

**THE**  
***NMR***  
**NEWSLETTER**

**No. 504**  
**September 2000**

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<b>The NMR Newsletter: 'New' Way to Submit Technical Contributions</b>	<b>. Shapiro, B. L.</b>	<b>2</b>
A Remedy When Your Digitizers Are Not Fast Enough	<b>Gan, Z.</b>	<b>5</b>
More Than One Way to Spin a Rat: MAS <sup>1</sup> H NMR Spectra of Rat Testicular Tissue	<b>Griffin, J., Troke, J., Nicholson, J., and Lindon, J. C.</b>	<b>7</b>
BIRD-HMBC	<b>Burger, R., Schorn, C., and Bigler, P.</b>	<b>11</b>
Actively Shielded Magnets	<b>Nakashima, T.</b>	<b>12</b>
Synchronized Adiabatic Decoupling	<b>Zhang, S., and Gorenstein, D. G.</b>	<b>13</b>
Low-Level Sample Performance Comparison: 3mm Conventional vs. 3mm Cryo NMR Probes	<b>Martin, G. E., Russell, D. J., Hadden, C. E., Gibson, A. A., Zens, A. P., and Carolan, J. L.</b>	<b>17</b>
Solvent-Solute Interactions	<b>Diaz, D., and Berger, S. T.</b>	<b>23</b>
Experiences with a Home-Built High-Performance Computer Cluster	<b>Brüschweiler, R. P., Johnson, G., Prompers, J., Roe, D., and Scheurer, C.</b>	<b>27</b>
<sup>31</sup> P NMR of Brain Phospholipids in Schizophrenia	<b>Komoroski, R. A.</b>	<b>31</b>
Position Available	<b>Haines, T. H.</b>	<b>32</b>
Diffusion Tensor Analysis of Erythrocyte Suspensions	<b>Kuchel, P. W., Regan, R., and Chapman, B. E.</b>	<b>35</b>
Tracking Down Strange B <sub>0</sub> -Related Artifacts in PSGE NMR Experiments	<b>Furó, I., Price, W. S., and Stilbs, P.</b>	<b>37</b>
Temperature Dependence of Lead-207 Tensor Elements	<b>Dybowski, C.</b>	<b>40</b>
Positions Available	<b>Westbrook, J.</b>	<b>41</b>
Position Available	<b>Pines, A./Carmichael, D.</b>	<b>41</b>

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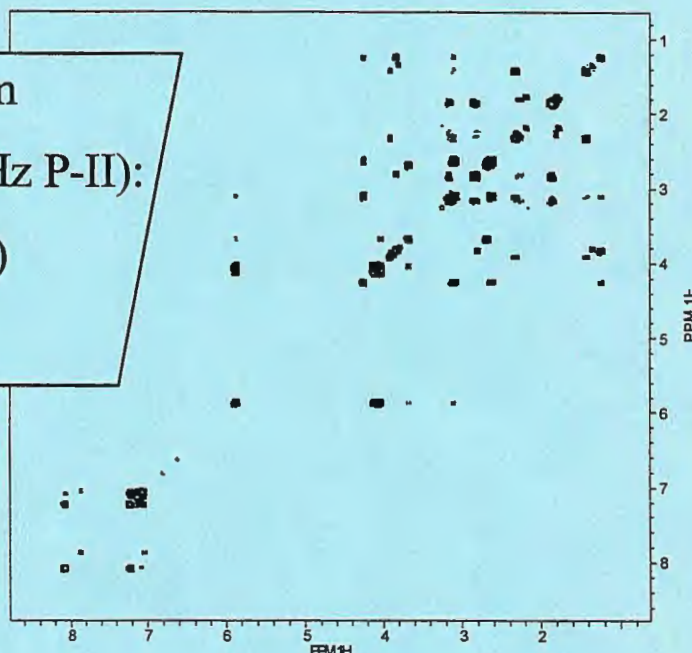
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THE NMR NEWSLETTER		NO. 504, SEPTEMBER 2000		AUTHOR INDEX	
Berger, S. T. . . . .	23	Gan, Z. . . . .	5	Lindon, J. C. . . . .	7
Bigler, P. . . . .	11	Gibson, A. A. . . . .	17	Martin, G. E. . . . .	17
Brüschweiler, R. P. . . . .	27	Gorenstein, D. G. . . . .	13	Nakashima, T. . . . .	12
Burger, R. . . . .	11	Griffin, J. . . . .	7	Nicholson, J. . . . .	7
Carmichael, D. . . . .	41	Hadden, C. E. . . . .	17	Pines, A. . . . .	41
Carolan, J. L. . . . .	17	Haines, T. H. . . . .	32	Price, W. S. . . . .	37
Chapman, B. E. . . . .	35	Johnson, G. . . . .	27	Prompers, J. . . . .	27
Diaz, D. . . . .	23	Komoroski, R. A. . . . .	31	Regan, R. . . . .	35
Dybowski, C. . . . .	40	Kuchel, P. W. . . . .	35	Roe, D. . . . .	27
Furó, I. . . . .	37			Russell, D. J. . . . .	17
				Scheurer, C. . . . .	27
				Schorn, C. . . . .	11
				Shapiro, B. L. . . . .	2
				Stilbs, P. . . . .	37
				Troke, J. . . . .	7
				Westbrook, J. . . . .	41
				Zens, A. P. . . . .	17
				Zhang, S. . . . .	13

THE NMR NEWSLETTER		NO. 504, SEPTEMBER 2000		ADVERTISER INDEX	
Acorn NMR, Inc. . . . .	inside front cover	Isotec Inc. . . . .	29		
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Bruker Instruments, Inc. . . . .	3				

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### FORTHCOMING NMR MEETINGS

- 5th International Workshop on Magnetic Resonance (Spectroscopy and Tomography)**, Rostov State University, Rostov-on-Don, Russia, **September 19-22, 2000**. Contact G. S. Borodkin, Yu. E. Chernysh, Tel: +7-8632-280894; Fax: +7-8632-285667; E-mail: [nmr@ipoc.rnd.runnet.ru](mailto:nmr@ipoc.rnd.runnet.ru).
- MOOT 13 NMR Minisymposium**, University of Toronto, Toronto, Canada, **September 30 - October 1, 2000**. Contact: Hiltrud Grondy, Dept. of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON M5S 3H6, Canada. Tel: 416-978-0448. On-line registration: <http://www.chem.utoronto.ca/facilities/nmr/moot13.html>.
- The Future of Solid State NMR in Biology**, Leiden University, Leiden, The Netherlands, **October 4-8, 2000**. Contact: SSNMR Secretariat, Leiden Institute of Chemistry, Leiden University, Faculty for Mathematics and Natural Sciences, Gorlaeus Lab, Einsteinweg 55, 2333 CC Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands. Tel: +31-71-527-4539; Fax: 31-71-527-4603.
- Contributions of NMR to Structural Biology**, Biozentrum Basel, Switzerland, **October 18, 2000**. Contact: S. Frauenknecht, Tel: +41-61-267-21-01; E-mail: [sabine.frauenknecht@unibas.ch](mailto:sabine.frauenknecht@unibas.ch).
- NMR: Drug Discovery and Design Conference - Post-Genomic Analysis**, McLean, Virginia, **October 24-26, 2000**. Contact: Mary Chitty, Cambridge Healthtech Institute, [mchitty@healthtech.com](mailto:mchitty@healthtech.com); Fax 617-630-1325.
- Protein Structure: Models, Fold, and Function Analysis Applications for Target Validation**, McLean, Virginia, **October 26-27, 2000**. Contact: Mary Chitty, Cambridge Healthtech Institute, [mchitty@healthtech.com](mailto:mchitty@healthtech.com); Fax 617-630-1325.
- International Conference on Structural Genomics 2000**, Yokohama, Japan, **November 2-5, 2000**. Contact: ICSG2000 Secretariat Protein Research Group, Genomic Sciences Center, RIKEN, 2-1 Hirosawa, Wako, Saitama, Japan. Tel: +81-(0)48-467-9427; Fax: +81-(0)48-462-4675; E-mail: [icsg@icsg2000.riken.go.jp](mailto:icsg@icsg2000.riken.go.jp).

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**'New' Way to Submit Technical Contributions.**

22 August 2000

As a step in modernizing the Newsletter, we are now asking that, when possible, technical contributions are submitted as **attachments to e-mail messages**. The attachments should be in WORD7 or WORD2000 formats, as **.doc files**. We will attempt to accommodate other formats as well, but please check with us in advance. (If the WORD or other pre-approved format is not available, we will reluctantly accept plain ASCII II text files or contributions embedded in standard e-mail, in which case formatting will be at our discretion.)

Graphics (including letterheads), drawings, spectra and your signatures should be embedded in the WORD files or included as separate file attachments when possible. If letterhead is not available as a graphic file, we will attempt to create a reasonable facsimile. To that end, please provide a faxed copy of the letterhead.

In any event, please include your preferred **e-mail address** below the signature line in your contributions.

Many thanks for your cooperation.

Barry Shapiro.  
shapiro@nmrnewsletter.com



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July 31, 2000

(received 8/7/00)

Dr. B. L. Shapiro

The NMR Newsletter

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## **"A Remedy When Your Digitizers Are Not Fast Enough"**

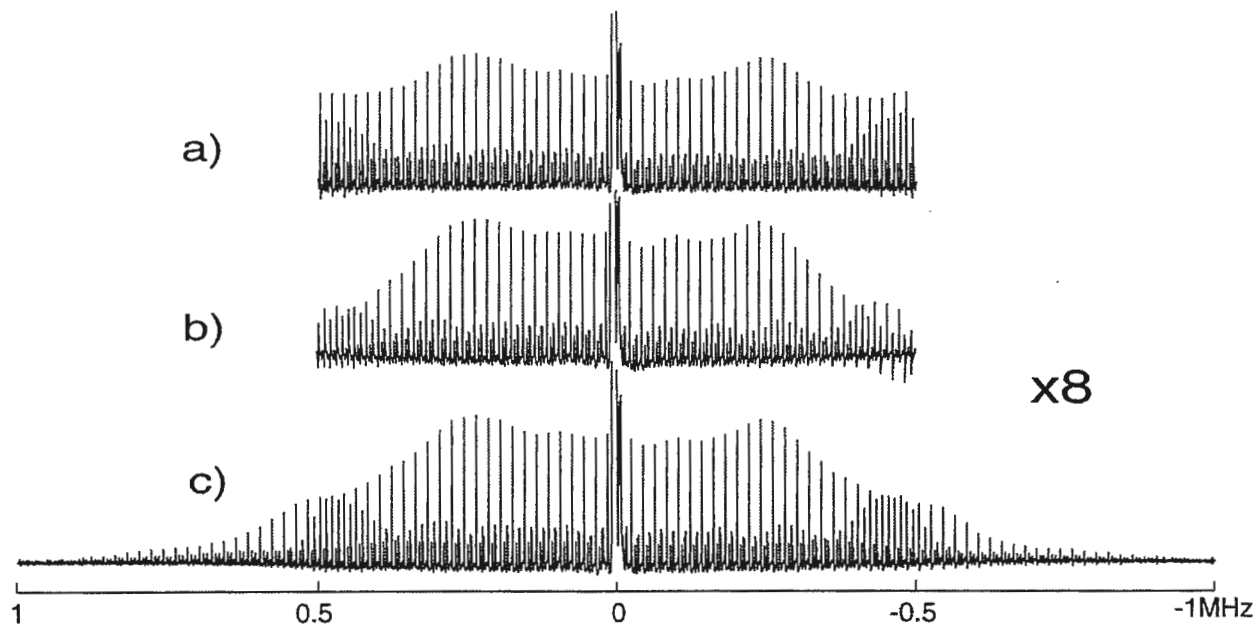
Dear Dr. Shapiro

The high magnetic fields available at National High Magnetic Field Laboratory (NHMFL) are particularly useful for high resolution solid state NMR of half-integer quadrupolar nuclei. Recently, we have been exploring the use of satellite transitions for further line narrowing. For  $5/2$  spins, the second-order quadrupolar effect for the  $\pm 3/2 \leftrightarrow \pm 1/2$  satellite transitions is more than three times smaller than the commonly observed central transition, therefore satellite transition spectra offer better spectral resolution (1-4). By transferring coherence from satellite to central transition, the 2D satellite transition MAS (STMAS) experiment can lead to isotropic NMR spectra if the magic-angle is accurately set (5,6).

Satellite transition spectra often span several megahertz which may exceed the maximum spectral window of NMR spectrometers. Figures 1(a) and (b) show the  $^{27}\text{Al}$  satellite transition MAS spectra of  $2\text{Al}_2\text{O}_3 + 9\text{B}_2\text{O}_3$ , a sample kindly provided by Dominique Massiot, CNRS of France. The quadrupolar coupling constant,  $e^2 q_{zz} Q/h$ , for the four aluminum sites ranges from 6~9 MHz in this compound (7). The 1MHz spectral window, maximum available on the 833MHz Bruker DRX console, is not enough to the satellite transition spectra and the spinning sidebands outside the spectral window are folded back.

The problem of spectral folding can be solved by the following method using the existing digitizer. Two FIDs are acquired under identical conditions except a shift to the data acquisition by a half of dwell-time. New FID can be generated by filling the data points from the two FIDs alternatively. The effective sampling rate of the generated FID is twice of the speed of the

digitizer therefore doubles the spectral window. The 2MHz window in (c) unfolds the satellite transition spinning sidebands showing the powder patterns excited by a  $1\mu\text{s}$  pulse with  $\gamma B_1/2\pi = 80\text{kHz}$ . The unfolding avoids the problems of incorrect spectral intensity and phase



which are evident in Figs. 1 (a) and (b).

Please credit this contribution to Nagarajan Murali's account.

Sincerely yours,

Zhehong Gan

- 1 A. Samoson, *Chem. Phys. Letters*, **119**, 29, (1985).
- 2 H.J. Jakobsen, J. Skibsted, H. Bildsoe, and N.C. Nielsen, *J. Magn. Reson.*, **85**, 173, (1989).
- 3 C. Jäger, *J. Magn. Reson.*, **99**, 353, (1992).
- 4 Z. Gan, T. Cross, R. Fu, A. Samoson and D. Massiot, manuscript in preparation.
- 5 Z. Gan, 41st ENC, Asilomar, CA, April 9-14, 2000.
- 6 Z. Gan *J. Am. Chem. Soc.*, **122**, 3243, (2000).
- 7 D. Massiot, D. Muller, Th. Hubert, M. Schneider, A.P.M. Kentgens, B. Cote, J. P. Coutures and W. Gessner, *Solid State NMR*, **5**, 175 (1995).



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15/08/2000  
 (received 8/21/00)

Dr. B.L. Shapiro  
 The NMR Newsletter  
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Dear Barry,

**More than one way to spin a rat: MAS  $^1\text{H}$  NMR spectra of rat testicular tissue**

MAS  $^1\text{H}$  NMR spectroscopy bridges the gap between magnetic resonance spectroscopy *in vivo* and conventional NMR spectroscopy of tissue extracts. The technique is well-suited to biological tissues in that high resolution spectra can be obtained without the destruction of the sample, and thus the spectra are not biased according to the extraction method used. By spinning tissue at the magic angle ( $54.7^\circ$ ) at a speed in excess of line-broadening factors, the effects of dipole-dipole couplings, chemical shift anisotropy, and bulk magnetic susceptibility inhomogeneities are minimised. In biological tissue the fluidic nature of the cytosol provides additional averaging of the anisotropic interactions so that only modest rotation speeds are necessary. As part of an on-going study we have been using this technique to investigate the biochemical profiles of testicular tissue in disease and as a result of xenobiotic toxicity.

The 600 MHz spectra obtainable using either conventional solvent suppression or the CPMG sequence had typically 1 Hz line-widths for the mobile small molecules (Figure 1). The spectra are comparable to those obtained by solution-state NMR and would clearly be the envy of any *in vivo* spectroscopist. Using a Bruker 4 mm rotor and a spacer insert, the tissue sample size can be as little as 10 mg. When compared with the need to use around 100 mg of tissue for the preparation of extracts, then MAS  $^1\text{H}$  NMR spectroscopy can be viewed as a more sensitive technique than its solution state counterpart. For testicular tissue with many endogenous metabolites giving easily assigned sharp resonances, including the singlet of creatine and the doublets of lactate and alanine, there are many suitable candidates for referencing and shimming purposes.

The testes are remarkable in composition, possessing in particular high quantities of creatine, in excess of even skeletal muscle. Given the use of creatine as a food supplement taken by many sports men and women, it might be that athletes may find a cheaper substitute for such food supplements in the form of animals testes, considered, we believe, a delicacy in some diets. Alternatively, increasing the levels of creatine through food supplements might have, as yet unknown but beneficial (?), effects on testicular function.

Potentially one of the largest benefits of MAS  $^1\text{H}$  NMR spectroscopy is that the environment of the tissue can be investigated directly. We have used the LED sequence with bipolar gradients along the magic angle axis to attenuate signal from fast-diffusing molecules. Figure 2 demonstrates that the main lipid signals detected at the maximum gradient strength are assignable to phosphatidylcholine rather than triglycerides whereas in tissues such as the liver and kidney, we and other workers have detected high levels of triglycerides. This might indicate that the lipids detected were mobile structural components of the cell membrane and not energy reserves for the organ. This is in keeping with sperm cell metabolism, which appears to favour citrate oxidation over other energy sources.

With best wishes,

*Jules*

Jules Griffin

*Jeff*

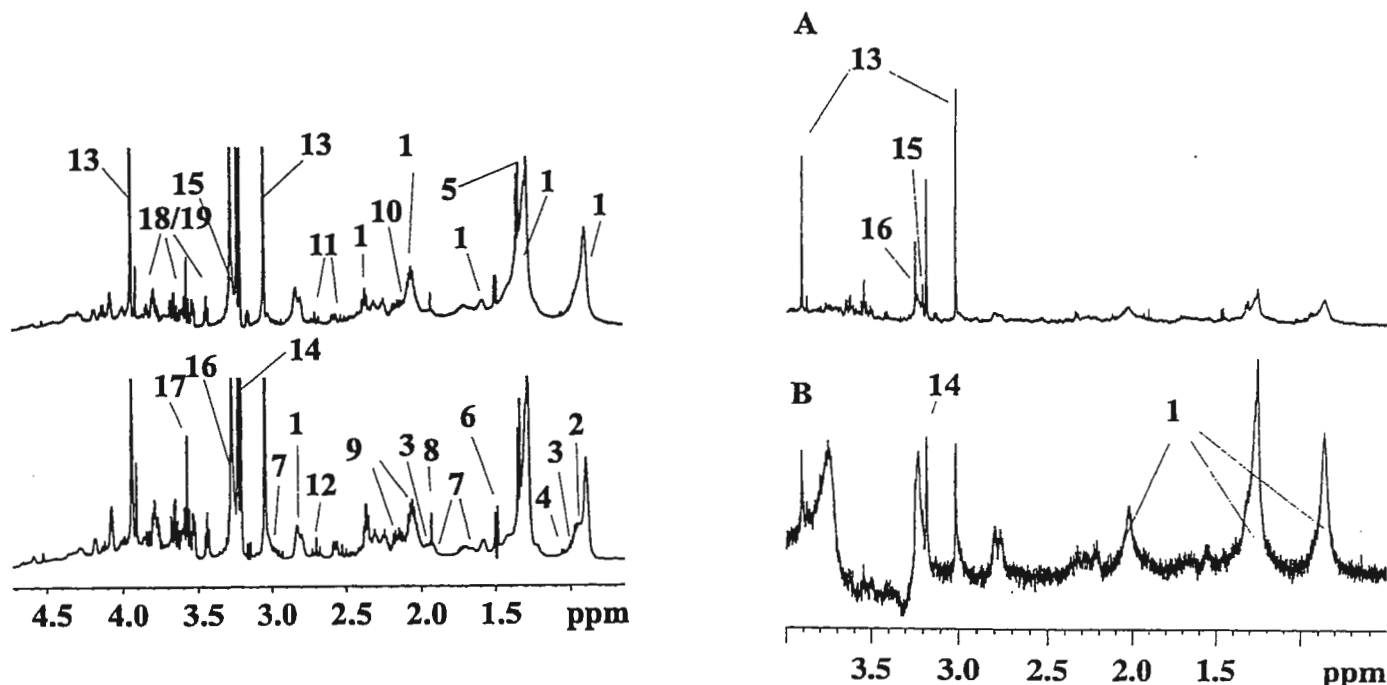
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**Figure 1:** High resolution MAS  $^1\text{H}$  NMR spectra of  $\sim 10$  mg of rat testicular tissue. Conventional solvent presaturation pulse sequence (A) and using the CPMG pulse sequence (B). Key: 1 lipid; 2 leucine; 3 isoleucine; 4 valine; 5 lactate; 6 alanine; 7 lysine; 8 acetate; 9 glutamine; 10 glutamate; 11 citrate; 12 sarcosine; 13 creatine; 14 choline; 15 phosphocholine; 16 phosphatidylcholine; 17 glycine; 18 glucose; 19 myo-inositol.

**Figure 2:** Attenuation of resonances as the gradient strength was increased from  $21 \text{ mTm}^{-1}$  (A) to  $1000 \text{ mTm}^{-1}$  (B). For key see Fig. 1.

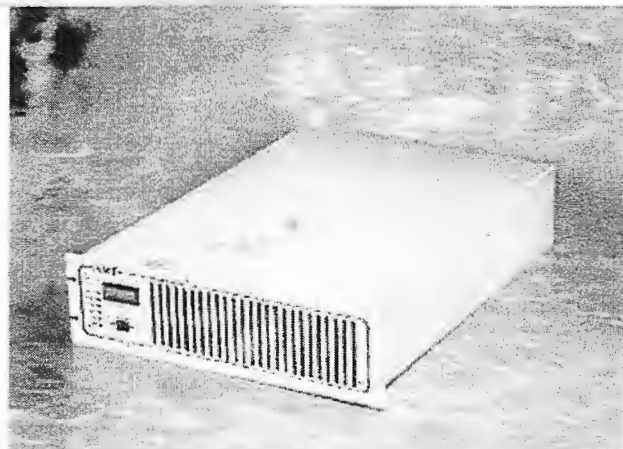
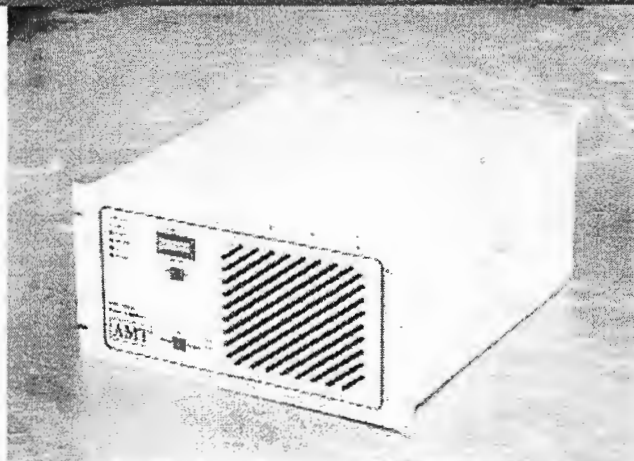
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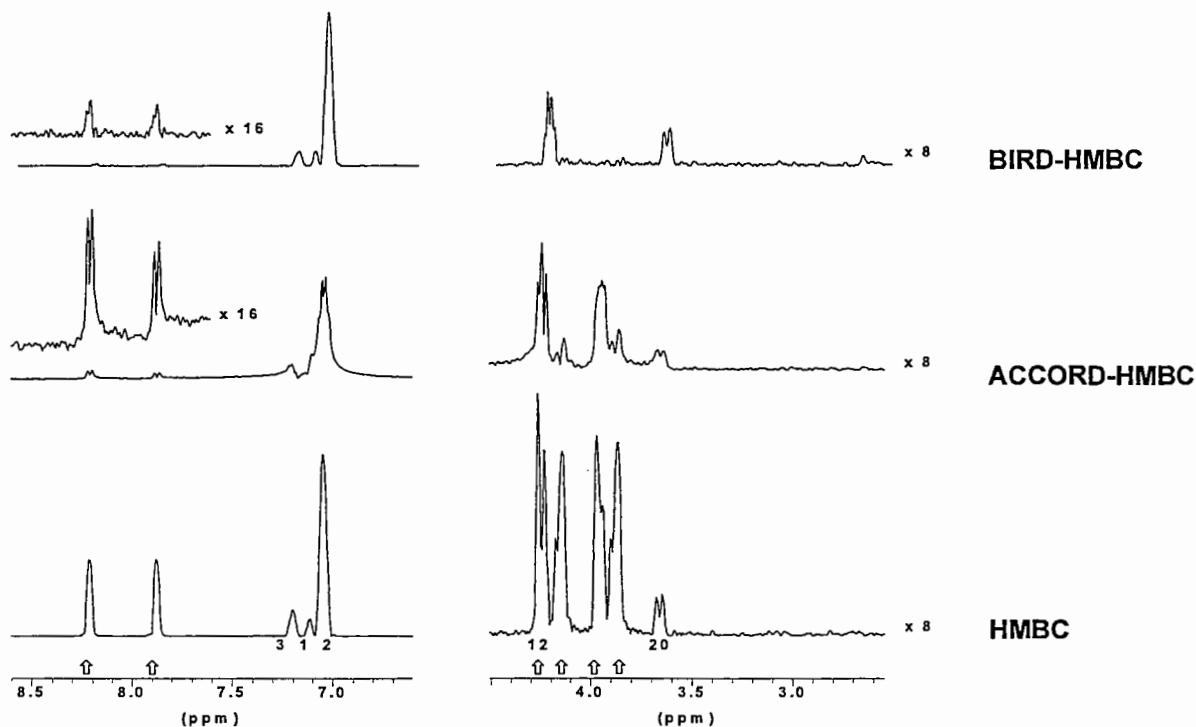
 August, 11<sup>th</sup> 2000  
 (received 8/11/00)

## BIRD-HMBC

BIRD-HMBC is a very useful heteronuclear 2D experiment for measuring heteronuclear long-range coupling connectivities (1). The sequence provides high sensitivities comparable to the basic HMBC experiment, but superior to the ACCORD-HMBC experiment. Following a new concept for efficient low-pass filtering, with the unwanted  $^1J_{CH}$  signals retained and cancelled in subsequent scans, it offers excellent suppression degrees for the whole range of residual  $^1J_{CH}$  peaks, allowing even small  $^4J_{CH}$  peaks to be recognized and yields the same narrow lineshapes as obtained with the HMBC experiment.

These attractive features, and the easy set-up, make BIRD-HMBC a valuable alternative to the HMBC experiment and its known variants for standard routine applications.

Two representative rows (C-4 left, C-23 right) extracted from the strychnine spectra measured with the HMBC, the ACCORD-HMBC and the BIRD-HMBC experiment respectively are shown for comparison. Residual  $^1J_{CH}$  signals are denoted by arrows. Signals of protons coupled to C-4 and C-23 respectively are assigned.



The BRUKER pulse program may be downloaded from: <http://www.nmr.unibe.ch/>

(1) to be published in Magn. Reson. Chem.

Yours sincerely

Remy Burger, Christian Schorn and Peter Bigler

an acquisition time and a relaxation delay of 100's ms to seconds that is sufficient for substitution of a new sequence. In this way, each sampling point corresponds to its own decoupling sequence, which allows the data to be acquired at the end of a complete decoupling period. Consequently, all decoupling sidebands disappear and the centerband increases correspondingly as demonstrated in Fig. 1.

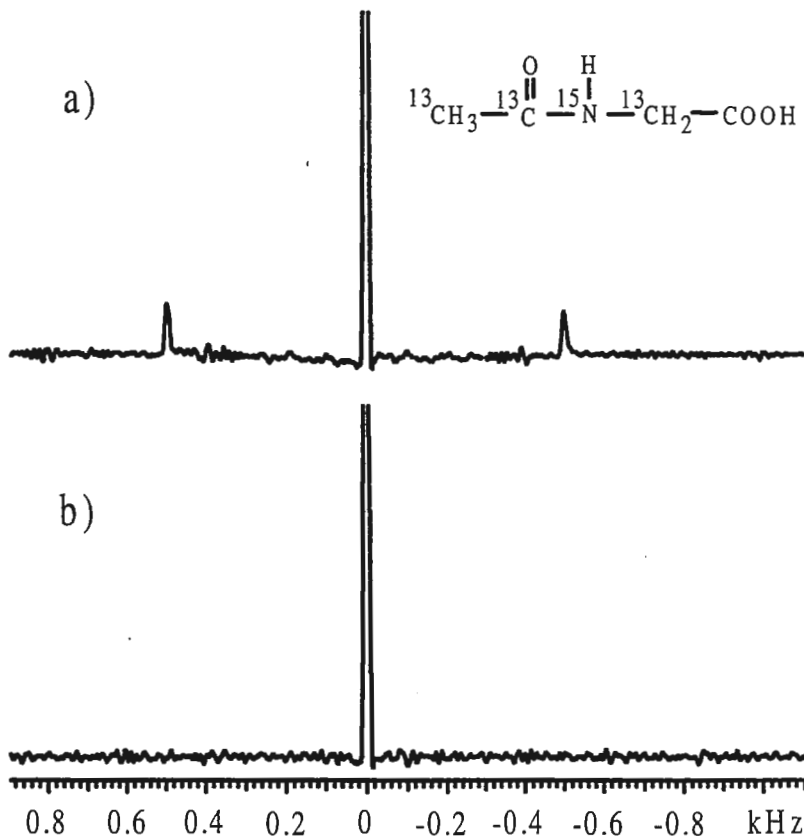


Fig. 1. Methyl  $^1\text{H}$  spectra of N-acetylglycine in the  $F_1$  dimension from the traces of two-dimensional gradient COSY spectra with a single scan per increment and with  $^{13}\text{C}$  adiabatic decoupling ( $T = 2\text{ms}$ ) (a) and with SAD (b). A total of 128 increments and a spectral width of 2 kHz in the  $t_1$  dimension are used in the experiments. The center peak is truncated at about 31% level.

Best regards,

Shanmin Zhang

Shanmin Zhang

David Gorenstein

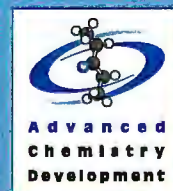
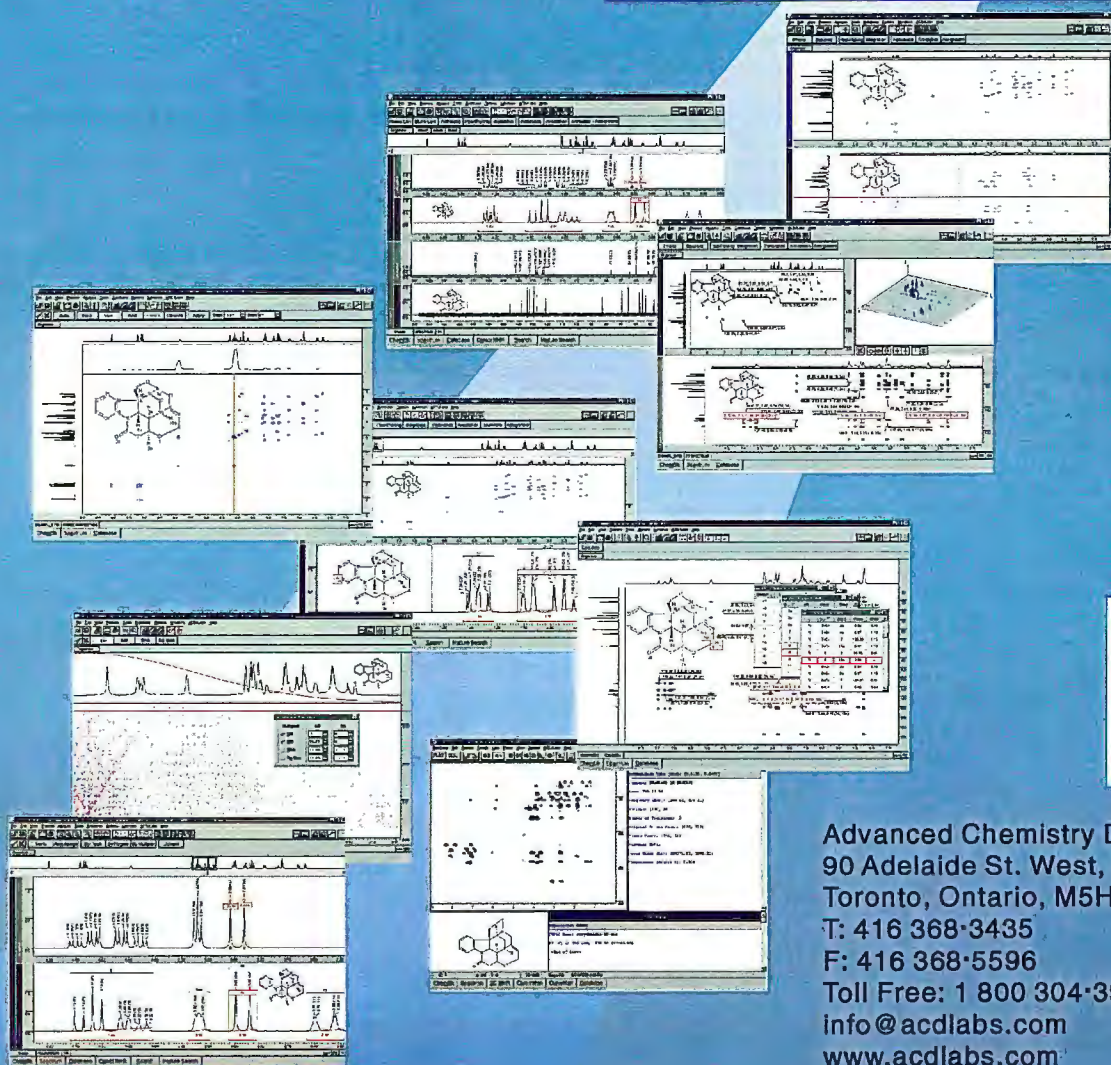
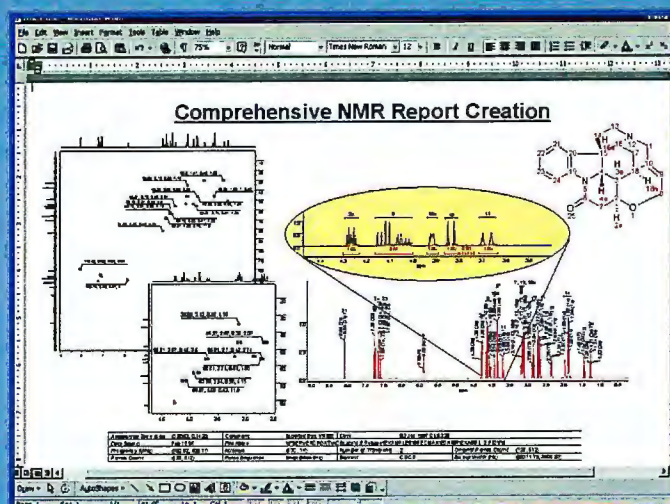
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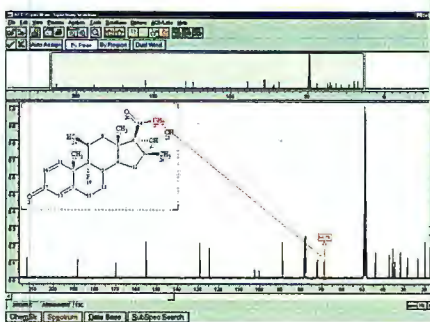
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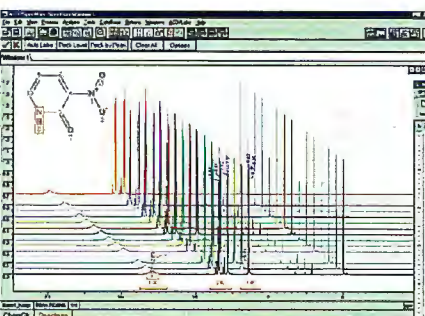


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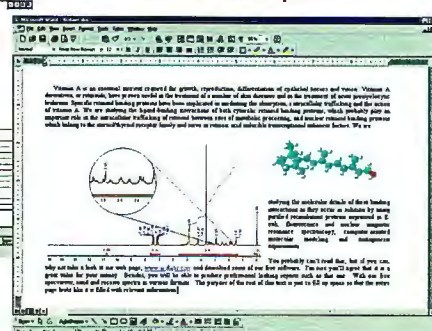
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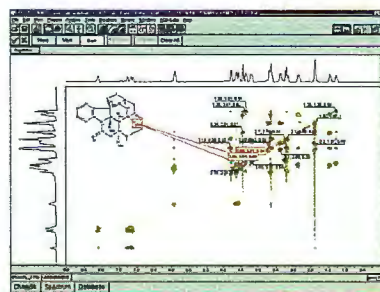
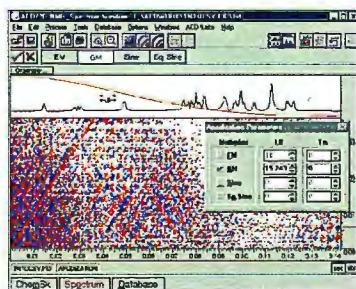
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(received 8/26/00)  
August 21, 2000

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

**Low Level Sample Performance  
Comparison: 3 mm Conventional vs.  
3 mm Cryo NMR Probes**

Dear Barry,

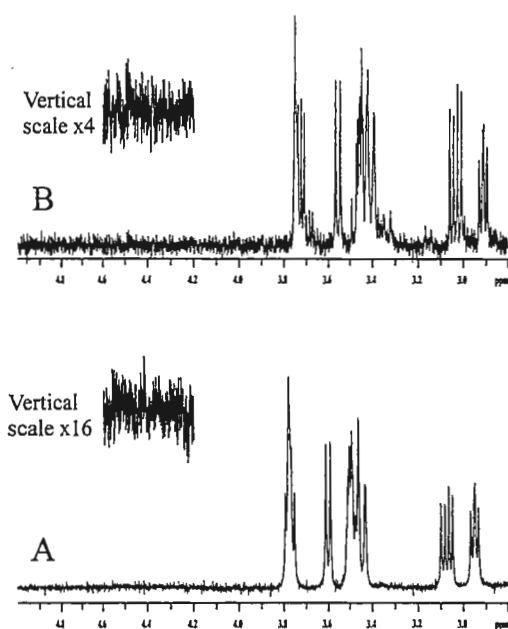
Within the pharmaceutical industry, there is continual pressure to shorten development times in an effort to get drugs to market more efficiently, thereby lengthening their patent lives. Within this context, the task of identifying process impurities and degradation products arising from stability studies required to meet FDA and ICH guidelines is made correspondingly more time critical. These considerations prompted us to collaboratively explore the development of 3 mm micro NMR probes with Nalorac staff in 1992.<sup>1,2</sup> More recently, to further enhance our ability to structurally characterize small samples of impurities and degradation products we have been engaged in the development and use of 1.7 mm SUBMICRO™ NMR probes.<sup>3-7</sup> We'd now like to highlight the next step on this pathway in our laboratories with the advent of 3 mm cryo NMR probes.

The idea of improving NMR sensitivity by resorting to cryo-cooled NMR probes is by no means new. A number of early reports explored the gains in sensitivity that could be realized by cooling the rf coils and associated electronics of NMR probes to temperatures in the range of 25°K.<sup>8-11</sup> Efforts have largely been aimed, thus far, at the development of 5 mm probes. In the small molecule area of interest, a report by Logan and co-workers<sup>12</sup> addressed the acquisition of low level nOe difference data in a 5 mm cryo probe using taxol™ (2, paclitaxel) as a model compound. To date, posters dealing with the characterization of metabolites have been presented at the 40<sup>th</sup> ENC<sup>13</sup> and SMASH 2000<sup>14</sup> meetings, which utilized 2.5 and 3 mm cryogenic NMR probes, respectively.

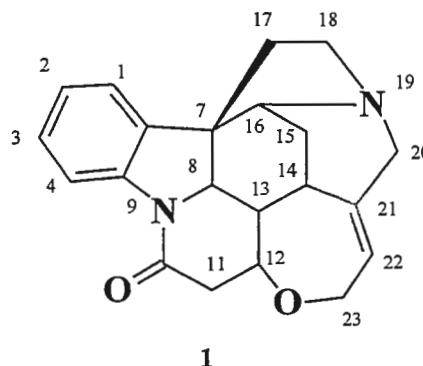
Cryo nmr probes developed thus far have generally delivered a sensitivity gain in the range of 3 to 4 fold, which translates to a factor of from 9 to 16 in time to achieve the same signal-to-noise ratio in a given experiment. We recently installed a prototype of a 3 mm Cryo•Spec™ micro inverse NMR probe being developed in collaboration with Nalorac on our Varian INOVA 500. As the tasking of this group at Pharmacia is aimed at the low level characterization of small samples of process impurities and degradants of potential candidate drugs in development, we elected to make an initial comparison of the performance of the 3 mm Cryo•Spec probe with that of a conventional, state-of-the-art Nalorac 3 mm MIDTG500-3 micro inverse probe. For this comparison, a sample consisting of 40 µg of strychnine (1, 120 nanomoles) was prepared in 150 µL *d*<sub>6</sub>-benzene (99.96% d, Cambridge Isotope Laboratories) by serial dilution and then flame sealed.

Figure 1 shows segments of the aliphatic region of the proton spectra recorded using the sealed sample of strychnine acquired in 16 transients in both probes. The noise regions shown as vertical expansions with both spectra were plotted at 16x for the Cryo•Spec probe and as a 4x vertical expansion for the conventional probe. The actual improvement in the s/n ratio realized with the cryo probe was a factor of 3.5 fold for the sealed sample of strychnine used for this comparison.





**Figure 1.** Comparative performance spectra recorded using a sealed 40  $\mu\text{g}$  sample of strychnine (**1**) in 150  $\mu\text{L}$   $d_6$ -benzene (99.96% $d$ , Cambridge Isotope Laboratories). Both spectra were recorded by accumulating 16 transients. Data from the 3 mm Cryo•Spec probe are shown in Panel A. Corresponding data from the conventional Nalorac MIDGT500-3 micro inverse probe are shown in Panel B. The expanded noise regions were plotted with vertical expansions of 16x and 4x, respectively. The s/n gain with the 3 mm Cryo•Spec probe was 3.5 fold for this sample.






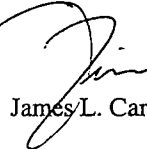


More germane to the structural characterization of impurities and degradants of pharmaceuticals, metabolites, or natural products are the results obtainable for heteronuclear shift correlation experiments. A series of three HSQC experiments were also performed on the 40  $\mu\text{g}$  strychnine sample. First, an HSQC spectrum was acquired using the 3 mm Cryo•Spec probe. Usable data were acquired in 45 min; the noise-free spectrum shown in Figure 2A was recorded in 90 min. The 90 min experiment was then repeated using the conventional 3 mm MIDTG500-3 micro inverse probe using exactly the same parameters. The results of this experiment are shown in Figure 2B. Some of the responses shown in Figure 2A were observed but many were not. There was also considerable noise in the spectrum. Taking into account the difference in the s/n comparison of the two probes shown in Figure 1, a 17.5 hr HSQC acquisition was undertaken using the conventional 3 mm probe, which gave the result shown in Figure 2C. The s/n ratio of the data shown in Figures 2A and 2C is comparable.

While a 17.5 hr HSQC experiment is by no means time prohibitive, acquiring the corresponding HMBC experiment on such a sample, if these data were necessary to characterize an unknown, which is frequently the case, would take approximately 4 times more instrument time. Thus, to acquire the data to fully characterize an unknown with this quantity of sample would require approximately 100 hrs of instrument time, in contrast to about 8 when using a cryo probe.

In addition to the heteronuclear performance of the probe, we were also interested in the low level proton performance. To test this, a sample was prepared by serial dilution containing 2.9  $\mu\text{g}$  of Taxol (**2**, paclitaxel) / 165  $\mu\text{L}$  of  $\text{CDCl}_3$  (99.96%  $d$ , Cambridge Isotope Laboratories). Using this sample, a pair of COSY spectra were acquired. The first spectrum was acquired in ~45 min (Figure 3B); while all of the expected responses were contained in the spectrum, the spectrum was somewhat noisy. A second COSY spectrum was acquired in ~3 hr with higher  $F_1$  digital resolution and more transients/ $t_1$  increment (Figure 3C). This spectrum was essentially free of noise. No suppression of the residual protio chloroform resonance or the water resonance was done for either of the spectra. Despite the potential of a dynamic range problem (the  $^{13}\text{C}$  satellite resonance of the 0.04% residual protio chloroform was essentially equal in height to the Taxol (**2**, paclitaxel) NH doublet) there were no problems associated with the acquisition of the data. These observations suggest that there is considerable potential for the use of cryo NMR probes in the structural characterization of metabolites and other applications where structural questions can be resolved by a proton or homonuclear 2D NMR spectrum.

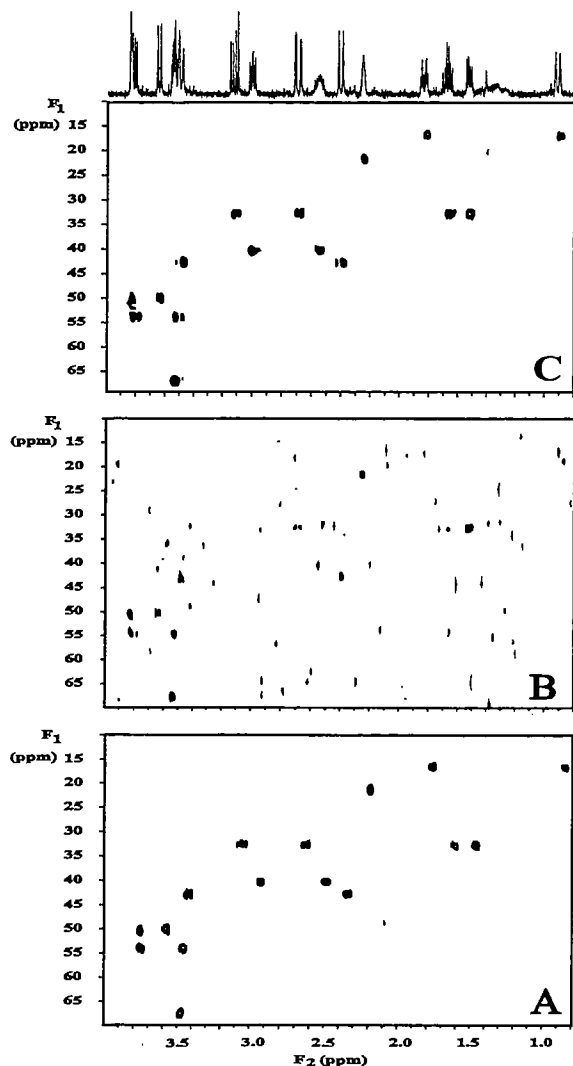
Clearly, as cryo NMR probe technology becomes more refined it will undoubtedly be broadly embraced for the characterization of small samples such as rare natural products, metabolites of drug molecules, potentially labile species where data must be acquired very rapidly, *etc.*

Gary E. Martin   David J. Russell   Chad E. Hadden   Atholl A. Gibson   Albert P. Zens   James L. Carolan

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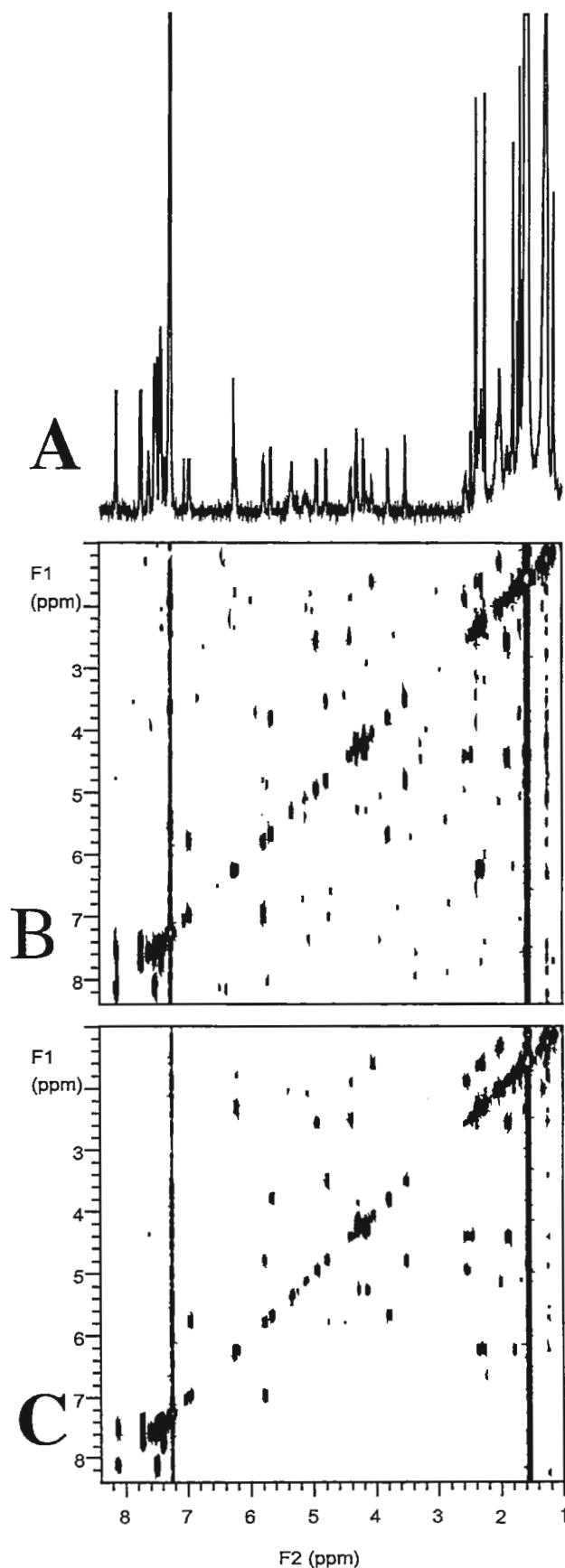


**Figure 2.** Comparative HSQC spectra recorded using Nalorac 3 mm Cryo•Spec and conventional Z•SPEC® MIDTG500-3 micro inverse NMR probes. All of the spectra were recorded using a Varian INOVA 500 MHz three channel NMR spectrometer. All of the data sets were 2048 x 48 (hypercomplex x 2) files. Data were linear predicted in the second frequency domain to 192 points and zero filled to 256 points during processing. Weighting factors used during processing and vertical scaling in the preparation of the plots were identical.

A.) HSQC spectrum recorded in 90 min using a Nalorac 3 mm Cryo•Spec (CryoM[H]C500-3) NMR probe operated with an open loop helium gas delivery system. Data were acquired by accumulating 32 transients for each of the 48 increments of the evolution time.

B.) HSQC spectrum recorded in 90 min using a Nalorac Z•SPEC MIDTG500-3 3 mm gradient inverse probe. The data were acquired identically with those shown in Panel A, accumulating 32 transients/ $t_1$  increment.

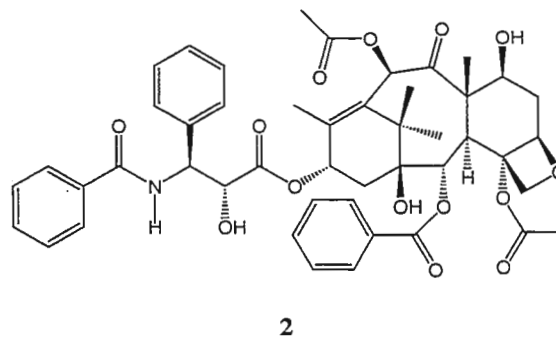
C.) HSQC spectrum recorded in 17.5 hrs using a Nalorac Z•SPEC MIDTG500-3 probe. Data were acquired by accumulating 352 transients/ $t_1$  increment. The s/n from the projections of the data in Panels A and C are comparable, consistent with the 3.5 fold increase in s/n of the cryo probe over the conventional NMR probe.



**Figure 3.** A.) Proton reference spectrum of a 2.9  $\mu\text{g}$  sample of Taxol (paclitaxel) in 165  $\mu\text{L}$   $\text{CDCl}_3$  (99.96% d, Cambridge Isotope Laboratories) prepared by serial dilution using volumetric glassware. The proton reference spectrum was acquired in 32 transients with no solvent or residual water suppression employed. All of the spectra shown in this figure were recorded using a Nalorac 3 mm Cryo•Spec (CryoM[H]C500-3) NMR probe. Cryogenic operation was identical to that described in the caption to Figure 2.

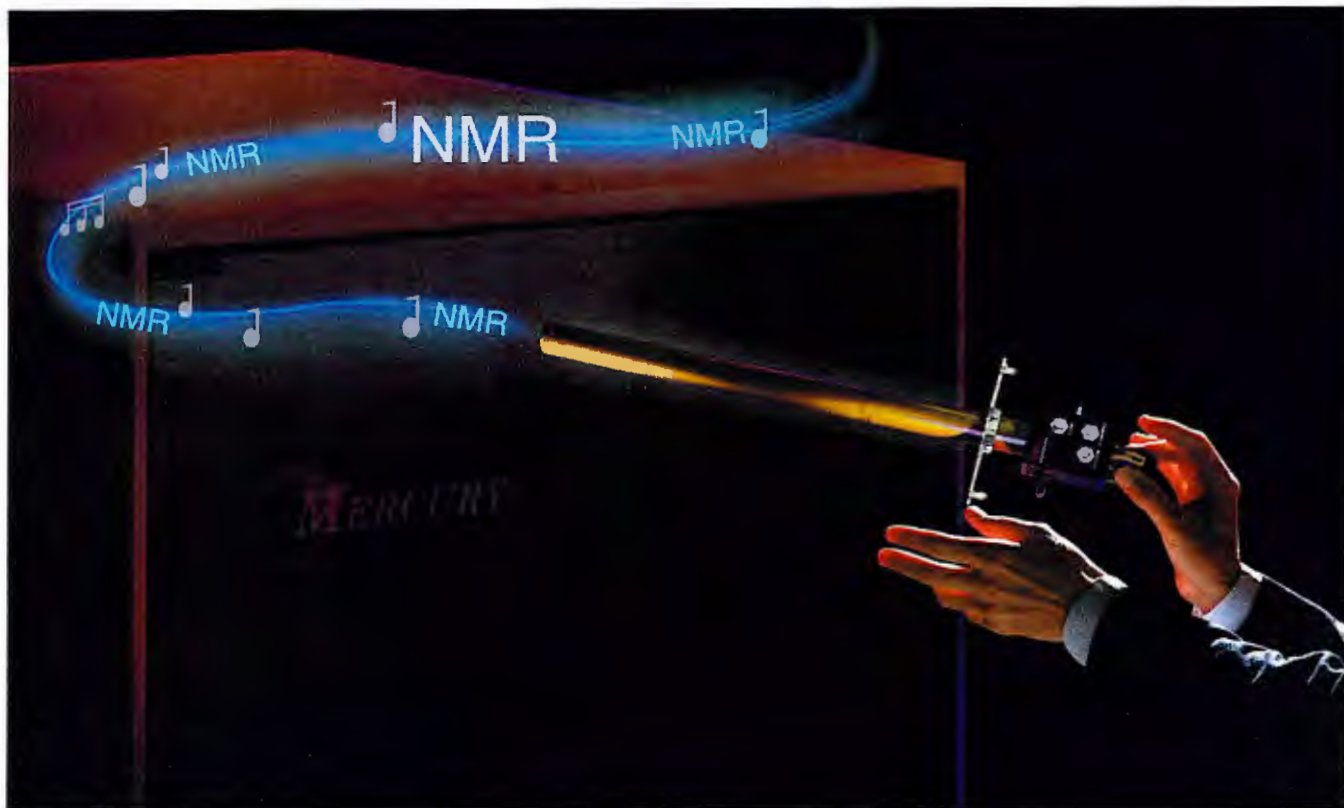
B.) COSY spectrum acquired in 46 min as 2048 x 128 point files accumulating 12 transients/ $t_1$  increment. The spectral width was 6286.3 Hz with an acquisition time of 0.163 sec and an interpulse delay of 1.6 sec.

C.) COSY spectrum acquired in 3 hr 4 min as 2048 x 192 point files, accumulating 32 transients/ $t_1$  increment. Spectral width and other acquisition parameters were identical to those for the spectrum shown in Panel B.





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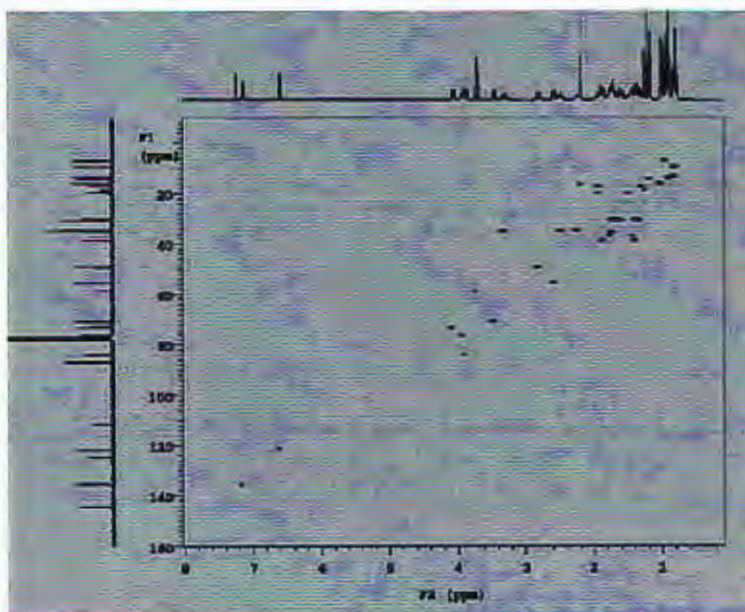
$^{13}\text{C}$  nutation profile of DMSO in  $\text{DMSO}-d_6$ ...

**...to Benzene...**



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 The NMR Newsletter  
 966 Elsinore Court  
 Palo Alto, CAL. 94303  
 USA



Leipzig, 15.08.00

## Solvens-Solute Interaction

(received 8/21/00)

Dear Barry,

we are currently interested in the study of solvens-solute interactions and try to learn about these by performing *intermolecular* NOE measurements [1]. Of special importance are solutions of peptides in water/trifluorethanol (TFE) mixtures, where it is known, that TFE induces  $\alpha$ -helical conformation of peptides above a certain TFE concentration [2]. The molecular cause and mechanism of this conformational transition is still under debate.

We have started our study with a simple tetrapeptide NAc-Ser-Phe-Val-Gly-OMe, which, of course, has no distinct conformation in solution, and we are observing in 90% H<sub>2</sub>O/10% D<sub>2</sub>O solution some interesting intermolecular NOE effects by irradiating the water signal. As NMR technique we use the DPFGE method published by Keeler and Shaka [3] with an additional water filter [4] after the NOE mixing period. A typical spectrum is shown in (a). The NOE-spectrum changes quite dramatically, if one adds 10% TFE to this solution and this is displayed in (b). Obviously, now only NOE's to the Phe side chain are observed. There is also the possibility to observe heteronuclear NOE's by irradiating the fluorine atoms of TFE (data not shown). The procedures become even more interesting, when using larger peptides which indeed change their conformation in the presence of TFE.

We are certainly quite far from understanding these spectra in detail, but feel that they may be worth pursuing with some effort.

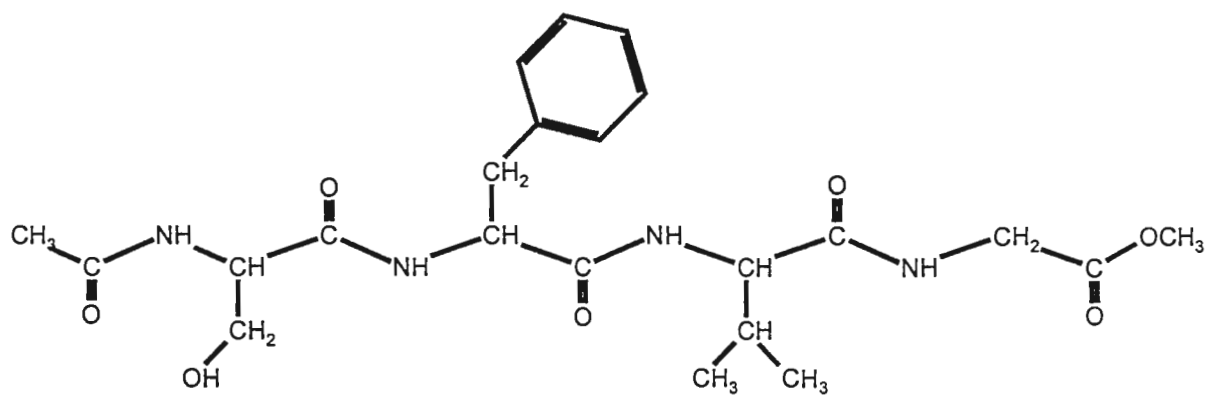
Sincerely yours

Dolores Díaz

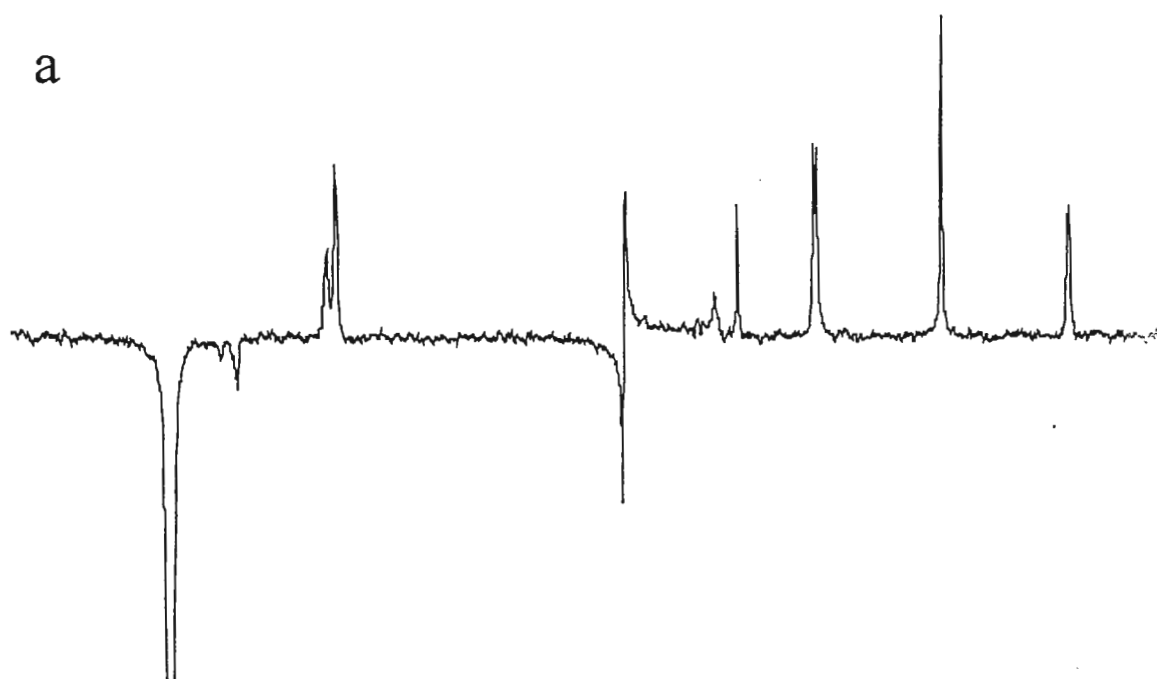
[Dr. Dolores Diaz]

[stb]

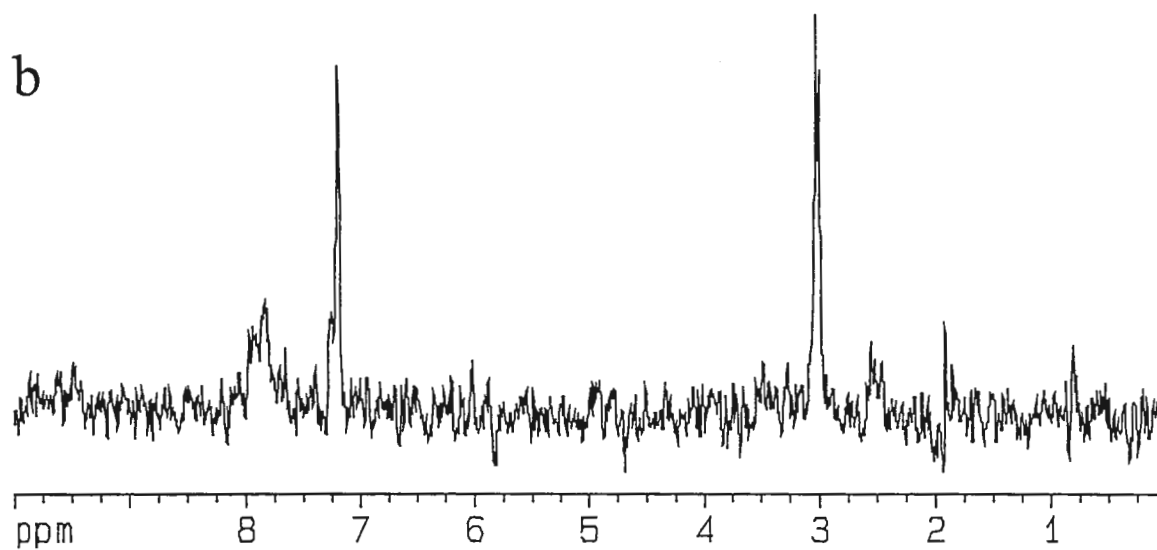
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a



b



*Intermolecular* NOE effects between water and tetrapeptide (a) in 90% H<sub>2</sub>O/10% D<sub>2</sub>O, (b) with additional 10% TFE-d<sub>2</sub>



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5 mm	HIP-7*	60	7 in	0.015"	nominal	nominal	\$95.00	100.00	\$85.00
5 mm	HIP-8*	60	8 in	0.015"	nominal	nominal	105.00	100.00	95.00

Size	Product Number	MHz	Length	Wall Thickness	Concentricity	Camber	Each	Qty.	Bulk Each
3 mm	335-PP-7	500	7 in	0.015"	0.0005"	0.00025"	\$11.75	+100	\$10.00
3 mm	335-PP-8	500	8 in	0.015"	0.0005"	0.00025"	12.90	+100	10.90
3 mm	327-PP-7	400	7 in	0.012"	0.0010"	0.0010"	9.10	+100	7.80
3 mm	327-PP-8	400	8 in	0.012"	0.0010"	0.0010"	10.10	+100	8.60
3 mm	307-PP-7	360	7 in	0.012"	0.0020"	0.0010"	8.45	+100	7.20
3 mm	307-PP-8	360	8 in	0.012"	0.0020"	0.0010"	8.95	+100	7.70

Size	Product Number	MHz	Length	Wall Thickness	Concentricity	Camber	Each	Qty.	Bulk Each
10 mm	513-7PP-7	400	7 in	0.018"	0.0015"	0.0005"	\$23.25	+25	\$20.95
10 mm	513-7PP-8	400	8 in	0.018"	0.0015"	0.0005"	24.10	+25	21.70

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5 mm	528-JY-7	400	7"	0.015"	0.0010"	0.0005"	75.70	+10	68.10
5 mm	528-JY-8	400	8"	0.015"	0.0010"	0.0005"	75.70	+10	68.10
5 mm	507-JY-7	360	7"	0.015"	0.0020"	0.0010"	72.45	+10	65.25
5 mm	507-JY-8	360	8"	0.015"	0.0020"	0.0010"	72.45	+10	65.25

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(received 8/24/00)

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

### *Experiences with a home-built high-performance computer cluster*

Dear Barry

Since I moved to Clark University in the Fall of 1998 acquisition of new hardware has added excitement to everyday campus life. For the experimental part of our research, we have got an INOVA 600 spectrometer whose installation and operation has been very smooth. NMR data processing and analysis is primarily done on a Sparc-Ultra 60/10 work station cluster.

For a better understanding and interpretation of experimental data we continue to develop and apply computational methods that require non-negligible computer power. In particular, we perform molecular dynamics (MD) simulations of proteins and quantum-chemical calculations of NMR parameters. Due to their favorable performance-to-price ratio, Linux clusters have become an attractive alternative to traditional supercomputers. We therefore decided to build our own Beowulf cluster in collaboration with Harvey Gould's group from the Physics department. For testing purposes we started with 4 Compaq DEC Alpha processors (533 MHz, 164LX2 motherboard) and based on the performance, which by far exceeded my original expectations, we added another 16 processors (600 MHz, 164LX4). The nodes run Debian Linux and they are connected via fast ethernet to a 24 port 3Com SSII3300 switch. The stability of the cluster has been further increased by the addition of a UPS system, where we found it most cost effective to use one

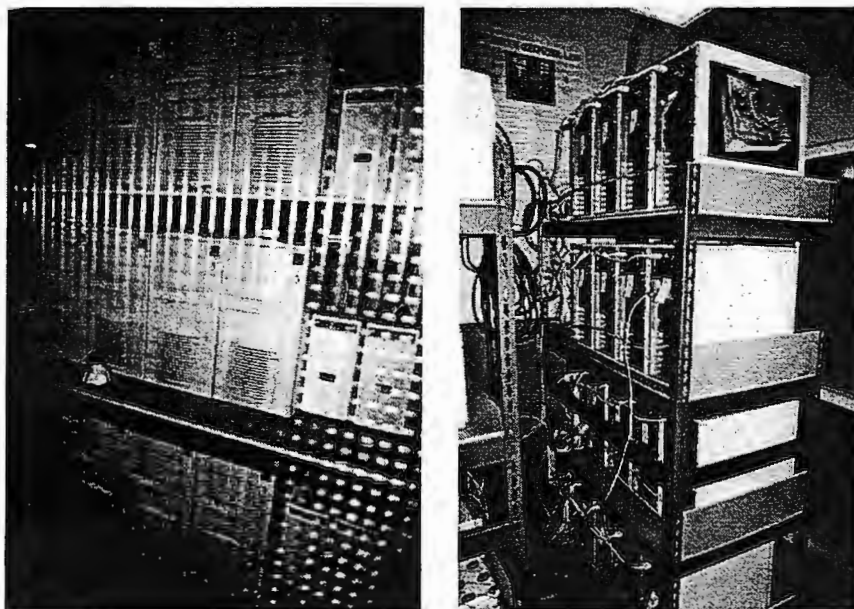


Figure 1. Beowulf cluster "Arthur" at Clark University (named after Arthur Gordon Webster, former Clark Professor and one of the three co-founders of the American Physical Society).

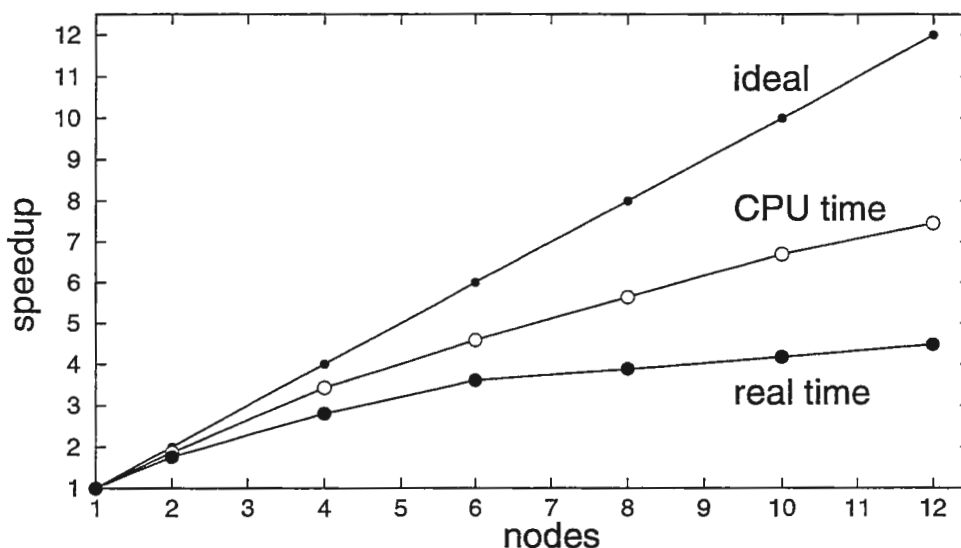


Figure 2. Speedup of a MD simulation of ubiquitin on our Beowulf cluster running under PVM as a function of the number of nodes.

600 VA UPS per two nodes. Figure 1 shows the current setup of the cluster, which is placed on two utility shelves purchased at Home Depot. The cluster is operational and running for about 99% of the time. More information and some useful links, in case somebody is interested in building this type of cluster, can be found on our home page ([nmr.clarku.edu](http://nmr.clarku.edu)).

A Beowulf cluster is by its very nature optimally suited for computational problems that involve a large number of jobs running on single processors only. An application in our group, where such ideal scaling is achieved, involves the investigation of the influence of molecular motion on NMR parameters such as CSA's, isotropic shifts, and scalar J couplings. For this purpose, quantum-chemical computations of these parameters using density functional theory (DFT) are performed for dozens to hundreds of molecular fragments and their environments extracted from a MD trajectory using a protocol described recently (Scheurer et al., *J. Am. Chem. Soc.* 121, 4242 (1999)).

Parallelization of a MD simulation of a protein is possible by distributing a single job over multiple processors. As is well-known, the scaling becomes less ideal for an increasing number of nodes due to the extensive communication that takes place between the nodes. The situation is illustrated in Figure 2 for a MD simulation using CHARMM of ubiquitin in a box of solvent containing a total of 13050 atoms under periodic boundary conditions. The speedup under PVM levels off at about 6 nodes. It is thus better to run several simulations at the same time than to use more than 6 - 8 nodes for a single job. Fortunately, there are now faster communication networks available (Myrinet, Gigabit ethernet) that improve the situation (at costs, however, that can reach 50% of the expenses of all other hardware).

Even with "only" fast ethernet we are able to generate on our cluster extensive MD simulations of proteins under different conditions (the longest simulation is now over 30 ns) that I did not even dream about only a few years ago.

Yours sincerely,

*Rafael*  
R. Bruschweiler

*Greg*  
Greg Johnson

*Jeanine*  
Jeanine Prompers

Dan Roe

C. Scheurer



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August 21, 2000

(received 8/24/00)

Barry Shapiro  
The NMR Newsletter  
966 Elsinore Court  
Palo Alto, CA 94303-3410

Title:  $^{31}\text{P}$  NMR of Brain Phospholipids in Schizophrenia

Dear Barry:

It has been hypothesized that schizophrenia arises from cell membrane abnormalities due to changes in phospholipid (PL) composition and metabolism (1). Also, *in vivo*  $^{31}\text{P}$  NMR studies suggest alterations of PL metabolism in the frontal lobes in schizophrenia. My colleagues John Pearce, Sue Griffin, Robert Mrak, Masao Omori, and Craig Karson, and I have used high resolution, *in vitro*  $^{31}\text{P}$  nuclear magnetic resonance (NMR) to characterize the PLs in left frontal cortex (gray matter) of postmortem brain from 5 schizophrenics and 5 controls. High resolution  $^{31}\text{P}$  NMR spectra were obtained at 121.65 MHz in an organic-solvent system to resolve PL classes (headgroups) and in a sodium-cholate, aqueous dispersion system to resolve phosphatidylcholine (PC) molecular species. Details of the sample preparation procedures have been published (2).

The Table below gives the PL compositions for the two groups. Phosphatidyl-inositol (PI) was significantly higher in the schizophrenic group than in the control group ( $p < 0.045$ ). There were no differences between the two groups for other individual PL classes, or for individual PL subclasses determined by the linkage type at the sn-1 position on glycerol. Total phospholipids were higher in schizophrenics relative to controls ( $p < 0.05$ ). There was no evidence for elevated lysophosphatidylcholine or lysophosphatidylethanolamine in schizophrenia. The intensity of the PC peak representing molecular species with one saturated and one unsaturated (one or two double bonds) acyl chain was higher for the schizophrenic group than for the control group ( $p < 0.043$ ). Although these results are not in complete agreement with previous studies, they support the idea that PL abnormalities occur in the brain in schizophrenia, and that fatty acid metabolism may be abnormal.

Our observations have a number of advantages. First, they pertain directly to frontal cortex, and not to peripheral tissue or body fluids, which are often studied. Second, they contain information on many PLs, including PL subclasses and molecular species. Lastly, they are relatively rapid and quantitative. Disadvantages of the present study are those usually associated with the use of postmortem tissue. These include 1)

the subjects were old; 2) the patients had been treated with antipsychotic medications for a long time; and 3) the possible presence of perimortem factors.

Table: Phospholipid Concentrations<sup>a</sup> (mM) in Left Frontal Cortex of Schizophrenics and Controls

Phospholipid	Controls	Schizophrenics
Cardiolipin, CL	0.50±0.10	0.58±0.17
Alkylacyl-phosphatidylethanolamine, PE <sub>e</sub>	0.76±0.18	0.80±0.22
Phosphatidylethanolamine plasmalogen, PE <sub>p</sub>	9.20±1.06	11.20±2.86
Phosphatidylethanolamine, PE <sub>a</sub>	7.72±0.56	8.35±0.83
Phosphatidylserine, PS	5.90±1.38	6.90±1.47
Sphingomyelin, SM	3.72±0.71	4.35±0.41
Phosphatidylinositol, PI	1.44±0.28	1.80±0.29 <sup>b</sup>
Phosphatidylcholine (both chains saturated), dsPC	4.34±0.63	4.10±0.73
Phosphatidylcholine (one saturated + one unsaturated chain, m=1,2), su <sub>L</sub> PC	8.66±0.70	9.95±0.85 <sup>c</sup>
Phosphatidylcholine [su <sub>H</sub> (m>3) + both chains unsaturated, m=1,2] (su <sub>H</sub> + du <sub>L</sub> )PC	2.58±0.48	2.88±0.45
Total phospholipids	46.3±2.9	52.6±5.0 <sup>d</sup>

<sup>a</sup>Mean ± standard deviation.

<sup>b</sup>Significantly different from controls, p<0.045.

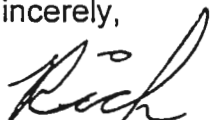
<sup>c</sup>Significantly different from controls, p<0.043.

<sup>d</sup>Significantly different from controls, p<0.050.

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2. Pearce, J. M., Komoroski, R. A. Analysis of phospholipid molecular species in brain by <sup>31</sup>P NMR spectroscopy, *Magn. Reson. Med.* **44**, 215-223 (2000).

Sincerely,



Richard A. Komoroski

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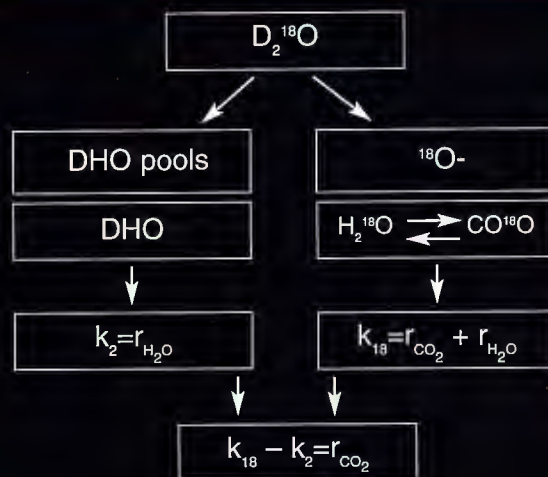
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References: (1) North American Society for the Study of Obesity, J 21, 1999. (2) Schoeller D.; Santen van, E. J. *Appl. Physiol.* 1982, 53, 955. (3) Urey, H *Science* 1948, 108, 489. (4) Cole, T. J. et al. *The Doubly Labeled Water Method for Measuring Energy Expenditure: A Consensus Report by the IDECG Working Group*, NAHRES-4, 1990, International Atomic Energy Agency



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DEPARTMENT OF BIOCHEMISTRY  
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(received 8/21/00)

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

## Diffusion Tensor analysis of Erythrocyte Suspensions

Alignment of biconcave-shaped human erythrocytes, in aqueous suspension, in the magnetic field of an NMR spectrometer, has been shown by the presence of coherence peaks in q-space plots obtained from pulsed-field-gradient spin echo (PGSE) NMR experiments, along the z-axis parallel to  $B_0$  (1). The experiment requires a probe that generates large magnetic field gradients of the order 2 to 10 T m<sup>-1</sup>. Erythrocytes are orientated in a strong magnetic field with their long axis parallel to the field direction. A simple mathematical relationship exists between the position of the minima in these q-space plots, obtained from a PGSE experiment along the z-axis, and the average mean diameter of the cells aligned parallel to the main field. If one could obtain q-space plots along the orthogonal x- and y-axes, a measurement of the length of the short axis of the erythrocyte would be obtained, thus confirming the alignment direction of the erythrocytes in the magnetic field. However three axis probes that generate such high magnetic field gradients are not readily available.

Diffusion tensor analysis has been used (2) for characterizing the orientation of microstructures in tissues *in vivo* during magnetic resonance imaging experiments. Three axis gradients for imaging and high resolution NMR, generating magnetic field gradients of the order 5 to 50 mT m<sup>-1</sup>, are readily available. We have used diffusion tensor analysis to provide corroborating evidence of erythrocyte alignment in high magnetic fields (3).

For an erythrocyte aligned with its long axis parallel to  $B_0$ , the z direction, and its short axis orientated randomly in the xy plane, the restriction to the diffusion of water molecules would increase in the following order. The least restriction would be along the z direction, then along the xz or yz directions, followed by the xyz direction, with the most restricted directions being along the x, y and xy axes. This may be seen in Fig. 1 which shows plots of water signal intensity vs the Stejskal-Tanner parameter for water diffusion along the seven directions in a suspension of erythrocytes.

Previous methods for determining the values of the elements of the diffusion tensor seemed to us to be unduly complicated. We have developed a new method of data analysis using the well known *Mathematica* software package. The program is outlined in reference 3. For a typical experiment using normal cells the diffusion coefficients along the principle x-, y- and z- directions were  $6.88 \pm 0.17$ ,  $7.07 \pm 0.17$  and  $10.20 \pm 0.17 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ .

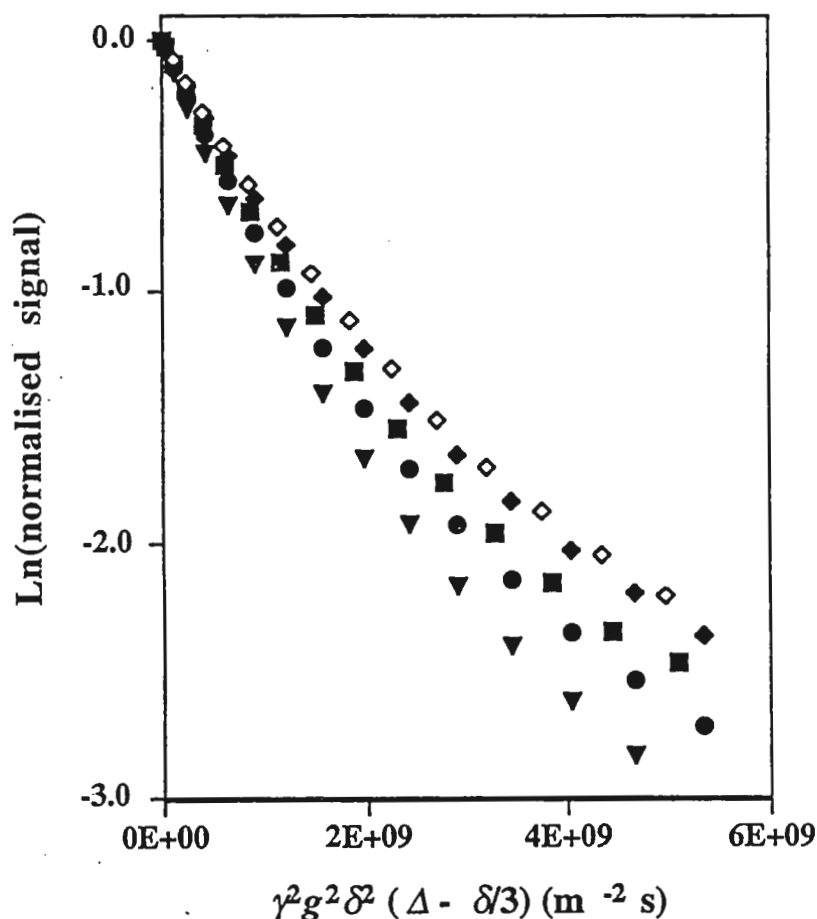


Fig. 1. Plots of water signal intensity as a function of the magnitude and direction of the magnetic field gradient pulses in  $^1\text{H}$  NMR PGSE experiments on a suspension of normal human erythrocytes. Seven data sets were acquired for each of 16 different values of the gradient pulses. The gradients and their corresponding data sets are denoted by the symbols:  $g_x$   $\diamond$ ;  $g_y$   $\diamond$ ;  $g_z$   $\nabla$ ;  $g_{xy}$   $\diamond$ ;  $g_{xz}$   $\bullet$ ;  $g_{yz}$   $\bullet$ ;  $g_{xy}$   $\blacksquare$ . Note the data for  $g_x$  were superimposed on that for  $g_y$ , and similarly for  $g_{xz}$  and  $g_{yz}$ .

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3. P. W. Kuchel, C. J. Durrant, B. E. Chapman, P. S. Jarret, and D. Regan. (2000). *J. Magn. Reson.* **145**, 291-301.

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10 August 2000  
(received 8/21/00)

Dr. B. L. Shapiro  
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USA

### Tracking Down Strange $B_0$ -related Artifacts in PGSE NMR Experiments

Dear Barry,

Due to the desire for obtaining every more accurate diffusion coefficients we have carried much research into artifacts that can degrade the quality of a measurement (e.g., see refs. (Furó and Jóhannesson, 1996; Hedin and Furó, 1998; Price et al., 1999)). However, several months ago something caught us by surprise. We noticed that all was not well with some of our PGSE NMR diffusion experiments of simply diffusing species with reasonably modest gradient strengths in our wide bore (89 mm) Bruker AMX 300 spectrometer. In particular, some points in the normal semi-log attenuation plots were subject to artifactual attenuation and that the narrow peaks of a molecule were more affected than the broad peaks.

After further thought and experimentation we realized that our artifacts were the result of either unstable rf generation or  $B_0$  field instability. We also noticed that these effects were independent of the diffusion gradients – and thus were not the usual problematic  $B_0$ -shift effect commonly observed with very high gradient pulses. In our case the instability of the  $B_0$  field/rf generation instability resulted in less than optimal refocussing of the echo and this effect was more obvious with the narrow peaks with a significant diminution of amplitude and broadening of the resonance. By repeatedly acquiring FIDs after single rf pulses frequency shifts of up to 6 Hz were observed when running unlocked. We note that for a wide bore magnet the shifts should be less than 2 Hz.

We investigated temperature control in the room and found that the situation was somewhat improved by moving the temperature sensor for the air conditioner closer to the magnet and also by replacing the air conditioner intake filters. We then turned our attention to other possible sources of error and found that by swapping rf generation components we were able to exclude unstable rf as being the origin of our problems and thus we turned our attention solely to isolating a  $B_0$ -based problem. Interestingly, the instability was not merely the inherent random instability of the of the  $B_0$  field and only some spectra in series of echo spectra were seriously affected. We then methodically investigated likely causes of non-random  $B_0$  instability, including sources of sample vibration such as too much VT air, and threatened people in surrounding rooms with extreme physical violence if they even thought about moving metal objects around. We found that the bore was slightly loose and was able to wobble slightly. To solve this problem we had a new Teflon spacer made which held the bore tube more securely to the magnet. But this did not completely solve the problem. As a last ditch effort we switched to using a very small volume in a capillary as our test sample (so that we would still observe a reasonably narrow signal) and electrically disconnected the shims. However, the instability still remained.

To gain more insight into the origin of the large instabilities we then acquired test spectra with a rather short recycle delay of  $\sim 3$  s for a few hours. Curiously we observed that the major 'spikes' of instability occurred reproducibly about every 7 minutes. Finally we fell to the conclusion that the instability was related to the operation of the dry air supply. In our lab the compressed air is fed into a cylinder of zeolite and then every 7 min the supply is rapidly switched to a second cylinder of zeolite whilst the first cylinder is 'regenerated'. The dried compressed air is then fed through a pressure reductor and a number of filters before being used for both VT and gradient coil cooling (although at this time the VT air was disconnected). The spikes of instability started shortly after the rapid switching between zeolite drying cylinders and then abated over the subsequent 10 s or so and with a smaller slower component decaying over the subsequent few minutes. Why this would affect the field/stability was unclear as firstly the air goes into the gradient coil and does not 'touch' the sample and secondly the flow is very small. We installed an air buffer made out of a large PVC pipe which significantly decreased the amplitude of the spike. To our surprise, the slower decaying small amplitude disturbance disappeared after we replaced the zeolite and some associated gaskets.

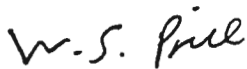
Finally after we had resolved the above sources of artifactual frequency shift we noticed that the Hall Effect Current probe that we had around the current line to the gradient coil to monitor the gradient pulse generation was another source of noise. Thus, after assuring ourselves that all functions correctly we remove this probe before starting an actual diffusion measurement.

Some 2D plots of the midpoints of the water resonance in dispersion mode (i.e., 1 D spectra) acquired using a pulse and acquire sequence with a small flip angle whilst we were investigating the origin of the artefacts are shown on the following page. Spectrum A was acquired after we had improved the temperature stability in the lab (note the large spikes resulting from the gradient cooling air), Spectrum B was acquired after bypassing the air dryer (consequently no large spikes) and Spectrum C was acquired after all of the above sources of artefacts were removed and represents our 'baseline' unlocked stability. Field frequency locking improved this stability by a further order of magnitude (i.e., to  $\sim \pm 0.1$  Hz).

Yours sincerely



István Furó



William S. Price



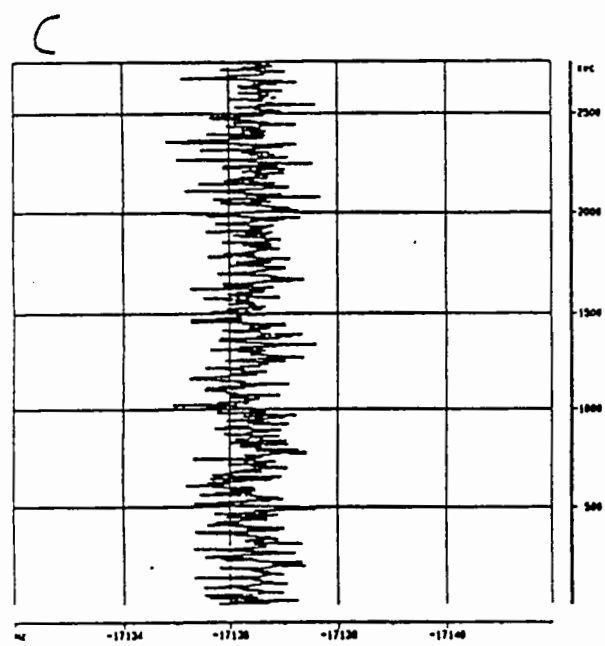
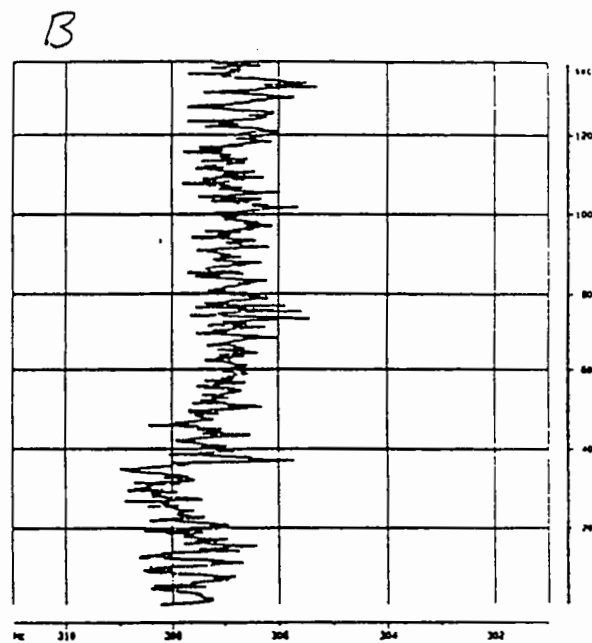
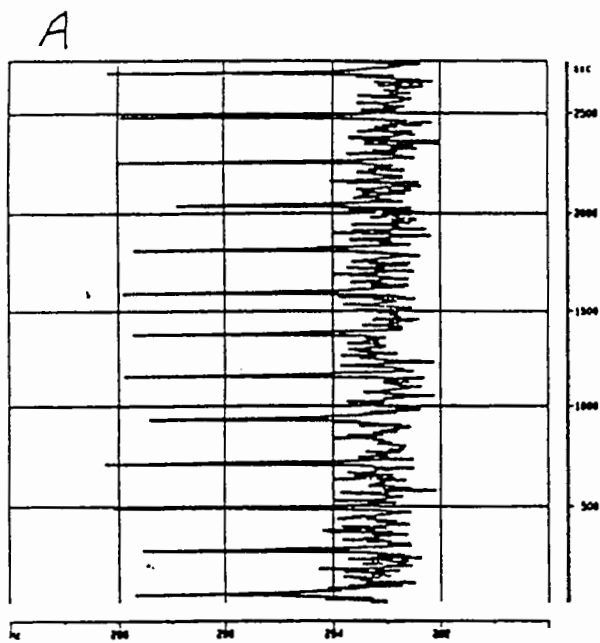
Peter Stilbs

Furó, I. and H. Jóhannesson. 1996. Accurate anisotropic water-diffusion measurements in liquid crystals. *J. Magn. Reson. A* 119:15-21.

Hedin, N. and I. Furó. 1998. Temperature imaging by  $^1\text{H}$  NMR and suppression of convection in nmr probes. *J. Magn. Reson.* 131:126-130.

Price, W. S., K. Hayamizu, H. Ide, and Y. Arata. 1999. Strategies for diagnosing and alleviating artifactual attenuation associated with large gradient pulses in PGSE NMR diffusion measurements. *J. Magn. Reson.* 139:205-212.





**Forthcoming NMR Meetings**, continued from page 1:

- NMR Spectroscopy of Biofluids and Tissues**, Imperial College, London, England, **November 13-17, 2000**. Contact: Hersha Mistry, Centre for Continuing Education, Imperial College, 526 Sherfield Building, Exhibition Road, London, SW7 2AZ, UK. Tel: +44 (0)20 7594 6884; Fax: +44 (0)20 7594 6883; Email: [h.mistry@ic.ac.uk](mailto:h.mistry@ic.ac.uk); <http://www.ad.ic.ac.uk/cpd/nmr.htm>
- Frontiers of NMR in Molecular Biology VII**, Big Sky, Montana, **January 20-26, 2001**. Contact: Keystone Symposia, Drawer 1630, 221 Summit Place, Suite 272, Silverthorne, CO 80498. Tel: 800-253-0685 or 970-262-1230; Fax: 970-262-1525; E-mail: [keystone@symposia.com](mailto:keystone@symposia.com). <http://www.symposia.com>.
- PITTCON 2001**, New Orleans, LA, **March 4-9, 2001**. Contact: THE PITTSBURGH CONFERENCE, Dept. CFP, 300 Penn Center Blvd., Suite 332, Pittsburgh, PA 15235-5503. Tel: 412-825-3220; Fax: 412-825-3224; E-mail: [pittconinfo@pittcon.org](mailto:pittconinfo@pittcon.org).
- 42nd ENC (Experimental NMR Conference)**, Rosen Plaza Hotel, Orlando, Florida, **March 11-16, 2001**; Arthur G. Palmer, Chair: [Agp6@columbia.edu](mailto:Agp6@columbia.edu); Contact: ENC, 1201 Don Diego Avenue, Santa Fe, NM 87505; (505) 989-4573; Fax: (505) 989-1073; E-mail: [enc@enc-conference.org](mailto:enc@enc-conference.org); Web: [www.enc-conference.org](http://www.enc-conference.org).
- Magnetic Resonance in Chemistry and Biology, XIth International Conference**, Zvenigorod, Russia, **April 20-27, 2001**. Contact: <http://www.nmr.de/html/conf/zelino.shtml>.
- ISMARM 9th Scientific Meeting and Exhibition; ESMRMB 18th Annual Meeting and Exhibition, Joint Annual Meeting**, Glasgow, Scotland, **April 21-27, 2001**. Contact: ISMARM Central Office, 2118 Melvia Street, Suite 201, Berkeley, CA 94704. Tel: 510-841-1899; Fax: 510-841-2340; E-mail: [info@ismarm.org](mailto:info@ismarm.org).
- Computational Aspects of Biomolecular NMR**, Gordon Conference, "Il Ciocco", Barga (Pisa) Italy, **May 6-11, 2001**. Contact: Michael Nilges [nilges@embl-heidelberg.de](mailto:nilges@embl-heidelberg.de), or Dave Cast [case@scripps.edu](mailto:case@scripps.edu).
- Gordon Research Conference on Magnetic Resonance**, **June 17-22, 2001**, Roger Williams University, Bristol, Rhode Island (note the new, improved location !!!). Contacts: Rob Tycko, Chair, 301-402-8272, [tycko@helix.nih.gov](mailto:tycko@helix.nih.gov), and Kurt Zilm, Vice-Chair, [kurt.zilm@yale.edu](mailto:kurt.zilm@yale.edu). Site description and application information available at <http://www.grc.uri.edu>.
- IXth International Symposium on Magnetic Resonance in Colloid and Interface Science**, St. Petersburg, Russia, **June 26-30, 2001**. Contact: Mrs. L. Ya. Startseva, Secretariat of ISMRCIS, Boreskov Institute of Catalysis, 5, Prosp. Akad. Lavrentieva, Novosibirsk, 630090, Russia. Tel: +7 (3832) 34-12-97; Fax: +7 (3832) 34-30-56; E-mail: [star@catalysis.nsk.su](mailto:star@catalysis.nsk.su).
- Royal Society of Chemistry: 15th International Meeting on NMR Spectroscopy**, 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](mailto:conferences@rsc.org)
- ESR and Solid State NMR in High Magnetic Fields**, Stuttgart, Germany, **July 22-26, 2001**. Contact: Prof. Hans Paus, 2 Physikalisches Institut, Universität Stuttgart, Pfaffenwaldring 57, D-70550 Stuttgart, Germany. Tel: ++49-711-685-5223; Fax: ++40-711-685-5285; E-mail: [ampere2001@physik.uni-stuttgart.de](mailto:ampere2001@physik.uni-stuttgart.de).
- ISMAR 2001**, Jerusalem, Israel, **August 19-24, 2001**; See <http://www.tau.ac.il/chemistry/ISMAR.html>.
- 14th European Symposium on Polymer Spectroscopy**, Dresden, Germany, **September 2-5, 2001**. Contact: Institut für Polymerforschung Dresden e. V., ESOPS 14, Postfach 12 04 11, 01005 Dresden, Germany. Tel: +49 351 4658-282; Fax: +49 351-4658-214; E-mail: [espos@ipfdd.de](mailto:espos@ipfdd.de).
- Fourth International Conference on Molecular Structural Biology**, Vienna, Austria, **September 5-9, 2001**. Contact: Andreas Kungl, Austrian Chemical Society (GÖCH), Biochemistry Subgroup, c/o Institute of Pharmaceutical Chemistry, University of Graz, Universitätsplatz 1, A-8010 Graz, Austria. Tel: +43 316 380 5373; Fax: +43 316 382541; E-mail: [andreas.kungl@kfunigraz.ac.at](mailto:andreas.kungl@kfunigraz.ac.at).

Additional listings of meetings, etc., are invited.

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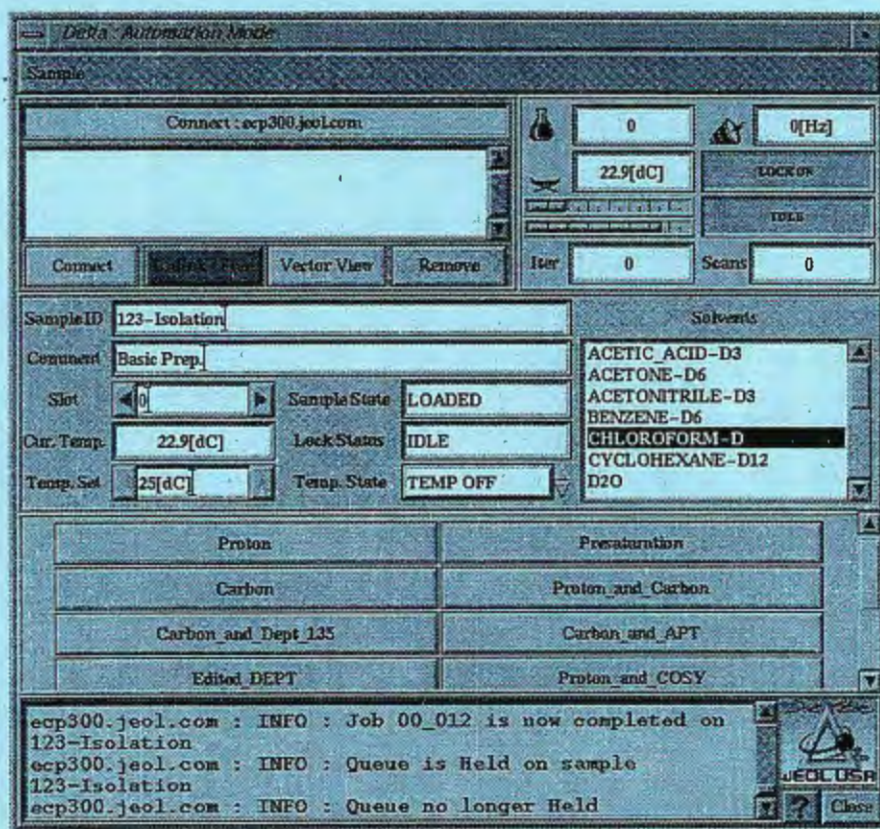
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