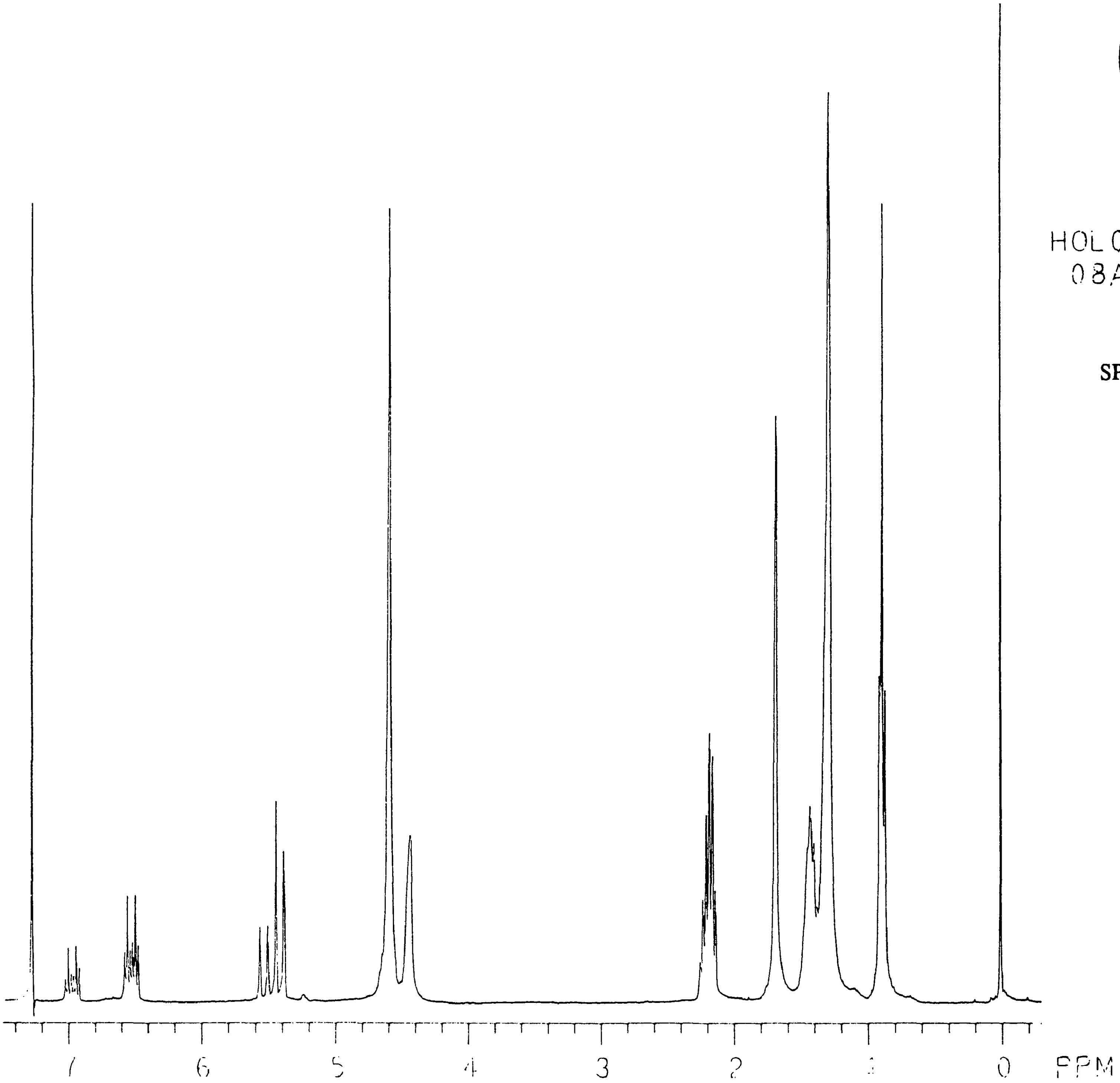
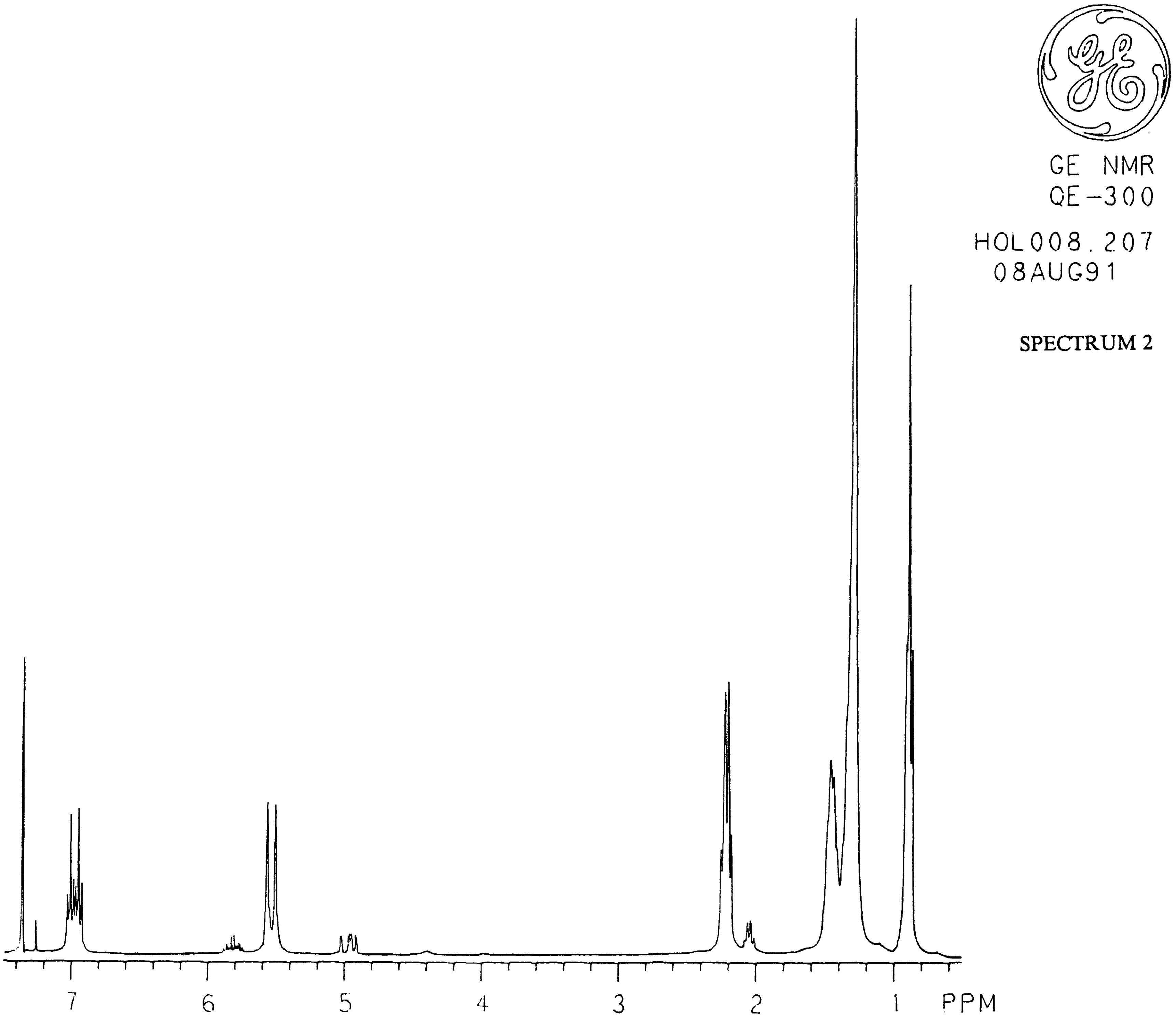


Figure 14

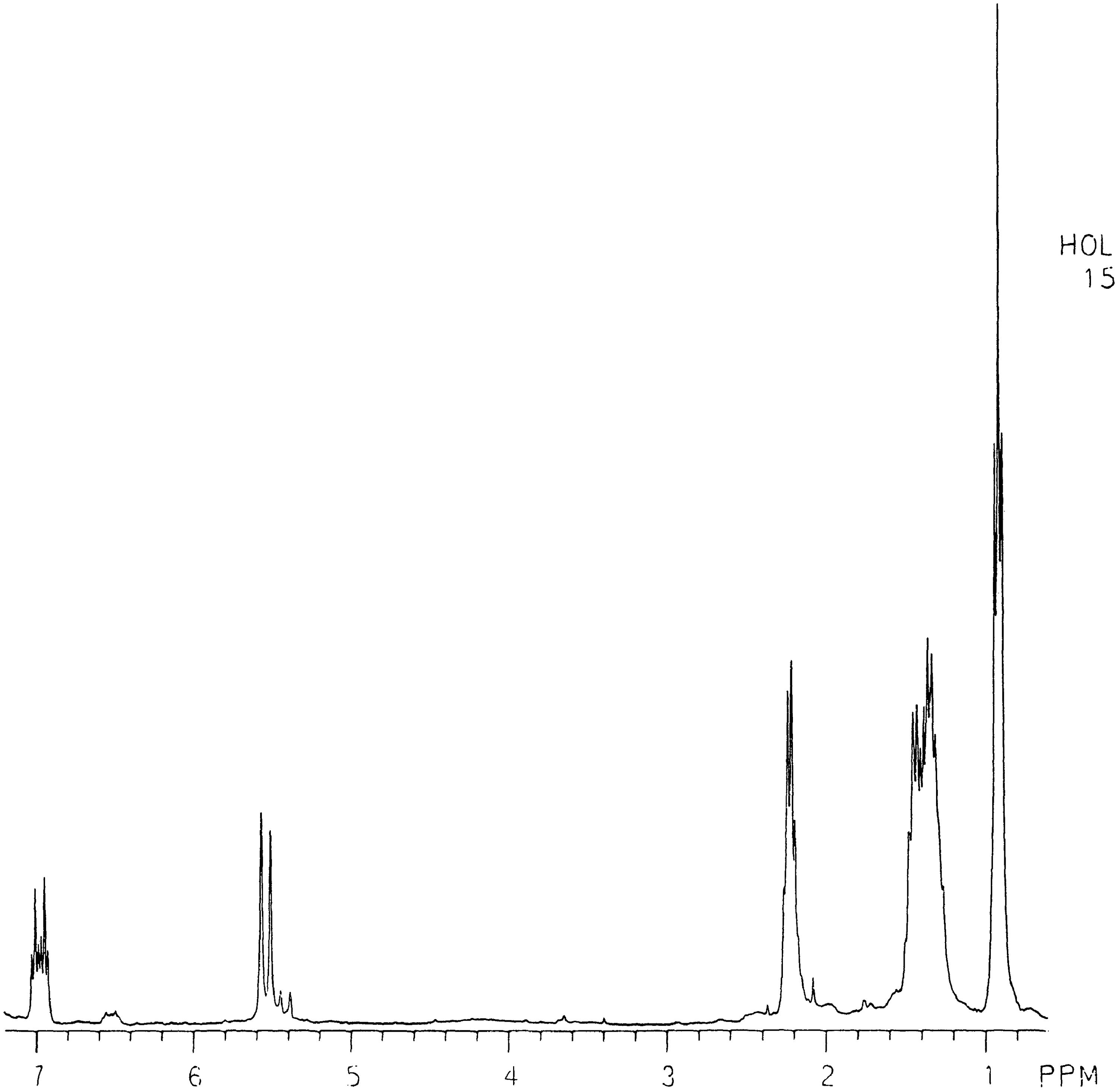
protonolysis type reaction. In either case, the desired products would not have been generated



SPECTRUM 1



SPECTRUM 2

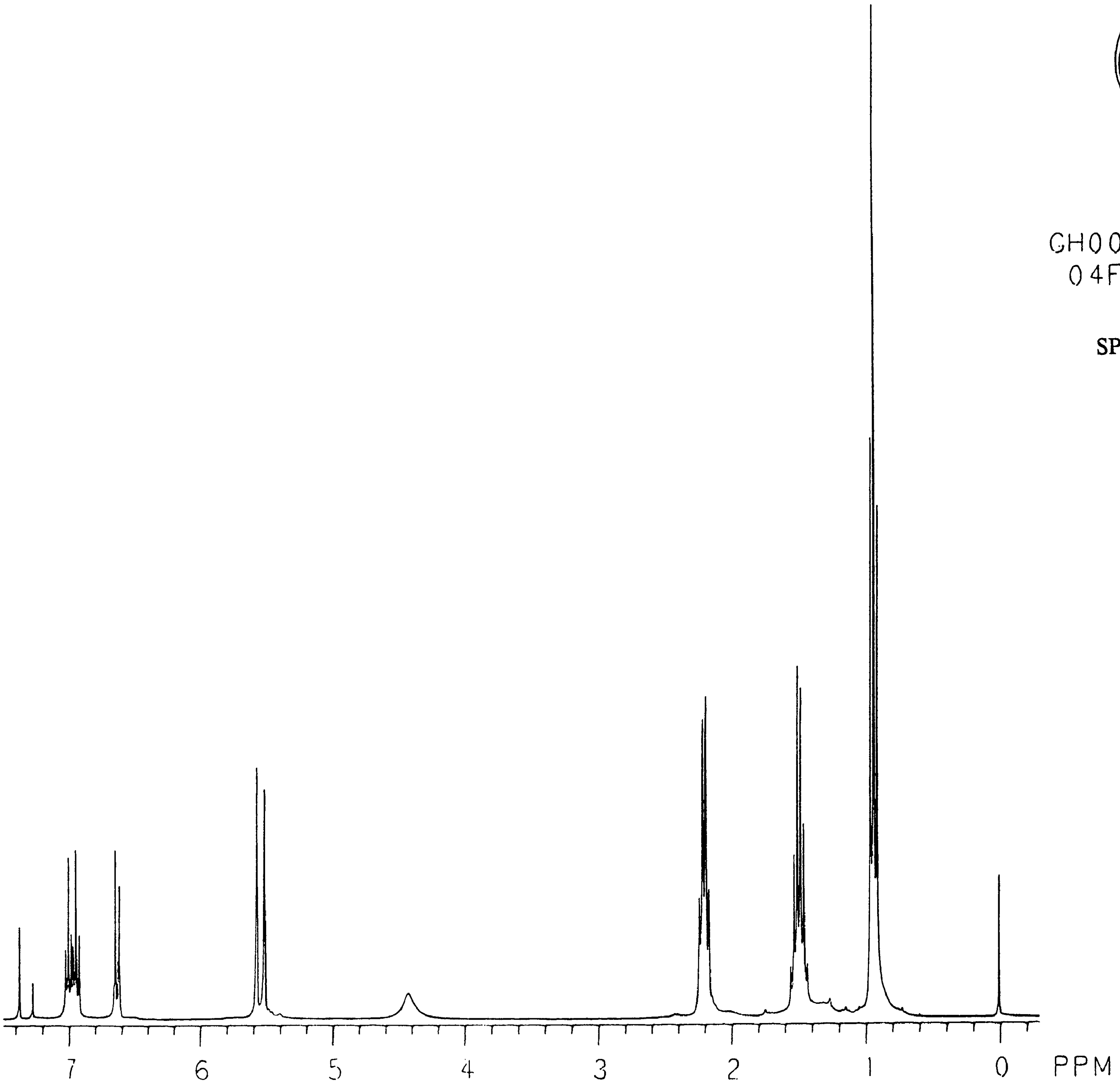


SPECTRUM 3

GE NMR
QE-300

GH002.707
04FEB90

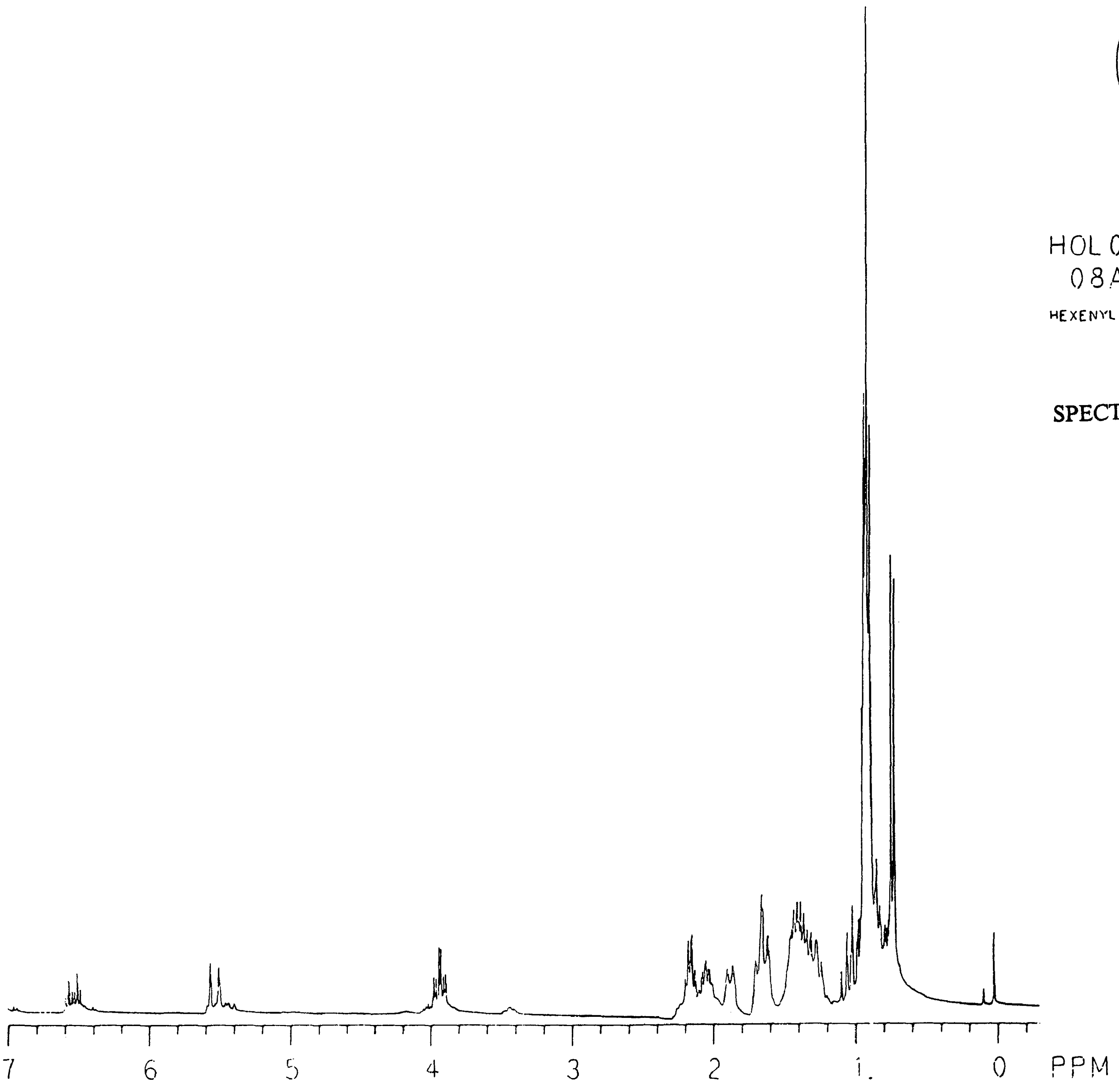
SPECTRUM 4

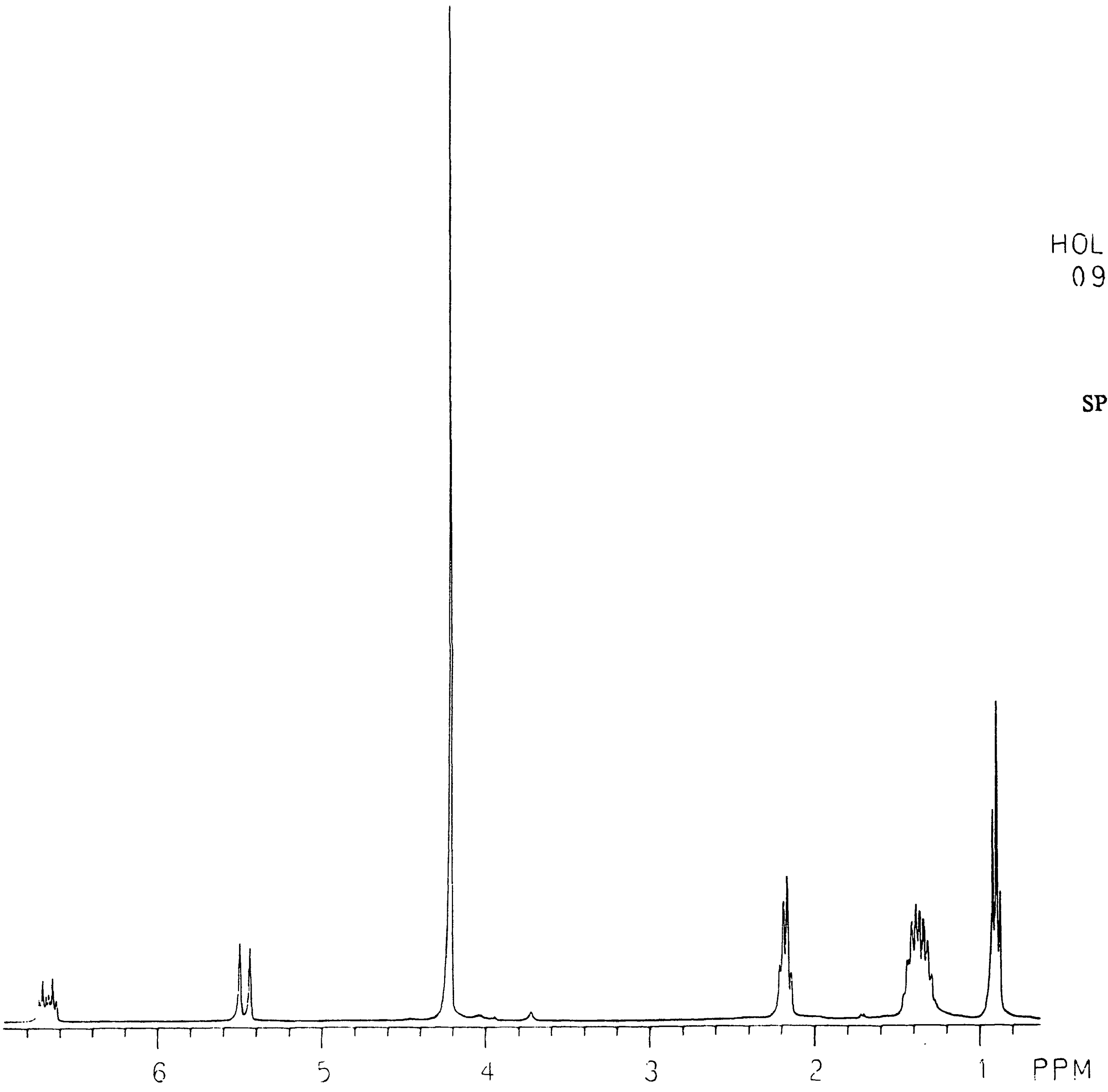


GE NMR
QE-300

HOL008.204
08AUG91
HEXENYL-DI(L-MENTHOL) EST

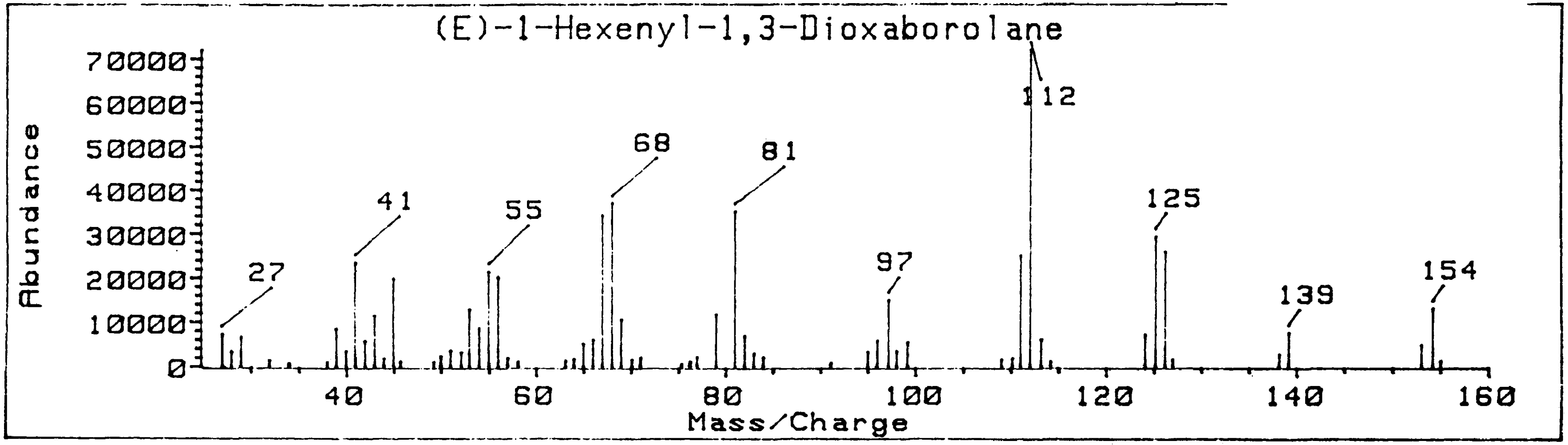
SPECTRUM 5





SPECTRUM 6

SPECTRUM 7


(E)-1-Hexenyl-1,3-Dioxaborolane
Abundance
70000
60000
50000
40000
30000
20000
10000
0
27
41
55
68
81
97
112
125
139
154
40
60
80
100
120
140
160
Mass/Charge

EXPERIMENTAL

Unless otherwise noted, all reaction were performed under nitrogen using previously dried glassware. Syringes and needles were stored in a dry-box until just prior to use. Proton and carbon NMR spectra were obtained with a GE QE-300 spectrometer. GC/MS analysis was performed using a Hewlett Packard 5988A mass spectrometer with accompanying HP 5890A gas chromatograph and HP Chem Station running under the Pascal environment. All injections onto the GC for mass spectral analysis were performed manually. Gas chromatography was performed on a Supelco fused silica capillary column, 30 meters, 0.32 mm internal diameter, and 1 μ film thichness. Melting points were taken using a MEL-TEMP melting point apparatus. Chromatography plates for thin layer chromatography were aluminium sheets coated with silica gel, 60W, with 0.2 mm layer thickness.

(E)-1-Pentenyl Boronic Acid:

The syntheses of pentenyl boronic acid and pentenyl boronic anhydride are representative of the procedures employed in the preparation of all boronic acids and anhydrides.

A 500 mL three neck round bottomed flask is equipped with a magnetic stir-bar, septum, and 125 mL addition funnel. Methylene chloride (50 mL) is added and the system is then placed under nitrogen. Via syringe, 9.9 mL (0.10 mole) 1-pentyne is added and the reaction flask is chilled in an ice-water bath to 0°C. Once the system has cooled, 100 mL (0.10 mole) 1M $HBBr_2$-Me_2S is added slowly via syringe. After addition of the $HBBr_2$-Me_2S is complete, the ice-water bath is removed and the reaction is allowed to continue at room temperature for three hours. The reaction mixture may become deep green or light pink.

The reaction flask is once again placed in an ice-water bath and chilled to 0°C. An aqueous solution of 8.8 g NaOH (0.22 mole) in 100 mL water is prepared, chilled to 0°C, and placed in the addition funnel. The nitrogen line is removed, leaving the system open, and the NaOH solution is added slowly over 15 to 20 minutes. During the addition, the reaction mixture turns pink and HBr gas is evolved. Toward the end of the addition, solid pentenyl boronic acid will precipitate (white flakes). Once all the base has been added, the ice-water bath is removed and the reaction allowed to stir at room temperature for one hour.

The reaction mixture is transferred to a 500 mL separatory funnel. The reaction flask is rinsed with 50 mL methylene chloride which is also added to the separatory funnel. The organic layer (bottom) is collected and the remaining aqueous layer is extracted with 300 mL (3 x 100 mL) of 5:1 ether/methylene chloride. The combined organic layers are then dried with anhydrous sodium sulfate.

The drying agent is removed and the dried organic layers are placed in a 500 mL single neck round bottomed flask. The solvents are removed under reduced pressure yielding 6.18 g of pentenyl boronic acid (white solid) and some pentenyl boronic acid anhydride (yellow oil). ^{1}H NMR ($CDCl_3$): δ 6.51 (dt, 1H, *J* = 17.9, 6.4 Hz), δ 5.41 (d, 1H, *J* = 17.9 Hz), δ 4.2 (s,2H), δ 2.07-2.27 (m, 2H), δ 1.37-1.55 (m, 2H), δ 0.77-0.98 (t, 3H).

(E)-1-Pentenyl Boronic Acid Anhydride:

The preparation of pentenyl boronic anhydride from pentenyl boronic acid is simply a continuation of the previously outlined synthesis: To 6.18 g of pentenyl boronic acid/anhydride in a 500 mL single neck round bottomed flask, 350 mL of benzene is added along with a magnetic stir bar. A Dean-Stark distillation apparatus with condenser and nitrogen line is assembled, using a mantle as a heating source. The flask is heated to reflux. The benzene/water azeotrope is removed periodically from the collection arm of the Dean-Stark apparatus until well after the collected solvent is clear, indicating that all the water had been driven off.

The remaining benzene is removed under reduced pressure yielding 5.30 g (0.0035 mole, 55% yield) pentenyl boronic anhydride. The product is stored under nitrogen. ^{1}H NMR ($CDCl_3$): δ 6.93 (dt, 1H, *J* = 17.9, 6.8 Hz), δ 5.56 (d, 1H, *J* = 17.9 Hz), δ 2.22 (dt, 2H, *J* = 7.8, 7.8 Hz), δ 1.60 - 1.38 (m, 2H),
δ 0.86 (t, 3H, *J* = 6.8 Hz).

(E)-1-Hexenyl Boronic Acid:

^{1}H NMR ($CDCl_3$): δ 6.52 (dt, 1H, *J* = 17.8, 6.55 Hz), δ 5.42 (d, 1H, *J* = 17.44 Hz), δ 4.37 (s, 2H), δ 2.12-2.17 (m, 2H), δ 1.27-1.49 (m, 4H), δ 0.86-0.95 (t, 3H).

(E)-1-Hexenyl Boronic Acid Anhydride:

^{1}H NMR ($CDCl_3$): δ 6.97 (dt, 1H, *J* = 17.6, 5.8 Hz), δ 5.53 (d, 1H, *J* = 17.6 Hz), δ 2.36-2.12 (m, 2H), δ 1.60-1.12 (m, 4H), δ 0.91 (t, 3H, *J* = 5.9 Hz).

(E)-1-Octenyl boronic acid:

^{1}H NMR ($CDCl_3$): δ 6.51 (dt, 1H, *J* = 17.2, 6.4 Hz), δ 5.40 (d, 1H, *J* = 17.2 Hz), δ 4.50 (s, 2H), δ 2.11-2.26 (m, 2H), δ 1.16-1.51 (m, 8H), δ 0.88 (t, 3H, *J* = 6.6 Hz).

(E)-1-Octenyl boronic acid anhydride:

^{1}H NMR ($CDCl_3$): δ 6.96 (dt, 1H, *J* = 17.1, 5.9 Hz), δ 5.53 (d, 1H, *J* = 17.1 Hz), δ 2.11-2.26 (m, 2H), δ 1.16-1.51 (m, 8H), δ 0.88 (t, 3H, *J* = 5.9 Hz).

(E)-1-Pentenyl-1,2-propanediol boronate ester ((E)-1-pentenyl-1,3-dioxa-4-methylborolane):

The preparation of pentenyl-1,2-propanediol boronate ester is typical of the procedure employed for all ester preparations. In a 300 mL single neck round bottomed flask is placed 3.19 g (0.028 mole) boronic acid, 2.03 mL (via syringe, 0.028 mole) 1,2-propanediol, 250 mL benzene and a magnetic stir bar. A Dean-Stark distillation apparatus with condenser and nitrogen line is assembled, using a mantle as a heating source. The flask is heated to reflux. The benzene/water azeotrope is removed periodically from the collection arm of the Dean-Stark apparatus until well after the collected solvent is clear. The remaining solvent is removed under reduced pressure (aspirator). The crude product is transferred to a 25 mL single neck round bottomed flask and Kugelrohr distilled. The pure product is collected at 70°C at 0.1 torr yielding 3.71 g of pure product (86%, clear oil). ^{1}H NMR ($CDCl_3$) δ 6.62 (dt, 1H, *J* = 6.6, 18.1 Hz), δ = 5.42 (d, 1H, *J* = 18.1 Hz), δ = 4.42-4.62 (m, 1H), δ 4.32 (dd, 1H, *J* = 7.8, 7.8 Hz), δ 3.73 (dd, 1H, *J* = 7.8, 7.8 Hz), δ 2.14 (dt, 2H, *J* = 31.7, 6.8 Hz), δ 1.38-1.60 (m, 2H), δ0.91 (t, 3H, *J* = 6.8 Hz).

(E)-1-Hexenyl Ethylene Glycol Boronate Ester ((E)-1-Hexenyl-1,3-Dioxaborolane):

86% yield ^{1}H NMR ($CDCl_3$): δ 6.66 (dt, 1H, *J* = 6.84, 17.58 Hz), δ = 5.47 (d, 1H, *J* = 17.55 Hz), δ = 4.23 (s, 1H), δ 2.18 (m, 2H), δ 1.20-1.53 (m, 4H), δ 0.89 (t, 3H, *J* = 7.81 Hz). Mass Spectrum: 154 amu (M^+) 14.4%, 139 amu 11.2%, 125 amu

36.9%, 112 amu (base peak) 100%, 97 amu 27.6%, 81 amu 46.4%, 68 amu 51.4%, 55 amu 27.8%, 41 amu 18.5 %, 27 amu 6.9%.

Hexenyl-(di-*l*-Menthol) Boronate Ester:

^{1}H NMR ($CDCl_3$): δ 6.52 (dt, 1H, *J*= 17.58, 6.83 Hz), δ 5.25 (d, 1H, *J*= 17.58 Hz), δ 3.93 (dt, 2H, *J*= 10.74, 3.91 Hz), δ 2.25-0.4 (mm, 45H).

CHAPTER THREE

REACTIONS OF ORGANOBORON COMPOUNDS WITH NITRONES

OVERVIEW

Prior to this work, no previously reported research documents the reactions of organoboron compounds with 1,3-dipolar type molecules. Specifically, reactions of organoboron compounds with nitrones have not previously been addressed in the literature. This chapter documents the synthesis of N-(1-phenylpropyl)-N-phenylhydroxylamine, a novel compound, produced via a rearrangement type reaction between diphenylnitrone and triethylborane (obtained commercially). The reaction proceeds with the formation of a new carbon-carbon bond with concurrent generation of a new asymmetric.

Interest arose in reacting unsaturated boron compounds with nitrones as an alternative route to synthesizing cyclic adducts via 1,3-dipolar cycloadditions. During the course of this work, it was discovered that more than one possible mode of addition existed. An alkylation reaction via rearrangement seemed to be occurring in competition with cycloaddition. In order to determine if, indeed, an alkylation reaction was proceeding, triethylborane was reacted with diphenylnitrone. The use of this borane eliminated the possibility of cycloaddition due to the lack of a π-bond. The product afforded upon work-up and analysis, N-(1-phenylpropyl)-N-phenylhydroxylamine, could have been formed only as a result of a rearrangement reaction. This new type of reaction if between nitrones and organoboron compounds is being further investigated for its synthetic potential.

Literature Review of Rearrangement Reactions at Boron

Trigonal boron often acts as a Lewis acid due to its low-energy empty p-orbital. Lewis bases will therefore attack boron, quaternizing it, and giving it a negative charge. If a leaving group is present within the complex, then a group attached to boron may migrate, with retention of configuration, to that position with the loss of the leaving group.[22,23]

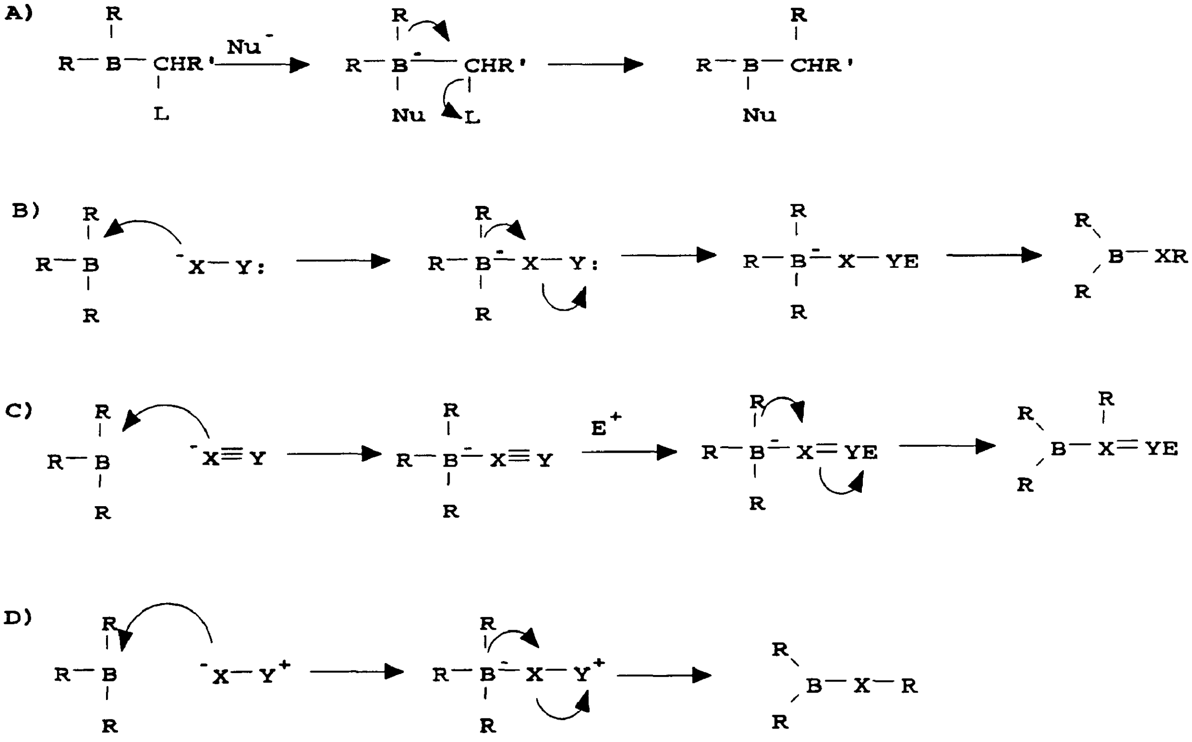


Figure 15

The factors that seem to accelerate the rearrangement process are: 1) increased negative charge on boron and 2) positive charge development on the atom receiving the migrating group. The commonly observed types of rearrangement reactions are presented in Figure 15.[22]

The rearrangement reaction is a very useful technique employed in numerous synthetic strategies.[22,23] For example, the reaction of trialkylborane with trimethylammonium methylide results in loss of trimethylamine and the homologation of one of the alkyl groups (see Figure 16).

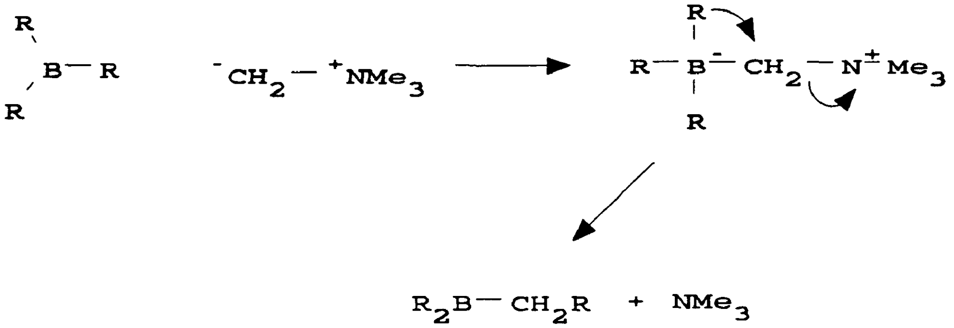


Figure 16

This type of reaction has been used in the ring expansion of boron heterocycles. Borapane, for example, is a seven membered boron heterocycle. It may be sequentially expanded by the addition of methylenes from chloromethyllithium to form larger rings of varying size up to twelve atoms.[23a]

Preparation of Nitrones

Nitrones may be prepared from a variety of nitro and amine containing compounds.[24] Synthesis from N,N-disubstituted hydroxylamines has been performed using numerous types of oxidizing agents.[24] These 1,3-dipolar compounds have also been prepared through the condenssation reaction between N-substituted hydroxylamines and a variety of aldehydes or ketones (see Figure 17 and Table 8).[24]

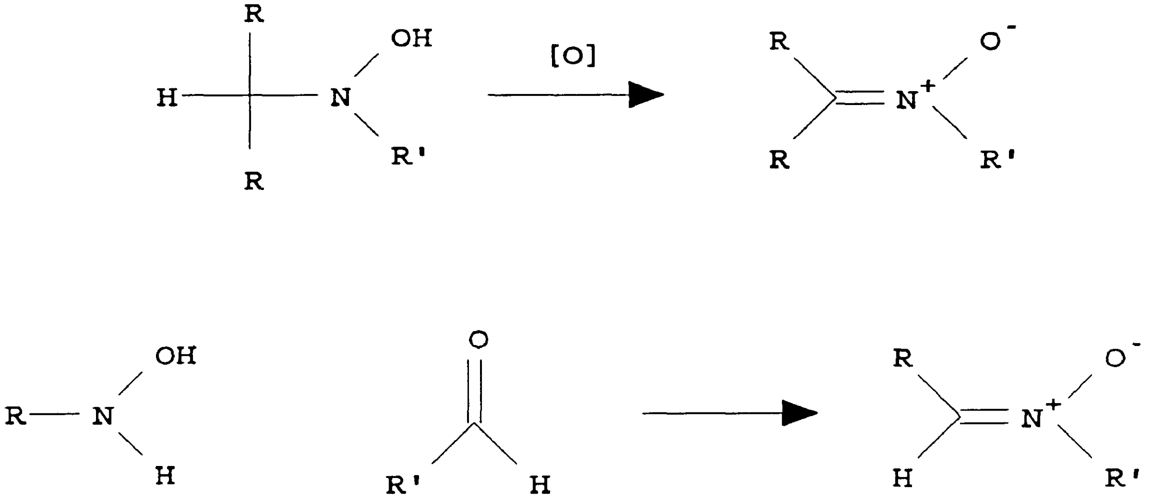


Figure 17

Table 8 lists some some nitrones that were prepared by the condensation reaction of monosubstituted hydroxylamines and carbonyl compounds.

Table 8

Substituents	N-Substituent	Yield%
n-C_3H_7, H	Phenyl-	21 - 80
Phenyl-, H	Methyl-	
Phenyl-, H	Phenyl-	>90
Phenyl-, H	CH(Phenyl)$_2$-	80
Phenyl-, Phenyl	CH_2-Phenyl-	65

Nitrones may be characterized using mass spectroscopy[25] and NMR.[26] The typical mass spectrum of nitrones lacks a molecular ion peak due to the lability of the nitrogen-oxygen bond giving rise to a prominent M-16 peak.

Table 9

Diphenylnitrone
Mass Spectral Data[30]

m/e	Composition
91	C_6H_5N (60%) C_7H_7 (40%)
104	C_7H_6N
105	C_7H_5O
168	$C_{12}H_{10}N$
169	$C_{12}H_{11}N$
180	$C_{13}H_{10}N$
181	$C_{13}H_{11}N$

Many types of rearrangements of the nitrone skeleton are possible under mass spectral conditions. Frequently observed fragments arise with weights of M-H, M-

CO, M-HCO, M-OH, and M-CHNO. All these are produced by a rearrangement of the nitrone skeleton. The spectra of aromatic nitrones will contain phenyl ions and tropylium ions and, possibly, fragments arrising M-C_7H_5O, M-C_6H_5N, and M-C_6H_4CO.[25]

The proton NMR spectra of phenylnitrones have been studied by Kayano and Suzuki.[26] The chemical shifts of the α-protons of nitrones typically appear 0.8 to 1.1 ppm farther downfield than those of sunstituted ethylenes. For comparison, the vinyl protons of dialkyl substituted ethylenes normally reside between 5.78 and 5.73 ppm. Those of styrene appear at 6.3 ppm and 7.1 ppm for *trans*-stilbene. The *meta* and *para* protons aromatic nitrones appear slightly upfield from benzene (7.2 ppm) between 7.45 and 7.37 ppm and are unresolved. The *ortho* protons of the N-phenyl ring appear slightly upfield relative to both the *metha* and *para* ring protons. This is caused by the electron withdrawing nature of the nitrone functionality.

RESULTS AND DISCUSSION

A new and relatively simple procedure was discovered that yields N,N-disubstituted hydroxylamines in good yield. The reaction affords a new chiral center with concurrent formation of a carbon-carbon bond. This reaction appears to be the first reported reaction between an organoboron compound and a nitrone. Currently, the synthetic utility of this reaction is being investigated more fully.

The two main obstacles encountered in this investigation were preparation and purification of the starting materials and isolation of the products that were synthesized. In particular, the preparation of diphenylnitrone was frustratingly difficult due to out initial inability to synthesize the N-phenylhydroxylamine.

Two previoulsy reported methods for preparing N-phenylhydroxylamine were used[27,28,29] but neither, in our hands, generated the hydroxylamine in reasonable yields. Less than 2% was obtained where 65% or better were reported. The first method attempted was a general procedure for the synthesis of N-arylhydroxylamines from nitrobenzenes. In this preparation, zinc dust was used with ammonium chloride to reduce the nitro function to a hydroxylamine.[27] Nitrobenzene was added to a solution of water, ethanol, and ammonium chloride. The mixture was stirred vigorously as the zinc dust was added slowly over 15 to 20 minutes. The temperature of the mixture rose upon addition of the zinc to *ca.* 40°C.

The reaction was halted when the formerly yellow solution became colorless. The reaction mixture was filtered and diluted with water until its volume had been doubled. The hydroxylamines were then recovered by extraction with methylene chloride and crystallized from hexanes or petroleum ether. The attempted preparations using this procedure yielded less than 2% of the desired product.

The second procedure attempted[28] was very similar to the first. Water was used as the solvent medium for the reaction. This posed a minor problem: Nitrobenzene and water are immiscible. The use of a mechanical stirrer or a very large magnetic stir bar alleviated much of this impediment by vigorously churning the reagents, keeping the nitrobenzene from collecting at the bottom of the flask. The zinc dust was once again added over a period of 15 to 20 minutes, during which the temperature of the mixture rose to *ca.* 56°C. After all the zinc had been added, stirring was continued for an additional 15 minutes or until the temperature began to decrease. The hot mixture was filtered to remove the zinc oxide by product which was washed with hot water (80-95°C). The filtrate was placed in a beaker and chilled in an ice/water bath. Sodium chloride was added until the solution became saturated. Yellow crystals of N-phenylhydroxylamine, which were expected to crystallize out of solution, were not observed. Numerous attempts using this method failed to yield any product.

The two methods were combined and modified to give a new preparative method that produced the hydroxylamine in 50 to 65% yield based on starting nitrobenzene. The initial steps of the second procedure were followed to the point of filtering the reaction mixture and washing the zinc oxide with hot water. The filtrate was then chilled in an ice/water bath and salted with sodium chloride. The hydroxylamines were recovered via extraction with methylene chloride. Removal of the solvent under reduced pressure (aspirator) affording light yellow crystals which were then dissolved in a minimum amount of warm methylene chloride. Addition of hexanes upon cooling caused rapid recrystallization of pure phenylhydroxylamine. The crystals were collected by vacuum filtration and washed with ice-cold hexanes. Any residual solvent was removed under vacuum at 0.2 torr. The melting point of the product, 78-80°C, was in good agreement with the literature value of 80°C.[30]

Diphenylnitrone[29] was prepared by combining N-phenylhydroxylamine with benzaldehyde in a one to one stoichiometric ratio in ethanol solvent. Upon addition of the two reagents, the mixture was swirled to promote dissolution. Within minutes, solid, white diphenylnitrone precitipated. The reaction mixture was chilled in an ice/water bath. The crystals were collected on a Buchner funnel and washed with cold ether. Complete removal of the solvent was accomplished at reduced pressure (0.2 torr, 10 minutes). Typical yields were 95% or better. See Table 10 for spectral data.

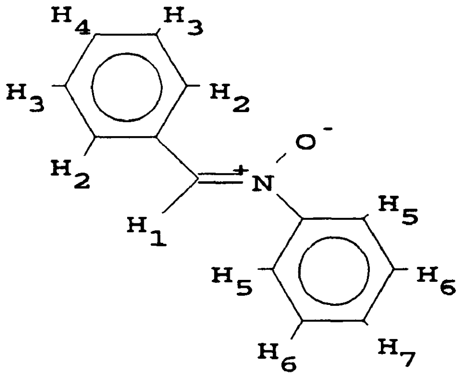


Table 10

Diphenylnitrone

Mass Spectral Data		
m/e	Abundance	
77	48	
51	18	
104	11	
152	5	
180	100	
181		

^{1}H NMR Chemical Shifts
In ppm Relative to TMS[28]

Position	Shift(ppm)
H^1	7.84
H_2 (2H)	8.28-8.31
H_3 (2H), H_4	7.36-7.46
H_5 (2H)	7.56-7.78
H_6 (2H), H_7	7.36-7.46

See Figure 18 for position labels.

Diphenylnitrone and triethylborane were combined in a three to one ratio (nitrone to borane) in methylene chloride. The three ethyl groups of the borane were each expected to react with nitrone. The mixture was heated to reflux and product formation was followed using TLC (20% ethyl acetate in hexanes as eluent on silica gel). After 24 hours, TLC showed that the one major product had formed but most of the starting material had still not reacted. Additional borane was added, increasing the mole ratio to three to two. The reaction was allowed to continue for an additional 24 hours upon which TLC indicated that most of the nitrone had been consumed.

The reaction was quenched upon the addition of water which served to hydrolytically sever the boron oxygen bonds thus forming the hydroxylamine. Extraction with ether/methylene chloride and subsequent recrystallization with ethanol/water afforded pure N-(1-phenylpropyl)-N-phenylhydroxylamine (see Figure 19).

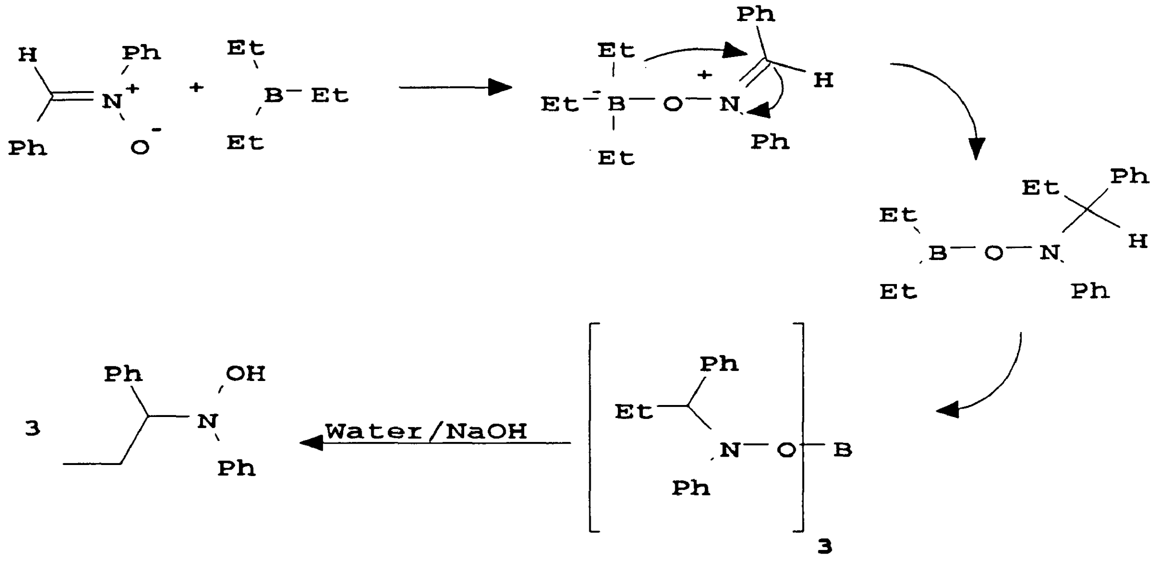


Figure 19

The N-(1-phenylpropyl)-N-phenylhydroxylamine was characterized using ^1H and ^{13}C NMR. An gated-decoupled ^{13}C NMR spectrum (decoupler off during acquisition) was taken along with a normal decoupled spectrum in order to determine the C-H coupling constants and to verify the structure of the compound. Data obatined from ^1H and ^{13}C NMR spectra are tabulated in tables 11 and 12 using the numbering scheme in Figure 20.

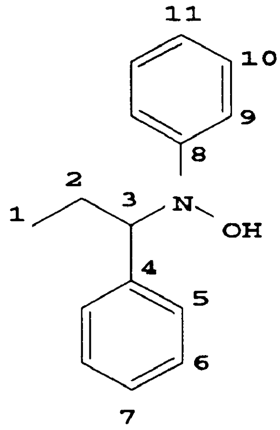


Figure 20

Table 11

Proton NMR Data

(Hz)	Shift (ppm)	Coupling Multiplicity	Constant
Methyl	0.86	triplet	6.83
Methylene	2.17-1.77	multiplet	
Methine	4.54	triplet	6.84
Aromatic	6.63-7.50	multiplet	
-OH	8.46	singlet	

The three upfield signals of the gated-decoupled spectrum corresponding to the methyl, methylene, and methine carbons appear as a quartet, a triplet, and a doublet respectively. Six sets of doublets are observed between 115 and 127 ppm corresponding to the ten aromatic carbons bearing one proton each. Four of these

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^{13}C NMR Data

Coupling Nucleus	Chemical Shift	Multiplicity	Constant (Hz)
C1	11.73	quartet	125.73
C2	25.50	triplet	128.18
C3	69.07	doublet	133.06
C4	140.72	singlet	
C5	128.38	doublet	157.47
C6	127.73	doublet	158.69
C7	119.55	doublet	159.19
C8	152.87	singlet	
C9	115.65	doublet	159.91
C10	128.85	doublet	155.03
C11	126.78	doublet	159.91

Multiplicity from an off-resonance decoupled spectrum
Coupling Constants are for C-H coupling

---

carbons (two sets of two) are symmetrical so only six signals appear for the a total of ten carbons. Finally, the two tertiary aromatic carbons appear at δ 139 and 153; both are singlets.

Mass spectral data was also used to confirm the identity of the hydroxylamine. These data are tabulated above. The largest ion fragment of 211 corresponds to the molecular ion minus the hydroxyl group. The base peak, with a weight of 182 amu, arrises from the loss of the ethyl group and loss of the hydroxyl group from the molecular ion. The peak at 77 and 91 arrise from the phenyl cation and the the tropilium ion respectively.

Table 13

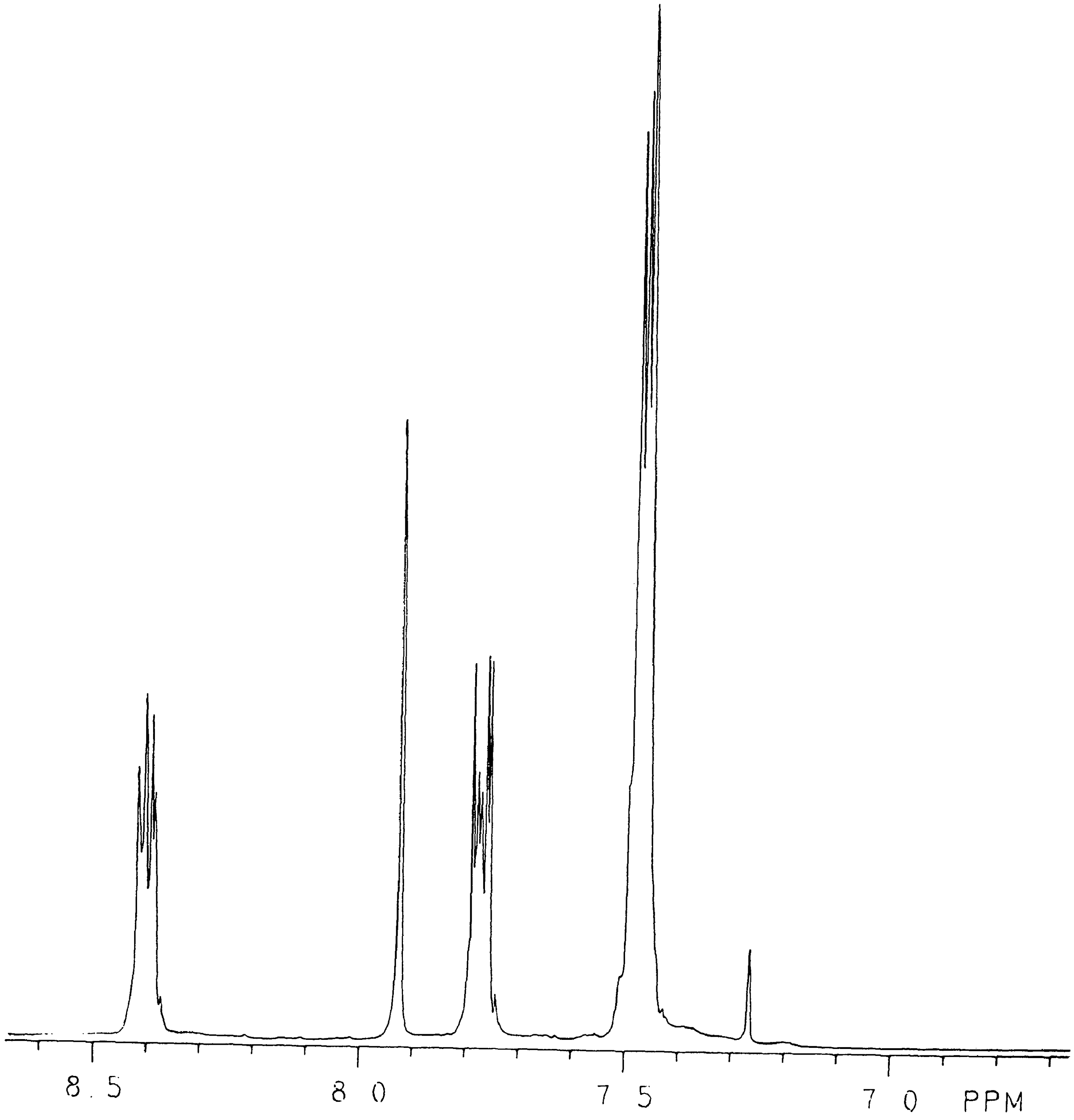
Mass Spectral Data

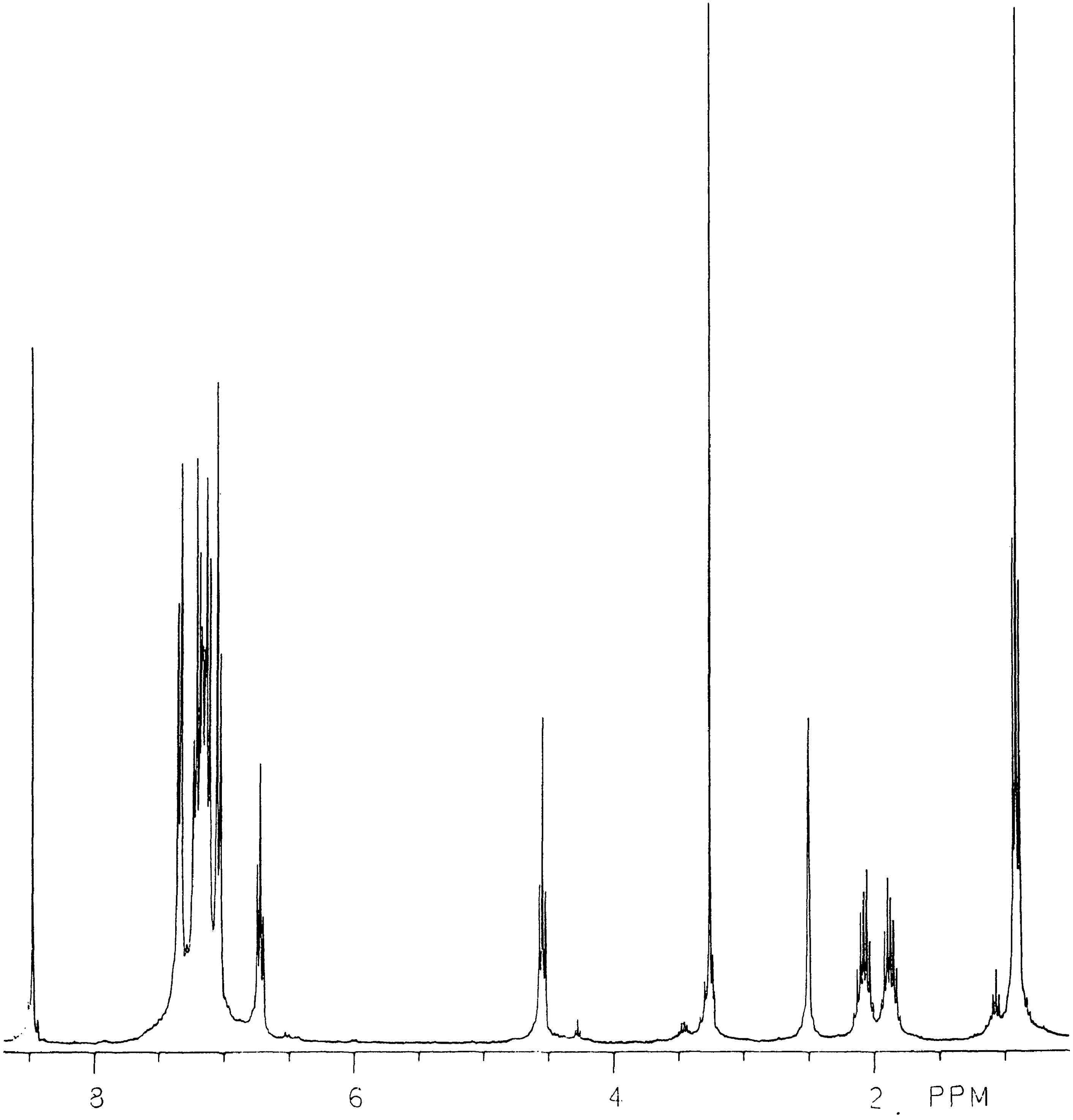
Peak	Composition	Normalized Abundance
77	C_6H_5	41
91	C_7H_7	38
104	C_7H_6N	18
182	$C_{13}H_{12}N$	100
211	M-OH	11

GE NMR
QE-300

HOL008 117
15AUG91

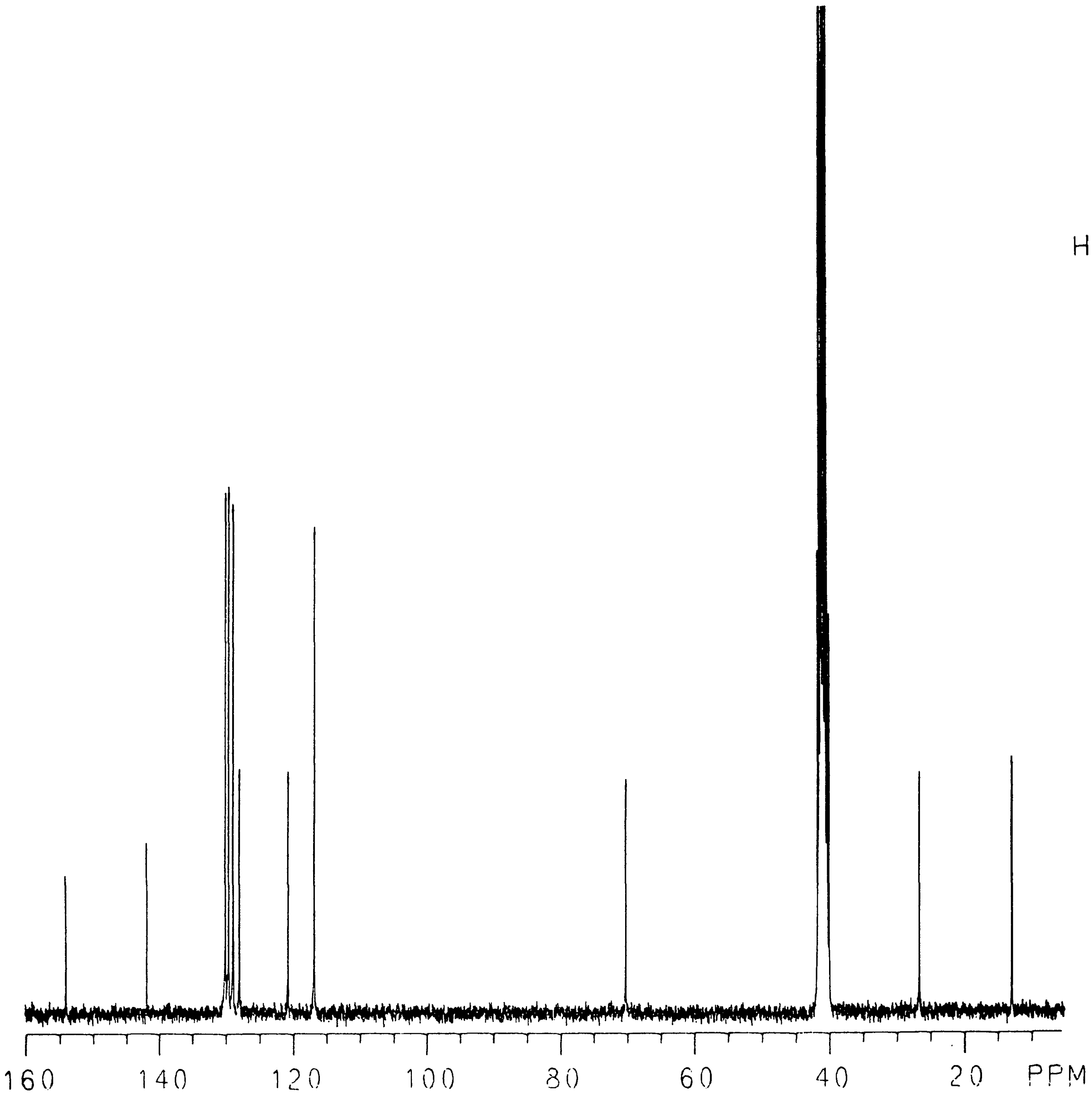
SPECTRUM 8





SPECTRUM 9

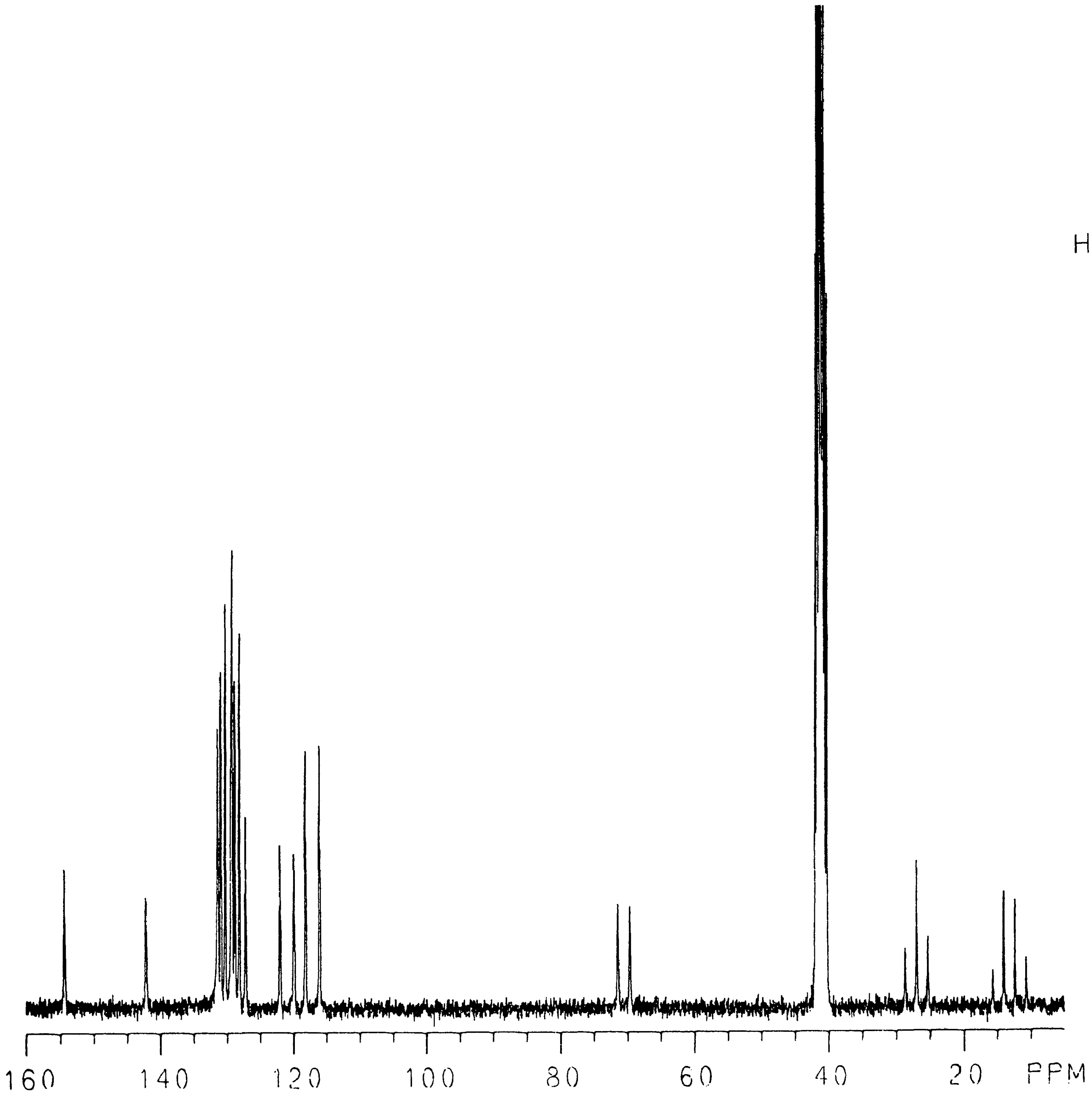
SPECTRUM 10



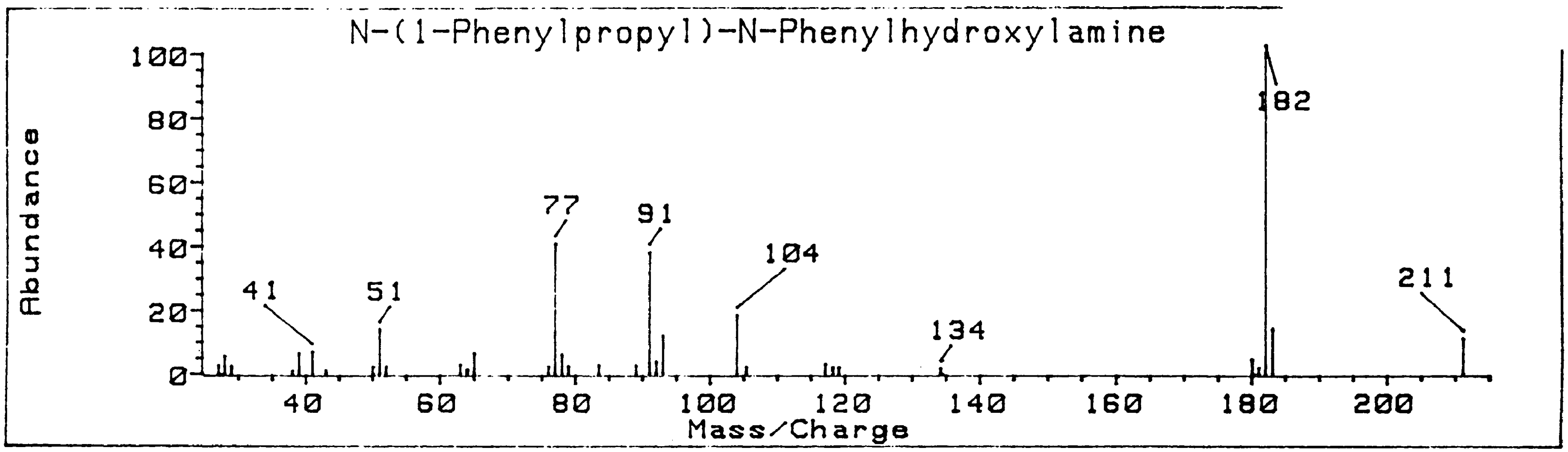
GE NMR
QE-300

HOL007 270
31JUL91

SPECTRUM 11



SPECTRUM 12


N-(1-Phenylpropyl)-N-Phenylhydroxylamine
Abundance
100
80
60
40
20
0
41
51
77
91
104
134
182
211
40
60
80
100
120
140
160
180
200
Mass/Charge

EXPERIMENTAL

Unless otherwise noted, all reaction were performed under nitrogen using previously dried glassware. Syringes and needles were stored in a dry-box until just prior to use. Proton and carbon NMR spectra were obtained with a GE QE-300 spectrometer. GC/MS analysis was performed using a Hewlett Packard 5988A mass spectrometer with accompanying HP 5890A gas chromatograph and HP Chem Station running under the Pascal environment. All injections onto the GC for mass spectral analysis were performed manually. Gas chromatography was performed on a Supelco fused silica capillary column, 30 meters, 0.32 mm internal diameter, and 1 μ film thichness. Melting points were taken using a MEL-TEMP melting point apparatus. Chromatography plates for thin layer chromatography were aluminium sheets coated with silica gel, 60W, with 0.2 mm layer thickness.

N-Phenylhydroxylamine from nitrobenzene:

In a 1000 mL three neck round bottomed flask, equipped with stir bar, thermometer, and large powder funnel, is placed 5 g (0.10 mole) NH_4Cl, 160 mL H_2O, and 10 g (0.081 mole) nitrobenzene. Stirring is started and zinc dust 10.62 g (0.162 mole) is added slowly over 20 to 30 minutes. The temperature rises to *ca.* 56 °C. When the temperature starts to fall, the reaction is halted. The hot mixture is filtered through celite and the solid is washed with 75 mL of hot water.

The filtrate is chilled in an ice-water bath, saturated with NaCl, and transferred to a separatory funnel. The aqueous mixture is extracted with 400 mL (4 x 100 mL) methylene chloride. The solvent is removed under reduced pressure yielding yellow crystals.

Methylene chloride (approximately 15 mL) is added until all the crystals dissolve. The flask is placed in an ice bath and hexanes are added until the white crystalline N-phenylhydroxylamine precipitates from the solution. The product is collected on a Buchner funnel and washed with ice-cold hexanes. The wet-crystals are quickly transferred to a pre-weighed Erlenmeyer flask. The remaining hexanes are removed at reduced pressure (0.1-0.2 torr, 2 hours) giving 11.46g (0.105 mole) N-phenylhydroxylamine with a yield of 65%. Typical yields range from 50 to 65% based on starting nitrobenzene. Melting point 78-80°C.

α,N-Diphenylnitrone:

In a 50 mL Erlenmeyer flask is placed 9.50 g (87.1 mmole) N-phenylhydroxylamine in 10 mL absolute ethanol. Benzaldehyde (9.24 g, 87.1 mmole, distilled) is added dropwise. The mixture is swirled, stoppered and placed in a freezer overnight. The white crystalline product is collected in a Buchner funnel and washed with 20 mL ice-cold ethyl ether. Any remaining ether is removed under reduced pressure (0.10 torr, 20 minutes). The pure α,N-diphenylnitrone (15.6 g, 79.1

mmole, 91% yield) is stored under nitrogen. ^{1}H NMR ($CDCl_3$): δ 8.4-8.4 (m, 2H), δ 7.9 (s, 1H), δ 7.7-7.8 (m, 2H), δ 7.4-7.6 (m, 6H). Mass spectrum: 181 amu 83%, 180 amu (base peak) 100%, 152 amu 5%, 104 amu 11%, 77 amu 48%, 51 amu 18%.

Reaction of triethylborane with α,N-diphenylnitrone: Preparation of N-phenyl-N-(1-phenylpropyl)-N-hydroxylamine

In a 100 mL three neck round bottomed flask are placed 1.00 g (5.07 mmole) and 25 mL benzene (or methylene chloride). The flask is then equipped with reflux condenser, nitrogen line, one septum, and glass stopper (with one additional stopper on hand). The triethyl borane, 3.4 mL (3.4 mmole, 1.0 M solution in hexanes) is added via syringe. The nitrogen flow in increased as the septum is quickly replaced with a glass stopper. The flask is heated to reflux using a mantle and variac. Reaction is allowed to continue at reflux overnight.

The reaction mixture is transferred to a 100 mL single neck round bottomed flask (water sensitivity is now irrelevant). The reaction flask is washed with ether which is added to the reaction mixture. The solvent is removed under reduced pressure. Water and one pellet of NaOH is added and the reaction is stirred for 4 hours.

The product is recovered by extraction with methylene chloride. The solvent is subsequently removed under reduced pressure yielding yellow crystals. Ethanol, 5 mL, is added and the crystals dissolve readily. Water is then added dropwise until crystallization of the pure hydroxylamine: 0.23g collected, 20% yield. ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1H), δ 6.63-7.50 (m, 10H aromatic), δ 4.54 (t, 1H, J= 6.8 Hz), δ 1.97-2.17 (m, 1H), δ 1.77-1.97 (m, 1H), δ 0.86 (t, 3H, J= 6.8 Hz). ^{13}C NMR (DMSO-d_6): δ 12.7 (q, 1C, J_{CH}= 125.7 Hz), δ 26.5 (t,1C, J_{CH}= 128.2 Hz), δ 70.07 (d, 1C, J_{CH}= 133.1 Hz), δ 141.7 (s, 1C), δ 129.38 (d, 2C, J_{CH}= 157.47 Hz), δ 128.73 (d, 2C, J_{CH}= 158.69 Hz), δ 120.55 (d, J_{CH}= 159.91 Hz), δ 153.87 (s), δ 116.65 (d, 2C, J_{CH}= 159.91 Hz), δ 129.85 (d, 2C, J_{CH}= 155.03 Hz), δ 127.78 (d, 1C, J_{CH}= 159.91 Hz). Mass Spectrum: 211 amu 11%, 182 amu (base peak) 100%, 77 amu 41%, 91 amu 38%, 104 anu 18%.

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