THE NMR NEWSLETTER

No. 498

March 2000

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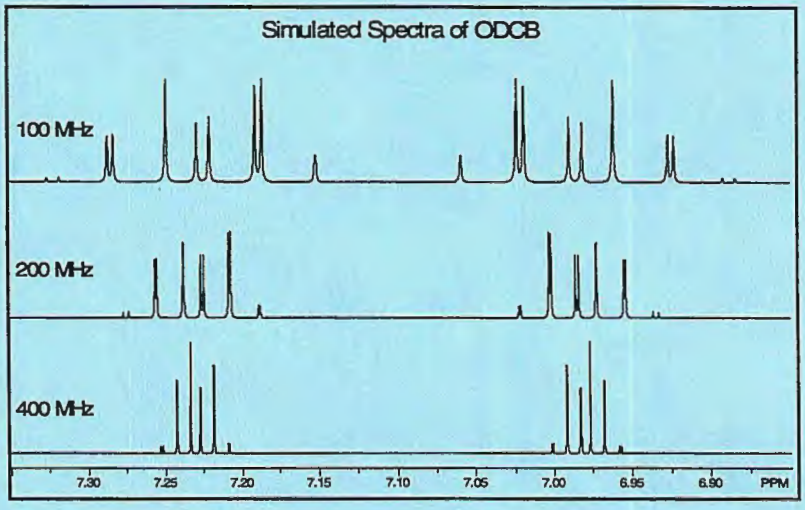

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FORTHCOMING NMR MEETINGS

8th Scientific Meeting and Exhibition, International Society for Magnetic Resonance in Medicine, Denver, CO, **April 1-7, 2000**; Contact: ISMRM, 2118 Milvia Street, Suite 201, Berkeley, CA 94704. Tel. 510-841-1899; Fax. 510-841-2340; E-mail: info@ismrm.org; http://www.ismrm.org.

Symposium on Advances in NMR Applications, Naval Postgraduate School, Monterey, CA. Shuttle service to and from Asilomar will be provided. **April 9, 2000**; Contact: V. Davies, Nalorac Corporation, 837 Arnold Drive, Suite 600, Martinez, CA 94553; 925-229-3501; Fax: 925-229-1651; Email: victoria.davies@nalorac.com; http://www.nalorac.com. See Newsletter 495, 28.

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. Web: enc-conference.org

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.

15th European Experimental NMR Conference, Leipzig, Germany, **June, 2000**. For information, see http://eenc.uni-leipzig.de.

XEMAT 2000, a Conference on "Optical Polarization and Xenon NMR of Materials", Sestri Levante, Italy, **June 28-30, 2000**. For information, see http://www.mater.unimib.it/xemat2000/

NMR Course: Part 1 - NMR-based Metabonomics; Part 2 - Hyphenated Spectroscopic Techniques, Imperial College, London, England, **July 10-14, 2000**; Contact: Hersha Mistry,Centre for Continuing Education, Imperial College, 526 Sherfield Building, Exhibition Road. London, SW7 2AZ, UK. Tel: +44 (0)20 7594 6884; Fax: +44 (0)20 7594 6883; Email: h.mistry@ic.ac.uk; Website: http://www.ad.ic.ac.uk/cpd/nmr.htm

continued on inside back cover

UNIVERSITY OF THE PACIFIC

College of the Pacific

Department of Chemistry

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

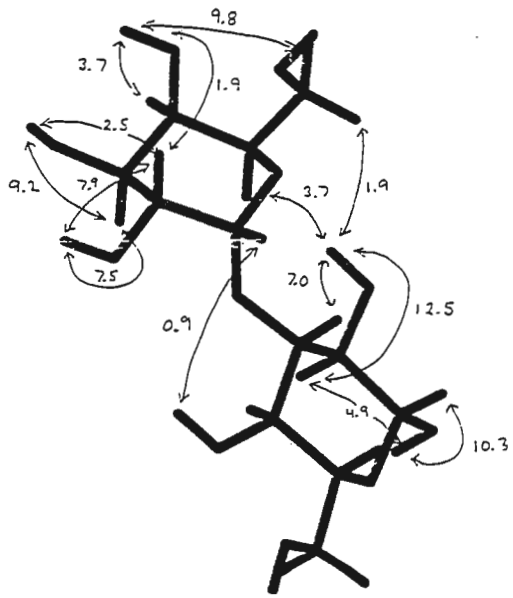
(received 2/17/2000)

The use of H_2O/ D_6-DMSO mixtures to study carbohydrate hydroxyl proton resonances at low temperatures

Dear Barry

The unusual property that H_2O/ D_6-DMSO mixtures can have freezing points more than eighty degrees below that of pure DMSO or sixty degrees below that of water permits this mixture to be used as a solvent that significantly slows down the exchange rate between bulk solvent water to reveal individual hydroxyl proton resonances and their coupling constants with neighbors. This means that the 13 ring protons visible in a disaccharide can be supplemented with up to 8 hydroxyl resonances. Moreover NOE information is also available, including NOES between rings. This trick has been used for a number of years but we recently found that it works very nicely with various galactose dissaccharides and that all the OH lines of compounds like lactose can be fully assigned using TOCSY and NOESY methods operating at –13° C with Watergate suppression to clean up the spectra. Of especially interest to us was the Alpha Gal (1→3) Gal disaccharide in which a large number of intra- and inter-ring OH NOEs distances can be deduced. The work described here was done during a sabbatical in the laboratory of Hans Vliegenthart at the University of Utrecht (Bijvoet Center for Bio-organic Chemistry) and the NOE data should prove useful to disaccharide molecular modeling work of Hans-Christian Siebert and Hans-Joachim Gabius in Munich at the Institut für Physiologische Chemie, Veterinary Faculty, Ludwig-Maximilians-University Munich, Veterinaerstr. 13. The following illustrates some, but not all the interactions, observable using this solvent mixture at 500 MHz.

α Gal (1→3) Gal-β-OH Selected NOES in 60% D_6-DMSO. Numbers are cross peak volumes x 10^{-6}.



Michael J. Minch Hans Vliegenthart Hans-Christian Siebert Hans-Joachim Gobius

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February 1, 2000 (received 2/9/2000)

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

Re: Swimming in the Aromatic Alphabet Soup

Dear Barry:

Aromatic sidechains in proteins are often involved in long-range hydrophobic interactions, and their NOE connectivities can provide valuable solution-state structural restraints if one can establish unambiguous proton assignments. One of the most popular methods[1] correlates the H_δ and H_ε shifts with C_β resonances. While the C_β shifts of Phe and Tyr are readily distinguishable from those of His and Trp residues, there is substantial overlap of the C_β resonances for each subclass of aromatic amino acid. In **Figure 1**, we show hbCBcgcdHD and hbCBcgcdceHE spectra measured on oleate-bound rat liver fatty-acid binding protein (LFABP). The C_β resonances of 6 Phe and 3 Tyr are fairly broad and span a range of less than 5 ppm (~40 ppm), thus precluding definitive assignments.

We have been working with a series of aromatic experiments developed by Prompers et al.,[2] which correlate C_γ resonances with aromatic as well as β-protons. This strategy is attractive for three reasons. First, the C_γ resonances are diagnostic for each type of aromatic residue. Second, the experimental design allows protonated carbons to fully develop anti-phase magnetization and then be destroyed by purge and gradient pulses while leaving the unprotonated carbons unaffected. The resulting spectral simplicity makes it very easy to visualize the connectivities of interest. Third, the correlation with a pair of H_β shifts in contrast to a single C_β shift allows the residue of interest to be identified more confidently.

In **Figure 2** we show the results of such experiments with LFABP. The separation of Tyr and Phe C_γ resonances is at once clear, facilitating the assignments. However, there are a few surprises. In the region downfield of 140 ppm, crosspeaks can be observed in the CGcdceHE and CGcdHD spectra, but there are no corresponding peaks in the CGcbHB spectrum. A brief inspection suggests that these peaks arise from aliasing of the nonprotonated Tyr ζ-carbons located at ~158 ppm. Indeed, one finds complete agreement of H_ε shifts from the (C_γ, H_ε) crosspeaks in the CGcdceHE spectrum and from the (C_ζ, H_ε) crosspeaks in the CGcdHD spectrum. Interestingly, no C_γ correlation is detected for Y54, which is located in the lipid portal region and therefore may have motional characteristics that are unfavorable for detection. Nevertheless, its aromatic proton assignments can be deduced through the C_ζ resonance.

A second surprise is the finding of peaks with negative intensities in the CGcbHB and CGcdHD spectra, an anomaly not discussed in the original literature report.[2] As judged by their H_β shifts, these intriguing features appear to arise from His residues. Furthermore, crosspeaks appear in the CGcdHD and CGcdceHE spectra that can only be attributed to *protonated* δ2 and ε1 carbons of histidine. This puzzle was solved by realizing that the destruction of anti-phase $C_{x,y}H_z$ magnetization is optimized for $^1J_{CH}$ = 160 Hz. With $^1J_{CH}$ values of ~200 and 220 Hz for histidine δ2 and ε1 carbons, respectively, we can predict 38% and 55% of the in-phase magnetizations will be retained and thus develop C-H correlations.

The disadvantage of carbon-initiated sequences is their lower sensitivity as compared with those starting from protons. For our 0.5 mM [U-^{13}C, ^{15}N]-LFABP sample, we found that decent spectra could be acquired in 6 hours for the CGcdHD experiment, and 24 hours each for CGcbHB and CGcdceHE. When augmented by an aromatic HCCH-TOCSY experiment,[3] this approach can provide complete ^{13}C and ^{1}H aromatic assignments. Considering the wealth of information these experiments provide, we feel that the requirements in instrument time are not unreasonable.

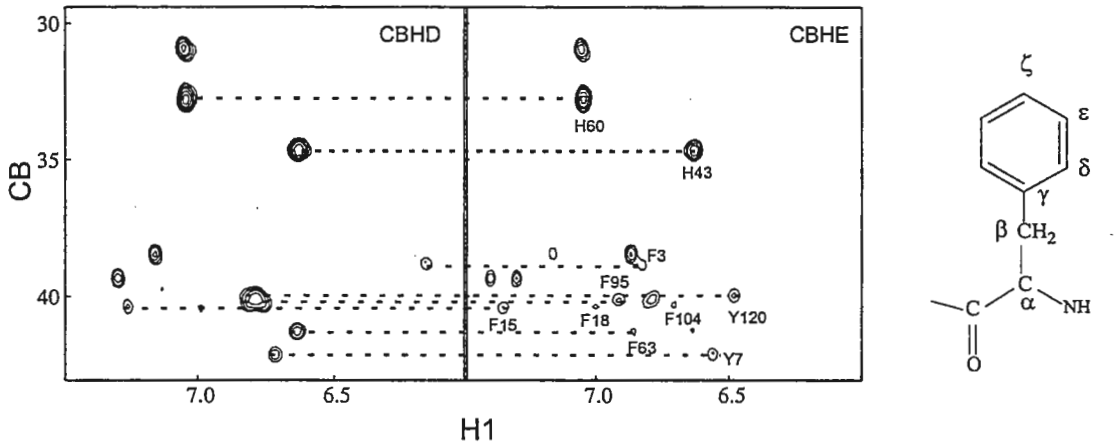

Figure 1

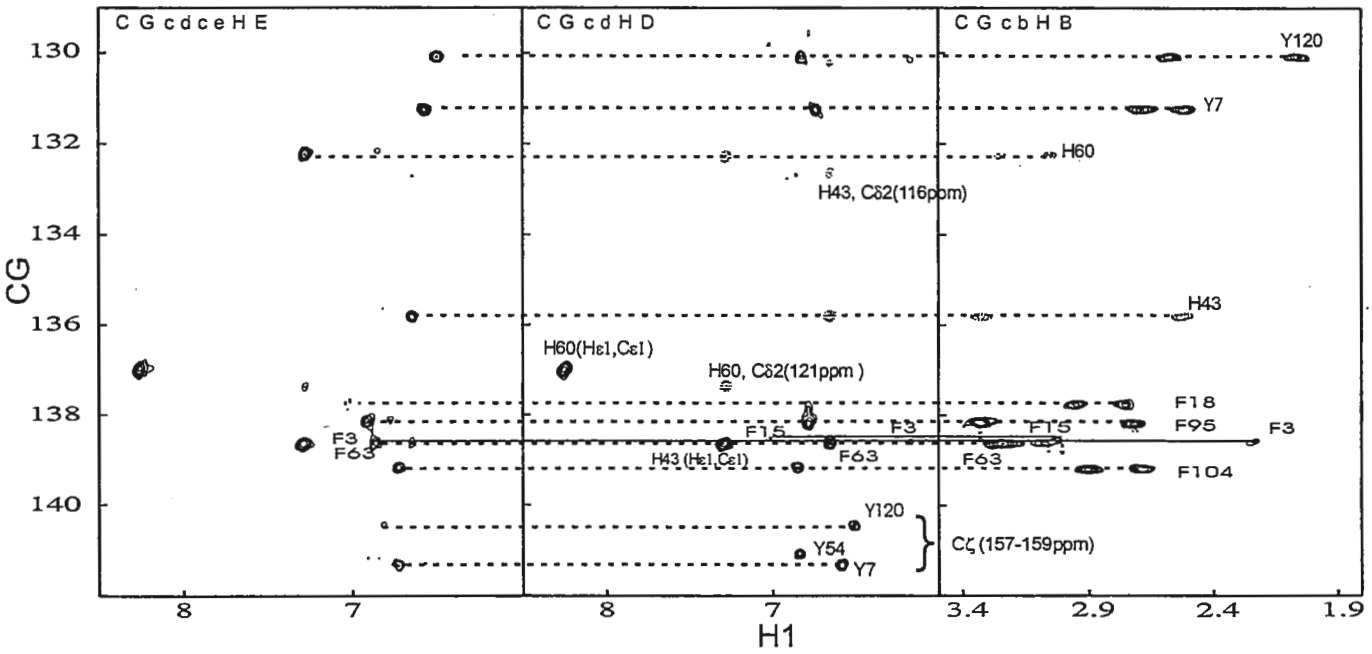

Figure 2

1. Yamazaki, T, Forman-Kay, JD, and Kay, LE (1993) *J. Am. Chem. Soc.* **115**, 11054-11055; 2.Prompers, JJ, Groenewegen, A, Hilbers, CW, and Pepermans, HAM (1998) *J. Magn. Res.* **130**, 68-75; 3. Löhr, F and Rütherjans, H (1996) *J. Magn. Res.* **112B**, 259-268.

Sincerely,

Hsin Wang	Xiaomin Yang	Yan He	Ruth E. Stark
NMR	Postdoctoral	Ph.D.	Professor of Chemistry

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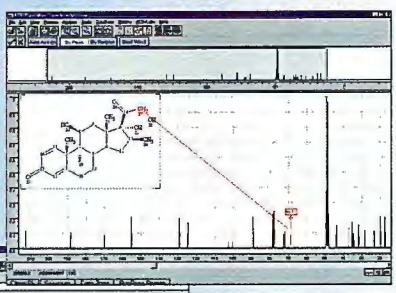

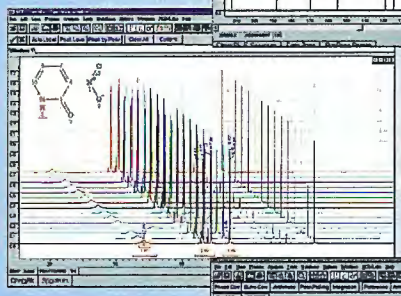

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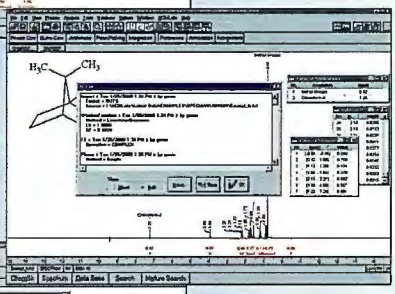

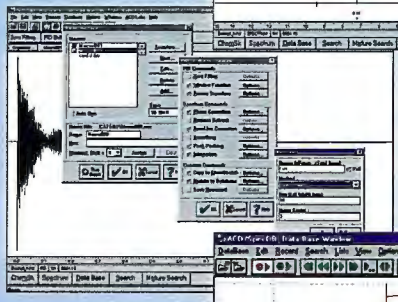

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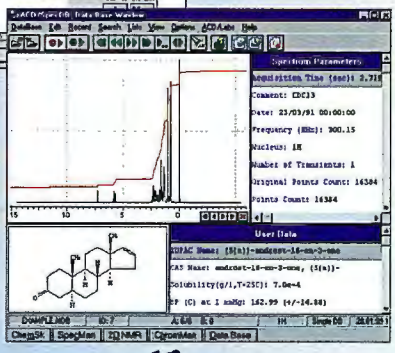

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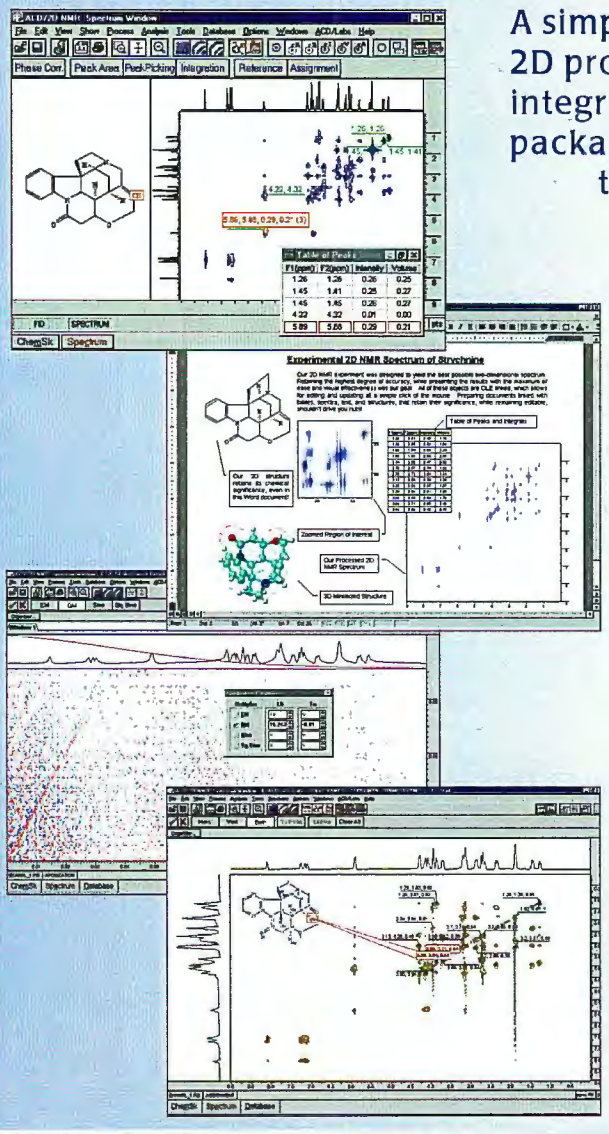

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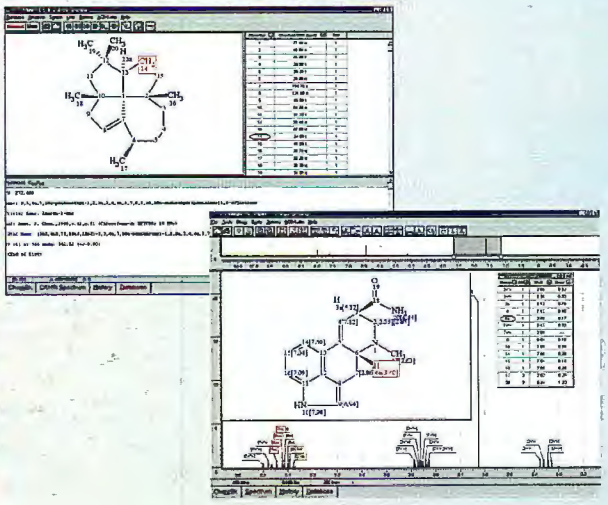

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Queen's University
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K7L 3N6

Dr. B. L. Shapiro
The NMR newsletter
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Palo Alto, CA 94303
USA

(received 2/19/2000)
February 11, 2000

Probing the Origin of Disorder in Polynuclear Aluminum Complexes by ^{27}Al MQMAS

Dear Dr. Shapiro:

The invention of multiple-quantum magic-angle spinning (MQMAS) methodology [L. Frydman, J.S. Harwood, *J. Am. Chem. Soc.* **1995**, *117*, 5367] has triggered a new wave of solid state NMR studies for half-integer quadrupolar nuclei. Recently, we have found that ^{27}Al MQMAS NMR is very useful in identifying the origin of ligand disorder in polynuclear aluminum 7-azaindolyl complexes.

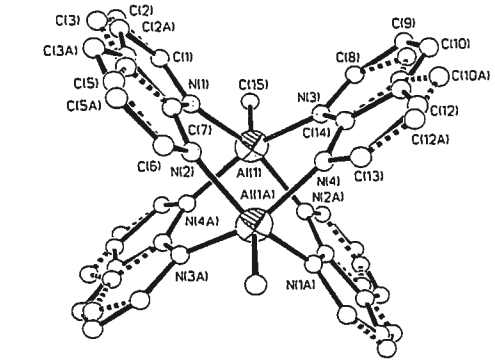
The molecular structure of $Al_2(CH_3)_2(7\text{-azaindole})_4$ is shown in Figure 1. This compound has a crystallographically imposed inversion center and all four 7-azaindolyl ligands are disordered in the crystal lattice. The origin of the disorder could be due to either the coexistence of different structural isomers or the presence of one isomer having different orientations in the crystal lattice. The low-temperature solution ^{1}H NMR spectrum suggests that the two Al atoms in the compound are chemically equivalent. The two possible symmetrical isomers are depicted in Figure 1, one with a C_{2h} symmetry (**1**A) while the other with a D_{2d} symmetry (**1**B). Now the question becomes whether isomers **1**A and **1**B coexist in the crystal lattice or only one of them is present with two different orientations. These situations are indistinguishable by X-ray crystallography.

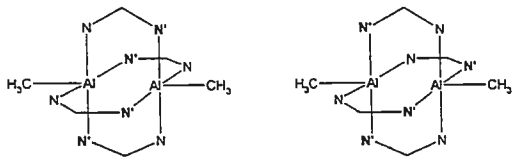
The 2D ^{27}Al MQMAS spectrum of this compound (shown in Figure 2) exhibits two isotropic peaks with a 1:1 intensity ratio. This immediately suggests that the 7-azaindolate disordering is due to the coexistence of two symmetrical isomers, **1**A and **1**B, in the crystal lattice. The remarkable site-resolution in the ^{27}Al MQMAS spectrum helps resolve to very similar Al sites that would be difficult or impossible to separate from the normal MAS spectrum. The methodology demonstrated here is clearly applicable to other systems where half-integer quadrupolar nuclei can be used as a probe of ligand disordering.

Please credit this contribution to the account of Francoise Sauriol.

Sincerely,

Gang Wu





1A 1B

Fig.1. Molecular structure of $Al_2(CH_3)_2$(7-azaindole)$_4$.

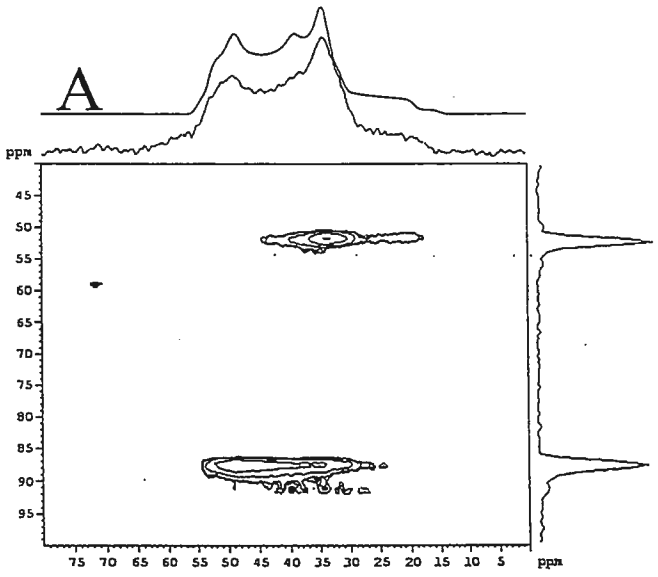


Fig. 2 ^{27}Al triple-quantum (3Q) MAS NMR spectrum of $Al_2(CH_3)_2$(7-azaindole)$_4$.

Family Matters

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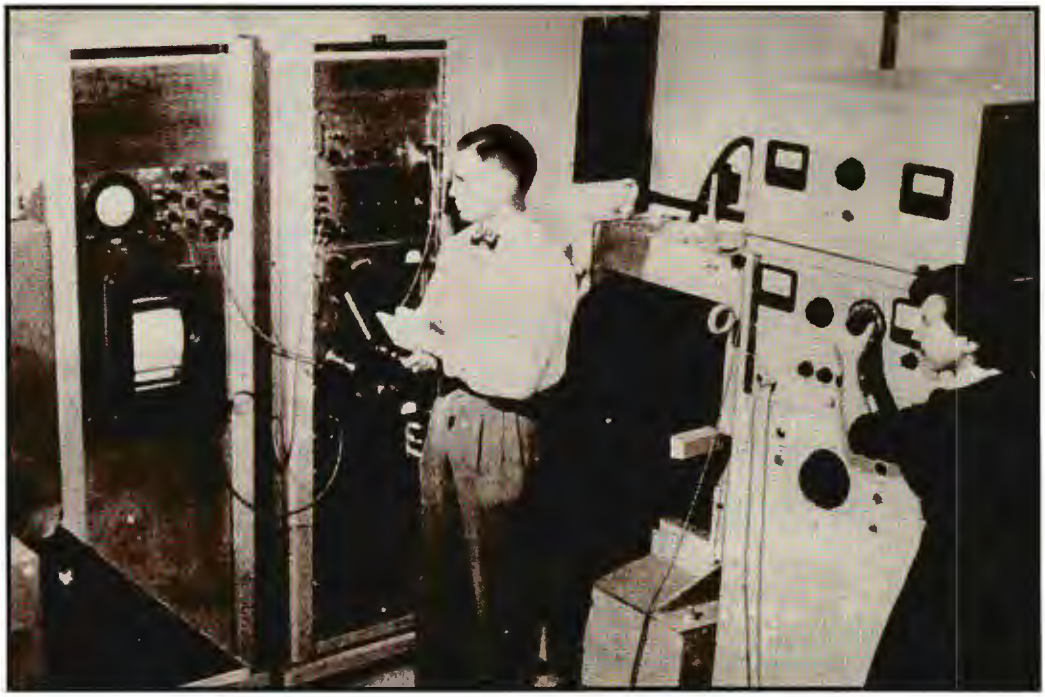

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Department of Physics

2 February 2000
(received 2/9/2000)

Dear Dr. Shapiro:

Together with colleagues at Boeing Co., we have been exploring the potential of NMR relaxation time measurements to help in the production and maintenance of epoxy-graphite aircraft components. We note that the Super Hornet (F-18 update) and the Harrier (VTOL jet) have substantial percentages of this composite material. The idea is to monitor the curing process and detect thermal damage to the epoxy.

We have constructed a small permanent magnet of just a couple of pounds weight that puts proton resonance at 13 MHz. Like the MOUSE of Blümich and Blümler,[1] this is a 1-sided magnet: signals are obtained with the magnet pressed against a flat piece of the material to be inspected.

In making measurements on rigid epoxy at 13 MHz, the short T_2 signal (~ 15 μs) is easily obscured by L-C ringing of the tuned circuit. The poor field homogeneity (1 MHz or more!) causes the S/N to be low, so we were not eager to reduce (dump) the Q to fix the ringing problem. Our original strategy was to use the magic-echo sequence[2] (τ_x-$\tau_{\bar{x}}$-$(\pi/2)_y$-delay-echo) with an extra π-pulse to refocus H_o inhomogeneity, locating it in the middle of the delay period of length τ. This π-pulse does not redress the large resonance offset **during** the rf excitations ($\tau_x, \tau_{\bar{x}}$) and the echo amplitude is thus a small fraction of what we expected.

Our solution was to use a hardware Q-switch.[3] This design resulted in a ringdown time of about 3 μs, quite good for a $Q = 65$ or greater coil at 13 MHz. To refocus the H_o inhomogeneity, a $\pi/2$-t-π sequence was used with a short t of 3 microseconds, locating the echo peak just outside the recovery window, but well inside the T_2 time limit. We noticed some acoustic ringing (coil disease); preceding every other pulse sequence with a π-pulse to invert M_z and add/subtract signal averaging eliminated all non-NMR signals. We second A. J. Vega's remark here (January 2000 issue) that the "blinking π-pulse" is underappreciated. All in all, the Q-switch, simple $\pi/2$-t-π pulse sequence, and blinking π-pulse give excellent signals from this unusual configuration.

1. G. Eidmann, R. Savelsberg, P. Blümler, and B. Blümich, J. Magn. Reson. **A122**, 104 (1996).
2. R. C. Bowman, Jr. and W.-K. Rhim, J. Magn. Reson. **49**, 93–98 (1982), and references therein.
3. Mark S. Conradi, "Fet Q-Switch for Pulsed NMR", Rev. Sci. Instrum. **48**, 359 (1977).

Sincerely,

Joseph P. Dugas

Mark S. Conradi

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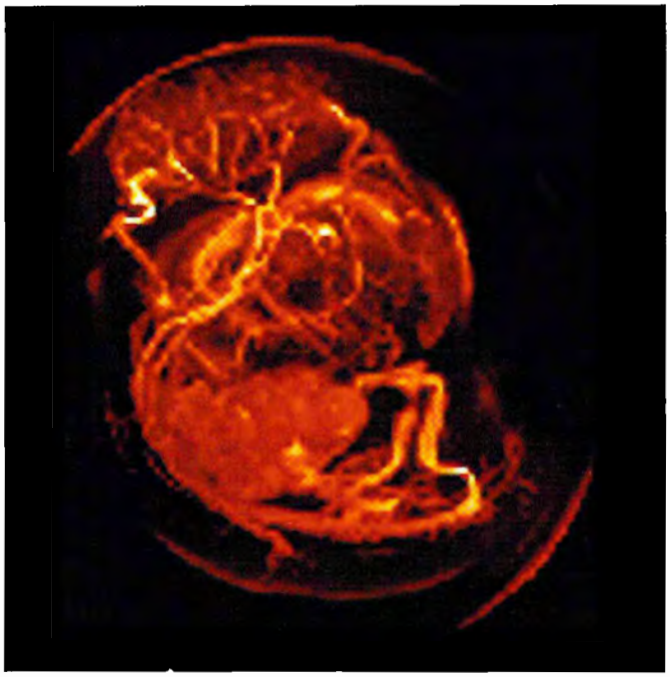

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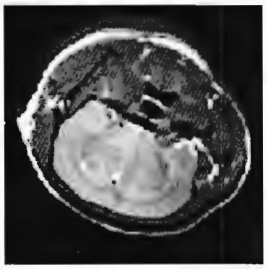
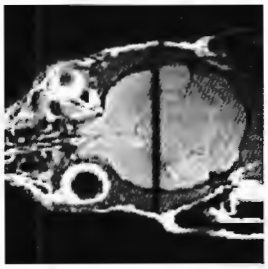
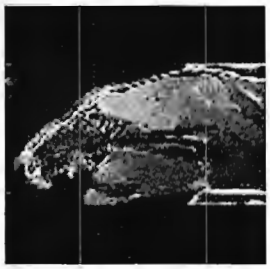
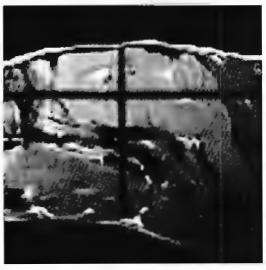


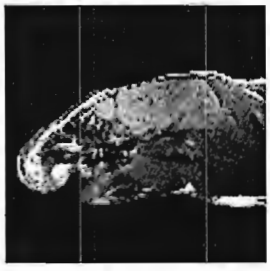




RARE mouse head image
- 256x128,
- 117 um pixels
- 500 um slice
- TR 3s,
- TE 5.5 ms
- Rare factor 8
- 2 averages



Spin echo images through a mouse head. The dark stripes indicate the position of the three intersecting orthogonal slices.



MSME, Sum of 8 echoes,
- 512 x 256,
- 59 um pixels,
- 500 um slice,
- TR 2s,
- TE 9.3 ms
- 4 averages

We gratefully acknowledge the valuable collaboration with "Spin System (Qld)" for support in developing the imaging probes and in-vivo accessories.

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Deuterium Gradient Shimming : a Tool for Automation

Wissembourg, February 8th 2000.
(received 2/15/2000)

Dear Barry,

Since their appearance in NMR, ten years ago, pulsed field gradients became one of the most widely used technique and their popularity is still increasing. The opportunity of rejecting the long and painful shimming procedure to the past of NMR raised a huge enthusiasm into the NMR community.

The "Gradient Shimming" tool was previously described in the *NMR Newsletter*[1]. It is based on the acquisition, with a gradient echo sequence, of profiles(1D)(fig1) or images(3D)[2]. A previous mapping of the probehead gives access to the action of each shim coil. The quality of the results depends critically of the signal/noise ratio of the profile. Best results were obtained at high field on water sample where the huge proton signal could be used to acquire the profiles and the images. In organic solvents, selective excitation of the main peak in the spectrum is used, in this case, the spectroscopist has to change manually the excitation frequency for each sample. This drawback prevents an easy implementation of ^{1}H Gradient Shimming in automation.

Consequently, for low field spectrometers, mainly dedicated to routine, deuterium gradient shimming seems to be a better choice. In fact, ^{2}H signals of deuterated organic solvents like DMSO, acetone or benzene are intense enough to allow the fast acquisition of profile with satisfactory S/N ratio. Observation and irradiation of the deuterium profile takes place on the lock coil, and is permitted thanks to a lockswitch unit . An AU program, **zg_2Hoffon** is running in the background and carries out the following tasks :

1. Switches off the lock during the acquisition of ^{2}H profiles
2. Gives to the carrier frequency the value of the lockshift
3. Switches on the lock at the end of the process.

The parameter set to call back is **gradshim1d2h.** Depending on the probehead, some parameters like D1, NS, PL1 or SW may be optimized to get a better profile. So, with one 90 degree excitation pulse, one scan and one iteration step (Z, Z^2, Z^3, Z^4, Z^5) it is possible to shim several samples in different organic solvents in less than a minute each.

The Bruker automation software Iconnmr allows the spectrometer administrator to define the shimming procedure, Gradient Shimming or the well known simplex process. In order to verify the reliability of the method and the quality of the shim, a set of test samples were chosen to simulate a "true" automation run. The spectra shown in figure 2 were obtained on an AVANCE 300, two channels, equipped with a ^{2}H lockswitch., using the Iconnmr Automation routine.

Fast process, good shim quality and reproducibility of the results make Deuterium Gradient Shimming as the future standard for all NMR automation systems.

Sincerely,

T RICHERT

C. BREVARD

Christian

References

1. Piotto, M. and C. Brevard, *B_0 gradients : A spectroscopist's best friend?* The NMR Newsletter, 1996. **451**: p. 17-18.
2. Van Zijl, P.C.M.., *et al.*, *Optimized Shimming for High-Resolution NMR Using three-dimensional Image-Based Field Mapping.* J. Magn. Reson., 1994. **111**(Series A): p. 203-207.

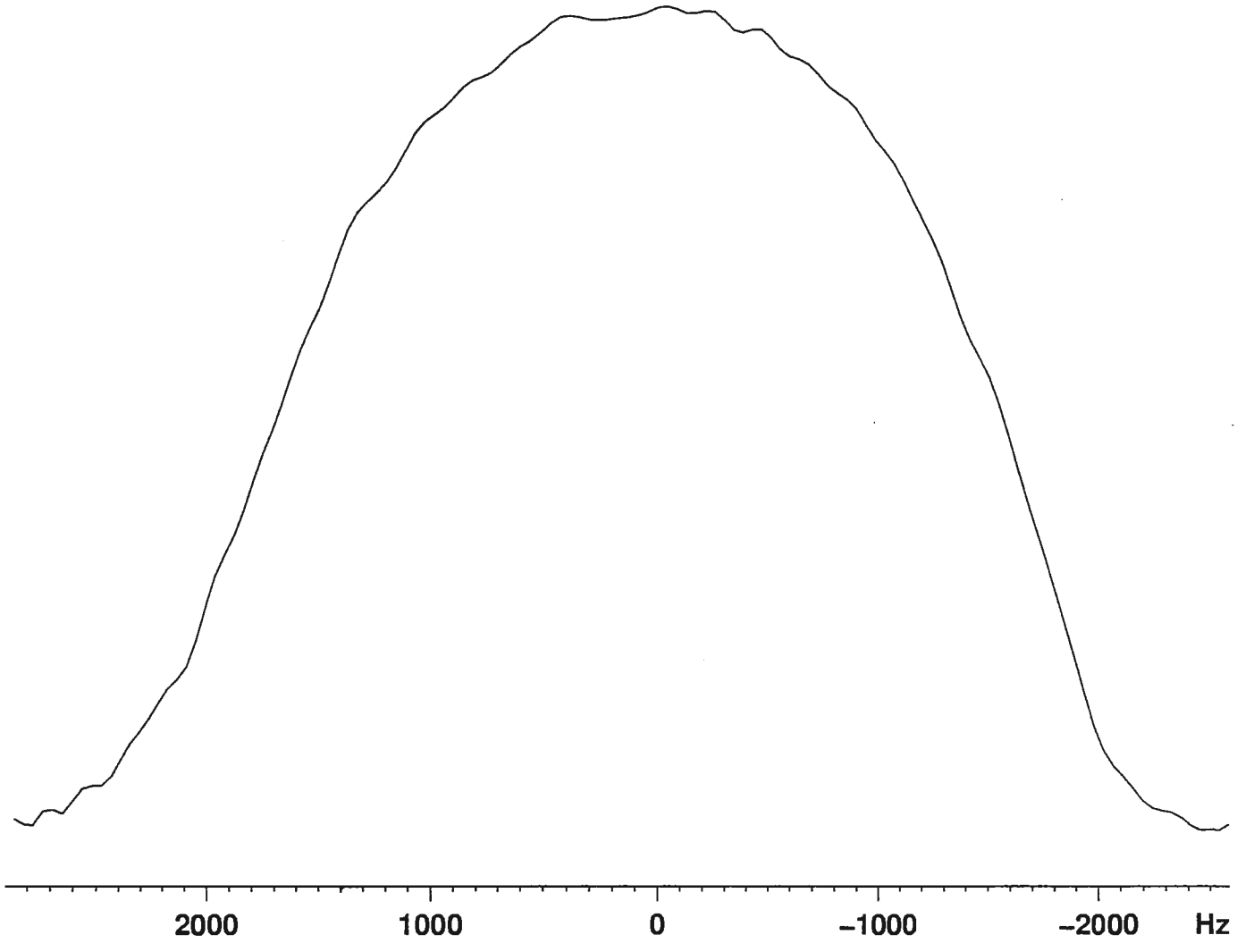

Figure 1: 1D Deuterium profile – QNP probehead

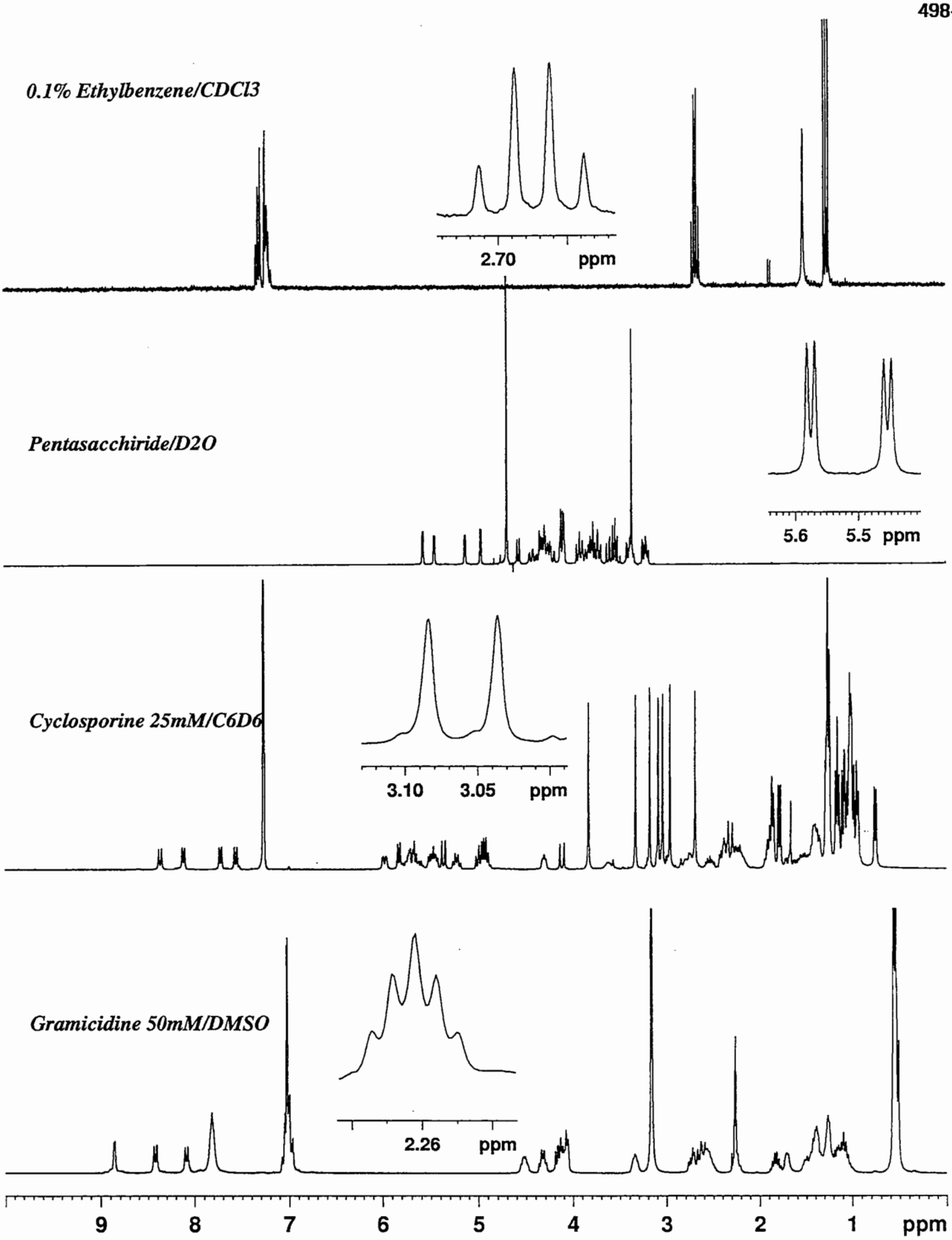

Figure 2: Deuterium Gradient Shimming in Automation.
Automation run simulation with 4 samples on AVANCE 300, 2 channels.
BBI Z gradients probehead, 1 scan, 1 iteration step.

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Rapid Analysis of Protein Structure Using Field Induced Orientation and NMR

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Protein Structure Modeling using Chemical Shifts and Residual Dipolar Coupling Homology

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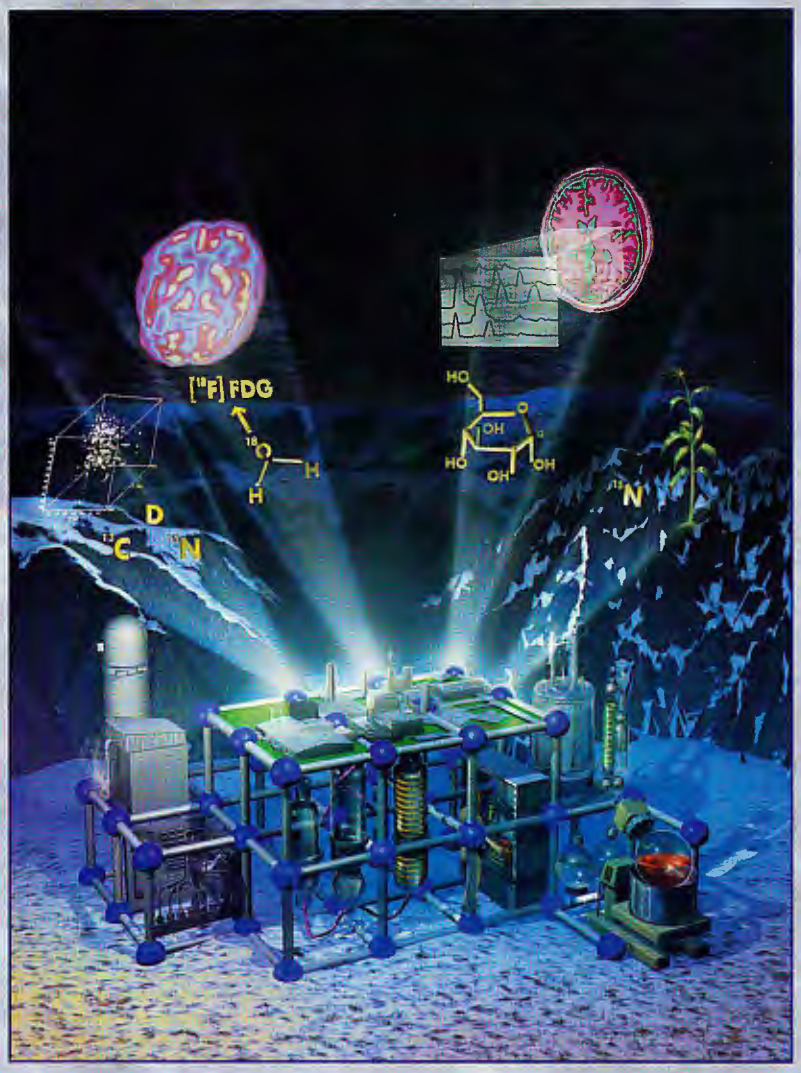

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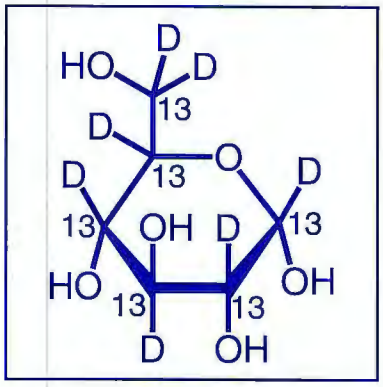

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The NMR Newsletter - Book Reviews

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

"NMR Techniques in Catalysis"

edited by

Alexis T. Bell and **Alexander Pines**

Marcel Dekker, Inc. .New York, Vol. 55 of the Chemical Industries Series, 1994;
ISBN 0-8247-9173-8; $199.00 (hardcover); available at http://www.dekker.com

This book is devoted entirely to applications of NMR to investigations of the various aspects of heterogeneous catalysis. It consists of a Preface and an Introduction written by the editors, followed by seven chapters over 407 pages, each chapter citing, on average, about 140 references, and then ends with a 14 page subject index.

Chapter 1 (Fyfe, Mueller, and Kokotailo) exploits the use of multinuclear NMR to characterize zeolites and related materials. A brief introduction of the various kinds of zeolites is presented, focusing on the differences of their lattice structures. The methodology for determination of the Si/Al ratio using ^{29}Si MAS NMR is delineated. Inasmuch as ^{27}Al spectra reflect the coordination state of aluminum, NMR is ideal to follow the several steps in the dealumination process of zeolites. For highly siliceous zeolites, ^{29}Si MAS NMR reveals that their framework is sensitive to adsorbates. Also, ^{29}Si MAS may be used to follow temperature-induced phase transformation in ZSM-5 and ZSM-39. ^{29}Si,^{29}Si–COSY may be used to establish the connectivities among the T-sites in zeolites. The authors compare ^{29}Si,^{29}Si-COSY and INADEQUATE experiments, highlighting advantages of the latter, due to the cleaner connectivities among T sites. ^{31}P NMR is presented as a tool for the characterization of VPI-5, and one may resort to ^{17}O DAS NMR to confirm the single Si-^{17}O-Si environment of cristobalite (SiO_2). At the end, it is shown that CP may be carried out between ^{31}P and ^{27}Al, and is pointed out that CP *from* quadrupolar *to* spin-1/2 nuclei is an important experimental feature because it shortens the total acquisition time.

Chapter 2 (Kärger and Pfeifer) deals with the diffusion aspects of the catalytic phenomena. Methodologies for the determination of intracrystalline diffusion are presented, such as tracer exchange, spin counting and ^{129}Xe NMR. The relevant diffusion theory is presented in a considerable part of this chapter. The text also discusses how PFG-NMR examines the problem of barriers to the diffusion process. PFG-NMR may also be employed to determine long-range diffusivity for cases where the crystallite diameter is smaller than the r.m.s. displacement observed by NMR.

Chapter 3 (Haw) addresses the experimental setup and results of *in situ* NMR. A design of a flow probe is presented, and the feasibility of executing *in situ* experiments using a regular RT or VT MAS probe is scrutinized. The CAVERN apparatus is described for sample preparation and. several studies have used this method, such as in olefin oligomerization and hydrocarbon cracking. The chapter also focuses on the use of ^{13}C chemical shifts of adsorbed species to measure catalyst acidity. The formation of cyclopentenyl cation during the cracking of an olefin over H-ZSM-5 is thoroughly discussed, in the light of the VT ^{13}C MAS results. ^{13}C MAS may indeed unravel intermediate species, such as those in the reaction of $^{13}CH_3I$ over the zeolite CsX. The chapter points outseveral ways to proceed in this area, among them carrying out *in situ* experiments at higher pressures in order to mimic actual reaction conditions, and execute flow studies under MAS conditions.

continued

Chapter 4 (Eckert) introduces the application of multinuclear NMR for the characterization of bulk oxide catalysts. ^{51}V static NMR has been used somewhat for the inspection of several oxides, since it reflects vanadium's unique environments, as well in the study of mixed catalysts. The characterization of aluminas is also discussed. ^{1}H, ^{13}C, ^{15}N, and ^{31}P NMR have been used to differentiate Bronsted from Lewis sites on γ-alumina (N_2O is argued to be a better alternative to quantify Lewis sites, using ^{15}N CP-MAS). The chapter moves into the use of both ^{29}Si and ^{27}Al NMR for the characterization of silica-aluminas. ^{27}Al is also mentioned for the characterization of HDN and HDS catalysts, which consist of Ni-Mo/γ-alumina, with P as a promoter.

Whereas chapter 4's focus is on the bulk of catalysts, chapter 5 (Maciel and Ellis) deals with the characterization of the surfaces of silica and alumina. Chapter 5 concentrates on the discrimination of nuclei at the surface from those in the bulk. Among the techniques to differentiate surface nuclei from nuclei in the bulk, $^{1}H \rightarrow ^{29}Si$ CP-MAS has been used on silicas. Results highlight the difference of ^{29}Si spectrum of hydrated silica with respect to the dehydrated one, and how silylation may be used to immobilize specific moieties at surfaces. The quantitation aspects of the $^{1}H \rightarrow ^{27}Al$ CP experiments are also investigated. The study of alumina surfaces via ^{1}H CRAMPS is also presented and the authors discuss the effects of the quadrupolar interaction of ^{27}Al on the multiple-pulse narrowing and MAS.

Chapter 6 (Haddix and Narayana) reviews the literature of the 1980s and early '90s regarding the application of NMR to layered materials, such as clays, aluminophosphates and derivatives, and metal sulfides. Among other things, the authors cite the difficulty of using ^{27}Al MAS in clays to determine, quantitatively, the Al_t/Al_o ratios. Also, ^{29}Si MAS has been extensively used to obtain detailed morphology of clays. ^{29}Si and ^{27}Al have been employed to study pillared clays.

In the last chapter (Kolodziejski and Klinowski), a forecast of the new NMR techniques for the study of catalysis is presented. Promising results with spin diffusion and rotational resonance are also discussed. MQ NMR may be used to characterize homonuclear spin clusters. New techniques for the investigation of quadrupolar nuclei are mentioned, involving ^{2}H NMR, nutation, DAS and DOR. The authors mention ^{129}Xe and force detection of MR to study surfaces, extending into imaging applications.

The chapters in "NMR Techniques in Catalysis" were written by very prominent researchers in the field of heterogeneous catalysis and cover all facets of this extremely important field, including from the industrial standpoint. The book is not a snapshot of the state-of-the-art NMR in 1994; rather it surpasses its inherent chronology, to set up the rationale for the design and the development of new NMR techniques for probing any catalytic reaction. It is doubtlessly still an invaluable source of information for chemists and chemical engineers.

Carlos R. N. Pacheco, Ph.D*
Department of Chemistry
Princeton University
Princeton, NJ 08544-1009
cpacheco@Princeton.edu

*Dear Barry: It is my great pleasure to introduce Carlos Pacheco, our new colleague at Princeton University. Carlos, a graduate from the group of Prof. Daniel Traficante, came to us from PETROBRAS Research and Development Center in Rio de Janeiro, Brazil.

István

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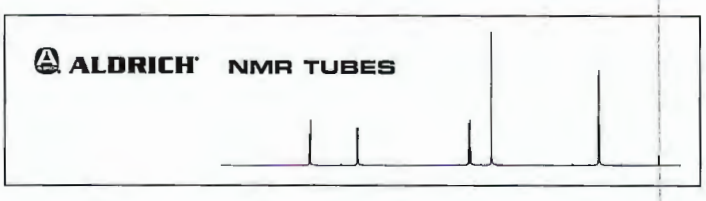

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Disposable	7	—	—	**Z41,277-5**	$12.40	—
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Series 400	7	0.0010	0.0005	**Z41,284-8**	61.20	977.60
	8	0.0010	0.0006	**Z41,285-6**	67.20	1,074.80
Series 500	7	0.0005	0.00025	**Z41,286-4**	86.90	1,389.50
	8	0.0005	0.00035	**Z41,287-2**	97.20	1,553.60
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February 25, 2000
(received 2/25/2000)

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

Early Days of NMR in the Southwest:
Sixth (and Final) Installment

Dear Barry,

As I mentioned previously, the petroleum industry in Texas quickly perceived the potential of NMR to solve practical problems. In the fourth installment of this history, I related the very early NMR research at Texaco in Houston with roots that extended to Felix Bloch himself. Houston was (and still is) the hub of the petroleum industry in Texas, and I start this installment with another early NMR project in Houston.

HUMBLE/EXXON IN HOUSTON

Humble (Humble Oil and Refining Company, a company owned by ESSO which later became EXXON) was an active participant in Varian's early NMR activities. Even before NMR was born, Russell Varian joined Humble in Houston in 1929 as a research scientist to improve the design of a vibrating magnetometer for oil exploration. He successfully completed this work and patented it. In January, 1930 he left Humble (dismissed by the laboratory manager) and returned to the San Francisco Bay area. It is amusing to speculate that this brief contact with oil exploration might have inspired him, in the late 1940's, to suggest the use of proton free precession in the earth's magnetic field for well logging in oil exploration (see the second installment of this history).

Later, scientists in the Analytical Section of Baytown R and D (part of Humble), located near Houston, were interested in exploring analytical applications of NMR. In early 1952, Rollie Williams ordered their first NMR instrument, the Varian 30 MHz high resolution NMR spectrometer, designed by Jim Shoolery. While awaiting delivery, Williams and a technician, R. K. Saunders, actually built a low resolution machine to get a feel for the capabilities this new tool. The machine then arrived and Shoolery installed it in September, 1952. They also obtained a low resolution accessory for elemental analysis of H and other elements such as F, P, Na, and whatever else they could measure.

This Varian NMR spectrometer was the first commercial high resolution unit. Although it was very crude by today's standard, they were still able to accomplish their objectives in (a) characterizing petroleum fractions for structural features, in (b) proving molecular structures in synthesis work by some of the division researchers, in (c) identifying contaminants in waste waters, in (d) learning the composition of additives in competitors' products, and in many other similar

applications.

When better high resolution instrumentation became available they always upgraded, first to 60 MHz, then to 100 MHz Varian spectrometers, and so on to today's several hundred MHz units with superconducting magnets. The newer instruments featured improved resolution and magnet stability so that they could do a better job. To do an even better job, Humble researchers themselves improved various aspects of their commercial instrumentation, such as field stabilization and magnet shimming; but in the end, Varian always came up with something better. They were the first to use electronic integration for measuring high resolution peak areas; this became standard on Varian machines. Humble also built spectrometers for electron spin resonance (ESR). These were used in measuring ESR signals of heavy petroleum fractions and in trying to understand what they represented.

In the beginning, Williams and Saunders worked alone. Later, other professionals, such as Ferd Stehling, Lowell Westerman, and Ken Bartz, worked with them for short periods of time. Nugent Chamberlain joined the group sometime in the mid 1950's and concentrated on high resolution NMR while Williams was busy with ESR. Chamberlain became leader of the group when Williams became Section Head about 1960. Other professionals worked in the group later on.

In those early days there was widespread interest in analytical applications of NMR and Williams made invited presentations at universities and at a number of professional society meetings. These included an American Chemical Society speaking tour, talks at Gordon Research Conferences, Bureau of Mines seminars in Wyoming, Institute of Petroleum conferences in London, a New York Academy of Sciences symposium, Analytical Symposia at LSU, ASTM meetings, and many more. Later on, Chamberlain was also an active speaker.

Elsewhere in Houston, Humble scientists were involved in evaluating Schlumberger's early NMR well logging efforts. They also had a low-key (i.e., technology monitoring) effort on the effects of porosity on the NMR of liquids in rocks.

RICE UNIVERSITY

Charles F. Squire received a Ph.D. in chemistry from The Johns Hopkins University in 1940 and was in the Rice physics department from about 1947 until 1960, when he left Rice to become Director of Research at United Technologies in Connecticut. Squire initiated NMR research at Rice around 1952-1954 and then administered it. NMR has been going on at Rice ever since that time. The Varian twelve-inch magnet and power supply (and probably also the console) from the discontinued Texaco NMR well logging project (see the fourth installment) was loaned to Rice for Squire's use. His early work was in low temperature physics, on systems such as solid hydrogen and simple crystals. In 1962, Squire went to Texas A&M University and stayed there until 1969.

After Squire left Rice in 1960, the Texaco magnet with power supply was purchased by Texas A & M university for Melvin Eisner's use. Soon afterwards, Harold Rorschach of the Rice physics department started research on liquid ^{3}He and ^{3}He - ^{4}He mixtures and, in 1963, was the only person in the deparatment doing NMR. He used a home made NMR spectrometer with a twelve-inch electromagnet operating at a proton NMR frequency of 30.3 MHz. In the spring of 1970 his student, Donald Chang, completed his Ph.D. thesis research on diffusion of ^{3}He in ^{3}He - ^{4}He solutions at 4°K. Around this time, Carlton Hazlewood of the Baylor University College of Medicine in Houston met with Rorschach and Chang (more about this in the next section). Chang then accepted a postdoctoral appointment from Hazlewood to perform biophysical NMR research.

continued on p.31

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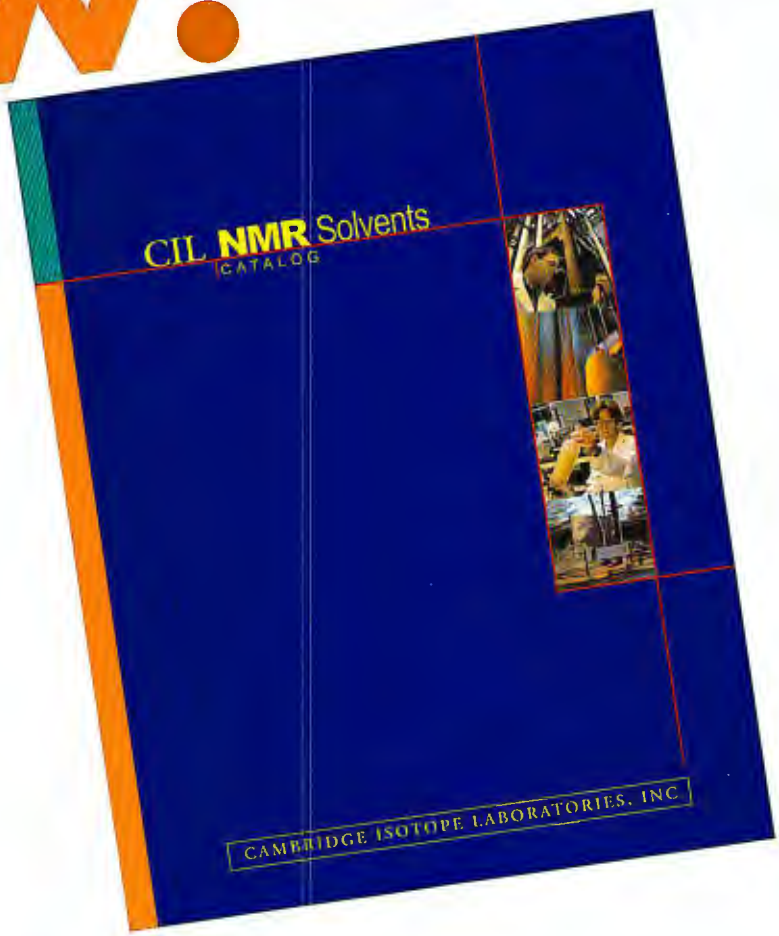

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continued from p.28

A few years later, Rorschach also extended his interests into NMR biophysics research and collaborated with Hazlewood in NMR diffusion measurements in biological tissue. This collaboration subsequently (1984-1985) branched out to include quasi-elastic neutron scattering (QNS) studies to obtain "obstruction free" measurements of water diffusion . QNS experiments were important in determining whether the lowered diffusion coefficient of water in tissue is caused by obstruction of motion by the presence of biomacromolecules or by an intrinsic, long-range effect on water characteristics caused by macromolecular interfaces.

Elsewhere at Rice, sometime between 1961 (when the Varian A-60 was introduced) and 1964 (when Ronald Magid arrived) the chemistry department had purchased a Varian A-60 and a Varian A-56/60. Later, Otto Gansow operated a higher field Fourier Transform instrument. In 1975 he collaborated with Hazlewood and Chang in a FT NMR study of ^{23}Na spectra from skeletal muscle of immature and mature rats.

BAYLOR UNIVERSITY COLLEGE OF MEDICINE

Much of the early biomedical NMR in the southwest involved collaboration between Hazlewood and researchers at several different locations. In the spring of 1962, Hazlewood received his Ph.D. in physiology from the University of Tennessee in Memphis (Progressive Muscle Electrolyte Changes in Normal and Dystrophic Mice). He then went to The Johns Hopkins University School of Medicine and studied the electrolyte changes in the postnatal development of rat skeletal muscle. On July 1, 1964 he joined the Department of Pediatrics at the Baylor College of Medicine in Houston and continued his studies on the distribution of electrolytes in developing rat skeletal muscle. By 1967 he perceived a "need to know" the physiological states of water and electrolytes in skeletal muscle in order to test several different views on intracellular function.

Hazlewood's first learned about NMR from an article by Freeman Cope on NMR studies of Na^+ in rat tissue that appeared in the May, 1967 issue of ***The Journal of General Physiology***. In the summer, he attended a workshop on classical proton high resolution NMR analysis of organic liquids that was given by Robert Willcott of the University of Houston. At the workshop he asked people about ^{23}Na NMR, but he encountered disinterest because it was "known" that NMR could not be used for studying biological tissue. However, Chamberlain, one of the speakers, expressed interest in his biological problem and, after the meeting, they continued their discussion of it. Then, about August, Hazlewood shifted his ideas from using ^{23}Na NMR to study sodium in biological tissue to using proton NMR to study the water in tissue. After much discussion concerning the difficulties of obtaining meaningful results from biological tissue, Chamberlain agreed to measure the proton NMR spectrum of rat muscle on his Varian A-60 and obtained Humble's clearance to do so. In September the first spectrum was obtained. It was a beautiful but somewhat broadened singlet that they included in a paper that was later (December, 1968) submitted to ***Nature***. This observation spurred them to discuss possible mechanisms for line broadening and Hazlewood's experiments became directed towards determining the reason for their observations.

However, access to the Humble spectrometer was limited and was insufficient for Hazlewood's needs. In early 1968 he learned about Paul Srere at the Veteran's Administration Hospital in Dallas. Srere was very busy at the time and, since his Varian A-60 was not in heavy use, he allowed Hazlewood liberal access to it. Use of this instrument enabled him to determine that most of the possible reasons for line broadening that Chamberlain had mentioned were not operative. He also made a trip to Argonne National Laboratory to use Stephen Danyluk's spectrometer. These spectra were useful and were also included in the paper that he and Chamberlain submitted to ***Nature*** in December, 1968 and was published in 1969. In this paper, the

spectra showing the broadening of the water NMR line in tissue were presented as evidence for the existence of at least two phases of ordered water in skeletal muscle.

About that time, Hazlewood met Robert Curl of the Rice chemistry department. Curl was in charge of the NMR spectrometers that the students used and allowed him rather liberal access to them The graduate student who was in direct charge of the instruments was very helpful. Mack Harvey of Shell Oil Company in Houston also provided instrument time on a Varian T-60 NMR spectrometer. Collaborations with Chamberlain, Harvey, Curl, and Terry Swift allowed Hazlewood to carry out a temperature dependence study. Chamberlain also provided sufficient instrument time for him to complete a study that demonstrated a difference in the NMR line widths of water in normal and dystrophic muscle.

Soon afterwards, Hazlewood embarked upon different types of NMR measurements. At the 11th Experimental NMR Conference (ENC) held in Pittsburgh, PA, on April 22 - 24, 1970, Ted Becker (National Institutes of Health) chaired a session on "Structured Water in Biological Systems" that dealt with NMR experiments that were relevant to Hazlewood's research. The topic of the session was "hot" at that time; articles on the characteristics of cell water were being published in many different scientific journals and professional magazines. Interest was widespread, geographically; the speakers at the ENC were from various locations and had different perspectives: Freeman Cope (Aerospace Medical Research Laboratory, Warminster, PA), Chamberlain (Humble, Houston), Woessner (Mobil, Dallas), John Hansen (Procter and Gamble, Cincinnati), and Ronald Dehl (National Bureau of Standards). Several of the talks emphasized pulse NMR methods, but continuous wave NMR spectroscopy and other physical techniques were adequately represented. The presentations were summarized in an article in ***Chemical and Engineering News*** (June 1, 1970, pages 48 - 49).

After the ENC, Chamberlain discussed the papers with Hazlewood and convinced him to switch from measuring proton spectra to determining relaxation times. At the suggestion of G. King Walters of the physics department of Rice, Hazlewood met with Rorschach and his graduate student Donald Chang, as mentioned above. Chang became a postdoctoral student of Hazlewood and modified the Rice home made spectrometer. They then conducted their first studies of T_1, T_2, and D of water in rat skeletal muscle. Around this time, Hazlewood visited me in Dallas and invited me to present a paper at the upcoming New York Academy of Sciences (NYAS) meeting on the "physicochemical state of ions and water in living tissues and model systems" (January 10 - 12, 1972).

The invitations to present the papers at the ENC and the NYAS conference stemmed from my collaboration with Brinkley Snowden in projects on using aqueous biopolymer solutions for enhanced oil recovery. Dilute solutions of Kelzan (xanthan gum) were being used in water flooding experiments to force petroleum to flow through the smaller pores of oil-bearing rocks so as to enhance oil production. We observed nonlinear increases in deuteron $1/T_2$ values with xanthan concentration when the concentration was increased above a threshold value while the $1/T_1$ values continued to change linearly. To get a benchmark to help determine whether a phase transition might be involved, we decided to measure the temperature dependence of water relaxation in agar systems which exhibit sol-gel and gel-sol transitions (in viscosity measurements) as the temperature is adjusted. There is a temperature hysteresis of this transition, just as there is a temperature hysteresis in the order-disorder lambda transition in the temperature dependence of the heat capacity of ammonium chloride. In the case of aqueous agar systems, the temperature of the sol-gel transition is about 38 °C (decreasing temperature), which is close to the temperature of the human body. The transition of the proton T_2 value is sudden; over a very small temperature range the

proton T_2 suddenly decreases by a factor of about 20. The topic of my presentation at the ENC was these experiments and our interpretation.

Snowden was intrigued by the closeness of the temperatures of the agar sol-gel transition and of the human body and thought that both of them might be due to a structural transition in water, the common component. He convinced me that such a transition could be important both in biology and in the behavior of water in oil exploration and production. To search for such a transition, we did NMR relaxation experiments to detect a transition in the behavior of water at this temperature and to detect a change in slope in the relaxation behavior as a function of concentration of various inorganic salts in water. Also, in further measurements on deuteron transverse relaxation in samples containing up to 20% xanthan, we observed residual quadrupole splitting of the deuteron resonance which indicated that the xanthan macromolecules were organized into spatial domains of nonrandom ordering. This was the topic of our paper at the NYAS conference.

After this conference, Hazlewood visited me in Dallas and invited me to collaborate in pulse NMR experiments on rat skeletal muscle. I obtained Mobil's clearance to carry out short-term, well-focused NMR measurements that did not interfere with my company responsibilities. This commenced my decade-long collaboration with Chang and Hazlewood and Hazlewood's students involving ^{1}H and ^{23}Na pulse NMR measurements on the rat gastrocnemius muscle.

UT SOUTHWESTERN MEDICAL CENTER AT DALLAS/V A HOSPITAL

Paul Srere started NMR research at the Veteran's Administration Hospital in Dallas (VA) after his arrival in July, 1966 from the Lawrence Livermore Laboratory. At Livermore, he had worked with Raymond Ward and James Happe, using a home made instrument. He had also carried out experiments with (a) Morales of the University of California in San Francisco on ^{15}N NMR to determine whether the metal ions that chelate with adenosine triphosphate (ATP) bind at the ring nitrogen and with (b) Melvin Klein of Berkeley to study exchange involving glucagon (an enzyme found in the pancreas). Srere was interested in diabetes and in using NMR to study enzyme reactions at the VA. Soon after arriving in Dallas he ordered a Varian A-60 spectrometer with a Computer of Average Transients (CAT). The CAT was needed to enhance the signal-to-noise ratio of weak spectra such as those expected when studying the effect of binding on ^{15}N NMR. The machine was delivered in 1967.

Gene L. (Larry) Cottam of the department of biochemistry of the University of Texas Southwestern Medical Center at Dallas (UTSW) talked with Srere about studying small polypeptides at low concentration to obtain the structures by NMR. The structural determination of glucagon, as revealed by the nonexchanging protons, was already done, but further structural refinement was elusive because higher sensitivity and higher resolution was needed. Unfortunately, funds were not available for a higher field instrument. Nevertheless, Cottam started working with Srere in February, 1967.

Srere was discouraged in his NMR research because the spectrometer turned out to be inadequate for his needs. The A-60, therefore, was idle much of the time so that it was available in 1968 for Hazlewood's experiments on water in biological tissue. About this time, Srere got out of NMR research and then returned to it many years later.

Cottam's interests were somewhat different from Srere's. Mildred Cohn's 1964 observation that metal ions bound to proteins can change the NMR relaxation times of the water got Cottam interested in the relaxation effects of bound metal ions. Also, attendance at a small Gordon

Research Conference on magnetic resonance related to biology and biochemistry, attended by people such as W. D. Phillips, Terry Swift, Robert Shulman, and Kurt Wüthrich, excited his interest in intra- versus extra-cellular water in tissue. He also became interested in the broadening of the water proton NMR line in tissue and decided to study the phenomenon by measuring relaxation times instead of spectra.

Cottam took over Srere's instrument for a while, but he soon purchased (in 1969 or 1970) an NMR Specialties PS 60AW pulsed NMR spectrometer that operated at 24.3 MHz Later, he acquired another magnet that operated at 28 MHz with six-inch pole faces and a wide gap (2½ - 3 inches) for measurements on large samples. Throughout the 1970's, and into the 1980's, this instrument was heavily used to measure the longitudinal and transverse water proton relaxation rates for a variety of research projects. The T_1 values were determined from 180° - 90° pulse sequences and the null point of Carr and Purcell, and the T_2 values were determined from the echo envelope of a Carr-Purcell pulse sequence.

After the 1971 publication by Raymond Damadian on tumor detection by NMR, Cottam and coworkers published a paper (1972) on water proton relaxation rates in various tissues. They explored the measurement of relaxation times in both normal and human tumor tissues as a diagnostic technique to distinguish between benign and malignant tissue.

In another project, Cottam found that transitions between soluble oxyhemoglobin S and polymeric oxyhemoglobin S cause changes in the water proton transverse relaxation and that the transition could be directly and continuously monitored by proton T_2 measurements. This allowed the study of polymerization kinetics and the effects of various parameters on polymerization in solution and, more importantly, in intact red blood cells. These parameters include pH, temperature, hemoglobin concentration, presence of other non-sickling hemoglobins, and the presence of anti-sickling compounds.

Other experiments involved the shortening of water proton relaxation times by paramagnetic ions. For example, water proton relaxation rate measurements were used to determine both the number of metal ion binding sites and the dissociation constant (Kd) for those sites on purified enzymes (e.g., liver and muscle pyruvate kinase, phosphofructokinase, alkaline phosphatase, and concanavalin A) that required metal ions for activity by using the paramagnetic metal ion manganese and some of the paramagnetic rare earth ions. These magnetic resonance techniques were used to analyze formation of both binary (enzyme-metal ion complexes) and ternary (enzyme-metal-substrate) complexes. ESR measurements were also used in titration experiments and graphically analyzed with Scatchard plots to determine the concentration of "free" manganese which was not "bound" to the protein molecule.

This concludes my narrative of the early days of NMR in the southwest. I welcome any corrections, additions, suggestions, and comments the readers of this newsletter may have.

Sincerely,

Don

Donald E. Woessner
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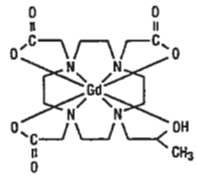

Each mL of ProHance contains 279.3 mg gadoteridol, 0.23 mg calteridol calcium, 1.21 mg tromethamine and water for injection. ProHance contains no antimicrobial preservative.

ProHance has a pH of 6.5 to 8.0. Pertinent physicochemical data are noted below:

PARAMETER		
Osmolality (mOsmol/kg water)		
	@ 37° C	630
Viscosity		
(cP)	@ 20° C	2.0
	@ 37° C	1.3
Specific Gravity		
	@ 25° C	1.140
Density		
	(g/mL) @ 25° C	1.137
Octanol: H_2O coefficient		–3.68 ± 0.02

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CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of intravenously administered gadoteridol in normal subjects conforms to a two-compartment open model with mean distribution and elimination half-lives (reported as mean ± SD) of about 0.20 ± 0.04 hours and 1.57 ± 0.08 hours, respectively.

Gadoteridol is eliminated in the urine with 94.4 ± 4.8% (mean ± SD) of the dose excreted within 24 hours postinjection. It is unknown if biotransformation or decomposition of gadoteridol occur *in vivo*.

The renal and plasma clearance rates (1.41 ± 0.33 mL/min/kg and 1.50 ± 0.35 mL/min/kg, respectively) of gadoteridol are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys and that the drug is essentially cleared through the kidney. The volume of distribution (204 ± 58 mL/kg) is equal to that of extracellular water, and clearance is similar to that of substances which are subject to glomerular filtration.

It is unknown if protein binding of ProHance occurs *in vivo*.

Pharmacodynamics

Gadoteridol is a paramagnetic agent and, as such, develops a magnetic movement when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

In magnetic resonance imaging (MRI), visualization of normal and pathologic brain tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadoteridol decreases T1 relaxation times in the target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

Gadoteridol does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier, e.g., cysts, mature post-operative scars, etc. However, disruption of the blood-brain barrier or abnormal vascularity allows accumulation of gadoteridol in lesions such as neoplasms, abscesses, and subacute infarcts. The pharmacokinetics of ProHance in various lesions is not known.

CLINICAL TRIALS

ProHance was evaluated in two blinded read trials in a total of 133 adults who had an indication for head and neck extracranial or extraspinal magnetic resonance imaging. These 133 adults (74 men, 59 women) had a mean age of 53 with a range of 19 to 76 years. Of these patients, 85% were Caucasian, 13% Black, 2% Asian, and < 1% other. The results of the non-contrast and gadoteridol MRI scans were compared. In this database, approximately 75–82% of the scans were enhanced. 45–48% of the scans provided additional diagnostic information, and 8–25% of the diagnoses were changed. The relevance of the findings to disease sensitivity and specificity has not been fully evaluated.

ProHance was evaluated in a multicenter clinical trial of 103 children who had an indication for a brain or spine MRI. These 103 children, (54 boys and 49 girls) had a mean age of 8.7 years with an age range of 2 to 20 years. Of these 103 children, 54 were between 2 and 12 years of age. Also, of these 103 children, 74% were Caucasian, 11% Black, 12% Hispanic, 2% Asian, and 2% other. The results of the non-contrast and gadoteridol MRI scans were compared. ProHance was given in one single 0.1 mmol/kg dose. Repeat dosing was not studied. In this database, MRI enhancement was noted in approximately 60% of the scans and additional diagnostic information in 30–95% of the scans.

INDICATIONS AND USAGE

Central Nervous System

ProHance (Gadoteridol Injection) is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues.

Extracranial/Extraspinal Tissues

ProHance is indicated for use in MRI in adults to visualize lesions in the head and neck.

CONTRAINDICATIONS

None known.

WARNINGS

Deoxygenated sickle erythrocytes have been shown in*in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by ProHance may possibly potentiate sickle erythrocyte alignment. ProHance in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of ProHance to exclude the possibility of increased hemolysis.

Patients with a history of allergy, drug reactions or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration. (See **PRECAUTIONS—General**).

PRECAUTIONS

General

Gadoteridol is cleared from the body by glomerular filtration. The hepato-biliary enteric pathway of excretion has not been demonstrated with ProHance®. Dose adjustments in renal or hepatic impairment have not been studied. Therefore, caution should be exercised in patients with either renal or hepatic impairment.

In a patient with a history of grand mal seizure, the possibility to induce such a seizure by ProHance® is unknown.

The possibility of a reaction, including serious, life threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic reactions (see **ADVERSE REACTIONS**), should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders.

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

When ProHance (Gadoteridol Injection) is to be injected using nondisposable equipment, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. After ProHance is drawn into a syringe, the solution should be used immediately.

Repeat Procedures: Repeated procedures have not been studied. Sequential use during the same diagnostic session has only been studied in central nervous system use. (See **Pharma-cokinetics** under **CLINICAL PHARMACOLOGY** and **Central Nervous System** under **DOSAGE AND ADMINISTRATION**).

Information for patients:

Patients scheduled to receive ProHance should be instructed to inform their physician if the patient;

1. is pregnant or breast feeding
2. has anemia or diseases that affect the red blood cells
3. has a history of renal or hepatic disease, seizure, hemoglobinopathies, asthma or allergic respiratory diseases.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadoteridol or potential effects on fertility.

ProHance did not demonstrate genotoxic activity in bacterial reverse mutation assays using *Salmonella typhimurium* and *Escherichia coli*, in a mouse lymphoma forward mutation assay, in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in Chinese hamster ovary cells, nor in an *in vivo* mouse micronucleus assay at intravenous doses up to 5.0 mmol/kg.

Pregnancy Category C

ProHance administered to rats at 10 mmol/kg/day (33 times the maximum recommended human dose of 0.3 mmol/kg or 6 times the human dose based on a

mmol/m^2 comparison) for 12 days during gestation doubled the incidence of postimplantation loss. When rats were administered 6.0 or 10.0 mmol/ kg/day for 12 days, an increase in spontaneous locomotor activity was observed in the offspring. ProHance increased the incidence of spontaneous abortion and early delivery in rabbits administered 6 mmol/kg/day (20 times the maximum recommended human dose or 7 times the human dose based on a mmol/m^2 comparison) for 13 days during gestation.

There are no adequate and well-controlled studies in pregnant women. ProHance (Gadoteridol Injection) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ProHance is administered to a nursing woman.

Pediatric Use

Safety and efficacy in children under the age of 2 years have not been established. The safety and efficacy of doses > 0.1 mmol/kg; and sequential and/or repeat procedures has not been studied in children. (See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections)

ADVERSE REACTIONS

The adverse events described in this section were observed in clinical trials involving 1251 patients (670 males and 581 females). Adult patients ranged in age from 18–91 yrs. Pediatric patients ranged from 2–17 years. The racial breakdown was 83% Caucasian, 8% Black, 3% Hispanic, 2% Asian, and 1% other. In 2% of the patients, race was not reported.

The most commonly noted adverse experiences were nausea and taste perversion with an incidence of 1.4%. These events were mild to moderate in severity.

The following additional adverse events occurred in fewer than 1% of the patients:

Body as a Whole:	Facial Edema; Neck Rigidity; Pain; Pain at Injection Site; Injection Site Reaction; Chest Pain; Headache; Fever; Itching; Watery Eyes; Abdom-inal Cramps; Tingling Sensation in Throat; Laryngismus; Flushed Feel-ing; Vasovagal Reaction; Anaphylac-toid Reactions (characterized by cardiovascular, respiratory and cutaneous symptoms)
Cardiovascular:	Prolonged P-R Interval; Hypotension; Elevated Heart Rate; A-V Nodal Rhythm
Digestive:	Edematous and/or itching tongue; Gingivitis; Dry Mouth; Loose Bowel; Vomiting
Nervous System:	Anxiety; Dizziness; Paresthesia; Mental Status Decline; Loss of Coor-dination in Arm; Staring Episode; Seizure; Syncope
Respiratory System:	Dyspnea; Rhinitis; Cough
Skin and Appendages:	Pruritus; Rash; Rash Macular Papular; Urticaria; Hives; Tingling Sensation of Extremity and Digits
Special Senses:	Tinnitus

OVERDOSAGE

Clinical consequences of overdose with ProHance have not been reported.

DOSAGE AND ADMINISTRATION

Central Nervous System

ADULTS: The recommended dose of ProHance (Gadoteridol Injection) is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min–60 mL/min) or bolus (> 60 mL/min). In patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose.

CHILDREN (2–18 years): The recommended dose of ProHance® is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min). The safety and efficacy of doses > 0.1 mmol/kg, and sequential and/or repeat procedures has not been studied.

Extracranial/Extraspinal Tissues

ADULTS: The recommended dose of ProHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min–60 mL/min) or bolus (> 60 mL/min).

CHILDREN: Safety and efficacy for extracranial/extraspinal tissues has not been established.

Dose adjustments in renal and liver impairment have not been studied.

To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL normal saline flush. The imaging procedure should be completed within 1 hour of the first injection of ProHance (Gadoteridol Injection).

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present. Any unused portion must be discarded in accordance with regulations dealing with the disposal of such materials.

HOW SUPPLIED

ProHance (Gadoteridol Injection) is a clear, colorless to slightly yellow solution containing 279.3 mg/mL of gadoteridol in rubber stoppered vials. ProHance is available in boxes of:

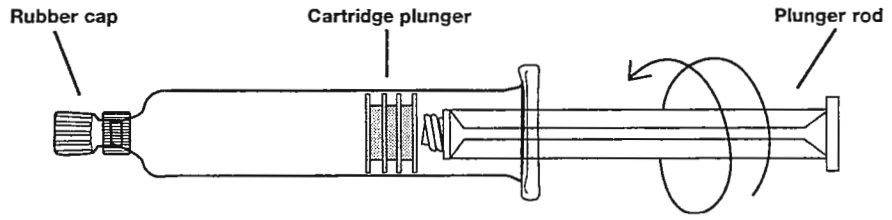
Five 5 mL fills in single dose 15 mL vials	(NDC 0270-1111-04)
Five 10 mL fills in single dose 30 mL vials	(NDC 0270-1111-01)
Five 15 mL fills in single dose 30 mL vials	(NDC 0270-1111-02)
Five 20 mL fills in single dose 30 mL vials	(NDC 0270-1111-03)
Five 10 mL fills in single dose 20 mL prefilled syringes	(NDC 0270-1111-16)
Five 17 mL fills in single dose 20 mL prefilled syringes	(NDC 0270-1111-45)

STORAGE

ProHance (Gadoteridol Injection) should be stored at controlled room temperature, between 15° and 30° C (59°–86° F) and protected from light. DO NOT FREEZE. Should freezing occur in the vial, ProHance should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 60 minutes, ProHance (Gadoteridol Injection) should return to a clear, colorless to slightly yellow solution. Before use, examine the product to assure that all solids are redissolved and that the container and closure have not been damaged. Should solids persist, discard vial. Frozen syringes should be discarded.

Directions for Use of the
ProHance®(Gadoteridol Injection) *single dose syringe**

1) Screw the threaded tip of the plunger rod clockwise into the cartridge plunger and push forward a few millimeters to break any friction between the cartridge plunger and syringe barrel.



2) Holding syringe erect, aseptically remove the rubber cap from the tip of the syringe and attach either a sterile, disposable needle or tubing with a compatible luer lock using a push-twist action.
3) Hold the syringe erect and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filled. Following the usual aspiration procedure, complete the injection. To ensure complete delivery of the contrast medium, the injection should be followed by a normal saline flush.
4) Properly dispose of the syringe and any other materials used.

*The syringe assembly is a HYPAK SCF® single dose syringe supplied by Becton Dickinson.

This product is covered by US Patent Nos.: 4,885,363 and 4,963,344.

Manufactured for
Bracco Diagnostics Inc.
Princeton, N.J. 08543
by E.R. Squibb & Sons Inc.
New Brunswick, N.J. 08903

Positions Available

Director, Computational Biology and Bioinformatics

The University of Pittsburgh, School of Medicine is developing a new Program in Computational Biology and Bioinformatics that will both integrate the diverse activities in these areas that are ongoing across the University and build additional expertise and capacity in computational solutions to key biological questions. This Program builds on major new investments in genome sciences and structural biology across the six schools of the Health Sciences and takes advantage of strong collaborations between the School of Medicine and the Faculty of Arts and Sciences. The Pittsburgh Supercomputing Center is a key resource, in terms of both faculty and support services, for the Program.

Director, Program in Computational Biology and Bioinformatics: An accomplished professional is being sought for the position of Director, Program in Computational Biology/Bioinformatics. It is anticipated that this tenurable position will be filled at the Associate or Full Professor rank, with a primary appointment in the Department of Molecular Genetics and Biochemistry, or in one of the other basic science departments of the School of Medicine, as appropriate. The successful candidate will have a doctoral degree (M.D. or Ph.D.) with extensive training and experience in computational science and in biochemistry, genetics, structural biology, neuroscience, or related fields. Postdoctoral experience in computational methodologies applied to biological/biomedical problems is essential.

The Director is expected to build on existing resources to advance the establishment of the University as a center of excellence in computational biology and bioinformatics, working within the framework of the six schools of the Health Sciences (School of Medicine, School of Dental Medicine, Graduate School of Public Health, School of Pharmacy, School of Nursing, School of Health and Rehabilitation Sciences) but with outreach to other schools on the main campus of the University of Pittsburgh. In this context, computational biology is the application of computational methodologies in support of understanding complex biological systems; computational biology includes, but is not restricted to, aspects of genomics and proteomics; of combinatorial chemistry and biology; of functional imaging; of structural biology; of neurobiology. Bioinformatics is focused on both methodological development and methodological application for extraction and analysis of data from very large and complex data sets. The Director is expected to provide leadership for the Program by building on his/her own active research program to establish a nucleation point for research activities across the Schools of the Health Sciences in computational biology; to develop a broad research agenda for the Program that capitalizes on the extensive basic and clinical research programs at the University; to establish a reliable, state-of-the-art set of computational biology and bioinformatics "core services" in support of biomedical research, including but not restricted to molecular, genome, and protein database services. Establishment of graduate and postgraduate training programs in computational biology and bioinformatics will be a key aspect of the Program.

Additional Positions Available: Two additional tenure track positions in computational biology or bioinformatics will be available, with each recruitment expected to be at the assistant professor level with primary appointment in an appropriate basic science department. Specific recruitment for these positions will be deferred until a Director has been selected, but successful candidates will be expected to develop their individual research programs while contributing to the synergistic efforts of the comprehensive Program. Additionally, three staff positions will be made available to support the service component of the Program, as will be a secretary to support the Director and the overall Program.

Support: The Senior Vice Chancellor, Health Sciences has committed to providing initial support for three years for the establishment of the Program, including the additional positions noted above. Support for the program in years beyond that period will come from grants and fee-for-service activities, with necessary additional subsidies coming from the Senior Vice Chancellor. Thus, the Director will be expected to seek significant external funding to maintain and expand the research activities and the research personnel as the Program develops.

If you are interested in this position, please send your curriculum vitae, a brief statement of your research interests, the names and contact information for at least three references, and reprints of three selected papers to **Dr. Michelle S. Broido, Assistant Vice Chancellor for Research, Health Sciences, 3471 Fifth Avenue, Suite 201, Pittsburgh, PA 15213.** Nominations for this position are also welcome. All application/nomination material must be received by March 17, 2000. The University of Pittsburgh is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

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- **Dave Giffin**, VP & MRI Division Manager
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  for Cryofill scheduling
- **Kathleen Crisafulli**, Office & Accounts Manager
  Email Kathy@cryomag.com
  for accounts receivable, payable & insurance information

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Peg Kotun, Roche Carolina

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Positions Available

NIH POSTDOCTORAL POSITION AVAILABLE

A postdoctoral position is available for combined work in the Nuclear Magnetic Resonance Unit (Richard Spencer, Chief) and in the Laboratory of Clinical Investigation (Darrell Abernethy, Chief) of the National Institute on Aging of the National Institutes of Health, located in Baltimore, Maryland. The work will center on spectroscopic and imaging studies of cartilage tissue derived from tissue engineering protocols and from animal studies. Other research opportunities may be available depending on the interests and background of the successful candidate.
NMR instrumentation consists of a double-resonance Bruker ABX 1.9T/31 cm Biospec with shielded gradients, and a triple-resonance wide-bore Bruker DMX 400 Avance system with microimaging and solids capability.
A background in NMR spectroscopy or imaging of connective tissue is preferred, although applicants with expertise in cartilage biology who have the desire to learn NMR techniquesare also strongly encouraged to apply. We also invite applications from individuals with experience in other areas of biological NMR. The appointment will be as an IRTA Postdoctoral Fellow for US citizens, or as a Visiting Fellow for US non-citizens. Accordingly, applicants must have fewer than five years of postdoctoral experience.
Interested individuals should send or e-mail their CV and the names, telephone numbers, and e-mail addresses of at least three references to: Dr. Richard Spencer, NMR Unit, NIH/NIA, GRC 4D-08, 5600 Nathan Shock Drive, Baltimore, MD 21224; Tel. 410-558-8226; e-mail: spencer@helix.nih.gov; website: http://www.grc.nia.nih.gov/branches/lcmb/nmr/nmr.htm

NIH TENURE-TRACK INVESTIGATOR POSITION AVAILABLE

A Staff Fellowship (assistant professor equivalent) position is available for work related to cartilage biology and physiology in the Laboratory of Clinical Investigation (Darrell Abernethy, Chief) of the National Institute on Aging (NIA) of the National Institutes of Health, located in Baltimore, Maryland. This recruitment is part of an ongoing expansion of the existing connective tissue research program at the National Institute on Aging.
The NIA has excellent research facilities including state-of-the-art cores in flow cytometry, confocal microscopy, DNA array studies, and NMR/MRI. In addition, the Baltimore Longitudinal Study on Aging is centered at the GRC, providing a ready population suitable for detailed longitudinal investigations.
The appointment will be as a Staff Fellow for US citizens or as a Visiting Scientist for US non-citizens, and will have a highly competitive salary. Applicants must have an excellent publication record demonstrating the potential for developing an independent research program.
Interested individuals should send or e-mail their CV and the names, telephone numbers, and e-mail addresses of at least three references to: Dr. Darrell Abernethy, Chief, Laboratory of Clinical Investigation, NIH/NIA, GRC 3C-02, 5600 Nathan Shock Drive, Baltimore, MD 21224; Tel. 410-558-8226; e-mail: abernethyd@grc.nia.nih.gov

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Position Available

DuPont Pharmaceuticals Research Labs

San Diego, CA

Has an immediate opening for a Research Scientist to work in collaboration with a team of analytical scientists in a multidisciplinary problem-solving environment to apply NMR methods to the structure characterization and elucidation of organic molecules in support of drug discovery. The successful candidate will have a B.S. or
M. S. in Analytical Chemistry with a minimum of 2-4 years experience in modern one- and two-dimensional nuclear magnetic resonance (NMR) and high throughput NMR analysis. The successful candidate must possess excellent NMR interpretation skills as applied to the structure characterization of small organic molecules. The candidate will develop and integrate high throughput flow probe analysis on a Varian 400 MHz NMR spectrometer for an open access environment. Contribution to the maintenance of open access instrumentation is also required. The incumbent will participate in project team efforts dealing with increased productivity, efficiency, and enhanced communication. The successful candidate must possess a demonstrated ability to work well in a team environment, and have the flexibility to succeed in a dynamic and rapidly growing work place. Excellent problem solving, oral, and written communication skills are required.

Please send resumes to:
E-mail: rrourick@combichem.com
Fax: 858-625-9293
US mail: DuPont Pharmaceuticals Research Labs
4570 Executive Drive
Suite 400
San Diego, CA 92121

Position Available

Our location, near Wilmington, DE, offers an attractive lifestyle with easy access to all the cultural, academic, and recreational activities of the Eastern Seaboard. The DuPont Company can offer you an excellent compensation and benefits package. To be considered, please forward your resume to:

DuPont Resume Processing Center
Attention Job Number FCRD818PNMR
P O Box 540117
Waltham, MA 02453-0117

NMR Spectroscopist

We are looking for an experienced NMR spectroscopist to join our Central Research and Development Department in the Corporate Center for Analytical Sciences at the Experimental Station in Wilmington, Delaware. Qualified candidates must possess a Ph.D. or M.S. degree in analytical, physical, or organic chemistry with a minimum of 5 years of experience in applying NMR chemicals, polymers, or materials science (industrial preferred). Experience using NMR skills for structural determination of polymers and small molecules is required. Knowledge of Unix operating systems and applications is necessary. Familiarity with LC/NMR and fluorine NMR is a plus. Good organizational, interpersonal and communication skills are also required. Responsibilities of the position include daily operation of the NMR facility, working directly with chemists, engineers, and material scientists in applying NMR to solve structural problems and collaborating with other analytical groups in order to solve structural problems. An Equal Opportunity Employer.

Positions Available

Postdoctoral Positions in Biological Magnetic Resonance

Two postdoctoral positions are available in the design and biological applications of microcoils for small volume NMR. The first position is funded through the National High Magnetic Field Laboratory in Tallahassee, Florida, in collaboration with Dr. Timothy Logan. The applicant will be responsible for the design of small radiofrequency probes for biomolecular spectroscopy for use at field strengths of 720 MHz and 833 MHz. Primary location will be at the University of Illinois at Urbana-Champaign. Previous experience in probe design or multidimensional NMR techniques is desirable. The second position is funded through the National Institutes of Health, and is centered at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign. This researcher will be responsible for applying our new microprobe technology to cellular analysis using the model system *Aplysia californica* in collaboration with Dr. Jonathan Sweedler. Experience in probe design, microimaging and/or hyphenated NMR-liquid chromatography is highly desirable. Applicants for both positions should send resume and the names of three references to Dr. Andrew Webb, Beckman Institute, 405 N.Mathews, Urbana. IL 61801. Both universities are equal opportunity employers.

Philosophical Points to Ponder – or Not

It is easier to get forgiveness than permission.

For every action, there is an equal and opposite government program.

Age is a very high price to pay for maturity.

A closed mouth gathers no feet.

If you look like your passport picture, you probably need the trip.

Men are from earth. Women are from earth. Deal with it.

Address all Newsletter correspondence to:

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

Deadline Dates

No. 499 (Apr.)	24 Mar. 2000
No. 500 (May)	28 Apr. 2000
No. 501 (June)	24 May 2000
No. 502 (July)	21 June 2000
No. 503 (Aug.)	25 July 2000

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

* E-mail: shapiro@nmrnewsletter.com

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

Forthcoming NMR Meetings, continued from page 1:

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

SMASH-2000, Argonne, IL, **July 16-19, 2000**. Contact: G. E. Martin (gary.e.martin@amu.pnu.com). See Newsletter 493, 21.

42nd Rocky Mountain Conference on Analytical Chemistry, Omni Interlocken Resort, Broomfield, CO, **July 31 – August 3, 2000**. NMR Symposium Chair: Lucio Frydman, Univ. of Illinois at Chicago, Dept. of Chemistry (M/C 111) 845 West Taylor St., Room 4500, Chicago, IL 60607-7061; 312-413-1053; Fax: 312-996-0431; lucio@samson.chem.uic.edu

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

NMR Spectroscopy of Biofluids and Tissues, Imperial College, London, England, **November 13-17, 2000**. Contact: Hersha Mistry, Centre for Continuing Education, Imperial College, 526 Sherfield Building, Exhibition Road. London, SW7 2AZ, UK. Tel: +44 (0)20 7594 6884; Fax: +44 (0)20 7594 6883; Email: h.mistry@ic.ac.uk; http://www.ad.ic.ac.uk/cpd/nmr.htm

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

Additional listings of meetings, etc., are invited.

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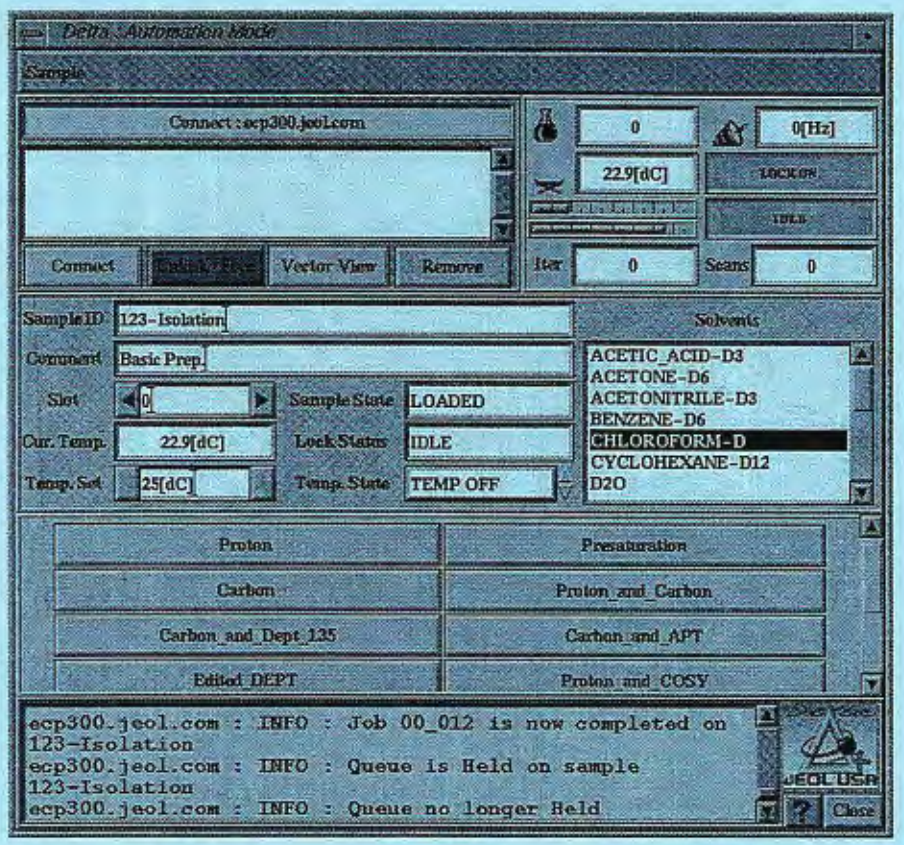

The **Eclipse+** NMR Spectrometer can be operated anywhere there is a computer on the local network. The **Single Window Automation** pictured above can be used with a single mouse click to select the sample from the auto-sample changer, gradient shim on any probe, run the selected experiment, and plot 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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