THE
NMR
NEWSLETTER

No. 490

July 1999

New! Internet Isolation for your NMR

Small-footprint device is placed on your network, between the spectrometer and the connection to the Internet.
Device is pre-configured for easy installation.

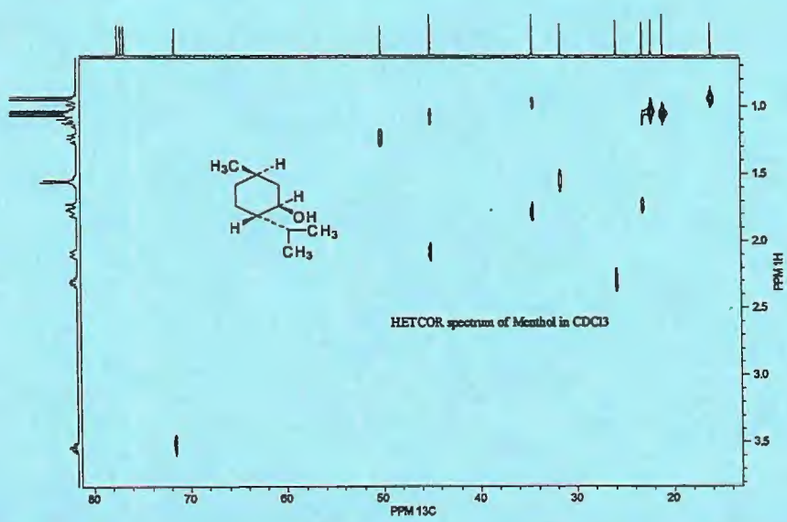
PROTECTION *WITHOUT* COMPROMISING UTILITY

Unhindered access ***TO*** the Internet and local network
Isolation ***FROM*** everyone outside the local network

See **http://www.acornnmr.com/NCII.htm** for details

New NUTS features

* 10-step Un-Do
* Flexible options for displaying contour plots
    - Projections on top, bottom, left and/or right
    - Projections can be scaled and clipped
    - Gridlines
    - Plot can be resized
    - Editable axis labels
    - Contour levels and colors set within NUTS



Acorn NMR Inc.
46560 Fremont Blvd. #418
Fremont, CA 94538

(510) 683-8595
(510) 683-6784 FAX
info@acornnmr.com

ftp.acornnmr.com
http://www.acornnmr.com

SPONSORS OF *THE NMR NEWSLETTER*

Abbott Laboratories
Aldrich Chemical Company, Inc.
AMT
Amgen, Inc.
Anasazi Instruments, Inc.
Astra AB
Avanti Polar Lipids, Inc.
Bruker Instruments, Inc.
Cambridge Isotope Laboratories
Cryomag Services, Inc.
The Dow Chemical Company
E. I. du Pont de Nemours & Company
Hewlett-Packard Company
Isotec, Inc.
JEOL (U.S.A.) Inc., Analytical Instruments Division
The Lilly Research Laboratories, Eli Lilly & Company
Merck Research Laboratories
Nalorac Corporation
Oxford Instruments
Pharmacia & Upjohn, Inc.
Programmed Test Sources, Inc.
SINTEF Unimed MR Center, Trondheim, Norway
Tecmag
Unilever Research
Union Carbide Corporation
Varian, Inc.
Zeneca Inc.

FORTHCOMING NMR MEETINGS

Rocky Mountain Conference NMR Symposium, Denver, CO, **August 1-5, 1999**. See Newsletter 487, 36 and http://india.cchem.berkeley.edu/~rmc/.

SMASH No. 1 (*S*mall *M*olecules *A*re *S*till *H*ot), Argonne, IL, **August 15-18, 1999**; Contact: Ms. Karen McCune , (mccune_karen_a@ lilly.com, 317-276-9783) or S. R. Maple (maple_steven_r@lilly.com) or G.E.Martin (gary.e.martin@am.pnu.com) or A. G. Swanson (alistair_swanson@sandwich.pfizer.com. See Newsletter 487, 17.

Applications of NMR to Complex Systems, symposium at the American Chemical Society Meeting, New Orleans, LA, **August 22-26, 1999**; Contact: R. E. Botto, Symposium Chair, Chemistry Division, Argonne National Laboratory, 9700 South Cass Ave., Argonne, IL 60439; 630-252-3524; Fax: 630-252-9288; E-mail: robert_botto@qmgate.anl.gov

Medical Imaging: NMR and Nuclear Tracers, colloquium at the 12th Entretiens Jacques Cartier, Lyon, France, **December 5-8, 1999**; See http://jade.univ-lyon1.fr/JacquesCartier/ and Newsletter 488, 38.

PITTCON 2000, New Orleans, LA, **March 12-17, 2000**; Contact: The Pittsburgh Conference, 300 Penn Cemter Blvd., Suite 332, Pittsburgh, PA 15235-5503; Phone: 412-825-3220; Fax: 412-825-3224; Email: expo@pittcon.org.

41st ENC (Experimental NMR Conference), Asilomar Conference Center, Pacific Grove, CA, **April 9-14, 2000**; Contact: ENC, 1201 Don Diego Avenue, Santa Fe, NM 87505; (505) 989-4573; Fax: (505) 989-1073; E-mail: enc@enc-conference.org.

XIX International Conference on Mag. Res. in Biological Systems, Florence, Italy, **August 20-25, 2000**. Contact: Profs. Ivano Bentini or Lucia Banci, Chem. Dept., Univ. of Florence, Via G. Capponi 7, I-50121, Florence, Italy; Phone: +39-055-2757600; Email: icmrbs@lrm.fi.cnr.it; Fax: +39-055-2757555; http://www.lrm.fi.cnr.it//icmrbs.html.

Royal Society of Chemistry: 15th International Meeting on NMR Spectroscpy, Durham, England, **week of July 8-13, 2001**; Contact: Mrs. Paula Whelan, The Royal Society of Chemistry, Burlington House, London W1V 0BN, England; +44 0171 440 3316; Email: conferences@rsc.org\

Additional listings of meetings, etc., are invited.

Washington
WASHINGTON · UNIVERSITY · IN · ST · LOUIS

Campus Box 1105
One Brookings Drive
St. Louis, Missouri 63130-4899

(314) 935-6276
FAX: (314) 935-6219

Department of Physics

May 24, 1999 (received 6/4/99)

Spin Magnetization: Easy to Lose

Dear Dr. Shapiro,

Our group produces laser polarized Xe-129 and He-3 gases for polarization-transfer experiments and for human lung MRI. For He-3 in particular, the process is slow, requiring 12-20 hr of optical pumping to obtain 0.5 litre STP of 40-50% polarized He-3.

Quite by accident, we found a location on a workbench (in the earth's field) where the spin polarization decayed rapidly (95% loss in 5 minutes). Other locations in the same laboratory did not have this problem. This mystifying loss of spin magnetism was a real concern, since we routinely move polarized cells from one magnet to another in the earth's field.

Now it is well known that diffusion (D) through a gradient G causes a relaxation,

$$T_1^{-1} \simeq DG^2/B^2,$$

with B the field strength. This mechanism has been discussed (1 and 2) and arises from the lack of complete adiabaticity of spins, as they try to follow the changing field direction (the existence of $G \neq 0$ prevents the field lines from all being parallel to each other). But crude measurements of G and B showed that this mechanism was not strong enough to cause our effects.

Instead, it turns out that ac magnetic fields from a nearby Varian power supply (for the electromagnet we use to measure the spin polarization) are saturating the He-3 spins. A pick-up coil and oscilloscope show the magnetic field to be very non-sinusoidal; presumably, high harmonics are responsible for the saturation. We note that He-3 in the earth's field of 0.5 Gauss precesses at 1600Hz.

We have confirmed the above explanation in several ways. First, turning off the power supply kills the effect. Second the largest effect on spin polarization is obtained very close to the power supply. Third, putting the glass cell with He-3 in a thick-walled aluminum tube kills the effect, through eddy-current shielding of the ac fields.

This finding has explained a few events of the past in which the spin magnetization disappeared mysteriously—we must have taken the spins too close to the power supply. It suggests that spins should be transported in conducting shields.

Thank you,

JLW
Jason LeaWoods

Brian T. Saam

Mark S. Conradi
Mark S. Conradi

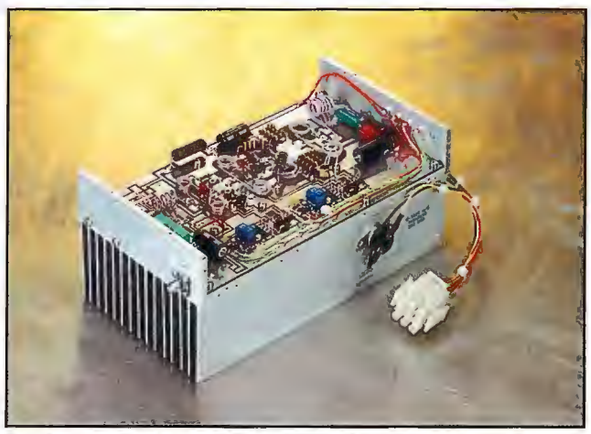
(1) R.L. Gamblin and T.R. Carver, Phys. Rev. A 138, 946 (1965)
(2) L.D. Shearer and G.K. Walters, Phys. Rev. A 139, 1398 (1965)

AMT

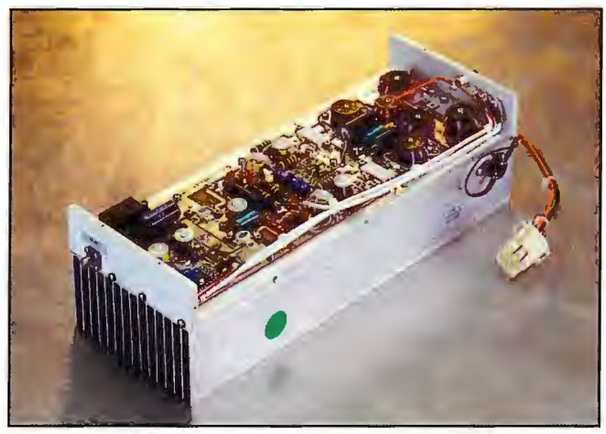
SCIENTIFIC & MEDICAL PRODUCTS

Model 3205 – 6 MHz to 220 MHz, 300 W, NMR Amplifier

Model 3445 – 10 MHz to 130 MHz, 2.0 kW, MRI Amplifier



200 MHz to 500 MHz, 50 W, NMR Module



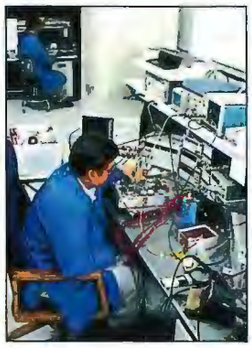
6 MHz to 220 MHz, 300 W, NMR Module

Model 4T70 – 25 MHz to 175 MHz, 7.0 kW, MRI Amplifier

AMT's scientific products are used extensively in Nuclear Magnetic Resonance (NMR) systems. These amplifiers cover the frequency ranges of 6 MHz to 950 MHz, with power levels as high as 2.0 kW peak power at 10% duty cycle.

AMT's medical products are employed in Magnetic Resonance Imaging (MRI) systems. These amplifiers cover the frequency ranges of 10 MHz to 200 MHz with power levels as high as 12.0 kW peak power at 10% duty cycle.

All amplifiers have dual mode capability and can be operated in either a pulsed or CW mode. Scientific and Medical customers include both OEM system manufacturers and end users.



COMPANY

AMT designs, develops and manufactures custom radio frequency (RF) and microwave power amplifiers for the wireless, scientific/medical and application specific industries. The company has been in business since 1984 and currently has over 60 employees, including 20 experienced engineers.

AMT has a worldwide reputation as a leading supplier of high power, solid state power amplifier products that operate at frequencies between 1 MHz and 3 GHz and provide RF power from several watts to several kilowatts. Its products are noted for their exceptional performance, highest quality and superior reliability.

The company's products are sold to numerous major corporations, universities and research centers throughout the world.

FACILITIES

AMT is located in Anaheim, California and occupies a 25,000 square foot facility allocated to engineering, manufacturing, quality assurance, marketing/sales, administration and finance.

Engineering areas include an R & D laboratory, a tool and die shop, mechanical design and drafting areas, an environmental testing laboratory and document control. The R & D laboratory is equipped with all of the latest design and testing equipment including intermodulation distortion simulators, network analyzers, spectrum analyzers, signal generators, noise figure meters and infrared (IR) scanners. The environmental testing laboratory includes equipment to simulate shock, vibration and thermal environments.

Manufacturing areas include a controlled access stock room, a 10,000 square foot assembly area and a production test area employing automatic testing. Also included is an environmental laboratory used for environmental stress screening of production products.

PRODUCTS

AMT's products vary in complexity from single modules, to rack-mounted amplifiers, to complete transmitter systems. The rack-mounted amplifiers and complete transmitter systems typically include detection/protection circuitry, built-in power supplies, front panel metering and digital and/or analog interface controls. Both forced air and/or water cooling are used, depending on the customer's requirements.

AMT's products feature highly reliable technical solutions designed for producibility and reliability. Producibility is enhanced through the use of surface mount components and circuit designs that eliminate the need for excessive alignment during the production cycle. High reliability is accomplished through the implementation of conservative thermal and RF circuit design and sophisticated self-protection schemes. Reliability is further enhanced during the design phase by employing detailed environmental testing.

These factors, along with computer driven automatic testing and environmental stress screening of the final product, ensure that the performance, quality and reliability meet AMT's exacting standards.

AMT

An Employee Owned Company

2570 East Cerritos Avenue, Anaheim, CA 92806•• Tel: (714) 456-0777•• Call Jerry Toll Free: (888) 545-4AMT ••Fax: (714) 456-0778

Varian NMR Systems
3120 Hansen Way, M/S D-298
Palo Alto, CA 94304-1030 USA

Phone: 650.424.4526
Fax: 650.852.9688

http://www.varianinc.com

Dr. Barry Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

June 7 , 1999
(received 6/11/99)

A New ProteinPack Featuring Bio-NMR Pulse Programming

Dear Barry,

We have recently placed a new version of ProteinPack in the on-line User Library (www.nmr.varian.com). Robin Bendall has implemented sensitivity-enhanced TROSY capability in a large number of NH-detected triple-resonance backbone assignment experiments (ghn_co, ghn_ca, ghn_co_ca, ghn_ca_co, ghn_cacb, gc_co_nh, gcbca_co_nh, gcbca_nh and ghc_co_nh) as well as gNhsqc.

New pulse sequences have been added, including ghca_co_canh ,hcch_cosy, ghnha, (fast) gNhsqc and magic-angle dqfcosy. Further optimization of menus and macros was done as well.

The most prominent addition to ProteinPack is "BioNMR Pulse Programming" which can make pulse programming of new experiments much simpler. This concept was developed by Boban John of our NMR Applications Lab in Palo Alto and further developed and enhanced by Robin. Bionmr pulse sequences use Erik Kupce's Pbox program (Pandora's Box) to generate all the shaped pulses "on-the fly". All Pbox needs is an accurate pw90/power for the nucleus, i.e. tpwr/pw/compH, pwC/pwClvl/compC and pwN/pwNlvl/compN (where comp* is the amplifier compression factor at the specified power).

The new PSG elements then use the Pbox output file (in shapelib) to obtain and set the proper attenuator and modulator power levels for pulses and decoupling. The 13C offset is set at the carbonyl frequency for all experiments (thus avoiding a possible source of operator error) and the PSG elements handle any needed offsets. A large number of new PSG statements have been added and included in the "bionmr.h" include file. These sequences do not use the normal ProteinPack shape files, nor do they require the user to generate any shaped pulse files or the pulse sequence code to figure out offsets or power levels.

For example, a 13C 180 sinc x-pulse on alpha carbons with a null at the carbonyls would have the syntax

```
c13pulse("ca","co","sinc",180.0,zero,rof1,rof2);
```

No pulse width or power settings need to be specified for this pulse statement.

In BioNMR pulse programming, all power levels and pulse widths are derived from "hard-pulse" calibrations and amplifier compression factors. Statements below generate the pulse shapes and decoupling patterns using Pbox and extract argument values for pulse and decouple functions from the shape and pattern files as generated by Pbox.

The BioNMR functions use keywords to select typical signal regions:

"ca"	C(alpha)
"aliph"	aliphatic carbons
"cb"	C(beta)
"cab"	alpha and beta carbons
"allch"	all (protonated) carbons
"arom"	aromatic carbons
"co"	carbonyls

Below is a quick overview of the new functions. For all pulses, the excitation region can be selected by using one of the above keywords.

Offset Statements (excitation region specified as argument):

set_c13offset	Moves 13C transmitter frequency to the desired position, e.g., "ca"

Pulse functions (excitation region and bandwidth, pulse shape and 13C flip angle or width (1H, 15N) are specified as arguments):

c13pulse	C13 pulse
c13adiab_inv_pulse	adiabatic C13 inversion pulse
sim_c13pulse	simultaneous 1H/13C pulses
sim_c13adiab_inv_pulse	simultaneous 1H/13C adiabatic inversion pulses
sim3_c13pulse	simultaneous 1H/13C/15N shaped pulses
sim3_c13adiab_inv_pulse	simultaneous 1H/13C/15N adiabatic inv. pulses

Band-selective pulses (excitation regions, flip angles and frequency shift are specified as arguments):

shiftedpulse	1H pulse
decshiftedpulse	13C pulse
dec2shiftedpulse	15N pulse
sim3shiftedpulse	3 simultaneous, centered band-selective pulses

13C Decoupling:

c13decon/c13decoff	controls/specifies band and shape
c13decouple	same but specifies the duration as well

1H Decoupling:

h1decon/h1decoff	controls/specifies band and shape
h1decouple	same, but specifies the duration as well
h1waltzon/h1waltzoff	same as h1decon, but adds 90 degree pulse

15N t2 evolution with 13C refocusing and sensitivity enhancement:

nh_evol_se_train	Function which takes care of 13C refocusing pulses for specified 13C band / null point; does 15N (t2) evolution, reverse-inept, gradient control, optional TROSY, and sensitivity enhancement for NH-detected triple resonance experiments.

Functions that create shape / pattern files using Pbox:

fshapefiles	Makes .RF shape of pw/bw, flip angle, shift
c13decfiles	Makes .DEC file for specified decoupling band
h1decfiles	Makes .DEC file for specified decoupling band
c13shapefiles	Makes Pbox files for specified excitation band, null band, shape type and flip-angle
c13adiab_files	Makes Pbox files for specified excitation band, null band, shape type and flip-angle

Tools to extract parameters from Pbox-generated shapes:

c13pulsepw/c13decpw	Return C13 pulse width
h1decpw/h1decpw90	Return 1H pulse widths

Sincerely Yours,

George A. Gray
NMR Applications Lab

Boban K. John
NMR Applications Lab

M.Robin Bendall
Melbourne University

UNIVERSITY OF CALIFORNIA, BERKELEY

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF CHEMISTRY BERKELEY, CALIFORNIA 94720-1460

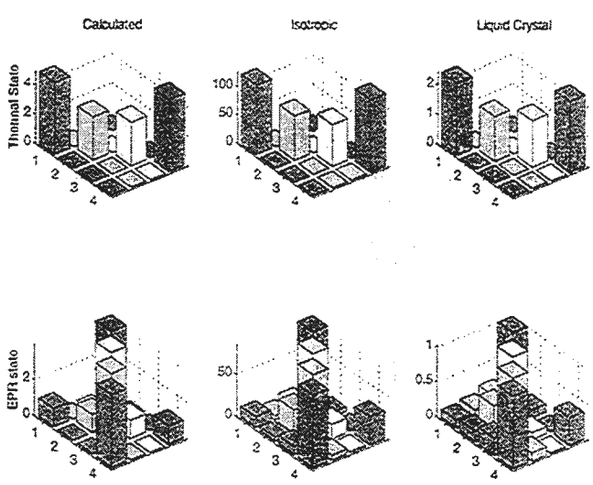
D62H Hildebrand Hall
email: mkubinec@uclink4.berkeley.edu

Dr. Barry L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

Subject:NMRQC in Liquid Crystals

Dear Barry,

We are working on exploiting the properties of liquid crystal solvents to enhance NMR quantum computing (NMRQC). NMRQC in isotropic solution is hindered by the relatively small and short–range scalar coupling among the nuclei. Liquid crystals frequently impart a larger and further reaching dipolar coupling which leads to a superior computational clock speed (the NMRQC clock speed is $\approx 2\Delta$, where Δ is the coupling strength). Furthermore, since relaxation times are shorter in liquid crystals, the system is reset to the initial state more rapidly allowing for more computations or signal averaging. The shorter relaxation times do not affect the efficiency of the computation because the faster clock speed more than compensates for the increased decoherence rate. We define efficiency here as $\Delta * L$, where L is a state lifetime paramter, i.e. T_2 for the single quantum lifetimes and the corresponding decay parameter for the other basis states discribed below. Computational efficiency defined in this way is a measure of the number of computations possible within the lifetime of the state.



To demonstrate the efficiency of the liquid crystal approach, we dissolved a small amount of ^{13}C–chloroform in a nematic liquid crystal and generated the EPR state of the ^{13}C and ^{1}H spins. The result, mapped out using state tomography, is shown here along with the corresponding isotropic result and a calclulation of the ideal two spin EPR state density matrix.[1] Using these data, we are able to compare relative efficiency between isotropic and liquid crystal computers. It turns out the computationally efficient subspaces within this two spin system are more easily identified in the natural singlet/triplet basis of two spins (S, T_0, T_+, T_-), rather than the more fammiliar sum of zero and double quantum coherences (ZQC and DQC) and dipolar order (ZZ). The relationship between the two basis is (ignoring normalization):

$$ZQC \approx S - T_0,\ DQC \approx T_+ - T_-,\ ZZ \approx T_+ + T_- - S - T_0$$

UNIVERSITY OF CALIFORNIA, BERKELEY

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF CHEMISTRY BERKELEY, CALIFORNIA 94720-1460

Computational Efficiency of Isotropic and Liquid Crystal Quantum Computers

Sample	Δ	$\Delta * T_2$ (^1H)	$\Delta * T_2$ (^{13}C)	$\Delta *$ (S or T_0)	$\Delta *$ (T_+ or T_-)
$CHCl_3$ (ISO)	215 Hz	2500	120	80	120
$CHCl_3$ (LC)	4731 Hz	2200	2200	1300	1500

To calculate efficiency, we measured the lifetimes of the singlet/triplet states and the single quantum lifetimes using state tomography. The table summarizes the results which suggest that certain subspaces in the liquid crystal (LC) are more efficient for processing quantum information than those in the corresponding isotropic (ISO) case. These efficient subspaces, however, are difficult to use as quantum bits because the transitions are not easily accesible. Nevertheless, we are optomistic that in more complex molecules, we will find NMR accessible subspaces with these same desireable properties.

Hope to hear back from you soon.

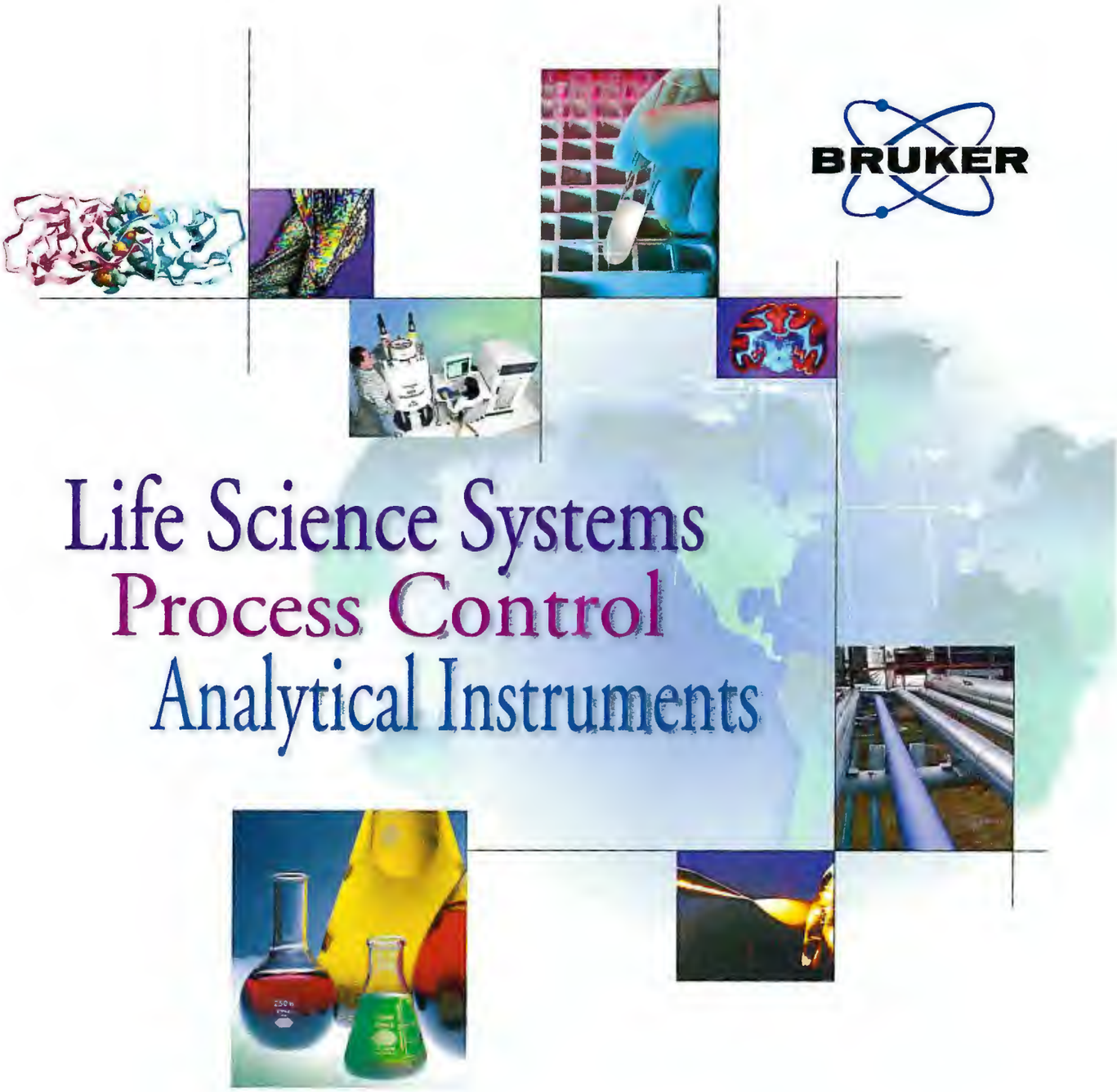
Best Regards,

Mark Kubinec

P.S. Please credit this contribution to the account of Alex Pines.

---

[1] I.L. Chaung, N. Gershenfeld, M.G. Kubinec, D.W. Leung, *Bulk Quantum Computation with Nuclear Magnetic Resonance: Theory and Experiment*, **Proc. R. Soc. London Ser. A–Math Phys. Eng. Sci.**, 454 (1998)



System Solutions and Precision Instruments from Bruker:

Bruker NMR/EPR	Bruker AXS	Bruker Optics	Bruker Daltonics
NMR	Single Crystal Diffraction (SCD)	FT-IR	MALDI-TOF & ESI-TOF
MRI	X-Ray Diffraction (XRD)	FT-Raman	FTMS
Process Control NMR	X-Ray Fluorescence (XRF)	FT-NIR Quality Control	Ion Trap LC/MS/MS
EPR		FT-NIR Life Sciences Systems	Proteomics & Genomics Systems

***Innovation** for customers*
*delivered with **Integrity***

www.bruker.com

Bruker Worldwide

Bruker is a global group of companies designing, manufacturing and distributing systems for the Life Science, Process Control and Analytical Chemistry markets with production sites in Europe and North America. A network of applications, sales and service offices around the world assures extensive high level customer support.

Our People

are our strength. Through them, Bruker continues to grow and prosper as a leading force in the scientific community. Our scientists, engineers, production staff, and sales team maintain close communication with customers, learning the latest requirements for cutting edge experiments, and incorporating that information into our next generation products. We actively support the exchange of information between our staff and the scientific community through participation in conferences, seminars, symposia, and exhibitions.

Our Solutions

are thorough and complete, concentrating on meeting your analytical requirements. The versatility of Bruker systems and accessories embrace a full range of applications. We offer sophisticated automation products adding high throughput capabilities for industrial applications as well as specialty instruments for unique experiments. Every year brings greater innovations, enhancing the productivity of the labs we serve. Software tools are highly integrated into every product allowing true ease-of-use for both routine as well as research environments.

Our Support

is extensive. The Bruker organization has a well-earned reputation of responsiveness to customers' demands for excellence in every area. Our worldwide organization features offices for sales, application and engineering support in every major area of the world. Whether you need information on new products and accessories, enhancements of existing products, or routine service and support, your local Bruker office is just a quick phone call away.

***Innovation** For Customers*
*Delivered With **Integrity***

BRUKER

BRUKER INSTRUMENTS, INC.
44 Manning Road
Billerica, MA. 01821-3991
Phone: (1) 978 667-9580
Fax: (1) 978 667-0985
http://www.bruker.com
http://www.bruker.de

LIFE SCIENCE SYSTEMS PROCESS CONTROL ANALYTICAL INSTRUMENTS

INDIANA UNIVERSITY
PURDUE UNIVERSITY
INDIANAPOLIS

June 17, 1999

(received 6/24/99)

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

SCHOOL OF SCIENCE

IUPUI

NMR vs X-ray Determination of substrate Structures

Dear Barry:

Thanks for your reminder.

ATP-utilizing enzymes are ubiquitous in a variety of critical cellular processes. They come in three categories based on the transferable moiety, viz., phosphoryl transfer, adenylyl transfer, and pyrophosphoryl transfer. All of them require a divalent cation, Mg(II) *in vivo*, for activity. Because of their importance, ubiquity and diversity these enzymes have been subjects of intensive structural investigations by X-ray crystallography and solution NMR. For some time now, we have been trying to characterize the conformation of the enzyme-bound substrates of a group of these enzymes. We recently did this for the enzyme, *E. coli* adenylate kinase, which catalyzes the reaction ATP+MgATP $\Leftrightarrow$ ADP + MgADP. This enzyme is unique in that both the substrates are adenine nucleotides. In the reverse direction two diphosphates are converted into one mono- and one triphosphate, the distinction between the acceptor and donor of the phosphoryl group being achieved by the selective binding of cation to the acceptor ADP.

We determined the enzyme-bound conformations by employing two high-resolution NMR methods: (i) TRNOESY for measurement of interproton distances in the adenosine fragment, and thereby determine the glycosidic rotation, and sugar pucker in this moiety, and (ii) ^{31}P and ^{13}C spin relaxation measurements in the presence of activating substituent paramagnetic cations, Co(II) and Mn(II), to determine the location of the cation with respect to the phosphate chain, and to determined the orientation of the phosphate chain with reference to the adenosine. Shown in the figure below is the enzyme-bound conformation of AMP determined by NMR, overlaid (by superposing the ribose) with that previously determined by crystallography. The important point is that these two conformations are quite different. Such differences are found for every ATP-utilizing enzyme investigated thus far. The distinction between the conformations determined by NMR and X-ray methods raises number of interesting questions. since the NMR measurements are made in solution phase

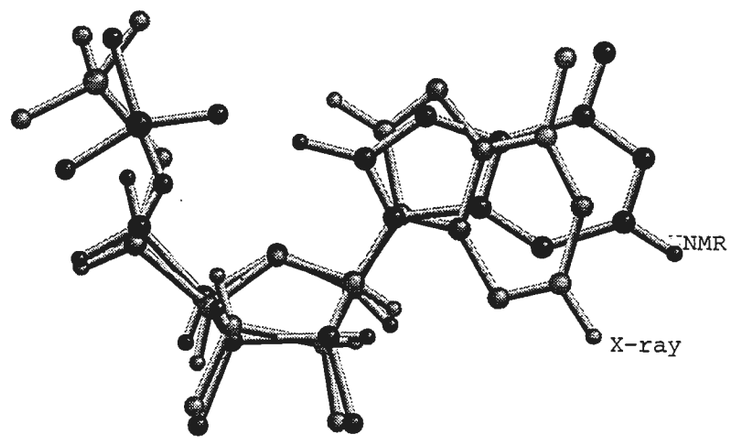
NMR CENTER

DEPARTMENT OF PHYSICS

402 North Blackford Street
Indianapolis, Indiana
46202-3273

317-274-6900
Fax: 317-274-2393

under conditions in which the reaction actually takes place, the NMR-determined conformations are the productive ones. On the other hand, the crystallization process and the attendant packing effects may have trapped the substrate in a different and unproductive conformation. It appears that, while the X-ray crystallography is undeniably the best means to acquire the protein structure, the NMR-determined structures are probably more reliable for the substrate conformations. It make sense, therefore, to combine these results of the two methods to gain insight into the structure-function relationships of these enzymes. This is our goal in the near future.



Conformations of AMP bound to *E. coli* adenylate kinase determined by NMR (atoms in darker color) and X-ray crystallography (Berry, M. B., Meador, B., Bilderback, T., Liang, P., Glaser, M. and Philips, G. N., Jr. (1994) *Proteins: Structure, Function, and Genetics 19*, 183-198).

Best regards.

Sincerely,

Yan Lin

B. D. Nageswara Rao

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

9 June, 1999
(received 6/12/99)

The Inside-Out Rule

Dear Barry:

CASE programs[1] make the generation of molecular structures a rigorous mathematical exercise. That is good, since it assures that no structural candidates will be overlooked. The bad side is that this process does not model the human insight we use in interpreting our data. If we could find a way to code some of this insight into the computer (that is, use "artificial intelligence"), we might be able to reduce the size of the problem considerably.

For example, human spectroscopists use what I call the "Inside-Out Rule" to aid in the interpretation of HMBC data. With this rule, one begins with substructures obtained from the COSY or proton NMR data and extend them by starting at the nuclei farthest from the free valences and looking at their long range correlations. By doing this the ambiguities regarding the number of bonds through which the HMBC correlations are transmitted can often be simplified. This may sound complicated, but really it is merely human common sense. It has always seemed to me, however, that this is an instance of common sense that could be programmed into a computer.

Table 1: HMQC/HMBC Correlations

Peak:	δ_C:	Mult:	HMQC	HMBC
1.	189.192	s		7.388
2.	169.535	s		4.776 3.710
3.	167.988	s		7.743 7.388
4.	151.607	s		7.063 6.581 4.776
5.	149.407	s		5.526 2.906 1.080
6.	137.516	s		7.063
7.	137.319	s		7.319 5.526
8.	128.688	d	7.319	7.042
9.	127.354	d	7.259	7.042
10.	126.080	d	7.042	7.259 5.526
11.	123.061	d	7.063	
12.	116.221	s		7.099 6.581
13.	109.774	s		2.906
14.	104.633	d	7.099	6.581
15.	104.269	d	6.581	
16.	64.954	t	4.776	
17.	51.804	q	3.710	
18.	46.010	t	5.526	7.042
19.	18.436	t	2.906	1.080
20.	14.189	q	1.080	2.906

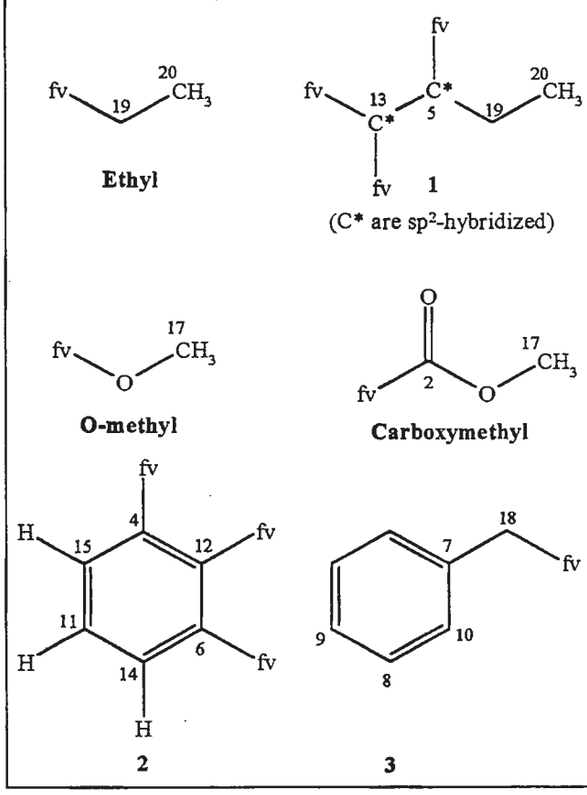
Let's show how this works with some examples (see Table 1). Methyl groups are particularly simple starting points for the Inside-Out Rule. For example, from the proton NMR spectrum of our example (not shown) it is clear that peaks 19 and 20 comprise an ethyl group. Clearly, the methyl protons are farthest from the free valence, and if we can find a carbon other than C-19 that is long range correlated to these protons, this *must* be due to a three-bond correlation. So we scan down the HMBC column looking for a carbon that is correlated to the methyl protons at 1.080δ, and we find that C-5 fits this constraint. Hence we can attach C-5 to C-19. We can extend this growing substructure further by looking for a carbon resonance that is correlated to the protons of CH_2-19, and on this basis we can attach C-13 to C-5. Thus we have enlarged the ethyl to substructure 1 of

[1] See NMR Newsletter, December 1998, #483, p. 19 and references cited therein.

Figure 1. From their chemical shifts we know that C-5 and C-13 are sp^2-hybridized, even if we do not know enough yet to specifically locate the double bond(s).

We can identify a second methyl (C-17) as an O-methyl group. Again, if we can find a carbon that is long-range correlated to the protons of this methyl, this must be due to three-bond coupling, so that the usual ambiguity in the meaning of HMBC data is resolved. We see from the data of Table 1 that C-2 shows such a correlation. Since the chemical shift of C-2 indicates that it is a carbonyl, our use of the Inside-Out Rule has allowed us to extend the O-methyl to a carboxymethyl group (Figure 1).

Figure 1:Substructures



We regularly use the Inside-Out Rule to extend our aromatic substructures (Table 1). From the proton NMR spectrum we can deduce the presence of the 1,2,3-trisubstituted benzene ring (**2**, Figure 1). To assign the resonances of carbons 4 and 6, we simply seek the resonances which are long-range correlated to H-11. Similarly, the resonance of C-12 is that which is correlated to both H-15 and H-14. Thus we "back out" of the substructures derived from the proton NMR data, filling out the carbon assignments as we go.

In a final example taken from this data set, the proton resonances of carbon 8, 9, and 10 show that these nuclei comprise a phenyl group. To identify the resonance of C-7 we look for a resonance with a long-range correlation to H-8. Finally, by looking at the list of protons long-range coupled to C-10, we can extend the phenyl substructure to a benzyl group (**3**, Figure 1). In this last case we select a carbon which cannot be within two bonds of any proton outside the phenyl group, so that any correlation found has to be a three-bond coupling. Hence we can use either carbon or proton resonances as our starting point. Our only constraint is that the nucleus chosen cannot be correlated through two bonds to nuclei of the free valence portion of the molecule.

Again, this is not mathematics, but intelligence. Sometimes such intelligence is difficult to program, but I would very much like to see some of our CASE program vendors give it a try.

Doug Dorman
doug_dorman@lilly.com

Dr BL Shapiro
The NMR Newsletter

11 May 1999

ASTRA
ASTRA CHARNWOOD

Dear Barry

GRAPHICAL VISUALISATION OF NMR DATA

Automated synthesis and High Throughput Screening (HTS) have changed the face of Drug Discovery over the last 5 years or so. Mainly because of speed and ease of interpretation, HPLC-UV/VIS and MS have become the analytical methods of choice.[1]

Medicinal Chemists have traditionally relied heavily on NMR for proof of structure and purity, but this paradigm has been somewhat lost. The prospect of measuring the NMR spectra of an array of compounds presented in microtiter plates ("tubeless NMR") has seen quite considerable uptake. In essence, one uses a conventional high-resolution NMR spectrometer fitted with a flow probe, and a robot to move the solute and wash solvents.

Although there are well-refined methods for measuring NMR spectra of these compounds, a new bottleneck has emerged: data analysis. One may consider methods which rely on a comparison of experimental- and calculated data and this is certainly appealing. Any scheme that relies solely on operator judgement will be both faulted and extremely tiresome.

In addition to the "analytical" approach, there may well be quite considerable merit in considering *graphical* methods for displaying spectroscopic information contained within an array of perhaps 96 ^{1}H NMR spectra. Such an overview of a plate may quickly provide the operator with information on:

1. the presence of impurities at significant concentration,
2. reaction completion (*e.g.*, removal of signal intensity in a characteristic spectral region, or its generation),
3. performance of automated data processing procedures (*e.g.* baseline flattening)

We are planning to implement these approaches with in-house programmes, but for the moment we can use the data mining capabilities of Spotfire Pro[2] to give an indication of the merit of the approach. Spectra were divided into 30 Hz "buckets" of signal integral and the data written to a delimited ASCII file.

In the first instance we were inspired by a graphical representation of MS data.[1] Here a representation of the spectrum of each well can be viewed. Each bucket is represented by a spot whose size is proportional to the signal integral in that frequency range; a logarithmic scale was used. Simple "sliders" (see http:\\www.spotfire.com) allow one to easily limit the amount of data viewed. The vertical ppm axis could, for example, be limited to a region of interest, and the Intensity slider can be altered to adjust the lower- or upper threshold. Note, for example, the presence of an impurity (I) in each spectrum at *ca* 3 ppm (DMS in the DMSO solvent). A couple of rows can be seen where no spectrum was collected (➔).

In the second example we have depicted a 96-well plate. Here, the size of each circle is proportional to the NMR signal intensity in the proton aromatic region.

Methods for dealing with the large amounts of NMR data produced by such equipment will undoubtedly increase in sophistication and ease-of-use. One can envisage interfaces with statistical methods to assist with multi-spectral analysis. For now, we offer these thoughts on the use of graphical analyses for rather simple questions and overviews.

---

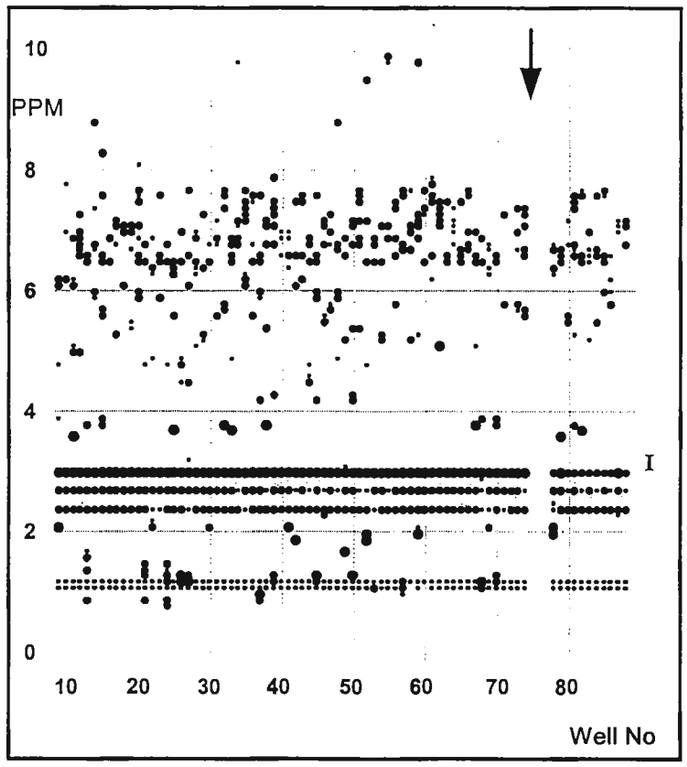
[1] E Görlach, R Richmond, and I Lewis, *Anal. Chem.* **1998**, *70*, 3227.
[2] Spotfire AB, Första Långgatan 26 S-413 28 Göteborg, Sweden

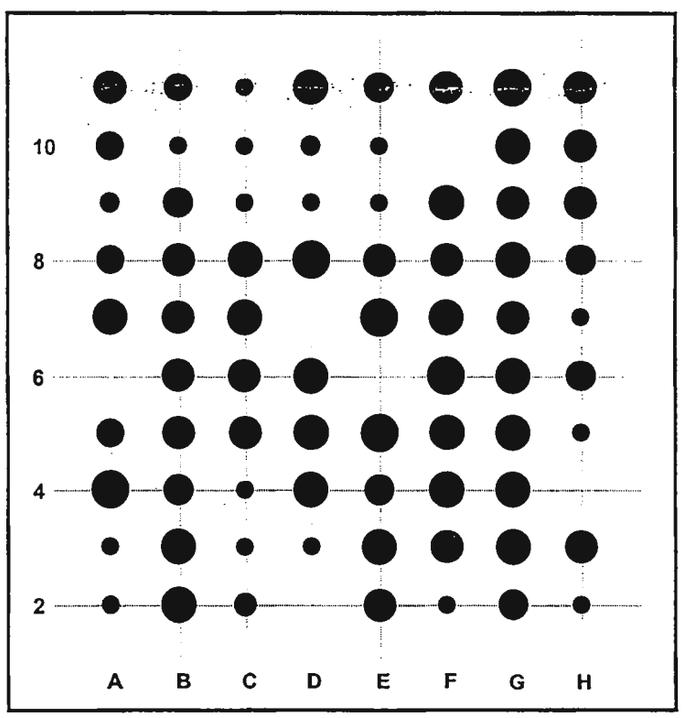
MAILING ADDRESS:
Astra Charnwood
Bakewell Road, Loughborough
Leics LE11 5RH England

TEL:
01509 64 4000
+44 1509 64 4000

FAX:
01509 64 5555
+44 1509 64 5555

[redacted]





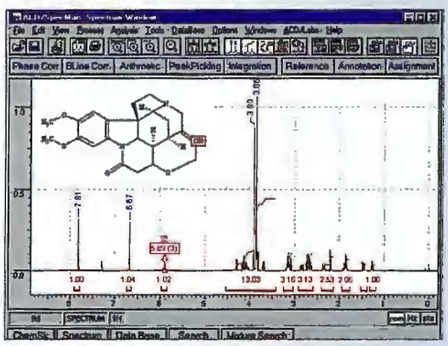
Yours sincerely
ASTRA CHARNWOOD

Mike
Michael A Bernstein

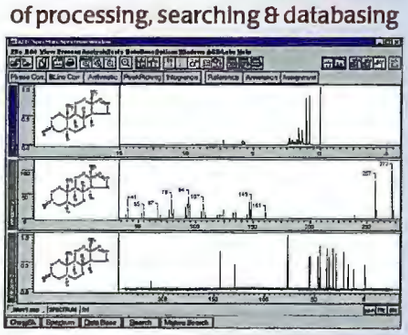
D. Hardy
David L Hardy

John Mark Dixon
J Mark Dixon

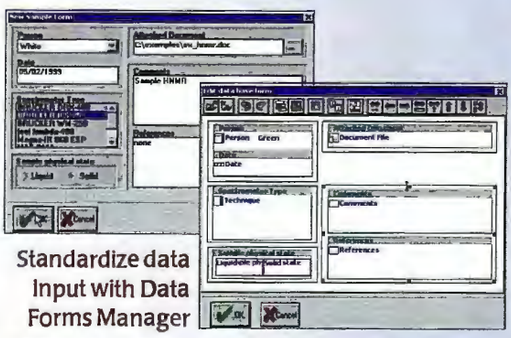
ACD/NMR Manager



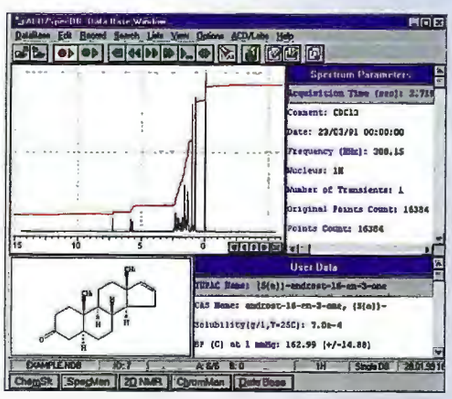
Intuitive interface for all kinds of processing, searching & databasing



Tile feature in Spectrum Window lets you view several spectra at once



Standardize data input with Data Forms Manager



Comprehensive Database Window

Take raw NMR data directly from the spectrometer and process it using a wide array of tools!

- Import the major FID and FT formats, including Varian, Bruker, JEOL, Chemagnetics, WinNMR, Nuts, Lybrics, JCAMP, etc.
- Use zero filling, weighting functions, Fourier Transform.
- Apply automated or manual phase and baseline correction, peak referencing.
- Automated or manual peak picking and integration.
- Manual or automatic peak assignment.
- Annotate the spectrum using either peak or region selection, offering unique capabilities to assign and annotate polymer spectra and other complex spectral curves.
- Create macro programs for completely automated data processing.
- Dual Window display of calculated and experimental spectra.
- **Plus** - All new capabilities of NMR Processor

SpecViewer
www.acdlabs.com
FREE!

Innovative storage and management software for all kinds of experimental data!

Create a *comprehensive* database of experimental spectra:

- Store different kinds of spectra in the same data base;
- **New!** - Assign several spectra to a single data base entry;
- Establish over 16,000 fully searchable user-defined fields;
- Protect databases with view-only and read-write passwords;
- Search database according to:
  - spectrum, sub-spectrum, spectral parameters;
  - molecular structure or sub-structure;
  - formula, molecular weight and user-defined fields; and any special fields corresponding to spectrum type
- Search through several databases at a time.
- Generate and save lists from searches, perform various manipulations with lists (duplication, merging, subtraction, intersection) to make complex searches.
- **New!** - Standardize and simplify record entry with the Data Forms Manager.

MS, UV-IR, 2D-NMR Modules also available.

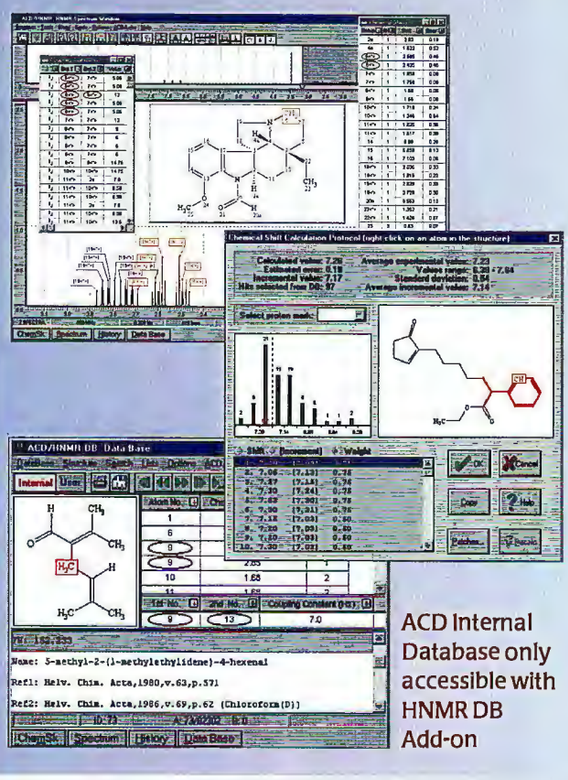
Advanced Chemistry Development
T: 416 368·3435
F: 416 368·5596
Toll Free: 1 800 304·3988
info@acdlabs.com
www.acdlabs.com

NMR
IR
UV-VIS
MS
Raman

NMR
IR
UV-VIS
MS
Raman

ACD/HNMR

Calculate the proton NMR spectrum for any organic chemical structure to very high accuracy.



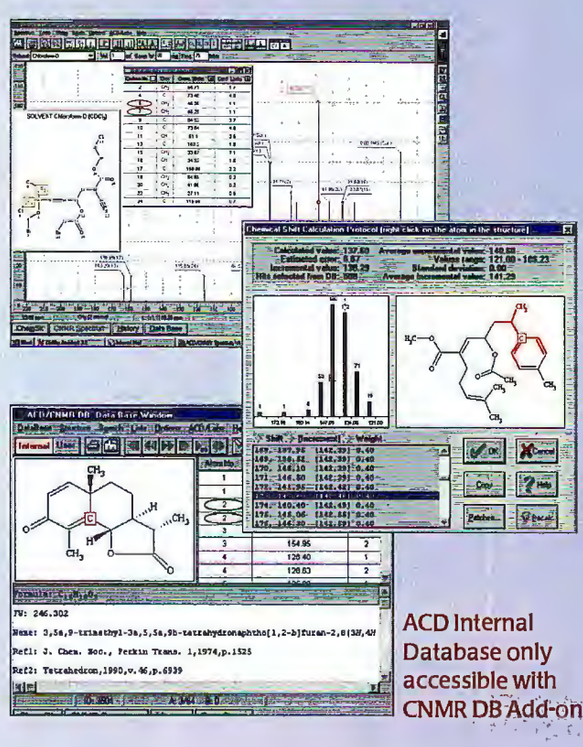
ACD Internal Database only accessible with HNMR DB Add-on

- Takes into account second order interactions (strong coupling effects) and long-range coupling constants.
- Uses 3D molecular structure minimization and Karplus relationships to predict proton-proton coupling constants.
- Allows you to calculate exact spectra for any strongly coupled system with up to 8 magnetically non-equivalent nuclei (spin 1/2) or more if some nuclei are magnetically equivalent.
- Prediction based on an internal datafile with over 600 000 experimental chemical shifts and 110 000 coupling constants.
- Self-training system lets you create your own database of chemical shifts, for improved prediction accuracy.
- **NEW!** Data Forms Manager streamlines and standardizes record entry as you build your own databases.
- **NEW!** Include multiple user databases in system training
- **NEW!** Calculate missing shifts in Database Window.
- **NEW!** Enter unassigned shifts or automatically transfer peak table into HNMR database from SpecManager.
- **NEW!** Modify or delete shifts in the internal DAT file.

ACD/CNMR

Calculate the carbon-13 NMR spectrum for any organic molecule to very high accuracy.

- Calculates spin-spin interactions, simulates off-resonance, DEPT, J-modulation and much more.
- Prediction based on an internal data file with over 900 000 experimental chemical shifts.
- Self-training system lets you create your own database of chemical shifts, for improved prediction accuracy.
- **NEW!** Data Forms Manager streamlines and standardizes record entry as you build your own databases.
- **NEW!** Include multiple user databases in system training
- **NEW!** Calculate missing shifts in Database Window.
- **NEW!** Modify or delete shifts in the internal DAT file.
- **NEW!** Enter ^{13}C-X coupling constants, where X = ^{19}F, ^{31}P, etc.
- **NEW!** Enter unassigned shifts or automatically transfer peak table into CNMR database from SpecManager.



ACD Internal Database only accessible with CNMR DB Add-on

The University of Texas Medical Branch at Galveston

School of Medicine
Graduate School of Biomedical Sciences
School of Allied Health Sciences
School of Nursing

Marine Biomedical Institute
Institute for the Medical Humanities
UTMB Hospitals and Clinics

Department of Human Biological Chemistry & Genetics
&
Sealy Center for Structural Biology

Dr. Bernard L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

"BEST" Homonuclear Adiabatic Decoupling for ^{13}C- and ^{15}N-Double-Labeled Proteins

June 16, 1999
(received 6/22/99)

Dear Dr. Shapiro,

As in heteronuclear adiabatic decoupling, homonuclear adiabatic decoupling also introduces significant sidebands. They are, however, not generated mainly by the modulation of the coupling but by the direct cyclic irradiation of the nearby decoupling RF field. Besides, the decoupling pulse also introduces severe nonlinear frequency (Bloch-Siegert) shift of all peaks.

The Bloch-Siegert shift can be reduced by a compensating decoupling pulse applied on the other side of the peak (1, 2), resulting in a spectrum contraction by a factor of $\lambda = [1-(f_{1rms}/\Delta f)^2]$, which can be eliminated by a dilated evolution time $t_1' = [1+(f_{1rms}/\Delta f)^2]t_1$ in the indirectly detected dimension (2). This double-adiabatic decoupling also reduces significantly the cyclic irradiation sidebands, especially for peaks in the central region of the spectrum. For large offset, ±3 kHz for example, there are about 2% residual sidebands with sideband number $n = \pm 1$. By inserting an initial decoupling period T_{ini} (= $T/2$) (Fig. 1), the residual sidebands ($n = \pm 1$) will be inverted and therefore be canceled as shown in Fig. 2. The initial decoupling period should have the same f_{1rms} as the main decoupling, making the Bloch-Siegert shift invariant during decoupling and therefore to be compensated more effectively.

This double-adiabatic decoupling is referred to as ***B***loch-Siegert Shift ***E***liminated and Cyclic ***S***ideband ***T***rimmed Double-Adiabatic Decoupling, or "BEST" decoupling for short (3).

DOCKSIDE BUILDING 301 UNIVERSITY BOULEVARD GALVESTON, TEXAS 77555-1157 (409) 747-6800 FAX (409) 747-6850

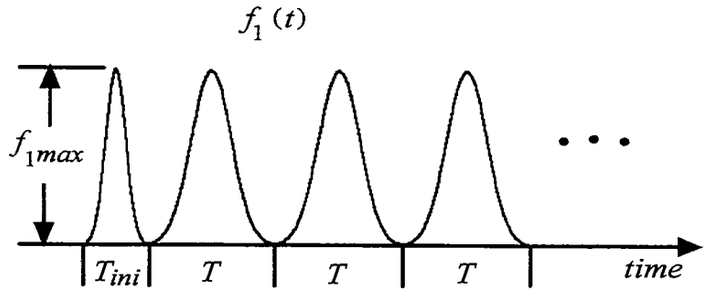


Fig. 1. Gaussian shaped adiabatic decoupling with an initial decoupling period T_{ini} and the main decoupling period T. As T_{ini} varies, the phases of sidebands will change accordingly while the phase of the central peak remains unchanged. In particular, the sidebands ($n = \pm 1$) are inverted if $T_{ini} = T/2$.

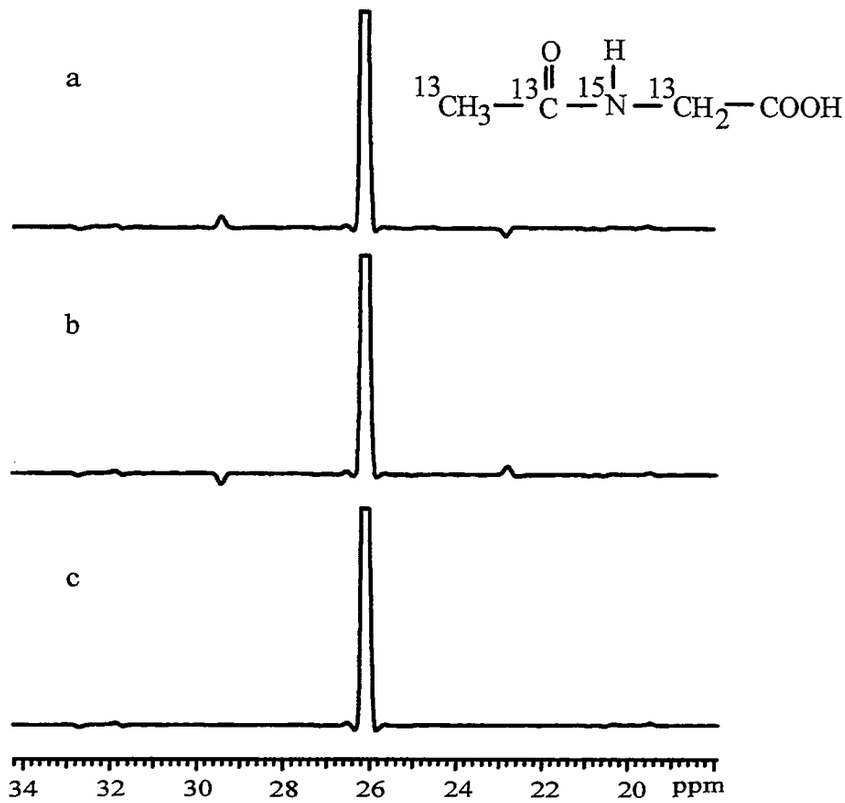


Fig. 2. Methyl ^{13}C spectra from the traces of two-dimensional HSQC spectra using a sample of double-labeled *N*-acetylglycine. The spectra are obtained using "BEST" decoupling, with a ^{13}C decoupling offset of –2.5 kHz and $T_{ini} = 0$ (a) and $T_{ini} = T/2$ (b). Spectrum (c) is the sum of spectra (a) and (b). The central peak is truncated at 40% level.

Best regards,

Shanmin Zhang David. G. Gorenstein

References:
1. M. A. McCoy and L. Mueller, *J. Magn. Reson.* **98**, 674 (1992).
2. S. Zhang and D. G. Gorenstein, *J. Magn. Reson.* **132**, 181 (1998).
3. S. Zhang and D. G. Gorenstein, *J. Magn. Reson.* in press (1999).

When You Need the Best.

From left to right:

Lisa Deuring:
UNITY*INOVA*
Product Manager

Matt Commens:
Sr. Probe Engineer

Debra Mattiello:
Sr. Engineer, R&D

Paul Keifer:
Sr. Applications Chemist

Varian is the Leader in High-Field NMR.

When you step up to high-field NMR, you expect the finest instrumentation — quality without compromise. Engineered to the tightest tolerances, all UNITY*INOVA*™ systems deliver the industry's highest levels of performance and reliability for your complex chemical and biomolecular applications.

An NMR system is only as good as the people who stand behind it. Each Varian system is backed by a team of experts — the best of the best. Known worldwide for their research and design achievements, our highly respected team of NMR scientists has one goal: to keep you on the forefront of cutting-edge scientific investigation.

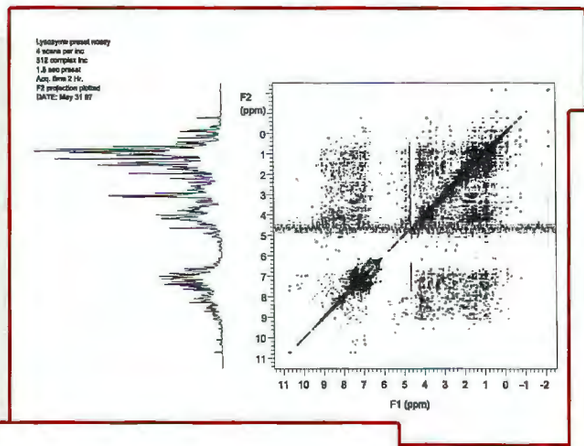
From the development of NMR 50 years ago to today's high-field systems, Varian is second to none. For more information on how you can achieve your best, contact Varian today.

varian

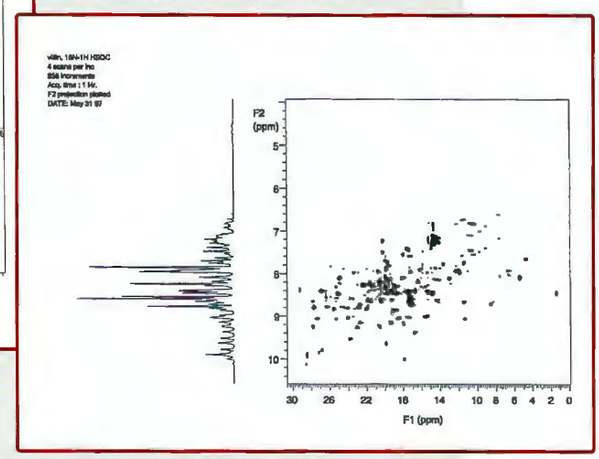
GC • GC/MS/MS • HPLC • AAS • ICP-AES • ICP-MS • UV-Vis-NIR • NMR • Sample Preparation • Vacuum Products

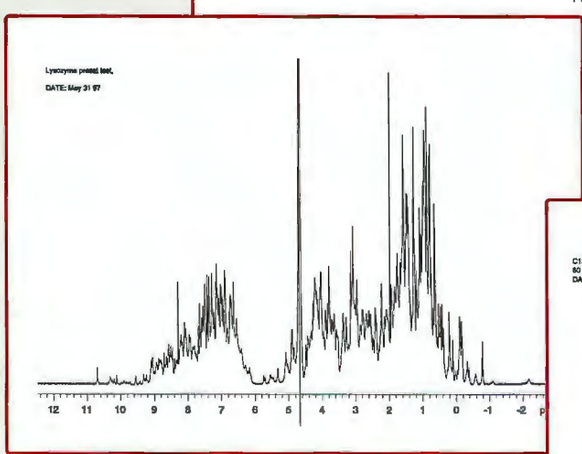
UNITY*INOVA*: Outstanding Performance at 800 MHz

Multidimensional Homonuclear NMR

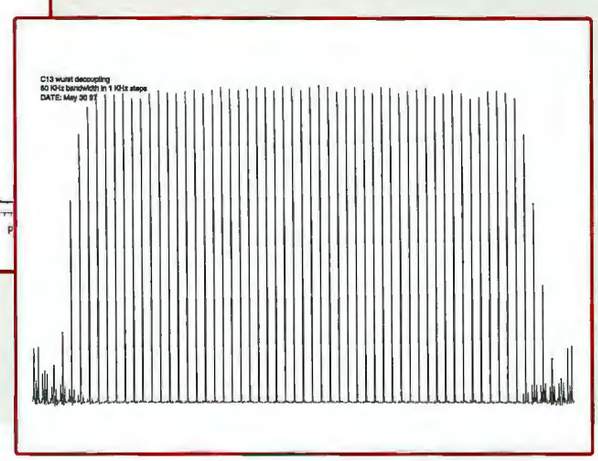


Multidimensional Heteronuclear NMR





Water Suppression Using Presaturation



Ultra-Broadband Decoupling

Varian's tradition of outstanding high-field NMR performance continues at 800 MHz. UNITY*INOVA*'s modular, wideband RF system makes the expansion to higher and higher frequencies fast and easy, with excellent performance and flexibility. Innovative probe design, utilizing 52-mm (2-inch) diameter probes, provides short pulse widths for large excitation bandwidths (required at 800 MHz), and exceptional ^{1}H sensitivity, with multiple-resonance and pulsed field gradient capability.

Manufacturing Facilities Varian NMR Instruments, Building 4, 3120 Hansen Way, Palo Alto, California 94304-1030, Tel 650.424.4876, Fax 650.852.9688 • http://www.varian.com • **Argentina** Buenos Aires, Tel 1.783.5306 • **Australia** Mulgrave, Victoria, Tel 3.9566.1133 • **Brazil** São Paulo, Tel 11.820.0444 • **Canada** Mississauga, Ontario, Tel 1.800.387.2216 • **France** Les Ulis, Tel 1.69.86.38.38 • **Germany** Darmstadt, Tel 06151.7030 • **India** Mumbai, Tel 22.837.3281 • **Italy** Milan, Tel 2.921351 • **Japan** Tokyo, Tel 3.5232.1211 • **Korea** Seoul, Tel 2.3452.2452 • **Mexico** Mexico City, Tel 5.523.9465 • **Netherlands** Houten, Tel 3063.50909 • **Switzerland** Basel, Tel 61.295.8000 • **Taiwan** Taipei Hsien, Tel 2.698.9555 • **United Kingdom** Walton-on-Thames, Tel 1932.898.000 • **United States** California, Tel 800.356.4437 • **Venezuela** Valencia, Tel 4125.7608 • **Other sales offices and dealers throughout the world**

varian

MAG-8758A/233

SIMON FRASER UNIVERSITY

INSTITUTE OF MOLECULAR
BIOLOGY AND BIOCHEMISTRY

8888 UNIVERSITY DRIVE
BURNABY, BRITISH COLUMBIA
CANADA V5A 1S6
Telephone: (604) 291-5630
Fax: (604) 291-5583

June 8, 1999 (received 6/18/99)

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court

Spectral Estimation of NMR Relaxation;
In the Limit of Small Error

Dear Barry,

The continuous Fourier Transform serves as a starting point for the treatment of the discrete Fourier Transform of small order, in the estimation of monoexponential decay. The observation[1] that a Fourier Transform approach gives the best correlation with other experimental observables suggests that this approach yield estimates, which may be of minimum variance and of minimum bias. We restrict our attention to monexpontential decay of the following form:

$$I(t) = Ae^{-Lt} + B \qquad [1]$$

which will encompass both transverse and longitudinal NMR relaxation. We can construct a family of spectral estimators at one half the Nyquist frequency, $(1/2)\omega_N$. If $(1/2)\omega_N$ is an integer, then N is a multiple of four. By extension of the continuous FT estimator[1], these DFT estimators have the following forms:

$L = \ln((f_1 - f_3)/(f_2 - f_4))/dt$, $\ln((f_1 - f_3 + f_5 - f_7)/(f_2 - f_4 + f_6 - f_8))/dt$,...,etc. (Hz)

where $f_1 \ldots f_k$ are intensity values measured at equal time increments, dt, starting at time, $t = 0$. A careful numerical study of Gaussian error propagation in the limit of small error, of this family and related divisor formulae[1], reveals that it is the four point spectral estimator which is of minimum variance. If we assume that each measured intensity has error of the same standard deviation, σ, then, in the limit of small error, each partial derivative contributes error of the amount, $(\partial L / \partial f_i)\sigma$, and the total estimation error is the root squared sum of all contributions. In the limit of small error, L is unbiased and each of $f_1 .. f_4$ can be substituted for its expression derived from equation [1]. This lead to an expression for the standard deviation of the estimate:

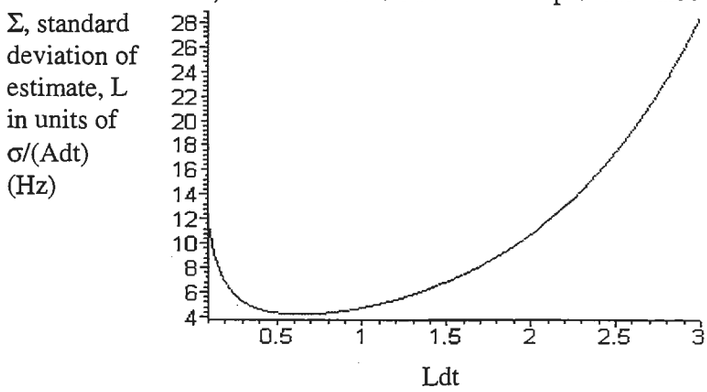
$$\Sigma = \frac{\sigma}{Adt} \frac{\sqrt{2}e^{2Ldt}\sqrt{1+e^{2Ldt}}}{(e^{2Ldt}-1)} \qquad [2]$$

This last expression [2] can be optimized in L. It is minimal when:

$$Ldt = \frac{1}{2}\ln(\frac{3}{2} + \frac{1}{2}\sqrt{17}) = 0.6350983165 \qquad [3]$$

Thus, if we have a prior estimate L (Hz) of the relaxation rate, we can obtain an estimate of minimal variance if we choose dt, the sample period such that Ldt=0.6350983165. This is very near to the relaxation half life based on the prior estimate. This is not an abstract issue. Very often we wish to study NMR relaxation as a function of some independent variable like ligand concentration, temperature or Carl-Purcell period. We will have a prior estimate. Spectrometer time may be very valuable and we may

have a valuable biological sample. This insight tells us how to design a relaxation experiment for optimal variance. However, nature is not so strict. We can plot the value of Σ as a function of Ldt:



Σ is very flat at the bottom. It can be seen that we will have nearly optimal variance when 0.5<Ldt<0.8. A/σ can be identified with the signal to noise ratio, S/N. Thus, the estimation variance can be reduced linearly with decrease in N/S. L gives a point estimate. Interval estimation can be obtained by a separate measurement of S/N.

It is of interest to consider the spectral implications of this insight. L is a complex frequency. In the complex plane it is close to some real frequencies and hence there is some optimal sample period. Since a relaxation decay dies away quickly, only a limited number of samples are needed. Rather than oversampling, it is better to put effort into signal averaging at the optimal four points so as to reduce N/S. The four point spectral estimator can be thought of as a kind of digital filter which ignores irrelevant information.

Nonlinear least squares estimation, NLS is most commonly applied to studies of NMR relaxation. It is worthwhile to compare the estimation strategy of NLS with that of the four point spectral estimator. An analytical solution of the NLS problem for four points can be derived[2].

$$L = -\frac{\ln(RootOf((f_2 - 2f_3 + f_1)Z^4 + (2f_4 - 2f_2 + 4f_1 - 4f_3)Z^3 + 3(f_4 - f_3 - f_2 + f_1)Z^2 + (4f_4 - 4f_2 + 2f_1 - 2f_3)Z - 2f_2 + f_3 + f_4))}{dt}$$

It can be seen that this expression has similarity to that of the four point spectral estimator. However, since a quartic with real coefficients may have up to four real roots there may be uncertainty whether the global minimum has been achieved by numerical optimization. If the minimum is very flat the minimizer may not be completely converged which makes the statistical analysis suspect. NLS strives to estimate all the parameters, which is more than we desire. Analysis of error propagation or of bias is an intractable problem in NLS. In summary, rigorous mathematical statistics requires that we use four point spectral estimation rather than NLS for the estimation of NMR relaxation.

Sincerely,

David Naugler
dnaugler@sfu.ca

Robert J. Cushley
cushley@sfu.ca

[1] "Exponential Analysis of physical phenomenon", Andrei A. Istratov, Oleg F. Vyvenko, Review of Scientific Instruments, Vol. 70, No. 2 , Feb. 1999, p1233-1257.
[2] "Die Methode der kleinsten Quadrate bei einem dreiparametrigenExponentialansatz.", S.Oberlander, ZAMM 43 (1963), p493-506.

SIMON FRASER UNIVERSITY

INSTITUTE OF MOLECULAR
BIOLOGY AND BIOCHEMISTRY

8888 UNIVERSITY DRIVE
BURNABY, BRITISH COLUMBIA
CANADA V5A 1S6
Telephone: (604) 291-5630
Fax: (604) 291-5583

June 8, 1999 (received 6/18/99)

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court

Spectral Estimation of NMR Relaxation;
Unbiased Estimation

Dear Barry,

If the quantity (A/σ) can be identified with the signal to noise ratio, S/N, then the number of significant bits provided by this S/N is $\log_2(S/N)=n$. Given a prior estimate of exponential relaxation rate, L (Hz) then the optimal variance is obtained if we select the sample period dt, such that Ldt=0.6350983165. Let us say that dt is the unit of time used in the measurement of L. Then, at the optimum, the estimation variance, Σ will be calculated to be 4.199595152σ/A. This says that the number of significant bits $\log_2(L/\Sigma)$ in the estimate L will be very nearly equal to n-2. Thus, a minimum of 3 significant bits are required of S/N in order to have any significance in an estimate L, even under the best of circumstances.
The bias of an estimator $\boldsymbol{L}$, can be determined by evaluation of its expectation value, E($\boldsymbol{L}$). It is reasonable to assume a normal, i.e., Gaussian probability density function for measurement error. For our four point spectral estimator, $\boldsymbol{L}$ we can combine variation terms in the numerator and denominator and express its expectation value as:

$$E(\boldsymbol{L})=\frac{1}{2\pi}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\ln\left(\frac{(f_1-f_3+\sigma' x)}{(f_2-f_4+\sigma' y)}\right)e^{-(x^2+y^2)/2}dxdy \qquad [1]$$

where $\sigma'=\sqrt{2}\sigma$. The integrand can be expanded as a power series in σ' and the integral evaluated term by term[1]. All the terms in odd powers of σ' evaluate to zero.

$$E(\boldsymbol{L})=\ln\left(\frac{(f_1-f_3)}{(f_2-f_4)}\right)+\frac{\sigma'^2}{2}\left(\frac{1}{(f_2-f_4)^2}-\frac{1}{(f_1-f_3)^2}\right)+\frac{3\sigma'^4}{4}\left(\frac{1}{(f_2-f_4)^4}-\frac{1}{(f_1-f_3)^4}\right)+O(\sigma'^6)$$

The coefficients, C_k, of the even order terms can be computed to higher order. The exponential generating function $\frac{1}{\sqrt{1-2x}\left(1+\sqrt{1-2x}\right)}$ and the general coefficient $C_k=(2k-1)!/\left(2^k k!\right)$ can be computed[2]. This allows the bias to be expressed in closed form:

$$\Delta=\Psi\left(\frac{\sigma'^2}{(f_2-f_4)^2}\right)-\Psi\left(\frac{\sigma'^2}{(f_1-f_3)^2}\right)$$

and where

$\Psi(X)=X\text{hypergeom}([3/2,\ 1,\ 1],[2],2X)/2$

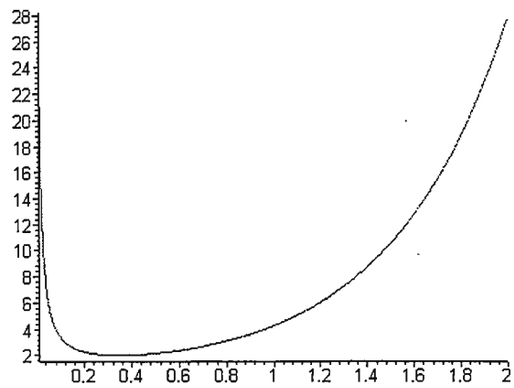
in which 'hypergeom' is the Barnes's extended hypergeometric function.

The first term $\ln\left(\frac{(f_1 - f_3)}{(f_2 - f_4)}\right) = L$, is the true value of L, and the other terms are the bias terms. Thus, the four point spectral estimator alone is a biased estimator of relaxation rate, L. This is an unavoidable aspect of nonlinear estimation, which has the potential to rectify noise power into bias. However, with a separate measurement of noise statistics we can calculate the bias and subtract away the bias to give an unbiased estimate of L. Further insight can be derived by focusing on the form of the second order bias term, Δ_2. After substitution it can be expressed as:

$$\Delta_2 = \frac{\sigma'^2 e^{2Ldt}}{2A^2 dt(1 - e^{-2Ldt})}$$

and plotted below.

Second order bias, in units of $\frac{\sigma'^2}{A^2 dt}$, (Hz)



Ldt

This function has a minimum at Ldt=1/2ln(2)= 0.3465735903. Thus, it can be seen that the objectives of minimum variance and minimum bias are contradictory experimental design objectives. It is probably better to aim for minimum or near minimum variance and to subtract off the bias.

Spectral estimation of NMR relaxation is an exact treatment. Other treatments are not exact. The purpose of an exact treatment of NMR relaxation is to allow the relaxation estimates to be used as if they were measurement data, in further mathematical modeling in the nature of nonlinear estimation. For this purpose it is necessary that the values estimated be unbiased and that reasonable estimates of the standard deviation of each estimate be available. Spectral estimation of NMR relaxation provides a rigorous mathematical framework in which this can be achieved.

Sincerely,

David Naugler
dnaugler@sfu.ca

Robert J. Cushley
cushley@sfu.ca

[1] Dr. Richard Lockhart, private communication.
[2] Dr. Jonathan Borwein, private communication.

UNIVERSITY OF THE PACIFIC

18 51

College of the Pacific

Department of Chemistry

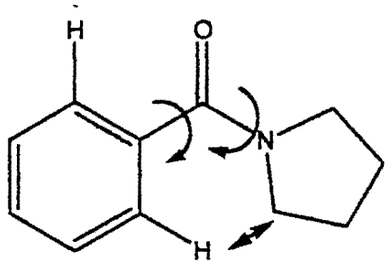
Dr. B. L. Shapiro
The NMR Newsletter
966 ElsinoreCourt
Palo Alto, CA 94303

(received 5/24/99)

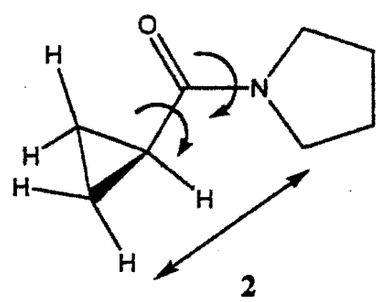
Amide Bond Rotation in a Teaching Experiment

Dear Barry

Many of your readers have as part of their responsibility the training of NMR users often in a formal course. At UOP we offer a course on NMR theory and practice combined with molecular modeling and stereochemistry for advanced undergraduates and graduate students. As the final activity in this course we require students to work on a project that combines as many NMR techniques as possible to resolve the conformational features of some small but interesting molecule and to compare these results with predictions obtained by molecular mechanics or dynamics calculations. One such set of problems is the amide bond rotation in pyrrolidine amides **1** and **2**.



1



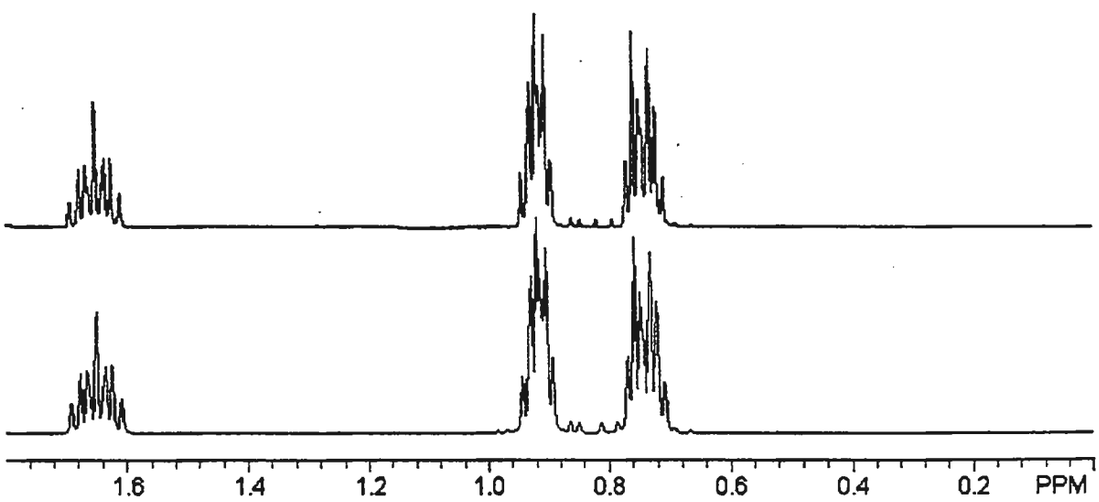
2

Yes, there are thousands of amide bond rotations described in the literature, why burden the world with another one? This project is interesting because there are multiple coalescence temperatures to give $\Delta G^{\ddagger}_{rot}$ at various temperatures, and one can combine lineshape measurements and DNMR simulations to get a fairly detailed picture of this rotation rate across a wide temperature range. Moreover truncated NOE measurements can be used to probe the average distance between nearby protons as a function of temperature. The four methylene proton pairs of the pyrrolidine ring appear as separate resonances for each compound and these resonances broaden then merge with temperature. Students H. V. Pham and Ting Wang showed from the temperature dependence of the proton spectra of **1** that the β-methylene multiplets merge at +37.7° and the α-methylene triplets merge at +61.5° C. When the ortho resonances are irradiated in a series of NOEDIF experiment with variable irradiation times, the α and α'-methylene signals (they are separated by 0.2 ppm at lower temperatures) show different buildup curves; the difference being more pronounced at lower temperatures. At low temperature (-30°)

3601 Pacific Avenue, Stockton, California 95211 • (209) 946-2271

only one of the α-methylene proton pairs shows a significant NOE (5%) which builds up quickly. At higher temperatures both just above and just below the coalescence temperature the observed NOE is small (1%) with a slow buildup. MM+ (Spartan) calculations show that in the energy minimized structure one of the ortho protons is quite close to one pair of α-methylene protons (2.39 and 3.09 Å) and to the other significantly more distant (4.45 and 5.09 Å). At low temperature where the rate of amide bond rotation is slow, the buildup is rapid and the NOE between the nearby protons is strong. At higher temperatures the average geometry is different but there is more to the problem. A theoretical treatment is far from trivial for the transfer of saturation in two-site exchange, where each pair of methylene protons is scalar coupled to one of two other pairs of methylene protons that are also exchanging positions. This is the sort of student project that is open-ended and requires students to pull together all sorts of diverse material.

The cyclopropylcarboxamide **2** presents yet another interesting issue. The coalescence behavior at high temperatures is similar to that of **1** but the temperatures are significantly higher (90° and >100° C). Moreover the cyclopropyl proton resonances also change as a function of temperature. At 25° we have the observed and calculated cyclopropyl proton resonances given below permitting a complete assignment of this five spin system. At higher temperatures the protons resonating at 0.9 ppm become a broad singlet. At lower temperatures the NMR can only be rationalized if all five cyclopropyl protons are non-equivalent.



Andreas Franz has rationalized these observations by calculating the potential energy surface defined by the two dihedral angles in structure **2**. There are two low energy orientations of the cyclopropyl ring with respect to the amide bond and each of these structures differs in the distances between the protons for one side of the five- and six-membered ring systems and that of the other side. A complete treatment is in preparation but this note may suggest that student teaching projects may lead to interesting things.

Respectfully

Mike Minch — Andreas Franz — Ting Wang — H. V. Pham

NEW

LOW COST DISPOSABLE NMR TUBES DESIGNED FOR HIGH THROUGHPUT NMR

WILMAD=NMR

WHY TAKE A CHANCE IN USING DISPOSABLE TUBES THAT COULD HAVE QUALITY VARIATION OR PHYSICAL DEFECTS RESULTING IN TUBE FAILURE?

Can your current tube manufacturer assure you that each tube is individually tested to pass all specifications, including a glass stress test? **Wilmad, the world leader in NMR tube manufacturing**, uses advanced laser technology to measure every single tube to specification.

We also test every tube for glass stress by utilizing a scanner that uses polarized light to check for defects. Every tube is checked and must meet our critical standards, or it is rejected. Don't take a chance with a tube manufacturer that cannot claim these high standards.

WILMAD NMR TUBES OFFER...

- Manufactured under Wilmad's strict quality standards
- Every tube checked using advanced laser technology
- Stress checked for physical defects that could result in tube failure
- Ideal for auto-samplers or High Throughput NMR
- Manufactured from quality borosilicate glass
- Scouting and one time use at an affordable price

Catalog No.	Tube Length	Tube O.D.	1-4 Packs**	5-9 Packs**	10 Packs**
HIP-7*	7"	5 mm	$95.00	$90.00	$85.00
HIP-8*	8"	5 mm	$105.00	$100.00	$95.00

* Tube Caps are not included, order tube caps separately under part no. 521-100, priced $3.50 per 100 caps. (specify color when ordering)
** One pack contains 100 tubes

PLACE YOUR ORDER NOW: 1-800-220-5171

WILMAD® LABGLASS™

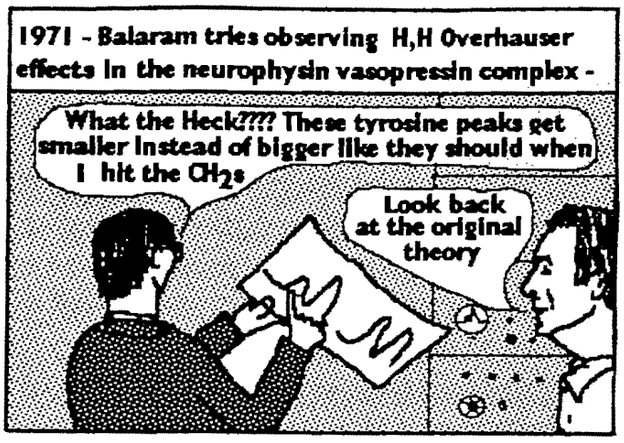
an SP Industries Company

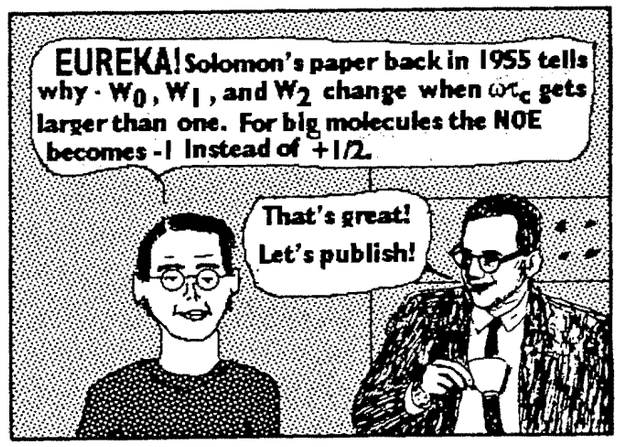
PO Box 688 • Buena, NJ 08310
Ph: 609-697-3000 • Fax: 609-697-0536
email: cs@wilmad.com

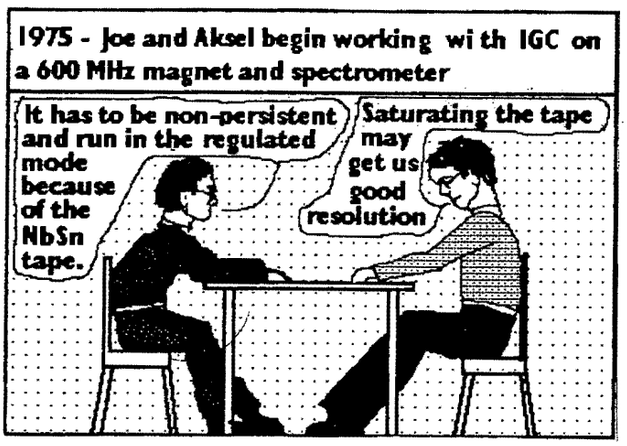
For further information...
VISIT OUR WEBSITE
www.wilmad.com

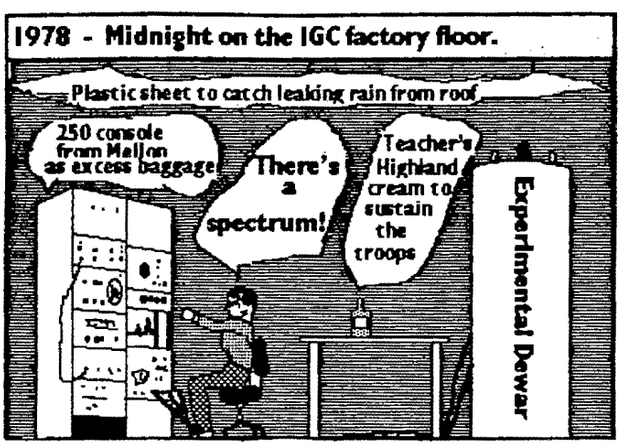
W 1/99 14K – SM 10K

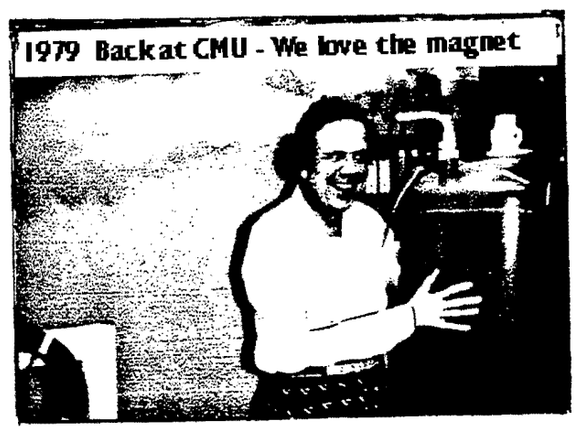
40 YEARS IN SHOW BUSINESS









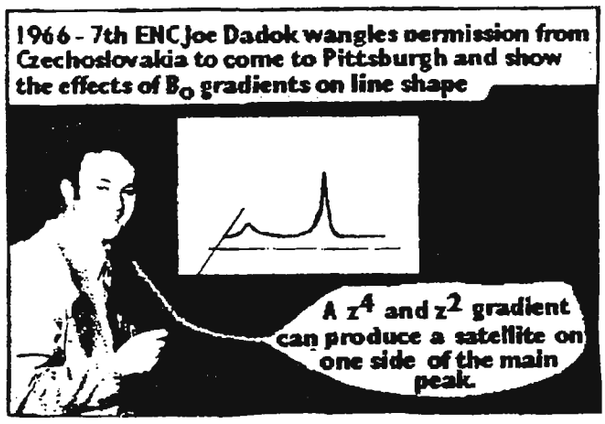


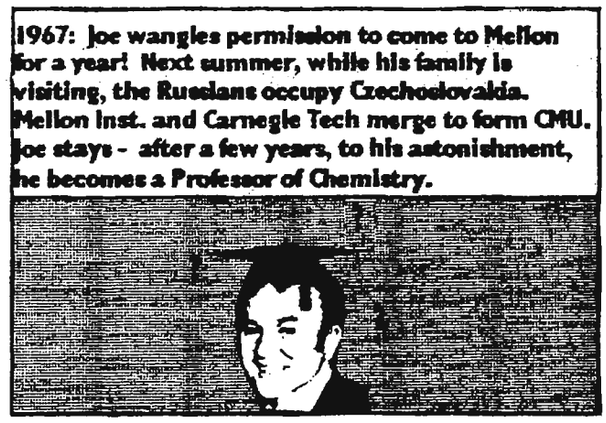
21 June 1999
Aksel A. Bothner-By
ab6d@andrew.cmu.edu

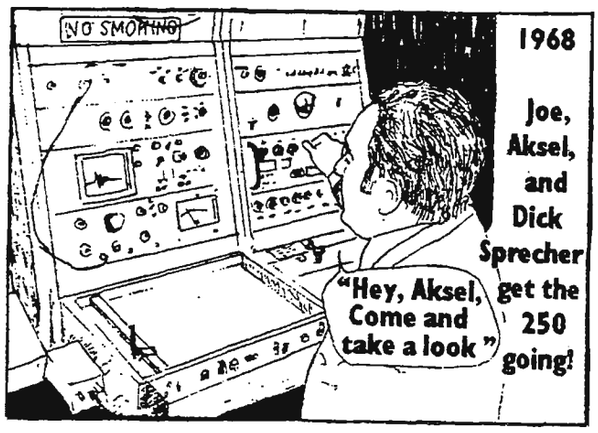
40 YEARS IN SHOW BUSINESS

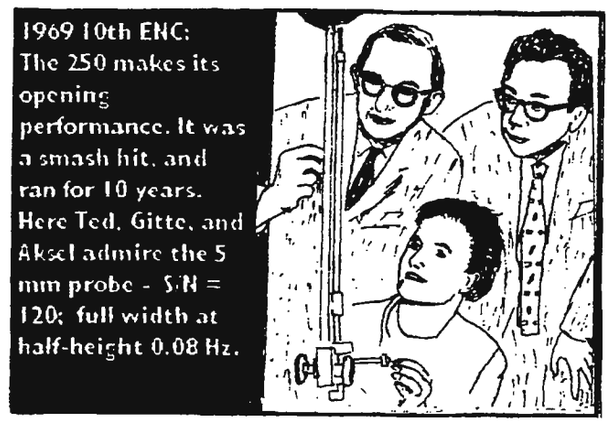
Dear Barry: Episode 3

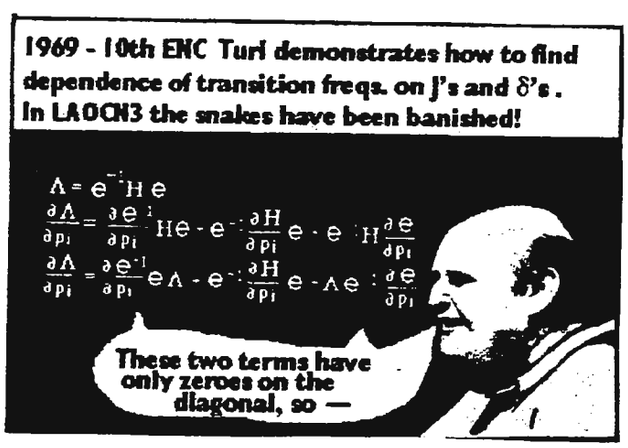
(received 6/23/99)

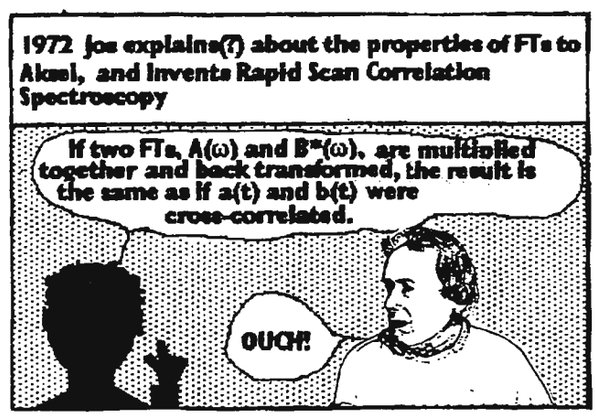












UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

Michael J. McCarthy
Department of Food Science and Technology
University of California
One Shields Avenue
Davis, California 95616-8598

TELEPHONE: (530) 752-8921
TELEFAX: (530) 752-4759
mjmccarthy@ucdavis.edu

(received 6/4/99)

Dr. B.L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303-3410

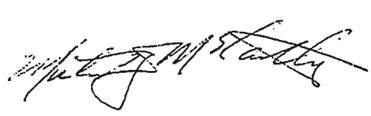
Dear Dr. Shapiro:

Detection of internal browning in 'Fuji' apples using NMRI.

Internal disorders in fresh fruits and vegetables result in significant losses to growers, packers, sellers and consumers. We have been investigating the use of NMRI as an in-line sensor for detecting defects if fruits and vegetables. The development of a nondestructive imaging sensor would be beneficial to packinghouses, as it would facilitate testing of representative samples or sorting of entire lots of apples and other agricultural products before marketing or further storage.

We utilized NMRI to detect internal browning, IB, an internal postharvest disorder that affects 'Fuji' apples (*Malus domestica*). The apples most susceptible to this type of disorder are those that have been harvested late in the season and stored in controlled atmospheres (CA). We carried out spin echo based NMRI experiments on apples which were stored in two CA: 3% CO_2 at 0° C and 18% CO_2 at 20° C in order to detect and monitor the progression of internal browning (IB). The NMR images of apples with IB detected three distinct regions: healthy, light and dark IB tissue. The in-plane spatial resolution of the images was 0.5 mm. Light brown regions had lower signal intensity than healthy tissue, whereas dark brown regions displayed the highest signal intensity (Fig 1). T_2 and proton density maps (Fig 2), revealed that the difference in signal intensity corresponded variations in proton density and T_2 values among the different regions. Low proton density and T_2 values of light IB regions explained their low signal intensity in the NMR image. Dark IB regions have significantly larger T_2 values than that of the other tissues and hence higher signal intensity in the NMRI images (the images were T_2-weighted). It is difficult to explain the difference in proton density and T_2 values among the tissues because the physiological changes that occurred during storage in CA are not understood.

Sincerely



Michael J. McCarthy

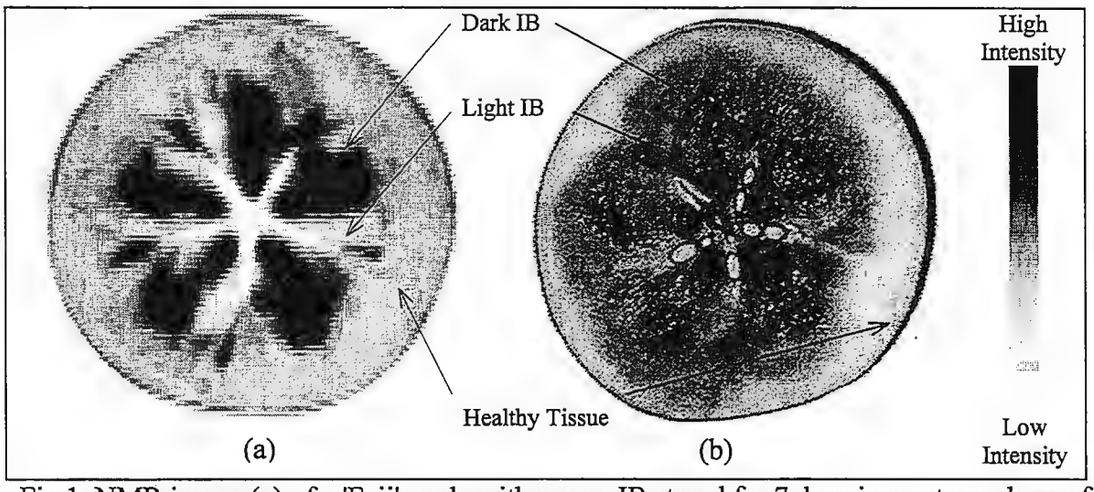


Fig 1. NMR image (a) of a 'Fuji' apple with severe IB stored for 7 days in an atmosphere of 18% CO_2 at 20°C. A photograph (b) of the same apple cut open immediately after the NMRI experiment.

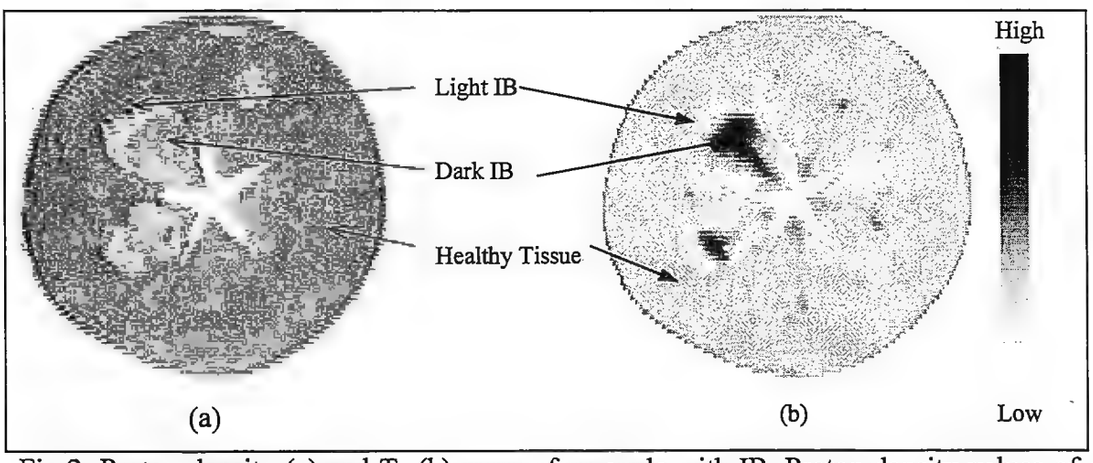
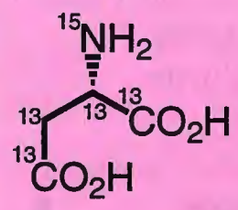
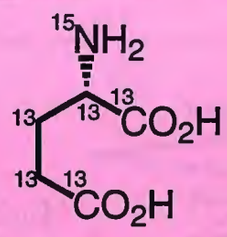


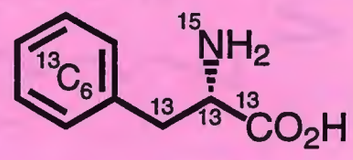
Fig 2. Proton density (a) and T_2 (b) maps of an apple with IB. Proton density values of normal tissue are larger than those of dark and light IB. T_2 values of dark and light IB and healthy tissues are 230 ± 20, 37± 7 and 54 ± 5 ms, respectively.



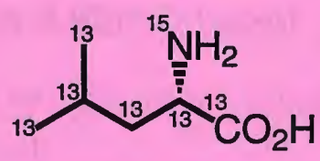
L-Aspartic Acid-$^{13}C_4$, ^{15}N



L-Glutamic Acid-$^{13}C_5$, ^{15}N



L-Phenylalanine-$^{13}C_9$, ^{15}N



L-Leucine-$^{13}C_6$, ^{15}N

The fully ^{13}C, ^{15}N labelled amino acids shown above are just a few examples of the extensive line of laballed amino acids that Isotec offers.

A Comprehensive Line of Fully ^{13}C, ^{15}N Labelled Amino Acids

From the Premier Producer of Isotopically Labelled Amino Acids

ISOTEC, the world's leading producer of isotopically labelled compounds continues to expand its extensive product line. Isotec offers a comprehensive line of fully ^{13}C, ^{15}N labelled amino acids for different applications including the production of specifically labelled proteins and polypeptides.

Please request information on the availabillity of fully ^{13}C, ^{15}N labelled amino acids and their derivatives including N-FMOC, N-t-BOC & CBZ.

THE ISOTEC ADVANTAGE

As the world's leading commercial producer of stable isotopes, including Carbon-13, Nitrogen-15, Oxygen-17 and-18, we provide our own starting material for the production of fully ^{13}C, ^{15}N labelled amino acids. We are expanding our Carbon-13 production capacity to meet your needs.

Our ability to separate and enrich more than 30 stable isotopes gives us a distinct advantage. We can be the one source for all of your stable isotope products, such as ^{15}N-Ammonium salts, D-Glucose-$^{13}C_6$, D-Glucose-^{13}C, C-d_7, Isogro™ and fully ^{13}C, ^{15}N labelled amino acids for protein expression and polypeptide synthesis. With the entire production process under our control, you can count on consistent, high quality products that are always available.

FULLY ^{13}C, ^{15}N AMINO ACIDS INCLUDES

L-Alanine-$^{13}C_3$, ^{15}N
L-Arginine-$^{13}C_4$, $^{15}N_4$
L-Asparagine-$^{13}C_4$, $^{15}N_2$
L-Aspartic Acid-$^{13}C_4$, ^{15}N
L-Glutamic Acid-$^{13}C_5$, ^{15}N
L-Glutamine-$^{13}C_5$, $^{15}N_2$
Glycine-$^{13}C_2$, ^{15}N
L-Isoleucine-$^{13}C_6$, ^{15}N
L-Leucine-$^{13}C_6$, ^{15}N
L-Lysine-$^{13}C_6$, $^{15}N_2$
L-Phenylalanine-$^{13}C_9$, ^{15}N
L-Serine-$^{13}C_3$, ^{15}N
L-Threonine-$^{13}C_4$, ^{15}N
L-4-Hydroxyphenylalanine-$^{13}C_9$, ^{15}N
L-Valine-$^{13}C_5$, ^{15}N

For more information, technical assistance, or to place an order, please call us toll-free at **1-800-448-9760**.

ISOTEC INC.
3858 Benner Road
Miamisburg, OH 45342 U.S.A.
(937)859-1808
Fax (937)859-4878
isosales@isotec.com
http://www.isotec.com

ISOTEC INC.
A Matheson, USA Company
PROMOTING RESEARCH AND DISCOVERY

18 June 1999 (received 6/19/99)

Bernard L. Shapiro
Editor, The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

VARIAN

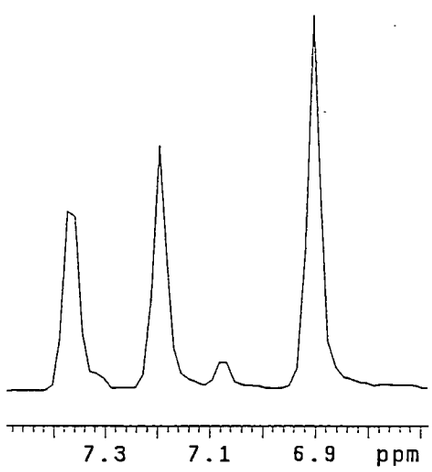
Carbon Pulse Widths For 800 MHz Applications

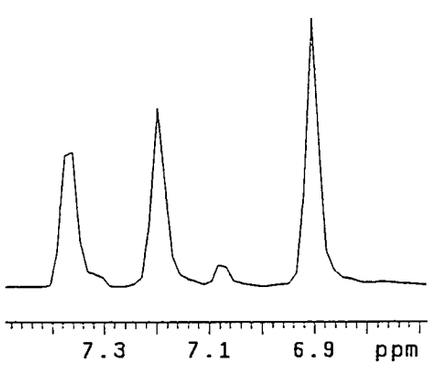
Dear Barry,

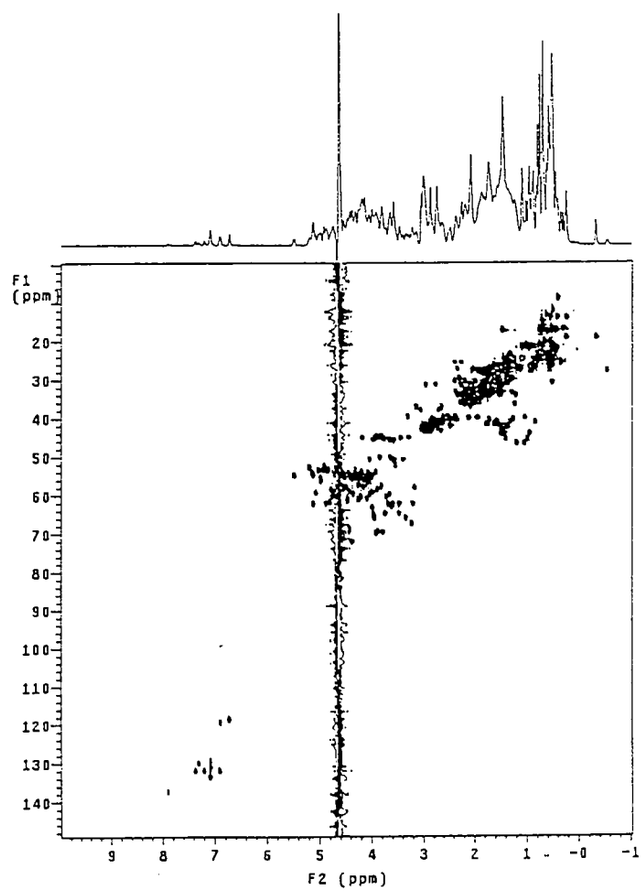
Recently we quantified the increased sensitivity across the carbon bandwidth as a result of short 90 degree carbon pulse widths with the Varian Inova 800 MHz NMR spectrometer in the department of Structural Biology at Stanford University. The customer's probe was the newest generation of 5mm triple axis (XYZ) gradient, triple resonance (^{1}H,^{13}C,^{15}N and ^{2}H) 800 MHz probes. The Inova console was equipped to provide up to 1 kWatt of power for both the carbon and the nitrogen channels.

The first set of experiments was proton-carbon single quantum correlation. In addition to careful power and pulse width calibrations, the goal of the exercise was to quantify the improved sensitivity with a 7.7μs carbon 90 degree pulse as compared with a 9.7μs carbon 90 degree pulse. The proton 90 degree pulse width was 6.5μs. The nitrogen 90 degree pulse width was 27μs. Carbon decoupling was accomplished with an adiabatic WURST-style modulation sequence with an effective bandwidth of 30 kHz. The sample was 850μM ^{13}C,^{15}N labeled ubiquitin in 90% H_2O/10% D_2O.

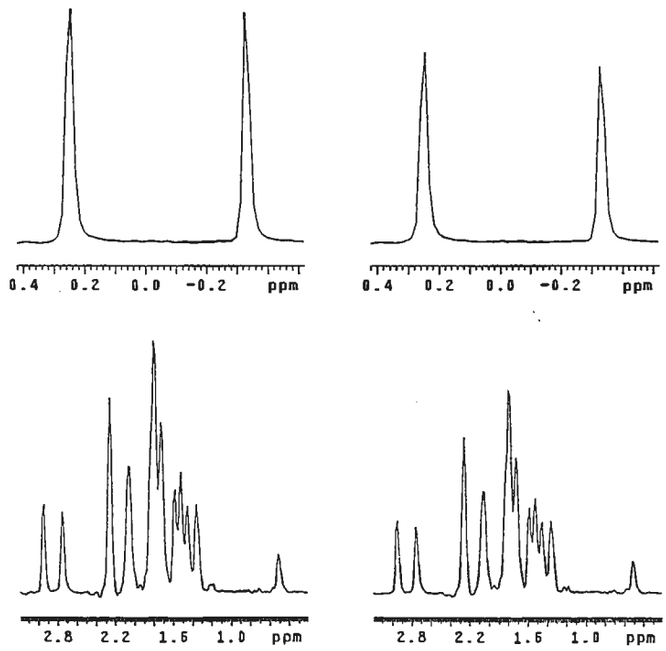
The 2D ^{1}H-^{13}C HSQC is shown below (right) in order to orient the traces in the carbon dimension. The results from selected traces follow. The first trace, from the aromatic region at F1=132 ppm, shows in the range of 35% sensitivity improvement for the 7.7μs pulse (top left) as compared with the 9.7μs pulse (bottom left). The carbon transmitter was centered at 70 ppm.



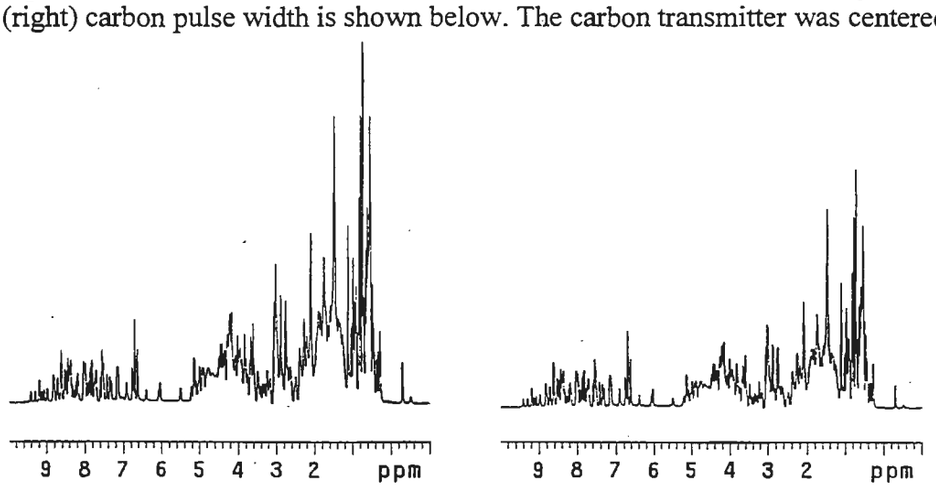




490-38 The trace from the methyl region at F1=19 ppm (top) and the trace from the alpha/beta region at F1=31 ppm (below), show 28% and 16-26%, respectively, sensitivity improvement with the shorter carbon 90 degree pulse. The results from the 7.7μs pulse (left) and the 9.7μs pulse (right) are shown below.



The second experiment was CN-NOESY-HSQC with simultaneous carbon and nitrogen pulses and simultaneous decoupling during acquisition. The nitrogen 90 degree pulse width was 27μs. The nitrogen decoupling field was 1 kHz. GARP decoupling was used. Carbon decoupling was accomplished with an adiabatic sequence with a bandwidth of 30 kHz. First increment CN-NOESY-HSQC with a 7.7μs (left) and 9.7μs (right) carbon pulse width is shown below. The carbon transmitter was centered at 67 ppm.



The degradation in sensitivity, across the entire carbon bandwidth, for carbon pulse widths in the neighborhood of 10μs, was investigated in order to quantify the benefits of much shorter pulses for 800 MHz applications.

Sincerely,

Debbie

Debbie Mattiello
Scientist

Matt

Matt Commens
Probe Engineer

Mark

Mark Van Criekinge
Systems Engineer

Mobil Technology Company

MARKETING, REFINING AND CHEMICAL
TECHNICAL CENTER (MRCTEC)
P.O. BOX 480
PAULSBORO, NEW JERSEY 08066-0480

June 17, 1999

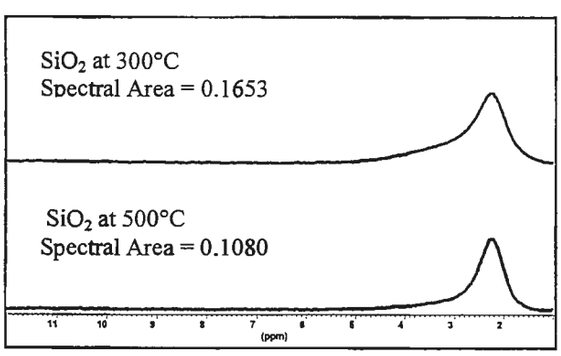
(received 6/21/99)

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

Solid state ^{1}H NMR methodology to measure absolute silanol contents on a silica support.

High resolution ^{1}H MAS NMR techniques are now routinely used to study the various distinct hydrogen species in many commercially important inorganic solids such as zeolites, silicas, and aluminas. The quantitative characterization of these protons is important because they are expected to relate to the catalytic and sorption properties of the material. However, the absolute quantitation of the various proton types in these systems has been difficult. The two major hurdles are the preparation of suitable absolute quantitation standards and to exclude water that will obscure the resonances of interest. Described in this contribution are details of a NMR methodology to quantitatively measure absolute hydrogen contents in solid supports and some representative examples of the application of this methodology.

The key factors in sample preparation for the NMR measurements are the exclusion of water and accurate sample weights. All NMR sample preparation (i.e. packing of MAS rotors) is done in a dry box. All samples are packed into 7.5mm Pencil® rotors that are previously dried at 300°C for 12 hours under vacuum. The rotor drive tips and end caps are dried overnight at room temperature under vacuum in the dry box antechamber. Weights are recorded on the empty and packed rotors, sample weight determined by difference. The external standard chosen for this work is an 83.8/16.2 mixture of D_2O (99% deuterated) and H_2O, resulting in a 17.038 % H_2O solution. The absolute quantitation standard was a 0.1067g aliquot of this standard mixture. This aliquot was sealed in a Kel-F® insert specially designed to fit inside a MAS rotor. The absolute amount of hydrogen in this aliquot is calculated to be equal to 2mmole of H. Shown below are representative ^{1}H MAS NMR spectra of silica supports that have been dehydroxylated at 300°C and 500°C.



The absolute amount of H in each sample is determined by directly ratioing the experimental spectral areas to that of the quantitation standard and then weight normalizing. This results in absolute SiOH contents of 1.10 and 0.71 mmole/g for the 300°C and 500°C silicas, respectively. As expected, the absolute silanol contents decrease with increasing dehydroxylation temperature. These values determined directly by H NMR are in excellent agreement with indirect wet chemical determinations.

This direct spectroscopic approach should be generally applicable and is being extended to quantitatively measure the various chemically distinct hydrogen types in other inorganic materials.

Gordon J. Kennedy

Gordon J. Kennedy

NEW MEXICO RESONANCE
A nonprofit research corporation

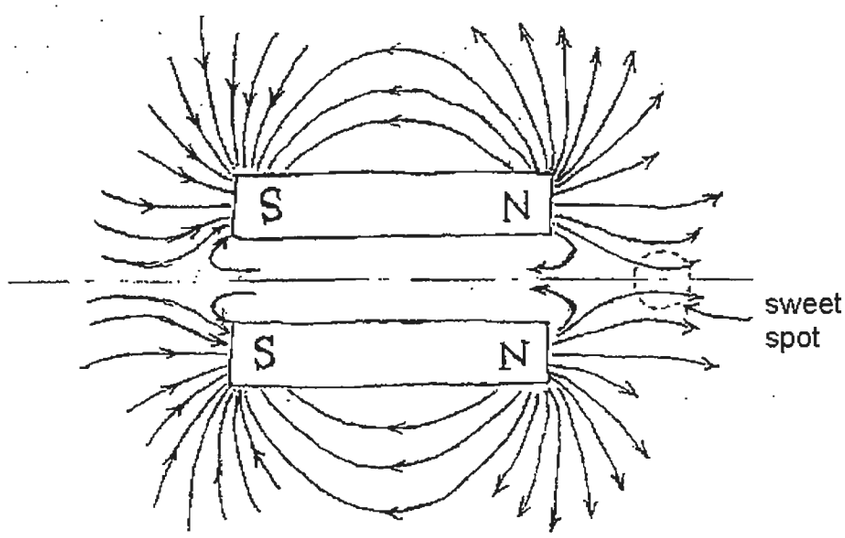
(received 6/23/99)
June 22, 1999 Unilateral magnets: An idea and some history

Dear Dr. Shapiro,

We at New Mexico Resonance still like to do "odd-ball" NMR. Our "normal" NMR studies of complex fluid flows is odd enough but we are now interested in outside-the-laboratory NMR in weak magnetic fields. Because of the novelty, we will embellish our project description with some history as we know it; it is incomplete but, we hope, interesting.

Due to space limitations, we will only mention, in passing, "sophisticated" experiments that are essentially laboratory experiments done under severe conditions such as MRI [J. Stepisnik, et al., MRM 15, 386 (1990)] and PGSE diffusion measurements [P. T. Callaghan, et al., RSI 68, 4263 (1997)] in earth's field. We will also not cover bore-hole devices that are extensively used by oil industry. Reference is made to a comprehensive description by Bob Kleinberg in Encyclopedia of Nuclear Magnetic Resonance.

We got our idea, however, from one of the bore-hole instruments [R. L. Kleinberg, et al., JMR 97, 466 (1992)]. They use a pair of permanent magnet slabs as shown in the sketch of a transverse cross-section. A pair of magnets arranged in that way will have a region removed from each set of poles where the field lines converge before diverging, thus providing a local maximum (which is actually a saddle point). The magnets are arranged in such a way that NMR signals can be obtained from a line parallel to but outside the bore-hole.

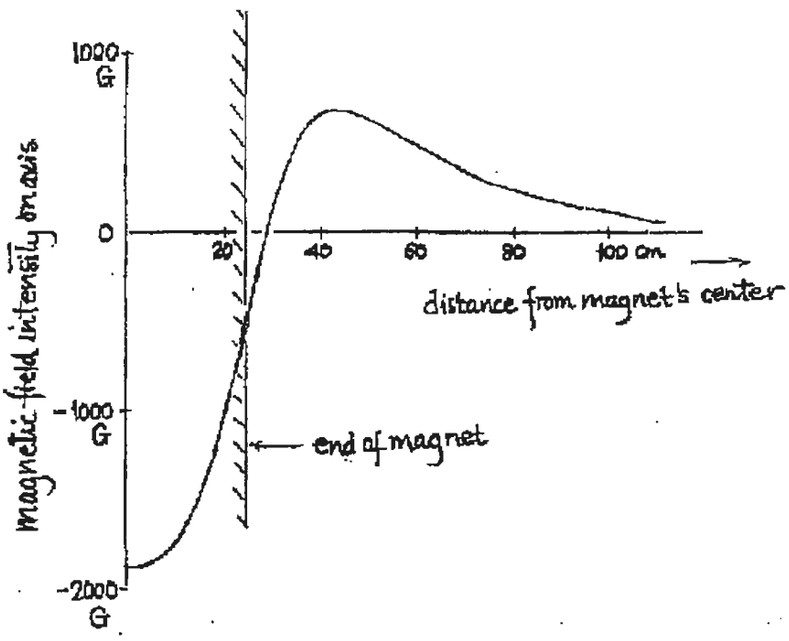


Consider the arrangement in the sketch to be of a pair of bar magnets (rather than slabs that extend out of the paper). Now add additional identical pairs, rotated about the two-fold axis to get a stronger field at the sweet spot. Thus, the permanent magnet pairs will lie within a hollow cylinder whose diameter is equal to the separation between the bar magnets. The strongest field will result when the hollow cylinder is 100% filled with the magnetic material

2425 Ridgecrest Drive SE • Albuquerque, New Mexico 87108-5127
Phone: (505) 262-7575, ext. 5025 • Fax: (505) 262-7043
http://nmr.org/

with opposite ends of the cylinder being opposite poles. There are many variants to this basic idea: nested cylinders, an additional dipole at the center, pairing up these things to make an "open architecture" magnet, etc.

We present computer simulations of a hollow tube of NdFeB that is 50 cm long with outer diameter 60 cm and wall thickness 10 cm. The sketch below shows the magnetic field along the axis with the origin at the center of the magnet. It is negative inside the tube but reaches a maximum of 675 gauss, 19.4 cm past the end of the cylinder. The distance to the sweet spot scales with the overall size of the tube and the field strength at the sweet spot is independent of the magnet size if everything, including the amount of magnetic material, scales.



We are designing a prototype, not with a solid hollow cylinder of magnetic material but with "columns" of 5 x 5 x 2.5 cm NdFeB blocks that are commercially available. We hope to make a magnet of overall cross-section of 40 cm with a remote spot around 15 cm past the end of the magnet. The magnet will be mounted under a table so we can place samples on top. We will not cover the subject of the rf coil, in this note.

So, what is the history of remote NMR and what are the potential uses for such a magnet? Closely related past applications include several projects at Southwest Research Institute (SwRI) and recent applications of NMR MOUSE from the Aachen group. The SwRI efforts, initiated by the late Bill Rollwitz, included a tractor-driven NMR device that monitored moisture just below the ground surface as well as an instrument that monitored drying of concrete. [Design News, May 5, 1986: One-sided NMR sensor system.measures soil/concrete moisture.] Other SwRI applications include mine detection and aging and moisture measurements in asphalt. The applications that demonstrate unique advantage of the MOUSE include examination of car tires (even with steel cords!) and thin PVC coatings on iron sheets (!). [See, for example, Magn. Reson. Imaging 16, 479-484 (1998).]

The SwRI and Aachen devices are essentially U-shaped magnets (similar to horse-shoe magnets) with a surface coil between the ends of the U. The maximum in the field of a U-shaped

magnet along the symmetry axis is too close to the end to be useful. Therefore, these instruments are designed to detect the NMR signal in the decaying part of the field, similar to stray-field NMR (STRAFI). A Larmor frequency is chosen to localize the signal at a distance which is a relatively small fraction of the overall size of the magnet. For example, the SwRI devices were designed to detect moisture ~6 cm below the surface.

More than 25 years ago, there were proposals also from SwRI for unilateral magnets that projected a uniform, i.e., with first derivative equal to zero, field to one side. One design consisted of two identical circular loops of wire coaxially displaced from each other and carrying currents in opposite directions. The fields from the loops subtract differently at different distances along the axis, resulting in a local maximum outside the pair of loops.

Alan Rath came up with an "inside-out-Helmholtz (IOH)" design in his thesis some years back. [RSI 56, 402 (1985).] It uses the fact that the magnetic field along the axis of a circular loop has an inflection point at ½ of the radius. [The Helmholtz coil uses two identical loops separated by a radius so the inflection points from the two loops overlap, making the first three derivatives zero.] The IOH design takes two unequal size loops, axially offset from each other so that the inflection points coincide on one side of the pair (rather than between the loops). The currents flow in opposite directions and their magnitudes are adjusted to make the first derivatives equal and opposite. The second derivatives are zero by definition so the first nonzero derivative is the third. This magnet has never been built. Because the formalism holds for an idealized loop of wire, the effect is not so clean for any real wires with significant cross-sections.

There have been other efforts at unilateral NMR as reflected by some US patents, e.g., Pissanetzky, 1995 (5,382,904) and Pulyer, 1998 (5,744,960).

It is clear that unilateral magnets can not be as homogenous nor generate as strong a field as "bilateral" magnets because they sacrifice bilateral symmetry. Therefore, the most appropriate uses, at least for the time being, are to detect whether something is there or not and how much is there. Another use would be to monitor changes rather than make absolute measurements. Applications include "remote" sensing of materials behind barriers for reasons of extreme temperatures, toxicity, sensitivity to air, geometrical confinement for transport or storage, etc., as well as large objects that will not fit into a magnet. Another possibility is to pair these unilateral devices and hope for a very wide-gap magnet with good field homogeneity.

In summary, our "invention" advances the art of remote sensing NMR by significantly increasing the relative distance out to the sweet spot. Several hundred gauss can be obtained at approximately 1/3 of the diameter along the axis. The field homogeneity and the localization at the sweet spot are not the greatest because it is only a saddle point. However, these parameters can be improved with shim coils and with rf coils that have different field profiles than the magnet.

We thank Armando De Los Santos for providing a summary of SwRI activities in this area over the past 25 years.

Sincerely,

Eiichi Fukushima and Jasper Jackson

The NMR Newsletter - Book Reviews

Book Review Editor: István Pelczer, Dept. of Chemistry, Princeton University, Princeton, NJ 08544

"Basic One- and Two-Dimensional NMR Spectroscopy"

by

Horst Friebolin

Translated from the German by **Jack K. Becconsall**

3rd, revised edition; Wiley-VCH (www.wiley.com); 1998. ISBN 3-527-29513-5; US$59.95

Today's NMR methods and instrumental equipment offer possibilities almost beyond the imagination just two decades ago. However, there is a price to pay for an ability to use the wonderful tools of modern NMR spectroscopy. Anyone wishing to use them with reasonable efficiency needs to acquire a solid knowledge of basic principles as well as of an array of experimental techniques. This is the point where Professor Friebolin's book comes to the rescue.

Basic One- and Two-Dimensional NMR Spectroscopy is exactly what the title says, namely a basic textbook for a beginner or someone who needs to refresh the understanding of the basics and/or to expand his/her repertoire of NMR techniques. The book deliberately refrains from using complicated mathematics so as not to scare away its intended audience – synthetic organic chemists. Indeed, the mathematical

What every organic chemist should know about NMR.

sophistication of the book does not go beyond logarithms. Superoperator-lovers and density matrix aficionados need to turn elsewhere. The approach works most of the time. The only real problem arises with the polarization transfer, which cannot be adequately explained using just magnetization vector diagrams. Here the reader simply has to believe that the spin system behaves as described.

The author treats the subject in 14 chapters. The first three deal with the fundamentals: the physical basis (1), the chemical shift (2) and indirect spin-spin coupling (3). Then, the attention turns to extracting information from the spectra in chapter 4 (spectrum analysis and calculations), chapter 5 (double resonance experiments) and chapter 6 (assignment of ^{1}H and ^{13}C signals). Relaxation is discussed separately in chapter 7. The next two chapters are devoted to more advanced techniques – one-dimensional methods in chapter 8 and the two-dimensional ones in chapter 9. These two chapters are the longest in the book with 48 and 54 pages, respectively. Separate descriptions of the nuclear Overhauser effect (chapter 10) and dynamic NMR spectroscopy (chapter 11) follow. Traditionalists will be pleased to see the chapter 12 on shift reagents alive and well into the time of triple-resonance experiments and magnetic fields approaching 1 GHz. The book concludes with a brief treatment of macromolecules (synthetic polymers only, chapter 13) and NMR spectroscopy in biochemistry and medicine (chapter 14, including *in vivo* spectroscopy and tomography but not the spectroscopy of proteins and nucleic acids).

continued

The greatest asset of the book is, in my opinion, in the clear and detailed description of the multipulse experiments. It provides the reader with an intuitive understanding of the processes without the need to perform any calculations. Suitable examples and hints then accompany the theoretical explanations on the use of the particular method in practice.

With a concise treatment on just 386 pages (including an 8-page Subject Index and a 4-page Index of Compounds), the author obviously needs to skip a lot of details, and any opinion on what should be included is necessarily a matter of personal taste. I myself miss two things in the book: at least a basic explanation of phase sensitive 2D spectra and the ROESY experiment as an alternative to NOESY for medium sized molecules. Others could argue for including the principles of multiple-quantum spectroscopy, long-range heteronuclear correlation experiments, inverse detected editing techniques or NMR of the nuclei other than ^{1}H and ^{13}C, especially ^{15}N. Overall, however, *Basic One- and Two-Dimensional NMR Spectroscopy* is an excellent introductory book that every chemistry student should read.

Radovan Fiala
Laboratory of Biomolecular Structure and Dynamics
Masaryk University
CZ-611 37 Brno, Czech Republic.

NMR Lab Manager

The Department of Chemistry at the University of Iowa invites applications for an NMR Specialist position. This individual will assume technical operation, management, service, training, and maintenance of six superconducting NMR spectrometers (300-600 MHz). Applicants should hold a Ph.D. in chemistry, or a related science and have extensive experience in the area of NMR spectroscopy. A minimum of three years of experience as an NMR spectroscopist is expected. The individual must have experience with application of modern NMR techniques to solve chemical problems. Familiarity with NMR hardware and software is essential. Excellent interpersonal, communication, and instructional skills are expected. The individual must have an ability to function in a service role, but should also have an interest in professional growth through technique development and collaborative activities. Other desirable qualifications include experience as an NMR facility manager, and familiarity with Bruker instruments, solid state NMR spectroscopy, solution gradient spectroscopy, and solution spectroscopy of biomolecules. Applicants should submit a letter of application, a resume, and have three letters of recommendation sent to: NMR Staff Search Committee, Department of Chemistry, University of Iowa, Iowa City, IA 52242 (FAX: 319 335-1270. e-mail: harold-goff@uiowa.edu). Screening of applications will begin August 16. *The University of Iowa is an Equal Employment/Affirmative Action employer. Women and minorities are encouraged to apply.*

Address all Newsletter correspondence to:

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303.
650-493-5971* - *Please call only between 8:00 am and 10:00 pm, Pacific Coast time.*

Deadline Dates

No. 491 (Aug.)	23 July 1999
No. 492 (Sept.)	20 Aug. 1999
No. 493 (Oct.)	24 Sept. 1999
No. 494 (Nov.)	22 Oct. 1999
No. 495 (Dec.)	26 Nov. 1999

* Fax: 650-493-1348, at any hour. Do not use fax for technical contributions to the Newsletter, for the received fax quality is very inadequate.

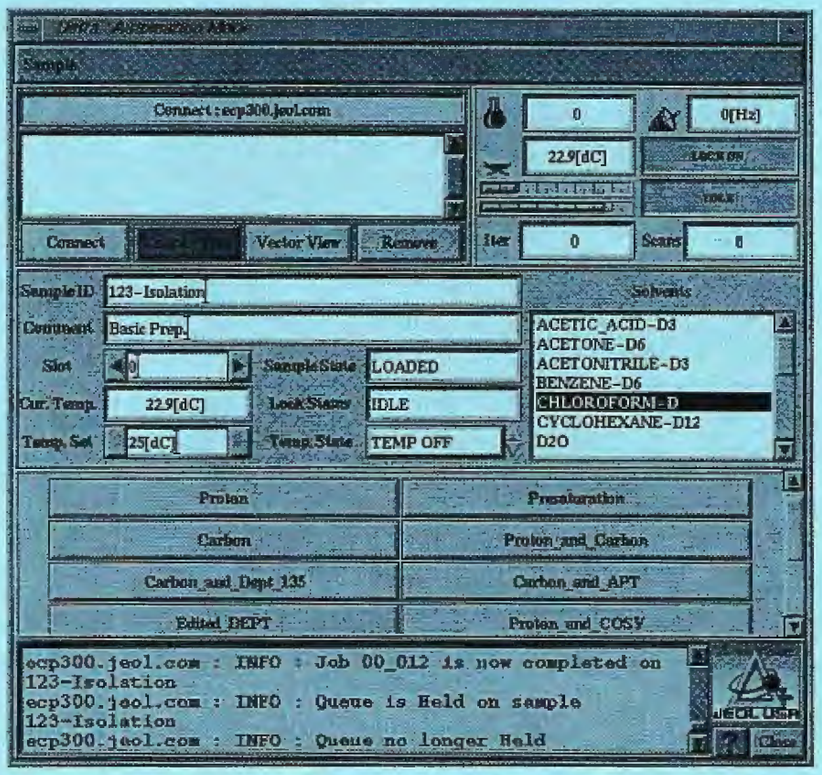
* E-mail: shapiro@nmrnewsletter.com

The Newsletter's fiscal viability depends very heavily on the funds provided by our Advertisers and Sponsors. Please do whatever you can to let them know that their support is noted and appreciated.

Mailing Label Adornment: Is Your Dot Red ?

If the mailing label on your envelope is adorned with a large **red dot**: this decoration means that you will not be mailed any more issues until a technical contribution has been received.

JEOL Can Give You the Data You Need From Your Desktop PC or MAC



The **Eclipse+** NMR Spectrometer can be operated anywhere there is a computer on the local network. The **Single Window Automation** pictured above can be used with a single mouse click to select the sample from the auto-sample changer, gradient shim on any probe, run the selected experiment, and plot the data on any network postscript printer. Need more data, click another button and the **Eclipse+** is off to do your work - and you have not left your office. Contact us at nmr@jeol.com or visit or web site at www.jeol.com.

JEOL USA, Inc., 11 Dearborn Road, Peabody, MA 01960
Tel: 978-535-5900 Fax: 978-536-2205
email: nmr@jeol.com www.jeol.com

JEOL