THE NMR NEWSLETTER

No. 484

January 1999

NUTS

SEE US AT ENC
SALON 10

NEW! Math functions for automated analysis

Macros can measure integrals and calculate results such as

- weight %
- mole fraction
- impurity levels

Totally automated!

The new macro commands function as an RPN-type calculator, with

- multiple memory locations
- add, subtract, multiply, divide, reciprocal, exponential, log
- 10-entry "stack"

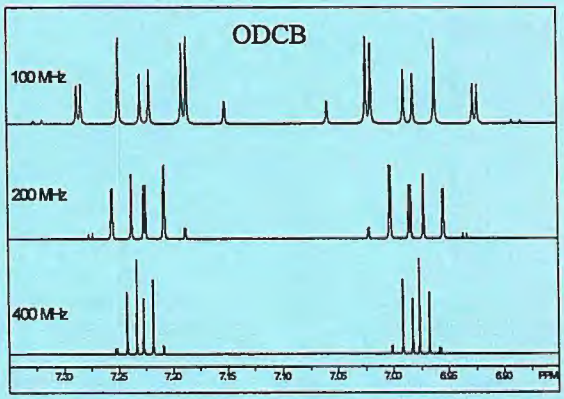
Other macro commands have been added to:

- prompt for user input at runtime
- automatically measure integrals of preset regions
- output calculated values as text annotation on the spectrum

NEW! Buffers for displaying multiple spectra

Spectra displayed on the same ppm scale
*even with **unequal***

- number of data points
- spectrometer frequency
- sweep width



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FORTHCOMING NMR MEETINGS

NMR Spectroscopy of Polymers, Breckenridge, Colorado, **January 24-27, 1999**; an International Symposium Sponsored by the Division of Polymer Chemistry, American Chemical Society; Organizers: P. T. Inglefield and A. D. English: Registration contact: Neta L. Byerly, Division of Polymer Chemistry, Inc., Virginia Tech, 201 Hancock Hall, M.C. 0257, Blacksburg, VA 24061; 540-231-3029; Fax: 540-231-9452; email: nbyerly@vt.edu.

7th Annual "Advances in NMR Applications" Symposium, Omni Rosen Hotel, Orlando, Florida, **February 28, 1999;** Contact: Kathy Bishop, at the Nalorac Corp.; 510-229-3501; kathy.bishop@nalorac.com; See Newsletter 484, 30.

40th ENC (Experimental NMR Conference), Clarion Plaza Hotel, Orlando, Florida, **February 28 - March 5, 1999**, immediately preceding Pittcon in Orlando; Contact: ENC, 1201 Don Diego Avenue, Santa Fe, NM 87505; (505) 989-4573; Fax: (505) 989-1073; Email: enc@enc-conference.org.

Pittcon '99, Orlando, FL, **March 7-12, 1999** (50th year celebration of the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy.) Contact: The Pittsburgh Conference, Dept. CFP, 300 Penn Center Blvd., Suite 332, Pittsburgh, PA 15235-5503; 412-825-3220; Fax: 412-825-3224; e-mail: pittconinfo@pittcon.org:

Spin Choreography - a symposium in appreciation of Ray Freeman, Cambridge, England, **April 8-11, 1999**; web site: http://mchsg4.ch.man.ac.uk/mcmr/RF.html; fax: c/o M.H.Levitt +46-8-15 2187; email: mhl@physc.su.se.

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

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

continued on p. 18

Carlsberg Laboratory

Danish Instrument Center for NMR Spectroscopy of Biological Macromolecules

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

December 11, 1998
(received 12/18/98)

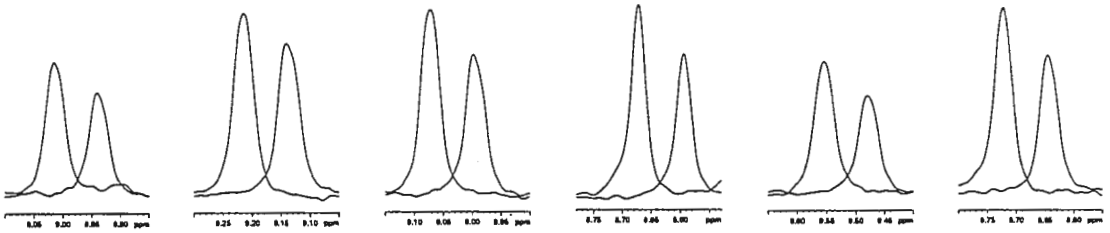
Superimposing TROSY and anti-TROSY

Dear Barry:

A subject of great current interest in the biomolecular NMR community is TROSY introduced by Pervushin et al. (PNAS **94**, 12366 (1997)). Here at Carlsberg we have been working on different ideas around TROSY. A paper with a new pulse sequence doing the same as earlier versions but with improved pulse economy is due to appear very soon in a Richard Ernst honory issue of Molecular Physics. Something else that intrigued us right from the beginning is that TROSY does a fine job of selecting the peak of highest intensity but it also eliminates the rest of the cross peak components. That leads to the thought that it might be possible to put the eliminated coherence or spin order to good use.

What it amounts to is finding a way of suppressing heteronuclear one-bond coupling constants in indirect dimensions of multidimensional experiments. In other words, the low-frequency component must be shifted by $|J|/2$ while the high-frequency component must be shifted by $-|J|/2$. That is possible using the novel technique of TIG-BIRD (JMR **135**, 44 (1998)) that allows arbitrary and independent manipulations of the two magnetizations of a doublet. Hence the solution is Spin-State-Selective Time-Proportional Phase Incrementation (S^3 TPPI), i.e. to apply different TPPIs on the two components so as to achieve the desired shifts in frequency. This is what we have been working on most recently in a joint project with Jacques Briand.

We want to share with you some preliminary results of comparing TROSY with a new experiment combining TIG-BIRD with the standard gradient version of HSQC. Currently, the comparison between S^3 TPPI HSQC and HSQC is not satisfactory. The results are obtained on a Bruker DRX 600 MHz spectrometer using a protein of MW about 20 kDa (NCAM modules 1 and 2, courtesy of Flemming M. Poulsen). F_2 sections from the ^{15}N-^{1}H TROSY spectrum are to the right and the corresponding ones from the S^3 TPPI HSQC spectrum (TROSY and anti-TROSY peaks superimposed) to the left.



Sincerely yours,

Ole W. Sørensen — Axel Meissner — Thomas Schulte-Herbrüggen

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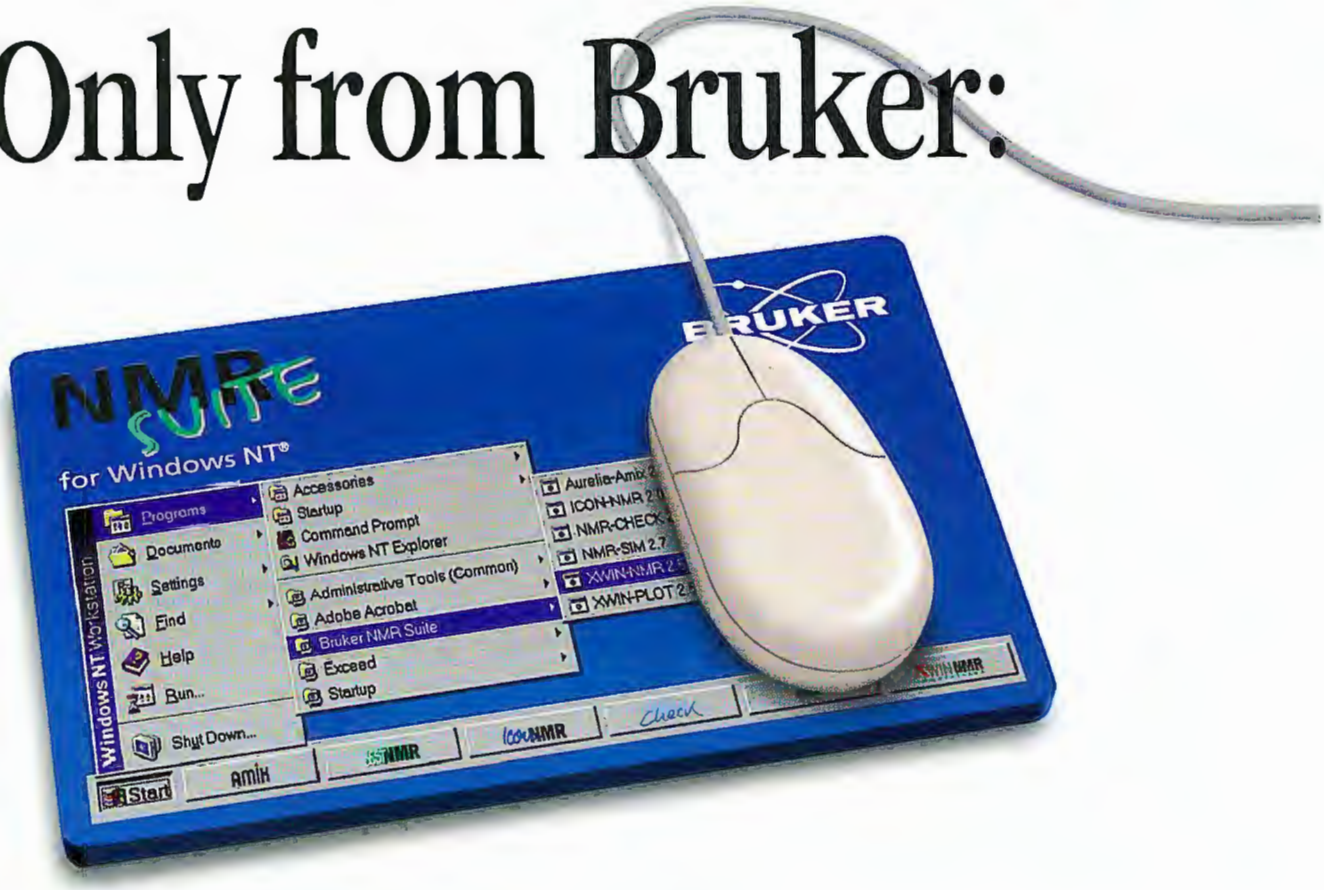

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NMR-Sim (numerical simulation of NMR spectra)

NMR-Check (diagnostic software).

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Q: Can NMR Suite for Windows NT control the spectrometer?

A: Yes! NMR Suite for Windows NT running on a PC has full control of the spectrometer and also does the data processing and data manipulation.

Q: Can I import spectra generated in NMR Suite for Windows NT into Windows programs such as MS Word or MS PowerPoint?

A: Yes! Our programs can write the plots into the Windows Clipboard or into a Windows Enhanced Metafile. From there the files can be imported into Word, PowerPoint and other Windows programs.

Q: Does NMR Suite for Windows NT replace NMR Suite running on the Silicon Graphics computers?

A: No! Bruker continues to support the SGI/IRIX platform. NMR Suite for Windows NT is an option, and the choice is yours!

Q: Is special hardware required for the PC to control the spectrometer?

A: No! The PC is connected to the spectrometer by a standard ETHERNET card. We require a second ETHERNET card to connect the PC to the INTERNET/INTRANET.

Q: Is NMR Suite for Windows NT "Year 2000 compliant"?

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- 3 button mouse for PS/2 port
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18th December 1998 (received 12/18/98)

Dear Barry,

Diffusion and peptide proton exchange

The work outlined here follows an idea from John Lindon. We have recently used ^1H diffusion experiments to monitor peptide proton (N*H*) exchange in the cyclic peptide viomycin (see below). The experiment used was the 1-D longitudinal eddy-current delay (LED) modification[1] of the pulse field gradient spin-echo experiment[2], incorporating WATERGATE[3] and bipolar gradients[4] to further reduce the eddy-currents. For non-exchanging protons the signal intensity follows a single exponential[5]:

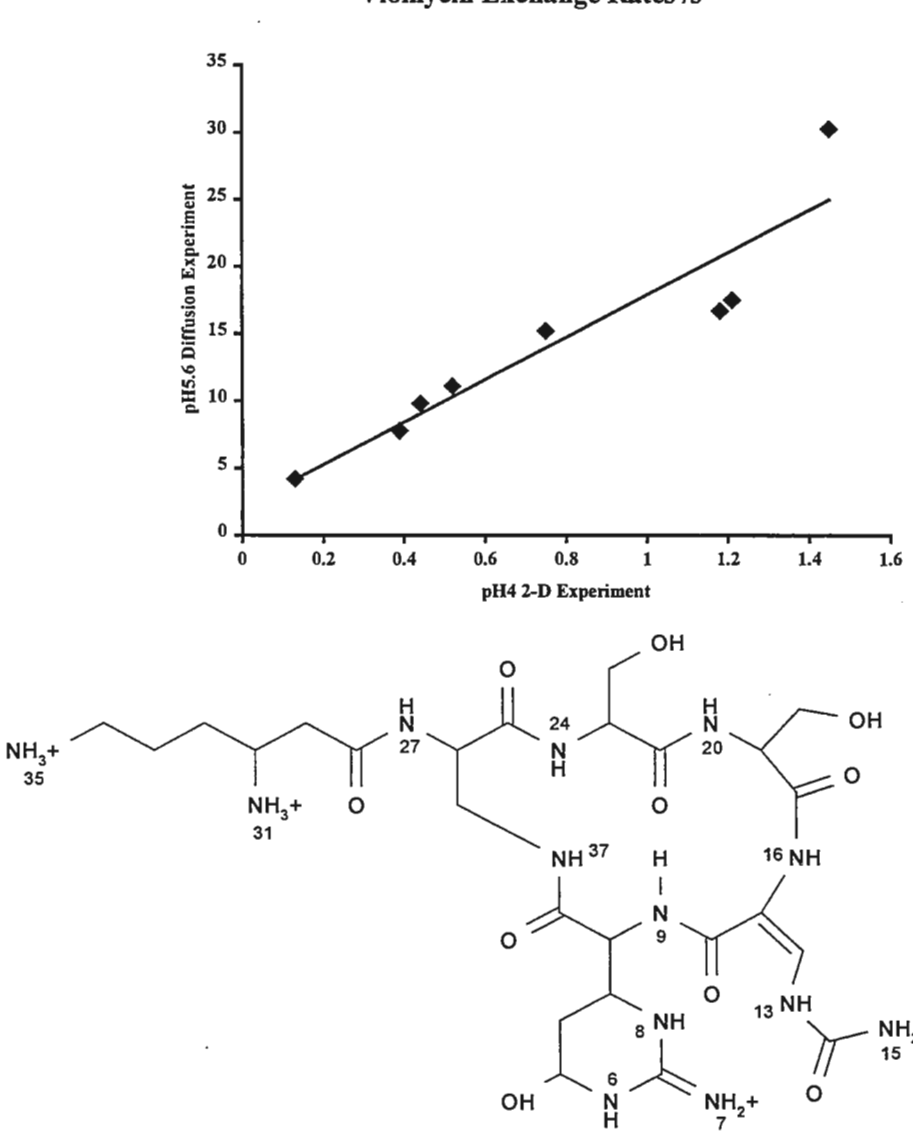
$$I_i = I_{0i} \exp(-K^2 D \Delta)$$

where $K = \gamma G \delta$; γ is the gyromagnetoc ratio, G and δ are the strength and duration of the gradient, D is the diffusion coefficient and Δ is the diffusion period. For intermediate rates of exchange - when the residence time (t_p) of the labile proton on the peptide is less than, but not a lot less than Δ, the signal intensity follows a more complicated function, and following Moonen *et al.*[6] we derived:

$$I_i = I(E)_{0i} \exp\{[-K^2(D_w f_w + D_p f_p)\Delta]\} + I(N)_{0i} \exp\{-K^2 D_p \Delta\}$$

where I(E) and I(N) are constants, f_p and f_w are the fractions of the diffusion period that the proton spends on the peptide and water respectively ($f_w = 1 - f_p$) and D_w and D_p are the diffusion coefficients of water and the peptide respectively. We determine D_p from the resonances of non-exchanging protons and D_w from a separate experiment without WATERGATE. A double exponential fit of the I_i data for the N*H* protons then gives values for f_p, then $t_p = f_p \Delta$, and the pseudo first order rate coefficient for the exchange may be estimated as t_p^{-1}.

We have tested the validity of the method by comparing the rate coefficients we obtained from this experiment with those obtained[7] some time ago in Chris Dobson's group (see attached graph) using 2-D magnetisation transfer (NOESY). Our measurements were made on a sample at pH = 5.6 while the published data were from a sample at pH = 4.2 - much slower exchange. The correlation is good, but another important feature is that the 'diffusion' method clearly can determine much faster rates than the NOESY (EXCSY) method, which seems to have an upper limit around 5 to 10 s^{-1}.



All credit to John Lindon and Jeremy Nicholson for this, which is now accepted for publication.[8]

Best wishes.

[1] Gibbs and Johnson, (1991), *J. Magn. Reson.*, **93**, 395-402; [2] Stilbs, (1987), *Prog. NMR Spectrosc.*, **19**, 1-45; [3] Piotto *et al.*, (1992), *J. Biomol. NMR*, **2**, 661-665; [4] Wu *et al.*, (1995), *J. Magn. Reson.*, **A115**, 260-264; [5] Stejskal and Tanner, (1965), *J. Chem. Phys.*, **42**, 288-292; [6] Moonen *et al.*, (1992), *J. Magn. Reson.*, **97**, 419-425; [7] Dobson *et al.*, (1986), *J. Magn. Reson.*, **69**, 201-209; [8] Liu *et al.*, *J. Biomol. NMR*, in press.

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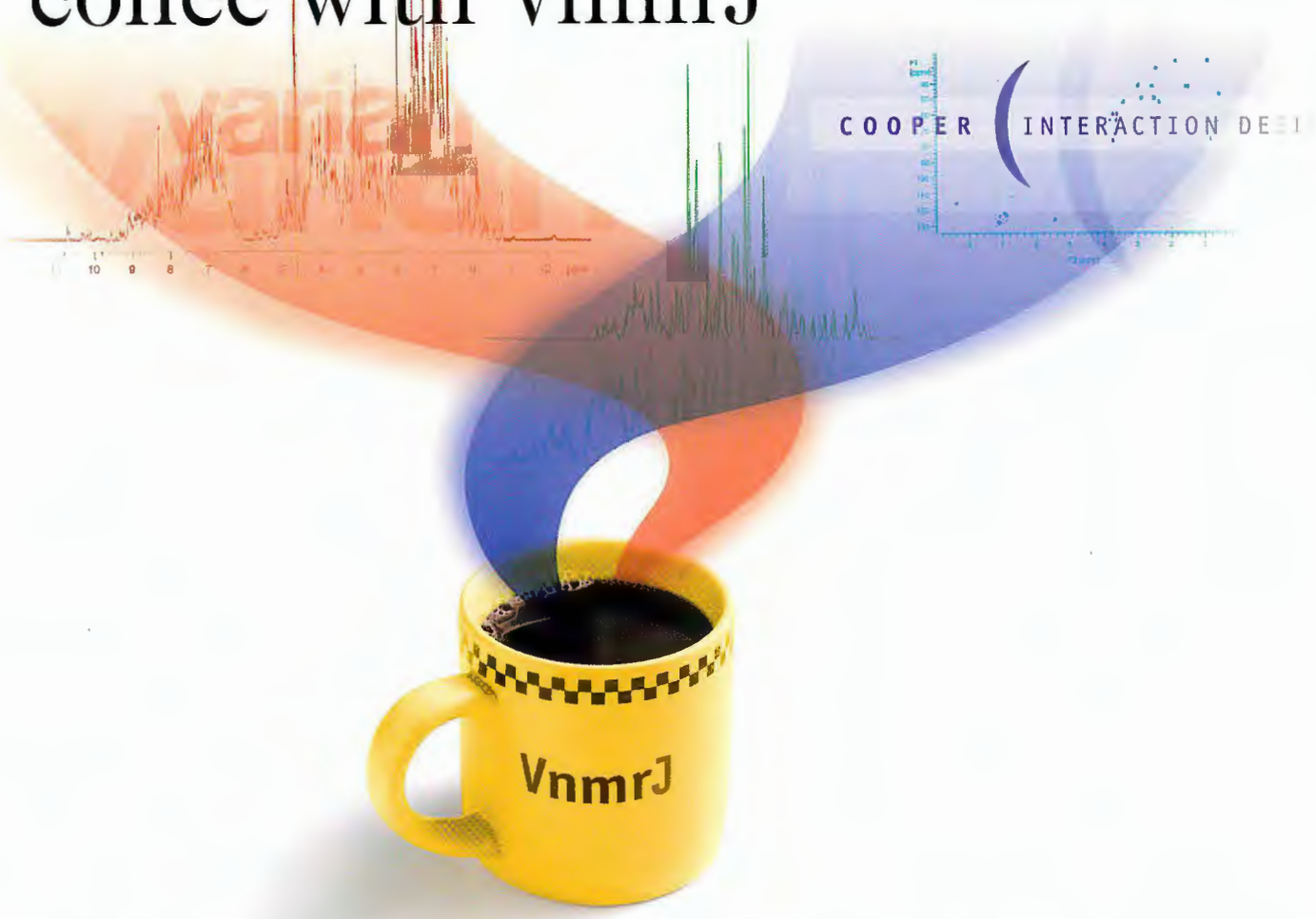

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Professor B.L. Shapiro, Publisher
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December 22, 1998
(received 12/23/98)

TIG-BIRD : Arbitrary and Independent Manipulations of I, IS^{α} and IS^{β} Spin Systems

Dear Barry:

Recently we have described our new pulse sequence element dubbed TIG-BIRD (Triselective Independent Gyrations BIRD) (*J. Magn. Reson.* **135**, 44-49, 1998) for simultaneous and independent rotations with arbitrary flip angles and phases for isolated I, IS^{α} and IS^{β} resonances without the use of selective radiofrequency pulses. TIG-BIRD generalizes earlier pulse sequence elements like BIRD, TANGO, BANGO, and BIG-BIRD, the latter of which allows for arbitrary selection of flip angles and phases for I and IS spin systems without discriminating between IS^{α} and IS^{β} resonances. TIG-BIRD also generalizes the Spin-State-Selective (S^3E) element which can selectively excite only one of the IS^{α} and IS^{β} resonances.

When isolated I spin systems are irrelevant, α,β TIG-BIRD is a four-pulse sequence element, as shown in Figure 1a, for arbitrary and independent manipulations of IS^{α} and IS^{β} resonances. When isolated I spin systems do also need to be considered, the full TIG-BIRD pulse sequence, as shown in Figure 1b is used. The full TIG-BIRD can be considered as a combination of BIG-BIRD and α,β TIG-BIRD. The flip angles and phases of the rf pulses on the proton channel are calculated in such a way that the cumulative effect of the pulse sequence element generates the desired flip angles and phases for I, IS^{α} and IS^{β} resonances:

$$\begin{cases} I & : & (\gamma^I)_{\varphi^I} \\ IS^{\alpha} & : & (\gamma^{\alpha})_{\varphi^{\alpha}} \\ IS^{\beta} & : & (\gamma^{\beta})_{\varphi^{\beta}} \end{cases}$$

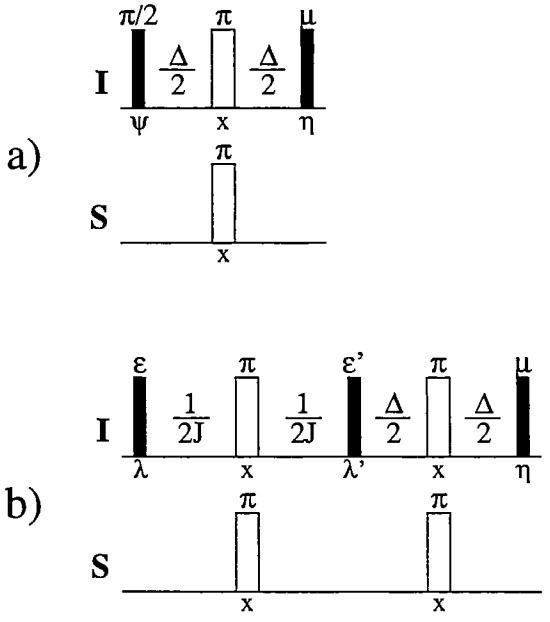


Figure 1

Figure 2 illustrates the enhanced capability obtained with TIG-BIRD in being able to arbitrarily and independently vary the phases and flip angles for the three resonances. A series of one-dimensional spectra was recorded for different combinations of desired flip angles (γ^I, γ^α, γ^β) and phases (φ^I, φ^α, φ^β) for I, IS^α and IS^β resonances, respectively. These spectra were recorded on a sample containing 1% iodomethane with about 60% ^{13}C-labeling in $CDCl_3$. All spectra were phase-corrected with the same zero- and first-order phase corrections and plotted with the same scaling factor.

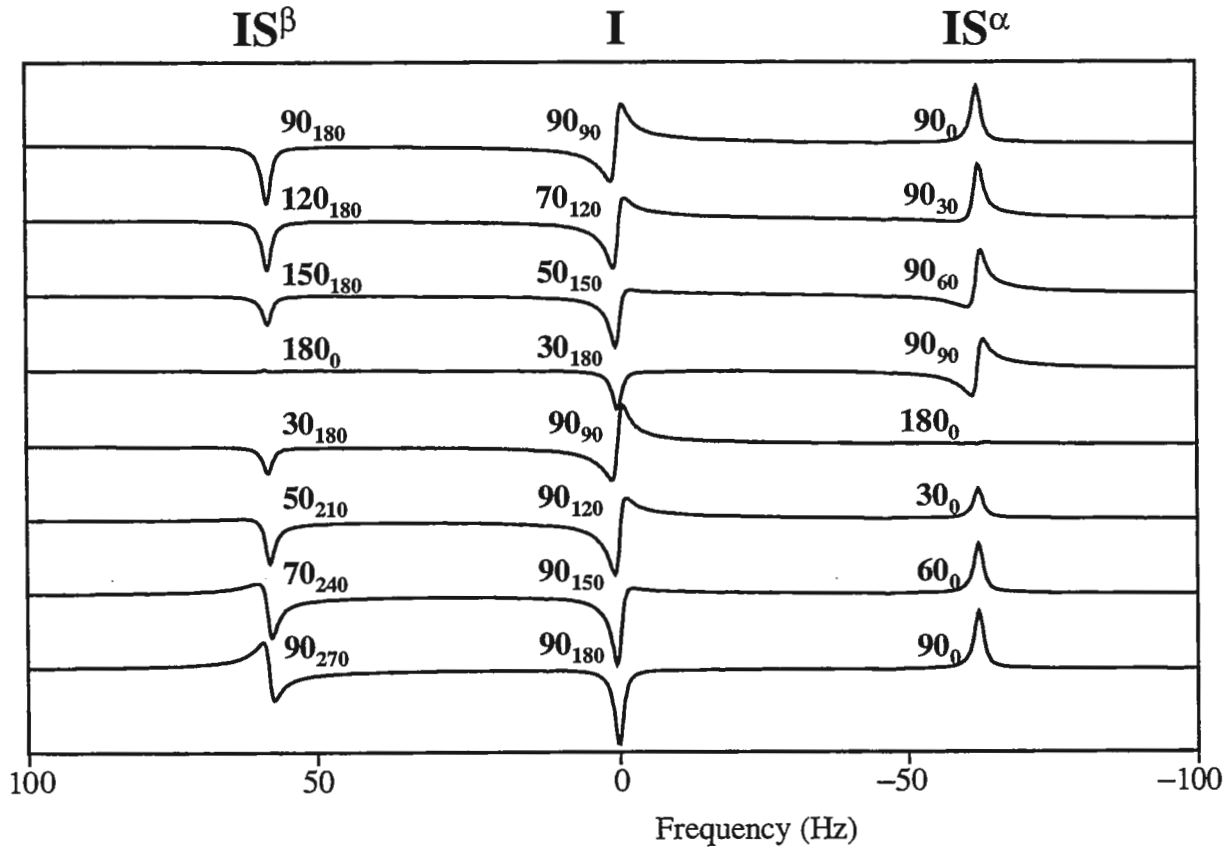
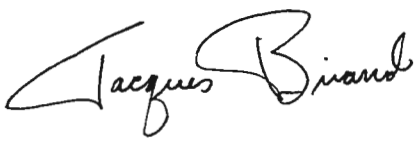


Figure 2

We are currently evaluating applications that could exploit this new feature.

Sincerely yours,



Jacques Briand & Ole W. Sørensen (Carlsberg Laboratory, DK-2500 Valby, Denmark)

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UAMS MEDICAL CENTER

December 17, 1998
(received 12/21/98)

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

Title: ^{19}F NMR of Metabolites of Trifluoperazine in Rat Brain
Also: **NEW PHONE NUMBERS**

Dear Barry:

Fluorine-containing, psychoactive drugs have been studied *in vivo* in both human subjects and animal models using ^{19}F NMR spectroscopy. The drugs, which typically contain a trifluoromethyl group, usually yield a single ^{19}F resonance *in vivo.* However, a psychoactive drug is often metabolized in brain and other tissues to a variety of compounds, which themselves may have therapeutic or toxic activity. It would be valuable to observe these compounds independently *in vivo*. The relatively large line widths encountered *in vivo* usually preclude observation of separate resonances for primary metabolites because their molecular structure is often very similar to the drug itself.

With Sabine Strohschein, Ursula Breyer-Pfaff, and Klaus Albert of the University of Tübingen, Roger M. Hawk of the University of Arkansas at Little Rock, and Craig N. Karson of the Little Rock VA Hospital, we have studied the ^{19}F *in vivo* NMR spectra of the heads of rats given the antipsychotic drug trifluoperazine (TFP). Resonances from unidentified metabolites were observed at about -57 and -75 ppm from CCl_3F in a number of spectra, in addition to the primary peak at about -62 ppm. Tissue extracts were studied to confirm metabolite contributions to the *in vivo* spectra. Contributions to the spectrum from tissues other than brain were shown to be minimal. Although the -57 ppm metabolite was not confirmed in any extract, the resonance at about -75 ppm was confirmed in brain and muscle. Several previously identified TFP metabolites were found to contribute to the primary *in vivo* ^{19}F resonance at about -62 ppm for rat head. The Figure on the next page shows the ^{19}F spectrum from rat brain with some assignments, confirmed by spiking, and the corresponding molecular structures.

We also wanted to alert you to our new phone numbers, which are given above.

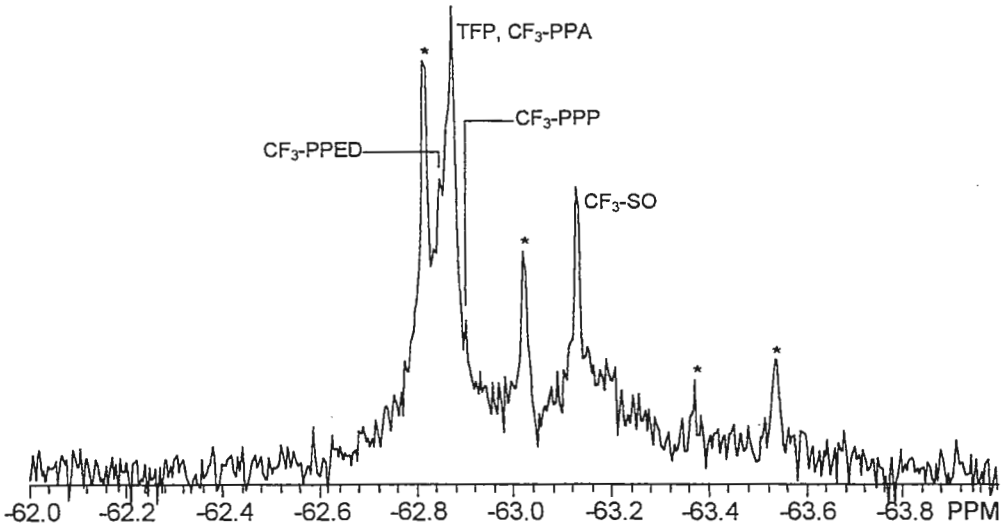
With best regards,

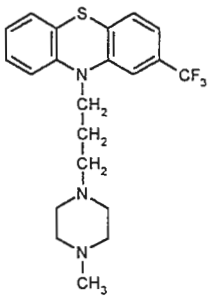
Rich

Richard A. Komoroski

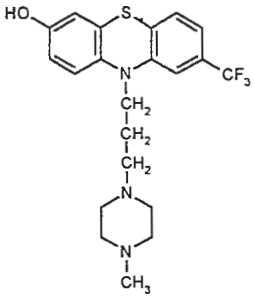
Diana Lindquist

Diana Lindquist

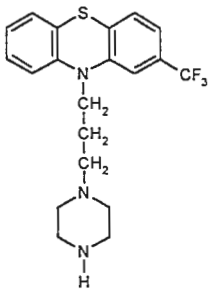




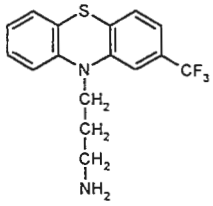
Trifluoperazine
(TFP)



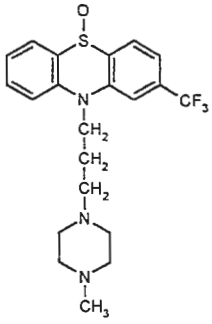
7-Hydroxytrifluoperazine
(CF_3-OH)



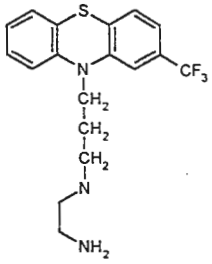
Desmethyltrifluoperazine
(CF_3-PPP)



N-[γ-(2-trifluoromethyl)phenothia-zin-10-yl)-propyl]amine
(CF_3-PPA)

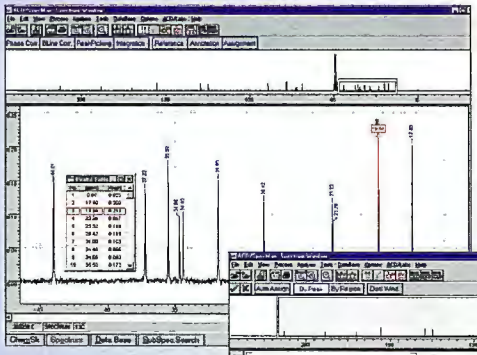


Trifluoperazine sulfoxide
(CF_3-SO)

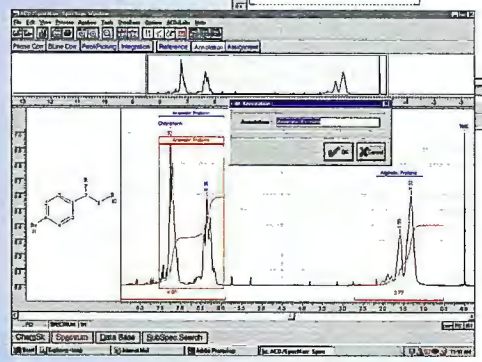


N-[γ-(2-trifluoromethyl)phenothiazin-10-yl)-propyl]ethylenediamine
(CF_3-PPED)

Advanced/NMR Processor



Standard display showing zoom window and peak table



Assign a spectrum by selecting either peak or region—simply select the nucleus and drag towards the peak

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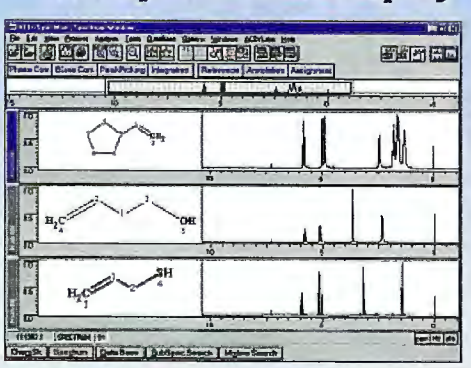
Multiple window display



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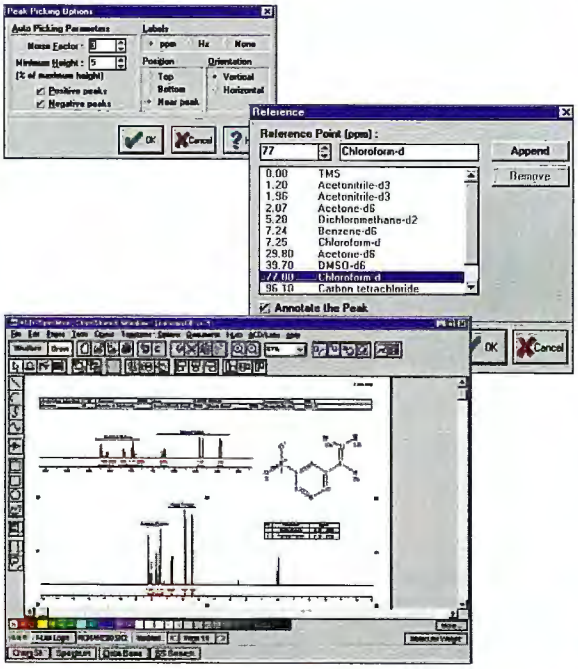

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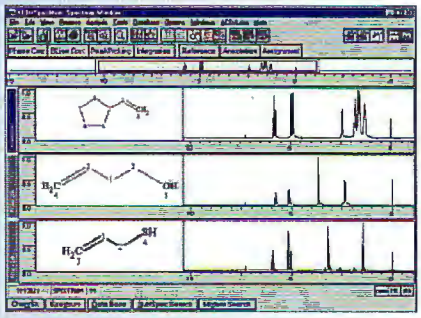

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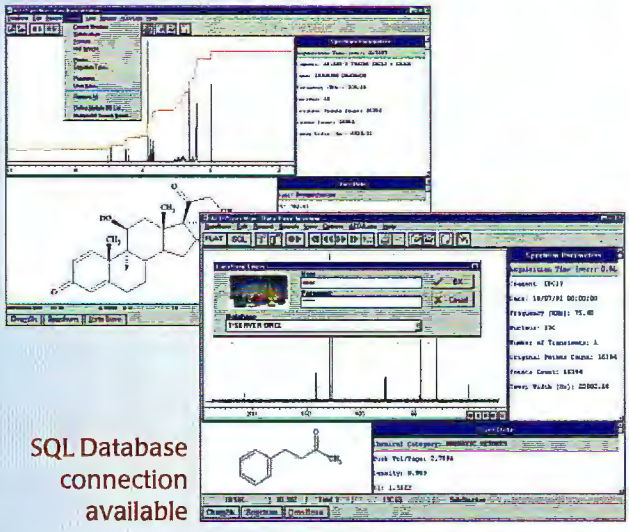

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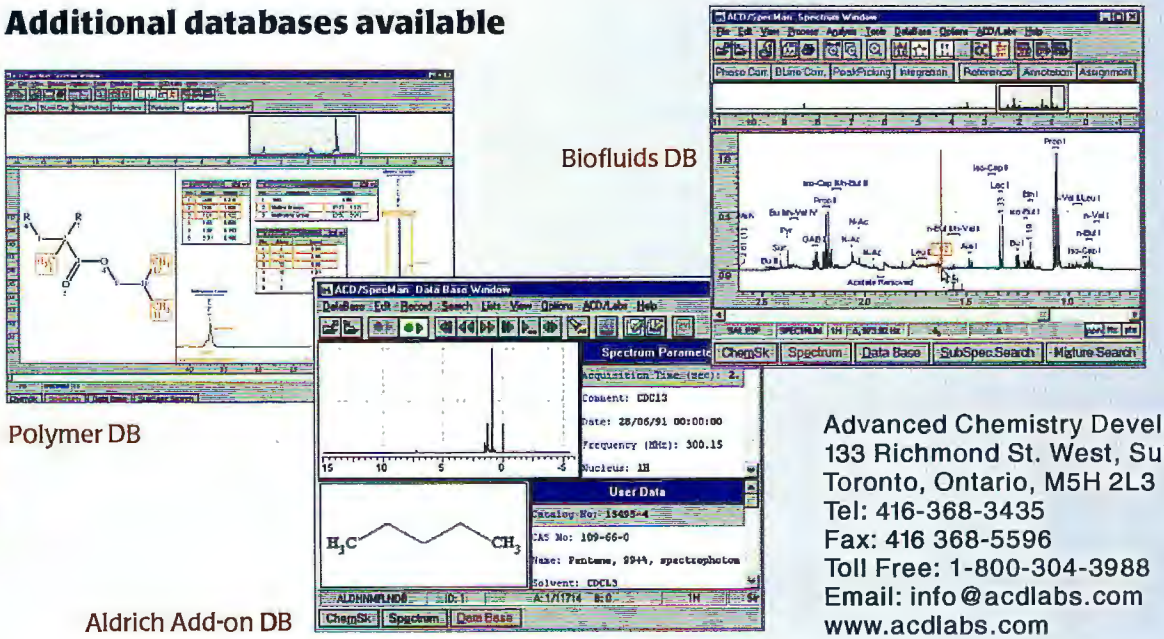

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B.L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

18 December 1998
(received 12/18/98)

"Two Dimension ^{129}Xe NOESY in Polymers"

Dear Barry:

In a continuation of our work using ^{129}Xe NMR to probe polymer morphology we have revived a long time interest in Poly (2, 6 - dimethyl - 1, 4 - phenylene oxide) (PXE) . Depending on the method of preparation highly porous forms of PXE can be prepared. At low temperatures (ca -90° C) two peaks are observed for the ^{129}Xe sorbed in the polymer. These resonances are centered around 180 ppm from the free gas resonance, and can be ascribed to different sorption sites or different pore sizes in the PXE.

2D NOESY shows exchange of the xenon between the two resonances. Exchange is produced by translational diffusion between the two environments; and the exchange process is spread over at least four decades in time indicating a broad distribution of time constants associated with this diffusion based process. The broad distribution of time constants for exchange could arise either from a distribution of length scales or a distribution of local diffusion constants. Note that the exchange starts in the two-dimensional pattern with a broadening in the middle of the shift range and only at very long times and high temperatures is exchange between all environments detected. Remembering that low shift values correspond to lower density regions and high shift values correspond to more dense regions, it appears that exchange begins by movement of the xenon gas between regions of only modestly different densities. This would account for the thickening of the two-dimensional pattern in the mid range of shifts. Exchange between regions of significantly different densities is observed only after long periods of time at high temperature.

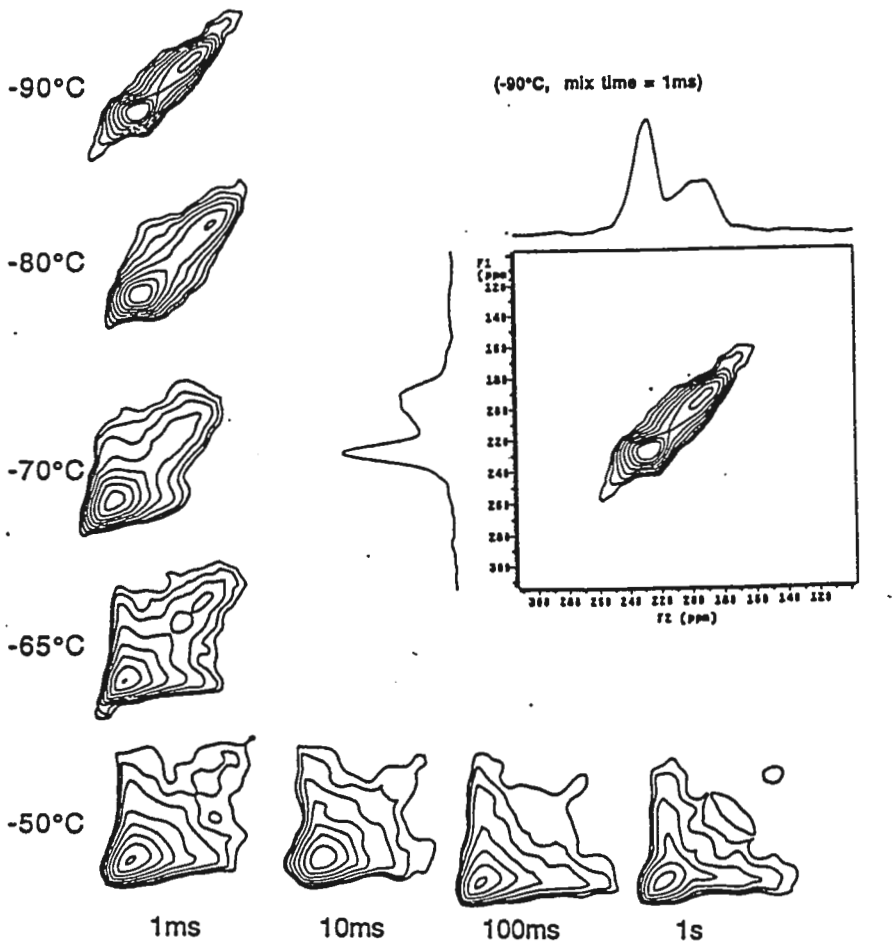
These results argue that there is a spatial pathway where the gas diffuses from a low density region through an intermediate density region and then on to a higher density region. Jumps directly from a high density region to a low density region are not observed. This information is indicative of the kind of insights on local processes available from NMR.

Sincerely,

Paul T. Inglefield

Yingzi Wang

2D ^{129}Xe NOESY as a Function of Temperature and Mix Time



Forthcoming NMR Meetings, continued from page 1:

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

SMASH No. 1 (*S*mall *M*olecules *A*re *S*till *H*ot), Argonne, IL, **August 15-18, 1999**; Contact: Ms. Karen McCune , (mccune_karen_a@lilly.com, 317-276-9783) or S. R. Maple (maple_steven_r@lilly.com) or G.E.Martin (gary.e.martin@am.pnu.com) or A. G. Swanson (alistair_swanson@sandwich.pfizer.com. See Newsletter 484, 29

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

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

Additional listings of meetings, etc., are invited.

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NMR Operating Frequency (MHz¹H)	200			300				400		500	
Field Strength (Tesla)	4.7			7.0				9.4		11.7	
Nominal Room Temperature Bore Access (mm)	54		89	54		89	150	54	89	51	89
Magnet Type (Standard or shielded)	Standard		Standard	Standard		Standard	Standard	Actively Shielded	Actively Shielded	Actively Shielded	Actively Shielded
Field Stability (Hz/hour ¹H)	<2		<2	<3		<3	<15	<8	<10	<10	<10
Axial 5 Gauss Stray Field Contour (Metres)	1.81		2.65	2.19		2.75	4.2	1.5	1.8	1.8	2.5
Radial 5 Gauss Stray Field Contour (Metres)	1.42		2.0	1.7		2.2	3.3	1.0	1.3	1.3	1.75
Cryostat Type	Compact	T3	T3	Compact	T3	T3	T5	T3	T4FB	T4FB	T5FB
Minimum Helium Refill Interval (Days)	80	235	203	80	235	203	120	183	150	150	140
Helium Refill Volume (Litres)	26	79	68	26	79	68	101	62	83	83	120
Year Hold Cryostat Option Available	X	✓	✓	X	✓	✓	X	X	X	X	X
Nitrogen Refill Interval (Days)	14	14	14	14	14	14	22	14	15	15	14
Minimum Nitrogen Refill Volume (Litres)	32	61	61	32	61	61	135	61	81	81	136
* Minimum Operational Ceiling Height (Metres)	2.69	2.92	.2.92	2.69	2.92	2.92	4.16	2.9	3.1	3.1	3.16
System Weight (kg) Including Cryogen's	120	315	391	133	325	399	1050	400	610	625	1200

NMR Operating Frequency (MHz1H)	600		750	800		900	
Field Strength (Tesla)	14.0		17.6	18.8		21.1	
Nominal Room Temperature Bore Access (mm)	51	89	51	63		63	
Magnet Type (Standard or shielded)	Actively Shielded	Standard	Standard	Standard	(2.2K) Pumped	(2.2K) Pumped Standard	(2.2K) Pumped With Iron Shield
Field Stability (Hz/hour ¹H)	<10	<12	<15	<15	<15	<15	<15
Axial 5 Gauss Stray Field Contour (Metres)	2.5	5.0	7.6	8.69	6.3	12.2	8.73
Radial 5 Gauss Stray Field Contour (Metres)	1.75	3.9	6.1	6.89	5.0	9.7	3.81
Cryostat Type	T5FB	T4FBL	T6	T6L	T7	T8	
Minimum Helium Refill Interval (Days)	120	90	60	60	60	60	
Cryostat Helium Refill Volume (Litres)	101	60	187	216	328	1200	
Minimum Nitrogen Refill Interval (Days)	15	15	14	14	14	15	
Nitrogen Refill Volume (Litres)	136	100	137	162	167	1800	
* Minimum Operational Ceiling Height (Metres)	3.16	3.4	3.78	3.97	3.97	8.75	
System Weight (kg) Including Cryogen's	1180	1200	3000	4000	4000	18000	

Room Temperature Shim Specifications

Shim Type (Model)	Number of Channels	Dimensions	
		External Diameter (Cryostat Bore Size)	Internal Diameter (NMR Probe Diameter)
23/54/45	23	54mm	45mm
18/89/73	18	89mm	73mm
26/89/73	26	89mm	73mm
28/51/40	28	51mm	40mm
40/51/40	40	51mm	40mm
29/51/45	29	51mm	45mm
36/63/51	36	63mm	51mm

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Laboratory of Chemical Physics, NIDDK
Building 5, Room 112
Bethesda, Maryland 20892-0520
November 30, 1998
(received 12.4.98)

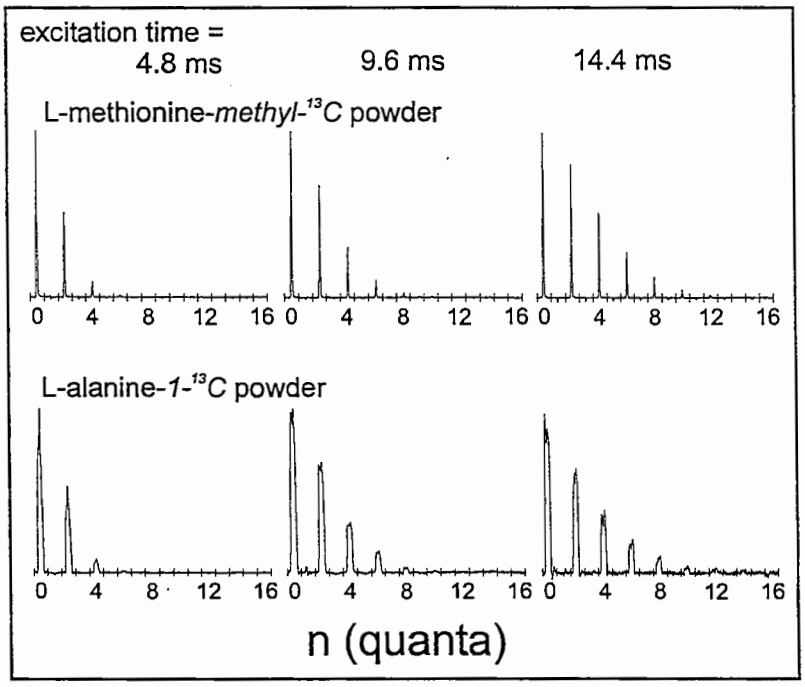
Dr. B.L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

High-Order Multiple Quantum Excitation in Solid State ^{13}C NMR

Dear Barry:

By now, there are many solid state NMR techniques for investigating local structural features of complex molecules, such as specific internuclear distances or dihedral angles. These techniques generally depend on specific isotopic labeling, usually with pairs of ^{13}C and/or ^{15}N nuclei. Local structural measurements are particularly useful for testing specific structural models or predictions. Recent work on an HIV-related peptide/antibody complex by David P. Weliky et al., which will appear in *Nature Structural Biology* in the near future, provides a good example of the importance of these techniques in biological problems. This work is the first application of solid state NMR in a structural investigation of a peptide/protein complex.

In cases where no credible structural models are available, no localized region is of principal interest, and the overall structural organization is unknown, solid state NMR techniques that provide more long-range or global structural information are needed. Solid state multiple quantum spectroscopy, as originally developed over 15 years ago by Alex Pines' group and subsequently investigated and applied by Jeff Reimer, Karen Gleason, Bernie Gerstein, James Yesinowski, Al Garroway, Serge Lacelle, and others, may provide such information. As shown by these people and their colleagues, multiple quantum spectroscopy can be used to determine the number of spins in a coupled group, thereby providing useful structural information. We have recently



shown that the time-reversible multiple quantum excitation pulse sequences that have been employed in earlier ^{1}H and ^{19}F multiple quantum NMR experiments, where dipole-dipole couplings are large and chemical shifts are small, can be easily modified for ^{13}C multiple quantum spectroscopy of dilutely-labeled organic systems and biopolymers, where dipole-dipole couplings are small and chemical shifts can be large. Examples of ^{13}C multiple quantum excitation spectra, obtained at 9.4 T on a Chemagnetics Infinity spectrometer, are shown here. Multiple quantum coherences up to tenth order, corresponding to simultaneous flipping of ten ^{13}C spins, are observed. ^{13}C-^{13}C distances are roughly 4 Å. This work will appear soon in the *Journal of Chemical Physics*.

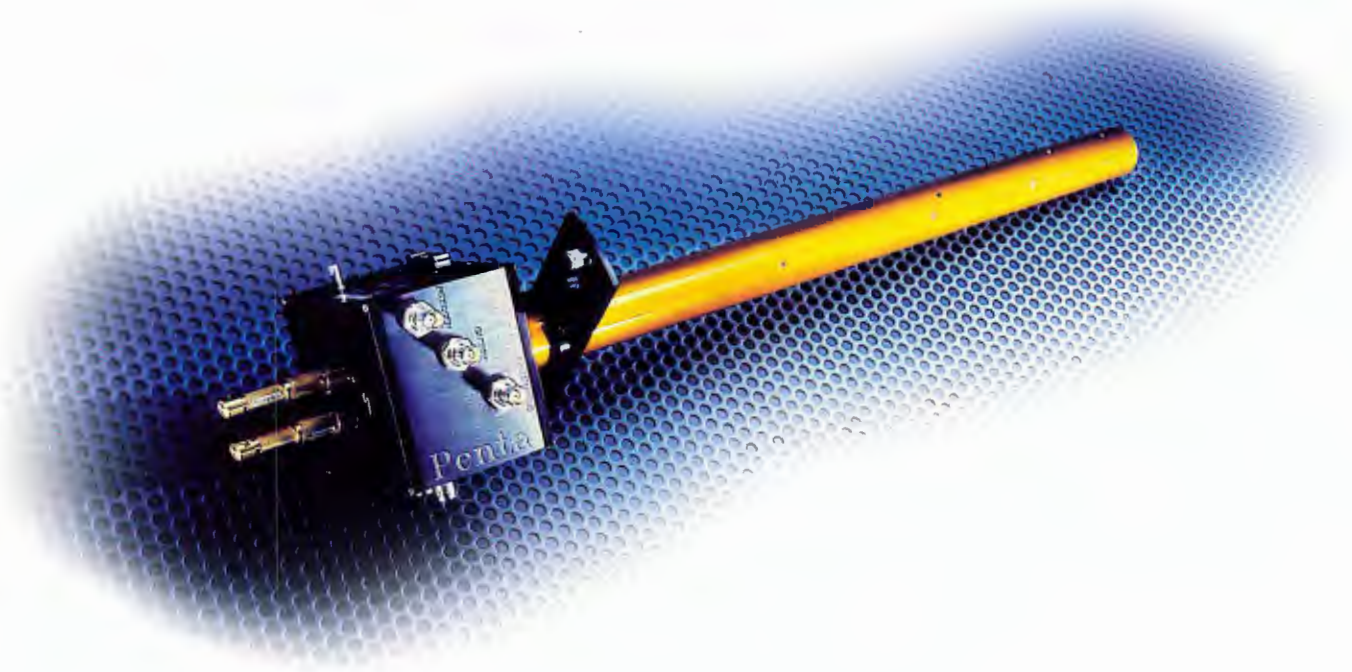
We can imagine many applications of ^{13}C multiple quantum spectroscopy in structural studies of peptides and proteins. For example, one could introduce a single ^{13}C label at each alanine (or other amino acid) in a protein of unknown structure. Multiple quantum measurements might then reveal the sizes and geometries of clusters of coupled ^{13}C nuclei that are formed when the protein adopts its native secondary and tertiary structure. Information about ^{13}C cluster sizes and geometries would place strong, long-range constraints on the global protein structure. As another example, multiple quantum spectroscopy could be used to investigate helix-coil transitions in helix-forming synthetic peptides. If one places a single ^{13}C label at every third amino acid residue in a peptide, then the labels will form a coupled chain with 5-6 Å spacings when the peptide is fully α-helical. When the peptide is in an extended or random coil conformation, the spacings will be significantly larger, up to about 12 Å, and the labeled sites will be uncoupled. Multiple quantum excitation spectra may then be used to determine the lengths of helical segments, or the distribution of these lengths, under conditions where the peptide is only partially helical. This information is not available from more traditional measurements, such as circular dichroism.

Sincerely yours,

Rob Tycko
phone: 301-402-8272
fax: 301-496-0825
e-mail: tycko@helix.nih.gov

Oleg Antzutkin
(on leave from Division of Inorganic Chemistry,
Luleå University, Luleå, Sweden)

Solve Biomolecular Problems



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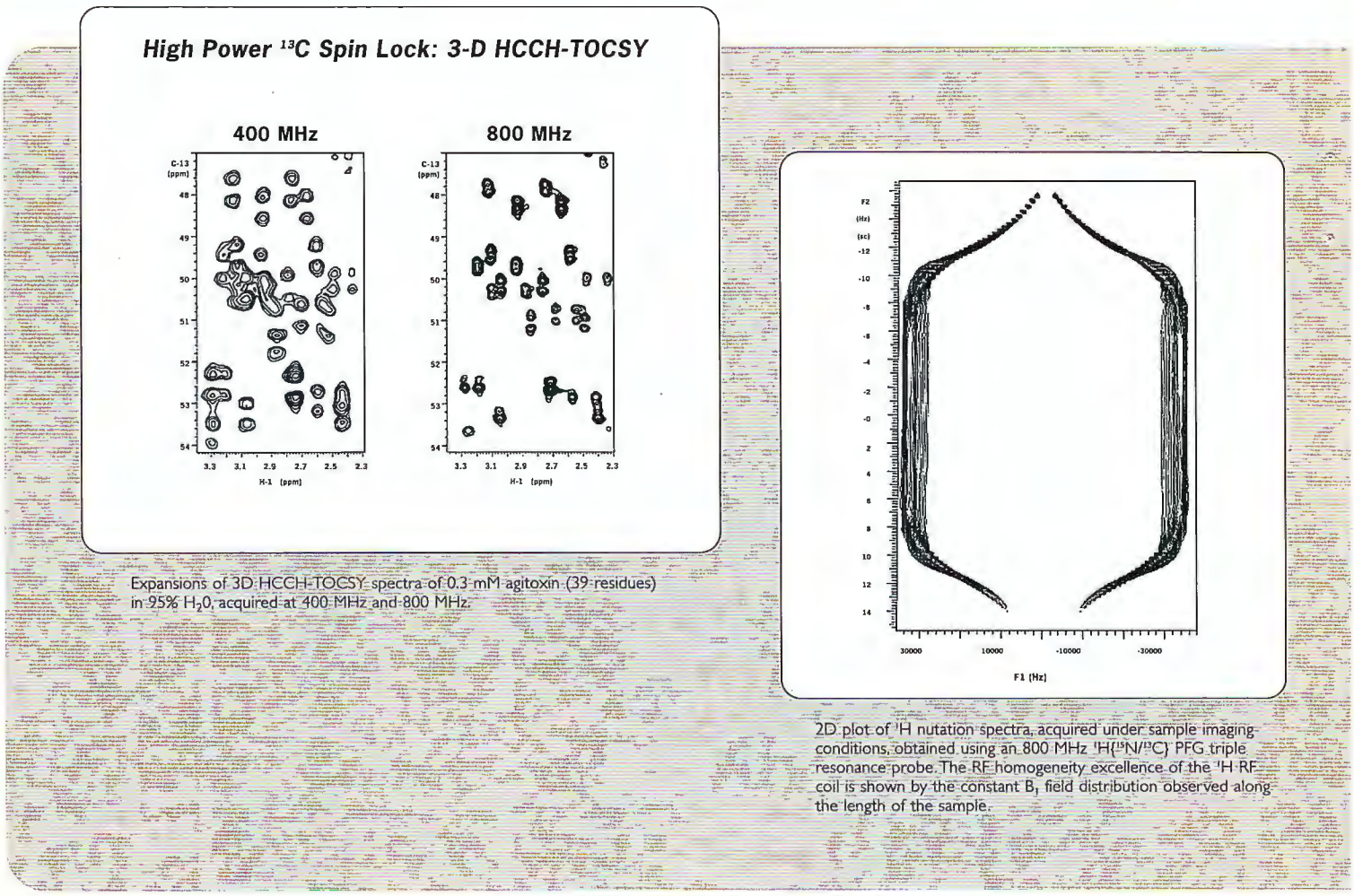

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(received 11/28/98)

A Probe for Deform Polymer Networks in NMR Experiments

Dear Dr. Shapiro,

We describe here a home-built NMR probe which is used to perform ^{2}H NMR experiments of polymer networks under deformation. The important features of this probe for deforming the polymer networks is its simplicity, easy to build and accurate measurements of deformation.

Rubber sample **s** is driven through the **RF** coil and then turn down to verticle direction from both sides over the freely rotatable rollers **b** and **b′**. Both ends of the sample are clamped tightly by the clamps **c** and **c′**(opposite to the c) respectively. These two clamps are fixed to the plate **e**.

A threaded rod **f** goes freely through the plate **g** and again it goes through the female threads in the plate **e**.

The top end of the rod **f** is free to rotate and the bottom end of it is fixed to a lever **h**.

Suppose the distance between two threads of rod **f** is x. When the lever **h** is turned clockwise one round, the plate **e** is moved vertically downward by an amount of x (and vise versa). Since **c** and **c′** are fixed to **e** , the sample **s** is extended from both sides by amounts of x. Therefore, one clockwise turn of the lever **h** corresponds to $2x$ macroscopic deformation of the sample. Since the distance x between two threads can be made in sub millimeter scales, the above described probe can be used as one of the accurate tools of deforming the rubber samples in NMR experiments. In our ^{2}H NMR experiments we are using this probe and one example is shown.

P. Ekanayake H. Menge M. Knörgen

Please credit this contribution to the subscription of Prof. H. Schneider, Department of Physics, Martin-Luther-University Halle Wittenberg, Halle/Saale, Germany

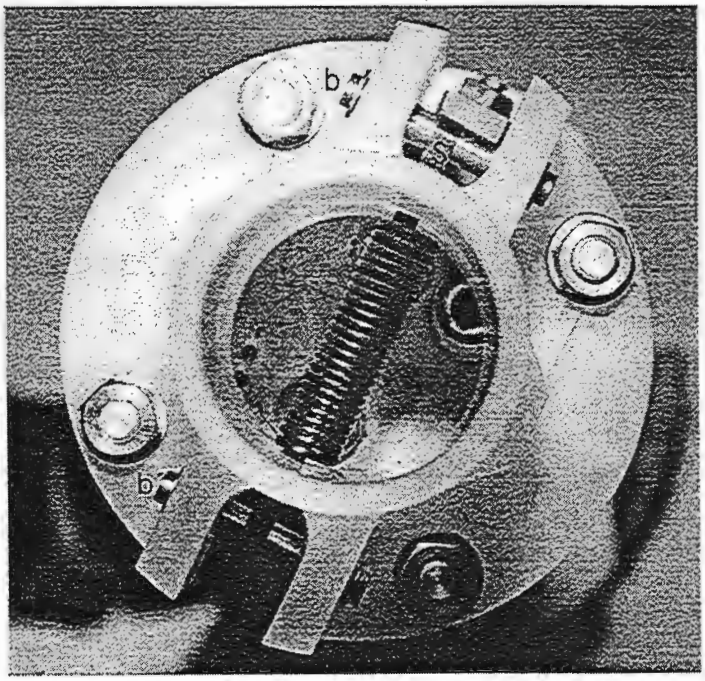

Fig. 1 View from the top

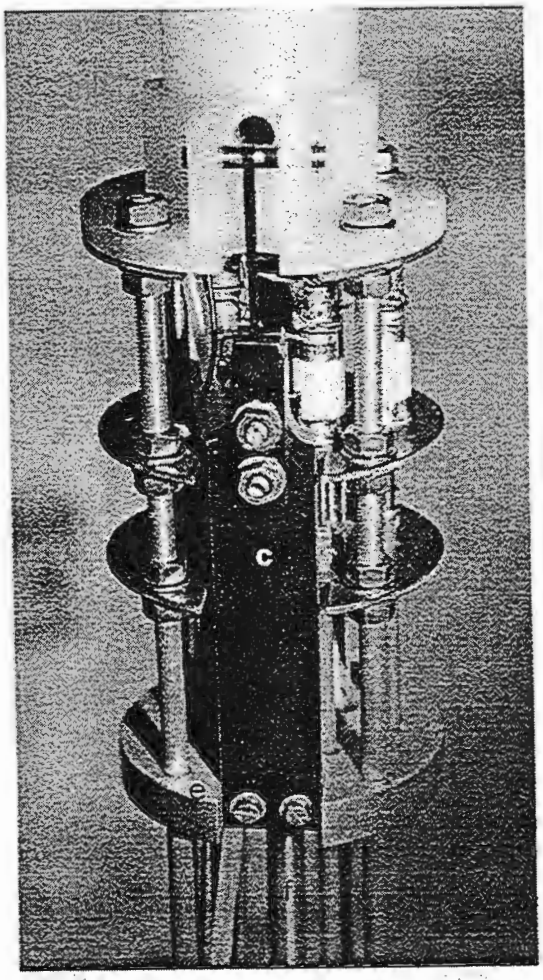

Fig. 2 View from the side

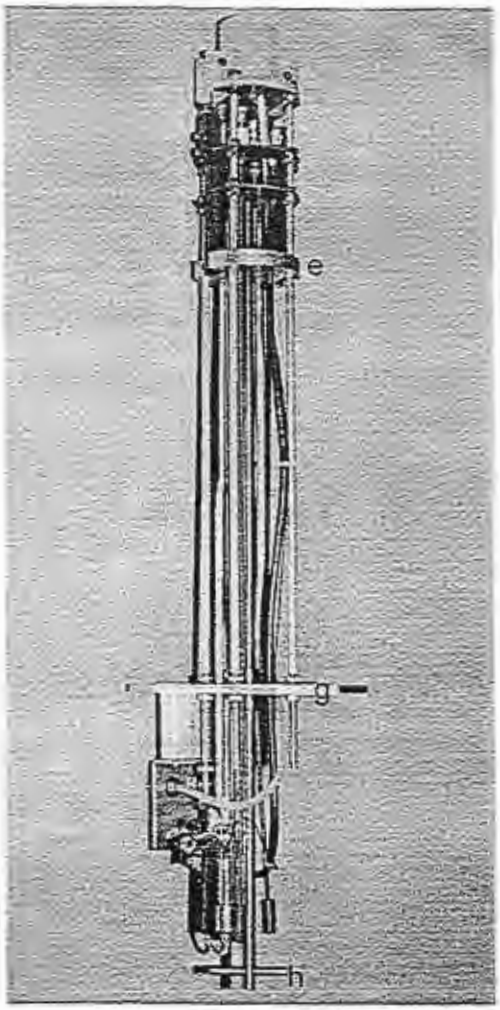

Fig. 3 The complete probe

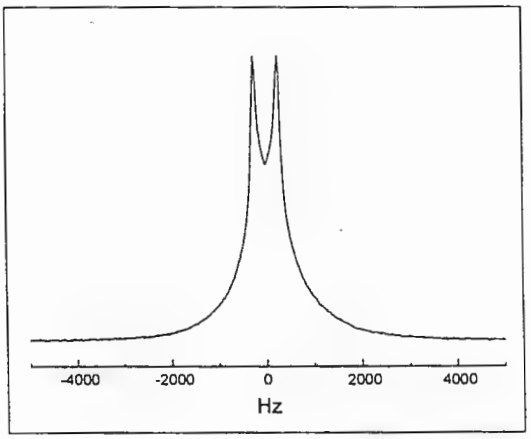

Figure 4 A deuterium NMR spectrum obtained from a cis-1,4 polybutadiene network (Mc=6500g/mol) under deformation(deformation ratio is 2.0), using the above described probe.

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5 mm	542-PP-8	800+	8 in	0.015"	0.00010"	0.00015"	37.50	+100	35.00
5 mm	541-PP-7 New!	800	7 in	0.015"	0.00015"	0.00015"	25.50	+100	23.85
5 mm	541-PP-8	800	8 in	0.015"	0.00015"	0.00015"	27.50	+100	25.85
5 mm	535-PP-7	500	7 in	0.015"	0.0005"	0.00025"	15.15	+100	12.85
5 mm	535-PP-8	500	8 in	0.015"	0.0005"	0.00025"	16.65	+100	14.15
5 mm	528-PP-7	400	7 in	0.015"	0.0010"	0.0005"	10.50	+100	9.25
5 mm	528-PP-8	400	8 in	0.015"	0.0010"	0.0005"	11.95	+100	10.15
5 mm	507-PP-7	360	7 in	0.015"	0.0020"	0.0010"	6.95	+100	5.90
5 mm	507-PP-8	360	8 in	0.015"	0.0020"	0.0010"	7.75	+100	6.60
5 mm	506-PP-7	100	7 in	0.015"	0.0020"	0.0020"	5.40	+100	4.80
5 mm	506-PP-8	100	8 in	0.015"	0.0020"	0.0020"	6.45	+100	5.45
5 mm	506-IM-7 New!	100	7 in	0.015"	0.0020"	0.0020"	3.85	+100	3.45
5 mm	506-IM-8	100	8 in	0.015"	0.0020"	0.0020"	4.05	+100	3.65
5 mm	WG-5MM-THRIFT-7*	60	7 in	0.015"	nominal	nominal	1.49	+100	1.30
5 mm	WG-5MM-THRIFT-8*	60	8 in	0.015"	nominal	nominal	1.70	+100	1.50
3 mm	307-PP-7	360	7 in	0.012"	0.0020"	0.0010"	7.70	+100	6.90
3 mm	307-PP-8	360	8 in	0.012"	0.0020"	0.0010"	8.70	+100	7.85
3 mm	327-PP-7	400	7 in	0.012"	0.0010"	0.0010"	10.20	+100	9.20
3 mm	327-PP-8	400	8 in	0.012"	0.0010"	0.0010"	11.65	+100	10.55
10 mm	513-7PP-7	400	7 in	0.018"	0.0015"	0.0005"	23.25	+25	20.95
10 mm	513-7PP-8	400	8 in	0.018"	0.0015"	0.0005"	24.10	+25	21.70

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5 mm	535-JY-7	500	7"	0.015"	0.0005"	0.00025"	79.85	+10	71.90
5 mm	535-JY-8	500	8"	0.015"	0.0005"	0.00025"	79.85	+10	71.90
5 mm	528-JY-7	400	7"	0.015"	0.0010"	0.0005"	75.70	+10	68.10
5 mm	528-JY-8	400	8"	0.015"	0.0010"	0.0005"	75.70	+10	68.10

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520-1A	0.0010"	0.0005"	185 µl	2.16 mm	2.50 mm	30.40	27.35

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BROCHURE #NMR 998-2 14M 9/98

SMASH No. 1

We are pleased to announce August 15-18, 1999, as the dates for the Small Molecules Are Still Hot (SMASH) conference. The Argonne Guest House, located on the grounds of the Argonne National Laboratory, has been selected as the site for the inaugural meeting. The Guest House offers excellent meeting facilities and accommodations, in addition to being located in Chicago, IL, which provides an international gateway for many of our colleagues.

The tentative schedule of events is arrival on Sunday, August 15, 1999 followed by an evening mixer. The bulk of the conference will be held on Monday and Tuesday (August 16-17) and will conclude at noon on Wednesday, August 18, 1999. The Argonne Guest House will handle all accommodation reservations. Details on the types of accommodations, pricing, and the methods for making reservations will be available in January 1999.

We would like to solicit your immediate assistance in two ways. (1) Please respond via e-mail or telephone to Dr. Gene Mazzola (epm@vm.cfsan.fda.gov or em105@umail.umd.edu; 301-405-1826) with your intentions regarding this conference. Specifically we would like for you to indicate ONE of the following in your response:

(i) I will definitely attend the SMASH conference
(ii) I may attend the SMASH conference
(iii) I will not be attending the SMASH conference

Your immediate response to this request is very important in putting together a successful SMASH conference. (2) Please give careful consideration to the types of information you would like to see included in the program, whether or not you would like to share new developments in your laboratories, and which colleagues you would enjoy hearing from during the conference. Your comments and suggestions regarding the program should be sent to Ms. Karen McCune (mccune_karen_a@lilly.com and 317-276-9783) by no later than the end of January 1999.

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

Steven R. Maple Eli Lilly and Company Lilly Corporate Center, DC3811 Indianapolis, IN 46285 (317) 276-1389 maple_steven_r@lilly.com	Gary E. Martin Pharmacia & Upjohn MS 4821-259-277 Kalamazoo, MI 49001-0199 (616) 833-6283 gary.e.martin@am.pnu.com	Alistair G. Swanson Pfizer Central Research Ramsgate Road, Sandwich Kent CT13 9NJ, United Kingdom 44 1304646637 alistair_swanson@sandwich.pfizer.com

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Partial Agenda Includes:

METHODS FOR IMPROVING NMR STRUCTURE DETERMINATIONS OF RNA
Arthur Pardi, University of Colorado

PROGRESS IN AFFINITY NMR
Aidi Chen and Michael Shapiro, Novartis Institute for Biomedical Research

OH MY GOD, THEY SHRUNK THE SAMPLE
Gary Martin, Pharmacia & Upjohn, Inc.

LC-NMR-MS: IS THE INFORMATION WORTH THE INVESTMENT?!
Steven R. Maple, Andreas Kaerner, Craig A.J. Kemp, Edward G. Groleau, and Karen A. McCune, Eli Lilly and Company

TRIPLE RESONANCE NMR: PRACTICAL CONSIDERATION OF ^{13}C / ^{19}F / ^{1}H EXPERIMENTS ON SMALL MOLECULES
Jim Beery, BASF Corporation

NEW PROBE TECHNOLOGY FOR AUTOMATED NMR
Claude Jones, Monsanto Company
Ron Crouch, Atholl Gibson, and Toby Zens, Nalorac Corporation

FROM ALIGNMENT TO STRUCTURE IN HIGH RESOLUTION NMR
Nico Tjandra, National Institutes of Health

USE OF CHEMICAL SHIFT FOR DETERMINATION OF PROTEIN STRUCTURES
Gabriel Cornilescu, Frank Delaglio, and Ad Bax, National Institutes of Health

APPLICATIONS OF THE TROSY TECHNIQUE
Arthur G. Palmer and J. Patrick Loria, Columbia University
Mark Rance, University of Cincinnati

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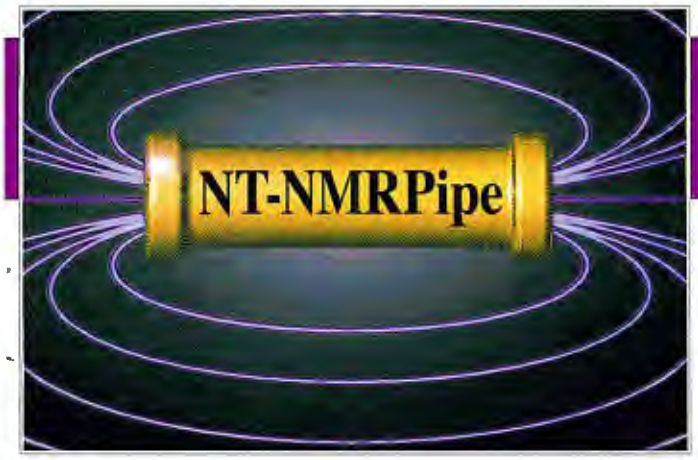

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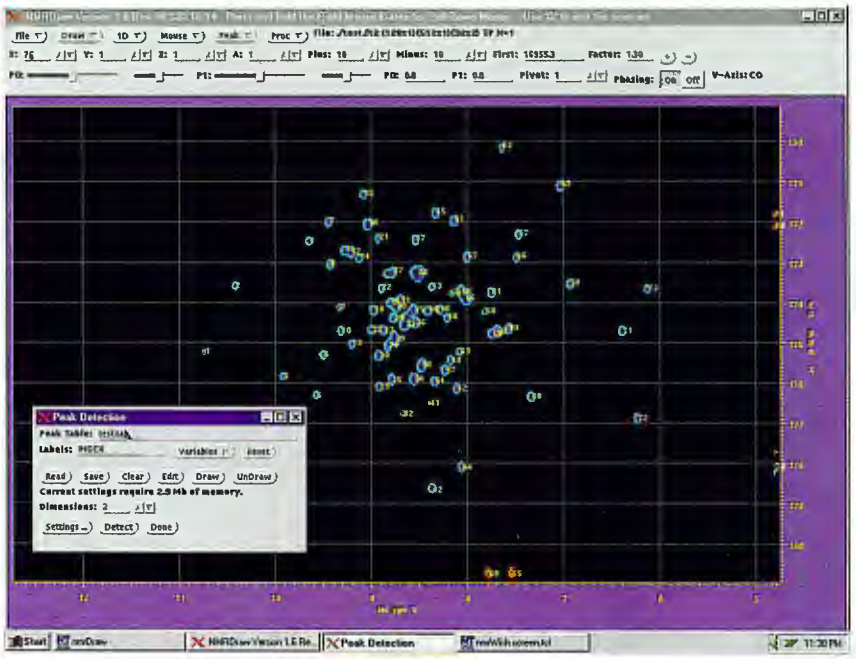
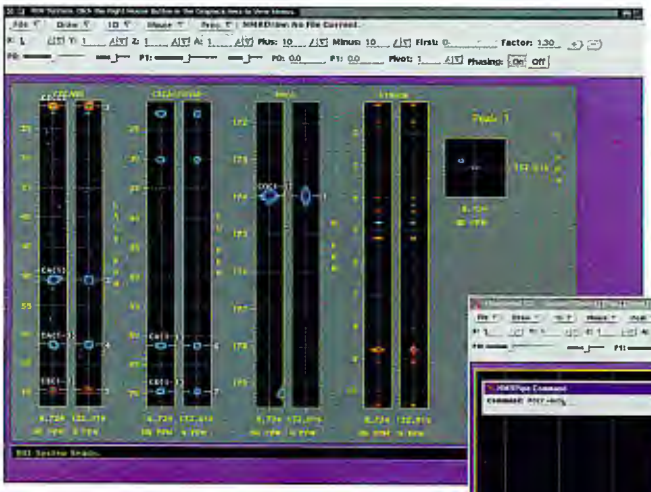
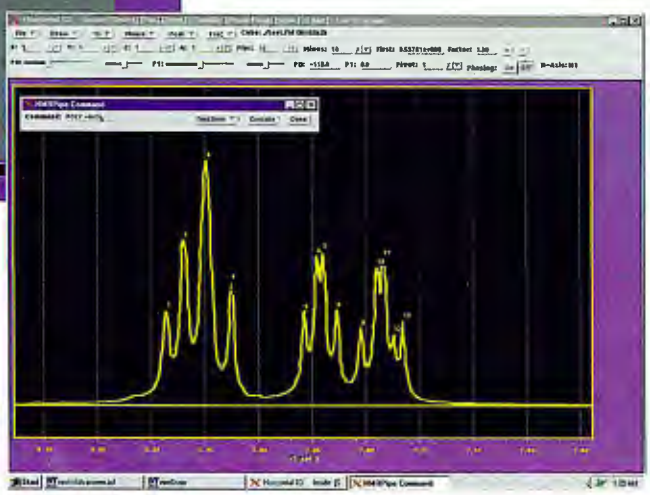
- Superior processing times.







- Open data formats that are fully compatible with popular UNIX-based software solutions for spectral analysis.
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- Automated peak detection in one to four dimensions with effective classification of noise peaks and truncation artifacts. Peak table data is fully accessible to other spectral analysis programs.
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- On-line HTML-based documentation and tutorials.

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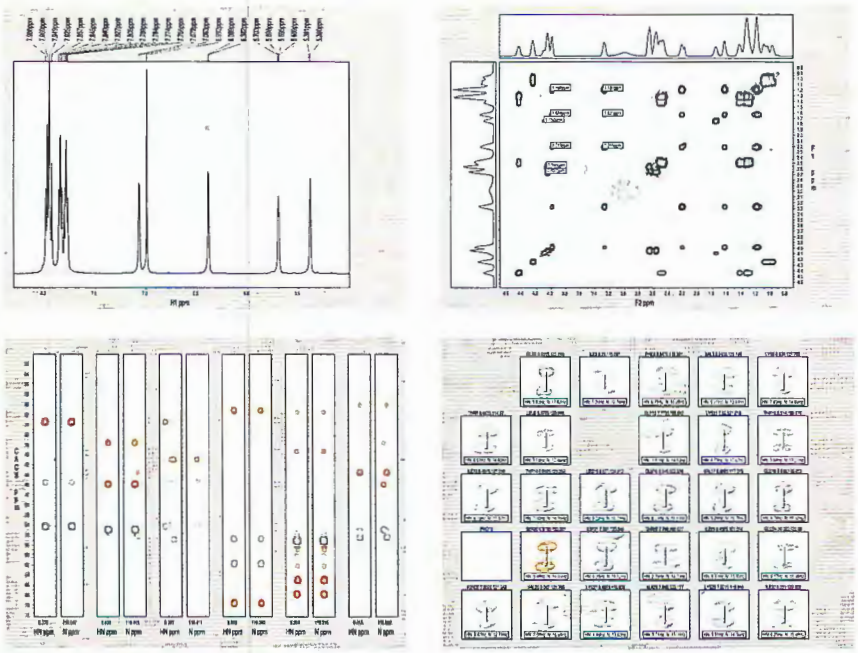

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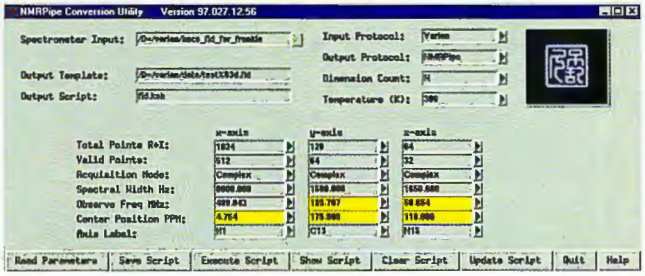
General purpose spectral analysis implemented by enhancements to the powerful Tcl window shell (wish)

- NT-NMRWish facilities include extraction of arbitrary regions and projections, complete access to spectral processing and peak detection, and a relational database engine for manipulating peak tables and PDB structure files.
- NT-NMRWish applications have included custom hardcopy format design, strip plot generation, computer-assisted assignment tasks, automated coupling constant measurement, and 'SAR-by-NMR' (Shuker, Hajduk, Meadows and Fesik, *Science* 274, 1531-1534, 1996).

Processing Times: NT-NMRPipe and UNIX Implementations

Task	Platform	Time
1D processing; 8k* → 128k*, with automated baseline correction	Pentium Pro 200	6 sec
2D processing; 512*x256* → 1024x1024	Pentium Pro 200	9 sec
	SGI R4000 (UNIX)	18 sec
	Sparc 10 (UNIX)	23 sec
2D processing; 512*x256* → 1024x1024 with automated baseline correction in both dimensions	Pentium Pro 200	25 sec
	SGI R4000 (UNIX)	57 sec
	Sparc 10 (UNIX)	71 sec
Amide-detected 3D processing scheme; 512*x64*x32* with solvent filtering and one zero-fill in each dimension	SGI R10000 (UNIX)	73 sec
	Pentium Pro 200 (2 cpu)	144 sec
	Pentium Pro 200 (1 cpu)	244 sec
	SGI R4000 (UNIX)	381 sec
	Sparc 10 (UNIX)	662 sec
Linear prediction (forward-backward); 512x128x32* → 64*	SGI R10000 (UNIX)	525 sec
	Pentium Pro 200 (2 cpu)†	1438 sec
	Pentium Pro 200 (2 cpu)	2074 sec
	Pentium Pro 200 (1 cpu)	2510 sec
	SGI R4000 (UNIX)	3292 sec
	Sparc 10 (UNIX)	5837 sec

†*explicitly parallelized scheme*



- Conversion facilities specifically for Varian and Bruker binary time-domain data are provided, as well as flexible, general-purpose facilities accommodating many other formats. All data is converted to a common format with uniform organization of real and imaginary points.
- Dedicated Varian conversion interface reads the *procpar* file and automatically extracts critical acquisition parameters. Interactive graphical interface enables customization for even the most sophisticated acquisition schemes.
- Dedicated Bruker conversion interface reads and interprets *pulseprogram* and *acq* files to deduce critical acquisition parameters. Full compensation for Bruker digital filter format data is performed during conversion.
- All conversion facilities support special options for complex acquisition schemes, including gradient-enhanced spectroscopy (Rance-Kay, echo:anti-echo) and accommodation for interleaved data formats.

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

December 11, 1998
(received 12/19/98)

Phase and Coherence Level Decoding - A New Computer Program

Dear Barry;

As we all know, vendors of NMR spectrometers supply with their software an entire battery of pulse sequences with phase cycles for coherence selection. Determining the pathway selection is extremely difficult in certain cases. We have devised a computer program, DECODE95, for extracting the coherence pathways and tested this program on a number of Bruker and Varian pulse sequences. In doing so we were surprised to find anomalies in the phase cycles for some of these standard pulse sequences. Some of your readers may be interested in our findings. In the Varian cosyps.c sequence for the TPPI implementation (phase=3), the pulse sequence is coded to select only one pathway which leads to, upon Fourier transformation, the well known phase twist problem. To correct the problem, replace the statement in the pulse sequence:
if ((iphase == 1) || (iphase == 2)) with: if (iphase > 0).
We also found a problem with the phase cycle for the Bruker DEPT.AU pulse program. If the carbon-13 180 degree pulse is imperfect, two extraneous pathways can give signals, and this can lead to possible phase anomalies in the final spectrum. The standard Bruker phase cycle allows these pathways to sneak through. The following phase cycle allows only the desired pathways.

H1 90	3 2 3 2 1 2 1 2 1 0 1 0 3 0 3 0
H1 180	2 1 0 3 3 2 1 0 0 3 2 1 1 0 3 2
H1 theta	3 0 3 0 1 0 1 0 1 2 1 2 3 2 3 2
C13 90	0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3
C13 180	3 3 1 1 0 2 2 0 3 3 1 1 0 2 2 0
Receiver	0 1 2 3 0 1 2 3 0 1 2 3 0 1 2 3

The computer program, DECODE95, runs on Windows 95/98 platforms, and reads Bruker AM and Varian Unity programs, generates a coherence transfer diagram (HPGL format file) and lists the full phase cycle. Copies of DECODE95 may be requested by e-mail to nmrlab@sunfun.chem.ualberta.ca and full details of the program are to be published in the December issue of Concepts in Magnetic Resonance. Please credit this contribution to Tom Nakashima's account.

Sincerely

Ted McClung Jason Ollerenshaw

Department of Chemistry
Buchtel College of Arts and Sciences
Akron, OH 44325-3601
(330) 972-7372 Office
(330) 972-6085 Fax

December 16, 1998

(received 12/26/98)

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

SUBJECT: 3D Triple Resonance NMR of Organic Mixtures

Dear Barry:

Although much of our recent work has involved NMR of polymers, we have recently found use for 3D NMR in characterizing complex mixtures of small molecules.

Silylation of vinyl cyclobexene leads to a 6 component mixture of stereo – and regio-isomers (Figure 1). The 600 MHz 1D ^{1}H, ^{13}C and ^{29}Si spectra (Figure 2) are very complex, making it impossible to do much more than say it is a complex mixture. Twelve separate resonances are resolved in the ^{29}Si 1D spectrum, as expected for a 6-component mixture.

A $^{1}H/^{13}C/^{29}Si$ 3D chemical shift correlation experiment similar to the HNCA experiment used by biochemists can disperse ^{1}H-^{13}C HSQC-type correlations into a third dimension based on the ^{29}CSi chemical shifts of the atoms which are part of the same spin system. The experiment can be run in three ways, with Csi to provide H-C-Si fragments, with CSi to provide H-C-C-Si fragments, and with CSi to provide H-C-C-C-Si fragments (Figure 3). The combined information from the three experiments permits assignments of all the resonances and the complete structure determinations for all 6 components in the mixture.

Unlike the experiments done in biochemistry, all of these data were obtained without the benefit of isotopic labeling. The experiments each require 4-8 hours of spectrometer time (not for sensitivity, but to obtain a sufficient number of increments in each of the evolution times) and the use of pulsed field gradients for coherence selection.

For the past year, we have been preoccupied with the replacement of our 600 MHz spectrometer with a 750 MHz instrument and many new accessories. Hopefully, we will show you some results from that equipment in our next contribution.

Best regards,

THE UNIVERSITY OF AKRON
Peter L. Rinaldi
Professor of Chemistry
Director of the Molecular Spectroscopy Laboratory

DUPONT AUTOMOTIVE
Laurine Galye
Joan Hansen
Leck Wiczek

Weixia Liu
Graduate Research Associate
The University of Akron

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Bruker AC-200, including broadband electronics, $^{1}H/^{13}C$ switchable probe.	$45,000.
GE QE-300, including dual $^{1}H/^{13}C$ electronics, $^{1}H/^{13}C$ switchable probe.	$45,000.
Varian VXR-300, including broadband electronics, $^{1}H/^{13}C$ switchable probe.	$58,000.

In addition, any of these systems may be purchased under lease, with typical payments as low as $627. per month for the XL-200.

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The NMR Newsletter - *Software* Reviews

Software Review Editor: István Pelczer, Dept. of Chemistry, Princeton Univ., Princeton, NJ 08544

NMRPipe*

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

December 15, 1998
(received 12/21/98)

Dear Dr. Shapiro,

I have been meaning to write for the past seven years since I joined the faculty at the University of Toronto to get my subscription underway but I am just a bit behind! One of the primary research interests in my laboratory focuses on the development of NMR methods for the study of the structure and dynamics of high molecular weight proteins and protein complexes. This requires (*a*) the production of proteins with optimal labeling, such as ^{15}N, ^{13}C, ^{2}H with protonation at key sites such as methyl groups and (*b*) the development of NMR methodology which exploits the labeling strategy employed. Our long term goal is to develop an approach facilitating the rapid generation of global folds of high molecular weight molecules (in the 50 kDa range). Obviously we record large numbers of data sets and having the right tools at our disposal for data processing is absolutely critical.

My initial experience with the development of data processing software for multi-dimensional NMR came when I was a post-doc in Ad Bax's laboratory. In those days everything was new (and exciting!) and we had to write our own processing software from scratch. Although the software that Dominique Marion and I wrote was usable and quite flexible, it quickly became apparent that large numbers of improvements were necessary. Fortunately for me (and for that matter the whole NMR community) Frank Delaglio joined Ad Bax's lab at the NIH in 1991 and began the process of writing processing software. The end result was the creation of an extremely elegant and very flexible program called **NMRPipe** for processing N-D data sets.

Processing begins with the conversion of data from the format stored on the spectrometer to NMRPipe format using a simple script. It inserts the number of points in each dimension, spectral widths, frequencies, carrier positions, axis labels and dimensionality of the data set in a header to be used by the program later. Subsequently the data can be processed without the bother of remembering the number of points and hence the size of the matrix that is necessary or will be necessary once zero filling, linear prediction, etc., are done. All of the standard processing tools are available (and more) including a number of post-acquisition water removal schemes, excellent baseline correction modules, as well as several linear prediction (and MEM) functions. Basically, the user writes a simple UNIX shell script, which takes the unprocessed data and 'flows' it through a pipeline of processing programs. Each pipeline corresponds to a particular function such as baseline correction, Fourier transformation or water suppression. Scripts are easily modified from one application to the next. Visualization routines are, of course, also available (called NMRDraw) so that one can study the effects of application of a particular window function prior to the actual data processing, for example. In my experience an average post-doc can master the essentials of the program to be able to process his/her data in about 15 minutes!

continued

An example from our own work on maltose binding protein (MBP, a 370-residue protein) will illustrate the power of the program. We have prepared [Val, Leu, Ile (δ1)]-methyl protonated ^{15}N, ^{13}C, ^{2}H-labeled protein and Kevin Gardner assigned the backbone ^{15}N, $^{13}C^{\alpha}$, HN and the sidechain $^{13}C^{\beta}$ and methyl (^{13}C, ^{1}H) chemical shifts. Naturally we wanted to obtain as many NOEs as possible to define the global fold. Catherine Zwahlen developed a number of NOE experiments for measuring NOEs to methyl groups with high resolution, necessary in the case of MBP with 122 methyl groups. In one experiment designed in collaboration with Andy Byrd's group we measured the methyl-methyl NOEs by recording the ^{13}C methyl chemical shift of the methyl from which the NOE originates together with the ^{13}C and ^{1}H chemical shifts of the destination methyl.

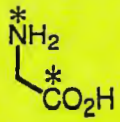
In order to squeeze out the last NOE from our data set, resolution is paramount and we employ a scheme in which linear prediction is carried out in both of the indirect detection dimensions. It is important, however, that linear prediction be performed on a data set in which two of the three dimensions are already processed in order to minimize the number oscillators. This necessitates undoing a whole set of transformations in one of the dimensions and redoing them after linear prediction. Frank's program handles this in a completely straightforward manner by including 'inverse' commands which undo previous processing. The 3D methyl-methyl NOE dataset on MBP was thus processed with minimal user effort.

NMRPipe has many other features, including routines for peak picking, volume fitting, analysis of J-coupling, dipolar coupling, and relaxation data and software for the analysis of data for structure determination. The program is reasonably well documented. Frank should be congratulated in writing what I think is the processing system of choice. The software has made a big contribution to the research in my lab.

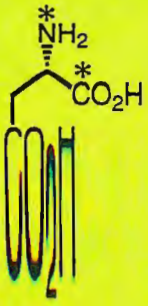
Sincerely yours,

Lewis E. Kay
Protein Engineering Centers of Excellence
Departments of Medical Genetics,
Biochemistry and Chemistry
University of Toronto
Toronto, ON M5S 1A8
Canada.

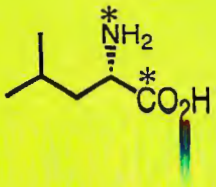
*(from the Software Review Editor) NMRPipe is available for free for Unix from LCP/NIDDK at NIH.Send an email for ftp access to Frank Delaglio (delaglio@speck.niddk.nih.gov). A commercial version for Windows-NT is available from Resonance Designs, Inc.) For additional information see the ad in this issue of the Newsletter, or see http://www.resdesigns.com.



Glycine-1-^{13}C,^{15}N
>99 atom % ^{13}C
>99 atom % ^{15}N



L-Aspartic Acid-1-^{13}C,^{15}N
>99 atom % ^{13}C
>99 atom % ^{15}N



L-Leucine-1-^{13}C,^{15}N
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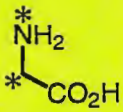
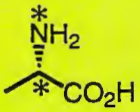
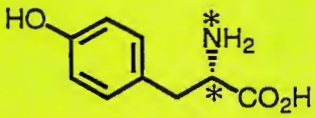
>99 atom % ^{15}N



Glycine-2-^{13}C,^{15}N
>99 atom % ^{13}C
>99 atom % ^{15}N



L-Alanine-2-^{13}C,^{15}N
>99 atom % ^{13}C
>99 atom % ^{15}N



L-4-Hydroxyphenylalanine-2-^{13}C,^{15}N
>99 atom % ^{13}C
>99 atom % ^{15}N

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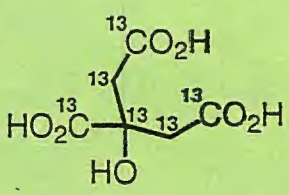
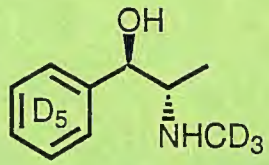
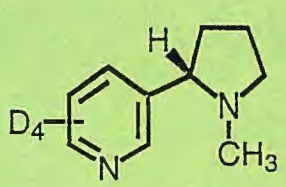


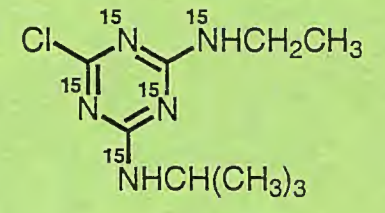
Citric Acid-$^{13}C_6$



(1R, 2S)-(-)-Ephedrin-d_8



S-(-)-Nicotine-2,4,5,6-d_4



Atrazine-$^{15}N_5$

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•Protein crystallography
•Multisubunit allosteric proteins

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•Principles of NMR and dynamics
•Protein dynamics and reactions •The energy landscape of proteins

Theoretical Analysis of Internal Motions in Biological Molecules
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•Simulating protein and nucleic acid molecular dynamics
•New programs in MD simulations •Calculation of free energy and binding constants

Motions in Nucleic Acid
•Nucleic acids structure and dynamics
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Deadline Dates

No. 485 (Feb.)	22 Jan. 1999
No. 486 (Mar.)	19 Feb. 1999
No. 487 (Apr.)	23 Mar. 1999
No. 488 (May)	23 Apr. 1999
No. 489 (June)	21 May 1999

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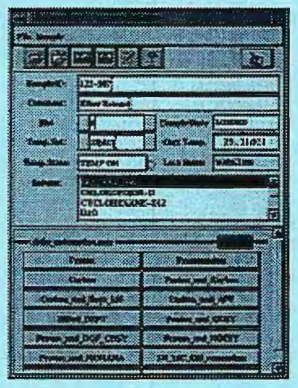

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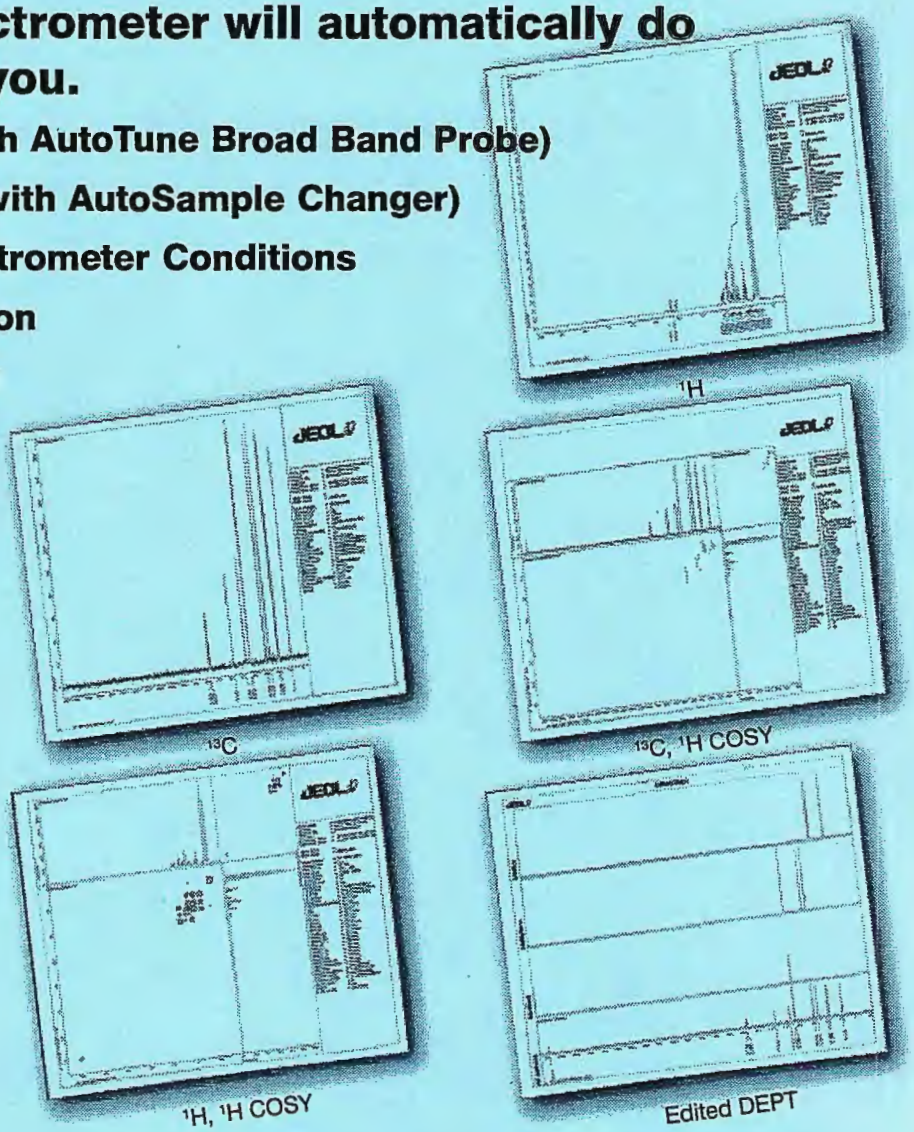

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