THE NMR NEWSLETTER

No. 502

July 2000

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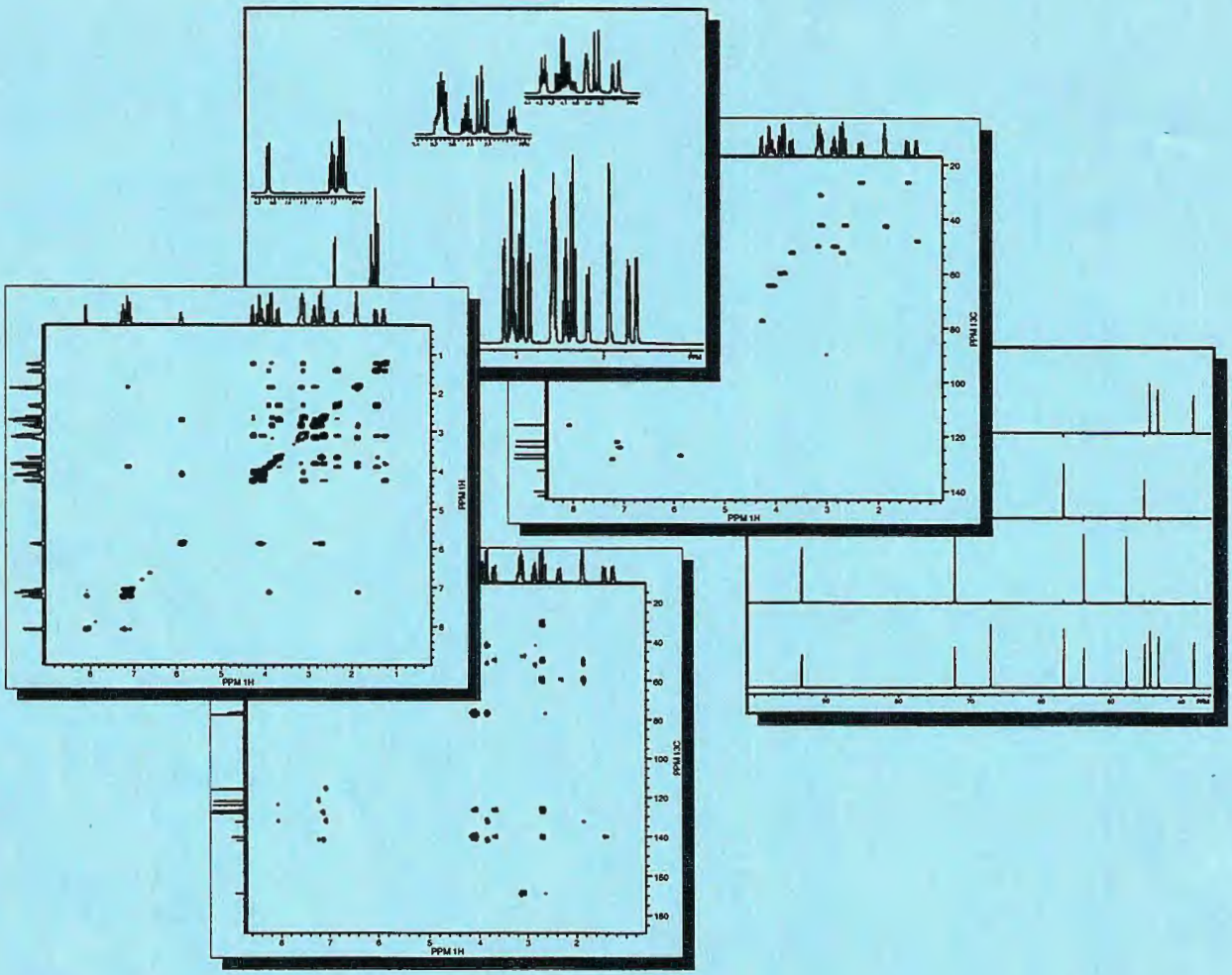

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FORTHCOMING NMR MEETINGS

SMASH-2000, Argonne, IL, **July 16-19, 2000**. Contact: G. E. Martin (gary.e.martin@amu.pnu.com). See Newsletter 493, 21.

Second Annual EMSL Workshop on Structural Genomics, Richland, Washington, **July 28 – 29, 2000**; Contact: Michael, A. Kennedy, Pacific Northwest Mational Laboratory, P. O. Box 999, K8-98, Richland, Washington 99352; 509-372-2168; fax: 509-376-2303; email: ma_kennedy@pnl.gov. See Newsletter 502, 13.

42nd Rocky Mountain Conference on Analytical Chemistry, Omni Interlocken Resort, Broomfield, CO, **July 31 – August 3, 2000**. NMR Symposium Chair: Lucio Frydman, Univ. of Illinois at Chicago, Dept. of Chemistry (M/C 111) 845 West Taylor St., Room 4500, Chicago, IL 60607-7061; 312-413-1053; Fax: 312-996-0431; lucio@samson.chem.uic.edu

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.

NMR: Drug Discovery and Design Conference – Post-Genomic Analysis, McLean, Virginia, **October 24-26, 2000**. Contact: Mary Chitty, Cambridge Healthtech Institute, mchitty@healthtech.com; Fax 617-630-1325.

NMR Spectroscopy of Biofluids and Tissues, Imperial College, London, England, **November 13-17, 2000**. Contact: Hersha Mistry, Centre for Continuing Education, Imperial College, 526 Sherfield Building, Exhibition Road. London, SW7 2AZ, UK. Tel: +44 (0)20 7594 6884; Fax: +44 (0)20 7594 6883; Email: h.mistry@ic.ac.uk; http://www.ad.ic.ac.uk/cpd/nmr.htm

42nd ENC (Experimental NMR Conference), Clarion Plaza Hotel, Orlando, Florida, **March 11-16, 2001**; Arthur G. Palmer, Chair: Agp6@columbia.edu; Contact: ENC, 1201 Don Diego Avenue, Santa Fe, NM 87505; (505) 989-4573; Fax: (505) 989-1073; E-mail: enc@enc-conference.org.
Web: enc-conference.org

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 inside back cover

The NMR Newsletter - Book Reviews

Book Review Editor: István Pelczer, Dept. of Chemistry, Princeton University, Princeton, NJ 08544

High Resolution NMR Techniques in Organic Chemistry

by

Timothy D. W. Claridge

Pergamon (an Imprint of Elsevier Science Ltd), Oxford, 1999, pp xiv + 382
ISBN 0-08-042798-7 (Paperback) £28.20, $49.50, Nil Guilder 95.00
ISBN 0-08-042799-5 (Hardbound) £78.66, $134.50

This book is a worthy successor to the late Andrew Jerome's *Modern NMR Techniques for Chemistry Research*. It is not just a new edition of that book, although the format and layout are similar.

Claridge identifies three classes of potential readers: (1) NMR users who have no direct contact with the spectrometer, (2) those who have also been trained to acquire their own spectra, and (3) those who may in addition be responsible for the maintenance of the equipment but who are not necessarily trained spectroscopists. The inclusion of this last class, which could include employees of the smaller universities and start-up firms, makes the book unique. (There are even hints as to how one should negotiate with instrument manufacturers!!)

The coverage can be gauged by the titles of the chapters: (1) Introduction, (2) Introducing high-resolution NMR, (3) Practical aspects of high resolution NMR, (4) One-dimensional techniques, (5) Correlations through the chemical bond I: Homonuclear shift correlation, (6) Correlations through the chemical bond II: Heteronuclear shift correlation, (7) Separating shifts and couplings: J-resolved spectroscopy, (8) Correlations through space: The nuclear Overhauser effect, (9) Experimental methods. There is a useful glossary of acronyms as an appendix together with a comprehensive index.

The book concentrates on the practical aspects of NMR, and there are many useful tips on sample preparation (for example). The business of setting up the spectrometer is also treated very well, and there is an excellent account of shimming techniques.

This book provides a clear, readable, and comprehensive introduction to NMR, and deserves to be read by both tyros and old hands. I can thoroughly recommend it.

Peter Bladon
Interprobe Chemical Services
Gallowhill House, Larch Avenue
Glasgow G66 4HX Scotland

Email: cbas25@strath.ac.uk

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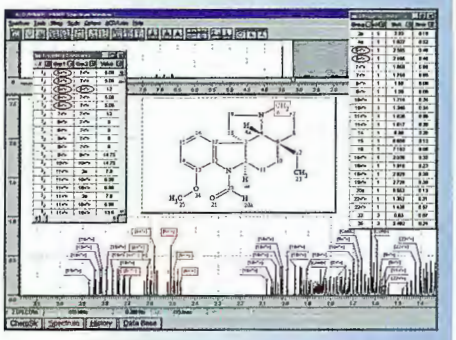
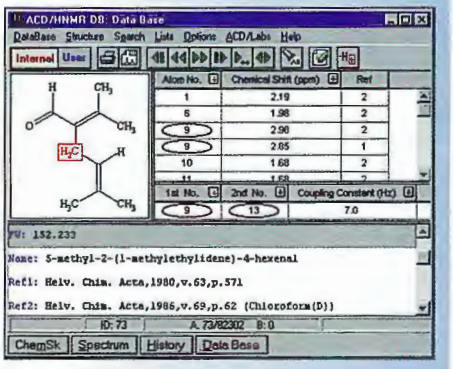


View coupling constants with highlighted atoms



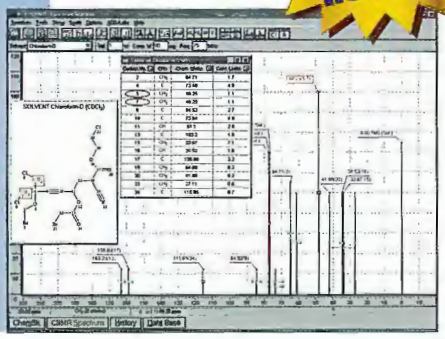
Access the internal database with full searching capability

Calculate the ^{1}H or ^{13}C NMR spectrum for any organic chemical structure. The Calculation Protocol Window lets you see exactly which fragments were used in the prediction. Self-training system lets you create your own database of chemical shifts for improved prediction accuracy.

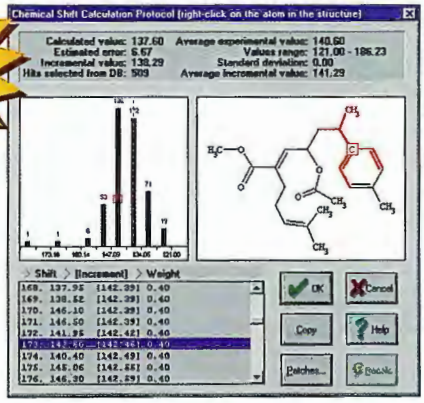
- **NEW**- Proton prediction now based on an internal data file with over 800,000 experimental chemical shifts and 180,000 coupling constants. Carbon prediction based on 1,200,000 chemical shifts.
- **NEW**- Improved algorithm for the prediction of diastereomers.
- **NEW**- Display predicted chemical shifts directly on the chemical structure.
- Data Forms Manager streamlines and standardizes record entries as you build your own databases.
- Include multiple user databases in the system training.
- Modify or delete shifts in the internal DAT file.
- **NEW**- Ability to export the database entries in JCAMP format.

- **NEW (H only)** - Option for chemical shifts calculation allows the merging of exchangeable OH and NH signals.
- Transfer the peak table from ACD/SpecManager (which processes and organizes experimental spectra) into the NMR Predictor user database with the click of a button.

- **ALSO AVAILABLE!** The proton and carbon NMR DB Add-ons now contain the user-accessible ACD databases of over 100,000 structures (**NEW**- an increase in size of 20% for HNMR, and an increase of 50% for CNMR, compared to version 4.0). These DBs include original references, molecular formula, molecular weight, IUPAC name, coupling constants (if applicable), NMR experiment (technique, frequency, temperature) and trivial name, all of which can be viewed and printed out.
- For CNMR, the ACD/Natural Products DB Add-on contains over 5,200 structures from marine and terrestrial sources.



Verify shifts & coupling constants with on-screen structural relation



Protocol Window explains the calculation procedure

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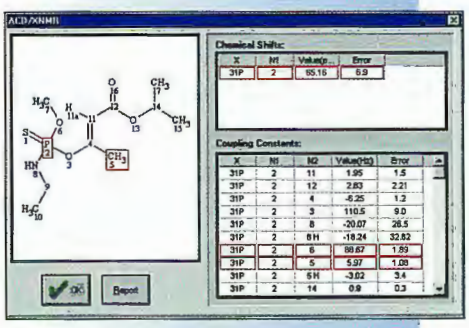
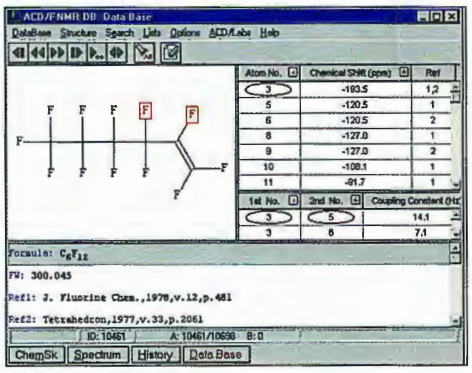
- ^{31}P NMR spectra for over 18,500 structures with over 23,300 chemical shifts and 8,600 coupling constants.

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.

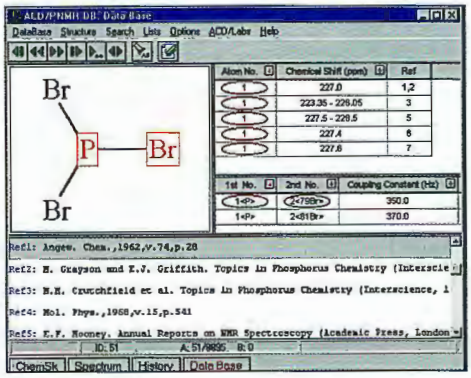


Display the predicted structure, interactively related to assigned shifts & coupling constants



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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Zürich, 2.3.2000

2515

Dr. B.L. Shapiro
The NMR Newsletter
966 Elsinore Court

Palo Alto, Ca 94303-3410
U.S.A.

(received 4/10/2000)

Dear Dr. Shapiro,

As we all know, but usually do not mention, the rf inhomogeneity over the volume of the sample in a (MAS) NMR probe is considerable.
Recently we were interested in an experiment where rf inhomogeneity is an important factor for the performance. In order to take this into account properly we decided to determine the rf inhomogeneity experimentally.

We did this with a simple nutation experiment on the carbons with cross polarisation from protons in order to enhance the polarisation and reduce the recycle time. As a sample we used hexamethylbenzene and we spun it at the magic angle with a frequency of 10 kHz. A schematic of the experiment is shown in Figure A. After Fourier transformation the lineshape in ω_1 is a direct measure of the rf inhomogeneity profile over the sample volume.

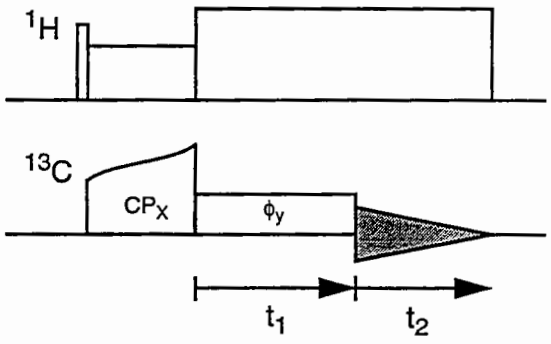


Figure A: CP nutation experiment.

Although we expected some inhomogeneity, the size of the variation somewhat surprised us. The results are shown in Figures B and C (top row). We then performed the

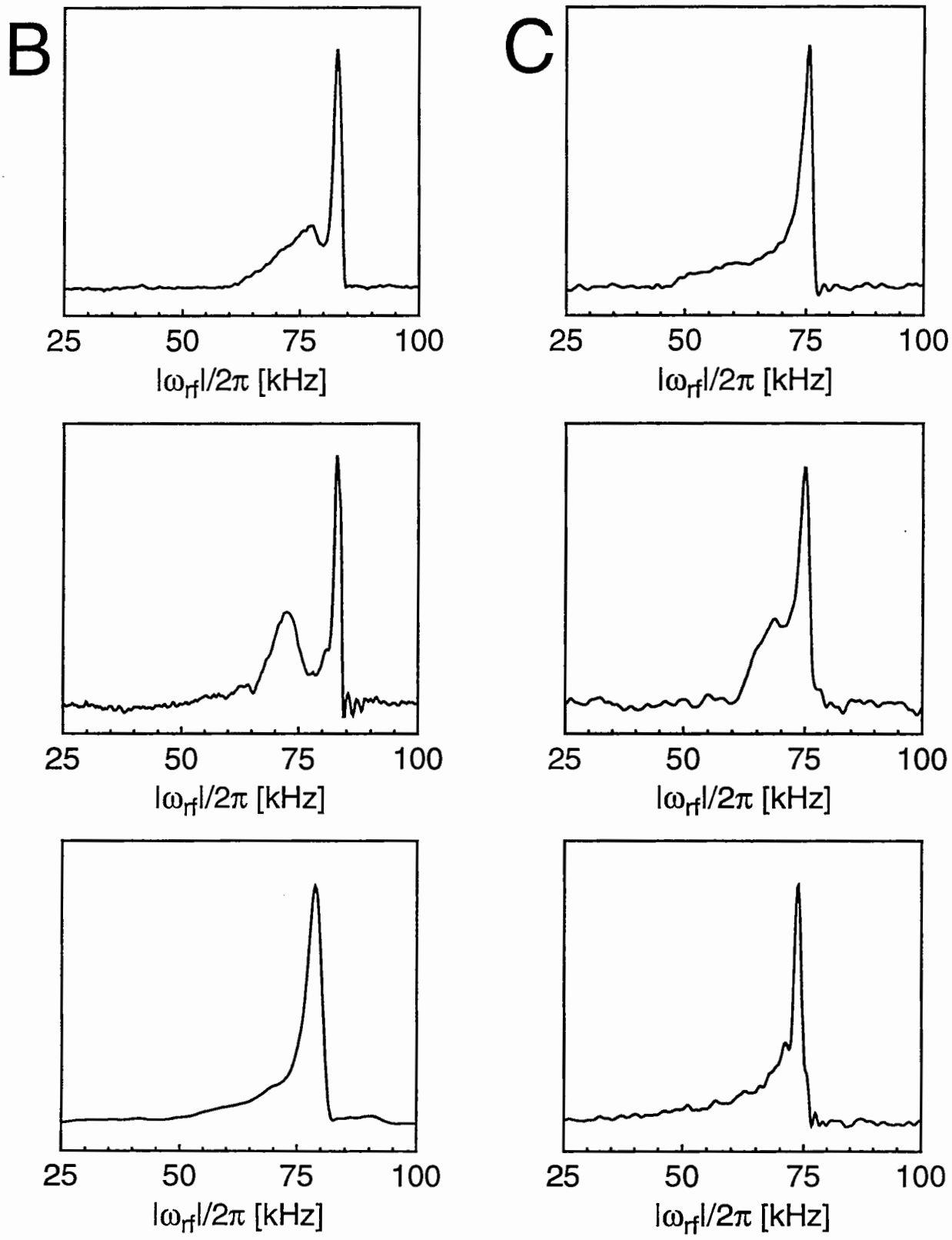
same experiment again but this time without the amplitude variation on the carbon pulse during CP. This resulted in a narrower profile in ω_1 (Figures B and C, center row) but also in a lower S/N. Finally the bottom row of Figures B and C shows the results for an experiment where the initial CP period was replaced by a single $\pi/2$ pulse on the carbon channel. The resulting lineshape in this case reflects the "true" rf inhomogeneity profile for the carbons. Considerable variation in rf field strength is observed, clearly demonstrating that multi pulse experiments need to be very robust with respect to rf inhomogeneity. Compared to a conventional CP experiment, a tangential or linear ramp during the mixing time will increase the integrated signal intensity considerably because one (sequentially) matches the difference between the proton and carbon rf fields to a small integer multiple of the rotor frequency over the *whole* sample volume.

The lesson one can learn from this is that the effects of rf inhomogeneity on an experiment should not be dismissed lightly.

Sincerely yours,

Beat H. Meier Matthias Ernst Jacco van Beek René Verel

Figure B and C: Experimental results for Hexamethylbenzene at $\omega_r/2\pi$ = 10 kHz. The data were taken with two brands of 4mm double resonance MAS probeheads. Top row: data obtained with the pulse sequence as depicted in Figure A. An almost linear amplitude variation was applied during the CP period (+/- 5 kHz around the -1 Hartmann-Hahn matching condition). Center row: no amplitude variation was applied during CP. Bottom row: CP was replaced by a single $\pi/2$ pulse on the carbon channel.


B
C
25
50
75
100
$|\omega_{rf}|/2\pi$ [kHz]

Positions Available

Industry leader seeks leading scientists

We are expanding our structural chemistry and analytical sciences team in AstraZeneca at Macclesfield in the UK and require additional scientists to help us meet our long term goals. The structural chemistry and analytical sciences team is charged with the characterisation and identification of our drug development candidates and is built around NMR, MS, IR, and separation techniques. In addition we have the key task of developing the analytical science required for the future.

In 2000 we have opportunities for two talented scientists to further develop the core expertise of the team in the following areas:

Physical aspects of NMR spectroscopy

The use of vibrational/Raman spectroscopy to characterise solid state materials and interactions.

Both roles offer an opportunity for good scientists to continue to develop their research in an industrial environment. We are looking for individuals who can offer us novel solutions to tomorrow's problems and can help us broaden our scientific base.

You would be involved in the initiation and execution of research programmes designed to identify and satisfy the unmet analytical needs in pharmaceutical development.

You should have a good track record in independent thinking, research, and publication and will probably have good experience of collaboration and communication with scientists from a range of other disciplines. You will be an expert in your own field but will also have a general interest in detection, measurement, and characterisation.

Our ideal candidate will probably have 2-3 years post doctoral experience but could also be a more experienced academic or industrial scientist who is looking for a new challenge.

Macclesfield is located next to the rolling hills of the peak district national park with its attractions for outdoor enthusiasts, and is 25 miles south of Manchester, England's third largest city.

If you are interested in finding out more about either of these positions please send a summary of your research interests and achievements to Dr Stephen Wren at:

Stephen.Wren@AstraZeneca.com

PAR&D, AstraZeneca, Silk Business Park, Macclesfield, Cheshire, SK10 2NA, UK.

Family Matters

From left to right:

Don McReynolds
Earthy Lee Young
Remonda Lavinghouse
James Brewer
Gary Skidmore

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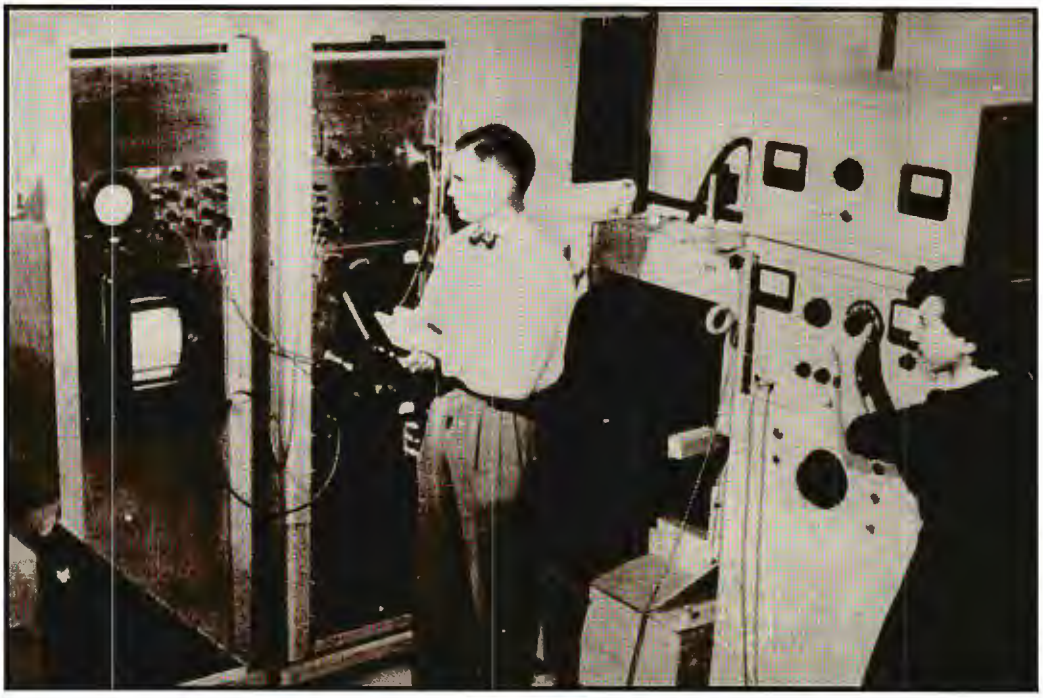

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Kevin H. Gardner, Ph.D.
Assistant Professor
W.W. Caruth, Jr. Scholar in Biomedical Research

Department of Biochemistry

June 19, 2000
(received 2/23/2000)

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

On the merits of protein NMR without purifying the protein first

Dear Barry,

A challenge to structural biologists embarking on studies of new proteins is the identification of fragments that are well behaved for biophysical study. For most NMR spectroscopists (aside from our brave colleagues working on unfolded proteins!), we're generally looking for good chemical shift dispersion and uniform peak linewidths. As part of establishing my research group at UT Southwestern, I've been evaluating these parameters for fragments of several new proteins that my group is working on. To do this, I've using an extremely handy --- but surprisingly underdiscussed/referenced --- method originally described by Gronenborn and co-workers several years ago (1,2). As I've found this method to be quite helpful, I'd like to share some recent results in the hopes that other readers of the *NMR Newsletter* might find it similarly useful.

The basis of this method is surprisingly simple: grow a ^{15}N-labeled culture of *E. coli* overexpressing the protein of interest, lyse these cells and acquire ^{15}N-^{1}H HSQC spectra on the soluble fraction of the resulting cell extract. These spectra are dominated by peaks from the overexpressed protein on account of the high fractional abundance of this molecule and the peak broadening of proteins in large complexes. From these spectra, one can rapidly use the amide proton chemical shift dispersion as a qualitative indicator of protein folding: poor dispersion (7.8-8.4ppm) suggests the protein is random coil, while good dispersion suggests secondary structure formation.

To complement the prior descriptions of this method, I'd like to add comments from our experience:

-*Protein molecular weight:* most of the proteins we have screened with this approach are 15-20kDa, including any attached fusion proteins. However, we've been able to acquire usable spectra on proteins as large as 40kDa --- which I find somewhat amazing given the viscosity that one might expect from a whole *E. coli* cell lysate.

-*Fusion proteins:* we've routinely screened most of our proteins as C-terminal fusions to proteins that are routinely used to aid purification or solubility. While this approach increases the apparent molecular weight of the protein being screened, this allows one to omit the time required for purification and fusion cleavage. As well, the presence of a soluble, well-folded fusion partner in the cell lysate provides an important positive control --- if peaks are not observed from this protein, then one must consider problems with solubility or aggregation. We have had success working with two fusion proteins for this purpose: *E. coli* thioredoxin (~100aa) and the protein G β1 domain (~60aa, suggested in reference 2).

Southwestern Medical School 5323 Harry Hines Blvd. / Dallas, Texas 75235-9038 / 214-648-8916 Telefax 214-648-8947 / email: kgardn@biochem.swmed.edu

-Required quantity of protein: we routinely screen extracts from 80-100mL of *E. coli* (strain BL21(DE3) grown in M9 media, concentrating the cell lysate to 0.5-1.0mL before running the HSQC spectra. Almost all of the proteins used in these screens have been overexpressed from high-level T7-based promoters, but our expression levels are usually lower than those shown in reference 1. With these parameters, we often obtain sufficient protein concentrations to record high-quality HSQC spectra in 15-60 minutes on our 500MHz instrument (4-16 scans/t_1, 64 complex increments).

A demonstration of the spectra obtained from this method is presented in Figure 1. Each panel in this figure shows an overlay of spectra obtained from the Gβ1 fusion protein alone (black) and Gβ1 fusions to fragments of a small protein domain that we are studying (gray). As such, the peaks of interest are those shown in gray without any corresponding black peaks nearby. The shortest construct (1-77) is clearly unfolded given the poor amide proton chemical shift dispersion observed in Fig 1A. Adding approximately 30 amino acids to the C-terminal side of this domain leads to significantly improved chemical shift dispersion, suggesting that this longer fragment is well folded (Fig 1B). Additional residues added on to the C-terminus appear to be unfolded, as marked by the increased congestion in the center of the 1-135 spectrum (Fig 1C).

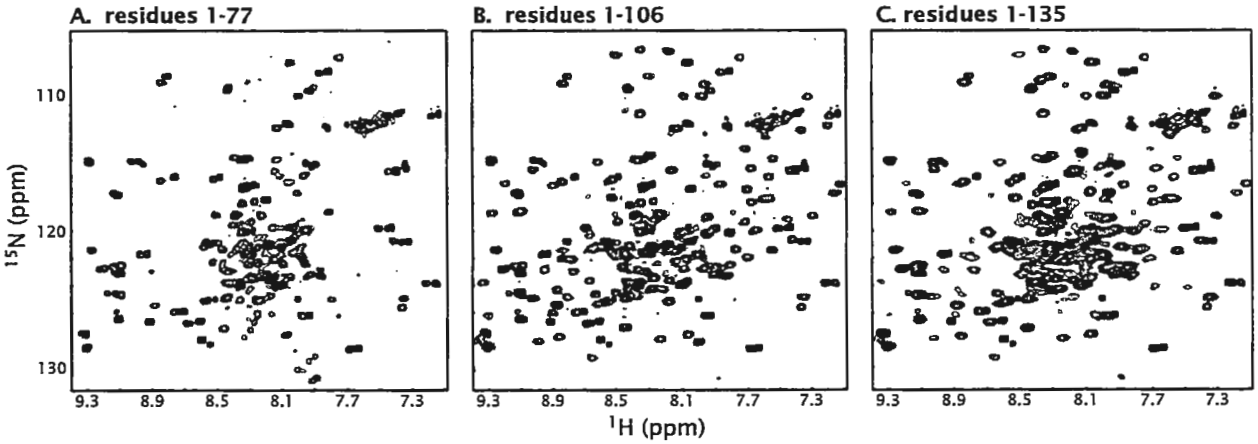

Figure 1: ^{15}N-^{1}H HSQC spectra acquired from lysates of *E. coli* cultures overexpressing various truncated forms of a Protein of Interest.

Sincerely,

Kevin Gardner

References:

1. Gronenborn, A.M. and Clore, G.M. (1996) Rapid screening for structural integrity of expressed proteins by heteronuclear NMR spectroscopy. *Protein Science* 5: 174-177.

2. Huth, J.R., Bewley, C.A., Jackson, B.M., Hinnebusch, A.G., Clore, G.M. and Gronenborn, A.M. (1997) Design of an expression system for detecting folded protein domains and mapping macromolecular interactions by NMR. *Protein Science* 6: 2359-2364.

Second Annual EMSL Workshop on Structural Genomics

Pacific Northwest National Laboratory
William R. Wiley Environmental Molecular Sciences Laboratory
Richland, Washington
July 28-29, 2000

This year, the workshop has the following objectives:

1. To bring representatives from DOE labs together to build new interactions and collaborations to meet the challenge of Structural Genomics.

2. To bring together members of the NMR community from around the country and world to discuss:
   - the role that NMR spectroscopy will play in Structural and Functional Genomics,
   - the technical challenges NMR faces for Structural Genomics, and
   - progress in meeting those challenges.

3. To bring together scientists from the Pacific Northwest region to build new interactions and collaborations.

4. To bring Principal Investigators of pilot projects in Structural Genomics to the meeting to provide updates on progress and stimulate exchange of information.

5. To discuss the need for dedicated nationally supported NMR facilities for Structural Genomics.

The workshop is organized to mix strong scientific presentations on Structural Genomics together with a workshop discussion at the end of the meeting to focus on the most pressing questions each year for the role of NMR in structural genomics.

Speakers

David Cowburn (Rockefeller University)
Cheryl Arrowsmith (University of Toronto)
Tom Szyperski (SUNY Buffalo)
Frank Delaglio (NIH)

Guy Montelione (Rutgers University)
Andrezj Joachimiak (Argonne National Laboratory)
Geoff Waldo (Los Alamos National Laboratory)
Rich Withers (Bruker Instruments)
Michal Linial (the Hebrew University in Israel)
Shigeyuki Yokoyama (University of Tokyo)
Iain Campbell (University of Oxford)
Hartmut Oschkinat (Protein Structure Factory, Berlin)
David Baker (University of Washington)
Michael A. Kennedy (PNNL)
Janna Wehrle (NIH)
John Markley (University of Wisconsin)
Abraham Levy (NIH) (tentative)
Roland Hirsch (DOE) (tentative)

More details about the workshop can be found at the following web site:

http://www.emsl.pnl.gov:2080/docs/msd/workshop2000/

The workshop is an open meeting and interested students, postdocs, staff, and faculty are encouraged to attend.

Contact:

Michael A. Kennedy, PhD
Sr. Research Scientist
Macromolecular Structure & Dynamics
William R. Wiley Environmental Molecular Sciences Laboratory
Pacific Northwest National Laboratory
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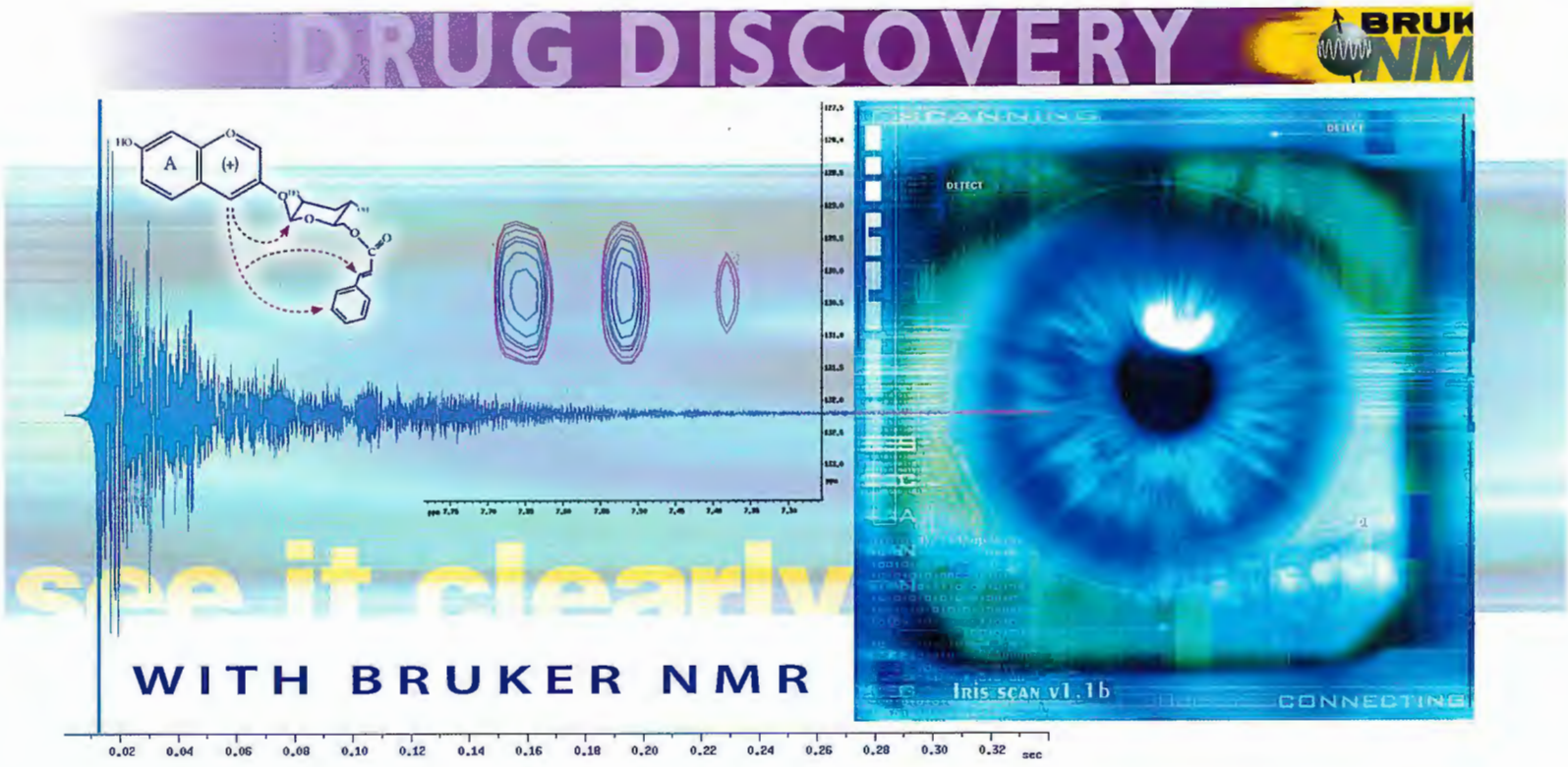

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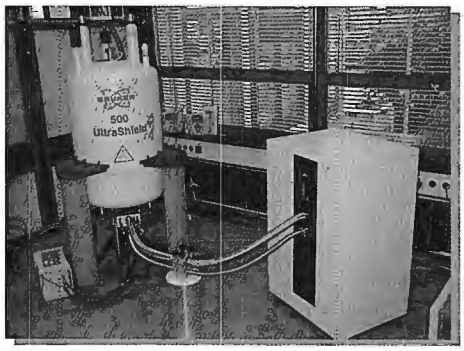

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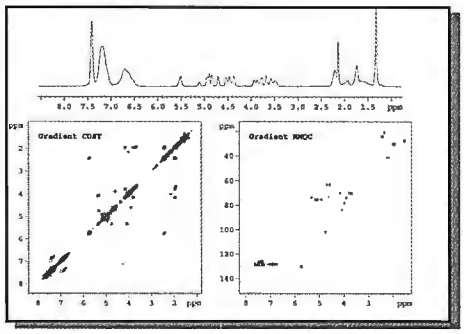

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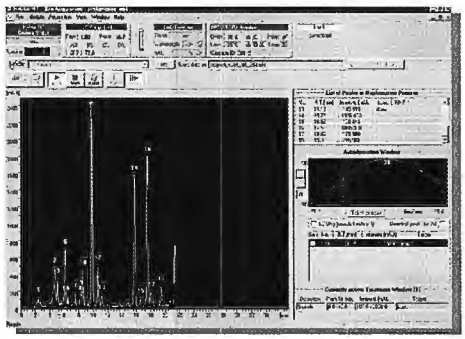

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May 30, 2000
(received 06/05/2000)

The DUAL Cryoprobe

PHARMACIA

Dear Barry:

Just prior to the ENC a DUAL cryoprobe was installed at our site in Kalamazoo and has been performing admirably since then. The following specifications were achieved:

^{13}C sensitivity: 10% EB in $CDCl_3$ --- 938:1
ASTM --- 1183:1

^{1}H sensitivity: 0.1% EB in $CDCl_3$ --- 1581:1 (2ppm); 1747:1 (200Hz)

Pulse widths: ^{1}H 90 -- 14.0μs @ 1dB ^{13}C 90 -- 9.3μs @ 4dB

According to a copy of the latest Bruker probe specifications, a 600 MHz is listed as having a 0.1% EB of 1100:1 (on a standard TXI, 200 Hz noise) and an ASTM of 290:1 (on a standard Dual). Extrapolating from these figures, the Dual cryoprobe, on our AVANCE 500 MHz, is achieving the equivalent of a 1500 MHz NMR on the carbon channel and an 800 MHz on the proton channel.

To get a sense of the improvement in sensitivity, experiments were performed on a 185ug sample of Prednisone prepared in a 5mm shigemi tube. The lower spectrum in Figure 1 represents 1024 transients of a composite pulse decoupled ^{13}C experiment and the upper represents 256 transients of a DEPT90. Signal to noise in each case is quite reasonable considering the short duration of the experiments. Noticeable in the DEPT spectrum is a solvent artifact at ~39 ppm, see discussion below.

We have observed two "idiosyncrasies" in the spectral data one of which we've termed, the solvent breakthrough problem, Figure 2. It occurs in DEPT spectra and manifests itself as the appearance of solvent signals in a dispersive manner. We have seen this type of behavior in normal probes when B_1 or B_2 needed to be calibrated, however, this is not the case here. The problem is environmental and caused by floor vibrations being introduced to the magnet via the cryotransferline isolation post. The post is meant as a sink for vibrations produced by the cryocooling unit. In our case it is transfering vibrations from the building to the magnet, i.e. bypassing the magnet stand TMC posts. A workaround is to reduce the number of "spins" subject to the problem by using a 3mm shigemi and restricting the solvent to the active coil length. The workaround, however, revealed the second idiosyncracy; a spike at the beginning of the FID which manifests itself as baseline distortions after transformation. The spike is not observed when using 5mm tubes.

Rather than the brute force method described above, a better solution is to manipulate the sign of the real signals in respect to the solvent artifact. This can be accomplished by modifying the phase cycling of Bruker's DEPT pulse programs to the following:

```
1 ze
2 d1 do:f2
  d12 pl2:f2
3 (p3 ph1):f2
  d2
  (p4 ph2):f2 (p1 ph4 d2):f1
  (p3 ph3):f2 (p2 ph5 d2):f1
  DELTA pl12:f2
  go=2 ph31 cpd2:f2
  d12 do:f2
  wr #0
exit

ph1=0
ph2=0 1
ph3=1 1
ph4=0 0
ph5=0 0
ph31=1 3
```

PHARMACIA

A comparison of the DEPT90 before and after the phase cycle modification is presented in Figure 3. The minimum phase cycle in the standard Bruker pulse program is NS = 4. The top spectrum in Figure 3 shows that after NS = 8 the solvent breakthrough artifact is attenuated by approximately 80%. For comparison see Figure 2 which shows the intensity of the artifact with an NS = 1. The minimum phase cycle for the aforementioned modification is NS = 2. The bottom spectrum shows that after NS = 8 the artifact is barely detectable. In practice, the solvent breakthrough artifact is not much worse with the minimum phase cycle of NS = 2. (Of course who uses an NS of 2 to collect carbon data?)

Similar modifications can be expected to be needed for other carbon observe polarization transfer experiments. This problem may be annoying but it does not seriously impact the ability to identify trace impurities. All in all, the Cryoprobe represents a tremendous advance in capability for those needing to identify less than µmole amounts of material.

Sincerely,

Stephen H Grode

Mark R Mowery

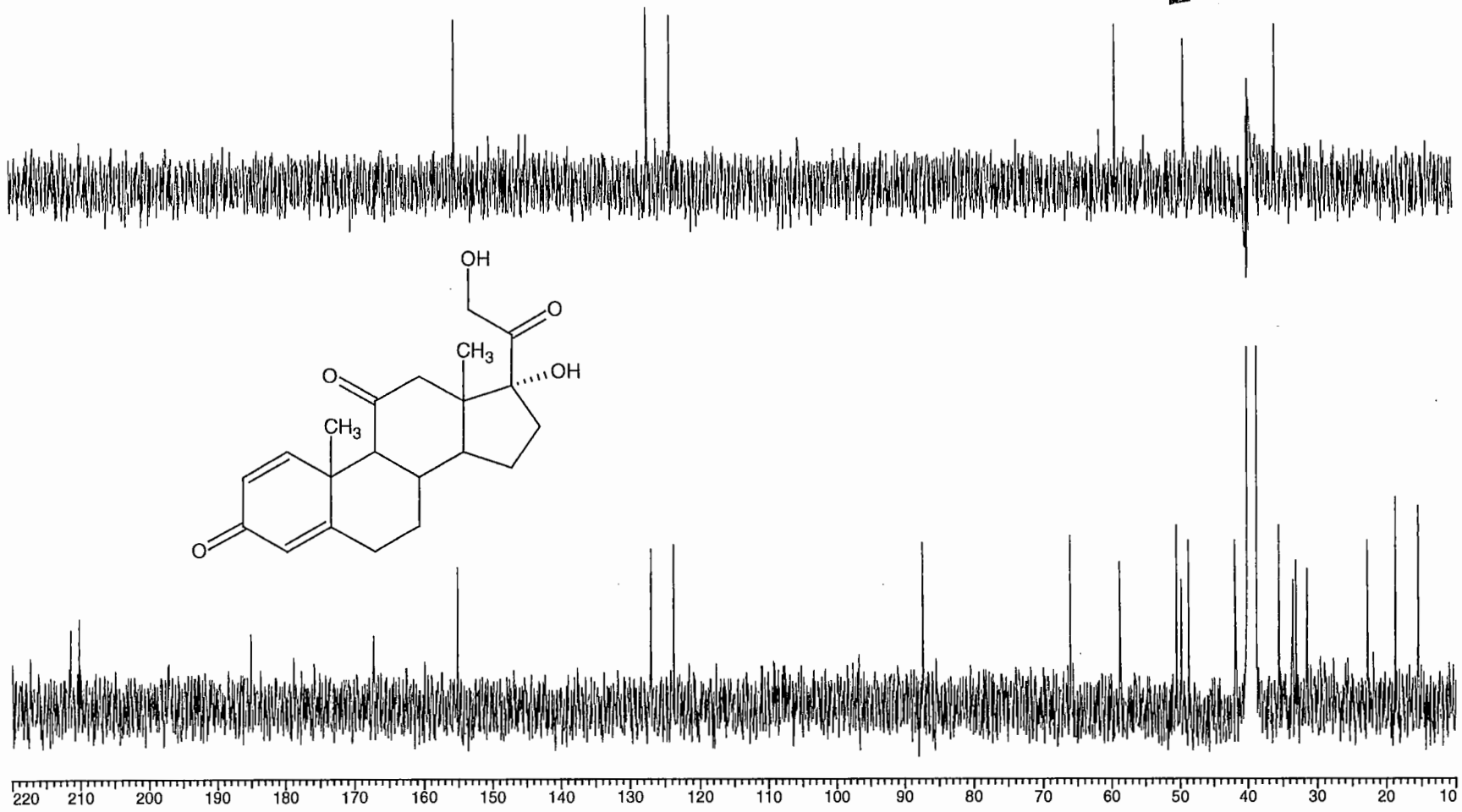

Figure 1. NMR spectra of 185µg Prednisone prepared in a 5mm shigemi tube. The lower spectrum is a composite pulse decoupled ^{13}C (NS=1024) and the upper is a DEPT90 (NS=256). Note the presence of a solvent artifact at ~39 ppm in the DEPT90, see text.

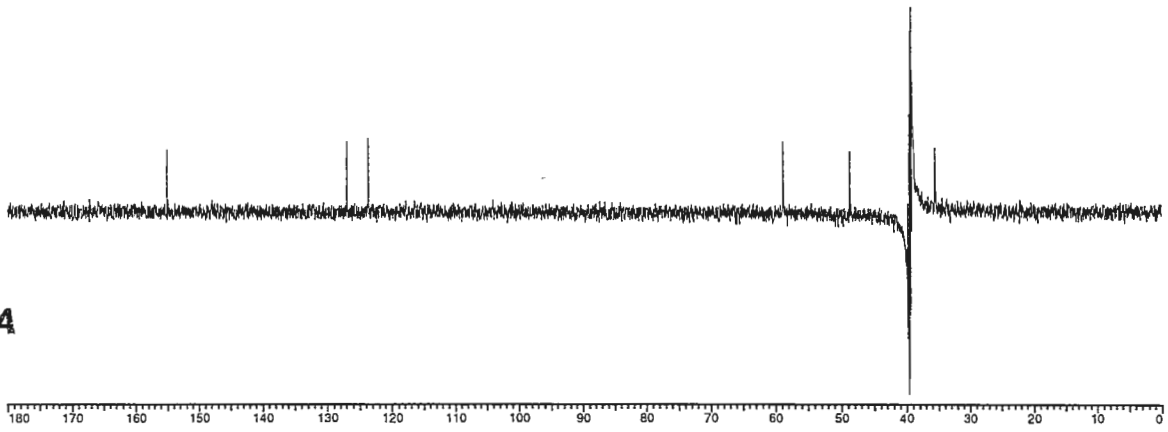

Figure 2. DEPT90, NS=1, showing the solvent breakthrough artifact, as described in the text.

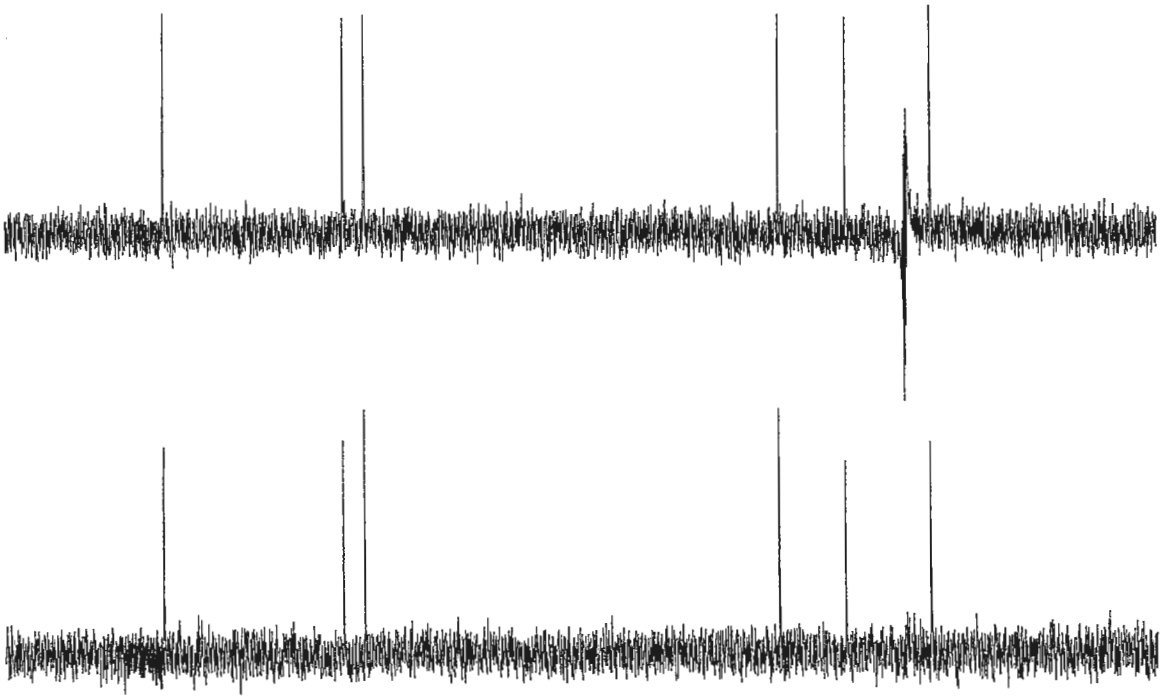

Figure 3. The top spectrum is a standard Bruker DEPT90 pulse program, NS=8. The bottom spectrum is the same pulse program with phase cycling modified to remove the solvent breakthrough artifact, NS=8.

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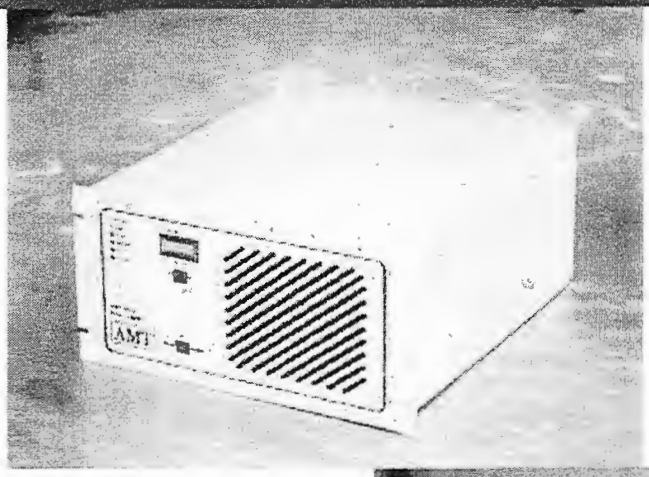

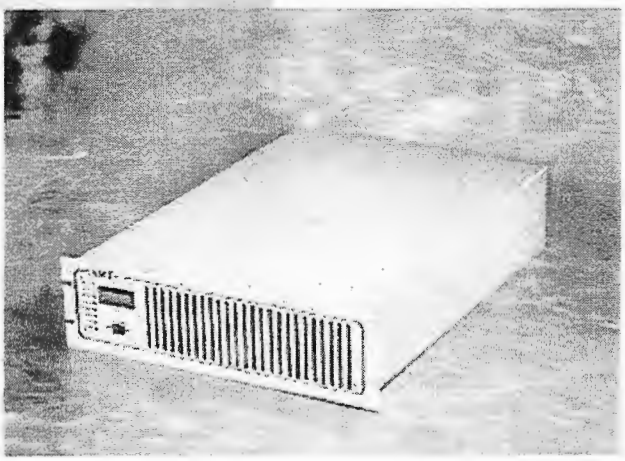

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The NMR Newsletter - Book Reviews

Book Review Editor: István Pelczer, Dept. of Chemistry, Princeton University, Princeton, NJ 08544

"High Resolution NMR. Theory and Chemical Applications" (3rd edition)

by

Edwin D. Becker

Academic Press (www.hbuk.co.uk/ap, www.academicpress.com – USA site)
San Diego, 2000, ISBN 0-12-084662-4, 400 pages, $83.00

The reviewer is humbled when a book like Ted Becker's updated work, the third edition of the first version from 1969, appears. This work not only bridges the decades and generations in NMR spectroscopy, but is also an exceptional handbook and reference resource. It simultaneously represents and illustrates the amazing – and still ongoing – enhancement of NMR, which has become an indispensable tool for so many applications in science, medicine and engineering.

Ted Becker, one of the great pioneers of NMR, has been encouraged by Ad Bax (fortunately with success) to put together this volume, which is new by more than two-thirds of its content. It fills the gap between very sophisticated and more specialized publications and those of an introductory nature. Becker has accomplished the virtually impossible tasks of joining historical perspective with up-to-date subject content, introducing basics and more advanced methods, theory and a great variety of applications. All this is presented quite clearly, in a conversational, yet enjoyably classic style. I found this book exceptionally rich in information, but also compact and easy to handle. The focus of the book is on high-resolution liquid state NMR, but brief overviews of solid-state NMR and imaging are also presented. Each chapter is followed by a list of additional reading and resources, and by a carefully crafted problem set, a great teaching resource. Citations mainly point to good reference books and reviews, often from the *Encyclopedia of Nuclear Magnetic Resonance*, rather than individual papers. This is an intentional strategy, which adds to the value of this work. Those papers referenced individually are often exceptional historical pieces.

The volume consists of a ***Preface to the Third Edition*** (worth reading, too!), fourteen chapters on 380 pages, five appendices on additional 30 pages, six pages of numbered references and finally eight pages of Index. The ***Introduction*** (Chapter 1) gives a short, yet comprehensive overview of the history of NMR spectroscopy from the early experiments of Rabi in the 30's. It presents a compressed overview of high resolution NMR and introduces some of the outstanding representatives of this field. An unusual but charming feature of this chapter is the small photos of Rabi, Bloch, Purcell, Gutowsky, Waugh, Pines, Ernst, Freeman, Hahn, Wüthrich, Bax and Lauterbur.

Chapter 2 introduces basic theory of NMR, all major approaches for describing its phenomena (quantum mechanical, vector model, density matrix, product operators – which are also treated more extensively later), methods of obtaining NMR spectra, and dynamic processes. The summary of terminology, symbols, units, and conventions at the end of this chapter is especially useful, and clarifies many confusing appearances in the literature. Chapter 3 deals with practical aspects of instrumentation and various techniques of data acquisition and processing. In Chapter 4 chemical shifts are discussed from both theoretical and practical points of view. This is probably the section that has changed the least over the last three decades or so. It remains, however, essential reading and presents a thoughtful

continued

summary of important details, such as those about susceptibility effects in external referencing (pp.90-92). The chapter is enhanced by a quite up-to-date compilation of databases and spectral data resources.

Spin-spin coupling, its theory, correlation of coupling constant values with chemical structure and other physical properties, effects of exchange, and double resonance techniques are subjects of the next chapter, with the focus on the electron-coupled spin-spin interactions (or *J* coupling).

Many new users of NMR spectroscopy have access to quite high field instruments that often provide closely first order multiplets, and/or use correlation spectra, where fine multiplet structure is not much of a concern. This may easily lead to a significant misconception that fine multiplet features can be neglected and are not very informative. That's why the following chapter, under the title ***Structure and Analysis of Complex Spectra***, carries so much of educational value. It deals with various coupling patterns (once the subject of extensive individual books), magnetic and chemical equivalence, and spin simulation. Some typical examples are also analyzed, including the often overlooked, yet very useful "satellites" from heteronuclides.

NMR in solid state and other oriented systems, such as liquid crystals, is the subject of Chapter 7. Introduction and analysis of dipolar coupling effects and the solid state lineshape is followed by discussion of technical aspects, such as dipolar decoupling, cross-polarization, line narrowing methods, and various pulse applications.

It is a unique feature of NMR to provide a window into the dynamics of individual spins, and smaller and more extended structures through analysis of relaxation properties. Chapter 8 leads us through the various relaxation mechanisms, their effects and contribution to the overall picture, as well as a few practical aspects of their interpretation. ***Pulse Sequences,*** the next chapter, is not just a list of various experiments, but rather a compilation of the most important modular elements. Spin-echo variants, spin-locking, selective excitation, filtering pulse combinations, such as BIRD and X-filters, various solvent suppression, and polarization transfer pulse methods are discussed.

Two-dimensional (and implicitly *n*D) NMR spectroscopy is presented in Chapter 10 from a very general, but comprehensive point of view, including technical aspects of data acquisition and data processing. The general discussion of NMR principles concludes with a highly educational chapter (Chapter 11) on density matrix and product operator formalism treatment of NMR phenomena. Selected examples include polarization transfer experiments, solid echo coherence pathway selection/rejection by phase cycling and pulsed field gradients.

Chapter 12 gives an overview of some 1D, and 2-4D experiments. Chapter 13 presents the application of NMR to molecular structure and macromolecular conformation. The final, chapter briefly describes imaging and spatially localized spectroscopy, such as chemical shift imaging, *in vivo* spectroscopy, and imaging in solids. These three chapters strongly illustrate the coordinating nature of the author's approach, and at the same time the cohesiveness of NMR principles and applications. Reading these pages, we can truly appreciate the tremendous power and usefulness of this technique – in large part due to the clear and systematic, yet conversational presentation of our guide, Ted Becker.

This book is an outstanding coordinating work, an excellent resource, and a reference for further studies in the field of NMR. I consider it as a must for all NMR spectroscopists and teachers who deal with the subject. Also, I wholeheartedly recommend it to students, and to anyone else who wants to receive an enjoyable introduction to the exciting field of NMR spectroscopy and its applications.

István Pelczer
Department of Chemistry
Princeton University
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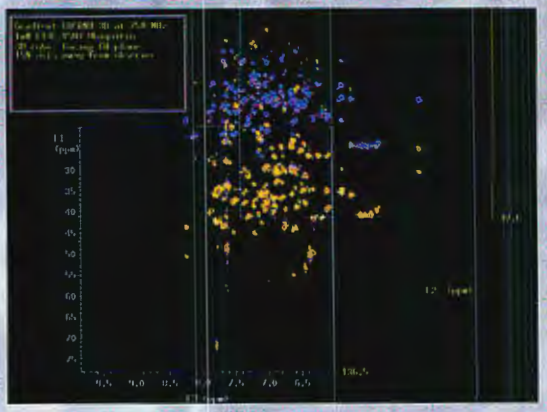

Gradient CBCANH 3D at 750 MHz 1mM Ubiquitin [^{13}C, ^{15}N] 3D cube facing CH plane ^{15}N axis away from observer. (Spectra courtesy of Varian Associates, Inc.— Palo Alto, CA.)

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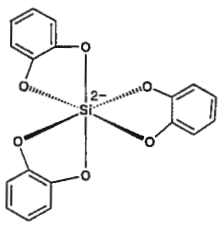
June 14, 2000
(received 6/19/2000)

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

Dear Barry:

The interplay of the inorganic and organic silicon worlds is only beginning to be understood. The universe of sand, clay, and computer chips has not interacted strongly with the organosilicon world of synthetic reagents, elusive intermediates, adhesives, lubricants, and medical implants. One reason is the essential lack of solubility of the inorganic materials in most solvents, including water. Although silica is not soluble in neutral water, silicic acid, $Si(OH)_4$, does have considerable aqueous solubility in base. This solubility has been associated with deprotonation to $Si(OH)_3O^-$, analogous to the polyprotic equilibria of phosphoric acid. In a recent report in *Science* (**285**, pp. 1542-1545, 1999), Kinrade et al. stated that pentacoordination was unknown in water and hexacoordination rare. These higher coordination numbers are well known in organic solvents and in crystals retrieved from organic solvents. Kinrade's report documented hypervalent species present when carbohydrates with at least four consecutive hydroxy groups were placed in aqueous media with silicic acid under basic conditions. Their only structural tool was ^{29}Si chemical shifts, with tetracoordination at ca. δ -75, pentacoordination at ca. δ -100, and hexacoordination at ca. δ -140. Each of the regions for penta- and hexacoordination contained several peaks, indicating complex mixtures.

We have examined under similar conditions unsaturated systems containing two hydroxy groups capable of chelating to silicon. For example, catechol (1,2-dihydroxybenzene) in alkaline silicic acid solution produces a single, sharp peak at δ -144, indicating the presence of the hexacoordinate species **1** as the only



1

material present in solution. We have found that other 1,2-dihydroxybenzenes (pyrogallol, L-DOPA) similarly form pure hexacoordinate species under these conditions. In addition to catechols, we have been examining tropolones, 1,3-diketones, 2-hydroxypyridine *N*-oxides, and other water soluble unsaturated chelates. We have found numerous examples of hypercoordination both in solution and in insoluble materials that drop out of solution, based on ^{29}Si chemical shifts respectively in solution and the solid state.

Biological implications of these observations include uptake of silica in plants, treatment of silicosis conditions, and interaction of silicone implants with the body.

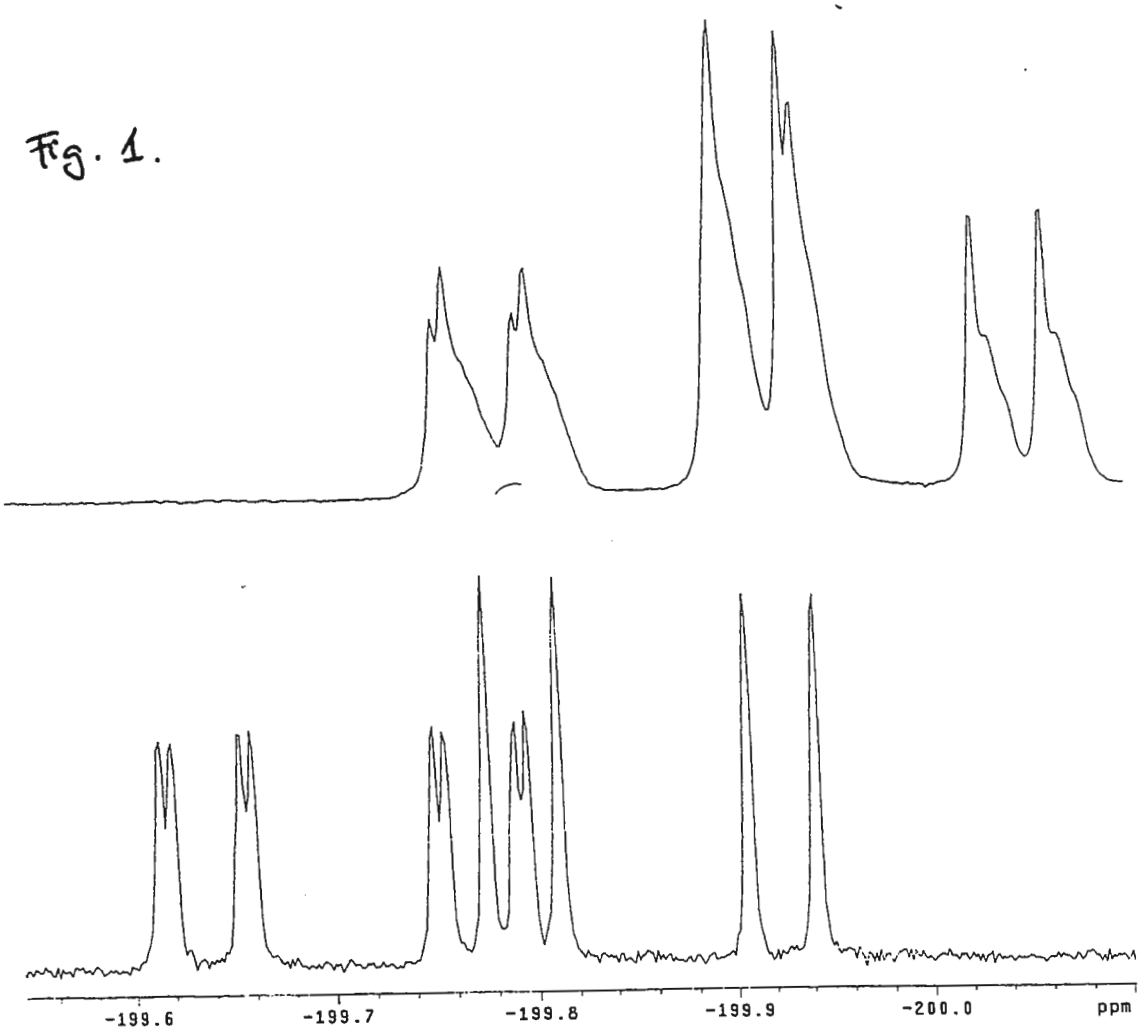
Sincerely,

Joseph B. Lambert

Stephanie R. Roder

CONTINUED FROM PAGE 29

Fig. 1.



Princeton University **Department of Chemistry**
Princeton, New Jersey 08544-1009

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

06/18/2000
(received 6/21/2000)

Re: ^{19}F as a probe to differential concentration

Dear Barry,

During our recent visit to Varian for a demo, we ran into some interesting, and potentially useful, behavior of ^{19}F. We added more D_2O to a previously prepared 2-fluoro-2-deoxy-D-glucose sample, and took spectra of both ^{1}H and ^{19}F, and did some double-resonance experiments, too. In the course of the regular protocol, we used ^{2}H gradient shimming, and observed a nice 1D ^{1}H spectrum, as expected.

However, we experienced some distortions in the lineshape of the ^{19}F resonances, as shown in Figure 1 (upper spectrum). This sample contains both the alpha and beta anomers, so seeing two doublets with further long-range couplings added is what we would expect. The distortion looked very much like caused by poor Z2 shimming, but we saw no similar effects in the repeated ^{1}H spectrum. Repeated gradient shimming ended up with the same feature also.

After some head scratching, we concluded that what we see is likely to be the effect of differential concentration along the sample. When we added more solvent, we ***did not*** shake the sample or made other particular effort to equilibrate the concentration, which people (including ourselves) usually do – to our benefit this time! In fact, when we did shake the sample few times and repeated the experiment, we ended up with the spectrum at the bottom of Figure 1. (Small chemical shift differences originate from the slightly elevated temperature in the second case.) Therefore, the lineshape of the first spectrum reflects the chemical shift distribution in the sample (more accurately in the active area with some additional weighted contribution from outside of it).

In retrospective, this observation is not that surprising. The extreme sensitivity of ^{19}F to the chemical environment is expressed in its large chemical shift range. We could not see any effect in the ^{1}H spectrum because it all was lost in the lineshape, let alone the ^{2}H spectrum, which also proves the robustness of ^{2}H shimming.

This observed behavior of ^{19}F makes it a potential probe to chemical shift (and perhaps temperature, etc.) distribution in the sample. The same principle can be applied to other systems and other phenomena, too, such as diffusion. We are planning to take a closer look at this possibility.

With our best regards,

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Chemistry
Princeton University

Carlos Pacheco
Chemistry
Princeton University

Steve Cheatham
Applications
Varian NMR Systems

CONTINUED ON PAGE 28

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Prof. Dr. B. L. Shapiro
Department of Chemistry
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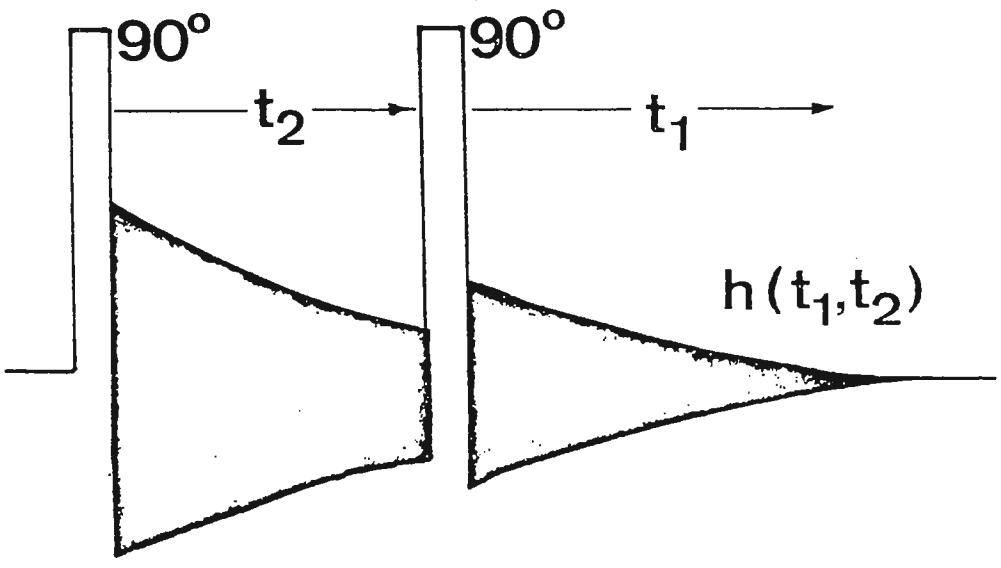
College Station, Texas

TWO-DIMENSIONAL SPECTROSCOPY

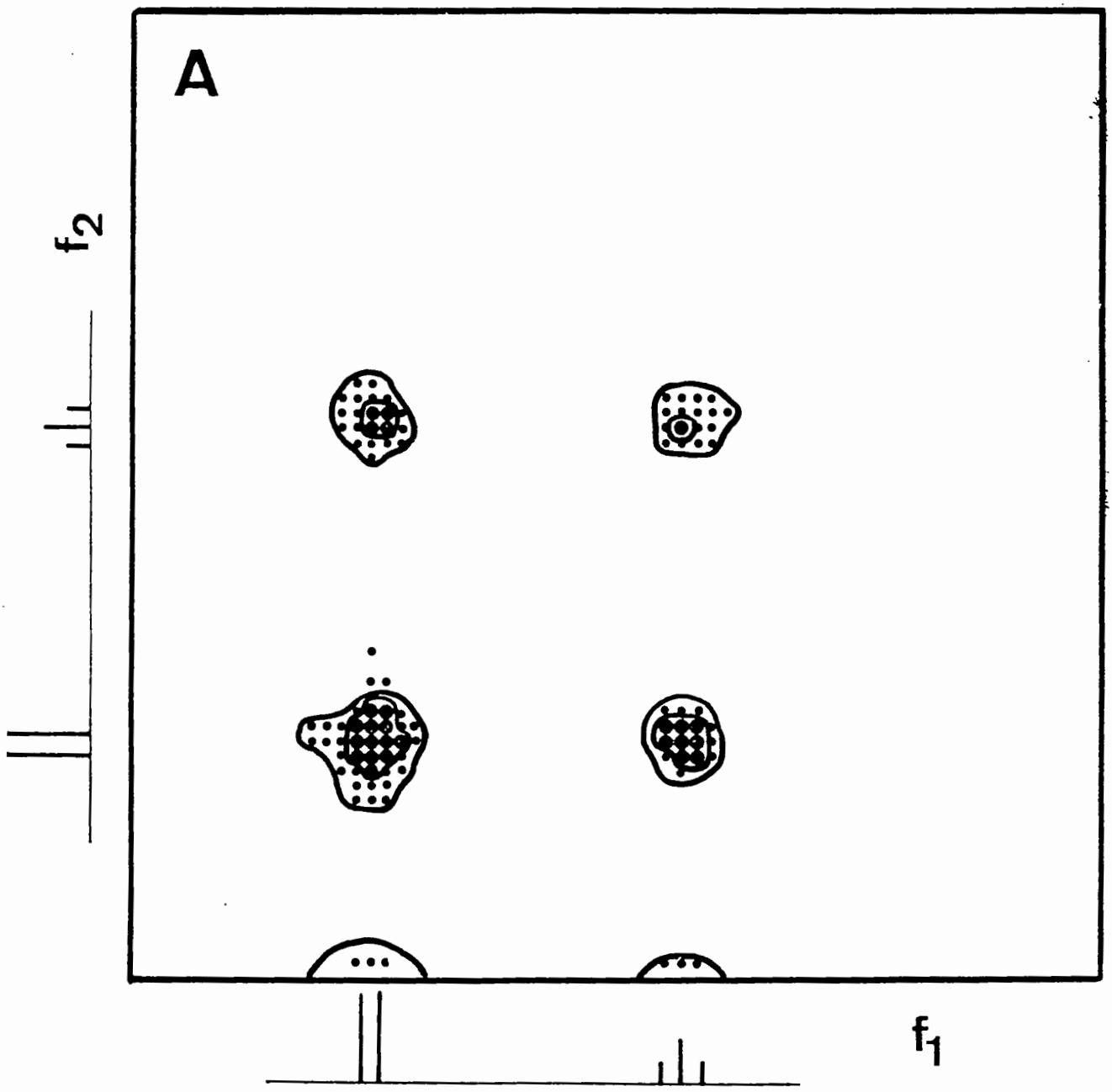
Dear Barry,

In 1971, J. Jeener has formulated the idea of pulse pair Fourier spectroscopy (Ampère International Summer School II, Basko Polje, unpublished). As we could not yet find results of an experiment of this kind in literature, we recently tried the experiment with some success.

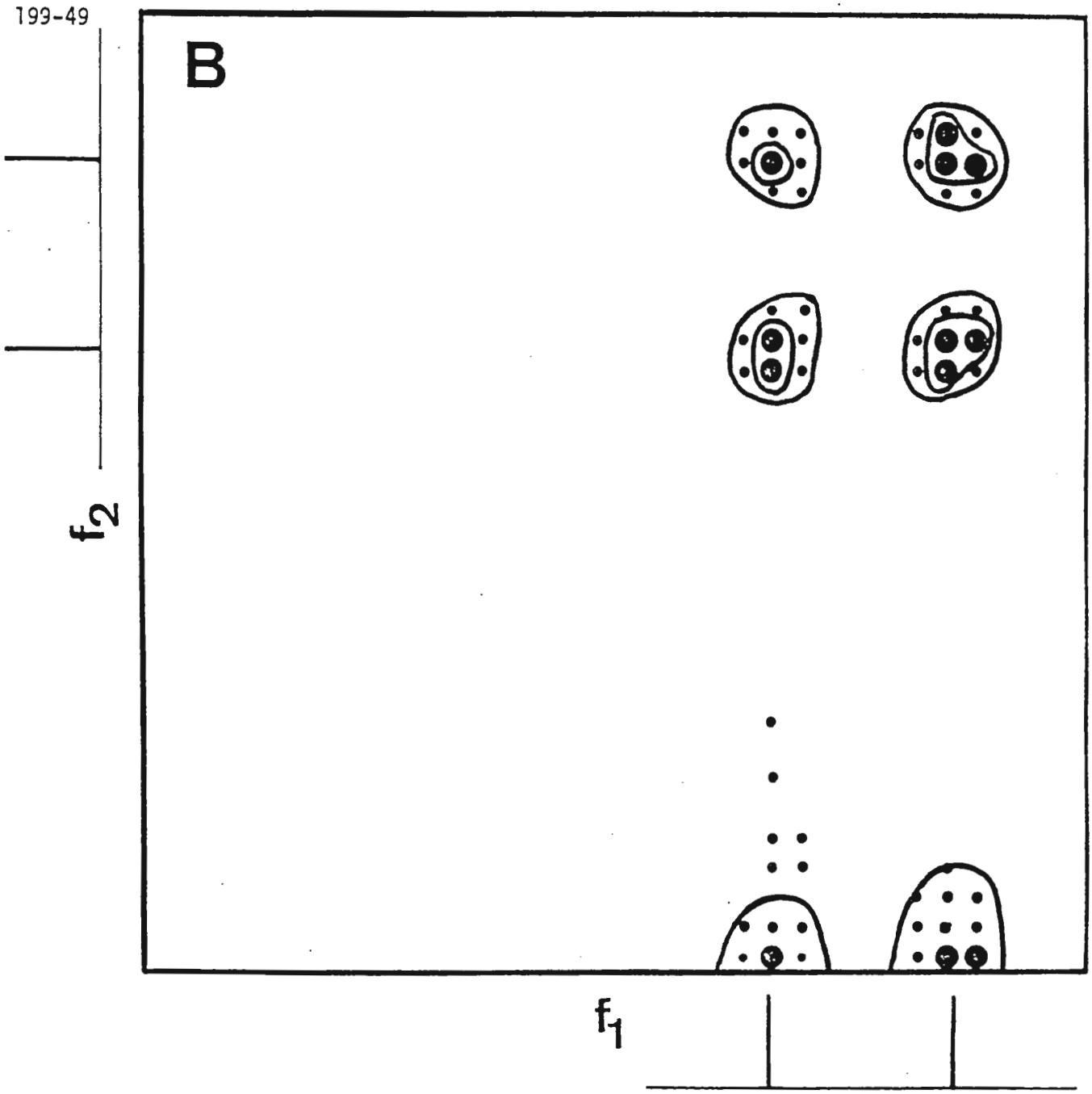
Pulse pair Fourier spectroscopy is an alternative to double resonance. It characterizes the nonlinear properties of spin systems and permits, for example, to trace out the energy level diagram in a manner similar to a tickling experiment. One measures the response to a pair of 90° pulses with separation t_2 as a function of the time t_1 elapsed after the second pulse. By varying the pulse separation t_2, one obtains a two-dimensional impulse response $h(t_1,t_2)$:



The 2D Fourier transform of $h(t_1,t_2)$ produces a 2D spectrum in a manner analogous to Fourier Zeugmatography (TAMU-NMR Letter 191, 36). An example of a low resolution 2D spectrum of 1,1,2-trichloroethane is given in the following figure. It consists of two peaks on the f_1 axis which represent the original spectrum, peaks on the diagonal and off-diagonal peaks which contain the "double resonance" information. In this example, they demonstrate at least that the two peaks belong to the same spin system.



More detailed information can be obtained by means of a blow-up of a partial 2D spectrum. The next figure gives the enlarged lower left corner of the above figure showing the CH_2 doublet.



These spectra are preliminary in several respects. First of all, resolution is severely limited by the available computer memory. A 64x64 data matrix was used. Secondly, the absolute value of the 2D spectrum is plotted disregarding phase information which may be of particular interest. This experiment has several further interesting aspects which we presently are investigating.

Sincerely yours

Richard

Richard R. Ernst

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650-493-5971* - *Please call only between 8:00 am and 10:00 pm, Pacific Coast time.*

Deadline Dates

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No. 504 (Sept.)	24 Aug. 2000
No. 505 (Oct.)	27 Sept. 2000
No. 506 (Nov.)	27 Oct. 2000
No. 507 (Dec.)	24 Nov. 2000

* 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.

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Forthcoming NMR Meetings, continued from page 1:

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\

ISMAR 2001, Jerusalem, Israel, **August 19-24, 2001**; See http://www.tau.ac.il/chemistry/ISMAR.html.

Additional listings of meetings, etc., are invited.

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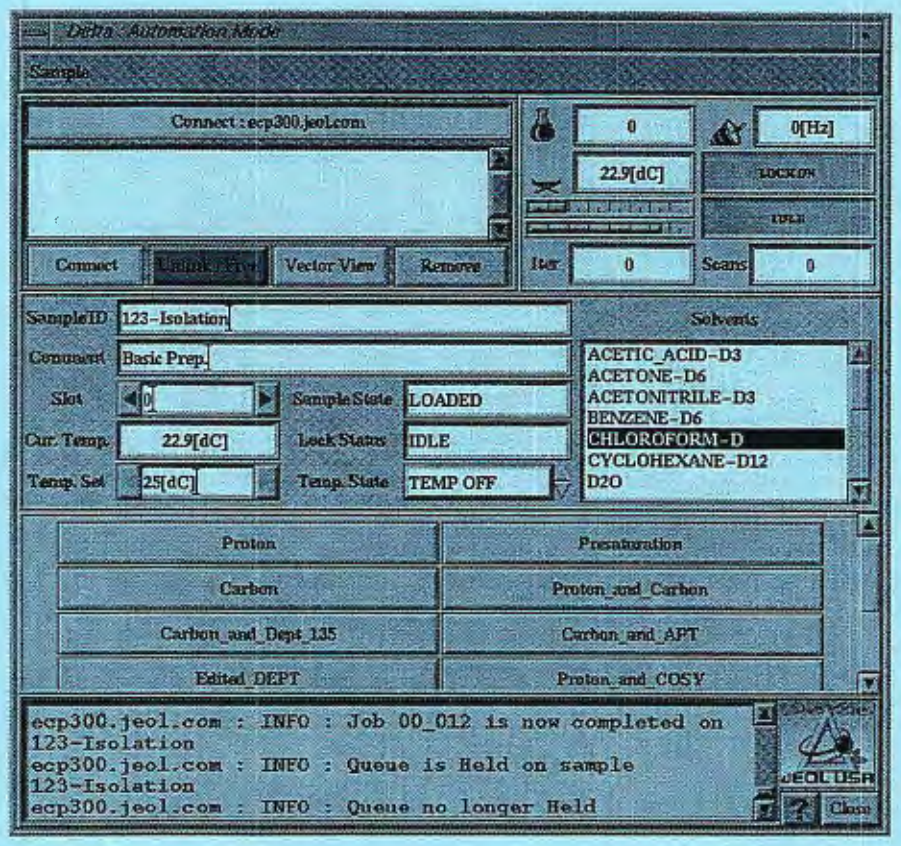

The **Eclipse+** NMR Spectrometer can be operated anywhere there is a computer on the local network. The **Single Window Automation** pictured above can be used with a single mouse click to select the sample from the auto-sample changer, gradient shim on any probe, run the selected experiment, and plot 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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