

APPLICATIONS OF QUANTITATIVE D-NMR IN ANALYSIS OF DEUTERIUM ENRICHED COMPOUNDS

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March 2004

INTRODUCTION

For highly deuterated compounds (Deuterium enrichment greater than 98 atom%), conventional Proton NMR analysis is limited by the residual proton signal intensities. The greater the deuterium enrichment, the weaker the signal detected. For structure verification and enrichment determination, Deuterium NMR proves to be an appealing alternative technique for highly Deuterium enriched chemicals.

Applications of D-NMR in study of highly Deuterium enriched compounds were explored at Isotec in the past. With the proper system configuration, D-NMR experiment can be performed with no additional probe tuning and no quarter wave cable interchanging. With the proper NMR parameter settings, D-NMR spectra provide rich information for structure verification and impurity identification.

Typical applications of D-NMR in study of highly Deuterium enriched compounds are presented in this poster presentation. We hope our experimental results stimulate more interest from our NMR colleagues, so that fruitful applications in D-NMR can be further explored.

THE EXPERIMENTAL SETTINGS OF DEUTERIUM NMR

1. D-NMR experiments are carried on Varian 400 MHz Mercury VX spectrometer with a 5 mm indirect detection probe. No additional instrument modification is needed.
2. With proper configurations, lock coil serves as the transreceiver coil. No probe tuning is required for each D-NMR experiment. One can switch from ^{13}C -NMR, to D-NMR, to H-NMR without tuning the probe for a two channel (high and low) probe.
3. In D-NMR, only the Deuteron signal is observed. The typical solvent used in the D-NMR experiment is non-deuterated solvents, such as pure, Natural Abundance H_2O and DMSO. This choice of solvent is indeed unconventional.
4. D-NMR experiment can be incorporated into the sample automation protocol. With a two channel probe, one can run ^{13}C -NMR, D-NMR and H-NMR automatically without probe tuning.

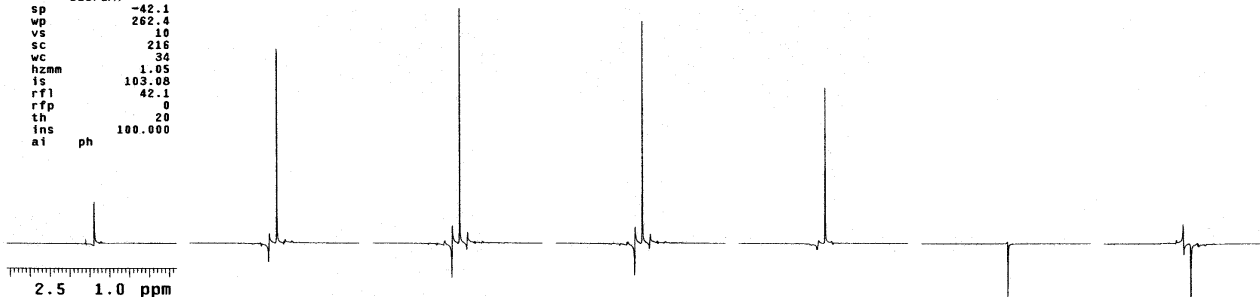
COMPARISON OF PROPERTIES BETWEEN PROTON AND DEUTERON

	<u>Proton (H)</u>	<u>Deuteron (D)</u>
Natural Abundance	99.985%	0.015%
Magnetogyric ratio (γ)	$26.7519 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$	$4.1066 \times 10^7 \text{ rad T}^{-1} \text{ s}^{-1}$
Resonance Frequency (9.4 T)	399.939 MHz	61.393 MHz
Resolution (FWHM)	0.3 Hz	1.3 Hz
Spin Quantum Number	$\frac{1}{2}$	1

90 DEGREE PULSE WIDTH DETERMINATION IN D-NMR

04-0379_151866_EQ1176_DNMR
DNMR T1 STUDY
ALDRICH NO:151866
ISOTEC BATCH NO: EQ1176
SUBMITTED BY: JK
NMR OPERATOR: JK
pw=10 100 200 300 400 500 600
guessed pw90 = 225 micro seconds

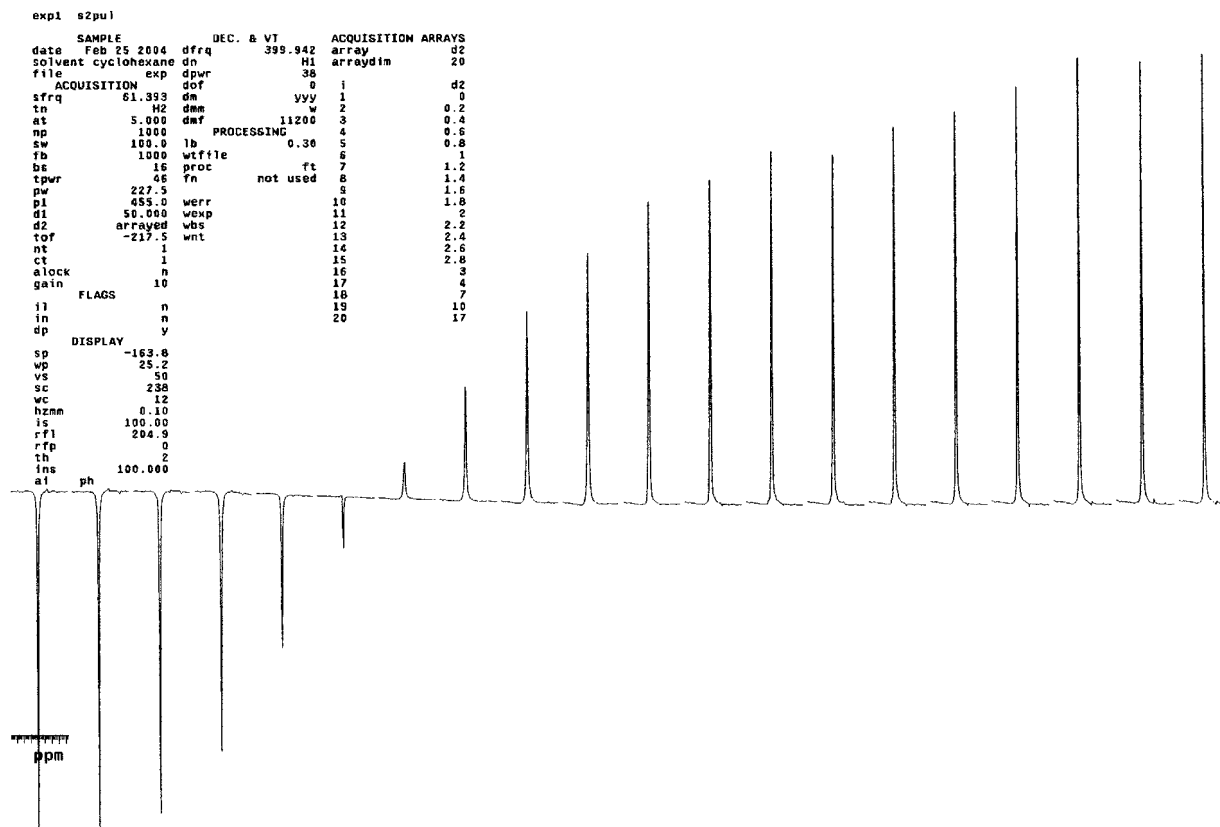
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exp8 s2pu1
SAMPLE          DEC. & VT      ACQUISITION ARRAYS
date   Feb 25 2004  dfrq      399.942  array      pw
solvent cyclohexane dn          H1          arraydim   7
file   /export/home/~ dpwr      38
isotec/vnmrsvs/409~ dot        0            1            pw
data/04-0379_15186~ dm          vvy          1            10
6_EQ1176_DNMR.fid  dmm          w            2            100
ACQUISITION      dmf          11200        3            200
sfrq      61.393      PROCESSING   4            300
tn         H2         lb          0.30        5            400
at         4.999      wtfile      6            500
np         2624       proc         ft          7            600
Sw         262.4      Tn          not used
fb         1000
bs         16         werr
tpwr       46         wexp
pw         arrayed   wbs
d1         0         wnt
tof        -210.5
nt         1
ct         1
alock      n
gain       10
FLAGS
i1         n
in         n
dp         y
DISPLAY
sp         -42.1
wp         262.4
vs         10
sc         216
wc         36
hzmm      1.05
is         103.08
rf1        42.1
rfp        0
th         20
ins        100.000
a1         ph
```



The 90 degree pulse width is 227 microseconds at tpwr=46 (Varian suggested maximum).

T₁ DETERMINATION FOR D-NMR (INVERSE RECOVERY METHOD)

04-0361_151866_EQ01176_T1_STUDY
T1 STUDY
ALDRICH NO:151866
ISOTEC BATCH NO: EQ01176
SUBMITTED BY: JK
NMR OPERATOR: DHS
T1 = 1.88 seconds



While T_1 values of Deuterium varies depending on solvent and chemical environment, it is typically in the range of 1 - 2 seconds, which is short enough for fast pulse data acquisition.

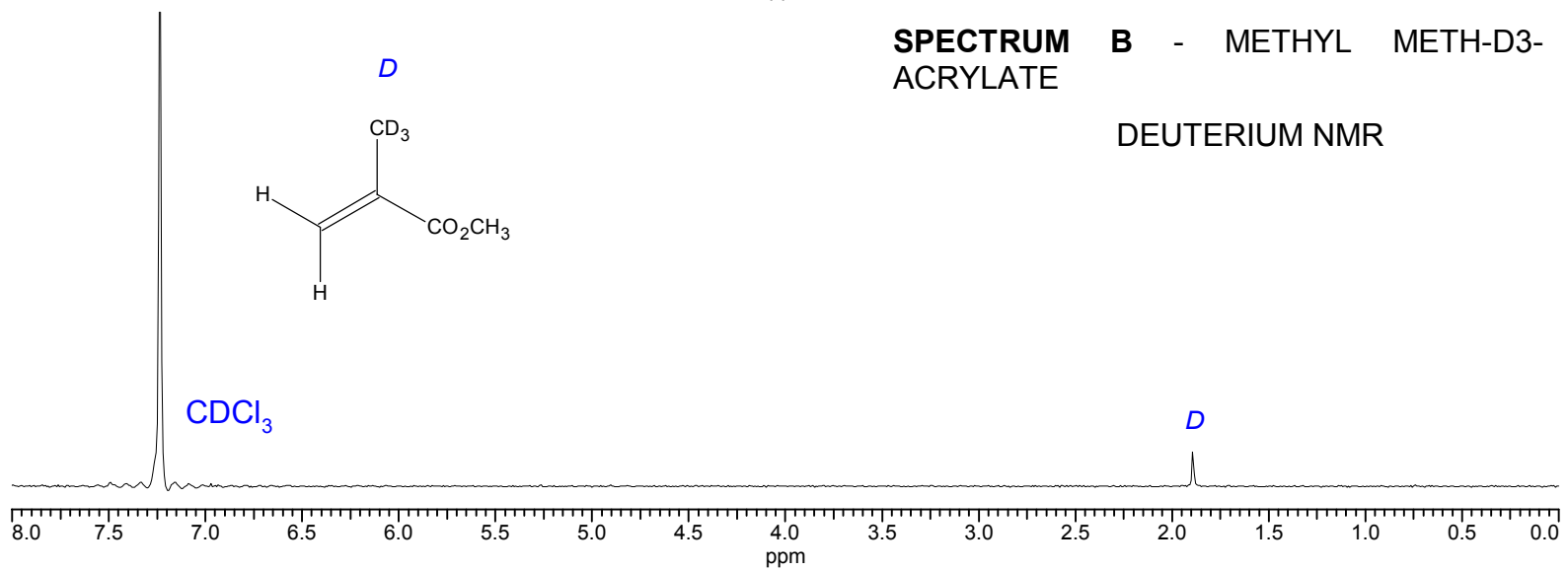
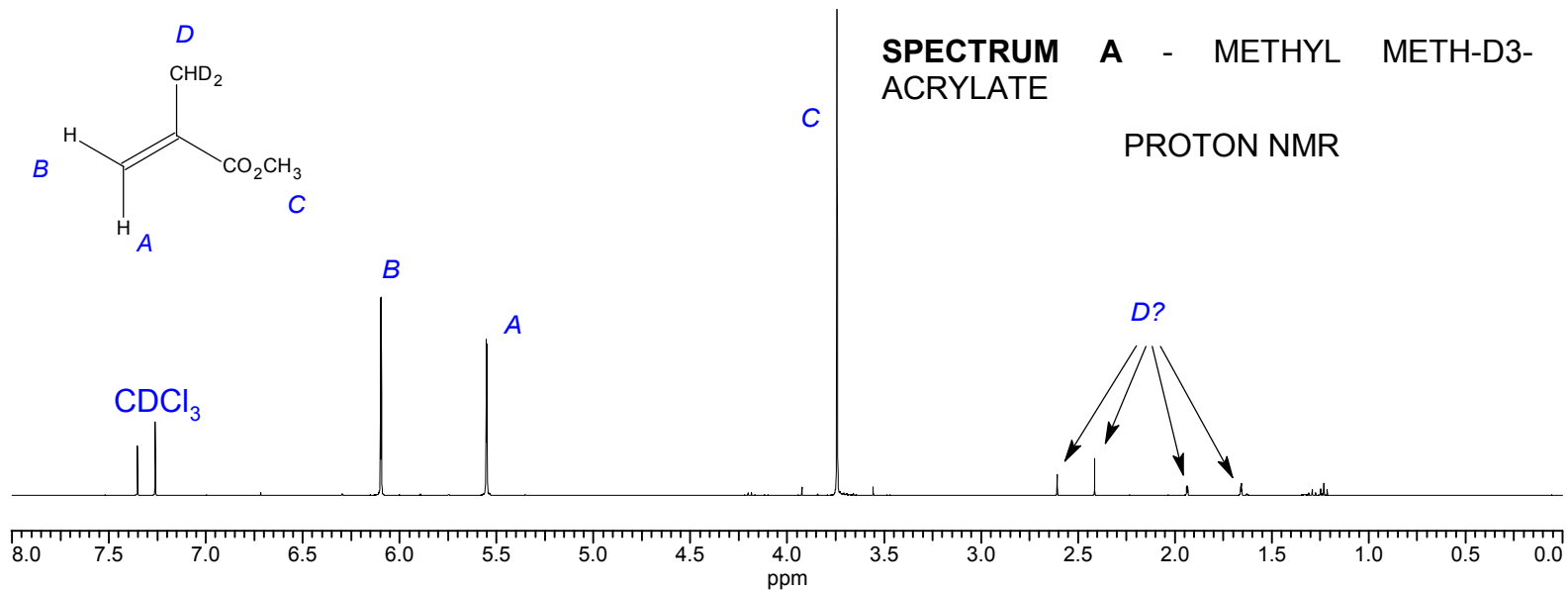
APPLICATION I

USE OF DEUTERIUM NMR FOR SPECTRAL INTERPRETATION

For a given chemical species and its deuterium isotopomer, their chemical shifts in H-NMR and D-NMR are very similar, with minor isotope effect. This similarity is due to the fact that their local chemical environments are nearly identical. Therefore, spectral interpretation can be easily extrapolated from the knowledge of H-NMR to D-NMR, or vice versa.

One application of D-NMR is to distinguish the residual peak from neighboring impurities in H-NMR. For example, impurity peaks are shown in methyl meth-d₃-acrylate H-NMR spectrum, leads to difficulty in spectrum interpretation.

Proton NMR spectrum of Methyl Meth-d₃ Acrylate (Spectrum A) can easily be interpreted for the natural abundance hydrogens, assigning protons A, B, and C. However, the residual protons cannot be easily identified, for structure verification and deuterium enrichment determination. Spectrum B is a Deuterium NMR of methyl meth-d₃-acrylate. Since the methyl group is the only moiety that is deuterated, it is very easy to find its chemical shift (1.9 ppm). With the help of D-NMR, the residual proton peak in H-NMR can be easily identified.



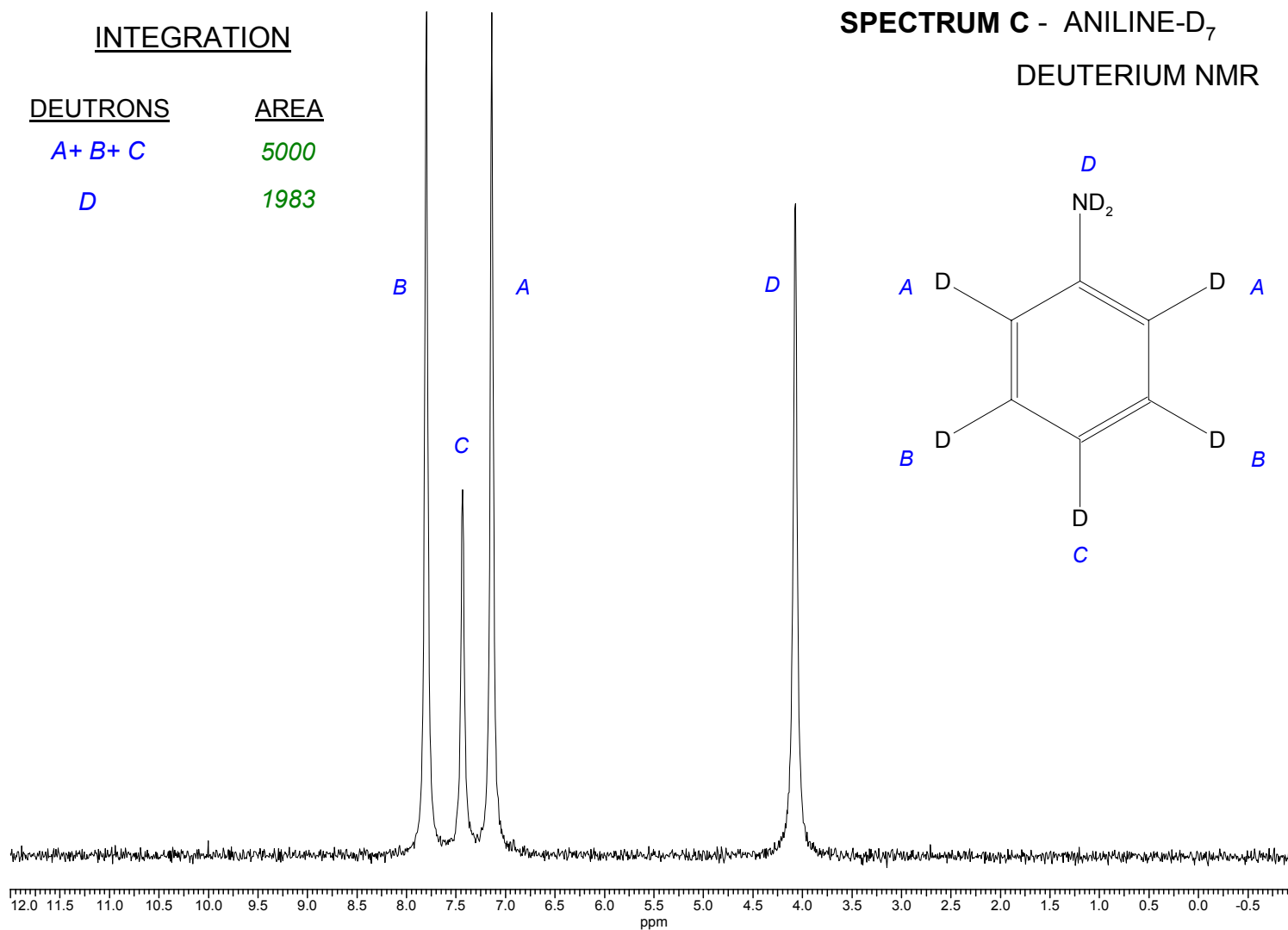
APPLICATION II

VERIFICATION AND QUANTITATION OF DEUTERIUM AT LABILE POSITIONS

It is known that deuterium at labile positions (such as -ND_2 and -OD) can be exchanged with environmental protons readily. Conventionally, the enrichment of the labile deuterium is determined indirectly by analyzing the Deuterium Oxide from the same source, assuming D-H exchanges reaches equilibrium.

With D-NMR, the deuterium at labile positions can be observed directly. In selected non-protonated solvents (such as Natural Abundance DMSO) or running the sample neat, the existence and quantitation of labile deuteriums can be determined by the D-NMR experiment.

An example of the determination of the deuteration of the labile position is the case of Aniline- d_7 . It was speculated that the -ND_2 group on Aniline- d_7 was in fact an -NH_2 group. As seen in Spectrum C, the Amino group was deuterated and very close to the enrichment of the Benzene ring, which is 99.6 atom% Deuterium.

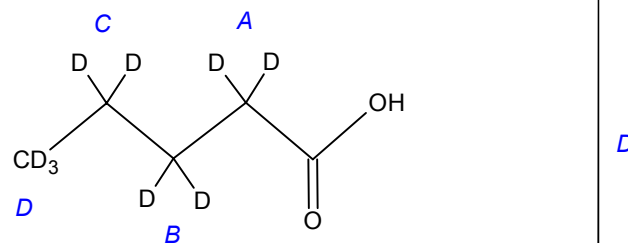


D-NMR verifies amino group of aniline is indeed -ND₂!

APPLICATION III

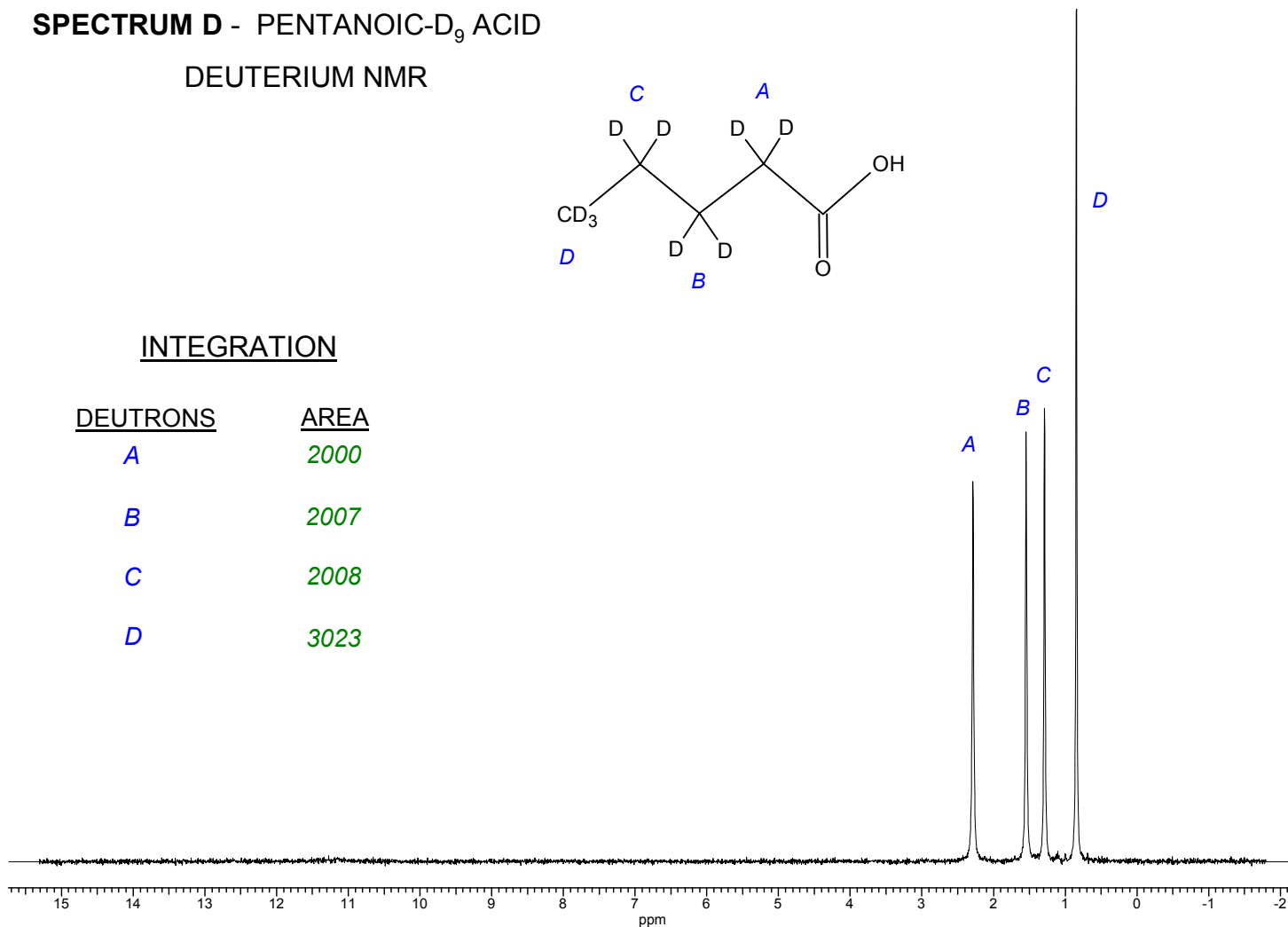
SPECTRUM D - PENTANOIC-D₉ ACID

DEUTERIUM NMR



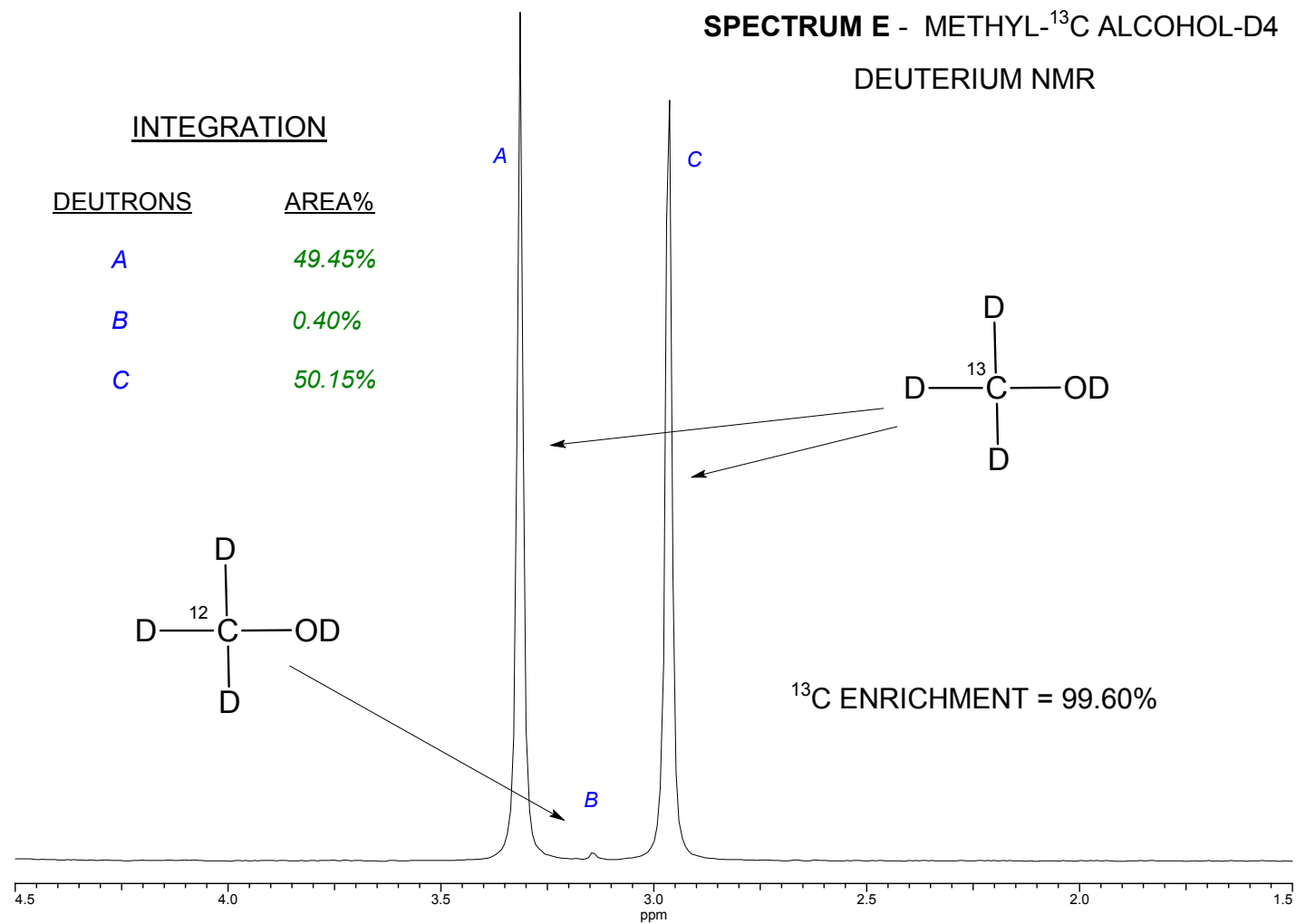
INTEGRATION

<u>DEUTRONS</u>	<u>AREA</u>
<i>A</i>	2000
<i>B</i>	2007
<i>C</i>	2008
<i>D</i>	3023



Through properly selected D-NMR parameter settings, the peak integrals are relatively quantitative, which can be used for chemical quantitation.

APPLICATION IV



For a ¹³C/ D doubly labelled compound, D-NMR provides a practical tool for ¹³C atom% determination.

ADVANTAGES IN D-NMR

1. D-NMR proves to be a useful technique in the study of highly Deuterium enriched chemicals.
2. It allows use of 100% natural abundance solvents in the NMR experiment.
3. All the proton signals are transparent in D-NMR, yielding a clean spectrum.
4. Under proper experimental settings, D-NMR is relatively quantitative in peak integration, which can be used for Deuterium atom% determination, and even ^{13}C enrichment determination for doubly labeled compounds.

LIMITATIONS IN D-NMR

1. Due to low magnetogyric ratio of Deuteron, D-NMR is better when applied to compounds that are highly deuterated.
2. It takes longer time to achieve desired S/N.
3. With 100% natural abundance solvent, D-NMR has to be run in unlocked mode, and shimming has to be manually done.

ACKNOWLEDGEMENT

The authors would like to thank the following:

Dr. Lisa Roth for her cooperation, discussion, and contribution to the ISOTEC NMR laboratory.

Tony Dodaro, Chris Robosky, Dan Larson, and Michael Hissett (Varian Engineers) for Varian NMR system installation.

Phil Darragh, Mark Dennis, Stephanie Long, Bhaskar Samant, and the rest of the ISOTEC Production group for sample synthesis.

The pioneering scientists in the field of D-NMR, whose research results are scattered in the NMR literature.