THE NMR NEWSLETTER

No. 473

February 1998

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PTS 120	90-120 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$5,330.00 (1 Hz resol., OCXO freq. std.)
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Type 1 PTS 310 Type 2	.1-310 MHz	1 Hz	1-20μs	standard	3½"H×19"W	BCD (std) or GPIB (opt)	1 Hz resol., OCXO: $6,425.00 1 Hz resol., OCXO: $5,850.00
PTS 500	1-500 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$8,720.00 (1 Hz resol., OCXO freq. std.)
PTS 620	1-620 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$9,625.00 (1 Hz resol., OCXO freq. std.)
PTS 1000	0.1-1000 MHz	optional .1 Hz to 100 KHz	5-10μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$11,830.00 (1 Hz resol., OCXO freq. std.)
PTS 3200	1-3200 MHz	1 Hz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$14,850.00 (1 Hz resol., OCXO freq. std.)
PTS x10	user specified 10 MHz decade	1 Hz	1-5μs	standard	3½"H×19"W	BCD (std) or GPIB (opt)	$3,000.00 (1 Hz resol., OCXO freq. std.)
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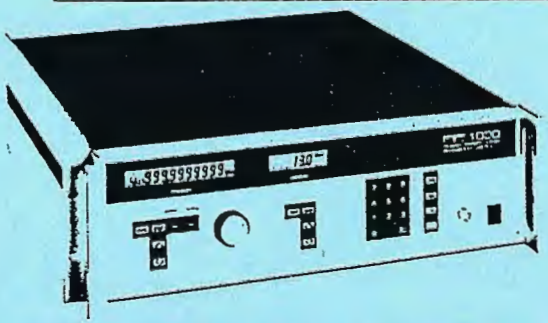

1 Switching Time is dependent on digit (decade) switched; see detailed instrument specifications.

2 For applicable digits, see detailed instrument specifications.

3 Bench cabinets are 17" wide.

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FORTHCOMING NMR MEETINGS

Tsukuba NMR 98, Tsukuba Science City, Japan, **March 10 - 12, 1998**. Contact: Professor Yoji Arata, Water Research Institute; +81-298-58-6183; Fax: +81-298-58-6166; e-mail: arata@wri.co.jp; http://www.wri.co.jp

39th ENC (Experimental NMR Conference), Asilomar Conference Center, Pacific Grove, CA, **March 22 - 27, 1998**; Contact: ENC, 1201 Don Diego Avenue, Santa Fe, NM 87505; (505) 989-4573; Fax: (505) 989-1073; Email: enc@enc-conference.org. See Newsletter 460, 41.

Sixth Scientific Meeting and Exhibition, International Society for Magnetic Resonance in Medicine, Sydney, Australia, **April 18 - 24, 1998**. Contact: International Society for Magnetic Resonance in Medicine, 2118 Milvia St., Suite 201, Berkeley, CA 94704; 510-841-1899.

NATO ARW "Applications of NMR to the Study of Structure and Dynamics of Supramolecular Complexes", Sitges (Barcelona), Spain, **May 5 - 9, 1998**. Contact: Prof. M. Pons, Dept. Quimica Organica, Univ. de Barcelona, Mart I Franques 1, 08028 Barcelona, Spain; http://www.ub.es/nato/nato.htm; e-mail: miguel@guille.qo.ub.es.

^{13}C in Metabolic Research, Symposium at the University of Texas Southwestern Medical Center, Dallas, Texas, **May 7, 1988**; For more information, contact Jean Cody at 214-648-5886 or www.swmed.edu/home_pages/rogersmr.

Workshop on Magnetic Resonance of Connective Tissues and Biomaterials, Philadelphia, PA, **June 18-20, 1998**; For more information. Contact International Society for Magnetic Resonance in Medicine, 2118 Milvia Street, Suite 201, Berkeley, CA 94704; (510) 841-1899; fax (510) 841-2340; info@ismrm.org; http://www.ismrm.org.

Fifth International Conference on Heteroatom Chemistry, London, Ont., Canada, **July 5 - 10, 1998**. For details, see Newsletter 468, 40.

XIVth International Conference on Phosphorus Chemistry, Cincinnati. OH, **July 12 - 17, 1998**. For details, see Newsletter 468, 40.

KARL-FRANZENS-UNIVERSITÄT GRAZ
Institut für Organische Chemie
Dr.Heinz Sterk

A-8010 Graz, 5.12.97
Heinrichstraße 28
Tel. (0316) 380 DW. 5321 bzw. 5320

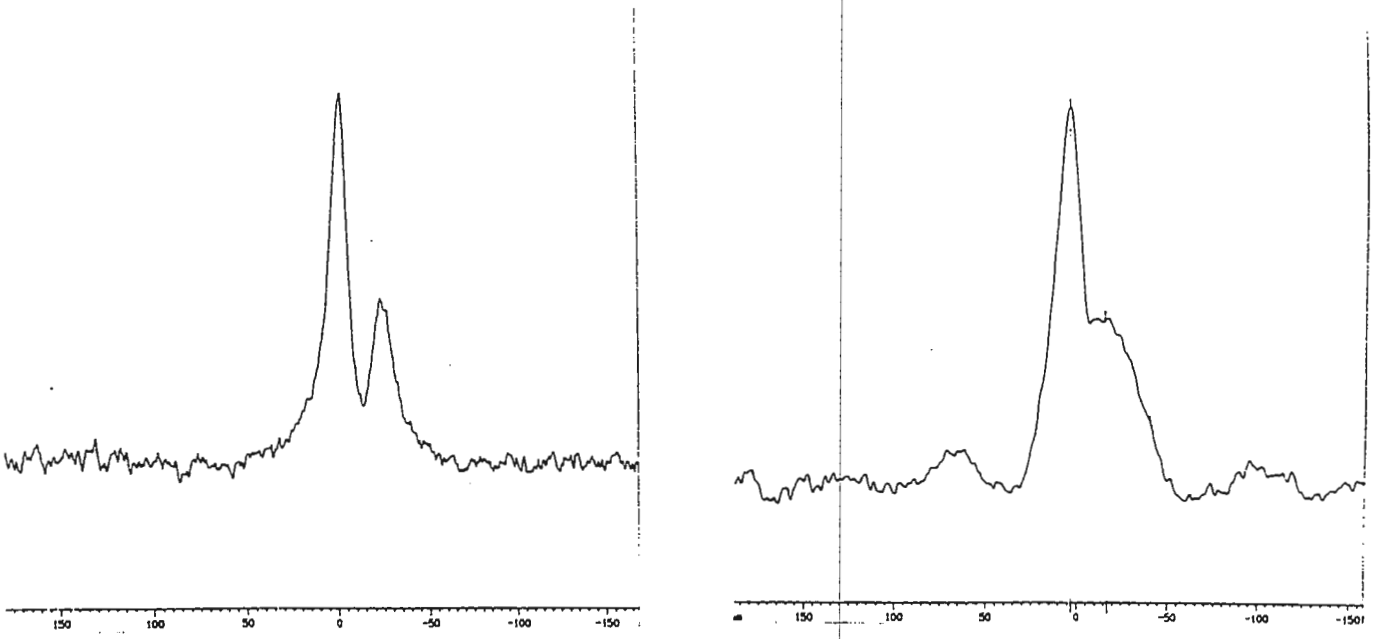
Unser Zeichen:
(received 12/26/97)

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

Potassium-Complexes

Dear Dr. Shapiro :

Very often questions about the strength of complex formation constants between complexing agents like crown ethers and alkali ions are being asked. In our case the difference between valinomycin, an peptide which is part of a potassium transport membrane protein, and the 18crown6 was of interest. To get information about the complex formation constants as well as about the competition between the two ligands, we titrated a mixture of both compounds with a potassium salt. Although potassium is not one of the well behaved nuclei, due to it´s quadrupol moment, it was more or less a straight forward exercise to get useable spectra. Thereby it turns out that 18crown6 - K complex has at least in $CHCl_3$ the higher complex formation constant than valinomycin and that the two species are in slow exchange as can be seen in figure1. Although the chemical shift differences are not huge, the intensities and shapes can be calculated easily and thus offer a chance to use this approach as a quick test on the different complex formation behaviours.



Yours sincerely

G.Stranzl

H.Sterk

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

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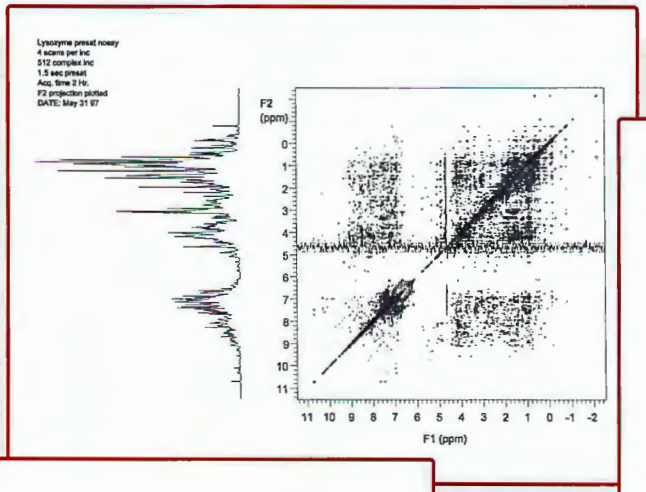
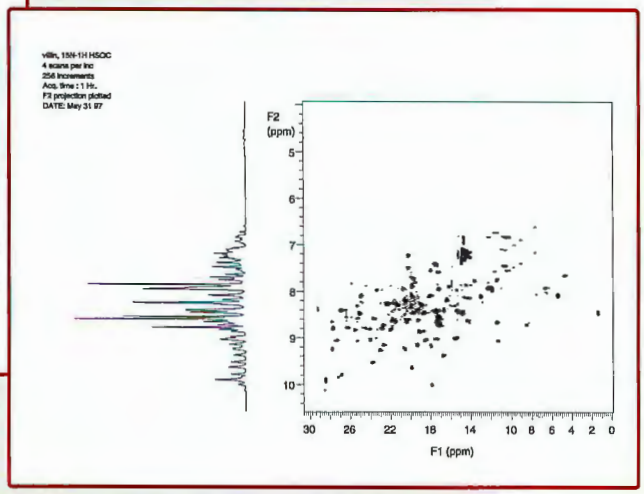
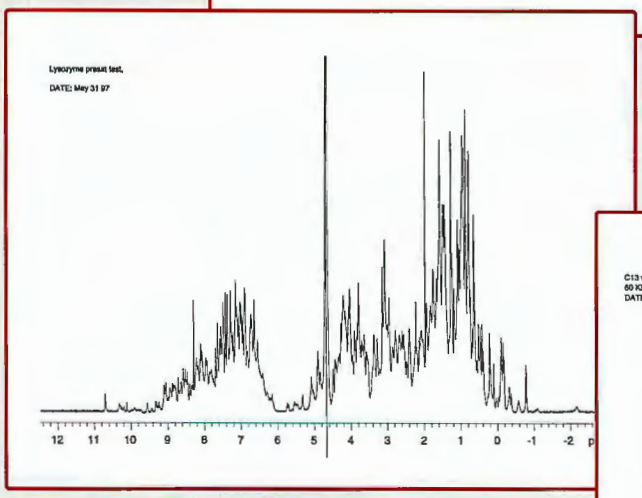
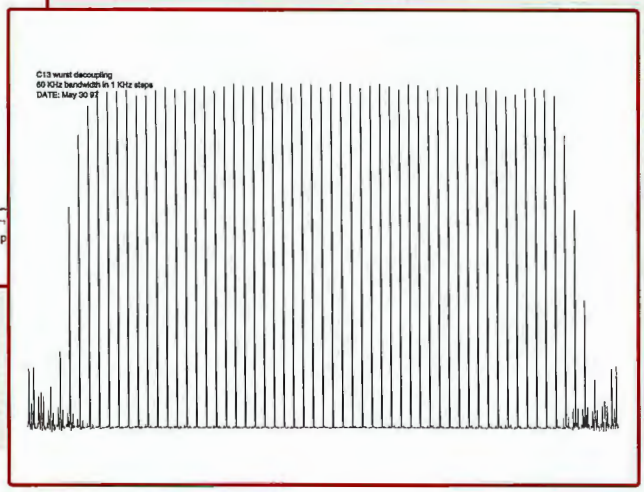


Multidimensional Heteronuclear NMR





Water Suppression Using Presaturation



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December 15, 1997
(received 12/23/97)

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

ANALYSIS OF BRAIN MICRODIALYSATES BY NMR

Dear Barry:

It was very nice to hear from you again. And, I might add, we admire the delightful shade of pink stationary you used for your latest correspondence.

We recently became interested in brain excitatory amino acids and their role in formation of toxic free radicals during focal brain ischemia and reperfusion. We sample the brain extracellular fluids using a microdialysis technique where we position a dialysis fiber in an appropriate region of the brain. Artificial cerebral spinal fluid is continuously perfused through the fiber at a rate of 2.1 μl per minute during baseline, ischemia and reperfusion and collected every 30 minutes. Having completed our initial analysis of dialysates by high performance liquid chromatography (HPLC), we wondered whether NMR would be useful for this purpose. We combined the dialysates from five rats (of which we used 175 μl), matching the time periods during the ischemia/reperfusion protocol. A small amount of D_2O was added for lock and shim. Water suppressed proton NMR was run at 750 MHz (128 transients, 10 sec repetition time). Spectra were run at 4°C (which affects chemical shift) in order to minimize chemical decomposition. The residual water peak was set to 4.70 ppm.

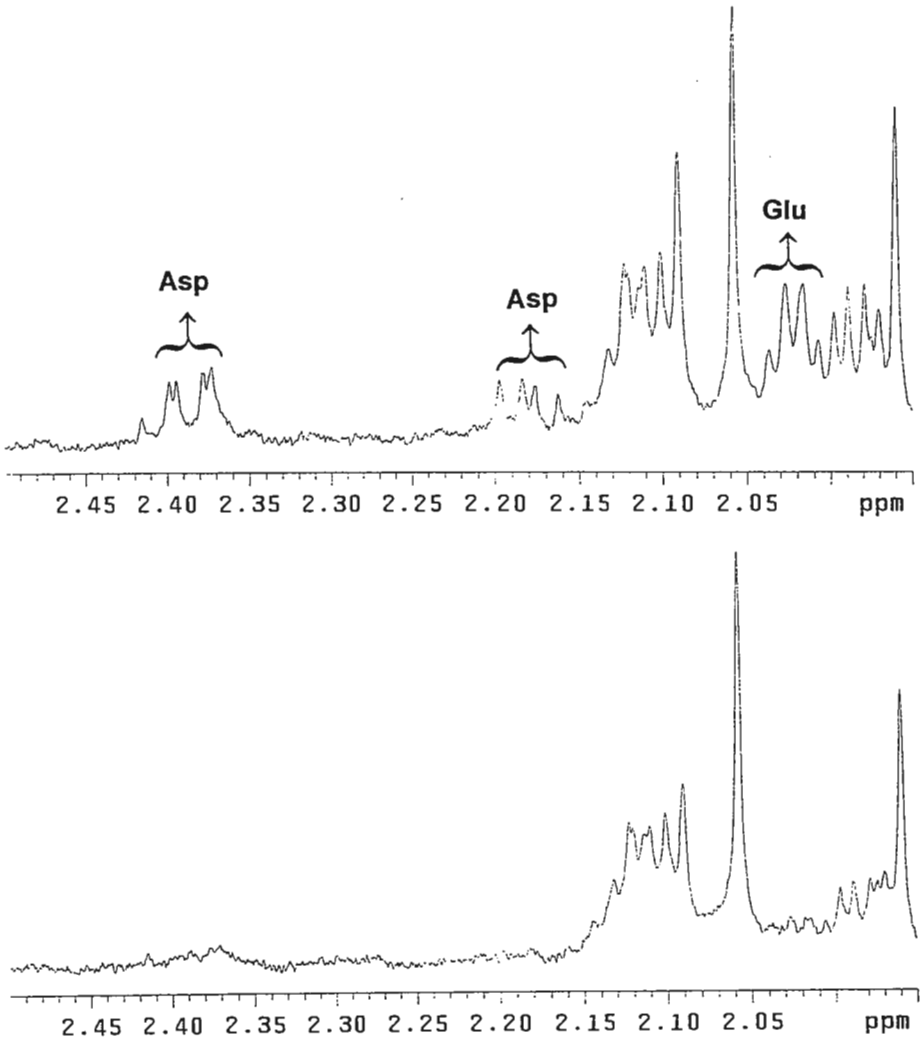
Numerous peaks corresponding to small molecule metabolites, amino acids and adenine nucleotide breakdown products were observed in the proton spectra of the microdialysates. We have assigned some of the peaks by comparison with external standards run at the same temperature. Many of these peaks have yet to be definitively assigned. Several of the peak intensities, notably the protons on the C4 glutamate (Figure) and lactate methyl change under ischemic conditions.

When I asked my microdialysis guru if he had ever considered NMR as an alternative to HPLC for analysis of microdialysates, he replied that he was under the impression that NMR was not sensitive enough to be useful. He was pleasantly surprised to learn that NMR can readily detect small metabolites down to single digit micromolar concentrations. Unlike analysis by HPLC where amino acids must be chemically derivatized prior to measurement, the NMR technique requires no further sample manipulation other than adding a small amount of D_2O. NMR allows the analysis of several classes of compounds over a wide concentration range to be assayed in one measurement, which would require several different HPLC assays, each with different columns, mobile phase etc. Furthermore, the samples are not destroyed by NMR and thus can be further analyzed by HPLC for other compounds whose concentrations are below the detection limit of NMR (e.g. serotonin).

For these reasons, as well as for the fact that we are NMR spectroscopists, we believe that NMR will prove to be a valuable tool in the analysis of microdialysates.

We wish you the best and we hope to see you at the ENC next March.

Figure: A 0.6 ppm region of the ^{1}H spectra of intracerebral microdialysates during baseline (bottom) and middle cerebral artery occlusion (top). These spectra show how cerebral ischemia produces increases in extracellular levels of glutamate (Glu) and aspartate (Asp).



Best Regards,

Michael Quast, Jingna Wei, Nishanta Illangasekare, Jose Gonzalez and Ed Ezell

THE UNIVERSITY OF UTAH

David M. Grant
Distinguished Professor

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

(received 1/21/98)

Dear Barry,

Investigation of Nitrogen-Containing Compounds at Natural Abundance with a 40 GHz DNP/ESR Spectrometer

A combined Dynamic Nuclear Polarization (DNP) and Electron Spin Resonance (ESR) spectrometer operating at a magnetic field of 1.41 T was built in the NMR laboratory at the Chemistry Department of University of Utah in collaboration with Robert A. Wind and Paul D. Ellis at the Pacific Northwest National Laboratory. The corresponding Larmor frequencies for the electron, ^{1}H, ^{13}C and ^{15}N nuclei are about 40 GHz, 60MHz, 15 MHz and 6 MHz, respectively. In contrast to the previously constructed DNP spectrometers where field sweep were used, [1-3] in our system, frequency sweep is employed. The microwave frequency is generated by a frequency synthesizer which is amplified to 10w by a traveling wave tube amplifier (TWT). Specifically, a quick in-situ ESR measurement is employed to set up the optimum DNP condition. The spectrometer can be readily switched from the ESR to the DNP condition with a single switch. A large volume sample (d = 10 mm & ℓ = 10 mm) is also used to enhance the overall NMR sensitivity.

Preliminary results are obtained on carbazole and purine. A ^{1}H DNP enhancement of 36 was obtained on carbazole doped with BDPA free-radicals and a ^{1}H DNP enhancement as large as 72 was obtained on purine doped with a mixture of BDPA and DPPH free-radicals. With such a large ^{1}H DNP enhancement, it is possible to obtain the ^{15}N Chemical shift anisotropy (CSA) powder patterns at ^{15}N natural abundance in minutes instead of days using the ^{15}N DNP-CP experiment.

Results of experiments on carbazole are demonstrated in Figs. 1 and 2. Figure 1 displays the ^{1}H DNP enhancement of carbazole as a function of microwave irradiation frequencies. Three types of DNP mechanisms can be identified, i.e., the solid state, the thermal mixing and the Overhause effects. The solid state effect is anti-symmetric about the electron Larmor frequency ω_e=39.136 GHz with the maximum enhancements occur at $\omega_e \pm \omega_n$, where ω_n = 59.444 MHz, the ^{1}H Larmor frequency. The thermal mixing effect is also anti-symmetric about ω_e, and the maximum enhancements are found to be at $\omega_e \pm \omega_o$, where ω_o is apparently less than 59.444 MHz. The Overhause effect is symmetric about ω_e, though its contribution is quite small in this case as the intensity at ω_e position is positive.

The ^{15}N CSA powder pattern of carbazole (shown in Figure 2) was obtained at -120 ℃ using ^{1}H-^{15}N cross polarization at the optimum ^{1}H DNP condition, i.e., the microwave frequency was set at the maximum solid state effect condition of the enhancement curve (39.074 GHz). The ^{1}H polarization was thus enhanced by a factor of 36. A spectrum with good S/N for this ^{15}N powder pattern was obtained in approximately 20 minutes.

References

1. R. W. Wind, F. E. Anthonio, M. J. Duijvestijn, J. Smidt, J. Trommel and G. M. C. De Vette, *J. Magn. Reson.*, **52**, 424 (1983).
2. J. Z. Hu, J. Zhou, B. Yang, L. Li, J. Qiu, C. Ye, M. S. Solum, R. A. Wind, R. J. Pugmire and D. M. Grant, *Solid State NMR.*, **8**, 129 (1997).
3. D. A. Hall, D. C. Maus, G. J. Gerfen, S. J. Inati, L. R. Becerra, F. W. Dahlquist and R. G. Griffin, *Science*, **276**, 930 (1997).

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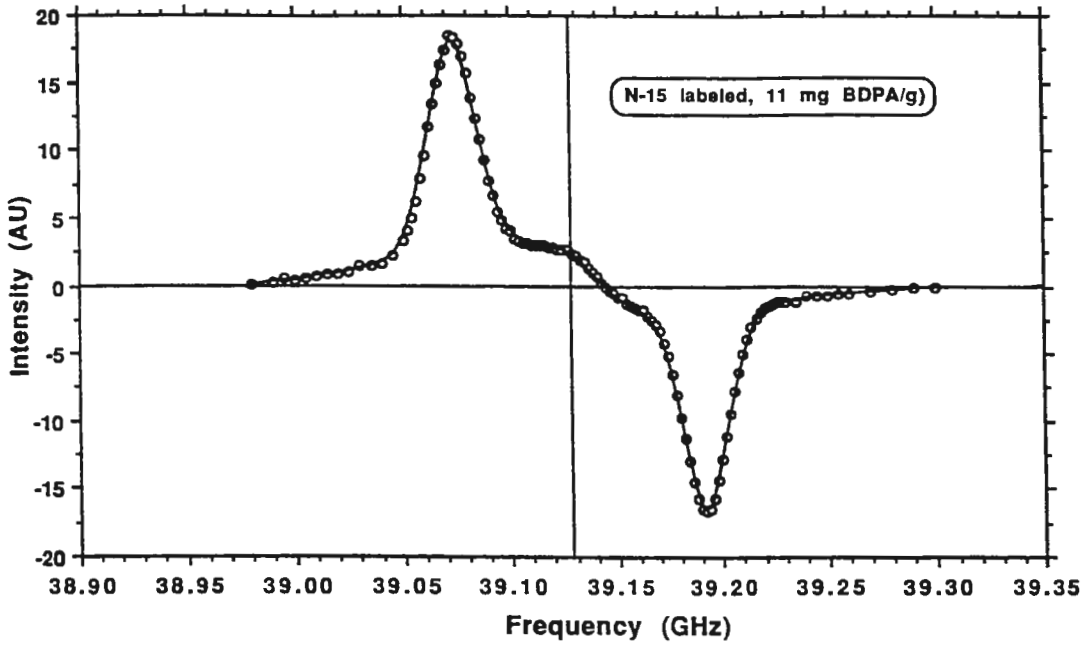

Figure 1. The ^{1}H DNP enhancement curve of a carbazole sample as a function of microwave irradiation frequencies at room temperature. The vertical scale is in arbitrary units. The carbazole sample was obtained by desolving 1g of carbazole and 11mg BDPA in acetone and then evaporate.

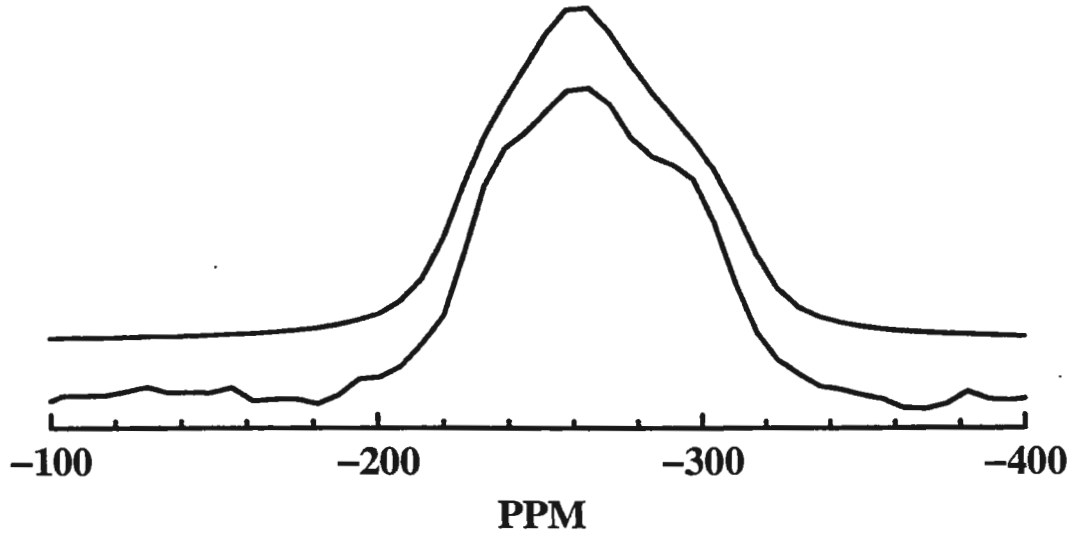

Figure 2. The ^{15}N CP-DNP specta (bottom: experimental, top: simulation) of carbazole (same as that in Figure 1) at a temperature of -120 °C. The experimental conditions were: contact time 0.5 ms, recycle delay time 2s, and a total of 596 scans were accumulated. The cross polarization field strength is 42 KHz for both the ^{15}N and ^{1}H channel; the decoupling field during data acquisition was 62 KHz.

Jian Zhi Hu

Mark S. Solum

Yi Jin Jiang

Ronald J. Pugmire

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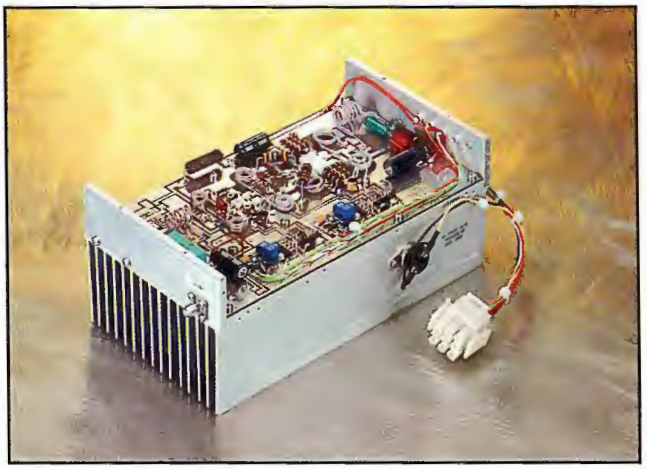

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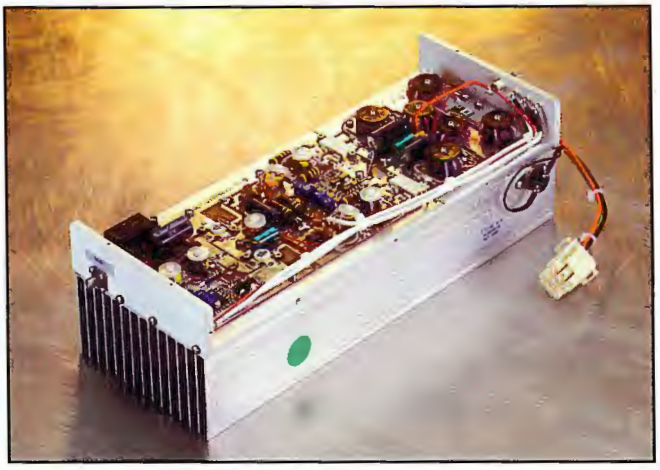

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SCIENTIFIC & MEDICAL PRODUCTS

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(received 12/22/97)
December 17, 1997

TWO-SITE EXCHANGE REVISITED

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

Dear Barry,

Another Canadian postal strike has probably preserved me from the wrath of your ultimatums, but I know they are coming. Let me tell you what we have been doing with good old two-site exchange, following up on Len Reeves's work (Reeves, L.W. and Shaw, K.N. *Can. J. Chem.*, **1970**, *48*, 3641-3653). In this paper, Len showed that you could always deconstruct the Gutowsky-Holm lineshape into two normal lines, which are distorted in phase, intensity, position and linewidth.

It is quite easy (Bain, A.D. and Duns, G.J. *Can. J. Chem.*, **1996**, *74*, 819-824) to derive the form of this in the time domain, since the lines are given by the eigenvectors and eigenvalues of the Liouville matrix, which is given in [1]. In this equation, M_A and M_B are the magnetizations of the two sites and we have made $\delta = (\omega_A - \omega_B)/2$.

$$\frac{d}{dt}\begin{pmatrix} M_A \\ M_B \end{pmatrix} = -\begin{pmatrix} i\delta + \frac{1}{T_2} + k & -k \\ -k & -i\delta + \frac{1}{T_2} + k \end{pmatrix}\begin{pmatrix} M_A \\ M_B \end{pmatrix} \qquad [1]$$

Equation [1] is a set of first-order differential equations, so its formal solution is given by [2], in which exp()

$$\begin{pmatrix} M_A(t) \\ M_B(t) \end{pmatrix} = \exp(-Lt)\begin{pmatrix} M_A(0) \\ M_B(0) \end{pmatrix} \qquad [2]$$

means the exponential of the matrix, L in [1]. In practice, we diagonalize L with a matrix of eigenvectors, U, as in [3] to give a diagonal matrix, Λ, with the eigenvalues of L down the diagonal.

$$\Lambda = U^{-1} L U \qquad [3]$$

Equation [3] becomes [4].

This is fine for numerical work, but it would be nice to have a tidy analytical expression for the

$$\begin{pmatrix} M_A(t) \\ M_B(t) \end{pmatrix} = U \exp(-\Lambda t)\ U^{-1} \begin{pmatrix} M_A(0) \\ M_B(0) \end{pmatrix} \qquad [4]$$

simple two-site case. This is not straightforward, since the eigenvectors of a non-Hermitian matrix are not orthonormal and may be complex numbers. All sorts of expressions are possible. Let us just give the form in [5].

$$U = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \qquad [5]$$

Regardless of whether U is unitary, its inverse is given by [8], where Δ is the determinant of [5] (which we would like to be pure real).

$$U^{-1} = \frac{1}{\Delta} \begin{pmatrix} d & -b \\ -c & a \end{pmatrix} \qquad [6]$$

Equation [4] then says that the signal is given by [7], regardless of slow or fast exchange.

$$signal = \frac{(a+c)(d-b)}{\Delta} e^{\lambda_1 t} + \frac{(b+d)(-c+a)}{\Delta} e^{\lambda_2 t} \qquad [7]$$

The values of the eigenvectors have two forms, depending on whether $\delta > k$ (slow exchange), or $\delta < k$ (after coalescence). For slow exchange, the eigenvalues are given in [8],

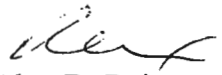
$$eigenvalues = -(\frac{1}{T_2}+k) \pm i \sqrt{\delta^2-k^2} \qquad [8]$$

and a convenient matrix of eigenvectors is given by [9].

$$\begin{pmatrix} k & i\,(\sqrt{\delta^2-k^2} + \delta) \\ -\,i\,(\sqrt{\delta^2-k^2} + \delta) & k \end{pmatrix} \qquad [9]$$

Using these in equation [7] gives us the FID, and an FT of that recovers the Reeves and Shaw expressions.

Yours truly,



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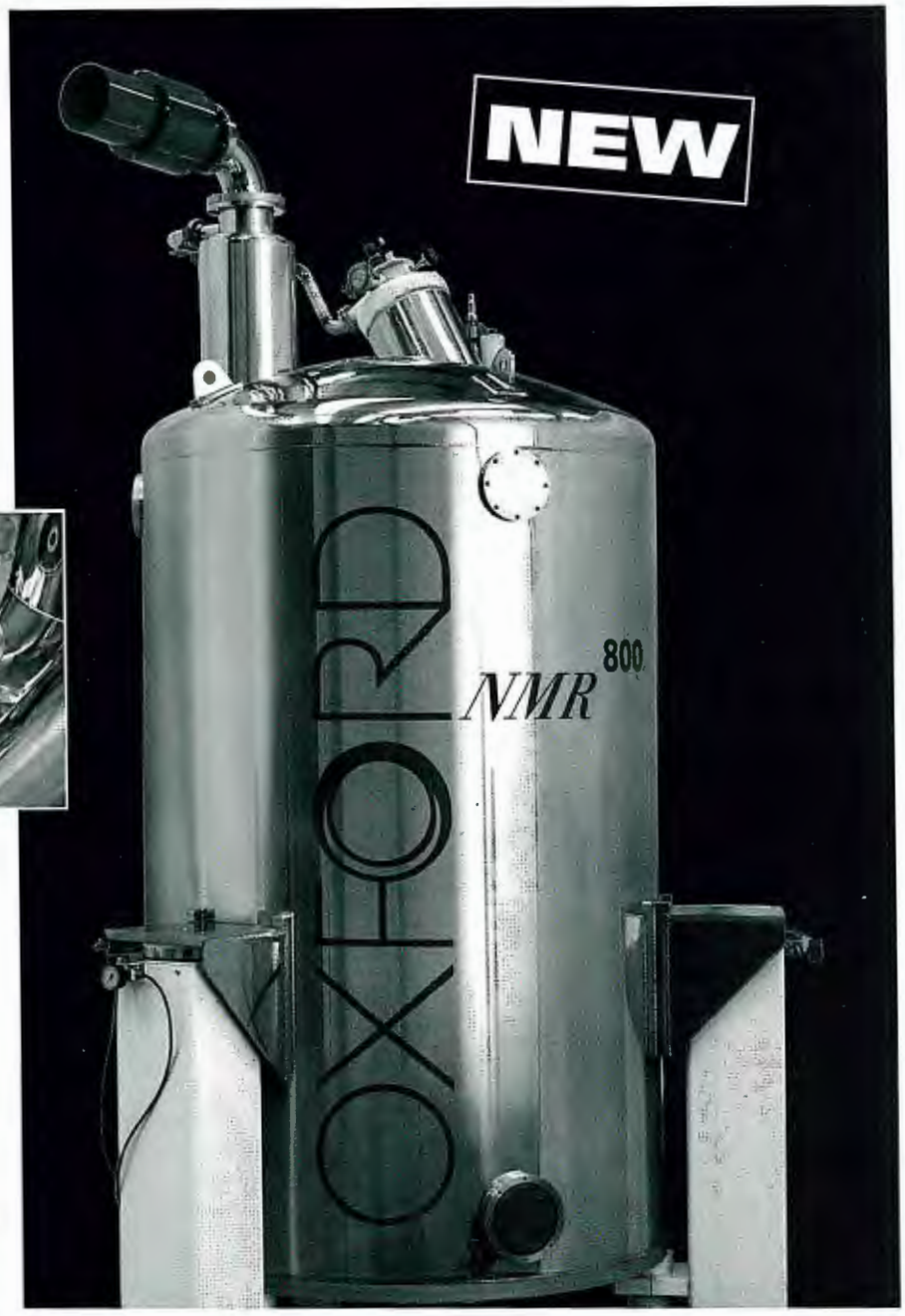

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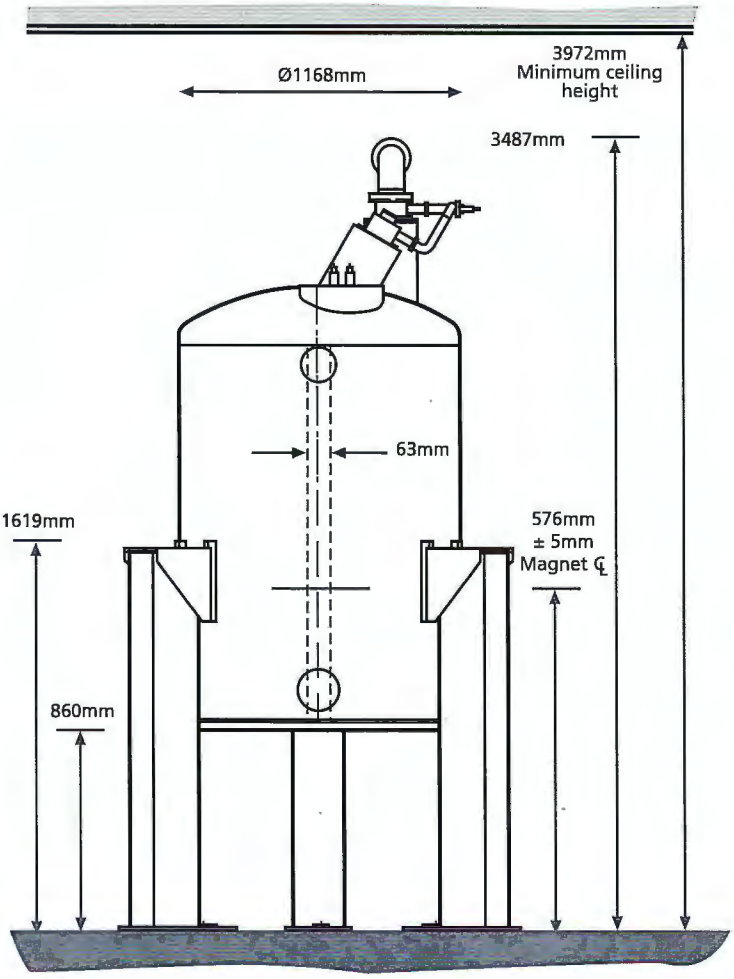

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(received 1/3/98)

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

Interleaved Heteronuclear Acquisitions on a Bruker DMX Spectrometer

Dear Barry,

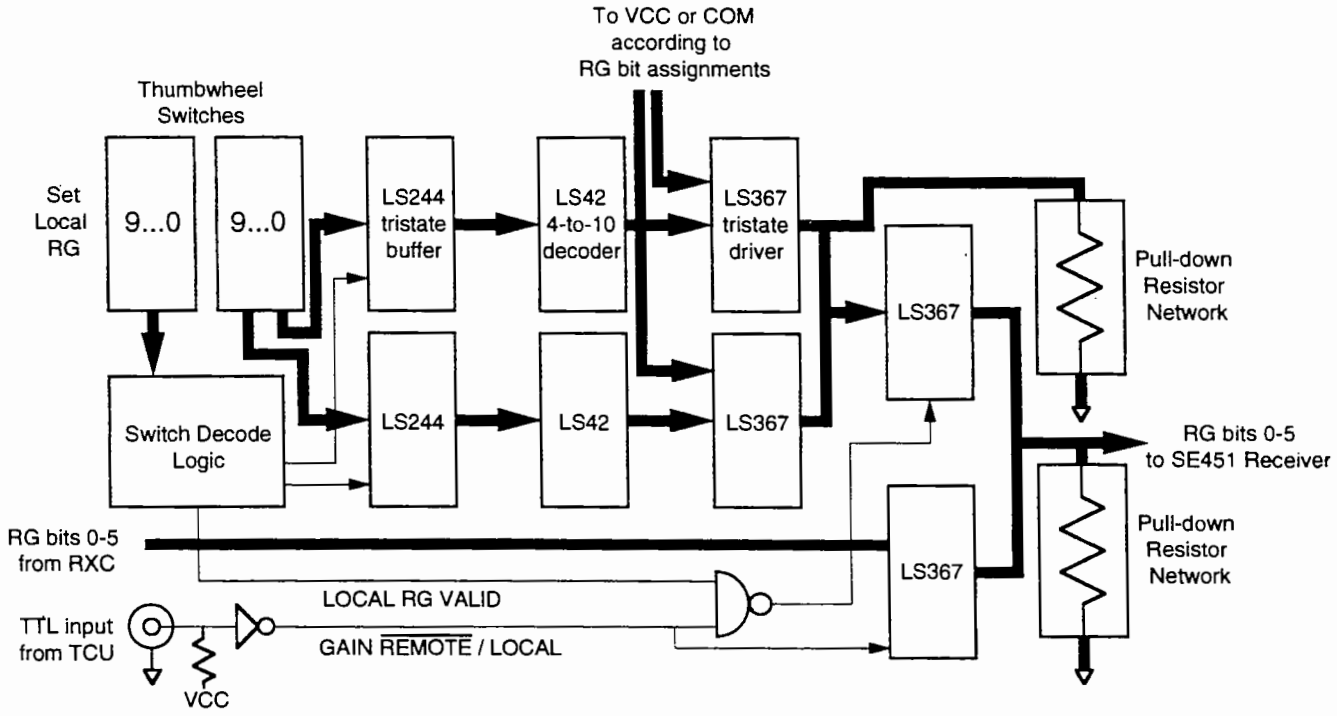
A common problem which arises in both *in vivo* and chemical kinetic studies is the need to acquire NMR spectra of two or more nuclei on a system which is varying or evolving in time. For example, it is frequently desirable to obtain both a ^{31}P and a ^{13}C spectrum on an isolated perfused mouse heart to study the correlation between the uptake of a given substrate and the metabolic activity of the cardiac myocytes. Unfortunately, this often mandates long acquisition times due to limited sensitivity, especially for ^{13}C. Since the heart preparation is not stable over long acquisition times, we cannot assume that the ^{31}P and ^{13}C spectra correspond to the same physiological conditions if these spectra are acquired sequentially. However, if the two spectra are acquired in an *interleaved* manner (i.e. ^{31}P FID - ^{13}C FID - ^{31}P FID, etc.), then they will reflect an average over the same physiological conditions. Thus, interleaved acquisition permits more reliable correlations to be made between spectra acquired for different nuclei. Finally, since ^{13}C T_1 values are generally quite long, interleaved acquisition allows one or more ^{31}P scans to be performed during the relaxation of ^{13}C spins. Conversely, the ^{31}P spins can undergo relaxation during the ^{13}C acquisitions. This is permissible in typical *in vivo* systems since the J and dipolar coupling between ^{13}C and ^{31}P spins is very small, especially in unlabeled systems. In this way, it is possible to acquire spectra for both ^{13}C and ^{31}P in the same time as would be required to collect a single ^{13}C spectrum.

To perform an interleaved heteronuclear acquisition on a general system, one must be able to set different excitation pulse lengths, relaxation delays, total number of scans, and receiver gain values for the two or more nuclei sampled. Moreover, the ability to rapidly switch observe frequencies, preamplifiers, and probe channels is necessary. With the exception of receiver gain (RG) switching, all of these capabilities are present in Bruker's DMX spectrometers without modification. A typical pulse program for interleaved acquisition of two heteronuclei with proton composite pulse decoupling is shown below:

```
;selzgdc.f1_f3
; parmode 2D
; 1 TD 2
; NBL 2
; 2 obschan 0 0
; 2 obschan 1 1
; 2 obschan 2 0
; 2 obschan 3 2
; 2 obschan 4 0

#include <observe.incl>

10u pl1:f1
10u pl2:f2
10u pl3:f3

1 ze
  10u st0                ;initialize acquisition buffer pointer
  30m cpd2:f2            ;1H composite pulse decoupling on
2 d1
```

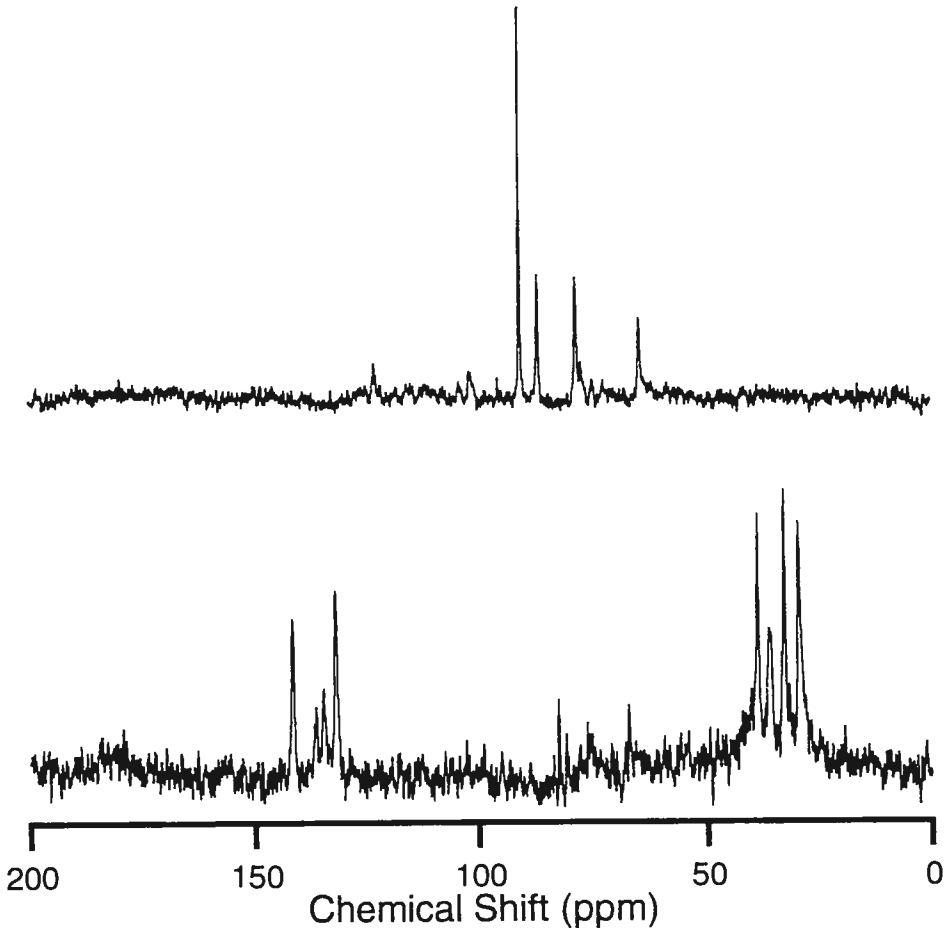
```
obsf1
 5u setnmr2|7              ;reset to obschan1 (13C)
 1u setnmr2^7
 5u setnmr5|14             ;select software RG with switchbox
p1:sp1:f1 ph1              ;pulse on 13C
 3u
 1u adc ph11               ;sample 13C FID
 aq
1m eoscnp
 1m ipp1 ipp11             ;increment 13C transmitter and receiver phases
 lo to 2 times l1          ;l1=number of 13C FID's per l0 iteration
 1m st                     ;set pointer to next block  of acquisition memory
 1u setnmr2|7              ;set obschan3 (31P)
 1u setnmr2^7
 5u setnmr5^14             ;select manual RG
obsf3
3 d3
 p3:sp3:f3 ph3             ;pulse on 31P
 3u
 1u adc ph31               ;acquire 31P FID
 aq
1m eoscnp
 1m ipp3 ipp31             ;increment 31P transmitter and receiver phases
 lo to 3 times l3          ;l3=number of 31P FID's per l0 iteration
 1m st                     ;set pointer to next block of acquisition memory
 lo to 2 times l0          ;l0=loop over l1 13C FID's followed by l3 31P FID's
 1m do:f2                  ;decoupler off
 100m wr #0 if #0
exit

ph1=0 2 2 0 1 3 3 1
ph3=0 2 2 0 1 3 3 1
ph11=0 2 2 0 1 3 3 1
ph31=0 2 2 0 1 3 3 1
```

In this pulse program, the commands "setnmr 5|14" and "setnmr 5^14" set the state of a spare logic output which drives a home-built receiver gain switching box. While the hardware architecture of the DMX allows the receiver gain to be rapidly changed simply by changing the state of six logic inputs to the receiver, the receiver control interface (RXC) will not process the necessary software commands arriving on the RS485 bus once an acquisition is underway. While this lock-out feature provides protection against accidental acquisition parameter changes during an experiment, switching the receiver gain in an interleaved heteronuclear experiment requires that we bypass this protection. We have done this by introducing logic circuitry between the RXC and receiver. A block diagram of this external device is shown below:



When the TTL input to the RG switchbox is high or disconnected, the six receiver gain control signals from the RXC proceed to the receiver module unchanged. In this state, the receiver gain is set by software just as in a conventional, non-interleaved acquisition. If a pulse program sets the TTL input to the low state, then the RXC gain control inputs are disconnected and the RG switchbox generates the six RG control signals according to the setting a front-panel thumbwheel switch. In this way, one can perform an interleaved heteronuclear experiment with receiver gain values optimized for each nucleus. This ability is especially important when ^{1}H spectra are to be collected in an interleaved fashion with low-sensitivity nuclei such as ^{15}N or unenriched ^{13}C.

We have applied the $^{13}C/^{31}P$ interleaved acquisition technique to studies of the metabolic effects of nitric oxide synthase (NOS) inhibitors in isolated perfused rat hearts. The figure below shows ^{31}P (top) and ^{13}C (bottom) spectra acquired under low-flow perfusion with buffer containing the NOS inhibitor L-NAME. These spectra were collected in a 1:1 interleaved fashion with an effective relaxation delay of 2 seconds between successive pulses on the same nucleus. For each nucleus, 128 FID's were collected under WALTZ-16 ^{1}H decoupling.



We wish to thank Henry Luhrs, Hans Förster, Charles Barthel, and Georges Billman of Bruker for their help in implementing the interleaved pulse program and designing the RG switchbox.

Sincerely,

Ken Fishbein
Facility Manager, NMR Unit

Guenter Baartz
Electronics Engineer

Richard G. S. Spencer
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Lineshape 3% $CHCl_3$ 5 mm non-spinning	
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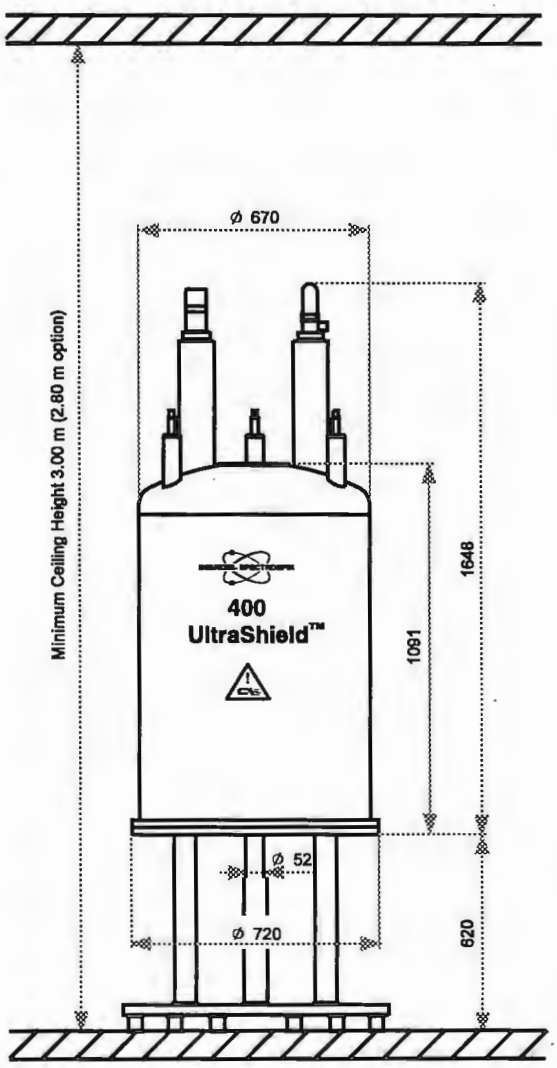

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Department of Chemistry, Physical Chemistry
Professor Peter Stilbs

Stockholm January 20, 1998

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

Re: Troubleshooting FT-PGSE hardware / Nomenclature pollution

Dear Barry - thank you again for the yellow ultimatum. Time really flies these days.

For quite some time we had recurring and intermittent problems with our FT-PGSE self-diffusion setup on our Bruker WB AMX-300 system. Although the hardware was custom-built, similar problems could occur on any type of field gradient instrumentation. Perhaps some readers may learn from our recent experiences. A recommended procedure is to permanently connect a DC current probe around one of the gradient leads, and display the gradient pulses continuously on a digital storage scope. This helps in the process of monitoring major malfunctions of the system. Tektronix sell a quite adequate current probe (A622) at a reasonable price. The A622 uses a 9V battery that only lasts a few hours, however. We replaced this with a simple permanent 'wall plug type' power supply.

However, routinely monitoring gradient pulses is not sufficient. In a proper pulsed-gradient spin-echo experiment subsequent gradient pulse areas/shapes should match at the ppm level. Of course, this makes normal troubleshooting with a scope or voltmeter inapplicable, and the the NMR signal appearance alone will tell if everything is OK. So, if the gradient pulses do not match the echo will attenuate or move in the time-domain (and attenuate, distort and phase shift in the frequency domain), as a result of the mismatch.

What we noted periodically on our setup were highly irregular FT-PGSE spectra, especially at higher gradient settings. At times everything was 'fine', however, except that one could not normally run good stimulated-echo based measurements with shorter first rf pulse intervals than 20 ms. Sometimes such experiments were OK down to 7 ms, however. It all seemed very weird, and it took us quite some time to find the answer.

So what could it be ? : a) Timing or other problems in the spectrometer itself - perhaps, since it was definitely erratic too at that time, even during simple one-pulse data acquisition. Subsequent signal amplitudes could differ by several percent. b) Some problem in the gradient generator - perhaps, since it is the actual current source, with lots of electronic components. c) Some mechanical (gradient coil moving ?) or electric malfunction in the probe - perhaps d) Eddy current problems in the probe - perhaps, since the shorter rf pulse interval stimulated echo experiments did not work.

'd' could be ruled out from the fact that one could produce a good, distortion-free NMR spectrum by a 90 degree pulse, less than 0.5 ms after a powerful gradient pulse. For a long time we suspected the spectrometer timing, since other instabilities were definitely present, and good measurements could occasionally be made after switching off/on all units. Later, we became confident that it was the gradient unit (it has bipolar pulse capability, although it is almost always used with a single polarity), since replacing it with another (monopolar) unit 'cured' the problems. However, the crucial troubleshooting test

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was to cross the leads on the monopolar unit, so as to create gradient pulses of the opposite polarity (which just happened to be the default polarity of the bipolar generator). Now the problems were all back.

So, the problems were all in the probe. The gradient leads inside are isolated from ground, but have a decoupling network, using a ferrite core followed by a capacitor to ground - one for each lead. Evidently, one of these capacitors partially failed, and due to some slight leakage to ground - especially at higher currents (at transient voltages of about 200 V) some slight and irreproducible fraction of the gradient current went to ground, instead of going through the gradient coil. Capacitors may self-heal to some extent, which explains why the problems were occasionally absent and why we noted 'hysteresis effects' with regard to actual measurement quality when changing from positive to negative gradient pulses.

Yours Sincerely

Peter

Peter Stilbs

PS: In my opinion there is a lot of 'nomenclature pollution' in the NMR field gradient self-diffusion field. Personally I always have always used the notation PGSE (pulsed-gradient spin-echo), since the spin-echo component is completely essential in this context. The use of 'PFG' for the same experiment has unfortunately become widespread, and should be stopped. Also, the use of the new notation 'diffusion ordered spectroscopy' or DOSY for the FT-PGSE experiment (first suggested 30 years ago) is equally unjustified. Many newcomers to the this field tend to use this unfortunate notation.

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January 14, 1998 (received 1/16/98)

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

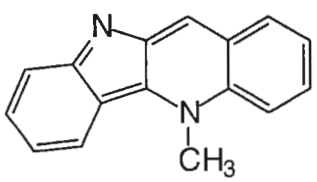
Big Magnets & Little Teeny Probes

Dear Barry,

Since our last contribution, the installation of our Varian Inova 600 has been completed. The instrument is being heavily used in the elucidation of the chemical structures of small samples. During the course of developing potential drug candidates, it becomes necessary to isolate and identify impurities and degradation products arising from subjecting the drug to various stress challenges per ICH mandate. Generally, anything at levels >0.1% will eventually be isolated and characterized. The sample requirements for impurity and degradation characterization were substantially reduced following the development of 3 mm micro probes reported from the laboratories of two of the authors in 1992.[1,2] Usefully, gradient micro probes have made the acquisition of heteronuclear shift correlation data frequently necessary for characterization a more facile undertaking at the submicromole level. In addition, the natural products chemistry community has also begun to enjoy the benefits of being able to characterize much smaller samples, allowing the identification of novel compounds present at levels too low to be characterized by more conventional NMR spectroscopic technologies.

We now wish to report some initial results of further reductions in probe scale with a commensurate decrease in sample volume coupled with our 600 MHz instrument. Using the now fairly widely employed (at least within the pharmaceutical industry) 3 mm gradient micro inverse and dual probes, sample volumes are typically in the range of 130-150 µl. Further reduction of optimal sample volumes to about 70-80 µl can be achieved by resorting to Shigemi micro sample NMR tubes matched to the magnetic susceptibility of the solvent being employed (D_2O, DMSO, $CDCl_3$). The benefits of this approach have been demonstrated with ~0.1 µmole of Caribbean ciguatoxin[3] as well as in a study by Reynolds and co-workers.[4] Recently, we installed the first prototype of a new generation of submicro gradient inverse probe on our 600, a Nalorac SMIDG-600-1.7. This probe reduces the optimal sample volume still further from the 70-80 µl attainable with a 3 mm Shigemi micro NMR cell to ~20-25 µl in a 1.7 mm NMR tube made from precision 1.7 mm capillary tubing (Wilmad Glass). The thrust of this effort, obviously, is to allow the characterization of still smaller samples as well as the identification of impurities and degradants earlier in the drug development process when supplies of the candidate drugs are more limited. Ideally, early stress testing of potential drug candidates can be used to provide the basis for more rational decisions as to the most stable candidate molecules when the information is passed back to the synthetic chemists developing potential lead molecule templates.

As an initial test of the SMIDG-600-1.7 probe, we elected to use the small alkaloid cryptolepine (**1**), the same molecule used in our initial report on the performance of the 3 mm micro inverse probe.[1] Since our Rapid Structure Characterization Group is typically able to chromatographically prep samples in the range of 0.5-1 µmole, we felt that a 0.5 µmole sample (prepared by serial dilution) of cryptolepine dissolved in 25 µl of 99.992% (Isotec) d_6-DMSO in a glove box (a flexible teflon needle and a Hamilton gas-tight syringe were used to introduce the sample into the 1.7 mm capillary NMR tube) under an inert argon atmosphere and sealed would provide an adequate test of the new probe's capabilities. Figure 1 shows a proton reference spectrum of cryptolepine acquired using 1 transient. Shown in Figure 2 is a GHSQC[5] spectrum of the aromatic region of the molecule acquired as 2048 x 16 (2 x 16 hypercomplex files in F_1 to



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USA

Telephone (616) 833-4000

digitize the 30 ppm F_1 spectral width) acquired in 12 minutes using 16 transients/t_1 increment. Pulse widths for proton and carbon were 6.65 and 11.6 μsec, respectively, at tpwr = 46 and dpwr = 58, respectively. GARP decoupling was used at a power of 40 with an 81 μsec 90 degree pulse affording a decoupling field strength of 3084 Hz. For comparison, an identical quantity of **1** dissolved in 150 μl of d_6-DMSO in a 3 mm NMR tube gave a spectrum using a Nalorac MIDTG-600-3 probe in 2.5 hr. that compared in terms of F_2 projection signal-to-noise with data acquired using the SMIDG-600-1.7 probe in ~20 min. This performance ratio is consistent with the reduction in sample volume in going from 3 mm to 1.7 mm probe format and the commensurate increase in concentration afforded by the same quantity of material in the 25 μl sample volume used in the 1.7 mm capillary NMR tube. The projection through F_2 of the GHSQC spectrum is presented in Figure 3. Signal-to-noise in the projection was 20:1 for the 12 min. acquisition.

To explore the versatility of this new probe format, two additional spectra were also acquired. First, an inverted direct response (IDR) GHSQC-TOCSY[6-9] spectrum of **1** was acquired and is shown in Figure 4. The spectrum was acquired using 2048 x 48 (2 x 48 hypercomplex files in F_1) points with 80 transients/t_1 increment in 2.3 hr. The mixing period had a duration of 24 msec and was flanked by 2 msec trim pulses. The 90 pulse 9 dB down used during the mixing period was 21 μsec.

Finally, a GHMBC[10] spectrum of **1** was acquired and is shown in Figure 5, with an expansion of the aromatic region shown in Figure 6. The spectrum was acquired as 4096 x 64 (2 x 64 hypercomplex files in F_1 used to digitize an F_1 spectral width of 110-170 ppm) points with 16 transients/t_1 increment giving an acquisition time of 1.1 hr. Signal-to-noise in the F_2 projection of the GHMBC data was 30:1. The same 200 Hz region between the two upfield aromatic multiplets was used to define representative noise in the determination. The spectrum was optimized for an assumed 8 Hz long-range heteronuclear coupling constant and gave data comparable to those we have reported previously.[1]

In conclusion, the SMIDG-600-1.7 submicro gradient inverse probe offers considerable promise to groups engaged in the regular characterization of submicromole quantities of material irrespective of their origins. Sample preparation if one finds it necessary to work in a glove box under an inert atmosphere is challenging due to the loss of manual dexterity imposed by heavy rubber gloves when working with the 1.7 mm capillary NMR tubes. Irrespective of the difficulties of sample preparation, we are of the opinion that the results obtainable with this probe format amply offset any difficulties inherent to the preparation of the sample. In fact, to obtain comparable results in a 3 mm format it is necessary to employ Shigemi sample tubes in a fairly aggressive manner. In practice, the routine use of a sealed 1.7 mm capillary NMR tube at 25 μl volume is a very simple task in comparison to aggressively employing a 3 mm Shigemi micro NMR sample tube to work at perhaps a 60-70 μl sample volume. Further details will be reported elsewhere.

Gary E. Martin

Kenneth D. Visscher

Ronald C. Crouch
Nalorac Corporation

Toby Zens
Nalorac Corporation

Acknowledgement: The authors would like to thank Professor Paul L. Schiff, Jr. of the University of Pittsburgh, School of Pharmacy, Pittsburgh, PA 15261 for kindly providing the samples of cryptolepine used in this and our previous studies.

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Figure Captions following page:

Figure 1. ^{1}H reference spectrum of 0.55 μmole of cryptolepine (**1**) dissolved in 25 μl 99.1996% d_6-DMSO recorded in one transient following a 90 degree pulseusing a Nalorac SMIDG-600-1.7 mm submicro gradient inverse detection probe in a Varian Inova 600.

Figure 2. GHSQC spectrum of 0.55 μmole of cryptolepine (**1**) using the Nalorac SMIDG-600-1.7 mm gradient submicro inverse. the data were acquired in 12 minutes as ni = 16 (2 x 16 hypercomplex files) to digitize a 30 ppm spectral width in F_1 acquiring 16 transients/t_1 increment.

Cryptolepine 0.5 umole/25 ul
Malorac SMIDG-600-1.7
Varian Inova600
1 transient 1H ref

exp8 s2pul

SAMPLE		DEC. & VT	
date	Jan 14 1998	dfrq	150.821
solvent	DMSO	dn	C13
file	exp	dpwr	47
ACQUISITION		dof	0
sfrq	599.753	dm	nnn
tn	H1	dmm	c
at	2.497	dmf	32222
np	24000	dseq	
sw	4806.5	dres	1.0
fb	3000	homo	n
bs	4	temp	30.0
tpwr	48	DEC2	
pw	6.7	dfrq2	60.778
d1	1.503	dn2	N15
tof	521.2	dpwr2	1
nt	1	dof2	0
ct	1	dm2	n
alock	n	dmm2	c
gain	60	dmf2	200
FLAGS		dseq2	
il	y	dres2	1.0
in	n	homo2	n
dp	y	PROCESSING	
hs	nn	wtfile	
DISPLAY		proc	ft
sp	1125.6	fn	not used
wp	4806.5	math	f
vs	119		
sc	6	werr	
wc	140	wexp	
hzmm	34.33	wbs	
is	33.57	wnt	wft
rfl	4236.2		
rfp	5361.8		
th	43		
ins	1.000		
ns ods ph			

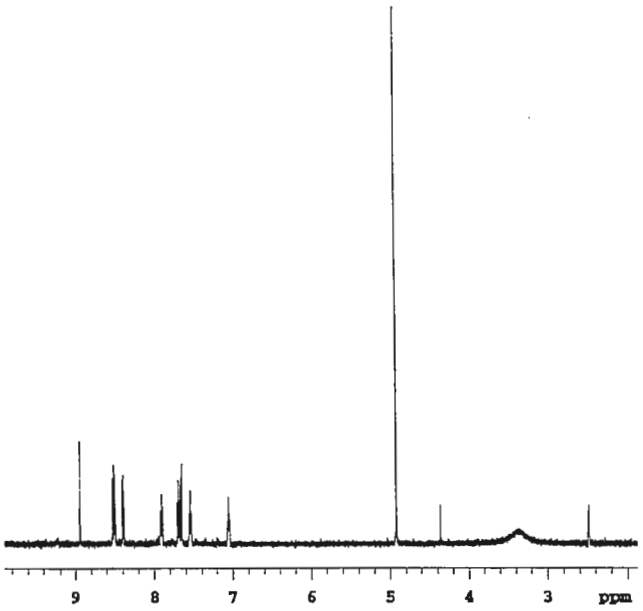

Figure 1.

Cryptolepine 0.55 umole/25 ul
Malorac SMIDG-600-1.7
Varian Inova600
GHSQC 12 min acq
ni=16 nt=16
1H ref 1 transient

exp1 gHSQC

SAMPLE		FLAGS		ACQUISITION ARRAYS	
date	Jan 14 1998	hs	n	array	phase
solvent	DMSO	sspul	y	arraydim	32
sample	undefined	PFGflg	y		
ACQUISITION		hsg1v1	6587	i	phase
sw	4806.5	SPECIAL		1	1
at	0.213	temp	30.0	2	2
np	2048	gain	60		
fb	3000	spin	0		
ss	64	GRADIENTS			
d1	1.000	gzlvl1	6587		
nt	16	gt1	0.002000		
2D ACQUISITION		gzlvl3	3306		
sw1	4524.6	gt3	0.001000		
ni	16	gstab	0.000500		
phase	arrayed	F2 PROCESSING			
TRANSMITTER		gf	0.107		
tn	H1	gfs	not used		
sfrq	599.753	fn	2048		
tof	521.2	F1 PROCESSING			
tpwr	48	gf1	0.014		
pw	6.650	gfs1	not used		
DECOUPLER		fn1	512		
dn	C13	DISPLAY			
dof	4722.3	sp	4093.1		
dm	nny	wp	1339.1		
dmm	ccg	sp1	17065.3		
dmf	12346	wp1	2395.4		
dpwr	40	rfl	365.0		
pwxlvl	58	rfp	1493.4		
pwx	11.600	rfl1	3175.5		
HSQC		rfp1	18732.5		
j1xh	165.0	PLOT			
nullflg	y	wc	150.0		
		sc	6.0		
		wc2	90.0		
		sc2	0		
		vs	40858		
		th	3		

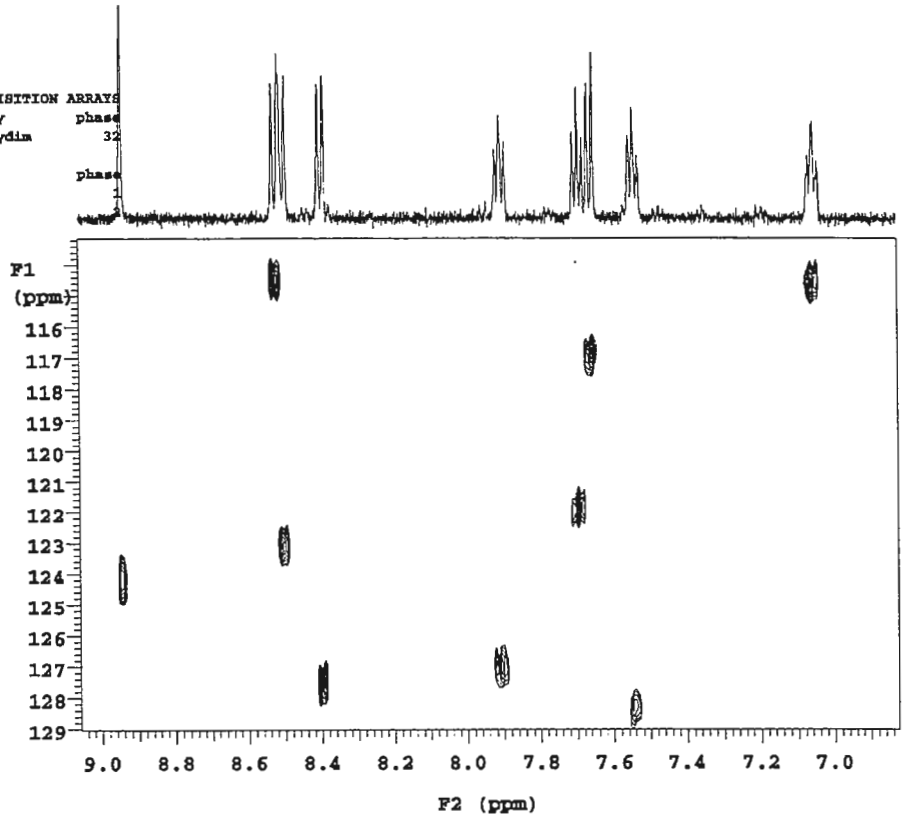

Figure 2.

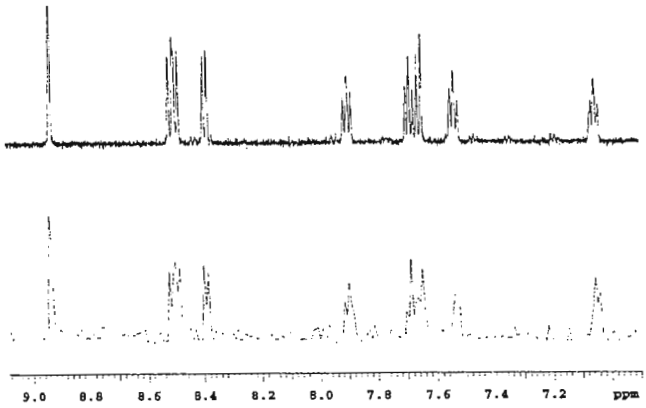

Figure 3. Bottom trace (left): F_2 Projection of the GHSQC spectrum of 0.55 µmole of cryptolepine (**1**) shown in Figure 2. The signal-to-noise ratio in the projection is 20:1 for the 12 min 2D acquisition. The region of the projection chosen for representative noise was a 200 Hz region between the two upfield multiplets.

Top trace (left): Expansion of the one transient ^1H reference spectrum of cryptolepin (**1**) shown in Figure 1.

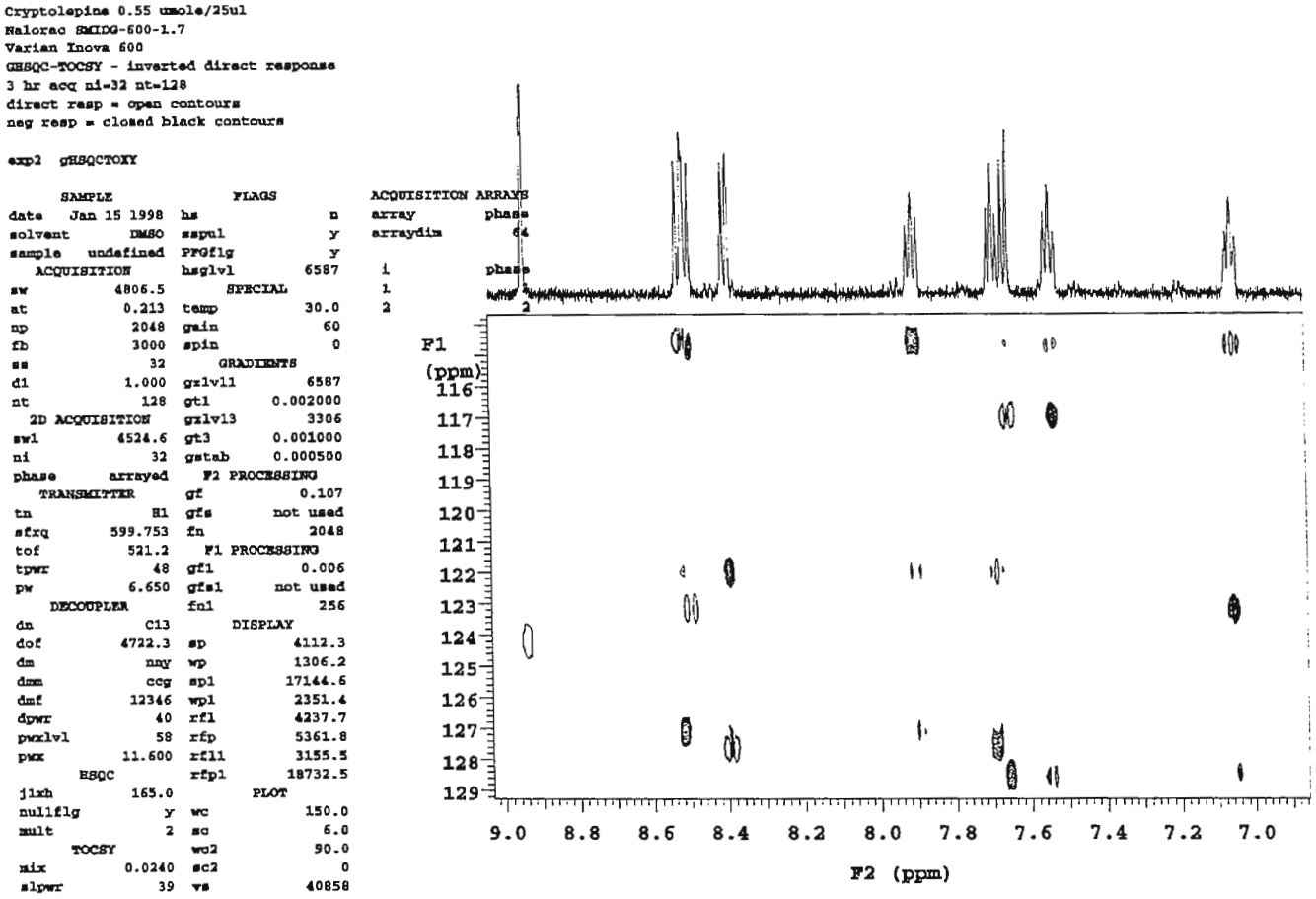

Figure 4. IDR-(Inverted Direct Response)-GHSQC-TOCSY spectrum of 0.55 µmole of cryptolepine (**1**) with a mixing time of 24 msec recorded using a Nalorac SMIDG-600-1.7 mm gradient submicro probe in a Varian Inova 600. The data were acquired as 2048 x 32 (2 x 32 hypercomplex files) accumulating 128 transients/t_1 increment. The acquisition time was 3 hr. Direct responses are negative in phase and are presented as open contours (see for example the response for the singlet resonating at 8.94/ 124.2 ppm corresponding to the H11 resonance of the quinoline portion of the molecule). Relayed responses have positive phase and are shown as the more intense, closed contours.

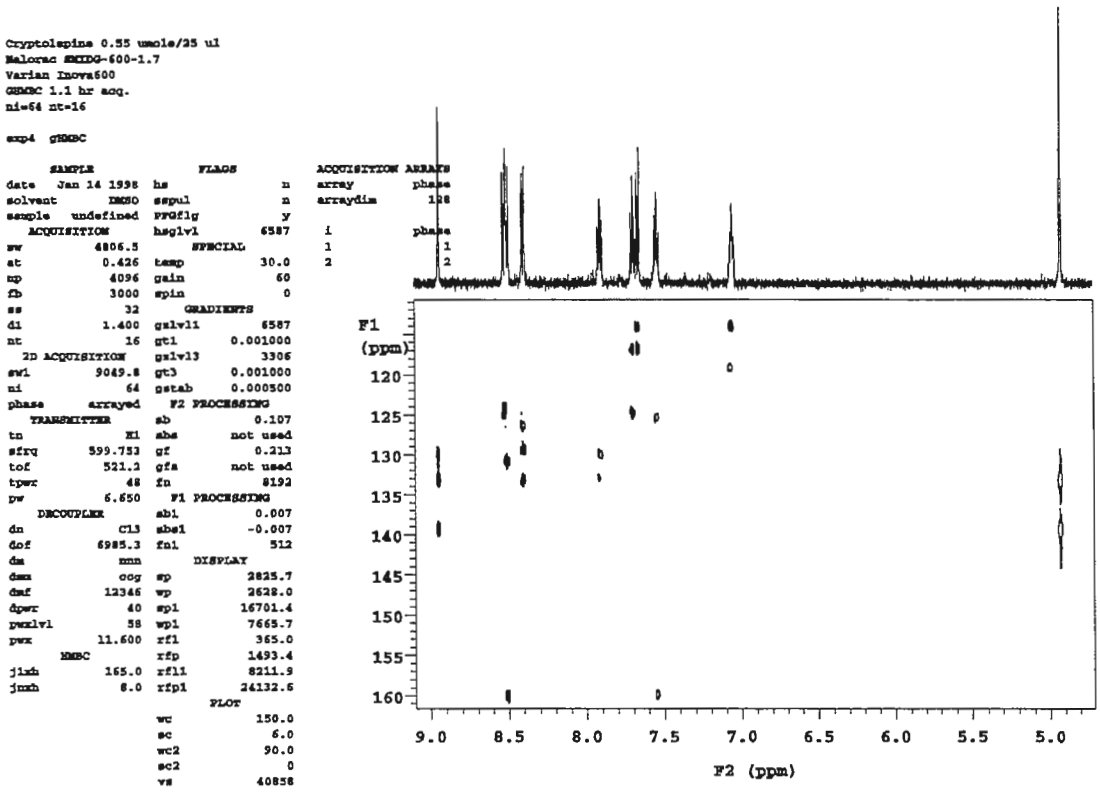

Figure 5. GHMBC spectrum of 0.55 μmole of cryptolepine (**1**) acquired using a Nalorac SMIDG-600-1.7 submicro gradient NMR probe in a Varian Inova 600. The data were acquired in 1.1 hr. as 4096 x 64 (2 x 64 hypercomplex files) using 16 transients/t_1 increment. Signal-to-noise in the F_2 projection was 30:1.

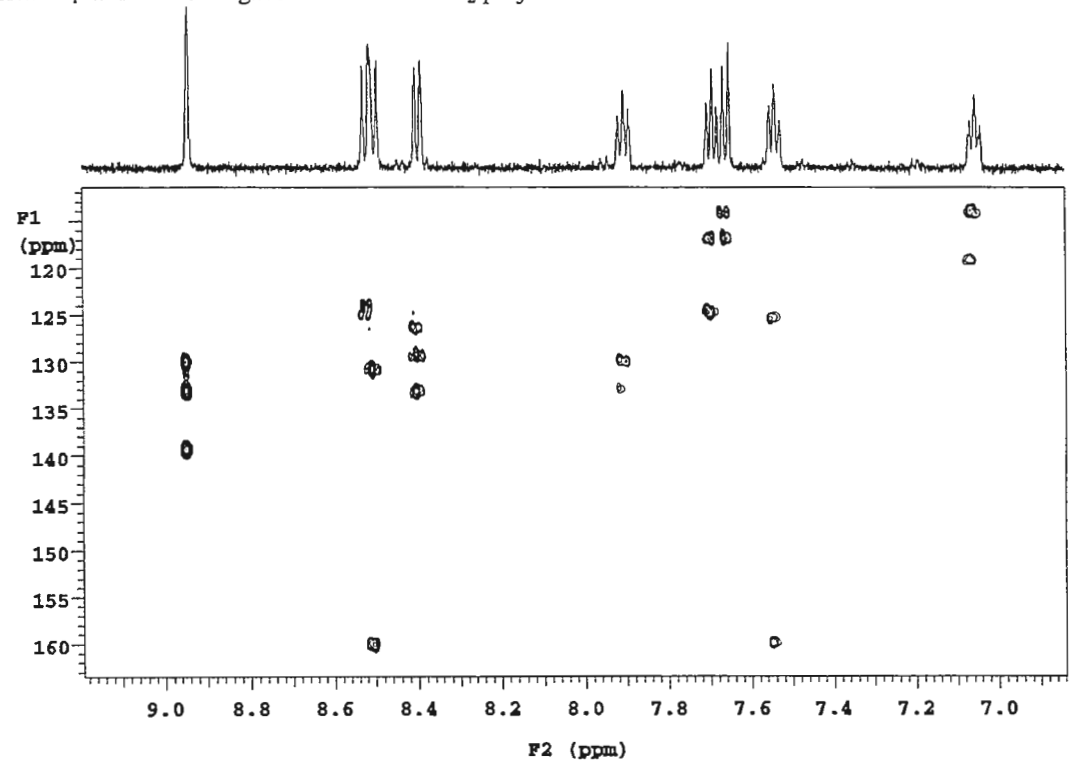

Figure 6. Expansion of the aromatic region of the GHMBC spectrum of cryptolepine (**1**) shown in Figure 5.

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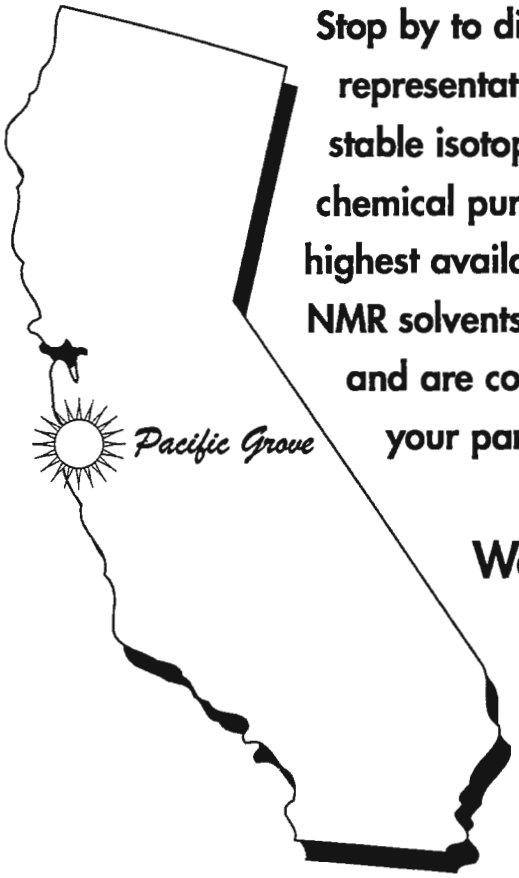

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Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

January 15, 1998 (received 1/22/98)

Dear Dr. Shapiro,

A while back (NMR Newsletter, no.370, 1989) we described our implementation of the P. COSY experiment as described by Bax (D. Marion and A. Bax, J. Magn. Reson. 80, 528-533 (1988)). Over the years this experiment has proved to be very useful for our users. It has undergone several changes during this time including: modifications of the phase cycling to reduce artifacts generated by incomplete relaxation (C. J. Turner and W. C. Hutton, J. Magn. Reson. 100, 469-483 (1992)) and to shift F1-axial peaks to the edge of the spectrum (D. Marion etal, J. Magn. Reson. 85, 393 (1989)) and modification of the pulse sequence such that odd transients are collected with a mixing pulse and for even transients, the mixing pulse is omitted and the receiver phase is shifted by 180° thus obviating the need for post-acquisition manipulation of the data.

Since this experiment is used extensively in our biological NMR work, the latest modification is to replace pre-saturation of the solvent (generally 9:1 H2O:D2O) with WET (*w*ater suppression *e*nhanced through *T1* effects) (R. J. Ogg etal, J. Magn. Reson. 104, 1-10 (1994)). The WET sequence uses a series of four variable-tip-angle solvent-selective RF pulses optimized to be insensitive to T1 differences and B1-field inhomogeneity with each RF pulse followed by a dephasing field gradient. Gradient echoes are minimized by halving the intensity of each subsequent gradient pulse (S. H. Smallcombe etal, J. Magn. Reson. 117, 295-303 (1995)). Even though WET is a solvent-saturation technique, its advantage, when compared to pre-saturation, is that resonances undergoing slow to medium exchange with the solvent are still observable.

P. COSY spectra of a 108 amino acid protein with pre-saturation (Fig. 1A) and the WET solvent-saturation (Fig. 1B) technique are shown below. The data, 1K x 2K complex points, were collected on a Varian INOVA 600 MHz spectrometer. The number of points in t_1 were extended to 2K points using linear prediction. The data were zero-filled to 4K x 4K and apodized with a 90° phase-shifted Gaussian function. Other than baseline correction in F1, the data were not modified by the use of solvent deconvolution software.

Sincerely,

John J. Likos

Shengtian Yang

John J. Likos

Shengtian Yang

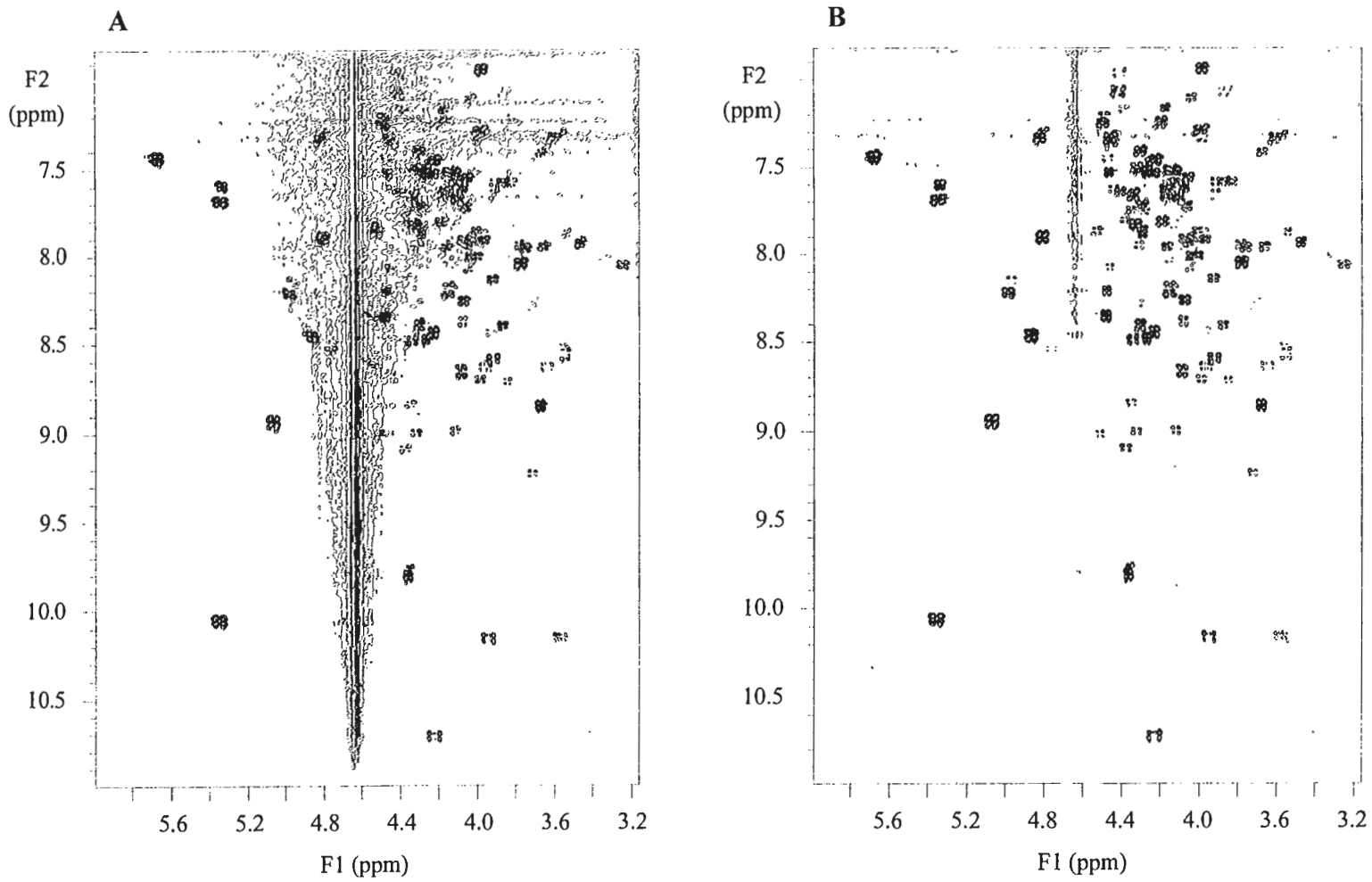
A
F2
(ppm)
7.5
8.0
8.5
9.0
9.5
10.0
10.5
5.6
5.2
4.8
4.4
4.0
3.6
3.2
F1 (ppm)
B
F2
(ppm)
7.5
8.0
8.5
9.0
9.5
10.0
10.5
5.6
5.2
4.8
4.4
4.0
3.6
3.2
F1 (ppm)

Figure 1

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Fernando Arias-Mendoza, M.D., Ph.D.
Nuclear Magnetic Resonance
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Prof. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA., 94303

(received 12/30/97)

Principal Component Analysis of ^{31}P Magnetic Resonance Spectroscopy of Human Non-Hodgkin's Lymphomas *In Situ.*

Dear Barry:

In order to acquire non-contaminated spectra from human tumors *in situ*, spectral localization is needed. It is agreed that the best localization is 3-dimensional to facilitate comparison between different tissues[1,2]. However, such localization presents difficulties in analyzing a large number of spectra. To overcome these difficulties, we have studied localized data sets with principal component analysis (PCA) to extract their statistically significant components[3]. Here we report the extension of the PCA application to a combined data set of 8 patients and 16 examinations of localized ^{31}P MRS of human non-Hodgkin's lymphomas (NHL) *in situ*.

Localized ^{1}H-decoupled ^{31}P MRS of human NHL was acquired at 1.5 T after collection of referencing images and adjustment of the magnetifc field shims[4]. Data analysis comprised the identification of the tumor on the images, extraction of the corresponding spectra, and application of PCA on the combined data set of extracted spectra after frequency and phase correction[5]. The resultant information was then reassigned to the corresponding patient and compared with imaging and clinical information. Figure 1 shows an example of tumor identification and the extraction of the corresponding spectra.

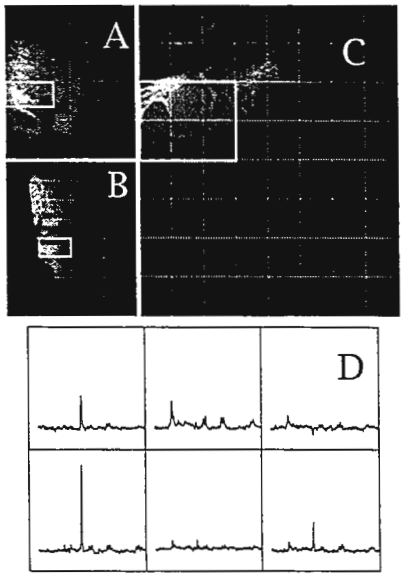

Fig. 1: Panels A, B, and C correpond to MR images in coronal sagittal and axial orientation respectively. Each image shows the 3D grid that demonstrates the volumes where each phosphorus spectrum was aquired from. Panel D shows 6 spectra subsampled from the localized data set matching the 6 volumes highlighted in panel C. The highlights in panels A and B show the coronal and sagittal projections of these same volumes.

The first 2 principal components of the corrected data set showed a signal component of the total variance of ~69% (Fig. 2A). They clearly suggested a possible re-expression into a muscle and a tumor component (Fig. 2b). The spectral tumor component (STC, upper spectrum of Fig. 2B) was measured in each spectrum and a total STC per patient examination was obtained and compared to the tumor size by imaging and by palpation. An acceptable correlation was found between STC and imaging (r^2=0.7), while no correlation was found with the clinical data (r^2=-0.3). Also, the total STC was analyzed before and after treatment and correlated to clinical response. In this small sample, the 4 patients that clinically responded to treatment showed a reduction of total STC while the 3 that did not respond showed an increase in total STC. One patient was not able to be evaluated.

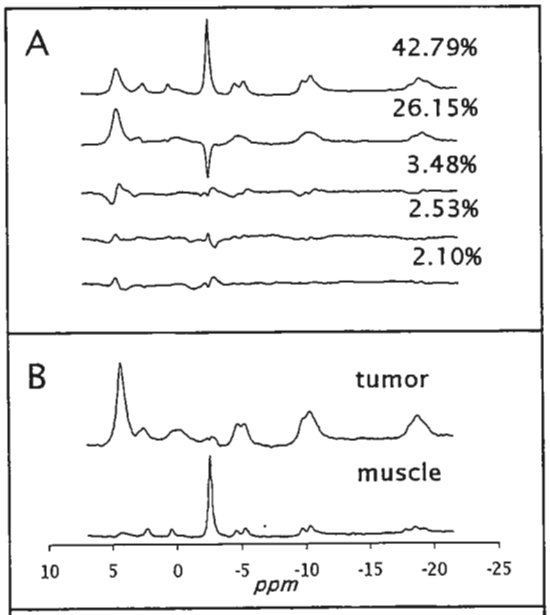

Fig. 2: Panel A, first 5 principal components obtained from the corrected and extracted data set. The numbers represent the total variance of the signal per component; Panel B is the addition and subtraction of the first two principal components of panel A demonstrating their re-expression as tumor and muscle spectra.

These preliminary results suggest that: 1) PCA is a suitable technique to analyze large quantities of spectra; 2) The PCA analysis of localized ^{31}P MRS of NHL is an objective and accurate way of determining tumor size and treatment response with a possible application in a clinical setting; and 3) The remaining principal components with significant variance (Fig. 2 panel A) may be related to biological and/or treatment variability in NHL an are still under investigation.

References:
1. Brown, T. R., *Chemical Shift Imaging* in Encyclopedia of NMR (Eds. D. M. Grant, R. K. Harris, I. R. Young) John Wiley & Sons, *pp*1261-72, 1995.
2. Arias-Mendoza, F., Javaid, T., Stoyanova, R., Brown, T. R., and Gonen, O., *NMR in Biomed.* **9**:105-13, 1996.
3. Stoyanova, R., Kuesel, A. C., and Brown, T. R., *J. Magn. Reson.* **115**:265-9, 1995.
4. Negendank, W. G., Padavic-Shaller, K. A. Li, Ch-W. *et al*, *Cancer Research* 55:3286-94, 1995.
5. Brown, T. R., and Stoyanova, R., *J. Magn. Reson.* **112**:32-43, 1996.

Sincerely yours,

Dr. Fernando Arias-Mendoza
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37,207-2 **Sodium deuteroxide,** 40 wt. % solution in D_2O, 99.9 atom % D — **10g $21.20; 50g $70.85**

32,994-0 **Tris(hydroxy-*d*-methyl)amino-d_2-methane,** 98 atom % D — **1g $24.90; 10g $135.70**

NMR Standards

T2,400-7 **Tetramethylsilane,** 99.9+%, NMR grade, A.C.S. reagent (TMS) — **25g $19.90; 100g $56.30**

17,883-7 **3-(Trimethylsilyl)-1-propanesulfonic acid, sodium salt,** 99% (DSS) — **1g $17.00; 5g $67.10**

26,991-3 **3-(Trimethylsilyl)propionic-*2,2,3,3-d_4* acid, sodium salt,** 98 atom % D (TSP-d_4) — **1g $36.75; 5 x 1g $116.75**

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42,619-9 **Algal amino acid mixture, uniformly ^{13}C labelled,** 99 atom % ^{13}C — **250mg $280.90; 1g $879.80**

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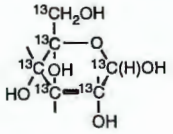
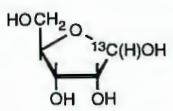
29,925-1 **Ammonium-^{15}N chloride,** 98 atom % ^{15}N — **250mg $33.00; 1g $80.00** — $^{15}NH_4Cl$

36,459-2 **Carbon-^{13}C dioxide,** 99 atom % ^{13}C **250mL $75.00; 1L $150.00**

38,937-4 **D-Glucose-$^{13}C_6$,** 99 atom % ^{13}C — **100mg $91.00; 250mg $175.00; 1g $482.30**



31,083-2 **D-Ribose-*1*-^{13}C,** 99 atom % ^{13}C — **100mg $124.85; 250mg $225.00**



Labelled Products for Mechanistic Studies

Aldrich offers a variety of products, including stable isotopes, that can be utilized in kinetic and mechanistic studies.[1-3] A few of the labelled products we offer are listed here.

References: (1) Okuyama, T. et al. *J. Am. Chem. Soc.* **1994**, *116*, 6480. (2) Diamond, G.M. et al. *ibid.* **1996**, *118*, 8024. (3) Jia, L. et al. *ibid.* **1996**, *118*, 7900.

17,586-2 **Acetone-d_6,** 100.0 atom % D — **5g $57.50; 25g $224.80**

17,587-0 **Benzene-d_6,** 100.0 atom % D — **5g $57.90; 25g $211.00**

15,185-8 **Chloroform-*d*,** 100.0 atom % D — **10g $18.30; 50g $61.20**

15,189-0 **Deuterium oxide,** 100.0 atom % D — **10g $25.40; 50g $76.15; 250g $205.00; 1kg $609.00**

23,336-6 **Dichloromethane-d_2,** 99.95 atom % D — **1g $29.50; 5g $97.20; 25g $361.50**

19,310-0 **Lithium aluminum deuteride,** 98 atom % D — **1g $19.10; 5g $75.30**

19,416-6 **Methyl-d_3 alcohol-*d*,** 99.96 atom % D **1g $28.60; 10g $175.00**

29,309-1 **Methyl-d_3-magnesium iodide,** 99+ atom % D, 1.0*M* solution in diethyl ether — **100mL $73.00; 800mL $371.00**

15,691-4 **(Methyl sulfoxide)-d_6,** 100.0 atom % D — **1g $12.80; 5g $48.60; 25g $173.80**

32,935-5 **(Methyl-d_3)triphenylphosphonium iodide,** 99 atom % D — **1g $15.40; 10g $84.60**

29,767-4 **Phenyl-d_5-magnesium bromide,** 99+ atom % D, 0.5*M* solution in THF — **50mL $51.40; 800mL $498.00**

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23,338-2 **Toluene-d_8,** 100.0 atom % D — **1g $33.40; 5g $118.80; 10g $196.00; 25g $460.00**

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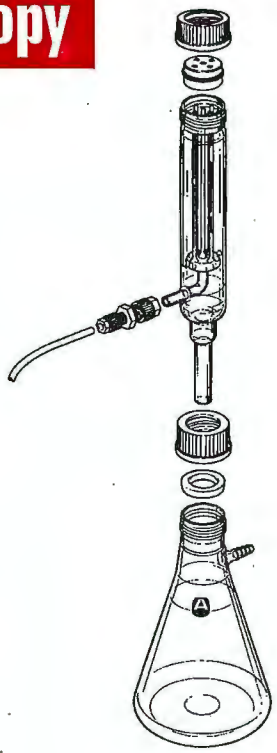
Techware Equipment for NMR Spectroscopy



Aldrich 5-Position NMR Tube Cleaner System

Washes up to five 5mm (i.d.) x 7in. (L) NMR tubes in a single cleaning cycle. NMR tube caps can be used to plug holes if less than five tubes are to be cleaned. Cleaning solvent is pulled from an external container via PFA tube, eliminating repetitious filling of side-mounted reservoirs. *Note: Bottle for cleaning solvent is not supplied.*

- Totally inert — cleaning solvents contact only borosilicate glass, PTFE, and PFA
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- No ground glass joints to freeze; no grease contamination
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Description	Cat. No.	Each
NMR tube cleaner system, complete	**Z28,838-1**	$299.00

Replacement Parts:	Cat. No.	Each
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NMR tube holder, 5-position, PTFE	**Z28,841-1**	45.00
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Cap with hole, GL-45 (cleaner to flask)	**Z28,844-6**	5.30
PTFE seal (tube cleaner to flask)	**Z28,845-4**	18.00
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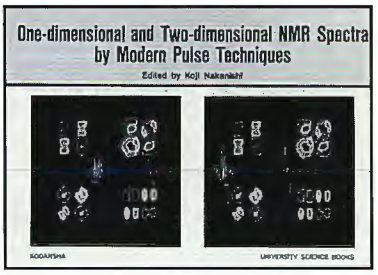
Compression fitting, PFA, ⅜ in. to ¼ in.	**Z28,847-0**	34.00
PFA tubing, ¼ in.(o.d.) x 2ft (L)	**Z28,848-9**	14.00

One-dimensional and Two-dimensional NMR Spectra by Modern Pulse Techniques

K. Nakanishi, Ed., University Science Books, Sausalito, CA, 1990, 234pp. Softbound.
Presents theory and clear-cut examples of modern NMR pulse techniques.

Z27,419-4 $39.00



Modern NMR Techniques for Chemistry Research

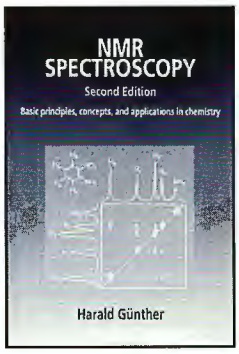
A.E. Derome, Pergamon Press, Oxford, UK, 1987, 280 pp. Softbound.
Serves as a practical guide to the use of NMR spectroscopy in terms suited to organic and inorganic chemists engaged in the solution of structural and mechanistic problems.

Z22,402-2 $55.40

The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra

C.J. Pouchert and J. Behnke, Aldrich Chemical, Milwaukee, WI, 1992, 4300pp.
Three-volume set of 12,000 high-resolution 300MHz proton and 75MHz ^{13}C FT-NMR spectra, arranged according to functionality.

Z23,103-7 $975.00



NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry

2nd ed., H. Günther, John Wiley & Sons, New York, NY, 1995, 581pp. Softbound.
This edition provides a comprehensive introduction to the basic techniques, combined with advanced applications to organic chemistry. Includes a new chapter on two-dimensional methods and an expanded treatment of Fourier transform methods.

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January 14, 1998
(received 1/20/98)

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

Estimation of Paramagnetic Complex Concentration from Bulk Magnetic Susceptibility Shifts

Dear Dr. Shapiro,

We employ NMR Spectroscopy to study the structure and dynamics of paramagnetic lanthanide complexes which are of potential interest as contrast agents for MRI. A common problem in the preparation of these compounds in aqueous media is the formation of hydrates and/or NaCl salts. Typically, the concentrations of stock solutions are standardized by complexometric titrations with EDTA and xylenol orange as indicator.[1] Further complexities arise when isolated compounds are required. In order to determine the composition of isolated complexes, the ligand is "burned" at 600°C leaving the metal oxide. The oxide must then be converted to the chloride species, neutralized and finally diluted to the appropriate concentration for the titration. The entire procedure must be carried out quantitatively to ensure reliable results. The method itself is laborious, time consuming (2-3 days) and requires the need for relatively large quantities of material to be sacrificed. In addition, color changes are often obscure and subjective. Titrations have been reported using up to 3 indicators to obtain definitive color changes.[2]

For these reasons, we were interested in an alternative method for estimating the content of paramagnetic complex in solution and to ultimately determine the molecular weight of isolated materials. The Evans Method is a simple and useful technique for the accurate determination of the

[1] Woyski, M.M. and Harris, R.E. "Treatise on Analytical Chemistry" Vol. 8, Part II, **1963**, 54.
[2] Brunisholz, G. and Randin, M. Helvetica Chimica Acta **1959**, 1927.

susceptibility of paramagnetic molecules in solution.[3] The method utilizes the bulk magnetic susceptibility shift of an inert compound (eg. *t*-BuOH or dioxane) caused by the presence of a paramagnetic solute. To a first approximation, the bulk magnetic susceptibility shift (Δ_χ) is given by:[4]

$$\Delta_x = \frac{4\pi cs}{T}\left(\frac{\mu_{eff}}{2.84}\right) \times 10^3$$

Here, the concentration of paramagnetic solute is given by c in mol l^{-1}, s is dependent on the shape and position in the magnetic field (S=1/3 for a cylinder parallel to the main field), T is the absolute temperature and μ_{eff} is the effective magnetic moment for a particular lanthanide ion.

In a typical case, we measure Δ_χ for a reference compound (*t*-BuOH) and solve for c after substitution of the other constants in the equation. The experimental procedure requires 2 separate measurements and the use of an inner co-axial tube in addition to a normal NMR tube. In the first measurement, a solution containing the *t*-BuOH in D_2O is placed in the outer tube with TMS in CCl_4 or $CDCl_3$ in the inner tube. The spectrum is calibrated on the TMS signal from the inner tube. The second measurement is made in an identical manner except that the outer tube now contains the paramagnetic complex and *t*-BuOH in D_2O. The observed frequency shift of the *t*-BuOH is the bulk magnetic susceptibility shift.

The method was tested with a standard $TmCl_3$ solution and results obtained are in very good agreement with the actual concentrations (less than a 2% error). We have obtained accurate results for both Tm(III) and Gd(III) complexes. Apart from ICP, this method for determination of concentration of paramagnetic solute is the most accurate and requires only a small amount of sample. For us, it is also the fastest and most convenient method since the NMR Sprectrometer is readily available and ICP (located outside of our department) results may take from several days up to weeks to be returned.

Sincerely Yours,

Daniele M. Corsi

Daniele M. Corsi

Please credit this contribution to the account of Dr. J.A. Peters.

---

[3] Evans, D.F. *J. Chem. Soc.* **1959**, 2003.

[4] Springer, Jr., C.S., *et.al. Magnetic Resonance in Medicine* **1990**, *13*, 239.

Austin & Repatriation
Medical Centre

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

December 17, 1997
(received 12/29/97)

Observation of Intracellular Cation Compartmentation in Rat Tissues by ^{133}Cs NMR Spectroscopy

Dear Dr Shapiro,

Potassium NMR is not readily used for intracellular studies of cations because of its low NMR sensitivity and broad linewidths, relative to chemical shift. Caesium–133 NMR, with its 100-fold greater NMR sensitivity and narrow linewidths, has been used as a potassium substitute to study the intracellular cation environment [1-3]. A further advantage of ^{133}Cs, compared with ^{39}K, is that intra- and extracellular caesium have distinct chemical shifts.

Our interest in the role of intracellular cation compartmentation lead to the study of ^{133}Cs in isolated perfused tissues. Examination of spectra from Langendorff-perfused hearts from caesium-fed rats suggested that the intracellular signal was composed of poorly-resolved multiple-components 1.51 and 1.12 ppm to higher field, relative to the extracellular (perfusate) caesium(Figure 1). The poor resolution of the overlapping intracellular peaks lead us to examine another tissue, isolated rat hepatocytes from caesium-fed rats. Trapped in agarose threads they could be perfused for several hours without loss of ATP signal intensity. The ^{133}Cs NMR spectrum from hepatocytes demonstrates more clearly the presence of at least two intracellular cation peaks 2.0 and 0.87 ppm to higher frequency than the extracellular caesium (Figure 2). The observation of distinct peaks from the intracellular environment indicates slow exchange on the NMR chemical shift timescale and offers an opportunity to study homeostatic regulation of cation distribution within the cell.

Sincerely,

Wellard, R.M. Bicknell, W. Adam, W.R.

1. Davis, D.G., Murphy, E., London, R.E., *Biochem.* **1988**, *27*, 3547-3551.
2. Shehan, B.P., Wellard, R.M., Adam, W.R., Craik, D.J., *J. Magn. reson. Med.* **1993**, *30*, 573-82.
3. Neil, J.J., Duong, T.Q., Ackerman, J.J.H., *J. Magn. Reson. Med.* **1996**, *35*, 329-335.

Austin & Repatriation Medical Centre, Heidelberg West 3081 Australia (Tel. 613-94962964)
Monash University (Parkville Campus) 3052 Australia. (Tel. 613 -99039546)

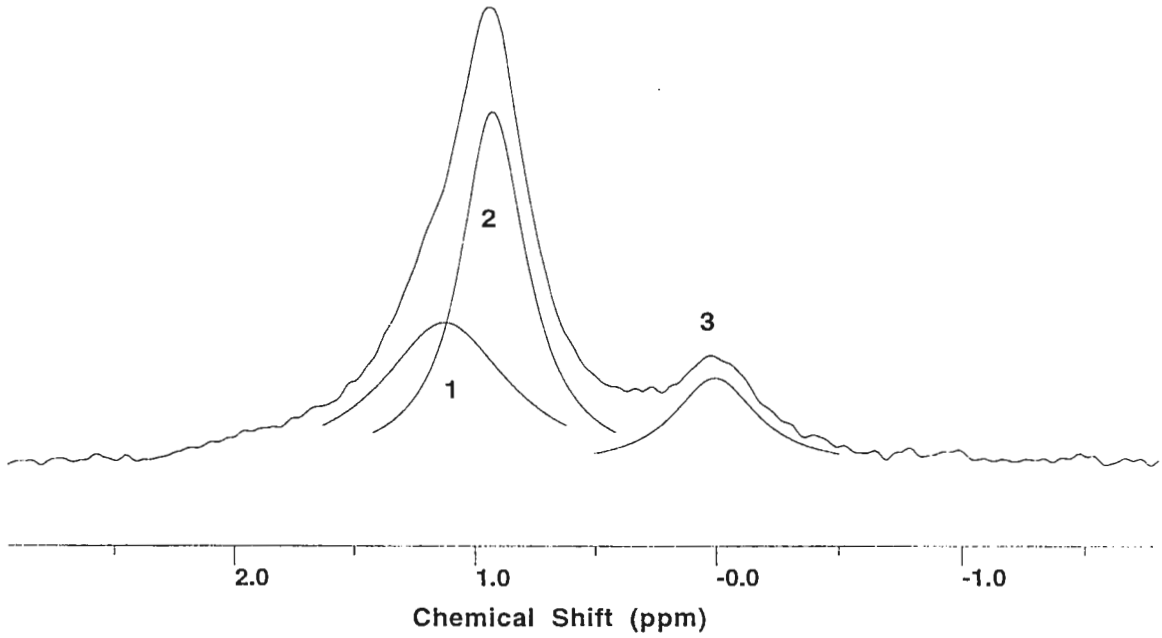

Figure 1: Cs spectrum of an isolated Langendorff-perfused heart showing two fitted intracellular components (peaks 1 and 2) when perfused with buffer containing 0.6 mM CsCl (peak 3). Acquisition parameters: 2560 transients; 8192 data points; spectral width, 5000 Hz and repetition time, 6.5 s. Signal-to noise was 75:1. Prior to processing, 1 Hz exponential linebroadening was applied. The solid lines show fitted Lorentzians of linewidth (and chemical shift): (1) 24.2 Hz (1.13 ppm), (2) 11.9 Hz (0.92 ppm) and (3) 15.6 Hz (0.00 ppm).

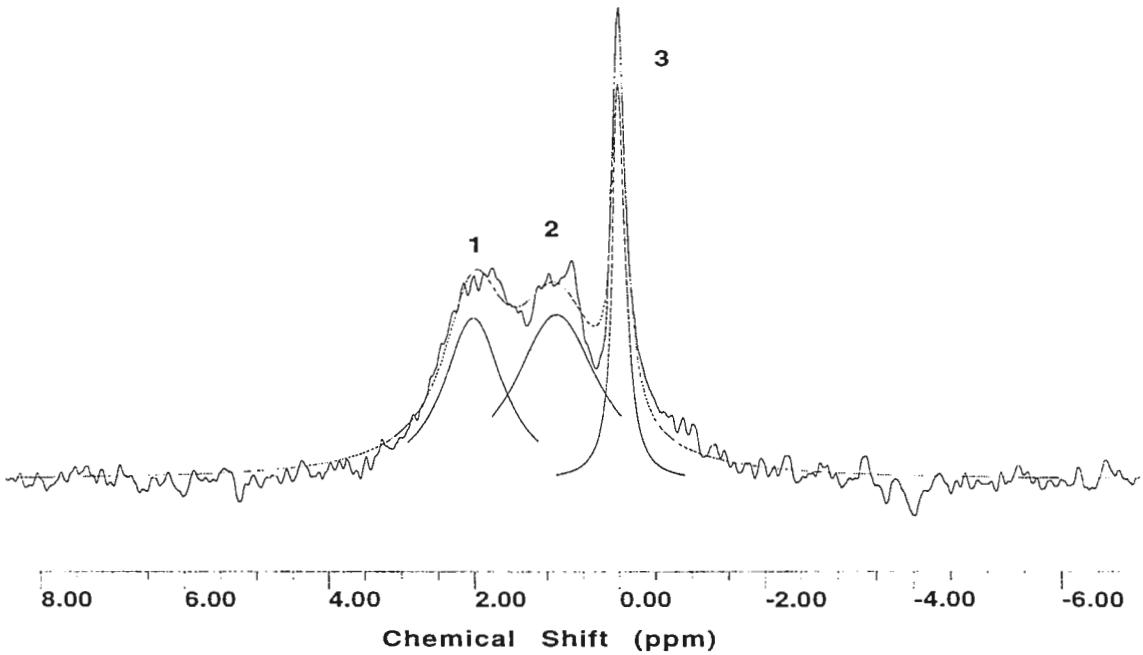

Figure 2: ^{133}Cs spectrum acquired from hepatocytes in agarose threads at 39.37 MHz and 27°C. The spectrum is well described by three overlapping Lorentzian lines at 2.00, 0.87 and 0.00 ppm of linewidth 37, 21 and 7 Hz, respectively (superimposed). The narrow peak at 0 ppm is from caesium in the perfusing buffer. Acquisition parameters: 1424 scans; repetition time 5.7 s; 8k data points acquired over a spectral width of 2500 Hz with a pulse length of 90 µs. Total experiment time was 2 1/4 h. 3 Hz exponential linebroadening was applied prior to processing.

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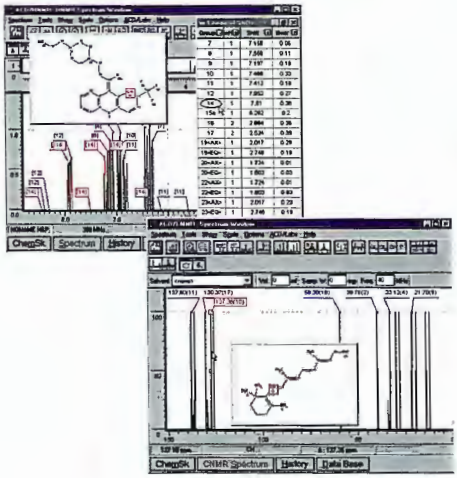

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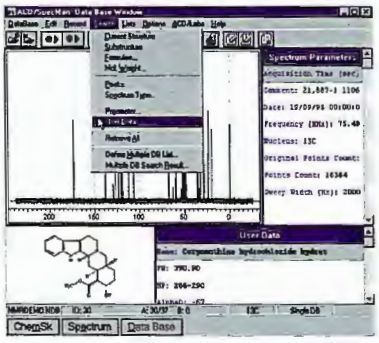
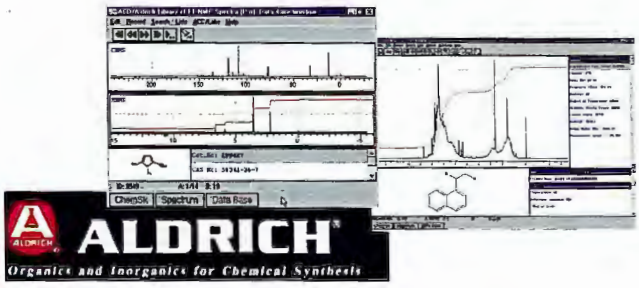
NMR Manager 3.0



NMR Databases from ACD



ACD NMR Databases:

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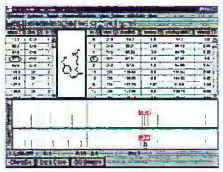

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- provide suggested structures from two atom fragment overlap
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- include filters for ^{1}H NMR, IR and MS information
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- HNMR shifts and coupling constants
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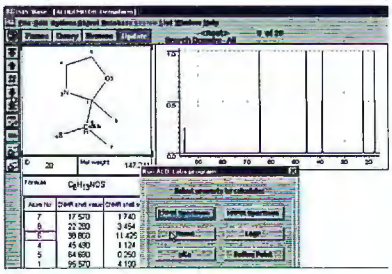
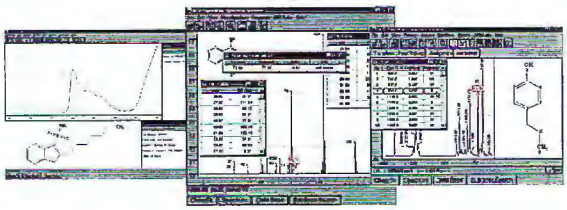
ACD/ISIS integrates MDL ISIS/Draw and ISIS/Base



ACD/SpecManager 3.0



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ACD/NIST Spectral Databases

The ACD/NIST IR Database contains FT-IR spectra for over 5200 compounds compiled by the National Institute of Standards and Technology and the Environmental Protection Agency. *(Spring release)*

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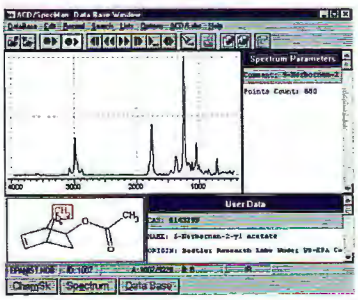
NIST Spectral Databases



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The NMR Newsletter - Book Reviews

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

NMR Spectroscopy and Its Application to Biomedical Research

Edited by

Susanta K. Sarkar

Elsevier, Amsterdam, The Netherlands, 1996. http://www.elsevier.nl
406 pages, $230. ISBN 0-444-89410-1

I am not a military man whatsoever, but the metaphor "heavy artillery" truly fits this excellent book edited by Susanta K. Sarkar (SmithKline Beecham Pharmaceuticals). Sarkar has managed not only to bring together a group of top-level authors with outstanding contributions, but also to keep the volume tight and compressed. It takes only 380 pages of text to deliver this concentrated dose of up-to-date NMR spectroscopy and a closely related issue of isotope labeling in Chapter 3. A well-organized seven-page subject index extends the book. There is a brief Foreword by Richard Ernst.

A unique virtue of this book is that it comprises pretty much all areas of applications of modern multidimensional NMR in eight chapters, including structural studies of nucleic acids and carbohydrates, and solid state applications, beside more common aspects of protein studies. Most references for each chapter are from the nineties, according to the nature of the subject.

The first chapter, written by William M. Westler, carries perhaps the most educational value. This attempt to summarize coherence pathway flow in multidimensional experiments in a consistent, systematic, and very visual protocol should be welcomed with enthusiasm.

Fasten your seat belts for the next chapter, written by Luciano Mueller and N. Vasant Kumar. We have read much about multidimensional experiments for proteins, but Chapter 2 will impress you. It is not easy reading due to the concentrated material, but that is exactly the benefit to the reader. Beside learning about all important issues of such experiments in general "on the sideline", one will receive advice on practical issues, such as how *not to fry* your probe.

Chapter 3 by Brian J. Stockman is a unique type of contribution, fitting very well with the overall picture. I believe it was only the famous NMR volumes of Methods in Enzymology, which gave extensive practical advice on isotope labeling methodology before this work.

In Chapter 4, Paul L. Weber gives a thorough and exhaustive assessment of structure calculations from input NMR data. It is not only a practically useful, professional, and highly educational chapter, but is a pleasant reading as well, in spite the complicated subject. Perhaps more could have been included about chemical shift as an input and constraint, since such values, as well as chemical shift index (CSI) have become quite widely used tools for characterizing secondary structure.

Linda K. Nicholson, Lewis E. Kay, and Dennis A. Torchia joined to present Chapter 5 on protein dynamics as studied by NMR. The chapter is as good as the list of authors would suggest. One receives a great introduction both to theory and to carefully crafted experimental approaches. Particular attention is paid to AX_3 spin systems, e.g., sidechain methyl groups, and related data processing. Perhaps the comparison to the approach taken by Peng and Wagner could have deserved a bit of more than a half a page in this chapter.

David E. Wemmer presents the next chapter on nucleic acid structure and dynamics. Although most techniques for multidimensional NMR data acquisition, processing, and data analysis, as well as structure calculation approaches are quite similar, or closely related to those applied to proteins, nucleic acids are usually left out, or are presented as a sideline of the discussion. Pleasantly, it is not the case for this book.

continued

The same can be said about Chapter 7 about carbohydrate structure and dynamics, by Laura E. Lerner. Carbohydrates present a special challenge for NMR spectroscopy due to the high complexity of the information. Such studies are now gaining importance, oligosaccharides being part of the recognition process in many biochemical processes.

The closing chapter by Alexandra Simmons, Susanta K. Sarkar, and Lynn W. Jelinski gives an ambitious, yet very concentrated overview to solid state applications in biomolecular NMR. This chapter provides a good introduction to solid state NMR in general, then tells us about particular applications, such as those for bone, lipid bilayers and membranes, and interactions of drugs with membrane lipids. Structure studies of membrane proteins, DNA, fibrous proteins, and ligand-protein complexes are also discussed.

It is often difficult to choose a book title; in this case the title promises a bit more than what is delivered -- there is no discussion of imaging, which is, of course, an essential part of biomedical research. But I think most readers will be more than happy to accept this (and the relatively high price) in return the exceptional value of this book.

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UNIVERSITY OF ILLINOIS
AT CHICAGO

College of Medicine at Urbana-Champaign

Department of Medical Information Sciences
BIOMEDICAL MAGNETIC RESONANCE LABORATORY (MC-008)
2100 South Goodwin Avenue
Urbana, Illinois 61801

January 5, 1998
(received 1/12/98)

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

Dear Barry:

POSITION AVAILABLE

We have an immediate opening for an individual to carry out research and to modify and maintain instruments and software in our laboratories, primarily supported as an NIH NCRR Biomedical Technology Research Resource. Some details of our facilities and programs may be found in the January issue of this Newsletter, at our Web site (URL http://bmrl.med.uiuc.edu:8080/), or obtained by fax (217-244-1330), phone (217-244-0600) or e-mail (bmrl@bmrl.med.uiuc.edu).

Paul C. Lauterbur

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Oleg Jardetzky, M.D., Ph.D.
Professor of Molecular Pharmacology

Tel.: 650/723-6153
Fax: 650/723-2253
Email: jardetzky@stanford.edu

January 21, 1998

POSTDOCTORAL POSITION

Immediate opening for a first or second year Postdoctoral Fellow to work on the physical mechanisms of allosteric control in proteins. Good programming skills and familiarity with Molecular Dynamics Simulations of allosteric transitions in proteins, Monte Carlo methods and NMR relaxation theory are essential. To apply send c.v. to Prof. Oleg Jardetzky by fax at 650/723-2253, as an email attachment to jardetzky@stanford.edu or mail to above address.

THE OHIO STATE UNIVERSITY

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

corrigenda
December 17, 1997
(received 12/26/97)

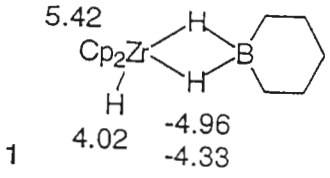
Dear Barry,

My colleagues have gleefully pointed out serious errors in my last letter ~~#417~~ 471, p. 23. The structures, corrected below, are indeed different. Also the relaxation term is,

$$R_q\varrho = \Sigma J_\alpha[\vartheta^\alpha, [\vartheta^{-\alpha}, \varrho]] \quad .$$
$$\alpha=0, \pm1, \pm2$$

With my regrets
Yours sincerely,

Gideon Fraenkel
Professor of Chemistry



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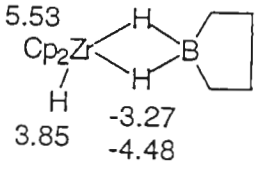

2

POSTDOCTORAL POSITION AVAILABLE

Department of Chemistry, National Taiwan University

A post-doctoral position is available for utilizing multiquantum NMR relaxation technique to study adsorption in zeolite systems. Our laboratory is well equipped with a Bruker MSL-500 spectrometer and a Bruker MSL-300 spectrometer. The equipments for zeolite synthsis are also available in our group. Interested applicants for this postdoctoral position should have backgound in NMR relaxation. Interested parties should submit their CVs and a list of references to :

Lian-Pin Hwang
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Phone: 886-2-23668287 Fax: 886-2-23620200
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Address all Newsletter correspondence to:

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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. 474 (Mar.)	27 Feb. 1998
No. 475 (Apr.)	27 Mar. 1998
No. 476 (May)	24 Apr. 1998
No. 477 (Jun.)	22 May 1998
No. 478 (July)	26 June 1998

* 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.

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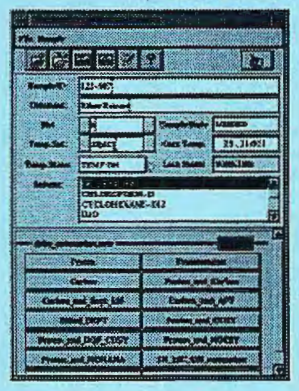
How To Run JEOL's Eclipse+ Spectrometer



Step 1: Enter your sample name and the solvent.

Step 2: Click the mouse button on the data you want.

Step 3: Walk away with your data.

JEOL's Eclipse Spectrometer will automatically do everything else for you.

- ✔ Auto Probe Tuning (with AutoTune Broad Band Probe)
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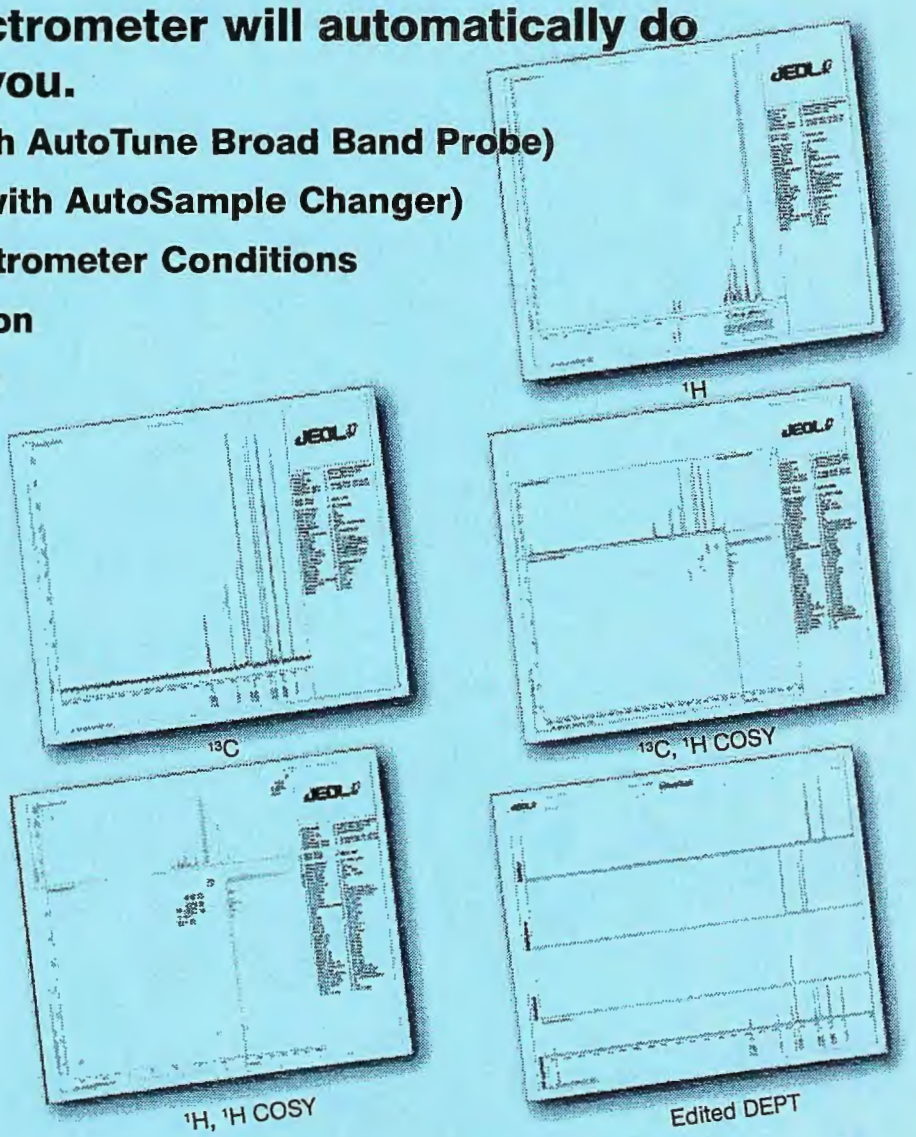

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