THE NMR NEWSLETTER

No. 481

October 1998

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PTS 250	1-250 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$7,440.00 (1 Hz resol., OCXO freq. std.)
Type 1 **PTS 310** Type 2	.1-310 MHz	1 Hz	1-20μs	standard	3½"H×19"W	BCD (std) or GPIB (opt)	1 Hz resol., OCXO: $6,425.00 1 Hz resol., OCXO: $5,850.00
PTS 500	1-500 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$8,720.00 (1 Hz resol., OCXO freq. std.)
PTS 620	1-620 MHz	optional .1 Hz to 100 KHz	1-20μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$9,625.00 (1 Hz resol., OCXO freq. std.)
PTS 1000	0.1-1000 MHz	optional .1 Hz to 100 KHz	5-10μs	optional	5¼"H×19"W	BCD (std) or GPIB (opt)	$11,830.00 (1 Hz resol., OCXO freq. std.)
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PTS x10	user specified 10 MHz decade	1 Hz	1-5μs	standard	3½"H×19"W	BCD (std) or GPIB (opt)	$3,000.00 (1 Hz resol., OCXO freq. std.)
PTS D310	two channels .1-310 MHz	.1 Hz	1-20μs	standard	5¼"H×19"W	BCD (std) or GPIB (opt)	$8,560.00 (.1 Hz resol., OCXO freq. std.)
PTS D620	two channels 1-620 MHz	.1 Hz/.2 Hz	1-20 μs	standard	5¼"H×19"W	BCD (std) or GPIB (opt)	$13,240.00 (.1 Hz/.2 Hz resol., OCXO freq. std.)

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FORTHCOMING NMR MEETINGS

NMR Technologies: Development and Applications for Drug Design and Characterizations, Baltimore, MD, **October 29-30, 1998**; Contact: J. Laakso, Cambridge Healthtech Institute, 1037 Chestnut St. Newton Upper Falls, MA 02164; 617-630-1300; Fax: 617-630-1325; chi@healthtech.com; http://www.healthtech.com/conferences/.

NMR of Polymers and Biopolymers, Symposium at the 54th SouthWest Regional ACS Meeting, Baton Rouge, LA, **November 1-2, 1998**, For Symposium schedule: members.aol.com/ACKolbert/symposium.html; Contact: A. C. Kolbert mailto:ackolbert@aol.com or Xiaolian Gao, xgao@uh.edu

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

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

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

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

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

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

UNIVERSITY OF THE PACIFIC

College of the Pacific

Department of Chemistry

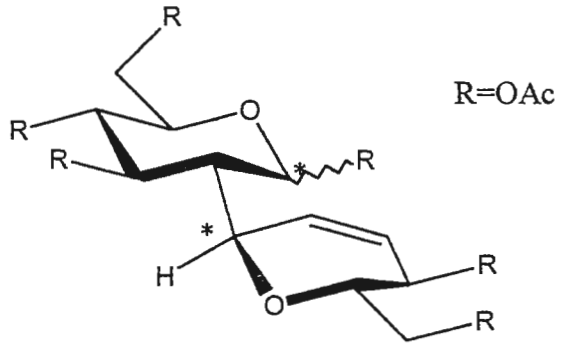
(received 9/17/98)

^{13}C-^{13}C Couplings in Doubly Labeled Ferrier Dimers

Andreas Franz, Paul Gross and Mike Minch

Dear Barry:

As we pointed out earlier (NMR Newsletter Dec 1997, ENC March 1998) Ferrier Dimers contain a carbon-carbon bond linking a pyranoside ring to a 2,3-dideoxyhex-2-ene pyranose ring. This linkage cannot freely rotate like a conventional O-glycosidic bond so that these C-glycosides can show one dominant rotamer. This was born out by our vicinal proton coupling constants and inter-ring NOE studies and more recently by an X-ray crystal structure.



Starting with [1-^{13}C] glucose we can prepare doubly-labeled gluco Ferrier Dimers with labels at C(1) and C(1'). Such molecules permit the convenient measurement of carbon-carbon and carbon-proton couplings. The following are some observed couplings for the α and β anomers of this compound:

Coupling	J-observed (Hz)	
$^{2}J_{C(1)C(1')}$	0	
$^{1}J_{C(1)H(1)}$	177.3	α
	168.9	β
$^{1}J_{C(1')H(1')}$	147.2	α
	–	β
$^{1}J_{C(1')C(2')}$	161.7	α
	171.9	β
$^{1}J_{C(1)C(2)}$	167.4	α
	159.3	β

Serianni [J. Magn. Reson. B *112*, 69 (1996)] has proposed a set of empirical rules predicting the magnitudes and signs of $^{2}J_{CCC}$, and $^{2}J_{CCH}$ values in carbohydrates based on the orientation of electronegative substituents about the Newman projections of the C-C bonds transmitting the coupling. One of our current research efforts is to prepare a series of doubly-labeled Ferrier Dimers from different pyranoses since the coupling constants observed for such compounds constitute a good test of the applicability of this empirical rule to linkages between rings. Because of the greater rigidity of our compounds compared with the more flexible pyranosides used by Serianni, these coupling constants can be assumed to be free from contributions of other rotamers about the C-C bonds transmitting coupling information. We point out that the observed $^{2}J_{C(1)C(1')}$ value for the compound above is consistent with the Serianni rule.

Family Matters

From left to right:

Don McReynolds
Earthy Lee Young
Remonda Lavinghouse
James Brewer
Gary Skidmore

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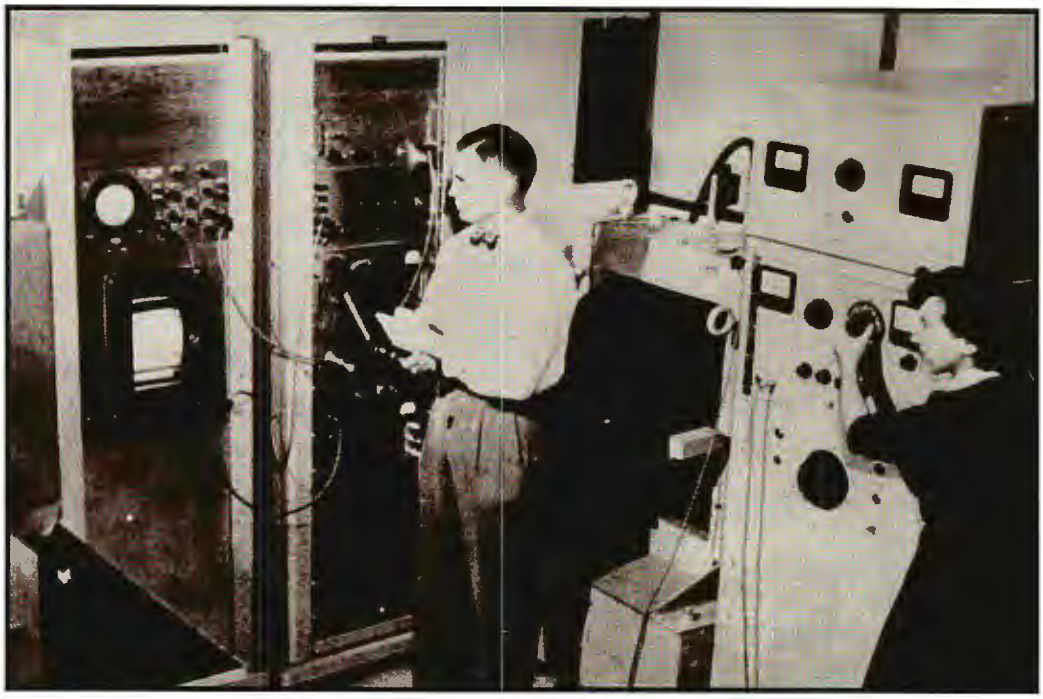

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Prof. Bernard L. Shapiro
Editor/Publisher, The NMR Newsletter
966 Elsinore Court
Palo Alto, CA 94303

August 20, 1998
(received 9/8/98)

Re: MQ tools for NMRView – developed over the net

Dear Barry,

We use NMRView (1, and see: www.nmrview.com) for analysis of multidimensional NMR spectra at the first place. One of the advantageous features of this software is its openess and flexibility, which can not be valued highly enough. In the following we want to report on some progress we are making in developing custom tools for handling homonuclear multiple quantum correlations (HoMQC).

HoMQC spectra can be very useful in structure elucidation of complex molecules (2,3). In a single experiment one obtains both connectivity and topology information. No diagonal (autocorrelation) peaks are present. High level of redundancy is an additional help when peak overlap is a concern. However, this technique is not used at the level as one would expect.

Beside historical and technical reasons this could be attributed to the fact that the connectivity patterns are quite different from those in the well known and familiar, diagonally symmetric COSY or TOCSY spectra. Also, the missing diagonal removes an 'anchor point', which can be especially helpful when folding/aliasing was applied. We (T.M. is graduate student of Prof. Ferenc Fülöp, and has been working under the supervision of Prof. György Dombi at "Albert Szent-Györgyi" Medical University, Szeged, Hungary) decided to develop some custom tools for NMRView. One early result is shown in Figure 1. The spectrum widget is difficult to access directly for annotation, but with a little trick (raising temporarily few points' intensity) a 'diagonal' can be drawn by a new button-tool, assisting spectrum analysis. We have additional tools built already, which include a 2Q-cursor, which moves connected crosshairs over symmetric locations by the pseudo-diagonal, and an MQ peak picker. A library-based graphical spin-topology tool is also in the works.

The fun part of this development is that we have never met in person (yet)... – we discuss development and exchange results for testing over the Internet.

Sincerely, with our best regards,

(Tamás Martinek) (István Pelczer)
...now both former students of "Attila József" University, Szeged, Hungary

(1) Johnson, B. A., and Blevins, R. A.; "NMRView: A computer program for the visualization and analysis of NMR data" *J. Biomol. NMR* 4(1994)603-614.

(2) Pelczer, I., and Bishop, K. D.; "Optimal acquisition and presentation of HoMQC spectra" In: "*Methods for Structure Elucidation by High-Resolution NMR*" (Eds.: Kövér, K. E., Batta, Gy., and Szántay, Jr., Cs.), in the Series: "Analytical Spectroscopy Library Series", Elsevier, 1997, pp. 187-207.

(3) Nooren, I. M. A., Wang, K. Y., Borer, P. N., and Pelczer, I.; "Full ^{1}H NMR assignment of a 24-nucleotide RNA hairpin. Application of the 3D-NOE/2QC experiment" *J. Biomol. NMR* 11(1998)319-328.

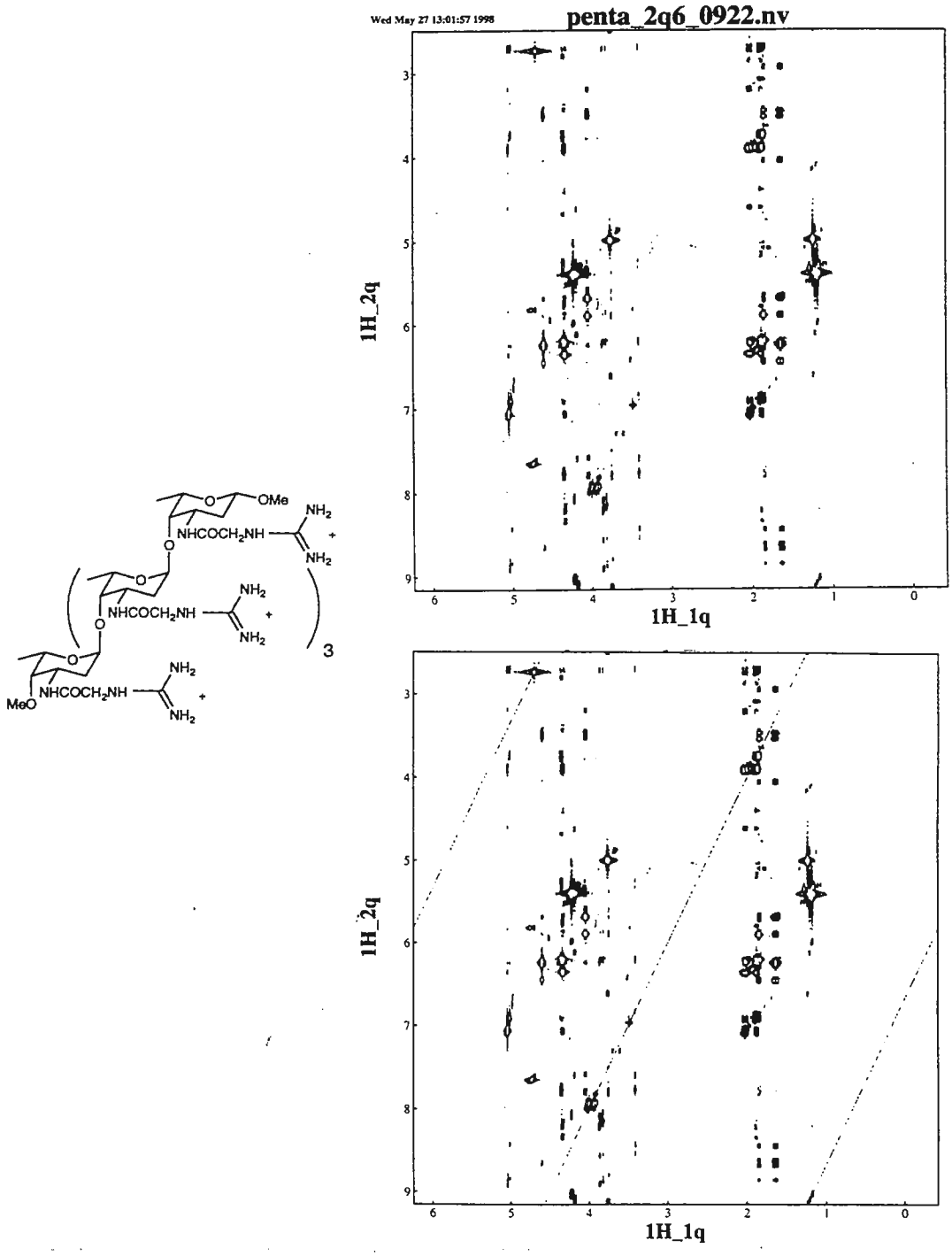

Figure 1. Gradient selected 2QC spectrum of a pentasaccharide (shown on the left, from Prof. Daniel Kahne and Dr. Minja Maletic), acquired at 600 MHz in $^{2}H_{2}O$. The spectrum on the top is the regular presentation in NMRView. The "2Q-diagonal" is turned on for the bottom spectrum using the new custom tool. The spectral window was set the same in both dimensions, therefore there is one times of aliasing.

KARL-FRANZENS-UNIVERSITÄT GRAZ
Institut für Organische Chemie
Dr.Heinz Sterk

A-8010 Graz, 15.9.98
Heinrichstraße 28
Tel. (0316) 380 DW. 5321 bzw. 5320
(received 9/23/98)

Unser Zeichen:

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

A Script to import Ansig data into Aria

Dear Dr. Shapiro :

People who don't have a lot of money are often forced to combine different program packages. This task is not something extremely difficult but it is tedious and needs sometimes a lot of work. Here we will offer a script to the reader of the Newsletter which enables one to import data from the Ansig program (written by Kraulis) into the Aria program package written by Nilges. In our opinion both concepts - Aria to treat overlapping crosspeaks in the modelling step and Ansig to have a single platform for the discussion of 2D and 3D spectra (Varian and Bruker) - are based on clever ideas, not too complicated in use and - very important - free of charge, and thus extremely useful. Their use is certainly wide spread. If one needs this script please give us a note via email. Either thomas.stockner@kfunigraz.ac.at or heinz.sterk@kfunigraz.ac.at.

Yours sincerely

Th.Stockner

H.Sterk

p.S.
The Pharmacologists at our University have extracted some polymerized silicic acid from a plant which shows astonishing anti inflammatory behaviour. To get some knowledge about the structure I tried to measure some Si spectra. However, I failed as the signal stemming from the NMR-tube is much stronger than the signal from the product. If somebody has knowledge about tubes manufactured using a different material or knows some trick which allows me to circumvent my problem it would be nice if he/she would give me a note.
Thanks !

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Dr. B.L. SHAPIRO
The NMR News Letter
966 Elsinore Court
Palo Alto, CA 94303

27.8.1998
(received 9/2/98)

Installation and Testing of a Commercial FFC NMR Relaxometer

Dear Dr. Shapiro,

To answer to your reminders, we would like to show some test results of our recently installed fast-field-cycling relaxometer. A relaxometer is an NMR instrument designed to measure T_1 relaxation times over a wide range of magnetic fields (typically from 5×10^{-4} to 1 T). To overcome the serious sensitivity problem at low magnetic fields, one can either shuttle the sample between a high polarization field and a low relaxation field or switch rapidly the magnetic field (fast-field-cycling, FFC). Recently, such an FFC relaxometer became commercially available, and we were lucky to install one in our laboratory.[1] Some typical performances of the instrument are given in Table 1. T_1 relaxation times are measured automatically as a function of magnetic field and the measurement of a whole relaxation profile takes about 1h (depending on the relaxation times).

Magnetic field:	from 50 μT to 0.5 T
Homogeneity:	< 200 ppm over 1 cm^3
Field switching rate:	0.3 ms/MHz
Sample diameter:	10 mm
Temperature range:	-140 to + 140°C

Table 1 Selected Specifications of the Fast-Field-Cycling Relaxometer

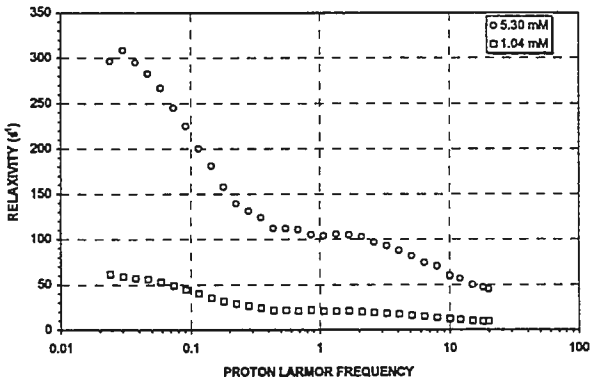

Figure 1 NMRD profiles of two aqueous solutions of $MnCl_2$; observation frequency: 5.6 MHz; 20 kHz – 6 MHz: prepolarized field-cycling sequence; 6 – 20 MHz: non-polarized field-cycling sequence.

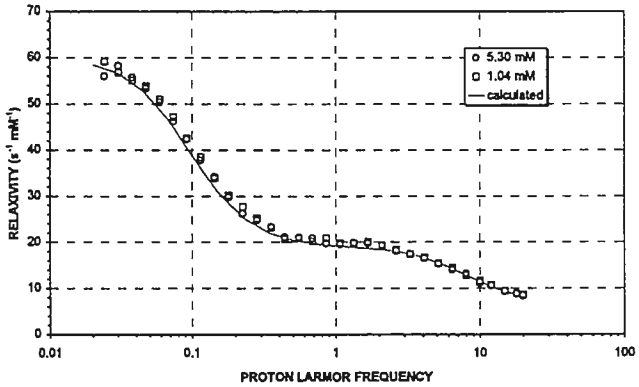

Figure 2 NMRD profiles of two aqueous solutions of $MnCl_2$ normalized to 1mM solutions.

To test the relaxometer, we measured the proton ***n***uclear ***m***agnetic ***r***elaxation ***d***ispersion (NMRD) of the water molecules of two aqueous solutions containing $MnCl_2$. (Figure 1). Relaxation rates up to 300 s^{-1} could be measured routinely. The linearity of the system is shown in Figure 2 where the relaxivity per mM concentration of $MnCl_2$ is reported. On the same figure we report also a curve calculated from literature parameters.[2]

T. Helm

Lothar Helm

Éva Tóth

Éva Tóth

Please credit this contribution to the subscription of Prof. A.E. Merbach, University of Lausanne

[1] Spinmaster FFC Relaxometer, Stelar s.n.c, Mede (Italy)
[2] S.K. Sandip, R.G. Bryant, J.Phys.Chem. 1995, 99, 6301-6308.

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Specifications for Vertical Bore, High Resolution NMR Magnet Systems

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

NMR Operating Frequency (MHz1H)	600		750	800		900	
Field Strength (Tesla)	14.0		17.6	18.8		21.1	
Nominal Room Temperature Bore Access (mm)	51	89	51	63		63	
Magnet Type (Standard or shielded)	Actively Shielded	Standard	Standard	Standard	(2.2K) Pumped	(2.2K) Pumped Standard	(2.2K) Pumped With Iron Shield
Field Stability (Hz/hour ¹H)	<10	<12	<15	<15	<15	<15	<15
Axial 5 Gauss Stray Field Contour (Metres)	2.5	5.0	7.6	8.69	6.3	12.2	8.73
Radial 5 Gauss Stray Field Contour (Metres)	1.75	3.9	6.1	6.89	5.0	9.7	3.81
Cryostat Type	T5F8	T4FBL	T6	T6L	T7	T8	
Minimum Helium Refill Interval (Days)	120	90	60	60	60	60	
Cryostat Helium Refill Volume (Litres)	101	60	187	216	328	1200	
Minimum Nitrogen Refill Interval (Days)	15	15	14	14	14	15	
Nitrogen Refill Volume (Litres)	136	100	137	162	167	1800	
* Minimum Operational Ceiling Height (Metres)	3.16	3.4	3.78	3.97	3.97	8.75	
System Weight (kg) Including Cryogen's	1180	1200	3000	4000	4000	18000	

Room Temperature Shim Specifications

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

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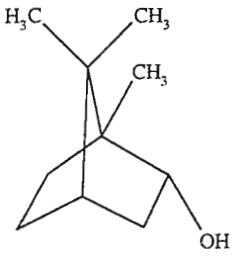
1 September 1998
(received 9/4/98)

A "Non-Classical" CASE Program

Dear Barry,

In my last contribution[1] we saw that with "classical" Computer Assisted Structure Elucidation (CASE) programs we are required to interpret the NMR spectra ourselves and to convert the resulting substructural data to a form understood by the program. We saw that sometimes the latter step can be more difficult than we might expect. In this contribution I will demonstrate a new type of software (SpecMan and NMRSAMS[2]) that attempts to help the molecular structure scientist by storing some "intelligence" in programmed form. We will again use borneol as our example.

SpecMan is a sophisticated peak picking program. It includes facilities for picking peaks in both manual and automated modes and editing the resulting peak table. In my experience the automated peak picking works fine with 1D carbon and HMQC spectra. It has the same problems I have with second order spectra in the 1D proton and COSY and t_1 ridges in HMBC spectra. In the case of borneol the proton spectrum is first order and the data set collected for me by Ross Johnson used gradient enhancement, so that automatic peak picking worked well. SpecMan writes ASCI peak list files which are readable by humans, but not in a format that one would choose for a report.



Borneol

In fact these peak listings are designed to be read by NMRSAMS, a program that "interprets" the data to assemble substructures, using logic very similar to that we humans use. Thus, the 1D carbon and DEPT spectra are interpreted to identify the multiplicities of the carbon resonances. The HMQC peak listing is used to assign the resonances of the proton(s) on each carbon, and homonuclear correlation experiments (COSY or INADEQUATE) are interpreted to assemble these building blocks into substructures when possible. The program understands that some COSY and all HMBC peaks include ambiguities in the number of bonds separating the correlated nuclei. The user has control over most of the parameters used in interpreting the data, but as in so many powerful programs the new user will find the control of all these parameters daunting. NMRSAMS is designed to use a data set consisting of proton and carbon 1D, DEPT, COSY, HMQC, and HMBC spectra, from which it can construct all candidate molecular structures consistent with the data. In the example below I shall initially *mis*use NMRSAMS, providing only a subset of this list of experiments, so that I can compare it more directly to my earlier contributions.

In the first example I input the peak tables for the 1D ^{13}C and DEPT spectra into NMRSAMS, which used these data to construct the "building blocks" and assigned the carbon chemical shifts to each of the carbon-centered nodes. These data accounted for all but one of the protons of the molecule, so the program automatically constructed a hydroxyl group to account for the last proton. At that point I instructed NMRSAMS to generate all two-dimensional structures consistent with this input. The program noted that I had not provided any correlation data and warned me that there were potentially a large number of structures consistent with the limited data that I had provided. In fact MolGen created 8,295 structures which were consistent with the results of the DEPT spectra,[1] so the program was right, but I was insistent and structure generation began. The results dramatized the differences between MolGen and NMRSAMS:

---

[1] See NMR Newsletter, July 1998, #478, p. 19.
[2] Spectrum Research LLC., Madison, WI, tel. 608 233 4882

while the former generated 8,295 structures in about 1.5 seconds, NMRSAMS took 1.5 minutes to build only 193 candidates.

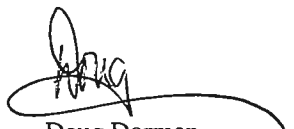
NMRSAMS works more slowly and gets fewer answers in this structure generation because it is using three examples of programmed intelligence: 1. From its default parameters it "knows" that a double or triple bond is associated with carbon chemical shifts greater than 60δ. In fact there is a chemical shift at 77.3δ, but of course two such resonances are needed to build the multiple bond, so the program rules out such bonds. When we limited MolGen to using only single bonds during structure generation,[1] the number of possible structures was reduced to 2,191, so much of the reduction in the number of structures must be due to this feature. 2. Many of the candidate structures will have a hydroxyl group attached to a methylene carbon. From its built-in knowledge of chemical shift theory, NMRSAMS knows that this would require a methylene chemical shift greater than 44δ. In fact the lowest field methylene comes into resonance at about 39δ, so this substructure is ruled out. Similar reasoning rules out structures with the hydroxyl group attached to quaternary carbons. 3. The constraints above can be thought of as examples of chemical shift knowledge. The program also uses chemical knowledge. A built-in BadList, or list of substructures that are considered too strained to be chemically feasible, is also used to prune the candidate list.

As a result of this "knowledge" used during structure generation, NMRSAMS comes up with only about 2% as many structural candidates as does MolGen. Of course, the use of these features is under the control of the user and can be "turned off," and in fact I have confirmed that by doing so one can duplicate the results of MolGen or even GENOA. This is not the way to use NMRSAMS, but it was an important step in my developing confidence that the program really does generate all reasonable structures.

In the second example I read the peak lists for the 1D carbon, DEPT, proton, and HMQC spectra into NMRSAMS. The carbon and DEPT spectra identified the methyl carbons (and other multiplicities, of course), and the HMQC carries those assignments over to the proton NMR spectrum. This is necessary because in its present form NMRSAMS does not use integration to identify the resonances of methyl groups. NMRSAMS assigns a default multiplicity of "u" (unassigned) to each of the resonances of the proton NMR spectrum, but facilities are provided to edit these assignments. I used these to change the multiplicities of the three methyl resonances to "s," from which the program deduced that these methyls must be connected to quaternary sites and reduced the number of candidate structures to 50. Clearly this is a simpler way to specify information derived from multiplicities in the proton NMR spectrum than we experienced with MolGen.[1]

As I mentioned earlier, a normal data set to use with NMRSAMS would also include COSY and HMBC spectra. When peak lists from these spectra are added to the data set, NMRSAMS generates two structures. In fact these two structures have identical connectivities, differing only in the assignments of the resonances of the quaternary carbons. Examination of the structure of borneol shows that this is an expected result, if there are no HMBC correlations to the exchangeable proton, as was the case in the chloroform solution we used.

SpecMan and NMRSAMS are examples of a new generation of CASE programs which attempt to put some of the spectroscopist's experience and knowledge into the process of spectrum interpretation and structure generation. As such they provide the spectroscopist the opportunity to work more efficiently and rapidly. These programs do not replace the spectroscopist, since it takes an experienced molecular structure scientist to use these programs intelligently. And, of course, someone has to generate new "intelligence" for the programmers to add to the program. I am convinced that such programs will be a part of our futures, and I hope my colleagues will explore their use...and report their experiences in Newsletters such as this one.



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School of Allied Health Sciences
School of Nursing

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Institute for the Medical Humanities
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Department of Human Biological Chemistry & Genetics
&
Sealy Center for Structural Biology

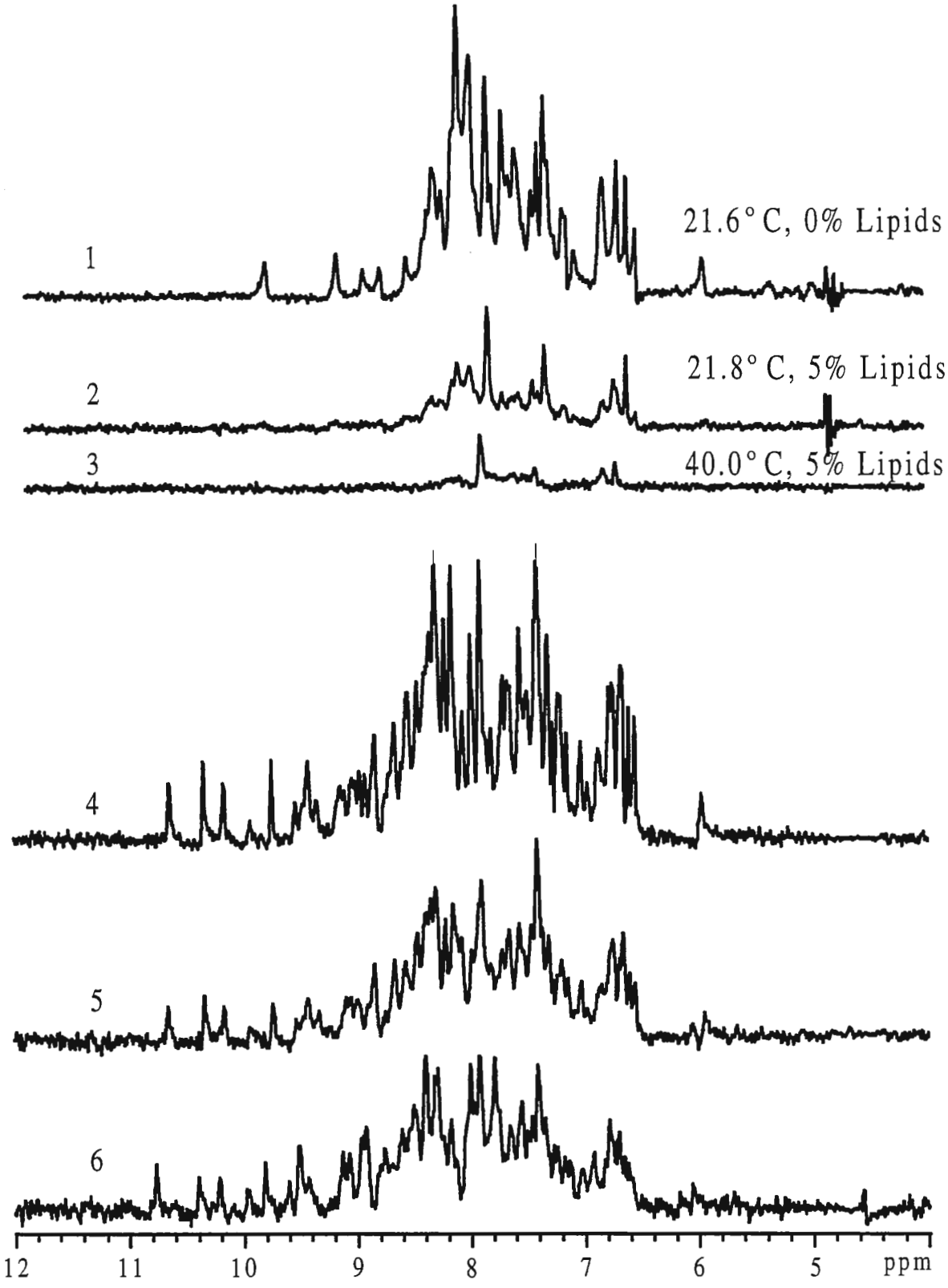
September 1, 1998
(received 9/8/98)

Orienting proteins with phospholipids bicelles: a warning.

Dear Barry:

The technique described by Tjandra and Bax (Science 278 (1997), 1111-1114) to impose a time averaged orientation on macromolecules by means of phospholipid bicelles which orient in the magnetic field is attractive because it gives access to residual dipolar splittings, which can serve as extra constraints in molecular dynamics structure calculations. However, the utility of this technique is possibly limited to proteins that do not interact directly with the phospholipid bicelles. To illustrate this point we show here results on two DNA binding proteins in 5% DMPC/DHPC (2.9:1) solutions, N-terminal domain of DNA Polymerase β and N-terminal domain of MutY of E. Coli. Shown are ^{15}N-^{1}H HSQC spectra of β-Pol at 0% lipids and 21.6°C, 5% lipids and 21.8°C, and 5% lipids and 40.0°C, respectively (1,2,3). Clearly, β-Pol interacts strongly with the lipids, especially at 40.0°C. Shown also are similar spectra for MutY (4,5,6). With this protein, the spectra maintain their high resolution character, except possibly for a lengthening of T_1 caused by increasing viscosity of the medium. Nevertheless, transient binding of MutY to bicelles cannot be definitely excluded. The moral: before basing conclusions about protein structure on measured dipolar splittings in phospholipid bicelle phases, one has to ascertain that these dipolar splittings are not affected by protein-phospholipid interactions.

Jan Post Shanmin Zhang David Gorenstein


21.6° C, 0% Lipids
1
21.8° C, 5% Lipids
2
40.0° C, 5% Lipids
3
4
5
6
12
11
10
9
8
7
6
5
ppm

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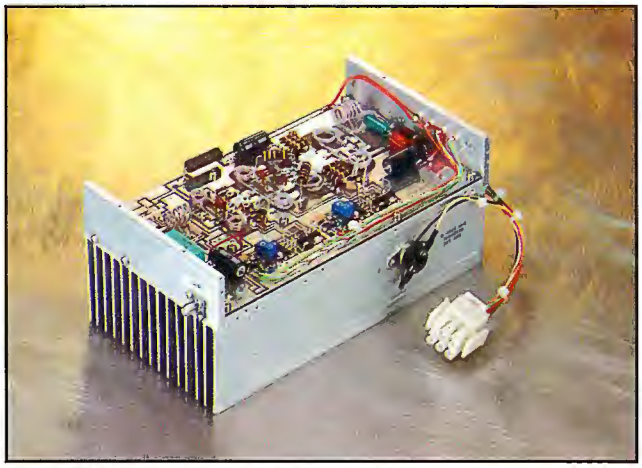
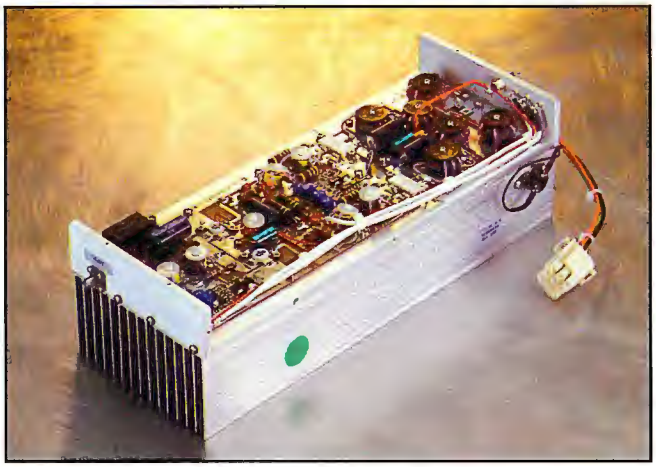


200 MHz to 500 MHz, 50 W, NMR Module



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nuclear magnetic resonance instruments

Dr. Barry Shapiro
The NMR Newsletter
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September 18,1998
(received 9/21/98)

New Versions of ProteinPack and AutoTest

Dear Barry,

I have been working this summer on additions and enhancements of two packages of pulse sequences, macros, menus, etc. and we are about to release them to the on-line user library (www.nmr.varian.com) and in the next major release of VNMR, 6.1B. These are ProteinPack and AutoTest. Your readers will recall that these were described in a couple of letters (AutoTest, **472**, p. 21; ProteinPack, **468**, p.23) within the last year.

AutoTest:

AutoTest has been substantially redone so that each test stands alone, initiated by a single macro which also contains all processing, plotting, statistical analysis etc..This permits the execution of a single test or selected group of tests, either once or in a repetitive loop. This structure makes it easy for users to develop and integrate their own tests. For example, if someone wanted to test the amplitude stability of the signal following 1 and 3 usec pulses and to store the stabilities and standard deviations in history files "stab1usec" and "stab3usec", the macro to do this would look something like this:

```
"AT_1_and_3_usec_stab"
 if ($#=0) then                          "Test starts with macro AT_1usec_stab  (no arguments)"
   Atrtp('standard')                                          "recalls standard parameter set"
   pw=1 array('nt',20,1,0)                                    "sets up 20 separate acquisitions"
   wexp='AT_1_and_3_usec_stab(`PART1`)'          "specifies what to do at end of experiment"
   au                                                         "begins first experiment"
 elseif ($1='PART1') then                  "This part executes at end of first experiment"
   wft Atplot:$stab,$stddev                                   "plots spectra, calculates statistics"
   ATrecord('stab1usec','1 usec stability','stability',$stab,'std_dev',$stddev)   "stores results"
   pw=3                                                       "changes pulse width for new experiment"
   wexp='AT_1_and_3_used_stab(`PART2`)'          "specifies action at end of experiment."
   au                                                         "begins second experiment"
 elseif ($1='PART2') then                "This part executes at end of second experiment"
   wft Atplot:$stab,$stddev                                   "plots spectra, calculates statistics"
   ATrecord('stab3usec','3 usec stability','stability',$stab,'std_dev',$stddev)   "stores results"
   ATnext                                                     "permits calling of next test"
 endif                          "new MAGICAL construct elseif permits use of only one endif"
```

The user interface is probably the most apparent change. It consists of a tcl/tk-generated graphics interface initiated by a macro command or menu button. The interface has three major displays: configuration, test library, and test history. The configuration panel permits the selection of test "packages". The original AutoTest series is initiated by just "clicking" on the "All Tests" checkbox. The automated test begins when the "Begin" button is pressed. Other "packages" are selectable as well, for example, such as "All Channel 1 Tests" or "Gradient Tests" just to name a couple. User-created packages may be added as well.

The second ("Test Library") panel shows groups of checkboxes, clustered by category, such as "Channel 2 Tests", "Channel 1 Shaped Pulse Tests", "C13 Tests", "Lock Tests", etc. . This collection includes all defined tests. Again, just selecting one or more checkboxes (from any groups), followed by the "Begin" button, starts the AutoTest run. The Atrecord macro has been written to store the test results in the performance history files (these document previous AutoTest results for the same test). Any user-defined test may be added to this library since the source file for the "Test Library" panel is just a text file listing the initiating macro name and a comment line. Tests may be grouped by category and given group names.

The third ("History") panel shows a scrollable list of history files, with a graphics display area showing a graph of the performance measurement over time or a text display of the selected history file. The graph also shows the average value of the result for all the previous runs, along with the corresponding standard deviation. The user can rapidly scroll through the graphs and note any trends which might signal changing hardware performance.

The generalized nature of this interface lends itself nicely to anyone who wishes to "automate" any experiment since it is really an interface for letting the user select any experiment or combination of experiments of any nature.

ProteinPack:

This package has been substantially enhanced with new pulse sequences and automated calibrations. Weixing Zhang of St.Jude's Children's Research Hospital in Memphis, Tenn. has contributed HCACO, HCA(CO)N and (HCA)CO(CA)NH pulse sequence codes and these have been integrated into the package with corresponding parameter sets, macros and menus, including full autocalibration. Kay's double-edited 13C,15N noesy has also been integrated.

A new automated experiment has been incorporated in which no calibrations are done (relying on the last calibrated values). The user can input 1H power and pw90, if desired, and all 1D first increments of the 13Chsqc, 15Nhsqc and all triple-resonance experiments are acquired and plotted, taking about 5-10 minutes.

A major addition is the inclusion of a whole family of water suppression capabilities for 1D and 2D experiments. Full autocalibration is included for presat, soft-pulse watergate, 3919 watergate and wet experiments. Noesys with wet, watergate and "quiet" options are also provided.

All experiments have associated tcl/tk "dg" screens that facilitate easy operation with high-level "non-jargon" parameter labels.

Availability:

VNMR6.1B is now undergoing beta test and it should be released in the October/November timeframe. ProteinPack will be submitted to the on-line userlib in the same timeframe. Users should check VNMR news for the announcement.

Sincerely Yours,

George A. Gray
NMR Applications Lab

The NMR Newsletter - *Software* Reviews

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

A New View Review:

A Look at the NMRView Software Package

Most macromolecular NMR spectroscopists form a very tight bond with the software they use to process and display their data. Its understandable – given the long hours spent using such packages and learning the latest tricks and quirks, it's easy to become rather dogmatically attached for better and for worse. With this disclaimer in mind, Id like to offer the closest thing to a non-biased review as I can about NMRView, given that this has been my primary data analysis program over the past two years or so.

A quick introduction is in order: NMRView was initially written by Bruce Johnson and Richard Blevins, with Bruce having produced ***version 3**** in 1997. An earlier version was described in a 1994 Journal of Biomolecular NMR article (B. A. Johnson and R. A. Blevins, *J. Biomol. NMR* 4(1994)603-614) but there have been a number of substantial changes since then.

Note that NMRView's forte is the visualization and analysis of multidimensional data. Although some vector/matrix processing functionalities are available in NMRView, I've preferred to process datasets with Frank Delaglio's NMRPipe package. Felix datasets are also easily accessed in NMRView.

Some features I've found useful are:

customizable in a well-established language, Tcl (tool command language). This is one of the best features of NMRView – no need to learn YAPSL (Yet Another Package-Specific Language). NMRView commands are built on top of the previously existing set of Tcl commands, giving you the benefits using a language that's used for many applications: regular expression matches, array/string handling functions and plenty of graphics-oriented capabilities via the tk toolkit. With Tcl integrated into NMRView, virtually any task can be run interactively (via window-based interfaces) or in a batch mode (using Tcl scripts). Finally, Tcl is well documented and rather easy to learn.

freely available from http://www.nmrview.com, precompiled for a wide variety of platforms including Sun/Solaris, SGI/Irix, Linux and MacOS. Documentation and a few other pieces of information are also available from this site.

multiwindow: an unlimited number of windows are available, with automatic cursor tracking between commonly named dimensions in these windows. Spectral display parameters can be easily set, controlled either by Tcl script (great for opening groups of spectra) or via a nice graphical interface that allows you to rapidly move/resize the viewable region, change the dimensions being viewed in a window, etc. On the Sun and SGI workstations that I've used, new contour plots are drawn reasonably fast in the default display mode, with a speedier playback mode available. Data can viewed as 1D traces or 2D contour plots of multidimensional sets.

specialized windows for common tasks: these include

- a CBCA window for managing strip-based views of multiple datasets (useful for making assignments with triple resonance or isotope-edited spectra)
- a Strip Plot window for printing groups of strips as above
- a Rate Analysis window for tracking peak intensities over multiple datasets (NOE buildup curves, relaxation series) and subsequently fitting these.

Continued

a nice database facility stores a veritable cornucopia of information, ranging from peak lists to chemical shift assignments to structure coordinates. Given that NMRView is rooted in Tcl, one can easily write Tcl scripts that use NMRView commands to search and modify this database in fairly sophisticated ways. Importing data from and exporting data to text files is trivial, with file formats easily customized in Tcl. There are also decent window-based interfaces to most of the information.

useful features of the NMRView datafile format include machine- portability and built-in headers, keeping the original spectral parameters together with data in one file.

a mailing list for NMRView users has been organized and maintained by Gary Thompson (Univ. of Leeds). There's a decent amount of conversation on this list, enough for me to have picked up a few tricks over time.

a great author: last but not least, I'd definitely list this as a plus of NMRView. Bruce has invested quite an effort into the development of this package, and continues to be a source of help to those using it (including me). He's a frequent contributor to the mailing list and has gone out of his way to get feedback from NMRView users at user meetings hes organized at various conferences.

In all fairness, there are several shortcomings of NMRView that deserve comment. In my opinion, most of these are common of many scientific freeware/shareware packages but here I focus on their impact with NMRView:

documentation lags behind development: as NMRView is still evolving, a number of new features (both positive and negative) have been introduced in the time that I've been using it. Unfortunately, a fair number of these have remained under-/undocumented for significant amounts of time, slowing their use (or avoidance) by the user community. This has been remedied somewhat by increased use of the mailing list, but it still remains a drawback.

learning curve could be steep if you're trying to learn how to use NMRView on your own. In defense of NMRView, this is probably the case for most packages in this area. However, the development of a more complete tutorial/example analysis would probably go a long way to helping ease this significantly. Additionally, more users (myself included!) need to contribute Tcl scripts and tips to a library provided on the NMRView WWW page to help those learning the program.

At this point, the future of NMRView seems bright with the development of a Java-based version. According to Bruce, the migration to Java will significantly ease the ability to introduce new features into the program and reduce the amount of time required to maintain versions for multiple platforms.

In summary, I've found NMRView* to be a valuable tool for interpreting multidimensional NMR data and would recommend it to others, especially if one can sit down with an NMRView expert for a while to while learning the ropes.

Kevin H. Gardner
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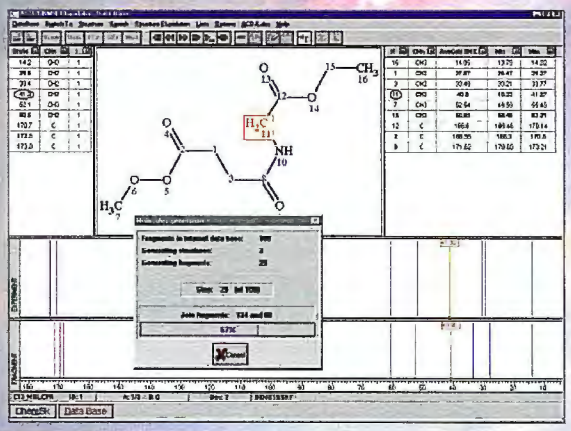
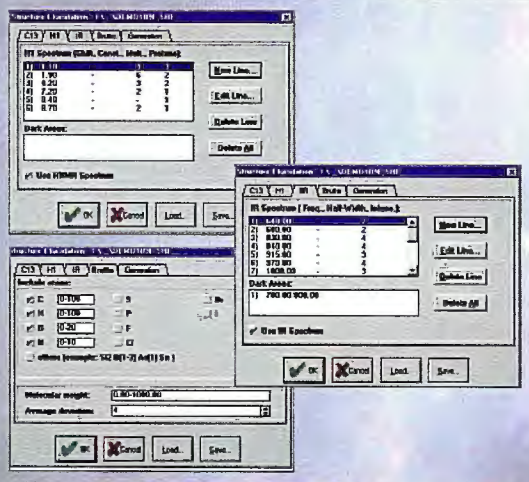
*Recently, ***version 4*** has become available. It will be reviewed and compared to version 3 in due course.

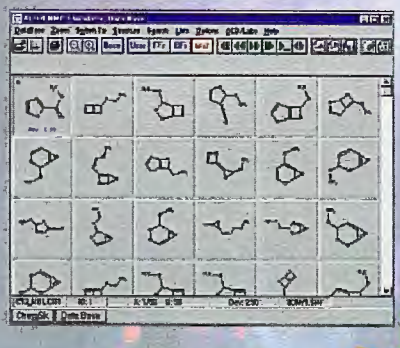
ACD/Structure Elucidator

Generate a molecule from experimental spectra

Obtain suggested molecular fragments and final molecules from a ^{13}C NMR peak list!







Partial list generated by Classical Structure Generator

ACD/Structure Elucidator generates lists of fragments which are consistent with the ^{13}C NMR chemical shifts and (if available) other chemical information. Using proven algorithms for merging structure fragments, **complete molecular structures** can be generated.

To use ACD/Structure Elucidator, you will require a ^{13}C NMR spectrum. It is helpful (but not necessary) to have multiplicity information available from DEPT or APT experiments, and ^{1}H NMR and IR spectral data. Molecular weight and elemental composition data provide further refinement.

ACD/Structure Elucidator provides suggested structures from fragment overlap using the unique fragment-based rules system at the heart of the highly successful ACD NMR predictive packages.

Observe the process of structure identification: ACD/Structure Elucidator will display a number of possible structures or (if a complete structure cannot be found) a set of structural fragments corresponding to portions of the spectrum. You can then use the fragment list on your own to help assemble the structure of the unknown compound.

Make use of other data: ACD/Structure Elucidator contains filters for ^{1}H NMR resonances, IR peaks, mass spectrometer (MW) data and elemental composition.

Fine-tune the search: ACD/Structure Elucidator will let you customize the fragment generation procedure by assigning spectral dark areas.

Test the hypothesis: Once a structure or fragment list is generated, you can compare experimental and predicted spectra in a single screen.

ACD/Structure Elucidator is fully integrated with NMR Manager, NMR Predictors and Databases and ChemSketch.

FREE NMR VIEWER is now available at www.acdlabs.com

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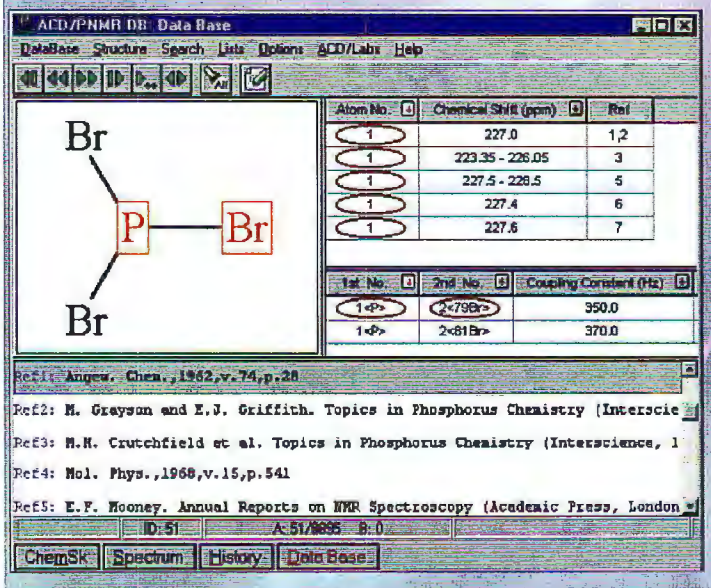
ACD/NMR Predictors provide the ability to calculate chemical shifts and, where appropriate, coupling constants for a variety of chemical structures. The ACD/NMR prediction suite has expanded now to include ^{1}H, ^{13}C, ^{19}F and ^{31}P prediction capability. The programs utilize our proprietary prediction algorithms developed over a period of many years, in conjunction with internal databases of experimental data collected from the open literature and verified for quality by our compilation team. The optional user-accessible internal data bases add-ons contain:

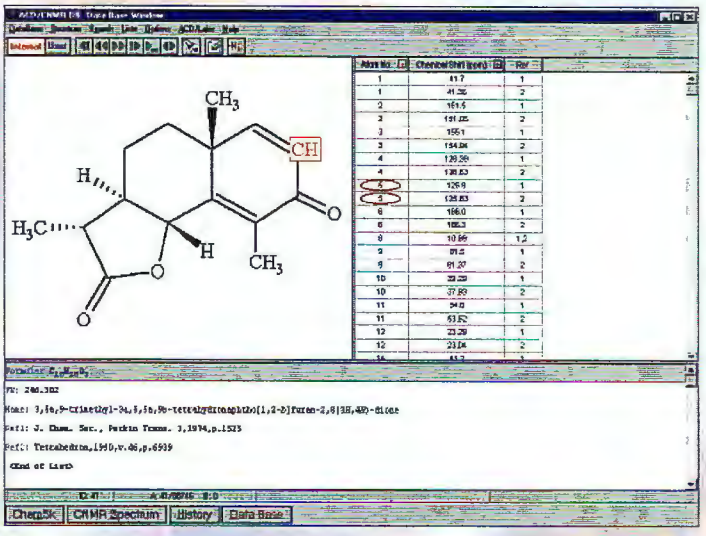
- ^{1}H NMR DB: over 81,000 structures
- ^{13}C NMR DB: over 67,000 structures
- ^{19}F NMR DB: over 11,500 structures
- ^{31}P NMR DB: over 19,000 structures
- ^{13}C NMR DB of Natural Products and analogs : over 5200 structures

Each database includes original literature references, molecular formula, molecular weight and IUPAC names which can be searched and viewed. All data have been collected from Literature Articles been verified for quality of careful screening by our database team.

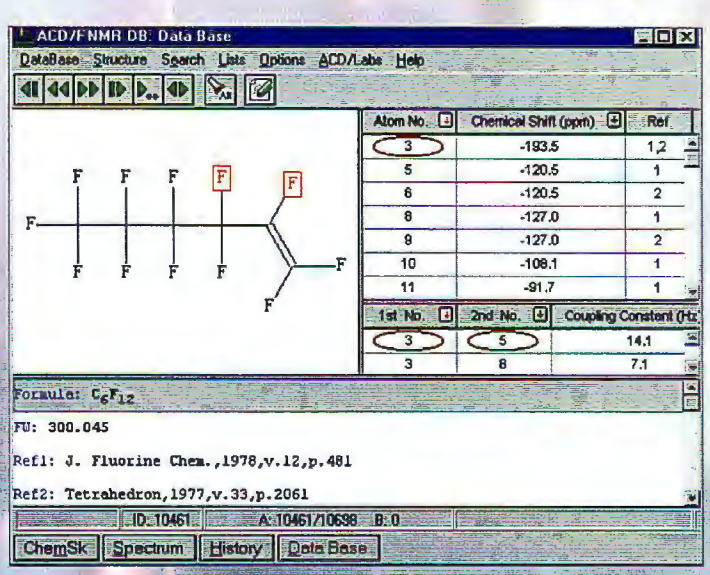
Search capability also includes structure and substructure, and searching by chemical shifts and coupling constants. Search capability also includes structure and substructure, and searching by molecular weight, molecular formula, chemical shifts, coupling constants and IUPAC name.



Phosphorus Database window showing chemical shifts, coupling constants, and references



CNMR DB window showing chemical shifts, references, formula and IUPAC name



Fluorine Database window showing chemical shifts, coupling constants, and references

(received 9/21/98)

Sandia National Laboratories
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P.O. Box 5800
Albuquerque, NM 87185-1407

Dr. B. L. Shapiro
The NMR Newsletter

Chemometric Analysis of ^{17}O NMR Spectra[†]

Sandia National Laboratories, Aging and Reliability, Bulk Materials Department,
Materials and Process Computation, and Modeling Department, Albuquerque, NM 87185-1407.

At Sandia the use of ^{17}O NMR spectroscopy to investigate polymer degradation continues to be an area of interest. While ^{17}O NMR shows a wide chemical shift range of approximately 800 ppm, there are several experimental difficulties commonly encountered; in particular low natural abundance and significant line broadening. The problem of low natural abundance for ^{17}O NMR investigations of polymer degradation has been avoided by utilizing labeled $^{17}O_2$ during the oxidative degradation step. The line broadening is dominated by the quadrupolar relaxation of the ^{17}O nucleus, and is proportional to the molecular correlation time(τ_c). Even at elevated temperatures significant overlap between resonances is commonly observed making quantitative analysis of the experimental spectra difficult. We have recently investigated the use of Chemometric techniques to improve the analysis of the ^{17}O spectra.

As a model system, a mixture of five primary alcohols (3-methyl butanol, butanol, propanol, pentanol, and ethanol) having similar chemical shifts and line widths were investigated. Figure 1 shows the natural abundance spectrum for equal molar concentrations of these five primary alcohols, demonstrating the level of spectral overlap commonly encountered. Fitting the spectrum using standard peak fitting routines resulted in poor results. The insert of Figure 1 shows the variation of the standard deviation of fit versus the number of resonances used in the peak fitting routine. No constraints were placed on the fitting procedure *a priori*. The first two components fit comprise the majority of the signal in the best fits, with approximately 80 and 12 % of the total integration, compared to the true value of 20%. Obviously the severe overlap limits the utility of routine peak fitting routines unless specific constraints can be incorporated. To address this difficulty we have investigated the use of chemometric techniques to improve the quantitative analysis of the ^{17}O NMR spectra.

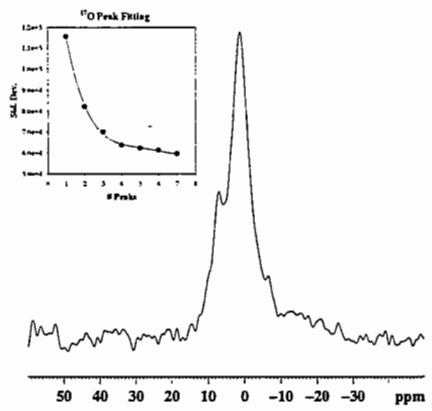

Figure 1. The ^{17}O NMR spectrum for an equalmolar mixture of five primary alcohols (3-methyl butanol, butanol, propanol, pentanol, and ethanol) is shown. Spectra were obtained at 54.4 MHz on a Bruker AMX using a 5mm broadband probe, using 4K scans and 500 ms recycle delay. Experiments were performed at 50°C to help reduce the line width. Spectral overlap of the 5 resonances is severe. The standard deviation for simple peak fitting routines decreases for the first 2 to 3 components, with little improvement for higher number of peaks used in the fitting. The concentrations obtained using this simple peak fitting method do not correctly predict the actual experimental concentrations.

[†] Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States department of Energy under Contract DE-AC04-94AL85000.

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Figure 2 shows the experimental spectra for a simple cubic lattice experimental design, specifying 21 mixtures, including a center point composed of equal portions of each alcohol, and pure component spectra for a total of 26 different ^{17}O NMR spectra. This experimental design allowed a thorough examination of spectral interactions between alcohols, plus variations in the ^{17}O NMR spectra between pure components and mixtures. As an example, the net analyte signal (NAS) of six propanol subsets was used to interpret the interaction between propanol and the other alcohols. The NAS is that part of the spectral signal which is unique to the analyte of interest, and thus available for quantitative analysis ("Net Analyte Signal Calculation In Multivariate Calibration",Lorber A., Faber K., Kowalski B. *Analytical Chemistry* V. 69(#8) Pg. 1620-1626, 1997). The size of the NAS is indicative of the strength of the signal. Shown in Figure 3 are the six net analyte signals for propanol. Inspection shows that there are two distinct subsets visible. At approximately 1 ppm the signal strength is decreased in three cases, indicating the propanol signal is degraded due to interactions with other species in the mixtures. Butanol was common to the three mixtures from which a degraded NAS was observed, indicating that the overlap between the butanol and propanol signal is large compared to the overlap between the other alcohols and propanol. Indeed, quantitative estimates of propanol for each of the six mixtures provided poor results for those mixtures containing butanol. Determination of the NAS allows these interactions to be corrected for, allowing more accurate quantitative results to be obtained. A detailed discussion of these NAS corrections is being prepared and will be published elsewhere.

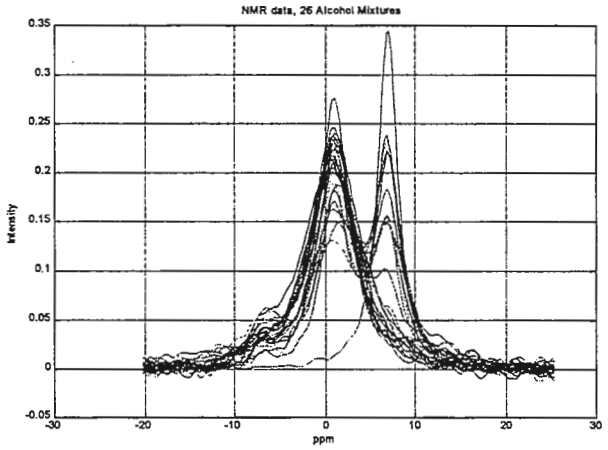

Figure 2. The 26 ^{17}O NMR sub-spectra obtained for a simple cubic lattice experiment designed for 5 primary alcohols (3-methyl butanol, butanol, propanol, pentanol, and ethanol). Except for ethanol, all the subsituent chemical shift (SCS) effects are for δ-hydrogen substitution or higher, and are not expected to produce any large changes in the ^{17}O chemical shift.

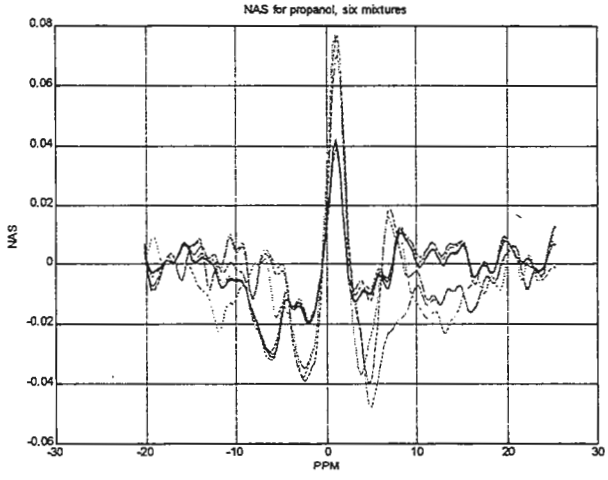

Figure 3. Net analyte signal (NAS) for the proponal component in various alcohol mixtures. Analysis of the NAS signal allows the interactions between the different alcohols to be determined. In addition, variations in the observed ^{17}O line width due to changes in the mixture viscosity can also be assessed using NAS analysis. Knowledge of these interactions can be used to improve the quantitative analysis of these complex mixtures.

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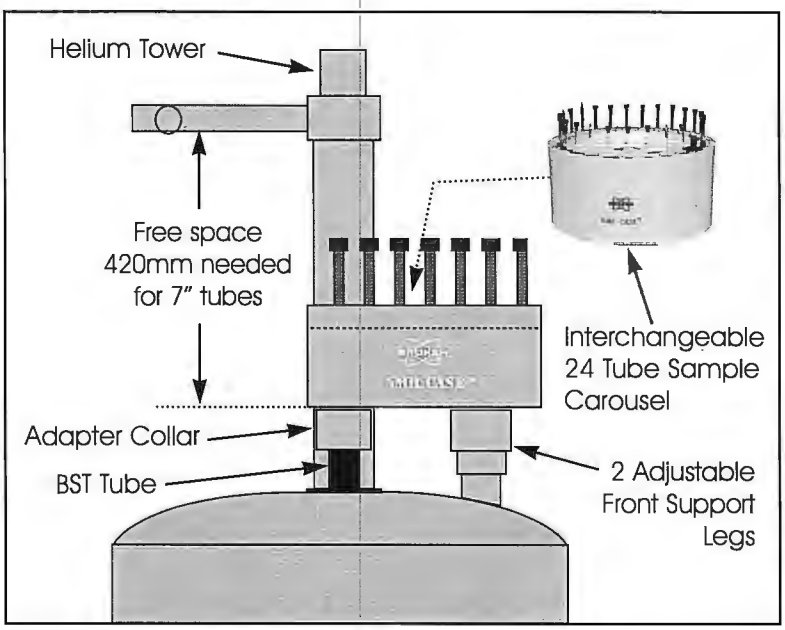

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September 24 1998
(received 9/25/98)

Very Low-Field MRI - Laser-Polarized ^{3}He imaged at 21 Gauss

Dear Barry,

Congratulations on the 40th anniversary of the Newsletter, an impressive milestone. To 'celebrate', I have enclosed another colorful contribution, which I hope will reproduce satisfactorily for your readers. In addition, this work will appear in detail, soon, in Physical Review Letters.

As I eluded to in the previous contribution (issue 475), one of our major studies here recently has been to use laser-polarized ^{3}He at what, for traditional NMRists, are very low fields. As the extremely high laser-polarization in a noble gas is artificially produced outside the magnet, there is no real need for an expensive, high field magnet as is used on traditional NMR systems. Therefore, we built a wire-wound solenoid that produces a field strength of 21 Gauss, as well as gradient coils for the magnet configuration, and the rf coils needed to operate at a frequency of 67 kHz for ^{3}He. This was a complete homebuilt spectrometer based on the audio-frequency equipment regularly used in atomic physics studies here at the CfA.

However, the system lacked adequate gradient control to take MR images, and so we transferred it, in entirety, to MIT, and interfaced it to an AMX console in David Cory's lab. The new system was designed so that the AMX would trigger our home-built kHz rf system that pulsed the sample in the magnet, and did heterodyne signal detection. Gradient control, signal averaging, data acquisition, etc. was all under the control of the AMX in normal acquisition mode. Images of ^{3}He cells were obtained in 10-30 sec with a standard FLASH sequence, and compared well in terms of signal-to-noise and resolution with images taken at 4.7 T in a commercial magnet. Some examples are shown in Fig. 1, where a cell shaped as an "H" (for helium) has been imaged at low field. It is compared to images of a cylinder of laser-polarized helium, and of water, obtained at 4.7 T, as well as an "image" of water at 21 G (i.e., nothing) in a similar experimental time.

Aside from proving the point, there are a number of advantages to working at low fields, if suitable NMR signal can still be obtained (e.g., by laser-polarization). Most notably, many problems at high field occur due to susceptibility differences in heterogeneous media, often between solids and liquids or gases. Such differences result in background gradients that scale with the square of the field strength, and result in broadened spectral lines and distorted images at high field. To produce such an effect artificially, we taped vials of paramagnetic salts to a triangle-shaped cell of laser-polarized ^{3}He. Fig. 2, shows that the presence of the salts makes no difference to the quality of the images obtained at 21 G. However, when the same vials were placed on top of a sample of water at 4.7 T, the image is distorted almost beyond recognition.

Similarly, the high rf frequencies used in high-field MRI have wavelengths too short to penetrate layers of conductive metals. Therefore, signal is rarely seen from such samples at high field. However, the lower frequency used at low fields is able to penetrate such layers, and so opens up the potential for imaging within such samples. We placed a cell of laser-polarized ^{3}He inside a thin brass shield, and imaged it 21 G. The signal is reduced ~ factor of 5 compared to the image in the absence of the shield, however, it is still very visible, unlike the cell of water similarly imaged at 4.7 T. (Figure 3). We feel these examples illustrate well the experimental benefits possible from a cheap, low-field MRI system using laser-polarized noble gas.

Best Regards,

Ross Mair Ching-Hua Tseng Glenn Wong Ron Walsworth

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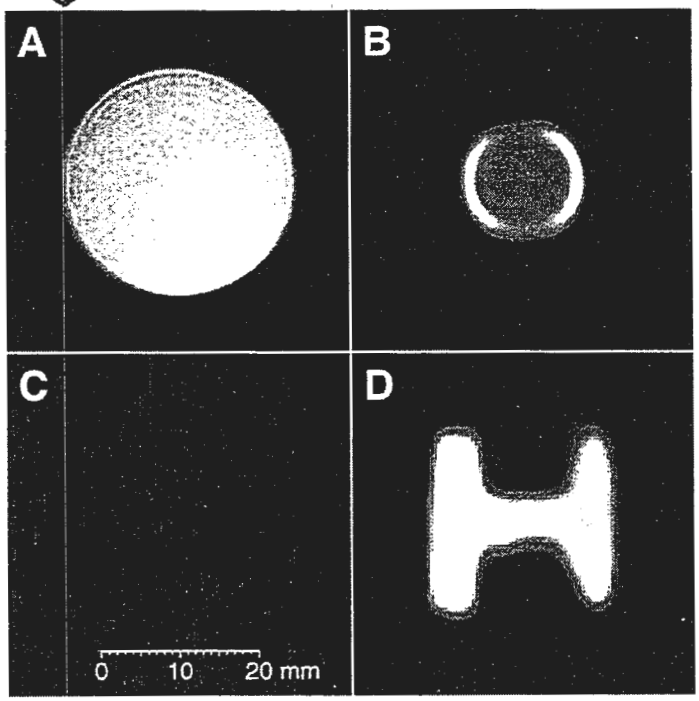

Fig. 1: Comparison of images at 4.7 T and 21 G. (A) Cylinder of water at 4.7 T. (B) Cylinder of laser polarized (lp) ^{3}He at 4.7 T, exhibiting extreme "edge-enhancement" due to diffusive attenuation of most of the sample from the read gradients. (C) water "image" at 21 G in ~ 10 mins. (D) lp ^{3}He at 21 G.

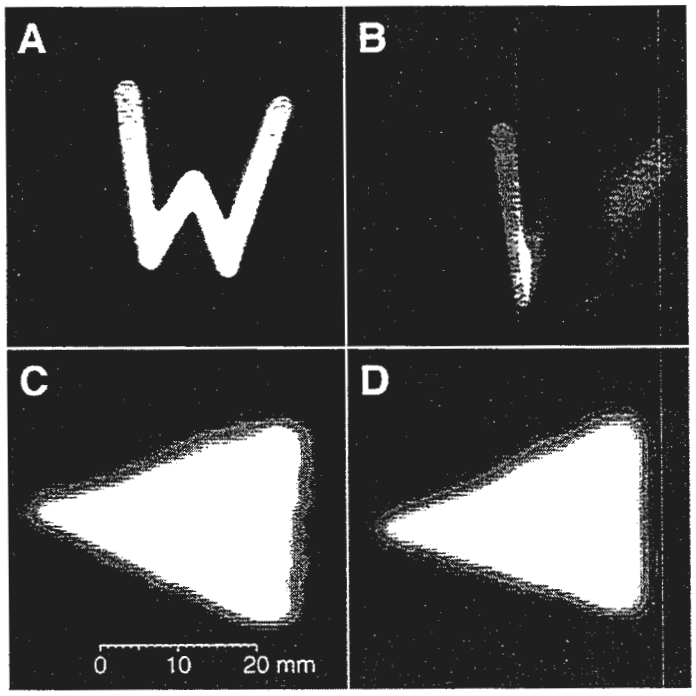

Fig. 2: Images in the presence or absence of paramagnetic salt creating artificial background gradients (A) Water at 4.7 T. (B) Water at 4.7 T in presence of salts. (C) lp ^{3}He at 21 G in the absence of salts. (D) lp ^{3}He at 21 G in the presence of salts.

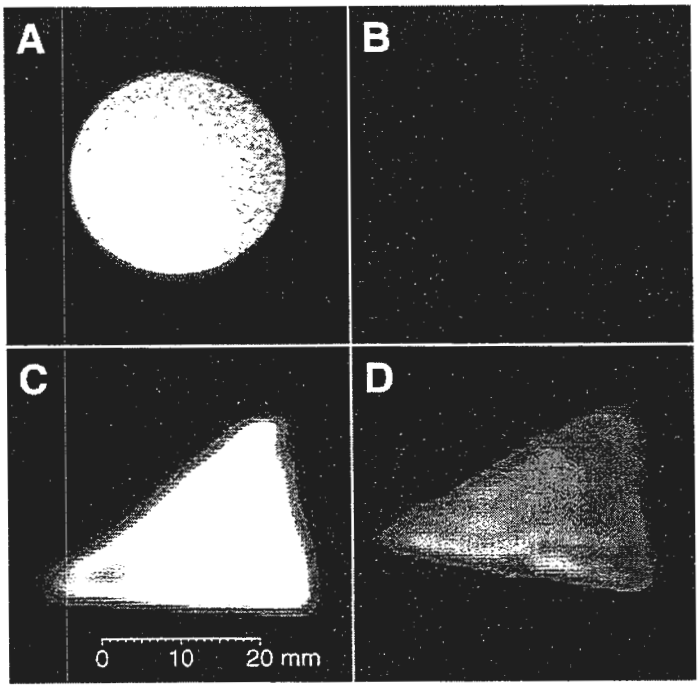

Fig. 3: Images in the presence or absence of a thin (25 μm) brass shield, demonstrating the effect of Faraday shielding of rf pulses at high frequencies. (A) Cylinder of water at 4.7 T. (B) Image of same water sample once encased inside brass shield. Spectral signal was reduced by 3 orders of magnitude. No image was observed. (C) cell of lp ^{3}He at 21 G. (D) Image of same cell of lp ^{3}He at 21 Gauss once encased inside brass shield. The image intensity is reduced by a factor of 5.

We thank Prof David Cory at MIT, for many useful discussions, assistance, and making available his lab space and AMX console for this work; and Vance Pomeroy and Bill Hersmann from University of New Hampshire, for assistance with ^{3}He cells for laser-polarization

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Postdoctoral Position Available:
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Department of Biochemistry

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Candidates should have experience in one or more of the following areas: molecular biology/protein expression, multidimensional NMR spectroscopy or computationally-based structure determination or modelling. Positions will initially be for a period of one year, with the possibility of extensions past that point.

Applicants should send a brief description of their prior research along with a C.V. to the address below and arrange for three letters of recommendation to be sent as well. Please feel free to call or email for further information:

Dr. Kevin Gardner
Department of Biochemistry
UT Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75235-9038

kgardn@biochem.swmed.edu
phone: (214)648-8916

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reference:
1: Kay, L.E. and Gardner, K.H. (1997) Solution NMR spectroscopy beyond 25 kDa. *Curr. Op. Struct. Biol.*, **7**, 722-731.

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September 24, 1998
(received 9/25/98)

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

Order Parameters

Dear Barry:

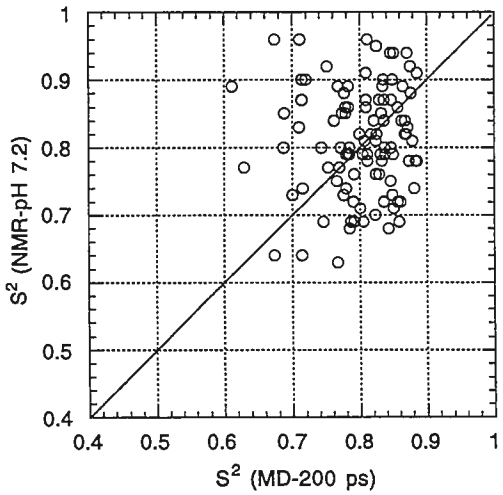
For some time we have been using heteronuclear (^{13}C and ^{15}N) relaxation measurements to monitor internal motion in proteins in liquid solution. The relaxation rates are analyzed with the Lipari and Szabo motional model-free formalism (G. Lipari & A. Szabo *J. Am. Chem. Soc. 104*, 4559-4570 (1982)). These techniques normally are applied to ^{13}C or ^{15}N nuclei having a single attached proton, and in the simplest version, the spectral density is expressed in terms of two correlation times and an order parameter. The parameters of the Lipari and Szabo formalism then describe the motion of a C-H or N-H vector. One of the correlation times is that for the overall rotational motion of the molecule, and the other gives an idea of the time scale of the motion of the given vector relative to a frame of reference fixed in the molecule (the internal motion). The order parameter (S^2) is the average of second-order Legendre polynomials over the motion of the vector in the molecule-fixed frame. S^2 varies from 0 (generally complete freedom of internal motion) to 1 (complete restriction of the internal motion). By far, the majority of work to date has focused on the motion of vectors in protein backbones. A problem that arises is that the backbone motion is usually quite restricted with most S^2 values being > 0.7. Thus there is not much of a range of measured S^2 values which places added importance on the accuracy of the values if patterns of motion along the backbone are to be deduced. One approach to gain some insight into the reliability of S^2 in reflecting the actual internal motions is to compare values obtained from more than one technique, for example, NMR and molecular dynamics (MD) simulations. This still does not answer the question of how accurate the values are, but at least it has the potential to increase confidence in the results provided the techniques yield similar values.

We have been examining the dynamics of rat intestinal fatty acid binding protein (I-FABP). I-FABP is a relatively small protein (mol. wt. ~ 15,000) that tightly binds a number of long-chain fatty acids, one at a time. The protein has a general β-barrel, or β-clam, shape and there is particular interest in details of the binding and release of the fatty acids. We and others (M. E. Hodsdon & D. P. Cistola *Biochemistry 36*, 2278-2290 (1997)) have measured the backbone dynamics of ^{15}N-enriched I-FABP and found limited correlation between the magnitude of S^2 values and residues thought likely to show motions important in fatty acid binding. We have also carried out an 800-ps MD simulation of completely solvated apo-I-FABP using

the CHARMm force field and periodic boundary conditions. The simulations showed what appear to be concerted fluctuations of the protein backbone on a time scale of around 300 ps that are suggestive of how the protein may open to accept and release a fatty acid molecule. This is a difficult time scale for NMR to access so these fluctuations may not "appear" in the NMR measurements. We calculated S^2-values from the MD simulation and compared those with values derived from NMR for individual backbone N-H vectors in the apo-protein. An example of the results is shown in the figure which is a plot of S^2 obtained from the two techniques for given residues where the values from the simulation were based on 200-ps intervals. (Generally, S^2 values from the simulation decrease the longer the interval employed to calculate them.) The 45° line in the figure is just to serve as a guide since ideally the values would be equal. Interestingly, the average values of the order parameter are in good agreement (0.79-MD, 0.81-NMR) as also found recently in staphylococcal nuclease (D. C. Chatfield, A. Szabo, & B. R. Brooks, *J. Am. Chem. Soc. 120*, 5301-5311 (1998)), but the correlation coefficient for a linear fit of the data is only ~ 0.05. In other words, the individual residue variations in S^2 do not track very well. In some cases this may relate to the correlation functions from the MD simulations not reaching a well-defined plateau in the time interval examined. Also the errors in the values need to be taken into account. Both techniques are of course experimental and could have their individual problems. We are in the process of looking further into the details and are comparing results with a second simulation.

Apo-I-FABP

S^2 Comparison



Please credit this to the account of B. D. Nageswara Rao.

Best regards,

L. Zhu V. Likic E. Kurian M. D. Kemple F. G. Prendergast

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(received 9/26/98)

Methodological Standardization for a Multi-Institutional *In Vivo* Trial of Localized ^{31}P MR Spectroscopy in Human Cancer Research

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

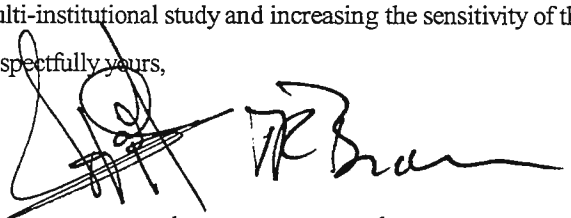
Dear Dr.. Shapiro,

We are nine clinical institutions that have made a group effort to gather localized ^{1}H-decoupled ^{31}P spectra from human non-Hodgkin's lymphomas, breast carcinomas, soft tissue sarcomas, and head and neck carcinomas *in situ*. Preliminary analysis of these spectra has shown high levels of phosphomonoesters in all tumor types, however, considerable variations in the levels of other phosphate-containing metabolites have also been observed. In order to validate and evaluate these clinical findings a large number of patients need to be observed through a controlled multi-institutional trial where intra- and inter-institutional comparisons can be done. Thus, standardization of the methodology with the aim of obtaining high quality control has been the main initial concern of our group.

The steps taken to minimize the problems inherent to a multi-institutional study and to increase reliable comparisons are: 1) A custom-built dual-tuned probe with a flexible ^{1}H coil and a fixed surface ^{31}P coil was supplied to all institutions. Each probe has a similar B_1 field for ^{31}P, and has MRI-visible markers that facilitate the recognition of its position in quantification analysis. 2) A 2 ml bulb with a known amount of triphenylphosphite (TPP; 1.9 M solution in chloroform doped with copper-acetoacetate; $T_1 < 0.2$ s) was placed inside the probe housing, isocentric with the ^{31}P coil. This allows rapid collection of signals from a known ^{31}P external reference during human studies. 3) The TPP concentration was calibrated against a commercially-available triphenylphosphate standard (Isotec, Inc. USA) tested for concentration to a $\pm$ 0.05 % accuracy by the supplier and a second independent laboratory (Galbraith Laboratories, Inc. USA). The commercially available standard was not suitable for human studies due to an extremely long T_1 value.

A fast and easy quantification quality control protocol has been implemented to monitor acquisition at each institution without compromising valuable machine time. This test uses a 2 ml bulb with a known amount of phosphoric acid (Pi; 1mM solution in water doped with 7mM $NiCl_2$; $T_1 < 0.2$ s) mounted in a fixed support containing a 0.2% NaCl loading solution which also supports the probe. Images and shimming are performed while in ^{1}H mode; determination of the 90° pulse and spectral collection of TPP and Pi while in ^{31}P mode (TR = 1 s; pulse length = 250 μs; 512 points). When 9 Pi samples were tested in one institution (FCCC) with this protocol, the RMS error vs. the actual amount in each sample was 2.8 %. One each of these samples was then distributed to each institution. The multi-institutional RMS value recorded so far is 3.6% (n = 4). Quality control tests for performance of adiabatic (BIRP) pulses, ^{1}H decoupling, and chemical shift imaging localization have also been implemented to assure their correct performance at each institution. The careful and systematic performance of these tests will ensure comparable results between the different institutions, thereby decreasing the possible problems generated by a multi-institutional study and increasing the sensitivity of the data analysis.

Respectfully yours,



F. Arias-Mendoza[1], and T. R. Brown[1],
H. C. Charles[2], K. Zakian[3], M. O. Leach[4],
J. R. Griffiths[5], S. J. Nelson[6], A. Heerschap[7], J. D. Glickson[8], and J. L. Evelhoch[9].

Fox Chase Cancer Center[1], U.S.A., Duke University Medical Center[2], U.S.A., Memorial Sloan Kettering[3], U.S.A., The Royal Marsden Hospital[4], U.K., St. George's Hospital Medical School[5], U.K., University of California at San Francisco[6], U.S.A., University Hospital Nijmegen[7], The Netherlands, University of Pennsylvania[8], U.S.A., and Wayne State University[9], U.S.A.

The NMR Newsletter - Book Reviews

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

"Spectra Interpretation of Organic Compounds"

by

Ernö Pretsch and Jean Thomas Clerc

Wiley-VCH, Weinheim Germany. 1997. pp xiii +175 + CD.
ISBN 3-527-28826-0 (hbk). £50.00, $80.00, DM138.00

This book contains fifteen structural elucidation problems. Each consists of a set of IR, ^{1}H and ^{13}C NMR, and mass spectra, together with an interpretation of this data leading to a solution. There are three useful chapters (Additional Remarks) giving some of the finer points for interpreting IR, NMR, and mass spectra. Of these the one on NMR is the longest and deals well with questions of isochronicity, magnetic equivalence, chemical equilibria, and spectra classification, points that often are stumbling blocks to the uninitiated. There are chapters on SpecTool and ChemWindow (which SpecTool uses).

The compact disc which accompanies the book is in effect a demonstration disc for the SpecTool 2.1 system (Chemical Concepts, GmbH, Weinheim, Germany). This is a PC or Macintosh computer-based system of spectra interpretation. However, this demonstration version has been doctored to make it of use only in solving the problems in the book, thereby restricting its usefulness. The doctoring also has the (surely undesired) effect of guiding the reader toward the correct solution. The disc also contains copies of problem spectra, and these can be manipulated (expanded) on the user's computer screen, which is useful when measuring peak separations, etc.

The problems themselves are not graded; they all are moderately difficult (only three involve compounds with molecular mass below 150). The logic of the interpretation is well presented in each case. However, I would question whether a problem book like this is relevant to actual practice, since in most problems (even in the natural product field) there is usually background information which provides a basis for starting a solution. Furthermore, nowadays most MS laboratories could provide high-resolution data to limit the range of molecular formulae; this type of data is not provided in these problems. In one of the problems, the identification of the compound as the hydrochloride of a base, depends on the presence of peaks in the region *m/z* 35-38 of the mass spectrum. It would be brave to put reliance on this in practice.

The authors state in their preface:-*"This volume is not an introductory textbook that proves basic knowledge in the various spectroscopic techniques. It rather is intended for undergraduate students and technicians who want to gain experience in the combined application of spectroscopic methods. It will also be useful for specialists in other fields and non-chemists who want to get acquainted with the modern approach to structure elucidation. Finally, experts interested in learning about the possibilities provided by multimedia tools will also profit from this book."* I am not sure that it caters for any of these groups. Students would be better served by a book with more problems and a range of difficulties. As an introduction to multi-media tools, it leaves much to be desired.

I have real reservations about this book. The glimpses of the SpecTool program that the CD reveals are tantalizing but I cannot help feeling that the book is an expensive (to the purchaser, that is) advertisement for this program. Much better to hang onto the money and get a complete version of SpecTool instead (the price of this for students is DM195).

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Policies and Practical Considerations

(Slightly revised September 1998)

The NMR Newsletter (formerly the **TAMU NMR Newsletter**, the **IIT NMR Newsletter**, and originally, the **Mellon Institute NMR Newsletter**), now in its forty-first year of consecutive monthly publication, continues under the same general policies as in the past.

1. **Policy**:

The NMR Newsletter is a means for the rapid exchange of information among active workers in the field of NMR spectroscopy, as defined broadly, including imaging. As such, the Newsletter serves its purpose best if the participants impart whatever they feel will interest their colleagues, and inquire about whatever matters concern them. Technical contributions should always contain a significant amount of information that has not already been published or that will appear in the formal literature within a few weeks of the appearance in the Newsletter.

Since the subscriber/participant clearly is the best judge of what he or she considers interesting, our first statement of policy is "We print anything." (This is followed by the reservation, "that won't land us in jail or bankruptcy court.") Virtually no editorial functions are performed, although on rare occasions there is the need to classify a contribution as 'not for credit'. The Newsletter is not, and will not become, a journal. We merely reproduce and disseminate exactly what is submitted.

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3. **Participation is the prime requisite for receiving the Newsletter: In order to receive the Newsletter, you must make at least occasional technical contributions to its contents.**

We feel that we have to be quite rigorous in this regard, and the following schedule is in effect: Seven months after your last technical contribution, you will receive a "Reminder" notice. If no technical contribution is then forthcoming, nine months after your previous contribution you will receive an "Ultimatum" notice, and then the next issue will be your last, absent a technical contribution. Subscription fees are not refunded in such cases. If you are dropped from the mailing list, you can be reinstated by submitting a contribution, and you will receive back issues (as available) and forthcoming issues at the rate of nine per contribution.

Frequent contributions are encouraged, but no advance credit can be obtained for them. In cases of joint authorship, only one contributor may be credited. Meeting announcements, as well as "Position Available," "Equipment Wanted" (or "For Sale"), etc., notices are very welcome, but only on a not-for-credit basis, *i.e.,* such items do not substitute for a *bona fide* technical contribution.

4. **Finances**: The Newsletter is wholly self-supporting, and its funding depends on Advertising, Sponsorships, and individual Subscriptions. The **Subscription fee** for the October 1998 - September 1999 year is US$190, with a 50% academic or personal subscription discount. Subscriptions are available for a minimum of the twelve monthly issues which end with a September issue. However, a subscription can be initiated at any time, with the price for more than twelve issues being prorated.

continued

Corporations are also invited to join the list of **Sponsors** of the Newsletter. Sponsors' names appear in each month's Newsletter, and copies of the Newsletter are provided to all Sponsors. The continuation of the Newsletter depends significantly on the generosity of our Sponsors, most of whom have been loyal supporters of this publication for many years. We will provide further details to anyone interested.

Another major, indeed most essential, source of funds for the Newsletter is **Advertising**. We earnestly encourage present and potential participants of the Newsletter to seek advertising from their companies. Our rates are very modest. Please inquire for details.

5. **Practical Considerations**:

a) All technical contributions to the Newsletter will be included in the next issue if received on or before the published deadline dates.

b) Please provide short titles of all topics of your contributions, to ensure accuracy in the Table of Contents.

c) Contributions should be on 8.5 x 11" (21 x 27.5 cm) pages, *printed on one side only*. Contributions may not exceed three pages without prior approval. Each page must have margins of at least 0.5" (1.3cm) on all four edges. Black ink for typing, drawings, etc., is essential. All drawings, figures, etc., should be mounted *in place* on the 8.5 x 11" pages. We are not equipped to handle pieces of paper larger than 8.5 x 11" (21 x 27.5 cm).

d) Please include your e-mail address on your contribution.

Please do not fold, clip, or staple your pages. Protect the condition of your letters from the ravages of the mails by enclosing what you send in a cardboard or plastic folder, etc.

Foreign subscribers are reminded that regardless of the standard paper length you use, *all material* - letterhead, text, figures, addresses printed at the page bottom, *everything - must not exceed 10" (ca. 25.3 cm) from top to bottom.*

When formatting your contributions, please consider the following:

i) Try using a smaller type font: The body of this page is printed in 10 point type, which I believe is adequate for most purposes. Even 11 or 12 point type is acceptable if the particular font is not too large. Type smaller than 8 point should not be used.

ii) **PLEASE** avoid excessive margins. *Instruct your secretaries to avoid normal correspondence esthetics or practices, however time-honored or 'standard'!* This page has margins on both sides of 0.6" (*ca.* 1.55 cm), which is very adequate. Margins of the same size at the top and bottom are sufficient also, but don't worry if there is more space at the end of your document, for I can often use such spaces for notices, etc.

Also, please avoid large amounts of unused space at the top of letters. Give thought to the sizes of figures, drawings, etc., and please mount these so as to use the minimum space on the page.

iii) 'Position Available', 'Equipment Wanted', and Similar Notices. These are always welcome, but not for subscription credit. Such notices will appear, however, *only* if received with these necessarily rigid constraints: a) Single spaced; b) both side margins 0.6 - 0.7" (1.5 - 1.7 cm.)- NOT WIDER; c) the minimum total height, please, but definitely no more than 4.5" (11.5 cm.).

iv) AVOID DOUBLE SPACING LIKE THE BLACK PLAGUE ! ! ! This is extremely wasteful of space.

6. **Suggestions**: They are always welcome.

Lee W. Shapiro

B. L. Shapiro
September 1998

*Telephone: 650-493-5971. Please confine telephone calls to 8:00AM-10:00PM, *Pacific Coast Time.*
*Fax: 650-493-1348 (Do not use for technical contributions which are to appear in the Newsletter, for Fax quality is not adequate.)
*Email: shapiro@nmrnewsletter.com
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Deadline Dates

No. 482 (Nov.)	23 Oct. 1998
No. 483 (Dec.)	27 Nov. 1998
No. 484 (Jan.)	24 Dec. 1998
No. 485 (Feb.)	22 Jan. 1999
No. 486 (Mar.)	19 Feb. 1999

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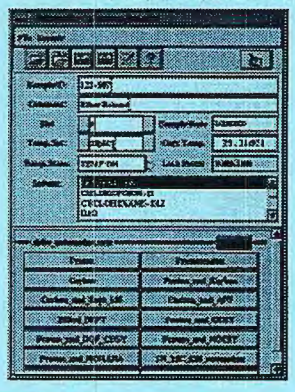
How To Run JEOL's Eclipse+ Spectrometer



Step 1: Enter your sample name and the solvent.

Step 2: Click the mouse button on the data you want.

Step 3: Walk away with your data.

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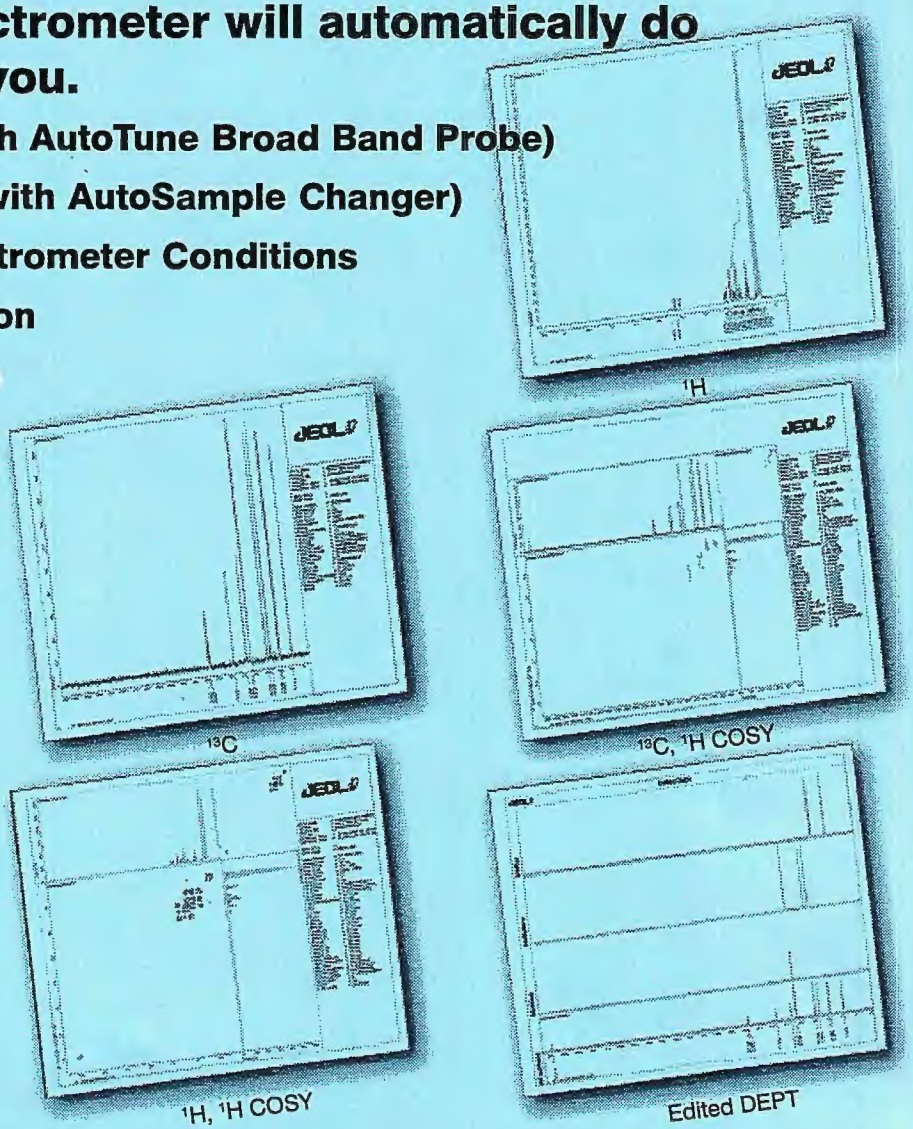

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