THE
NMR
NEWSLETTER

No. 487

April 1999

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PTS 120	90-120 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$5,330.00 (1 Hz resol., OCXO freq. std.)
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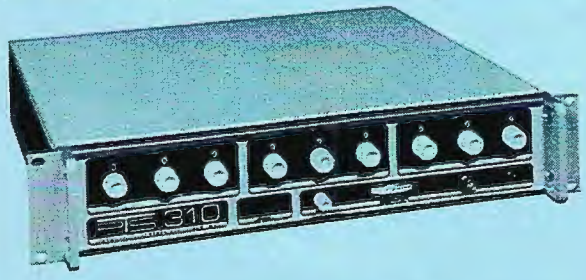

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FORTHCOMING NMR MEETINGS

Seventh Scientific Meeting and Exhibition of the Intl. Soc. for Magnetic Resonance in Medicine (ISMRM), Philadelphia, PA, **May 22 - 28, 1999**; Contact: International Society for Magnetic Resonance in Medicine, 2118 Milvia St., Suite 201, Berkeley, CA 94704.

International School of Structural Biology and Magnetic Resonance, 4th Course: Dynamics, Structure and Function of Biological Macromolecules; Erice, Sicily, Italy; **May 25 - June 5, 1999**; Contact: Ms. Robin Holbrook, Stanford Magnetic Resonance Laboratory, Stanford University, Stanford, CA 94305-5055; (650) 723-6270; Fax: (650) 723-2253; Email: reh@stanford.edu. See Newsletter 483, 8.

Gordon Conference on Magnetic Resonance, Henniker, NH, **June 27 - July 2, 1999**. Contact: the chairperson: (Regitze Vold, rvold@ucsd.edu) or vice-chairperson (Robert Tycko, tycko@helix.nih.gov. See Newsletter 487, 37.

Royal Society of Chemistry: 14th International Meeting on NMR Spectroscpy, Edinburgh, Scotland, **June 27 - July 3, 1999**; Contact: '99NMR14' c/o Mrs. Paula Whelan, The Royal Society of Chemistry, Burlingtom House, London W1V 0BN, England; +44 0171 440 3316; Email: conferences@rsc.org\

Rocky Mountain Conference NMR Symposium, Denver, CO, **August 1-5, 1999**. See Newsletter 487, 36 and http://india.cchem.b4rkeley.edu/~rmc/

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

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

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

Additional listings of meetings, etc., are invited.

Duke University

Duke Nuclear Magnetic Resonance Spectroscopy Center

Leonard D. Spicer, Director 919 684 4327
Anthony A. Ribeiro, Manager 919 613 8887

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

March 15, 1999
(received 3/24/99)

Re: SIDDS NMR Analyses of Purified Lipid A (Endotxin)

Dear Barry,

We have been working with Prof. Chris Raetz (Duke, Biochemistry) to study bacterial glycolipids like Lipid A (endotoxin) that are potent toxins for Gram-negative infections in mammalian hosts. Determination of phosphorus linkages and sequential ordering of phosphosugars are crucial steps in establishing the covalent structure of Lipid As, which are phosphorylated glucosamines that are heterogeneous with respect to number of acyl chains, phosphorus groups, and attached substituents.

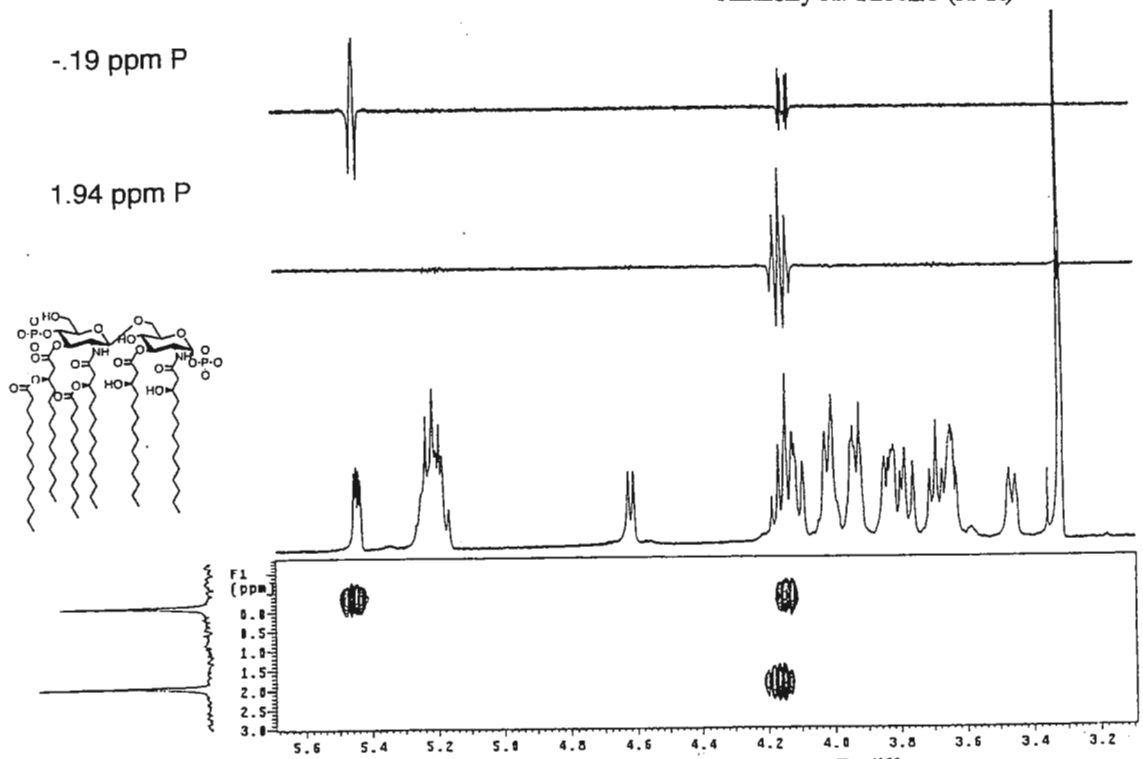
We have recently implemented selective inverse (31P) decoupling difference spectroscopy (SIDDS) as a simple 1D NMR strategy for establishment of the phosphorus attachment sites and the sequential ordering. Results for wild type Lipid A from *E. coli* are shown below. Selective 31P decoupling of the -0.19 ppm phosphorus signal while observing the 1H NMR spectrum and subtraction from an off-resonance control yields a diagnostic "doublet" at 5.44 ppm (H-1) and a "double-doublet" at 4.14 ppm (H-2), clearly establishing the -0.19 ppm signal as the anomeric phosphate of the proximal sugar. Selective decoupling of the 1.94 ppm phosphorus signal in contrast yields a diagnostic "triplet" at 4.16 ppm which derives from H-4' of the distal sugar. The SIDDS spectra were recorded in ~103 minutes. 2D H-P HMQC gives the same result, but took ~ 18 hrs.

It should be noted that membrane-associated molecules like Lipid A are amphipathic and generally show poorly resolved NMR resonances in solution due to aggregation. Purified Lipid As are also sometimes unstable in solution with the tendency to undergo hydrolysis at the anomeric phosphate under acid conditions and ester deacylation under base conditions. We have recently discovered purified Lipid A molecules to display sharp NMR signals (illustrated below) and to be chemically stable for days in a CDCl3:CD3OD:D2O mixed solvent system.

Regards,

Tony

Anthony A. Ribeiro (A^2R)



31P decouple, 1H observe 1D difference spectra and H,P 2D NMR of wild type Lipid A.

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Lineshape 1% $CHCl_3$ 5mm non-spinning	
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* Typical values obtained with the BOSSII™ shim system.

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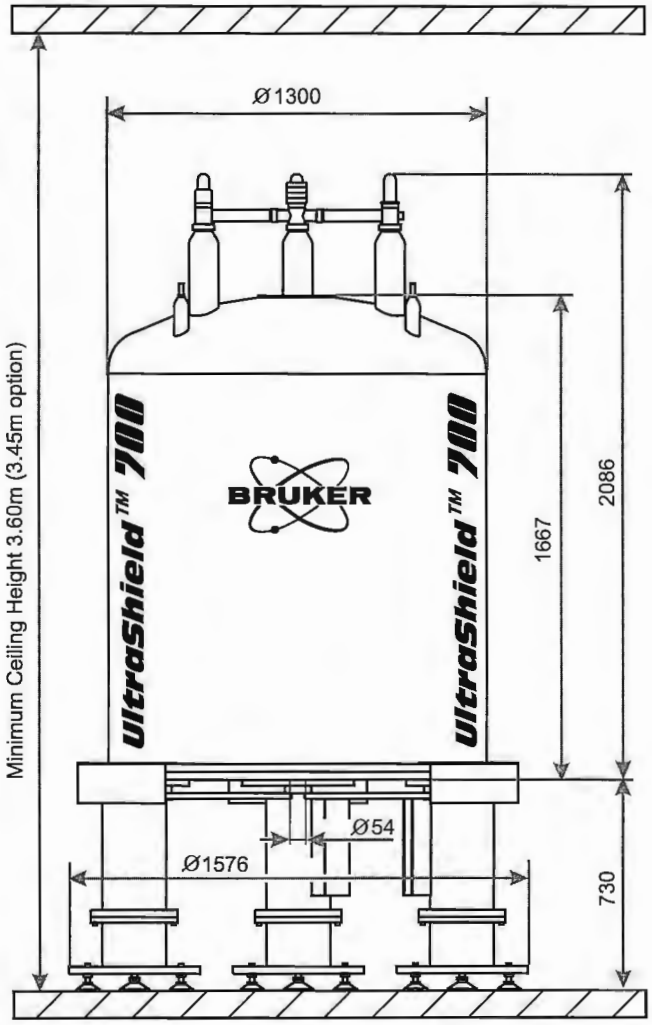

Dimensions in millimeters unless stated otherwise

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March 13, 1999
(received 3/18/99)

Sparky - A Graphical NMR Assignment Program

Dear Barry,

We've developed a graphical assignment program for proteins and nucleic acids called Sparky. It displays multi-dimensional NMR spectra in separate windows and assists peak picking, peak integration and assignment. The spectrum windows provide optional display of resonance labels or 1D cross-sections along the edges of contour plots (Fig. 1), interactive contour level adjustment, overlaying of multiple spectra, synchronizing the displayed regions between different windows, subtracting off profiles of fit peaks, publication quality printing, ... There are capabilities for strip plot display (Fig. 3), picking peaks selectively along strips, suggesting peak assignments using assigned resonances, Gaussian and Lorentzian fitting. handling multiple sets of resonances for different experimental conditions, etc. A manual and numerous help buttons in the program provide explanations of all the features. Sparky is easy to use, reliable, and extendable. It runs under Microsoft Windows or Linux on PCs, and on SGI, Sun and DEC Unix workstations. Spectra processed with NMRPipe, Felix, or Bruker software are used as input. Resonance and peak assignments are output for subsequent distance geometry calculations.

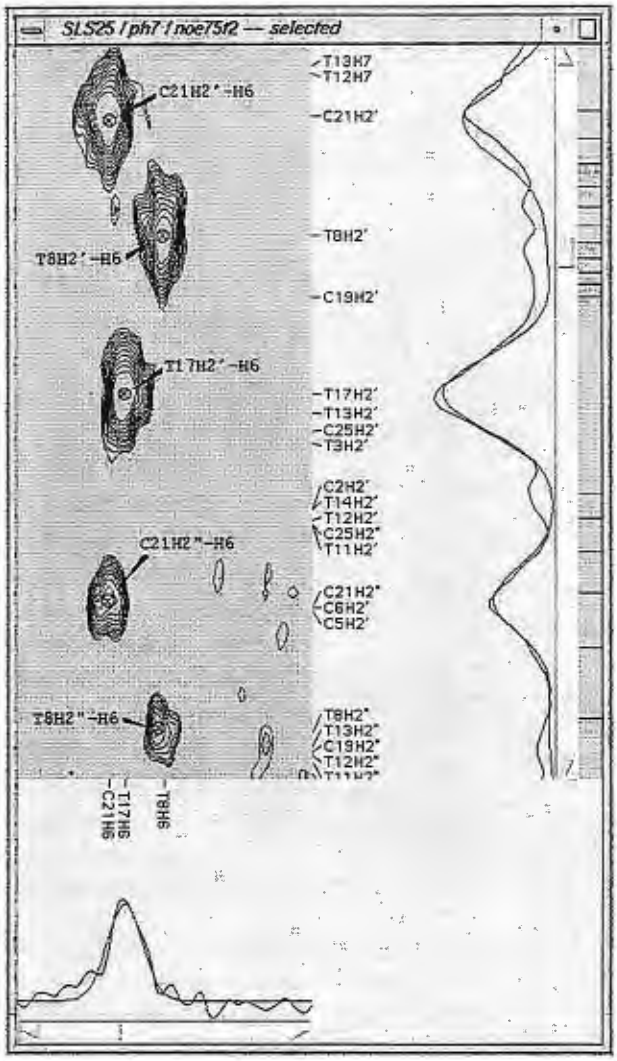

Figure 1 Spectrum window displaying resonances, 1D slices, and scale for adjusting contour levels.

Sparky is extendable using a general purpose interpreted language called Python. We are currently working on a spin graph extension. This diagram has dots that represent atoms and lines that represent peak connectivities (Fig. 2). It is like a chemical structure diagram but lines show NMR interactions instead of covalent bonds. A peak in an HNCA spectrum is represented as a line from the amide proton to the nitrogen and another line from nitrogen to alpha carbon. Peaks from different spectra are shown as different color lines. This gives a quick view of which peaks support the current resonance assignments. The diagram is interactive. Clicking on a line will bring up a spectrum window showing the peak. Or if a peak is missing, clicking on the atoms will show in a spectrum contour plot the place where the peak should be. This should be particularly useful for assessing the results of automated assignment programs. It can be used to complete the assignments manually, or to improve peak lists and rerun the automated assignment program.

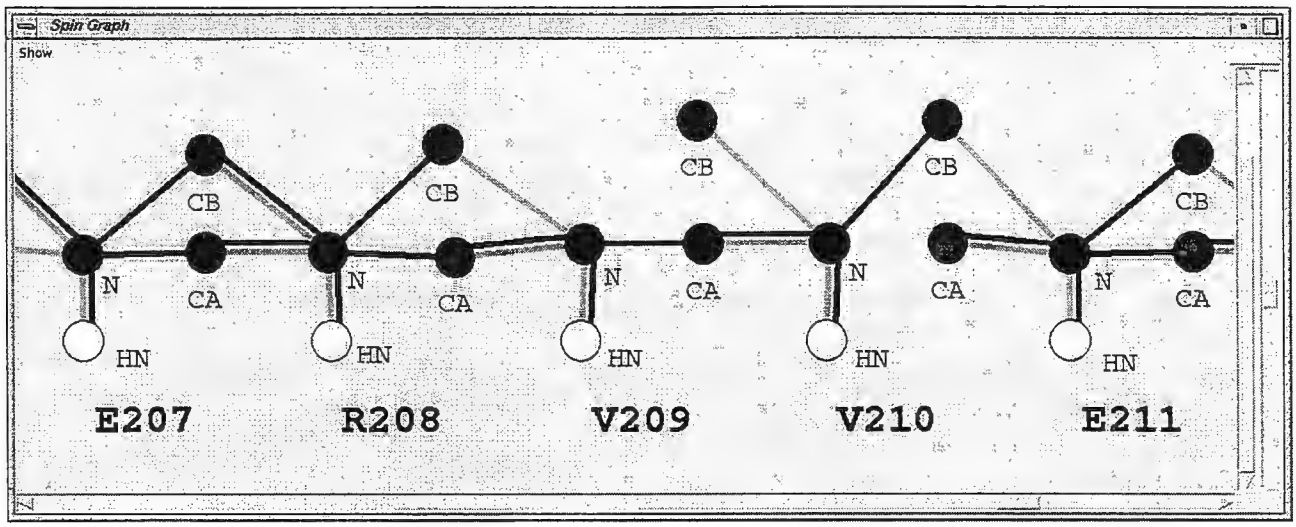

Figure 2 Spin graph showing CBCA(CO)NH peaks (light lines) and HNCACB peaks (dark lines) for protein backbone. Clicking on line shows corresponding peak in contoured spectrum plot.

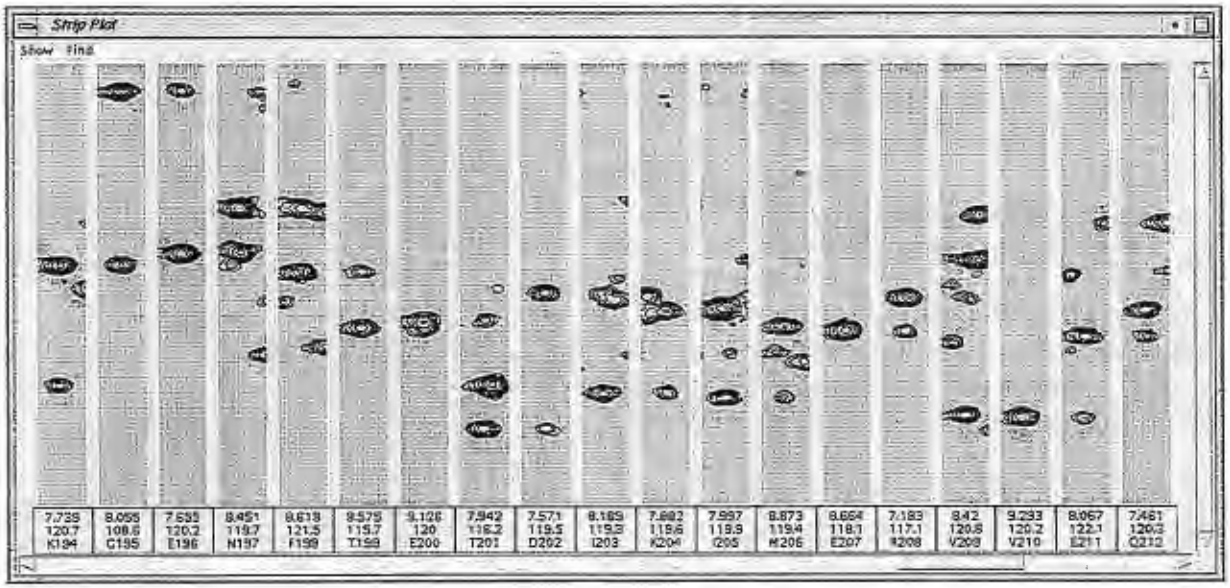

Figure 3 Strip plot showing HNCA protein backbone strips. The x and y axes are the amide proton and alpha carbon. Each strip shows the a peak for the alpha carbon of this residue and the previous residue. The horizontal scrollbar allows scrolling through all residues.

To try Sparky or find out more about it, see our web site http://www.cgl.ucsf.edu/home/sparky

Sincerely,

Tom Goddard

Tom

Thomas Goddard

Thomas L. James
Professor of Chemistry, Pharmaceutical Chemistry, and Radiology
Chairman, Department of Pharmaceutical Chemistry

UNIVERSITY of PENNSYLVANIA

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March 5, 1999
(received 3/14/99)

Membrane protein architecture from solid-state NMR spectra

Dear Barry,

Thank you for the many colorful and timely reminders.

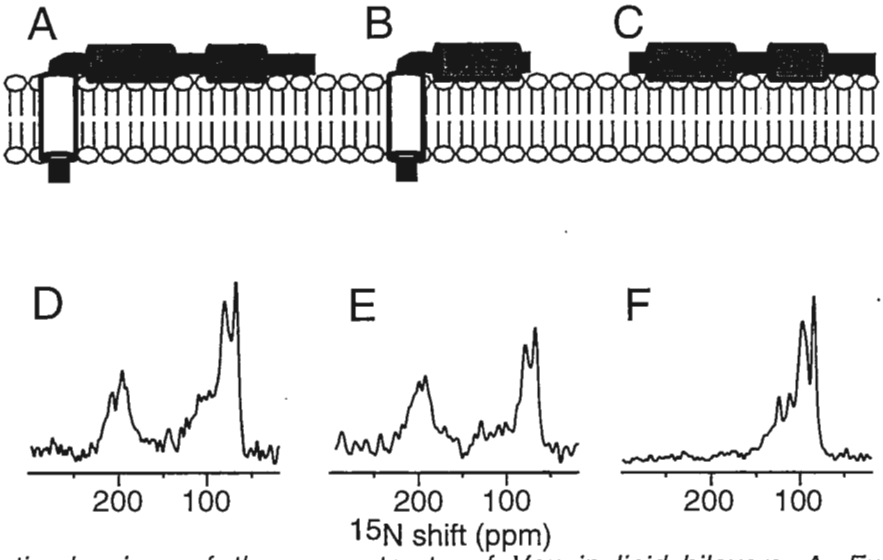
A major goal of our research program is to determine the three-dimensional structures of proteins in biological supramolecular assemblies, including virus particles and membrane bilayers. Because these proteins are immobile on the relevant NMR timescales, solution NMR experiments are ineffective, and high resolution solid-state NMR methods must be developed and applied to oriented protein samples. Recent progress includes the complete resolution in two- and three-dimensional solid-state NMR spectra of uniformly ^{15}N labeled proteins in virus particles (1, 2) and membrane bilayers (3). With the development of systematic assignment methods based on triple-resonance (4) and dilute spin-exchange (5) experiments, we have been able to determine the structure of a polypeptide that functions as an ion channel in membrane bilayers (6).

In this letter, we demonstrate that at an early stage of the structure determination process simple one-dimensional solid-state NMR spectra of uniformly ^{15}N labeled proteins in oriented bilayer samples provide valuable information about the architecture of helical membrane proteins. This relies on the well-characterized angular dependence of the ^{15}N chemical shift interaction, but requires that the secondary structure be characterized by independent methods.

As an example, we use the 81-residue membrane protein Vpu from HIV-1. This protein has two biological activities that appear to be associated with different structural domains. The protein facilitates the budding-out of new virus particles; a function that correlates with the ion channel activity associated with the oligomerization of the N-terminal hydrophobic α -helix. The protein also enhances the degradation of CD4/gp160 receptor complex through interactions of its cytoplasmic domain, which consists of two amphipathic α helices as determined by solution NMR studies of the protein in DHPC micelles (unpublished results).

The Figure shows schematic structures of three constructs of Vpu in lipid bilayers. The one-dimensional ^{15}N NMR spectra associated with the constructs are remarkably effective at mapping out the protein architecture. The 80 backbone amide resonances of full-length Vpu are clearly segregated into two discrete resonance bands. About one-third have chemical shift frequencies associated with N-H bonds perpendicular to the membrane surface (200 ppm), which is attributable to the trans-membrane hydrophobic helix, and about two-thirds have frequencies associated with N-H bonds parallel to the membrane surface (70 ppm) from both cytoplasmic in-plane helices. The corresponding results from the two smaller constructs provide strong additional support for these conclusions. Further, they indicate how the domains of Vpu are effectively independent in terms of both folding and associating with the surface of the membrane.

These results are similar to those we have previously obtained on a variety of membrane associated peptides and proteins where the hydrophobic trans-membrane helices have N-H bonds parallel to the applied magnetic field and the amphiphatic in-plane helices have N-H bonds perpendicular to the field. Most of these initial studies have involved proteins with 22 – 50 residues. One of our most important results reported in 1998 was obtained in collaboration with W. Cramer (Purdue). By using two-dimensional PISEMA experiments, we were able to show that the membrane-bound form of the 190-residue colicin E1 channel polypeptide has a 38-residue helical hairpin inserted into the bilayer, which is consistent with the "umbrella" model for its interaction with the membrane (7).



Top row: Schematic drawings of three constructs of Vpu in lipid bilayers. A. Full-length Vpu (residues 2 – 81). B. Transmembrane helix and one cytoplasmic amphipathic helix (residues 2 – 51). C. Cytoplasmic domain (residues 28 – 81). Bottom row: Solid-state NMR spectra of uniformly ^{15}N labeled constructs of Vpu in oriented lipid bilayers. D. Full-length Vpu (residues 2 – 81). E. Transmembrane helix and one cytoplasmic amphipathic helix (residues 2 – 51). F. Cytoplasmic domain (residues 28– 81).

This research is supported by a Program Project grant (PO1 GM56538-02) from the National Institute of General Medical Sciences and involves related research by M. Klein, J.K. Blasie, and P. Loll at the University of Pennsylvania, and M. Montal at the University of California, San Diego. It benefits from substantial interactions with K. Strebel and U. Schubert at the National Institute of Allergy and Infectious Disease. The research utilizes the Resource for Solid-State NMR of Proteins at the University of Pennsylvania.

S. J. Opella F. M. Marassi C. Ma S. Straus

1. High resolution three-dimensional solid-state NMR spectra of a uniformly ^{15}N labeled protein, R. Jelinek, A. Ramamoorthy, and S. J. Opella, J. Amer. Chem. Soc. 117, 12348-12349, 1995
2. Effects of temperature and Y21M mutation on conformational heterogeneity of the major coat protein (pVIII) of filamentous bacteriophage fd, W. M. Tan, R. Jelinek, S. J. Opella, P. Malik, T. D. Terry, and R. N. Perham, J. Mol. Biol. 286, 797-808, 1999.
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5. Dilute spin-exchange assignment of solid-state NMR spectra of oriented proteins: acetylcholine M2 in bilayers, F. M. Marassi, J. J. Gesell., A. P. Valente, Y. Kim, M. Oblatt-Montal, and M. Montal, and S. J. Opella, J. Biomol. NMR, in press, 1999.
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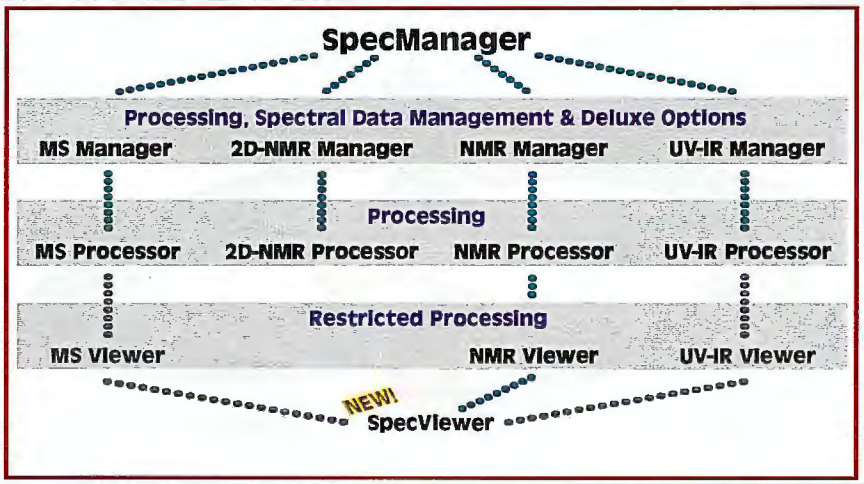

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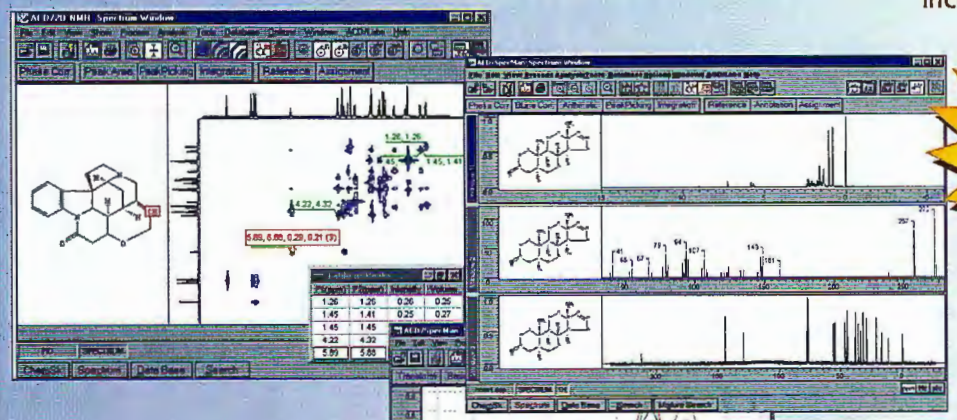

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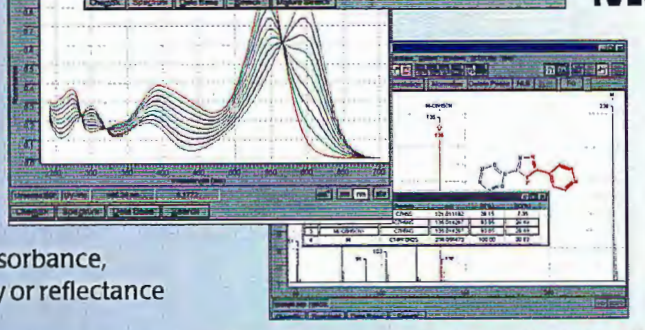

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February 22, 1998
(received 3/25/99)

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

ACCORD-HMBC: A Potentially Powerful Alternative to GHMBC - Praises and Pitfalls

Dear Barry,

There has recently been a resurgence in the exploration of new, inverse-detected long-range heteronuclear shift correlation experiments. Although this is hardly the place for a review of the experiments now contained in the literature, a brief survey for the reader interested in this area is warranted. Experiments include the D-HMBC sequence of Furihata and Seto[1] which incorporates broadband heteronuclear decoupling during acquisition. Furihata and Seto followed their initial foray into this area with a 3D-HMBC experiment that was designed to sample a range of potential long-range couplings in the 3rd dimension of a 3D experiment in which each individual plane contains a long-range spectrum for a given long-range coupling optimization.[2] In 1997 Marek, Králík, and Sklenář reported on the GHSMBC experiment which is capable of providing experimental access to long-range correlation responses based on the single quantum GHSQC experiment.[3] Sheng and van Halbeek also reported a phase-sensitive variant of GHMBC during 1998.[4] A novel approach to sampling a potentially broad range of long-range heteronuclear coupling constants was reported in mid-1998 by Wagner and Berger[5] in the form of the ACCORD-HMBC experiment, which serves as the focal point of this contribution. Most recently, in late 1998, Furihata and Seto[6] reported a pair of constant time long-range experiments, CT-HMBC-1 and CT-HMBC-2.

The ACCORD-HMBC experiment of Wagner and Berger[5] employs the accordion-principle[7] in the form of a variable delay used to select the long-range coupling optimization of the experiment. In successive increments of the evolution time, t_1, the variable delay, vd, is systematically decremented from τ_{max} to τ_{min} in steps of $(\tau_{max} - \tau_{min})/ni$, where ni is the total number of increments to be performed in the second frequency domain of the experiment. Through the use of the variable delay incorporated into the ACCORD-BC pulse sequence shown in Figure 1, it is possible to sample a potentially broad range of long-range heteronuclear coupling constants. Unfortunately, as a consequence of the use of the accordion principle, as noted by Wagner and Berger,[5] responses are subject to modulation in F_1 resulting in a "skewed" appearance. (See Figure 2). Wagner and Berger further comment that the benefits of the use of the accordion principle, in terms of the numbers of new responses observed, outweighs any disadvantages of the "skew" introduced in the second frequency domain.

The "skew" of responses in the second frequency domain of ACCORD-BC spectra can be both beneficial and detrimental. First, in the case of weak responses or in a noisy spectrum, legitimate long-range correlations are identifiable by virtue of their skewed appearance. A point which Wagner and Berger[5] did not address in their initial report were factors influencing the extent of the skew of responses in F_1. During the variable delay, vd, ^1H-^1H frequency modulation occurs which is scaled by a scaling factor, N, in a manner analogous to the EXSIDE experiment developed by Krishnamurthy.[8] The scaling factor, N, is dependent on both the spectral width in F_1 and the number of increments of the evolution time, ni, used to digitize F_1 according to the expression:

$$N = 2\tau/\Delta F_1 \qquad [1]$$

where

$$\tau = (\tau_{max} - \tau_{min})/ni. \qquad [2]$$

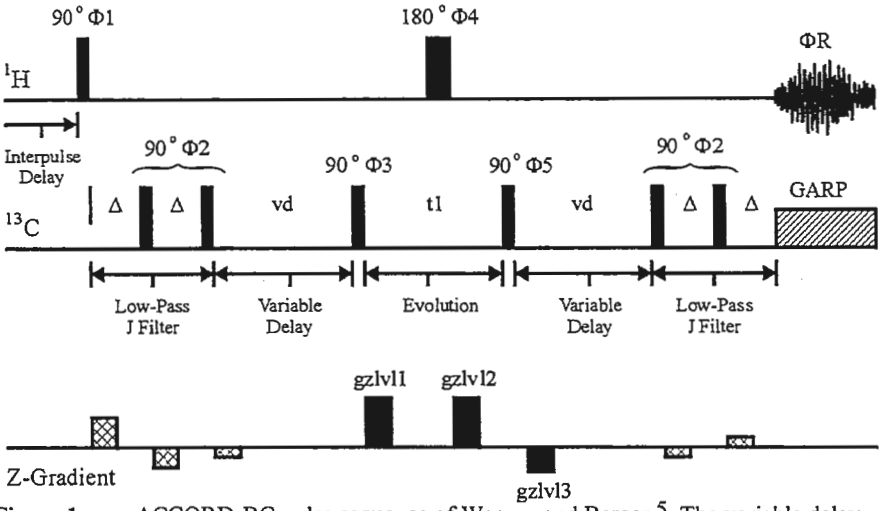


Figure 1. ACCORD-BC pulse sequence of Wagner and Berger.[5] The variable delay, vd, is systematically decremented as the evolution period, t_1, is being systematically incremented. The gradients gzlvl1, gzlvl2, and gzlvl3 are applied in the ratio 2:2:±1 for ^{1}H-^{13}C long-range correlation or in the ratio 5:5: ±1 for ^{1}H-^{15}N long-range correlation.

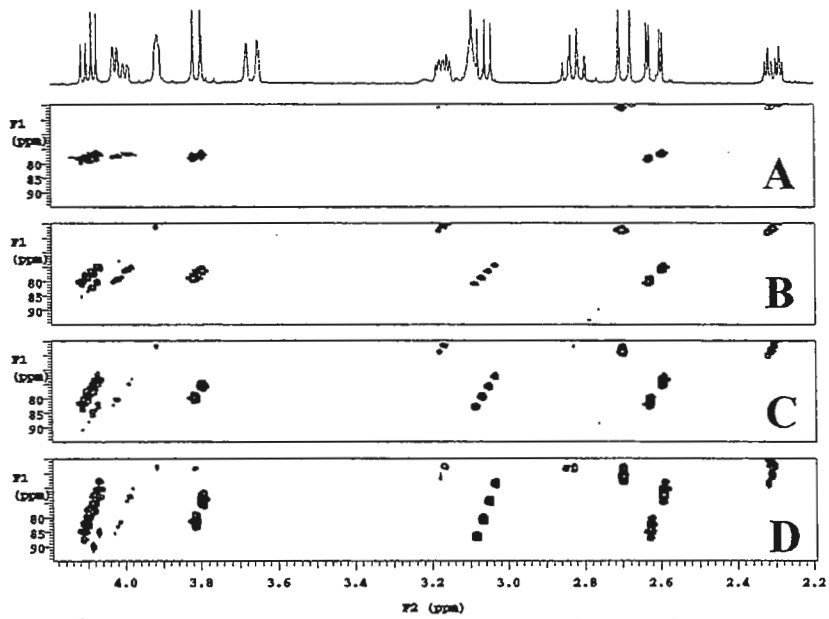


Figure 2. Comparison ACCORD-BC plots from a series of spectra digitized in F_1 using ni = 128. The optimization of the variable delay were A) 6-10 Hz; B) 4-12 Hz; C) 3-16 Hz; and D) 2-25 Hz. As will be noted by comparison of the response at ~4.1 ppm which correlates H23a to C12 of strychnine, the F_1 "skew" increases substantially as the optimization range is widened, keeping the digitization in F_1 constant at 128 increments. In the case of the response at ~3.05 ppm there is no long-range correlation to C-12 observed in the 6-10 Hz experiment, the response observed weakly in the 4-12 Hz experiment, and strongly in the 3-16 and 2-25 Hz experiments.

These expressions lead to the expectation that when broad spectral widths are used in F_1 and/or when low levels of digitization are employed in F_1 that there will be considerable "skew" associated with long-range responses in the second frequency domain.[9] This behavior is illustrated by comparing the four panels shown in Figure 2. All were acquired using 128 increments to digitize the second frequency domain; the accordion optimization range was varied from 6-10, 4-12, 3-16, and 2-25 Hz.

Varying the number of increments used to digitize the second frequency domain, ni, has a similar impact on the "skew" of responses in F_1. The responses for the individual multiplets shown in the panels of Figure 3 illustrate this behavior. The three sets of responses shown are for the same multiplet from each of 24 separate ACCORD-BC experiments. The H8-C12 $^3J_{CH}$ response was selected in this case. The horizontal rows were from experiments various optimized at 6-10, 4-12, and 2-25 Hz, with ni varied as shown in the legend. Again, for a given optimization, as the level of digitization in the second frequency domain increases, the "skew" of the response is correspondingly diminished.

The ability of the ACCORD-BC experiment to sample a wide variety of potential long-range correlations is dramatically illustrated by considering the structure of strychnine (**1**) shown below. The arrows shown on the structure represent only the very numerous four-bond ($^4J_{CH}$) long-range correlations observed in a 2-25 Hz optimized ACCORD-BC experiment digitized with 512 increments in the second frequency domain to minimize the "skew" of the observed multiplets.

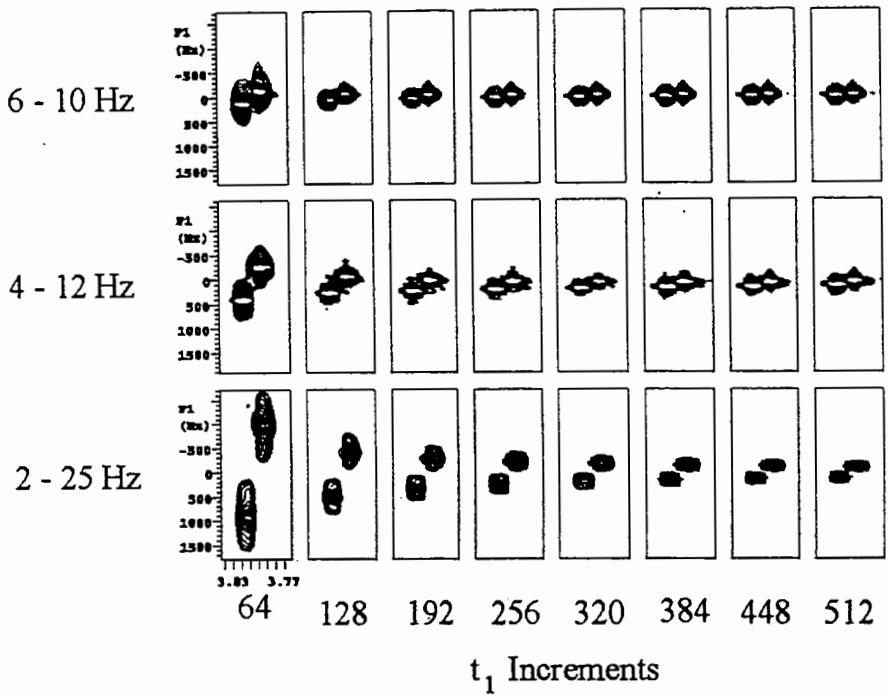
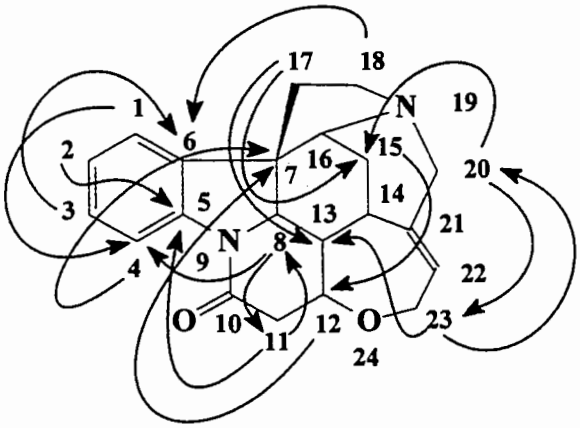


Figure 3. (Left) Segments from a series of accordion-optimized ACCORD-BC experiments illustrating the effect of digitization in the second frequency domain on F_1 response modulation. The correlation of H-8/C-12 is used to illustrate the effect of increasing the number of increments used to digitize the second frequency domain from 64 to 512 increments in steps of 64. The results obtained for the H-8/C-12 response for optimizations of 2-25, 4-12 and 6-10 Hz are shown. The observed F_1 modulation frequencies range from 1944 Hz for the 2-25 Hz experiment digitized with only 64 increments to 33 Hz for the 6-10 Hz experiment digitized with 512 increments. By counterbalancing the desired range of the accordion-optimization with digitization in the second frequency domain, it is possible to minimize the adverse consequences of F_1 modulation associated with the use of accordion-optimization.



1

In conclusion, the ACCORD-BC experiment provides a powerful means of accessing long-range heteronuclear correlations that can be vital to the successful determination of a structure, particularly when dealing with proton deficient molecules in which the normally utilized two- and three-bond correlations do not provide enough "reach" to establish critical connectivities. The "skew" of weak multiplets or in noisy spectra provides a unique means of differentiating legitimate long-range responses from wishful interpretation of random noise. However, the choice of parameters for use in acquiring ACCORD-BC experiments must be made judiciously. As shown in Figures 2 and 3, the "skew" of multiplets is dependent on a scaling factor, N, which is a function of the optimization range and the spectral width in F_1. The use more modest optimization ranges for the variable delay, vd, is recommended when the size of the sample will preclude extensive digitization in the second frequency domain to avoid the potential overlap of long-range responses.

Gary E. Martin

Chad E. Hadden

Ronald C. Crouch
Nalorac Corporation

Krish Krishnamurthy
Varian NMR Instruments

References: **1.)** K. Furihata and H. Seto, *Tetrahedron Lett.*, **36**, 2817 (1995). **2.)** K. Furihata and H. Seto, *Tetrahedron Lett.*, **37**, 8901 (1996). **3.)** R. Marek, L. Králík, and V. Sklenář, *Tetrahedron Lett.*, **38**, 665 (1997). **4.)** S. Sheng, and H. van Halbeek, *J. Magn. Reson*, **130**, 296 (1998). **5.)** R. Wagner and S. Berger, *Magn. Reson. Chem*, **36**, S44 (1998). **6.)**K. Furihata and H. Seto, *Tetrahedron Lett.*, **39**, 7337 (1998). **7.)** G. Bodenhausen and R. R. Ernst, *J. Am. Chem. Soc.*, **104**, 1304 (1982). **8.)** V. V. Krishnamurthy, *J. Magn. Reson.*, **121**, 33 (1996). **9.)** G. E. Martin, C. E. Hadden, R. C. Crouch, and V. V. Krishnamurthy, *Magn. Reson. Chem.*, submitted (1999).

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Feb. 21, 1999
(received 3/2/99)

Diffusion Behavior of the Benzene Molecule in Faujasite-Type Zeolite Studied by Double Quantum Filtered NMR

Dear Professor. B. L. Shapiro,

Double quantum filtered (DQF) spectral analyses has been examined for the dynamics of benzene molecules adsorbed into faujasite zeolites.[1] The application of modified cone model to site-to-site hopping and wobbling motion processes is essentially similar to the model of benzene orientation randomization (BOR) used by Auerbach and Metiu.[2] The wobbling motion is induced by the diffusive motion and therefore the diffusion coefficients of benzene can be estimated from the correlation time of wobbling motion of benzene adsorbed into NaY, DAY, USY and NaX at 298 K. The long time behavior of orientational correlation function, identified as the rate of cage-to-cage motions,[2] may be correlated to the τ_w process in present model since the wobbling motion is induced by the barrier of zeolite framework in the course of benzene diffusion through the cage. In the light of these obvious connections between the long time orientation randomization and the wobbling motion concerning the cage-to-cage diffusion, we establish a new approach to estimate the self-diffusion coefficient of benzene in faujasite-type zeolites. The estimation of self-diffusion coefficients may be made with the relation $D = \langle \ell^2 \rangle / 6\tau_h$ where $\langle \ell^2 \rangle$ is the average distance between the adsorption site in two adjacent cages and τ_h is the correlation time for intercage hopping. The distance between the centers of two supercages ℓ is set to be 11 Å. In accordance with the kinetic Monte Carlo calculation,[2] the long time BOR rate, k_{BOR}, in NaY is controlled by cage-to-cage motion. Considering the resident time on site is much longer than the flight time of a hop, we have that k_{BOR} is equal to the intercage hopping rate k_{cage}. In terms of present model one obtains $k_{BOR}=1/\tau_w$. Since $k_{cage}=1/\tau_h$, the self-diffusion coefficient of benzene may be calculated from $D = \langle \ell^2 \rangle / 6\tau_w$. Comparing the estimated self-diffusion coefficients in NaX and NaY system with those from PFG NMR and T_2 measurements, the result yields satisfactory agreement. However, the self-diffusion coefficients of benzene estimated from T_1 measurement in NaY and ZDDAY may reflect the effect from the fast motional mode such as the site-to-site hopping or/and the internal rotation rather than from the slow mode of the wobbling motion. The estimated self-diffusion coefficients are about one order larger than the values estimated from T_2 studies.

1. (a) Y.-H. Chen, W.-T. Chang, P.-C. Jiang and L.-P. Hwang *Microporous and Mesoporous Mater.* **21**, 651 (1998). (b) Y.-H. Chen and L.-P. Hwang *J. Phys. Chem.* (1999) submitted.
2. S. M. Auerbach and H. I. Metiu *J. Chem. Phys.* **106**, 2893 (1997).

Sincerely Yours,

Yu-Huei Chen

Yu-Huei Chen

Lian-Pin Hwang

Lian-Pin Hwang

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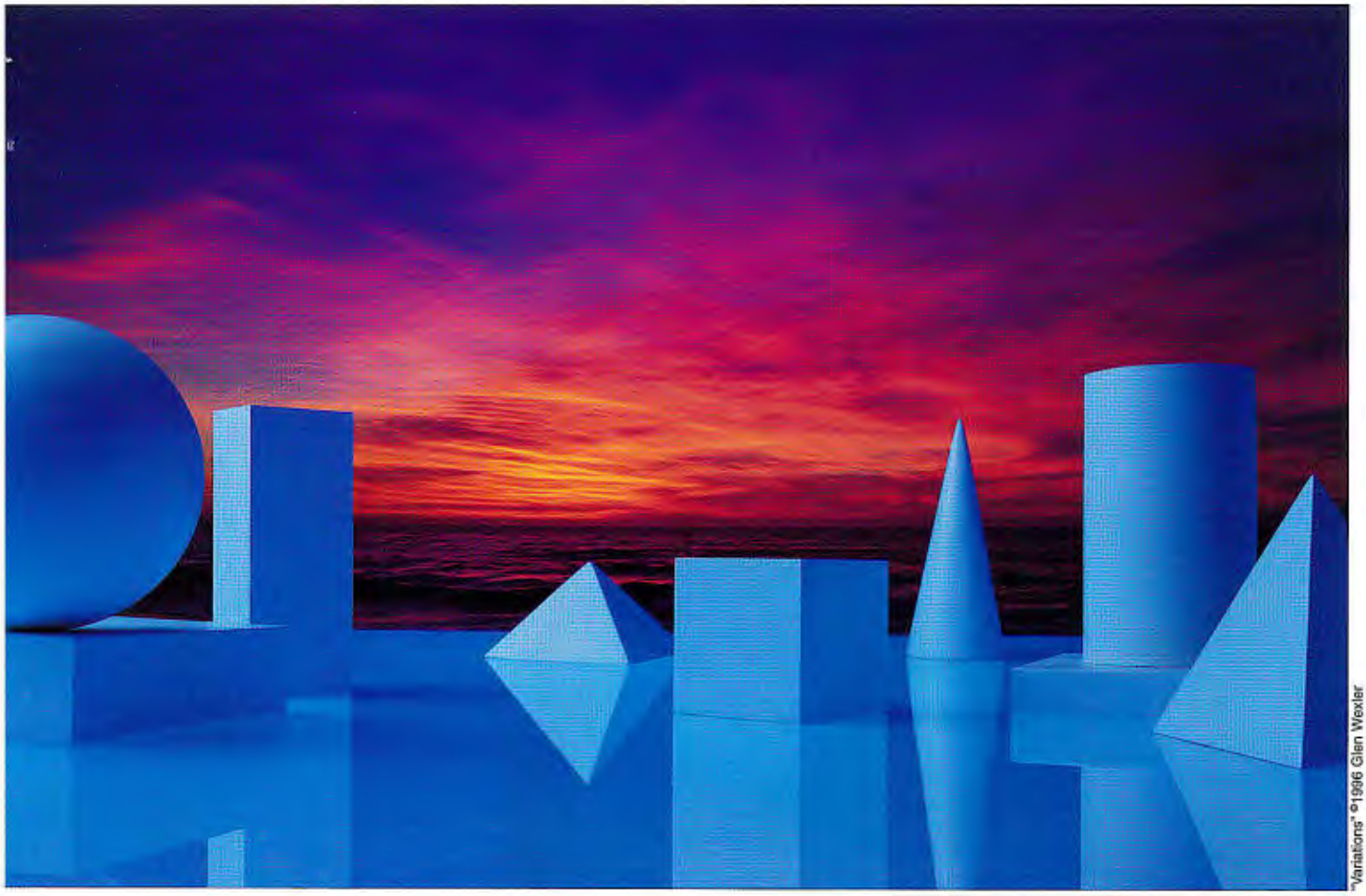

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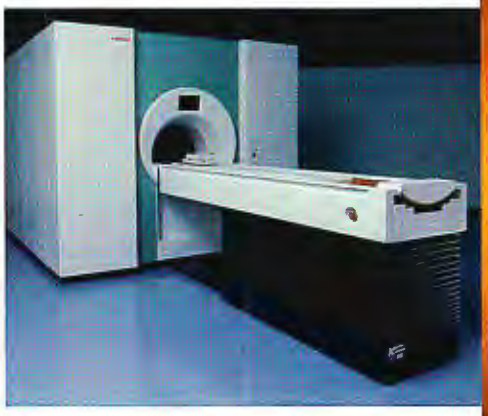

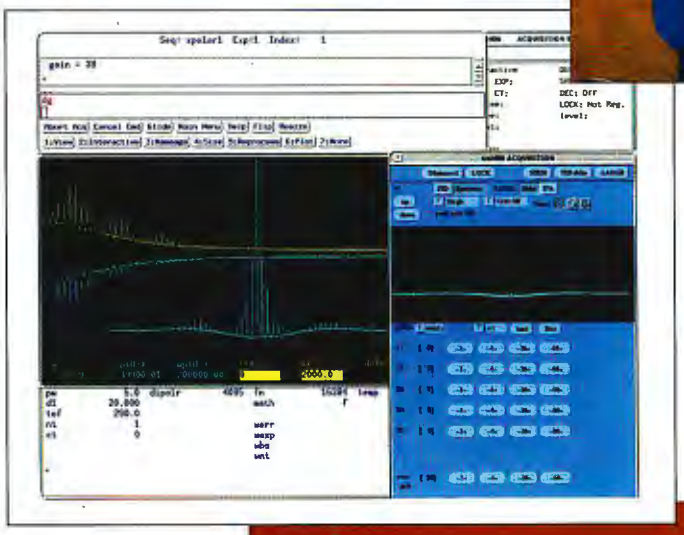

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SMASH: Small Molecule NMR Conference
(Small Molecules Are Still Hot)

Sunday, August 15 – Wednesday, August 18, 1999
Argonne Guest House,
Argonne National Laboratory, Argonne IL (outside Chicago, IL)

Sunday		
Noon – 5:30 pm		Arrival and registration
5:30 – 7:00 pm		Introductory Plenary Lecture by Dr. James Shoolery Sponsored by Varian NMR Instruments
7:00 – 9:00 pm		Social Mixer
Monday		
7:00 – 8:30 am		Breakfast
8:30 – 10:30 am		**Session 1: Natural Products** Chairman: G. E. Martin
10:30 – 11:00 am		Morning Break
11:00 – 12:30 pm		**Session 2: Pulse Sequences** Chairman: K. Krishnamurthy
12:30 – 2:00 pm		Lunch
2:00 – 4:00 pm		Free Afternoon
4:00 – 6:30 pm		**Session 3: New Probe and Magnet Development** Chairman: A. Zens
6:30 – 8:00 pm		Dinner Dinner lecture by Dr. Ray Freeman Sponsored by Advanced Chemistry Development
Tuesday		
7:00 – 8:30 am		Breakfast
8:30 – 10:30 am		**Session 4: Applications of Flow NMR** Chairman: A. Swanson
10:30 – 11:00 am		Morning Break
11:00 – 12:30 pm		**Session 5: Metabolism** Chairman: J. Shockor
12:30 – 2:00 pm		Lunch
2:00 – 4:00 pm		Free Afternoon
4:00 – 6:30 pm		**Session 6: Applications of NMR to High Throughput Screening and Combinatorial Chemistry** Chairman: M. Shapiro
6:30 – 8:00 pm		Dinner Dinner lecture by Dr. Tom Farrar
7:30 – 9:30 pm		**Session 7: Posters** Chairman: D. Lankin Refreshments sponsored by Bruker Instruments
Wednesday		
7:00 – 8:30 am		Breakfast
8:30 – 11:00 am		**Session 8: Post acquisition data processing, databasing and spectral prediction** Chairman: A. Evans
11:00 – 11:30 am		Conference wrap-up

(received 3/18/99)

Fees, Reservations, and Transportation

Conference Registration Fee: $100

Reservations/Accommodations:

Reservations for the event must be made by individual call to Argonne (800-632-8990 or 630-739-6000). Reservations include meals but can be made with or without overnight accommodations (see rate schedule below). Please refer to "SMASH" when making your reservation.

Cut-Off Date for Reservations: June 15, 1999
Reservations made after the cut-off date will incur an additional $25 fee.

Check-in Time: 3:30pm Check-out Time: Noon

Rate Schedule

Conference 3-day accommodation packages:

Single Occupancy	$570
Double Occupancy	$480 (per person)
6 to a Quad	$420 (per person)
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Double Occupancy with Spouses	$885
Single day attendance rate	$80 per day

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Abstract Submission

Abstracts for talks and posters must be submitted in electronic format. The submission format will involve transmitting the required information via email to: david.c.lankin@monsanto.com.

Instructions

1. First indicate the abstract is for a POSTER. Include the title, authors, and affiliation information.

2. Then create the body of the abstract with the following provisions:

   Length: 500 words (maximum)

   Figures: Do not include any figures or tables.

   Editing: Be sure that your abstract is in final form. Except for formatting and font selection, the content of the abstract will be printed in the Program as you have submitted it.

   Submission Deadline. The final date for abstract submission will be May 15, 1999. In order to avoid a last minute surge of submissions, we ask that you submit your abstract as early as possible. Acknowledgement of abstract receipt will be sent to you via email.

   Posters. The poster session will be held Tuesday evening August 17. The posters can be displayed on Monday August 16. The poster presentation space will be 4 feet x 4 feet. Posters must be taken down immediately following the Poster Session.

Your participation in the SMASH conference is vital for its success. We encourage our industrial colleagues to consider a corporate financial contribution, and **we would like to encourage you to spread the notice of this conference to interested individuals in academia, industry, and government agencies.**

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U. S. Department of Energy

March 16, 1999
(received 3/25/99)

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Hello From Washington

Dear Barry,

Recently, I have taken on a temporary assignment as a rotator within the Division of Chemical Sciences, Basic Energy Sciences in the Office of Science at the Department of Energy (DOE). The purpose of this letter is to acquaint you and your readership with program funding within this office, whose mission is to support fundamental research in areas relevant to energy and the environment. By the way, the level of support for basic research at the National Labs and universities funded by Basic Energy Sciences is on par with that from the Math and Physical Sciences Directorate within NSF, and the basic research program in catalysis within Chemical Sciences is by far the largest sponsored among all government agencies.

The program in Chemical Sciences is divided into two major sections: Fundamental Interactions and Molecular Processes. I am involved in managing programs for the latter section. The Molecular Processes Section funds fundamental research in the areas of homogeneous & heterogeneous catalysis, organometallic chemistry, surface science, materials precursor chemistry, heavy element chemistry, separations science, analytical sciences including applied physics aspects, electrochemistry and electrochemical storage systems.

To learn more about the staff, research programs and future solicitations within the Office of Science, visit our Website at *http://www.er.doe.gov/*.

Sincerely,

Robert E. Botto

UMEÅ UNIVERSITET
Organisk kemi
Dr. Jürgen Schleucher

UMEÅ UNIVERSITY
Department of Chemistry
1999-03-25
(received 3/25/99)

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

Deuterium NMR bridges Chemistry, Botany and Environmental Research

Dear Barry:

Signal intensities in natural-abundance ^{2}H NMR spectra are influenced by kinetic ^{2}H/^{1}H isotope effects. These isotope effects are large and can easily be detected by NMR. This has been used to distinguish natural products of different origins (Grant et al., 1982; Martin et al., 1982; Toulemonde et al., 1983).

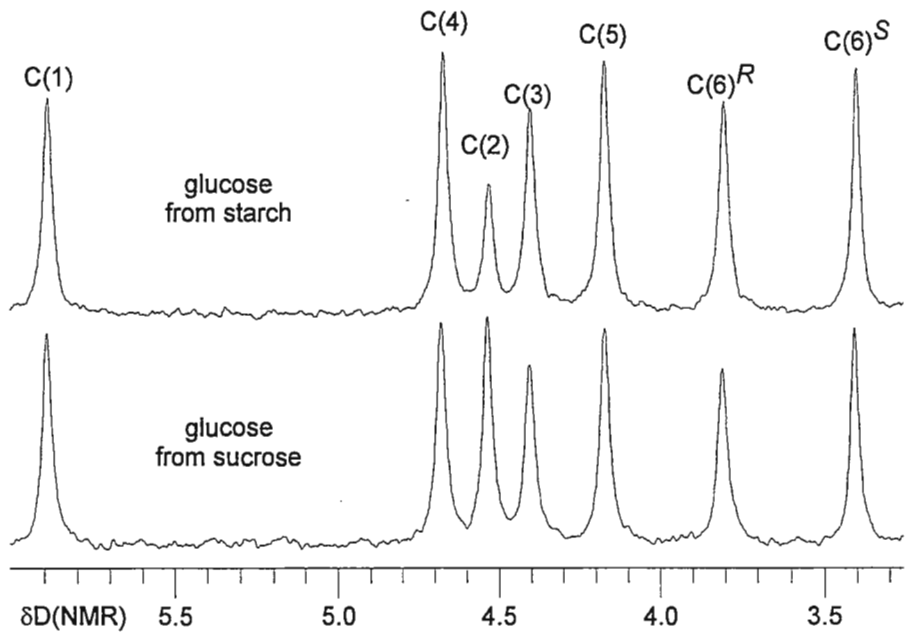

Figure 1: Deuterium NMR spectra of 3,6-anhydro-1,2-*O*-isopropyliden-α-D-glucofuranose, isolated from bean leaf starch and sucrose. Note the huge difference in ^{2}H abundance of the C(2) positions.

We have developed a way to obtain resolved ^{2}H NMR spectra of glucose derivatives (Schleucher et al., 1999). This opens the way to study ^{2}H NMR spectra of this metabolite, which has applications in plant physiology, climate research and medicine. Two conditions have to be met

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to resolve all ^2H signals: The ^1H spectrum must be resolved, and sufficiently narrow ^2H lines must be achieved. The first condition is met by preparation of a glucose derivative. The second condition is met by using solvents of very low viscosity (acetonitrile or acetone) at temperatures close to the boiling point. This is possible if evaporation of the solvent is suppressed using NMR tubes with PTFE valves.

Figure 1 shows ^2H NMR spectra of 3,6-anhydro-1,2-*O*-isopropyliden-α-D-glucofuranose in acetonitrile. The solubility of this derivative is so high that good S/N can be obtained in a few hours on a 5 mm probe. These spectra were recorded in unlocked mode using an NMR system with a stable magnet, solvent line widths of a fraction of 1 Hz can be maintained over hours.

There is a striking depletion of the C(2) position of glucose from leaf starch by ≈ 40%, relative to C(2) of sucrose-derived glucose. A 40% D depletion can only be caused by a reaction that breaks the C(2)-H bond. In the biosynthetic pathway of starch, this happens only in the phosphoglucose isomerase reaction. Sucrose and starch are synthesised in the cytosolic and chloroplastic cellular compartments, respectively. From this follows that phosphoglucose isomerase does not cause a ^2H discrimination in the cytosol, but in the chloroplast. This means that the phosphoglucose isomerase reaction is in equilibrium in the cytosol, but not in the chloroplast.

This demonstrates that biochemical information can be obtained from ^2H NMR. Methods to study plant physiology without sampling during growth are useful for plant breeding and paleobotany, because information can be obtained from plants that grew at past times, e.g. from prehistoric samples.

Reconstruction of climates of past times and elucidation of how vegetation and climate interacted in past millenia is a pressing question, because this information might allow to tell how vegetation and climate are responding to current man-made changes in the atmosphere. The exact natural abundance of ^2H is correlates with climate, colder climates lead to more ^2H-depleted precipitation, antarctic snow is depleted by ≈ 40% in ^2H relative to sea water. The $^2H/^1H$ ratio of annual ice layers extracted from glaciers around the world can therefore serve as a paleo-thermometer. The $^2H/^1H$ ratio of tree rings should contain similar information. However, the 40% depletion of C(2) in starch, averaged over seven carbon-bound hydrogens of glucose, corresponds to a ≈ 6% reduction in the average $^2H/^1H$ ratio of starch, relative to sucrose. This shows that the intramolecular ^2H distribution, measurable by ^2H NMR, is essential to understand the average $^2H/^1H$ ratio of plant matter.

We plan to combine measurements of average $^2H/^1H$ ratios of tree rings and of intramolecular ^2H distributions by ^2H NMR. We hope that this will allow us to obtain both climate and plant-physiological information, and therefore help to unravel the question how climate and vegetation interacted in the past millenia.

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Jürgen Schleucher Ulf Edlund

BICELLE PREPARATION

Buffer: An effective and convenient method for preparing bicelles makes use of a buffer solution containing 10mM phosphate buffer, pH 6.6, 3.0 mM sodium azide, 93% H_2O (HPLC-grade), 7% D_2O (99.9%). Below, this solution will simply be referred to as buffer.

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

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.

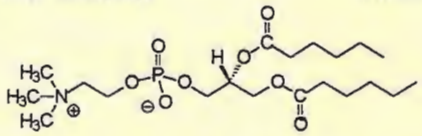
Protein-Bicelle Mix: Two volumes of protein solution are added to one volume of bicelle solution.

Tjandra, N., & Bax, A., "Direct Measurement of Distances and Angles in Biomolecules by NMR in a Dilute Liquid Crystalline Medium" *Science* (1997) **278**:1111-1113.

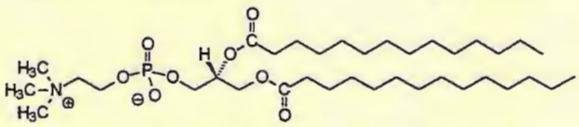
Ottiger, M., & Bax, A., "Characterization of Magnetically Oriented Phospholipid Micelles for Measurement of Dipolar Couplings in Macromolecules" *J. Biomol. NMR* (1998), in press.

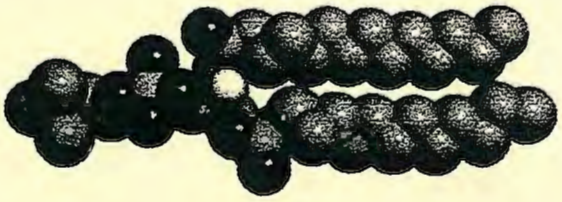
BICELLE FORMING LIPIDS

1,2-dihexanoyl-*sn*-glycero-3-phosphocholine (DHPC)
Cat No. 850305 MW 453.51



1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC)
Cat No. 850345 MW 677.95





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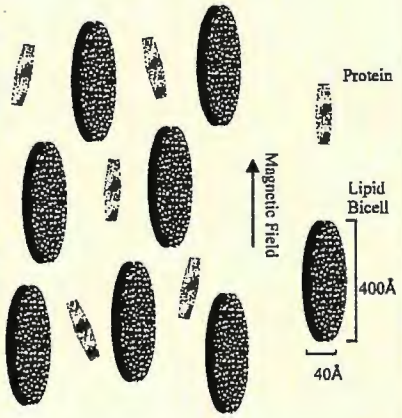

Two of the most common phospholipids used for bicelle formation are **1,2-Dimyristoyl-*sn*-Glycero-3-Phosphocholine (DMPC)** and **1,2-Dihexanoyl-*sn*-Glycero-3-Phosphocholine (DHPC)**. Preparation of defined mixtures of these lipids can be technically difficult and time consuming. Also, specialized equipment is required for handling the materials due to the hygroscopic nature of DHPC. To assist researchers in utilizing this technique, Avanti now offers these components in **pre-mixed units ready for hydration.** Just add buffer and protein solution and you can be ready to take measurements in less than 1 hour.

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Vienna, March 8, 1999
(received 3/13/99)

^{15}N NMR SPECTROSCOPY NONSTOP: ^{1}H,^{15}N-*ge*-HMBC EXPERIMENTS ON HETEROCYCLES

Dear Dr. Shapiro,

due to the increasing availability of modern NMR spectrometers allowing the routine use of proton-detected techniques and, in many cases, coherence selection by pulsed field gradients, ^{15}N NMR spectroscopy seems to experience a renaissance both with synthetic chemists working in the field of heterocyclic chemistry and theoreticians. Here in Vienna, the latter species has persuaded me to collect chemical shift data of some 30 nitrogen containing compounds, most of them commercially available in any amount desired, in different solvents with the purpose of checking (sometimes ancient) literature data and to establish a sound data base for comparison with their theoretical calculations. Thus, different from the investigations described earlier in this journal [1], we were not interested in recording ^{15}N NMR spectra of microamounts, but in producing as many data as possible in a minimum of time.

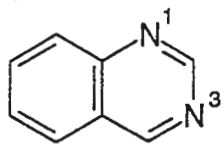
From the beginning it was obvious that the required measurements could only be mastered in a reasonable time utilizing the techniques mentioned above. However, more than 90% of the compounds involved in the study contained tertiary aliphatic or - more frequently - aromatic nitrogen atoms, restricting the applicability of experiments based on direct connectivities (and thus large ^{1}J values) to a minority of cases. A standard ^{1}H,^{15}N-*ge*-HMBC experiment was therefore designed on our upgraded Bruker DRX 400 spectrometer which has already been dealt with in another Newsletter story [2]. Some typical parameters were: measurement frequency 40.53 MHz, 5 mm sample tubes, ca. 100 mg substance in ca 0.6 cm^3 solvent, ^{15}N 90° pulse width 22.5 µs at -6 dB, relaxation delay 2 s, 1 k data points in ω_2, 64 experiments à 2 scans in ω_1, sweep with 3 - 6 ppm (as required) in ω_2, 40 ppm in ω_1, transform size 1 k x 512 data points, no decoupling, magnitude mode, unshifted sinebell in both dimensions. The necessary long-range ^{1}H,^{15}N coupling constants and ^{15}N chemical shifts were taken from the literature if available [3] or estimated based on those of related compounds; $^{1}J(^{1}\text{H},^{15}\text{N})$ was assumed as 90 Hz (*J*-filter). The time required for an experiment was about 6 min depending on the delay $1/^{1}J(^{1}\text{H},^{15}\text{N})$ for evolution of long-range couplings and on acquisition time.

Some features of the experiments seem worth mentioning:

- The sensitivity of the technique is high enough to produce 2D spectra practically free of noise (some t_1-noise was observed in cases where no appropriate coupling constant was available, though). Measurement time cannot be reduced further due to the phase cycle of the pulse program employed (2 scans minimum) and the number of experiments required to give a sufficient representation of ω_1 (64). The other way round, this obviously means that the amount of substance used by us was by far too high; indeed, in a case of restricted solubility we got absolutely satisfying results for a sample of only 10 mg using the above parameters.

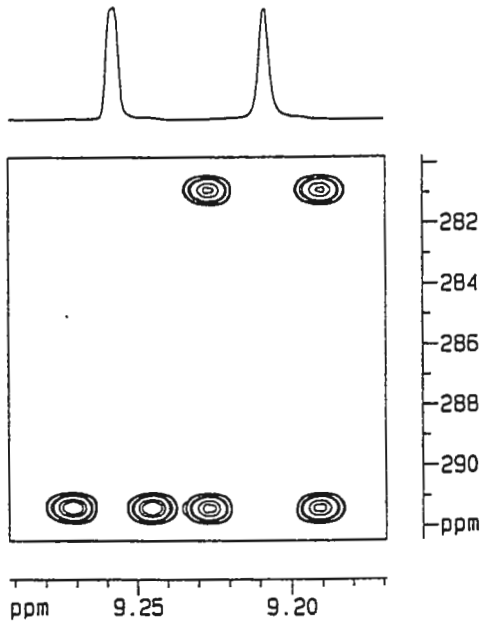
- As the long-range couplings the experiments rely on were rather small in some cases (below 2 Hz), it was expected that sensitivity would suffer dramatically from relaxation during delays of up to 300 ms (corresponding to $J(^1H,^{15}N)$ = 1.7 Hz). However, no noticeable decay of *S/N* was observed.
- Quite some (if not to say many) of the long-range couplings taken from the literature turned out to be wrong (too small throughout) and yielded unexpected connectivities (*e.g.* via 4 bonds instead of 3). In experiments where no cross peaks could be observed, increasing the literature value by a factor of 1.5 to 2 usually settled the case.
- The throughput achieveable using the above technique is incredible, especially for somebody who learnt his job in times when it was absolutely useless to talk about ^{15}N NMR if you couldn't put half a gram of substance or more in a 10 mm tube and pulse at least overnight. At our best, we recorded 24 $^1H,^{15}N$-*ge*-HMBCs (including shimming and measuring of the corresponding ^1H spectra) within 8 h - perhaps some sort of world record, I guess.

Just to illustrate the quality of the results, one of the spectra (not the ugliest one, to be sure!) is given below (quinazoline, $CDCl_3$, optimized for 15 Hz (33.3 ms)).



Quinazoline
(1,3-Benzodiazine)

δ(H-C(2)) = 9.209 ppm
δ(H-C(4)) = 9.259 ppm
δ(N1) = 280.9 ppm [4]
δ(N3) = 291.3 ppm [4]
J(H-C(2),N(1)) = 14.7 Hz
J(H-(C2),N(3)) = 14.7 Hz
J(H-C(4),N(3)) = 10.8 Hz



Please credit this contribution to the account of Dr. Hanspeter Kählig.

Yours sincerely

H. Kalchhauser

Hermann Kalchhauser

References and notes

[1] The NMR Newsletter, December 1998, No. 483, p 11
[2] The NMR Newsletter, March 1998, No. 474, p 43
[3] S.Berger, S.Braun, H.-O.Kalinowski, "NMR-Spektroskopie von Nichtmetallen", Vol 2: "^{15}N-NMR-Spektroskopie"; Georg Thieme Verlag Stuttgart - New York, 1992
[4] ^{15}N chemical shifts relative to external ammonia

CENTRO DE INVESTIGACION Y DE ESTUDIOS AVANZADOS DEL I.P.N.

March 17, 1999
(received 3/24/99)

Dr. Bernard L. Shapiro
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~~TAMU~~ NMR Newsletter
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Push-pull and pull-push in 3-alkylidenindol-2-ones

Dear Professor Shapiro:

The 3-alkylidenindol-2-ones **1-6** are push-pull alkenes:[1, 2] In these compounds the sp^2-C-3 atom of the C-3=C-8 bond is part of an oxindole, while the other sp^2-C-8 atom carries in some cases one or two electron-donating groups (NMe_2, OH, Me) and in other cases one or two electron-withdrawing groups (CO_2Me, CN). These molecules are of interest since they represent a situation where the electronic behavior of the heterocycle may be reversed by the electronic nature of the substituent(s) at C-8, as can be seen in Table 1.

The push-pull substitution pattern is recognized by strongly polarizing the C=C bond and by reducing its double-bond character. The marked decrease of the activation barrier of (*Z*)/(*E*)-isomerization in **1**, **4** and **5** allows it to occur even at room temperature.

Table 1. ^{13}C NMR chemical shifts of the push-pull 3-alkylidenindol-2-ones **1-6**.[a]

No.	R^1	R^2	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	ΔδC-3–C-8
1*E*[b]	NMe_2	H	170.8	94.9	122.9	114.3	119.3	121.6	107.7	135.7	148.8	-53.9
1*Z*[b]	H	NMe_2	165.9	93.1	128.7	120.1	119.7	122.9	108.6	137.9	147.8	-54.7
2*Z*	OH	H	170.2	106.4	122.7	121.9	120.8	126.0	108.9	138.4	154.4	-48.4
3	Me	Me	168.5	122.7	123.6	123.5	120.8	127.5	108.9	140.3	153.8	-31.1
4*E*[b]	CO_2Me	CN	166.1	146.7	119.6	130.3	123.6	137.0	111.7	146.4	105.0	+41.7
5*E*[b]	CN	H	165.9	143.7	119.3	123.8	122.2	133.7	110.9	144.6	97.4	+46.3
5*Z*[b]	H	CN	164.6	144.2	120.6	123.0	121.9	133.5	110.5	143.3	97.4	+46.8
6	CN	CN	163.6	150.4	118.5	125.7	122.8	137.7	111.6	146.4	80.5	+69.9

[a] In ppm from TMS; DMSO-d_6 solution. [b] In *E*/*Z* mixture.

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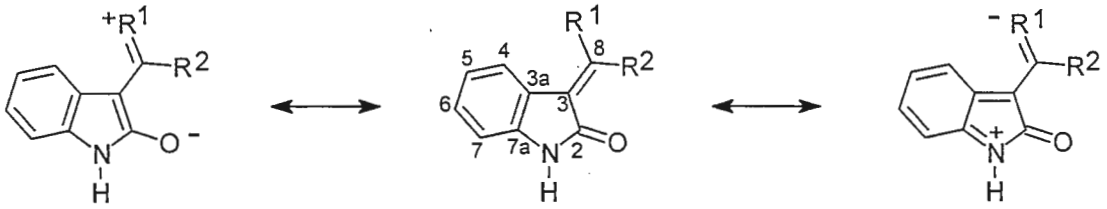
Unambiguous assignments for all carbon resonances were achieved on basis of fully ^{1}H-coupled ^{13}C NMR spectra, one-bond 2D-HETCOR and long-range FLOCK spectra. The stereochemistry at the C-3=C-8 double bond could be deduced by comparison of the ^{13}C chemical shifts of both isomers considering γ-effects due to steric compression,[3] long-range coupling constants ($^{5}J_{NH,\ H8}$), hydrogen-bonding and paramagnetic anisotropy effect from the ester carbonyl group.

The shifts for carbon C-3 of **1**, **2** are substantially upfield (at ~100 ppm) of the 144-150 ppm range of **4-6**. In contrast, the carbon shifts for C-8 of **1**, **2** are substantially downfield (at ~150 ppm) of the 80-105 ppm range of **4-6**. These dramatic changes occurring in the electronic structure of the molecule, can be explained by considering the highly polarizable nature of these cross-conjugated compounds, involving the C-2, C-3 and C-3a atoms. The reverse character of the push-pull effect in **1-3** as compared with **4-6** may reflect contributions by the 3-alkylidenindol-2-ones resonance canonicals depicted in Figure.



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Sincerely yours,

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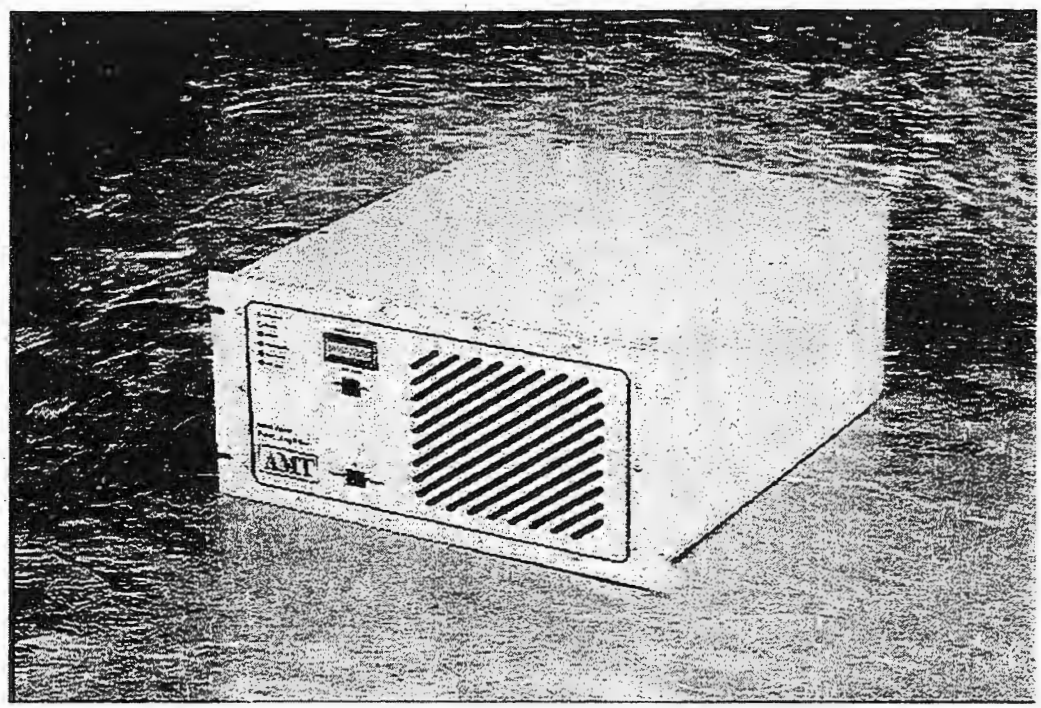

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March 17, 1999
(received 3/22/99)

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Early Days of NMR in the Southwest:
Second Installment

Dear Barry,

In the first installment of this history, I invited additional information from readers. I received the following items that concern the early NMR research at Los Alamos:

(a) Henry Taube continued consulting at Los Alamos until the late 1960's after moving to Stanford University about 1960.

(b) In 1964, Jackson and Rabideau obtained the first deuteron NMR spectrum of heavy ice. During a visit to Los Alamos, Warren Proctor aided in interpreting this data.

(c) From 1964 until 1969, NMR was used by Jackson in the physics division at Los Alamos to measure the polarization of microwave-pumped polarized nuclear targets. This was done first at accelerators and later in a physics experiment carried out by G. A. (Jay) Keyworth on an underground nuclear explosion.

INTRODUCTORY COMMENTS

As mentioned in the first installment of this series, Mobil did pioneering research on NMR relaxation of molecules on surfaces. This topic is of fundamental importance in biomedical magnetic resonance imaging and research and in the exploration of petroleum, two different areas of current exploitation of NMR.

Research in the petroleum industry is concerned with supporting three different areas of application: (a) finding petroleum in the rock formations of the earth (exploration), (b) moving the petroleum from the pore space of the rocks to the earth's surface (production), and (c) transforming the petroleum into useful products such as gasoline, lubricants, plastics, etc. (refining, plastics, and petrochemicals). Because of the proximity of major oil fields, the petroleum companies in the Southwest in the "early days" were particularly concerned with (a) and (b). Since finding the petroleum is fundamental, well logging people very early became interested in the possibility of using NMR in well logging (NML) to identify oil versus water in the rock formations and to discern those formations that have high permeability for the flow of oil from the pores of the rock into the

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borehole of the oil well. The means of distinguishing oil from water would depend on these fluids having different NMR properties, namely different relaxation times. Because these fluids are in contact with immobile rock surfaces, the effects of these surfaces on the relaxation properties were of great interest. Very little was known about this at that time, and most people had initially assumed that the surfaces would have little, if any, effect.

The beginnings of NML occurred in the early days of NMR and many of the NMR pioneers were involved. In the late 1940's, Russell Varian had demonstrated proton free precession in the earth's magnetic field (2 kHz Larmor frequency) and suggested the possibility of using it for well logging. The idea was that, because oil is more viscous than water, oil would have shorter NMR relaxation times than water. This difference would allow measurements of the amounts of each in a rock formation and, also, the signal amplitude would give the total porosity.

In the early 1950's people at several different places in the U.S. started to develop NML. Much of the early development of NML was done in California, which is outside the geographical area of this history. However, because this work has many connections with the efforts in the Southwest, I give a brief synopsis of it here. (Actually, the history of the development of NMR well logging and the use of NMR in petrophysics is extensive and deserves a separate article.) Byron Jackson Tools, Inc. sponsored experiments by Varian on the feasibility of using NMR in well logging. Up until that time, it was not generally recognized that contact with a solid surface decreases the proton NMR relaxation times of water. It was found that the water relaxation times were spread over a wide range of values, rendering part of the original Varian concept invalid. In addition, some of the relaxation times were so short that the NMR signals would be undetectable by earth's field NML, precluding even a measurement of total porosity.

Chevron began an independent NML development even though the original objectives of measuring total rock porosity and distinguishing between oil and water could not be achieved. The idea was to exploit the effects of the rock surface on NMR relaxation. Because the surface effects cause the relaxation times to be sensitive to the local surface-to-volume ratio, information related to pore size, permeability, producible fluid, etc., would be available. The term "free fluid" was adopted for the fluid that could be observed with the earth's field NML. Because the low frequency, 2 kHz, caused the electronics to respond slowly after NMR excitation, the first 35 msec of the free induction decay was lost. Then, Chevron, Byron Jackson, and Borg Warner (which had acquired Byron Jackson) carried out cooperative development of a well logging tool and made field tests in the late 1950's. D. O. Seevers did NMR research at high fields on fluids in rocks, and R. J. S. Brown did NMR research in the earth's magnetic field and developed the earth's field NML. The Chevron work was aided by several consultants who spent extended periods of time at Chevron: Henry C. Torrey of Rutgers University, Jean Uebersfeld (from France), and Jan Korringa of Ohio State University.

The California logging tool had important early success in locating oil in California in wells where the oil was extremely viscous and had a T_2 that was shorter than the 35 msec dead time of the tool. Consequently, it did not give an NMR signal from the oil, but it gave a good signal from zones that would have given unwanted production of water. In zones where other logging tools showed significant rock porosity, the NML tool indicated the oil formations by the absence of an NMR signal.

After it was found that rock surfaces greatly shorten the water relaxation times, the relaxation mechanism was sought. One school of thought held that the properties of water are drastically

modified out to great distances from the surface, up to hundreds of Angstroms, so that the relaxation time shortening was a "bulk" effect in the thick layer of surface water. In fact, there was a vast literature on the modification of water properties out to large distances, causing affects on many different types of physical measurements A review paper on the topic had been published in Reviews of Modern Physics in 1948. Even some years later, Walter Drost-Hansen [Ind. Eng. Chem, **61**, 10 (1969)] published a comprehensive review of the experiments. Water in biological tissue is also in contact with the "surfaces" of relatively immobile macromolecules, and some early biomedical researchers held that the above long-range effects occur in tissue and affect biological processes (there is more about this concept in a later installment). Hence, the relaxation properties of water were of concern to researchers in a wide range of interests.

In that general time frame, Nicolaas Bloembergen of Harvard University, in line with this general concept, published in the abstract of a talk for an American Physical Society meeting a curve that he interpreted to show long-range forces of surfaces in liquids that affected molecular diffusion and caused a shortening of water relaxation times. Schlumberger hired Bloembergen as a consultant because it had the general idea that NMR might be used for well logging. However, the problem of the surface relaxation effects caused Schlumberger to postpone the project. Nevertheless, in 1954 Bloembergen filed for a U.S. patent on a method and apparatus for NMR well logging, assigned to Schlumberger in Houston, Texas.

Another other school of thought held that the NMR relaxation time shortening was a short-range effect right at the surface. In fact, Conger and Selwood at Northwestern University showed that paramagnetic centers on catalyst surfaces drastically shorten the relaxation times of hydrogen in many liquids. Also, Wallace S. Brey showed analogous effects with thorium oxide as the substrate. In other research, relaxation effects of silica gel surfaces (which were taken as models for rock surfaces) were being investigated at Bell Telephone Laboratories in New Jersey and by Dr. Charles H. Holm at Shell Development Company in California. However, the most significant research took place in the Southwest. Parenthetically, the surface relaxation effect in rocks is still being investigated to properly interpret the modern high-frequency (i.e., 0.5 to 2.5 MHz) NMR oil well logs, notably by Schlumberger and also by Numar.

MAGNOLIA/MOBIL IN DALLAS

In the early 1950's, daring individuals in Mobil Corporation had keen interests in applications of NMR to industrial research. This interest started in the Field Research Laboratory (FRL) of Magnolia Petroleum Company, a Mobil subsidiary in Dallas, Texas. There were separate efforts in FRL to apply NMR to (a) petroleum exploration (well logging), and (b) petroleum production problems. In production research, Mr. Sidney M. Foulks became interested in NMR and promoted it strongly. The idea was to "look inside" a porous rock and measure the fluid flow paths under dynamic conditions. However, full realization of this idea occurred only some thirty years later with the development of NMR imaging.

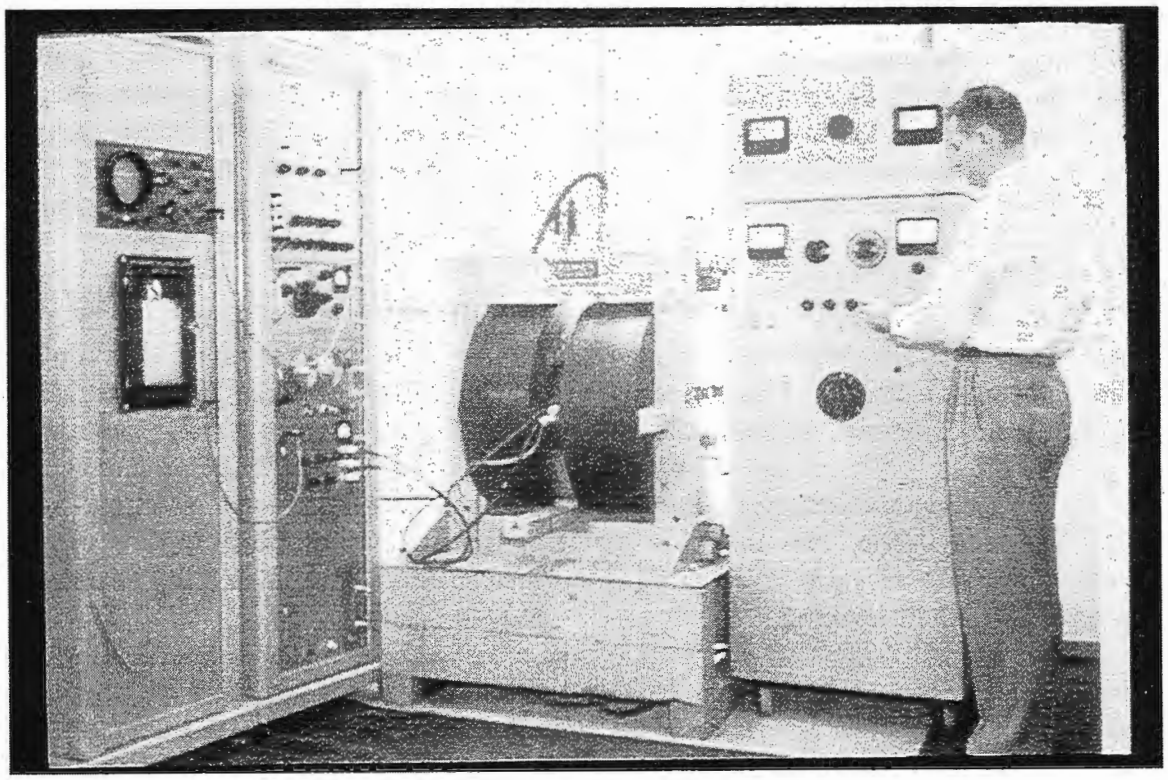
In petroleum exploration research, Robert A. Broding, manager of the well logging group, was interested in finding ways to get response from the different chemical elements in rocks to differentiate between different rocks. He was a physicist and had read Irwin L. Hahn's 1950 paper in Physical Review on spin echoes right after it was published. Broding decided that pulse NMR might be a good way to obtain response from hydrogen in rocks, using relaxation times to analyze the data. (It is not known whether Broding was aware of Varian's NML proposal.) He interested a young man with a Master's degree, named John O. Ely, in this work. In 1951 or early 1952, Ely

spent about six months in building a "breadboard" pulse NMR machine for making laboratory experiments to get proton NMR signals. With this instrument he demonstrated to Dr. Dayton H. Clewell, manager of FRL, that he could observe, in the laboratory, NMR signals from liquids in rocks at high magnetic fields and also measure the T_1 and T_2 of these protons. The work was not published, for proprietary reasons. These results were encouraging and Ely and co-workers filed a patent application on NMR well logging (January 19, 1952).

Foulks and Dr. Sam R. Faris visited Varian in late 1951 or early 1952 to look at their NMR equipment and inquire about purchasing it. Jim Shoolery was very helpful in describing Varian's NMR capabilities to them. As a result of this visit, Dr. Clewell signed a purchase order for three different Varian NMR machines. The total, around 50 to 75 thousand dollars, was a huge sum in those days -- especially for obtaining new technology without prior *proven* applicability to the research at hand. Before the equipment was delivered, in late 1952 Mr. Foulks took a leave of absence from FRL to attend graduate school. A Varian pulse NMR instrument was included in the purchase. It was delivered to Mobil in 1952 or 1953, after Ely had taken leave to attend MIT graduate school to get a Ph.D. so that he could better carry out this NMR research (Ely died before getting his degree).

The first machine to arrive was a Varian continuous wave, broad line (low resolution) spectrometer for the production research. It was the *first* commercial NMR machine. This instrument, before it was delivered to FRL, is shown in below.

Fig. 1. The first commercial NMR spectrometer.



This instrument had sufficient sensitivity to show the natural-abundance deuterium NMR resonance in ordinary water. The analog output of the receiver was plotted by the strip chart recorder, located in the left-hand console, as the magnetic field was swept through resonance. This was long before digitizers and minicomputers were developed. The unit on top of the electromagnet

power supply was a high voltage stabilizer that provided a fair degree of magnetic field stability. The magnet had 12-inch diameter pole faces with a two-inch gap and was Serial No. 4, made in San Carlos, CA. Dr. Ted Burdine, a physicist, used the machine to study fluid flow/displacement in porous rocks. This was done by detecting proton NMR and displacing the fluid with D_2O. Apparently, the results were less than spectacular. The combined effects of magnetic field inhomogeneity inside the rock samples and difficulties in making precise signal amplitude measurements with a cw spectrometer led to poor quantitation of fluid displacement in a given cross section of the sample. Research with this machine was discontinued and interest shifted to the pulse rf machine, that had been ordered, and then to use spin echoes and time-domain data collection to circumvent the inherent data collection problems of cw machines mentioned above. (The electromagnet was later used in a Varian electron spin resonance spectrometer. Years later after that, I cut down the pole faces to nine inches to increase the magnetic field and used it for pulse NMR with an in-house constructed console.)

The next installment of this history will finish the Magnolia/Mobil NMR saga, starting with the first commercial pulse NMR machine, Serial No. 1, built by Varian in San Carlos.

Again, I solicit comments, corrections, additional material, etc. on the topics covered in the first two installments.

Sincerely,

Don

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March 12, 1999
(received 3/17/99)

Dear Colleague:

Please take a moment and look at your calendar for August 1-5, 1999. The 1999 Rocky Mountain Conference* NMR Symposium is scheduled for that week and you will want to set aside time to participate!

The NMR Symposium for 1999 is pleased to announce that Professor H.W. Spiess of the Max-Planck-Institute for Polymer Research will be the Vaughan Lecturer. In addition, the symposium will feature technical sessions on Conformational and Structural Determination, Catalysis and Interfaces, Inorganic Materials/Glasses, Novel Detection Schemes, and Dynamics. At the present time our (incomplete!) invited speaker list includes (in random order) Ed Samulski, Robert Tycko, Huub De Groot, Jean-Paul Amoureux, Hellmut Eckert, Hironori Kaji, Niels Nielsen, Sarah Larson, Dominique Massiot, Dieter Freude, Bill Power, Geoff Barrell, Klaus Woelk, Zeev Luz and Dick Wittebort. We will also be sponsoring the Laura Marinelli Prize for outstanding student or postdoctoral paper or poster. Finally, you will not want to miss "vendor carnival" night in which vendors will present technical posters and demonstrate equipment over a delightful dessert.

Over the years the RMC has been one of the few conferences where emerging *and* established scholars have the time and opportunity to engage in intellectually stimulating discussions and cultivate personal growth. This summer is your chance to be a part of this great tradtion: why not prepare an abstract for the meeting? Then go to our web site (http://india.cchem.berkeley.edu/~rmc/) for instructions on how to submit the abstract and make your travel arrangements!

In closing, I note that in addition to having technical discussions with the many fine colleagues I have met and come to know over the years at the RMC, I have also enjoyed their company while strolling in the lovely Colorado sunshine, dining at the many affordable restaurants and shops along the"16th Street Mall", partying at Larimer Square, and sharing rousing cheers for the Colorado Rockies at Coors Field. Won't you join us this year?

Sincerely,

Jeffrey A. Reimer
1999 RMC NMR Symposium Chair

* in Denver, CO.

GORDON CONFERENCE ON MAGNETIC RESONANCE

The 1999 Gordon Research Conference on Magnetic Resonance will be held at New England College in Henniker, New Hampshire, June 27 through July 2, 1999. Invited lectures will cover topics that include new techniques in solid state NMR, high-resolution liquid state NMR, MRI, and high-field EPR, quantum computing with NMR, high-resolution NMR of biopolymers, biological EPR, and optical pumping. In addition, participants have the opportunity to present posters. As always, the Gordon Conference will be a forum for the presentation and discussion of the most sophisticated and freshest developments in magnetic resonance. Attendance is limited, so apply now!

Additional information and an on-line application form can be found at http://www.grc.uri.edu/ . Contact the chair (Regitze Vold, rvold@ucsd.edu) or vice-chair (Robert Tycko, tycko@helix.nih.gov) if this information is insufficient.

Field of Dreams

By Kip Shaffer

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650-493-5971* - *Please call only between 8:00 am and 10:00 pm, Pacific Coast time.*

Deadline Dates

No. 488 (May)	23 Apr. 1999
No. 489 (June)	21 May 1999
No. 490 (July)	25 June 1999
No. 491 (Aug.)	23 July 1999
No. 492 (Sept.)	20 Aug. 1999

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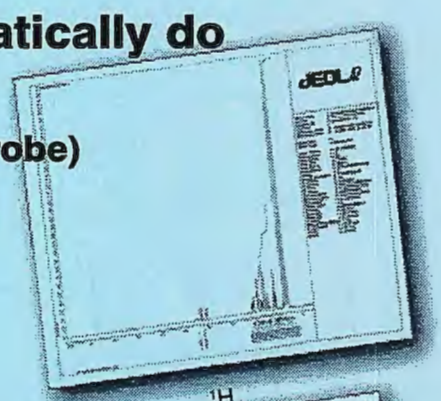
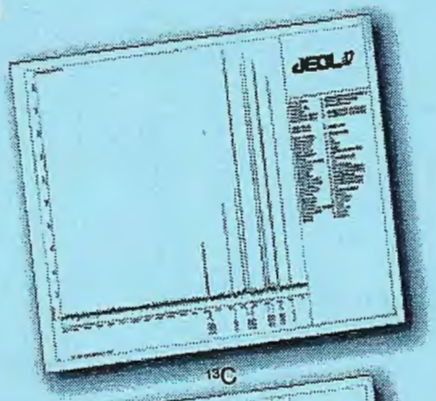
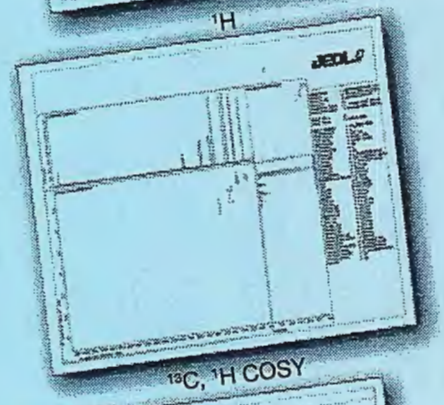


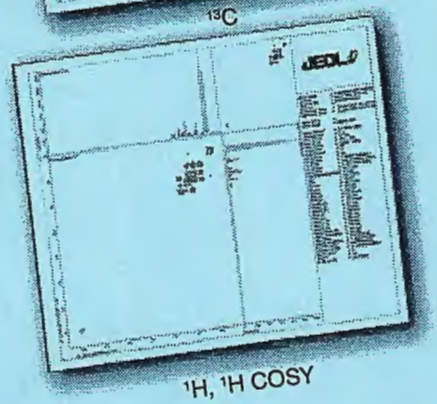
^{1}H



^{13}C



^{13}C, ^{1}H COSY



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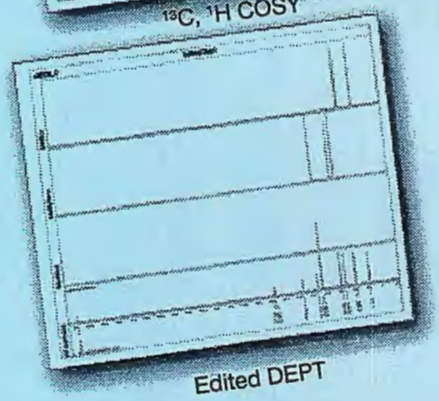

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