THE NMR NEWSLETTER

No. 511

April 2001

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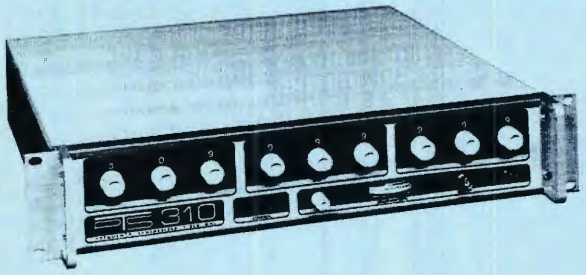

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FORTHCOMING NMR MEETINGS

Magnetic Resonance in Chemistry and Biology, XIth International Conference, Zvenigorod, Russia, **April 20-27,2001**. Contact: http://www.nmr.de/html/conf/zelino.shtml.

ISMRM 9th Scientific Meeting and Exhibition, and ESMRMB 18th Annual Meeting and Exhibition, Joint Annual Meeting, **April 21-27, 2001**; Contact: ISMRM Central Office, 2118 Melvia Street, Suite 201, Berkeley, CA 94704. Tel: 510-841-1899; Fax: 510-841-2340; 10th Annual Meeting of the Section for Magnetic Resonance Technologists, and 17th Annual Meeting of the British Association of MR Radiographers, **April 20-22, 2001** Glasgow, Scotland, UK; http://www.ismrm.org

Computational Aspects of Biomolecular NMR, Gordon Conference, "Il Ciocco", Barga (Pisa) Italy, **May 6-11, 2001**. Contact: Michael Nilges nilges@embl-heidelberg.de, or Dave Case case@scripps.edu.

13C Symposium and Training IX: Hepatic Gluconeogenesis, University of Texas Southwestern Medical Center, Mary Nell and Ralph B. Rogers Magnetic Resonance Center, Dallas, Texas, Thursday, **May 10, 2001**. Contact Janet Thach at janet.thach@utsouthwestern.edu. Please check our web page at http://www2.swmed.edu/rogersmr at a later date for details.

Spring New Mexico Regional NMR (NMR^2) Meeting, Albuquerque, NM, **May 12, 2001**; For further information contact Todd Alam (tmalam@sandia.gov) or Karen Ann Smith (karenann@unm.edu).

9th Chianti Workshop on Magnetic Resonance – Nuclear and Electron Relaxation, Tirrenia (Pisa), Italy, **May 26 – June 1, 2001**; http://www.cerm.unifi.it/chianti/chianti9.html. *Note: changed location.*

Fast Field Cycling Magnetic Relaxation Conference, Torino, Italy, **June 1-3, 2001**; http://nmr.ch.unito.it/meeting/ffcrelax/.

Gordon Research Conference on Magnetic Resonance, **June 17-22, 2001**, Roger Williams University, Bristol, Rhode Island (note the new, improved location !!!). Contacts: Rob Tycko, Chair, 301-402-8272, tycko@helix.nih.gov, and Kurt Zilm, Vice-Chair, kurt.zilm@yale.edu. Site description and application information available at http://www.grc.uri.edu.

continued on page 10

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Sensitivity Enhancement of Quadrupolar nuclei using RAPT

March 6, 2001
(received 3/12/2001)

Bernard L. Shapiro
The NMR Newletter
966 Elsinore Court
Palo Alto, CA 94303

Dear Dr. Shapiro:

While it was understood quite early in the history of NMR that the polarization of the central transition of quadrupolar nuclei can be enhanced by transferring polarization from the satellite transitions [1], attention was only focused on this possibility when Haase and Conradi[2] developed a technique for selective inversion of the outer satellite transitions using frequency swept adiabatic passages to enhance the central transition by a factor of 2I in static samples. Kentgens and Verhagen[3] later employed amplitude modulated double frequency adiabatic sweeps (DFS) to enhance the central transition polarization in samples under both static and MAS conditions. More recently we devised a simple technique called RAPT (Rotor Assisted Population Transfer)[4] where a fast 180 phase alternation pulse train during magic-angle spinning is used to prepare a selectively excited state in which the populations of all eigenstates $|m\rangle$ with the same sign of m are equal, resulting in an enhanced central $m = -1/2 \rightarrow 1/2$ transition polarization (see figure 1). Theoretically, the maximum enhancement factor of I + 1/2 can be obtained with this selective"saturation" of the satellite transitions (figure 2). Although polarization enhancement by selective saturation of the satellite transitions does not provide as high of an enhancement as selective inversion, it has the distinct advantage over selective inversion that it can be performed under sample rotation and obtained for all crystallite orientations simultaneously.

The sequence for obtaining the RAPT enhancement is shown in Fig 1. The relevant parameters in optimizing the RAPT pulse train are the rf field strength and modulation frequency. The optimum modulation frequency appears to be on the order of $\nu_m = C_q/4$ for a spin 3/2 nucleus, and may vary slightly depending on the value of η_q. We also found that the enhancement gradually increased with increasing rf field strength, and through numerical simulations we predict that the enhancement will diminish as one approaches the higher rf field strengths where the excitation of the central and satellite transitions are no longer selective. The enhancement factors are not critically sensitive to the RAPT pulse train modulation frequency or the rf amplitude, yielding a simple experimental protocol[4].

Such enhancement schemes can be easily combined with any solid-state NMR technique for quadrupo-

lar nuclei that draw their coherences from the polarization of the central transition. For example, we recently showed[5] that RAPT can enhance the sensitivity of the RIACT(II)[6] MQ-MAS experiment by a factor of 1.8 (figure 3). The spectrum of Fig. 3 was obtained with an rf field strength of 170 kHz, a modulation frequency(ν_m) of 695 kHz, and a RAPT pulse train duration of 90.7 μsec which is close to one rotor period, t_R = 83.3 μsec. The length of the selective central transition excitation pulse was 0.75 μsec, and the spin lock pulse was 20.83 μsec which is $t_R/4$, as specified by Wu et al.[5]. The interval τ between the RAPT preparation was increased to approximately 0.4 milliseconds to act as a z-filter, eliminating all transverse coherences and the need to modify the RIACT(II) phase cycle. The experimental enhancement factor of 1.8 is very close to the theoretical value of I + 1/2 = 2, showing the good agreement with theory. Moreover, it is particularly important to notice that the anisotropic MAS line shape observed using the RAPT enhancement is undistorted with respect to the conventional RIACT(II) experiment, indication that all the crystallites in the sample are affected in the same way by the RAPT preparation. Once again, the lack of distortion in the enhanced lineshape is one of the key advantages of this method.

We believe the RAPT sensitivity enhancement scheme will become a useful addition to the solid-state NMR spectroscopist's toolbox. Extension of these ideas to higher spin quadrupolar nuclei with greater enhancements has been possible, and such investigations are currently in progress.

Sincerely,

Hyung T. Kwak

Philip J. Grandinetti

[1] R. V. Pound, Nuclear electronic quadrupole interactions in crystals, *Phys. Rev.* **79** (1950) 685-702.

[2] J. Haase, M. S. Conradi, Sensitivity enhancement for NMR of the central transition of quadrupolar nuclei, *Chem. Phys. Lett.* **209** (3) (1993) 287-291.

[3] A. P. M. Kentgens, R. Verhagen, Advantages of double frequency sweeps in static, MAS, and MQMAS NMR of spin I=3/2 nuclei, *Chem. Phys. Lett.* **300** (1999) 435-443.

[4] Z. Yao, H. T. Kwak, D. Sakellariou, L. Emsley, P. Grandinetti, *Chem. Phys. Lett.* **327**(2000) 85-90.

[5] H. T. Kwak, S. Prasad, Z. Yao, J. R. Sachleben, L. Emsley, P. J. Grandinetti. *J. Magn. Reson.* (2001) in press

[6] G. Wu, D. Rovnyak, R. G. Griffin, Quantitative multiple-quantum magic-angle spinning NMR spectroscopy of quadrupolar nuclei in solids, *J. Am. Chem. Soc.* **118** (1996) 9326-9332.

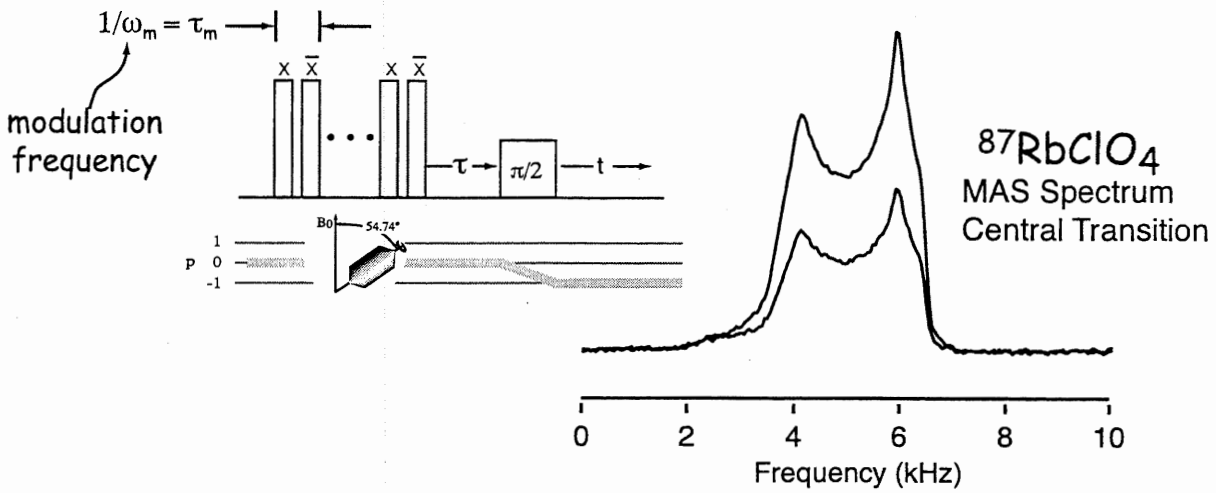

Fig 1. Pulsed Sequence for Rotor Assited Population Transfer (RAPT) from the satellites to the central transition for spin I = 3/2, and a experimental comparison of central transition spectra of ^{87}Rb in polycrystalline $RbClO_4$ with and without RAPT preparation. The spinning speed was 12 kHz. A RAPT modulation frequency and rf amplitude of ν_m=720 kHz and ν_1=175 kHz for $RbClO_4$ were employed. The RAPT pulse train duration was one rotor period.

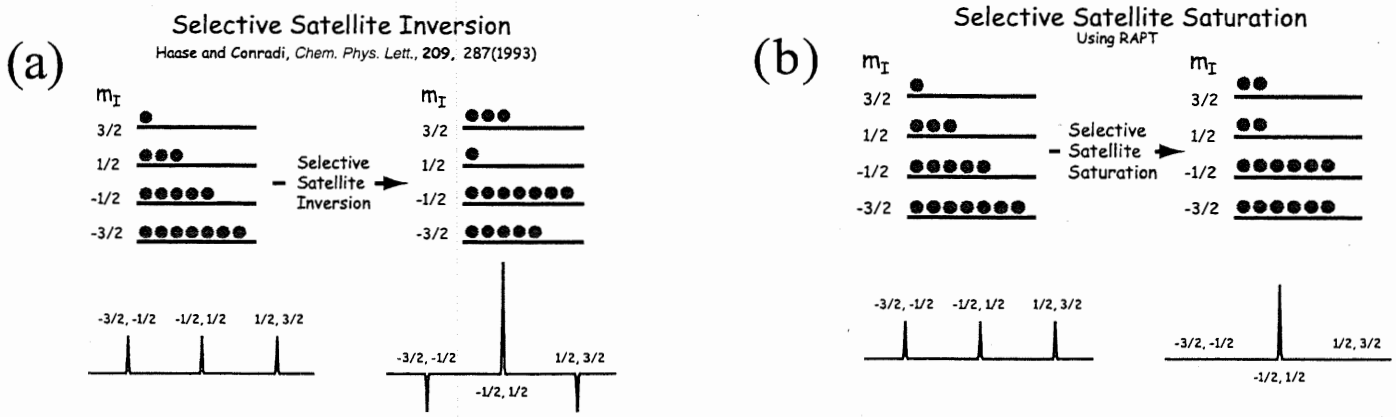

Fig 2. (a) Selective population inversion of the satellite transitions leads to a sensitivity enhancement of the central transition by a factor of 2I. (b) Selective excitation or saturation of the satellite transitions leads to a sensitivity enhancement of the central transition by a factor of I+1/2.

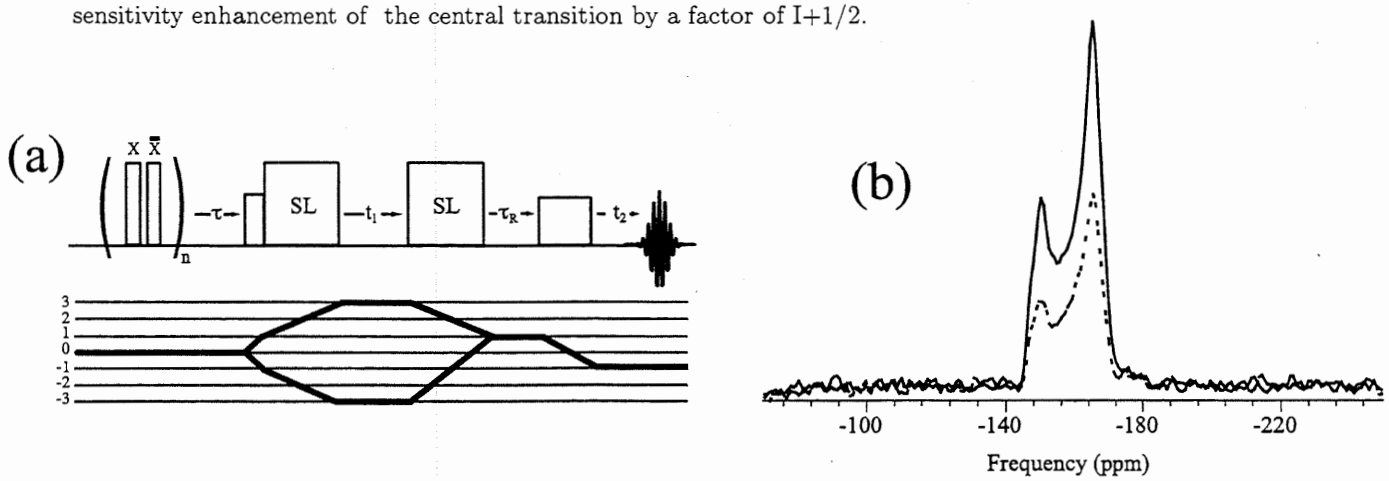

Fig 3. (a) RIACT(II) pulse sequence with RAPT pusle train. (b) A comparison of anisotropic MQ-MAS cross section of ^{87}Rb in polycrystalline $RbClO_4$ from RIACT(II) with and without the RAPT pulse train (solid line : RIACT(II) with RAPT, dashed line : RIACT(II) wihtout RAPT). A factor of 1.8 sensitivity enhancement was achieved by applying RAPT pulse train in front of RIACT(II).

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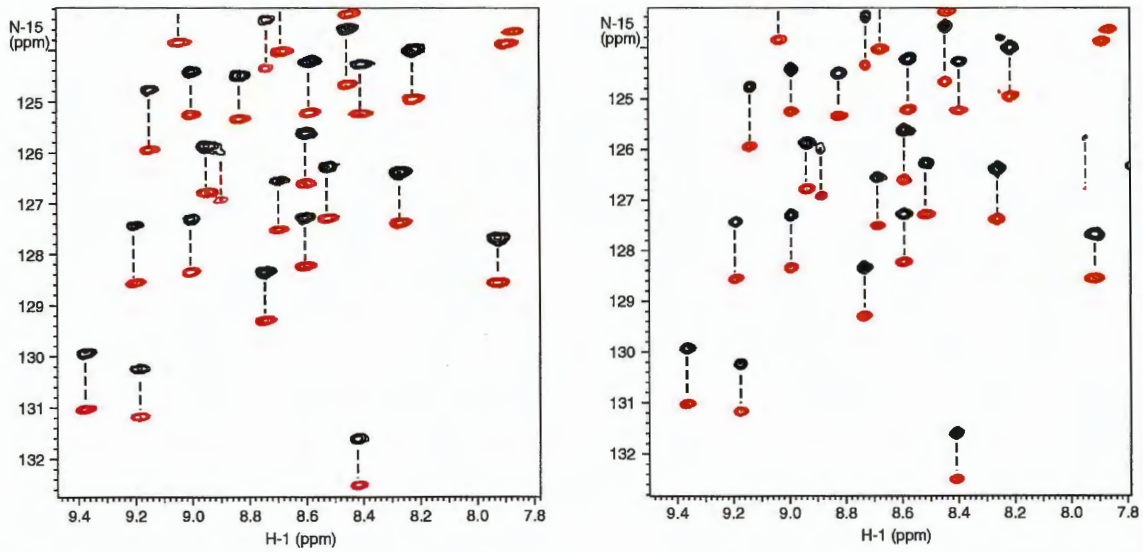
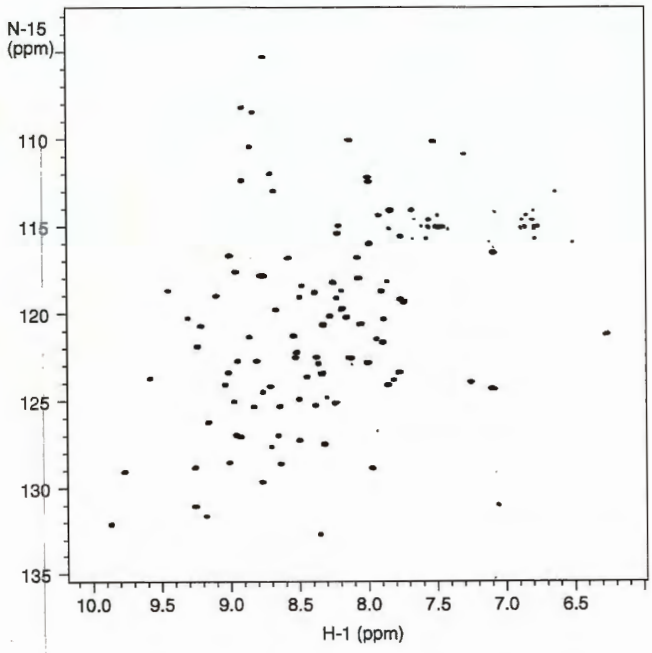


Measurement of residual dipolar N-H couplings at 900 MHz in partially oriented proteins with (right) and without the use of band-selective homonuclear decoupling.

TROSY at 900 MHz



The ^{15}N-^{1}H TROSY correlation spectrum of 6F1 1F2 module pair from the gelatin-binding domain of fibronectin. Sample courtesy of Prof. .I.D. Campbell of Oxford University.

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Princeton University **Department of Chemistry**
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(received 3/5/2001)

Re: Phasing COSY to all-dispersive (COSY^{DD})

Dear Barry,

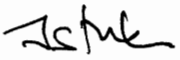
This is an old tune, but Frank Delaglio's recent contribution about an additional tool provided for the excellent software NMRPipe [1] encouraged me to remind COSY users to a simple trick.

Frank's enhancement makes it easy to remove diagonal resonances, which can be beneficial to many correlation experiments, especially to phase-sensitive COSY. In these spectra large diagonal peaks are phased dispersive, therefore can be overwhelming, and obscure cross peaks close to the diagonal. (See – a fairly old – COSY of cyclosporin in Figure 1, *top*.) Removing the diagonal peaks using data processing (either in frequency domain or in time domain) provides an attractive remedy to this problem (Figure 1, *middle*). Such applications were published for 1D application [2a], then for 2D simultaneously by Luciano Mueller's group using Felix [2b], and myself [2c] using ***NMRi*** software at that time (much of which was developed by Frank himself).

However, there is a trick, one can consider as an even simpler alternative, and provides additional benefits [3] also. The active coupling constant (which leads to antiphase character of the multiplet structure in cross peaks) is often comparable to, or is smaller than the linewidth. It happens either by the nature of the sample (larger molecules, viscous solvent, etc.), and/or by selecting relatively short acquisition times in both dimensions to save data size and acquisition time. In this case phasing the cross peaks dispersive in both dimensions (**COSY^{DD}**) leads to a simplified pattern and provides increased sensitivity ("for free") with decreasing ***J***/linewidth ratio. The ***DD*** phasing can be applied with the same benefit to all kinds of antiphase cross peaks.

As far as the diagonal is concerned, in a **COSY^{DD}** it becomes absorptive with much less interference with its neighborhood (Figure 1, *bottom*), therefore one can spare suppressing it. The procedure boils down to acquiring a pure-phase COSY and simply phasing the cross peaks dispersive (the diagonal absorptive) in both dimensions. Never say never... – but there is little justification left to collect DQF-COSY any more.

With my best regards,



(István Pelczer)
ipelczer@princeton.edu
Department of Chemistry
Princeton University

References:

[1] Delaglio, F., Wu, J., and Bax, A.; "Numerical Diagonal Suppression in COSY" *TNN* August 2000

[2] a) Tsang, P., Wright, P. E., and Rance, M.; "Signal Suppression in the Frequency Domain to Remove Undesirable Resonances with Dispersive Lineshapes" *J. Magn. Reson.*, 88(1990)210-215

b) Friedrichs, M. S., Metzler, W. J. Mueller, L.; "Removal of Diagonal Peaks in Two-Dimensional NMR Spectra by Means of Digital Filtering" *J. Magn. Reson.*, 95(1991)178-183

c) Pelczer, I.; "Correlation Spectroscopy at a Bargain: SIMPLE-COSY" *J. Am. Chem. Soc.*, 113(1991)3211-3212

[3] a) Pelczer, I., and Carter, B. G.; "Data processing in Multidimensional NMR" In: *"Protein NMR Techniques"* Vol 60. in the Series: *Methods in Molecular Biology* (Ed.: D. G. Reid), Humana Press, Totowa, NJ, 1997, pp. 71-156.

b) Also in: "*Protein Protocols*" on CD-ROM (Ed.: J. M. Walker), Humana Press, Totowa, NJ, 1998

Figure 1

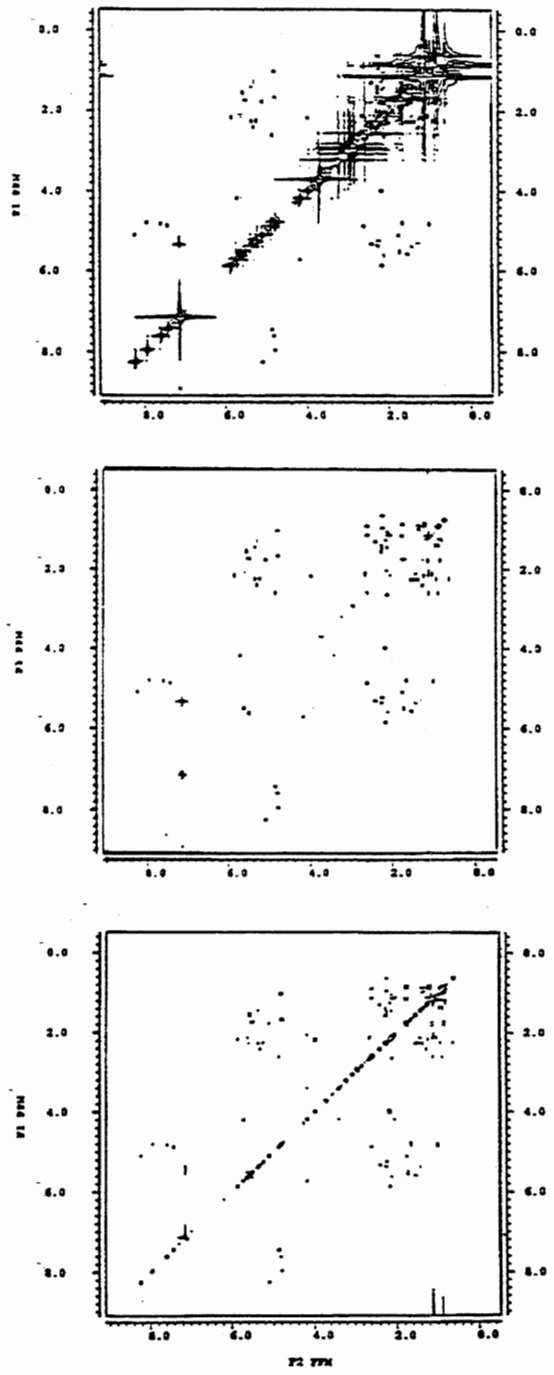


Figure 1. COSY spectrum of cyclosporin A dissolved in C_6D_6. (*top*) Result of conventional processing, the cross-peaks are phased pure absorptive. (*middle*) The same spectrum after the diagonal was removed through data processing. (*bottom*) All-dispersive COSY (***COSY***^{DD}), the cross-peaks are phased dispersive. Contour levels are cut identically for all spectra.

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

February 15, 2001
(received 2/26/2001)

"Deuterium exchange study revealed hydrogen bonding between N and C termini in the MMP-13/CGS27023 structure"

Dear Dr. Shapiro,

In our attempts to identify hydrogen bonds in MMP-13/CGS27023 complex structure (1), we have carried out a deuterium exchange experiment. As expected, very slow amide proton exchange was observed in 100% D_2O buffer for residues 134-149, 216-230, and 257-266, which define all three α-helices. For the five β-sheet strands, residues 118-121, 123, 124 in β-1, residues 151,152, 154, in β-2, residues 163-168 in β3, residues 185-187, 189 in β-4 and 197-201 in β-5, slow exchange in deuterated buffer was observed consistent with their hydrogen bonding interactions. Residues whose amide protons did exchange rapidly in the β-sheet regions included Ile 122, Phe 153, Arg 155, and Ala 188. In accordance with the three dimensional structure, these protons are in an unprotected environment and not involved in hydrogen bonding. The amide protons of loop residues Leu 239 and Met 240 did not undergo rapid deuterium exchange. These residues form a tight turn at the base of the S1' binding pocket, near the catalytic zinc which places them in a protected environment and therefore less susceptible to exchange with heavy water. It is interesting that tryptophan ring proton HE1 experienced slow exchange for residues 113, 145, 207. The side chains of residues 145 and 207 are buried in the core of the protein and protected from solvent exchange, however Trp 113 is near the N-terminus and not buried in the protein core. Examination of the structure reveals that this ring NH can form a hydrogen bond of approximately 2.07 Å with the carboxylate side chain of Asp 270. Also, the amide proton of Glu 271 does not undergo rapid deuterium exchange. Structure shows the amide proton to be surrounded by carboxylate groups from residues Asp 270, Glu 271 and Asp 272 that can act as hydrogen bond acceptors. In addition, Glu 271 [NH] resides in an environment protected by the Trp 113 ring moiety and oriented to hydrogen bond with the carbonyl oxygen of Trp 113 (Figure 1). This deuterium exchange data is corroborated by NOEs between Trp 113 [HA]-Glu 271 [HN], Trp 113 [HE3]-Glu 271 [HN], Trp 113 [HE1]-Asp 270 [HA], Trp 113 [HA]-Asp 270 [HN], Ser 114 [HA]-Glu 271 [HN], Ser 114 [HN]-Glu 271 [HA], Ser 114 [HB2]-Asp 272 [HN], Ser 114 [HA]-Asp 272 [HN], Ser 114 [HA]-Asp 270 [HN], Lys 115 [HN]- Asp 270 [HN], Lys 115 [HN]-Gly [HA2] and Met 116 [HN]-Glu 271 [HB2], Met 116 [HB1]-Gly 269 [HN], Met 116 [HN]-Tyr 266 [HE1] and Met 116 [HN]-Tyr 266 [HD1] which define the close proximity between the N- and C-termini.

Sincerely,

Ki-Yean Nam, Nina C. Gonnella, Ph.D. Xiaolu Zhang, Ph.D.

1. Zhang X., Gonnella N.C., Koehn J., Pathak N., Ganu V., Melton R., Parker D., Hu S., Nam K. (2000), *J. Mol. Biol.* **301**, 513-524.

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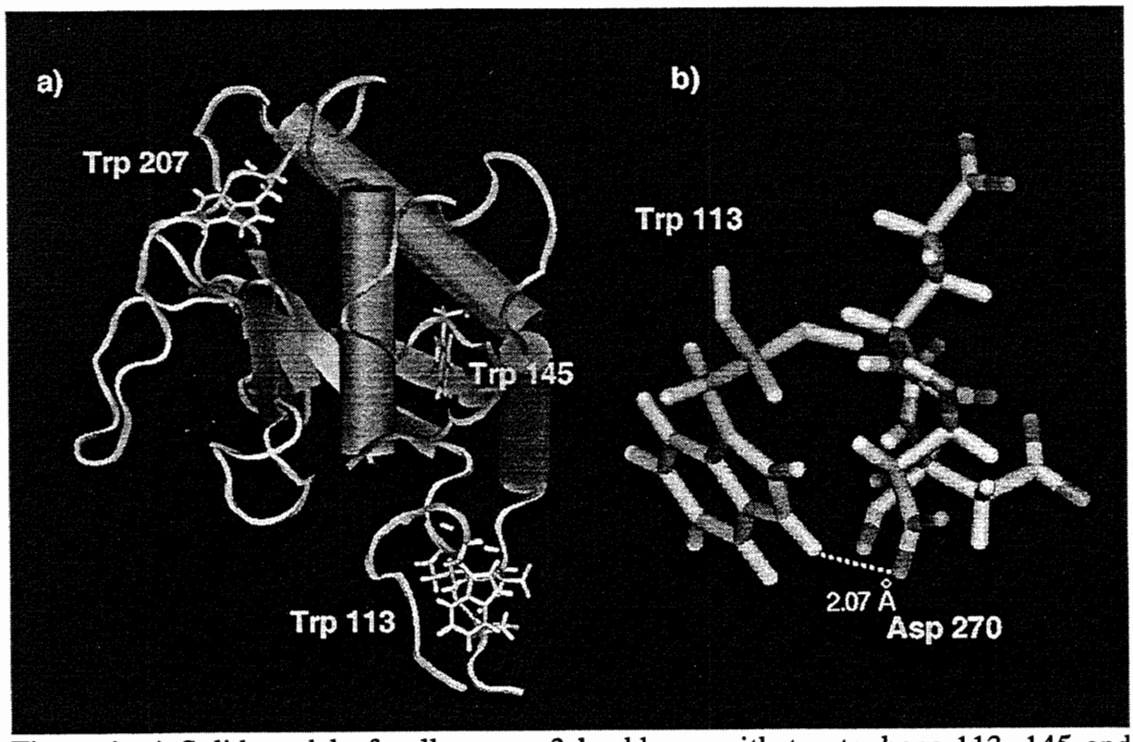

Figure 1. a) Solid model of collagenase-3 backbone with tryptophans 113, 145 and 207 that show slow deuterium exchange. b) Expanded view of Trp 113 which experiences slow exchange due to a hydrogen-bonding interaction with the carboxylate side chain of Asp 270.

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Forthcoming NMR Meetings, continued from page 1:

IXth International Symposium on Magnetic Resonance in Colloid and Interface Science, St. Petersburg, Russia, **June 26-30, 2001**. Contact: Mrs. L. Ya. Startseva, Secretariat of ISMRCIS, Boreskov Institute of Catalysis, 5, Prosp. Akad. Lavrentieva, Novosibirsk, 630090, Russia. Tel: +7 (3832) 34-12-97; Fax: +7 (3832) 34-30-56; E-mail: star@catalysis.nsk.su.

Royal Society of Chemistry: 15th International Meeting on NMR Spectroscopy, Durham, England, **July 8-12, 2001**; Contact: Mrs. Paula Whelan, The Royal Society of Chemistry, Burlington House, London W1J 0BA, England; tel: +44 (0) 207-437-8656; fax: +44 (0) 207-734-1227; Email: conferences@rsc.org\; Use the subject header '01NMR15'

ESR and Solid State NMR in High Magnetic Fields, Stuttgart, Germany, **July 22-26, 2001**. Contact: Prof. Hans Paus, 2 Physikalisches Institut, Universität Stuttgart, Pfaffenwaldring 57, D-70550 Stuttgart, Germany. Tel: ++49-711-685-5223 or -5217; Fax: ++40-711-685-5285; E-mail: ampere2001@physik.uni-stuttgart.de.

43rd Rocky Mountain Conference on Analytical Chemistry, Denver, CO, **July 29 – August 2, 2001**; www.milestoneshows.com/rmcac

ISMAR 2001, Rhodes, Greece, **August 19-24, 2001**; See http://www.tau.ac.il/chemistry/ISMAR.html. *Note: New Location. See Newsletter 511, 14.*

14th European Symposium on Polymer Spectroscopy, Dresden, Germany, **September 2-5, 2001**. Contact: Institut für Polymerforschung Dresden e. V., ESOPS 14, Postfach 12 04 11, 01005 Dresden, Germany. Tel: +49 351 4658-282; Fax: +49 351-4658-214; E-mail: espos@ipfdd.de.

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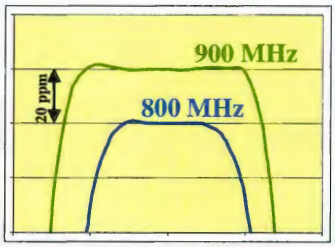

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Room temperature bore	54 mm
Cryostat height (with magnet stand)	3865 mm
Cryostat diameter	1688 mm
He evaporation rate He refill volume Helium hold time	< 250 ml/hr ~ 350 liters > 60 days
N_2 evaporation rate N_2 refill volume N_2 hold time	< 700 ml/hr ~ 400 liters > 21 days
Magnet stand	included
Vibration dampers	included
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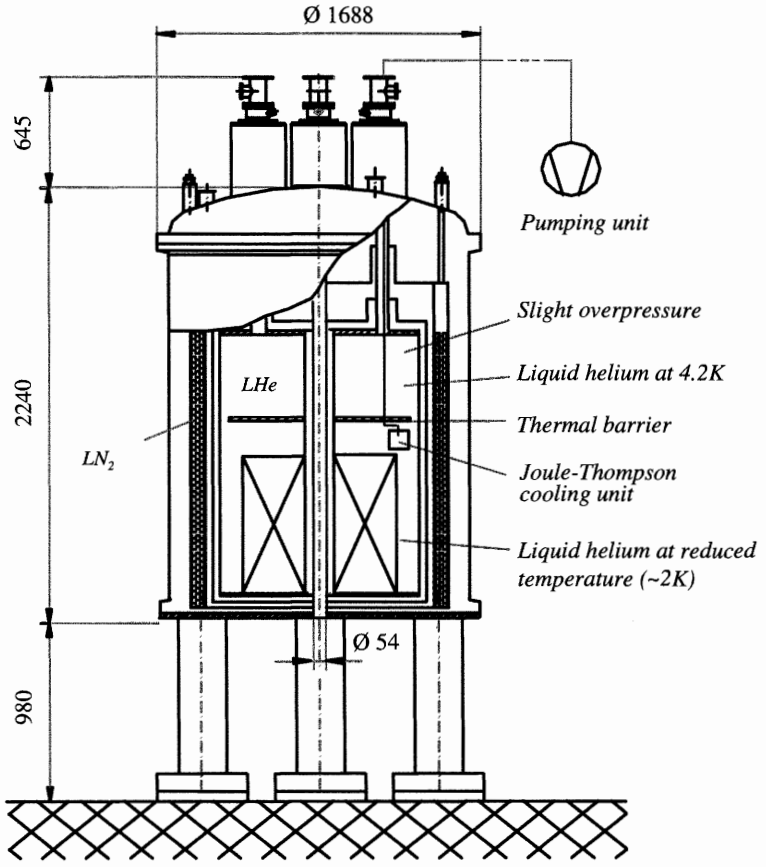

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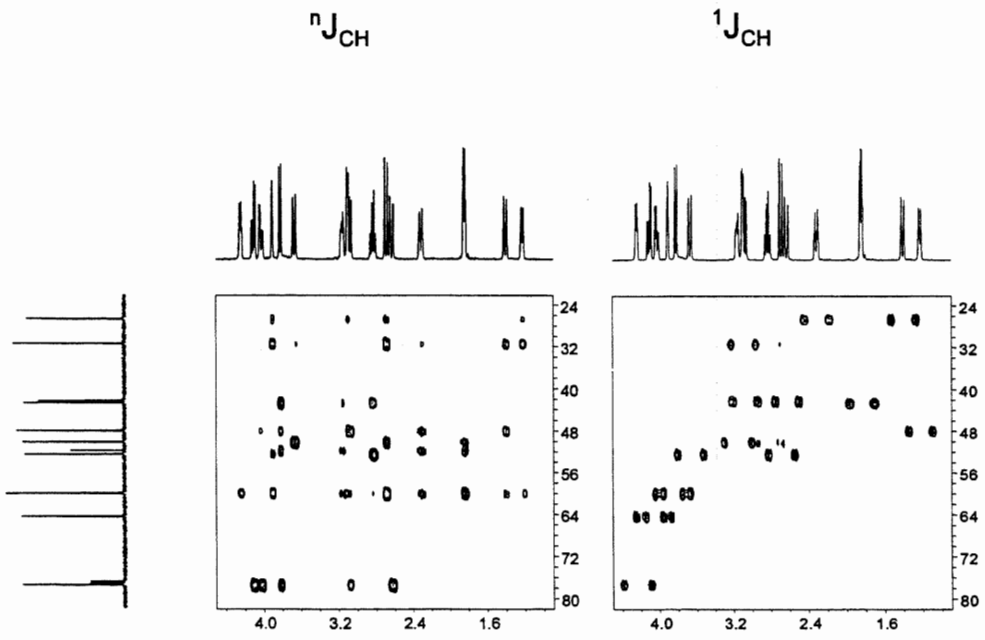
march, 16th 2001
(received 3/16/2001)

HMSC:

Very recently we proposed the BIRD-HMBC for measuring heteronuclear long-range coupling connectivities, which is the "precursor" for the HMSC (1) experiment, dedicated to detect simultaneously $^{n}J_{CH}$ a n d $^{1}J_{CH}$ connectivities in a single experiment and to disentangle the two types of heteronuclear J-coupling interactions by simple data processing. The sequence provides high sensitivities, comparable to the basic HMBC an HMQC experiments respectively, excellent $^{1}J_{CH}$ suppression factors in the $^{n}J_{CH}$ subspectrum, but some residual $^{n}J_{CH}$ "artifacts" in the $^{1}J_{CH}$ subspectrum. With HMSC "long-range" connectivity spectra with only minor sensitivity losses but almost complete elimination of unwanted $^{1}J_{CH}$ residual peaks compared to HMBC may be obtained within the same measuring time. Since no extra HMQC or HSQC has to be performed the coresponding spectrometer time is saved.

As an example HMSC has been applied to strychnine dissolved in $CDCl_3$ and the two subspectra have been calculated (below).



The BRUKER pulse program may be downloaded from: http://www.nmr.unibe.ch/

(1): R. Burger, C. Schorn and P. Bigler, J. Magn. Reson. **148** (1), 88-94 (2001)

Yours sincerely
Remy Burger, Christian Schorn and Peter Bigler

ISMAR 2001 – New Location

March 2001 (received 3/8/2001)

Dear Shapiro,

As I indicated in my previous letter, political developments in our area may require the re-location of the ISMAR 2001 venue. In view of the continuing local unrest, and the concern expressed by a number of potential participants, the Organizing Committee has now decided to hold the conference outside Israel.

As the new location we have selected the Convention Center of Rodos Palace Hotel in **Rhodes**. Rhodes is one of the largest islands of **Greece**, about one hour flight from Athens. There are daily scheduled flights from Athens and daily charter flights from most European capitals. Rhodes is a beautiful island, and a major tourist attraction, and the facilities in the Center are well suited for our meeting. The hotel web site is: http://www.rodos-palace.gr.

The dates of the conference (**August 19-24**), the scientific program and the registration details remain unchanged. Information about accommodation, travel and sightseeing will soon appear on the ISMAR homepage, which is now in a process of updating: http://www.tau.ac.il/chemistry/ISMAR.html. Please also notice the change in the deadline for submission of Abstracts to April 2.

I am sorry about the turn of events, which necessitated moving the conference away from our country. I hope very much that the situation will calm down and that one of the forthcoming ISMAR meetings will again take place in Israel.

On behalf of the Organizing Committee,

Gil Navon

****

Prof. Gil Navon
School of Chemistry Phone: 972-3-6408156
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****

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March 20, 2001
(received 3/22/2001)

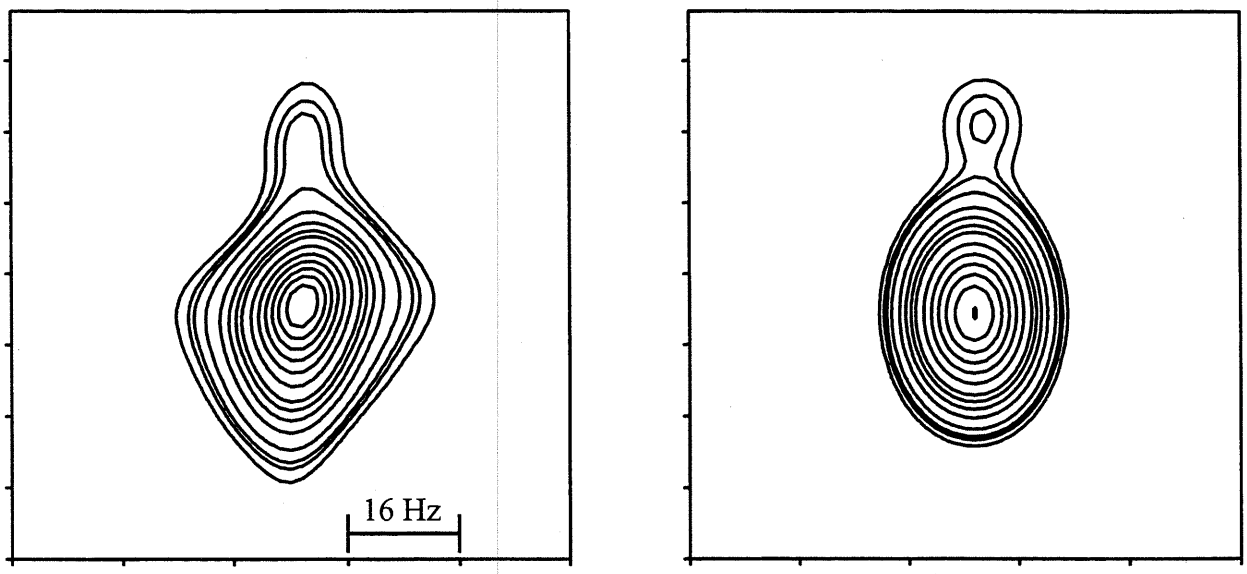
Deconvolution of superimposed 2D-NOESY resonance peaks

Dear Barry,

We routinely use two-dimensional nuclear Overhauser effect spectroscopy (2D-NOESY) in combination with magic angle spinning to determine the location of small molecules in the lipid matrix of biomembranes. Quantitative assessment of location is made through the determination of cross-relaxation rates between the proton resonances of lipid and the membrane-incorporated compound. This requires quantitative analysis of cross- and diagonal peak intensities of 2D NOESY spectra as a function of mixing time. Though ^{1}H NMR linewidth in our spectra is typically 10 Hz [1], superposition of peaks occur, making integration troublesome at best with our standard spectral integration software (XWIN-NMR, AURELIA). This is especially a concern when crosspeak intensities are very low, such as crosspeaks from molecules like ethanol that associate with lipids for brief periods of time. Low crosspeak intensities are often misread by standard integration packages. They are boosted in intensity by tails of a neighbored peak. We describe herein a quick and convenient procedure for deconvolution of superimposed 2D resonance peaks using a curve-fitting program based on the Marquardt-Levenberg algorithm [2] that can be run on a standard PC.

What follows is a brief description of the process: in XWIN-NMR the zoom feature is used to expand an area of the 2D spectrum containing only the superimposed peaks. Once the program has displayed this area, a new file called 'dsp.exp' is automatically created in the processed data directory of the experiment. This is a temporary file that contains the three-dimensional coordinates of the region that is currently being displayed. The file dsp.exp is copied, and transferred to a PC where it is converted into ASCII format. The data is then imported into a program that is capable of performing the deconvolution. (After sampling this procedure on various commercially available software packages, we prefer SigmaPlot version 5.0 (SPSS Inc.) for its stability, ease of use, and ability to display a graphical solution within seconds of initiating the deconvolution calculation). Once the data is in the program, it can be displayed as a two-dimensional contour- or surface plot that can be used to evaluate the peaks visually.

In our spectra, the resonances can be reasonably well approximated by Gaussian peaks. Peak position, peak width in x- and y-dimensions, and peak height are fitting parameters. Precision of the deconvolution procedure depends mostly on experimental artifacts, like residual t_1-noise, deviation of lineshapes from Gaussian, but also on the ratio of superimposed peak intensities. We have been able to determine superimposed peak volumes reliably that differ by more than one order in magnitude. It is strongly recommended to graphically evaluate the quality of the fit. Below is a pair of contour plots, the first being the superimposed two-peak system taken from the original spectrum, the second is the result of the deconvolution procedure.



The cross-relaxation data gathered from the more accurate measurement of superimposed peak volumes has allowed for unfettered comparison between our experimental values and those obtained through molecular dynamics simulation from the laboratory of Scott E. Feller [3].

A detailed description of the deconvolution procedure including the C-program for data conversion of XWINNMR binary files to ASCII, and templates for processing in SigmaPlot are available upon request.

Sincerely yours,

David T. Nizza Klaus Gawrisch

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References:

1. Holte, L.L., Gawrisch, K. *Biochemistry* 36:4669-4674, 1997.
2. Press, W.H., Flannery, B.P., Teukolsky, S.A., and Vetterling. W.T. (1986) *Numerical Recipes*, Cambridge University Press, Cambridge.
3. Feller, S.E., Huster, D., Gawrisch, K. *J. Am. Chem. Soc.* 121:8963-8964, 1999.

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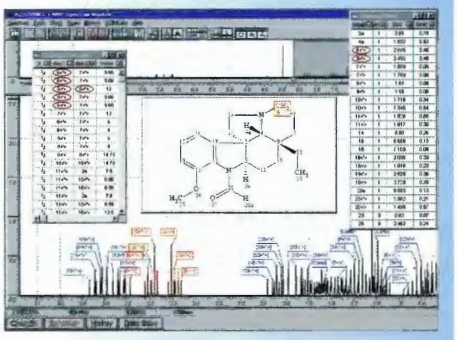
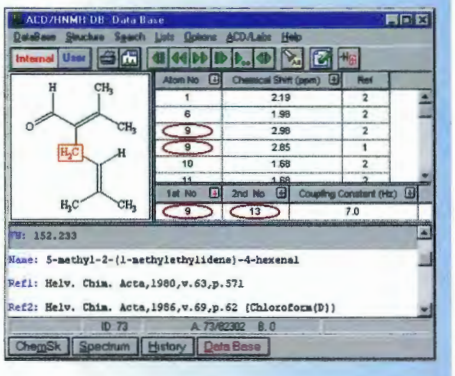


View coupling constants with highlighted atoms



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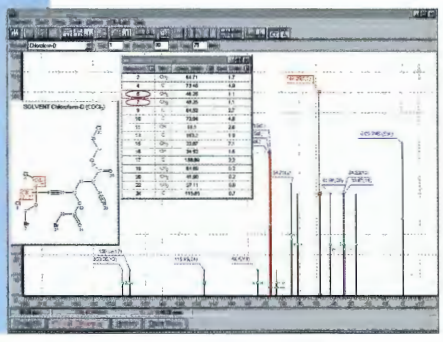

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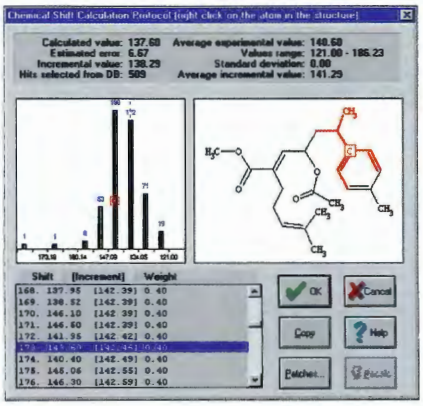
- For CNMR, the ACD/Natural Products DB Add-on contains over 5,200 structures from marine and terrestrial sources.



Protocol Window explains the calculation procedure

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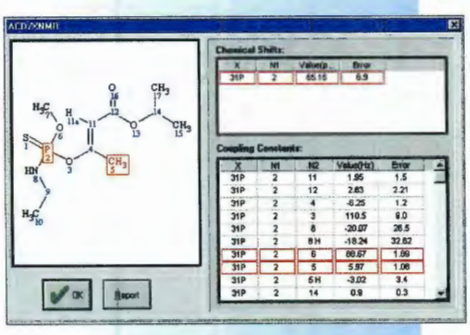
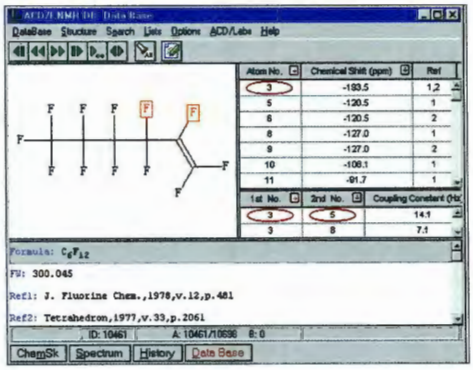
Each database includes original literature references, molecular formula, molecular weight and IUPAC names which can be searched and viewed. Search capabilities also include structure and substructure, and searching by exact value or range of values for chemical shifts and coupling constants.

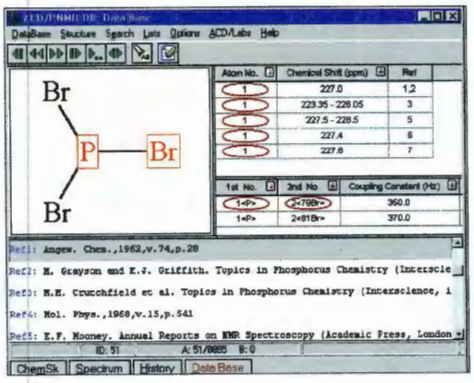


Display the predicted structure, interactively related to assigned shifts & coupling constants



Phosphorus database window showing chemical shifts, coupling constants, references, formula and IUPAC name

Fluorine Database window showing chemical shifts, coupling constants & references



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(received 3/20/2001)
March 9, 2001

Optimized coherence-order selective coherence transfer in IS spin systems

Dear Barry,

Most pulse sequences for heteronuclear coherence transfer have been derived under the assumption that relaxation can be neglected. The most commonly used approach to take relaxation into account is to simply reduce the mixing time of these pulse sequences in order to find a compromise between coherence transfer and relaxation losses. However, even if relaxation is taken into account only qualitatively, i.e. by an exponential dampening of the signal, one can do better than this.

For example, consider the coherence-order selective transfer of in-phase coherence (e.g. $S^- = S_x - i S_y$ to $I^- = I_x - i I_y$) in a heteronuclear two-spin system. If relaxation can be neglected, it is well known (1,2) that complete transfer is possible using heteronuclear isotropic mixing experiments with a mixing time of $3/(2J)$. However, it is less obvious whether or not the isotropic mixing experiments yields the best possible transfer also for reduced mixing periods $\tau < 3/(2J)$. Based on principles of geometric optimal control theory (3,4) analytical solutions have been derived (3) for the optimum transfer amplitude as a function of the transfer time τ. In addition the corresponding optimal mixing sequences can derived using this approach.

For the $S^- \rightarrow I^-$ transfer, a gain in signal amplitude of up to 12% is possible (3), simply by modifying the delays τ_x, τ_y, τ_z in commonly used heteronuclear isotropic mixing sequences (Fig. 1) of duration $\tau = \tau_x+\tau_y+\tau_z$. Whereas in isotropic mixing sequences $\tau_x=\tau_y=\tau_z= \tau/3$, in the optimum sequence τ_z is related to $\tau_\perp=\tau_x=\tau_y$ by $\tan(\pi J\tau_z)=2 \tan(\pi J\tau_\perp)$, see Fig. 2.

Fig. 3 shows the theoretically expected as well as the experimentally observed gain of the optimal transfer sequence compared to isotropic mixing as a function of the mixing time τ. Although the gain is relatively small, it can become quite significant if several such transfers are used in a given experiment and it comes basically for free because it simply requires to adjust the relative size of τ_x, τ_y, and τ_z in commonly used pulse sequences. We are currently extending the application of geometric optimal control to spin systems consisting of three coupled spins, where even more substantial improvements are found compared to known pulse sequence elements.

Sincerely,

Steffen J. Glaser — glaser@ch.tum.de
Timo Reiss — timo.teiss@ch.tum.de
Navin Khaneja — navin@arjun.dartmouth.edu

P.S. Please credit to Frank Köhler's subscription.

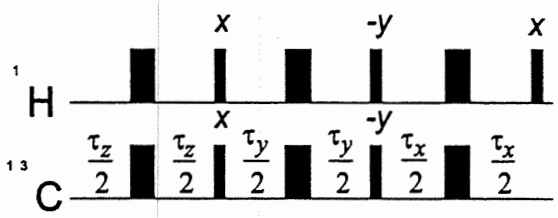

Figure 1: Schematic representation of a (simplified) isotropic mixing-type pulse sequence (1) for coherence-order selective coherence transfer from ^{13}C to ^{1}H. By adjusting the durations τ_x, τ_y, τ_z (see Fig. 2), the theoretical optimum of the transfer amplitude can be achieved for any given mixing time $\tau = \tau_x+\tau_y+\tau_z$.

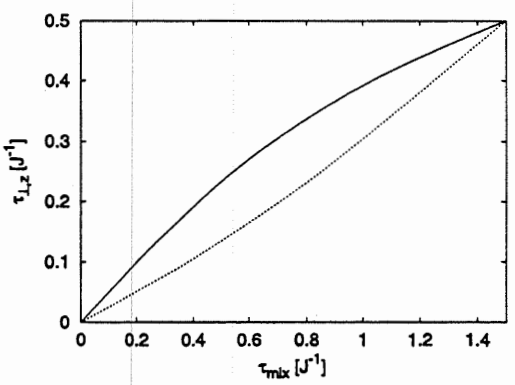

Figure 2: The optimal durations $\tau_\perp=\tau_x=\tau_y$ and τ_z as a function of the mixing time τ (3).

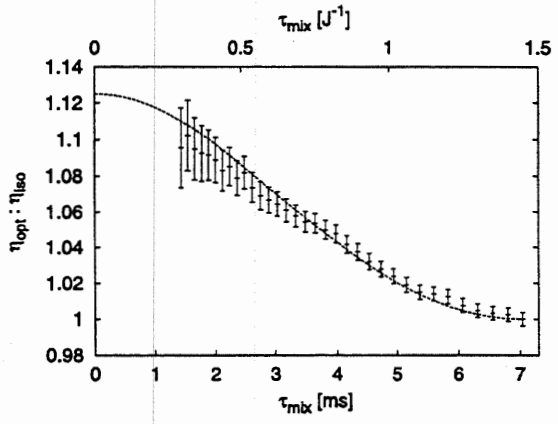

Figure 3: The ratio of the $S^- \rightarrow I^-$ transfer amplitudes η_{opt} and η_{iso}, which correspond to the optimal and the isotropic mixing experiment, respectively. Experimental data were acquired using the IS spin system of chloroforme.

(1) M. Sattler, P. Schmidt, J. Schleucher, O. Schedletzky, S. J. Glaser, C. Griesinger, *J. Magn. Reson.* B108, 235 (1995).
(2) S. J. Glaser, J. J. Quant, *Adv. Magn. Opt. Reson.* 19, 59 (1996).
(3) N. Khaneja, R. Brockett, S. J. Glaser, *Phys. Rev. A* 63, 032308 (2001).
(4) N. Khaneja, S. J. Glaser, *Chem. Phys.*, in press (preprint: quant-ph/0010100).

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Prof Barry Shapiro
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March 8 2001
(received 3/12/2001)

Constant time carbon HSQC and negative NOEs

Dear Barry

This contribution is an unusual one, in that (a) it's not prompted by the red letter, and (b) it's a comment on two recent contributions.

The first is from Brian Sykes' lab (Feb 2001, page 5), relating to constant time carbon HSQCs. Neri *et al.* (*Biochemistry* **28**, 7510-7516, 1989) first showed that if a protein is grown up using 90% U-^{12}C glucose and 10% U-^{13}C glucose as carbon source, then the labelling of amino acids as a result of the normal biosynthetic pathways is such that the *pro*-R methyl group of valine and leucine will almost always come out such that if it is ^{13}C labelled, then the adjacent carbon atom will also be ^{13}C labelled. By contrast, the *pro*-S methyl group will almost always *not* have a ^{13}C neighbour. This leads to a cunning method for stereospecific assignment. Brian's letter noted that if partially labelled proteins grown up in this way are examined using constant time HSQC [CT-HSQC], then the distinction is very straightforward, because the *pro*-R and *pro*-S methyls have opposite sign.

We have been using the CT-HSQC experiment in this way, and the results are indeed very clear and easy to interpret, as Brian's letter notes. There is however a further benefit of this experiment, which is in the distinction between the Me$^{\delta}$ and Me$^{\gamma}$ groups of isoleucines. One might think that these would be easy to distinguish using chemical shifts for example. However, it is surprisingly often that chemical shifts are ambiguous. The partial labelling route then becomes useful. When one examines the biosynthetic pathway for isoleucine, it's rather messy. Isoleucine is made from addition of pyruvate to threonine, which in turn is made from aspartate, which is generally made from transamination of oxaloacetate. This means that the Me$^{\gamma}$ and its attached carbon come from pyruvate: they will therefore either both be labelled or neither. By contrast, the Me$^{\delta}$ and its attached carbon come from the C$^{\beta}$ and C$^{\gamma}$ of aspartate. These may or may not be labelled together, depending on flux through the Krebs cycle. The result is that in CT-HSQC, the ^{13}Me$^{\gamma}$ of isoleucine will generally have a ^{13}C-labelled neighbour, and therefore be the same sign as alanine methyls and Val Me$^{\gamma 1}$/Leu Me$^{\delta 1}$. The isoleucine ^{13}Me$^{\delta}$ will sometimes have a ^{13}C-labelled neighbour, and sometimes not. In practice, this means that its signal is small, and usually opposite in sign to the Me$^{\gamma}$.

This is shown in the Figure. Negative peaks are filled in in black. Alanine methyls, and Val $Me^{\gamma 1}$/Leu $Me^{\delta 1}$ are positive, while Val $Me^{\gamma 2}$/Leu $Me^{\delta 2}$, as well as methionine methyls, are negative. It is striking that isoleucine Me^{γ} are positive, while Me^{δ} are small and negative.

This observation was made by Pete Simpson, a post-doc in the lab who has regrettably decided to leave the comforts of Sheffield for the bright lights of London.

My second comment is on a letter 'Negative NOEs in a steroid' by Arison and Doss (March 2001, p. 15). They noted that a steroid showed negative NOEs in chloroform, which was attributed to aggregation, leading to a long correlation time. This example is by no means unique. I thought it might be worth drawing your readers' attention to other similar cases, cited in 'The nuclear Overhauser effect in structural and conformational analysis' (D Neuhaus and M P Williamson, Wiley, 2nd Ed., 2000). Fig. 3.10 (p. 89) shows a macrolide antibiotic which has some positive and some negative NOEs, and another case is discussed on p. 90, from an alkaloid, which is charged and probably as a consequence has negative NOEs at ambient temperature.

Best wishes

Mike

Mike Williamson
(m.williamson@sheffield.ac.uk)

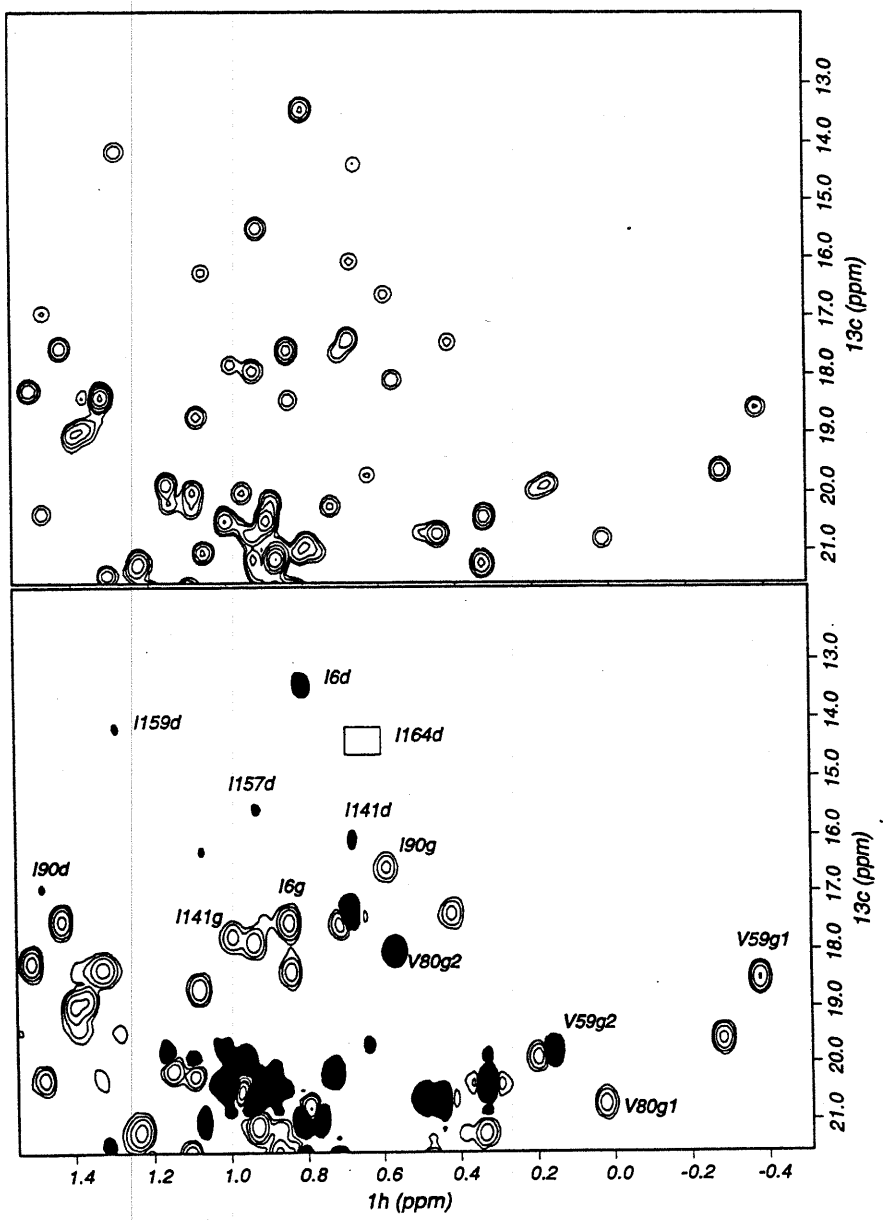

Figure Part of the methyl area from (top) normal ^{13}C HSQC, and (bottom) CT-HSQC from a sample of a carbohydrate binding module from *Rhodothermus marinus*, labelled by growth in 90% U-^{12}C glucose and 10% U-^{13}C glucose. Negative peaks are coloured black. The box shows the location of a very low intensity peak.

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February 6, 2001
(received 3/20/2001)

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High Throughput Structural Identification of a Combinatorial Library via NMR Pseudo 2D Plots

Dear Barry,

Recent advancement in combinatorial chemistry has brought the revolution in fast synthesis of a large number of compounds simultaneously in a very short period of time. However, it is well recognized that complete analysis of combinatorial library is a rate-limiting step. As part of our approach to develop NMR methods for HTP analysis of combinatorial products, we report here an application of pseudo 2D plots for quick reviewing the data for assisting structural verification of combinatorial library.

The 96 samples were dissolved in 200 ul protio DMSO and placed into a 96-well plate. The concentrations of these samples were about 4.0 mM. For each sample, 150 ul solution was injected into an actively shielded z-gradient 3 mm indirect detection flow probe. 1D spectra were recorded using WET pulse sequence on a Varian Inova500 NMR equipped with pulsed field gradient. A version of VNMR 6.1B is used throughout the study. We collected the spectra in the order from H1 to A1, H2-A2……(Figure 1). The two pseudo 2D plots were created using a modified procedure: we wrote a macro to transpose the 96 1D data sets to an order that we want (see below), and used the Varian macro 'vastglue' to stack the 96 1D spectra into a pseudo 2D data set. We found the most useful orders for stacking the data are either along the column or along the rows.

The 96 well plate numbering arrangement for NMR data collection in the submitted library are shown in Figure 1. The NMR results are shown in the pseudo-2D representation in Figure 2 and 3. Figure 2 shows the NMR spectra of the 96 compounds along the rows of the plate starting from position A1 to A12, then B1 to B12 etc (referred to as **row-view** 2D plot). Figure 2 shows the NMR spectra of the compounds in a column view of the plate e.g., starting from

position A1 to H1, then A2 to H2 etc (referred to as **column-view** 2D plot). These two different views allow the chemist to see trends in chemistry across rows or across columns. The characterization of the library was performed by analyzing the spectra of compounds in wells using these pseudo 2D plots along with the inspection of the individual spectrum in an interactive fashion. The following could be discerned:

- The **row-view** 2D plot, shown in Figure 2, provides a way to inspect whether the eight different R2 groups have been successfully incorporated onto the core structure. The characteristic NMR signature of these R2 groups can be seen in the aromatic region of the spectrum as eight different patterns in each of the boxes, indicating completion of reactions. As an example, from this 2D plot, the signals from 6.2 – 8.5 ppm are characteristic peaks for aromatic rings. As an example, the successful incorporation of groups 1' and 5' in wells A1-A12 and wells E1-E12, respectively, is highlighted in the figure.
- The **column-view** 2D plot, shown in Figure 3, provides a way to inspect whether the twelve different R1 groups have been successfully incorporated onto the core structure. The characteristic NMR signature of these R1 groups can be seen in the aliphatic region of the spectrum as twelve different patterns in each of the boxes, indicating completion of reactions. As an example, the successful incorporation of groups 1 and 9 in wells A1-H1 and A9-H9, respectively, is highlighted in the figure.

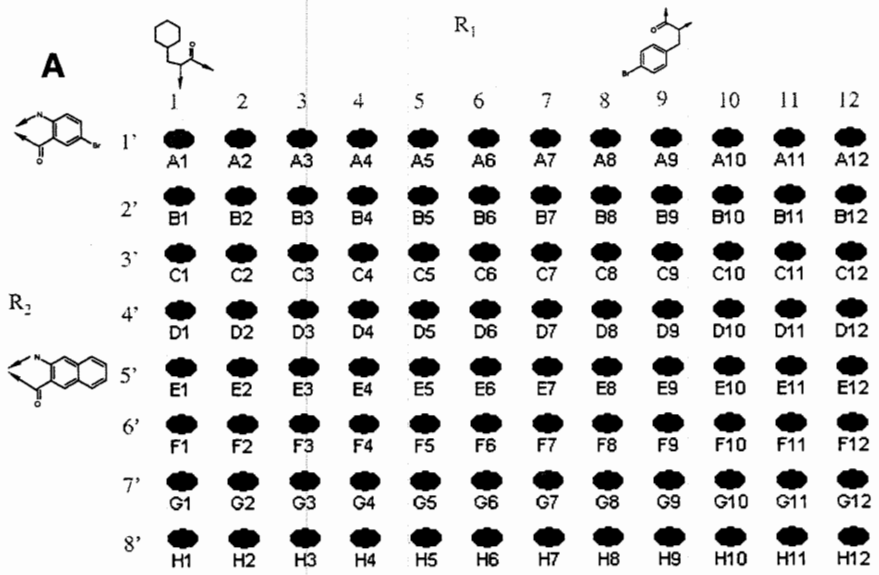

Figure 1

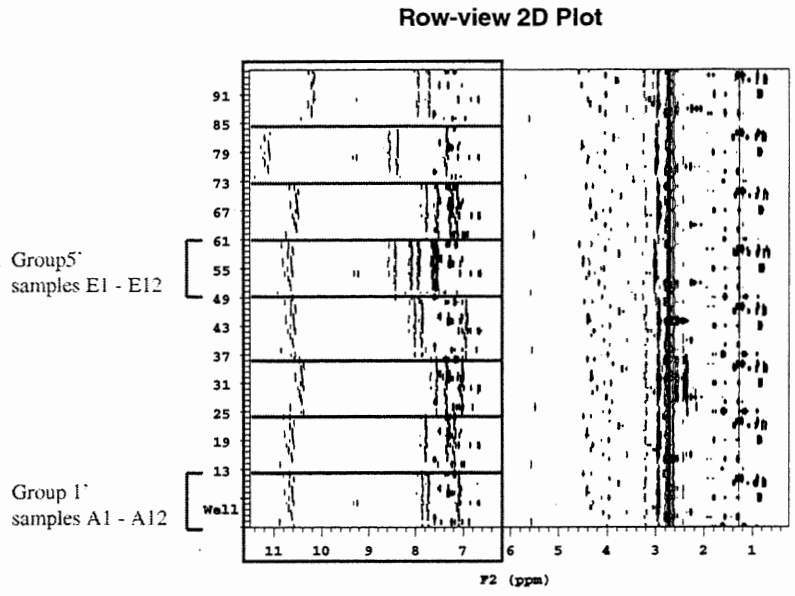

Figure 2

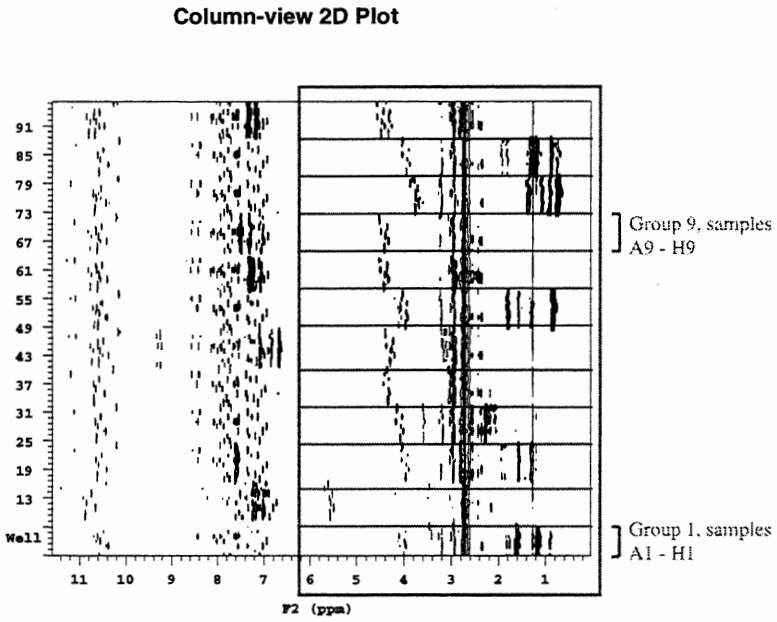

Figure 3

Sincerely,

Bing Wang, Allison K. Dunn, Maria A. Cichy-Knight,

Michael L. Moore, Susanta K. Sarkar

Washington University in St. Louis

ARTS & SCIENCES

Department of Physics

March 14, 2001

Dear Colleague,

I'm looking for a talented, highly motivated postdoc to join my NMR group here at Washington University. The group consists of 4 graduate students and 2 undergraduates. Two more graduate students will join this summer. Several different avenues are being pursued; a postdoc would become involved in one or more of these. Here are the three major projects:

1. MRI of human lungs with laser-polarized He-3. There is lots of room to improve the polarization process and the MRI techniques; the data analysis end of the project is particularly weak. See Magnetic Resonance in Medicine volume 44, pages 174-179 (2000) and MRM Volume 42, pages 507-514 (1999). We are moving towards the use of He-3 to detect pulmonary emboli (blood clots in the lung), a disease of major importance. The He-3 work also includes a small-animal component, aiming at genetically modified mice.

2. Polarization transfer from laser-polarized Xe-129 to spins of analytic interest (hydrogen, C-13, N-15, etc.). We have reported some progress in this effort in Chemical Physics Letters, Vol. 327, pages 359-364 (2000). If successful, the sensitivity of analytical NMR (solution-state) could be increased dramatically.

3. Metal-hydrides and -deuterides. We are now studying a phase transition in ZrBe2Dx and an unexpected resolved proton splitting in nanocrystalline-PdHx. We have plans for other systems such as LaDx (x=2 to 3), a material exhibiting the reflective-transparent transition (described in Nature volume 380, page 231 (1996)). There is lots of fun physics here.

The group has 3 solenoids (4.4, 8.0, and 8.4 Tesla) and 3 iron-core magnets. There is a Chemagnetics CMX-360 and two home-built spectrometers. We have access to a whole-body (human) research MR imager and two 4.7 Tesla Varian machines for small animals in Joe Ackerman's lab.

Life in Saint Louis is nice. The cost of housing is low and there is a fun night life. There are more bars per corner than most places. Serious culture includes art, music, and theatre. For sports fans, there is professional baseball, football, and ice hockey (Cardinals, Rams, and Blues). The nearby and beautiful Ozarks are great for hiking and canoeing.

Thank you for bringing this opening to the attention of your students and postdocs.

Mark Conradi
Professor of Physics

msc@howdy.wustl.edu

Position Available

Postdoctoral Position available June 1, 2001 to conduct NMR studies of molecular structure and dynamics in fatty acid-binding proteins. Requires Ph.D. in chemistry or biochemistry, with experience in one or more of the following areas: multidimensional NMR, protein resonance assignments, protein structure determination from NMR-based restraints, spin relaxation, protein expression and purification, pulse sequence modification. Send a *curriculum vitae*, two letters of reference, and copies of pertinent publications to: Dr. Ruth E. Stark, Department of Chemistry, City University of New York (CUNY), College of Staten Island (CSI), 2800 Victory Boulevard, Staten Island, NY 10314-6609. Inquiries may also be made to stark@postbox.csi.cuny.edu or http://www.chem.csi.cuny.edu/reslab/. *EEO/AA/ADA Employer.*

Research in the Chemistry Department at CUNY College of Staten Island focuses on polymers and biopolymers; it is conducted by a close-knit group of 10 faculty, 25-30 graduate and undergraduate students, and 10-12 postdoctorals. In addition to our own laboratories and instruments, we maintain close ties to other campuses within CUNY and to nearby institutions in the New York - New Jersey area. Our new 204-acre Willowbrook campus is centrally located in Staten Island, a pleasant and reasonably-priced suburban community with easy access to Manhattan and New Jersey.

The Stark research group has ample access to NMR spectrometers operated by the CSI Chemistry Department: 4-channel Varian Unity$_{INOVA}$ (600 MHz), 3-channel Unity*plus* widebore (300 MHz), 2-channel Unity (200 MHz). Also available locally are state-of-the-art 800 MHz NMR facilities, scheduled to open in late 2001 at the New York Structural Biology Center.

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On the next page is a strange contribution which somehow found its way into the Newsletter issue no. 225 of June 1977. I no longer recall the origin of this fanciful letter (not that it matters).

BLS

The Arcturus Society for Resonance
Galactic Science Foundation
Third Sector, 5th Octant
July 47, 3549
(received June 1977)

Prof. B. L. Shapiro, CCXLVI
Department of Chemistry and Stellarometry
The Alpha Centauri A&M University
University Station, New Texas 78695095867493940586

Dear Barry the two-hundred-forty-sixth:

We just received your pink notice that this contribution was overdue. Surely, you realize that hyperspace communications are not what they used to be and that, at least in this part of the galaxy, the Romulans have caused untold havoc in communications. But, in the spirit of better-late-than-never we shall tell you what has been going on in our laboratory lately.

1. Our new 14,349,456,200 Gauss FT spectrometer arrived last week. When we first turned it on, all wrist-watches were destroyed in this solar system. However, our spectra are so much simpler than ever before, it is certainly worth it. However, with only 556K of memory for our transforms, resolution is suffering. Also, we have found that liquid sodium does not work well in cooling the magnet system. However, we shall not discuss how we got around this problem since magnet cooling systems are not allowed in the Newsletter. Finally, you will note that we report the field strength in Gauss. The recently adopted cgs system of units is probably confusing to some, but we believe strongly that those unwieldy SI units should go.

2. The newly discovered element, no. 4539 (Nixonium), has very interesting properties in the NMR. So far, we have had superb spectra from the isotopes of spin 78, 45, and 33-1/3. The coupling patterns, especially across 48 bonds are magnificent.

3. Gamma-ray excited carbon-12 NMR seems to be a thing of the past. I have not seen any papers in the last 3 or 4 years employing this technique. Are any of your readers still active in this area?

4. Eka-eka-eka-eka-ekalanthanide shift reagents look to be very promising. Especially interesting is element no. 456. Those half-filled g and h orbitals give rise to shifts approaching 33,456.009 ppm. This should greatly help people studying conformations on the surfaces of black holes.

5. We recently discovered that hydrogen (element no. 1) has a nuclear spin. (So far, we can say it is only less than 3.5.) It has coupling patterns more complex than any seen recently. We are confident that this will present a great breakthrough and are proceeding with this work with a great deal of excitement. Unfortunately, the Galactic Academy has refused to fund the work until we have given further demonstration of its feasibility. Probably, the work would have been funded if we had not simultaneously mentioned a new technique we used in obtaining the spectra. It seems that sweeping with a slowly varying magnetic field gives spectra directly WITHOUT USING A FOURIER TRANSFORM. This upset the academy greatly; also, the computer companies were up in arms.

Well, nothing further to report. I hope that you can stop by sometime. After all, we are only 5000 light years from you.

Sincerely yours,

Bela Oxnyx, Director, Iotian-Arcturan Academy

Address all Newsletter correspondence to:

Dr. B. L. Shapiro
The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303.
650-493-5971* - *Please call only between 8:00 am and 10:00 pm, Pacific Coast time.*

Deadline Dates

No. 512 (May)	27 Apr. 2001
No. 513 (June)	25 May 2001
No. 514 (July)	22 June 2001
No. 515 (Aug.)	20 July 2001
No. 516 (Sept.)	24 Aug. 2001

* Fax: 650-493-1348, at any hour. Do not use fax for technical contributions to the Newsletter, for the received fax quality is very inadequate.

* E-mail: shapiro@nmrnewsletter.com

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If the mailing label on your envelope is adorned with a large **red dot**: this decoration means that you will not be mailed any more issues until a technical contribution has been received.

Forthcoming NMR Meetings, continued from page 10:

Sixth International Conference on Magnetic Resonance Microscopy, Nottingham, UK, **September 2-5, 2001**.http://www.magres.nottingham.ac.uk/conferences/2001/icmrm/

Fourth International Conference on Molecular Structural Biology, Vienna, Austria, **September 5-9, 2001**. Contact: Andreas Kungl, Austrian Chemical Society (GÖCH), Biochemistry Subgroup, c/o Institute of Pharmaceutical Chemistry, Univeristy of Graz, Universitätsplatz 1, A-8010 Graz, Austria. Tel: +43 316 380 5373; Fax: +43 316 382541; E-mail: andreas.kungl@kfunigraz.ac.at.

2nd Alpine Conference on Solid-State NMR, Chamonix-Mont Blanc, France, **September 9-13, 2001**; Contact: Alpine Conference Secretariat, Laboratoire STIM, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69364 Lyon Cedex 7, France; alpine.SSNMR@ens-lyon.fr; Tel. +33-(0)4 72-72-84-86/ 83 84; Fax. +33 (0)4 72 72 84 83;http://ens-lyon.fr/STIM/alpineweb,html

XXth International Conference on Magnetic Resonance in Biological Systems, Toronto, Ont., **August 25-30, 2002**. For further information check www.uwo.ca/chem/icmrbs/, or contact: mgordon@julian.uwo.ca

Additional listings of meetings, etc., are invited.

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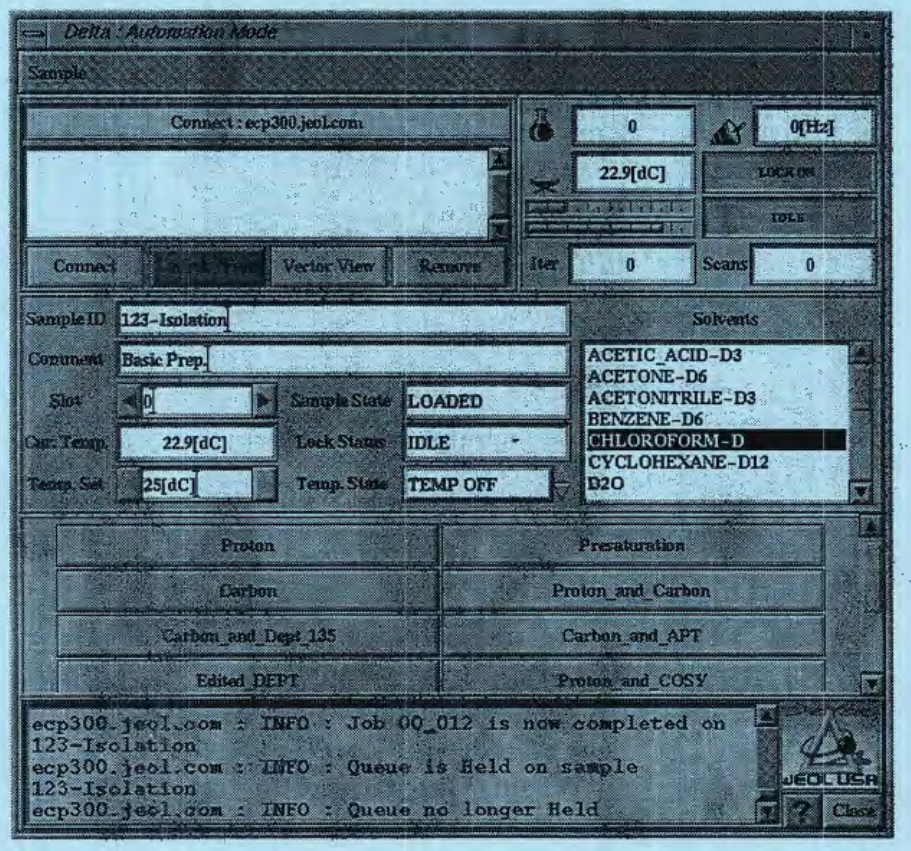

The **Eclipse+** NMR Spectrometer can be operated anywhere there is a computer on the local network. The **Single Window Automation** pictured above can be used with a single mouse click to select the sample from the auto-sample changer, gradient shim on any probe, run the selected experiment, and plot the data on any network postscript printer. Need more data, click another button and the **Eclipse+** is off to do your work - and you have not left your office. Contact us at nmr@jeol.com or visit or web site at www.jeol.com.

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