THE
NMR
NEWSLETTER

No. 492

September 1999

NUTS adds a whole new dimension in NMR data processing

New! ***NUTS-Pro does 3D!***

The data set shown is from a CBCA(CO)NH experiment, ^{1}H-detected (512 complex points), with ^{13}C in the 2nd dimension (110 total slices, hypercomplex) and ^{15}N in the 3rd dimension (96 total slices, hypercomplex) for a total size of 43 MBytes.

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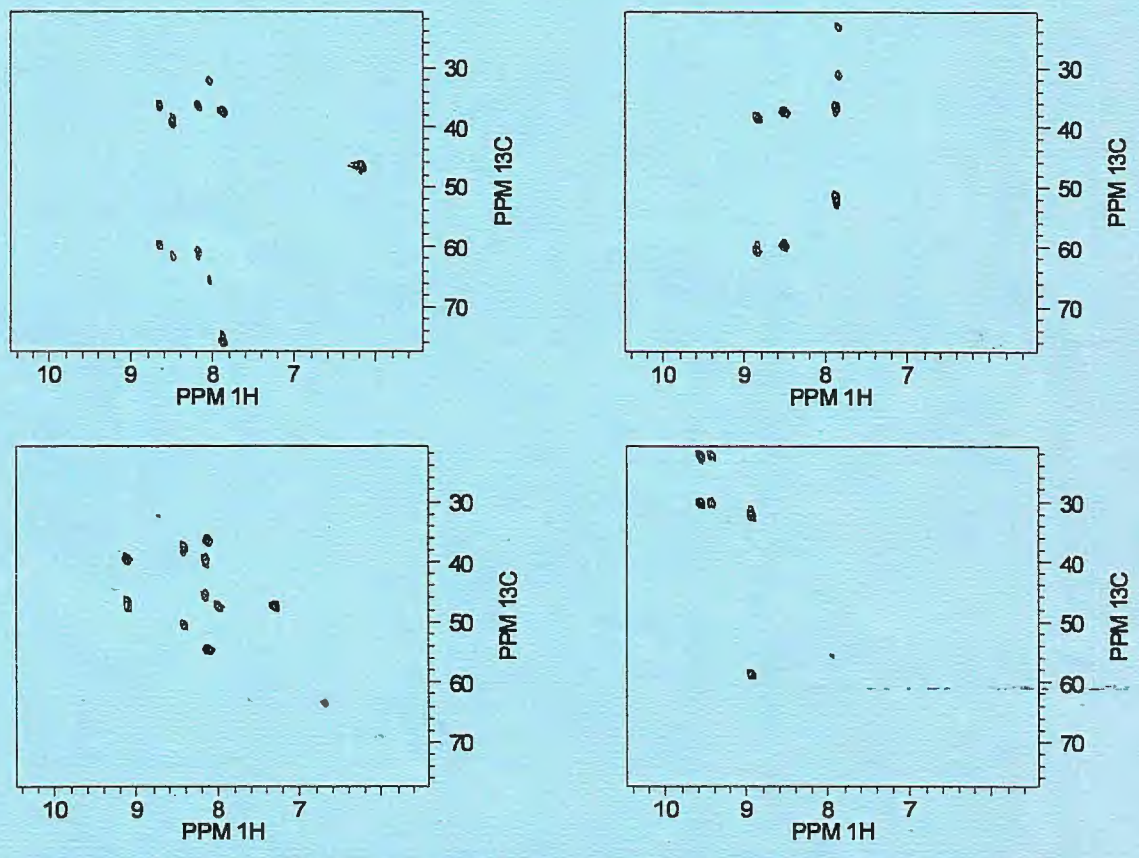
Below are C-H planes corresponding to selected ^{15}N frequencies



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FORTHCOMING NMR MEETINGS

"*In Vivo* Magnetic Resonance Imaging and Spectroscopy", Basel, Switzerland, **October 11-16, 1999**; Contact: Prof. J. Seelig, Biocenter of the University, Klingelbergstr. 70, CH-4056, Basel, Switzerland; E-mail: seelig1@ubaclu.unibas.ch; Phone: 41-61-267-2191; Fax: 41 61-267-2189; biozentrum.unibas.ch/~embo-nmr/.

NMR Technologies: Development and Applications for Drug Discovery, Baltimore, MD, **November 4-5, 1999**; Contact: Cambridge Healthtech Institute, 1037 Chestnut St., Newton Upper Falls, MA 02464; el. 617-630-1300 or (in U.S.) 888-999-6288; Fax. 617-630-1325; e-mail: chi@healthtech.com; www.healthtech.com; See Newsletter 492, 27.

Medical Imaging: NMR and Nuclear Tracers, colloquium at the 12th Entretiens Jacques Cartier, Lyon, France, **December 5-8, 1999**; See http://jade.univ-lyon1.fr/JacquesCartier/ and Newsletter 488, 38.

Biennial Meeting of the Australian and New Zealand Society for Magnetic Resonance (ANZMAG2000), Mt. Buller, Victoria, Australia; **February 13-17, 2000**; Contact: Dr. Jenny Wilson, Victorian College of Pharmacy, Monash University, Parkville, Victoria 3052, Australia; E-mail: anzmag@edda.vcp.monash.edu; vcp.monash.edu.au/chemistry/anzmag2k.

PITTCON 2000, New Orleans, LA, **March 12-17, 2000**; Contact: The Pittsburgh Conference, 300 Penn Cemter Blvd., Suite 332, Pittsburgh, PA 15235-5503; Phone: 412-825-3220; Fax: 412-825-3224; Email: expo@pittcon.org.

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

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.

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

continued on inside back cover

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**

August 2, 1999
(received 8/14/99)

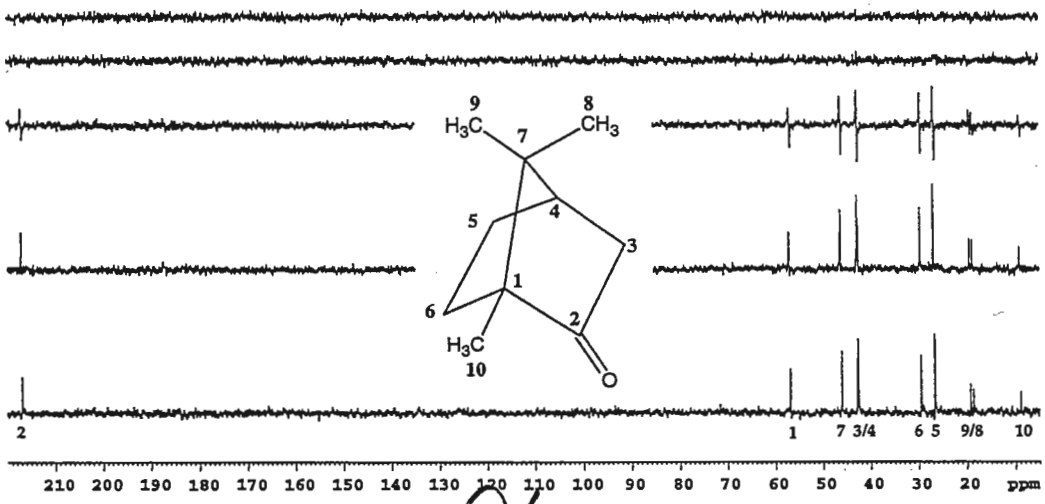
Doubling the Sensitivity of INADEQUATE with Off-Resonance Compensation

Dear Barry:

The INADEQUATE CR experiment[1-3] about doubles the sensitivity of conventional INADEQUATE. This sensitivity enhancement comes about by transferring the ^{13}C-^{13}C double-quantum coherence to only two of the four lines of the two-spin systems, i.e. either the two left or the two right doublet lines.

Apart from the inherently low sensitivity there is another severe problem with INADEQUATE, namely dramatically deteriorated performance in the presence of large off-resonance effects. In fact, INADEQUATE usually fails when it is applied to molecules exhibiting a wide range of ^{13}C chemical shifts.

Malcolm Levitt has long since showed that this problem can be remedied by use of composite pulses[4] and we recently implemented his refined scheme for global pulse sequence compensation[5] into INADEQUATE experiments with the results shown below. The molecule studied was camphor and the spectra were run on a Varian Unity Inova 500 MHz spectrometer. They are from top to bottom uncompensated INADEQUATE, uncompensated INADEQUATE CR, compensated INADEQUATE, compensated INADEQUATE CR with the left doublet lines, and compensated INADEQUATE CR with the right doublet lines. Clearly, the doubled sensitivity of INADEQUATE CR over conventional INADEQUATE is retained even in the presence of large off-resonance effects when the pulse sequences are appropriately compensated. Anybody interested in the 1D or 2D pulse programs can request them by email.



Sincerely yours, Ole W. Sørensen Ole Jakob Bunkenborg Jakob

[1]N.C. Nielsen, H. Thøgersen and O.W. Sørensen, *J. Am. Chem. Soc.* **117**, 11365-11366 (1995), [2]N.C. Nielsen, H. Thøgersen and O.W. Sørensen, *J. Chem. Phys.* **105**, 3962-3968 (1996), [3]N.C. Nielsen and O.W. Sørensen, *J. Magn. Reson. A* **123**, 135-139 (1996), [4]M.H. Levitt and R.R. Ernst, *Mol. Phys.* **50**, 1109-1124 (1983), [5]M.H. Levitt, *Encyclopedia of NMR*, 1396-1411 (1996).

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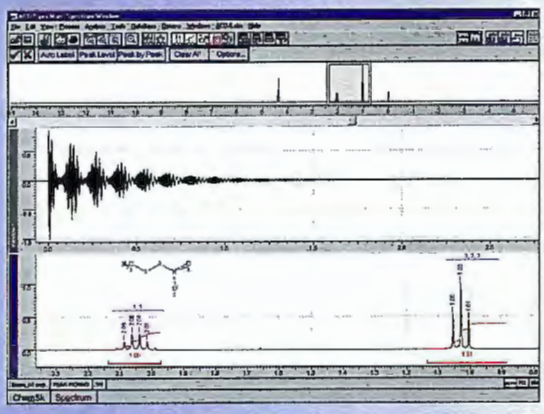

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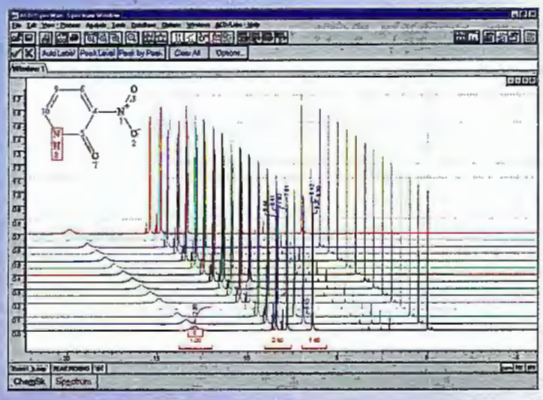
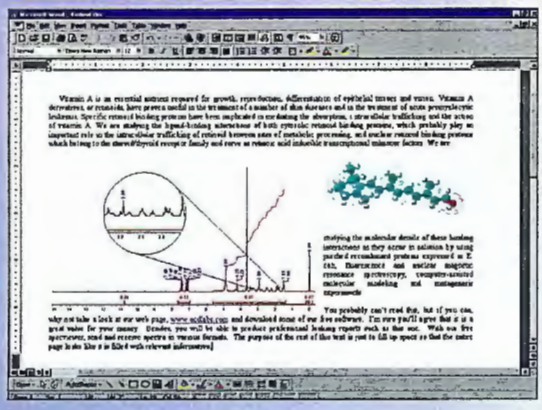


Multiple display options



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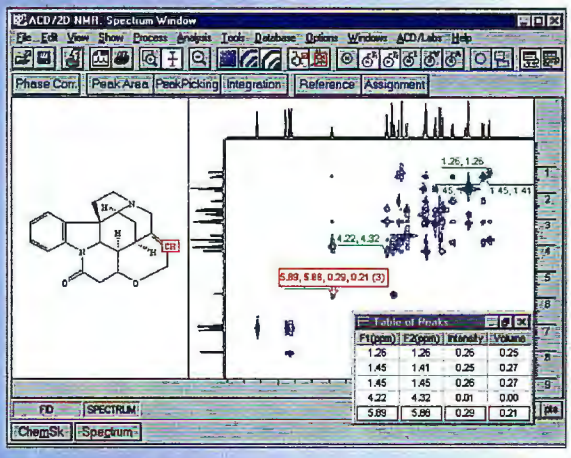

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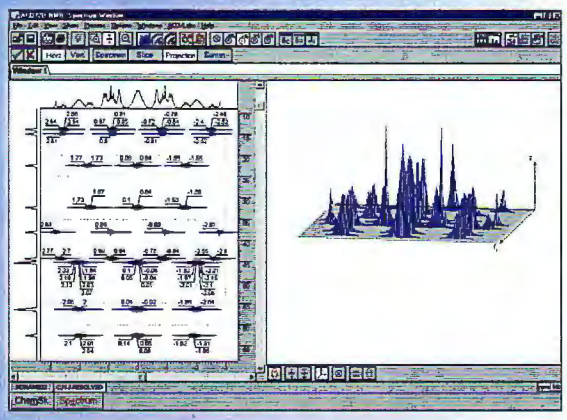

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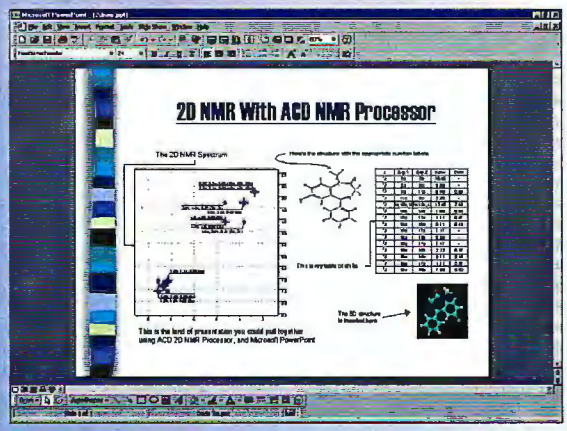

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NMR Newsletter
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(received 8/17/99)
August 14, 1999

Observation of $^{2h}J_{HC'}$, at last

Dear Barry:

About a year and a half ago, Stephan Grzesiek and his group in Germany startled the biological NMR community by reporting the presence of J_{NN} couplings across hydrogen bonds (H-bonds) in Watson-Crick base-pairs (1). The exceptionally large values (6-7 Hz), for a nucleus which normally only shows very modest one-bond (*ca* 20 Hz, max) and even much smaller two- and three-bond ^{15}N-^{15}N J couplings, came as a complete surprise. Stephan and his colleagues observed these values in a very large (69-nucleotide) fragment, but any initial skepticism about the authenticity of these couplings was laid to rest by the thoroughness of Grzesiek's analysis. Shortly thereafter, Kurt Wüthrich and co-workers reported similar couplings (2), including a smaller "one-bond" coupling between the hydrogen and the H-bond accepting ^{15}N (2-4 Hz) (Figure 1). Kurt suggested to insert the superscript "h", to differentiate these through-H-bond couplings from regular, through covalent bond couplings. So, Stephan observed $^{2h}J_{NN}$ couplings, and Wüthrich and co-workers reported $^{1h}J_{HN}$ (and also $^{2h}J_{NN}$) couplings.

I really should not have been as surprised as I was at the presence of these couplings because six years earlier, Michael Summers had shown that substantial (up to 4 Hz) J couplings could be detected between amide protons and the Hg or Cd metal in the protein rubredoxin. As we reported at that time, these couplings were mediated through a hydrogen bond between the amide proton and the sulfur of the cysteine residues coordinating the metal, and "suggest that these hydrogen bonds contain significant covalent character" (3). Such (misleadingly named) "through-space" couplings had been observed before in the literature, primarily for cases involving ^{19}F. Subsequently, Limbach and co-workers have studied a range of small model compounds, both by solution and solid state NMR, and also found evidence for such J couplings in non-F cases (4). The whole story was placed on solid theoretical footing in a recent landmark paper by Barfield and Grzesiek (5), which shows excellent agreement between density functional theory (DFT) calculations and experimental data.

After Mike Summers reported the through-H-bond J couplings, we made some serious effort to observe analogous J couplings between amide protons and their hydrogen-bond accepting carbonyls (Figure 1). Alas to no avail. The only conclusion we could draw was that if such couplings indeed existed, they fell below our detection threshold of about 1 Hz. This was actually the second time we tried to observe such couplings, this time in isotopically enriched proteins. In 1986 Don Davis, who spent a sabbatical year in my group, suggested that these couplings might be measurable and we tried for a long weekend to observe them at natural abundance in a cyclic peptide. Alas, to no avail.

When Grzesiek's and Wüthrich's results last year indicated that $^{2h}J_{NN}$ is larger than $^{1h}J_{HN}$, it occurred to me that conceivably in peptides too, $^{3h}J_{C'N}$ might be larger than $^{2h}J_{C'HN}$ couplings. Indeed, Gabriel Cornilescu and Jin-Shan Hu were readily able to detect across H-bond J couplings between ^{15}N and $^{13}C'$ in the protein ubiquitin (6). Unfortunately, we narrowly got scooped on this by the Grzesiek group, which had made exactly the same measurement (7). We subsequently

showed an exquisitely tight relation between hydrogen bond length and the magnitude of $^{3h}J_{C'N}$, which was masked in ubiquitin by the uncertainty in the atomic positions of the moderate resolution (1.8Å) X-ray structure of this protein. For a different protein, for which a 1Å X-ray structure was available, the correlation was much clearer, however, and yielded (7):

$$^{3h}J_{C'N} = -59000 \exp(-4R_{NO}) \pm 0.09 \text{ Hz}$$

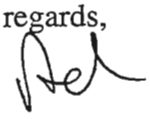
where R_{NO} is the distance between donor and acceptor atoms, in Ångstroms. For typical hydrogen bond lengths of 2.8 to 3.0 Å, this works out to couplings of -0.8 to -0.36 Hz.

After all this, I was left with the unsatisfying feeling we had missed the $^{2h}J_{C'N}$ coupling, even though by now I was certain it had to be there. I discussed the issue with Stephan Grzesiek, who agreed with me and he kindly sent me some perdeuterated $^{15}N/^{13}C$-enriched ubiquitin. The idea being that the T_2 of the amide protons is substantially (about two-fold) longer in perdeuterated proteins than in protonated ones, which should make it easier to detect such very small J couplings. A second problem in detecting the small $^{2h}J_{C'N}$ couplings is that they are "competing" with the much larger through-covalent-bond $^{2}J_{C'HN}$ (4-5 Hz), and the ϕ-angle dependent $^{3}J_{C'HN}$. The solution to this was to use selective pulses, where only coupling between H^N and its H-bond accepting $^{13}C'$ is allowed to de- and rephase during the HMQC delays.

Doing this, we observed some very nice correlations between amide protons and their H-bond accepting carbonyls, indicative of $^{2h}J_{C'HN}$ couplings of about 0.5-0.6 Hz (Figure 2). A subsequent, careful measurement of many other such couplings and comparison of $^{2h}J_{C'HN}$ with $^{3h}J_{C'N}$ by Florence Cordier in Stephan's group showed a beautiful linear correlation, with $^{2h}J_{C'HN}$ being about 6% smaller than the corresponding $^{3h}J_{NC'}$ value (its sign remaining undetermined).

Considering how painful the recording of multiple selective 2D experiments typically is, I don't expect observation of $^{2h}J_{C'HN}$ will become a routine method for establishing the presence of hydrogen bonds in proteins. However, it is conceivable that for other types of hydrogen bonds, particularly for very strong hydrogen bonds involved in catalysis, the $^{2h}J_{C'HN}$ value may be easier to detect. This could be particularly useful when studying H-bonds between enzyme inhibitors, which might be difficult to enrich isotopically, and protein carbonyl groups. In any case, I'm happy this old issue is finally laid to rest.

Kindest regards,



Ad Bax

(1) A. J. Dingley and S. Grzesiek, *J. Am. Chem. Soc.* **120**, 8293-8297 (1998).
(2) K. Pervushin, A. Ono, C. Fernandez, T. Szyperski, M. Kainosho, and K. Wüthrich, *Proc. Natl. Acad. Sci. USA* **95**, 14147-14151 (1998).
(3) P.R. Blake, M.F. Summers, M.W.W. Adams, J.-B. Park, Z.H. Zhou, and A. Bax, *J. Biomol. NMR* **2**, 527-533 (1992).
(4) Globulev, N.S.; Shenderovich, I.G.; Smirnov, S.N.; Denisov, G.S.; Limbach, H.H. *Chem. Eur. J.* **5**, 492-497 (1999).
(5) A. J. Dingley, J. E. Masse, R. D. Peterson, M. Barfield, J. Feigon, and S. Grzesiek, *J. Am. Chem. Soc.* **121**, 6019-6027 (1999).
(6) G. Cornilescu, J.-S. Hu, and A. Bax, *J. Am. Chem. Soc.* **121**, 2949-2950 (1999).
(7) F. Cordier and S. Grzesiek, *J. Am. Chem. Soc.* **121**, 1601-1602 (1999).
(8) G. Cornilescu, B.E. Ramirez, M.K. Frank, G.M. Clore, A.M. Gronenborn, and A. Bax, *J. Am. Chem. Soc.* **121**, 6275-6279 (1999).

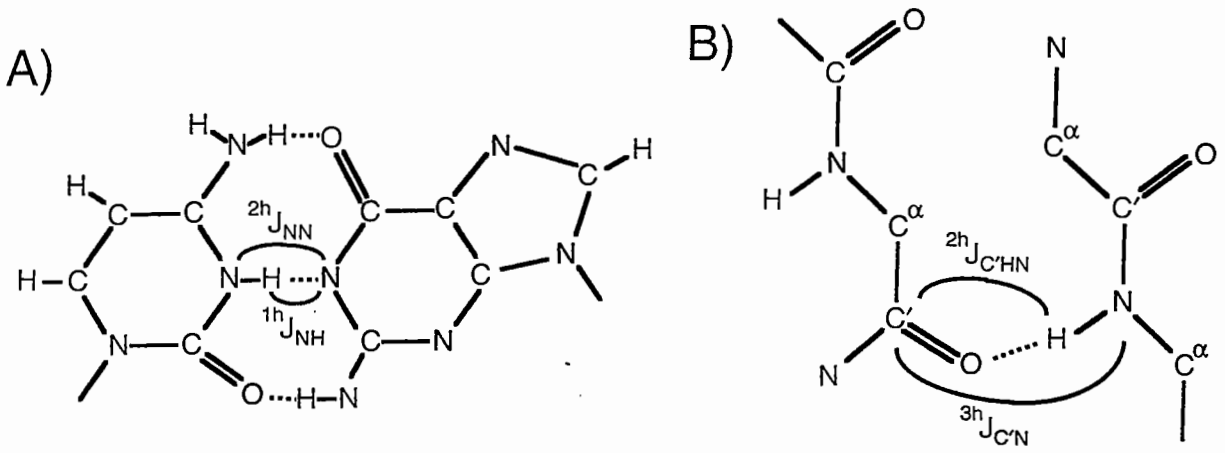


Figure 1. Sketch of the types of ^{h}J couplings observable in (A) oligonucleotides and (B) polypeptides.

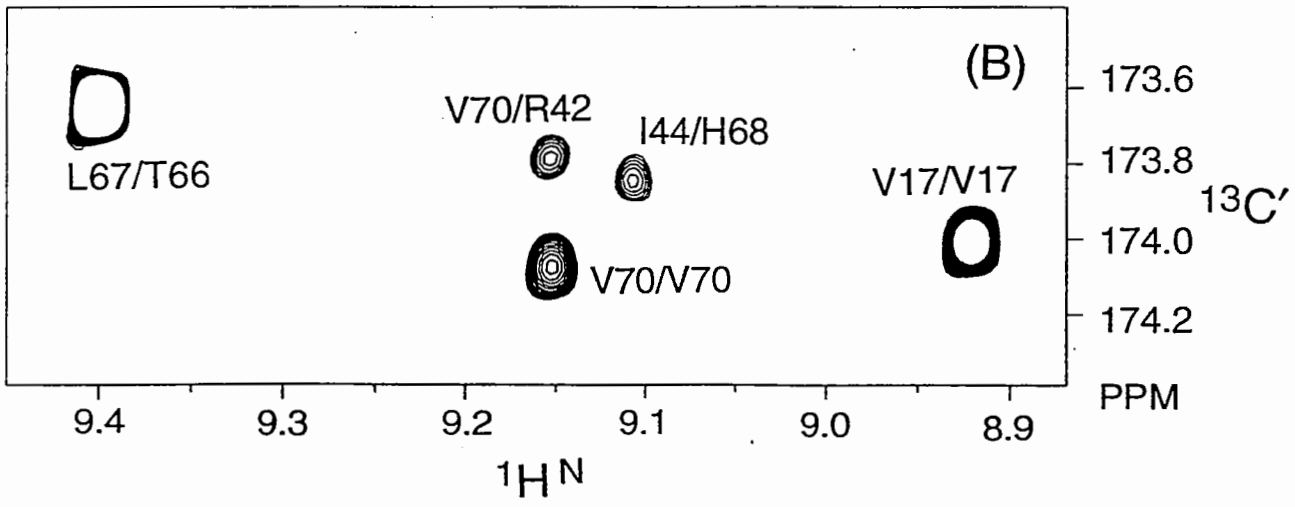


Figure 2. Small section of the 600 MHz 2D selective $^{1}H^{N}$-$^{13}C'$ HMQC spectrum of U-$^{2}H/^{13}C/^{15}N$ ubiquitin, recorded in H_2O. The $^{13}C'$ carrier was set to 175.3 ppm. The spectrum shows through-hydrogen bond J connectivities (V70/R42 and I44/H68), in addition to intraresidue correlations (V70/V70 and V17/V17), and one sequential correlation (L67/T66).

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(received 8/23/99) 17.8.99

Unser Zeichen:

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

Rotations or the Hausdorff equation

Dear Dr. Shapiro :

We all use with great benefit the product operator formalism and describe pulses, scalar couplings or offset phenomena by linear or bilinear rotations. I thought that it might be of interest to some reader to see the analytic way which can lead to these formulas. The central point thereby is the so called Hausdorff-equation (Hausdorff 1906) :

$$\exp(-i\hat{H}t)\,A = \Sigma_n\{(-it)^n/n!\}(\hat{H}^n A)$$

If we now assume that $(\hat{H}^0 A) = A$; and $(\hat{H}^1 A)$ = is the commutator [H, A] and so on, and further on use the so called Schmidt orthogonalization, these commutators can be replaced by a system of finite orthogonal operators (the system is finite as these spin problems are related to a finite Hilbert space). The analytical solution to the first and second order problem has been shown by Banwell and Primas 1963.

For a special second order problem it looks like this:

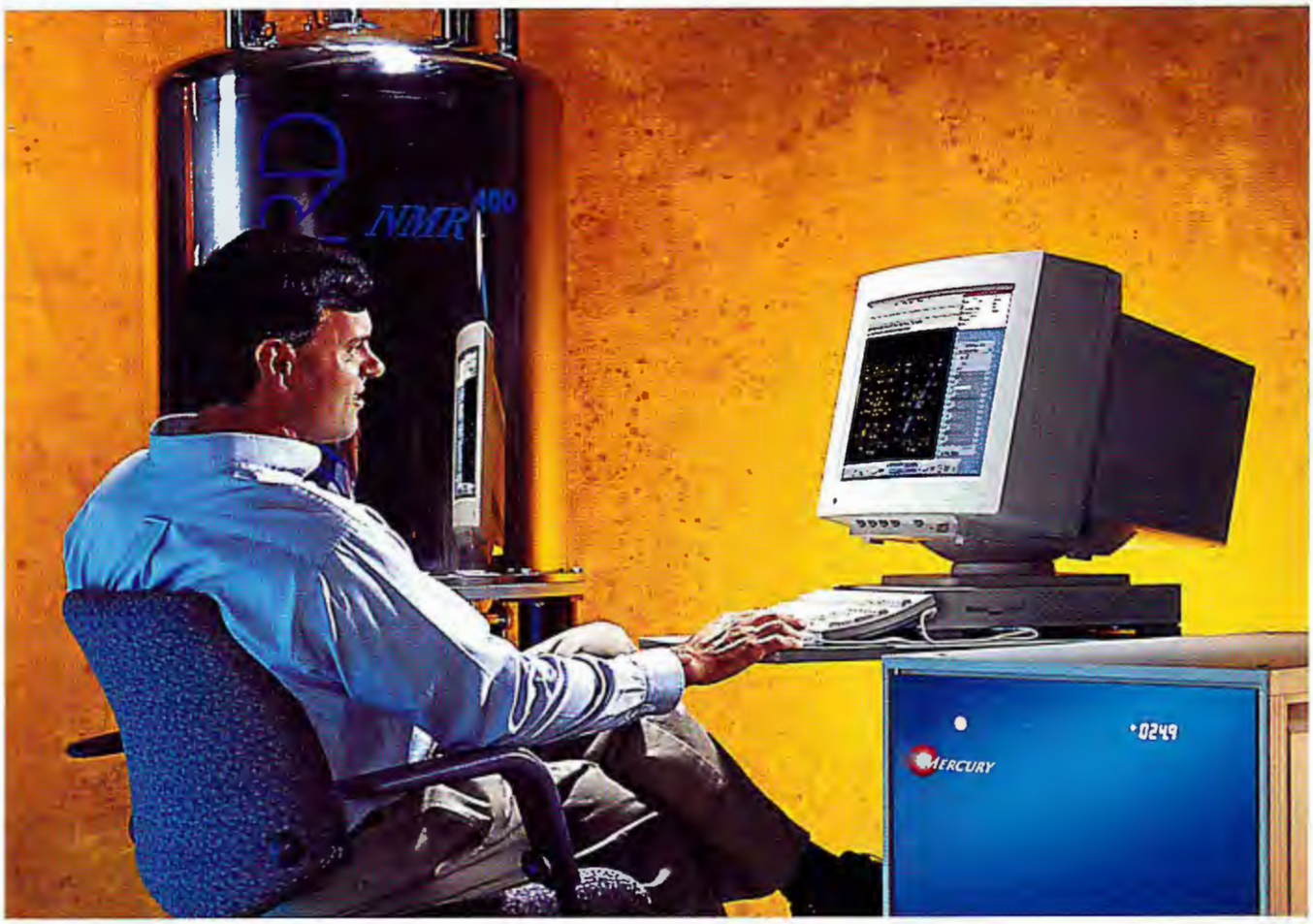
$\hat{H}A = \beta B$ and $\hat{H}B = \gamma A$ with Tr $\{A^+B\}$. we get

$$\exp(-i\hat{H}t)\,A = A\cos\lambda t - (i\beta/\lambda)B\sin\lambda t \text{ ; with } \lambda = (\beta\gamma)^{1/2}$$

H.Sterk

E.Königsberger

The Wait is Over.



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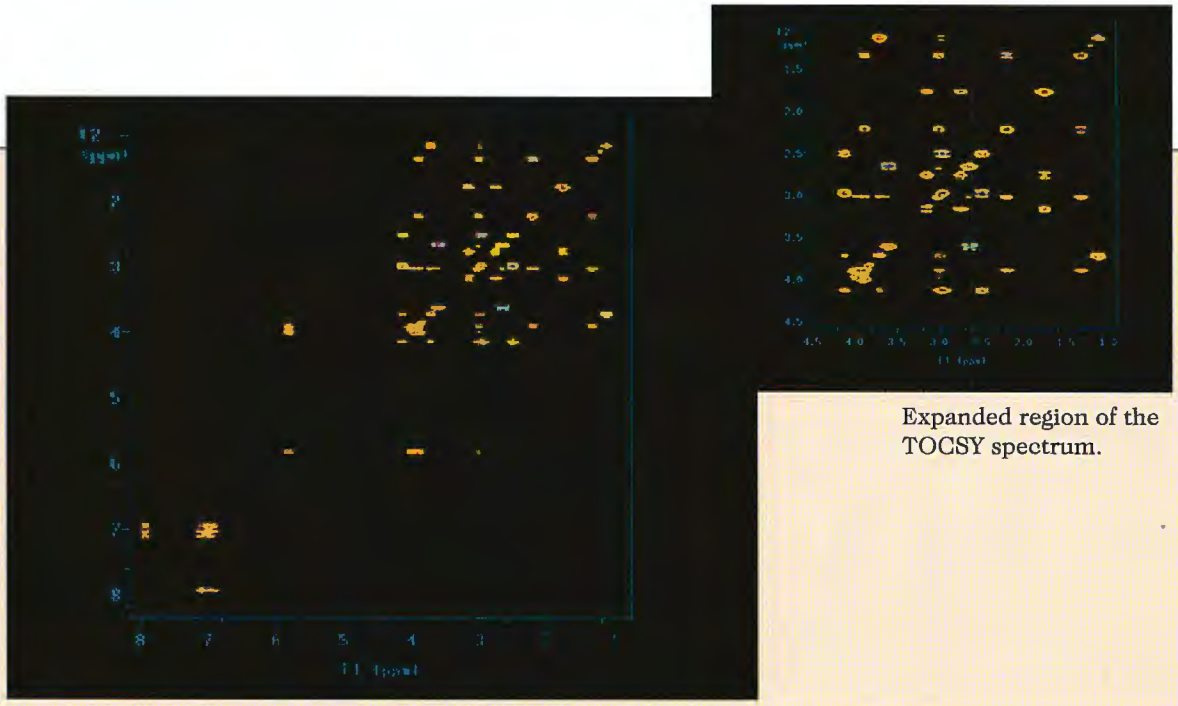
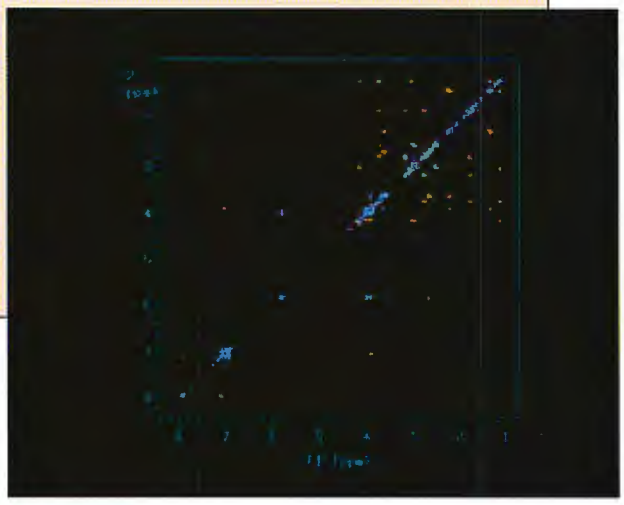


Expanded region of the TOCSY spectrum.

Spinlock experiments, such as this TOCSY spectrum of strychnine, are routinely performed with ***MERCURY***.



MERCURY features advanced experiment capability, as is demonstrated in this high-quality ROESY spectrum.

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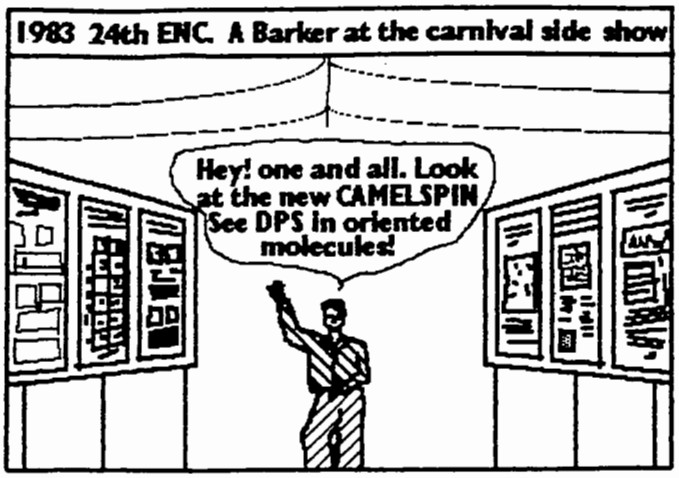

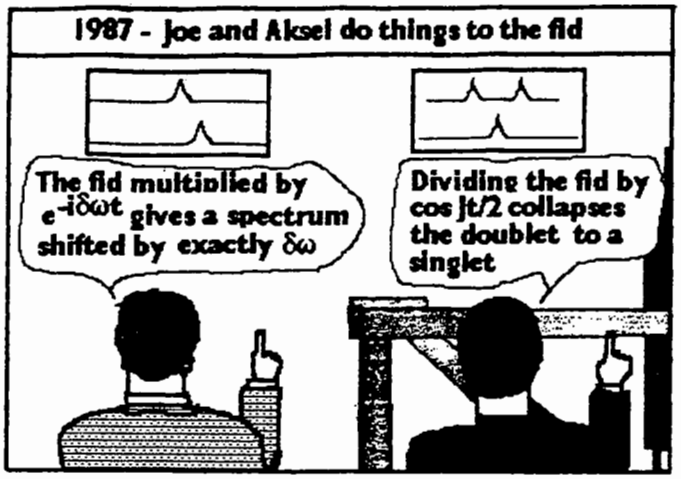

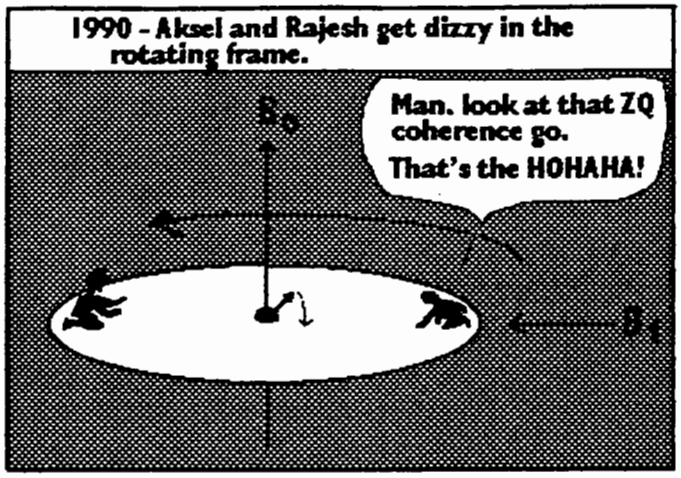

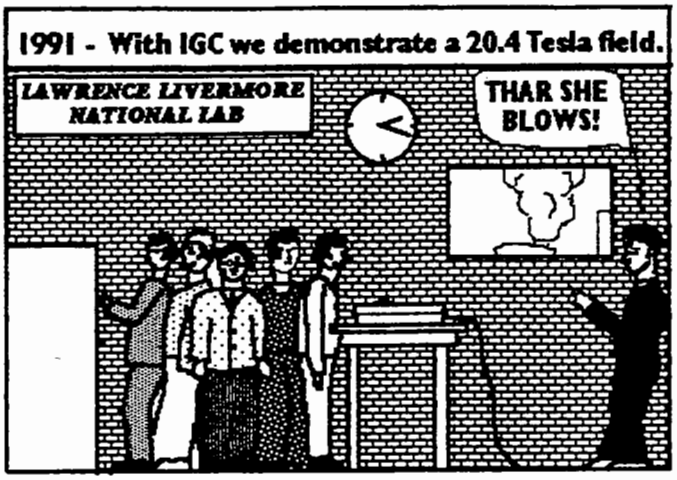

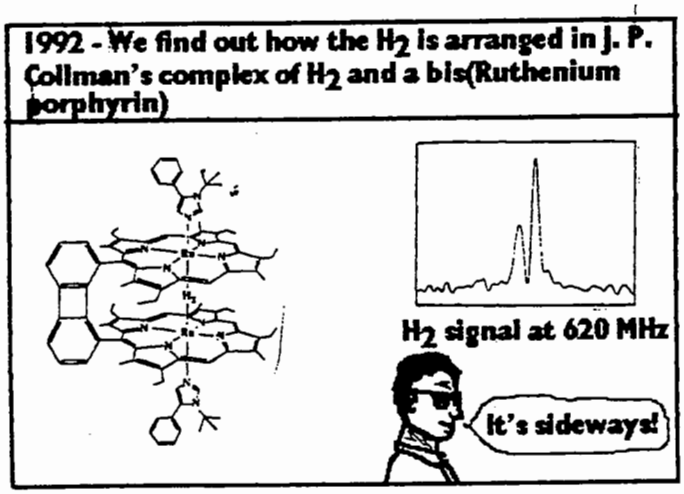

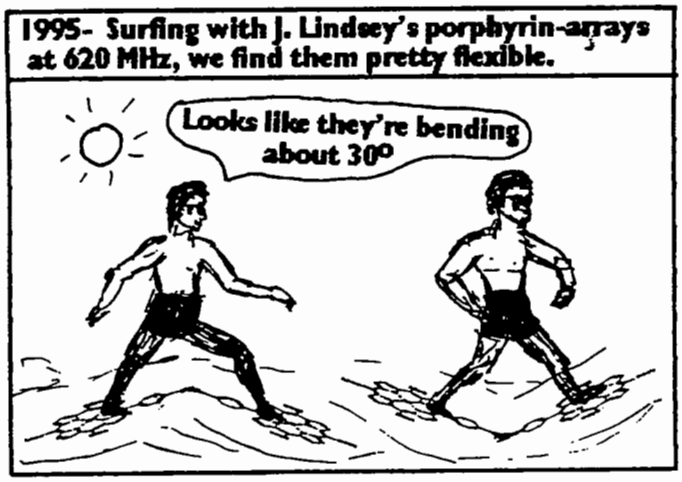

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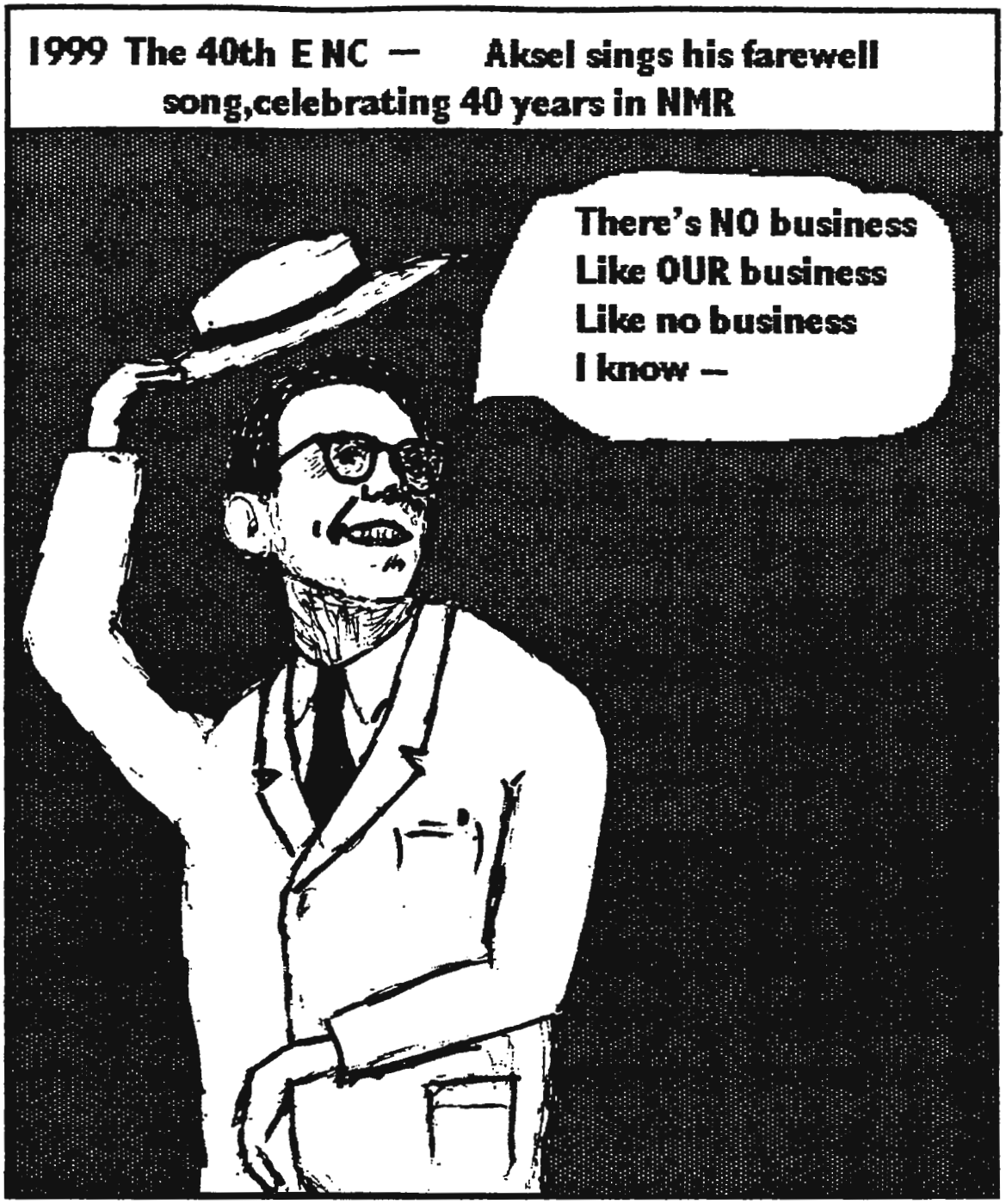

Sincerely,
Aksel A. Bothner-By
ab6d@andrew.cmu.edu

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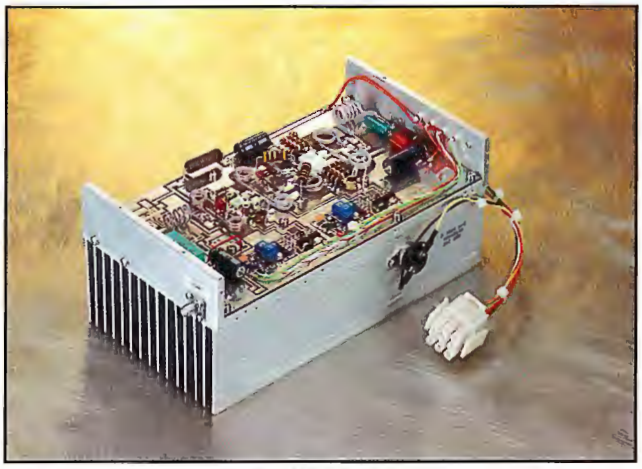
Model 3445 – 10 MHz to 130 MHz, 2.0 kW, MRI Amplifier



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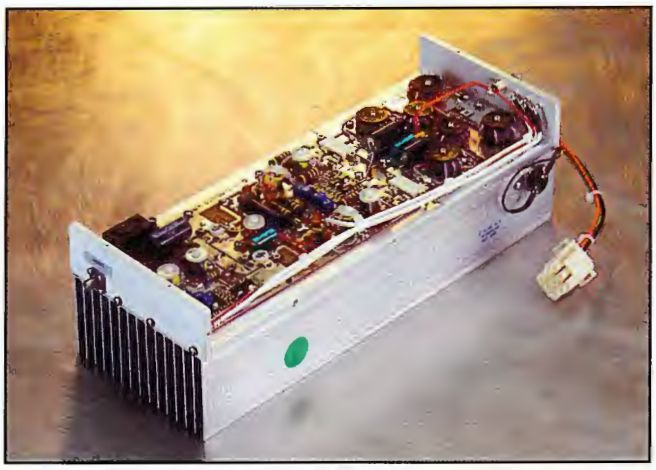

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SCIENTIFIC & MEDICAL PRODUCTS

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AMT designs, develops and manufactures custom radio frequency (RF) and microwave power amplifiers for the wireless, scientific/medical and application specific industries. The company has been in business since 1984 and currently has over 60 employees, including 20 experienced engineers.

AMT has a worldwide reputation as a leading supplier of high power, solid state power amplifier products that operate at frequencies between 1 MHz and 3 GHz and provide RF power from several watts to several kilowatts. Its products are noted for their exceptional performance, highest quality and superior reliability.

The company's products are sold to numerous major corporations, universities and research centers throughout the world.

FACILITIES

AMT is located in Anaheim, California and occupies a 25,000 square foot facility allocated to engineering, manufacturing, quality assurance, marketing/sales, administration and finance.

Engineering areas include an R & D laboratory, a tool and die shop, mechanical design and drafting areas, an environmental testing laboratory and document control. The R & D laboratory is equipped with all of the latest design and testing equipment including intermodulation distortion simulators, network analyzers, spectrum analyzers, signal generators, noise figure meters and infrared (IR) scanners. The environmental testing laboratory includes equipment to simulate shock, vibration and thermal environments.

Manufacturing areas include a controlled access stock room, a 10,000 square foot assembly area and a production test area employing automatic testing. Also included is an environmental laboratory used for environmental stress screening of production products.

PRODUCTS

AMT's products vary in complexity from single modules, to rack-mounted amplifiers, to complete transmitter systems. The rack-mounted amplifiers and complete transmitter systems typically include detection/protection circuitry, built-in power supplies, front panel metering and digital and/or analog interface controls. Both forced air and/or water cooling are used, depending on the customer's requirements.

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Joseph B. Lambert
Clare Hamilton Hall Professor of Chemistry

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Internet jlambert@nwu.edu
Facsimile (847) 491-7713
http://www.chem.nwu.edu/~lambert/

August 16, 1999
(received 8/19/99)

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

Dear Barry:

We are continuing our work in organosilicon chemistry, and the ratio of silicon to carbon seems to be increasing. We recently synthesized the largest dendritic polysilane (**1**, see *Organo-*

1 $MeSi[SiMe_2\text{-}Si(SiMe_3)_2\text{-}SiMe_2\text{-}SiMe_2\text{-}Si(SiMe_3)_3]_3$

metallics, **17**, 4904 (1998)) and proved its structure by X-ray crystallography. Polysilanes offer useful properties as materials, including conductivity and photolithography. Molecule **1** has 13 silicon atoms in the longest polysilane chain. Assignment of the ^{29}Si resonances of the eight distinct silicon atoms, however, is difficult. By comparison with other systems, ranges can be set for the four types of silicon: Me_3Si (δ ca. -9), Me_2Si (δ ca. -26), MeSi (δ ca. -66), and Si (δ ca. -120) (all other connections are to Si). The only definite assignment that can be made is for the unique MeSi resonance, δ -66.1. This atom in fact serves as the core of the dendrimer.

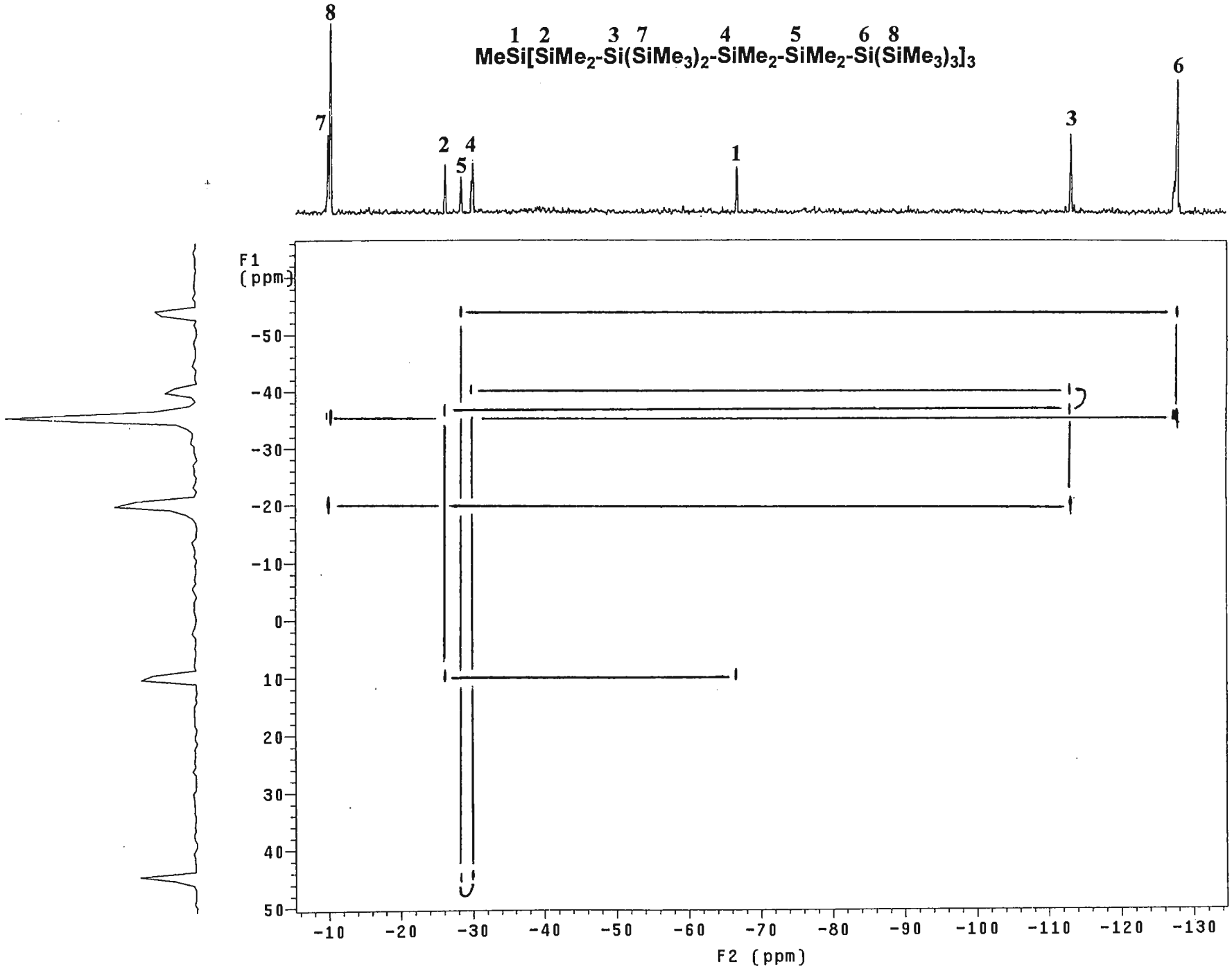
In order to complete all the assignments, we have used the ^{29}Si-^{29}Si 2D INADEQUATE method (*J. Organomet. Chem.*, **554**, 113 (1998)). The complete spectrum is shown on the next page. The INADEQUATE walk begins with the unique MeSi atom, labeled Si1 in the structure on the spectrum. The indicated series of horizontal and vertical lines then leads to an unambiguous assignment for each of the other peaks, as shown for the resonances in the 1D spectrum across the top. This 2D experiment is the structural method of choice for complex polysilanes. The 1D INADEQUATE experiment is not so useful, because of the close similarity of many of the ^{29}Si-^{29}Si coupling constants.

Sincerely,

Hongwei Wu

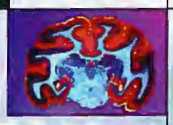
Joseph B. Lambert

Title: 2D INADEQUATE of Complex Polysilanes


8
1 2 3 7 4 5 6 8
MeSi[SiMe2-Si(SiMe3)2-SiMe2-SiMe2-Si(SiMe3)3]3
7
2 4
5
1
3
6
F1 (ppm)
-50
-40
-30
-20
-10
0
10
20
30
40
50
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130
F2 (ppm)







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(received 8/13/99)
5th August 1999

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

Dear Dr. Shapiro,

Mapping the Dynamics with TEMPO

Rac is a small GTPase regulating the NADPH oxidase activity in phagocytes by switching between inactive GDP and active GTP-bound form. Guanine nucleotide exchange inhibitor Rho-GDI binds to the inactive form of Rac and controls its partitioning between cytosol and membrane. The spatial structure of GDI is known and it consist of two domains, the folded C-terminal and a flexible N-terminal domain. The flexible domain is essential for binding Rac. Our results demonstrate the presence of small population of helical conformation in this unstructured region (manuscript in preparation).

To investigate further the residual structure of N-terminal domain, we used a paramagnetic relaxation reagent, 4-hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxy (HyTEMPO) to probe the surface exposure of amide protons. Longitudinal relaxation rates of amide protons were measured at different concentrations of HyTEMPO using inversion-recovery version of 2D ^{1}H-^{15}N-TROSY experiment for ^{15}N-labelled rho-GDI2. For all residues of N-terminal domain paramagnetic contributions of longitudinal relaxation rate $R_{1\rho}$ had linear dependence upon concentration of HyTEMPO (in the range up to 4 mM). The slopes of these dependencies measured for each residue, R_{TEMPO}, reflect the relative accessibility of residue to solvent (Fig. 1). Such analysis clearly revealed that two regions at N-terminal flexible domain - residues 12-22 and 34-47 - are less accessible to solvent. Regions 25-32 and 54-56 are more exposed to solvent; the last region is a protease cleavage site.

The method described here can be applied to study surface exposure of different parts of unfolded or partially folded proteins and complement currently widely used molecular dynamics techniques (i.e., measurement of relaxation parameters T_1, T_2 and NOE) using the same ^{15}N-labelled protein samples.

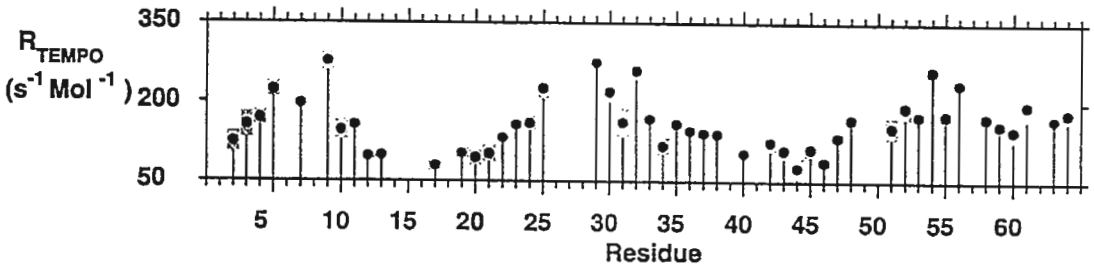

Fig.1

Please credit this contribution to Gordon Roberts's subscription.

Sincerely,

A.Golovanov, I.Barsukov, L.-Y. Lian, G.C.K. Roberts

POSTDOCTORAL POSITION

A NSF-funded position is open starting this fall to study protein dynamics by NMR relaxation and computation. Available equipment includes two new fully equipped 600 and 400 MHz spectrometers and DEC-alpha and SUN Sparc-Ultra workstation clusters. Applicants should have experience in either NMR of labeled proteins or molecular dynamics computer simulations or quantum-chemical calculations of NMR parameters. Send c.v. and names of three references to Prof. Rafael Brüschweiler, Gustaf H. Carlson Chair, Department of Chemistry and Biochemistry, Clark University, Worcester, MA 01610 (Clark University is about 1 hour from Boston by car). E-mail: bruschweiler@nmr.clarku.edu

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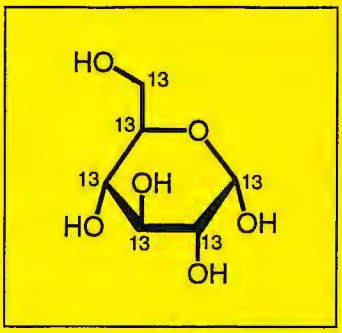

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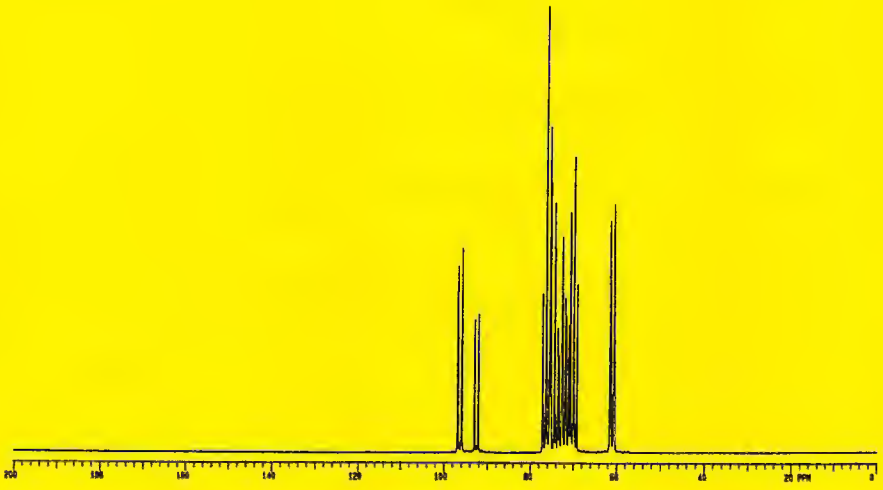
Isotopic Enrichment:	**min. 99 atom %**
Water Content:	<0.50%



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85-610-03-8	ISOGRO™-^{15}N Powder Growth Medium	99
81-610-02-4	ISOGRO™-^{13}C, ^{15}N Powder Growth Medium	99 ^{13}C 99 ^{15}N

Typical Batch Analysis of ISOGRO™ Powder

Isotopic Enrichment:	99 atom% ^{13}C and/or 99 atom% ^{15}N
Total Carbon:	~28%
Total Nitrogen:	~9%
Salts:	~30%
Water:	~3%
Glucose:	~1-3%

Typical Procedure for **Growing** *E. coli* Using ISOGRO™ Powder

To prepare **100mL** ISOGRO™ medium, we suggest the following:

1. Dissolve 1.0g of ISOGRO™ powder in about 90mL of Millipored water.
2. Make stock solutions of the following salts and use the quantities indicated in the medium preparation:

Salt	Conc. of Stock Soln.	Qty./100mL medium
K_2HPO_4	100g/L	1.8mL
KH_2PO_4	50g/L	2.8mL
$MgSO_4$	50g/L	2.0mL
$CaCl_2 \cdot H_2O$	37g/L	30µL

3. Adjust pH to 7.0 with NaOH and bring solution up to 100mL with Millipored water.
4. Pass the solution through a 0.22µM filter and transfer the filtrate to an autoclaved shaker flask (for example: 50mL medium in a 500mL flask).
5. The culture is inoculated with a loop of *E. coli* which has been maintained on a nutrient agar slant.
6. Shake the culture flask in a 37°C water bath.
7. The absorbance of the culture is measured at 600nM with a 1:3 dilution into water.

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FEBRUARY 1997

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Email: ldh11@hslmc.cam.ac.uk
www.hslmc.cam.ac.uk
10th August 1999
(received 8/16/99)

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

Dear Barry

The Herchel Smith Laboratory for Medicinal Chemistry

This contribution is largely intended to draw the attention of your readers to the range of research currently in progress in my Department and the possibility that some readers may be able to participate. I shall not attempt to give the basic facts since those are available directly on our web site. However, we currently have 5 MRI scanners in the HSLMC: one based on a 100cm bore 2 Tesla magnet; three on 31cm horizontal bore 2 Tesla magnets and one on a 8.9cm vertical bore 7 Tesla magnet. All scanners are driven by Bruker consoles based on MSL electronics and connected to a large network of Pentium computers running either LINUX or WINDOWS NT. All the gradient and radiofrequency coils are home built.

All three major research programmes are sponsored by industrial contracts.

1. Clinical Research
We have developed a range of MRI protocols which enable us to measure accurately the dimensions of different organs, and to quantitate the MRI parameters of their water and/or fat content. We are particularly interested in articular joints, brain and heart. For the former we now have "virtual arthroscopy", and also "virtual punch biopsy" of localised volumes.

2. Fluid Flow
MRI is an extremely powerful method for measuring in three dimensions the entire flow velocity field of opaque fluids in opaque vessels. We use this potential in a variety of ways including measurement of the rheology of complex fluids, and studies related to process engineering, such as filtration or temperature mapping.

3. Food
It is well know that NMR spectroscopy can be used to study the composition of many foodstuffs. Our interest is to extend that approach to study "real" foods which are spatially heterogeneous, and the effects of processing on their texture. Often we combine our interests in "food" with those in "processing"; for example, we have recently used MRI to map in three dimensions microwave heating.

Cont/...

Although the choice of these topics may appear to be strange for a "medicinal chemical laboratory" their selection is partly motivated by the fact that the income that they produce supports a great deal of our "medical" work. Furthermore much of the methodology developed for those industrial areas has been directly applied to our medical research.

I am currently well advanced in restructuring my entire group and hope to have a substantial number of new opportunities for PhD students and postdoctoral fellows. Their background training is far less important than their enthusiasm for research.

In any event, I look forward to providing you in the near future some examples of the results which continue to encourage me to push ahead with our studies in this area.

Yours,

Laurie

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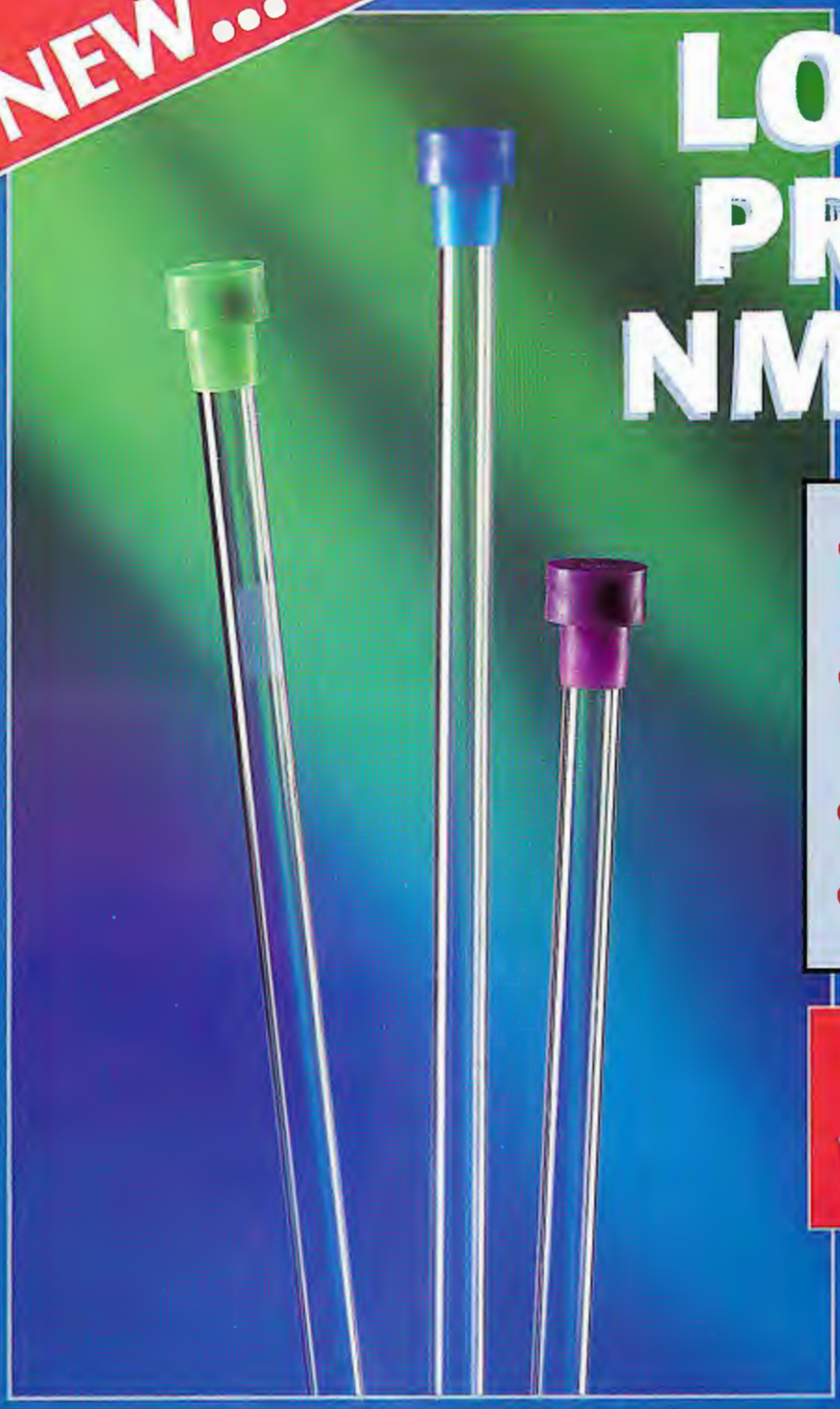

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Cambridge Healthtech Institute's Second International

LAB INSTRUMENTATION Series

NMR TECHNOLOGIES:

Development and Applications for Drug Discovery

November 4-5, 1999 • Sheraton Inner Harbor Hotel • Baltimore, Maryland

Major advances in NMR technologies continue to enable dynamic, molecular structure (SAR) studies leading to a greater understanding of some of the mechanisms of various diseases as well as targeted therapeutic drug design and discovery programs. New biomedical and materials sciences are fueling the development of high-field NMR spectroscopy as a more accessible tool for researchers. Researchers are continuing to develop new ways to share their NMR resources more efficiently and creatively, primarily over the Internet. Driving the interest in faster access to SAR analyses is genome research. Major emphasis will be placed on the application of NMR to drug discovery processes this year, including case studies and other examples from large pharmaceutical and biotech organizations.

SESSION TOPICS INCLUDE:

ADVANCES IN NMR TECHNOLOGIES AND METHODOLOGIES

Flow NMR Spectroscopy
Cryoprobes for NMR
Capillary-Based Microliter-Volume NMR
Solid-State NMR Approaches to the Study of Biomolecular Self-Assemblies
Autoscreen: Automated Processing and Analysis of Receptor/Ligand Binding NMR Data
Automated Analysis of Protein NMR Spectra
ASTER: Fast and Accurate NMR Structure Determination
High-Efficiency NOE Assignments and Structure Calculations

NMR FOR DRUG DISCOVERY

NMR Pattern Recognition of Biofluids
Structure-Based Drug Design
Structures, Interactions, and Dynamics of Protein-Ligand Complexes of Therapeutic Interest
PFG-NMR Detection of Anticancer Drugs Bound to Okazaki Fragments
Interaction of Cyclic Peptides with HIV-1 TAR RNA
SAR by NMR
Novel Applications of NMR SHAPES Screening in Drug Discovery
Application of NMR in High-Throughput Pharmaceutical Research and Development
Development of Affinity NMR
Alignment of Small Molecule Fragments That Interact with Protein Targets

Yes! Register me for NMR Technologies: Development and Applications for Drug Discovery **O96A9**

	Commercial	Academic, Government, Hospital-Affiliated
Advance Registration (by September 24, 1999)	☐ $895	☐ $445
On-site or Late Registration	☐ $995	☐ $470

☐ I cannot attend but would like to purchase a copy of the documentation binder for $195 (plus shipping).

☐ Please send information on exhibiting and opportunities to present workshops.

☐ I am interested in presenting a poster at **NMR Technologies: Development and Applications for Drug Discovery** and will submit an abstract by October 1, 1999.

Title_____

☐ Mr. ☐ Ms. ☐ Mrs. ☐ Dr. ☐ Prof.

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Invoices unpaid one week prior to conference will be billed to credit card at full registration rate.
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If you plan to register on site, please check with CHI beforehand for space availability.

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HOW DID YOU FIRST HEAR ABOUT THIS MEETING?

☐ Brochure
☐ Colleague
☐ Ad _____ (publication name)
☐ CHI Web Site
☐ Other_____

Please send information on related CHI programs:
☐ Protein Structure (PST)
☐ Molecular Diversity (MLD)
☐ Phage Display (PGD)
☐ Mass Spectrometry (MSP)

Register 3—4th Is Free

Individuals must register for the same conference or conference combination and submit completed registration forms together for discount to apply. Call for details on groups of 5 or more. (Applicable to paid registrations only.)

Additional Registration Details

Each registration includes all conference sessions, posters and exhibits, one luncheon and reception, continental breakfasts, all refreshment breaks, and a copy of the document binder.

Handicapped Equal Access: In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting.

Substitution/Cancellation Policy

In the event that you need to cancel a registration, you may:

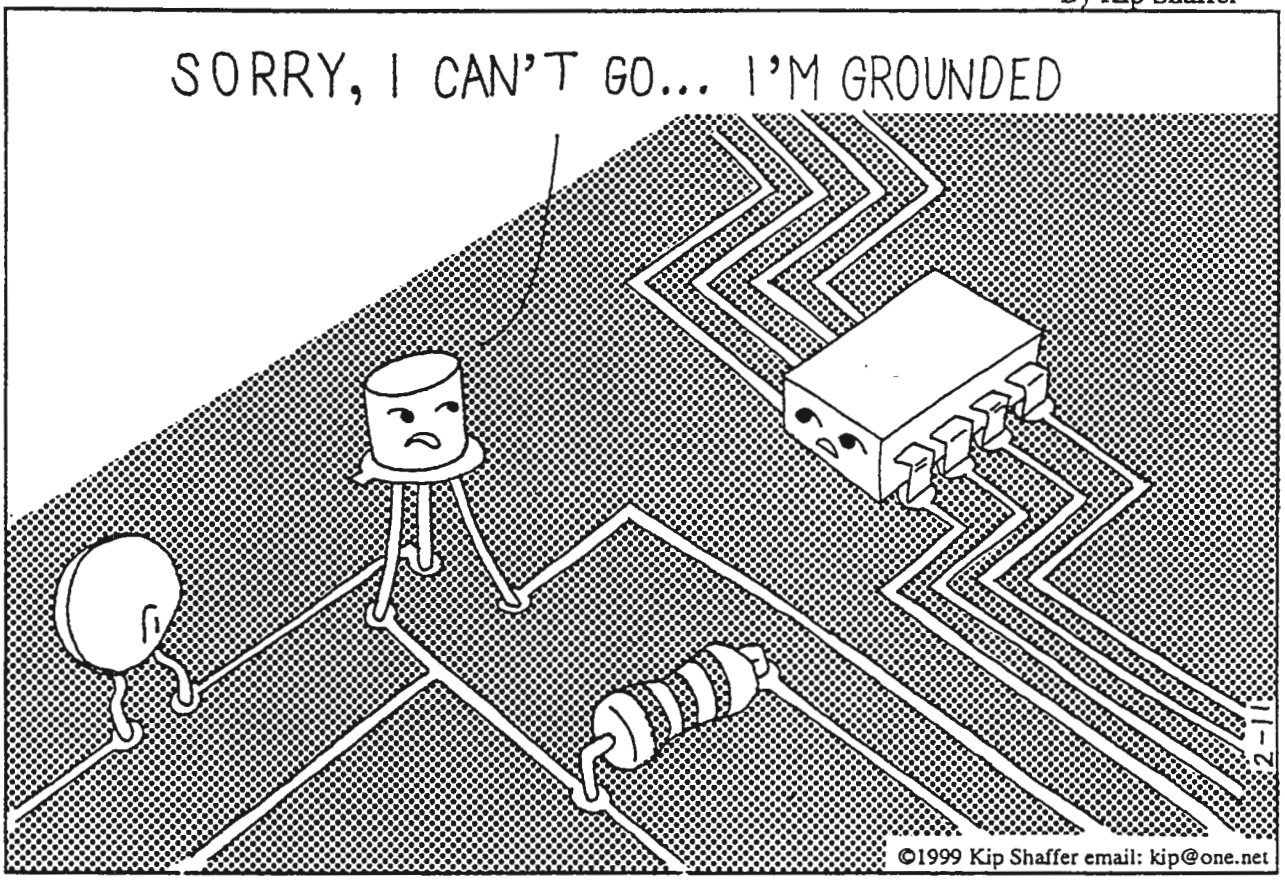
- Transfer your registration to a colleague within your organization
- Credit your registration to another Cambridge Healthtech Institute program
- Request a refund minus a $75 processing fee
- Request a refund minus the cost ($195) of ordering a copy of the document binder

NOTE: Cancellations will only be accepted up to one week prior to the conference.

Program and speakers are subject to change.

Field of Dreams

By Kip Shaffer



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Deadline Dates

No. 493 (Oct.) 24 Sept. 1999

No. 494 (Nov.) 22 Oct. 1999

No. 495 (Dec.) 26 Nov. 1999

No. 496 (Jan.) 24 Dec. 1999

No. 497 (Feb.) 21 Jan. 2000

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Forthcoming NMR Meetings, continued from page 1:

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

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

Additional listings of meetings, etc., are invited.

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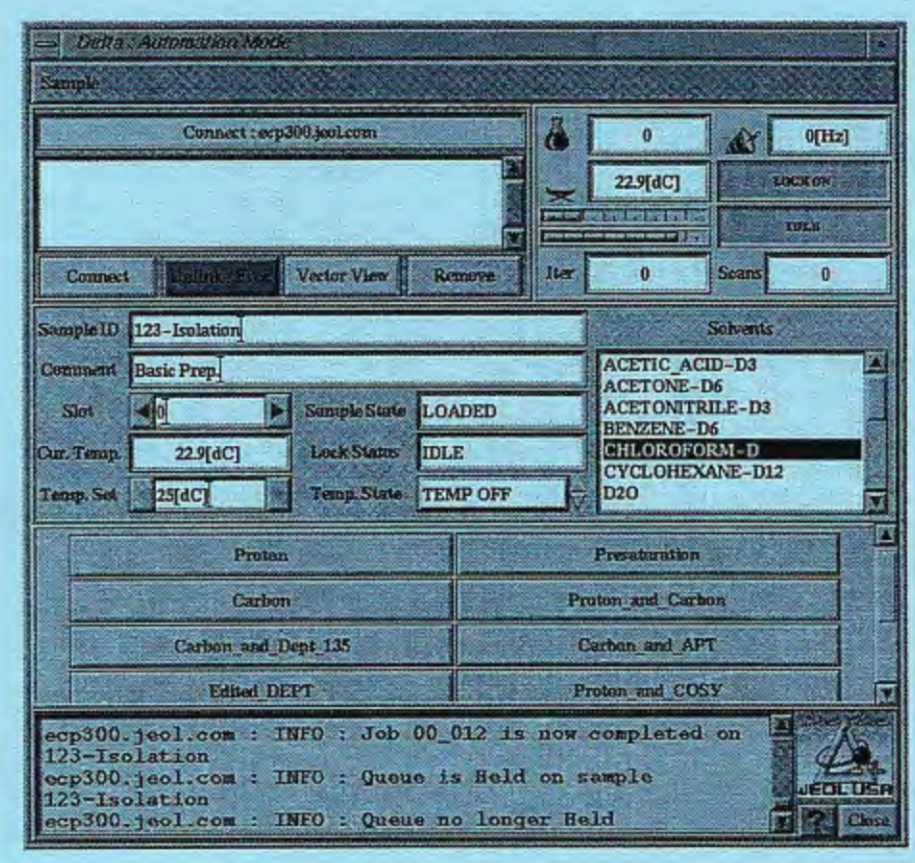

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