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NMR NEWSLETTER

NO. 313

OCTOBER 1984

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Should be Addressed to:

Professor Bernard L. Shapiro
Department of Chemistry
Texas A&M University
College Station, Texas 77843 U.S.A.

TEXAS A&M UNIVERSITY
NMR
NEWSLETTER

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AUTHOR INDEX ------ TAMU NMR NEWSLETTER NO. 313, OCTOBER 1984

The **Seventh International Meeting on NMR Spectroscopy,** sponsored by the Royal Society of Chemistry and the NMR Discussion Group of the U.K., will be held at the University of Cambridge, U.K., 8-12 July 1985. There will be Poster Sessions and a limited number of short Contributed Papers, in addition to the Invited Lectures.

Details will appear in a future issue of the TAMU NMR Newsletter.

For application forms, etc., please write to:

Dr. John F. Gibson
Secretary (Scientific)
The Royal Society of Chemistry
Burlington House
London W1V OBN, England

The Rockefeller University

1230 York Avenue,
New York, New York, 10021-6399

Bernard L. Shapiro,
Texas A & M University,
Department of Chemistry
College Station, Texas 77843-3255

22 Aug 1984

Dear Dr. Shapiro:

Thousand fold enhancement of ^{15}N NMR via Proton Detected Multiquantum Coherences.[1]

The severe sensitivity limitations associated with the observation of ^{15}N NMR signals, especially at natural abundance, make any improvement in sensitivity of considerable importance.[2,3] The potential advantages of using indirect detection via protons for nuclei like ^{15}N and ^{13}C over conventional direct detection methods have been recognized,[4-8] but the enhancement has not been explicitly measured.[8] It is important to know if the theoretical enhancement over simple direct detection $(\gamma_{^1H}/\gamma_{^{15}N})^3$, about 1000 fold, can be achieved, and, if so, whether this can be done routinely on samples of interest at natural abundance.

We wish to report here the quantitative determination of the enhancement under typical conditions for biological macromolecules using a 50 mM solution of 2-pyrrolidinone, (I), in water.[9] The spectrum of (I) with ^{15}N detection using INEPT[2] and with indirect ^1H detection of ^{15}N satelites using multiquantum coherence transfer[5,8] are shown in Fig 1. The signal to noise ratios (S/N) of the two spectra are comparable, but the directly-detected ^{15}N spectrum was obtained with 10-fold greater volume of sample, and 35-fold longer time. After correction for (a) different acquisition times, (b) relative sample volumes, (c) the INEPT enhancement factor[10], and (d) the total intensity of the doublets in Fig 1B, the enhancement between the direct and indirect detection is found to be about 1,230, compared to the theoretical 961.[11] The S/N of the ^{15}N projection of a two-dimensional data set gives a similar value for the sensitivity gain. The line width of the conventional amide proton spectrum of (I) is very broad (fig 1D), because of ^{14}N quadrupolar relaxation. The sharpness of the ^{15}N satellites suggests additionally that much more precise NMR measurments of the proton spectra of amides are possible by this method.

The demonstration of a thousand-fold sensitivity increase via heteronuclear multiquantum coherence transfer substantially reduces the restrictions on ^{15}N NMR arising from low sensitivity for compounds in which such coherence transfer can be obtained. It may be expected that important enhancements, though less dramatic, can be observed for other nuclei (e.g. ^{13}C, ^{29}Si, and ^{113}Cd). Preliminary results for ^{13}C support this expectation.

Sincerely,

David Cowburn David H. Live Donald G. Davis

(1) A longer report of this work will appear in *J. Am. Chem. Soc.*
(2) Morris , G.A.; Freeman, R. J. Am. Chem. Soc. 1979, 101, 760-762.
(3) Morris, G.A. J. Am. Chem. Soc. 1980. 102, 428-429.
(4) Aue, P.W.; Bartholdi, W.; Ernst, R.R. J. Chem. Phys. 1976, 64, 2229-2246.
(5) Müller, L. J. Am. Chem. Soc. 1979, 101, 4481-4484.
(6) Bodenhausen, G.; Ruben, D.J. Chem. Phys. Lett. 1980, 69,185-190; Freeman, R.; Marecl, T.H.; Morris, G.A.; J. Magn. Res. 1981, 42, 343-351.
(7) Redfield, A.G. Chem. Phys. Lett. 1983, 96, 539-543; Roy,S.; Apapstavros,M.Z.; Sanchez,V.; Redfield, A. G. Biochemistry,1984, in press.
(8) Bax, A.; Griffey, R.H.; Hawkins, B.L. J. Magn. Res. 1983, 55, 301-312; J. Am. Chem. Soc. 1984, 105, 7188-7190; Griffey, R.H.; Poulter C.D.; Bax, A. ; Hawkins, B.L.; Yamalzumi, Z.; Nishimura, S. Proc. Nat. Acad. Sci. 1983, 80, 5895-5897.
(9) The spectra were obtained on an NT-300Wspectrometer, with a top entry probe stack system. For indirect detection experiments, an additional synthesizer based radiofrequency generator was used. A ^{1}H 12 mm probe was modified by inclusion of a second coil matched for ^{15}N. The separate coil elimlnates lock interference previously observed by others in single coil designs, ref. 8 (Live, D.H.; Cowburn. D. , unpublished results). Sequences used were generally those described previously (ref. 8., Minoretti A.; Aue, W.P.; Reinhold, M.; Ernst, R.R. J. Mag. Res. 1979, 40, 175-186) , with proton excitation generated by a selective pulse (Redfield, A.; Kunz, J.; Ralph, E.K. J. Magn. Res. 1975, 19,114-119)
(10) In theory, the advantage of INEPT should be 10 fold,ref 2. We achieve experimentally a factor of 8.5.
(11) The third power dependence on (γ_H/γ_N) arises from the difference in spin polarization, magnetic moment, and detection frequency of the nuclei. We have neglected adjustments for instrumental effects such as differences in the Q factors of probes used, see Abragam, A. " The Principles of Nuclear Magnetism", Oxford U.P., (1961), p 83, or for integrated intensities.

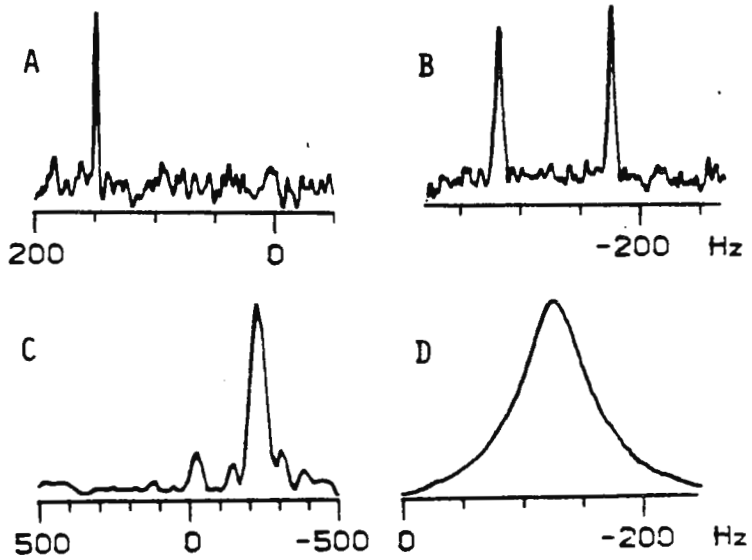
Figure. Comparison[9] of direct ^{15}N and indirect proton detected spectra of pyrrolidinone (I) (50 mM, 95%H_2O/ 5%D_2O).

(A) Directly detected INEPT [2,3] spectrum of 20mm o.d. sample, active volume 10 ml, 2180 scans in 28 min, S/N =9.

(B) ^{1}H detected ^{15}N spectrum of (I) taken in a 12mm tube in a modified 12mm ^{1}H probe, active volume 1 ml, 128 scans in 0.8 min, S/N =11. The signals are at the position of the ^{15}N satellites.

(C) ^{15}N projection of a complete two-dimensional data set for (I), as in (b). Total accumulation time 13 min(16 blocks), S/N =70.

(D) ^{1}H spectrum of (I) using Redfield pulse acquisition.



UNIVERSITY OF NEW HAMPSHIRE

Department of Chemistry
College of Engineering and Physical Sciences
Parsons Hall
Durham, New Hampshire 03824-3598
(603) 862-1550

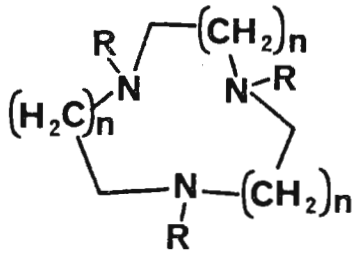
August 28, 1984

Professor Bernard L. Shapiro
Department of Chemistry
Texas A. & M. University
College Station, Texas 77843

Dear Professor Shapiro:

NMR Studies of Tripodand-Alkali Ion Complexation
and
A Two-Site DNMR Program in C

As part of our ongoing conformational studies of oligopodand-alkali metal ion complexation, we have examined Na^+ complexation by cyclic triamine based tripodands 1 and 2.



R = $CH_2CH_2OCH_3$
1: n = 1
2: n = 2

R = $CD_2CH_2OCH_3$
3: n = 1
4: n = 2

Each of the compounds solubilizes one equivalent of $NaBPh_4$ in $CDCl_3$ within experimental error. AA measurements have shown the solubilty of $NaBPh_4$ in $CHCl_3$ to be 2×10^{-6} M. After the method of Reinhoudt *et al.*[1,4], simple equilibrium considerations and ^1H NMR integrations allow us to place a lower limit of 10^7 on the association constants. Competition experiments are planned.

^{13}C chemical shifts (FX-90Q) of the tripodands and the corresponding complexes are given in the Table. Despite the simplicity of the ^1H spectra, selective ^1H decoupling did not allow unambiguous assignment of the ^{13}C resonances (N-$\underline{C}H_2$, ring *vs* sidearm). The assignments were easily made, however, on the basis of the carbon spectra of deuterated analogs 3 and 4, which were prepared by $LiAlD_4$ reduction of the corresponding amides. It is probably worthwhile for NMR spectroscopists to remember that chemistry can still be useful! 1:1 mixtures of free host and $NaBPh_4$-complexed tripodand exhibited slow exchange ^{13}C spectra at ambient probe temperature. All of the resonances of 1 were in the slow exchange limit; a lower limit of $\Delta G^{\ddagger}$= 17 kcal/mole (323°K.) may be placed on the Na^+ exchange barrier. The ^{13}C lines of 2 and its complex are slightly exchange broadened at ambient temperature. At the coalescence temperature of the -$\underline{C}H_2$-O- resonances (326° K.), $\Delta G^{\ddagger}$ = 16.0 kcal/mole. Thus, with the reasonable assumption that decomplexation is rate determining (which we have established in other similar cases), the difference between the free energies of association of 1 and 2

with $NaBPh_4$ may be estimated as >1 kcal/mole at room temperature,[1] 1 being the better host. The relatively large complexation induced shifts suggest substantial conformational changes upon complexation. The details of our interpretations of the spectra and MM2 molecular mechanics calculations will be reported in a future publication.

TABLE: ^{13}C Shifts of 1, 2, and $NaBPh_4$ Complexes in $CDCl_3$.

Compound	Free Host	Complex	$\Delta\delta$	Assignment
1	56.29	51.95	-4.34	NCH_2(ring)
	57.70	58.03	0.33	NCH_2(sidearm)
	58.73	59.16	0.43	OCH_3
	71.51	69.72	-1.79	OCH_2
2	21.67	25.90	4.34	$CH_2CH_2CH_2$
	50.00	59.48	9.48	NCH_2(ring)
	53.42	57.48	4.06	NCH_2(sidearm)
	58.67	58.73	0.55	OCH_3
	71.46	68.75	-2.71	OCH_2

During the course of these studies, one of us (PAP) has written a two site simulation program (DNMR.c) which handles both uncoupled and coupled systems using the Gutowsky-Holm equations and modifications[2]. There are lots of these programs around but this one is unique because of its portability. Written in C under Berkeley UNIX, DNMR.c can easily be moved to any machine supporting a standard C compiler. The program has been run on a VAX-780 and on a DEC Rainbow. The graphics routines also strive to be portable: Some simple definitions at the beginning of the program allow DNMR.c to interface with most hardware situations. Currently supported configurations are Tektronix 401X and BBN Bitgraph terminals, the Tektronix 4662 plotter, and any devices supported under the GSX graphics system. Our plan is to make DNMR.c publicly available soon (free).

Please credit this contribution to Kathy Gallagher's account (in the nick of time we hope).

Sincerely,

Gary R. Weisman
Associate Professor

David J. Vachon

Peter A. Petillo

References

(1) Reinhoudt, D. N.; Gray, R. T.; DeJong, F.; Smit, C. J. Tetrahedron 1977, 33, 563.

(2) Sandstrom, J. "Dynamic NMR Spectroscopy" 1982, Academic Press, New York.

CONCORDIA UNIVERSITY
DEPARTMENT OF CHEMISTRY

September 6, 1984

Professor Bernard L. Shapiro,
Department of Chemistry,
Texas A & M University,
College Station, Texas 77843
U.S.A.

Re: ^{19}F Spectra on the WP-80SY

Dear Barry,

Recently, we have been running many ^{19}F spectra at 75.4 MHz on our Bruker WP-80SY. The source of the samples is the Positron Emission Tomography (PET) group at the Montreal Neurological Institute, McGill University, under the direction of Dr. M. Diksic.

One of the short-lived radioactive nuclides used for labelling PET samples is ^{18}F. The chemists at the Neurological Institute work out their synthetic procedures using ^{19}F before incorporating the radioactive label. We monitor their reaction mixtures, and help to identify their products, using ^{19}F, supplemented by ^{1}H NMR. Proton spectra are usually taken on the XL-200 or 300 at McGill, rather than on our low-field instrument. The Bruker spectral simulation program PANIC has proved invaluable for spectral analysis.

The WP-80SY is equipped with a dual 5 mm $^{1}H/^{19}F$ probe, which we have found very satisfactory and convenient to use. Data are typically collected into 16K and zero-filled to 32K.

PET sample preparation at the Neurological Institute has led to improved ^{18}F-labelling procedures, and to new organo-fluorine chemistry. We have been able to identify previously unobserved intermediates, and to gain a better understanding of the course of some fluorination reactions. This work is being prepared for publication.

Best regards,

Yours sincerely,

L.D. Colebrook

LDC/dg

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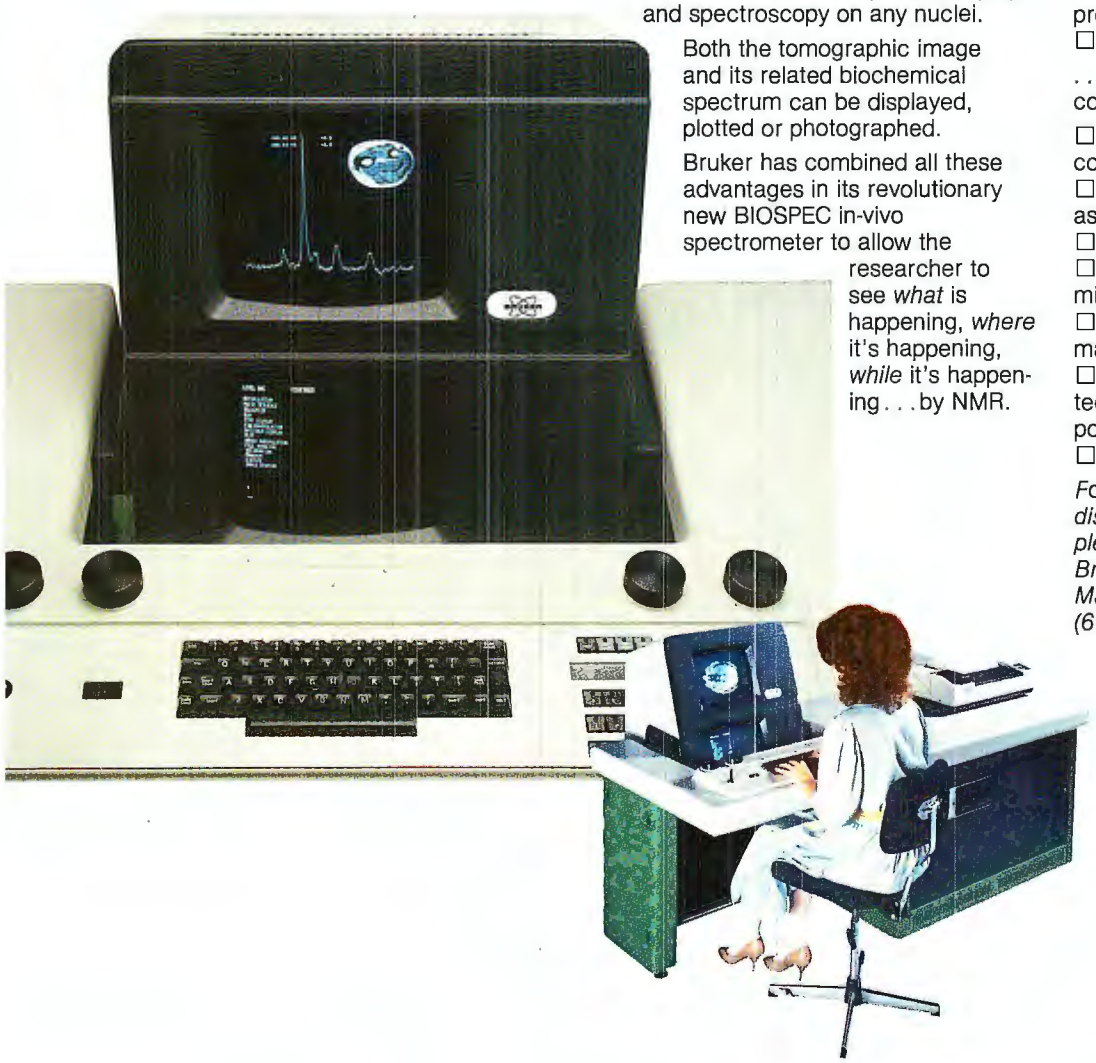

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LABORATOIRE DE CHIMIE ORGANIQUE PHYSIQUE

J.-E. DUBOIS, *Directeur*

Paris, September 20th, 1984

Dr. B.L. Shapiro
TAMU NMR Newsletter
Department of Chemistry
Texas A & M University
College Station
Texas 77843
U.S.A.

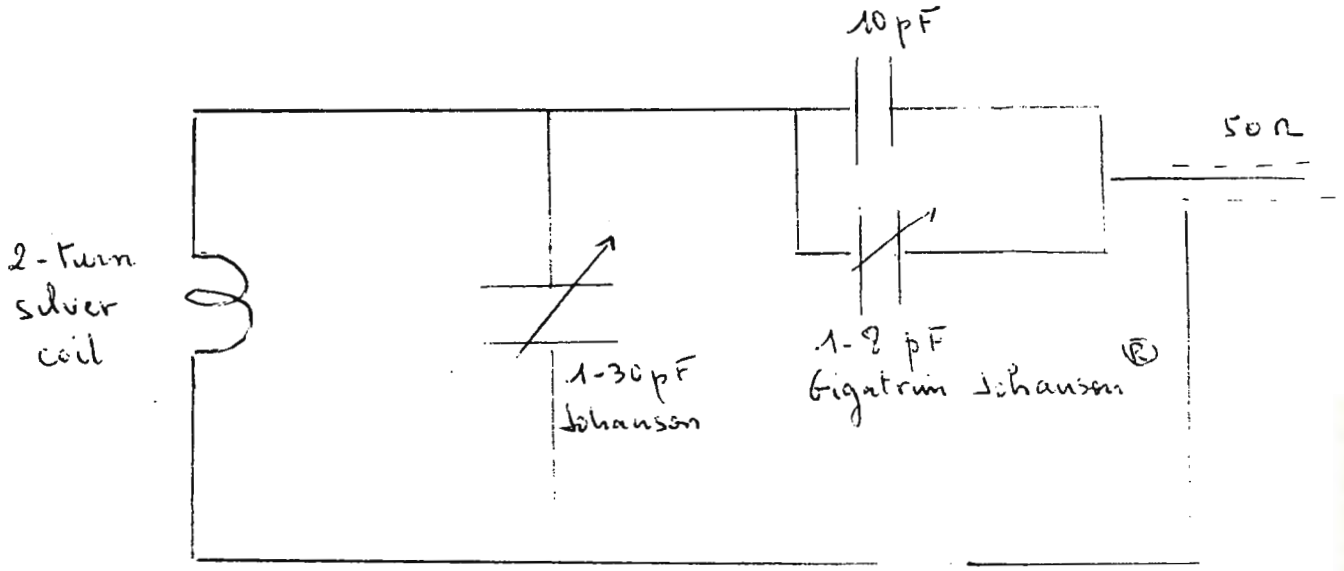
Surface Coil on a Narrow Bore Supercon Magnet

Dear Professor Shapiro,

Since last year we have been focusing our attention on biochemical applications of NMR, particularly on ^{13}C NMR studies of living tissues and organisms. We are developing a surface coil tuned at 50.32 MHz on our Bruker WP 200 spectrometer equipped with a narrow-bore (52 mm i.d. clear bore) supercon magnet.

To save space for placing small animals like mice, we have chosen to remove the original Bruker shim coil-holder. So, on an appropriate plexiglas cylinder (ϕ_{out} = 53 mm, ϕ_{in} = 47 mm) we have engraved x, y and z gradient shims, using a one-turn coil to minimize the room occupied by these circuits as described in the literature.[1] However, these shims require a rather high current (1 ∿ 2 A), so it is convenient to use the powerful current amplifiers (5 A max) normally feeding the original Bruker second-order shim coils.

The below-described circuit[2] has been used.



The probe is shielded using a thin copper sheet wound inside the plexiglas tube. This circuit can be easily tuned with the SWR meter of the Bruker pulse amplifier which gives a slightly better SWR ratio than our Bruker 15 mm broadband probe tuned for ^{13}C and a very low noise level.

Unfortunately, the magnet homogeneity of about 2 cm off-axis is rather poor, and gives a linewidth of ca. 12 Hz for a 0.5 g 90 % enriched CS_2 sample contained in a 8 mm o.d. glass tube, and a S/N ratio ≈ 160 for a pulse width of 70 µs giving the maximum signal; the same sample in the 15 mm ^{13}C probe gives a linewidth of ca. 4 Hz with a S/N ratio ≈ 360 with a single 90° pulse.

Some proton measurements on a very small sample using a similar circuit at 200 MHz placed at different off-axis points inside the original Bruker shim coil holder (ϕ_{bore} = 40 mm) convinced us that second and third order shims do not noticeably improve off-axis resolution. So we do not want to try to add second order shim coils to our probe.

Figure 1 shows the non-decoupled ^{13}C spectrum of neat acetone contained in a polyethylene bottle (o.d. ≈ 30 mm). On the onset recorded with only 10 Hz line broadening, the coupling between ^{13}C and the four hydrogens becomes apparent.

The next step will be broadband proton decoupling using a second proton tuned coil, also useful for shimming magnets, as developed by Ackerman et al.[3]

We hope this letter annuls the pink "ultimatum" we received just after the holidays!

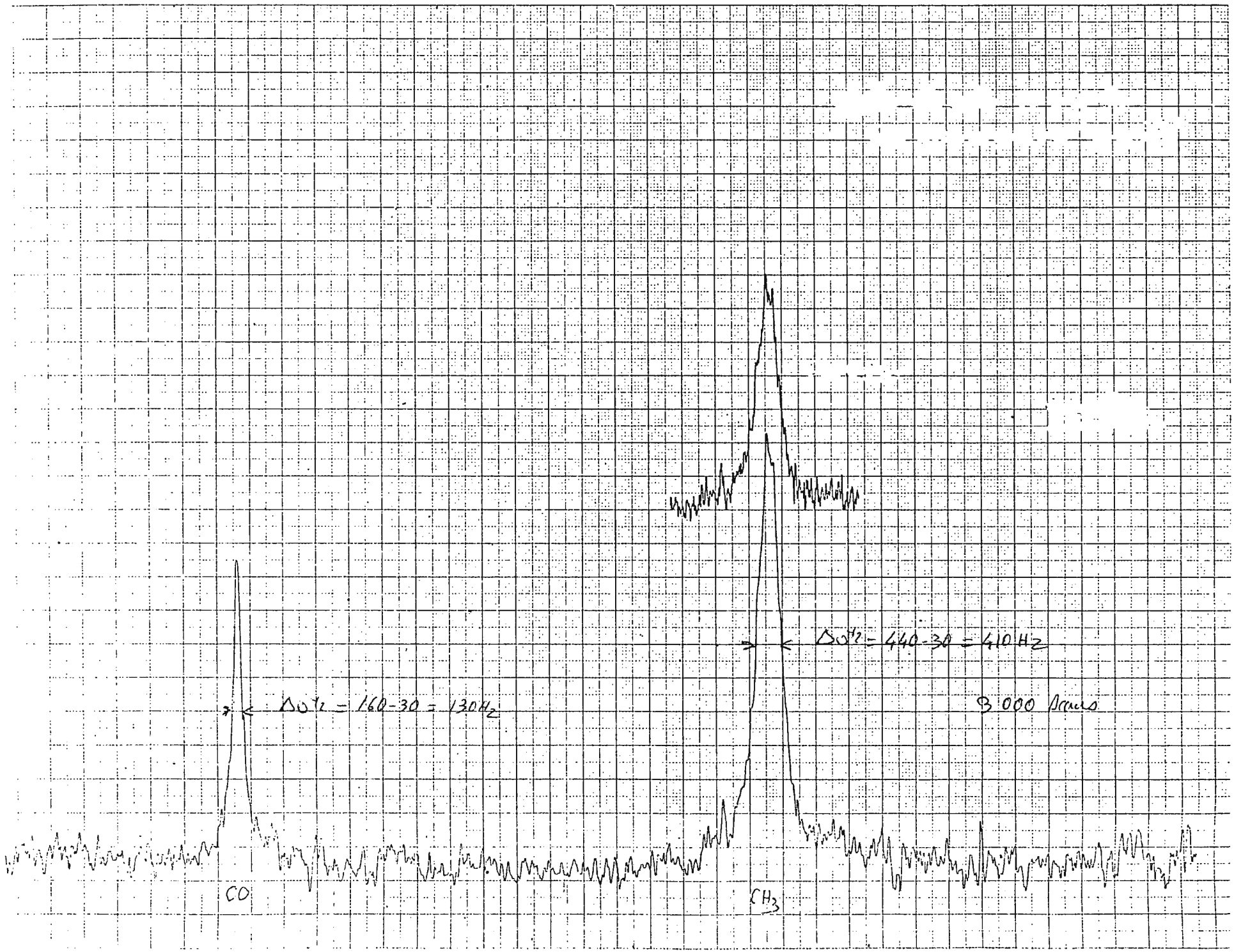
Sincerely yours, with best regards,

B. Tiffon

B. Ancian

A. Briguet
(Université C. Bernard, Lyon)

1. M.D. Sauzade and S.K. Kan, Adv. Electronics and Electron Physics, 34, 1 (1973).
2. D.I. Hoult, Progress in NMR Spectroscopy, 12, 41 (1978).
3. J.H. Ackerman et al., J.M.R., 58, 76 (1984).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August 29, 1984

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

Remote Connectivities From 2D Double Quantum NMR

Dear Barry,

In order to elucidate the structural requirements associated with antibacterial activity in a series of glycopeptide antibiotics, we have been investigating their conformational properties and interactions with Ac_2-Lys-D-ala-D-ala, a model for the antibiotics' site of action. A critical requirement for obtaining structural information from our ^1H NMR studies is the unambiguous assignment of the ^1H resonances. In order to assign the ^1H resonances, we have been using two-dimensional double quantum NMR and relayed correlation spectroscopy. Both methods proved useful in identifying the connectivities between remote nuclei belonging to the same spin system.

A contour plot of a 2D-double quantum NMR experiment of ristocetin aglycone alcohol (figure 1) is depicted in figure 2. The experiment was performed using a $(90^o\text{-}\tau\text{-}180^o\text{-}\tau\text{-}90^o\text{-}t_1\text{-}\alpha)_n$ pulse sequence in which the observation pulse, α, was chosen to optimize the direct connectivities in the lower quadrant (figure 2b).[1] Due to the magnitude of these cross-peaks, it was difficult to observe some of the connectivities between the remote spins in this quadrant. However, in the upper quadrant (figure 2a), the remote connectivities were easily identified and are indicated by the arrows in the figure. These cross-peaks appear at a ω_2 frequency of the common nucleus (middle number in the subscript) and at the sum of the frequencies of the remote spins (outer numbers) on the ω_1 axis.[2]

Sincerely yours,

Stephen W. Fesik

Stephen W. Fesik

1 T.H. Mareci and R. Freeman, J. Magn. Reson., 51, 531-535 (1983).

2 L. Braunschweiler, G. Bodenhausen, and R.R. Ernst, Molec. Phys. 48, 535-560 (1983).

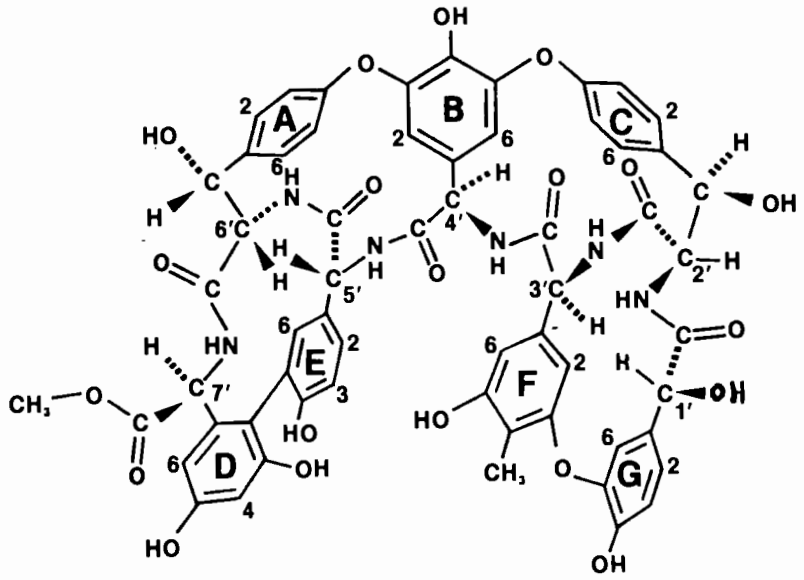

Figure 1. The structure of ristocetin aglycone alcohol.

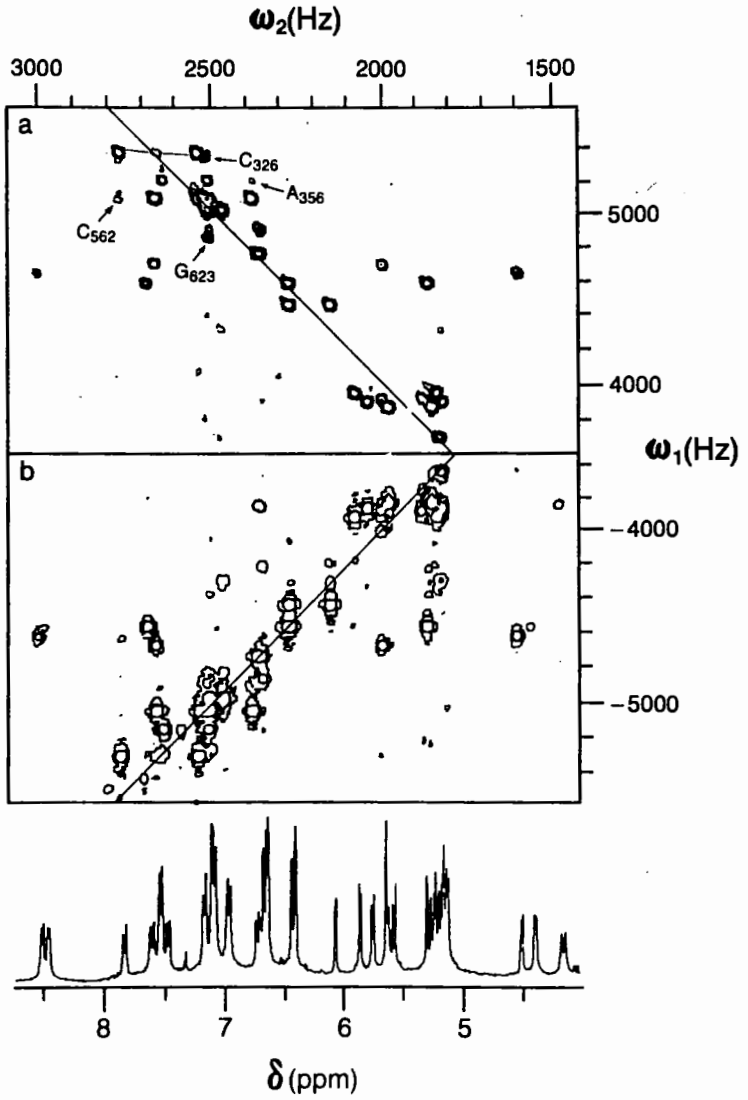

Figure 2. Contour plot of the a) upper and b) lower quadrants of a 2D double quantum NMR experiment of ristocetin aglycone alcohol. The arrows indicate the cross-peaks corresponding to connectivities between remote spins.

UNIVERSITY CHEMICAL LABORATORY,
LENSFIELD ROAD,
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CB2 1EW
TELEPHONE (0223) 66499

30 August 1984

Professor B L Shapiro
Department of Chemistry
Texas A and M University
College Station
Texas
U S A

Dear Barry

NMR of One Carbon Metabolism by Methanotrophic Bacteria

Following on our in vivo work on formaldehyde metabolism in E.coli,[1,2] we have been looking at a variety of different organisms. The spectra opposite show the time course (with 4 minute time resolution) of methanol oxidation through formaldehyde and formate in the obligate methanotroph Methylosinus trichosporium OB3b. All the added methanol (10 mM) is consumed in about 20 minutes, to generate formaldehyde which is itself all oxidised within half an hour or so. If the experiment is continued, the formate can be seen to go to bicarbonate/CO_2.

With this rather splendid analytical tool in hand we have been able, in collaboration with the Biotechnology group at Cranfield Institute of Technology, to elucidate many hitherto puzzling features of the relationship between growth conditions and metabolic behaviour. This work will shortly appear in the Journal of General Microbiology.

Yours sincerely

Jeremy Sanders

Dr J K M Sanders

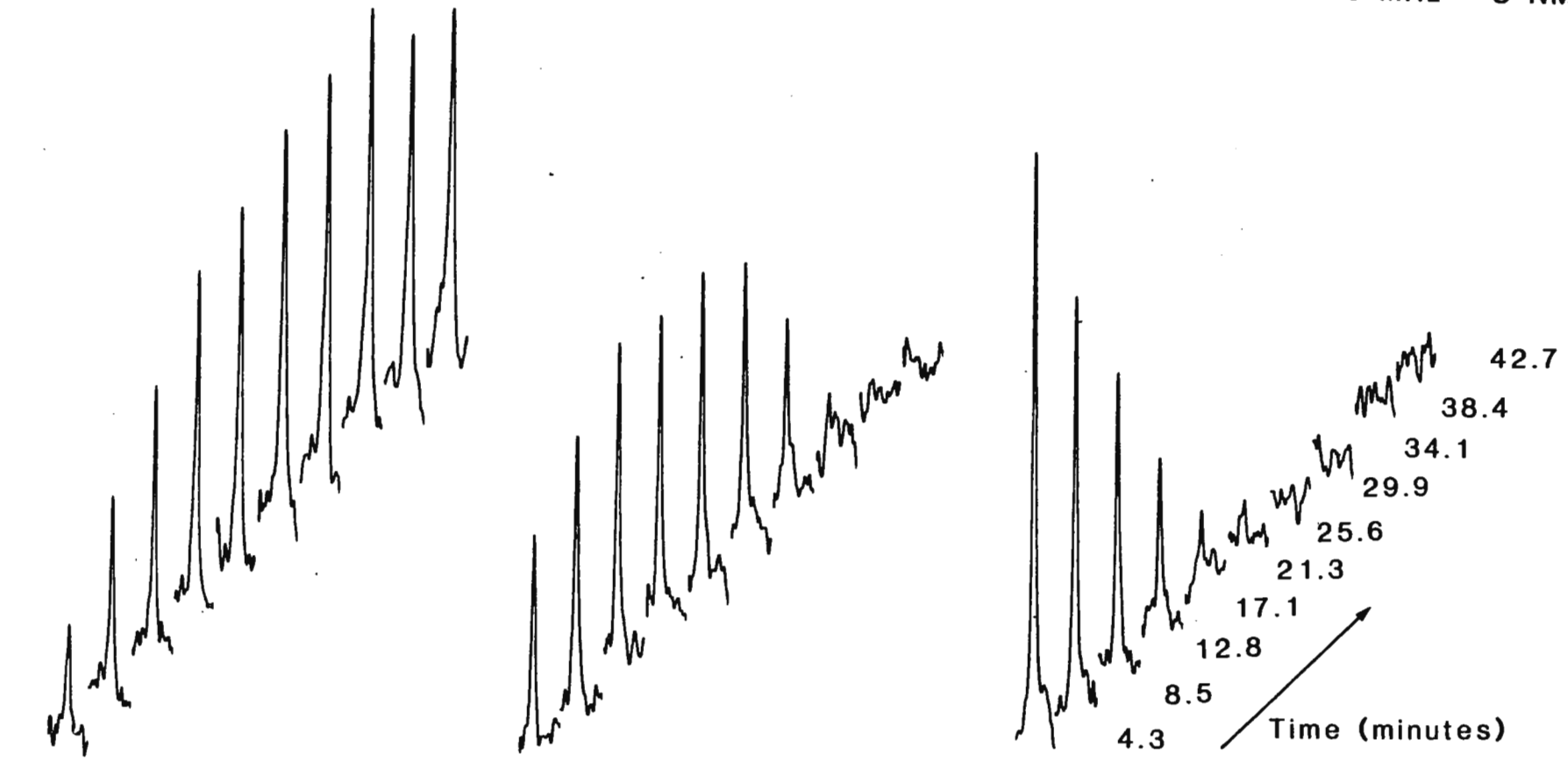
1. Hunter et al, Biochemistry, 23, 508 (1984).
2. Doddrell et al, FEBS Letters, 170, 73 (1984).

Methylosinus trichosporium OB3b

low biomass

10 mM $^{13}CH_3OH$ added

100 MHz ^{13}C NMR



INSTITUT FÜR PHYSIK DER UNIVERSITÄT BASEL
EXPERIMENTELLE KERNPHYSIK
Klingelbergstrasse 82, Telefon 061 - 44 22 80

CH - 4056 Basel (Schweiz) Sep. 3, 1984

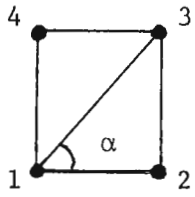
Prof. Dr. P. Diehl

Prof. B.L. Shapiro
Department of Chemistry
Texas A and M University
College Station, Texas 77843
USA

Simple relations for the structure of partially oriented molecules with C_2-symmetry, based on the use of two different solvents

Dear Barry

It is well known that the determination of molecular structure from the spectra of oriented molecules must generally be performed by computer, because already for a four spin system with D_2-symmetry the molecular shape is a relatively complex implicit function of the measured direct couplings (see eq. 1).



$$\frac{D_{23}}{D_{12}}\left(\frac{r_{23}}{r_{12}}\right)^5 - \frac{D_{13}}{D_{12}}\left\{1+\left(\frac{r_{23}}{r_{12}}\right)^2\right\}^{5/2} + 1 = 0 \qquad (1)$$

The situation is improved drastically if the same molecule is studied in two different liquid crystals. We then observe the direct couplings D_{12}, D_{23} and D_{13} in the first solvent and D_{12}', D_{23}', D_{13}' in the second. D_{13} and D_{13}' can be expressed in terms of the other direct coupling constants!

$$D_{13} = x\,D_{12} + y\,D_{23}$$
$$D_{13}' = x\,D_{12}' + y\,D_{23}' \qquad (2)$$

with

$$x = \left(\frac{r_{12}}{r_{13}}\right)^3 \cos^2\alpha\,, \qquad y = \left(\frac{r_{23}}{r_{13}}\right)^3 \sin^2\alpha$$

i.e. $$\frac{y}{x} = \left(\frac{r_{23}}{r_{12}}\right)^3 \operatorname{tg}^2\alpha = \left(\frac{r_{23}}{r_{12}}\right)^5$$

Now we derive from (2) :

$$\frac{y}{x} = \frac{D_{12}D_{13}' - D_{12}'D_{13}}{D_{13}D_{23}' - D_{13}'D_{23}} = \left(\frac{r_{23}}{r_{12}}\right)^5 \qquad (3)$$

so that the molecular structure can be expressed explicitly in terms of the measured quantities.

This approach is not limited to systems of D_2-symmetry but can be generalized for planar molecules of C_2-symmetry.

With best regards
Yours sincerely
Peter
(Peter Diehl)

Are you building your NMR research system?

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PULSkit: A powerful Pulse Programmer with 100 nsec resolution, 2K x 128 bits of memory and five loop counters.

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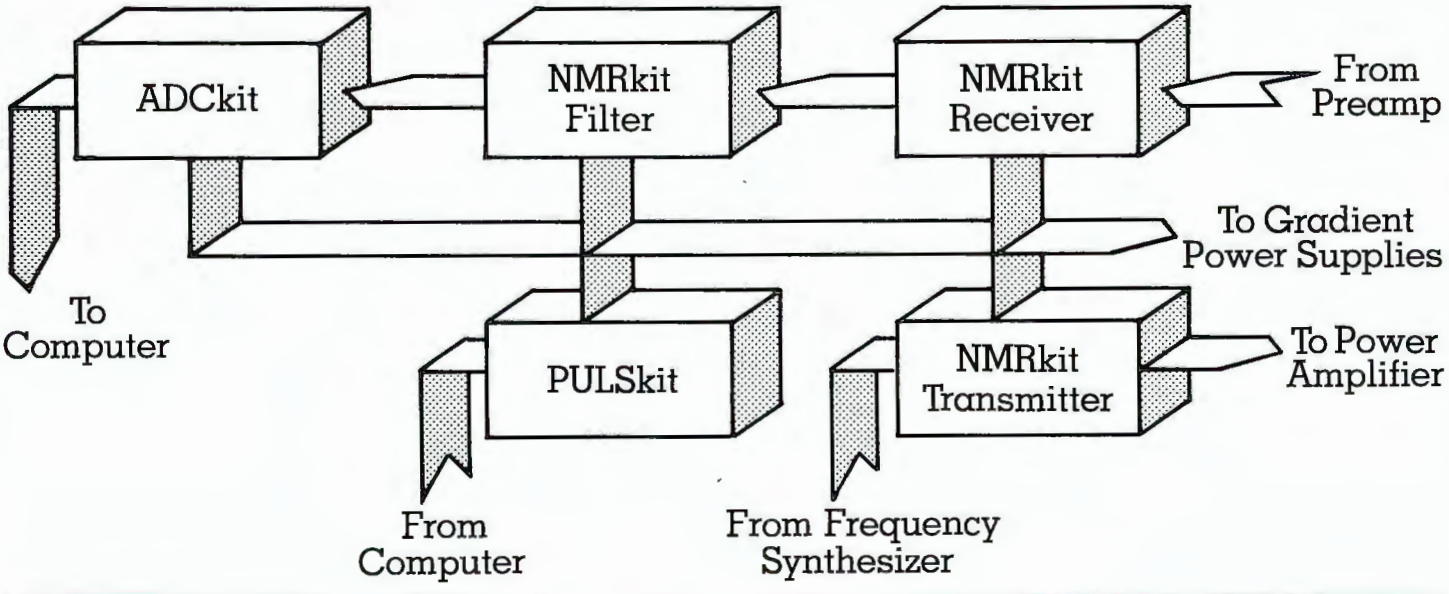

The **NMRkit** is the broadband control unit of the spectrometer. Four different bandwidths are available, including 2–32 MHz, 3.5–80 MHz, 7–160 MHz and 50–500 MHz, (other bandwidths are available on request). The **NMRkit** consists of three boards:

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—The **Receiver** board consists of three sections: the broadband amplification to bring the NMR signal at an acceptable level for the detection, the IF section with detection and amplification, and the quadrature detection with another stage of amplification.

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The **PULSkit** is a universal pulse programmer specifically designed for NMR applications. It generates the different intervals required in an NMR experiment, controls the magnetic field gradients and the shape of the selective pulse, and can also drive a two-channel analog-to-digital converter (the ADCkit, for example). Besides a time resolution of 100 ns and a minimum pulse width of 500 ns, the **PULSkit** has five, independent, 16-bit loop counters and a memory of 2K x 128 bits, providing 76 control lines for your instrument. The **PULSkit** can be interfaced to a VAX-11/750 or PDP-11 computer via a DR-11/W interface board, or any other 16-bit bus using the appropriate interface.

The **ADCkit** is a two-channel 12-bit Analog to Digital Converter Board, which consists of:

—Two high speed sample-and-hold amplifiers
—A two-channel analog multiplexer
—A 12-bit Analog to Digital Converter with a 3 μs conversion time
—A 16-bit adder/subtractor to control the sign of the output signal

Each of these components is controlled by a separate bit in the control word. This simplifies the acquisition software and allows maximum flexibility in the choice of the acquisition mode.
Controlled directly by the pulse programmer, the **ADCkit** offers an elegant solution to fast acquisition of NMR signals.
For maximum convenience, a 12-bit Digital-to-Analog converter is also included on the board.

The **DECkit-2** is a fully broad-banded decoupler: it allows homo- or hetero-decoupling (WALTZ-16) on any nucleus from 3.5 MHz to 80 MHz. Optional ranges (2–32 MHz, 7–160 MHz or 50–400 MHz) are also available. In order to operate properly, it requires an external frequency synthesizer as well as an appropriate broadband power amplifier.

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DELFT UNIVERSITY OF TECHNOLOGY
Laboratory of Organic Chemistry
Julianalaan 136
2628 BL DELFT
The Netherlands

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

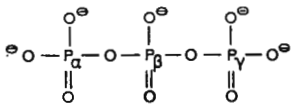
Delft, September 10, 1984

Dear Professor Shapiro,

The complexation of lanthanide(III) cations with sodium triphosphate

Previously, in a search towards new builders for detergent formulations, we have studied with the use of multinuclear NMR several (hydr)oxycarboxylates in the presence of Ln(III) cations as probes for Ca(II).[1]

Recently, we studied the complexation of Ln(III) cations with the classical builder triphosphate (TP) with the use of NMR shift and



TP

relaxation rate measurements (^{17}O and ^{31}P). Depending upon the choice of the Ln(III) cation, separate signals for the 1:2 Ln(III)-TP complex and the free TP ligand, or averaged spectra were obtained (see Fig. 1). The longitudinal relaxation rates, however, were always in the fast exchange region. In those cases where separate signals were observed for free and complexed ligand (TP) the ^{31}P relaxation rates for both signals appeared to be identical. The magnetization recovery curve after the inverting 180° pulse was always single exponential within the experimental accuracy. Application of a selective pulse on either the signals for the free or complexed TP gave analogous results: the magnetization transfer between free and complexed nuclei is fast on the experimental time scale. As far as

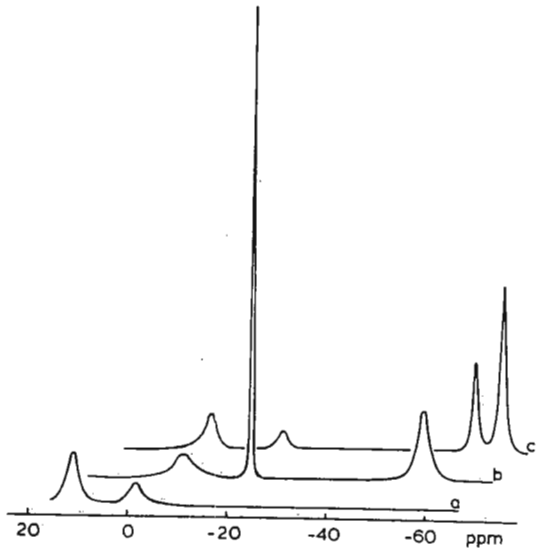


Fig. 1. Examples of ^{31}P spectra of $Ln(TP)_2$ complexes, illustrating fast and slow exchange on the ^{31}P NMR time scale (25 °C; $\rho = 0.25$).
a: Ce(III) fast exchange $\delta = 9.7$ ($P_{\alpha,\gamma}$), $\delta = -3.7$ (P_{β}).
b: Eu(III) fast exchange for P_{β}: $\delta = -13.9$, slow exchange for $P_{\alpha,\gamma}$: $\delta = 0.0$ (free ligand), $\delta = -48.3$ (complex).
c: Yb(III) slow exchange $\delta = 0.0$ ($P_{\alpha,\gamma}$, free ligand), $\delta = -14.4$ (P_{β}, free ligand), $\delta = -52.6$ (P_{β}, complex), $\delta = -58.6$ ($P_{\alpha,\gamma}$, complex).

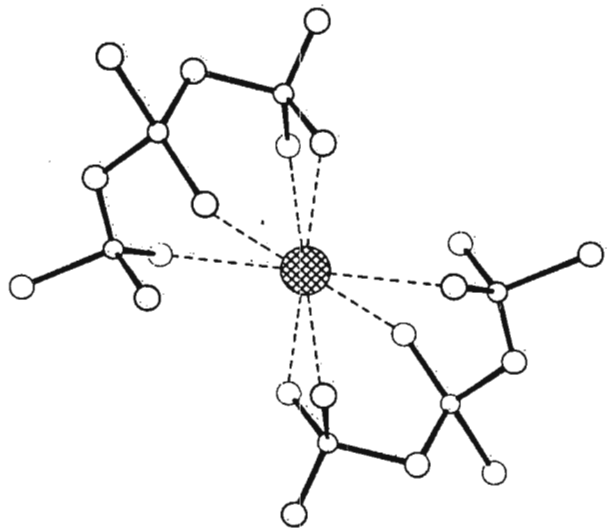


Fig. 2. Structure of the $Ln(TP)_2^{7-}$ system.

we know this phenomenon does not often occur when separate signals are observed for exchanging nuclei.

From the analyses of the ^{17}O and ^{31}P shift and relaxation data it is concluded that the Ln(III) ion is coordinated with two TP ligands and one water in the first coordination sphere, while from Ln(III) induced ^{6}Li relaxation rates it is concluded that 7 alkali counter ions are present in the second coordination sphere. TP is coordinated to Ln(III) via two oxygens of one PO_3 group, one oxygen of the other PO_3 group and one oxygen of the PO_2 moiety (see Fig. 2).

Sincerely yours,

M.S. Nieuwenhuizen

J.A. Peters

1. J.A. Peters and A.P.G. Kieboom, Recl. Trav. Chim. Pays-Bas 102, 381-392 (1983).

UNIVERSITÉ D'OTTAWA UNIVERSITY OF OTTAWA
OTTAWA ONTARIO
CANADA

September 7, 1984.

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

Dear Prof. Shapiro,

Le simple, c'est le beau?

Except in the extreme-narrowing conditions, the relaxation of quadrupolar nuclei results from the summation of several exponentials. Hubbard (1) has shown that, in an isotropic system, I + ½ (half-integral I) exponentials can describe the decay of the magnetization. If the 3/2 case was easily solved (1, 2), for I ⩾ 5/2 numerical solutions (3), or an analytical approximation resulting from a perturbational treatment (4) have to be used.

Al(III) forms long-lived complexes with ATP in aqueous solutions (5). With Dr. Alfred Delville, on leave from Liège for a few months (until the beginning of the canadian winter), we are investigating their stoichiometry, and their thermodynamic and kinetic properties. At 78.16 MHz (Varian XL-300), the Al-27 (I=5/2) spectrum of an Al(III)-ATP mixture (pH 7.4) is composed of several broad lorentzian lines which originate in the coexistence of different chemical species and/or of different relaxation exponentials characterizing a single large chemical species. At 20.72 MHz (Varian FT-80), a single broad line with an uncertain lineshape, is observed.

Our first approach to the problem has been to simplify it by "killing" as many lines as possible. And we were successful as it is shown on the figure. Using a long delay between the end of the pulse and the start of the acquisition (> 1500 µsec) we obtain one and only one resonance ($\nu_{\frac{1}{2}}$ = 500 ± 50 H_z) whose linewidth is independent of the field and which, plausibly, represents the aquated cation in fast exchange with a 1:1 Al-ATP complex.

Mais si, pour citer Edgar Morin, "la simplification contient de la mort", alors il ne nous reste plus, maintenant, qu'à partir à la recherche du temps perdu.

Département de chimie
Faculté des sciences et de génie

365 Nicholas
K1N 9B4

Department of Chemistry
Faculty of Science and Engineering

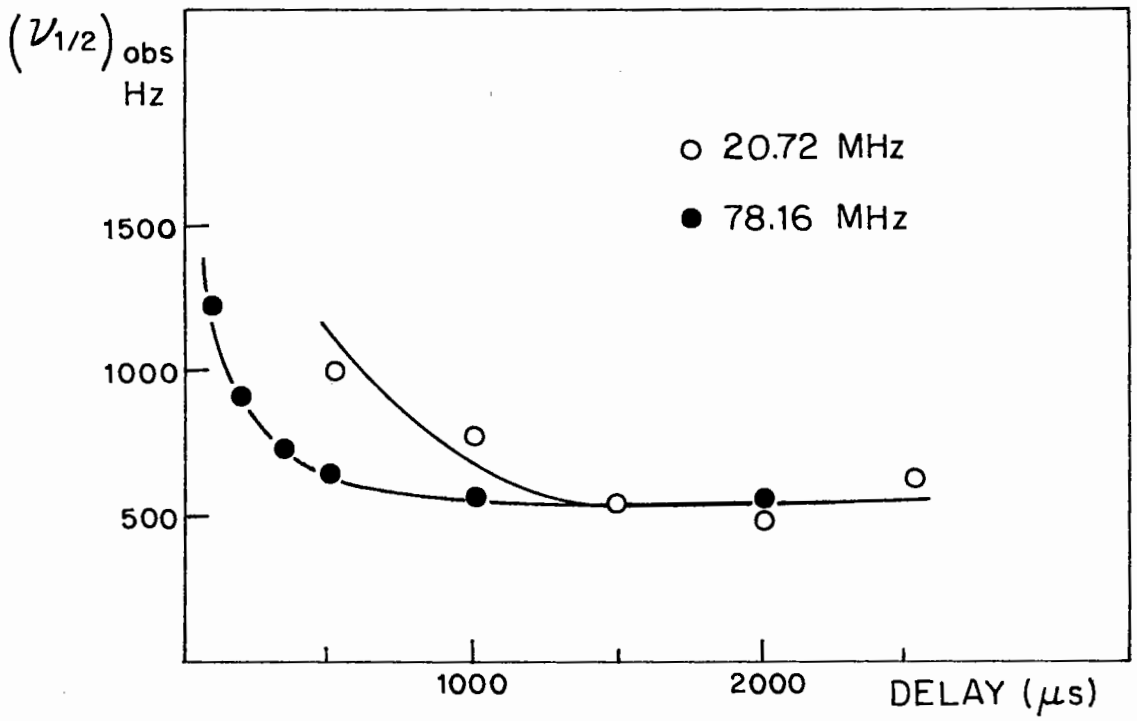
Please, credit this contribution to the subscription of Prof. R.R. Fraser.

Sincerely yours,

C. Dupressoir A. Delville C. Detellier

References

(1) P.S. HUBBARD, J. Chem. Phys., 53, 985 (1970).
(2) T.E. BULL, J. Magn. Reson., 8, 344 (1972).
(3) T.E. BULL, S. FORSEN, D.L. TURNER, J. Chem. Phys., 70, 3106 (1979); A.D. McLACHLAN, Proc. Roy. Soc., A 280, 271 (1964).
(4) B. HALLE, H. WENNERSTRÖM, J. Magn. Reson., 44, 89 (1981).
(5) S.J. KARLIK, G.A. ELGAVISH, G.L. EICHHORN, J. Am. Chem. Soc., 105, 602 (1983).



SYRACUSE UNIVERSITY

N.I.H. RESOURCE FOR MULTI-NUCLEI NMR AND DATA PROCESSING
DEPARTMENT OF CHEMISTRY, BOWNE HALL, SYRACUSE UNIVERSITY, SYRACUSE, NY 13210

September 10, 1984

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

TITLE: SOFTWARE AVAILABLE FOR NMR DATA REDUCTION; A PROGRESS REPORT.

Dear Barry,

Over the past six years, one part of our research has been involved in development of software for processing NMR FIDs on general purpose computers. **NMR1** is a large program designed for 32-bit computers such as DEC VAX or Data General MV systems. In 1983, we began supporting **NMR1** installations outside of our laboratory; Release 2.1 was mailed in August 1984 to 47 University Laboratories (8 in Europe). **NMR2**, our software for processing 2D FT NMR experiments has just gone into beta-test at five universities.

One of the design conditions for our software is its ability to adapt to various hardware configurations; most installations to-date are on VAX 11/750 or 11/780 systems.

Release 2.1 of **NMR1** has a number of major new features which are described below. Also, we are currently expanding support of peripherals to include: Raster Technology, Lexidata and AED DMA graphics systems as well as Tektronix 4107, Graphos, and DEC VT-240, 241 terminals. We also plan to support HP and Houston HiPlot plotters; currently Zeta and Watanabe plotters can be used.

NMR1 (and NMR2 after beta-testing) software is available <u>without charge</u> to academic or government laboratories. For information write or call us.

A PROGRESS REPORT ON NMR1

This TAMUNMR contribution will briefly summarize three new modules of **NMR1**:

1. The PRocess (PR) command language and its applications.
2. Regression (RG) Analysis.
3. Polymer analysis.

Work on the first and third modules was overseen by Chuck Dumoulin in his last few months at the Resource (Chuck is now at GE Corporate R&D in Schenectady).

1. The **PR** command allows experienced users to set up very complex data reduction protocols which can then be invoked by themselves or others. Protocols may include branching based on results of automatic operations and there is virtually no limit to the complexity of the automated sequence of operations. Release 2.1 includes a rolling demonstration of **NMR1** features which is actually a single **PR** command file.

2. **RG** is a large module which contains sophisticated automatic and interactive routines for non-linear regression analysis. Various modes of operation are possible, including the ability to automatically extract information about a specific peak (height, integration, linewidth, or position) from a set of spectra taken over time or through variation of experimental conditions. The user can fit the variation of the extracted quantity to any of several supplied equations or, using the **RG** parser-interpreter, the user can type in any desired equation (up to 8 variables). **RG** uses a modified Levenberg-Marquardt non-linear optimization to fit experimental data points to the proposed relationship. Extensive statistical information is provided, both numerically and graphically. As in other modules of **NMR1**, **RG** can operate totally automatically or users can select various levels of control over the processing.

3. **Polymer Analysis.** The polymer analysis module calculates tacticities for vinyl polymers using Bernoullian or Markov Statistics. Furthermore, the module, which is still under development, will calculate number average sequence lengths and block runs in copolymers. Polymer analyses are performed using internal user-supplied database assignments. The software matches observed peaks with database entries and, using **NMR1** quantitation, determines the statistical parameters best fitting the experimental data. Spectral simulations are also provided.

Our **NMR2** software system (pre-release version 0.0) for 2D FT NMR is currently limited to DMA graphics systems (Lexidata, Raster Technology, AED). The first general releases of **NMR2**, supporting DMA and serial graphics systems and integrating various array processors, will be announced later this year; laboratories wishing pre-release tapes for VAX or DG machines should contact us.

Best regards,

George C. Levy
Professor and Director

John H. Begemann, Ph.D.
Software Projects Manager

GCL/JHB:cma

MRC
Medical Research Council

MRC Biomedical Nuclear Magnetic Resonance Centre
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telephone 01-959 3666

reference

21st August 1984

Professor B.L. Shapiro
Department of Chemistry
Texas A and M University
College Station
Texas 77843

Dear Professor Shapiro,

^{31}P NMR Double Resonance Techniques for the Study of Living Tissue

In some tissues, notably brain and liver, measurement of the concentrations of phosphorylated metabolites is hindered by the presence of an underlying broad resonance. This arises from the chemical shift anisotropy of phospholipids which are present in large quantities in these tissues. By pre-irradiating this phospholipid resonance at a suitable point it is possible to selectively saturate the whole of it, thus providing a flat baseline against which the sharper peaks of the metabolites can be more easily observed. We have used this approach in conjunction with ^{31}P nmr surface coil methods in order to demonstrate the existence of phospho-

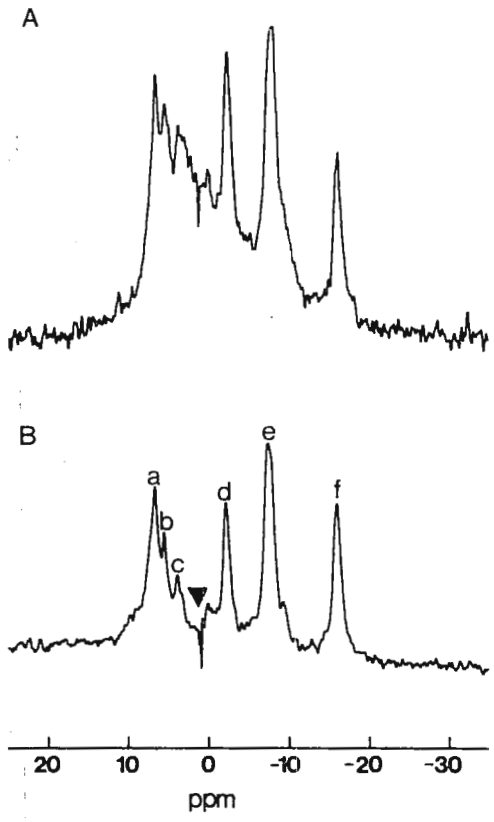

Fig. 1: ^{31}P nmr spectra of rat liver: A control; B with 1.71 s pre-irradiation

diesters in the in vivo rat liver which were previously masked by the rising edge of the phospholipid "hump" (figure 1). Quantitation, particularly of the sugar and inorganic phosphate region is also greatly simplified by this approach.

The same method has been applied to a superfused brain slice preparation (Cox et al 1983) using a conventional 25 mm ^{31}P probe (Fig. 2).

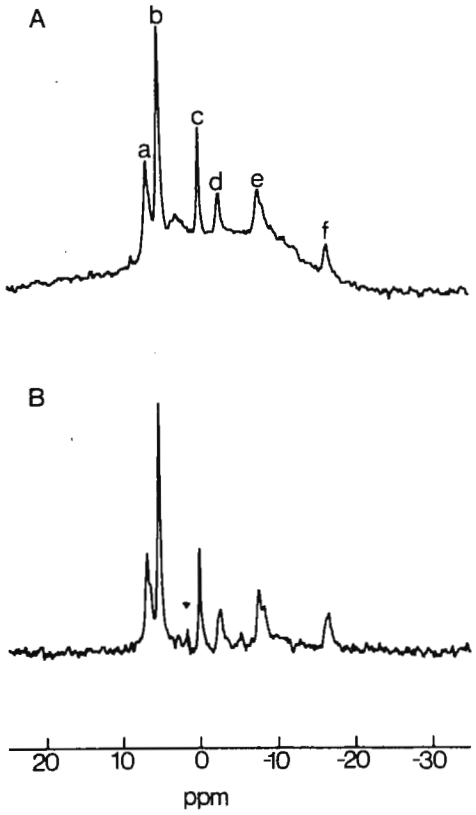

Fig. 2: Removal of the phospholipid resonance from the ^{31}P spectrum of superfused guinea-pig brain slices. Peak assignments are as for Fig. 1 with the exception of peak c which in this case is phosphocreatine.

The removal of the entire phospholipid resonance is itself an interesting phenomenon which occurs by virtue of the (slow) motion of the phospholipids enabling them to explore all possible orientations of the ^{31}P chemical shift tensor and hence experience the effects of the fixed frequency irradiation (De Kruyff et al 1980). Studies in which the length of the pre-saturation interval has been varied have enabled us to estimate the correlation time associated with this motion (Table 1).

Table 1: Effect of presaturation interval on phospholipid resonance.

Time (sec)	Relative area (± 0.06)
0	1
0.1	0.59
0.25	0.36
0.5	0.22
1.0	0.17
1.75	0.12
2.0	0

Thus the time constant associated with this motion is ∿ 0.25 s.

References

Cox, D.W.G., Morris, P.G., Feeney, J., and Bachelard, H.S. (1983) Biochem. J. 212, 365

De Kruyff, B., Morris, G.A., and Cullis, P.R. (1980) Biochim. et Biophys. Acta. 598, 206.

Yours sincerely,

Peter G. Morris

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CASE WESTERN RESERVE UNIVERSITY • CLEVELAND, OHIO 44106

September 10, 1984

Professor Bernard L. Shapiro
Department of Chemistry
Texas A & M University
College Station, Texas 77843

Title: Inversion Recovery Cross Polarization of Polymers.

Dear Barry,

Ther are many polymers that have both a crystalline and an amorphous phase in the solid state. When these systems are observed by CP/MAS, resonances for both phases are usually seen, and generally overlap. In previous studies, separation of these componets have been acheived by letting one dephase by dipolar or some relaxation process, and observing the other. The dephased signal may then be recovered by spectral subtraction.

Mike Melchior demonstrated, at the 22 nd ENC, that Inversion Recovery Cross Polarization (IRCP) may be used to suppress resonances selectively, based on differences in T_{CH}'s. The appropriate expression for the magnetization is given by

$$M(\tau_1,\tau_2) = [1-2e^{-\lambda\tau 2/T_{CH}} + e^{-\lambda\tau/T_{CH}}]e^{-\tau/T_{1\rho}{}^{H}}$$

$$\tau = \tau_1 + \tau_2$$

$$\lambda = 1 + \frac{T_{CH}}{T_{1\rho}{}^{C}} - \frac{T_{CH}}{T_{1\rho}{}^{H}} \approx 1$$

which is null at

$$2e^{-\lambda\tau 1/T_{CH}} - e^{\lambda\tau 2/T_{CH}} = 2$$

or if $\tau_1 >> T_{CH}$ the null occurs at

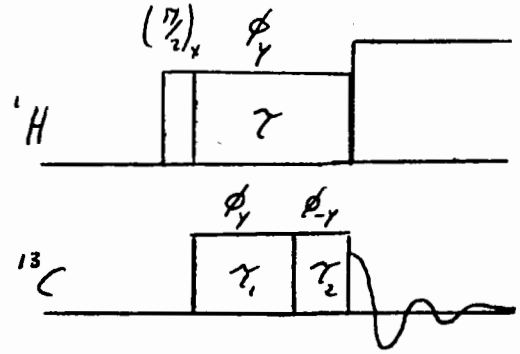
$$\tau_2 = T_{CH}\ln 2$$

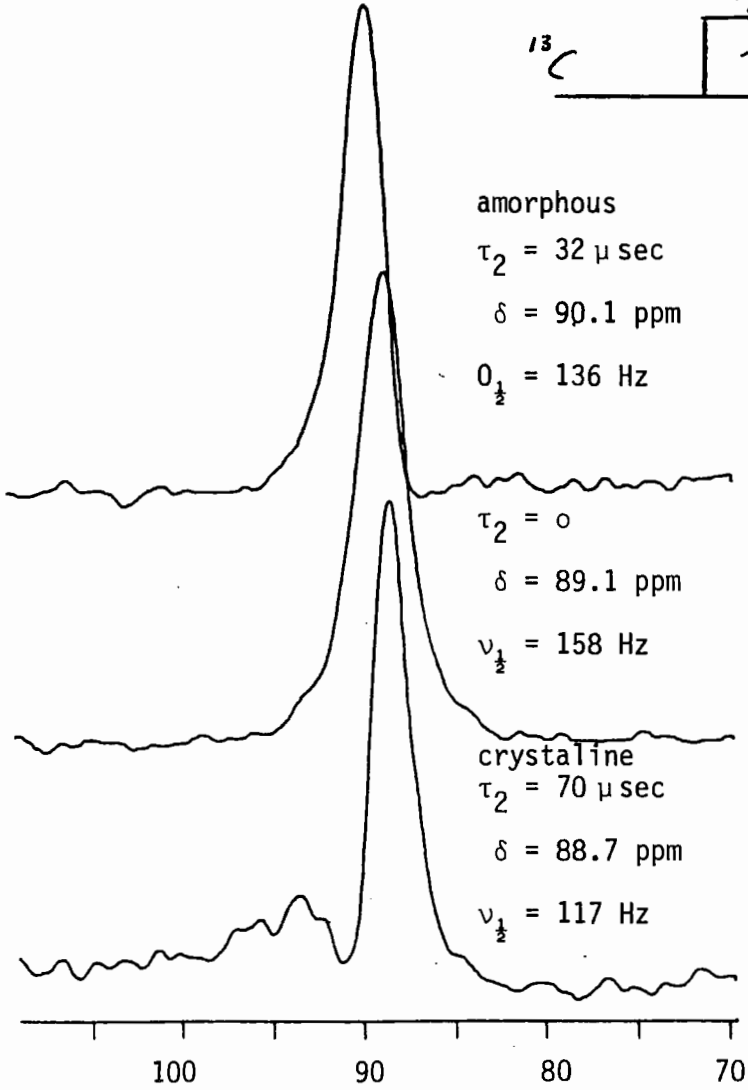
which is remaniscant of inversion recovery sequences in solution.

We have applied IRCP to resonace separation in several polymer systems. The figures shows the separation of amorphous and crystalline conponets for delrin (polyoxymethylene) (Fig. 1) and low density polyethylene (Fig. 2).

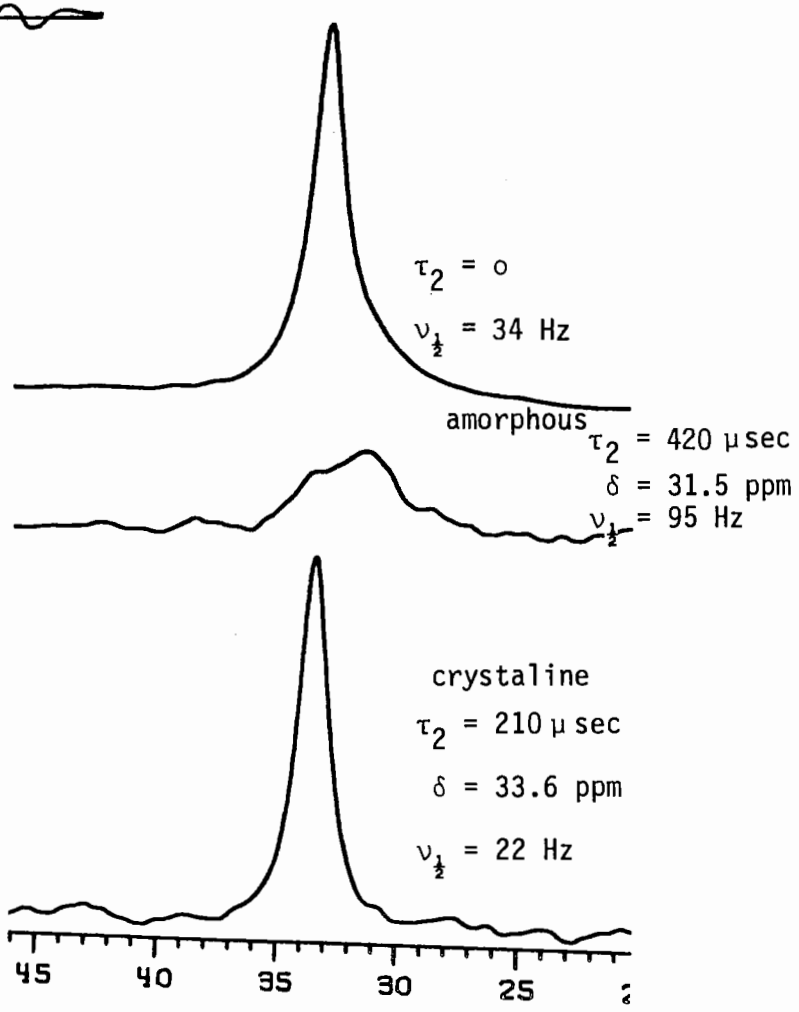
David Cory Dwight Patterson William M. Ritchey

Delrin





Polyethylene



313-31

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda, MD 20205

September 14, 1984

Professor B.L. Shapiro
Dept. of Chemistry
Texas A & M University
College Station, TX 77843

Dear Prof. Shapiro:

New Begining and ^2H Powder Spectra on a JEOL GX-400

It is a pleasure to initiate a subscription to the TAMU NMR Newletter from my new laboratory at the FDA. I have recently relocated here after six very pleasant years in Ottawa, Ontario at the National Research Council.

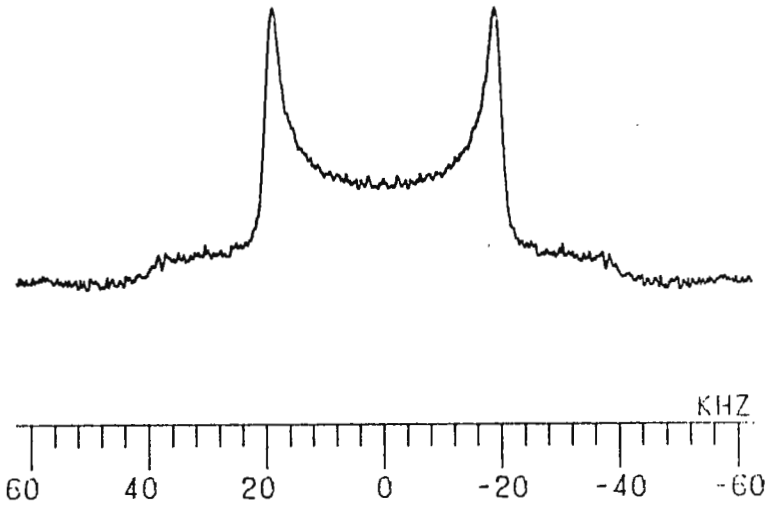
As a brief introduction, my laboratory is part of the Biophysics Branch within the Center for Drugs and Biologics. The Branch also includes Bill Egan (Branch director, chemist and NMR spectroscopist with interests in polysaccharides and in vivo cell metabolism studies) and Richard Pastor (a theoretician from Dr. Karplus laboratory, who is working in the molecular dynamics and graphics area). My laboratory is primarily involved with biological applications of solid state NMR. We are equipped with three spectrometers(JEOL GS-400 & FX-100, and Bruker WM-300) and a additional home-built spectrometer is under construction. This new spectrometer is mainly for solid state studies using all three magnets.

As an initial contribution to the Newsletter, I would like to illustrate what we have been able accomplish in observing ^2H powder spectra on the GX-400, with fairly minor modifications. First of all, a home-made probe was constructed of a fairly standard configuration, using a 5 mm diameter coil. Without any additional amplifiers other than the broadband unit in the spectrometer, we obtained a 90° pulse length of 4.7 usec. However, the sensitivity for broad powder spectra was very low. By replacing the normal duplexer and preamplifier system of the GX-400 with a simple quarter-wavelength duplexer and MITEQ preamp, this problem was solved and a representative spectrum is shown in the figure. The main problem at this point is the limitation of ADC speed (max. allowed spectral width). We have found that, although the system permits spectral widths up to 166 KHz, useful spectra are only obtained at spectral widths of 125 KHz or less. The use of a faster external digitizer would correct this problem. This approach has been implemented by others, and it will also be taken in our laboratory. All spectra to-date have been acquired with a simple phase cycled quadrupole echo sequence; attempts to implement a composite pulse version of this sequence (TAMU #309) have not been successful. The pulse shape and phase switching are quite adequate for solution sequences; however, the fast time scale of the solid-state sequence has presented difficulties. There are remaining problems to optimum performance; however this illustrates that certain projects may be pursued while solutions to these problems are being implemented!

By the way, the GX-400 is generally used for more conventional high-resolution studies. It's sensitivity and RF performance are quite good, and the software is steadily improving. We will report later on our research in this area.

Best regards,

R. Andrew Byrd



Perdeuterated plexiglass ^{2}H NMR spectrum at 61.4 MHz

UNIVERSITY OF CALIFORNIA, SANTA BARBARA

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DEPARTMENT OF CHEMISTRY
SANTA BARBARA, CALIFORNIA 93106

17 September 1984

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

"Fluorine NMR of Carbonmonoxyhemoglobin"

Dear Barry,

Hemoglobin isolated from rabbits receiving 0.3% by weight of D,L-4-fluorophenylalanine in their diet contains approximately one fluorophenylalanine per hemoglobin tetramer (1). Since fluorine nmr signals are particularly sensitive to environment, this fluorine "enrichment" provides useful spectroscopic reporter groups at several locations in each chain of the protein. Earlier our group reported tentative assignment of many of the 16 fluorophe resonances observed for rabbit cyanomethemoglobin; your readers may be interested in further work along these lines.

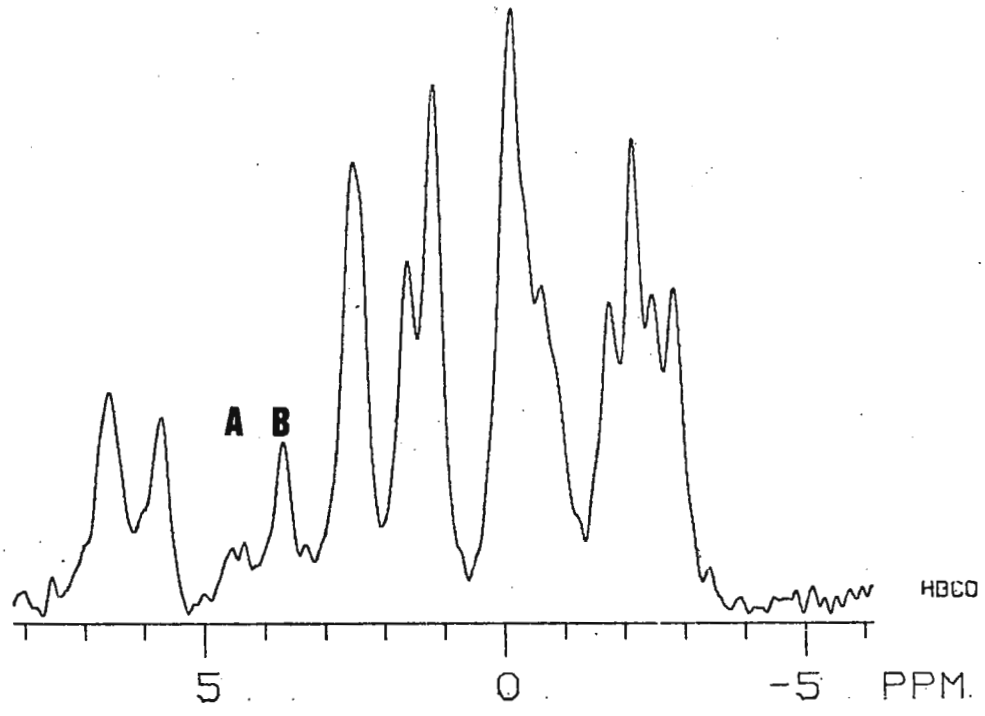

Figure 1. Fluorine-19 Spectrum of Rabbit Carbonmonoxyhemoglobin, pH 7.5, 0.1M Tris-HCl, 0.1M NaCl, 25 μM EDTA, 5% deuterium oxide.

A fluorine-19 spectrum of rabbit carbonmonoxyhemoglobin at 282 MHz is shown in the Figure. The spectrum is dramatically different from that of the paramagnetic cyanomet form and, unlike the cyanomet species, T_1 and $^{19}F[^1H]$ NOE values do not differ greatly from resonance to resonance. Several of the signals observed may be assigned to specific fluorophe residues from the dependence of their chemical shifts on pH and the effect of a nitroxide spin-label attached to the sulfhydryl group of cys-93 of the beta chain. An intriguing aspect of the spectrum is the presence of resonances of non-integral intensities even though the protein samples are homogeneous by a variety of chromatographic criteria; two of the most blatant are labelled A and B in the Figure. We felt that these might arise because of protein conformational changes that are in the slow exchange limit but there was no detectable transfer of saturation when these signals were selectively saturated by the DANTE sequence (2). A possible explanation is that there exists an appreciable amount of heme disorder, arising because of 180° rotation of the heme ring within its binding pocket. Such isomerism has been detected in a number of monomeric hemoglobins as well as horse and human hemoglobin (3,4). Assignment of the signals of the carbonmonoxy spectrum are still underway and we hope to be able to use these to examine changes in hemoglobin structure produced by ligand binding and variation of solution variables such as pH and temperature.

Sincerely,

Mike Gamcsik

M.P. Gamcsik
Postgraduate Research Chemist

Tom

J.T. Gerig
Professor of Chemistry

(1) Gerig, J.T., Klinkenborg, J.C., and Nieman, R.A. Biochemistry **22** 2076 (1983).

(2) Morris, G.A., and Freeman, R. J. Magn. Reson. **29** 433 (1978).

(3) Jue, T., and La Mar, G.N. Biochem. Biophys. Res. Commun. **119** 649 (1984).

(4) Docherty, J.C., and Brown, S.B. Biochem J. **207** 583 (1982).

Postdoctoral Research Associate

Applications are invited from chemists and biochemists for postdoctoral research involving high field nmr studies of enzymes, hemeproteins and calcium-binding proteins. Experience with organic synthesis, protein isolation, nmr and hplc desired. Salary commensurate with experience.

Please submit C.V. and names of two persons who may be contacted as references to J.T. Gerig, Department of Chemistry, University of California, Santa Barbara, CA 93106.

INSTITUTE OF CHEMICAL PROCESS FUNDAMENTALS
Czechoslovak Academy of Sciences
165 02 Prague, Czechoslovakia

August 27, 1984

Professor B. L. Shapiro
Department of Chemistry
Texas A&M University
College Station, TX 77843
U.S.A.

29

Subject: Application of Si-NMR to Stereochemical Diagnostics of Steroids

Dear Barry,

We continue our work on routine and practical applications of Si-NMR to trimethylsilylated products. The "new" techniques for signal enhancement (INEPT & DEPT) permit not only to measure compounds which are available in a small quantity (e.g. 5 mg of a compound with mol.wt. around 300 on our Varian XL-200 spectrometer) but also to measure compounds in sufficient supply at much lower concentrations than before. In Si-NMR lower solute concentrations in deuterichloroform solutions mean more pronounced effects of molecular structure on the silicon chemical shifts.

So we went back to steroid derivatives some of which were measured 10 years ago (Coll.Czech. Chem. Commun. 41, 360 (1976)) as neat liquids. The results show: (i) concentration and solvent effects up to 1 p.p.m. and (ii) clear stereochemical dependence of the chemical shift. For example, in trimethylsilylated cholestanol and coprostanol we have found the following shifts:

trimethylsilylated	cholestanol	coprostanol
3-alpha	13.23	15.26
3-beta	15.04	13.25

Clearly,the trimethylsiloxy group in the axial-axial arrangement with the gamma hydrogen atom on carbon 5 has the silicon shielded by some 2 p.p.m. more than in other arrangements.Hence , the silicon chemical shift indicates the stereochemical position of the original OH group in the parent compound that was trimethylsilylated.

We hope that this communication will reach you before the "Ultimatum" deadline.

With the best regards,

Sincerely,

Jan Schraml

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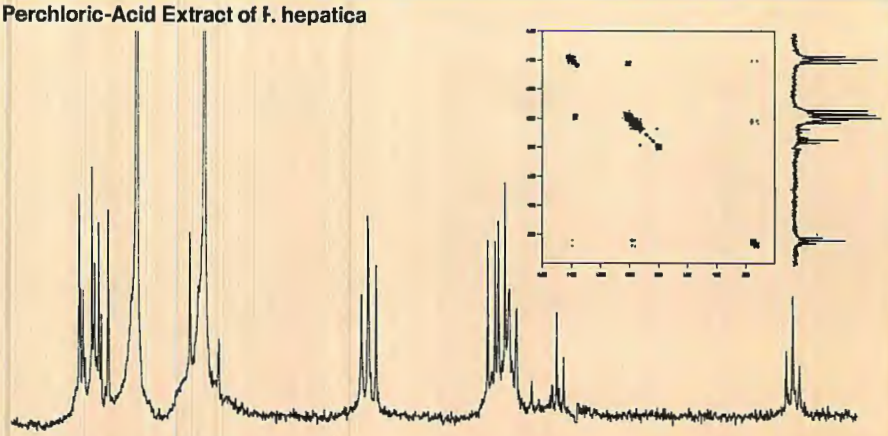
XL performance for demanding biological NMR studies

Recently, NMR has become an important tool for biochemists interested in studying metabolism *in vivo*. The applications shown on this page illustrate the broad range of capabilities required in an NMR spectrometer used in biological research. These capabilities demand superb sensitivity, flexibility in pulse programming, and software that permits taking advantage of available experiments and techniques.

Perchloric-Acid Extract of F. hepatica

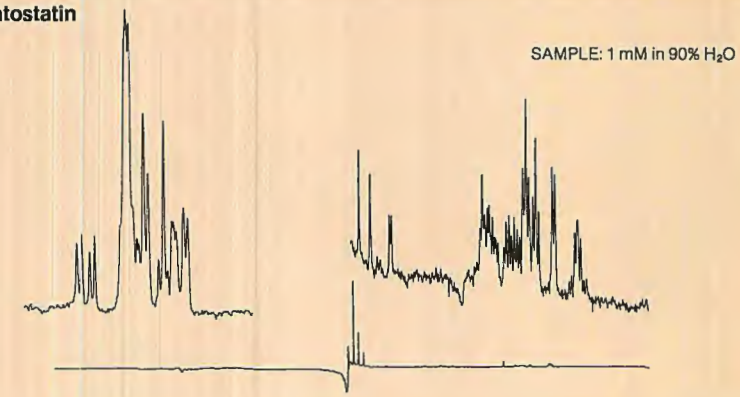


The high-sensitivity probes of the XL-200 allow spectra to be obtained from biologically relevant compounds at low concentration. The ^{31}P spectrum above is of a perchloric-acid extract of F. hepatica *(bovine liver flukes) and was obtained in 4 hours (1500 transients) at 81 MHz, using a 10-mm probe. The spectrum has been resolution-enhanced to facilitate the identification of the ^{31}P-containing compounds present. The average concentrations of metabolites present in the sample are submillimolar.*

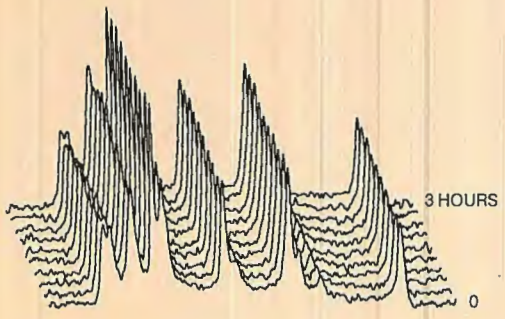
Two-dimensional NMR is a powerful method for analyzing complex mixtures. The contour plot shown above the spectrum is the result of a ^{31}P homonuclear shift correlation experiment carried out on a portion of the fluke extract using a 5-mm ^{1}H broadband switchable probe at 81 MHz. The total experiment time was approximately 12 hours. The experiment led to the discovery of a nucleotide pyrophosphate compound whose presence is indicated by the cross peaks between the P-α-nucleotide peaks and the peak at 800 Hz.

Biological NMR often requires the observation of protons in H_2O, particularly for observation of exchangeable protons. The strong signal from the solvent can be suppressed effectively by pulse sequences such as time-shared Redfield 2-1-4 or, as here, the Jump-and-Return pulse sequence. This XL-400 spectrum is the result of only 16 accumulations using a 1-millimolar solution. The aromatic expansion (rephased for upright presentation) shows the single-proton sensitivity that can be obtained in a half-minute period.

^{1}H Somatostatin

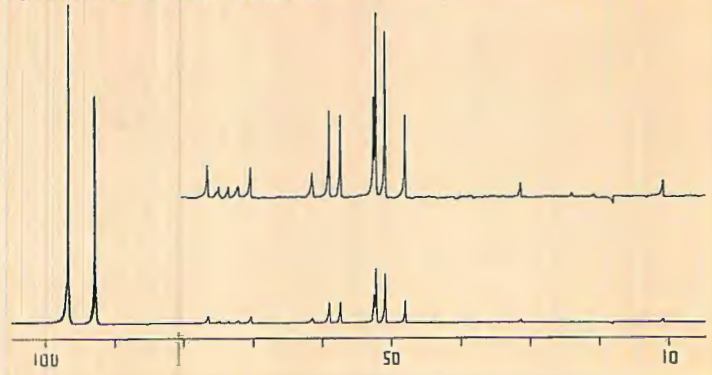


Perfusion of Tissue



Use of a modified 10-mm tube permits the NMR study of intact tissue while perfusing with temperature-controlled nutrient. No hardware modification of the spectrometer is necessary. The stacked plot shows the time course of ATP resonances during tissue perfusion with a nutrient medium and illustrates how tissue preparations can be maintained in a viable state during experiments. Insufficient or poor perfusion causes rapid degradation of the ATP and resultant cell or organism death. The ability to retain viability over many hours permits extensive study of metabolism in metabolic, nutrative, and cell research.

Spectrum of Perfusion Medium



NMR is a valuable tool for following metabolism in isotope labeling experiments. This spectrum is of the perfusion medium taken at the end of an experiment in which the bovine liver flukes (above) were perfused with (1-^{13}C) glucose. A large number of labeled species are formed as the (1-^{13}C) glucose is metabolized. Subsequent analysis of the sample using spectral editing pulse sequences and heteronuclear correlation experiments are essential for assignment of these resonances.

Wesleyan UNIVERSITY

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TEL.: (203) 347-9411

DEPARTMENT OF CHEMISTRY

September 21, 1984

Professor Bernard L. Shapiro
Department of Chemistry
Texas A&M
College Station, Texas 77843

"A few words on TPPI in phase sensitive correleation experiments"

Dear Barry:

A little while ago I became interested in a paper by Marion and Wutrich, BBRC 113, 967 (1983), which showed some of the advantages to be gained by using phase sensitive two-dimensional correlation experiments. After thinking about the approach, I did a couple of experiments and found out that there is an extra twist to time proportional phase incrementation (TPPI) which I had not been aware of. In a TPPI experiment the phase of the first proton 90° pulse in a conventional correlation experiment is increased by 90° in phase with each increment of the evolution time. The net result is allegedly to introduce the F_1 frequencies equal to the chemical shifts of the protons by TPPI. However, the F_1 frequencies introduced by this procedure are not the proton frequencies but rather are given by

$$f_1^{observed} = \frac{SW1}{2} + (SW_1 - SW_2) + f_1^{actual} \quad ; \quad SW1 = \text{spectral width of } F_1$$

Thus, to obtain the proper frequencies one must set SW2=3/2SW1. Marion and Wutrich were certainly aware of this since this is precisely the ratio of SW1 to SW2 that they used but anyone else trying to use the method may not. The reason for the offset is simply due to the precession which occurs during the evolution time and is not a feature of the two-dimensional experiment per se.

Sincerely,

Philip H. Bolton

PHB:lb

TECHNISCHE HOGESCHOOL DELFT
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Bereikbaar met buslijn 60 en 63 (station N.S.-Delft)

Professor B. L. Shapiro
Department of Chemistry
Texas A & M University
COLLEGE STATION TX 77843
U S A

Uw kenmerk	Uw brief van	Ons kenmerk	Datum
		SE.JC/1	26 September 1984

Delft, Lorentzweg 1
Doorkiesnummer (015) 78 6109

Onderwerp

HIGH RESOLUTION IMAGING IN SOLIDS

Dear Barry,

Your ultimatum prompted us to write this letter and to report on the results we got recently on spin imaging.

We found a simple method to remove all line broadening effects in imaging, just by observing the free induction decay signal at a fixed time while the experiment is repeated each time with incremented field gradient in equal steps. Details of the method and results are given in two forthcoming papers (1,2). Reprints will be available soon. With regard to the stepped gradient, this technique is commomly used in imaging of liquids (3), but the crucial aspect of using it to remove line broadenings has not been recognized before.

As an illustration we compare in Fig.1 the conventional method (Fig.1b) with our method (Fig.1c). In Fig.1b the images of the two tubes of adamantane are not resolved. In Fig. 1c the images of the two tubes are well-resolved. We thus obtained high resolution imaging in solids.

1. S. Emid, Physica B (in press).
2. S. Emid and J. H. N. Creyghton, Physica B (in press).
3. A. Kumar, D. Welti and R. R. Ernst, J. Magn. Reson. 18 (1975) 69.

Yours sincerely,

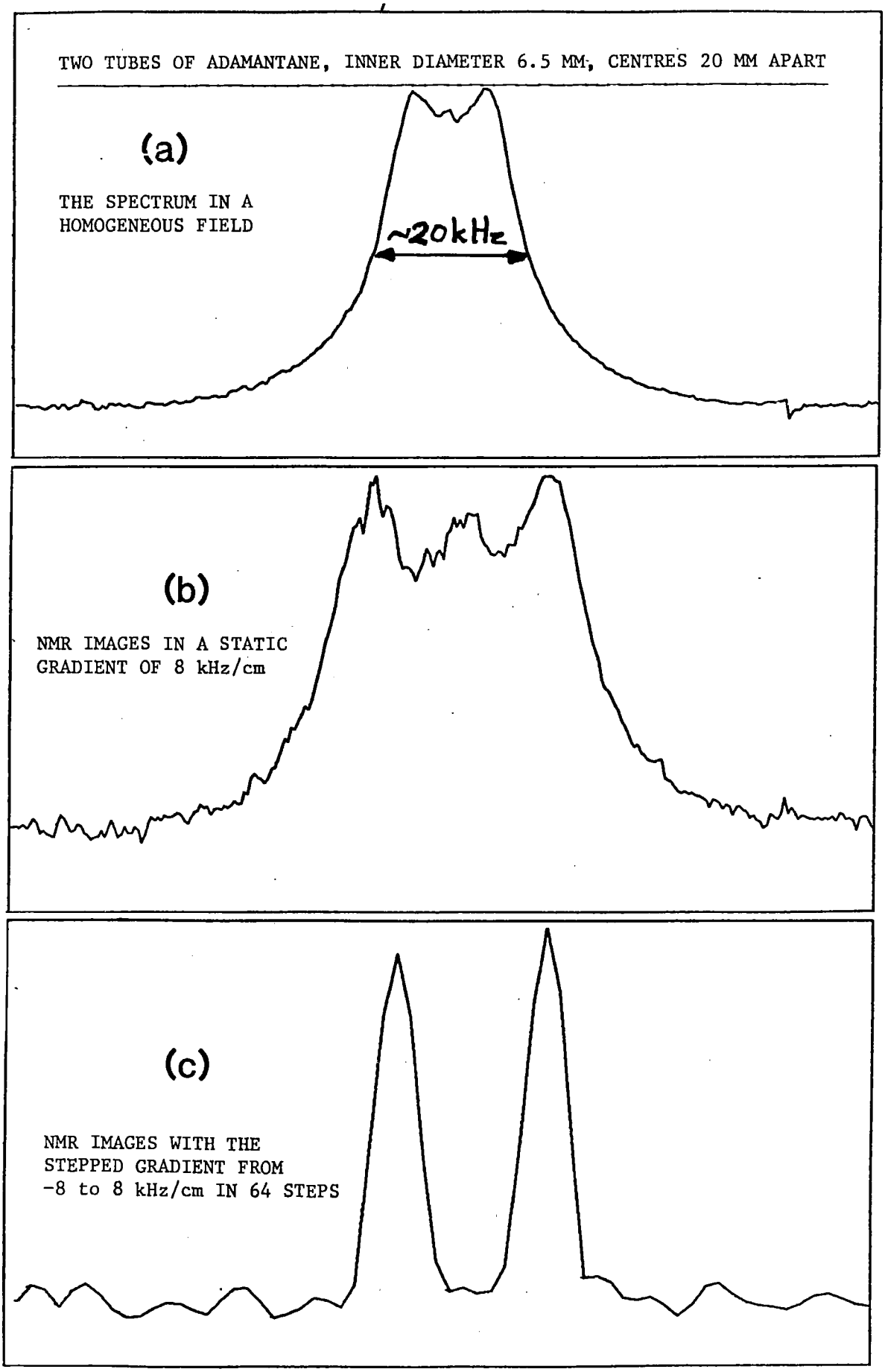
Dr. S. Emid Ir. J. H. N. Creyghton

Algemeen telefoonnummer T.H. (015) 789111
Correspondentieadres: Postbus 5046, 2600 GA Delft

812340

P.S.Please credit this contribution to the subscription of Prof. Smidt.
We hope this letter will arrive in time.

Fig.1 / S. Emid and J.H.N. Creyghton



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Professor Bernard L. Shapiro,
Department of Chemistry,
Texas A & M University,
COLLEGE STATION,
Texas 77843,
USA.

10th September 1984.

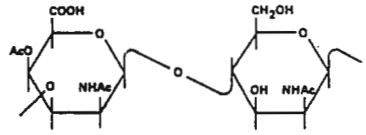
Dear Professor Shapiro,

STRUCTURES OF BACTERIAL POLYSACCHARIDES

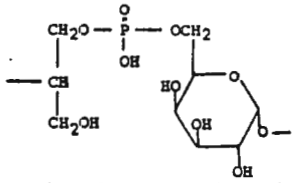
For the past couple of years we have been applying NMR spectroscopy, mainly using our WM-360, to the structuring of polysaccharides from the capsules of Gram-negative bacteria. In collaboration with Dr. Chris Adlam, a bacteriologist colleague, we have concentrated on Pasteurella haemolytica as an organism which causes pneumonia and septicaemia in sheep and cattle. This organism against which we are developing a vaccine exists as two biotypes known as A and T, with several serotypes in each.

Using principally NMR but backed up by other analytical techniques, we have elucidated the structures of the polysaccharides from five serotypes. All have fairly simple repeating units, some of them containing phosphate diester linking groups. Rather than rely solely on the use of degradation techniques for determining the sugar linkage positions we have managed using such techniques as ^{1}H-^{1}H COSY and ^{13}C-^{1}H 2D correlation to largely assign many of the resonances and through the use of chemical shifts, ^{1}H-^{1}H, ^{1}H-^{31}P and ^{13}C-^{31}P couplings to determine the structures, including positions of O-acetylation.

As examples, the A1 serotype polysaccharide has the repeating unit



but the T4 polysaccharide is quite different, in this case containing galactose, glycerol and phosphate, with non-stoichiometric O-acetylation.



These substances form the basis for publications accepted by the J.Gen.Microbiology in which the structures, their immunology and bacteriology are discussed.

Yours sincerely,

J.C. LINDON J.M. WILLIAMS
Department of Physical Chemistry

FACULTÉ DES SCIENCES
Université de Nantes · U E R DE CHIMIE

CHIMIE ORGANIQUE PHYSIQUE
E.R.A. nº 315 · C.N.R.S.

NANTES, le 20 Septembre 1984

Prof. B.L. SHAPIRO
Department of Chemistry
Texas A.E M. University
College Station
Texas 77843 U.S.A.

KETO-ENOL EQUILIBRIUM - ^{15}N STUDY

Dear Prof. Shapiro,

We have studied by ^{15}N NMR the rotation around the C-N bond for several amides. The introduction in the β-position of a second carbonyl group allows the detection of a keto-enol equilibrium and induces a variation of the rotational barrier of the amide function. The attribution of the two ^{15}N NMR lines observed for compound 1 was achieved by comparison with the values for compounds 3 and 4 (1), where the enol function is very disadvantaged.

$(Et)_2N - CO - CH_2 - CO - CH_3$ ⇄	1	250,9 ppm/CH_3NO_2
$(Et)_2N - CO - CH = C(OH) - CH_3$ ⇄	2	259,3
$(Et)_2N - CO - CH_2 - COOEt$	3	251,5
$(CH_3)_2N - CO - CH_2 - CO - N(CH_3)_2$	4	278,2

The 250,9 ppm value, comparable to the ^{15}N NMR chemical shift observed for compound 3, is assigned to the β-diketone form 1. Compound 4 leads to the same conclusion, if we consider the substituent effect (28,4 ppm between $N(CH_3)_2$ and $N(Et)_2$ for the amides) (1).
Furthermore the detection of an allylic coupling constant between CH_3 and the ethylenic proton shows the existence of form 2, assigned at 259,3 ppm by ^{15}N NMR. This form would have a lower rotational barrier around the C-N bond than form 1 (2). This consideration is confirmed by a ^1H NMR study.

Sincerely yours.

J. DORIE B. MECHIN J.P. GOUESNARD

References

(1) G.J. Martin, M.L. Martin and J.P. Gouesnard, ^{15}N-NMR spectroscopy, Springer-Verlag, Berlin, 1981.
(2) G.J. Martin, J.P. Gouesnard, J. Dorie, C. Rabiller and M.L. Martin, J. Amer. Chem. Soc, 99, 1381, 1977.

P.S. Please Credit this contribution to Prof. G. MARTIN account.

CHEMICAL CENTER
UNIVERSITY OF LUND
PHYSICAL CHEMISTRY 2

Lund, September 26, 1984

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

Dear Dr. Shapiro,

Shift reagents enhance resolution in ^{43}Ca NMR spectra

Various ^{43}Ca NMR studies of a variety of small calcium-binding proteins (MW < 25000) have demonstrated that it is feasible to observe slowly exchanging $^{43}Ca^{2+}$-ions bound to these proteins (1). Despite the fact that the chemical shift range measured for a series of low molecular weight Ca^{2+}-chelating agents is almost 80 ppm (2), we have found that the range for protein-bound $^{43}Ca^{2+}$ does not exceed 20 ppm (1). This situation gives rise to practical problems, since the protein-bound resonances are often broad (300 - 1000 Hz) and they overlap with those of free Ca^{2+} or Ca^{2+} in fast exchange with weak binding sites on the surface of these proteins. Although such spectra can in principle be resolved with the help of spectral simulation programs, we have found that different combinations of Lorentzians lead to equal fits in many instances. Hence, we felt the need to look for a method which would artificially increase the resolution in our spectra. To this end we decided to test the anionic shift reagents that have recently become popular through the *in vivo* ^{23}Na NMR work of the groups of C. Springer and R. Gupta. We have found that upfield and downfield shifts of -120 to 60 ppm can be obtained using these agents and standard calcium solutions. Figure 1 shows that these shift reagents are indeed successful at improving the resolution in ^{43}Ca NMR spectra of calcium-binding proteins. Fast exchanging Ca^{2+} ions are shifted, while tightly-bound slow exchanging resonances are not affected. The details of this method, as well as its application to the study of different calcium-binding proteins will be reported (3,4). It is conceivable that the same methodology could be useful in the study of other slowly exchanging quadrupolar nuclei with small chemical shift ranges.

Please credit this contribution to the subscription of Sture Forsén.

Yours sincerely,

HJVogel

Hans J. Vogel William H. Braunlin

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REFERENCES

1. Vogel, H.J., Drakenberg, T. and Forsén, S. (1983). In "NMR of newly accessible nuclei" (P. Laszlo Ed.) Vol. I, Academic Press, New York, 157-192.

2. Drakenberg, T. and Forsén, S. (1983). In "The multinuclear approach to NMR spectroscopy". (J. Lambert and F. Riddell, Eds.), Reidel Publ. Comp., Dordrecht, Holland, 309-329.

3. Vogel, H.J., Andersson, T., Braunlin, W.H., Drakenberg, T. and Forsén, S. (1984). Biochem. Biophys. Res. Comm. 122, 1350-1356.

4. Vogel, H.J. and Braunlin, W.H. (1985). J. Magn. Reson. (in press).

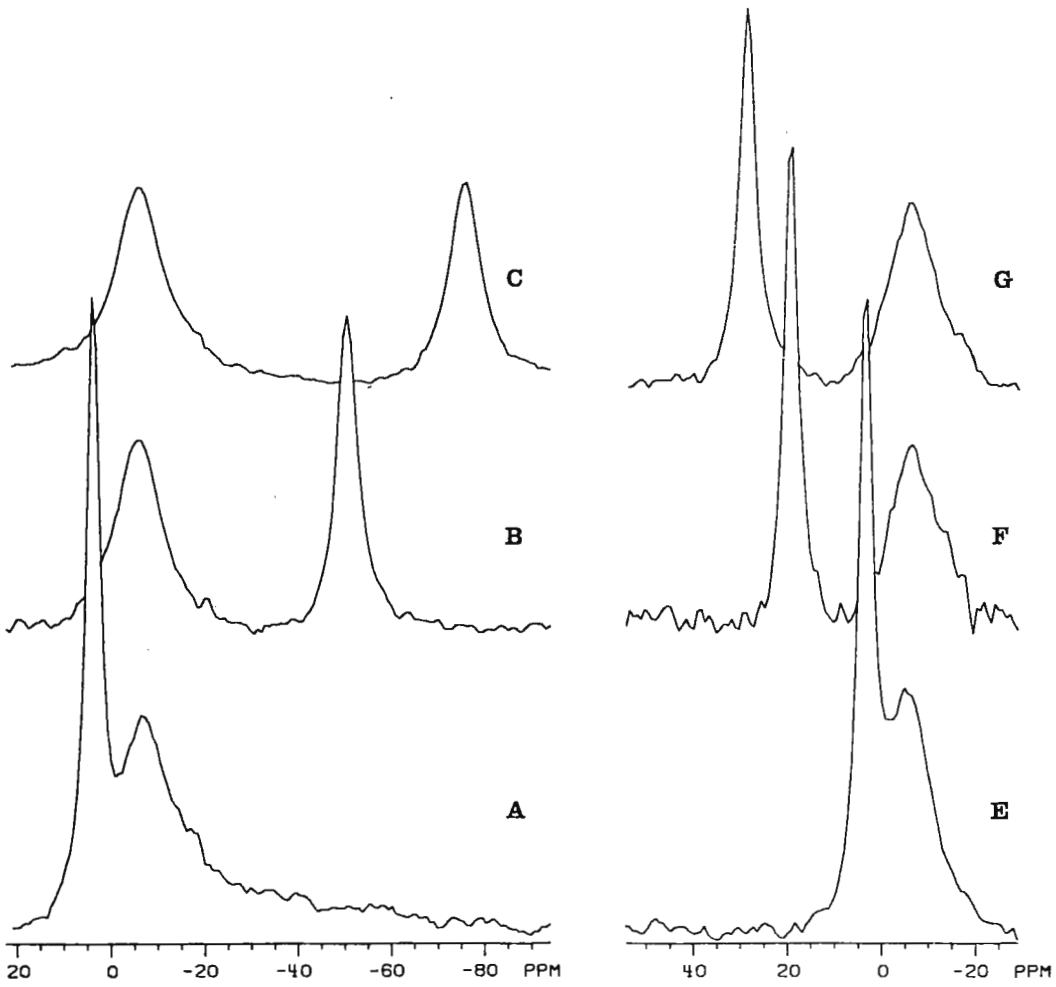

Fig. 1. 24.3 MHz NMR spectra of $^{43}Ca^{2+}$ (60 % isotopically enriched) bound to the bovine milk protein α-lactalbumin. This protein comprises one strong $^{43}Ca^{2+}$-binding site ($K_d \sim 10^{-8}M$), which gives rise to the ~ 300 Hz broad resonance at -6 ppm, and several weak Ca^{2+}-binding sites ($K_d \sim 10^{-3}M$) which give rise to the fast exchanging resonance at +3 ppm. (See Fig. 1A and 1E). Addition of different amounts of the upfield shifting shift reagent $Dy(PPP)_2^{7-}$ gives rise to spectra B and C. Addition of different amounts of the downfield shifting shift reagent $Dy(TTHA)^{3-}$ gives rise to spectra F and G.

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DEPARTMENT OF CHEMISTRY
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84.09.25

Prof. B. L. Shapiro
Department of Chemistry
Texas A & M University
College Station, TX 77843-3255

Dear Barry:

Methods have existed for several years to determine equilibrium constants and bound shifts resulting from the following NMR fast-exchange system:

$$A + B \leftrightharpoons AB$$

$$AB + B \leftrightharpoons AB_2$$

If we observe the shift behavior of molecule B, we can express the observed incremental shift as

$$\Delta\delta_{ij} = \alpha_i \Delta_{1j} + \beta_i \Delta_{2j}$$

where j is the shift index (for $\underline{s}$ total shifts) and i is a concentration index ($\underline{n}$ total concentrations). α_i and β_i are the bound fractions of the AB and AB_2 species and Δ_{1j} and Δ_{2j} are the bound shifts for nucleus j of these respective complexes.

The system is characterized in total by 2 equilibrium constants and by $2\underline{s}$ bound shifts. The best values for these parameters are found by minimizing the quantity

$$Q = \sum_{i=1}^{n} \left[\sum_{j=1}^{s} (\Delta\delta_{ij} - \alpha_i \Delta_{1j} - \beta_i \Delta_{2j})^2 \right]$$

Getting the best values of these various parameters is easily accomplished by any of a number of readily available computer programs. However, what is not generally known is the uncertainties of the parameters obtained. In this short note, we look at one such set of uncertainties, namely that for the bound shifts.

If we let

$$S_{\alpha\alpha} = \sum_{i=1}^{n} \alpha_i^2, \quad S_{\alpha\beta} = \sum_{i=1}^{n} \alpha_i\beta_i, \text{ etc.},$$

then, through a rather intricate argument, the uncertainties in the bound shifts can be easily derived. What is interesting here is that all the uncertainties for the Δ_1-values are equal to each other; this is true also for the Δ_2-values. That is, in a statistical analysis involving fits to multiple nuclei (such as with applications using LSR's), all bound shifts for a given complex (AB or AB_2) are the <u>same</u> in absolute uncertainty. Without further ado, we give the final result:

First, let the sample variance be

$$s_\epsilon^2 = Q/[(n - 2)s - 2]$$

then, if we let

$$D = S_{\alpha\alpha}S_{\beta\beta} - S_{\alpha\beta}^2$$

then the variances in Δ_1 and Δ_2 are given, respectively, by

$$s_1^2 = s_\epsilon^2 S_{\beta\beta}/D$$

and

$$s_2^2 = s_\epsilon^2 S_{\alpha\alpha}/D$$

These short formulas allow a rapid assessment of how good bound shifts are for a given set of data and allows one a more accurate estimate of how well such derived quantities may be applied to determining molecular structures.

Sincerely yours,

Milton D. Johnston, Jr.
Associate Professor

Suggested Title: Uncertainties in Bound Shifts

313-47

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Carnegie-Mellon University

Department of Chemistry
4400 Fifth Avenue
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September 24, 1984

Dr. B. L. Shapiro
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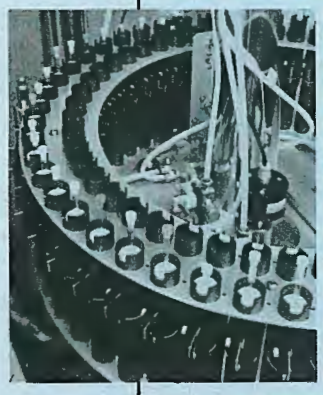

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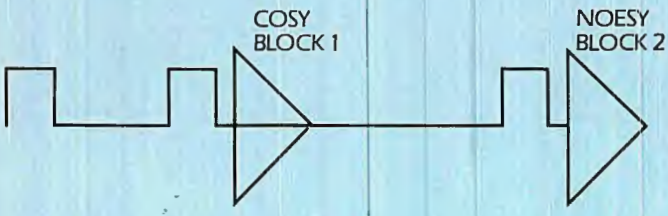
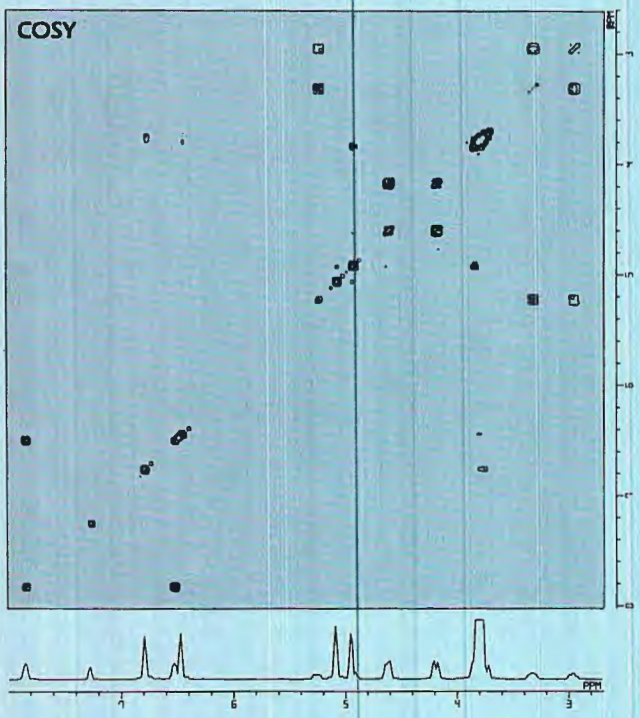
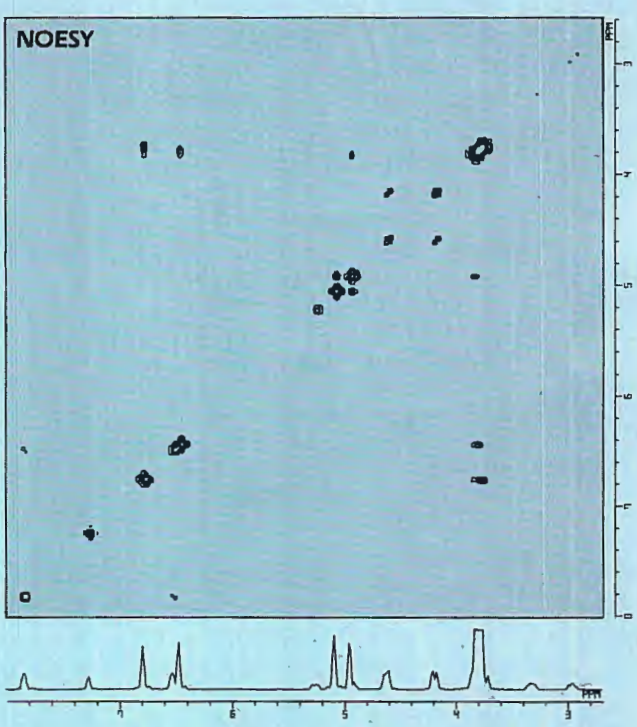


- Simultaneous acquisition of COSY and NOESY





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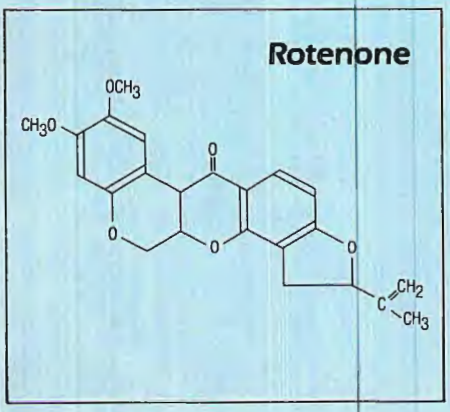
*COCONOSY (Haasnoot, et. al., J. Magn. Reson., 56,343 [1984])



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