TEXAS A&M UNIVERSITY

NMR NEWSLETTER

No. 393

June 1991

Continued on page 2

TABLE 1 DEUTERATED SOLVENTS

Cat. No.	Description	Formula	Min. Isotopic Purity (%D)	Density (g/mL)	MP (°C)	BP (°C)	$-\chi_v \times 10^6$ @ (°C)
D-11	Acetone-d_6	CD_3COCD_3	99.8%	0.87	-94	57	0.460 (20)
D-121	Aceonte-d_6 + 1% TMS		99.8%				
D-129							
D-14							543 (20)
D-21							0.611
D-122							
D-130							
D-28	Choloroform-d	$CDCl_3$	99.8%	1.50	-64	62	0.740 (20)
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WCV-XLFT-100	11" X 26"	XL-100 (CF and FT)	Gridded-Two Color
WCV-XL-200	11" X 26"	XL-200, XL-300, XL-400	Gridded-Two Color
WCV-20 (CFT-20)	11" X 16 3/4"	CFT-20, FT-80, FT-80A	Gridded-Two Color
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FORTHCOMING NMR MEETINGS

Tenth International Meeting on NMR Spectroscopy, St. Andrews, Scotland, **July 8-12, 1991**; Contact: Dr. John F. Gibson, Secretary (Scientific), The Royal Society of Chemistry, Burlington House, London W1V 0BN, England; See Newsletter 387, 69.

Gordon Research Conference on Magnetic Resonance, Brewster Academy, Wolfeboro, NH, **July 15-19, 1991**; Chairman: R. Griffin; Information from Dr. A. M. Cruickshank, Gordon Research Center, Univ. of Rhode Island, Kingston, RI 02881-0801; Tel.: (401) 783-4011 or -3372; FAX (401) 783-7644.

33rd Rocky Mountain Conference on Analytical Chemistry, Denver, CO, **July 28 - August 2, 1991**; For information on the NMR Symposia, contact Dr. H. Eckert, Dept. of Chemistry, Univ. of California at Santa Barbara, Goleta, CA 93106, (805) 893-8163; For general information, contact: P. Sulik, Conference Chair, Rocky Mountain Instrumental Laboratories, 456 S. Link Lane, Fort Collins, CO 80524, (303) 530-1169.

Tenth Annual Scientific Meeting and Exhibition, Society of Magnetic Resonance in Medicine, San Francisco, **August 10-16, 1991**; Contact: S.M.R.M., 1918 University Ave., Suite 3C, Berkeley, CA 94704; (415) 841-1899, FAX: (415) 841-2340; See Newsletter 391, 55.

Two-Dimensional NMR Spectroscopy (ACS Short Course), New York, NY, **August 23 - 25, 1991**; See Newsletter 392, 33.

New Developments and Applications of Magnetic Resonance and Optical Spectroscopies (ACS Symposium), New York City, **August 25-30, 1991**; See Newsletter 393, 48.

International Conference on NMR Microscopy, Heidelberg, Germany, **September 16 - 19, 1991**; See Newsletter 385, 28.

1991 Joint Meeting FACSS/Pacific Conference, Anaheim, California, **October 6-11, 1991**; NMR/EPR Program Section Chairman: Prof. Cecil R. Dybowski, Chemistry Dept., Univ. of Delaware, Newark, DE 19716. Contact: FACSS, P.O. Box 278, Manhattan, KS 66502-0003.

Eighth Australian NMR Conference, Lorne, Victoria, Australia, **February 2-6, 1992**; See Newsletter 391, 38.

Eleventh Annual Scientific Meeting and Exhibition, Society of Magnetic Resonance in Medicine, Berlin, Germany, **August 8-14, 1992**; Contact: S.M.R.M., 1918 University Ave., Suite 3C, Berkeley, CA 94704; (415) 841-1899, FAX: (415) 841-2340.

Additional listings of meetings, etc., are invited.

Table of Contents, cont'd.

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All Newsletter Correspondence

Should Be Addressed To:

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

(415) 493-5971

DEADLINE DATES

No. 395 (August)---------- 19 July 1991
No. 396 (September)-------- 16 August 1991
No. 397 (October) -------13 September 1991
No. 398 (November) -------11 October 1991

* * * * *

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April 29, 1991
(received 5/1/9])

Dr. Barry Shapiro
TAMU NMR Newsletter
966 Elsinore Ct.
Palo Alto, CA 94303

^{15}N NMR of Protonated Cytidine in Oligonucleotides

Dear Barry:

I am writing to inform you of my change of address (see letterhead) and describe some additional results in studies of ^{15}N NMR of oligonucleotides.

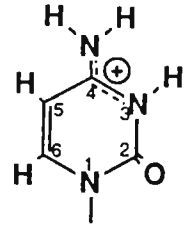
There is considerable interest in protonated cytidine (CH^+) in oligonucleotides due to the role it plays in the formation of triple helicies, and the implication of such structures in control of gene expression. The effects of protonation N3 of the base by itself had been examined using ^{14}N NMR and NQR, and ^{15}N NMR (e.g. G. Kupferschmitt et. al., Nuc. Acids. Res., 15, 6225 (1987)). In oligonucleotides, ^{15}N NMR is required because of the need to resolve multiple resonances in the same spectral region. The concentrations for the studies of oligonucleotides, and the difficulty of isotopic labeling has severely limited the accessibility of such studies until the advent of HMQC methods. We have applied these experiments to two samples, d(TCGA) at pH 4.51 (160 OD units/0.4ml), whose solution conformation is under study, and $d(G(AG)_8)$ and $d(C(TC)_8)$ in a ratio of 1:2 at pH 5.01 (322 OD units/ 0.4 ml) which has characteristics of a triple helix. Resulting 2D spectra are shown in figure 1. Shifts for the G and T imino nitrogens are respectively relatively constant for both samples, while the N3 of CH^+ shifts by about 20 ppm. Further, the $^1J_{NH}$ coupling for TCGA (Fig. 1a) is only 47 Hz, about half of the normal coupling. Whereas the N3 in the triple helix system is close to the position expected from model studies on protonated CMP, the shift for d(TCGA) is about half way between the positions of N3 for protonated and unprotonated CMP. The latter is not a manifestation of rapid exchange between the two states, since the coupling is well resolved and the satellite lines are sharp. The couplings can be related to s character of the NH bond as was pointed out some time ago by G. Binsch et. al. (JACS, 86, 5564 (1964)). Thus the reduced couplings and the intermediate shift suggest a delocalization of the positive charge in the d(TCGA), structure I, while the result in the triple helix system is more consistent with structure II. The ^{13}C shifts of the C5 from carbon HMQC change little with protonation, supporting the localization of the effects to the region between N3 and the amino nitrogen.

Sincerely yours,

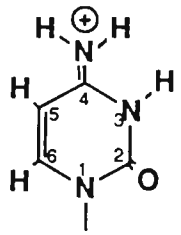
David Live

PASADENA, CALIFORNIA 91125

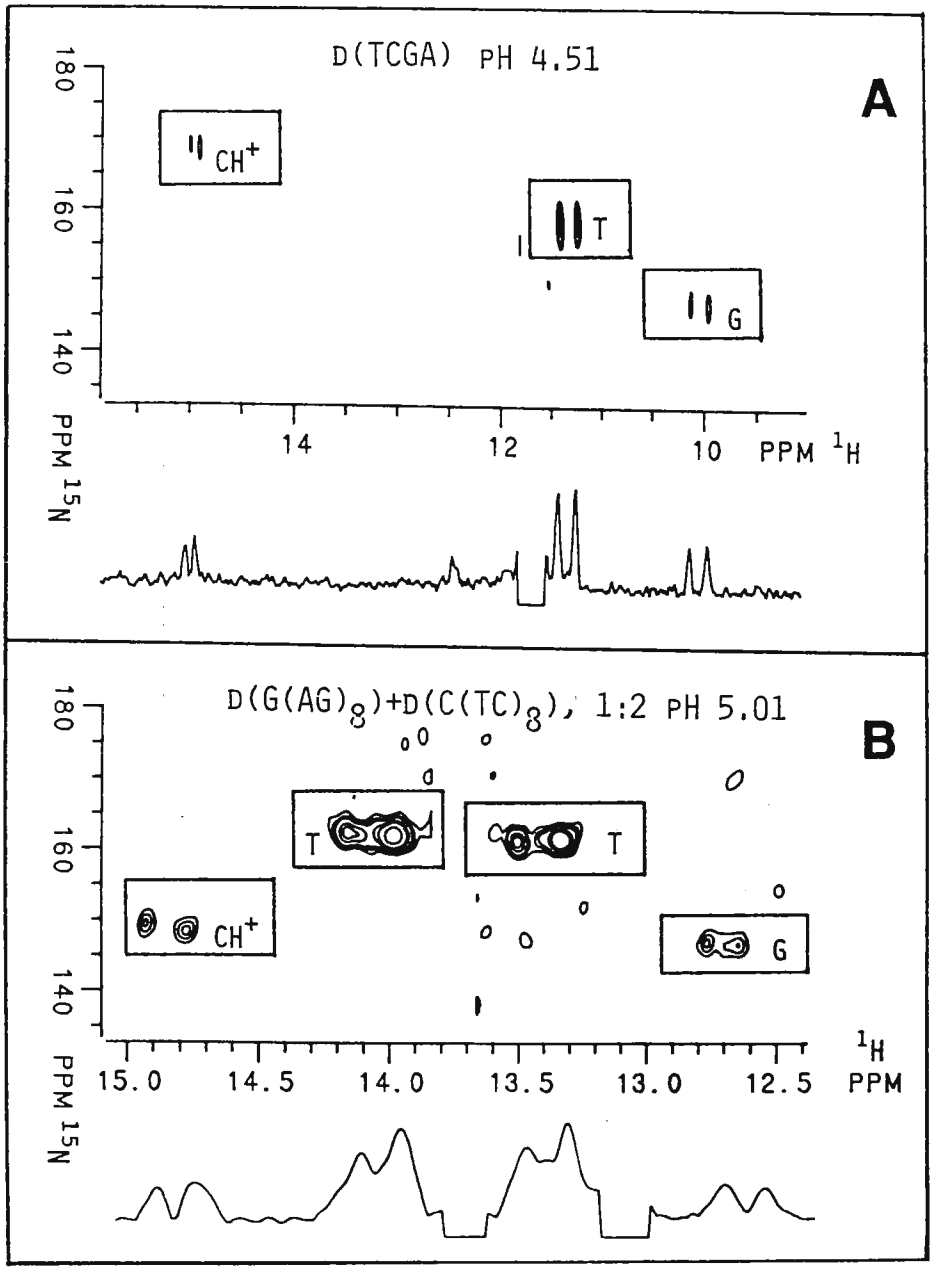
Figure 1



I



II


D(TCGA) PH 4.51
A
CH+
T
G
180
160
140
PPM 15N
14
12
10
PPM 1H
D(G(AG)8)+D(C(TC)8), 1:2 PH 5.01
B
T
T
CH+
G
15.0
14.5
14.0
13.5
13.0
12.5
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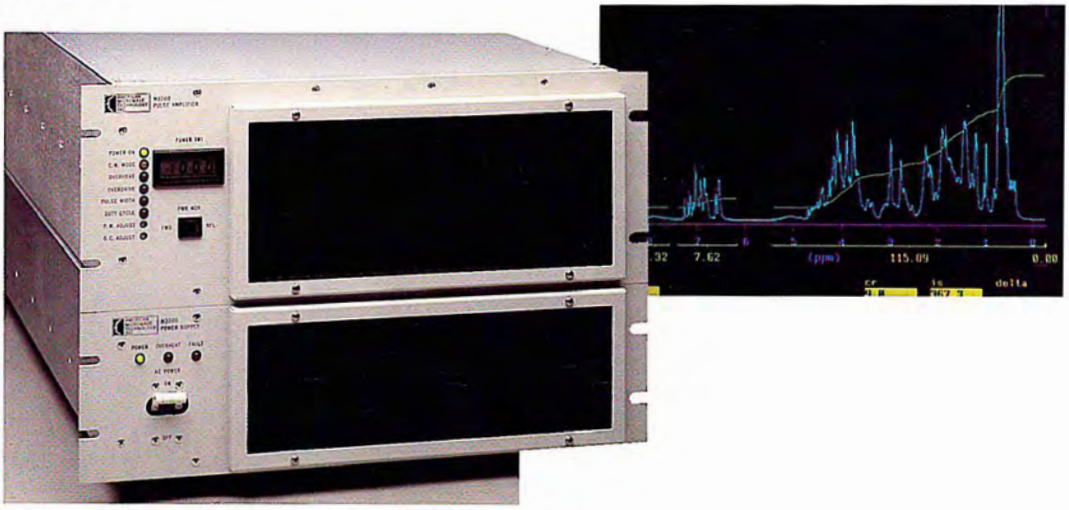

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Dr. B.L. Shapiro
TAMU NMR Newsletter

April 15, 1991
(received 4/24/91)

Dear Dr. Shapiro,

"EMBARKING" ON LIPID METABOLISM IN SPHEROIDS OF CANCER CELLS.

The importance of variations in the membrane lipid precursors phosphorylcholine (PC) and phosphorylethanolamine (PE) as a function of tumor growth and metabolism is increasingly observed. Following our initial studies of T47D human breast cancer spheroids (1,2) we proceeded to investigate systematically the different steps involved in choline and ethanolamine uptake and metabolism in small (150μ diameter) and large (300μ diameter) spheroids.

Spheroids were perfused inside the NMR spectrometer with 1,2 ^{13}C labeled choline and 1,2 ^{13}C labeled ethanolamine and the buildup of labeled PC and PE was monitored. To confirm these labeling experiments washout measurements were performed, namely the PC, phosphatidylcholine and glycerol-PC pools were prelabeled with ^{13}C and the reduction of PC label was monitored. Alternating ^{31}P (202 MHz) and ^{13}C (125.7 MHz) NMR spectra were recorded for approximately 48 hours using a 10 mm quadro nuclei (^{31}P, ^{13}C, ^{15}N, ^{1}H) software controlled probe. Fig. 1 shows a ^{13}C spectrum and time courses of PC and PE labeling of 14 day old T47D spheroids following perfusion inside the spectrometer with 1,2 ^{13}C choline and 1,2 ^{13}C ethanolamine at 36°C. The ^{31}P spectra provided information regarding the total pool sizes of PC and PE and the overall energetic status of the cells while the ^{13}C spectra yielded the kinetic parameters for the rate of the enzymes phosphocholine kinase, phosphoethanolamine kinase, CTP:PC cytidyltransferase and CTP:PE cytidyltransferase. The analysis of the kinetic data was perfored on a model based on the Kennedy pathway for lipid metabolism (3). In large spheroids (~300μ diameter) composed primarily of two cell populations - proliferating and non-proliferating compartments it was assumed that each signal represents a weighted average of signal from each compartment.

The results indicated that the average pool sizes of ATP and PC are significantly lower in the large spheroids while PE pool size is similar in small and large spheroids. This could be correlated with the kinetic results: choline incorporation was markedly reduced in the non-proliferating compartment of the large spheroids, while the kinetics of ethanolamine incorporation remained similar in both compartments.

We conclude that NMR presents a useful non-invasive tool for detecting variations in lipid metabolism. Specifically the use of ^{13}C NMR and the determination of kinetic parameters using the uptake of labeled lipid precursors can be used in trying to quantitate such changes in cells and tissues.

1. Ronen, S.M. and Degani, H., Magn. Reson. Med. 12, 274-281, (1989).
2. Ronen S.M., Stier, A. and Degani, H., FEBS Lett. 266, 147-149, (1990).
3. Kennedy, E.P., and Weiss, S.B., J. Biol. Chem. 222, 193-214 (1956).

Please credit this contribution to the account of Dr. Raphy Poupko.

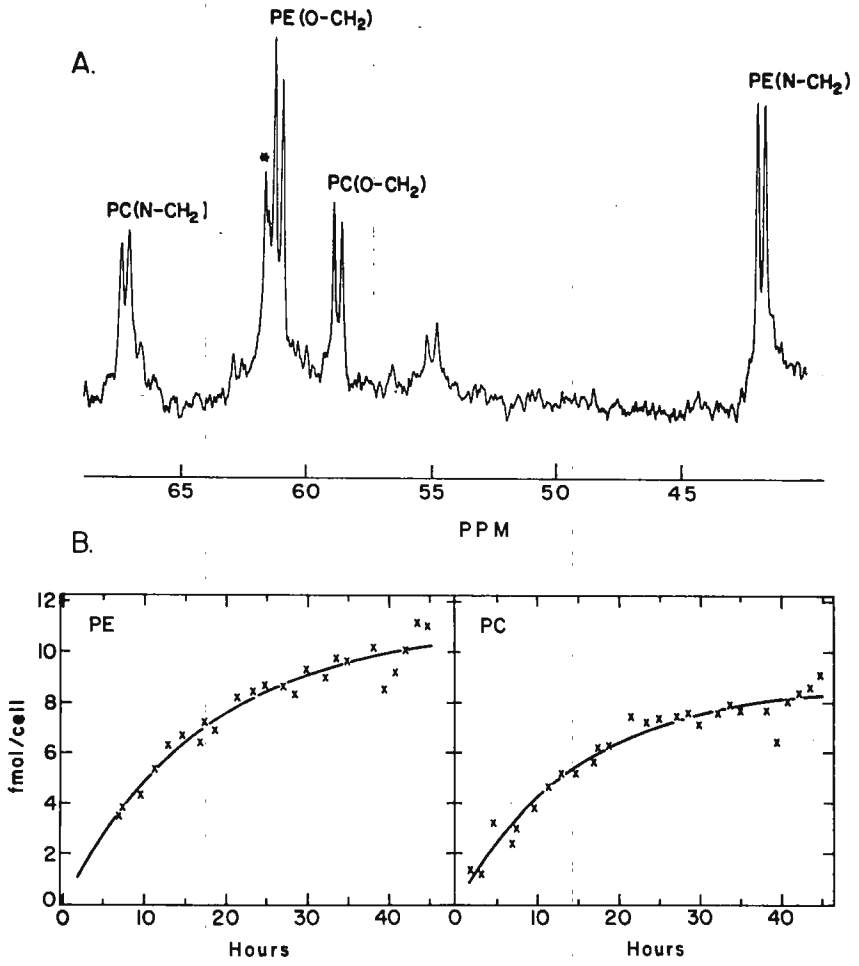

Fig. 1. A) ^{13}C NMR spectrum of 14 day old, large spheroids following perfusion for 42 hours with 1,2-^{13}C labeled choline and ethanolamine (0.028 mM) at 36°C. The $O-CH_2$ carbon of PC (PE) is derived from choline (ethanolamine) carbon 1 and the $N-CH_2$ carbon from choline (ethanolamine) carbon 2. The spectrum is the result of 1200 scans (40 min) recorded with 45° pulses, 2 sec repetition delay and a composite pulse proton decoupling. A line broadening of 8 Hz was applied.
B) Computer fit of the experimental data to its expected behavior. The cellular PE and PC contents were determined using the Bruker GLINFIT program. The theoretical curve is based on a model that estimates the NMR data to be a weighted average from 30% proliferating cells and 70% non-proliferating cells.

Sincerely yours,

Sabrina M. Ronen

Hadassa Degani

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Department of Chemistry

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13 May, 1991
(received 5/14/91)

Dr. Bernard L. Shapiro, Editor
TAMU NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

HARTLEY-HILBERT TRANSFORM SPECTROSCOPY: ABSORPTION-MODE RESOLUTION WITH MAGNITUDE-MODE PRECISION

Dear Barry,

FT of an N-point time-domain discrete signal produces, after phase correction, two independent data sets: an N/2-point absorption spectrum, A(ω), and an N/2-point dispersion spectrum, D(ω), each with the same information content. Usually only A(ω) is kept. The dispersion-mode information has conventionally been recovered in either of two ways [1]. First, the N/2-point *magnitude-mode* spectrum, M(ω), offers a $\sqrt{2}$ improvement in precision compared with the original N/2-point absorption spectrum, but with poorer resolving power (factor of $\sqrt{3}$ for Lorentzian peak shape). Alternatively, *zero-filling* the initial time-domain data to 2N data points prior to FT results in an N-point absorption-mode spectrum with the same peak width and peak-height-to-noise ratio as the original N/2-point absorption spectrum, but with a $\sqrt{2}$ improvement in precision [2]. Thus, magnitude-mode display improves FT spectral precision at the expense of a loss in resolving power, whereas zero-filling improves precision at the expense of having to store twice as many data points.

We here describe a third method of recovering the dispersion information. Specifically, discrete Hilbert transform of D(ω) (obtained by discrete Hartley transformation [3] of N time-domain data) yields an N/2-point "pseudo-absorption" spectrum which may be added to the original A(ω) to yield an N/2-point "enhanced" absorption spectrum with the same peak width and same number of data points, but with peak-height-to-noise ratio improved by a factor of $\sqrt{2}$ over the original N/2-point absorption spectrum. In other words, **the new procedure yields a FT spectrum with enhanced precision, without any attendant loss in resolving power (as for magnitude-mode display) and without any increase in the number of stored data points (as for zero-filling)**, as shown in Figs. 1 and 2. For best results, there should be no peaks within ~20 line widths of either end of the Nyquist bandwidth.

This work will be reported more fully elsewhere, [4] and was supported by N.I.H. (GM-31683) and Ohio State University.

Sincerely,

Alan G. Marshall

Christopher P. Williams
Ph.D. Candidate

Alan G. Marshall
Professor, Chemistry and Biochemistry
Director, Campus Chemical Instrument Ctr.

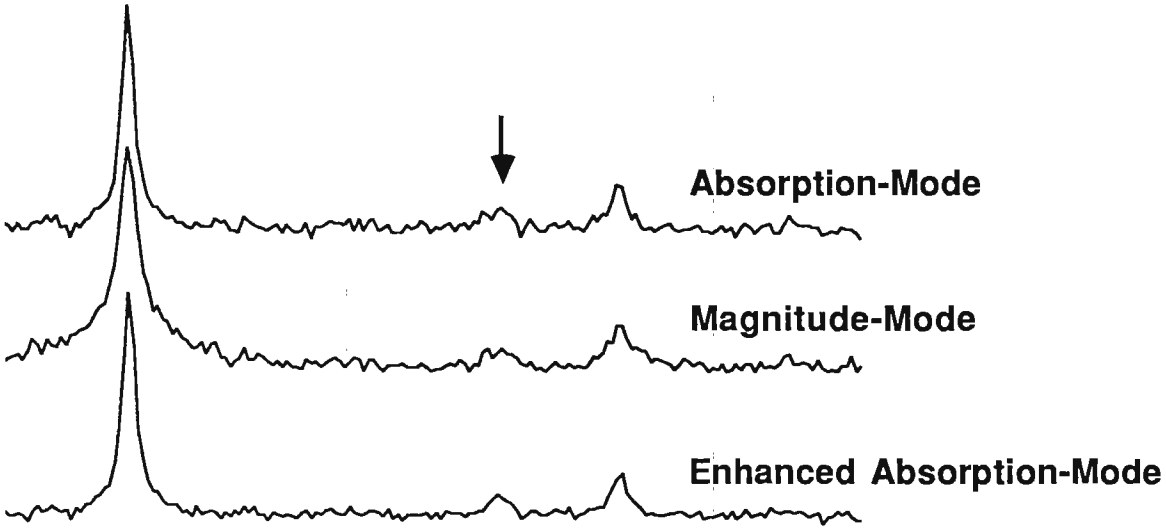

Figure 1. Absorption-mode, magnitude-mode, and enhanced absorption-mode FT spectra of a time-domain signal consisting of three exponentially damped sinusoids of relative amplitude, 10:1:3. The frequency of the weakest signal is shown by an arrow. Note the improved (peak height)/(rms baseline noise) ratio for the enhanced absorption-mode display (see text).

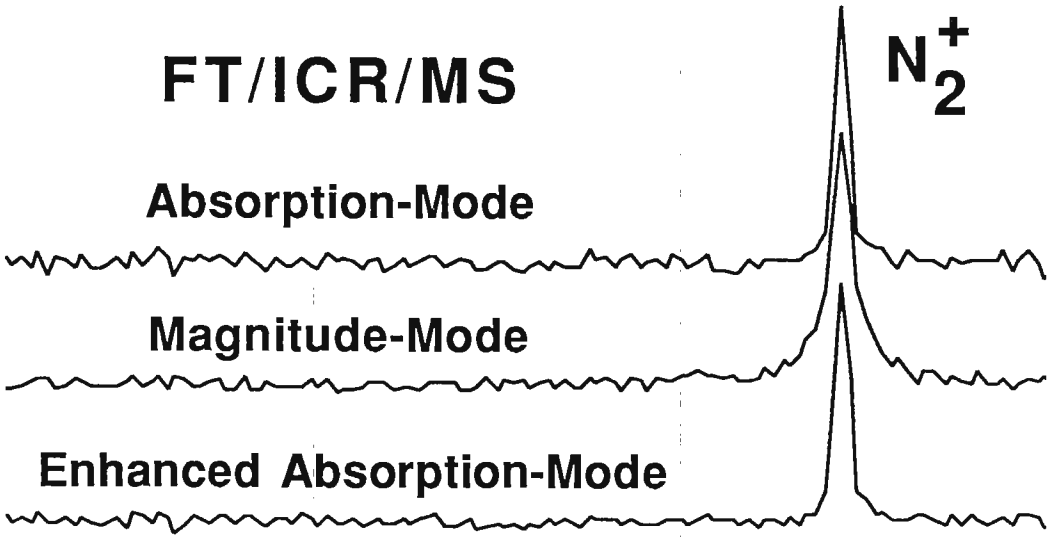

Figure 2. Absorption-mode, magnitude-mode, and enhanced absorption-mode FT/ICR mass spectra of an experimental time-domain N_2^+ signal. The higher resolution of the enhanced absorption-mode compared to magnitude-mode is especially obvious.

References

1. Marshall, A. G.; Verdun. F. R. *Fourier Transforms in NMR, Optical, and Mass Spectrometry* (Elsevier, Amsterdam, 1990).
2. Liang, Z.; Marshall, A. G. *Appl. Spectrosc.* **1990**, *44*, 766-775.
3. Williams, C. P.; Marshall, A. G. *Analyt. Chem.* **1989**, *61*, 428-431.
4. Williams, C. P.; Marshall, A. G.; submitted for publication.

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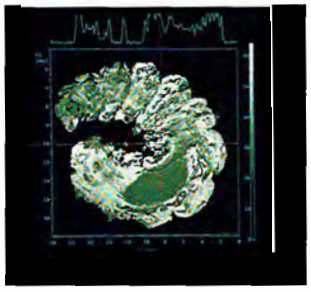

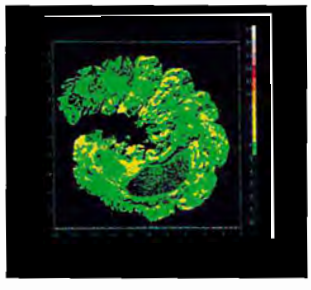

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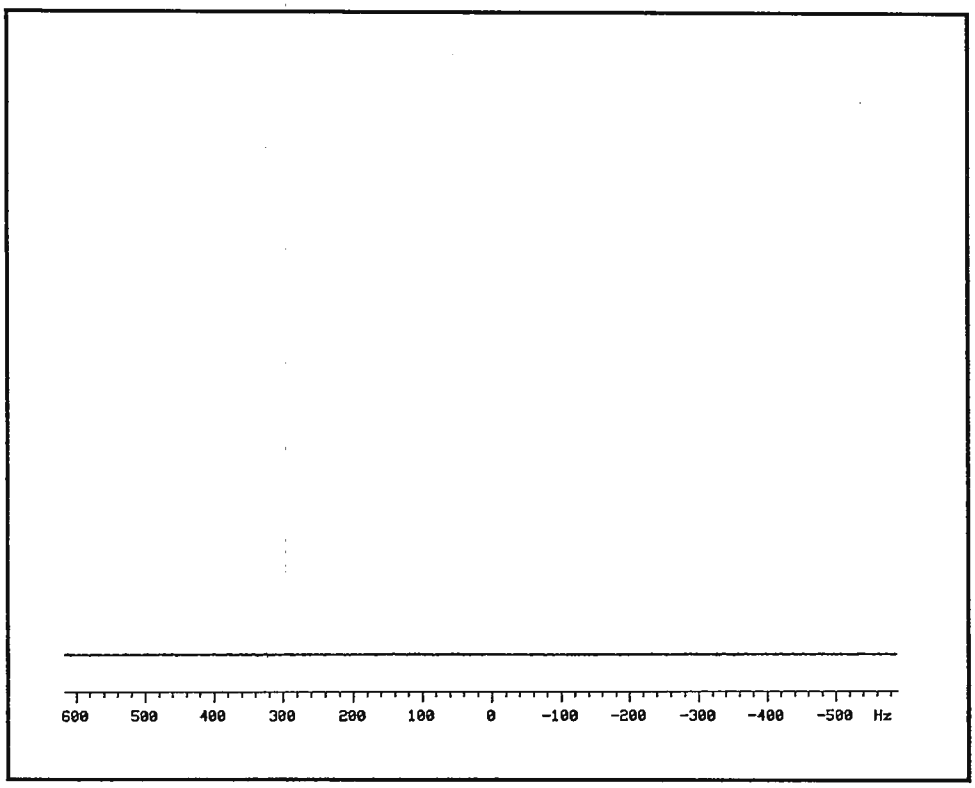

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AUSTRALIA

6th May, 1991 (received 5/14/91)

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

Dear Dr. Shapiro,

Configurational Assignments for 1,3-Disubstituted Cyclopentane Derivatives

The use of n.m.r. spectroscopy in establishing the configurations of 1,3-disubstituted cyclopentane derivatives has been of interest to us for some time. One approach to the problem follows from early observations[1] concerning the epimeric 1,3-dimethylcyclopentanes. After converting the original data to the TMS scale, the chemical shift of C1 and C3 is found to be greater for the *cis* than for the *trans* isomer. The shift difference (1.9 p.p.m.) is significantly less than that for the corresponding carbons of the epimeric 1,3-dimethylcyclohexanes ($\Delta\delta \simeq 6$ p.p.m.), however, due to the greater degree of conformational mobility of the 5-membered ring derivatives.

Differences in chemical shifts of ring methine carbons are also observed for 1,3-disubstituted cyclopentanes in which the two substituents are different, but the magnitude and sign of the differences vary according to which ring methine carbon (C1 or C3) is considered. Thus, data already published,[1,2,3] together with that now presented in the Table, indicate that the shift of C3 is always greater for the *cis* than for the corresponding *trans* isomers. No general trend is evident, however, in the shifts for C1.

The difference between the situations at C1 and C3 is surprising on two grounds. First, in all cases, the labelling of a particular carbon as C1 or C3 has been determined by empirical IUPAC rules of nomenclature. Secondly, semi-empirical force-field calculations have previously led[2] to the conclusion that the preferred conformations of 1,3-disubstituted cyclopentanes are essentially determined by the stereo-relation between the substituents (*cis* or *trans*) and not by the nature of those individual substituents. As such, *from a conformational point of view*, the time-averaged environments of C1 and C3 in any one given isomer should be the same, in which case any trends in the *differences* between the chemical shifts of C3 in epimeric pairs should be mirrored in the corresponding chemical shift differences at C1.

Please credit this contribution to Ian Rae's Monash "subscription".

Yours sincerely,

Syd Middleton

(Dr.) Syd Middleton

1. M. Christl, H.J. Reich, and J.D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3463 (1971).
2. H-J. Schneider, N. Nguyen-Ba, and F. Thomas, *Tetrahedron*, **38**, 2327 (1982).
3. N.F. Janes and B.P.S. Khambay, *Mag. Res. Chem.*, **27**, 197 (1989).

Chemical shifts for ring methine carbons of epimeric 1,3-disubstituted cyclopentane derivatives.

Substituent at C1	Substituent at C3	Stereochemistry	δc1	δc3
COOH	CH_3	cis	44.0	35.4
		trans	43.2	34.2
$COCH_3$	CH_3	cis	52.6	35.4
		trans	51.6	34.2
COOH	t-Bu	cis	43.8	51.5
		trans	43.6	50.2
OH	t-Bu	cis	73.3	49.2
		trans	73.6	48.0
OAc	t-Bu	cis	76.5	49.3
		trans	77.1	48.6

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April 15, 1991
(received 4/26/91)

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

Magnetization Transfer Imaging in Humans

Dear Dr. Shapiro:

Wolff and Balaban have demonstrated that the "narrow" signal from "free" water can be attenuated in MR images via prolonged presaturation of the broad resonance from water bound to macromolecules, etc. We have studied the implementation of magnetization transfer imaging on a General Electric Signa scanner operating at 1.5 T. We have studied the contrast differential between pathology and normal tissue produced by MTC in the knee and breast (1).

We have adapted MT prepulses onto the front end of a 3-dimensional, fat suppressed, imaging sequence. In our implementation, we use a sinc pulse placed 1.5 KHz off-resonance for generation of MTC. The sinc pulse is positioned such that no residual excitation is observed at the frequency of the main water signal. Fat suppression is achieved using a jump-return pair of shaped RF pulses. An echo time of 3.6 msec is used with a repetition time of 26 msec. The duty cycle of the MTC pulse is ~20%. When the MTC pulse has an amplitude corresponding to a π pulse, a 50% reduction in signal intensity from muscle and cartilage can be observed in 3-dimensional images of the knee. The signal from fluid (cyst) is reduced by less than 5%. While Wolff and Balaban have observed attenuation of over 95% in animal models, the 50% reduction in muscle signal is observed at the limit of power deposition for humans. Clinically, the MT 3D images of the knee did not provide additional contrast compared to conventional T1 or T2-weighted 2D or 3D images.

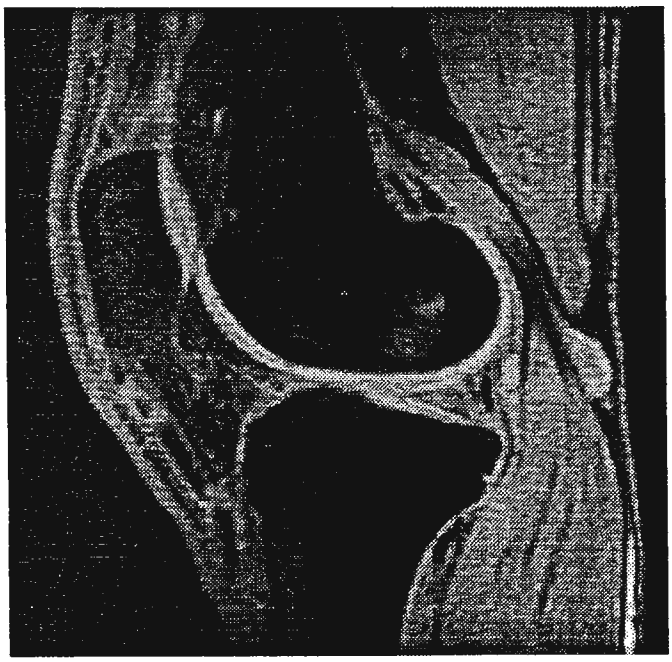
Initial application of 3D MT imaging to the breast showed that the contrast to noise ratio for pathology actually *decreased* using MTC. This

effect resulted from the ~30% reduction in signal from breast, and the apparent similarity in water exchange between tumor and normal parenchema. However, this attenuation dramatically improved the contrast to noise ratio observed in the breast following administration of Gd-DTPA. A 75% increase in contrast to noise has been observed in the Gd-DTPA MT images compared to their non-MTC counterparts. The 20-fold reduction in the signal from fat is maintained, and the resulting images have the appearance of MR "mammograms", with hyperintense pathology observed with hypointense breast parenchema over a dark background of "fat". The MTC-GdDTPA combination yields high quality MR angiograms from the same data set following maximum pixel ray casting on the same data set. Hence, MTC may prove useful for reduction of the background signal from normal tissue in 2D and 3D time-of-flight MR angiograms. Preliminary results also suggest that MTC may have clinical utility in differentiation of diseases in the brain.

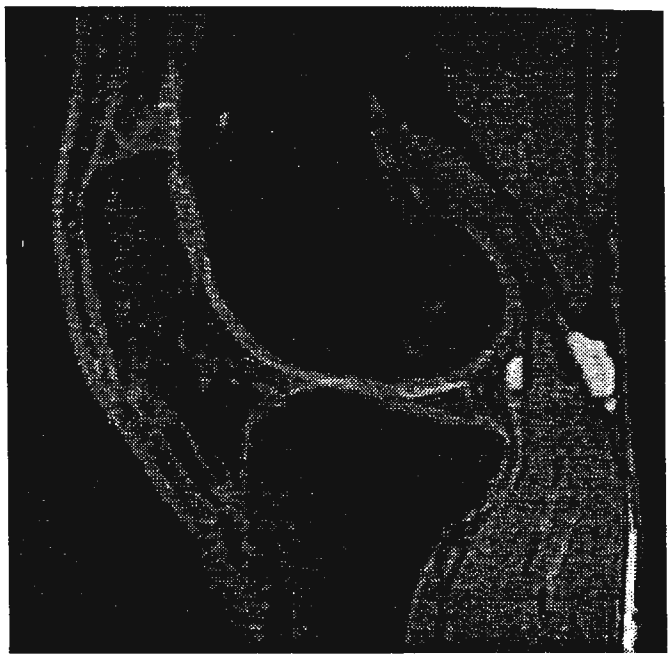
Sincerely,

Richard H. Griffey Duane P. Flamig

1. Flamig DP, Pierce W, Harms SE, and Griffey RH, submitted, Magn. Reson. Med., 1991.



3D FATS (NO MTC)



3D FATS W/ MTC (You need surgery, buddy)

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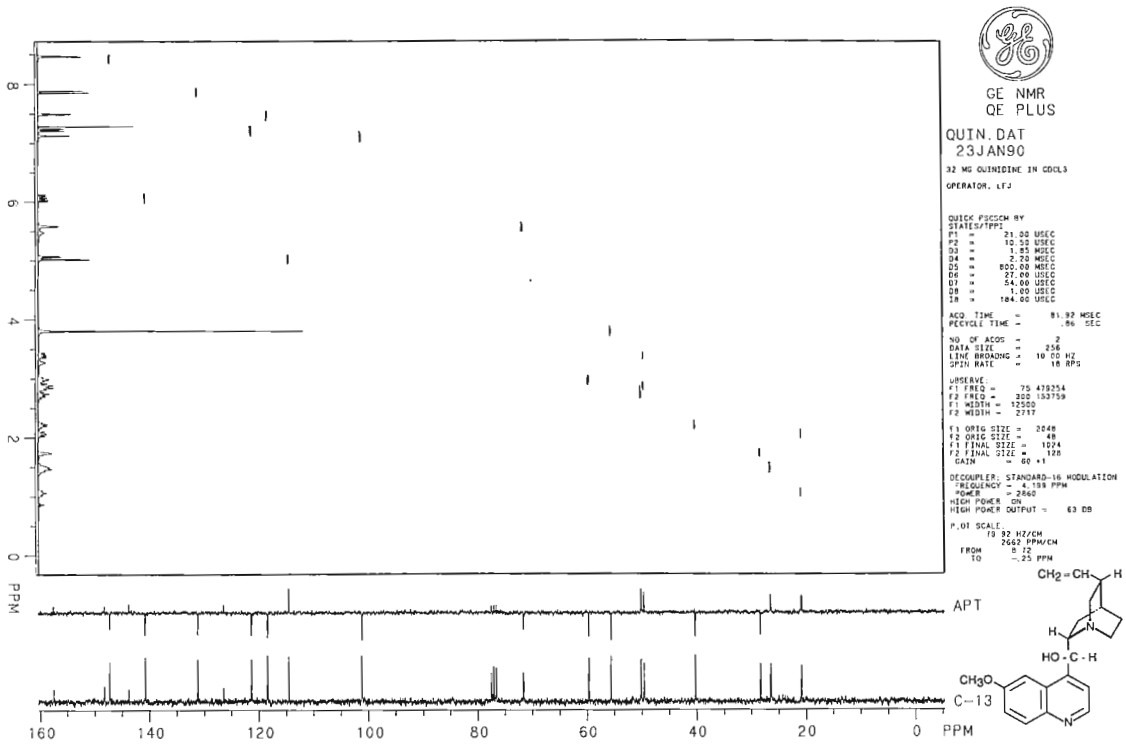

An automated run using MACRO mode operation on a sample of 32 mg of quinidine in 0.5 ml chloroform-d (0.20M). Data were obtained using the 5 mm broadband probe. ^{1}H, ^{13}C, APT and phase sensitive 2D data were collected, processed and plotted—including the 2D contour—in only 8.2 min.

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May 17, 1991
(received 5/17/91)

Dr. Bernard L. Shapiro
TAMU NMR Newsletter
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From CAT NMR in 1962 to DOG-EAT-DOG NMR in 1992[1]

Dear Barry,

In the tradition that all important observations in NMR in the last 30 years were first published in your Newsletter, making the Newsletter a chronicle of the spectacular rise of the field, I submit two more. These, however, suggest that we are now beginning to witness the downfall of the field, as the US biological NMR community is proceeding to kill itself off.

The first observation was reported to me by one of our NIH program directors. In his words: "The recent NMR proposals don't seem to have fared well with your peer review community." This was echoed by three of his colleagues at both the NIH and the NSF. By partial count, no fewer than seven major publicly funded NMR laboratories received nonfundable priorities in the past two years. One was funded, but with equipment funds cut to nothing.

The second observation I made by classifying the mass of reprints which many of our colleagues very kindly sent to me to help with the second edition of "NMR in Molecular Biology." 87% of the contributions are coming from laboratories that do not depend on the US granting system - those abroad, in the NIH intramural program, in industry and in private foundations.

The obvious conclusion to be drawn from the two observations taken together, is that the smartest people in this field know where to work. Tragically, the other conclusions are (1) that the grant supported NMR laboratories in this country are being strangled to death by the inadequacy of their resources, and (2) that it is not just the tight federal budget which is responsible, but the management of peer review. Only in the US granting system are the expert communities given a de facto decisive power.

When the cited observations tell us that this power is being used to destroy established laboratories, or to force them to work with obsolete instrumentation and inadequate resources so that they in fact *become* noncompetitive - we must at least stop and ask: Do we as a community fully understand what we are doing?

First: What is it that the peer reviewers don't like about the current NMR proposals? Is it really true that those of us working under the grant system have run out of good ideas or become unproductive? The 13% of the contributions from US academic institutions say no. They are, if anything, more original. In contrast, the message of the reviewers is far from clear.

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[1] My 1962 CAT NMR letter to you which ushered in the era of signal averaging in NMR was echoed, as you may remember, by a series of clever and good-humored technical modifications - DOG NMR, MOUSE NMR, etc. The spirit has changed.

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The uniformity of the experience among those recently reviewed is striking: high praise, few, if any criticisms - and a nonfundable priority score. Of the criticisms that find their way into the record at least half are irrelevant or outright wrong. This is alarming. The basic premise of peer review is that it is rational. Voting unfundable priorities for an otherwise highly praised proposal on the basis of minor, irrelevant or wrong criticisms is hardly rational.

Part of the problem is the priority score system itself. Any statistician can tell us that a numerical rating assigned by an ad hoc group reviewing only one proposal, without any comparative norms, cannot be compared to any other and is a meaningless number. Nevertheless, the NIH insists in normalizing these numbers against all those voted by totally different groups using totally different criteria and uses them as a decisive factor in funding. When words and numbers don't match, it is the number that counts. Here we are, a scientific community evaluating scientific merit by a completely unscientific method. It is - crazy.

The rules of peer review in Europe are vastly different from those in the US. Executive decisions in research institutes, public or private, and in industry may rely on some advice, but the advice is never binding. No one relies on arbitrary numbers except US granting agencies. There are few, if any, biological NMR laboratories in Western Europe, Canada and Australia whose proposals I had not reviewed at some point, but I have never been asked to give a numerical rating. The laboratories were funded on the judgment that they were proposing good work, and no reviewer was given the opportunity to undercut them by slipping a low score under a high compliment.

Working within a peer review framework gone crazy is our first handicap. Yet it is a handicap that our colleagues in several other fields have learned to conquer: according to them, most, if not all work in their field deserves only the highest priority. In the present system we are not so much competing with each other. We are competing against them.

Therein lies our real problem. The prevalent mentality in the NMR community seems to be that if one is asked to review a proposal, one is not doing one's job properly unless one can find some fault with it. (How else can the reviewers prove that they are better and smarter than the applicants?)

A specific analysis of one case from our own experience brings the point home. We have seldom been praised so highly: "Work of *extremely high scientific merit,*" "a *great accomplishment* ", "*enthusiastic* support for our *outstanding* science," our past contributions were "*distinguished*" and "*seminal.*" Pleasant reading, though too late - one glance at the priority score of 178 instantly said: not to be funded. The only *"serious weaknesses"* to account for the unfundable score were that for a resource we did not have a broad enough support base (only 12 projects) and not enough preliminary data for all of them. At first glance the criticism looks eminently reasonable. And yet if one takes it seriously and estimates what it would take to meet it, one discovers (1) that if one broadens the support base, one will have exceeded the capacity of the available instrumentation not by a factor of 2, which we already did, but by a factor of 5-10, and (2) it would require two to three man-years of work, as well as equipment and computer time well beyond those available.

Is it reasonable for a resource to promise to support more users than its instruments can support? Is it reasonable to expect an order of magnitude more work to have been done than the existing resources allow? I think not. Is it reasonable to raise such criticisms? I think not.

The striking feature of most criticisms one now reads - of which one could cite many more examples - is that they can easily be raised against *any and every* proposal. It is *always* possible to find *some* imperfections. They have nothing to do with scientific merit, but they suffice to destroy

a laboratory's funding. Is the NMR community engaging in fault finding for the sake of fault finding? And, if so, why?

In the days of very tight budgets self-interest may sound as an obvious answer (if he doesn't use up the budget, and doesn't get to do and publish very much, I have a better chance). In the short run this may even work. In the long run, it is a tragic miscalculation. If A and B shoot down C, and C, with D, shoots down E, and E and F shoot down G there will come a point when C and G, whose standards have been appropriately raised by the experience, will shoot down A.

One net result is that public funds, which could, should and would have been committed to biological NMR, go to other fields. Already program directors at the NSF and NIH are getting the message that no one in this field is quite good enough to get funded, so they place their priorities elsewhere. Those of us who have served time in industrial executive ranks know how sensitive industrial, foundation and research institute management are to federal funding trends. It is only a matter of time before non-federal sources of support for biological NMR begin drying up as well. So will jobs. What University will want to hire faculty members in a field in which support is notoriously difficult to get?

Our situation was very graphically put to me by a wise and distinguished colleague from another discipline: "Your people (in biological NMR) behave as if they were too many rats fighting over too few spoils. Is there any real future in biological NMR?"

I don't think this is the reputation we deserve or that we want to create. Clearly, we have a grim future if we insist on belittling each other's contributions and exaggerating each other's shortcomings. Constructive and destructive climates have an autocatalytic quality about them. If the experts testify too often that nothing in the field - except, of course, themselves - is quite up to snuff for public support, outsiders will believe that this applies to everyone in the field, *including* each critic. Perhaps we should consider that if none of us are good enough to be funded through the peer review system, none of us are good enough to sit on peer review committees.

I think the NMR community needs to wake up to reality. Today there is no operational distinction between an "excellent" priority of 1.5 and a disapproval score of 5.0. Both amount to a hanging. Second, most of the NMR proposals I have seen that have been rated in the 1.7 - 2.4 range by our colleagues are conceptually of much higher quality and made by individuals with a much more solid record in science than many of the proposals in preparative molecular biology, immunology or computer graphics that receive ratings between 1.0 and 1.2 and adequate funding. Third, most of the reasons given to justify a lesser priority score are contrived. Some border on the ridiculous. Many - so it would seem - are passed over in silence. The cloners have convinced the world that cloning is good. The NMR community is convincing the world of the opposite about itself. So, much more money is spent on cloning than on NMR facilities - even though much of the cloning is aimless without NMR or at least crystallography. But the crystallographers too have learned this lesson and do not cut each other down as we do. Result: grant support for crystallography is stable.

I would like to hear from everyone concerned about this problem. We need to form a National Committee for the peer review of peer review before Congress does it for us.

Yours sincerely,

Oleg Jardetzky

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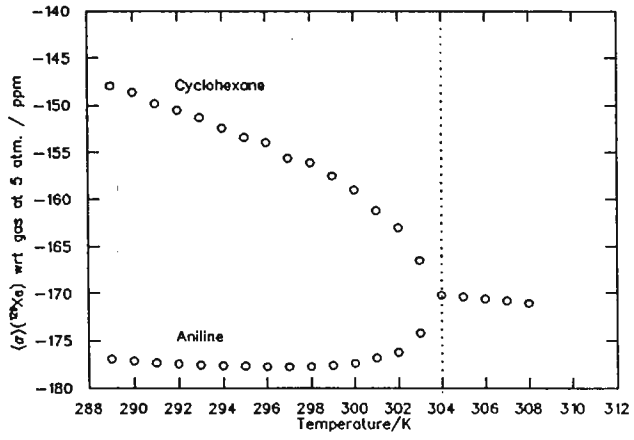
April 29, 1991
(received 5/3/91)

Phase Transition in two component liquid system observed by ^{129}Xe-NMR

Dear Barry

Having been interested lately in studying phase transitions of liquid crystals by the use of noble gas NMR [1] we also ran a series of phase transitions in two component liquid systems in which ^{129}Xe was used as a monitor. The figure which presents the chemical shift of ^{129}Xe in a mixture of aniline(47.3 wt%) and cyclohexane(52.7 wt%) as a function of temperature clearly shows the phase transition and allows the immediate determination of the relative concentrations of the two substances in the phases before and after the transition.



Best wishes, yours sincerely

P. Diehl Oliver Münster

[1] J. Jokisaari, P. Diehl and O. Muenster, *Mol. Cryst. Liq. Cryst.*,**188**, 189 (1990)

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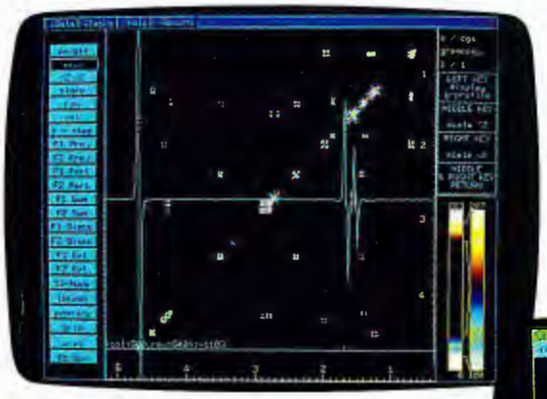

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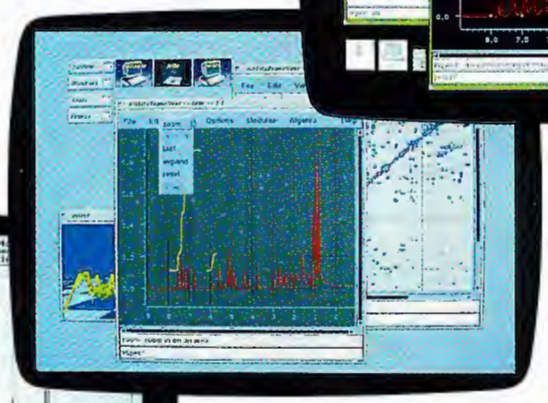

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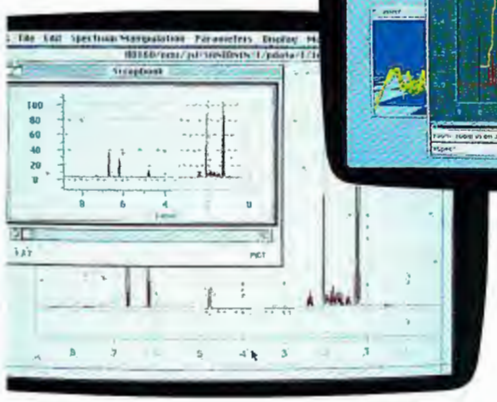

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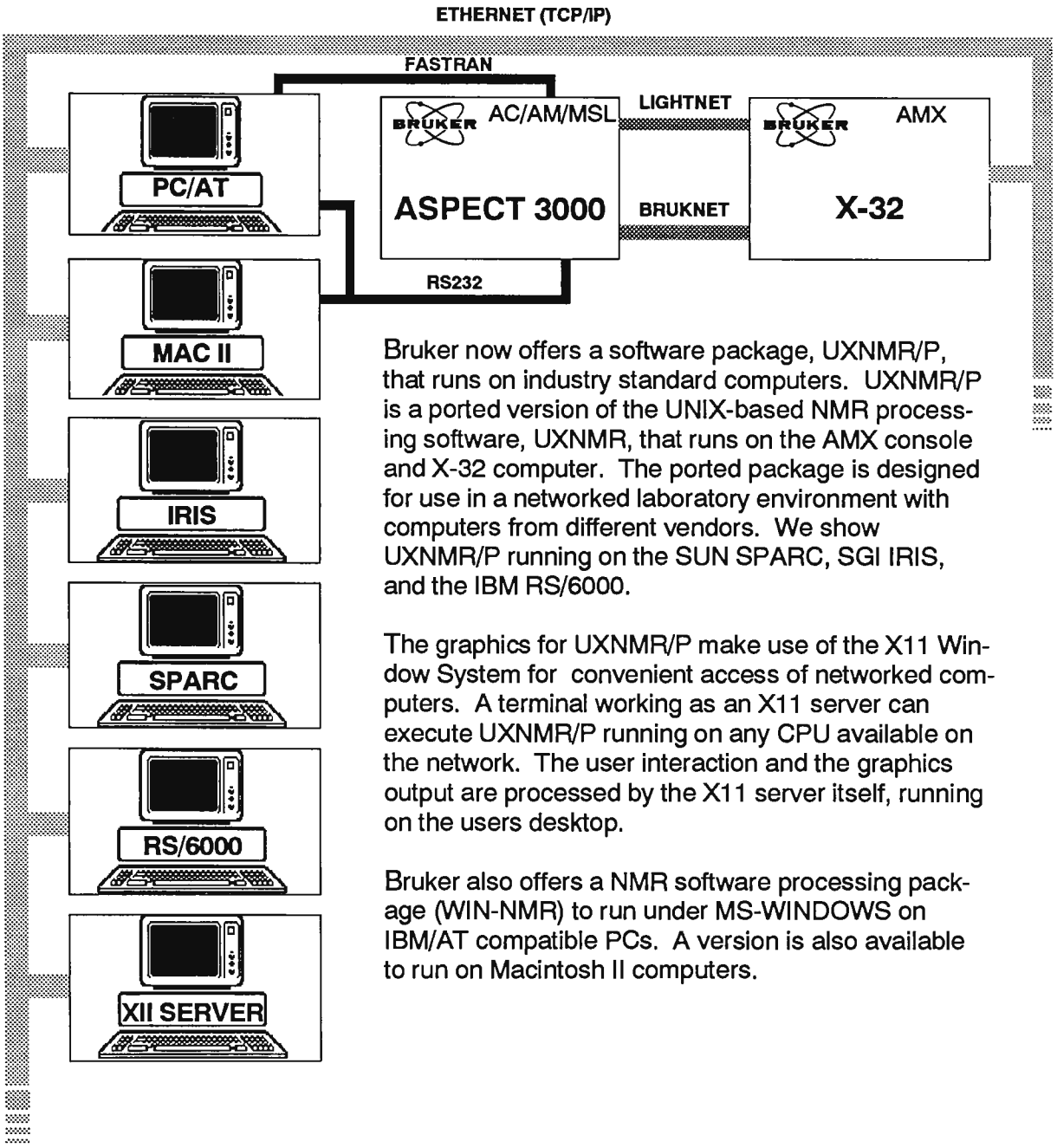
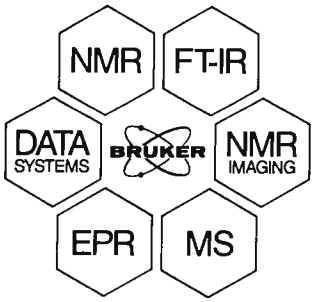


Bruker now offers a software package, UXNMR/P, that runs on industry standard computers. UXNMR/P is a ported version of the UNIX-based NMR processing software, UXNMR, that runs on the AMX console and X-32 computer. The ported package is designed for use in a networked laboratory environment with computers from different vendors. We show UXNMR/P running on the SUN SPARC, SGI IRIS, and the IBM RS/6000.

The graphics for UXNMR/P make use of the X11 Window System for convenient access of networked computers. A terminal working as an X11 server can execute UXNMR/P running on any CPU available on the network. The user interaction and the graphics output are processed by the X11 server itself, running on the users desktop.

Bruker also offers a NMR software processing package (WIN-NMR) to run under MS-WINDOWS on IBM/AT compatible PCs. A version is also available to run on Macintosh II computers.



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SCHOOL OF BIOCHEMISTRY

16th April 1991
(received 4/27/91)

Professor B.L. Shapiro
TAMU NMR Newsletter
966 Elsinore Court
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3D Homonuclear NMR: A Useful Step in Refinement of Small Protein Structures

Dear Dr Shapiro,

The refinement stages of our NMR structure of AP-A [1], a 49 residue polypeptide comprising four strands of β-sheet, have involved backcalculation of NOESY spectra. This process served to pinpoint some errors in the distance constraint list. In an effort to improve on the original (rather short) list, I have been re-analysing the 2D NOESY spectra which had been recorded and processed on our Bruker AM-500 spectrometer. Although the spectra were somewhat improved by off-line processing using Hare's FTNMR package, many peaks (eg. those of $C^{\beta}H$ and $C^{\gamma}H$) could still not be resolved sufficiently well to derive unambiguous NOE information and therefore useful distance constraints.

A very effective way of increasing the NOE restraint list has come instead from the results of a non-selective 3D TOCSY-NOESY spectrum [2]. This spectrum was recorded on a Bruker AM-500 instrument at the University of Utrecht, with the help of Geerten Vuister and Rolf Boelens. The sample used contained about 5mM AP-A in H_2O. The TOCSY (using a clean MLEV17 pulse sequence) and NOESY mixing times were carefully chosen to maximise magnetization transfer, and the values eventually used were 40ms and 200ms, respectively. The data array of 160 t_1 × 173 t_2 × 1024 t_3 points was acquired in a total of 69 hours.

After 5 days of processing using the TriTon software package developed at Utrecht, the transformed data set measured 256 × 256 × 512. The data set was of reasonably good quality, despite the relatively low sample concentration used. Data analysis involved plotting and analysis of the 512 ω_3 slices (or $\omega_1\omega_2$ planes), in which the vertical line represents TOCSY transfer, and the diagonal contains NOE transfer peaks. Each ω_3 slice corresponds to approx. 0.3ppm, which means that many slices contain information arising from more than one resonance, even for this small protein. In cases of overlap, it was necessary to check that an NOE observed between protons A and B was observed at both the ω_3 frequencies ω_A and ω_B. There was also overlap of intense crosspeaks from one slice to those adjacent, which complicated the analysis. Such problems could be overcome in the future by increasing the digital resolution in ω_3. It should be stressed that the spectrum of AP-A had been fully assigned previously from 2D data [3], which proved essential for me to analyse all the NOE information contained in the 3D spectrum.

The final list of NOEs is still being compiled, but the significant improvement in quality and quantity of this list is already evident. The increased number of distance constraints resulting from the unambiguous identification of previously unassigned or unobserved NOEs has made the recording of the 3D experiment very worthwhile. For instance, the region of AP-A encompassing Cys6-Asp7-Ser8-Asp9-Gly10 was previously thought to be essentially random coil in structure, but new NOEs seen in the 3D spectrum indicate that some type of reverse turn is present.

The Figure shows the ω_3 slice at 7.75ppm corresponding to NH resonances of Ser27 and Asp9. NOEs are seen on the diagonal and are identified from their coupled resonances appearing on the vertical. The following is a summary of the 'new' and 'old' NOE list for these amide protons:

	3D data	2D data
Ser27 NH.....	Gly28 NH Tyr 25 $H_2\beta$ Pro26 protons Ser27 protons	Gly28 NH Ser27 protons
Asp9 NH.....	Ser8 NH Asp9 Hβ	None

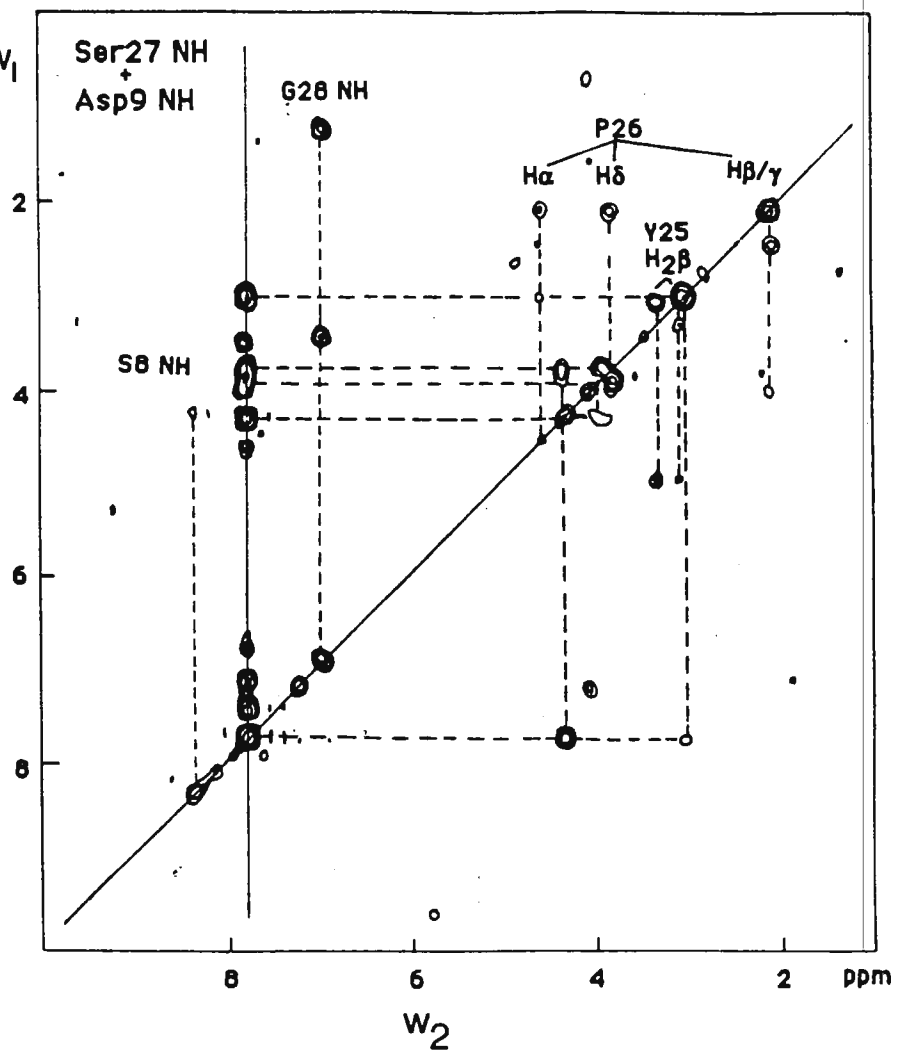
Please credit this contribution to the account of Ray Norton. Thanks to Geerten Vuister, Rolf Boelens and Rob Kaptein for helping to make my visit to Utrecht so fruitful.

1. Torda, A.E., Mabbutt, B.C., van Gunsteren, W.F. and Norton, R.S. FEBS Letts 239, 266-270 (1988).
2. Vuister, G.W., Boelens, R. and Kaptein, R. J.Magn. Reson. 80, 176-185 (1988).
3. Mabbutt, B.C. and Norton, R.S. Eur J. Biochem. 187, 555-564 (1990).

Yours sincerely,

Bridget Mabbutt

Bridget Mabbutt



Université de Lausanne - Faculté des Sciences

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Prof. Bernard L.Shapiro
966 Elsinore Court
Palo Alto, CA 94303
U S A

25.4.1991 (received 5/7/91)

^{14}N NMR ON LIQUID AMMONIA UP TO 330 K

Dear Prof. Shapiro,

After having studied solvent exchange on a variety of transition metal and main group element cations in aqueous and different non-aqueous solvents (like DMF, DMSO, methanol and others) we thought it could be interesting to look at liquid ammonia as solvent. The ammonia molecule is as small as the water one and has a relatively high dielectric constant (ca. 22). The capability of forming hydrogen bonds is less pronounced leading to the lower boiling point of -33.4 ° C .

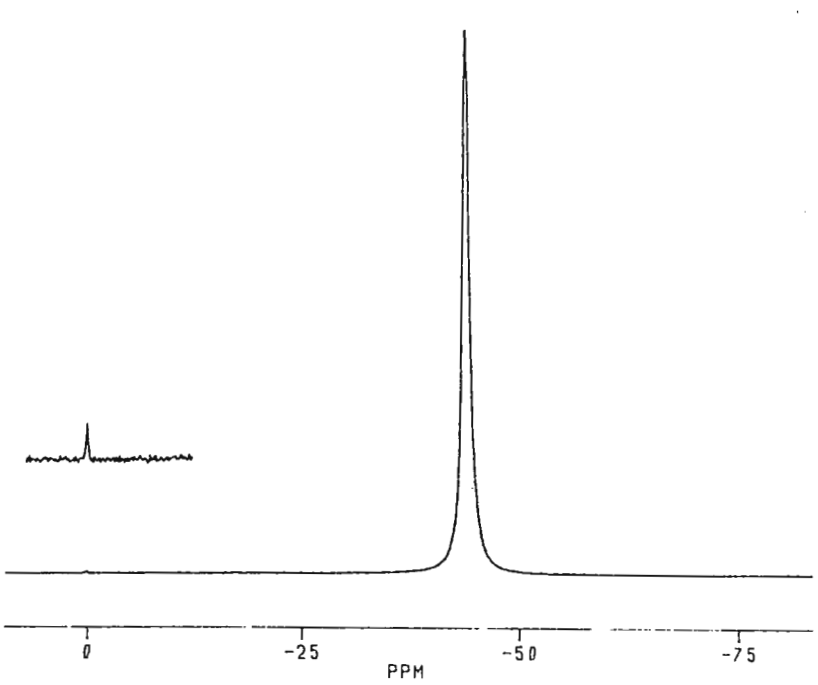
The study of the solvent exchange reaction mechanism in liquid ammonia using NMR suffers from the difficulty that NH_3 is a gas at temperatures above -34°C. To obtain informations on the reaction mechanism we measure solvent exchange rates over a wide range of temperatures and pressures leading to activation enthalpies, entropies and volumes.[1] Liquid ammonia and solutions in it can easily be studied over a wide temperature range starting close to the freezing point at about -77°C to about +60°C using sapphire tubes as described by Roe[2].

Because of the fast proton exchange in liquid ammonia we have to use ^{14}N NMR to study solvent exchange. We used in this preliminary work a 4.7T instrument equipped with a 10 mm broadband probe and 10 mm o.d. sapphire tubes. The observation frequency is 14.45 MHz. We looked firstly on neat ammonia containing $N(CH_3)_4ClO_4$ (saturated solution, ≈0.2m) as internal chemical shift reference and NH_4ClO_4 to vary H^+-concentration. The samples are prepared by giving a weighed amount of solid into the sapphire tube and then syphoning cold liquid NH_3 into it. The tubes were filled up to more than 50% to minimize concentration changes of the solution due to the strong increase of gas pressure in the upper part of the tube if temperatures higher than the boiling point are reached. The exact amount of liquid added to the sample was calculated from the filling height.

---

[1] A.E. Merbach; Pure & Appl. Chem. 59, 161 (1987)

[2] D.C. Roe, J. Magn. Res. 63, 388 (1985)



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MNNH31.301
DATE 8-2-91

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SY   14.0
O1   -5642.578
SI   16384
TD   16384
SW   10000.000
HZ/PT    1.221

PW      20.0
RD        .100
AQ        .819
RG          8
NS       1659
TE        230

FW   12500
O2    4195.605
DP   63L PD

LB        0.0
GB        0.0
CX       15.00
CY       10.00
F1        9.457P
F2      -83.675P
HZ/CM   89.762
PPM/CM   6.209
SR    -4648.93
```

Figure 1 shows a ^{14}N NMR spectrum recorded at 27.5°C at 14.45MHz using 16k data points and a spectral window of 10kHz. The $[NH_4]^+$ concentration was 0.207m. 1800 FID are added.

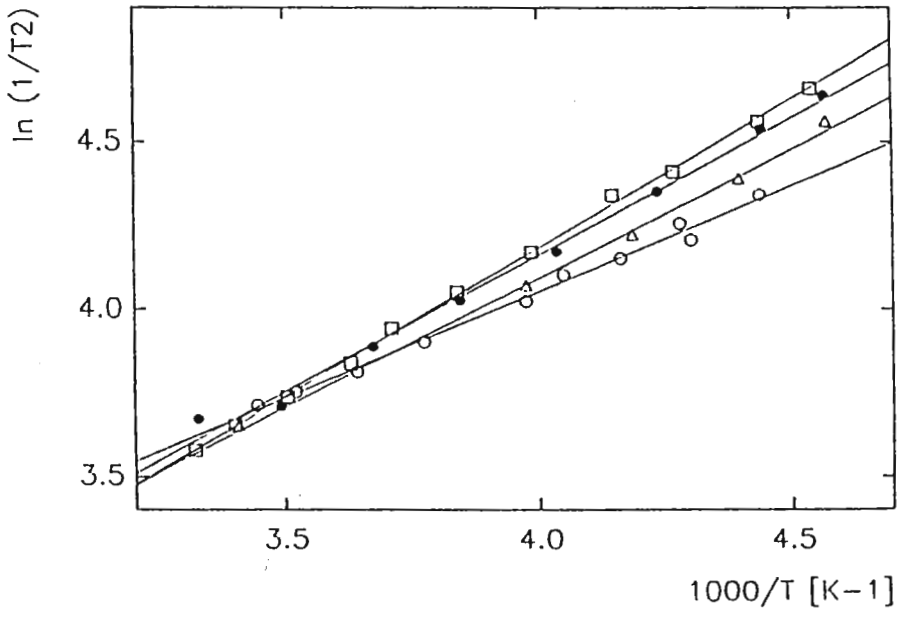

Figure 2: Temperature dependence of ^{14}N NMR transverse relaxation of liquid ammonia at various acid concentrations as obtained from linewidth measurements. The NH_4ClO_4 concentrations are 0.0334m (Δ), 0.042m (O), 0.207m (●), 0.317m (□).

V. Besançon Dr. L. Helm Prof. A.E. Merbach

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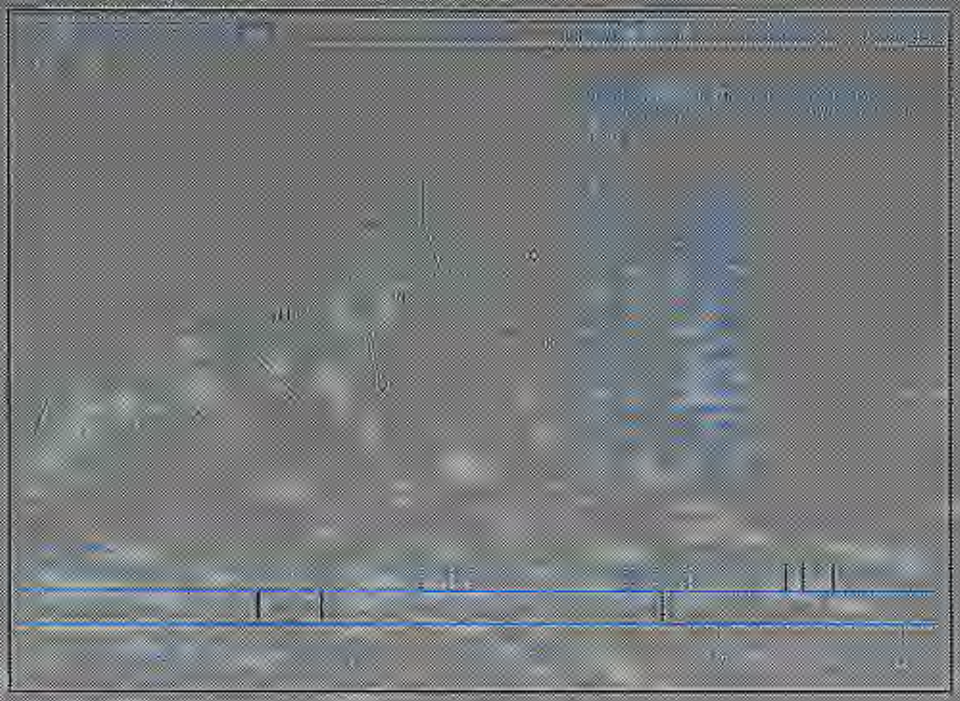

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CENTRAL RESEARCH & DEVELOPMENT
Experimental Station
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Wilmington, Delaware 19880-0328

April 19, 1991
(received 4/22/91)

Dear Barry, "Magnetization transfer data handling"

Our 11 year old Nicolet NT-360 widebore is still functioning, and in fact provides a number of utilities that are not available on our newer high field spectrometers. Chief among these capabilities is variable temperature work at "extremes" -- our work in catalysis and organometallic chemistry has required temperatures as low as -150C all the way up to +250C (albeit for different problems). This entire range is within the existing capabilities of the original VT unit, although we did have to disable the high-temperature limit switch that would otherwise restrict the heater current output to +160C. This upper limit was appropriate for our original probes, but with a specially built high temperature probe obtained from FMR we have been able to run at +250C for extended periods of time. Operation at either temperature extreme is facilitated by the widebore design feature of mixing lots of room temperature air (i.e., dry nitrogen) with the exiting VT gas so as to minimize any effects on the shim stack.

This preamble brings me to the main point of this note - namely how to handle the large volume of data that is produced by a reliable but isolated 1280 computer. One option is to transfer spectra (or fids) to our Vax cluster for processing via FTNMR (from Hare Research). However, the majority of our kinetic studies on discrete equilibria in catalytic cycles involves multi-site magnetization transfer, which requires an inordinate effort in data handling; e.g., a given case might involve 8K data sets times 32 time points times 4 separate site inversions (for a 4-site exchange problem), and this "complete data set" approach would then be repeated for a variety of conditions and temperatures. While it was possible to write an FTNMR macro that would produce integrated intensities for a series of spectra, and have these intensities written to a file (an obscure use for "assignment lists"), this approach suffers from the fact that the inversion transfer delay times are not carried along with the header information. In addition, we have suffered the overhead of transferring 4MB of data when we only want a total of 640 points (32 time values and 4 site intensities, all repeated 4 times for a complete data set). So much time was taken simply transferring the data sets that it was literally faster to type the results into a Vax file for subsequent analysis. A recent study (J.Am.Chem.Soc., 112, 7707 (1990)) ultimately required typing almost 10^4 such entries!

Fortunately, we have since installed a PC with appropriate communication software to replace the old Teletype. Thus, with output directed to the "teletype", the DR data sets can be directly captured into a log file in a matter of seconds. In this case, the resulting file contains all the information we need but is arranged in a somewhat inconvenient format. This situation is readily dealt with however; any number of such files can be accumulated on the PC and then transferred quickly and conveniently to a Sun 4/110 which is on the same Tops network as the PC. Matt O'Brien of this department has written a script which takes the raw data in these files and assembles the results in the desired format (namely time, intensity at site 1, intensity at site 2....,etc). In addition to being fast, this process was made even easier by an X-Windows interface that Matt developed to handle the other tedious chores associated with magnetization transfer data analysis (e.g., data file and plot file manipulation). With this effort, we have been able to greatly speed up the quantitative analysis of a variety of exchanging systems since this new interface has effectively removed the major activation barrier to this objective. Figure 1 illustrates a portion of the interface and indicates the nature of the operations which are now under mouse control.

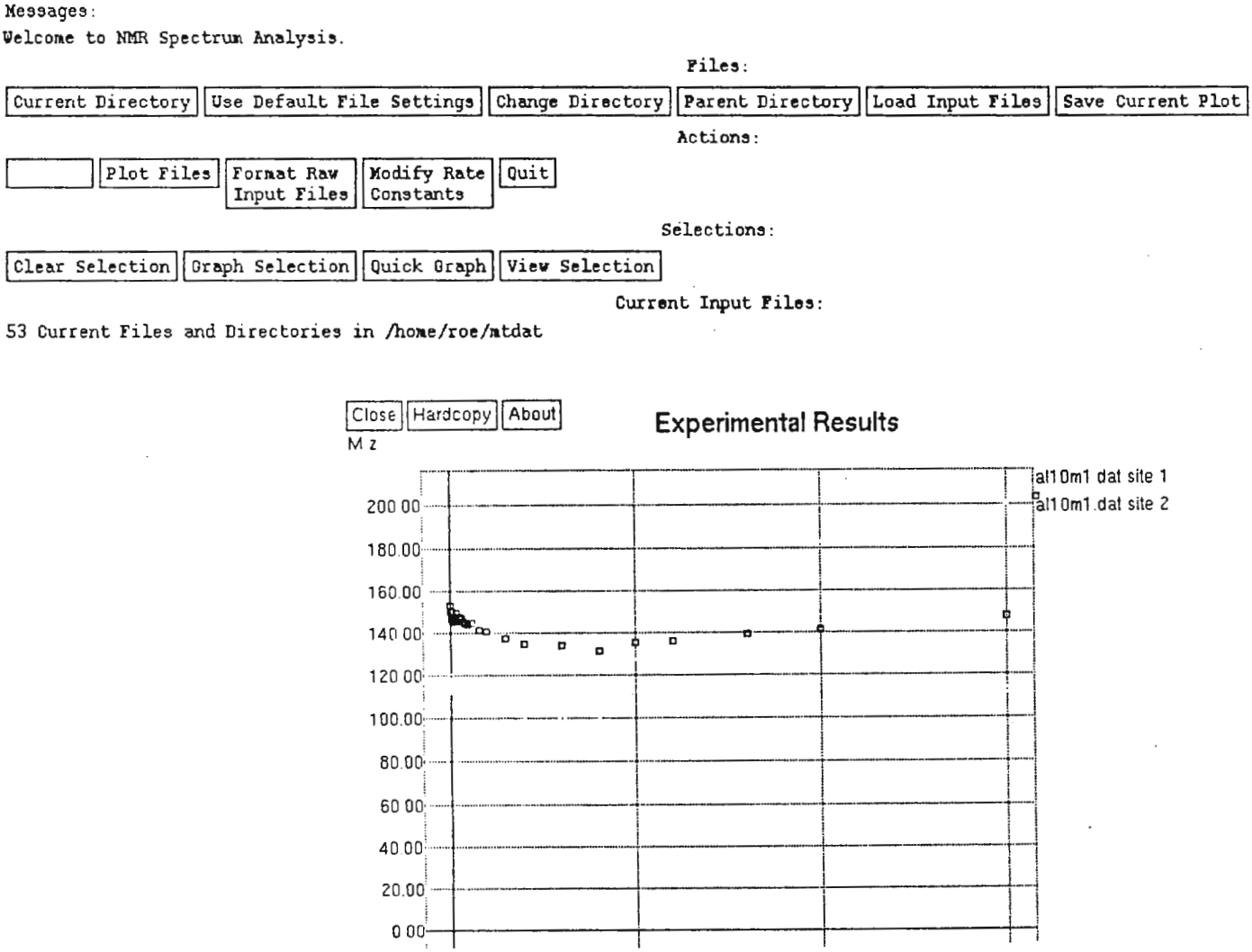
The nonlinear least-squares program that provides the best fitting rate constants and relaxation times was written some time ago in a Vax environment. The code has been ported to the Sun, and we are presently refining its operation under the new interface. We hope to report on further improvements in the optimization routines in the near future. Please credit this contribution to the account of Patricia Watson.

Sincere best wishes,

Chris

Chris Roe

Figure 1. Portion of X-Windows interface for manipulating magnetization transfer data sets. The plot of intensity vs time was produced by clicking on a filename, and then on the button "Quick Graph".



Amoco Corporation
Amoco Research Center
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312-420-5111

April 23, 1990(?) (received 5/6/91)

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

Data Transfer and Translation in a Networked Laboratory

Dear Dr. Shapiro:

Our laboratory currently contains seven spectrometers: four Sun-based Varian VXR/Unity series (500, 400, and two 300s), two Chemagnetics (a CMX-200 with an Intel computer running Xenix, and an M-100 which offloads its data to a Microvax running NMRi software), and a Nicolet 1280-based NT-300. An Aspect 3000-based Bruker 300 is located in another research area on our site. We also have several offline Sun computers which serve as data stations. All these different computers, running five different types of NMR software, cause real problems with data interchange and staff training. It became obvious that we needed some kind of common data processing capability.

We settled on our Sun computers for this purpose. These computers run Varian NMR software, and the open architecture of Varian's data files makes it easy to design translation programs to handle foreign data formats. Furthermore, the Sun computers are on an Ethernet network which includes the Varian and Chemagnetics spectrometers and many other computers throughout Amoco, raising possibilities of data transfer to our clients.

I wrote a data translation program which reads various data file formats and outputs Varian's "sread" import/export format. The program is written in modular fashion which makes it easy to design new translations, either from the command line or by building them into the program. Some of the possibilities include scaling or zeroing of the reals or the imaginaries; negation of the imaginaries (spectrum reverse); byte reversals; and VAX-, Bruker-, and IEEE-floating point to 32-bit integer conversions. Parameters are handled as well as data; all vital parameters are translated as are any non-vital parameters that I knew Varian equivalents for. New parameter translations are easy to add. Currently CMX 1-D and 2-D and NMRi 1-D formats are completely supported; Bruker Aspect 1-D is in principle but I have not had much opportunity to test it.

A simple automated data-transfer system was built around the conversion program to make operation as painless as possible. The data transfer is done by Unix shell scripts, executing on a data station, which log into the CMX or Microvax over Ethernet (FTP), copy the remote data file onto the data station, and feed it into the conversion program. The scripts are executed by VNMR macros, so all the operator has to do is run a macro named after the remote spectrometer and supply a file name. Transfer and conversion take only a few seconds even for large files, and the data appears, ready for manipulation, in the operator's current VNMR experiment.

The conversion program is written in portable C and should work on most platforms without modification. The data transfer scripts need only to be customized with

default directories and login protocols. I would be happy to provide copies of the program to anyone interested; simply send me a 1/4" magnetic tape cartridge (or for Sparcstation users, a 3.5" floppy disk).

Please credit this contribution to the account of G. J. Ray.

Sincerely,

Stephen T. McKenna

****

Department of Chemistry
University of Wisconsin

1101 University Avenue
Madison , Wisconsin 53706

May 8, 1991 (received 5/11/91)

Dear Barry,

We have been measuring exchange rates with water, in acetone-water mixtures, of the hydroxyl protons of sucrose, as a function of solvent composition and temperature. Conditions are adjusted to allow resolution of all eight hydroxyl resonances, which results in exchange rates being in the range studied by saturation transfer. The raw data from these experiments is of course peak intensities decaying exponentially with saturation time; we have been extracting decay rates simply by using the three parameter fitting routine supplied with the system software.

The latest version of the software (VNMR, version 3.2) features a significant advance in the flexibility of the fitting routine, by making a generalized regresion routine available. The specific feature of greatest use to us is that now different numbers of data pairs can be included in individual data sets, rather than having to have the same number of points in all sets. This allows two refinements in our procedures.

First, in spite of our best efforts, there is occasionally one bad point in one or another of the intensity versus time sets (i.e., for one peak), which should clearly be eliminated. This was possible before only by eliminating the corresponding time point from all data sets; now, only the offending point need be removed. The macro to do this was a bit of a challenge for this neophyte programmer, and will gladly be supplied on request.

Second, the activation parameters for the reaction are available from rate versus temperature data. Formerly this was accomplished using the linearized version of the Eyring equation and a linear least squares analysis. Now the data can be fit directly to an exponential function, presumably resulting in better estimates of the activation parameters. (The overlap of some peaks at various temperatures prevents getting independent rates for all peaks at all temperatures, hence the need for variable input capability.)

One caveat: the display and plot routines (expl and pexpl) do not always display all the points used in the regression calculations (although the printed results show that all input data is actually used). Varian is aware of the problem, but users should check results carefully until the bug is fixed.

Yours kinetically,
Bruce Adams

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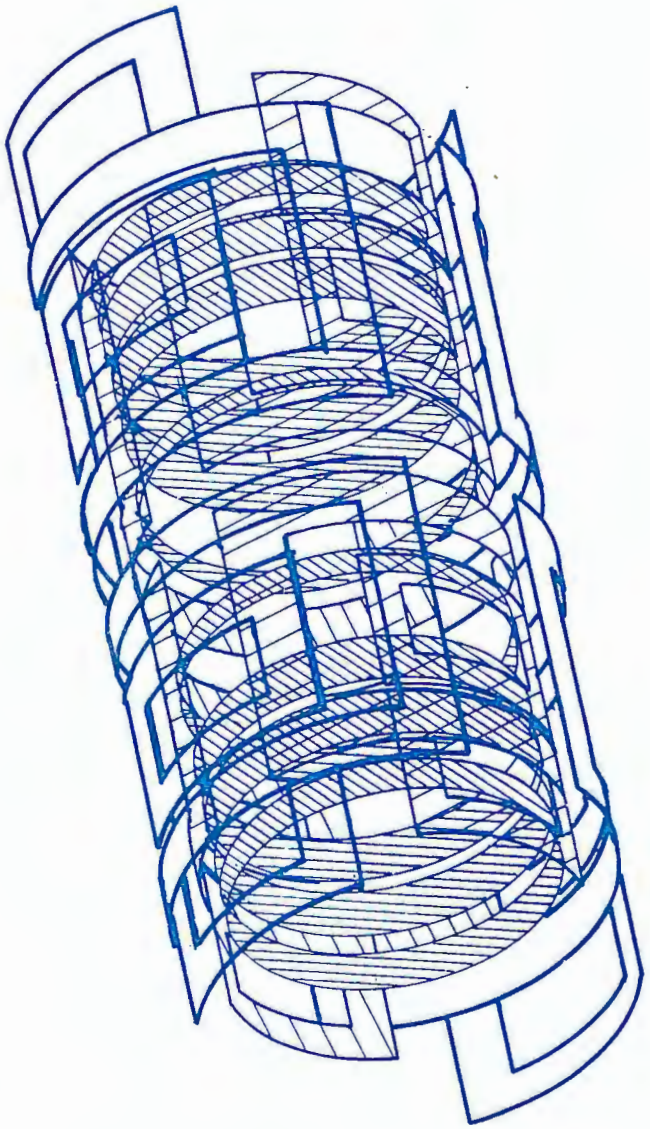

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GEORGETOWN UNIVERSITY MEDICAL CENTER

Cancer Pharmacology Section
Department of Pharmacology

April 29, 1990
(received 5/13/91)

Prof. B.L. Shapiro
TAMU NMR Newsletter
966 Elsinore Ct
Palo Alto, CA 94303

Gradient method for water suppression and separation of intra/extracellular signals in 1H NMR

Dear Dr. Shapiro,

A major problem encountered in the NMR study of cells and organs is discrimination between intra- and extra-cellular contributions to the spectrum. This problem depends on cell density and is more pronounced when the extracellular fraction increases. In *ex vivo* studies, this density may be orders of magnitude lower than *in vivo*. For instance, for breast cancer cells embedded in agarose gel, the extracellular water volume is about a factor of 100 larger than the total intracellular one. Thus, the NMR signal from a 0.1 mM metabolite in the perfusion medium will be comparable in intensity to 10 mM of this same metabolite in the cell, complicating the interpretation of signal intensity changes in terms of intracellular metabolite concentrations. For proton studies an additional problem arises due to the presence of the intense water resonance. For the typical example above, total intra- and extra-cellular water has a signal intensity that is a factor of about 10^6 higher than that for a 10 mM metabolite. As a result, proton spectra of intracellular metabolites in perfused cell cultures have never been reported. Proton spectra of cell suspensions have been reported, but separation of intra- and extracellular signals is not straightforward.

We address the problem using the difference in motional properties of these components (1-2). Intracellular species diffuse in the cellular matrix with an effective diffusion constant D_i, which depends on several factors, e.g. molecular size, bonding, viscosity, temperature, and possible restrictions due to compartmentation. When extracellular, these species have a diffusion constant D_e in neat medium, but also flow through the perfusion vial holding cells and their support system (an agarose gel), giving an apparent constant D_e^*. Application of a pair of pulsed magnetic field gradients sensitizes spin echo magnetic resonance experiments to diffusion. The first gradient G of length δ, disperses the complete signal, which is regained by application of a compensating gradient after time D (Fig. 2). However, when molecules move incoherently (e.g. diffuse) between application of these gradients, the signal is attenuated. For a single component, assuming unrestricted diffusion, the final intensity S is related to the initial S_o without weighting by

$$\ln(S/S_o) = -\gamma^2 G^2 \delta^2 (\Delta - \delta/3) D = -bD \qquad [1]$$

D is the apparent diffusion constant, b the diffusion-weighting factor. When describing multiple-compartment systems, corrections for relaxation-time differences and exchange have to be included (1-2). When restricted diffusion plays a role, the formula is no longer correct, but the signal-intensity decay as a function of diffusion time ($\Delta - \delta/3$) can be used to estimate cell dimensions.

When strong diffusion weighting is required with minimal loss of echo time (TE), it is convenient to use a stimulated echo (STEAM) sequence (Fig. 2). During TM, only T1-relaxation and multiple quantum relaxation (for coupled spins) occur. This is advantageous in vivo, where T1s are generally much longer than T2s. At the short TEs that we use here, multiple quantum contributions are small for protons with coupling constants in the order of 7 Hz. In most experiments, water suppression was performed with selective rf pulses followed by gradient dephasing (WS in Fig.2). Suppression was improved by application of the diffusion gradients. Fig. 3A shows the attenuation curve for water as a function of the diffusion-weighting factor b for drug-resistant MCF-7 cells embedded in an agarose gel and being perfused with growth medium. To prove that the slow component is intracellular, we repeated the experiment with gel and medium only, and no slow component of this order of magnitude was found. (Fig. 3B). Therefore, as a first approximation, we use the largest and

lowest rates to describe extra- and intracellular components, respectively. When fitting the last 8 points of this curve to a straight line, an intracellular diffusion constant $D_i = 0.11 \times 10^{-9}$ m^2/s is found. This value is comparable in magnitude with the one deduced for a model system of multicellular spheroids by NMR microimaging (3). Notice that this value need not be the diffusion constant for freely moving intracellular water, since a long diffusion time was used in the experiment. We are presently initiating experiments as a function of D, in order to study the influence of restriction on D_i. Fig. 4 shows metabolite spectra obtained with and without cells (only perfusion medium) and with and without diffusion-weighting in only 2 minutes.

A detailed paper describing these studies has appeared in Proc. Natl. Acad. Sci. USA (April 91) 88(8), 3228 (1991)

Peter van Zijl Chrit Moonen Pat Faustino James Pekar Ofer Kaplan Jack Cohen

1) Tanner JE & Stejskal EO (1968) J. Chem. Phys. **49**, 1768-1777; 2) Andrasko J (1976) J. Magn. Reson. **21**, 479-484; (1976) Biochim. Biophys. Acta **428**, 304-311; 3) Neeman M, Jarrett KA, Sillerud LO & Freyer JP (1991) Cancer Res., in press.

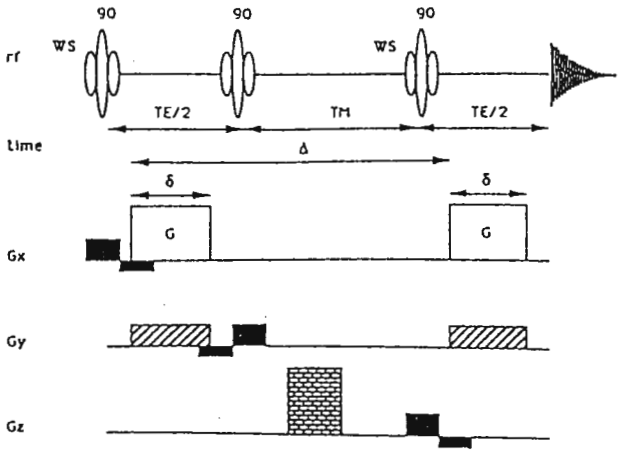

FIG. 2. Diffusion-sensitized stimulated-echo NMR localization experiment. Diffusion weighting can be adjusted by changing Δ, δ, *G*, or any other gradient contribution. Thus all experiments are at least slightly diffusion weighted. In our experiments, δ and Δ are constant, whereas *G* is used to change diffusion weighting. When needing long Δs, TM can be increased without lengthening TE, thus avoiding T_2 and J-modulation losses. For localization purposes, the rf pulses are selective sinc pulses, each in the presence of a different orthogonal gradient. The localization gradients and their compensations are in black. The TE crusher is matched and the TM crusher is the brick wall.

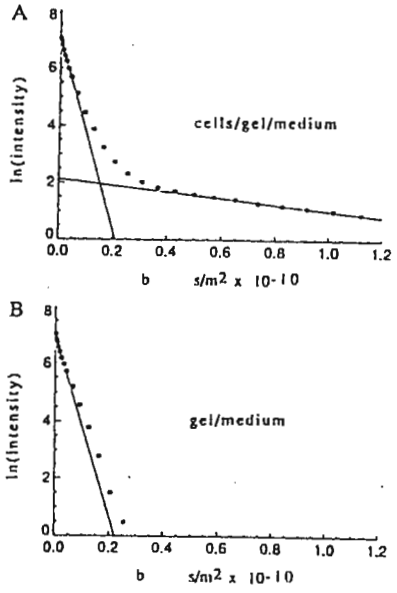

FIG. 3. Water signal intensity (arbitrary units) as a function of diffusion-weighting factor *b* for an experiment with perfused gel and cells (*A*) and one with only a perfused gel (*B*). The increase in *b* was attained by increasing *G*, while keeping Δ (150.5 ms) and δ (25 ms) constant. TE = 100 ms, TR = 2.44 s, and TM = 100 ms were used. The fast and slow asymptotes were used to determine extra- and intracellular diffusion constants, respectively.

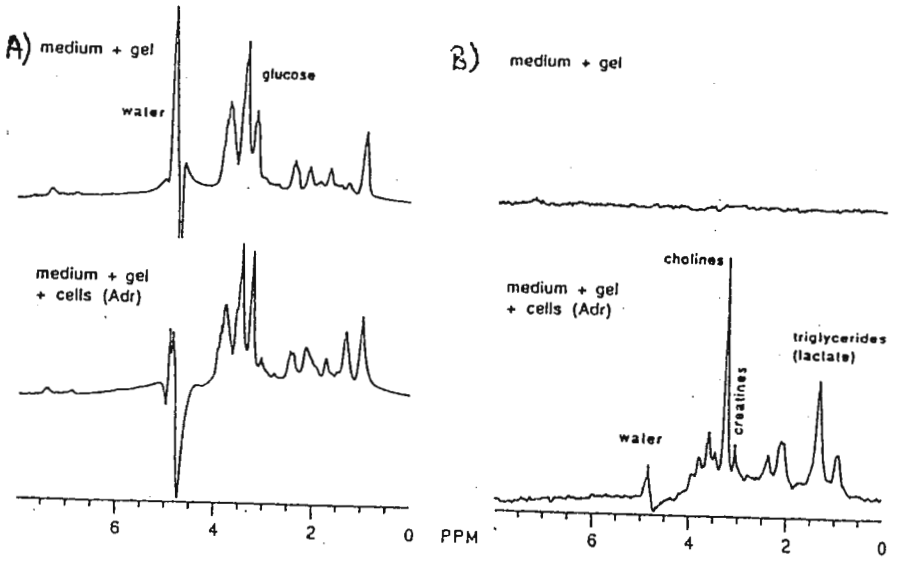

FIG. 4. Comparison of 200-MHz proton NMR spectra (TE/TR = 12/2440 ms; line broadening, 4 Hz) for perfusion experiments with only gel (top) and with gel and cells (bottom) using different diffusion-weighting factors: $b = 0.028 \times 10^{10}$ s/m^2 (*A*); $b = 0.770 \times 10^{10}$ s/m^2 (*B*). At high diffusion weighting, no signal appears when using a perfused gel only, whereas the complete intracellular spectrum appears when cells are present. Note that *A* (512 scans) and *B* (128 scans) are displayed at different scales for optimum display. Adr, Adriamycin.

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U. T. Mueller-Westerhoff

9 May 1991
(received 5/16/91)

Dr. B. Shapiro, TAMU Newsletter

***[STILL SOME MORE]* NMR Experiments on Protonated Ferrocene: Undecets and Fe-H Coupling Constants.**

Many NMR experiments have been reported on protonated ferrocene. This "old hat" nevertheless is not too old to have provided us now with a few surprises. We report here some of our observations.

^{1}H-NMR spectra were run at 270 MHz (IBM-Bruker) on concentrated samples of protonated ferrocene, prepared by dissolving (in an inert atmosphere, to strictly avoid the formation of the paramagnetic ferrocenium ion!), pure ferrocene in ice-cold $BF_3 \cdot H_2O$, which led to an orange-yellow homogeneous solution. Because this is a deuterium-free sample, the averaged acid/H_2O peak was defined (based on previous experiments) as 8.30 ppm, and no shimming on the FID was attempted.

In related work, we have been able to establish that in protonated ferrocenes a rapid equilibrium exists: the additional proton can reside on the metal ***and*** in the endo position of any one of the ten ring carbons. This leads to an averaged position of the "hydride" (in the lingo of organometallic chemists) proton, which appears at approximately -1.9 ppm. The ten ring protons appear at 5.1 ppm as one doublet due to their equal and averaged interaction with the hydridic proton ($J = 1.75 \pm 0.1$ Hz).

In principle, such an interaction should let us observe a rarity: the hydride signal should be an undecet. Looking at this signal carefully and in high, but reasonable, amplification lets us indeed discern most of the expected 11 peaks - and in the predictable ratio! Since the expected ratio of the central peak to the exterior peaks is 252:1, observation of all peaks would border on the miraculous. The strict exclusion of oxygen certainly helped us to avoid any line broadening and to detect this splitting (Fig. 1).

Decoupling at the observed peaks was done as a routine comparison but provided an interesting surprise. Irradiation at the "hydride" frequency showed the expected collapse of the 5.1 ppm doublet to a singlet. The irradiation at 5.1 ppm also showed the expected result: a singlet at -1.9 ppm; **BUT**: this singlet (Fig. 2) has satellites at ±10.8 Hz, each with about 1.5% of the intensity of the main signal. We attribute these peaks to Fe-H coupling. Indeed, the intensity corresponds closely to the 2.1% natural abundance of the spin 1/2 $^{57}_{26}Fe$ isotope. A careful look at the literature has convinced us that this seems to be the first observation of this type of coupling (will we stand corrected??). Any observable isotope effect is within the limits of our digital resolution. The measured J_{Fe-H} = 21.6 Hz may represent a reduced value, because the rapid exchange (of which we are convinced for other reasons) could diminish the observed coupling.

Thomas K. Leipert* Ulrich T. Mueller-Westerhoff

[* To whose account this letter should be credited.]

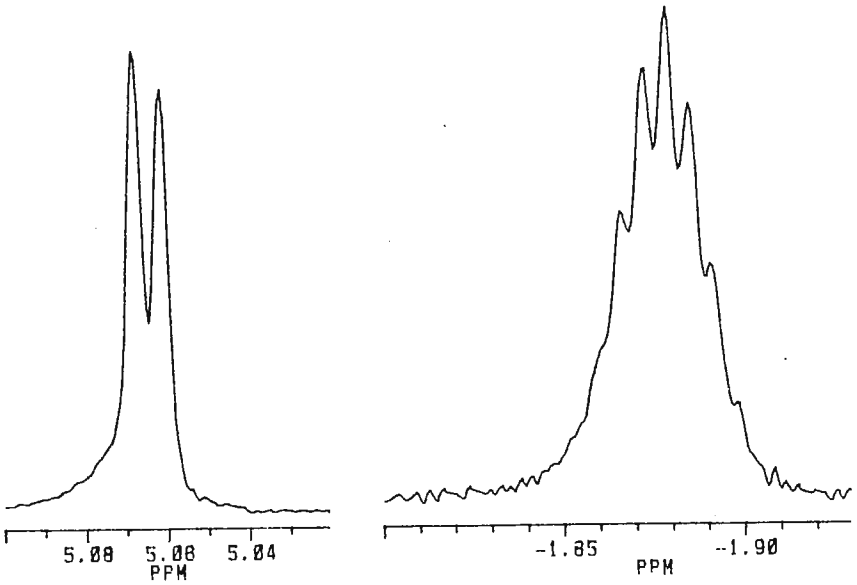

Fig. 1: Coupling in $Cp_2TiF / BF_3 \cdot H_2O$

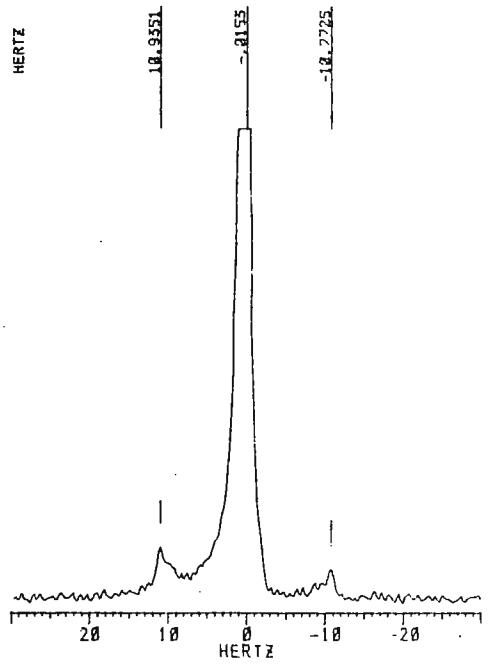

Fig 2: ^{57}Fe Satellites

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BRUKER

May 14, 1991
(received 5/17/91)

Dr. Barry Shapiro
TAMU Newsletter
966 Elsinore Court
Palo Alto CA 94303

Re: Positions Available

Dear Dr. Shapiro:

Our Software Development group in Billerica has immediate openings for two positions. The first is for an **NMR Software Specialist**. The ideal candidate for this position will have an advanced degree in Chemistry or Physics and extensive experience writing software for data processing. Familiarity with NMR spectroscopy and knowledge of the C programming language is essential.

The second position is for a **Postdoctoral Fellow** in NMR Data Processing. The ideal candidate for this position will have a recently earned Ph.D. in Chemistry or Physics and a strong mathematics background. The position will involve the development and implementation of lineshape analysis and spectrum simulation software for solidstate NMR spectra. Direct experience with the analysis of solidstate NMR spectra is preferred, however, candidates with related experience will be considered. Significant programming experience is required.

If you feel you qualify for either of these positions and would like to work in a pleasant suburban setting for the world leader in NMR spectroscopy, send your curriculum vitae to my attention at the above address.

Sincerely

Charles G. Thibault, Ph.D.
Manager of Software Development

Pfizer Limited, Sandwich, Kent CT13 9NJ
Telephone: Sandwich (0304) 616161 Telex: 966555
Facsimile: CCITT Groups II & III
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Central Research

Dr. Bernard L. Shapiro,
TAMU NMR Newsletter,
966 Elsinore Court,
Palo Alto, CA 94303,
USA.

May 13, 1991
(received 5/18/91)

tel. 0304-616672
fax 0304-616726

'FIDDLEing in FTNMR.'

Dear Dr. Shapiro,

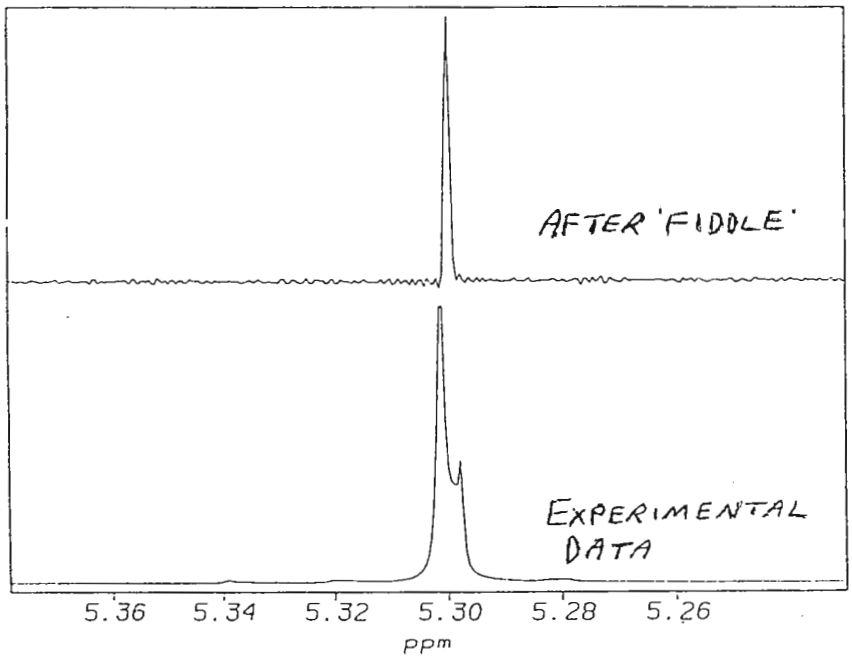
The FIDDLE algorithm[1] for deconvolution of an experimental data set with a reference line of known lineshape is potentially a very powerful tool for removing frequency-independent artifacts from spectra and for restoring an ideal lineshape.

We have recently had a number of different problems where we needed to use FIDDLE to clean up data. Since we could not program it on our GN500 spectrometer, we decided to implement the algorithm within the FTNMR program[2] which we run on our VAX cluster. This letter describes that implementation and shows a simple example of the power of the method for lineshape improvement.

The first step of the FIDDLE process is the digital extraction of a reference singlet from the experimental spectrum. This is then deconvoluted with a corresponding signal with idealised lineshape and the resulting function is applied to the entire experimental data set. Since FTNMR can perform complex number division and multiplication, the implementation of FIDDLE is relatively straightforward. Our approach has been to add to FTNMR a command *xrf* which zeros the region on either side of the chosen reference peak, and to use this command in a macro which performs the rest of the calculations. The entire correction process is fast, taking only a few seconds on a VAX 8800.

A typical macro to perform the FIDDLE deconvolution is shown below, together with its use for removing a substantial z^2 shimming error.

```
;fiddle.mac
get 'Initial FID filename?:' data1
get 'Reference FID filename?:' refdata
re &data1
bc 0.1
mpt 1 0.5 0
con      ;conjugate needed for GN data
ft
ph
xrf      ;zeros outside reference region
ift
xbf 1
re &refdata
dwb 1
xbf 1
re &data1
con
mwb 1
bc 0.1
mpt 1 0.5 0
ft
ph
dr
end
```



Helpful discussions with Gareth Morris are gratefully acknowledged. Please credit this contribution to David Bowen's account.

Dr. A. G. Swanson

---

1. G.A.Morris, *J.Mag.Reson.*, **80**, 547 (1988)
2. Hare Research Inc., Woodinville, WA.

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U.S.A

Fri, May 10, 1991
(received 5/18/91)

Professor B.L. Shapiro,
TAMU NMR Newsletter,
966 Elsinore Court,
Palo Alto, CA 94303

Quantitative Proton Spectra of the Human Brain

Dear Professor Shapiro,

Thank you for your reminder. Proton NMR spectroscopy of the brain appears to be one of the most promising areas for clinical applications of NMR spectroscopy. One of the key requirements for the analysis of the spectral data is the accurate conversion of NMR signal intensities to molar concentration units. For the human brain, previous quantitation methods have been based on either the use of an external reference (1), or on an assumed value for either total creatine and NAA concentrations (2,3). Both approaches may be problematical: external references are susceptible to error due to inhomogeneities in both the B_0 and B_1 fields, and creatine or NAA levels may change under pathological conditions. We have investigated the use of tissue water signal as an alternative internal reference signal for quantitation. Quantitation relative to water has been used for some time in ^{31}P NMR spectroscopy (4). For ^{1}H NMR spectroscopy, the implementation is somewhat simpler since no corrections are needed for variations in spectrometer sensitivity at different frequencies, and the potential for mis-calibration of flip angles is also reduced.

We have recorded preliminary data from volume of frontal cortex white matter in 5 volunteers. Spectra were recorded using the STEAM sequence on a 1.5 Tesla General Electric Signa scanner. Water signals consisted of 4 scans, with TR = 10 seconds, TM = 80 msec, and TE = 50,100,150 and 200 msec. Water-suppressed spectra were recorded using 16 scans (TR = 10 seconds) or 64 scans (TR = 3 seconds), with TM = 80 msec, and TE = 30,60,90,120,200 and 270 msec. Spectra were processed with a 3 Hz line broadening, and analyzed using a time domain non-linear least squares fitting procedure (5). Water signal intensities were corrected for the additional attenuation factor which was used to prevent overflow of the analog-to-digital converter. All signal intensities were corrected for T_1 and T_2 losses, partial saturation due to the water suppression pulses, and the number of protons per functional group. Concentrations were calculated assuming a cerebral water content of 80% (corresponding to a molar proton concentration of 88.9M) and density of 1.049 g/cm^3 (1).

Calculated concentrations were: Choline 2.6±0.6, Creatine 11.8±2.9, and NAA 15.4±2.8 (μmol/g ± standard deviation). NAA values in human white matter have been reported as 5.9μmol/g (1), 17 μmol/g (3) and 4 μmol/g (6). NAA has been determined by conventional biochemical techniques to be of the order 4.9 μmol/g in human brain. For creatine, values are 8.9 μmol/g (1), 10.0 mM (3), and 7.7 μmol/g (6) have been reported, while for choline, values of 2.2 mM (3) and 0.6 μmol/g (6) have been reported. The values reported here are in reasonable

agreement with those of Frahm et. al. (3), who based their values on a total creatine content of 10 mM. The higher NAA values obtained in vivo, compared to those determined from tissue extracts (6), would appear to reflect the overlap of NAA with resonances from glutamate and glutamine, as well as the presence of other N-Acetyl compounds (3).

Tissue water appears to be a suitable internal intensity standard for ^1H NMR spectroscopy of the brain. Pathological variations in cerebral water content occur over a reasonably small range (≈ 75 to 85%), and changes in water content can also be estimated from MR images. The method should be readily extendable to multiple-voxel chemical shift imaging studies to determine regional variations in concentrations and grey/white matter differences.

yours sincerely,

P.B. Barker.

Peter B. Barker, D. Phil.
Assistant Professor of Radiology

1. P.A. Narayana, L.K. Fotedar, E.F. Jackson, et. al., *J. Magn. Reson.*, **83**, 44-52 (1989).
2. J. Frahm, H. Bruhn, M.L. Gyngell, et. al., *Magn. Reson. Med.*, **9**, 79-93 (1989).
3. J. Frahm, H. Bruhn, M.L. Gyngell, et. al., *Magn. Reson. Med.*, **11**, 47-63 (1989).
4. K.R. Thulborn and J.J.H. Ackerman, *J. Magn. Reson.*, **55**, 357-371 (1983).
5. P.B. Barker and S. Sibisi, Proc. 9th SMRM, 1089 (1990).
6. O.A.C. Petroff, D.D. Spencer, J.R. Alger et. al., *Neurology*, **39**, 1197-1202 (1989).

****

POSITION AVAILABLE

A position has recently become available in my laboratory for a hardware-oriented NMR spectroscopist.

The position involves maintaining the high performance level of our VXR-500S spectrometer and of a 600 MHz instrument which will arrive in 1992. This includes implementation of novel techniques and upgrades in hardware and software; troubleshooting and repair when instrument failure occurs; and periodic replenishment of nitrogen and helium.

There will also be an opportunity for independent research in one or more of the following areas: analysis of NMR data of proteins and peptides; development of novel NMR experiments; development of data analysis programs on VAX or Silicon Graphics computers; and purification and isotopic labeling of proteins.

Interested applicants should send me a curriculum vitae and the names of two references.

Dr. David C. Fry
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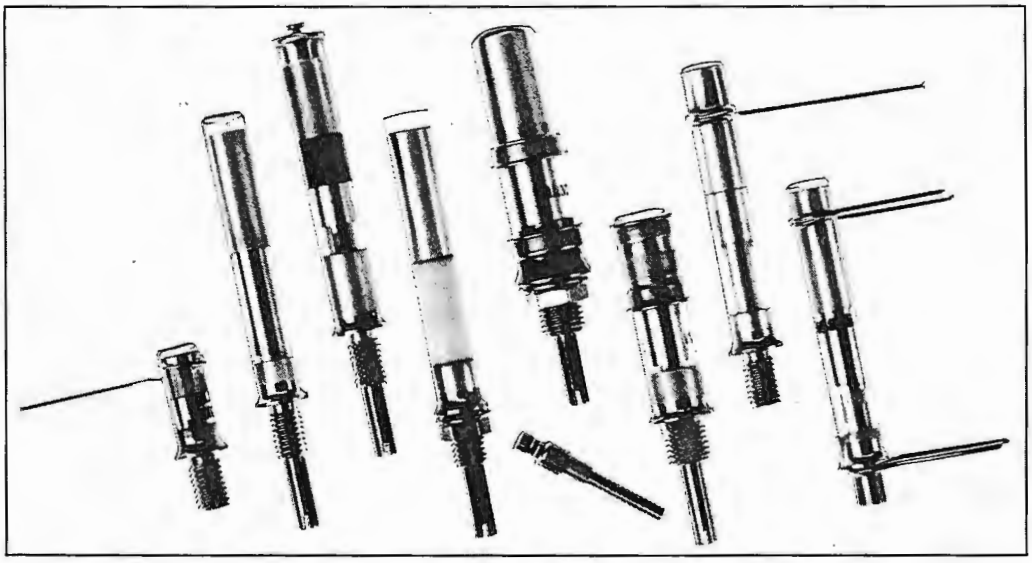

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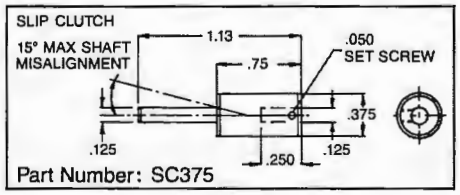

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May 15, 1991

SYMPOSIUM ANNOUNCEMENT:

The Physical Chemistry Division of the American Chemical Society will sponsor a symposium entitled "NEW DEVELOPMENTS AND APPLICATIONS OF MAGNETIC RESONANCE AND OPTICAL SPECTROSCOPIES" at the ACS National Meeting in New York City, August 25-30, 1991. The symposium will be devoted to recent technical and theoretical developments in NMR, EPR, and coherent optical spectroscopy and to the application of modern spectroscopic techniques to problems in biochemistry, polymer chemistry, physical chemistry, and materials science. Roughly two thirds of the talks will deal primarily with magnetic resonance and its applications. Speakers include W.S. Warren, D.P. Weitekamp, K.W. Zilm, J. Schaefer, C.S. Yannoni, A. Bax, J.H. Freed, M.K. Bowman, G.L. Hoatson, H.W. Spiess, M.D. Ediger, A.D. English, J. Baum, A.J. Wand, G. Drobny, R.G. Griffin, D.E. Wemmer, T.M. Duncan, C. Fyfe, C.A. Klug (Slichter group), K.T. Mueller (Pines group), A.J. Vega, J.M. Millar, and J.W. Zwanziger. Consult Chemical and Engineering News for the complete program and for registration materials. Please contact Rob Tycko at the address above if you require additional information.

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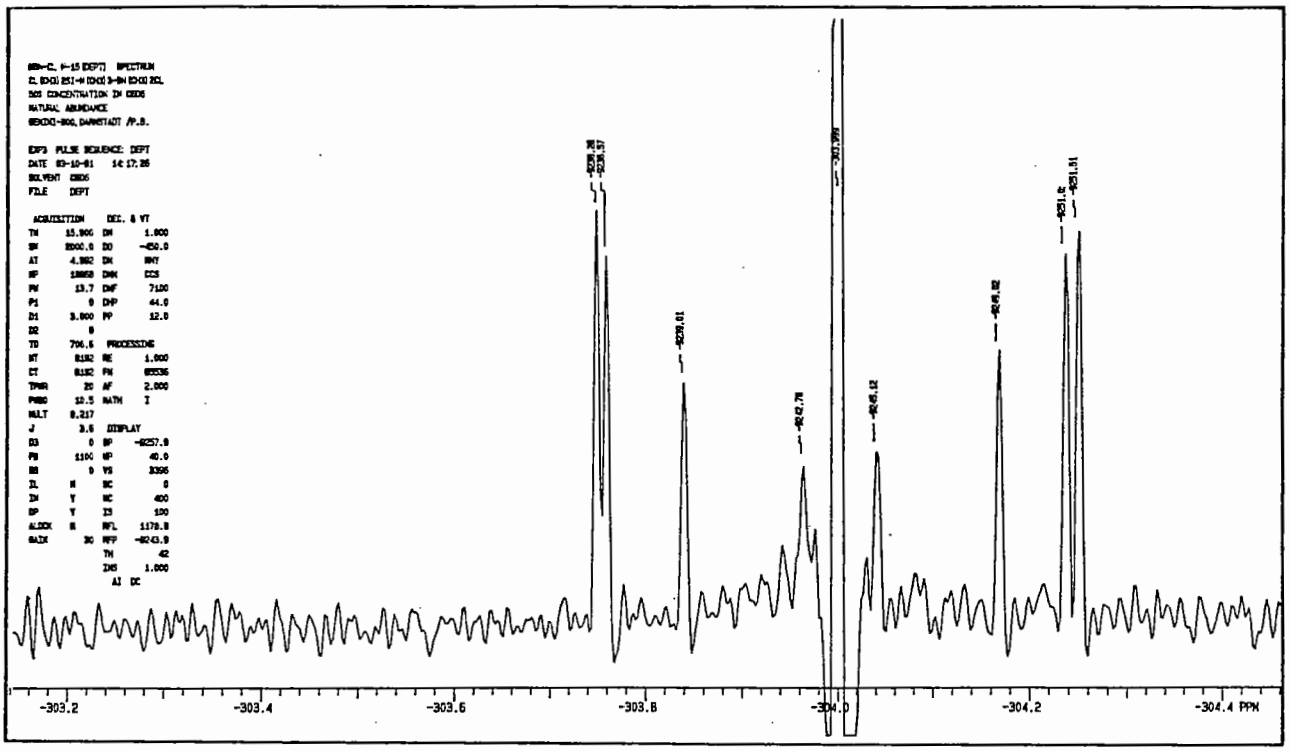
Dr. Bernard L. Shapiro
TAMU NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303, U.S.A.

April 29 1991 (received 5/6/91)

Satellite manifold in natural abundance ^{15}N spectrum

Dear Dr. Shapiro,

$Cl(Me)_2$-Sn-N(t-But)-Si-$(Me)_2Cl$ exhibits an interesting 15N spectrum, where the nitrogene line is fourfold sandwiched between satellites from i) the carbons, ii) the silicon, and iii) the two tin isotopes. The spectrum below was run using DEPT at natural abundance ^{15}N level within less than 7 h on a Varian GEMINI 300 broadband spectrometer using a 5 mm broadband probe and a 50% sample concentration. Some resolution enhancement was applied which distorts the base of the ^{15}N line.



Sincerely Yours

Peter Sandor
NMR Applications Laboratory

Position Available

Currently we have an opening for a NMR Applications Chemist in our European NMR Applications Laboratory in Darmstadt/Germany. Applicants should have a degree in Chemistry, a Ph. D. in state-of-the art high-field multinuclear liquids NMR, plus related post-doc or first industrial NMR experience. Applications with cv, publication list, and abstract of thesis, should be sent to Peter Meier, Manager Varian European NMR Applications Laboratory.

KUNGL TEKNISKA HÖGSKOLAN
ROYAL INSTITUTE OF TECHNOLOGY
Dept. of Inorganic Chemistry
Dr. Julius Glaser

Stockholm, May 3 1991

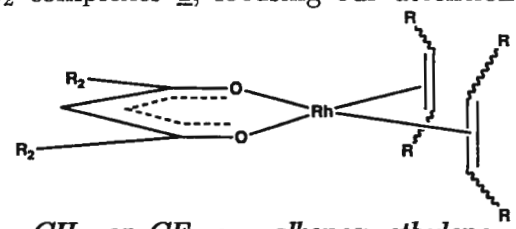
(received 5/13/91)

Prof. B.L. Shapiro
TAMU NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303, USA

^{103}Rh NMR of Rh-alkene complexes; an unexpected correlation

Dear Prof. Shapiro,

For a number of years our group has applied metal–NMR to a wide selection of problems in aquatic coordination chemistry. We have been looking at speciation, structural properties and kinetics. Recently, we have extended our field of interest to organometallics and ^{103}Rh–NMR. In our first investigation, we prepared a series of Rh(β–diketonato)(alkene)$_2$ complexes 1, focusing our attention on the Rh–alkene bonding.



Complex 1: $R_2 = CH_3$ *or* CF_3 ; ***alkenes: ethylene, cis–butene, trans–butene***

It has been demonstrated that metal–NMR chemical shift depends on the oxidation state, but would any information come out on structure or bonding? In ^{103}Rh NMR, the compound Rh(acetylacetonate)(ethylene)$_2$ gives a partly resolved multiplet at lower temperatures with the possibility to assign coupling constants and to gain hints on its structure. When we continued the study, we noted an unexpected correlation between the ^{103}Rh–shift of the complexes 1 and the $\pi \rightarrow \pi*$ excitation energy of the free alkenes (Figure 1).

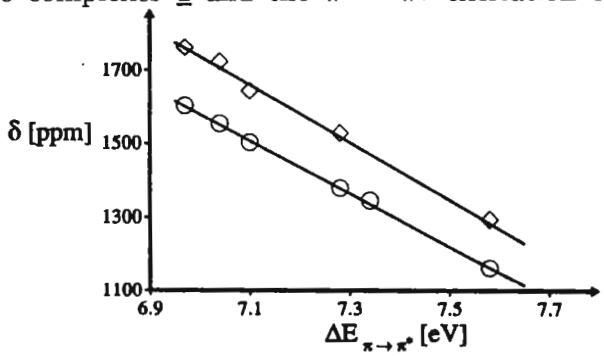


Figure 1. ***Excitation energy, π→π*, of the free alkenes vs. ^{103}Rh–NMR shift of 1.***

The question is, how do the excitation energies of the free alkenes relate to the electronic structure of the complex and the Ramsey equation? If we can figure that out, we will probably get some useful information on Rh–alkene bonding. If we can't, we will be left with only a curious straight line.

Sincerely,

B. Åkermark J. Glaser L. Öhrström K. Zetterberg

Postadress/Address S-100 44 STOCKHOLM
Besöksadress/Visitors address
Telefon Nat. Vx 08-790 60 00 Int. +46 8 790 60 00
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May 7, 1991

Dr. B.L. Shapiro, Editor
TAMU Newsletter
966 Elsinore Court
Palo Alto, CA 94303

Diagonal Suppression in Phase-Sensitive COSY by FTNMR

Dear Dr. Shapiro,

We have been interested in methods of digital signal processing for the improvement of the quality of multi-dimensional NMR data. We have discussed our implementation of various procedures for solvent suppression and baseplane flattening of NOESY and ROESY spectra of peptides and proteins (TAMU Letters, August, 1990). In this contribution, we would like to share with you our FTNMR implementation of diagonal suppression of phase-sensitive COSY by use of Hilbert Transforms and diagonal blanking (S.COSY, Pelczer, JACS 113,3211-3212,1991).

The crucial step in the S.COSY procedure involves the selective blanking of the diagonal of a phase-sensitive COSY spectrum which has been phased such that the diagonal peaks have absorptive lineshapes in both dimensions. We implemented the diagonal blanking procedure using the MACRO language available in the FTNMR program (v 5.1, Hare Research). Rows (or columns) of the 2D spectrum are loaded during the execution of the MACRO. The regions around the diagonal peaks are then set to zeroes before writing back to disk. With our version of FTNMR, we found that it is not easy to compute the index of the data points to be zeroed for each slice. We used a trick to accomplish the same task as shown in the following MACROs:

zrrf2.mac:

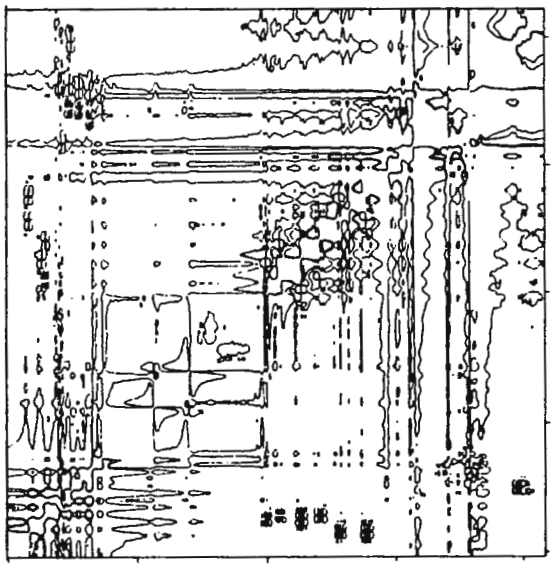
```
for row 1 &NROWS
lr &row
csl &row
csr &CENTER2
zrr &START2 &END2
csl &CENTER2
csr &row
sr &row
next
fl
end
```

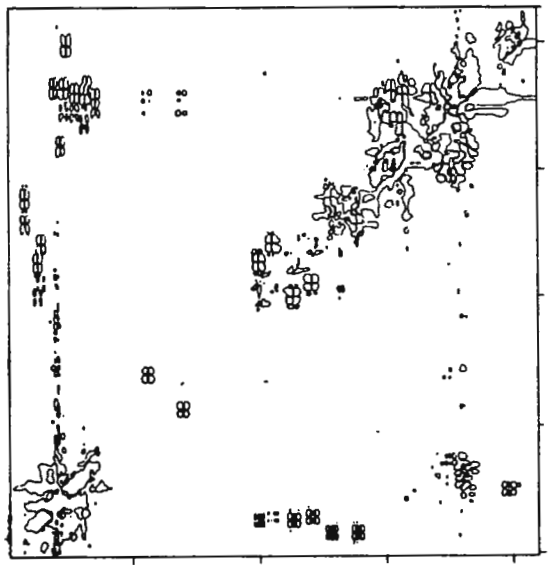
zrrf1.mac:

```
for col 1 &NCOLS
lc &col
csl &col
csr &CENTER1
zrr &START1 &END1
csl &CENTER1
csr &col
sc &col
next
fl
end
```

where CENTER1 = (NCOLS/2+1) and CENTER2 = (NROWS/2+1) and START1 and END1 and; START2 and END2 specify the range of data points to be zeroed along F1 and F2, respectively. These contants can be set outside the MACROs since the zeroed data points are always around the center of the shifted spectrum.

The following Figures show the same region of a phase-sensitive COSY spectrum of a peptide before and after diagonal suppression. The improvement is obvious especially around the diagonal. Incomplete diagonal suppression was observed for peaks with large linewidths or for spectra with very short acquision time along the t1 direction. Applications for processing spectra of proteins will be reported elsewhere.





Yours sincerely,

Feng Ni, Ph.D.

Enrico Purisima, Ph.D.

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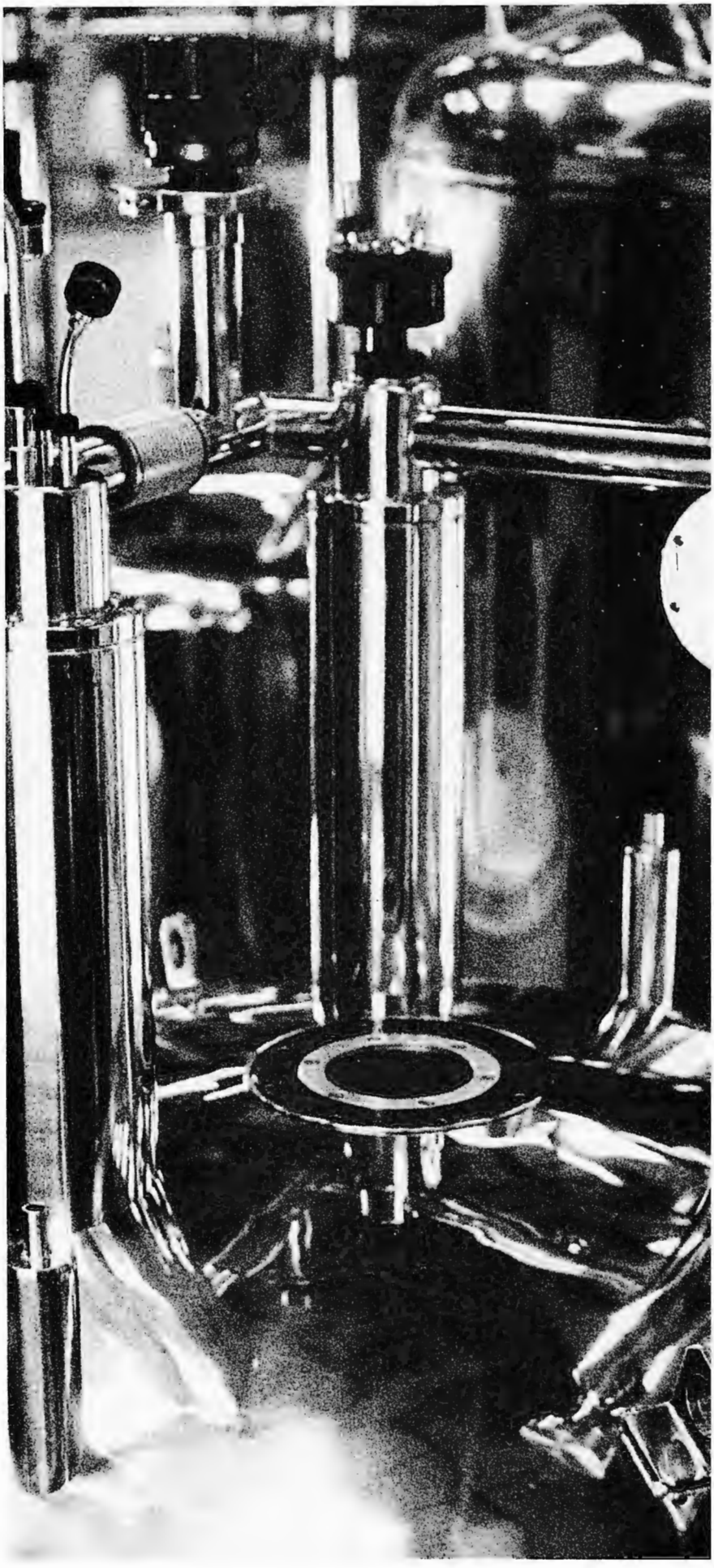

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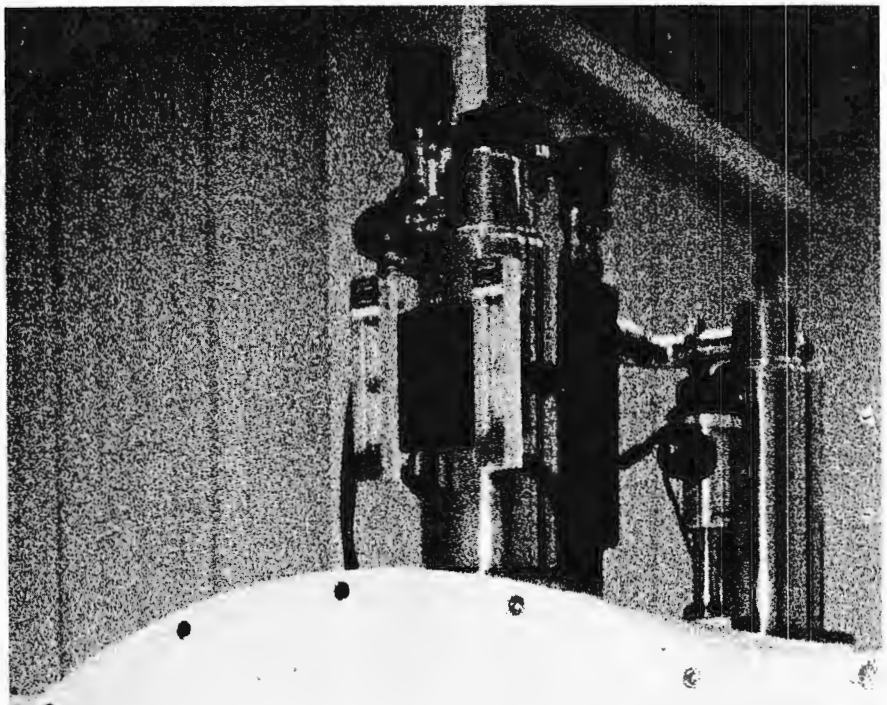

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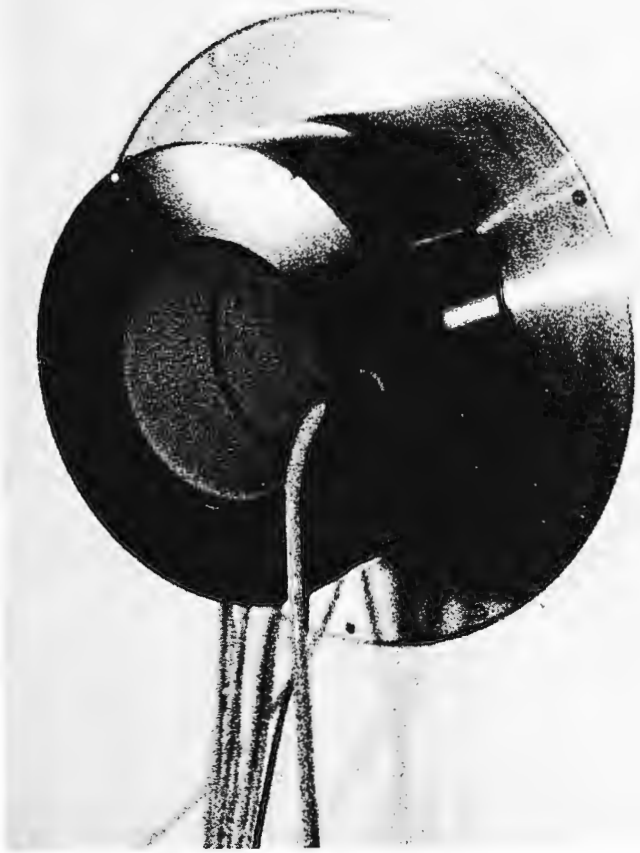

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393-55

UNIVERSITY OF LONDON

25th April 1991 (received 4/30/91)

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Telex 893750

Title: Symmetrised SECSY

Spin-echo correlated spectroscopy (SECSY) was at one time a widely used alternative to the COSY experiment. The drawbacks of the method are that it does not give pure phase line shapes (without use of a z-filter); correlations are less obvious; the total experiment time is longer but the sensitivity is lower; the total experiment time is longer but the sensitivity is lower; and commonly used enhancement methods such as symmetrisation cannot be used.

However, SECSY has recently attracted some attention for use in-vivo, since the cross-peak terms are a combination of in-phase terms (COSY gives anti-phase cross-peaks) and so in inhomogeneous fields do not necessarily cancel. What is not always appreciated is that the same software routines used to tilt and symmetrise J-resolved spectra can be applied to SECSY spectra.

Below is the simulated SECSY spectrum of an A_2X together with the tilted spectrum and the tilted/symmetrised spectrum. We feel that the correlations appear more obvious in the tilted spectrum, but for purists who want a "real" SECSY spectrum, it could always be tilted back again.

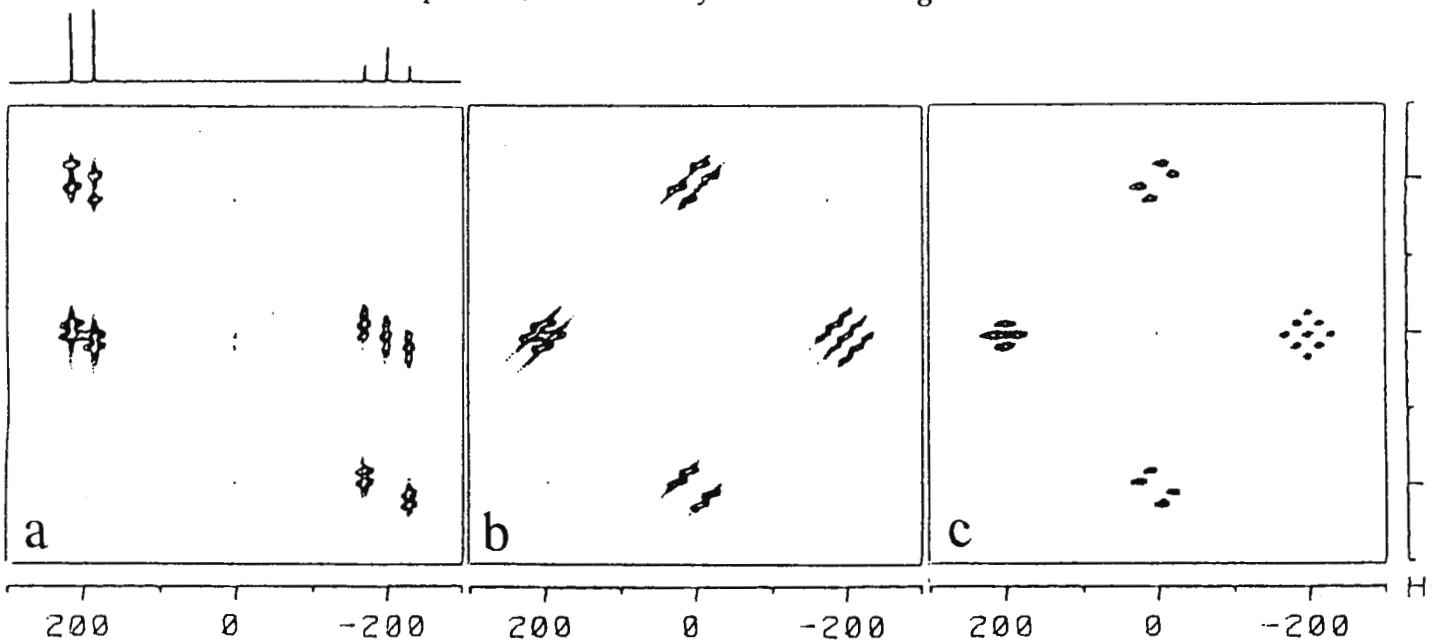

Figure a) normal, b) tilted, c) tilted and symmetrized.

Yours sincerely,

Harold Toms

Harold Toms

Geoff Hawkes

Geoff Hawkes

393-56

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

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Position in in-vivo NMR spectroscopy

A spectroscopist position is available in the in-vivo NMR Unit at the Institute on Aging of the NIH, in Baltimore. Research activities include studies of the effects of aging on skeletal muscle metabolism in humans, small animal work oriented towards cardiac, pulmonary, and brain physiology and metabolism, and NMR methodologic studies not directly related to aging. A Bruker Biospec 1.9T/31 cm spectrometer is available on-site, as is a Varian 200 MHz instrument suitable for in-vitro studies. In addition, the NMR facilities of the main NIH campus in Bethesda, as well as instrumentation at the nearby Johns Hopkins Medical School, are readily available. The appointment will be as an IRTA Postdoctoral Fellow or Staff Fellow, depending on experience and qualifications. In-vivo experience is preferred but not required; enthusiasm for in-vivo studies is essential. Interested individuals should send a curriculum vitae and bibliography to: Dr. Richard G. S. Spencer, NIH/NIA, GRC 4-101, 4940 Eastern Avenue, Baltimore, MD 21224, or telephone directly at 301-550-2912/-1805.

The Newsletter's fiscal viability depends very heavily on the funds provided by our Advertisers and Sponsors. Please do whatever you can to let them know that their support is noted and appreciated.

Please read the Notices on page 3 of the May issue regarding Newsletter finances and subscription renewal invoicing. The subject of raising Newsletter funds is not one of my favorite things - far from it - but the facts must be faced. Your efforts to help will be appreciated.

B.L.S.

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TAMU NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94393

May 8, 1991

(received 5/13/91)

Deuterium Quadrupole Coupling Constants and Asymmetry Parameters in Bridging Metal Hydrides

Dear Dr. Shapiro:

In this work solid-state deuterium NMR powder patterns were acquired for six bridging metal hydrides to obtain structural information on the M-^{2}H-M structure. This quest is based on the fact that the solid-state deuterium NMR spectrum is determined by two measurable parameters, the quadrupole coupling constant, $e^2q_{zz}Q/h$, and the asymmetry parameter, $\eta = (eq_{yy} - eq_{xx})/eq_{zz}$. The quadrupole coupling constant is a measure of the magnitude of the electric field gradient at the deuterium site while the asymmetry parameter gives information about the shape of the electric field gradient. Consequently, both parameters will be related to the M-H bond distance and the M-H-M bond angle.

The bridging metal hydride bonds are bent, even when the metal carbonyl framework has a pseudo D_{4h} geometry, as shown in Figure 1a. The metal carbonyl framework is sensitive to the counter-ion with a bent staggered geometry being relatively common as shown in Figure 1b.

Figures 2 shows the solid-state deuterium NMR powder patterns obtained at 300 K for two representative bridging metal hydrides and the nonlinear least-squares fits using the Levenberg-Marquardt algorithm. The spectra show that three bridging metal sites, $[Et_4N][^2HCr_2(CO)_{10}]$, $[(Ph_3P)_2N][^2HCr_2(CO)_{10}]$, and $[Et_4N][^2HW_2(CO)_{10}]$, have an eclipsed metal carbonyl geometry and another three, $[Ph_4P][^2HCr_2(CO)_{10}]$, $[(Ph_3P)_2N][^2HW_2(CO)_{10}]$, and $[Ph_4P][^2HW_2(CO)_{10}]$, have a bent staggered metal carbonyl geometry. The observed deuterium powder patterns are a result of the deuterium quadrupole coupling constant, the asymmetry parameter, and, for sites with an eclipsed metal carbonyl geometry, possible rapid four-site jump motion in the M-^{2}H-M unit. The apparent axial symmetry of the eclipsed metal carbonyl structure, $[Et_4N][^2HCr_2(CO)_{10}]$, was preserved to the lowest temperature studied, 140 K, but does not necessarily indicate rapid four-site jump motion.

The deuterium quadrupole coupling constants and asymmetry parameters were related to the M-H-M bond distance and the M-H-M bond angle with a point charge model shown in Figure 3 and by assuming that the sign of the quadrupole coupling constant is positive. Early on, a deficiency in the point charge model was found; an exaggerated dependence of the asymmetry parameter on the bond angle is apparent on comparison with the experimental results. Therefore, also shown in Figure 3b are the results from a set of *ab initio* molecular orbital calculations for a model system, $[Na\text{-}H\text{-}Na]^+$.

This work shows that solid-state deuterium NMR spectroscopy has the potential to investigate structure in metal hydrides. In particular, these NMR results are highly pertinent to NMR spectroscopy of adsorbed hydrogen on metal surfaces.

Sincerely,

Ae Ja Kim Leslie G. Butler

P.S. An outstanding graduate student (Ae Ja Kim, Ph.D in September 91, (504) 388-8248) seeks employment in the Houston area.

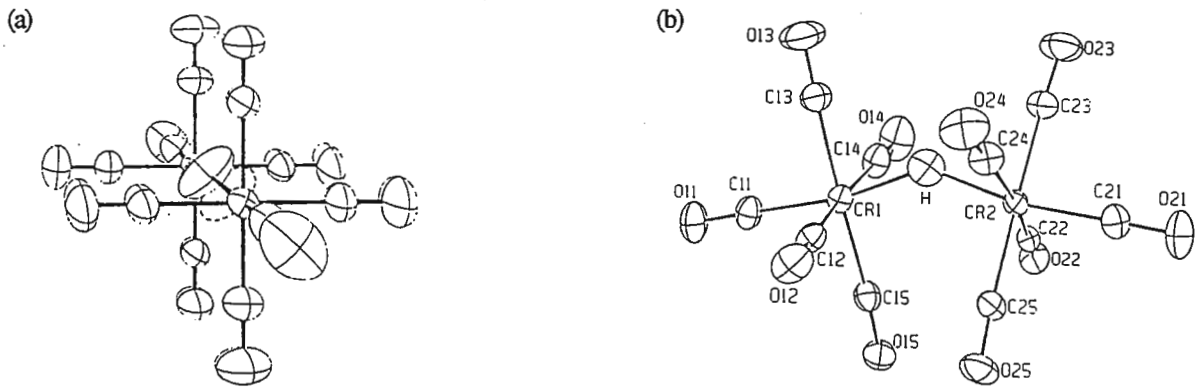

Figure 1. The flexible geometry of the M-H-M structure in the $[HM_2(CO)_{10}]^-$ anion is shown for two representative structures. (a) The eclipsed configuration for the anion of $[Et_4N][HCr_2(CO)_{10}]$. (b) The bent staggered metal carbonyl geometry for the anion of $[Ph_4P][^2HCr_2(CO)_{10}]$.

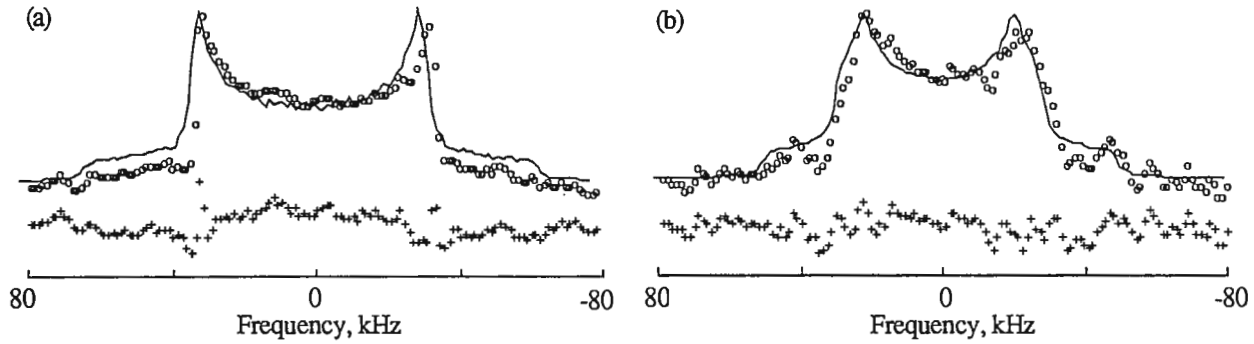

Figure 2. Solid-state deuterium NMR powder patterns obtained at 300 K for two representative structures and the corresponding nonlinear least-squares fits. Circles (o), solid lines (–), and crosses (+) represent the experimental deuterium powder pattern, the best calculated fit, and the residual between the experimental spectrum and the fit, respectively. (a) $[Et_4N][^2HCr_2(CO)_{10}]$ and (b) $[Ph_4P][^2HCr_2(CO)_{10}]$.

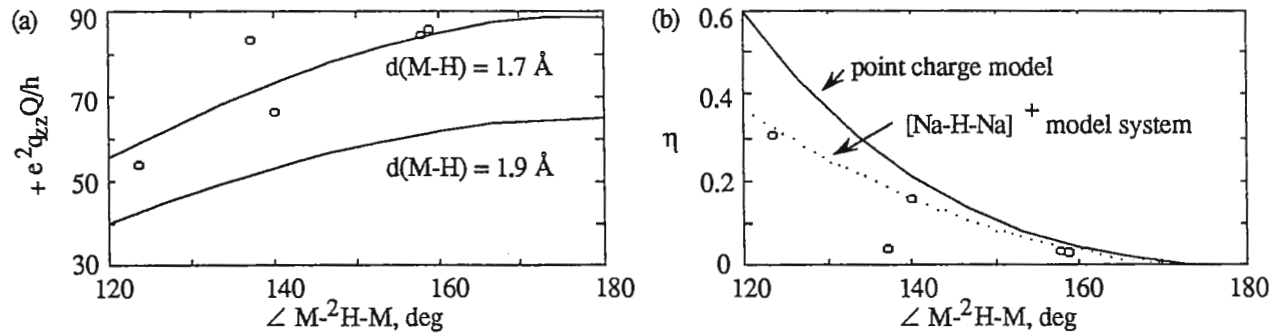

Figure 3. The effect of a nonlinear, symmetric M-^{2}H-M bond on the deuterium quadrupole coupling constant and the asymmetry parameter. (a) Two traces showing the quadrupole coupling constant as a function of M-^{2}H-M bond angle. The circles (o) represent the experimental deuterium quadrupole coupling constants. (b) The asymmetry parameter as a function of the M-^{2}H-M bond angle as computed for both a point charge model and an in *ab initio* SCF-HF calculation of a model system, $[Na\text{-}H\text{-}Na]^+$.

Gradient Enhanced Spectroscopy SWAT

GE introduces the use of Switched Acquisition Time (SWAT) gradients to achieve pure phase 2D spectra with quadrature detection in both the acquisition (ω_2) and evolution (ω_1) dimensions without any phase cycling and without an additional set of t_1 data.

One example of a pure phase gradient enhanced COSY spectrum of a solution of 2,3-dibromopropionic acid in benzene-d6 is shown in Fig. 1. SWAT gradients and a single acquisition per block were used. Data was collected on an Omega 300WB with Microstar actively-shielded gradients. A 5mm inverse probe was built for use within the gradient coils.

Digital resolution of 1.2 Hz in ω_1 and 2.4 Hz in ω_2 was achieved by collection of a 512 x 512 matrix with t_1 evolution time of 840ms and a t_2 acquisition time of 420ms. A single acquisition per t_1 evolution data block and an average recycle time of 1.84s resulted in a 15 minute total collection period.

Since the SWAT gradient method encodes the necessary information in a single t_2 acquisition time, it avoids the collection of additional data blocks required by traditional pure phase methods. This time efficiency is especially important for collection of large multidimensional data sets.

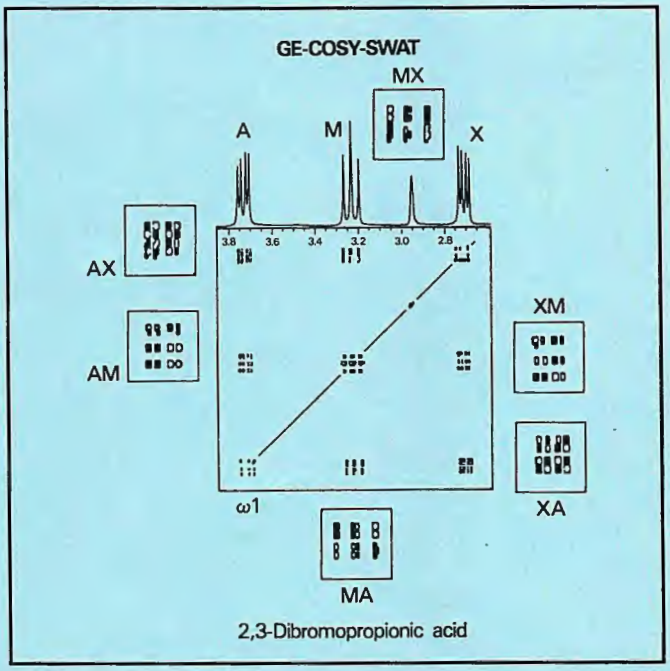

Fig. 1

Contour plot of a 300 MHz pure-phase COSY spectrum of a solution of 2,3-dibromopropionic acid in benzene-d6 acquired with only a single acquisition per t_1 evolution time increment using the GE-COSY-SWAT method. Cross peaks are shown in expanded insets with positive peaks as darkened contours and negative peaks as open contours. A one dimensional spectrum is plotted across the top of the 2D spectrum.

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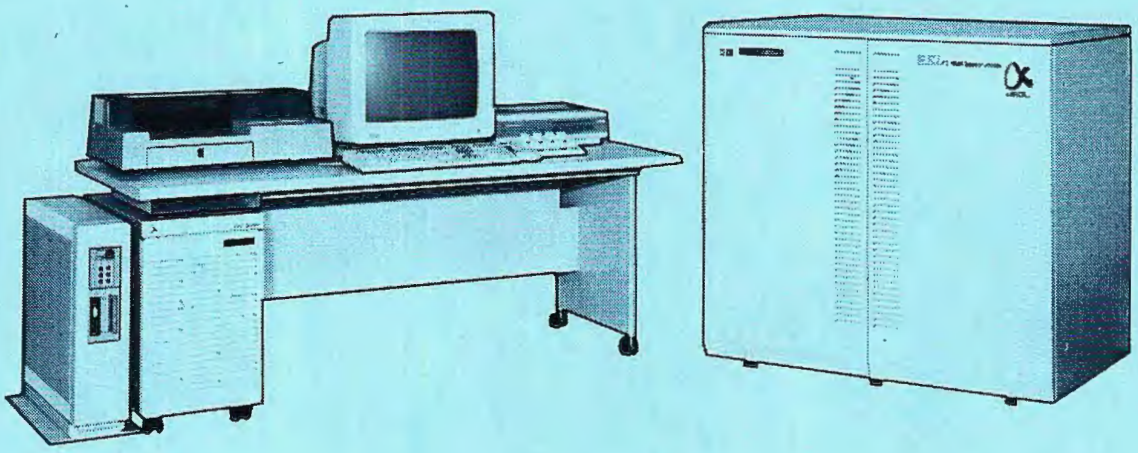

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