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Frequency-domain Hadamard spectroscopy

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Abstract

A new technique is proposed for multichannel excitation and detection of NMR signals in the frequency domain, an alternative to the widely used pulse-excited Fourier transform method. An extensive array of N radiofrequency irradiation channels covers the spectrum of interest. A selective radiofrequency pulse sequence is applied to each channel, generating a steady-state NMR response acquired one-point-at-a-time in the intervals between pulses. The excitation pattern is repeated N times, phase-encoded according to a Hadamard matrix, and the corresponding N composite responses are decoded by reference to the same matrix. This multiplex technique offers the same sensitivity advantage as conventional Fourier transform spectroscopy. The irradiation pattern may be tailored to concentrate on interesting spectral regions, to facilitate homonuclear double resonance, or to avoid exciting strong solvent peaks. As no free induction decay is involved, the new method avoids problems of pulse breakthrough or lineshape distortion by premature termination of the time-domain signal.

Keywords: Frequency-domain spectroscopy; Multichannel excitation; Hadamard spectroscopy; Multiplex advantage; Solvent peak suppression

1. Introduction

The frequency domain is the natural mode for observing NMR spectra, and the spectroscopist always visualizes high-resolution spectra in this dimension. Time-domain acquisition followed by Fourier transformation is essentially a roundabout process for achieving the same end. For many years the continuous-wave slow-passage method was universally accepted, until it was seen to be inefficient from the point of view of sensitivity. To counter this deficiency, Anderson [1] set out to explore the possibility of a multiplex spectrometer which employed a regular array of "channels"—each defined by a stationary excitation frequency and a matching synchronous detector. In principle, this provides a multiplex advantage [2] that improves the signal-to-noise ratio by a factor of $\sqrt{N}$, where N is the number of independent channels. Now, four decades later, Anderson's mechanical devices for generating a regular "comb" of closely spaced excitation frequencies and for demodulating the resultant signals may seem a little cumbersome, but the idea nevertheless served as the spur to the invention of the pulse-excited Fourier transform method [3] which revolutionized the practice of high-resolution NMR. The Anderson "Prayer Wheel" was quietly abandoned and consigned to the Smithsonian Institution in Washington, DC.

The extraordinary success of the Fourier transform technique has left very few viable alternatives for recording NMR spectra of high information content. The inherently poor sensitivity of magnetic resonance has been largely redressed by the orders of magnitude improvement afforded by pulse excitation and Fourier transformation. The few remaining shortcomings are generally accepted as inevitable; the goose is still laying the golden eggs. The main practical disadvantage is the serious dynamic range problem associated with aqueous solutions, a widespread limitation that has inspired the invention of an entire armoury of techniques for solvent peak suppression. Furthermore, wide-band excitation with a hard radiofrequency pulse imposes certain restrictions on the way NMR spectra are recorded by the conventional Fourier transform method. It is difficult to

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focus attention on particularly interesting regions of the spectrum while largely neglecting the rest of the frequency domain. Finally, there are some minor difficulties associated with Fourier transformation of a distorted free induction decay—the result of pulse breakthrough, acoustic ringing, or premature termination of the time-domain signal.

Because of these shortcomings there have been some attempts to find alternatives to the Fourier transformation stage, for example, least-squares fitting of the time-domain signal to a set of decaying sinusoids, or maximum entropy reconstruction. This paper proposes a new frequency-domain approach that enjoys the same multiplex advantage as conventional Fourier transform methods, and which offers certain practical advantages. This is frequency-domain Hadamard spectroscopy. The basic idea is related to a method of optical multiplexing suggested by Golay [4] where incident radiation from an infrared source is passed through a set of masks that have open or closed slits arrayed according to a suitable binary sequence $(1,0,0,1,1,1,\ldots)$ and where, after interaction with the sample, the exiting radiation passes through a related set of binary masks. In this way the conventional single-channel infrared spectrometer is converted into a multichannel device with a corresponding improvement in sensitivity.

The concept may be illustrated by analogy with the task of weighing several objects on a balance [5]. Suppose there are four different objects of weights A, B, C, and D. The "pedestrian" mode measures each one separately in four different weighings and gives the results directly. The Hadamard multiplex scheme also makes four weighings, but with all the objects on the balance at the same time, encoding the measurements according to whether the unknown weights are placed on the left-hand or right-hand pan (where the standard weights are placed). If the former is written +A and the latter −A, the four successive weighings (W) may be expressed as four equations:

$$W_1 = +\mathrm{A} + \mathrm{B} + \mathrm{C} + \mathrm{D}$$
$$W_2 = +\mathrm{A} + \mathrm{B} - \mathrm{C} - \mathrm{D}$$
$$W_3 = +\mathrm{A} - \mathrm{B} + \mathrm{C} - \mathrm{D}$$
$$W_4 = +\mathrm{A} - \mathrm{B} - \mathrm{C} + \mathrm{D}$$

This can be represented as a 4 by 4 Hadamard matrix:

$$\begin{matrix} + & + & + & + \\ + & + & - & - \\ + & - & + & - \\ + & - & - & + \end{matrix}$$

Recovery of the individual weights involves combining the four measurements according to the appropriate columns of this matrix; for example, $W_1 + W_2 - W_3 - W_4$ gives four times the weight B. The terms for A, C, and D cancel. If it can be assumed that weighing errors are random with mean value zero and independent of the loading of the balance, they increase only as the square root of the number of weighings (twofold in this case). Consequently the accuracy is doubled. For the general case of N objects, the improvement is $\sqrt{N}$, a considerable advantage when N is large.

2. Hadamard spectroscopy

The basic idea is to operate exclusively in the frequency domain—both excitation and signal acquisition. The excitation is stationary—there is no field or frequency sweep. The irradiation comprises an array of separate radiofrequency channels covering the entire NMR spectrum or, if desired, selected regions of it. A schematic diagram of the procedure is set out in Fig. 1.

2.1. Frequency-domain excitation

A single monochromatic radiofrequency, suitable for excitation of a single channel, is generated by a regular sequence of short pulses, similar to a DANTE sequence [6]. The selectivity in the frequency domain is set by the overall duration of the sequence, typically of the order of 1 s. The effective frequency is offset from the carrier by incrementing (or decrementing) the radiofrequency phase at an appropriate linear rate along the sequence [7–10]. An array consisting of N such monochromatic frequencies is generated by combining N pulse sequences with the same repetition rate but different rates of phase ramping. This is achieved by vector addition of the individual pulses at each time segment [9] thus generating "polychromatic" irradiation that feeds the appropriate radiofrequencies to all N channels.

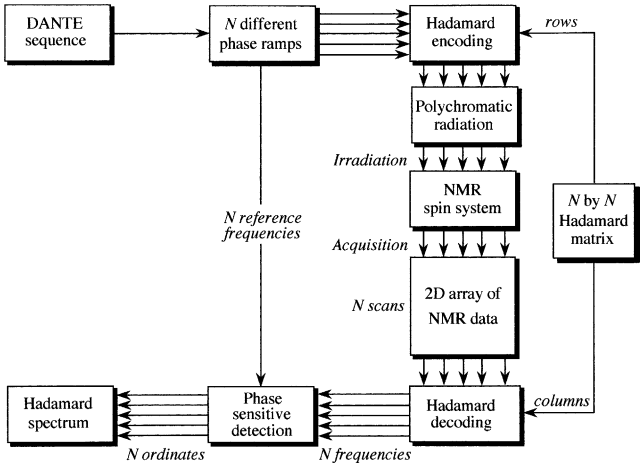

Fig. 1. Schematic diagram of frequency-domain Hadamard spectroscopy (see text).

The key to the Hadamard scheme is a binary encoding procedure, roughly similar to scrambling and then unscrambling a telephone message. The irradiation scheme is encoded according to a Hadamard matrix of dimension N by N. This entails setting the phase (0° or 180°) of the irradiation in each channel according to the signs in the appropriate row of the Hadamard matrix, changing the code for each new row. In practice, encoding is carried out before the individual DANTE sequences are combined into polychromatic radiation (Fig. 1).

For the purpose of illustration consider the very simple case of $N = 8$ and a very narrow spectral region spanning only 8 Hz. A suitable multiplex irradiation scheme might comprise eight separate radiofrequency components (eight channels) regularly spaced 1 Hz apart. Typically the selective radiofrequency pulses would have a duration of 1 s and an overall radiofrequency pulse flip angle of 10°. The pulse flip angle is adjusted to avoid saturation. The evolution of nuclear spins in a given channel can be considered in a reference frame unique to that channel, one that rotates about the Z axis at the appropriate irradiation frequency F. After a short rise time, the spin system settles into a steady state corresponding to a dynamic balance between weak pulse excitation and spin–lattice relaxation. This is virtually equivalent to continuous-wave excitation.

The excitation operation must then be repeated eight times; for want of a better term these will be called "scans". A new binary code is employed for each new scan.

Channel:	1	2	3	4	5	6	7	8
Scan (1)	+	+	+	+	+	+	+	+
Scan (2)	+	+	+	+	−	−	−	−
Scan (3)	+	+	−	−	+	+	−	−
Scan (4)	+	+	−	−	−	−	+	+
Scan (5)	+	−	+	−	+	−	+	−
Scan (6)	+	−	+	−	−	+	−	+
Scan (7)	+	−	−	+	+	−	−	+
Scan (8)	+	−	−	+	−	+	+	−

For example, during the second scan, the first four channels are irradiated with the same radiofrequency phase whereas in the last four channels the phase is inverted.

Now consider a more realistic experimental test case employing a 512 by 512 Hadamard matrix to examine part of the 500 MHz proton spectrum of a sample of 2-ethyl-1-indanone. Each polychromatic pulse excites an array of 512 frequency components, regularly spaced from +255.5 to −255.5 Hz with respect to the radiofrequency carrier. (This kind of symmetry in the frequency domain cancels the imaginary parts, so the polychromatic pulse phases are either 0° or 180°, but this is not essential to the method.) The experiment requires a total of 512 scans, each with a fresh coding pattern. Fig. 2a plots the time dependence of the amplitudes of the polychromatic pulses used in a typical scan, in this case scan 334.

2.2. Frequency-domain acquisition

The NMR signal is acquired one data point at a time in the intervals between the radiofrequency pulses [11], a total of 512 data points. The duty cycle of the pulse sequence is low, typically 5%, to allow the receiver gating to be open for most of the interpulse interval, thus acquiring the signal with a negligible loss of sensitivity. At this stage the response is a composite signal comprising all NMR frequencies within the excitation band. Fig. 2b shows the time course of the NMR

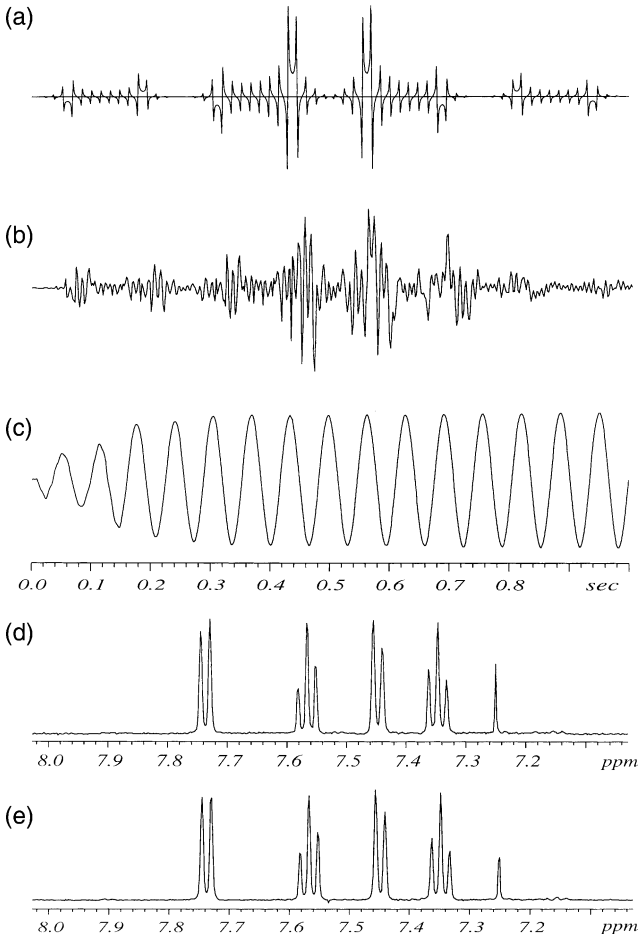

Fig. 2. Illustration of Hadamard spectroscopy by reference to part of the 500 MHz proton spectrum of 2-ethyl-1-indanone. (a) A typical encoded sequence of polychromatic pulses used to provide simultaneous irradiation in 512 radiofrequency channels. (b) The corresponding NMR responses acquired one point at a time in the intervals between the polychromatic pulses. A total of 512 records like this are acquired, forming the rows of a 512 by 512 data array. (c) The time course of the decoded signal from one particular frequency channel. After phase-sensitive detection this provides a single ordinate of the Hadamard spectrum. (d) The Hadamard spectrum obtained by reading out all 512 ordinates in sequence. (e) The conventional Fourier transform spectrum of the same region for comparison.

response during the 334th scan of the indanone spectrum, corresponding to the irradiation pattern illustrated in Fig. 2a. This "interferogram" has very little in common with a conventional free induction decay, not least because the various NMR frequency components carry different signs. When all 512 scans are completed, the results fill a 512 by 512 data array made up of rows representing the composite NMR responses as a function of time, repeated for each new scan (Fig. 1). This data array is now decoded column by column.

The decoding stage reads one of the columns of the NMR data array and adds or subtracts the responses from all 512 scans according to the signs in the corresponding column of the Hadamard matrix. This code exactly matches the one employed in the initial encoding stage and has the effect of combining the NMR data in a constructive manner, thus extracting the signal component carried at that particular frequency. Fig. 2c shows one such decoded response corresponding to the frequency of the central peak of the aromatic triplet at 7.57 ppm in the indanone spectrum. It is a clean monochromatic signal at the frequency F of the selective pulse used to excite that particular channel. Contributions from all other responses are rejected because they are modulated by different codes. The envelope follows a rising curve and then settles down to a constant level after about 0.2 s as the spin system reaches a steady state. Thereafter the signal does not decay with time; in principle it could be monitored for an arbitrarily long period, thereby increasing sensitivity. When this process has been completed for all N columns, a new two-dimensional data array can be constructed in which the rows now represent the N frequency channels and each column contains an oscillatory signal at the appropriate frequency F.

The Hadamard decoding process collects the total NMR signal in each channel but makes no distinction about the *phase* of that signal. Consequently nearby "off-resonance" channels pick up appreciable dispersion-mode signal components from the skirts of the NMR line, with the result that the lineshapes have long tails, as in an absolute-value display. The remedy is to employ the equivalent of phase-sensitive detection. Since each channel is associated with its characteristic excitation frequency F, this is used as the reference frequency for phase-sensitive detection. This involves multiplication of the NMR response by a sinewave of frequency F, followed by integration—equivalent to a single-point Fourier analysis. The phase of this reference signal is adjusted for pure absorption and the long dispersion tails consequently disappear.

Once all 512 frequency channels have been processed, each one is represented by a single ordinate, and when these are read out in sequence they form the expected Hadamard spectrum. Fig. 2d shows the partial Hadamard spectrum of indanone recorded in this manner; it compares well with the conventional Fourier transform spectrum of the same sample, illustrated in Fig. 2e. Note that in the Hadamard experiment no Fourier transformation is involved at any stage.

The soft-pulse excitation behaves in essentially the same way as the stationary continuous-wave irradiation scheme envisioned by Anderson [1] and the acquisition stage corresponds to his proposal for an array of separate phase-sensitive detectors. Because all possible signal components are acquired in each scan, and because random noise increases only as the square root of the number of scans, there is a theoretical improvement in sensitivity equivalent to the well-known multiplex advantage enjoyed by Fourier transform spectroscopy.

3. Operation in the frequency domain

Hadamard spectroscopy presents no serious challenge to conventional Fourier transform methodology for routine applications over a wide spectral width. It only comes into its own in situations where the irradiation envelope needs to be "tailored" or restricted in some manner. Because the Hadamard matrix is square, a frequency-domain experiment with N frequency channels requires N successive scans, and unless these are all completed, the decoding process breaks down. Except for situations where the NMR signal is particularly weak, requiring extensive multiscan averaging, this is an important limitation.

On the other hand, there are several applications where tailored excitation offers significant advantages. Hadamard spectroscopy does not require the excitation frequencies to be arrayed uniformly across the spectrum—they can be concentrated in the interesting regions while the remainder of the spectrum is examined with sparse sampling, or even overlooked entirely. For this purpose it might be useful to acquire an initial low-definition "search spectrum" with a small number of widely spaced channels in order to identify the signal-bearing regions. Furthermore, because the irradiation intensities need not have a uniform envelope, different regions of the spectrum can be scaled differently. For example, carbon-13 sidebands in a proton spectrum can be favored at the expense of the centerband. This kind of flexibility is not feasible in traditional pulse-excited Fourier transform spectroscopy.

Tailored excitation methods have hitherto been quite limited. Tomlinson and Hill [12] reported a scheme based on stochastic irradiation with pulses modulated according to the Fourier transform of the desired frequency-domain excitation pattern, a somewhat unreliable approximation. More recently, band-selective radiofrequency pulses [13] have been designed specifically for "zooming in" on one particular region of interest. Frequency-domain Hadamard spectroscopy goes

much further. It naturally lends itself to "designer" profiles with *arbitrary* excitation envelopes. It is a straightforward matter to tailor the excitation profile to pick out a subspectrum from a single component of a mixture; however complex that subspectrum might be. The desired subspectrum might be selected by a technique known as "template excitation" [14] where the irradiation pattern is derived directly from the NMR spectrum of the chosen component. This can be useful in applications where the selected subspectrum must be monitored as a function of time while the experimental conditions are varied. The Hadamard method may also prove useful in experiments where several different samples are examined in the spectrometer at the same time, to improve throughput.

Hadamard spectroscopy with sparse frequency-domain sampling may be used as a fast and direct means of data reduction, where the NMR spectrum is presented in the form of a low-definition histogram. For example, a proton spectrum might be divided into 0.1 ppm segments, displaying only the integral for each segment, with low vertical dynamic range, perhaps a single bit. Such a drastic reduction in information content could be a distinct advantage when creating or consulting a large reference library of NMR spectra, as in combinatorial chemistry, where too much detail is counter-productive. The process of matching an unknown spectrum to items in the library is more reliable when the unknown and reference "fingerprints" are in the same simple format and where slight relative shifts are not important. Simplifying the excitation pattern in this manner cuts down the overall size of the Hadamard matrix and speeds up the experiment.

Operation in the frequency domain has another crucial advantage—it can be made far less susceptible to the dynamic range problem. In conventional Fourier spectroscopy, an intense solvent signal can introduce digitization noise by interfering with the analog-to-digital conversion of the remaining signals. In Hadamard spectroscopy irradiation in the channels spanning the solvent response can be avoided simply by setting the appropriate pulse flip angles to zero. Any residual solvent-induced artifacts can be removed by nulling the same channels during the processing stage. One rotten apple does not spoil the whole barrel. In a similar manner, homonuclear double resonance experiments (for decoupling, chemical exchange, or cross-relaxation studies) can be implemented with strong irradiation in one frequency band, with Hadamard excitation and detection for the remainder of the spectrum, thus avoiding the response from the strongly irradiated spins.

All frequency-domain multiplex schemes are potentially susceptible to interference between closely spaced radiofrequency fields. This is normally analyzed in terms of the generalized Bloch–Siegert effect [15], where an adjacent off-resonance radiofrequency field induces a small shift of the frequency of the response in question. To a good approximation the shift is proportional to the square of the intensity of the offending radiofrequency field and inversely proportional to its offset. It is always in a direction *away* from that radiofrequency field. For a regularly spaced array of channels in the Hadamard experiment, the Bloch–Siegert shift from adjacent channels on the left and right would be expected to be equal and opposite and thus cancel. Uncompensated shifts should only occur at the extreme edges of the excitation spectrum, where there would normally be no NMR responses.

There are also advantages in avoiding the conventional hard pulse excitation. Detection of fast-relaxing quadrupolar nuclei (such as oxygen-17) is often bedevilled by acoustic ringing in the radiofrequency probe, which interferes with, or even obscures, the free induction decay [16]. The proposed Hadamard scheme is equivalent to continuous-wave excitation with a very weak level of irradiation, with signal acquisition interleaved between the excitation pulses. This circumvents any problem of acoustic ringing.

Hadamard spectroscopy in the frequency domain does not involve Fourier transformation of a global free induction decay. Thus spectral artifacts attributable to distortions of the free induction signal (due to pulse breakthrough or premature truncation) are absent. Quadrature phase detection is unnecessary because NMR frequencies above and below the carrier frequency are properly defined by the sense of the phase incrementation, hence there is no "quadrature glitch" at zero frequency.

4. Experimental

Frequency-domain Hadamard spectroscopy was tested on the proton spectrum of a sample of strychnine in deuterochloroform, recorded on a Varian INOVA 500 spectrometer. A Hadamard matrix of dimension 2048 by 2048 was used, with the individual rows of this matrix calculated during the intervals between successive scans. (Note that faster operation could be achieved by computing a look-up table for the entire matrix.) The duration of each polychromatic pulse was 1 s, corresponding to a frequency selectivity of approximately 1 Hz, which was also the separation between adjacent frequency channels, giving a spectral width of 2048 Hz. It is interesting to note that each experiment involved more than *four million* radiofrequency pulses. In any given frequency channel the flip angle at the end of the polychromatic pulse was $+10°$ or $-10°$, depending on the coding.

The NMR data array had dimensions 2048 by 2048, and after decoding and phase-sensitive detection, this generated a Hadamard spectrum of 2048 separate

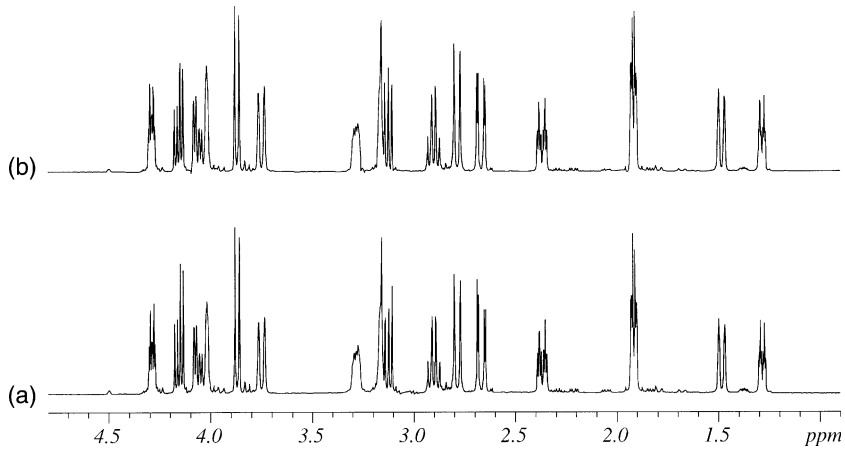

Fig. 3. (a) The Hadamard response from part of the 500 MHz proton spectrum of strychnine, excited by 2048 separate radiofrequencies spaced 1 Hz apart. (b) The conventional Fourier transform spectrum of the same region for comparison. The sample is partly decomposed.

ordinates (Fig. 3a). In principle, no baseline correction or frequency-dependent phase correction was required; in practice there may have been a slight timing error in the acquisition operations, necessitating a mild first-order phase correction. Sensitivity enhancement, conventionally carried out in the time domain by multiplication of a free induction decay with a decaying exponential, was implemented directly in the frequency domain. In this case the lineshapes and baseline noise were smoothed by application of a 1:2:1 convolution function, repeated if necessary.

Solvent suppression was illustrated for an aqueous solution of inosine. The excitation envelope was nulled in forty channels around the water resonance (at 4.3 ppm) and these same channels were blocked during processing. Fig. 4 illustrates the degree of water suppression achieved. If necessary, this scheme could be combined with one of the traditional solvent suppression methods such as presaturation.

As suggested above, Hadamard spectroscopy lends itself naturally to data reduction. The 500 MHz spectrum of strychnine between 1.0 and 4.7 ppm was excited with only 128 frequency channels, giving a trace with correspondingly sparse sampling (16 Hz steps). The intensity scale was limited to just one bit, creating a low-definition histogram (Fig. 5). This might serve as a "fingerprint" of reduced information content, suitable for storing in a large NMR spectral library, or it could provide a preliminary "search spectrum" as an aid to planning more detailed frequency-domain investigations.

5. Discussion

Although pulse-excited Fourier transform spectroscopy has served NMR spectroscopists well for the last three decades, there are some applications where

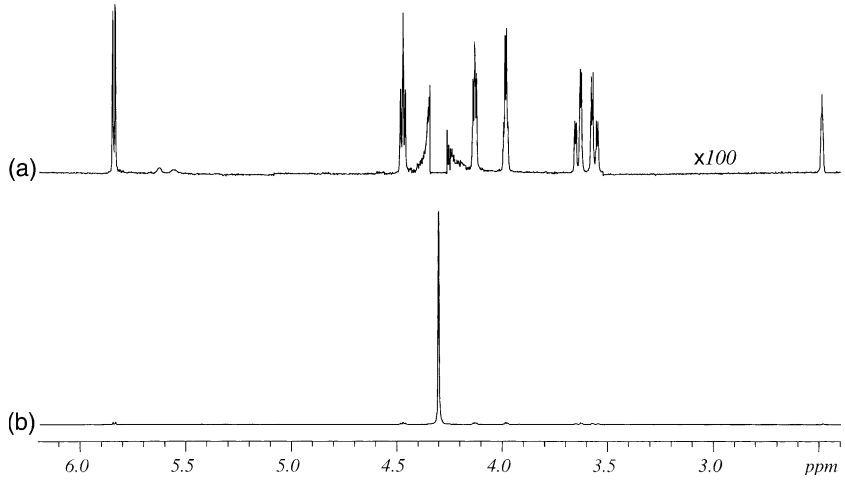

Fig. 4. (a) Water suppression in the proton spectrum of inosine by Hadamard spectroscopy. Forty channels spanning the water resonance at 4.3 ppm receive no radiofrequency excitation and the same forty channels are blocked during data processing. (b) The Hadamard spectrum without water suppression with the vertical scale reduced 100 times.

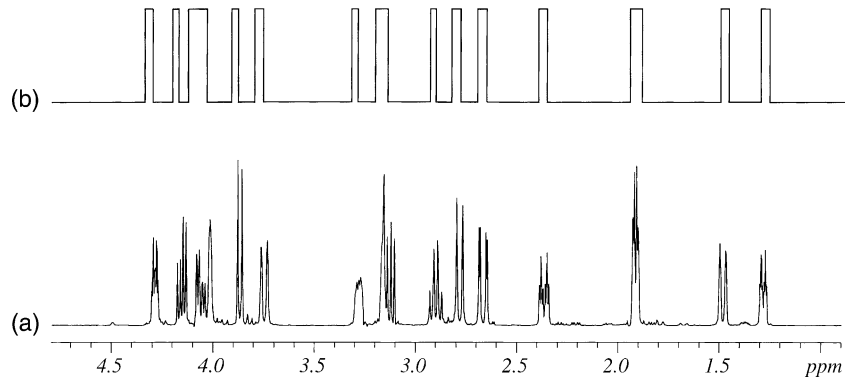

Fig. 5. Partial Hadamard spectrum of strychnine obtained (a) with 2048 channels and (b) with only 128 channels. The low-definition fingerprint (b) was recorded with the vertical scale limited to one bit (0 or 1).

operation exclusively in the frequency domain offers practical advantages. The concept of a multichannel NMR spectrometer, first proposed by Anderson [1], has been implemented by exploiting a new radiofrequency irradiation scheme encoded according to a Hadamard matrix, with the individual NMR responses separated by decoding with the same matrix. This makes it possible to tailor the excitation envelope in an arbitrary manner for the purpose of solvent peak suppression, homonuclear decoupling, data reduction, or for focusing attention on specific details of the high-resolution spectrum.

In principle frequency-domain Hadamard spectroscopy enjoys the same sensitivity advantage as the Fourier transform method, exciting all the spins all of the time. Indeed it may even offer a $\sqrt{2}$ improvement in sensitivity [17]. However, this approximate equivalence may not be entirely realized in practice owing to certain spectrometer shortcomings, those that give rise to t_1 noise in two-dimensional spectroscopy [18]. These artifacts are not significantly reduced by multiscan averaging. However, the technical performance of NMR spectrometers continues to improve, reducing the significance of the t_1 noise problem. For certain applications the much greater flexibility offered by frequency-domain operation may outweigh any minor sensitivity disadvantage. Hadamard spectroscopy should prove a useful adjunct to the ubiquitous Fourier transform method, but not a replacement for it.

Two-dimensional NMR spectroscopy has become an everyday tool in most chemical and biochemical laboratories. When all that is needed is a relatively small number of correlations (through spin coupling or cross-relaxation) the traditional two-dimensional spectra are rather too rich in extraneous detail, and they take a long time to complete. Hadamard encoding has already been used to perform several simultaneous one-dimensional correlation experiments, with a view to improving the rate of data gathering [19–24]. The new Hadamard method presented here should prove useful for excitation in the indirect frequency dimension of classic two-dimensional experiments. By focusing the irradiation on chemical sites of interest, leaving the rest untouched, it promises to speed up these experiments by a large factor. Preliminary tests bear out this suggestion and an investigation of these two-dimensional applications is underway.

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