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40 Years in Show Business (Second installment)

Use of $^1$H MAS NOESY to Determine Location and Diffusion in Small Molecules in Biomembranes

Early Adventures of Ray Freeman, Master of NMR Choreography

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Another Blast from the Past: Early Jurassic Digital Computers

Still Another Blast from the Past: Niveaux d’Energie $A_nX_m$

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Water Inversion Using a Radiation Damping Control Unit

Fast Lithium Sigmatropic Shift in an Otherwise Dynamically Frozen Allylic Lithium Compound

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Spectral Estimation of NMR Relaxation

Spectral Estimation of NMR Relaxation

Temperature Calibration of a Solid State NMR Probe

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FORTHCOMING NMR MEETINGS


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


SMASH No. 1 (Small Molecules Are Still Hot), Argonne, IL, August 15-18, 1999; Contact: Ms. Karen McCune, mccune_karen_a@lilly.com, 317-276-7983) or S. R. Maple (maple_steven_r@lilly.com) or G.E.Martin (gary.e.martin@am.pnu.com) or A. G. Swanson (alistair_swanson@sandwich.pfizer.com). See Newsletter 487, 17.

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


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


Additional listings of meetings, etc., are invited.
Comments.

1. "Spin Choreography, a Symposium in Appreciation of Ray Freeman". Starting on p. 11 with a narrative by Wes Anderson are some pages relevant to the April symposium at the University of Cambridge. The Newsletter also has reasons to appreciate Ray, for he holds the record - by a wide margin - for the number of technical contributions by one person in the Newsletter's pages: from his first missive in June of 1961 (issue no 33) to the present, Ray has authored no fewer than 68 letters! Several of these have featured not only first-rate science, but also writing distinguished by its literacy and wit, and also by screamingly funny and appropriate cartoons. For all of these aspects, and most especially for his loyalty over so many years, we are most grateful.

If any other participants (or indeed non-participants) in the Cambridge symposium would like to share thoughts/experiences/photos/cartoons/whatever concerning Ray, we would be happy to receive such pages (camera-ready, svp) for the July or August Newsletter issues (deadline dates are June 25 and July 23).

2. "40 Years in Show Business", by Aksel Bothner-By. This imaginatively formatted saga continues on p. 5. Although I am grateful for these efforts, allow me to correct the impression that the inception of the Newsletter in October of 1958 was solely my doing - my clear recollection was that it was a joint effort until I left Mellon Institute early in 1964. The first name of the newsletter, MELLONMR (Monthly Ecumenical Letters from Laboratories of NMR, pronounced 'mellonmer') was Aksel's doing. The operating ideas he and I settled on for the Newsletter have continued to this day.

3. "Blast from the Past". Are these of interest to anyone other than the authors and the publisher? Any suggestions for future examples.

4. Some small practical matters:
   a) Another plea to include in your technical letters your phone and fax numbers, and especially, your e-mail addresses, to facilitate communication.
   b) Subscription invoices and requests for Sponsorship renewals will be mailed on July 1, for your kind attention. Subscription rates will again remain unchanged.
   c) Reader feedback is always appreciated - even when I am unable to agree or acquiesce!

Barry Shapiro
June 1, 1999.
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1993 Varian provides undreamed of sensitivities for obtaining $^{13}$C NMR spectra for tiny amounts of solution-state samples.

1994 Varian brings high resolution NMR to chemists analyzing compounds still bound to solid-phase synthesis resins with the second generation Nano Probe. This capability has since blossomed into the rapidly growing field of HR-MAS, whereby a wide range of heterogeneous samples are yielding to NMR analysis.

1996 Varian publishes the definitive “High-Resolution NMR Spectra of Solid-Phase Synthesis Resins.”

1997 Varian announces the innovative NMS, bringing automation to Nano Probes.

1998 Varian announces the gHX Nano Probe which goes even further by offering indirect detection capabilities for even the most demanding experiments.
Dear Barry-
The adventures continued (2)

We wrote to G. Traverso, in Italy, and told him we could decide between two structures for him

A year later, X-ray diffraction

S. Berzi, M. Mammi, & C. Garbuglio

Obvious, huh?

Holy Shinola!

Aksel moves to Mellon Institute, in Pittsburgh 1958

Barry Shapiro and Cecile Naar came to Pittsburgh, and helped set up the new 60 MHz spectrometer.

Shower curtains to protect magnet from drafts (and soot/iron dust)

Cecile shims the 60. For the meaning of “chocolat”, consult a Belgian friend.

1958 began another 40 year show: In October Barry brought out

Monthly Ecumenical Letters from Laboratories Of N-M-A

No. 1

(received 5/20/99)
40 YEARS IN SHOW BUSINESS

Cleveland 1960 - Bill Ritchey organizes the first ENC, another 40 year travelling show.

Barry attends., and his enthusiasm convinces everybody we should hold the next ENC at Mellon Institute. Turned out to be ten ENCs.

SMASH HIT

2nd ENC

3rd ENC

With a lot of head-scratching and poring over John Pople's chapters in P.S.&B. we wrote FREQINT, to compute line freqs and intensities from J's and 8s.

We got a big boost in 1962 when Turi Castellano joined us.

5th ENC - LAOCOON - to get J's and 8's by fitting the line freqs. Lines often crossed over when J or 8 was varied, creating snakes.

Ahmed A. Berman
ahmed@andrew.cmu.edu
Use of $^1$H MAS NOESY to determine location and diffusion of small molecules in biomembranes

Dear Dr. Shapiro:

The location of small molecules in biomembranes, when combined with data on partitioning and interaction enthalpies, provides very valuable information about the nature of interaction of these molecules with biomembranes. We have investigated location of Trp analogs [1], alcohol [2] and benzene [in preparation] by two-dimensional nuclear Overhauser enhancement spectroscopy (NOESY) on biomembranes. High resolution conditions have been achieved by magic angle spinning (MAS).

For the quantitative analysis of cross-relaxation rates, the NOESY diagonal peak and crosspeak intensities are recorded as a function of mixing time. At short mixing times, each crosspeak and the corresponding diagonal peak of the lipid resonance are treated as a pair of interacting protons [3]. The corresponding cross-relaxation rate, $\sigma_{ij}$, has been calculated by fitting crosspeak volumes to the equation

$$A_{ij}(t_m) = \left(\frac{A_{ij}(0)}{2}\right)\left(1-e^{-2\sigma_{ij}t_m}\right)\exp\left(-t_m/T_{ij}\right)$$

where $A_{ij}(t_m)$ is the respective crosspeak volume at mixing time $t_m$, $A_{ij}(0)$ is the diagonal peak volume at mixing time zero, and $1/T_{ij}$ is the rate of magnetization leakage towards the lattice.

For both aromatic compounds and alcohol, the resulting per-proton cross-relaxation rates reflect a preferential interaction of these molecules with the membrane/water interface region. At the same time, there is weaker cross-relaxation to resonances that are located in the bilayer hydrophobic center, like the terminal methyl protons of hydrocarbon chains. We conclude that location of such molecules in the bilayer is more accurately described by a distribution function along the bilayer normal. Furthermore, the wide range of contacts is also a reflection of the tremendous disorder in lipid packing of a liquid-crystalline lipid matrix [2-4]. For all investigated substances, we were able to verify the preference for a biomembrane interface location by other spectroscopic means. We have strong evidence that the averaged magnitude of cross-relaxation rates depends on the diffusion rates of the small molecules in the lipid matrix. This allows new insights into diffusion of small molecules in the plane of the lipid matrix and across the bilayer. For example, the tryptophan analogs appear to have diffusion rates that are comparable to the lateral lipid
diffusion rates, while indene, benzene, and alcohol diffuse much more rapidly within the bilayer.


Sincerely yours,

[Signature]

Wai-Ming Yau

Klaus Gawrisch

Section of NMR
Laboratory of Membrane Biochemistry and Biophysics
National Institute on Alcohol Abuse and Alcoholism

Phone: (301) 594-3750
Fax: (301) 594-0035
e-mail: gawrisch@helix.nih.gov

Per-proton normalized cross-relaxation rates between selected lipid resonances and membrane-incorporated aromatic molecules.
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Early Adventures of Ray Freeman, Master of NMR Choreography
(as seen from Palo Alto)*

by

Weston A. Anderson
Varian, Inc.

This narrative* relates a selection of the many contributions Ray has made to NMR, and includes some of the interesting and sometimes humorous events that happened early in his career. It traces his path from his high school graduation up through his employment at Varian.

Ray was born in Derbyshire on January 6, 1932, and attended Nottingham High School, graduating in 1949. From high school, Ray went directly into the Air Force for a year and a half, and then went up to Oxford University to study chemistry, receiving his Bachelor of Science degree in 1955.

At Oxford he got his first taste of NMR, working in Rex Richards' group. As one of his projects, he prepared a sample of potassium amide and measured the spectrum of the solid. (He used the calculations of Pake to determine the inter-proton distance in the amide ion). This may have been more challenging than it appears, as Richards has recently commented, "Making the stuff without blowing yourself up is quite difficult, and nowadays would only be allowed with extreme precautions!" Ray's response: "All the compounds Rex suggested were dangerously explosive, or poisonous, or both. After the NMR measurements, we buried the samples in a grassy slope just outside the lab." As part of his D. Phil. work, Ray built a Pound spectrometer to measure the chemical shifts of compounds of gallium, thallium and cobalt, his first experience measuring chemical shifts in solution. He received his D. Phil. Diploma in 1957.

Saclay

After his D. Phil. Degree from Oxford, Ray went to Saclay, France, to work in Anatole Abragam's group. There he met Ionel Solomon and Bob Pound, who was on sabbatical from Harvard. At that time Pound was concerned with radiation damping. (The marginal oscillators used by Pound and others enhanced the radiation damping, causing line broadening of all high-resolution NMR lines). Based on some of Pound's ideas, Ray went to work to build a high-resolution spectrometer which included an internal lock to maintain field/frequency stability, and audio frequency field modulation and sideband detection to provide base line stability. This super-regenerative oscillator had the nice property that it would automatically lock onto an NMR line.

During Ray's time at Saclay, Prof. Abragam is known to have quipped: "In the midst of the broken English that is heard here, Ray, you remain our standard of English" to which Ray replied: "If I am to serve as a standard, it is high time I was sent home to be recalibrated". In French, the word for "standard" is étalon, which also means "stallion", so Ray suspected Abragam had a pun in mind!

*Excerpted from the talk presented by W.A.A. on April, 8, 1999 at the University of Cambridge in the "Spin Choreography, a Symposium in Appreciation of Ray Freeman."
Ray made several trips to Paris, during one of which he remembers a meeting where Varian's Jim Shoolery and Emery Rogers gave a talk announcing the Varian HR-60 NMR spectrometer. This was a great shock to Ray, who in 1957 was still working at 30 MHz.

National Physical Laboratory

In 1959, Ray went to the National Physical Laboratory at Teddington, England, where he became enchanted with NMR double resonance. He added a sideband double resonance device to NPL's HR-60 spectrometer. Later he added an additional sideband channel to provide a lock channel. Dennis Evans, a colleague from his graduate student days at Oxford, provided an interesting application. He had studied the proton-thallium spin couplings in the diethylthallium cation. There were two methyl groups and two methylene groups, both coupled to the thallium spin. Since the effects of selective irradiation of the thallium frequencies depended upon the magnitude and signs of the two thallium-proton coupling constants, Evans was able to determine the relative signs of the thallium-proton couplings. When Evans described this experiment, Freeman and David Whiffen realized that similar measurements could be carried out on any three-spin system, provided one could obtain adequate sensitivity. They demonstrated that in 2,3-dibromopropionic acid*, the gem- and vic- couplings have opposite signs.

Varian Sabbatical

In 1961, Ray took a sabbatical leave to work at Varian. He arrived in November, with his wife, Anne Marie, and two children, Dominique and Anne. One of the things that Ray had to contend with was the fact that there is "the English language" and there is "American English". Ray soon found out that 'Berkeley' is not pronounced 'Barclay'. It seems there is a town in Somerset called Berkeley but pronounced Barclay. There were a number of other words that apparently were not in Ray's vocabulary. Some of these became apparent when Ray purchased a house from another Varian employee. When inspecting the house Ray found the Telly was called a TV, the Tap was called a Faucet, the Gar'-rage was called a Garage'. Being a little bit intimidated Ray pointed to a hoe and asked what that was called, and found it was a hoe, and his friend asked him "Don't you have them in England?"

There were also the American holidays. One day Ray arrived at work at the usual time and found the parking lot empty and the doors locked. That was the time that he learned that Washington's Birthday was a holiday.

One of the activities of the R&D personnel in those days was an annual back-packing trip to the mountains. We would choose a scenic spot in the Sierra Nevada mountain range and then would backpack in for 4 or 5 days. We would carry all of our own food and supplies, and usually little tents made of plastic, as it often rains in late afternoon and at night. Ray heard about our plans and was eager to go. Although it was a hard climb, there were many scenic views along the way. However the next morning we found that one person had a hard time crawling out of his sleeping bag. I still remember Ray's words: "Leave me alone!"

At the end of Ray's sabbatical year he was offered a permanent job at Varian. He accepted, taking an eight-month leave of absence from Varian before starting.

*It is well known that Ray holds the world's record for publishing papers using this cheap, readily available compound.
Ray's Scientific Contributions while at Varian

While at Varian Ray made many contributions to the NMR field. His main emphasis was the development of techniques for analyzing complex NMR spectra. One of the questions that came out of some of our informal seminars was the idea we called "spin tickling": What happens when a second RF* field affects just one transition, i.e., if that RF field is too weak to cause decoupling?

Ray and I analyzed the basic idea, and showed that if one applies a weak perturbing RF frequency centered on one line, then all lines that had an energy level in common with the irradiated line would be split into doublets. This enabled one to trace out complex spin energy level diagrams. Furthermore, one could distinguish whether the two transitions were between levels with the same total magnetic quantum number \( M \), or whether the quantum number of one of the levels differed by 2 units. These were called 'regressive' or 'progressive' levels, respectively.

Ferretti and Freeman illustrated a variation of this technique. They centered an observing RF on one line and then swept a second RF field through the entire spectrum. An amplitude change followed by a Torrey oscillation was observed when the second RF field passed through a transition line that had a common energy level. In addition, one could distinguish between progressive or regressive arrangements by whether there was an initial increase or decrease of the observed line intensity.

Another interesting spin decoupling technique we called 'modulation through the spin coupling'. Ray was interested in exploring the technique to see if it could be useful to solve real problems. We showed how it could be useful to detect carbon-13 satellites in proton spectra that might be hidden under the much stronger signals of protons coupled to carbon-12.

Ray was also quick to pick up on the technique of Fourier Transform NMR. An important question in the early days of FT NMR was whether one could achieve a high resolution NMR spectrum with the limited memory sizes that were available on computers at that time. Freeman and Jones showed they could pick up some very small long-range couplings of the aldehyde resonances in 3-bromothiophene-2-aldehyde. Here they used the concept of 'zero filling' the data, to improve the definition with a limited number of data points.

Another question was if relaxation times could be measured. Freeman and Hill combined the well-known techniques developed by Hahn and others into a series of Fourier Transform experiments, to measure all of the relaxation times \( T_1 \) and \( T_2 \) in a spectrum more or less simultaneously. For \( T_1 \) measurements, a series of 180°-90° pulses were used, and a spin-lock sequence was used to measure \( T_2 \).

*RF = radio frequency or Ray Freeman or République Française or rinforzando? (Ed.)
Oxford and Cambridge

In October 1973, Ray returned to England to accept a lectureship at Oxford, and in 1987, he moved to Cambridge as professor of chemistry. Here he and his coworkers developed many innovative pulse sequences, easily recognized by their descriptive and clever acronyms including BURP, $\psi$-COSY, CUSPIDOR, DANTE, EXORCYCLE, GARP, GROPE, INADEQUATE, INEPT, MLEV, SLURP, SPITTOON, TANGO, TSETSE, WALTZ, WURST, etc.

Ray has published 2 books and over 200 scientific papers. Last July, the University of Durham gave him an honorary degree.

Today, then, we salute RAY FREEMAN, MASTER OF SPIN CHOREOGRAPHY.

Palo, Alto, California
April 1999.

(1998) Self-captioned. Those who were not at the Cambridge symposium may try to identify Ray’s companion - the first correct answer gets a prize.

(1958) Starting in September 1999, bookings for this stellar musical attraction are available for wakes, weddings, bar mitzvahs, etc. Apply to pescadero@marsals.com
Decomposition of Unresolved Multiplets

Dear Barry,

For some time we have been interested in the problem of generating "differential" double resonance spectra, where all resonances are cancelled except for those perturbed by the irradiation. Experimentally this entails pulse modulation of $B_0$ at a very low frequency, and inversion of the signal in synchronism with the pulses, either in a conventional lock-in detector or through the "add" and "subtract" functions of a time averaging computer. Although this proved to be straightforward for heteronuclear double resonance, our first attempts at proton-proton work could only be described in terms of a phenomenon first reported by Thurber's grandmother, i.e. "modulation was leaking out all over the molecule." Every transition appeared to be directly connected to every other. We feel this was due to the rapid transients induced in the internal lock field-frequency loop as $B_2$ was switched, displacing all the spectral lines. It can be cured by introducing a short blanking period during which both the "add" and "subtract" functions are inhibited:

Among the several possible applications we would like to describe the decomposition of an unresolved multiplet—a 0.05 Hz doublet in the spectrum of 3-bromothiophene-2-aldehyde due to long-range coupling between the proton at position 4 and the aldehyde proton. This doublet consists of transitions $X_1$ and $X_2$, distinguishable by the different ways in which they fit into the energy level diagram; $X_1$ is connected to $M_1$ while $X_2$ is connected to $M_3$. Thus weak irradiation of line $M_1$ causes $X_1$ to split into a doublet but leaves $X_2$ unaffected. Pulse modulation of the irradiating field on $M_1$, followed by synchronous detection of the signal results in a response with a central
positive peak (X1) flanked by two weaker, negative signals (X1 split and inverted) with negligible contributions from X2.

Our time averaging device was a Mmemotron CAT 400 which has the feature that signals in alternate channels may be steered into two quite separate regions of the memory (let us call them the odd and even locations). At read-out, first all the odd channels are displayed sequentially and then, starting again at the left-hand edge of the recorder, the even channels. We therefore alternately irradiated lines M1 and M3, storing the X1 response in the odd locations and the X2 response in the even locations. The resulting trace is shown in the Figure.

![Figure showing X1 and X2 responses](image)

Transient nutations of the magnetization vectors persist for a considerable time after H2 is switched. It should be pointed out that there are certain features about these transient effects that are incompletely understood—in particular, oscillatory signals could be detected at a frequency that appeared to depend on the levels of both H1 and H2. Unless the pulse period was increased sufficiently (22 secs) to minimize such transient effects, there was a detectable amount of "cross-modulation" between the X1 and X2 responses.

Yours sincerely,

Ray

Ray Freeman    Bo Gestblom

2 J. Thurber, My Life and Hard Times, Chapter II.
3 Varian Postdoctoral Fellow, on leave from the Institute of Physics, Uppsala.
Dear Barry,

Early Jurassic Digital Computers

I never quite understood how one manages to do long division on an abacus but I can imagine it can cause real difficulties when the denominator is zero. There were similar problems with digital computers in the 1960's; they seemed to blow all their fuses in this situation. Later computers checked one's arithmetic beforehand and sent a rather shirty error message. Division by zero was a crime almost as unforgivable as using double spacing in the Newsletter. *

Now there is a nice experiment suggested by Axel Bothner-By and Joe Dadok\(^1\) where they deconvolute J-splittings from individual spin multiplets by dividing the corresponding time-domain signal by \(\cos(\pi J^* t)\) where \(J^*\) is a trial coupling constant. Problems arise when the cosine wave is zero or near zero. Because of these numerical instabilities, a considerable amount of research has gone into alternative methods of deconvolution that avoid this problem. For example, we once advocated a method that carefully sampled the cosine wave in such a manner as to avoid the zero-crossings.\(^2\)

We have recently attacked this problem again from another angle. In this particular case the cosine wave is a noisy signal which makes the problem even trickier. We test each ordinate of the time-domain denominator to see if its modulus is less than a predefined threshold \(\theta\). If it is, it is replaced by \(\theta\), retaining the original sign. A good value of \(\theta\) seems to be something comparable with the peak-to-peak noise level, but in fact the method is surprisingly tolerant of the choice of \(\theta\) (over several orders of magnitude). It even works when \(\theta\) is so high that all the ordinates are replaced by \(+\theta\) or \(-\theta\) although in this case there are complications due to harmonics of the basic frequency. After division, any residual spikes in the quotient can be smoothed by a simple 1:2:1 convolution algorithm, repeated if necessary. We think that this might be one of the simplest solutions to the J-deconvolution problem.

 Kindest regards,

Ray Freeman

---


* Or misspelling Aksd, or leaving the last letter off Elsinor.

Thanks, Roy.

BLS.
Lors de votre récent passage à notre laboratoire, vous avez sollicité une communication digne de la centième édition de l'I.I.T.N.M.R.

Depuis quelque temps nous étudions les signes relatifs des constantes d'interaction spin-spin à longue distance dans certains extraits de l'huile de coprah. Au cours de ce travail nous avons éprouvé quelques difficultés à établir le réseau des niveaux d'énergie pour certains systèmes de deux groupes de spins nucléaires, par exemple $A_2X_3$ (selon la nomenclature de Pople). Le problème a été résolu par une nouvelle méthode de construction graphique qui s'explique par l'exemple suivant.

On trace d'abord sur le graphique (Fig. 1) le profil du spectre $A_2X_3$, se rappelant qu'un quadruplet 1:1:1:1 doit être décomposé en quadruplet (1:1:1:1) auquel on superpose un doublet (2:2) par dessus les deux lignes centrales, tandis qu'un triplet (2:2:2) avec un singulet central. Ainsi chaque résonance est en réalité deux sous-spectres qui doivent être traités séparément.

Avec un compas centré sur chaque ligne d'un sous-spectre $A$ quelconque, on trace des arcs qui se coupent avec d'autres arcs (à rayon $r$ égal) centrés sur les lignes d'un sous-spectre $X$. Les intersections de ces arcs définissent les niveaux d'énergie, et, dans ce cas particulier de deux sous-spectres $A$ et deux sous-spectres $X$, établissent quatre systèmes indépendants de niveaux (voir la figure ci-contre). Les transitions entre niveaux d'énergie peuvent être identifiées par l'origine de l'arc générateur.

Par dessus le marché, la méthode se prête facilement à la prédiction des spectres à deux quanta. Chaque parallélogramme sur le graphique engendre une transition à deux quanta dont la fréquence correspond à la mi-hauteur du parallélogramme (on doit tourner la figure pour que la direction énergie soit verticale). Le cas $A_2X_3$ donne naissance à un quadruplet de transitions à deux quanta, avec les intensités relatives 1:4:4:1, en accord avec l'expérience de KAPLAN et MEIBOON sur l'alcool éthylique.

Cette méthode s'étend sans difficultés à d'autres systèmes à couplage faible, $A_2X_n$. On laisse au lecteur le soin de construire (en deux dimensions) les graphiques appropriés aux systèmes $A_nM_2X_p$ (trois groupes de spins inégaux).

Sincères salutations,

Sue

(Mlle) Suzanne Perchery


Titre: Niveaux d'énergie $A_nX_m$. 

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HCN TROSY for Nucleic Acids

Dear Barry:

In our previous letter we reported the sensitivity gains obtained with the TROSY approach for $^1$H-$^{13}$C correlation in larger oligonucleotides at 500 MHz. The average sensitivity enhancement (TROSY/HSQC) at various sites in a fully $^{13}$C- and $^{15}$N-labeled ATP binding aptamer containing 40 nucleotides varied between 2.3 and 2.9 at 50°C in the case of aromatic carbons while for $^{13}$C' sugar carbons the enhancement was substantially smaller (1.3 on average). We did not find the results significant enough to warrant publication, especially since Brutscher and coworkers presented a comprehensive discussion of $^1$H-$^{13}$C TROSY correlation for labeled RNA.

Recently, we have decided to resuscitate our TROSY attempts to see the possible merits in applications to $^{13}$C labeled RNA and DNA oligonucleotides. In continuation of the effort to improve sensitivity of nD HCN and HCNCH experiments for intra-residual correlations of sugar H1' and C1' with N1/9, C6/8 and H6/8 in pyrimidine and purine bases, we have designed their TROSY versions. Previously, the conversion of single- to multiple-quantum evolution in HCN and HCNCH experiments, together with a careful control of homo- and heteronuclear scalar interactions, resulted in up to 400 % increase in signal-to-noise ratio. The first TROSY results obtained on our spectrometer at 500 MHz were a little bit disappointing. For ATP binding aptamer only pyrimidines showed substantial gains in sensitivity (enhancement factors 2.2 – 2.3) when out-and-back TROSY and MQ HCN experiments were evaluated. In the case of purines, the performance of both versions was comparable. For sugar carbons, the performance of the TROSY version of the HCN experiment is always inferior to MQ due to a small value of the chemical shift anisotropy (CSA) of C1'. The sensitivity of through-bond correlating HCNCH experiments, where we combined the MQ evolution on sugars with a TROSY step on bases, was also lower than expected.

Since 11.7 T is far from being optimal for applications of transverse optimized spectroscopy we were wondering what could be achieved at higher fields. Few weeks ago, by courtesy of Bruker Analytik and Wolfgang Bermel, we had a chance to test the experiments at 800 MHz on a AVANCE demo system in Karlsruhe, Germany. As predicted by theoretical calculations (Fig. 1), TROSY approach in both out-and back HCN and all-the-way-through HCNCH schemes showed considerable improvement in sensitivity and resolution. Average gain in signal-to-noise ratio was 300 - 400 % for uracils and cytosines and 200-300 % for adenines and guanines when TROSY and MQ versions were compared. The chemical shift labeling in the HCNCH experiment can be arranged as H6/8-to-H1' or H1'-to-H6/8 correlation. Depending on the choice, the TROSY step is placed in the first or second CN evolution interval. The transfer H1'-C1'-N1/9 is designed as the MQ evolution. The S/N gains are not as dramatic as in the case of HCN experiments but average gains of between 22 and 81% were obtained for purine and pyrimidine signals, respectively.
The enhancement factors are not uniform and vary across the RNA structure. To get better understanding of the relaxation properties of C1'(ribose), C6(U and C) and C8(G and A), we have calculated the values of principal components and orientation of CSA using DFT \textit{ab initio} method. The differences in relaxation rates based on the obtained CSA values are in good agreement with the sensitivity relations observed in experimental data. Significant variations observed for individual bases reflect differences of relaxation rates due to local variation of the relaxation environment and of the motional behavior.

Figure 1. Relaxation rates of single quantum coherence (dotted line), multiple-quantum coherence (dashed) and TROSY (solid line) of C6-H6 pair in cytosine (A) and C8-H8 pair in guanine (B) as a function of magnetic field. The calculation included the effect of neighboring protons.

References

Sincerely,

Radovan Fiala

Jiří Czernek

Vladimír Sklenár
Dear Barry,

One of the problems frequently encountered when working in aqueous solutions is the efficient inversion of the water signal. This is of particular importance when studying exchangeable protons or bound water molecules in protein samples. The phenomenon of radiation damping will oppose the effect of classical selective excitation pulses (Gaussian, E-BURP...) and will prevent a good excitation of the water signal. The methods that have been proposed in the literature to overcome this problem usually employ techniques that cancel the radiation damping field.

There is, however, another way to achieve a clean water inversion which is based on the excitation of the water signal by its own radiation damping field. The idea, originally proposed by Abergel et al.¹, uses an electronic circuit to detect and manipulate the radiation damping field. The net result is that the resulting field will not bring the water magnetization along the +z axis (classical radiation damping case) but along the −z axis (water inversion case).

The results we have obtained using our newly developed radiation damping control unit are quite impressive and lead to a very good water inversion. When taking the difference between two spectra recorded with the water magnetization along the +z or the −z axis, only the protons in interaction (chemical exchange or dipolar interaction) with water molecules appear in the resulting spectrum. The spectra we have obtained on a 10 mM Cytochrome c sample² (Figure 1) exhibit a signal to noise superior to the one obtained using alternative techniques³,⁴.

O. BORNET, F. GUERLESQUIN, C. BREVARD, M. PIOTTO

Figure 1: Comparison of the results obtained on a 10 mM sample of horse heart ferrocytochrome c in 90% H₂O and 10% D₂O at 300 K. A 500 MHz Avance Bruker spectrometer equipped with a HCN probe and self shielded triple axis gradients was used. A) Reference 1D spectrum recorded with 8 scans and presaturation. B) 1D NOE spectrum recorded using a selective spin echo for water inversion with 64 scans and a 100 ms NOE mixing time. A 50 ms Gaussian pulse was used to select the water magnetization. C) 1D NOE spectrum recorded using a radiation damping control unit for water inversion with 64 scans and a 100 ms NOE mixing time.
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Solvated allylic lithium compounds do not ordinarily exhibit one bond $^{13}$C, $^6$Li (or $^7$Li) coupling. With coordinated lithium sited normal to the allyl plane, the "s" contribution to any C, Li covalency would be minimized, hence spin coupling is too small to be detected. The exceptions which show $^{13}$C lithium coupling are the few allylic lithium compounds within which lithium is internally coordinated to a pendant ligand, see 1. In these latter cases we proposed\(^1\) (confirmed with X-ray crystallography\(^2\)) that restricted stereochemistry of lithium coordination favors lithium to be somewhat off the vertical axis ($40^\circ$) normal to the allyl plane. This increases the "s" character associated with a small C, Li covalence, allowing for detectable ($3$ Hz) $^{13}$C, $^6$Li coupling.

By lengthening the ligand tether by one carbon, we now have a system in which there is $^{13}$C, $^7$Li coupling to both termini of an allylic lithium compound. It is produced by metalating 2 with CH$_3$Li at CH$_2$Si.

The lithium compound is a monomer in solution (freezing point) and in the solid (X-ray). The latter shows a covalent species with Li bonded to the terminus with silyl endo. In solution, $^7$Li is coupled to the two $^{13}$C termini differently, 4.3 Hz and 4.9 Hz, up to 300 K. The terminal $^{13}$C shifts of 64.88 and 68.38 don't look like a localized system. However, all can be explained.

In contrast to the solid state, in solution there is an equilibrium mixture of two covalent species in similar concentration rapidly interconverting via a lithium 1,3-sigmatropic shift, see 3a$\leftrightarrow$3a', 3b$\leftrightarrow$3b'. Relative to the NMR time scale bimolecular C, Li exchange is slow as is also rotation around the C$_1$-C$_2$ and C$_2$-C$_3$ bonds. Our sample has $^{13}$C in natural abundance. Thus, the two pairs of separately interconverting isotopomers are 3a$\leftrightarrow$3a', 3b$\leftrightarrow$3b'. So each observed coupling constant is the average over two interconverting species, 3a, a' and 3b, b'. They are different because the bond rotation rates which convert 3a to 3b or 3a' to 3b' are slow in this sample. The observed shifts are likewise averages over 3a, a' and 3b, b'.
All of this comes from variations in the stereochemistry of lithium solvation.

Best regards,

Gideon Fraenkel
Professor of Chemistry

Roland Fleischer
Research Associate


2. Watch your JACS this summer.

---

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

Re: For Sale: 4.7 Tesla, 330 mm Horizontal Clear-Bore Magnet & Accessories

Dear Barry:

I am nearing the final step in my multiyear ease out of the *in vivo* NMR business. As a consequence, I have for sale a horizontal bore instrument which is adequate for studies with animals up to the size of young rabbits. While the console (Nalorac Quest) is aged and probably of little value to others, the Oxford magnet is really excellent. The magnet has actively shielded shim coils and gradient coils (15 G/cm maximum), and it has a nice "sweet" spot according to users. The magnet is currently operating, but we will probably decommission it within a month. Other components, such as frequency synthesizer and power amplifiers, may be useful to some people as well. More details about the available equipment and contacts regarding procurement can be found at the web site http://picasso.ucsf.edu/magnetforsale.pdf.

Sincerely yours,

Thomas L. James, Ph.D.
Chairman, Department of Pharmaceutical Chemistry
Professor of Chemistry, Pharmaceutical Chemistry and Radiology
April 12, 1999
(received 4/27/99)

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

Spectral Estimation of NMR Relaxation

Dear Dr. Shapiro,

If a monoexponential decay has the following form:
\[ f(t) = Ae^{-\lambda t} + B \]
then the one sided continuous Fourier Integral Transform gives the transform as:
\[ F(\omega) = A(\lambda - i\omega) / (\lambda^2 + \omega^2) + 2\pi B \delta(\omega) \]
and hence the decay rate \( \lambda \) can be extracted as:
\[ \lambda = -\omega \Re(F(\omega)) / \Im(F(\omega)) \]
for any nonzero angular frequency \( \omega \).

In "Exponential Analysis of physical phenomenon" by Andrei A. Istratov and Oleg F. Vyvenko, in Review of Scientific Instruments, Vol. 70, No. 2, Feb. 1999, p1233-1257, (with 344 references), the authors advocate this method as the best method for determination of a monoexponential decay rate. This relationship is a very good approximation where the discrete Fourier Transform is used with long records of 256 points but is not very approximate when short records like four, eight, twelve points are collected, like in NMR relaxation.

In our opinion, current wisdom in NMR is represented by the ideas presented in "Optimization of Magnetization Transfer Experiments to Measure First-Order Rate Constants and Spin-Lattice Relaxation Times", by H. Katki et al. in NMR in Biomedicine, 9, 135-139 (1996), and "The Effects of Imperfect Saturation in Saturation Recovery T1 Measurements" by A. Roscher et al. in J. Mag. Res. 118A p108-112 (1996).

However, it can be shown that for a short record DFT, the decay rate can be extracted from data as:
\[ \lambda = \ln(-\Re(F(\omega)) / \Im(F(\omega))) \]
where, \( \omega \) is selected to be at the half Nyquist angular frequency. The DFT can be thought of as a matrix of complex values and hence this latter expression can be used to construct a more rational expression for the extraction of \( \lambda \) from data. If the decay transient is measured at points with equal time increments and if the time increment is taken as the unit of time, \( \lambda \) can be extracted from data as follows:

For four points, \( f_1, \ldots, f_4 \)
for twelve point, $f_1 \ldots f_{12}$

$$\lambda = -\ln \left( \frac{(f_2 - f_4 + f_6 - f_8 + f_{10} - f_{12})}{(f_1 - f_3 + f_5 - f_7 + f_9 - f_{11})} \right)$$

These formulae provide a non iterative estimate of $\lambda$ which is independent of any assumption concerning the error distribution within the data.

Sincerely,

David Naugler
dnaugler@sfu.ca

Robert J. Cushley
cushley@sfu.ca

Reply by:

Dr. Andrei A. Istratov,
Institute of Physics of St. Petersburg State University
Ulianovskaya 1
St. Petersburg, 198904
Russia

Re: Spectral Estimation of NMR Relaxation

David,

This is indeed a good point. Equation of the form $\lambda = -\ln \left( \frac{(f_2 - f_4)}{(f_1 - f_3)} \right)$ appears in Sec. VI.A.2 of the review, and the obvious disadvantage of this formula is that it uses only four points, no matter how many are actually measured. Equation of the type $\lambda = -\ln \left( \frac{(f_2 - f_4 + f_6 - f_8 + f_{10} - f_{12})}{(f_1 - f_3 + f_5 - f_7 + f_9 - f_{11})} \right)$ is much better in this respect, and I agree that it deserved to be included in the review. Thank you for pointing this out. You know, after I read your e-mail I realized that we should have discussed in more detail in the review what to do if the number of experimental data points is limited to, e.g., 6, 8, or 10. This is a very special problem, and only few algorithms can be used.

Another point that was discussed in Sec. VI (page 1242, left column, at the top of the page), but was not emphasized in the discussion, is that all methods for multiexponential analysis are suitable for monoexponential analysis. For this reason, such a common technique as exponential nonlinear least squares fit would be a good algorithm to analyze a set of 8 or 10 data points. But it is surely not as fast as your formula.

Thank you for your comments,

Sincerely,

Andrei Istratov
istratov@socrates.berkeley.edu
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<tr>
<td>48,775-9*</td>
<td>99.9</td>
<td>5% chloroform in acetone-d$_6$</td>
<td>5mm x 8in.</td>
<td>1 ea (0.70mL)</td>
<td>66.90</td>
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</tr>
<tr>
<td>48,717-1*</td>
<td>99.9</td>
<td>1% chloroform in acetone-d$_6$</td>
<td>8mm x 8in.</td>
<td>1 ea (1.95mL)</td>
<td>128.70</td>
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<td>48,716-3*</td>
<td>99.9</td>
<td>1% chloroform in acetone-d$_6$</td>
<td>5mm x 8in.</td>
<td>1 ea (0.70mL)</td>
<td>66.90</td>
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<tr>
<td>48,714-7*</td>
<td>99.9</td>
<td>1% 1,2-dichlorobenzene in acetone-d$_6$</td>
<td>5mm x 8in.</td>
<td>1 ea (0.70mL)</td>
<td>77.20</td>
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<tr>
<td>48,712-0*</td>
<td>99.8</td>
<td>0.1% ethylbenzene and 0.01% tetramethylsilane in chloroform-d</td>
<td>8mm x 8in.</td>
<td>1 ea (1.95mL)</td>
<td>149.30</td>
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<tr>
<td>48,719-4*</td>
<td>99.8</td>
<td>0.1% ethylbenzene and 0.01% tetramethylsilane in chloroform-d</td>
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<td>92.70</td>
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<td>48,711-2*</td>
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<td>0.1% ethylbenzene and 0.01% tetramethylsilane in chloroform-d</td>
<td>3mm x 8in.</td>
<td>1 ea (0.23mL)</td>
<td>108.10</td>
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<tr>
<td>48,713-9*</td>
<td>99.9</td>
<td>0.1 mg/mL gadolinium(III) chloride, 0.1% DSS and 1% water in deuterium oxide</td>
<td>5mm x 8in.</td>
<td>1 ea (0.70mL)</td>
<td>154.50</td>
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<tr>
<td>48,715-5*</td>
<td>99</td>
<td>1% iodomethane-$^{13}$C, 1% trimethyl phosphite and 0.2% chromium(III) acetylacetonate in chloroform-d</td>
<td>3mm x 8in.</td>
<td>1 ea (0.23mL)</td>
<td>145.00</td>
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* Manufactured by ISOTEC, Inc.

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<table>
<thead>
<tr>
<th>Cat. No.</th>
<th>Name, Isotopic Purity</th>
<th>Unit Size and Price</th>
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<tr>
<td>44,486-3</td>
<td>Acetone-(d_6), 99.9 atom % D</td>
<td>100mL $175.10</td>
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<tr>
<td>15,179-3</td>
<td>Acetone-(d_6), 99.5 atom % D</td>
<td>100g $146.20</td>
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<tr>
<td>15,180-7</td>
<td>Acetonitrile-(d_3), 99.6 atom % D</td>
<td>100g $228.60</td>
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<tr>
<td>15,181-5</td>
<td>Benzene-(d_6), 99.6 atom % D</td>
<td>100g $175.10</td>
</tr>
<tr>
<td>15,182-3</td>
<td>Chloroform-(d_3), 99.8 atom % D</td>
<td>150g $31.90</td>
</tr>
<tr>
<td>22,578-9</td>
<td>Chloroform-(d_3), 99.8 atom % D (contains 0.03% v/v TMS)</td>
<td>150g $31.90</td>
</tr>
<tr>
<td>43,487-6</td>
<td>Chloroform-(d_3), 99.8 atom % D (contains 0.1% v/v TMS)</td>
<td>150g $31.90</td>
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<tr>
<td>15,183-1</td>
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<td>150g $31.90</td>
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<tr>
<td>15,189-0</td>
<td>Deuterium oxide, 100.0 atom % D</td>
<td>125g $169.90</td>
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<tr>
<td>15,188-2</td>
<td>Deuterium oxide, 99.9 atom % D</td>
<td>125g $72.10</td>
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<td>15,194-7</td>
<td>Methyl-(d_3) alcohol-(d_3), 99.8 atom % D</td>
<td>100g $451.10</td>
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<tr>
<td>15,187-4</td>
<td>(Methyl sulfoxide)-(d_3), 99.9 atom % D</td>
<td>100g $142.10</td>
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<tr>
<td>17,594-3</td>
<td>(Methyl sulfoxide)-(d_6), 99.5+ atom % D</td>
<td>100g $133.90</td>
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</table>

† This is the quantity packaged under nitrogen in the Sure/Seal™ bottle. We offer many other units and packaging options. Please contact us for more details.

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Temperature Calibration of a Solid State NMR probe

Dear Barry,

We have recently started using $^2$H solid state NMR at low temperatures and wanted to calibrate the temperature in the solids probe. Typically, for high resolution work, one uses methanol and measures the difference between the OH and CH$_3$ resonances. Since our solids probe is $^2$H, we were interested in how accurate this procedure would be using the OD and CD$_3$ resonances.

The central issue in transferring $^1$H temperature calibration curves to $^2$H NMR relates to whether $\gamma_H / \gamma_D$ remains constant as a function of temperature. If it does remain constant, our calibration of the probe temperature is simple. We expect a value for $\gamma_H / \gamma_D$ of approximately 6.51. Having carefully calibrated our $^1$H-indirect detection probe using methanol, we ran a spectrum of Val-H$_8$ at different temperatures and measured the difference between the HDO peak and the center of the Val-(CH$_3$)$_2$ resonances. Our calculations indicated that $\Delta \delta = -3.73T + 1223.8$ for the indirect detection probe (Figure 1A). Next, we measured the difference between the HDO peak and Val-(CD$_3$)$_2$ resonances in the solids probe. We found $\Delta \delta = -0.55T + 194.0$ (Figure 1B). The slope and y-intercept of the $^2$H curve is different from the $^1$H curve by an average factor of 6.5. This information indicates to us that $\gamma_H / \gamma_D$ is not a function of temperature. Therefore, we can use the calibration of the indirect detection probe to get an accurate temperature inside our solids probe.
Figure 1: Temperature calibration curves for (A) $^1$H indirect detection probe and (B) solid state $^2$H probe. Shown is the difference in chemical shift between the HDO peak and the center of either Val-(CH$_3$)$_2$ ($^1$H indirect detection probe) or Val-(CD$_3$)$_2$ ($^2$H probe) versus temperature. The calibrated temperature inside the $^1$H indirect detection probe is shown in (A) whereas the temperature reading on the VT console was used on the solids probe in (B).

Sincerely,

Carolyn Slupsky  
Brian Sykes
Dear Barry,

When doing diffusion measurements especially with very high amplitude gradient pulses, phase disturbances are often noted. One commonly used means of 'solving' this problem is to hide it by computing absolute value spectra. It is interesting to consider this situation and this 'solution' a little further. For example, if we perform an analysis based on the short gradient pulse approximation and include the effects of a phase-shift, \( \phi \), due to the effects of a gradient mismatch, \( \Delta q \), and sample movement, \( \Delta r \), between the first and second gradient pulses in the PGSE sequence we get

\[
E(q, \Delta) = \int \rho(r_0) \int P(R, \Delta) e^{i2\pi q \cdot R} dR dr_0
\]

where \( \rho(r_0) \) is the spin density, \( R \) is the dynamic displacement defined by \( r_1 - r_0 \) (the starting and finishing positions of a spin with respect to the first and second gradient pulses), \( P(R, \Delta) \) is the average propagator (i.e., the probability that a spin will move by a displacement \( R \) during the time interval \( \Delta \)) and the phase term can be expressed as

\[
2\pi q \cdot R + \phi = 2\pi[(q + \Delta q) \cdot (r_0 + R + \Delta r) - q \cdot r_0].
\]

Taking the gradient to be oriented along the z-direction and assuming that \( \Delta q \) is a magnitude mismatch (i.e., parallel to \( q \)), Eq. [1] can be re-written as

\[
E(q, \Delta) = \int P(Z, \Delta) e^{i2\pi q z} dZ \{ e^{i\pi q(z + \Delta z)} \} \int \rho(z) e^{i2\pi q z} dz.
\]

The first term is the attenuation due to diffusion, the second term is the residual (net) phase-shift due to sample movement (which can be removed by computing the absolute value spectrum), and the third term is the residual phase-twist resulting from the gradient pulse mismatch. For a cylindrical sample of length \( l \) centred in the gradient we obtain

\[
E_{\text{phase}}(\Delta q) = \text{sinc}(\pi \Delta q l).
\]

Some example plots of \( \ln|E(q, \Delta)| \) as they would appear if they were determined from absolute value spectra are shown in Figure 1. It has been simplistically assumed that \( \Delta q \) is a fixed proportion of \( q \). It can be clearly seen that as the mismatch increases, the measured (i.e., apparent) diffusion coefficient increases (i.e., compare the slopes at small \( q \) values).
Figure 1 Plots of $\ln(|E(q,\Delta)|)$ calculated using Eqs. [3] and [4] with $D = 1 \times 10^{-14}$ m$^2$s$^{-1}$, $\Delta = 20$ ms, $l = 5$ mm, $\Delta z = 0$ mm and $\Delta q = 0$ (---) (i.e., no mismatch, this corresponds to $E_{\text{diff}}(q,\Delta)$), $\Delta q = q \times 2 \times 10^4$ (-----) and $\Delta q = q \times 10^3$ (-----). With such a low value of $D$ the diffusive attenuation should be almost negligible as shown for the case of $\Delta q = 0$, however, the residual phase-shift resulting from gradient pulse mismatch causes enormous artifactual attenuation resulting in a huge increase in the apparent diffusion coefficient (i.e., if the attenuation data is interpreted assuming that all of the observed attenuation resulted from $E_{\text{diff}}(q,\Delta)$). At larger $q$ values (and therefore $\Delta q$) artifactual diffraction peaks are evident. The degree of mismatch strongly influences the position of the diffraction peaks with the diffractive peaks appearing at smaller values of $q$ as the degree of mismatch increases.

We note that the $E_{\text{phase}}(\Delta q)$ term is not removed by computing absolute value spectra. However, if absolute value spectra are used the negative excursions in the attenuation plot become positive. This results in an attenuation plot that contains sharp minima similar to the diffractive minima that can be observed for species undergoing restricted diffusion (2). Thus, it is important to observe the PGSE spectra in phase-sensitive mode to distinguish between real and artifactual diffraction peaks in PGSE attenuation plots.

References


Please credit this to the account of Prof. Y. Arata.

Yours sincerely

William S. Price
Oxygen contributions to magnetic relaxation are ubiquitous and very well known. Perhaps not so well known is the magnetic field dependence of the oxygen contribution to relaxation rates. For small molecule systems, the correlation time for the electron-nuclear coupling will become the electron $T_{1e}$ in the case that the electron relaxation rate is rapid compared with correlation times for translational diffusion. Our new MRD spectrometer permits an easy measurement that reports the $T_{1e}$ as the inflection point in a relaxation dispersion curve. Data for oxygen contributions in cyclohexane are shown in the Figure below for air and a sample prepared at 1 atm of oxygen. The oxygen g-factor is 2.0021, so that the top axis of the figure may be labeled easily with the electron Larmor frequency, $\omega_e$. On this axis, the inflection point corresponds to a correlation time of 5 ps, which is much shorter than translational correlation times for either the liquid or the dioxygen molecules in this sample. Thus, this inflection provides a convenient measurement of the oxygen $T_{1e}$. We have observed similar results in other solvents, such as water, methanol, etc.

Dear Dr. Shapiro,

NMR imaging is particularly sensitive to motion effects, especially functional imaging. Random gross motions of the patient may induce pseudorandom sampling when using cartesian scanning. In the present analysis, we assume that random motions do not occur during sampling along a trajectory but only during the time slots between successive k-space trajectories. Figure 1 shows the cells computed with the Voronoi algorithm (1) for a pseudorandom sampling distribution. The cell areas represent the inverse of the sampling density. In this example, random rotations, occurring in the time slots between successive k-space horizontal trajectories were only considered.

Figure 1: Voronoi cells associated with each sample of a pseudorandom k-space sampling distribution obtained in presence of rotation effects. In the absence of such rotation effects, the samples would be on a Cartesian grid, all the cells would be rectangular and would have the same area.

To reconstruct the correct image, the Bayesian estimator (2) was found more efficient than the gridding algorithm (3). A comparison between these two methods will be discussed during the defense of Marc Bourgeois' thesis on June 9.

Yours Sincerely,

Marc Bourgeois

Andre Briguet

Danielle Graveron-Demilly

Dear Dr. Shapiro,

Glycine (C2H5NO2) is perhaps the simplest of all amino acids. There is no center of chirality. While it has many uses in other areas, glycine is a useful and convenient sample for solid state NMR. In particular, it can be used to check and calibrate spectrometer performance or, with the various isotopic enrichments commercially available, to quickly implement and demonstrate a variety of different techniques, such as rotational resonance, REDOR, triple resonance experiments, etc.

Glycine is known to exist in three forms (α, β, and γ) in the solid state. These have been studied by both x-ray(1,2,3) and neutron diffraction(4). The α form has hydrogen bonded double layers of molecules which are packed by van der Waals forces. The β form is unstable. It has single molecular layers, whose internal arrangements are the same as in the α form. The γ form crystallizes with a trigonal hemihedral symmetry. The γ form is stable at room temperature but will convert to the α form upon heating to near its decomposition temperature of 165 °C. The unstable β form is reported to change to α upon heating, by mechanical shock, or by grinding. The three forms can also be identified by the N-H stretching frequency in the infrared spectra(2).

Figure 1 shows the 13C CP/MAS spectrum of glycine (as is). This sample, of unknown age and handling, originally came from Aldrich Chemical Company. The spectrum shows two carbonyl resonances. The α form is assigned to the resonance at 176.1 ppm while the γ form is assigned to 174.3 ppm. The methylene resonances overlap but may be separated by using the differences in the proton spin lattice relaxation rates. Relaxation time constants are given in Table 1.

Relatively pure samples of either the α or γ form are easy to prepare from such a glycine mixture. The α form can simply be recrystallized by slow evaporation from aqueous solution while the γ form is rapidly recrystallized from aqueous solution with the addition of ethanol. The literature values for the N-H stretching frequency in the infrared spectra have been used to identify the purified forms. The N-H stretch appears at 3173.4 wavenumbers for α glycine and at 3107.8 wavenumbers for γ glycine. The IR spectrum of each form is shown in Figure 2. The above 13C spectral assignments were made based upon the identification of these purified samples.

The NMR relaxation parameters differ significantly between the α and γ forms. However, the simple preparation of either allows the spectroscopist a choice of which to use.

Sincerely,

Robert E. Taylor
Research Instrumentation Specialist

Please credit this contribution to the subscription of Steve Silber.
Figure 1: $^{13}$C CP/MAS spectrum of glycine (as is) from Aldrich Chemical Company.

Figure 2: The infrared spectra using KBr pellets of $\gamma$ glycine (top) and $\alpha$ glycine (bottom).

Table 1: Relaxation Times

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<th>$^{1}$H T1</th>
<th>$^{1}$H T1 rho</th>
<th>$^{13}$C T1</th>
<th>$^{13}$C T1 rho</th>
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<tr>
<td>$\alpha$</td>
<td>0.21 sec</td>
<td>45 msec</td>
<td>12 sec (C=O)</td>
<td>220 msec (C=O)</td>
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<td></td>
<td></td>
<td>4.6 sec (NCH2)</td>
<td>37 msec (NCH2)</td>
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<tr>
<td>$\beta$</td>
<td>3.5 sec</td>
<td>5.7 msec</td>
<td>43 sec (C=O)</td>
<td>300 msec (C=O)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>20 sec (NCH2)</td>
<td>37 msec (NCH2)</td>
</tr>
</tbody>
</table>

All NMR measurements were made with a Bruker MSL-300 spectrometer with $^{1}$H and $^{13}$C ninety degree pulsewidths of 4 usec.

References:

Address all Newsletter correspondence to:

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

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No. 491 (Aug.)  23 July 1999
No. 492 (Sept.)  20 Aug. 1999
No. 493 (Oct.)  24 Sept. 1999
No. 494 (Nov.)  22 Oct. 1999

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