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NMR
NEWSLETTER

No. 513

June 2001

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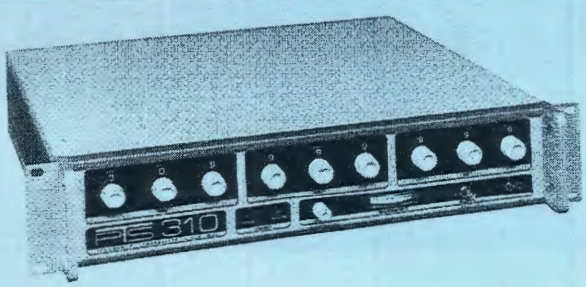

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FORTHCOMING NMR MEETINGS

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, and Kurt Zilm, Vice-Chair, kurt.zilm@yale.edu. Site description and application information available at http://www.grc.uri.edu.

ISMRM (International Society for Magnetic Resonance in Medicine) Workshop on "Limits of Detection in Nuclear Magnetic Resonance", Univ. Of California, Berkeley, **June 23-26, 2001**. For details of the program, registration, on-site accommodations, and call for papers, see http://www.ismrm.org/workshops/nmr/

IX 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.

Royal Society of Chemistry: 15th International Meeting on NMR Spectroscopy, Durham, England, **July 8-12, 2001**; Contact: Paula Whelan, 15th International Meeting on NMR Spectroscopy, Royal Society of Chemistry, Burlington House, Piccadilly, London W1J 0BA, United Kingdom. Tel: +44-(0)207-437-8656; Email: conferences@rsc.org\.

ESR and Solid State NMR in High Magnetic Fields, University 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: ++40-711-685-5282; E-mail: ampere2001@physik.uni-stuttgart.de.

43rd Rocky Mountain Conference on Analytical Chemistry, Denver Marriott City Center, Denver, CO, **July 29-August 2, 2001**. Email: milestone@bod.net. Web: www.milestoneshows.com/rmcac.

ISMAR 2001, *Note change of meeting location:* Convention Center of Rodos Palace Hotel in Rhodes, Greece. **August 19-24, 2001**; See http://www.tau.ac.il/chemistry/ISMAR.html.

Sixth International Conference on Magnetic Resonance Microscopy, Nottingham, UK, **September 2-5, 2001**. http://www.magres.nottingham.ac.uk/conferences/2001/icmrm.

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December 5, 1975

Dr. B. L. Shapiro
Department of Chemistry
Texas A&M University
College Station, Texas 77843

Dear Barry,

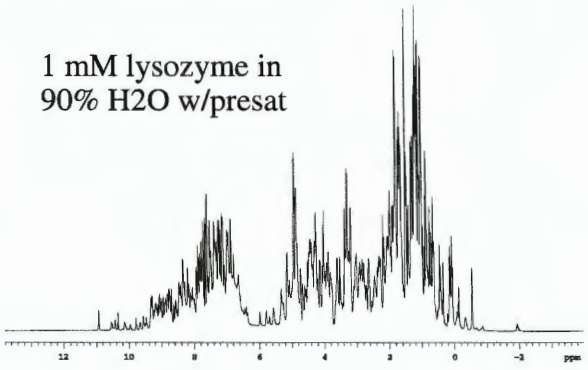
**SATURATION-RECOVERY T_1'S
REINVENTION OF THE WHEEL**

The accurate measurement of spin-lattice relaxation times is a problem which is on everyone's mind. As recently summarized by Levy[1], various techniques show different dependences on factors such as miscalibration of pulses, distance off-resonance, H_1 inhomogeneity, etc. The use of equations which include these factors is in many cases indispensable for obtaining accurate results. Nothing, however, can replace the selection of an experimental technique which minimizes the various difficulties. In this regard, the most critical factor in measuring accurate relaxation times is the preparation of the magnetization to a precisely known state at some time in the experiment. Any imprecision, caused by pulse miscalibration, distance off-resonance, H_1 inhomogeneity, or whatever, will introduce "distortion" into the observed behavior of the magnetization with time and will certainly reduce the expected accuracy.

Some time ago, Markley et al.[2] observed in a footnote that one could measure T_1's by a saturation-recovery technique, using white noise to saturate an entire spectrum. That paper focussed on the reduction in time made possible by such a technique in connection with the measurement of long relaxation times. We would like to focus on another aspect of that experiment, i.e., the fact that one can prepare a spin system to a known (M_0=0) state of magnetization at a known time (t=0). Furthermore, one can directly monitor that state to verify this. In the standard inversion-recovery T_1 sequence[3], for example, components of the magnetization left in the x-y plane by the 180° pulse complicate the immediate monitoring of the z-magnetization without the intervention of a homogeneity spoiling pulse, and the observation of spectra with $M(t)=-M_0$ is rarely possible. In a saturation experiment, however, there is no net x-y magnetization at time zero, so that an (almost) immediate monitoring of the z-magnetization is possible. At the same time one has dispensed with the need to calibrate pulse lengths and worries about H_1 inhomogeneity and distance off-resonance. The only requirement is a decoupler capable of saturating the spins of interest.

This experiment is demonstrated in the accompanying figure, which is a T_1 measurement of ribonuclease. We present the downfield (A) and the upfield (B)

Varian and Oxford Instruments are pleased to announce the establishment of a joint applications laboratory located in Oxford, U.K. The new laboratory features the Inova 900 MHz NMR spectrometer.



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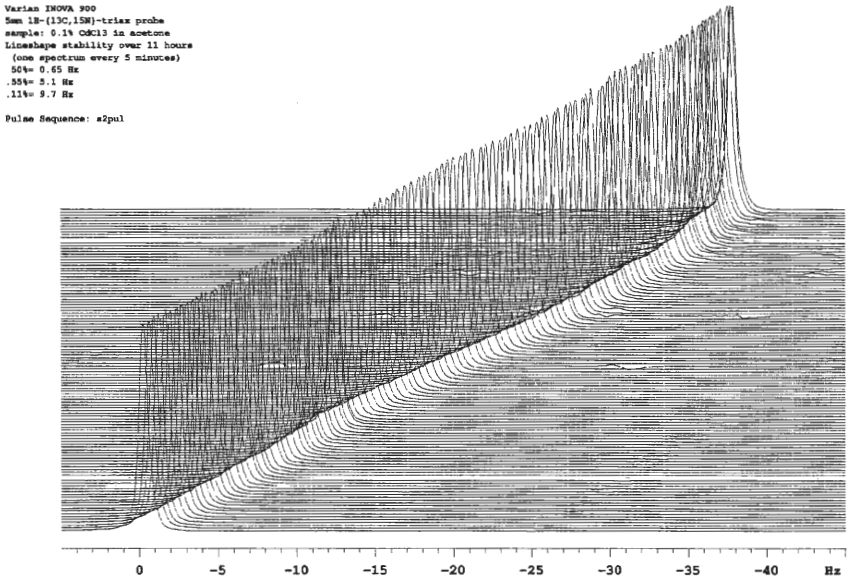
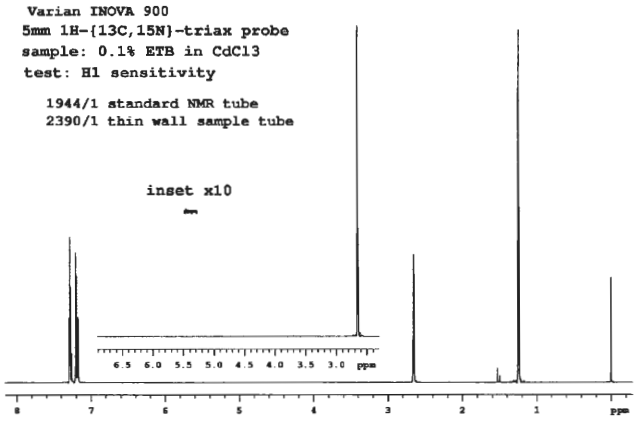
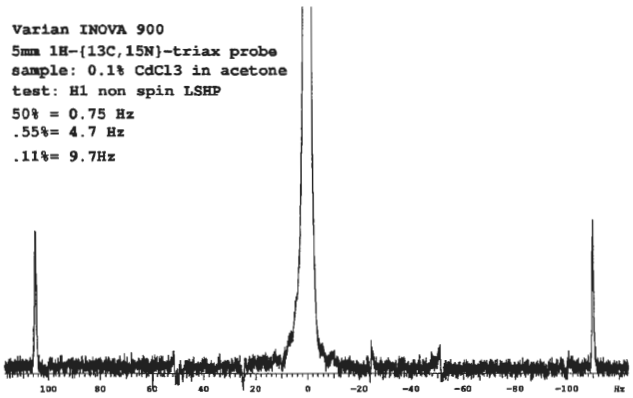
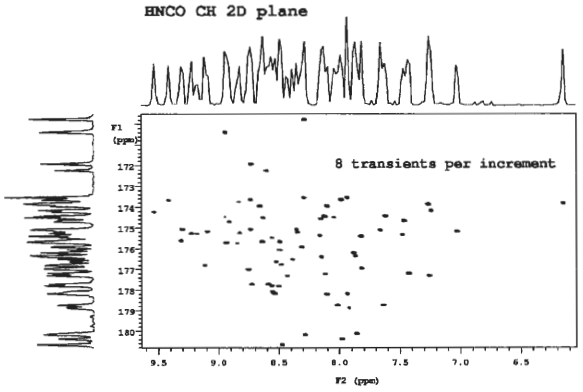
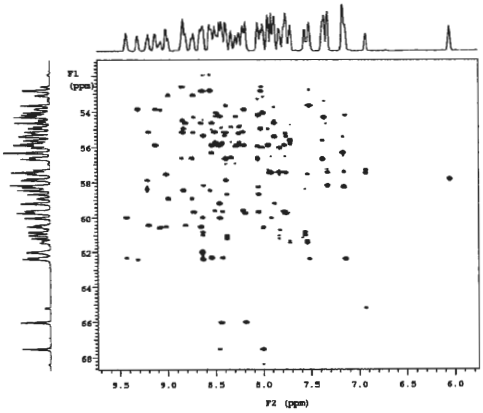










The 900 MHz magnet has been at field since early January and is fully persistent and stable with a measured drift rate of 2 Hz per hour. Fundamental NMR performance as well as triple resonance are illustrated by the spectra on this page.

The Inova 900 is currently available for scientific collaborations and customer demonstrations.

VARIAN

Dr. B. L. Shapiro
December 5, 1975

regions of the spectrum at 360 MHz, with τ values from bottom to top of .01, .04, .08, .1, .2, .4, .7, 1.0, and 1.5 seconds. Note that one can look at these spectra and be confident that at time zero the magnetizations did indeed start at 0. Decoupling power used in these experiments was approximately 20 times normal single frequency decoupling experiments. 0.5 second was allowed to re-saturate the spectrum after each pulse. The approach of spin systems to complete saturation is a non-trivial theoretical problem, given either single frequency[4] or white noise[5] decoupling (which is not used on our Bruker spectrometer in any case). The experimental approach of lengthening the time for saturation until no magnetization is seen at short values of τ is probably the best solution to the problem in general.

One additional feature should be noted. Like the progressive-saturation experiment[6], no estimate of T_1 is needed to begin the experiment, and thus no wastage of time is incurred. Unlike the progressive-saturation experiment, however, the acquisition time and/or the decay of magnetization in the x-y plane following the sampling pulse do not place a limitation of the selection of τ values, and hence there is no limitation on the T_1's which can be measured. The only limitation which must be mentioned is that, for white noise decoupling at least, the net z-magnetization in the presence of the decoupling is[5]

$$\overline{M_z} = M_0/(1+\sigma^2 T_1/2)$$

where σ^2 is the constant power spectral density. In other words, and as everyone knows intuitively, it is harder to saturate resonances with short T_1's. We repeat, however, that although this may interfere with the experiment, the state of magnetization at small values of τ is subject to direct experimental measurement.

Sincerely,

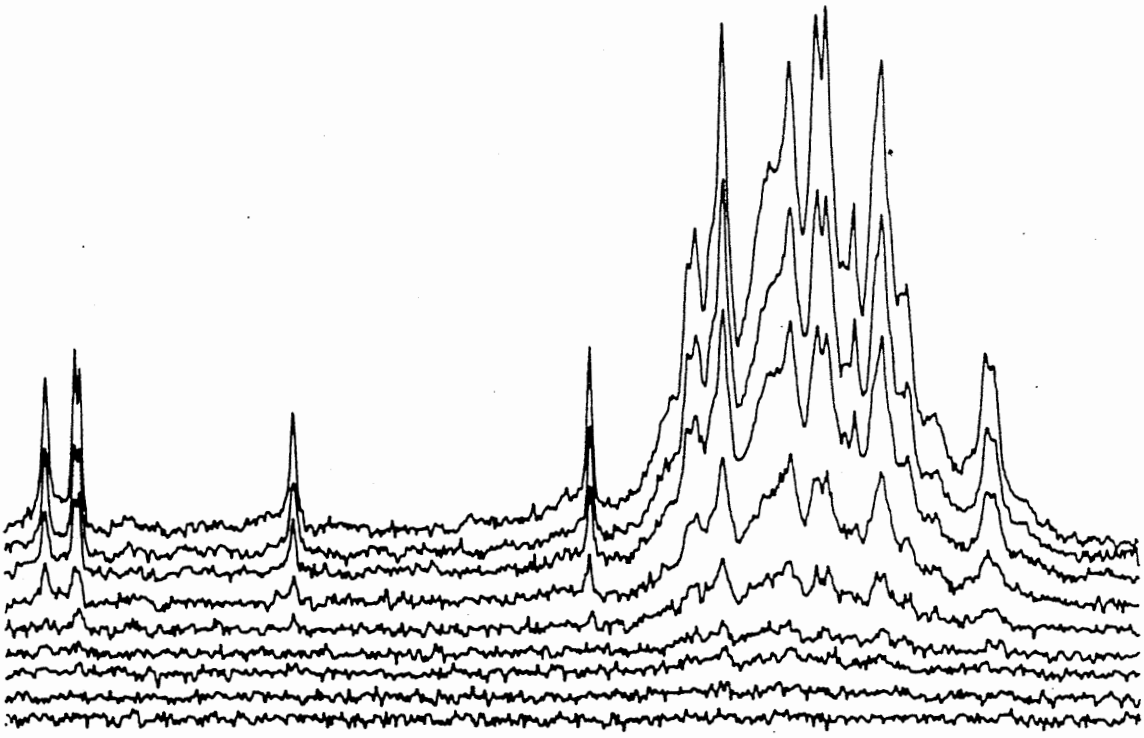
Steve Patt Oleg Jardetzky Woody Conover

Enclosure

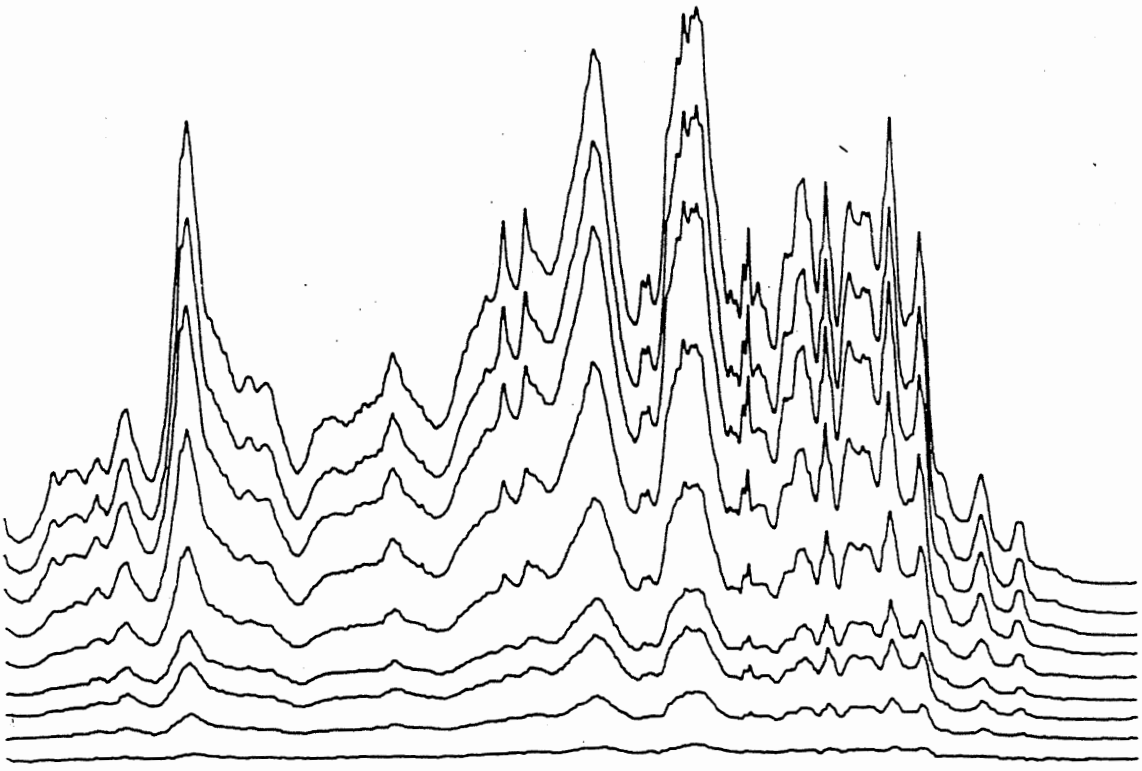
SP/OJ/WC/skh

[1]G. C. Levy and I. R. Peat, J. Mag. Res., 18:500 (1975)
[2]J. L. Markley, W. S. Horsley, and M. P. Klein, J. Chem. Phys., 55:3604 (1971)
[3]R. L. Vold, J. S. Waugh, M. P. Klein, and D. E. Phelps, J. Chem. Phys., 48:3831 (1968)
[4]H. C. Torrey, Phys. Rev., 76:1059 (1949)
[5]R. R. Ernst, J. Mag. Res., 3:10 (1970)
[6]R. Freeman and H. D. W. Hill, J. Chem. Phys., 54:3307 (1971)

A)



B)



RNAse A, 36 mg/ml, pH 2.07, 26°C, 200 75° pulses each,
taken on an HXS-360 spectrometer

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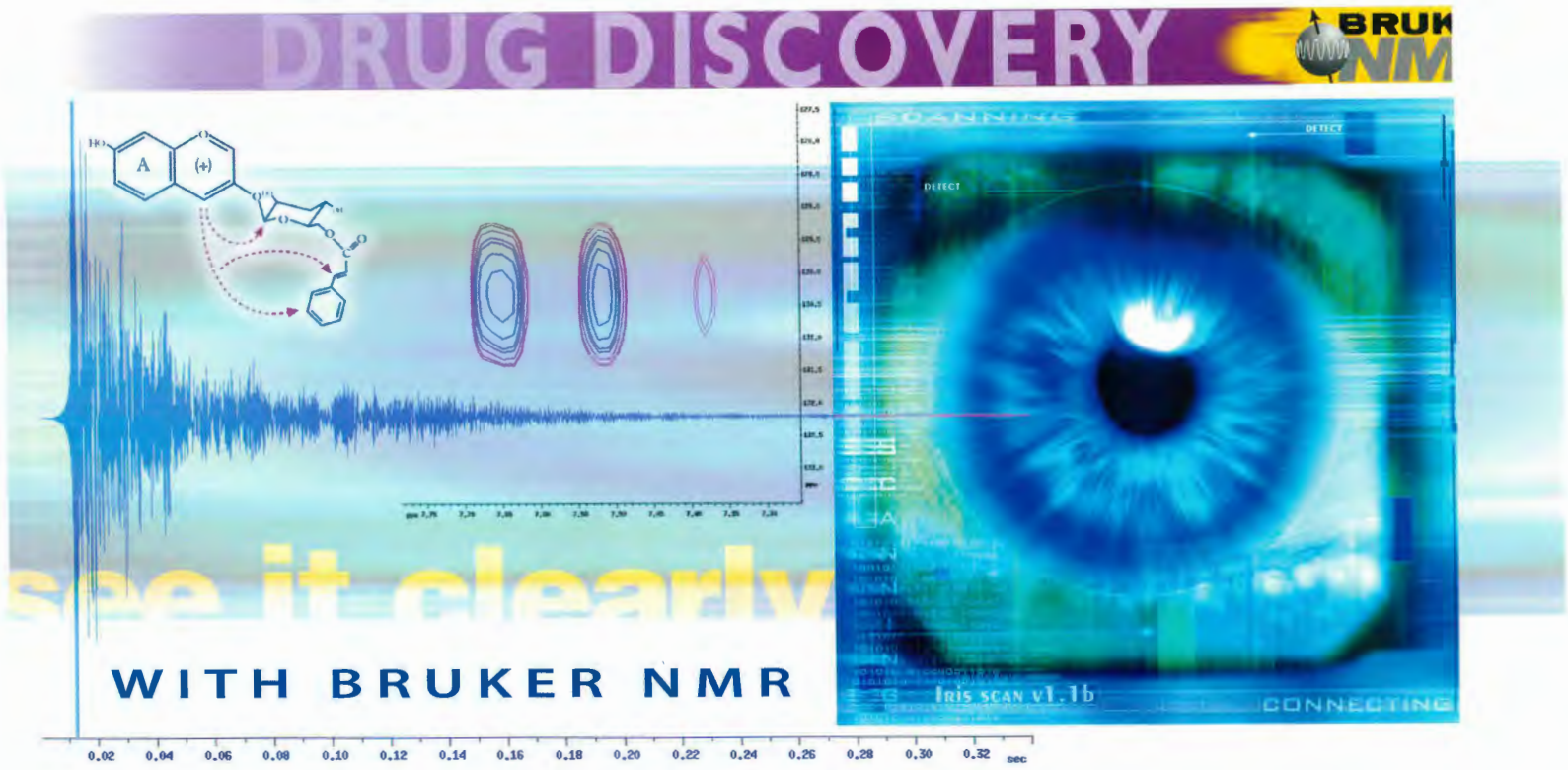
SEE IT CLEARLY



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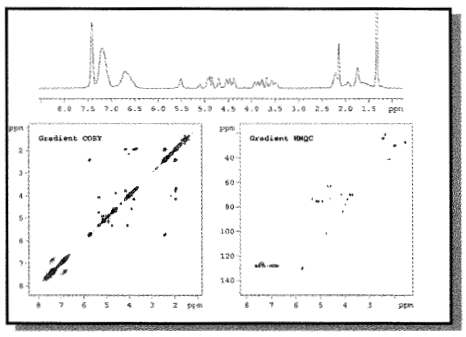

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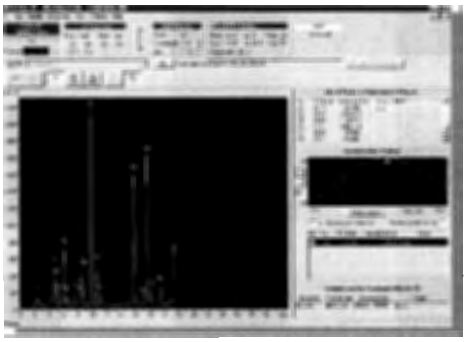

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April 12, 2001 (received 4/30/2001)

^{31}P-NMR Spectroscopic Assessment of the Viability of Tissue Engineered Cartilage

Dear Barry,

More and more attention is being given these days to tissue engineering. This includes many investigators who are seeking to replace damaged or diseased tissues with properly functioning tissue grown in laboratory cell culture.

One tissue engineering method expanding cartilage cell lines and then transplanting them into human articular cartilage is called Autologous Chondrocyte Transplantation (ACT) [1], [2]. ACT is receiving increasing attention due to the high morbidity associated with articular joint diseases such as osteoarthritis and the relatively few options currently available for treatment.

A major challenge to tissue engineers in general is the development of a non-invasive technique to assess the viability of cells grown in culture. This could enable them to ensure that, once transplanted, these cells would behave in a physiologically normal way. We have found that one non-invasive method of assessing viability in chondrocytes is ^{31}P-NMR spectroscopy. This technique has already been used to assess pancreatic tissue destined for transplantation [3]. ^{31}P-NMR has also been used in the assessment of liver transplants [4].

Few studies to date, however, have used ^{31}P-NMR spectroscopy to examine bioenergetics in cartilage [5], [6]. We have therefore initiated studies examining the bioenergetics of cartilage tissue engineered for transplantation.

Cartilage cells (chondrocytes) were harvested from the distal sterna of 16 day-old chick embryos and inoculated into hollow-fiber bioreactors (HFBRs), sealed glass tubes of 15 mm diameter that provide a chamber for cell growth [7]. The bioreactor contained twelve porous fibers and was continuously supplied with tissue culture media (TCM) containing 4.5 g/L glucose.

^{31}P-NMR spectroscopy was performed on bioreactors three weeks after inoculation. The bioreactor was then perfused with glucose-free medium for an additional week and analyzed spectroscopically again at week 4. A saddle coil was constructed for the experiments which were carried out on a 9.4 T Bruker DMX spectrometer. A reference sample of methylene diphosphonic acid (MDP) was built into each bioreactor.

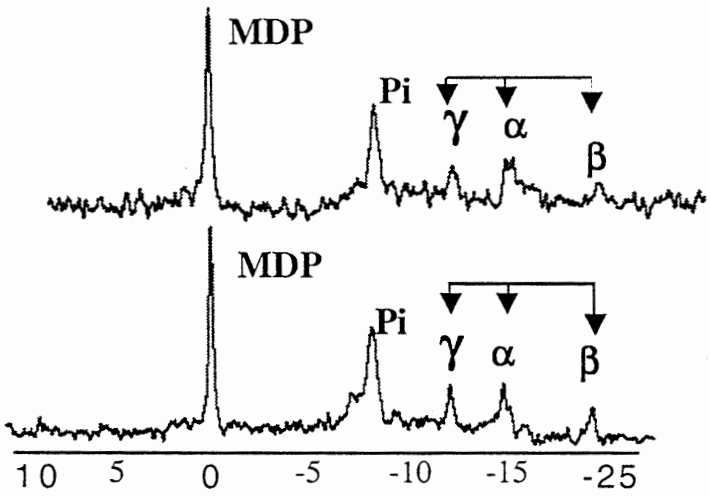

Figure 1. ^{31}P-NMR Spectra of neocartilage tissue: top) week 3 (4.5 g/L glucose) bottom) week 4 (after 1 week of 0 g/L glucose).

Spectra acquired before and after the suspension of glucose were similar with respect to the energy charge and metabolites detected (Figure 1). All three resonances associated with adenosine triphosphate as well as that of inorganic phosphate (Pi) were observed. Phosphocreatine (PCr) was not present in detectable concentrations. The energy charge (ATP/Pi) of the sample increased from 0.93 at week 3 to 0.97 at week 4 (Table 1). This increase may be due in part to a change to oxidative phosphorylation which allows for more efficient production of ATP. This phenomenon, known as the Crabtree Effect, has been previously observed in chondrocytes [7]. Unlike other cells such as myocytes, chondrocytes are much more flexible in using different types of metabolism to adapt to various energy substrates.

Tissue Culture Media	MDP	Pi	Gamma ATP	Alpha ATP	Beta ATP	ATP/Pi
with 4.5 g/L Glucose	19.0	9.74	2.35	4.62	2.15	0.93
with 0.0 g/L Glucose	19.0	9.33	3.90	3.97	1.72	0.97

Table 1. Peak intensities of spectra from bioreactors in presence and absence of glucose.

This data shows that ^{31}P-NMR spectroscopy provides useful information about the bioenergetics of cartilage grown in the HFBR system. The absence of detectable concentrations of PCr is consistent with previous studies [8].

^{31}P-NMR of bioreactors may be utilized in evoloving designs for future bioreactors. Optimal growth conditions may then be achieved with regard to cell number in the inoculate, bioreactor dimensions, and the number of fibers needed for adequate nutrient supply and waste product removal.

The current study is aimed at optimizing the viability of avian cells using the HBFR system. Future studies will apply the information gained towards the assessment of human cartilage viability. In addition, we will attempt to correlate the spectroscopic assessment of human cartilage used in ACT to outcome measures in order to allow the clinician to decide when engineered tissue is suitable for transplant.

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2. Schneider U., Breusch S.J., Von der Mark K., Z Fur Orth Grenz, 137(5), 386-392, (1999).
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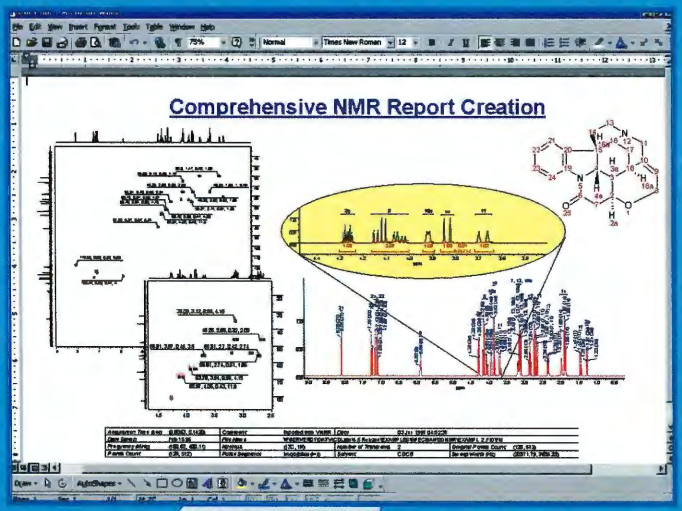

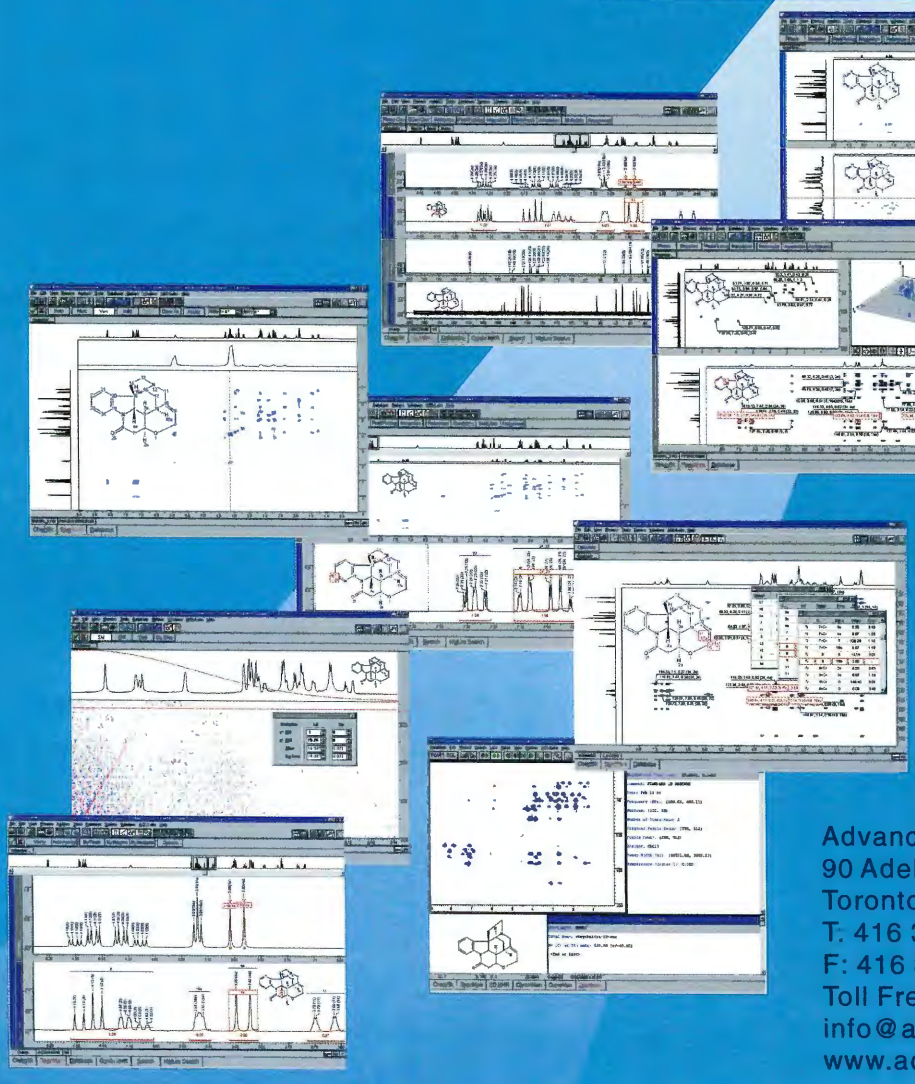

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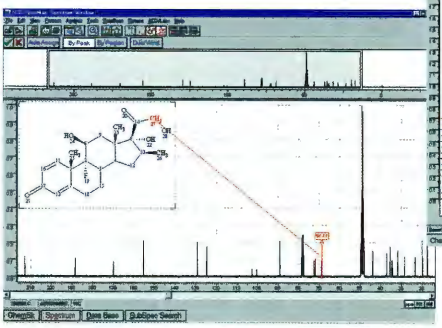

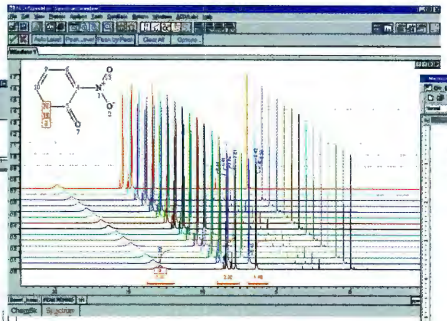

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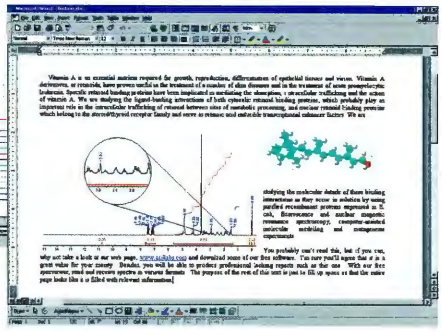

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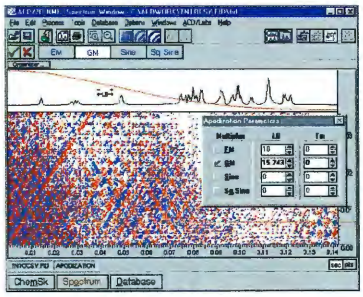

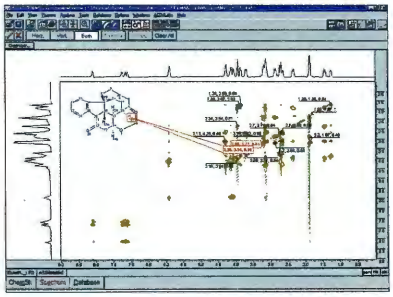

Assign 2D spectra to structures

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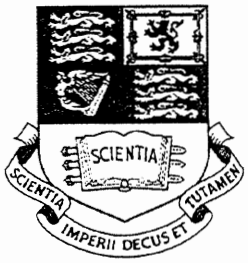


Imperial College
OF SCIENCE, TECHNOLOGY AND MEDICINE

14 May 2001
(received 5/21/2001)

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

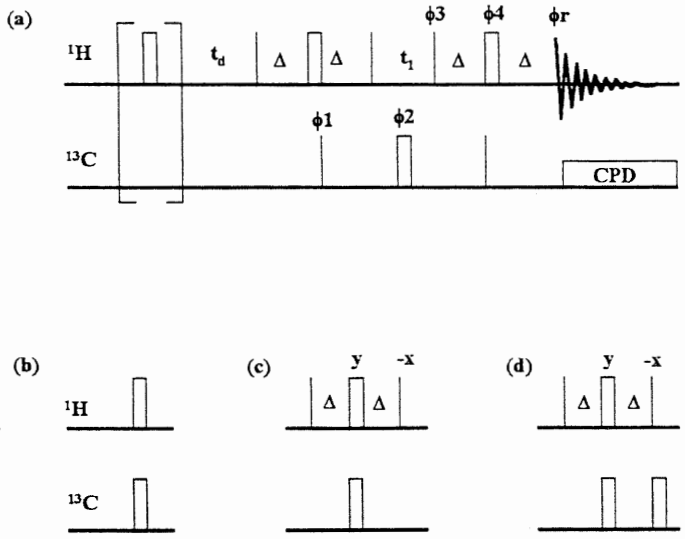
Dear Barry,

Proton T_1s in crowded ^1H NMR spectra

We have previously developed an NMR spectrum editing method, MAXY, based on filtering through the maximum quantum coherence of CH_n groups including the natural abundance ^{13}C spin, and combined it with a variety of one-, two- and three-dimensional ^1H, ^1H-^{13}C and ^{13}C-^1H NMR methods to give selective detection of CH, CH_2 or CH_3 resonances. The general approach has now been extended to allow the determination of ^1H longitudinal relaxation times in the situation of spectral overlap. The relaxation rate ($R_1 = 1/T_1$) is, in some circumstances determined by dipole-dipole interactions, and can be used to obtain the correlation time (τ_c) of the spin. However, determination of T_1 of individual resonances in a ^1H NMR spectrum is often difficult, especially in the case of large or complex molecules, where resonance overlap makes it impossible to distinguish one peak from another.

The pulse sequences used in the experiments are shown in the figure, where four types of inversion-recovery (IR) scheme have been used to achieve selective and non-selective inversion and the MAXY sequence is used to read out the magnetization to get selective spectra from CH, CH_2 or CH_3 groups. A single 180° pulse on ^1H (Fig. a) gives rise to a non-selective inversion effect similar to the conventional IR method. The contribution of the cross-relaxation from the ^{13}C to the attached proton is included by simultaneously applying a 180° pulse on ^{13}C (Fig. b). Selective inversion of the magnetizations of the directly bonded ^1H and ^{13}C can be achieved by a modified BIRD sequence (Fig. c), where the phase of the last 90°(H) pulse in the BIRD sequence has been changed from the x axis to the -x axis. By introducing a second 180° pulse on ^{13}C at the end of the BIRD sequence (Fig. d), only the magnetization of the protons in $^{13}CH_n$ systems will be selectively inverted resulting in a selective relaxation rate without any cross-relaxation term. It is, therefore, possible to derive the cross-relaxation rate between the directly attached ^{13}C and ^1H, or between the protons bonded to ^{13}C, and the protons bonded to ^{12}C by taking the difference of the

relaxation rates obtained from two of the measurements. The methods have been demonstrated using cholesteryl acetate since the molecular dynamics of cholesteryl esters in cell membranes and lipoproteins is a subject of considerable importance and the results will be published soon in Molecular Physics.



Pulse sequence used for proton longitudinal relaxation time measurements. This is essentially the 2D MAXY sequence or a 1D MAXY sequence if the variable delay (t_1) is fixed at the initial value (3 μs), with additional inversion-recovery schemes for inverting (a) all protons, (b) protons and ^{13}C, (c) only directly attached ^{1}H and ^{13}C with cross-relaxation from the ^{13}C (d) only ^{1}H attached to ^{13}C.

With best wishes,

Maili Liu

John Lindon

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The University of Sydney
DEPARTMENT OF BIOCHEMISTRY
Faculty of Science
College of Sciences & Technology

1st May, 2001 (received 5/18/2001)

dphilp@physics.usyd.edu.au
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Observation of Scalar Coupling with Quadrupolar Nuclei

Dear Barry,

We have been investigating scalar coupling with quadrupolar nuclei, from both theoretical and experimental points of view. The beryllium fluoride complexes are an excellent system for such study, because the large F–Be coupling constant ($J = 34$ Hz) leads to well resolved ^{19}F and ^{9}Be spectra. We thought that your readers might be interested in seeing how an expression for the evolution of a system can be used to predict spectra in a novel context.

Müller, Bodenhausen and Ernst [1] presented the expression [Eq. (1)] for the evolution of a spin $I = \frac{1}{2}$ nucleus coupled to a spin $S = \frac{3}{2}$ system, such as ^{9}Be, where scalar coupling acts for a period τ:

$$\begin{aligned}\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{00} \xrightarrow{2\pi J\tau \hat{I}_z\hat{S}_z} & \frac{1}{2}\left[\cos(\pi J\tau)+\cos(3\pi J\tau)\right]\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{00}+\frac{i}{2\sqrt{5}}\left[\sin(\pi J\tau)+3\sin(3\pi J\tau)\right]\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{10} \\ & -2\sin^2(\pi J\tau)\cos(\pi J\tau)\,\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{20}-\frac{2i}{\sqrt{5}}\sin^3(\pi J\tau)\,\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{30}. \qquad (1)\end{aligned}$$

The $\hat{T}^{\mathrm{I}}_{l_1\pm p_1}\hat{T}^{\mathrm{S}}_{l_2\pm p_2}$ are the modified irreducible tensor operator products [2], used for describing coupled spin systems where at least one nuclide has spin $S > \frac{1}{2}$.

Because the evolution matrix of a spin system is symmetrical, the terms on the right hand side of Eq. (1) themselves evolve into the term on the left hand side, and the expression for the evolution would have the same coefficient. For example, the evolution of the coherence $\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{20}$ must include the following:

$$\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{20} \xrightarrow{2\pi J\tau \hat{I}_z\hat{S}_z} -2\sin^2(\pi J\tau)\cos(\pi J\tau)\,\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{00}+\text{other terms}. \qquad (2)$$

In an experiment where the I nucleus is observed, only the coherence $\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{00}$ induces a signal in the coil. If we acquire an FID from a coherence that is not in itself observable, but evolves into the observable coherence during acquisition, then the shape of the FID will be described by an evolution function, such as in Eq. (2); and the spectrum is described by its Fourier transform. Figure 1 shows how these spectra may be observed experimentally.

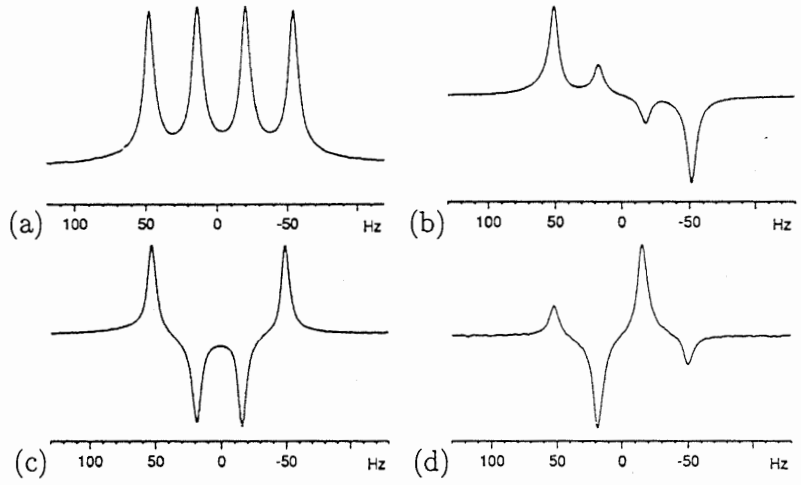

Figure 1: Experimental ^{19}F spectra of the density operator components in Eq. (1).

	coherence	FID	spectrum	experiment
(a)	$\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{00}$	$\frac{1}{2}\left[\cos(\pi Jt_2)+\cos(3\pi Jt_2)\right]$	$1:1:1:1$	pulse-acquire
(b)	$\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{10}$	$\frac{i}{2\sqrt{5}}\left[\sin(\pi Jt_2)+3\sin(3\pi Jt_2)\right]$	$3:1:-1:-3$	reverse INEPT
(c)	$\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{20}$	$-2\sin^2(\pi Jt_2)\cos(\pi Jt_2)$	$1:-1:-1:1$	2QF spin-echo
(d)	$\hat{T}^{\mathrm{I}}_{1\pm1}\hat{T}^{\mathrm{S}}_{30}$	$-\frac{2i}{\sqrt{5}}\sin^3(\pi Jt_2)$	$1:-3:3:-1$	3QF spin-echo

Regards,

David Philp Richard Kemp-Harper Philip Kuchel

References

[1] Müller, N., Bodenhausen, G., and Ernst, R. R. (1987) Relaxation-induced violations of coherence transfer selection rules in nuclear magnetic resonance. *J. Magn. Reson.*, **75**, 297–334.

[2] Kemp-Harper, R., Philp, D. J., and Kuchel, P. W. (2001) NMR of J-coupled quadrupolar nuclei: Use of the tensor operator product basis. *J. Chem. Phys.*, **in press**.

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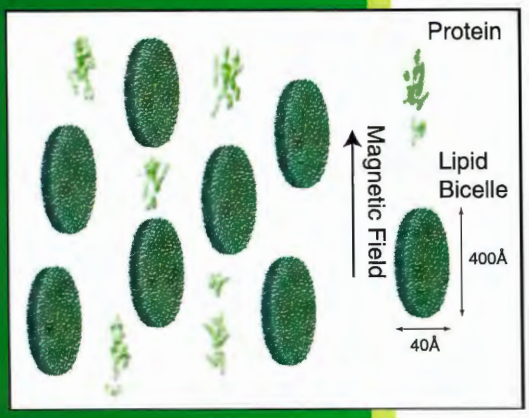
Determination of Water Soluble Protein Structure



Tjandra & Bax[1] recently developed a new nuclear magnetic resonance (NMR) technique that gently aligns protein molecules in a bath of liquid crystals, allowing researchers to determine how each bond between neighboring atoms is oriented with respect to the rest of the molecule. By compiling all such orientations between atoms,a precise map of the protein can be derived. In aqueous solution, just above room temperature, the lipids switch from a gel to a Liquid Crystal (LC) phase, where they form disc-shaped particles, often referred to as bicelles[2], with diameters of several hundred angstroms and thicknesses of ~40Å. The lipids are diamagnetic, and, as a result, the bicelles orient with their normal orthogonal to the magnetic field. However, the lifetimes and temperature ranges of orientation for these samples are critically dependent on sample composition and experimental conditions. Losonczi & Prestegard[3] demonstrated that doping dilute bicelle solutions with small amounts of charged amphiphiles substantially improves the stability and degree of alignment, as well as extends the temperature range of orientation for these systems.

1. Tjandra, N. and Bax, A. (1997). Direct measurement of distances and angles in biomolecules by NMR in a dilute liquid crystalline medium. *Science* 278:1111-3.
2. Sanders, C.R. II and Schwonek, J.P. (1992). Characterization of magnetically orientable bilayers in mixtures of dihexanoylphosphatidylcholine and dimyristoylphosphatidylcholine by solid-state NMR. *Biochemistry* 31:37,8898-905.
3. Losonczi, J.A. and Prestegard, J.H. (1998). Improved dilute bicelle solutions for high-resolution NMR of biological macromolecules. *J Biomol NMR* 12:447-51.

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Bicelle Preparation

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Bicelle Formation:
DMPC/DHPC stock solutions containing a total of 15% w/v (150mg lipid/ml) are prepared as follows: *Add buffer to the lyophilized lipid mixture* - 50mg lipid mixture/280µg buffer or 200mg lipid mixture/1130µg buffer. *Let the mixtures hydrate at room temperature (18-22°C) for several hours.*
Lipid mixtures with a "q" of 2.8 - 3.0, the hydration is complete in 2 - 3 hours. Lipid mixtures with a "q" of 3.25 - 3.5 require 24 hours for complete hydration. Accelerated hydration (one hour) may be effected by heating any mixture to 40°C for 10 minutes and cycling to 18°C twice, then briefly vortexing.
Protein-Bicelle Mix: Two volumes of protein solution are added to one volume of bicelle solution.

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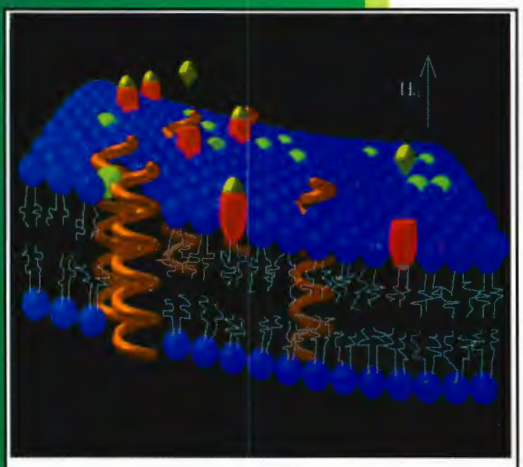
Magnetic Alignment of Biological Membranes



Blue, green, and red stylized molecules represent DMPC, DMPG, and DMPE-DTPA, respectively, and yellow represents the Yb^{3+} ion DHPC, which is believed to be sequestered in curvature defect regions, is not shown in this figure.

A phospholipid chelate complexed with ytterbium (DMPE-DTPA:Yb^{3+}) is shown to be readily incorporated into a model membrane system, which may then be aligned in a magnetic field such that the average bilayer normal lies along the field. This so-called positively ordered smectic phase, whose lipids consist of less than 1% DMPE-DTPA:Yb^{3+}, is ideally suited to structural studies of membrane proteins by solid-state NMR, low-angle diffraction, and spectroscopic techniques that require oriented samples. The chelate, 1,2-dimyristoyl-*sn*-glycero-3-phosphoethanolamine diethylenetriaminepentaacetic acid, which strongly binds the lanthanide ions and serves to orient the membrane in a magnetic field, prevents direct lanthanide-protein interactions and significantly reduces paramagnetic shifts and line broadening. Similar low-spin lanthanide chelates may have applications in field-ordered solution NMR studies of water-soluble proteins and in the design of new magnetically aligned liquid crystalline phases[1].

The addition of lanthanides (Tm^{3+}, Yb^{3+}, Er^{3+}, or Eu^{3+}) to a solution of long-chain phospholipids such as DMPC and short-chain phospholipids such as DHPC is known to result in a bilayer phase in which the average bilayer normal aligns parallel to an applied magnetic field. Lanthanide-doped bilayers have enormous potential for the study of membrane proteins by solid-state NMR, low-angle diffraction, and a variety of optical spectroscopic techniques[2].

The equimolar complex, consisting of the lipid-like, amphiphilic chelating agent DTPA-18 and Tm^{3+}, is shown by deuterium NMR to be useful in aligning bicelle-like model membranes, consisting of DMPC and DHPC. As shown previously, in the absence of chelate, the lanthanide ions bind loosely with the lipid phosphate groups and confer the membrane with a sufficient positive magnetic anisotropy to result in parallel alignment. Two conclusions could be drawn from this study: 1. The addition of Tm^{3+} to the bicelle system is consistent with a conformational change in the surface associated peptide, and this effect is shown to be reversed by addition of the chelate, and 2. The paramagnetic shifts are shown to be significantly reduced by addition of chelate[3].

1. Prosser, R.S., et al. (1998). Novel chelate-induced magnetic alignment of biological membranes. *Biophys J* 75:2163-9.
2. Prosser, R.S., et al. (1998). Solid-state NMR studies of magnetically aligned phospholipid membranes: taming lanthanides for membrane protein studies. *Biochem Cell Biol* 76:443-51.
3. Prosser, R.S., et al. (1999). Lanthanide chelates as bilayer alignment tools in NMR studies of membrane-associated peptides. *J Magn Reson* 141:256-60.

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(received 5/22/2001)

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The NMR Newsletter
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USA

18 May 2001

Classifying amino acid type from differences in ^{13}C chemical shifts

Dear Barry,

Identifying amino acid type is a key part of sequentially assigning proteins. Grzesiek & Bax (J. Biomolec. NMR (1993) **3**, 185-204) realised that C_α and C_β shifts are especially useful for this. They used a data base of about 600 spin-systems to generate a composite probability surface for C_α and C_β shifts relative to random coil values. This probability distribution can be used to classify unknown spin systems.
One problem with the approach is that it requires consistent ^{13}C referencing. This should not be a problem because there are straightforward methods of referencing all dimensions of multinuclear experiments. However, it is fairly clear that the methods are not universally used, especially in the early stages of assignment. An alternative approach which avoids the referencing problem is to use chemical shift differences ($\Delta\delta^{13}C$). If carbonyl chemical shifts are available, then shifts can be expressed as CO-C_α and CO-C_β. These values will be unaffected by referencing differences.
The graph overleaf shows the distribution of $\Delta\delta^{13}C$ for approximately 750 spin systems from 8 proteins randomly selected from the BioMagResBank. Points represent the average values for the different types of amino acid (tryptophan, cysteine, and histidine are not included, because less than 20 examples were present in the training set). From the distribution, it is clear that $\Delta\delta^{13}C$ are as well separated as absolute chemical shifts themselves (compare with Figure 6 from Grzesiek & Bax).
The crosses on the figure are the 49 phenylalanines in the training set. They're shown to give an idea about how much overlap there is between residue types. The oval surrounding the points is at 1.96 standard deviations, which is the 97.5% confidence limit for a normal distribution. The 1.96 standard deviation contour for serine is also shown, to demonstrate that variation is different for the different amino acid types.
For a normally-distributed population, the average and standard deviation of a population can be used to calculate the probability of another sample being a member of the population. However, assuming normality needs some justification as ^{13}C shift is strongly dependent on secondary structure so might be expected to have a bimodal distribution (this is the reason that Grzesiek & Bax calculated the distribution function instead of assuming a normal distribution). Visual inspection suggests the distributions of $\Delta\delta^{13}C$ are not too far from normal for most residue types. This is probably because secondary structure has a similar effect on both the C_α and carbonyl shifts, and its effect is much smaller than total variation in CO-C_β.
$\Delta\delta^{13}C$ appears to be at least as good at discriminating residue type as absolute shifts. The main disadvantage of using shift differences is that the it does require carbonyl shifts, which involves extra

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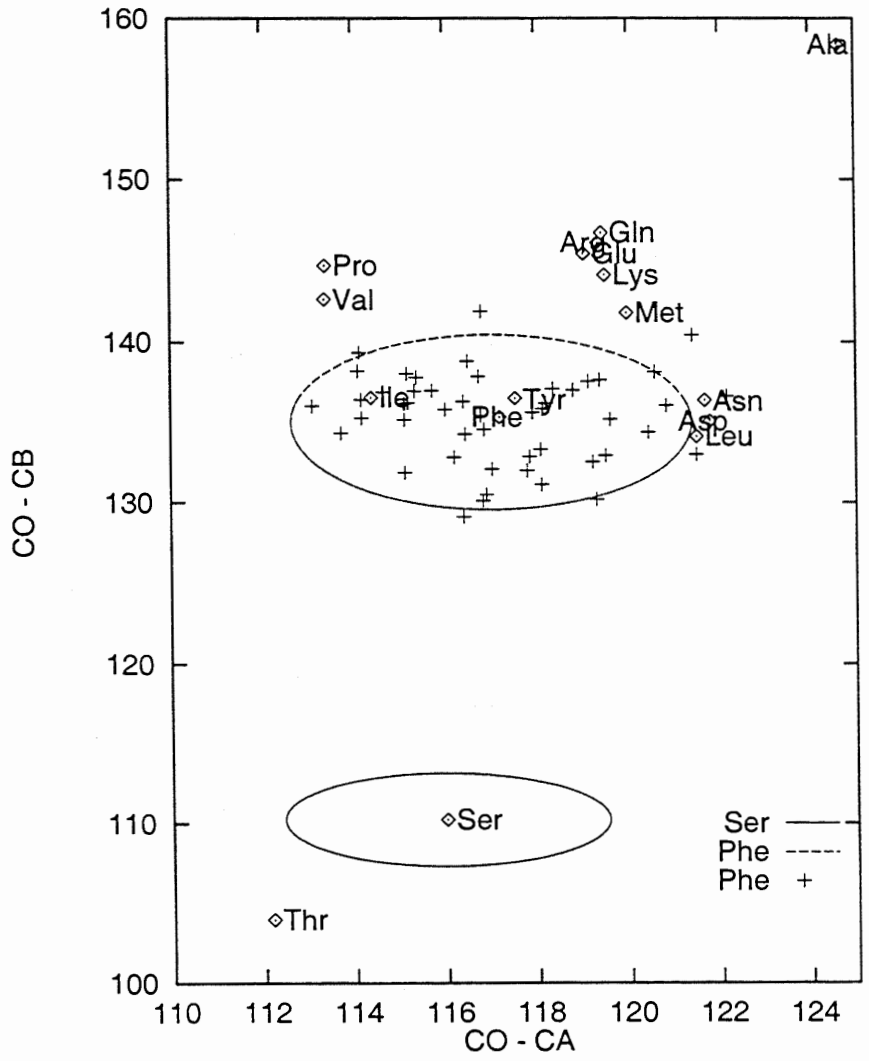
work and is also more difficult with larger proteins owing to the poor separation of carbonyl shifts and the role of CSA in relaxation. Using C_α-C_β would avoid the need for carbonyl shifts, but this would be expected to give poorer discrimination between residue types.
This is our first contribution from Jealott's Hill as part of Syngenta, the world's leading research-based agribusiness, which was formed in November last year from the agribusinesses of Novartis and Zeneca.

Yours sincerely,

Peter Howe

Peter Howe.

PS Anyone who'd like the values of the averages and standard deviations for $\Delta\delta^{13}C$ should get in touch.



Aventis Pharmaceuticals

Aventis

Professor Bernard L. Shapiro
Editor/Publisher
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94030-3410

May 14th, 2001 (received 5/16/2001)

Dear Professor Shapiro:

Getting Our Feet 'WET'

Recently, we implemented LC-NMR and VAST-NMR techniques on a Varian Inova 600 system at Aventis to support drug discovery activities. We would like to share some of our experiences regarding the utilization of WET pulse sequence and digital filters to suppress solvent peaks in LC-NMR and VAST-NMR.

It's widely recognized that suppression of solvent peaks is a primary requirement for any successful application of LC-NMR and/or VAST-NMR approaches. The solvent peaks in these experiments are usually several orders of magnitude more intense than the analyte peaks. Frequently, it also means suppressing multiple resonances resulting from either a binary solvent system used as the mobile phase in LC-NMR or other solvent used in VAST. Varian developed a solvent suppression technique called WET which is based on the application of selective pulses, ^{13}C decoupling and gradient pulses, to overcome these spectroscopic problems and is used routinely as an efficient solvent-suppress pulse to generate high quality LC-NMR and VAST-NMR spectra. We have used WET technique in case acetonitrile/water and DMSO as solvents in VAST. Typically, proton transmitter offset is set to the methyl resonances of the solvent (acetonitrile or DMSO). However, it will be inconvenient to use this approach if there are any resonances of interest which are close to these methyl peaks. It is possible, in such cases, to place the proton transmitter offset (tof) to the residual water peak and use soft digital filters to suppress the solvent's methyl resonances.

The following figure represents some typical ^{1}H spectra of a small organic compound in DMSO-*d*6. The top spectrum is acquired without any solvent suppression and the intense peak at 3.3 ppm corresponds to the water in "cheap" DMSO. The next spectrum is obtained with WET pulse applied at 2.5 ppm and 3.3 ppm with both solvent peaks suppressed significantly. However, not surprisingly, the peaks of interest around 2.5 ppm are "washed out" completely. The next spectrum shows the effect of further suppression of the residual peaks using digital filters. Finally, the WET pulse is applied only at the water peak (3.3 ppm) in the last (bottom) spectrum and the resonances close to 2.5 ppm are clearly observable. Thus, minor tweaking of WET pulse with digital filtering recovers the valuable spectral information around the solvent resonances.

Yours sincerely,

Jiping
Jiping Yang

Vasant
N. Vasant Kumar

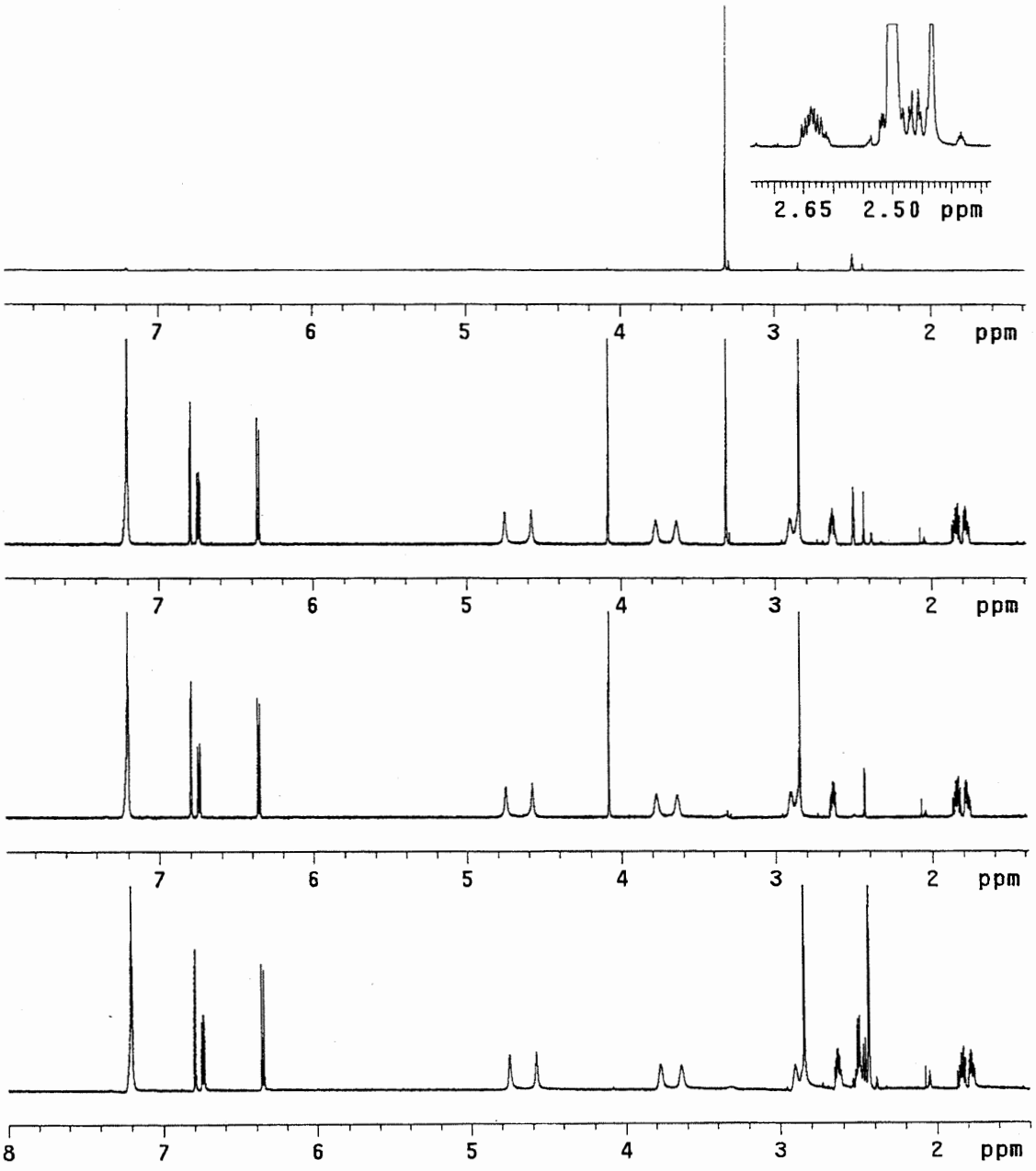


Figure 1. Four 1D proton spectra with and without solvent suppression and digital filter

Position Available

Tier I Canada Research Chair in NMR Studies of Materials

Dalhousie University (http://www.dal.ca) invites applications and nominations for a Tier I Canada Research Chair in NMR Studies of Materials. More details about this position are available at http://www.chem.dal.ca/nmrcrc/

The CRC in NMR Studies of Materials will be a world leader in NMR investigations of materials, with a proven ability to work with others in a wide variety of materials programmes. As a senior Chair, the appointment will be tenured and at the rank of Professor, in the Department(s) most suited to the candidate's research and teaching interests.

Applicants should send a *curriculum vitae*, a detailed research plan and names of three referees to: Professor Mary Anne White, Killam Research Professor in Materials Science and Chair of the NMR CRC Search Committee, Department of Chemistry, Dalhousie University, Halifax, Nova Scotia B3H 4J3, Canada, email: Mary.Anne.White@Dal.ca

Applications will be considered until the position is filled. Please note that the CRC nominations are subject to review and final approval by the CRC Secretariat. Dalhousie University is an Employment Equity/Affirmative Action employer. The University encourages applications from qualified Aboriginal people, persons with a disability, racially visible persons and women.

Position Available.

Postdoctoral Position – Michigan State University

Solid State NMR Studies of Viral Fusion Peptides

This is an NIH-funded project to investigate the structure and motion of membrane-bound viral fusion peptides. These studies will provide insight into the mechanism of peptide-induced liposome fusion and ultimately, viral/host cell membrane fusion. We have two 400 MHz solid state NMR spectrometers available for these studies, including triple resonance capabilities. We also expect to have access to a 900 MHz NMR spectrometer.

The ideal candidate would have experience in solid state NMR with some experience in solution NMR. Experience in biochemistry, peptide synthesis, and/or protein expression would also be valuable. Please send a curriculum vitae and names and contact information for two references to: Dr. David Weliky, Dept. of Chemistry, Michigan State University, East Lansing, MI 48824.

e-mail: weliky@cem.msu.edu

website: http://poohbah.cem.msu.edu/Faculty/Welikygrp/index.html

Forthcoming NMR Meetings, continued from page 1:

14th European Symposium on Polymer Spectroscopy, Dreikönigskirche – Haus der Kirche, Dresden, Germany, **September 2-5, 2001**. Contact: Institut für Polymerforschung Dresden c. 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.

Fourth International Conference on Molecular Structural Biology, Vienna, Austria, **September 5-9, 2001**. Contact: Dr. Andreas Kungl, Austrian Chemical Society (GÖCH), Biochemistry Subgroup, c/0 Institute of Pharmaceutical Chemistry, Univeristy of Graz, Universitätsplatz 1, A-8010 Graz, Austria. Tel: +43 316 380 5373; Faz: +43 316 382541; E-mail: andreas.kungl@kfunigraz.ac.at.

2nd Alpine Conference on Solid-State NMR, Chamonix-Mont Blanc, France, **September 9-13, 2001**; Contact: Alpine Conference Secretariat, Laboratoire STIM, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69364 Lyon Cedex 7, France; alpine.SSNMR@ens-lyon.fr; Tel. +33-(0)4 72-72-84-86/ 83 84; Fax. +33 (0)4 72 72 84 83; http://www.ens-lyon.fr/STIM/alpineweb/html.

EMBO Practical Course: Structure Determination of Biological Macromolecules by Solution NMR, EMBL, Meyerhofstr. l, D-69117 Heidelberg, Germany, **September 12-19, 2001**; Email: nilges@EMBL-Heidelberg.de; sattler@EMBL-Heidelberg.de; http://www.embl-heidelberg.de/nmr/sattler/embo.

EMBO Workshop on NMR and Molecular Recognition, Ravello, Italy, **October 3-7, 2001**; Contact: Dr. T. Tancredi: ttancredi@icmib.na.cnr.it, or Dr. P. Amodeo: pamodeo@icmib.na.cnr.it. Information: http://www3.icmib.na.cnr.it/ravello2001.

43rd ENC (Experimental NMR Conference), Asilomar Conference Center, Pacific Grove, CA, **April 14-19, 2002.** More information will be posted when available

XXth International Conference on Magnetic Resonance in Biological Systems, Toronto, Ont., **August 25-30, 2002**. For further information check www.uso.ca/chem/icmrbs/, or contact: mgordon@julian.uso.ca.

Additional listings of meetings, etc., are invited.

Position Available.

A postdoctoral position is available at **Novartis Institute for Biomedical Research**, located in Summit, New Jersey. The work will focus on utilizing NMR technology to identify lead chemical templates in drug discovery and drug design projects. Candidates must have considerable experience in NMR instrumentation, methods and pulse sequence development, as applied to ligand screening. Experience in all aspects of protein NMR spectroscopy, including data collection and analysis, is required. Strong publications history and communication skills are required. Thorough knowledge and experience in small molecule libraries for NMR screening are advantageous.

Please e-mail your resume as a 'Microsoft Word' attachment to: rd@recruitmentsolutions.com. Include in your e-mail message the following information: 1. In the subject area and in the main copy of your e-mail, reference the requisition # 10249 for sorting purposes. 2. In a brief note or cover letter, indicate where core competencies align with requisition.

As an alternate method of submission, fax your resume and cover letter to: 800-343-8850. If you would like to know more about openings available at Novartis, please visit our website at: www.joinnovartis.com. We are equal opportunity employers M/F/D/V.

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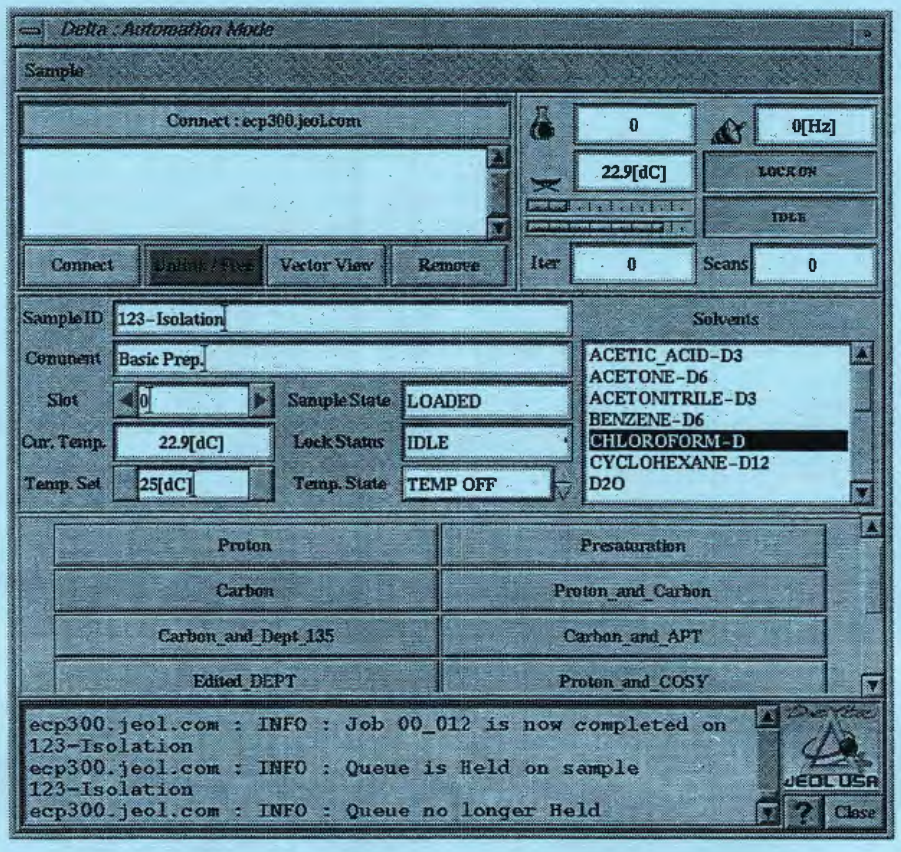

The **Eclipse+** NMR Spectrometer can be operated anywhere there is a computer on the local network. The **Single Window Automation** pictured above can be used with a single mouse click to select the sample from the auto-sample changer, gradient shim on any probe, run the selected experiment, and plot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

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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. 514 (July)	22 June. 2001
No. 515 (Aug.)	27 July 2001
No. 516 (Sept.)	24 Aug. 2001

* 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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