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Two Years of NMR Developments at the National High Magnetic Field Laboratory in Tallahassee, USA

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Abstract. The purpose of this contribution is to give an overview of the activities of the NMR program of the National High Magnetic Field Laboratory in Tallahassee, Florida. Several scientists who contributed to start this research program moved from the University of Lausanne to the United States in August 1994. Part of this group will move back to Lausanne in September 1996. This contribution focuses on the two-year time-span that the group was active in the USA.

Introduction

In some respects, this contribution may appear paradoxical, since this issue of CHIMIA is dedicated to the life of the Chemistry departments of the Université de Lausanne and the Ecole Polytechnique Fédérale. Most of the research that will be described was not actually carried out in Lausanne, but in the United States between August 1994 and September 1996, during a period where the authors of this contribution helped to set up the NMR program of the National High Magnetic Field Laboratory (NHMFL) in Tallahassee, Florida. Some members of this group will move back to the University of Lausanne in September 1996, others will move to the Ecole Normale Supérieure in Paris, and the remainder will continue to run the NMR program in Tallahassee. This contribution focuses on the time-span of the two years that the group was active in the USA. Some of the themes of the research of these American years flowed quite naturally from a variety of subjects that were initiated at the University of Lausanne. Many novel themes were inspired by the environment of the NHMFL, by the expectations of the *National Sci-* *ence Foundation* and the State of Florida, both of whom generously supported the laboratory, and of course by the personalities and interests of the faculty and staff who joined the NHMFL. Many of these themes are likely to be continued as *Leitmotivs* in future years in Lausanne, Paris, and Tallahassee.

Equipment and Facilities

The National High Magnetic Field Laboratory (NHMFL) was established in Tallahassee, Florida's capital, by the *National Science Foundation.* The decision to establish the new laboratory in Florida, rather than continue funding the *Francis Bitter National Magnet Laboratory* associated with the Massachusetts Institute of Technology, has been the subject of much controversy in the American media. Construction was started in 1991, and the laboratory was officially inaugurated by the Vice-President of the United States in October 1994. The laboratory has undergone a tremendously rapid growth, since it now employs *ca.* 350 people. The NHMFL is operated jointly by the Florida State University (FSU) in Tallahassee, the Uni- versity of Florida (UF) in Gainesville, and the Los Alamos National Laboratory (LANL) in New Mexico. All three institutions host faculty and staff that have been appointed in the context of the establishment of the NHMFL, and all three locations have specialized laboratories, such as pulsed magnetic fields in Los Alamos and a magnetic resonance imaging laboratory in Gainesville, but the main facility is located in Tallahassee in a building of *ca.* 30 000 m². In contrast to similar magnet laboratories around the world (located in Cambridge, Massachusetts, in Grenoble, France, in Nijmegen, Netherlands, and in Tsukuba, Japan), which tend to focus on making the highest possible magnetic fields

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available to the community of condensed-matter physicists, an important part of the NHMFL is dedicated to magnetic resonance. Three complementary programs have been brought together in the Center of Interdisciplinary Magnetic Resonance (CIMAR): Electron Magnetic Resonance (EMR), Ion Cyclotron Resonance (ICR), and Nuclear Magnetic Resonance (NMR). The latter two are housed in a building of *ca.* 3000 m² designed specifically for this purpose, using mostly aluminum, wood and stainless steel to avoid magnetic materials. Since August 1994, the NMR program in Tallahassee has acquired an impressive array of instruments with proton Larmor frequencies of 850, 720, 600, 500, 2 x 400 and 2 x 300 MHz. Some of these are specifically configured for solid-state NMR (the 850, the 600, a 400, and a 300 MHz), one instrument is equipped for micro-imaging and diffusion studies (the 600 MHz which has a large 89 mm bore), while the remaining systems (the 720, the 500, a 400, and a 300 MHz) are primarily used for high-resolution solution-state NMR. The NMR program is eagerly expecting the completion of a 900 MHz high-resolution NMR system, which is currently under development in a joint effort of the NHMFL and Intermagnetics General Corporation (IGC). This project

is scheduled to be completed by 1998. In addition, NMR is routinely used to calibrate the fields of the powerful water-cooled resistive magnets that are designed and built in the laboratory. Such magnets, thanks to a design that has greatly evolved since *Francis Bitter*'s original ideas, now can achieve fields of up to 33 T, which corresponds to more than 1400 MHz for proton NMR. A hybrid magnet (part resistive, part superconducting) is under construction and expected to achieve at least 45 T. Magnetic resonance applications of these magnets are currently limited to wideline NMR, EMR, and ICR, but a resistive 25 T magnet designed to have an improved homogeneity (*ca.* 1 ppm) is under construction.

Personnel

The magnetic resonance effort is carried by a large number of faculty, staff, post-doctoral associates and graduate students from all three institutions, supplemented by a steady stream of visitors, some of whom merely come for a few days to give a seminar or use an instrument, while others stay for up to a year to enjoy the stimulating scientific environment and to carry out sophisticated projects. Vari-

ous means of communication have been established, ranging from a CIMAR committee that meets once a week to a broad CIMAR faculty meeting that meets *ca.* four times a year. A large number of 'multi-disciplinary magnetic resonance seminars' have been given by external speakers, staff and faculty, often at a rate of two lectures per week.

Much of the burden of setting up the structure of the laboratory was carried by senior colleagues who joined the laboratory in the early stages, such as *Jack Crow* (director of the NHMFL), *Neil Sullivan* (co-principal investigator), *Tim Cross* (acting director of the NMR program until 1994), *Alan Marshall* (director of the ICR program), *Louis-Claude Brunel* (head of the EMR program), and affiliated faculty such as *Russ Bowers, Ross Ellington, Tim Logan, Tim Moerland*, and many others. Several new faculty were recruited more recently (*Naresh Dalal, Steve Gibbs, Betty Gaffney*, and *Nancy Greenbaum*), while others moved their research groups from FSU's main campus to the NHMFL (*Peter Fajer*). A number of courageous people moved from Lausanne to help build up the NMR program: *Martina Schwager, Catherine Zwahlen, Sébastien Vincent, Riqiang Fu, Thomas Meersmann*, and *Damien Jeannerat* joined *Geoffrey Bodenhausen* from the beginning. Others were recruited in the USA to strengthen the NMR program: *Scott Smith, Chen Peng, Nagarajan Murali, Benoit Boulat, Philippe Pelupessy*, and *Brian Cutting*. The team was greatly enhanced by the active participation of long- and short-term visitors such as *Hervé Desvaux, Isabella Felli, Pierre Mutzenhardt, Nikolai Skrynnikov, Ago Samoson, Miriam Gochin*, and many others.

Research

The expectations that the *National Science Foundation* and the scientific community at large placed in the NMR program were commensurate with the investments in equipment and personnel. At least four criteria had to be met: *1*) Establish the NHMFL as a major center of research that enjoys national and international recognition (easier said than done!); *2*) Foster an atmosphere where the scientific community of FSU and UF would feel supported in their role as 'internal users' of the facility, thus allowing new dynamics to develop in teaching and research; *3*) Build up a community of 'external users', *i.e.*, scientists from across the country and overseas who come to Tallahassee to carry out experiments, to benefit
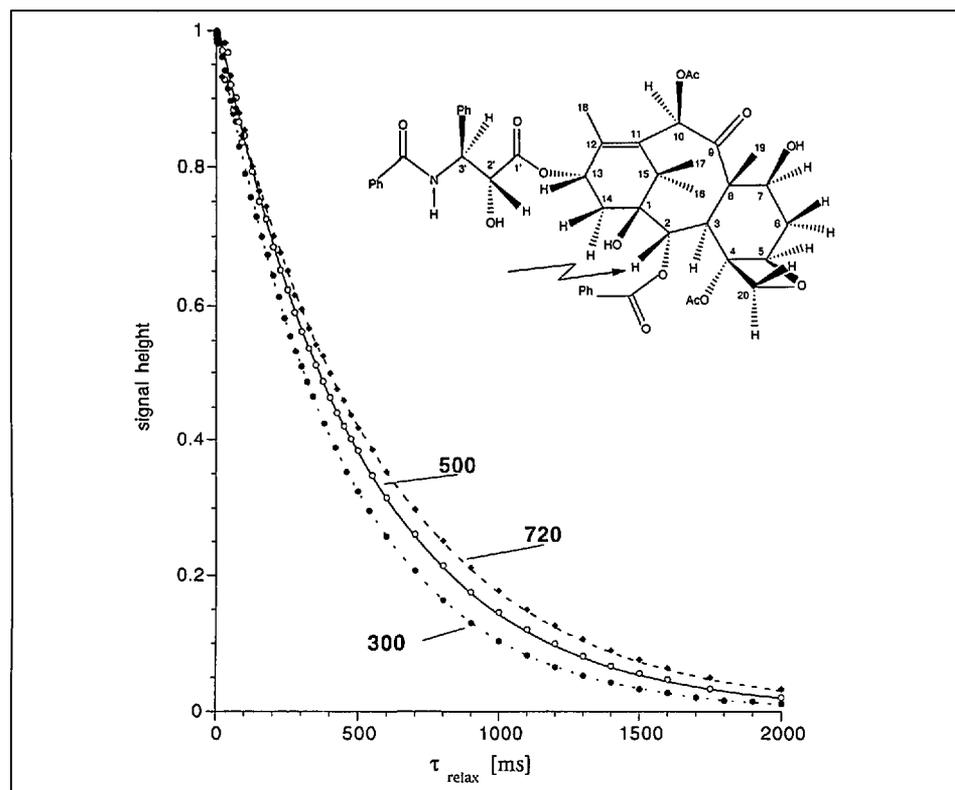

Fig. 1. *Field-dependence of transverse relaxation times* $T_{1\rho}$ *of a selected proton in Paclitaxel* (*'Taxol'*), *measured by spin-locking the in-phase magnetization with a selective RF field.* Experiments were carried out using *Bruker DMX 300, Varian Unity plus 500,* and *Varian Unity plus 720* spectrometers. The $T_{1\rho}$ values were found to be 442, 509, and 574 ms, corresponding to natural linewidths of 0.72, 0.63, and 0.55 Hz. Reproduced from [18] with permission of Academic Press.

from the exceptional instrumentation and stimulating intellectual environment of the NHMFL. Interested scientists from Switzerland and elsewhere should not hesitate to send inquiries to the coordinator of the CIMAR program, *Jo Ann Palmer* (palmerj@magnet.fsu.edu).

The references below [1–25], listed in chronological order, give an overview of the work that originated with the NMR program of the NHMFL in the first two-year period. We shall not attempt to cover the considerable amount of research carried out by internal and external users and affiliated faculty. We have tried to favor the emergence of research projects that would benefit specifically from the availability of very high fields. The best-known advantages, as discussed extensively in the abundant literature on this subject, are: improved sensitivity, increased chemical shift dispersion, enhanced resolution, more favorable relaxation properties, and greater sensitivity to chemical exchange and other dynamic processes. Unusual oriented phases may occur in high fields due to molecular alignment induced by an anisotropic magnetic susceptibility. For solid-state NMR, one should mention that second-order quadrupolar interactions of odd-integer spins such as ^{17}O, ^{23}Na, ^{27}Al are attenuated in inverse proportion to the Larmor frequency.

Beyond these well-known reasons for using high fields, we have identified some advantages that do not appear to be widely recognized [18]: *1*) The transverse relaxation times T_2 may increase with field strength B_0, thus leading to line-narrowing and enhanced peak heights, particularly for molecules of medium size such as natural products and oligosaccharides; *2*) Because of the increased dispersion of chemical shifts at high fields, soft pulses need not be so selective as in low fields, thus allowing the use of shorter pulses, so that losses due to relaxation during these pulses are greatly reduced; *3*) Cross-correlation effects due to correlated fluctuations of anisotropic chemical shifts and dipole-dipole interactions can be measured by selective spin-locking, in order to gain insight into the relative orientations of chemical shift and dipolar tensors. At high fields, selective spin-locking is less prone to artifacts because the amplitude of the RF field can be increased to achieve efficient spin-locking of all components of a chosen multiplet, while the risk of disturbing neighboring resonances is reduced.

In order to study transverse relaxation and its non-trivial field dependence, we have developed a number of methods to
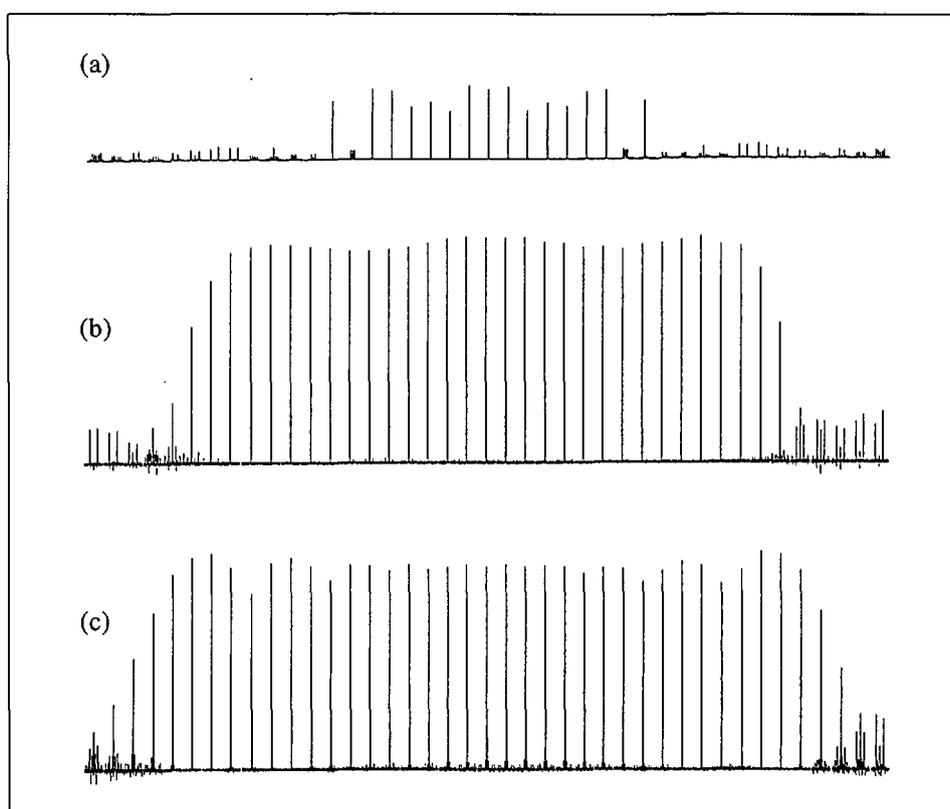

Fig. 2. *Comparison of decoupling bandwidths obtained with different methods.* Proton-decoupled ^{13}C spectra of formic acid (HCOOH) were recorded as a function of proton offset, stepped from –20 to 20 kHz. *a*) GARP decoupling with a constant RF amplitude of 2.7 kHz. The linewidth was 1.8 Hz in the center of the range, after exponential line broadening of 1.5 Hz, which was necessary to mask the residual splitting. *b*) WURST decoupling with a peak amplitude of 3.4 kHz. *c*) CHIRP-95 decoupling with a constant RF amplitude of 2.7 kHz. The linewidths in (*b*,*c*) were 0.6 Hz after exponential line broadening of 0.3 Hz. All spectra were recorded with a *Bruker DMX 300* spectrometer (unpublished work).

measure the relaxation rates of in-phase and antiphase components of the magnetization [7]. *Fig. 1* gives some examples of the favorable field-dependence of proton relaxation in Paclitaxel ('Taxol'), an anti-tumor agent which has been synthesized by *R.A. Holton* and coworkers in the Chemistry department of FSU. For medium-sized molecules such as Paclitaxel, the transverse relaxation times ('T_2') increase with the magnetic field, which implies that the lines become narrower, leading to a gain in both resolution and sensitivity. Further studies of transverse relaxation have lead to the discovery of a new type of echo modulation that is induced by relaxation [21].

Some aspects of relaxation tend to become simplified at high fields, while other aspects become more complicated. Until the advent of very high fields, nobody paid much attention to the chemical-shift anisotropy (CSA) of protons as a possible relaxation mechanism. Even at 800 MHz, CSA on itself is not of much concern for proton NMR, but cross-correlation of the fluctuations of CSA and dipole-dipole interactions may lead to surprising effects, such as asymmetric multiplets and multi-exponential relaxation. A detailed study

of such effects that was initially undertaken in Lausanne was continued in Tallahassee [12].

High fields present new technical challenges for the use of radio-frequency (RF) pulses, since the width of the spectra usually increases in proportion to the static field. In favorable cases, when relaxation is not too fast, broadband excitation can be achieved very effectively by sweeping rapidly through the spectrum with 'chirp' pulses. These ideas were extended to systems with quadrupolar splittings in the solid state, where modulated pulses can be used both to excite and refocus transverse magnetization [20].

In solution-state NMR at very high fields, broadband decoupling represents a strategic challenge. Not only does one need to decouple ^1H nuclei when observing ^{15}N and ^{13}C in routine NMR, but one also requires ^{15}N and ^{13}C decoupling during ^1H observation in isotopically-enriched proteins and nucleic acids. The range of chemical shifts of ^{13}C spectra is far greater than for ^1H spectra. It is not possible simply to increase the RF power without excessive heating of the sample. Major breakthroughs were achieved simultaneously and independently with the 'CHIRP-95'

decoupling scheme developed at the NH-MFL [11][13][16] and the 'WURST' method developed by *Freeman* and *Kupče* in Cambridge [26], both of which require much less power than the usual 'GARP' method [27]. *Fig. 2* shows a comparison of the bandwidths that can be achieved with various decoupling techniques.

In solid-state NMR, efficient decoupling represents an even greater challenge, particularly if one wishes to decouple nuclei such ^2D that have large quadrupolar interactions. In liquid crystalline phases, we have made significant progress in observing protons while decoupling deuterons, by using phase-alternated irradiation schemes [6]. True polycrystalline solids, however, remain a formidable challenge because they feature broad ranges of quadrupolar splittings.

At high fields, magic angle spinning (MAS) must be carried out with very high speeds (at least 15 kHz at 600 MHz) to overcome the increasing breadths of the powder patterns due to the anisotropies of the chemical-shift tensors. Unfortunately,

high spinning speeds tend to interfere with the efficiency of cross-polarization, and thus may lead to great losses in signal amplitude. We have found novel means to improve the efficiency of cross-polarization in spite of high spinning speeds, by modulating the RF carrier frequency adiabatically during spin locking [24]. These methods may be regarded as extensions of a scheme proposed by *Kolbert* and *Bielecki* [30]. *Fig. 3* illustrates how the amplitudes of ^{13}C signals in a polycrystalline powder sample of alanine spinning at 15 kHz in a 600 MHz spectrometer can be boosted and made more uniform for all ^{13}C sites by using frequency-modulation during cross-polarization. In contrast to the conventional scheme, where the signals strongly depend on the amplitudes of the two RF fields, the new scheme makes the accurate adjustment of the RF amplitudes to match the so-called *Hartmann-Hahn* condition essentially superfluous.

Cross-polarization can also be very useful in solution-state NMR to explore networks of scalar-coupled spins, particu-

larly if very weak RF pulses are employed. The efficiency of such experiments tends to suffer from 'passive' couplings to other nuclei. Selective decoupling in triple-resonance experiments [2] makes it possible to achieve a dramatic enhancement of the efficiency of cross-polarization. Techniques involving multiple-resonance (*e.g.* with three or more discrete frequencies applied within one and the same spectrum) set very high demands on the linearity of radio-frequency (RF) amplifiers. We have developed a simple test that might be adopted by instrument manufacturers as a means of establishing a health certificate of RF circuits [1].

One of the central themes of the NMR program in Tallahassee has been the determination of scalar coupling constants in solution-state NMR. This is also a subject of potential interest to instrument manufacturers: ideally, the spectrometers of the 21st century should be able to provide a fully automated interpretation of NMR spectra. The combination of new multiple-resonance experiments [15] with computer-supported data analysis based on convolution and deconvolution of two-dimensional multiplets [10][14][17][22] allows one to extract a great deal of reliable information from multiplet patterns that may appear exceedingly complex to the human eye. When used in combination with $^1H/^{13}C$ correlation spectroscopy, it is possible to generate proposals for the structures of unknown natural products.

Strong coupling effects are often considered to be an old-fashioned subject, since high fields are supposed to transform all strongly-coupled '*AB*' systems into well-behaved first-order '*AX*' systems. We have investigated a rather pernicious manifestation of strong coupling, which affects all experiments involving selective pulses. Unlike the behavior of magnetization under nonselective 'hard' pulses, individual transitions of a strongly-coupled system undergo different nutation angles in the course of a selective pulse [23]. It turns out that this undesirable effect is only slightly attenuated at the highest fields that are currently available.

Another central theme of the NMR program in Tallahassee has been the study of cross-relaxation (*Overhauser* effects), and, more specifically, the suppression of so-called spin diffusion effects, which are the chief limitation on the accuracy of structural studies of molecules in solution. If one could enhance the accuracy of the measurement of proton-proton *Overhauser* effects, this would improve all structural studies, not only for large proteins and nucleic acids [5], but also for smaller oli-
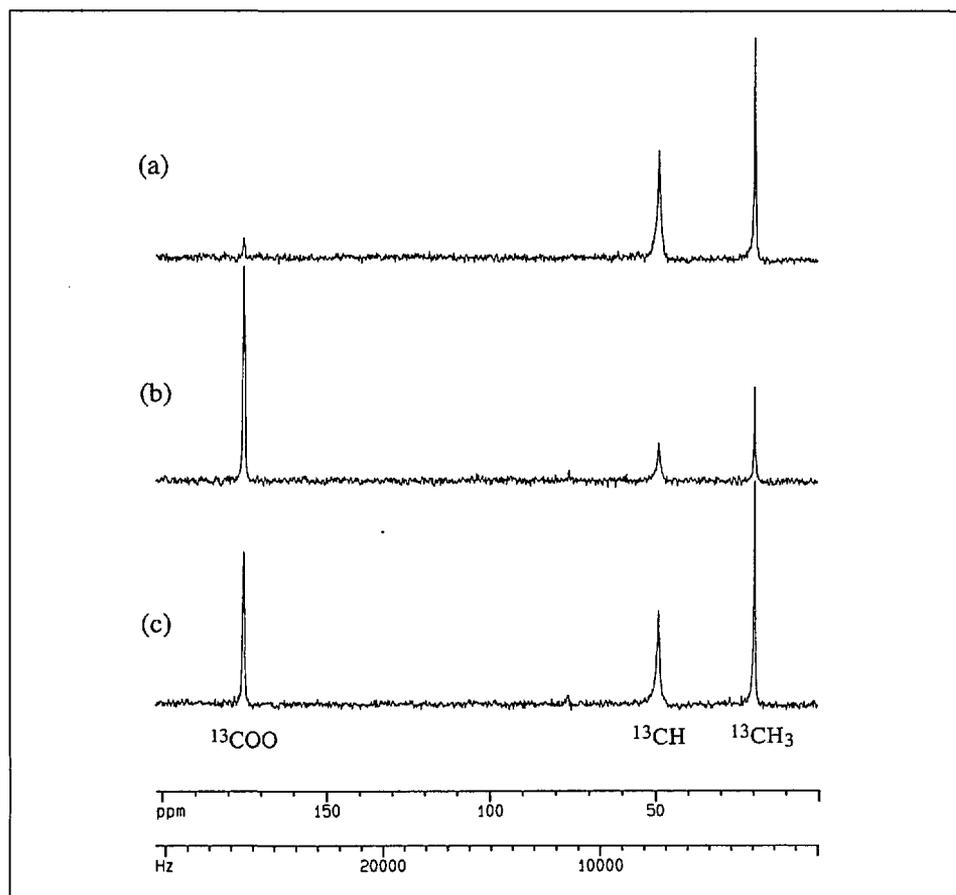

Fig. 3. *^{13}C Spectra of a polycrystalline sample of DL-alanine spinning at the magic angle at 15 kHz,* recorded with a Bruker 600 MHz spectrometer equipped with a 14 T 89 mm wide-bore magnet manufactured by Magnex (150 Hz/ppm for ^{13}C). *a*) Conventional CW spin-locking of both proton and ^{13}C spins, where cross-polarization is reasonably effective for ^{13}CH and $^{13}CH_3$ but not for ^{13}COO, because the *Hartmann-Hahn* condition cannot be matched for all three sites. *b*) Conventional spin-locking where the *Hartmann-Hahn* condition has been adjusted for ^{13}COO, but where cross-polarization largely fails for ^{13}CH and $^{13}CH_3$. *c*) The carrier frequency of the carbon spin-lock pulse was modulated adiabatically while a CW pulse was applied to the proton spins. This new scheme allows all three resonances to be polarized uniformly (unpublished work).

gosaccharides and peptides [3]. Several new methods were derived from the principle of 'QUIET-NOESY' (which stands for Quenching of Undesirable Indirect External Trouble) that was initially developed in Lausanne, thanks to a fruitful cooperation with *Malcolm Levitt* and *Lorenzo Di Bari* of the University of Stockholm [28]. We attempted to determine accurate cross-relaxation rates in a DNA fragment ('*Dickerson*'s dodecamer') by combining extensive one-dimensional experiments with a careful analysis of competing relaxation effects [8]. We also developed two-dimensional versions of 'QUIET-NOESY' using selective pulses [9] which yield cross-relaxation maps with frequency windows where, within certain approximations, all cross-peaks are free from spin-diffusion effects. These methods were applied to a study of the cofactor nicotinamide adenine dinucleotide (NAD+) in rapid exchange between a flexible conformation in free solution and a more rigid conformation when it resides in the binding pocket of the enzyme lactate dehydrogenase [25]. By suppressing spin diffusion, it was possible to eliminate indirect cross-relaxation pathways where the magnetization travels between two protons belonging to the NAD+ cofactor *via* protons that are attached to the binding pocket of the enzyme, thus providing an undistorted picture of the conformation of the cofactor in the binding site.

In combination with so-called bilinear rotation sandwiches, which allow one to invert the longitudinal magnetization of amide protons that have scalar couplings J_{NH} to ^{15}N nuclei, we have designed a method that makes it possible to measure *Overhauser* effects between amide protons in proteins, while suppressing all *Overhauser* effects involving aromatic or aliphatic protons [19]. These methods are closely related to schemes proposed by *Macura* and coworkers [29]. *Fig. 4* shows a comparison of NOESY maps of an ^{15}N-enriched protein obtained with and without suppression of spin diffusion. Provided suitable precautions are taken to account for relaxation-induced losses during the pulse sequence, such maps should make it possible to measure long-distance *Overhauser* effects between amide protons separated by as much as 5 Å without contamination by spin diffusion.

A generalization of such quenching techniques to systems in chemical exchange allowed us to simplify networks with multiple exchanging sites in an inorganic complex [4]. The exchange rates involving *cis*- and *trans*-ZrCl$_4$L$_2$ with excess ligand L = (CH$_3$O)$_3$PO in solution

could be measured very accurately by effectively excluding the effect of competing reactions on the migration of longitudinal magnetization.

Many investigations are still under way at the time of writing this overview, and are likely to become the subject of further
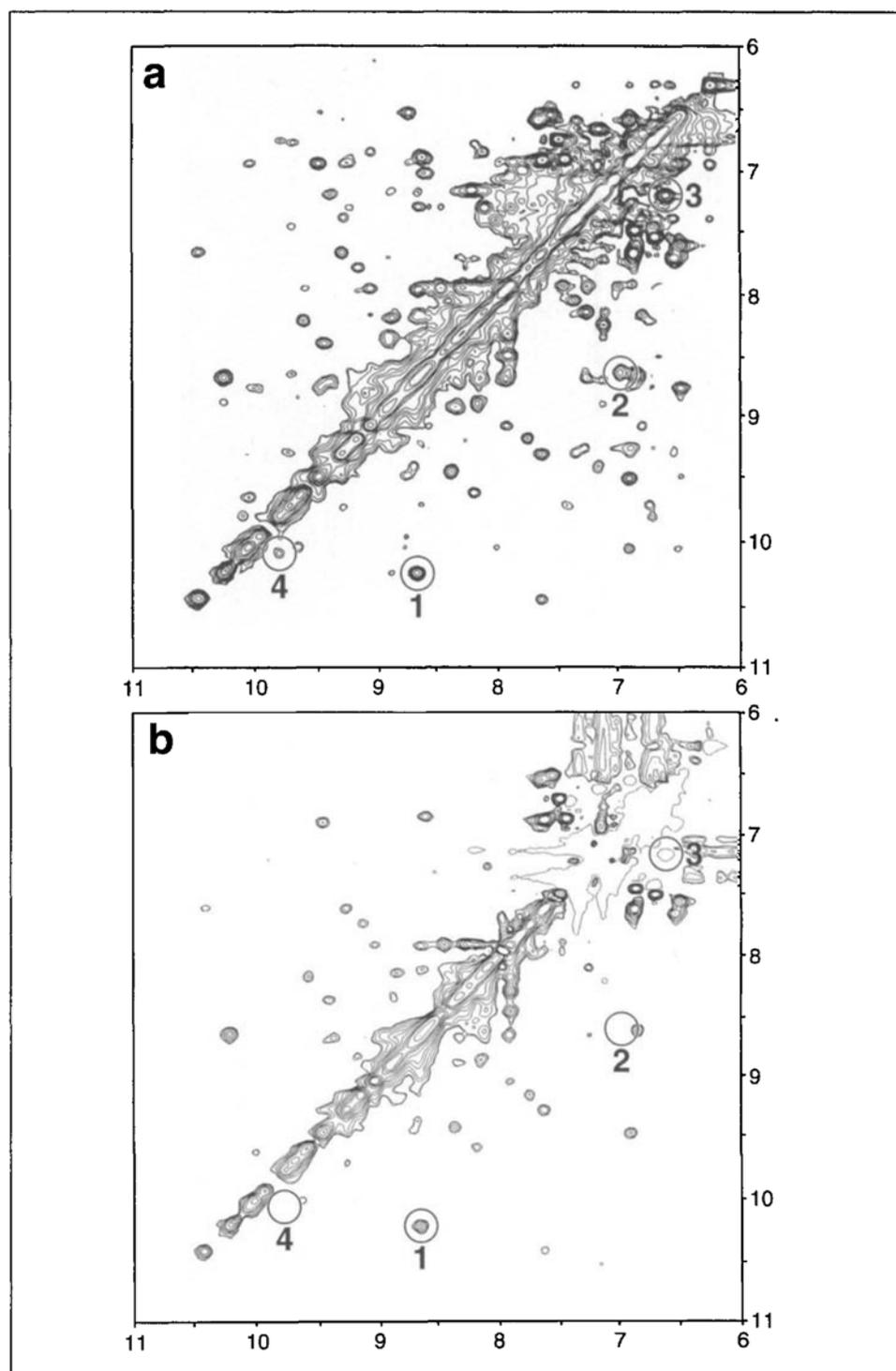

Fig. 4. *Comparison of NOESY maps of the ^{15}N-enriched form of the C22A mutant of the protein FKBP obtained with and without suppression of spin diffusion. a*) Amide region of a conventional NOESY spectrum. *b*) Corresponding region of a QUIET spectrum. Both were recorded with a *Bruker DMX 300* spectrometer. Four cross-peaks are emphasized for illustration, corresponding to different distances: *1*) H^N(R13) – H^N(T14) with $r = 2.06$ Å (retained, both partners being amide protons); *2*) H^N(F36) – H$^\delta$(F36) ($r = 1.77$ Å, suppressed because one partner is not an amide proton); *3*) H$^\delta$(Y82) – H$^\epsilon$(Y82) ($r = 2.44$ Å, retained, neither partners being amide protons); *4*) H^N(K73) – H^N(L74) ($r = 3.94$ Å, retained, both partners being amide protons). Reproduced from [19] with permission of the American Chemical Society.

publications in the near future. For example, various experiments have been explored that use NMR of ^{129}Xe ($I = 1/2$) and ^{131}Xe ($I = 3/2$). In the former case, the signals can be greatly enhanced by hyperpolarization induced by optical pumping [31][32], while in the latter case we have

Fig. 5. *Members of the NMR group near the 720 MHz magnet of the National High Magnetic Field Laboratory in Tallahassee, Florida.* Back row: *Scott Smith, Sébastien Vincent, Bill Moulton, Steve Gibbs, Geoffrey Bodenhausen, Jo Ann Palmer, Brian Cutting, Johannes Huth, Philippe Pelupessy, Hervé Desvaux, Benoit Boulat, Nagarajan Murali.* Front row: *Damien Jeannerat, Ashley Blue, Catherine Zwahlen, Charlotte Vincent, Isabella Felli, Riqiang Fu, Thomas Meersmann,* and *Chen Peng*

explored the role of multiexponential relaxation with multiple-quantum filters. *Hervé Desvaux* has worked extensively on new methods to study dipolar cross-correlations and anomalous coherence transfer processes in a complex of a DNA fragment with a paramagnetic drug. *Isabella Felli*, in collaboration with *Hervé Desvaux*, has developed new tools to study the dynamics of N–H fragments in paramagnetic proteins. *Pierre Mutzenhardt* is exploring new methods designed to quench spin diffusion in *Overhauser* measurements. *Nagarajan Murali* is working on the theory and experimental implications of relaxation in $^{13}C, ^2H$ systems encountered in isotopically enriched biological macromolecules [33]. *Benoit Boulat* is focusing on exchanging systems of biological interest [34], developing a new formalism to describe NMR phenomena [35], and exploring new aspects of solid-state NMR. In 'cyberspace', *Scott Smith* has provided generous support to a rapidly expanding community of users of the 'GAMMA' simulation platform [36], with applications ranging from the effects of frequency-modulation in correlation spectroscopy to the interference of relaxation effects in chemical exchange studies, and from simple grapefruit diagrams to sophisticated calculations in Liouville space. Potential users are vividly encouraged to visit the World Wide Web site of the NHMFL (HTTP://gamma.magnet.fsu.edu.)

· A cursory overview cannot possibly do justice to all the efforts that have gone into making these two years so successful and rewarding. Building up a large laboratory such as the NMR program of the NHMFL is only possible with a great deal of good-will, not only from the scientists, but also from the technical and administrative staff, including *Davis Prime, Janet Cox, Josette Mobley*, and many others, whose contributions can hardly be acknowledged in an adequate manner.

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