TEXAS A&M UNIVERSITY

NMR NEWSLETTER

No. 389

February 1991

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D-120	Acetone-d_6 + TMS	CD_3COCD_3	99.9%	1.13	-94	57	
D-13	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	Chloroform-d	$CDCl_3$	99.8%	1.50	-64	62	0.740 (20)
D-31	Chloroform-d + 1% TMS		99.8%				

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FORTHCOMING NMR MEETINGS

1991 Pittsburgh Conference & Exposition, Chicago, Illinois, **March 4 - 8, 1991**; NMR sessions and symposia on March 5 and 6; Information: Pittsburgh Conference, Dept. CE, 300 Penn Center Blvd., Suite 332, Pittsburgh, PA 15235.

In Vivo Magnetic Resonance Spectroscopy Tutorial and Participatory Workshop, St. Louis, Missouri, **April 4 - 7, 1991**; See Newsletter 385, 58.

32nd ENC (Experimental NMR Spectroscopy Conference), St. Louis, Missouri, **April 7 - 11, 1991**; Contact: ENC, 750 Audubon, East Lansing, MI 48823; (517) 332-3667.

1991 Keystone Symposia on Molecular & Cellular Biology, Keystone, Colorado: **April 8-14, 1991**, *Frontiers of NMR in Molecular Biology*; *Proteolysis in Regulation and Disease*; *Protein Folding, Structure and Function*; See Newsletter 384, 46.

Fifth Wasington University-ENI/Emerson Electric Co., Symposium on NMR, St. Louis, Missouri, **May 20, 1991**; See Newsletter 388, 52.

Contrast-Enhanced Magnetic Resonance, a workshop of the Society of Magnetic Resonance in Medicine, Napa, California, **May 23-25, 1991**; Contact: S.M.R.M., 1918 University Ave., Suite 3C, Berkeley, CA 94704; (415) 841-1899, FAX: (415) 841-2340.

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.

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.

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

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.

389-2

SmithKline Beecham
Pharmaceuticals

Phenylalanine-deuterated Calmodulin from Trypanosoma brucei

Direct Line:

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Dear Barry

(received 1/10/91)

Like many others, we are finding that the preparation of significant quantities of fully deuterated proteins, for NMR study of drug and other ligand binding, is far from trivial. We have been interested in calcium binding regulatory proteins of the calmodulin class for some time now, and in collaboration with neighbours of ours at the Hatfield Polytechnic, have been learning some of the lessons of protein perdeuteration the hard way, using a T. brucei calmodulin expression system devised at our Upper Merion Laboratories. However, we are fortunate in the sense that the drug we have chosen as a model calmodulin antagonist, calmidazolium (R24571, ', is predominantly aromatic, and Tryp calmodulin only contains a single tyrosine (138). We can thus obliterate most of the troublesome protein signals from the spectrum of the calmidazolium-calmodulin complex by simply growing the E. coli expression system on Phe-d_5 to which it seems quite partial. The Figure shows the very satisfactory improvement in the visibility of the drug signals in the complex with {Phe-d_5} calmodulin relative to isotopically normal protein. We are currently doing NOE experiments to add more detail to previous spin-probe elucidation of the drug binding sites of calmodulin and getting experience in ^{15}N and ^{13}C multinuclear techniques.

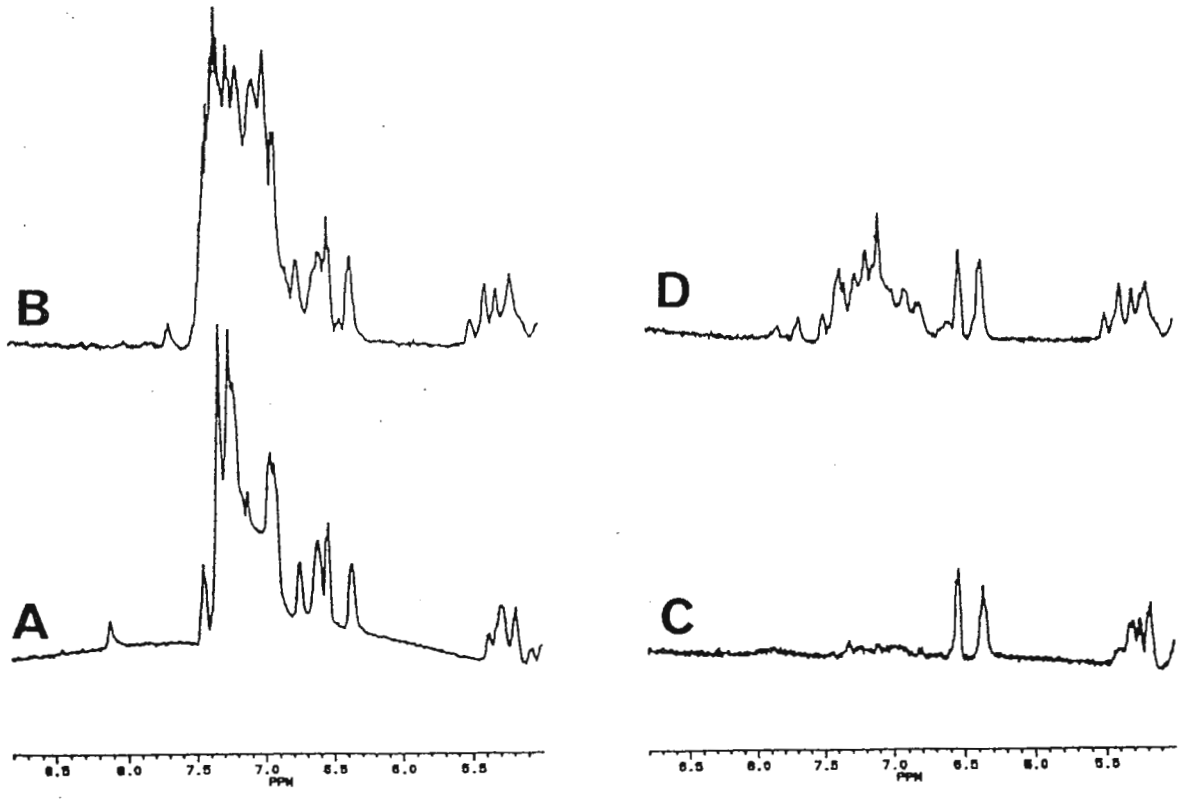

Figure Legend

Low-field regions of 360MHz ^1H NMR spectra at 37°C of (A) Isotopically normal Trypanosomal calmodulin; (B) As for A, with 1 equivalent of calmidazolium bound; (C) {Phe-d_5} calmodulin; (D) As for C, with 1 equivalent of calmidazolium bound.

David Reid Lesley MacLachlan Trish Sweeney (Hatfield) John Walker (Hatfield)

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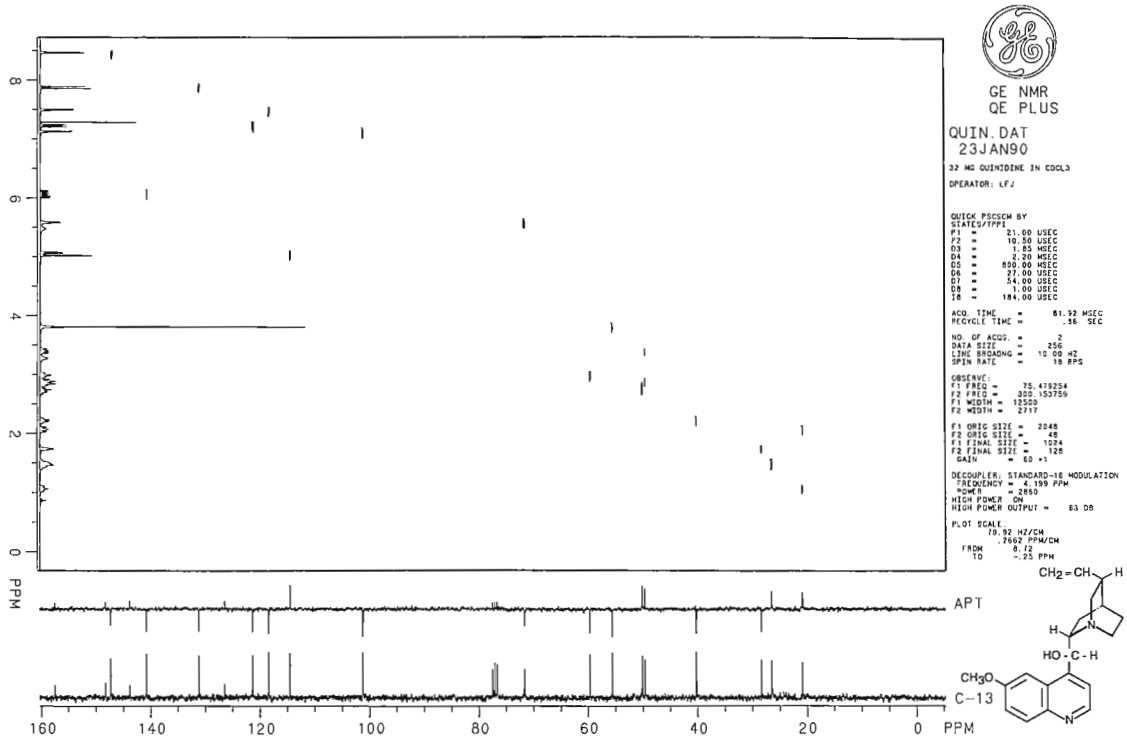

An automated run using MACRO mode operation on a sample of 32 mg of quinidine in 0.5 ml chloroform-d (0.20M). Data were obtained using the 5 mm broadband probe. ^{1}H, ^{13}C, APT and phase sensitive 2D data were collected, processed and plotted—including the 2D contour—in only 8.2 min.

University of Nottingham

Department of Chemistry

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

5th December 1990
(received 12/12/90)

Dear Dr Shapiro

^{1}H NMR Measurements of Interfacial Transfer Rates

We are interested in the properties of surfactant layers adsorbed at the interface between oil and water phases and in particular the nature of the barrier they present to a molecule crossing the interface. In order to study the permeability of the interfacial layers we have observed the ^{1}H nmr lineshape of a solute which is partitioned between the two phases and which, because of the different magnetic susceptibilities in the separate phases, produces two distinct chemically shifted signals. Exchange between the phases leads to the well known broadening and coalescence effects.[1]

Fig. 1 shows the 100 MHz ^{1}H spectrum of an emulsion of o-xylene in H_2O/D_2O containing 1,4 dioxane. The emulsion is stabilised by a sorbitan ester and has a mean oil droplet diameter of 2.3 μm. To prevent creaming and coalescence of the droplets during sample spinning, the aqueous phase was gelled by the addition of 1% agarose. The dioxane signal clearly represents broadened and partially coalesced lines arising from the exchange of dioxane molecules between the two phases of the emulsion. By varying the surfactant concentration used in preparing emulsions, mean droplet size can be altered and hence the mean residence time of dioxane molecules in oil droplets can be changed. Fig. 2 demonstrates the effect of changing the surfactant concentration. With a mean droplet diameter of 6.6 μm the exchange rate is sufficiently slow to reveal separate resonances whilst the emulsion with the smallest droplet size (2.2 μm) shows a band with the largest amount of coalescence. By simulating the dioxane spectra using a standard theoretical model relating the exchange rate between two chemically shifted sites to the bandshape[2] we calculate that the average residence time of a dioxane molecule in an oil droplet varied from 16.1 ms to 5.65 ms as the droplet diameter decreased from 6.6 μm to 2.2 μm. These data can be used to find the probabilities of dioxane molecules crossing the interface into the aqueous phase if we assume isotropic diffusion within the oil droplet. In the future we hope to apply the technique to diffusive exchange of dioxane across a variety of surfactant films.

Please credit this contribution to Dr H Booth's account.

Yours sincerely

M J Hey F Al-Sagheer

1. "Dynamic NMR Spectroscopy", J Sandström, Academic Press, London, 1982
2. M T Rogers and J C Woodbrey, J.Phys.Chem. 66, 540 (1962).

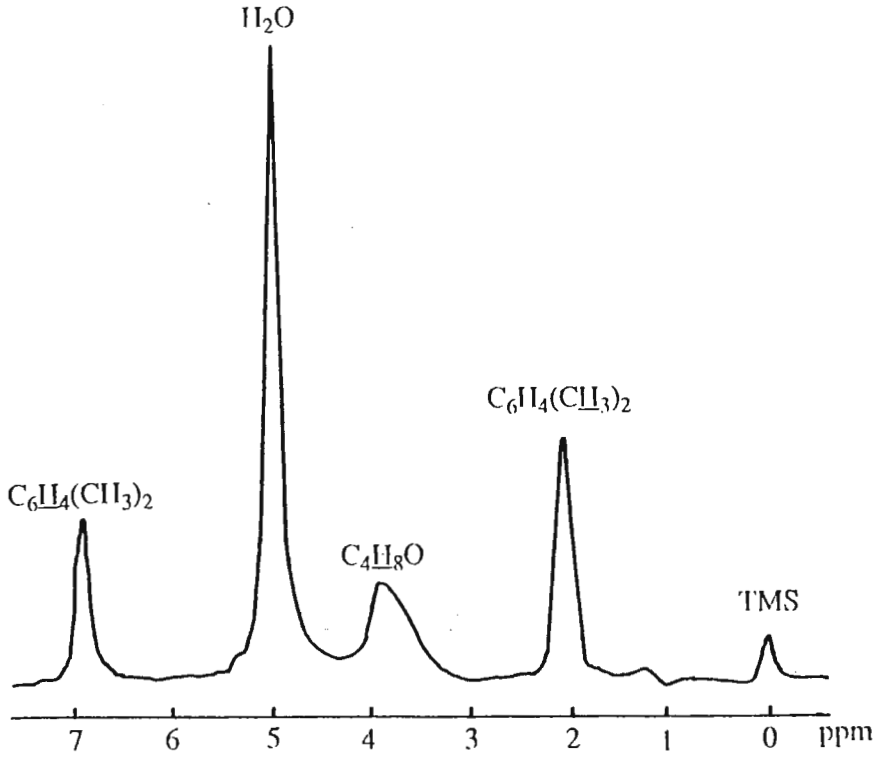

Fig. 1 100 MHz ^1H spectrum from a 44% (v/v) emulsion of o-xylene in water stabilised by 4% Span 40 and containing 2.4 mol dm^{-3} of 1,4 dioxane.

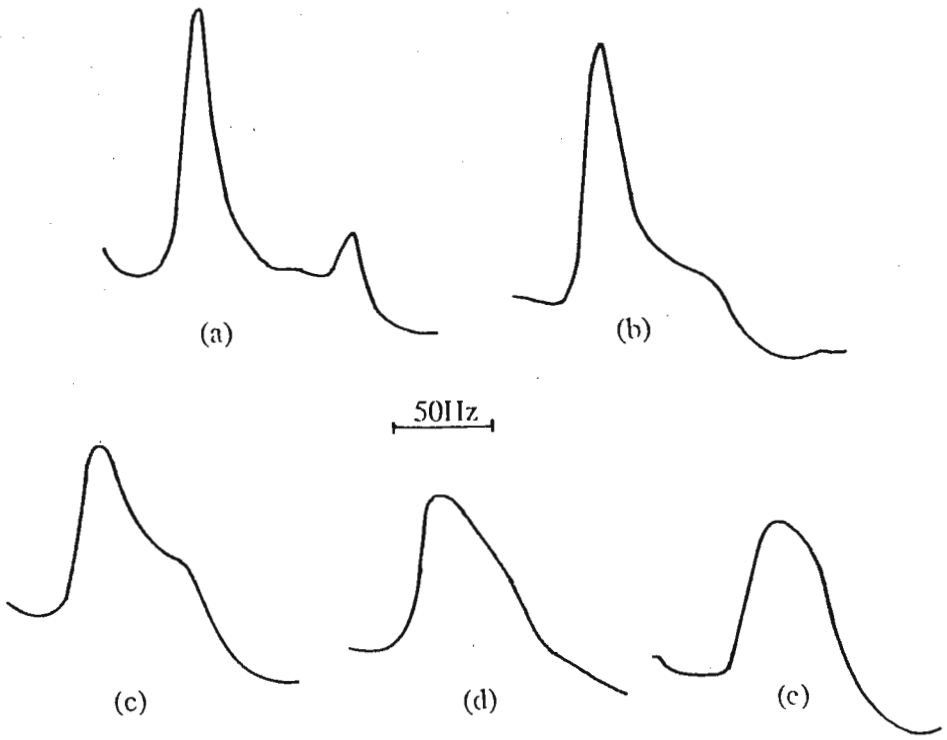

Fig. 2 Dioxane solute signal from a series of xylene/water emulsions stabilised by Span 40: mean droplet diameters/μm (a) 6.6, (b) 3.9, (c) 2.4, (d) 2.3 (e) 2.2.

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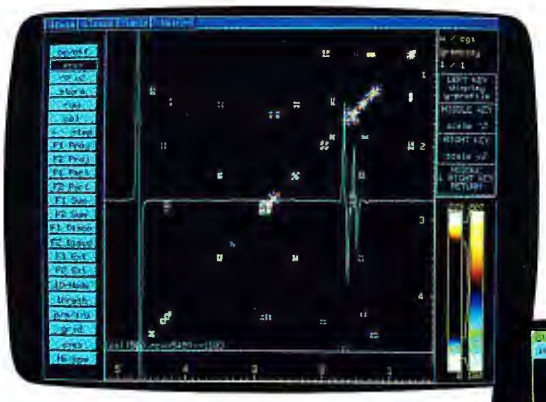

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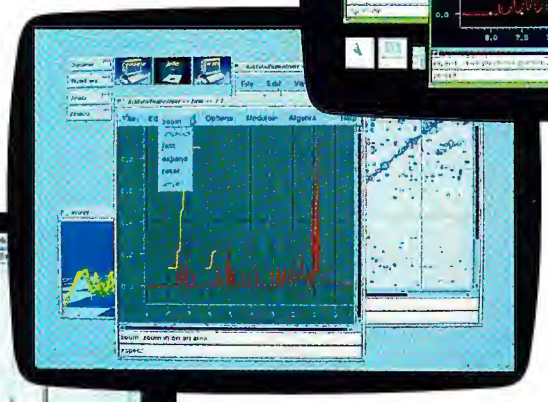
UXNMR on your IBM RS/6000.



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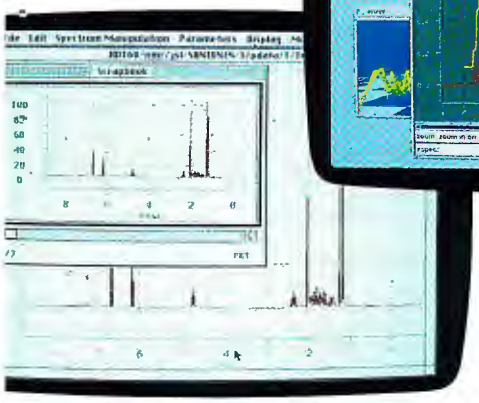

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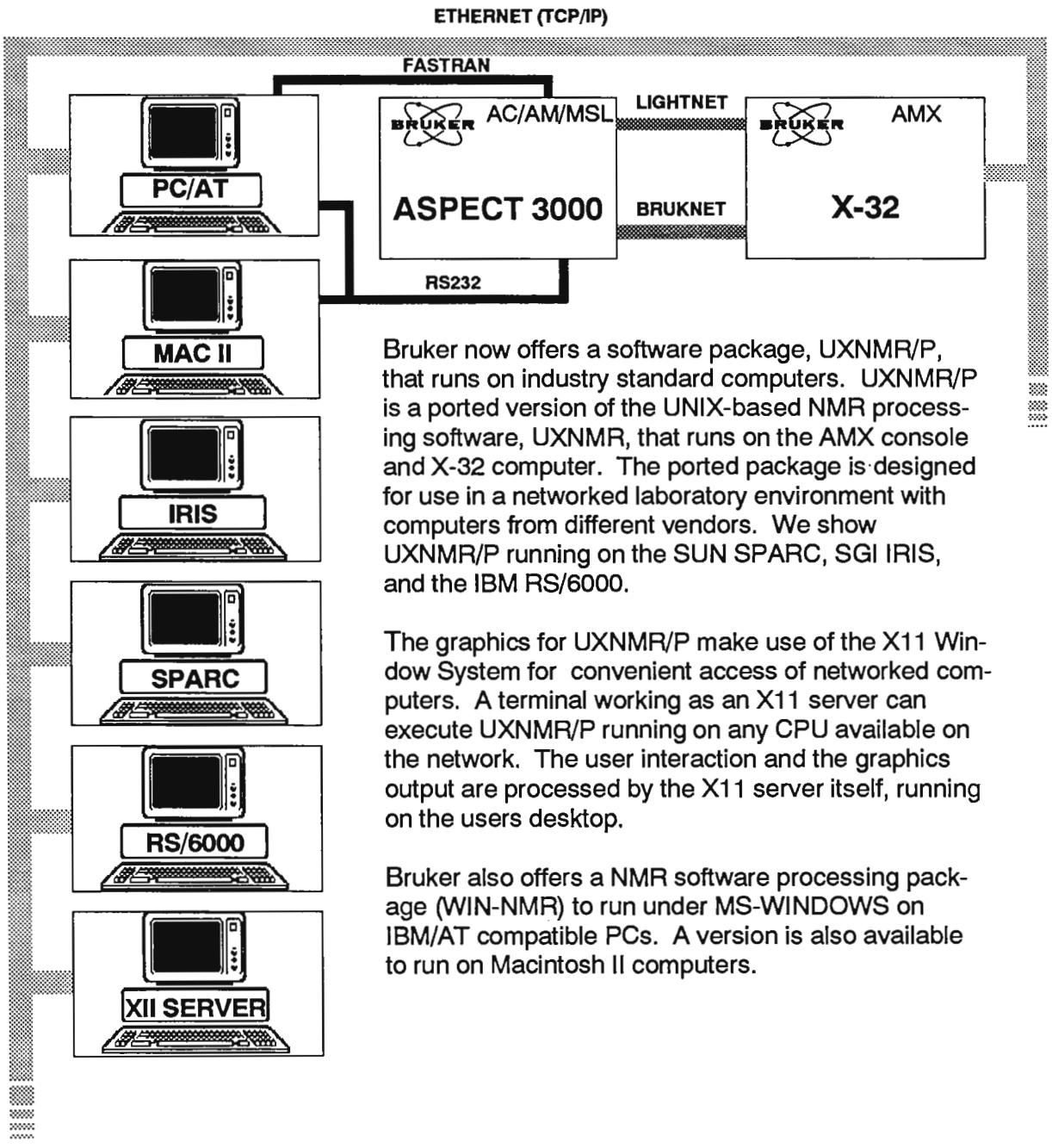

Bruker now offers a software package, UXNMR/P, that runs on industry standard computers. UXNMR/P is a ported version of the UNIX-based NMR processing software, UXNMR, that runs on the AMX console and X-32 computer. The ported package is designed for use in a networked laboratory environment with computers 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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10/90

DEPARTMENT OF THE NAVY
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IN REPLY REFER TO:

^{129}Xe NMR as a Probe of Polymer Blends

14 December 1990
(received 12/28/90)

Dear Barry,

Our group has recently started using ^{129}Xe NMR to assess the miscibility of polymer blends. The very large chemical shift range of ^{129}Xe provides a sensitive probe of its environment. ^{129}Xe NMR has been used extensively as a probe of zeolites but it has applicability to many materials. Recently, reports have appeared in the literature of ^{129}Xe NMR being used to study clathrates, silicates, liquid crystals, and polymers.

Our work concerns the use of ^{129}Xe as an indicator of the morphological heterogeneity of polymer blends. The systems we are working with (table 1) include polychloroprene (PC), polyisoprene (PIP), and two forms of epoxidized polyisoprene (EPI50) and (EPI25) where the random epoxidization is at 50 and 25 mole percent respectively. It has already been established by non-NMR methods that blends of PC and EPI50 are miscible whereas blends of PC and PIP are not. Manifestations of this miscibility and immiscibility clearly show up in the ^{129}Xe NMR as shown in fig. 1. The spectra were taken on a Bruker MSL 300 at 83 MHz where the peaks of the ^{129}Xe in the polymers are approximately 200 ppm down field from the gas. The PC/PIP blend exhibits two well-resolved peaks and the miscible blend of PC/EPI50 has only one ^{129}Xe NMR peak. Also shown is a blend of EPI50/PIP which exhibits two peaks. In the immiscible blends, the ^{129}Xe chemical shift is the same as in the pure polymers. More importantly, the single peak of the blend is between the two pure polymer peaks and the shape of the single peak is not what would be expected from the overlap of two peaks.

A word of caution at this point. Two peaks are direct evidence for an immiscible blend. One peak however is not definitive evidence for miscibility - it is only consistent with miscibility. It is easy to imagine a blend with small domains and rapid diffusion of the Xe atoms between domains, i.e. chemical exchange. If this model is assumed, the position of the resulting single line can be calculated and compared to the measured value. If the calculation does not agree with the measurement by a sufficient amount, then it can be inferred that the blend is miscible. While we already know PC/EPI50 is miscible, the status of blend PC/EPI25 is an open question. Conventional techniques cannot provide an answer because the T_g's of the two components are the same. ^{129}Xe NMR measurements to settle the question are currently underway.

Of further interest is that the ^{129}Xe NMR chemical shift in these polymers is very temperature dependent. The slope is about 0.21 ppm/K for all the polymers measured. This temperature dependence reflects the change in free volume in these polymers. We are currently investigating this aspect.

On a more practical note, the temperature dependence caused many headaches until we discovered that the temperature controller on our Bruker MSL 300 was not doing quite as good a job as we thought. It was not until we went to very high gas flow rates that we got stable temperatures close to the set point. When the controller was run per the manual's instructions, we experienced low frequency oscillations in the temperature with amplitudes of a degree or more. While this degree of control may be good enough for many purposes, it did affect our lineshapes and linewidths. The moral of the story is always have an independent check of the temperature.

Please credit this to A. N. Garroway's account.

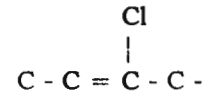
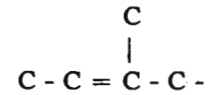
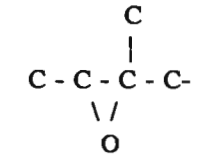
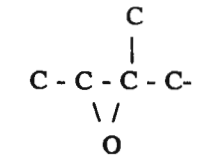
Sincerely yours,

J. H. Walton

J. B. Miller

C. M. Roland

Table 1
The polymers investigated in this work. Blends of PIP with the other three polymers are all immiscible. Blends of EPI50/EPI25 were not investigated.

Polymers	T_g	Repeat Unit	Miscible with PC?
Polychloroprene (PC)	239 K		Yes
Polyisoprene (PIP)	203 K		No
50% Epoxidized* PIP (EPI50)	258 K		Yes
25% Epoxidized* PIP (EPI25)	239 K		?

* Epoxidization is random by mole percent as indicated.

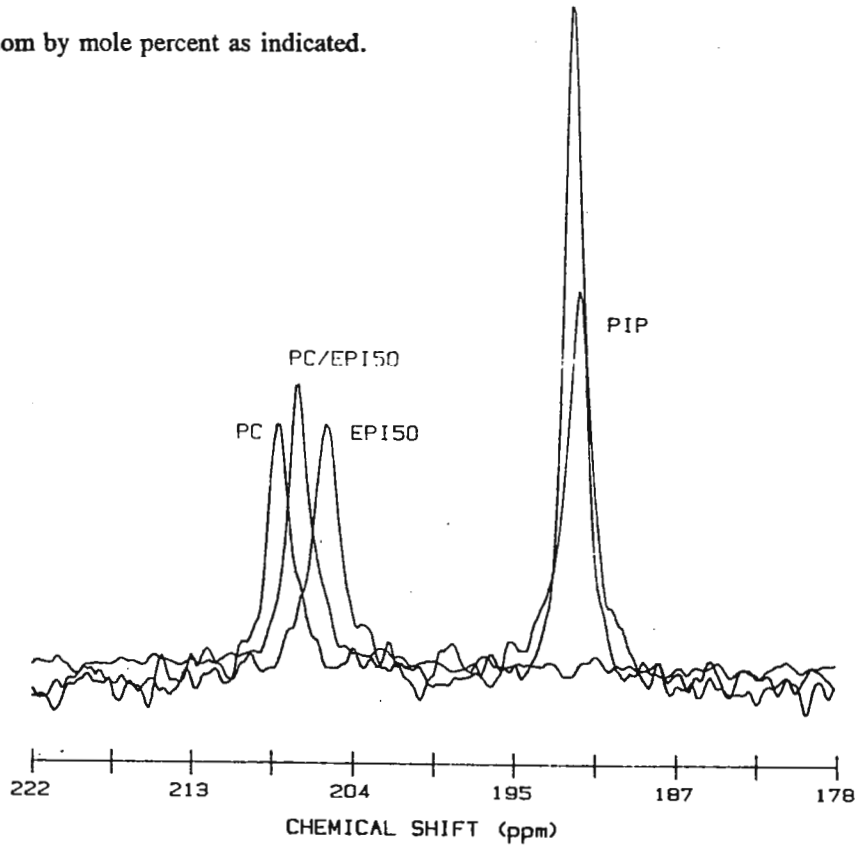
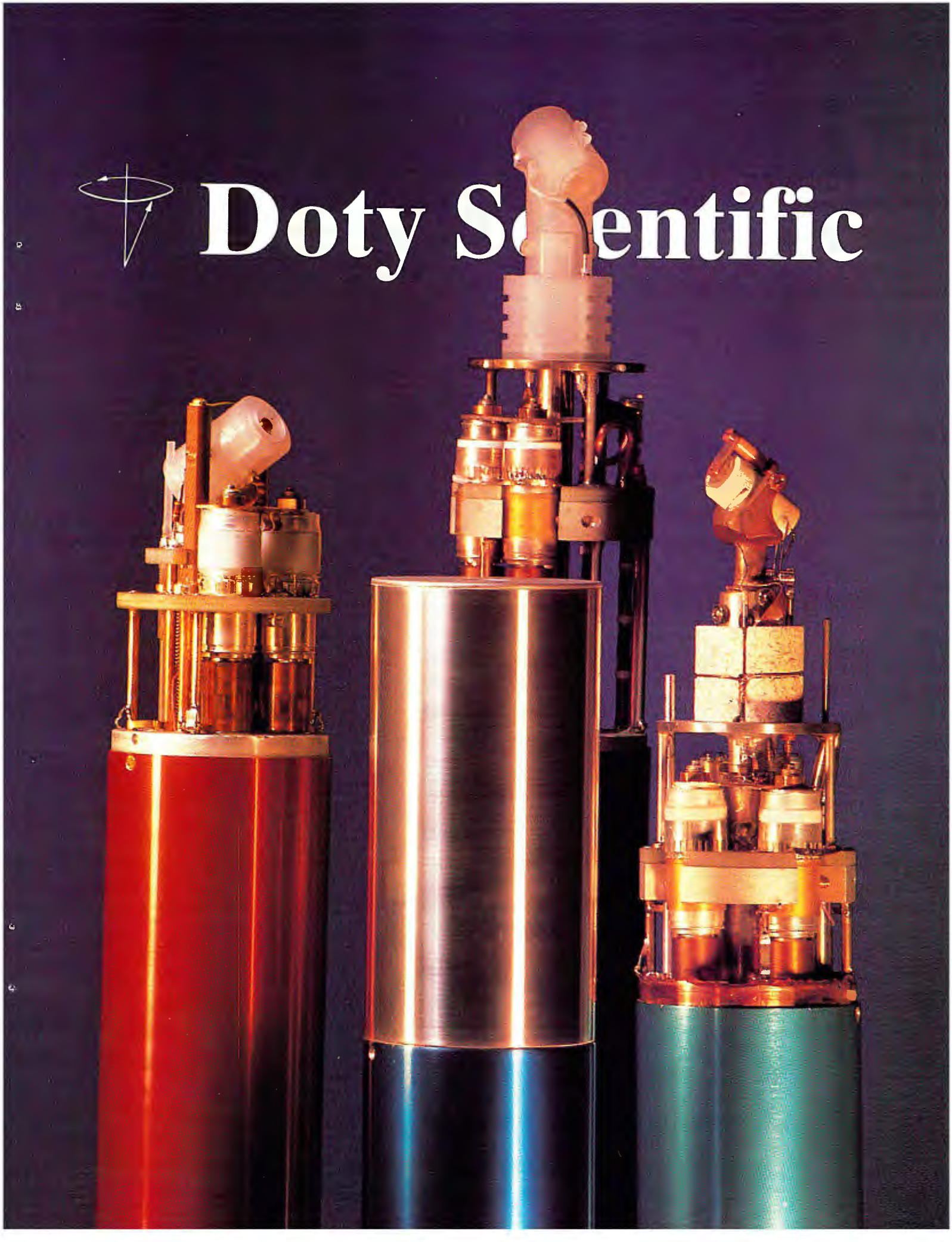


Fig. 1. Three ^{129}Xe NMR spectra of the blends PC/PIP, PC/EPI50, and PIP/EPI50 overlaid. The two immiscible blends PC/PIP and PIP/EPI50 exhibit two peaks. The miscible blend PC/EPI50 shows only one peak. The chemical shift scale is referenced to Xe gas at 12 atm.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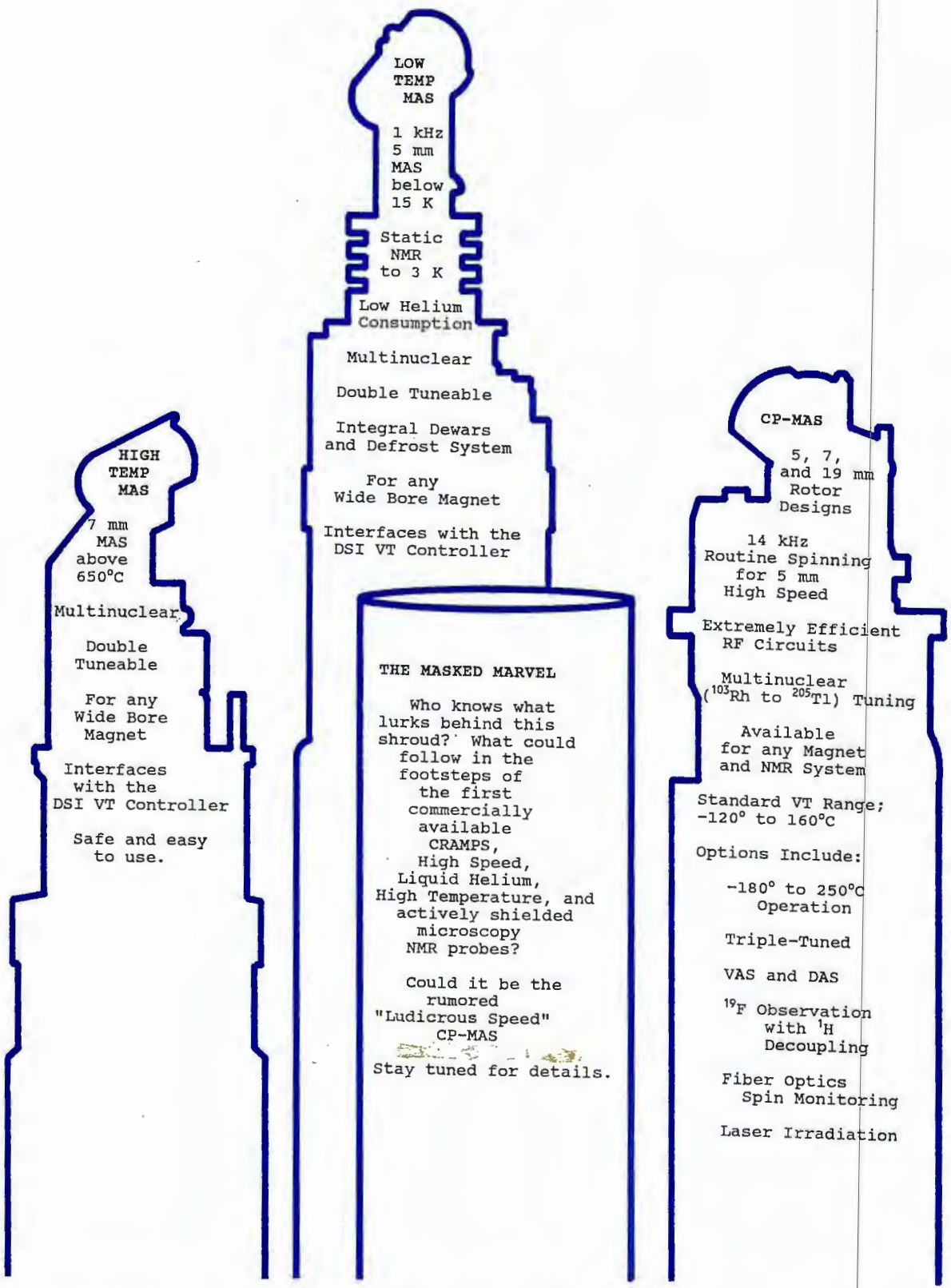

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(received 1/12/91)

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

Re: High Pressure ^{59}Co NMR

Dear Barry:

^{59}Co is a highly favourable nucleus for investigation by NMR. It is 100% abundant and has a detection sensitivity[1] of 1572 relative to ^{13}C. It has nuclear spin of I=7/2 and a quadrupole moment of 0.4×10^{-28}cm^2 making the NMR linewidth sensitive to the electric field gradients at the nucleus and therefore the symmetry about the cobalt nucleus. For octahedral symmetry the six ligands surrounding the nucleus result in low electric field gradients and the linewidths can be <10Hz. Chemical shifts for ^{59}Co cover >18,000 ppm, the reasons for which are extensively discussed in a number of papers[2-5].

The temperature dependence of the ^{59}Co chemical shift is linear, with an increase in temperature resulting in a decrease in shielding which moves the resonance to higher δ-values. Two groups of workers[6,7] determined that for $K_3[Co(CN)_6]$ $d\sigma/dT = -1.38$ ppm/K while we obtained $d\sigma/dT = -1.404 +/- 0.007$ ppm/K. In 1963 Benedek *et al.*[7] demonstrated that the ^{59}Co chemical shift is also pressure dependent. Increasing the pressure causes an increase in cobalt shielding which shifts the resonance to lower δ-values. At a temperature of 300K $d\sigma/dP = 21.38$ ppm/kbar[8].

While designing a high pressure vessel to perform studies up to 5kbar pressure we repeated the measurements of Benedek *et al.* performed on $K_3[Co(CN)_6]$ and confirmed their original results as to the dependence of the chemical shift on pressure (see Figure 1). We also obtained a more visual demonstration of the large pressure dependence of the shift on pressure by acquiring a ^{59}Co spectrum as the pressurising system applied the pressure. Each of the "spikes" corresponds to the resonance after each stroke of the pressurising pump. As the pressure reaches its set value the resonance no longer moves and the "spikes" are summed (pump strokes 18-20 on the figure). In actual fact, since the cobalt shift is so sensitive to temperature, the measurement of the shift as a function of pressure was delayed since the sample was heated slightly during compression and thermal equilibrium needed to be reestablished.

A manuscript with a full description of the experiments performed on $K_3[Co(CN)_6]$ as a function of temperature and pressure is in preparation[9].

Yours sincerely,

A.J. Williams

References

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2. N.F. Ramsey, Phys. Rev., 78, 699 (1950)
3. R. Freeman, G.R. Murray and R.E. Richards, Proc. Roy. Soc. A242. 455 (1957)
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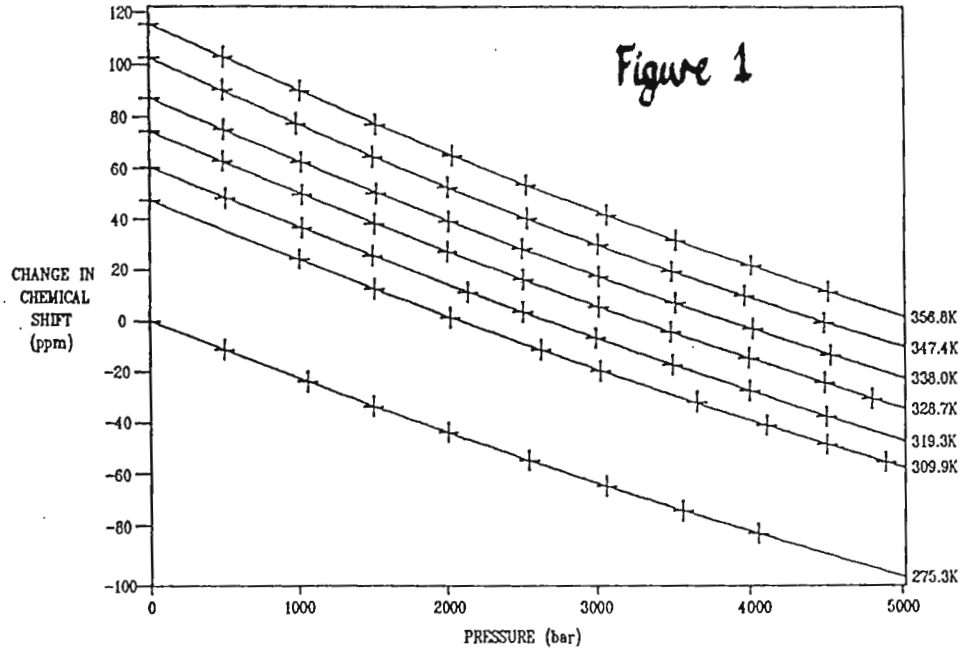
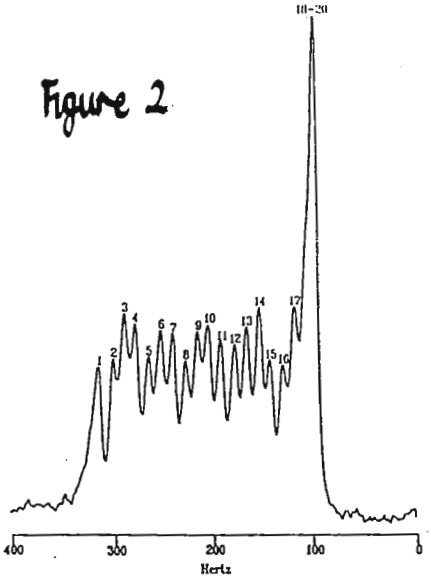
5. R. Bramley, M. Brorson, A.M. Sargeson and C.E. Schäffer, J. Am. Chem. Soc., 107, 2780 (1985)
6. W.G. Proctor and F.C. Yu, Phys. Rev. 81, 20 (1951)
7. G.R. Benedek, R. Englman and J.A. Armstrong, J. Chem. Phys., 39, 3349, (1963)
8. D.G. Gillies, L.H. Sutcliffe, A.J. Williams, unpublished -results
9. This work was performed during my Ph.D studies at Royal Holloway and Bedford New College, University of London, United Kingdom.

CHIMIE/CHEMISTRY

32 GEORGE GLINSKI, OTTAWA, ONTARIO, CANADA K1N 6N5
(613) 564-2430 FAX: +1(613) 564-6793

The change in chemical shift of the cobalt-59 resonance of $K_3[Co(CN)_6]$ as a function of pressure at a series of temperatures.





The effect of pressure pump strokes on the ^{59}Co chemical shift of potassium hexacyanocobaltate(III). Twenty scans were acquired while the pressurising system was pumping up to pressure. The acquisition time was 1s with no pulse delay. The numbers indicate each pump stroke during the acquisition time of the entire spectrum.

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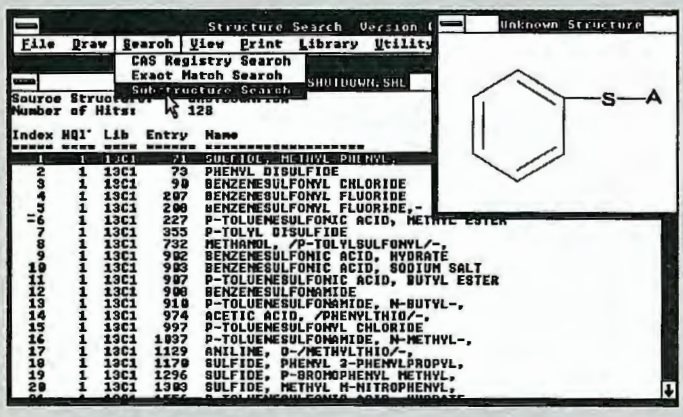

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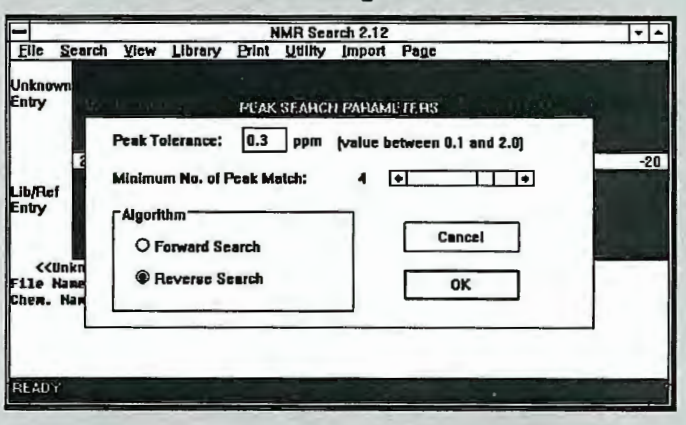

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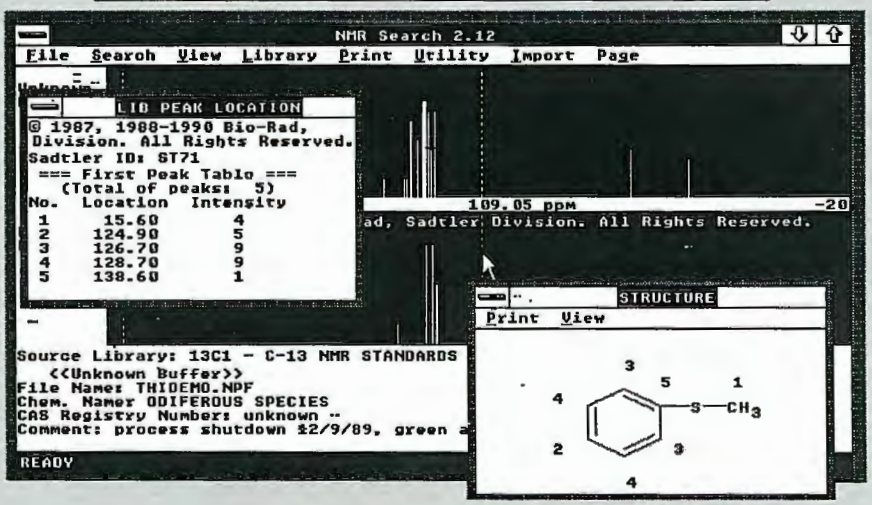

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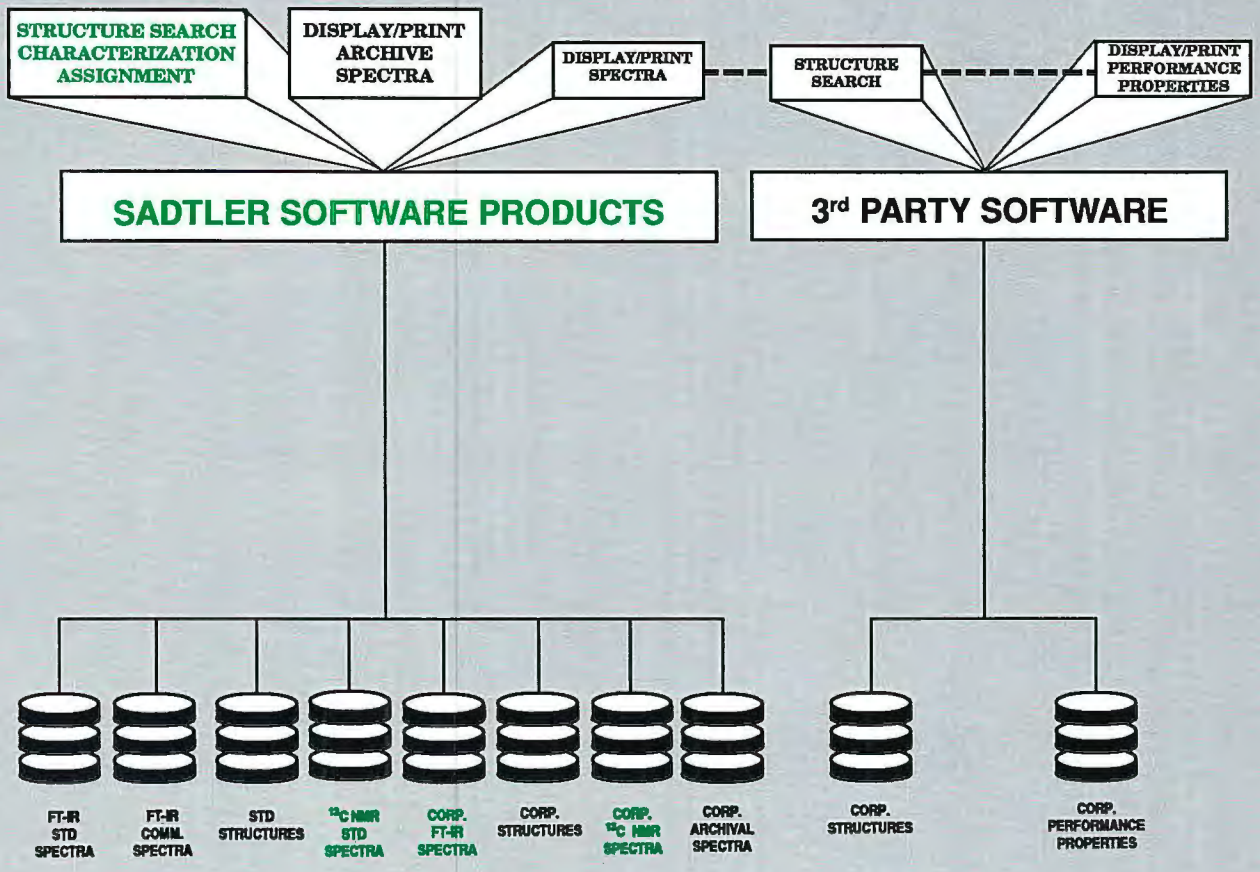

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Washington
WASHINGTON·UNIVERSITY·IN·ST·LOUIS

Department of Chemistry

(received 1/12/91)
January 8, 1990

Re: Further (Re)Discovery of Unexpected (?) Multiple Resonances in Tissue Extracts. Two ^{31}P Resonances for Phosphoethanolamine!

Dear Barry:

Last April (1990) we sent a short article to the *Newsletter* on the deuterium isotope induced splitting of the phosphocreatine ^{31}P resonance observed in high resolution NMR studies of tumor extracts. In the same studies we have observed also two ^{31}P resonances from phosphoethanolamine (PE), $H_2PO_4(CH_2)_2NH_2$. The (unexpected) presence of two resonances from PE in the tumor extracts, unlike that of phosphocreatine, was found to be due to a pH dependent bicarbonate effect. This was verified by experiments with standard PE samples (Fig. 1) and was found to be associated with both the pH and the amount of bicarbonate in the solution. The observations made (Figs 1A – 1C) appear to be consistent with the following chemical reactions:

$$RNH_2 + CO_2 \rightleftharpoons RNHCOO^- + H^+ , \qquad [1]$$

where R stands for $(PO_3)^{-2}$—O—$(CH_2)_2$ and the CO_2 is generated by reactions,

$$HCO_3^- + H_2O \rightarrow OH^- + H_2CO_3 \qquad [2]$$

and

$$H_2CO_3 \rightleftharpoons CO_2 + H_2O . \qquad [3]$$

In Fig. 1A, moving from bottom to top, one can see that with marked increases in the amount of bicarbonate (accompanied by small pH changes) the relative intensity of the peak corresponding to $RNHCOO^-$ (lower shielding) increases while that of the peak corresponding to RNH_2 (greater shielding) decreases. This phenomenon was present in all solutions of PE whose pH values were in the range of *ca.* 8.5 to 11 provided there was some bicarbonate present in the system. For example, Fig. 1B, in spite of the fact that the pH lies in the above mentioned range, fails to show the resonance at lower shielding due to the absence of bicarbonate and shows only the resonance at greater shielding corresponding to RNH_2. In Fig. 1C the bottom spectrum (note change in chemical shift scale) does not show the resonance at lower shielding despite a significant concentration of bicarbonate in the solution. At a pH value of 6.80 two phosphorus containing species are possibly present in solution: (i) primarily RNH_3^+, which does not react with CO_2 and whose ^{31}P resonance is shifted toward greater shielding due to the well known pH dependent (ionizable) phosphate chemical shift and (ii) minor amounts of RNH_2 which could react with CO_2 according to Rxn. [1] but because of the pH value the equilibrium is shifted towards the left {high $[H^+]$, low $[CO_2]$} and formation of $RNHCOO^-$ becomes negligible. As the species RNH_3^+ and RNH_2 are in fast exchange, one then observes a single resonance at a ^{31}P chemical shift which is the weighted average of the pH dependent phosphate chemical shifts of the individual species. The upper spectrum in Fig. 1C (note change in chemical shift scale) shows that under highly basic conditions the equilibrium Rxn. [1] is shifted far towards the right and in the presence of excess bicarbonate one will see only the ^{31}P resonance corresponding to $RNHCOO^-$.

Joseph J.H. Ackerman

Tedros Bezabeh

Tedros Bezabeh

Washington University
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One Brookings Drive
St. Louis, Missouri 63130-4899

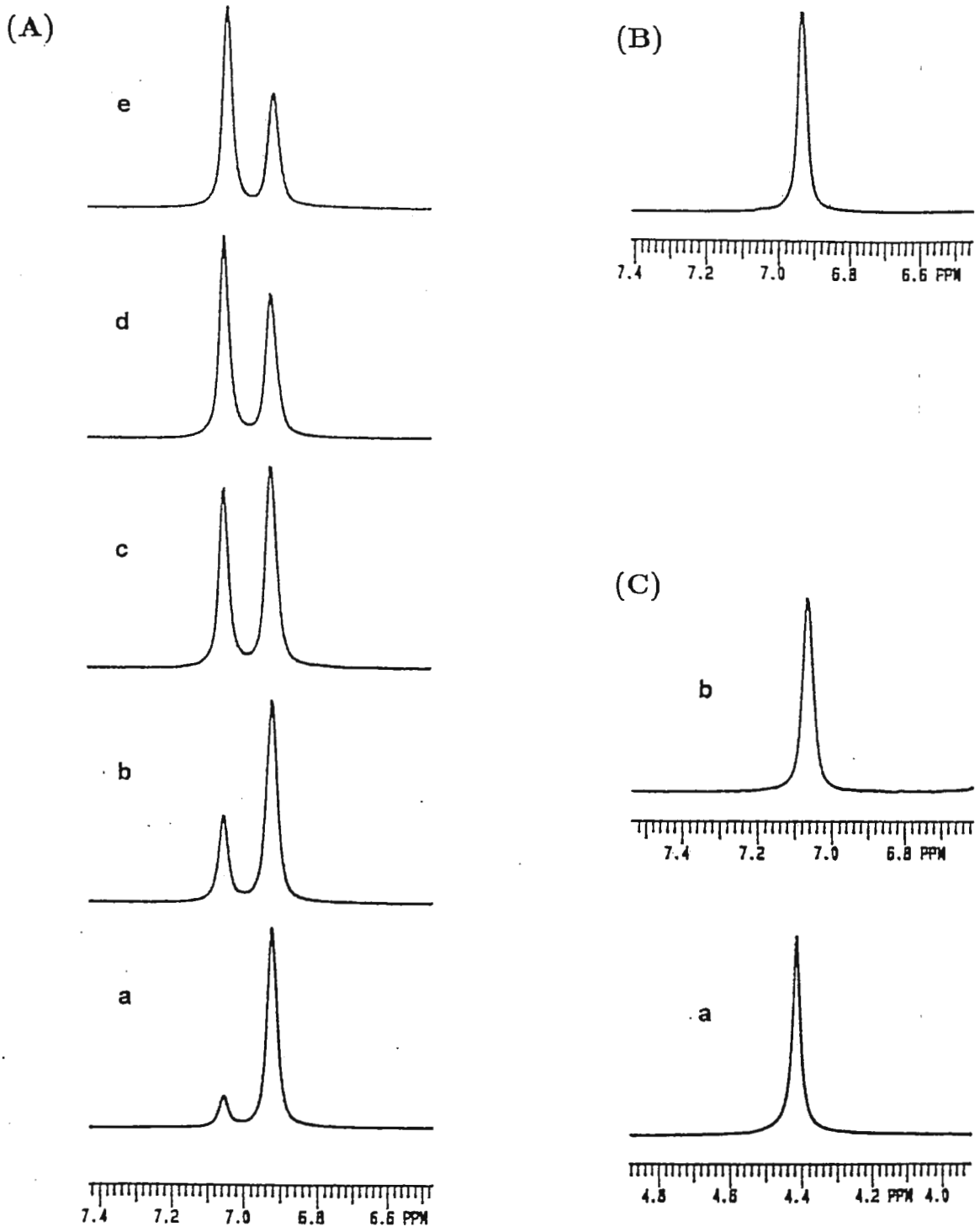

Fig. 1. Proton decoupled ^{31}P NMR spectra (202.3 MHz) showing the effects of bicarbonate and pH on the phosphoethanolamine resonance. Chemical shifts referenced to internal phosphocreatine (not shown) as 0.0 ppm. Panel (A) shows this effect with the addition of different amounts of a standard 2.0 M bicarbonate solution to a 0.6 ml 0.10 M solution of PE. The final bicarbonate concentration and the pH values for each of the subpanels were as follows: (a) 0.37 M, pH = 9.08 (b) 0.49 M, pH = 9.40 (c) 0.66 M, pH = 9.57 (d) 0.79 M, pH = 9.62 (e) 0.90 M, pH = 9.67. Panel (B) shows the spectrum of a PE solution that contained no bicarbonate but only NaOH (pH = 9.74). Panel (C) shows the spectra of 0.06 M PE solution with bicarbonate concentrations of 0.07 M and 0.21 M respectively at different pH values, *i.e.* (a) pH = 6.80 (b) pH = 11.04.

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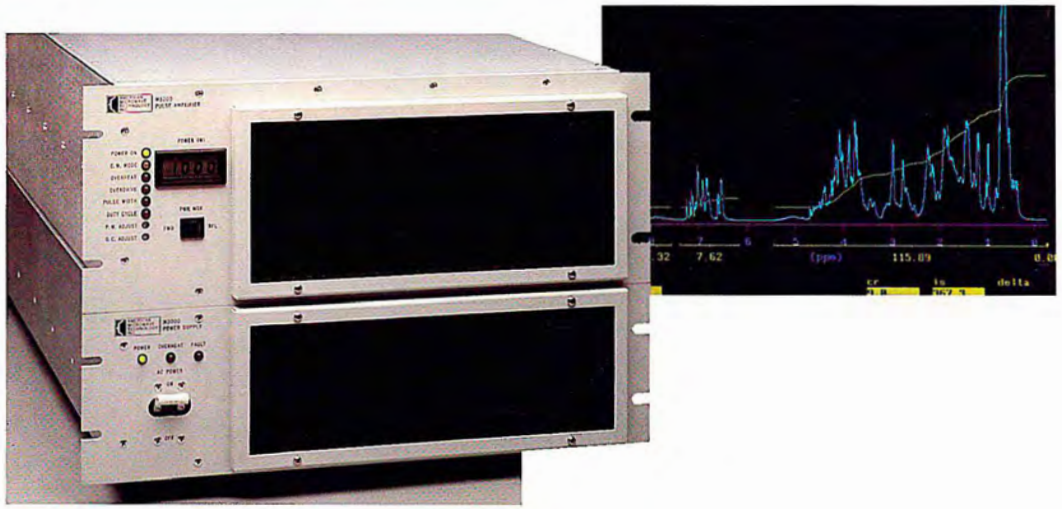

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Professor B.L.Shapiro
Tamu NMR Newsletter
966 Elsinore Court
Palo Alto CA 94303
USA

Your reference and date	Our reference	Office telephone	Date
		6041	January 3 1991.
			(received 1/10/91)

Subject

Sub-division

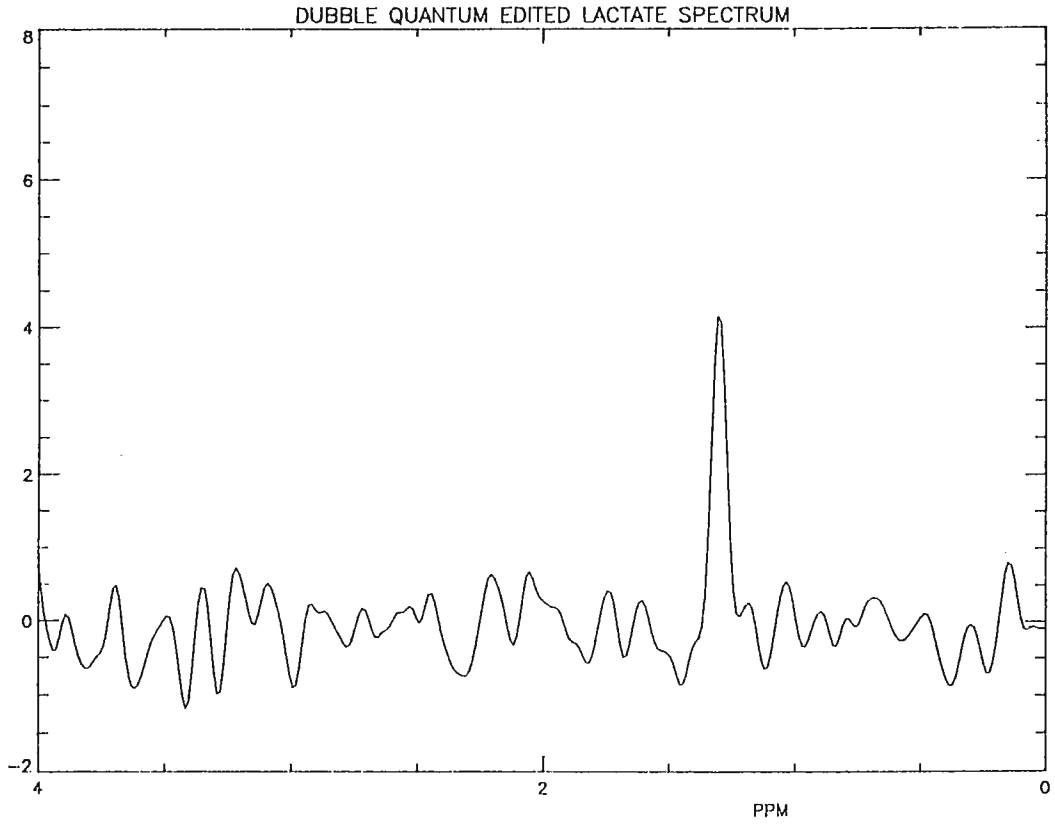
Dear Professor Shapiro,

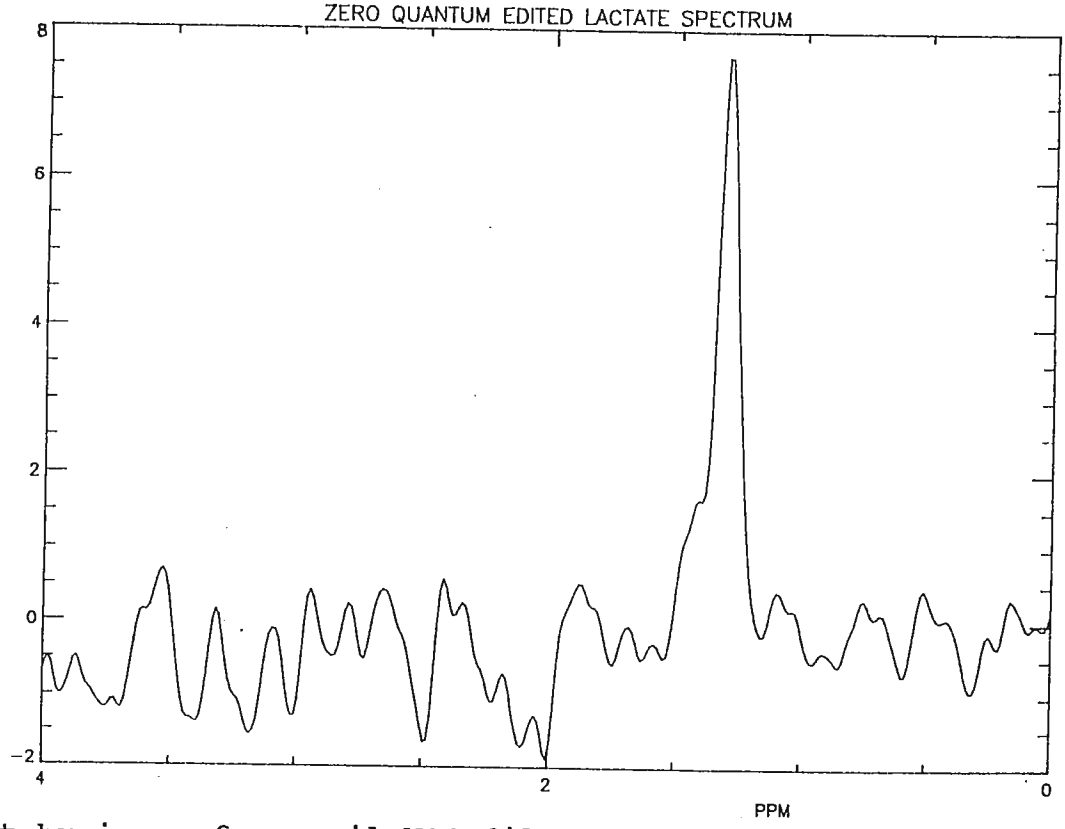
In vivo spectral editing by multiple quantum filtering.

Spectral editing methods can be based on the following properties:
1. Differences in relaxation times of overlapping lines.
2. J-modulation effects of coupled spins.
3. Multiple quantum coherence (MQC) filtering. This method separates spectral compounds on basis of the MQC order, and in some way on the magnitude of the coupling constants. To minimize motional artifacts in vivo, single shot methods to select a MQC order are preferable to phase cycling. B_0 field gradients can be used for this purpose. This results, however, in 75% signal loss for the detectable magnetization of the X_3 group of AX_3 systems like lactate. Using a selective readout pulse a factor two in signal strength is gained. A further factor two can be obtained by applying a selective 180° pulse symmetrically surrounded by gradient pulses in the middle of the t_1-interval (L.A.Trimble e.a., J.Magn. Reson.86, 191-198, 1990).
Besides the MQC editing properties mentioned above, further editing can be obtained by using the MQC modulation effects during t_1. In a two shot experiment, t_1 can be chosen in such a way that of two overlapping signals, X and Y, the X signal has both times the same phase, the Y signal differs 180° in phase. Addition or subtraction gives either the X or Y signal.
Examples of in vivo DQC and ZQC edited spectra are given in the figure.

Hans v. Dijk

Wim Bovée





Rat brain surface coil MQC filtered spectra, showing lactate.

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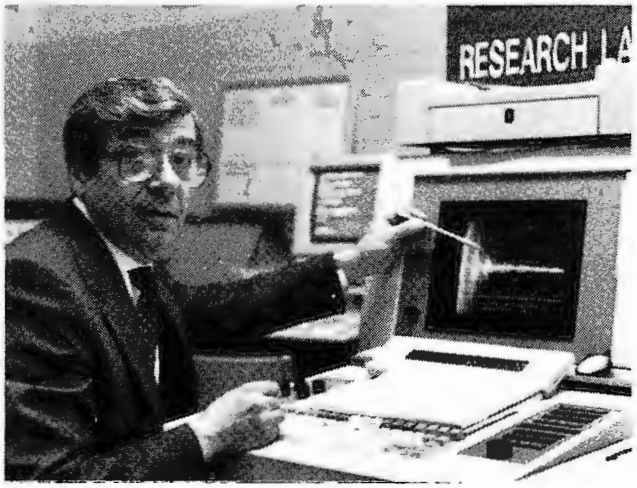

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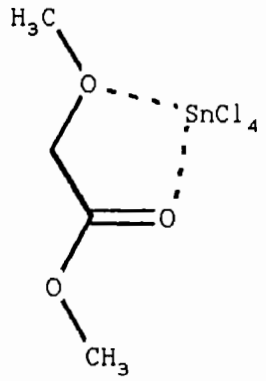
11 January, 1991
!!! (received 1/10/91 [sic])

Dr. Barry Shapiro
Texas A&M Newsletter
966 Elsinore Court
Palo Alto, CA 94303

A Chelate Complex of $SnCl_4$

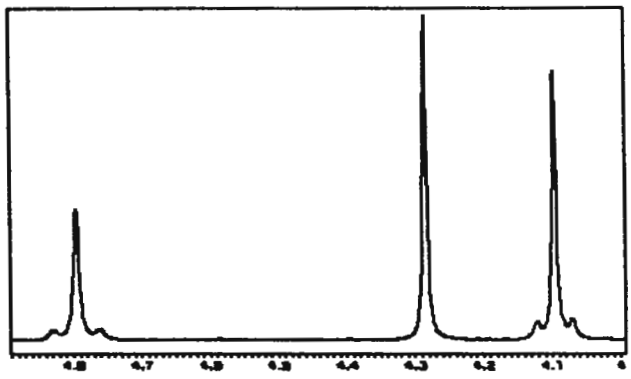
Dear Barry:

As part of an attempt to understand the way in which $SnCl_4$ catalyzes some of our reactions, we have studied its complex with methyl methoxyacetate (MMA). We thought this complex might be a good place to start, since from some X-ray crystallography results in the literature[1] of very similar complexes we thought that we could predict that the MMA complex would be a chelate of the type:



By studying mixtures of MMA and $SnCl_4$ in various mole ratios and temperatures[2] in CD_2Cl_2/CD_3NO_2 (4:1) solutions we were able to prove that the stoichiometry of this complex was 1:1. From the comparison of the ^{13}C NMR spectra of the complex and the free ligand we could see that complexation had led to a large change in the chemical shift of the carbonyl carbon, so that it was clear the carbonyl was involved in the complexation process. In support of this there was a large change in the chemical shift of the ester O-methyl protons. Other proton and ^{13}C chemical shifts around the molecule also showed changes, but they were smaller. There seemed to be no chemical shift changes that proved definitively that the ether oxygen was involved in the complexation process.

Fortunately, it turned out that there were some coupling data which solved this problem. The proton spectrum of a 1:1 mixture of MMA and $SnCl_4$ at -60°C looked like:



δ

It turned out that the "side bands" on the resonances of the methylene and the ether O-methyl were due to coupling to the ^{119}Sn of the $SnCl_4$. There are two magnetically active tin isotopes, and their total natural abundance is about 16%. Their couplings to other nuclei should differ by only about 5%, so that the two different couplings would not be resolved at the line-widths prevailing in the spectrum above. It was possible to confirm this interpretation by simply taking the ^{119}Sn NMR spectrum without decoupling, and by specific decoupling experiments. We believe that coupling between these nuclei, especially that between the tin nucleus and the protons of the ether O-methyl, prove the existence of a dative bond between the tin and the ether oxygen.

This is one of a very few complexes in which we have seen this sort of proton-tin coupling. However, one of our consultants (Prof. Desmond Cunningham, University of Galway) tells us that inorganic chemists are quite accustomed to observing this sort of thing.

Sincerely,

Frank Brown, Jr. Doug Dorman Perry Heath Larry Spangle

[1] M.T.Reetz, K.Harms, W.Reif, *Tetrahedron Letters*, **1988**, *29*, 5881.

[2] S.E.Denmark, B.R.Henke, and E.Weber, *JACS*, **1987**, *109*, 2512.

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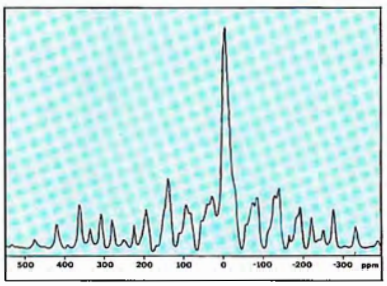

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15 mg / 0.7 ml (27 mmolar)
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of protons from different spin systems
U-500, 5 mm 1H/19F probe (#252)
P.S. Darmstadt

exp6 pulse sequence: tocsyid

SAMPLE		DEC. & VT		ACQUISITION ARRAYS	
date	Jun 25 90	dn	H1	array	(selfrq,m
solvent	D2O	dof	-174.2		ix)
file	exp	dm	ynn	arraydim	4
ACQUISITION		dmm	c		
sfrq	499.843	dmf	200	1	selfrq
tn	H1	dpwr	2	1	261.1
at	2.005	temp	29.0	2	51
np	12032	PROCESSING		3	-1603.4
sw	3000.1	gf	0.330	4	-395.7
fb	1700	gfs	not used		
bs	32	wtfile		1	mix
ss	4	proc	ft	1	.18
tpwr	60	fn	not used	2	.18
pw	0	math	f	3	.18
d1	2.000			4	.12
tof	-689.7	werr			
nt	32	wexp			
ct	32	wbs			
mix	arrayed	wnt	wft		
shape	tophat	DISPLAY			
selpwr	-4	sp	774.2		
selfrq	arrayed	wp	2199.8		
nisp	64	vs	1619		
pis	165.0	sc	0		
trimpwr	54	wc	250		
trim1	0.002	hzmm	8.80		
trim2	0.002	is	33.57		
slpwr	48	rfl	2013.2		
pw90	31.8	rfp	2374.3		
slock	n	th	7		
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FLAGS		si cdc ph			
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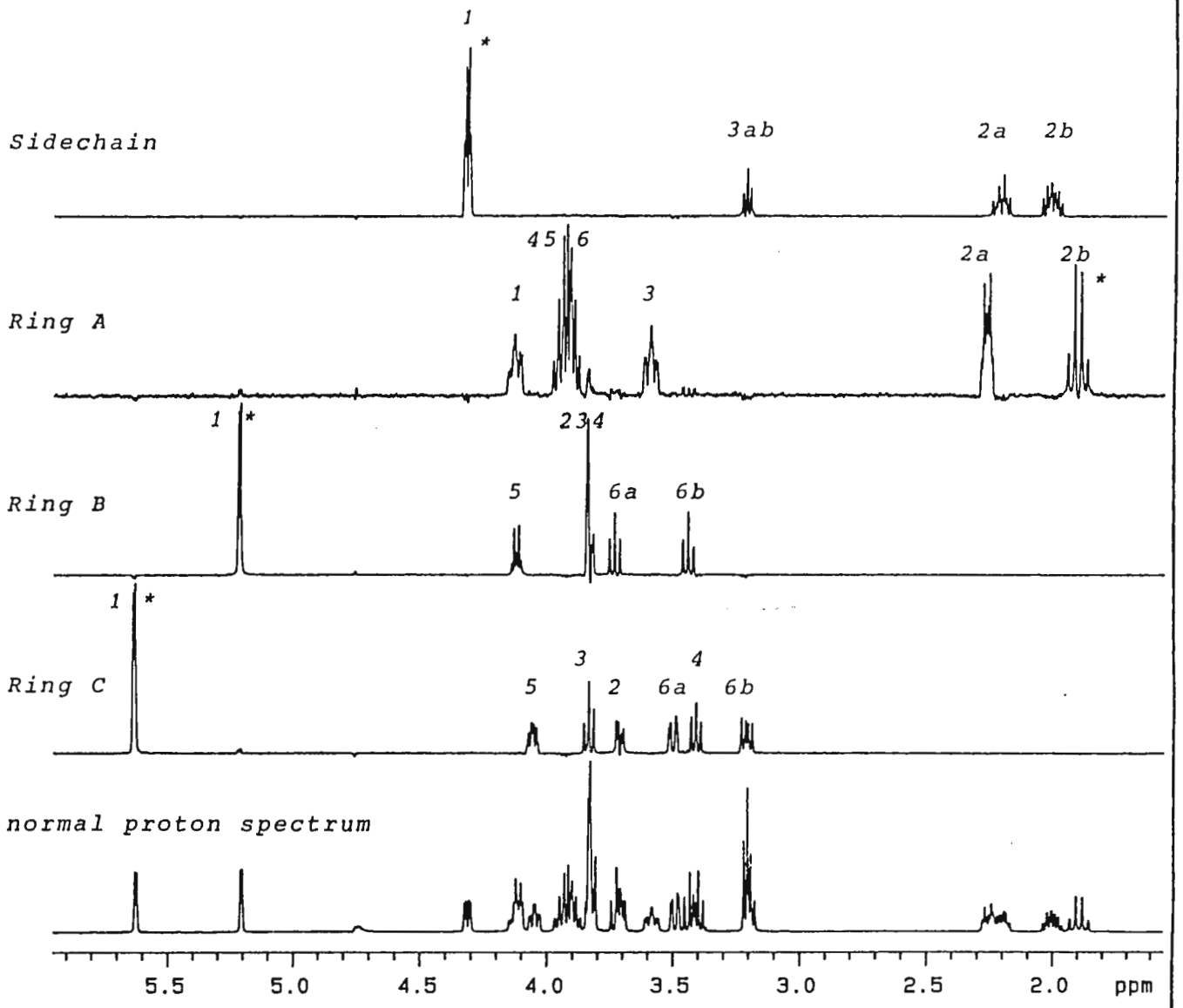
in	n				
dp	y				
hs	nn				



Dr B L Shapiro
TAMU NMR Newsletter
966 Elsinore Court
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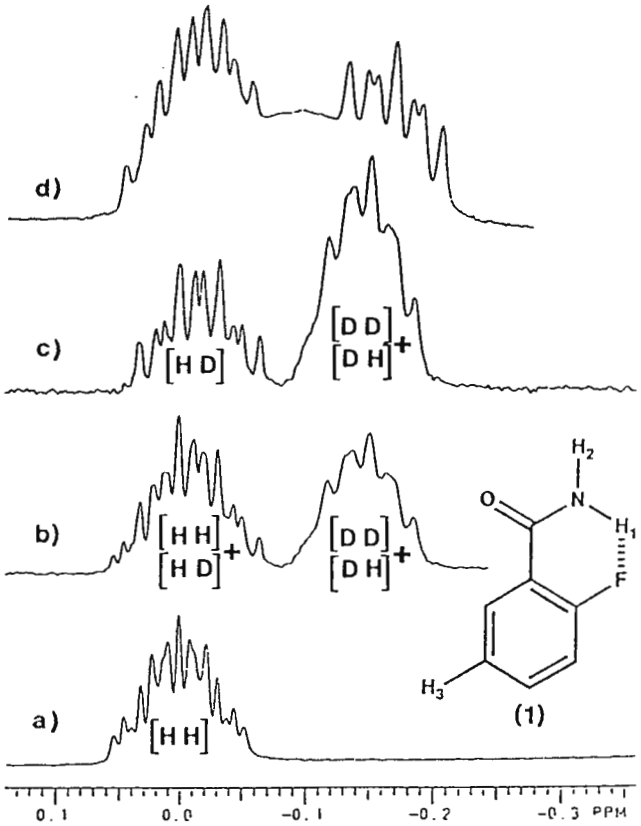
^{19}F DEUTERIUM ISOTOPE EFFECTS AND THROUGH SPACE COUPLING

(received 12/19/90)

Dear Dr Shapiro,

The use of fluorine as a Lewis base creates many interesting ways of using NMR to investigate the strength, geometry and electronic interactions in hydrogen bonds. This is of practical as well as academic interest, given the increasing number of fluorinated drugs which are designed to interact with polypeptide receptors.

2-Fluorobenzamide (1) illustrates most of the entertaining points. In $CDCl_3$ solution, the molecule adopts a conformation with a strong internal hydrogen bond. The ^{19}F spectrum (a) shows a complicated multiplet that cannot be simulated on the basis of the measured ^{19}F-CH coupling constants but must include additional 5-bond couplings to the amide protons. In a sample that has first been freeze-dried from 1:1 H_2O:D_2O, four species are present which can be labelled [H, H], [H, D], [D, H] and [D, D] according to the isotope present at the two amide sites, [H_1, H_2].



376 MHz NMR spectra of 2-fluorobenzamide (1) in $CDCl_3$. (a) Fully protonated. (b) 50% deuterated. (c) The difference spectum (a)-(b). (d) Coalescence of the [H,D] and [D,H] signals at 35°C

The ^{19}F NMR spectrum (b) of such a mixture shows two separate groups of signals. Those shifted to high field, compared with (a), are assigned to [D, H] and [D, D] illustrating the 0.14 ppm isotope shift which arises from substitution of the proximal hydrogen (H_1). Spectrum (c) is the difference spectrum, (b)-(a). The downfield multiplet now arises solely from the species [H, D]. Comparison of this multiplet with the [H, H] multiplet of (a) indicates a 0.016 ppm isotope shift (also upfield) on substitution of H_2 for deuterium and spectral simulation gives $^5J_{F\text{-}H1}$ = 11.3 Hz and $^5J_{F\text{-}H2}$ = 2.9 Hz.

These values should be compared with each other, and with $^5J_{F\text{-}H3}$ = 0.2 Hz, indicating a substantial 'through-space' contribution.

At higher temperatures (d), the ^{19}F NMR signals due to [H, D] and [D, H] coalesce due to rotation about the C-N amide bond. Lineshape analysis and saturation transfer between the H_1 and H_2 proton resonances gives a value of 82.4 ±2 kJ mol^{-1} for $\Delta H^{\#}_{rot}$. A similar analysis of the 4-fluorobenzamide spectrum gives $\Delta H^{\#}_{rot}$ = 63.5 ±2 kJ mol^{-1}; the difference in activation energy gives a value of 18.9 ±4 kJ mol^{-1} for the H...F hydrogen bond enthalpy in 2-fluorobenzamide.

Despite their name, through-space couplings are not isotropic but rely on overlap between (directional) orbitals (1); thus a much smaller proximal NH-^{19}F coupling is observed in 2-fluoroaniline. The nature of the orbitals is also important. Replacement of the amide group by two fused aromatic rings gives 4-fluorophenanthrene in which the proximal CH-^{19}F coupling is reduced to 2.6 Hz (2).

Integration of the ^{19}F and ^1H signals of partially deuterated samples of 2-fluorobenzamide has indicated that there is no preference for H over D at the proximal site (within experimental error), contrary to predictions based on the higher zero-point energy of H and the 'softer' potential at this site .

Please credit this contribution to Tony Thomas's account.

With all best wishes for 1991, the Chinese year of the Palindrome, from the Physical Methods Department at Roche, Welwyn.

Glyn Williams

(1) J Hilton and L H Sutcliffe, Prog. in NMR Spectroscopy, 10, 27-39 (1975).

(2) Li C Hsee and D J Sardella, Mag. Reson. in Chem, 28, 688-692 (1990).

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PTS 500

Range: 1–500 MHz
Resolution: 0.1Hz–100KHz (opt)
Switching: 1–20μs

Output: +3 to +13dBm; 50ohm
Spurious Outputs: –70dBc
Phase Noise: –63dBc (0.5Hz–15KHz)

Freq. St'd: OCXO, TCXO, Ext.
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PTS 620

Range: 1–620 MHz
Resolution: 0.1Hz–100KHz (opt)
Switching: 1–20μs

Output: +3 to +13dBm; 50ohm
Spurious Outputs: –70dBc
Phase Noise: –63dBc (0.5Hz–15KHz)

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PTS 1000

Range: 0.1–1000 MHz
Resolution: 0.1Hz–100KHz (opt)
Switching: 5–10μs

Output: +3 to +13dBm; 50ohm
Spurious Outputs: –70dBc (0.1–500 MHz), –65dBc (500–1000 MHz)
Phase Noise: –60dBc (0.5Hz – 15KHz)

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January 17, 1991
(received 1/18/91)

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

Re: ^{1}H Decoupled ^{31}P Three Dimensional Chemical Shift Imaging (3D CSI) of Human Brain at 1.5T.

Dear Dr. Shapiro:

We have developed a new dual-tuned $^{1}H/^{31}P$ quadrature transmit/receive birdcage head coil for studies of the human brain. Proton decoupling using Waltz-4 modulation and bilevel excitation was used to acquire full Nuclear Overhauser Effect (NOE) enhanced 8x8x8 3-D CSI phosphorous spectra at 64 (4x4x4) CC and 27 (3x3x3) CC voxel resolutions from normal volunteers. Using repetition times of 1 second and a flip angle of 40^{o} at the coil center, observation times were 35 minutes for a 4 acquisitions per phase encoding step. Fifteen watts of decoupling power was used during ^{31}P acquisition (0.256 sec) and 1.5 watts between acquisitions for an average power of 5 watts. In addition to acquiring decoupled ^{31}P spectra, this coil was also used to obtain high quality proton images of the brain in the same examination, without repositioning the subject.

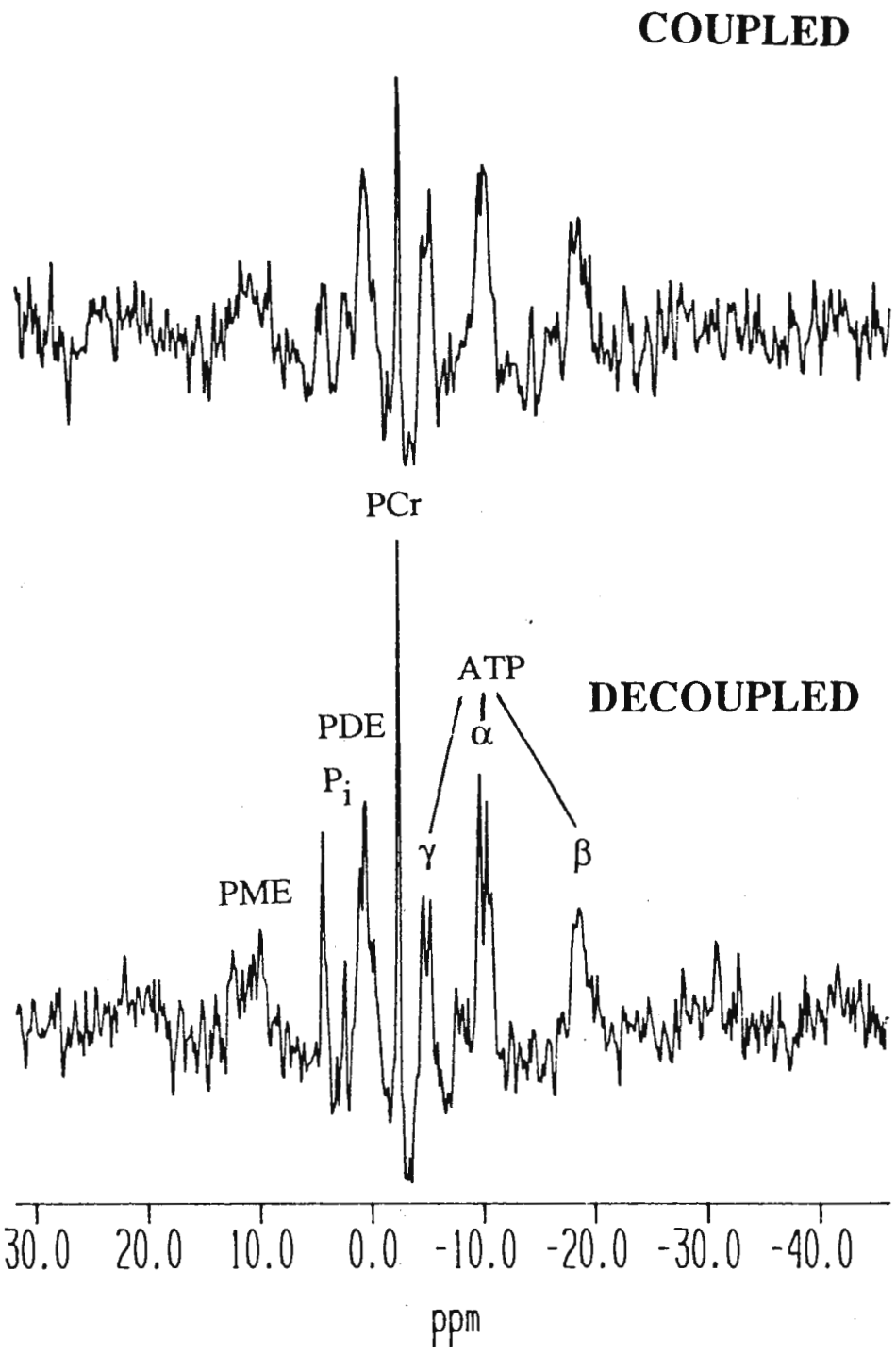
Sixty-four (4x4x4) cc voxel coupled and proton decoupled ^{31}P spectra from the human brain are enclosed. As can be seen from the spectra, the application of bilevel proton decoupling to 3D ^{31}P CSI results in a substantial improvement in both spectral resolution and sensitivity with substantial reduction in linewidth and increase in sensitivity for phosphomonoesters (PME) and phosphodiesters (PDE). With proton decoupling the small inorganic phosphate P_i peak now becomes clearly visible between the PME and PDE regions, which is normally hidden by the overlap of these peak regions in the coupled spectra. PCr also shows dramatic improvement in sensitivity and spectral resolution.

This increased ability to observe metabolites in the PME and PDE regions may be useful in studying tumors and other brain diseases for which the phospholipid metabolism may be altered.

Sincerely,

Ravi Srinivasan Joseph Murphy-Boesch Truman R. Brown

3-D CSI at 64cc



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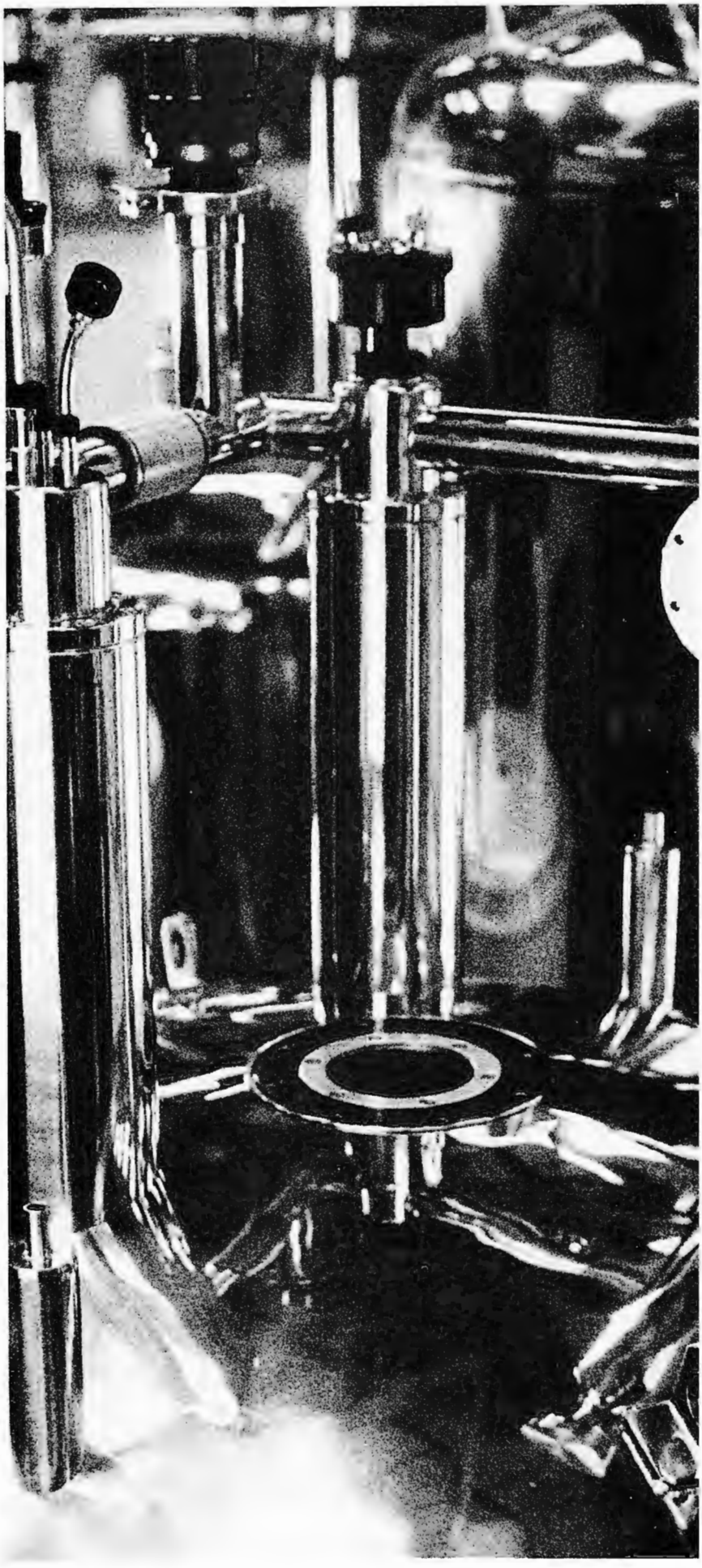

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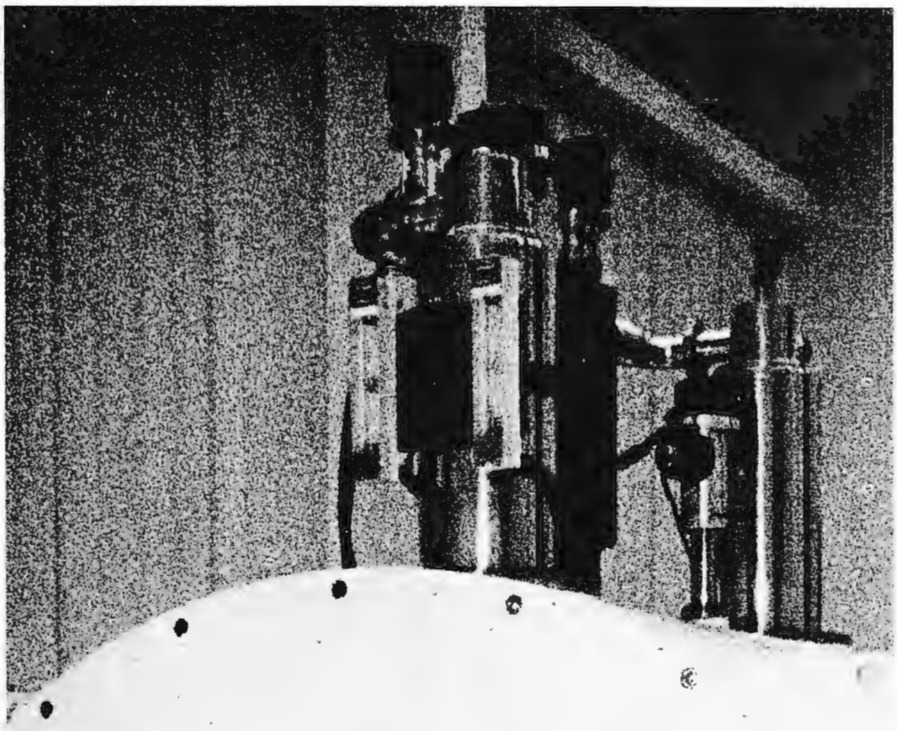

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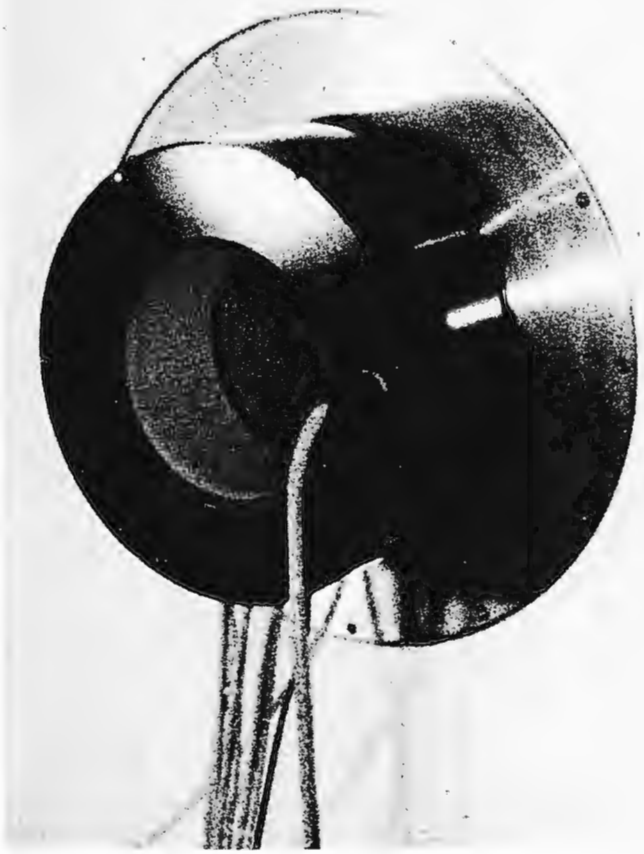

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January 11, 1991 (received 1/15/91)

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

Spin-Diffusion Measurements for MAS-NMR Assignments: A SPARTAN Approach

Dear Barry:

Measurements of spectral spin-diffusion from one peak in a MAS-NMR spectrum to another might be expected to provide useful information for assignment purposes. Ernst and co-workers first demonstrated[1] how a rotor-synchronized DANTE pulse sequence could be used to selectively excite a given ^{13}C MAS-NMR peak and its associated sidebands, and later demonstrated the existence of spin diffusion by using a related sequence in ^{1}H CRAMPS experiments (in the case where strong proton dipolar couplings are not averaged to zero by MAS).[2] We would like to show here that the simplest 1–D version of these experiments (not previously described) can demonstrate the existence of spin diffusion *even when the spinning speed exceeds the moderate homonuclear and small heteronuclear dipolar couplings of the spin system.* Since the basic idea is to selectively invert a given peak and measure the rate at which its magnetization "spin-diffuses" to another peak, we propose the acronym SPARTAN for this basic pulse sequence (**S**elective **P**opulation **A**nti-z and **R**ate of **T**ransfer to **A**djacent **N**uclei).[3]

The pulse sequence we use is shown in the top Figure, and contains a series of small flip angle pulses spaced at intervals of the rotor period, forming in total a 180° pulse, whose selectivity is governed by the total length of the pulse train. A mixing period allows cross-relaxation (via spin-diffusion or chemical exchange) to occur, and a final 90° observe pulse is applied. On our Varian VXR-400 spectrometer it is easy to use the optically detected spinning speed signal from our Doty ^{19}F MAS probe to gate the actual pulses. Shaped pulse trains (Gaussian, etc.) can also be produced by changing power levels, and can offer improved excitation profiles.

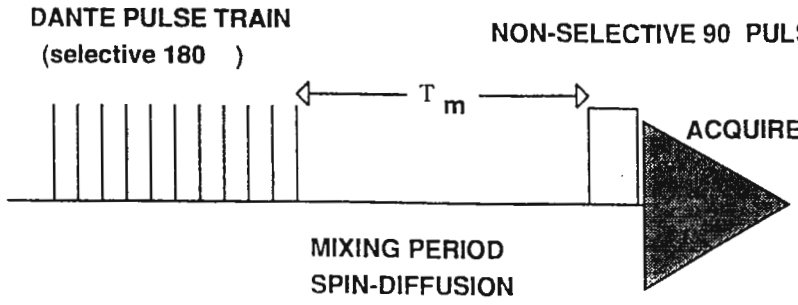
The system we were interested in was Sb^{3+}-doped fluoroapatite ($Ca_5F(PO_4)_3$), as described in our last TAMU contribution (March, 1990). Models for the ionic columns of linear fluoride ions are shown in the middle Figure. The ^{19}F MAS-NMR spectrum of fluoroapatite with 1.7% Sb^{3+} exhibits a main peak **"C"** at 64.0ppm (from C_6F_6), a weak shoulder **"B"** at 65.6ppm, and a small peak **"A"** at 68.6ppm resulting from the perturbation by the Sb^{3+} substitution in the lattice. Selectively inverting this last peak and obtaining spectra as a function of mixing times results in the superimposed plots shown in the bottom Figure. Since the T_1 relaxation time of the peaks (193sec) is much longer than the mixing times used, the recovery of the inverted peak **"A"** in a matter of seconds must be due to cross relaxation; indeed, a corresponding decrease in the intensity of the main peak **"C"** is observed. We conclude that spectral spin-diffusion between neighboring pairs of fluorine nuclei (separated by 3.44 Angstroms) is taking place. The energy-conservation requirement appears to be satisfied by having the frequencies of the two types of spins become equal at some point during the rotor cycle, due to unequal chemical shift tensors. Even more revealing from the point of view of assignments is the lack of intensity change (decrease) for the shoulder at 65.6ppm (peak **"B"**). We are able to assign this shoulder to an Sb-perturbed fluoride ion in an *adjacent* linear chain separated by 9.37 Angstroms, as shown in the rightmost middle Figure; this assignment helps confirm our conclusions that an SbO_3^{3-} group replaces the PO_4^{3-} group nearly midway between the two chains. The results will be submitted shortly for publication.

Sincerely yours,

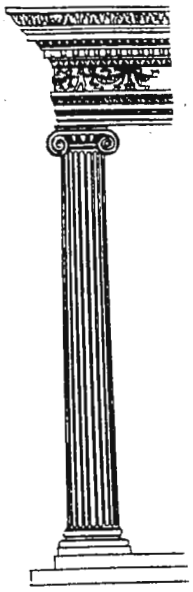
Liam Moran James Yesinowski

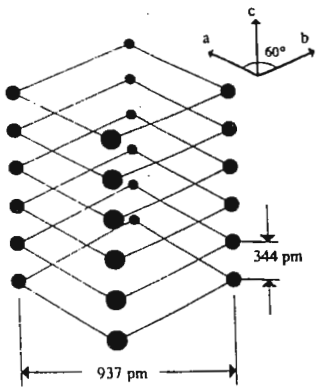
Liam B. Moran James P. Yesinowski

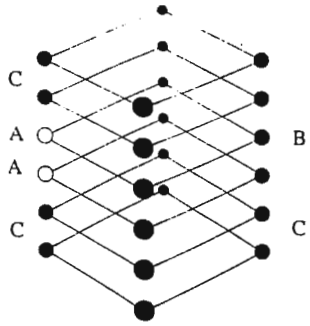
1. P. Caravatti, G. Bodenhausen and R.R. Ernst, *J. Mag. Reson.*, 55, 88 (1983).
2. P. Caravatti, M.H. Levitt and R.R. Ernst, *J. Mag. Reson.*, 68, 323 (1986).
3. A suitable acronym, based on the simplicity of the technique, and the incidental fact that it is the symbol of Michigan State University.



SELECTIVE
POPULATION
ANTI-Z and
RATE of
TRANSFER to
ADJACENT
NUCLEI

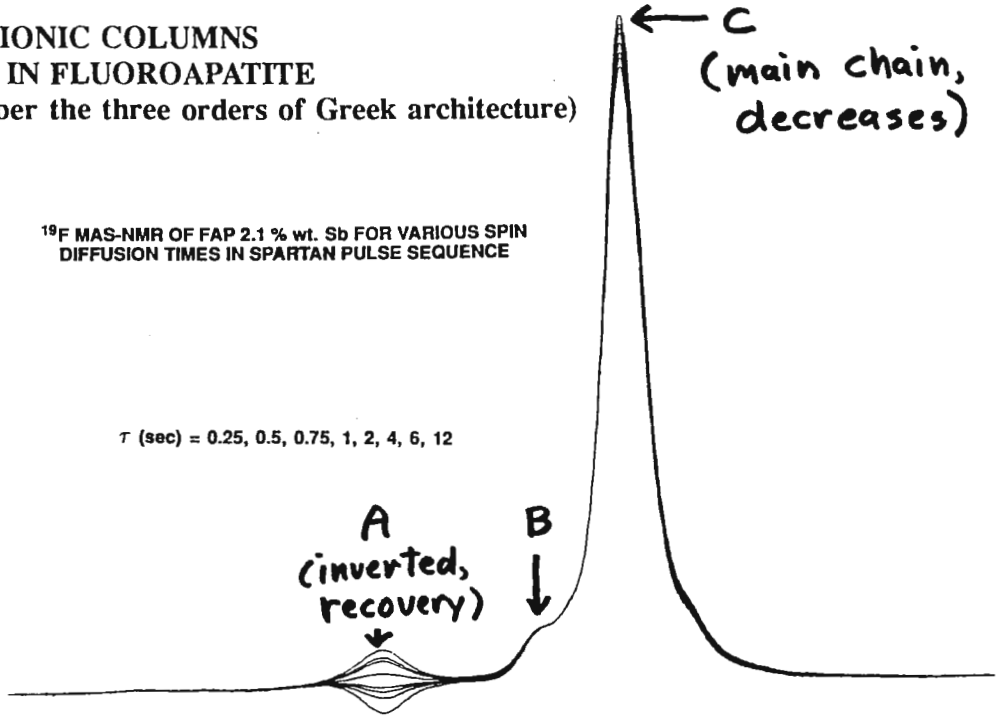






PEAK ASSIGNMENTS

TWO MODELS FOR IONIC COLUMNS OF FLUORIDE IONS IN FLUOROAPATITE
(for those who remember the three orders of Greek architecture)



PENNSTATE

College of Medicine • University Hospital
The Milton S. Hershey Medical Center

Department of Radiology

P.O. Box 850
Hershey, Pennsylvania 17033
(717) 531-6069

January 16, 1991
(received 1/18/91)

Dr. Bernard Shapiro
TAMU NMR Newsletter
966 Elsinor Court
Palo Alto, California 94303

Dear Barry:

Interleaved Acquisition Software for Bruker Spectrometers

We recently have had the need to obtain ^{1}H metabolic data in a time frame which corresponds with ^{31}P acquisition of **in vivo** neonatal rat brain. During the onset of hypoxia and subsequent recovery, rapid changes in the physiological state have been measured for our hypoxic-ischemic model (1). It is therefore optimal to acquire one of the nuclei during the relaxation delay of the other nucleus, which is typically 2 secs. for **in vivo** ^{31}P.

The following pulse sequence accomplishes interleaved acquisition on our Bruker AM 400 WB spectrometer with process controller.

```
        ZE
        RJ H1P          ;READ PARAMETERS FOR OUTER NUCLEUS (P31)
        RJSW P31P       ;MAKES INTERLEAVED NUCLEUS (H1) CURRENT PARMS
        STO             ;RESET DATA START TO FIRST BLOCK
1       ZE
        ST              ;MOVE DATA ADDRESS TO NEXT MEMORY BLOCK
LO TO 1 TIMES 2         ;ZERO BOTH MEMORY BLOCKS (NBL = 2)
2       STA0
        P1 PH1          ;PULSE INTERLEAVED NUCLEUS (H1)
        AQ              ;ACQUIRE AS IN GO (CP,ASTI=0) BUT NO RECYCLE
                        ;USES SAME PHASE AS IN THE GO BELOW
        D3 STA          ;MOVE TO 2ND BLOCK
        D5 SWJ          ;SWITCH TO 2ND PARAMETERS (P31)
;       II              ;INTIALIZE INTERFACE IF SWJ DOESN'T
        D1              ;REMAINDER OF RELAXATION DELAY FOR BOTH NUCLEI
        P1 PH2          ;PULSE OUTER NUCLEUS (P31)
3       GO=3 PH3        ;ACQUIRE WITH NS =1
        D4 SWJ          ;SWITCH BACK TO 1ST PARAMETERS (H1)
        IPHA            ;INCREMENT ALL PHASE PROGRAMS BY 90
LO TO 2 TIMES L1        ;REPEAT L1 TIMES
        STO             ;RESET DATA START TO 1ST BLOCK
        WR #1   /INTERLEAVED NUCLEUS
        ST              ;MOVE TO 2ND BLOCK
        D4 SWJ          ;SWITCH TO 2ND PARAMETERS (P31)
        WR #2   /OUTER NUCLEUS
EXIT
 PH1=0
 PH2=0
 PH3=R0
```

where STO, STA move between the two data blocks (set NBL=2), while SWJ swaps job parameters which were previously read-in with the RJSW command. The swap of parameters (which is supposed to also initialize the interface) requires 10 msecs (plus mechanical switching time), while STA requires 400 μsecs. The number of time domain points must be the same for both parameter sets. A Bruker AM 1990 version was required to successfully implement the pulse

program, as our DISR88 software was inadequate. Care should be used if preamp switching is necessary and PIN diode hardware (2) isn't available. Interleaved acquisition has recently been demonstrated on a Nicolet 1180 system with a 293B pulse programmer (3). Interleaved acquisition is desirable for all time dependent data collections of two nuclei which have similar sensitivities.

(1) Williams, Palmer, Roberts, and Smith; 9th Annual SMRM, New York, pg. 1029 (1990); TAMU 367, pg. 55 (1989).
(2) Ewing, Craig, Branch, Helpern, Smith, Butt, Welch; Stroke 20(2); 259-267 (1989).
(3) Chang, Shirane, Weinstein, and James; Magn. Reson. Med. 13; 6-13 (1990).

Sincerely,

Gerald D. Williams,
Radiology NMR Manager
Bitnet: JERRY@PSUHMED

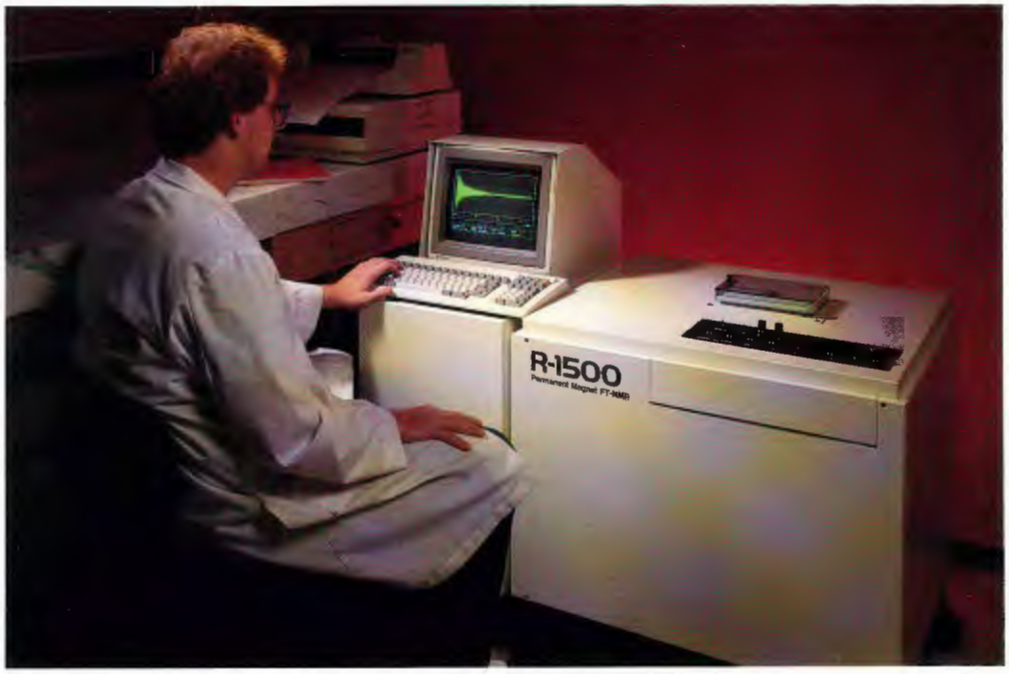
J. Mike Geckle
Bruker Instruments
Wilmington, DE

Michael B. Smith
Associate Professor
Chief, NMR Division

Postdoctoral Position at the Harvard Medical School Dept. of Biological Chemistry and Molecular Pharmacology

Applications are invited for a postdoctoral position devoted to the simulation of NMR data from models of molecular structure and dynamics. Applicants should have a sound knowledge of the physical principles on which NMR spectroscopy is based, and be experienced computer programmers. The successful applicant will be expected to apply these techniques to the interpretation of NMR data on biological macromolecules in solution, which is being collected on the Department's high-field NMR facilities. The Department is also in the process of acquiring extensive computational facilities to be used for this project, including graphics, vector and parallel supercomputers. Please send your resume, the names and addresses of two references, and copies of your two most relevant publications to: Dr. Timothy F. Havel, Dept. of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, 240 Longwood Ave., Boston, MA 02115.

Model R-1500
FT-NMR Spectrometer

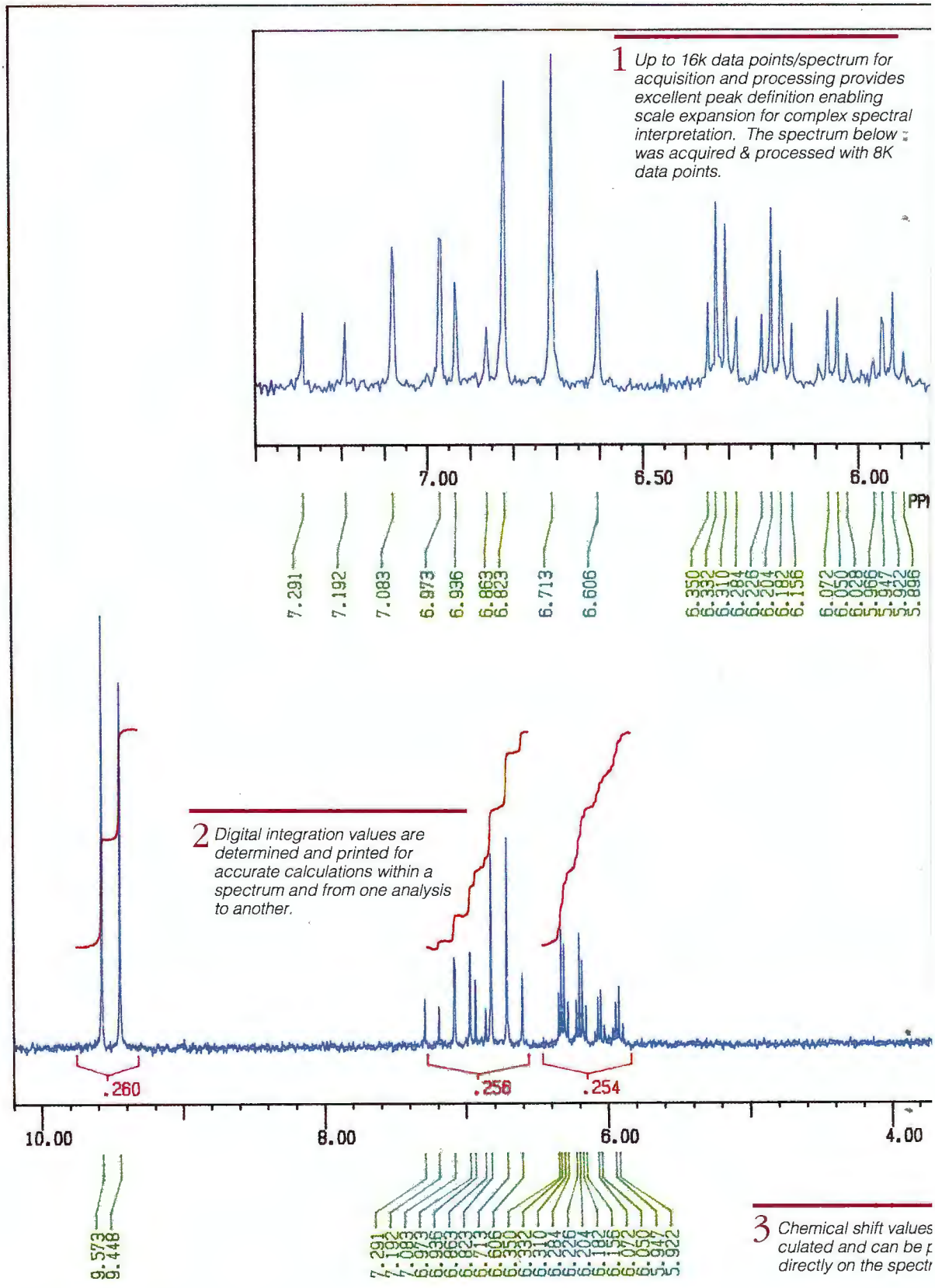


The Model R-1500 60 MHz Fourier Transform NMR Spectrometer. (Photo provided through the generous courtesy of the Department of Chemistry Teaching Laboratory, University of Massachusetts, Amherst, MA.)

- **FT system features high sensitivity, excellent resolution and accurate chemical shift measurements.** With field stability ensured by ^{2}D lock, the Model R-1500 delivers performance typically associated with higher field instruments.
- **As many as 16K data points per spectrum** can be utilized to provide optimum peak definition and accurate scale expansion for critical interpretations.
- **Homonuclear decoupling** simplifies spectral interpretation by removing splitting due to coupling of neighboring protons. **Gated decoupling** increases the dynamic range improving the interpretation of more dilute peaks.
- **Inversion recovery T_1 measurements** can be used to interpret complex spectra by removing overlapping chemical shifts.
- **WEFT measurement** capability expands the dynamic range by minimizing the large water peak and enables the interpretation of lower concentration components.
- **The multi-tasking data system** enables simultaneous acquisition and plotting or post run processing of spectral data to save time and increase productivity.
- **A complete data handling system** with 12-inch color CRT provides data archiving and post run processing. Data are conveniently stored on 5 1/4-inch floppy disks.
- **A menu system simplifies operation** by prompting the operator through standard acquisition parameters. As many as 32 methods can be stored to further simplify routine analyses.
- **Digital integration** combined with partial integration provides accurate calculations within a spectrum and from one analysis to another.
- **Chemical shifts, integration values, peak tables, and acquisition and processing parameters** are printed with the spectrum on the digital, 4-pen, 4-color printer/plotter in either A3 or A4 formats.
- **The R-1500 permanent magnet provides** minimal, low-cost maintenance.

HITACHI

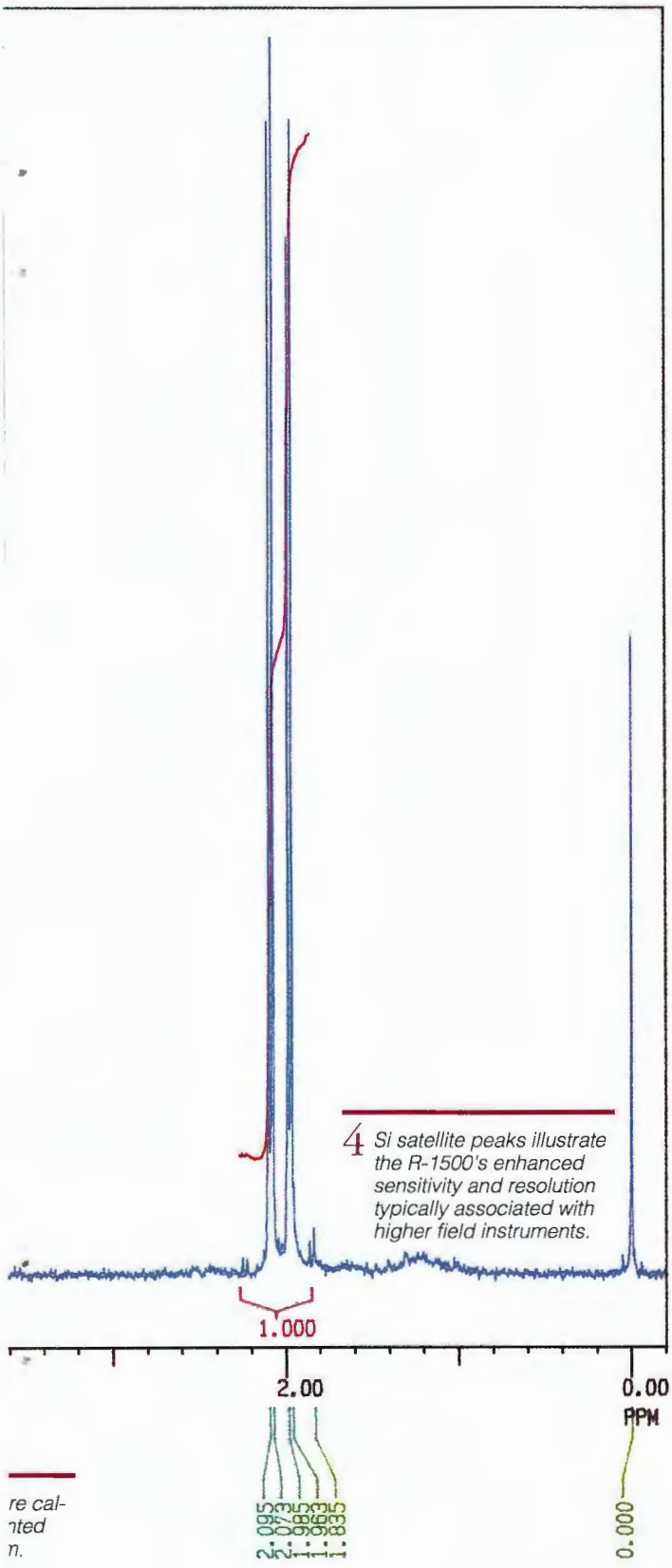
Hitachi Instruments, Inc.



1 *Up to 16k data points/spectrum for acquisition and processing provides excellent peak definition enabling scale expansion for complex spectral interpretation. The spectrum below was acquired & processed with 8K data points.*

2 *Digital integration values are determined and printed for accurate calculations within a spectrum and from one analysis to another.*

3 *Chemical shift values culated and can be p directly on the spectr*



4 *Si satellite peaks illustrate the R-1500's enhanced sensitivity and resolution typically associated with higher field instruments.*

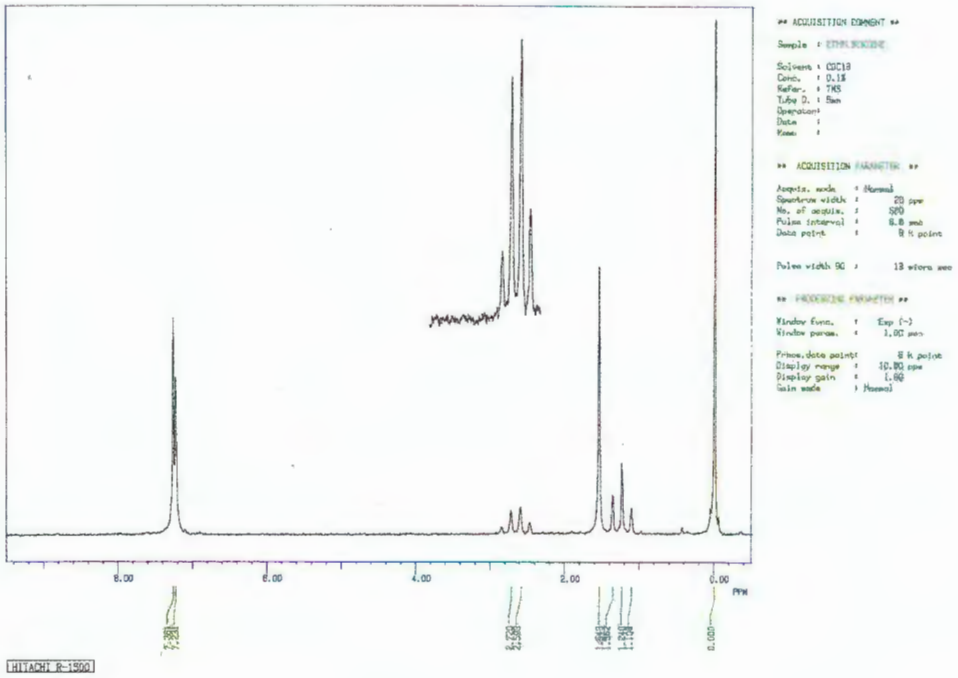
re cal-
nted
n.

```
** ACQUISITION COMMENT **

Sample  : Crotonaldehyde

Solvent : CDCL3
Conc.   : 4%

Tube D. : 5mm
Operator:
Date    : Feb 16 '88
Memo    :


**  ACQUISITION PARAMETER  **

Acquis. mode    : Normal
Spectrum width  :       15 ppm
No. of acquis.  :       16
Pulse interval  :      6.0 sec
Data point      :        8 k point


Pulse width 90  :       10 micro sec

**  PROCESSING PARAMETER **

Proce.data point:       8 k point
Display range   :    10.40 ppm
Display gain    :     1.00
Gain mode       : Normal
```

5 *Acquisition and processing parameters are stored and can be printed automatically so that all data and operating conditions are linked. Additionally, peak height tables including ppm to Hz conversion values can be printed.*

Technical Specifications

This spectrum of 0.1% ethyl benzene illustrates the excellent sensitivity and resolution obtained with the Model R-1500 FT-NMR. A S/N ratio of 77.5 was calculated for the quartet shown in the expanded portion of the spectrum. The silicon satellite peaks seen at the base of the TMS peak underscore the R-1500's outstanding resolution.



Nucleus	^1H
Resonance Frequency	60 MHz
Field Strength	1.41 Tesla; permanent magnet
Field System	Internal deuterium lock
Resolution	Better than 0.4 Hz
Sensitivity	Better than 20 (1% ethyl benzene, single pulse) Better than 120 (1% ethyl benzene, 150 pulses)
Pulse Sequence	90°, 180° -t-90° (T_1, WEFT)
T_1 Measurement	Inversion recovery method
No. Of Acquisition Points	30,000 or more (12 bit accuracy)
Data Density	1, 2, 4, 8, 16K points per scan
Decouple Modes	Homo decoupling; gated decoupling
Output	4-pen, multicolored printer/plotter for A3/A4
Double Resonance	Standard
Monitor	12 in., color CRT
Data Storage	5 1/4 in., floppy disk
Integration	Digital integration

Order Information

435-6671 R-1500 Permanent Magnet Fourier Transform NMR

AN0-0166 Sample tube 0.5 mm OD Pkg/100

AN0-0167 Sample tube caps-red Pkg/100

AN0-0168 Sample tube caps-white Pkg/100

671-7501 A4 100 sheets plotter paper.

671-7502 A3 100 sheets plotter paper.

642-7362 Ceramicron Pen (Red) 0.2 mm

642-7364 Ceramicron Pen (Black) 0.2 mm

642-7365 Ceramicron Pen (Green) 0.2 mm

642-7369 Ceramicron Pen (Blue) 0.2 mm

Installation Specifications

Room Temperature	16-30°C with <2° C/hr fluctuation, (10°C/24 hr)
Power Supply	115V ± 10%, 60 Hz, 4-5 Amp
Magnet Weight	250 kg (550lb)
Dimensions	1,630 mm (5'4") X 1,310 mm (4'3") X 800 mm (2'6") high

HITACHI

Hitachi Instruments, Inc.

For More Information Please Call or Write:
Hitachi Instruments, Inc.
44 Old Ridgebury Road
Danbury, CT 06810
(203)748-9001 - (800)548-9001

ETH Eidgenössische Technische Hochschule Zürich

Ecole polytechnique fédérale de Zurich
Politecnico federale di Zurigo
Swiss Federal Institute of Technology Zurich

Laboratorium für Physikalische Chemie
Prof. Dr. R.R. Ernst

0430

Universitätsstrasse 22
Durchwahl-Nr. 01/256 43 68
Telefonzentrale 01/256 22 11

Postadresse:
Laboratorium für Physikalische Chemie
ETH-Zentrum
8092 Zürich
Switzerland

Prof. B.L. Shapiro
966 Elsinore Court
P a l o A l t o, CA 94303
U.S.A.

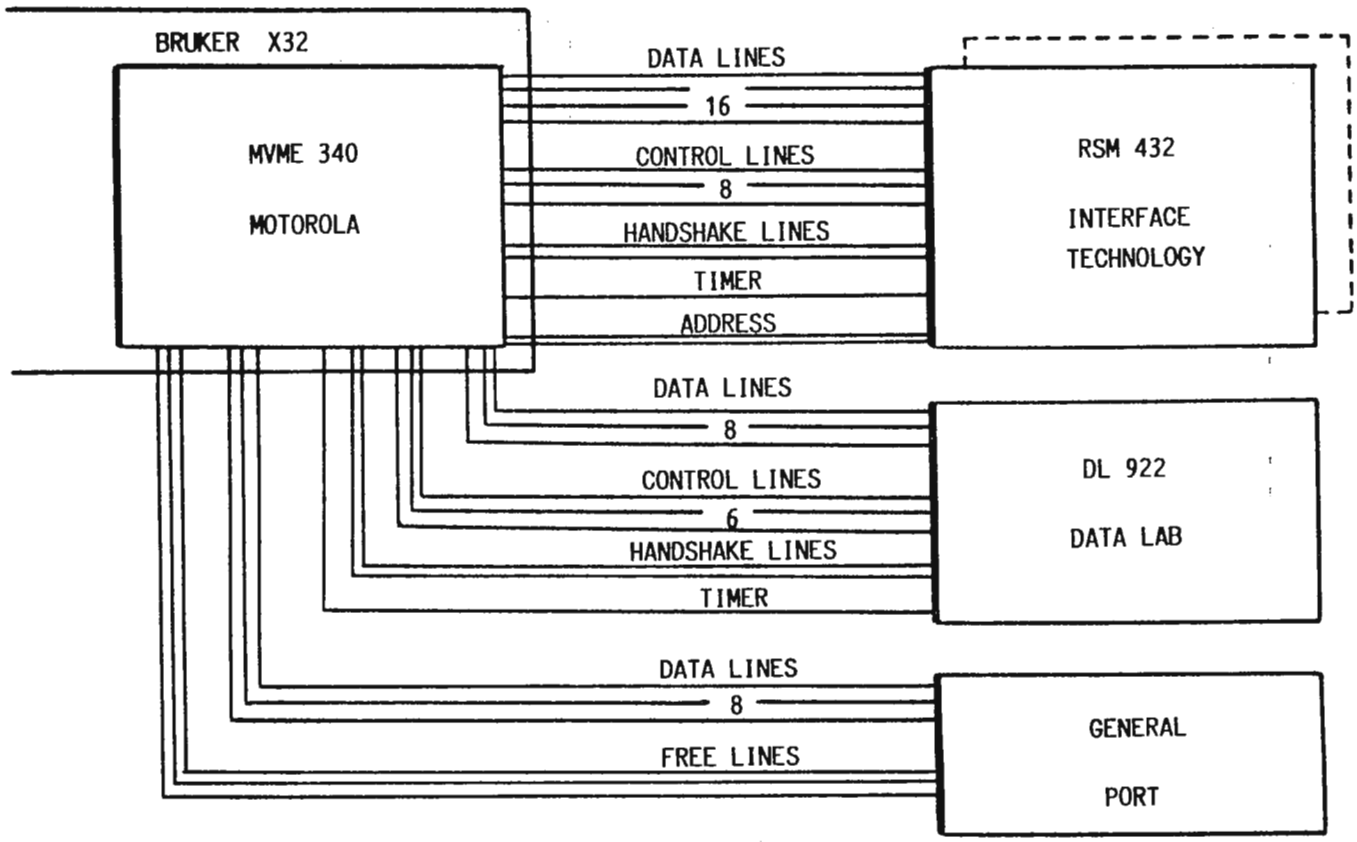
December 18, 1990
(received 12/29/90)

X-32 DRIVING A SOLID STATE NMR SPECTROMETER

Dear Barry,

Even at a time when excellent commercial solid state NMR spectrometers are available, it is frequently desirable to design one's own instrument. Reasons may be special requirements, hardware flexibility, or, as in our case, that an existing spectrometer should be upgraded. The availability of high-performance components makes the task quite manageable. A major aspect is the use of the proper computer system. Because no general software packages supporting both acquisition and data processing are available for open computer systems, we decided to base our development on the proprietary Bruker UXNMR software package for data processing and management of acquisition parameters which resides on top of the UNIX operating system. We developed our own pulse program interpreter (SINOMA, SIgnal and NOise MAschine, written by Dr. Roland Kreis, presently at Huntington Medical Research Institutes, Pasadena, California) which takes the acquisition parameters from UXNMR, assembles the code for an Interface Technology RSM 432 time sequence generator, loads and starts the pulse sequence, receives the FID data from the Data Lab 922 transient recorder, and transfers the data to the UXNMR program for processing and display. SINOMA loosely follows an earlier concept written by Dr. Malcom Levitt.

Hardwarewise, the interconnection between X-32 Computer, RSM 432 time sequence generator, and DL 922 transient recorder was realized by using a general purpose Motorola interface card MVME 340 which plugs directly into the VME bus of the computer. It was not too difficult to write a C code driver for the interface card and to incorporate it into the UNIX system. The interconnection diagram looks as follows:



The interface card has sufficient output lines to control at the same time a second RSM 432 time sequence generator. In addition, there are eight data lines that can be used for other purposes. Hardware and interface driver have been implemented by Gerhard Gucher (presently at Bruker Instruments, Billerica,Mass. USA).

The succession of experiments is timed by the interface card while the timing of the pulse sequence itself is performed by the time sequence generator. The pulse program interpreter supports a language which loosely follows the Bruker command language. It supports "C-like" looping possibilities and any type of arithmetic expressions for timing parameters as well as for phase values or loop variables. Although phase lists are supported, the mathematical power of the pulse interpreter virtually eliminates the need for them.

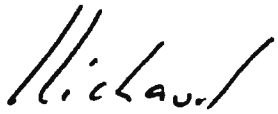
As an example, the pulse program for a solid state 2D spin diffusion experiment is listed below. The first five lines following "MAIN" contain some mathematical operations, the code for the pulse sequence follows. The first word of a line describes the pulse duration. Variables like "DØ" or "PW" are taken from the parameter list of UXNMR. The second word (following the backslash) specifies the pulses active during that period. Mnemonics like H(Φ) for proton pulse with phase Φ renders programming easier. On the other hand, it is possible to set all parameters, including the phase, by defining directly the 32 bit output pattern of the time sequence generator in binary, octal, or decimal notation. The integer variables Lx are also taken from UXNMR with the exception of LØ which contains the scan number and L1 which contains the number of the t_1-experiment presently in progress.

```
# Cross Polarization / 2D / Spin Diffusion along the z-axis
# 8 phase cycle + TPPI

MAIN

DR=.05;                                  # maximal duty ratio
MX=160*ms;                               # max. length of X-pulse
MH=160*ms;                               # max. length of H-pulse
D1=(L1-1)*IN0;                           # d1=d1+ino d1 : evol. time
L13=2*((L0-1)%2);
L14=(L0-1)/2+3;

D0      \IR;
PW      \H(L13)IR;                       # first pulse 90; phase +/-
P1      \H(1)X(L14)IYR;                  # CP time
D1      \H(1)IR;                         # t1
PW      \H(L13+2)X(L14+2+L1)IYR;         # 90-pulse store mag. along z
D15     \R;                              # mixing
PW      \IRY;
PW      \H(L13)X(L14+L1) YIR;            # 90-pulse flip mag. in xy-plane
DE      \H(1)I;                          # dead time
1e-6    \T(L13+L14+L1-1)H(1)I;           # trc trigger
D2      \H(1)I;                          # t2 under cw decoupling
PW      \H(L13+2)I;                      # flipback of protonmag. along z
D3      \;

MEND
```

Our arrangement has the great advantage that the extensive NMR software of the X-32 computer is available for data processing of 1D and 2D solid state spectra. The computer-spectrometer system has proved to be quite versatile for a great variety of experiments. At present a second spectrometer is under construction with the same interface and computer system.

Best regards.

Sincerely yours,



Richard R. Ernst Beat H. Meier

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ARIZONA
TUCSON ARIZONA

College of Arts & Sciences
Faculty of Science
Department of Chemistry

Tucson, Arizona 85721
(602) 621-6354
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Terry Matsunaga
Michael Barfield
University of Arizona
Department of Chemistry
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Tucson, AZ., 85721

January 7, 1991
(received 1/10/91)

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

Bruknet to Felix Data Conversion with Parameter Handling

Dear Dr. Shapiro,

We have been using, as a beta-test site, the Bruker ethernet transfer software, Bruknet, on the Silicon Graphics Inc. (SGI) Personal Iris 4D20G between the Iris and a Bruker AM500. We have also obtained the "Felix" software from Hare Research Inc. for offline multi-dimensional NMR data analysis on the SGI Personal Iris.

The conversion software provided by Hare Research Inc. for converting the Bruknet files on the Iris for use in "Felix" did not work properly. We modified the Dennis Hare program, "BRKSUN" so that Bruker AM500 files sent to the Iris via Bruknet with parameter handling enabled are successfully converted to "Felix" format with size, sweep width and frequency (parameter) information kept for use in "Felix".

The changes to brksun.for, a Fortran program, necessitated by differences in the Fortran input/output handling between Sun computers and Iris computers in the IRIX 3.3 version of Fortran 77, were as follows:
1. The "open" statements in brksun were changed to have "recl=192" rather than "recl=768" so that record lengths are in four byte words rather than in bytes
2. The statement "read(11,rec=n,end=99)buffer" was replaced with -
read(11,rec=n,IOSTAT=ios,err=99)buffer
if(ios.lt.0) go to 99
so that end-of-files are properly sensed when accessing the AM500 files on the Iris.
3. A write statement to give size, sweep width and frequency output on the Iris console was also added.
All changes have been forwarded to Hare Research Inc.

We hope that this information will be helpful to the users of "Felix" and Bruknet on the SGI Personal Iris.

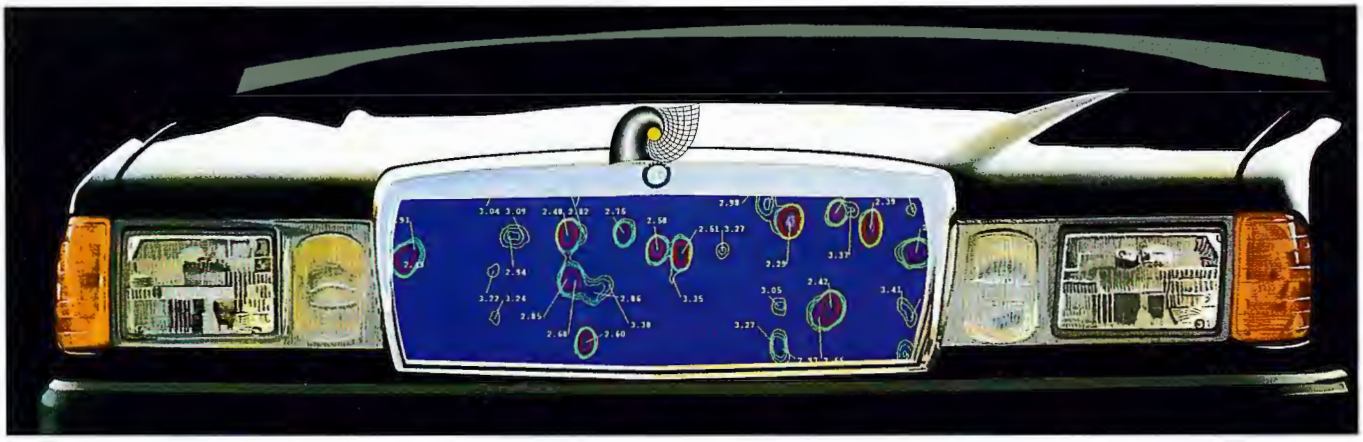
Sincerely,

Susan Yamamura Susan Yamamura

Terry Matsunaga Terry Matsunaga

Michael Barfield Michael Barfield

Experience the Science and Art of Our New Front End...



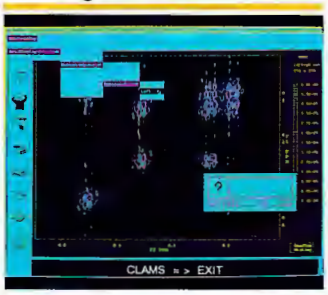
...Just Point and Click

Engineered Like No Other NMR Software in the World

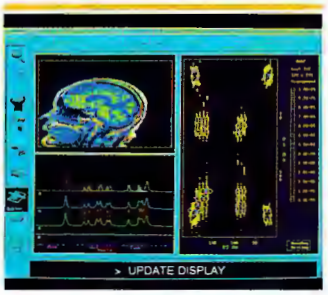
Customized Icons

Pop-up Menus

Dialog Boxes



Multi-Windows



The working environment of our software consists of a user-friendly Graphics User Interface (GUI), built on the X-window system. This working environment allows the user to execute commands without leaving the GUI, a feature which eliminates the need to shift between New Methods' software and the operating system. One can call a favorite editor, check mail, list directories, copy, move, rename files, and much more.

Interaction with the software is accomplished through icon symbols, pulldown or pop-up menus, and by "point-and-click." Keyboard-entered text and messages appear in dialog boxes. Any function can be executed from the keyboard as an alternative to the point-and-click.

New Methods' newly-created Graphics User Interface is easily customized. It has a built-in Geometry Manager which automatically adjusts the graphics when the windows are resized.

New Methods' new Front End: unprecedented speed and ease of use, backed by our dedication to excellence in customer support and quality assurance.

We invite your interest and inquiries.

The Science and Art of NMR Systems Integration

See us at the
Pittsburgh Conference
March 4-8, Chicago, IL
McCormick Place
Booth 3017

See us at the
32nd E.N.C.
April 7-11, St. Louis, MO
Adams Mark Hotel
Directors Row 29

NEW METHODS

IMAGINATION TRANSFORMING INFORMATION

NEW METHODS RESEARCH, INC. 6035 CORPORATE DRIVE, EAST SYRACUSE, NEW YORK USA 13057-1016
PHONE 800-333-NMRi (6674) • 315-437-7500 • FAX 315-437-1836

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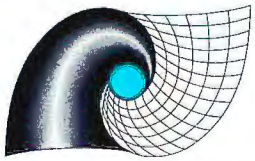

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Dr. Bernard L. Shapiro
TAMU NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

December 4, 1990
(received 12/12/90)

HIV-1 PEPTIDE INTERACTIONS WITH LIPID BILAYERS

Dear Barry:

I hope this contribution will be sufficient to restore our names to the TAMU NMR Newsletter mailing list. We have recently been using solid state NMR techniques to study the interaction of peptides with microsomal membranes. The peptide fragment 828 - 848 of the terminal fragment of the gp160 envelope glycoprotein associated with type I human immunodeficiency virus (HIV-1) has been synthesized and purified. This peptide fragment represents the region of gp41 with the highest hydrophobic moment assuming an α-helix. Such amphiphilic peptides could strongly interact with the hydrophobic/hydrophylic interface of cell membranes with their hydrophobic faces inserted into the hydrophobic lipid core region and the hydrophilic faces directed towards the membrane surface.

The synthesized peptide is highly soluble in water and contains an excess of six positive charges. It interacts strongly with negatively charged lipid membranes as demonstrated by electrophoretic mobility measurements. The energy of association of the peptide to a negatively charged phosphatidylglycerol membrane in an 0.1M NaCl solution is about 6 kcal/mole. Both ^{31}P - and ^{2}H NMR studies on deuterated and nondeuterated lipids were performed to investigate the impact of peptide binding on the lipid structure and mobility. Preliminary results indicate that only the lipid headgroup region is involved in that interaction. Also, NMR and circular dichroism experiments were carried out to study the impact of binding on the peptide structure. In water solutions the peptide exists as an extended chain or a random coil. Our CD spectra on the peptide in the membrane bound state differ very slightly from the solution results, but clearly show that the peptide does not form an α-helix. The experimental results favor a model where the peptide slides over the lipid surface with the positive peptide charges directed towards the lipid surface. This result is in disagreement with the prediction of the formation of an α-helix partly imbeded in the lipid bilayer. The theoretically predicted high amphiphilicity of an amino acid sequence is not sufficient for α-helix formation. Although care should be exercised when extending the results obtained on synthetic peptide fragments of proteins, these results suggest that the 828-848

region of gp41 could serve to teather the protein to the intracellular face of the viral membrane. The synthesis of other fragments of gp41 with different degrees of hydrophilicity and different amounts of charges is planned. In addition to the investigation of fundamental questions of peptide-membrane interactions, these studies could help to improve our understanding of the functional role of different fragments of the HIV viral envelope glycoprotein. Please credit contribution to Bob Highet's subscription renewal.

Sincerely yours,

Jim

James A. Ferretti

Klaus Gawrisch

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NMR Research and Development
December 3, 1990
(received 12/11/90)

Dr. Barry Shapiro
966 Elsinore Court
Palo Alto, CA 94303

PseUdo Triple Resonance via Indirect Detection

Dear Barry,

As you and most of the other practitioners of NMR know by now, triple resonance spectroscopy, with its myriad of supporting hardware and software components, is being touted as a definite means to addressing even larger biological macromolecules by NMR. Experiments in the research groups of Markeley, Bax, and Wagner clearly indicate the general power and importance of triple resonance spectroscopy (*1-3*). But what of those scientists not faced with such debilitating problems as assigning the NMR spectrum of a 250 GD protein: might they *too* be able to avail themselves of this technique (or at least hardware!) to some advantage? The answer to this question lies just below.

Pseudo triple resonance spectrosopy may be considered a variant of triple resonance spectroscopy in which, for example, only ^{1}H <--> ^{13}C and ^{1}H <--> ^{15}N correlations would be established, i.e., the ^{13}C <--> ^{15}N connectivity would be ignored. The absence of this latter connectivity allows the technique to be used to acquire a simultaneous [^{13}C, ^{15}N]-HMQC experiment using only natural abundance levels of ^{13}C and ^{15}N. In many cases, such a simultaneous experiment can reduce the acquisition time *by half* compared to acquiring ^{13}C-HMQC and ^{15}N-HMQC experiments sequentially. The spectrum in Fig. 1A is from such an experiment performed on a cyclic undecapeptide (30 mM in d_6-dmso) on a VXR500. The open circles represent the ^{1}H-^{13}C correlations; the closed circles, the ^{1}H-^{15}N correlations. In this particular experiment, the ^{1}H-$^{13}C_{\alpha}$ peaks were folded once in F_1; and the ^{1}H-$^{13}C_{arom}$ peaks, twice in F_1. The ^{1}H-^{15}N peaks were not folded at all. The F_1 axis is labeled with respect to the ^{15}N chemical shift. Figure 2A is an expansion of the boxed region in Fig. 1A.

In the case of Figs. 1A and 1B, both the ^{1}H-^{13}C and ^{1}H-^{15}N correlations *must* be present at the same time in the display. Figures 1C and 1D result from a modified experiment in which the two sets of correlations can be displayed either separately *or* together. The advantage to this is two-fold. First, there is absolute impunity in folding signals in F_1 in terms of accidental overlap and concomitant peak cancellation. Second, the effect of any dynamic range difference between the two sets of correlations is minimized in terms of display artifacts.A complete description of this experiment has been submitted for publication, including a pulse sequence. Finally, this technique can be generalized to more than two heteronuclei provided that certain connectivity conditions are met. As with all "good little" NMR experiments, it must be afflicted with a hopefully disgusting acronym. In this regard, I have done my best (or worst?).

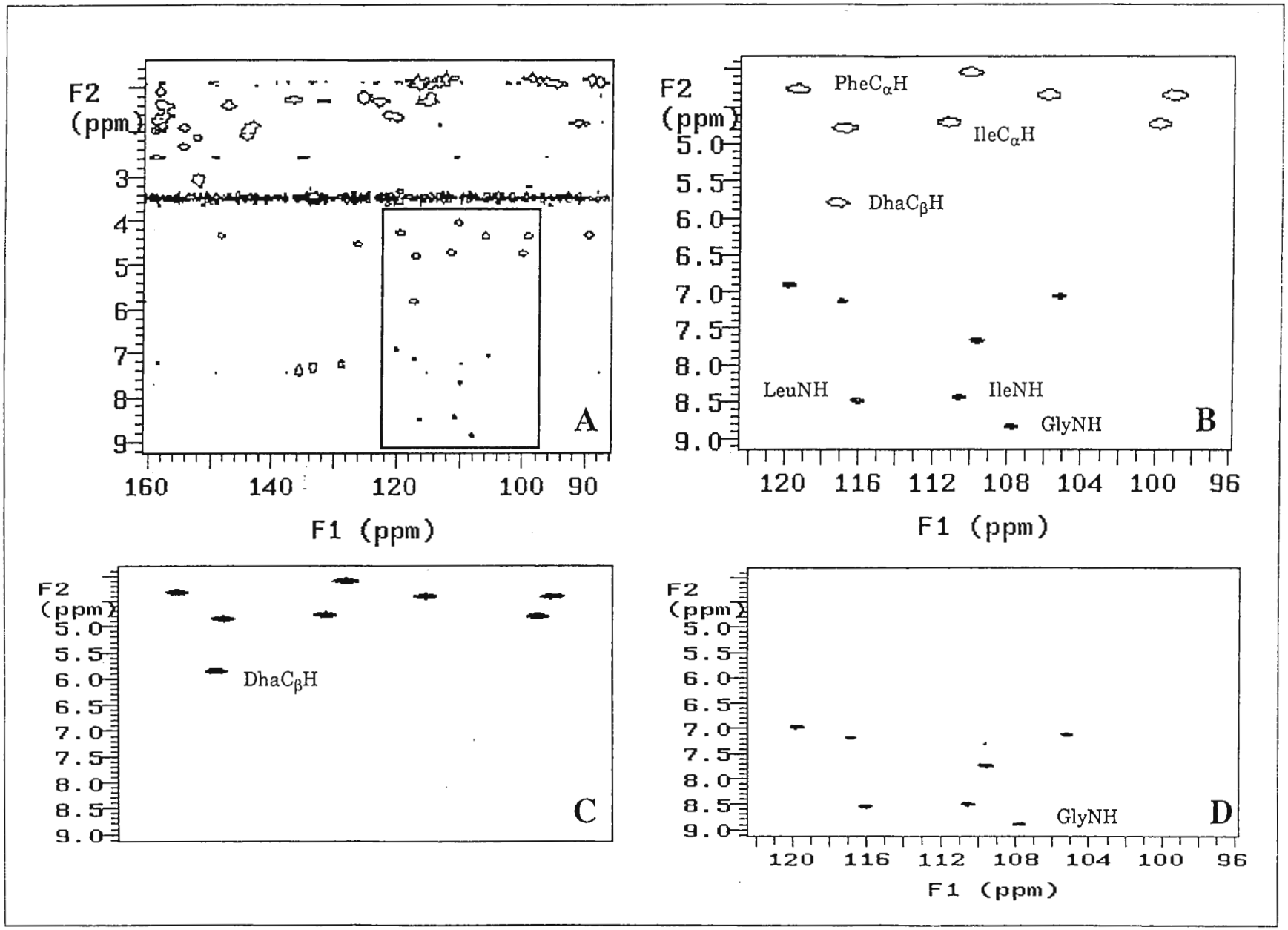
Sincerely yours,

Sandy Farmer

1. W. M. Westler, B.J. Stockman, J.L. Markeley, Y. Hosoya, Y. Miyake, and M. Kainosho, *J. Am. Chem. Soc.* **110**, 6256 (1988).

2. G.T. Montelione and G. Wagner, *J. Magn. Reson.* **87**, 183 (1990).

3. M. Ikura, L.E. Kay, and A. Bax, *Biochemistry* **29**, 4659 (1990).


F2 (ppm)
F1 (ppm)
A
PheCαH
IleCαH
DhaCβH
LeuNH
IleNH
GlyNH
B
C
D

2D NOESY SIMULATIONS OF EXCHANGEABLE PROTONS IN ACETAMIDO SUGARS

Perseveranda Cagas and C. Allen Bush

(received 1/10/91)

Department of Chemistry and Biochemistry
University of Maryland Baltimore County
Baltimore, Maryland 21228

Because of the flexibility of most small peptides, quantitative simulation of proton nuclear Overhauser effects (NOE) by relaxation matrix methods which ignore internal motion are not thought to be generally useful. But NOE simulations for the carbon-bound protons of certain complex oligosaccharides carried out as a function of geometry have produced an excellent fit to experimental data suggesting that these carbohydrates adopt relatively rigid conformations. Amide protons, the interpretation of whose NOE is crucial in determining the secondary structure of peptides, also occur in N-acetyl amino sugars which are prominent components of complex carbohydrates. While amides in sugars are not so strategically located as are those in peptides, quantitative interpretation of their NOE could yield useful information on oligosaccharide conformation. Therefore we have devised a method for simulation of amide proton NOE and applied it to the amide protons of GlcNAc in a milk oligosaccharide Lacto-N-fucopentaose-1 (LNF-1)† which has been proposed to adopt a rigid conformation (Rao et al., 1985)

Several salient features of amide protons complicate the measurement and interpretation of NOE. First, chemical exchange with solvent requires ^1H NMR measurements in H_2O, a technical problem which has been successfully addressed by solvent suppression pulse sequences commonly used in peptide and protein chemistry. Problems of non-uniform exitation in ω_2, which are characteristic of selective 1-1 pulses, can be avoided by choosing peaks on a single column for quantitation and normalization of NOESY intensities. Also one must consider the influence of chemical exchange of NH protons with solvent to the NOESY crosspeak volumes. Saturation transfer experiments show that the rate of chemical exchange of the amide proton with solvent (H_2O) is sufficiently slow under acidic conditions (pH $\approx$ 2.3) that the amide NOE intensities are essentially unaffected by chemical exchange.

The NOE of amide protons also differs from that of ^{12}C -bound protons as a result of the contribution of the ^{14}N dipole and quadrupole to ^1H relaxation. Scalar relaxation modulated by chemical exchange, which arises when one proton of a coupled pair is exchanging, is insignificant under our conditions of small coupling constants ($^3J_{NH\cdot H2} \approx 10Hz$) and the relatively long exchange lifetimes (seconds) for the amide proton. Rapid quadrupolar relaxation of the ^{14}N nucleus results in modulation of the ^{14}N-H spin-spin coupling which provides a scalar mechanism of the second kind for the proton attached to it. It may be shown, using reasonable values for the coupling constant J_{14N-H}, the assymetry parameter (η) and $\frac{e^2qQ}{\hbar}$ from formamide, that this contribution to the amide proton spin-lattice relaxation rate is negligible for a rotational correlation time (τ_c) of 1 ns, a value deduced for this small oligosaccharide from T_1 data. It is to be noted

† Fuc α-(1$\rightarrow$2)$-$Gal β-(1$\rightarrow$3)$-$GlcNAc β-(1$\rightarrow$3)$-$Gal β-(1$\rightarrow$4)$-$Glc

that although the scalar contribution to T_1 relaxation of the amide proton is small, the effect on T_2 relaxation can be significant.

Dipolar relaxation of the amide proton originates not only from other protons in the molecule, which provides information on geometry, but also from dipolar interaction with the directly bonded ^{14}N nucleus, which depends mainly on the distance r_{N-H} and correlation time τ_c. Assuming an isotropic model, the dipolar relaxation rate R_1 of an amide proton interacting with the ^{14}N to which it is bonded was estimated to be 0.67 s^{-1} at 500 MHz (^1H), assuming an N-H distance of 1.0 angstrom and τ_c of 1 ns. For the amide NOEs simulated for LNF-1 using the matrix method of Cagas and Bush (1991) which are $\approx$ 1 - 5 %, incorporation of this contribution reduced the values calculated from $^1H - ^1H$ interactions by $\approx$ 0.6 % from those calculated without the ^{14}N - H contribution.

The above considerations provided for incorporation of NH NOESY crosspeaks into our recently published simulation method, (Cagas and Bush, 1991). This modification yields significant new information on the glycosidic dihedral angles as well as information regarding the relative orientation of the amide sidechain in GlcNAc which is deduced to be in a *trans* arrangement based on the N-H to H2 coupling constant of 10.1 Hz. A contour plot and cross section through the amide resonance of the NOESY spectrum in water of LNF-1 at a mixing time of 250 ms and at 5 °C (Figure 1) show crosspeaks from the amide proton of GlcNAc to H1 of Gal[3], and to protons within the GlcNAc unit, H2, H3 and to the methyl group of the acetamido sidechain. Quantitative interpretation of the crosspeak involving the methyl group was not included in our simulation procedure because of complications introduced by internal rotation. Simulation of NOEs from exchangeable protons were consistent with the glycosidic Ψ and Φ angles derived by simulation of non-exchangeable proton NOEs providing additional support for our proposal of a single rigid conformation for LNF-1 reported previously, (Rao et al., 1985). The simulation was consistent with a nearly *trans* conformation of the NH proton relative to GlcNAc H2, with the value τ, defined by the atoms C_1-C_2-N-C, = 60°$\pm$30°for the amide dihedral angle. In this conformation the amide proton is closer to H3 than to H1 of the GlcNAc residue, and the calculated NOE to H1 (GlcNAc) was $<$ 1%.

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- Rao, B.N.N., Dua, V.K. & Bush, C.A. (1985) *Biopolymers* **24**, 2207- 2229.

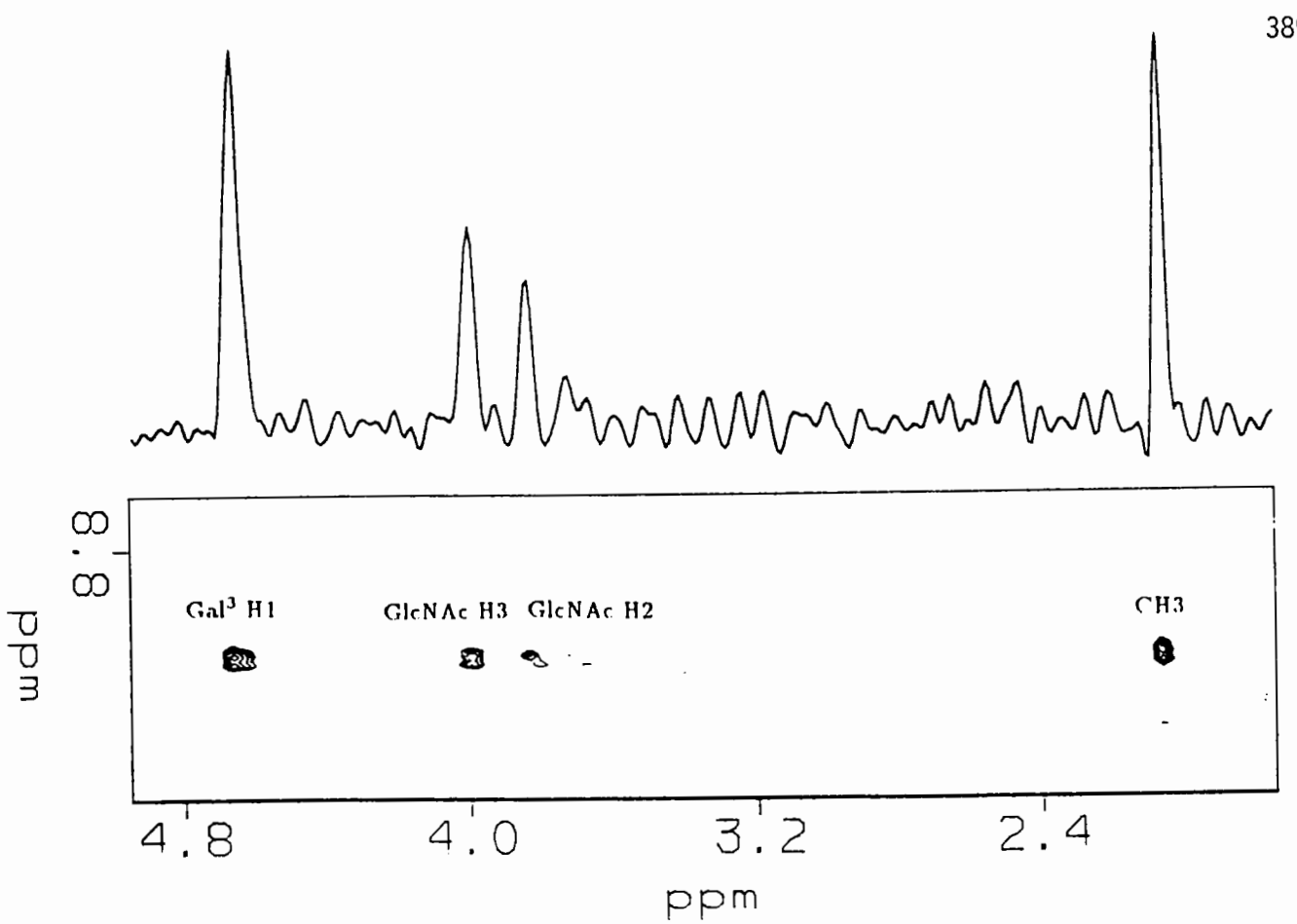

Figure 1. Contour plot and cross section through the amide region of the 500 MHz NOESY spectrum of LNF-I in 90% H_2O:10% D_2O with 0.01M trifluroacetic acid. Temperature was 5° C and a mixing time of 250 ms was used. Spectral width was ± 2304 Hz, and τ_1 and τ_2 delays of 139 and 278 μ s, respectively, were used in the water suppression scheme. Raw data size was 2 x 256 x 2048 complex points, with 64 transients per t_1 value.

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DEADLINE DATES

No. 391 (April) ---------- 15 March 1991
No. 392 (May) ---------- 19 April 1991
No. 393 (June) ---------- 17 May 1991
No. 394 (July) ---------- 21 June 1991

Texas A&M University NMR Newsletter - Book Reviews

Book Review Editor:
William B. Smith, Texas Christian University, Fort Worth, Texas

"The Nuclear Overhauser Effect in Stereochemical and Conformational Analysis"

by

David Neuhaus and **Michael Williamson**

VCH Publishers, New York
514+ pages: 1989 $95.00. ISBN 0-89573-343-9

This excellent book is organized in three parts and two appendices. The first part, Theory, has six chapters covering 208 pages. The second part, Experimental, has three chapters covering 142 pages and the third part, Applications, has three chapters covering 152 pages. The appendices, "Equations for Enhancements Involving Groups of Equivalent Spins" and "Quantum Mechanics and Transition Probabilities" fill 12 pages. There is a seven page subject index.

The authors have successfully produced a volume that covers stereochemical studies and conformational analysis using NOE. The section on theory has, by necessity, a large number of mathematical equations but the authors have kept this within the bounds of reason and anyone who has completed the first two years of a chemistry degree should have no difficulty understanding the equations used in these chapters. The authors have included a large number of well made figures illustrating critical points.

The three chapters on experimental techniques are especially valuable to people using NOE experiments on an infrequent basis and to those learning these techniques. The authors discuss sample preparation, solvent choices, solute concentration, sample purity and degassing requirements. The reader is given information on subtraction artifacts, phase instability, automated routines, irradiation power and selectivity, and pulse and delay timing, all essential points for the practicing spectroscopist. The authors then discuss two dimensional methods with a thorough discussion of the practical points of these methods and using examples from the real world. The third chapter in this section discusses heteronuclear experiments, rotating frame experiments, editing and spectral simplification, and solvent suppression.

The third section has a large number of applications of NOE experiments for the determination of structure and conformation taken from the recent literature and covering examples from aromatic substitution to biopolymers.

The references are listed at the end of each chapter instead of being contained in a reference list and the book lacks an author index but every laboratory using or contemplating using NOE techniques for the study of stereochemistry or conformations should have a copy of this book.

Michael L. Maddox
Analytical & Environmental Research
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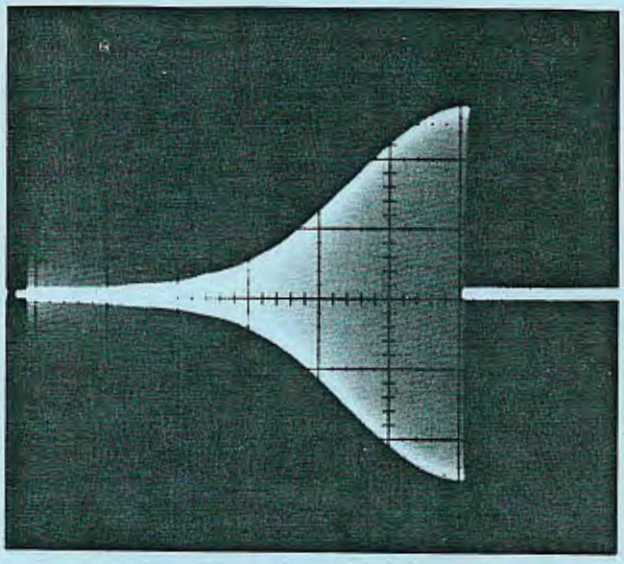
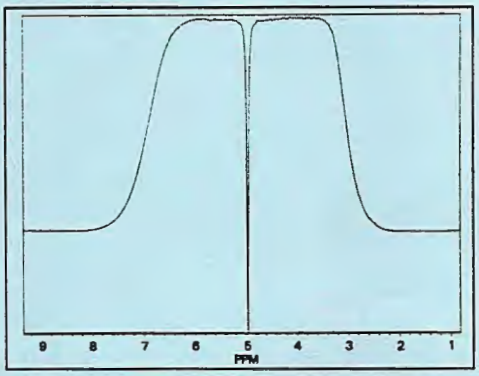
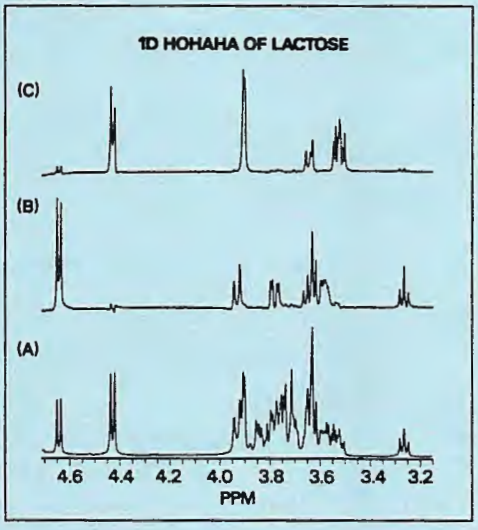


An oscilloscope trace of a half-Gaussian pulse. The pulse is defined by 250 points and the duration is 10 ms.



The result of applying a 180° half-Gaussian pulse to a sample of doped water. The water resonance has been broadened by introducing a large Z1 current in the room temperature shims. The half-Gaussian pulse width is 200 ms and the width of the "burned hole" is 12 Hz.



TOCSY of Lactose (10mM in D_2O).
Bottom spectrum (A) is a simple one pulse spectrum. Middle spectrum (B) is a 1D-TOCSY spectrum, where anomeric proton at 4.43 ppm has been selectively irradiated with a half-Gaussian pulse. Top spectrum (C) is a 1D-TOCSY spectrum when the anomeric proton at 4.65 ppm has been selectively irradiated with a half-Gaussian pulse.

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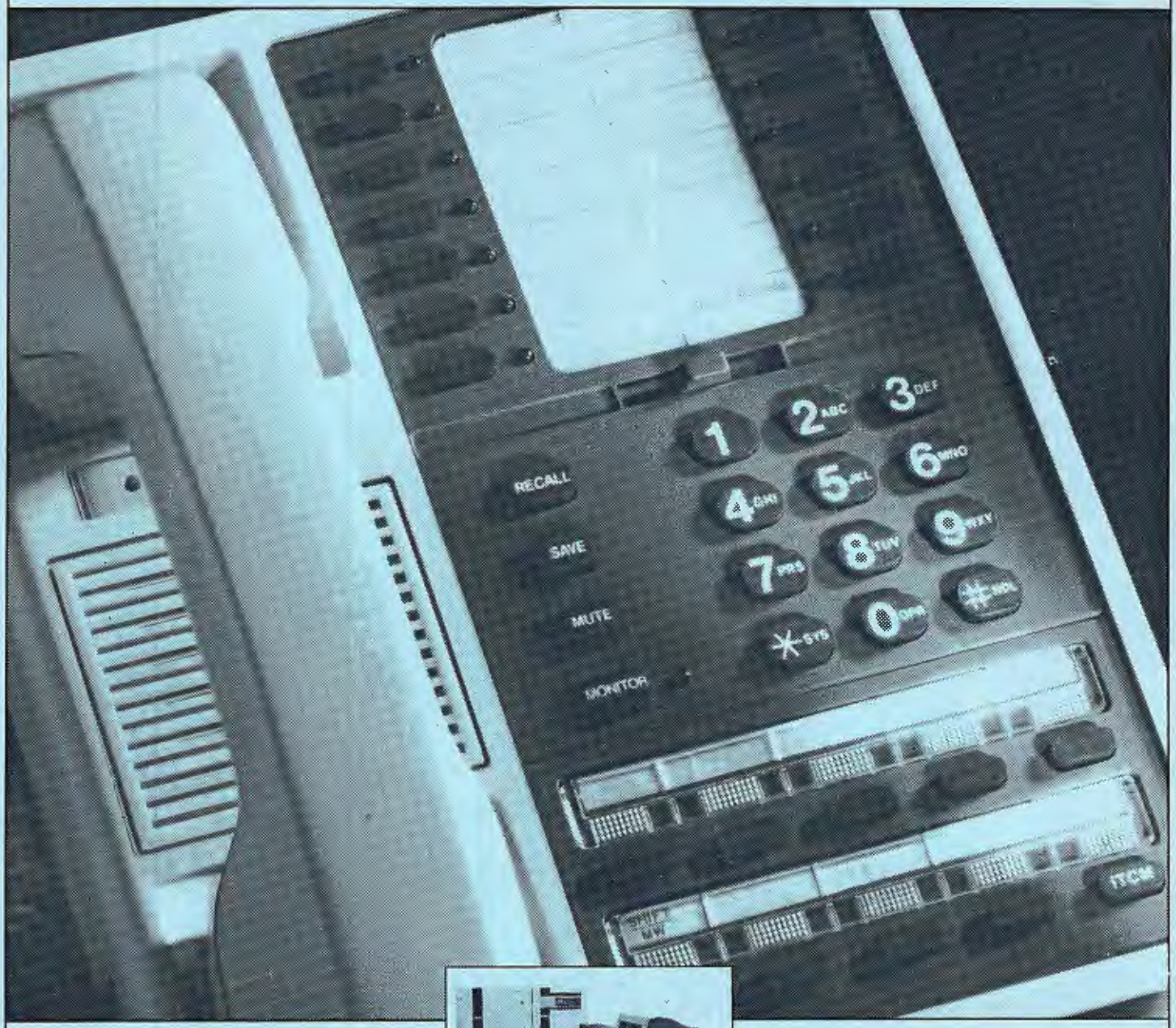

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