Journal of Magnetic Resonance 205 (2010) 171–176

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

A new gradient-controlled method for improving the spectral width of ultrafast 2D NMR experiments

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ARTICLE INFO

Article history:
Received 26 March 2010
Revised 29 April 2010
Available online 10 May 2010

Keywords:
Ultrafast 2D NMR
Spectral width
Folding
DQF–COSY
TOCSY
HSQC

ABSTRACT

Ultrafast 2D NMR allows the acquisition of a 2D spectrum in a single scan. Still, a limitation affecting these experiments rests in their inability to cover large spectral ranges while preserving an acceptable resolution, due to limitations in gradient amplitudes and filter bandwidths. Various approaches relying on selective pulses have been recently proposed to overcome this drawback, by "shifting" resonances into arbitrary positions. However, these methods are associated with a number of drawbacks characterizing selective pulses. Here, we propose a new strategy to increase the spectral width accessible in the ultrafast dimension without degrading the resolution. This method leads to "folded-like" spectra along the ultrafast dimension. It does not require any selective pulse, and relies on suitably chosen gradients placed on each side of the mixing period. Our gradient-controlled folding method can be applied to almost any ultrafast 2D experiment, and appears to be particularly promising for heteronuclear 2D NMR. The results obtained on different compounds and pulse sequences (DQF–COSY, TOCSY, HSQC) are presented, highlighting the efficiency and the robustness of our method.

1. Introduction

Nuclear Magnetic Resonance (NMR) is a powerful tool employed in a wide range of situations, including the structural elucidation of organic structures, biochemical studies, pharmaceutical analysis and *in vivo* spectroscopy. In particular, multidimensional (nD) spectroscopy [1,2] plays a central role among NMR techniques, as it brings a resolution enhancement that is essential to elucidate complex molecular structures. However, the length of the experiments (several hours), necessary to complete the acquisition of a nD FID, often hampers the implementation of nD spectra. This is a consequence of the nD acquisition process, which relies on the repetition of numerous transients with incremented delays. Beyond the timetable constraints caused by the subsequent experiment duration, this incrementation procedure makes nD NMR very sensitive to temporal instabilities, leading in particular to large noise ridges along t_1 dimension [3]. Moreover, it makes nD NMR unsuitable for the study of short timescale phenomena.

A number of strategies [4–8] have been proposed to overcome this time limit and to obtain 2D NMR spectra in a reduced time while preserving the spectral resolution. A straightforward and efficient approach has been developed by Jeannerat [9,10], based on the optimization of spectral aliasing. In this method, 2D peaks are folded along the indirect dimension, resulting in a smaller spectral range to be sampled. Consequently, the resulting 2D spectrum can be obtained in a shorter time without degrading the resolution.

Recently, Frydman and co-workers [11,12] proposed a new approach allowing the acquisition of 2D NMR spectra within a single scan. In the so-called "ultrafast" method, the usual t_1 encoding is replaced by a spatial encoding. After a conventional mixing period, the spatially encoded information is decoded by a detection block based on Echo Planar Imaging (EPI) [13]. The discrete spatial encoding scheme initially proposed was replaced in the past few years by several continuous encoding patterns [14–17] relying on the combination of continuously frequency-swept pulses applied during a bipolar gradient. The constant-time phase modulated encoding scheme proposed by Pelupessy [14] was shown to be the one leading to the optimum ratio between sensitivity and resolution [18,19], and it progressively became the method of choice to perform the spatial encoding required by ultrafast experiments [20,21].

In spite of its high potentialities, ultrafast 2D NMR still presents limitations in terms of sensitivity, resolution and spectral width, that have been described in recent papers [22,23]. It has been shown that a compromise was necessary between the spectral widths SW_1 and SW_2 that can be accessed in the ultrafast and conventional dimension, respectively, and the resolution $\Delta\nu_1$ characterizing the peaks along the ultrafast k-domain. Relation (5) in

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doi:10.1016/j.jmr.2010.05.002

Ref. [23] shows that for a given resolution $\Delta\nu_1$, the maximum spectral widths that can be sampled in both domains are limited by the maximum acquisition gradient amplitude G_a available. Moreover, increasing G_a leads to sensitivity losses due to larger filter bandwidths.

In order to face these limitations, several strategies have been proposed to increase the spectral range accessible by ultrafast NMR experiments without degrading SNR and resolution. Unfortunately, the spectral aliasing method described above [9,10] cannot be employed in the *k*-domain, as Fourier Transform is not applied in the ultrafast dimension. Therefore, Pelupessy et al. proposed to add a band-selective refocusing pulse flanked by a bipolar gradient pair before the mixing period to recover signals lying out of the observed range [22]. Shrot et al. have very recently suggested a spatial/spectral encoding approach [23] that was successfully applied to hyperpolarized samples [24]. However, both strategies require the implementation of additional selective pulses associated with a number of drawbacks (necessity for precise calibration, sensitivity to pulse imperfections) and whose implementation is not straightforward.

Here, we propose a simple method to increase the spectral width accessible in the ultrafast dimension without degrading the resolution. This method does not require any selective pulse, and relies on suitably chosen gradients placed on each side of the mixing period. The principle of the method is described, and applications to various samples and pulse sequences are presented.

2. Principle

The generic principle of the method is described in Fig. 1. It consists in a simple modification of the basic ultrafast scheme proposed by P. Pelupessy. The pulse sequence starts with a 90° non-selective pulse, followed by a pair of identical 180° chirp pulses applied during alternating gradients. At the end of the excitation block, a phase-modulated signal is obtained and spins are encoded over a length L with a spatially dependent evolution phase [25]:

$$\phi(z) = \frac{2T_e\Omega_1 z}{L} \tag{1}$$

where T_e is the duration of the encoding pattern. After a mixing period which is identical to the one employed in conventional 2D experiments, this spatial winding is read out by the detection block, leading to chemical shift dependent echoes for $k = -C\cdot\Omega_1$, where Ω_1 is the resonance frequency, $k = \gamma_a\int_0^t G_a(t')dt'$ a wave number describing the ultrafast dimension [11], and $C = 2T_e/L$ [25].

In a vast majority of cases, the mixing period added between the spatial encoding and the detection block transforms the phase-modulated spatially encoded signal into an amplitude-modulated signal, like in conventional NMR experiments. The resultant signal detected during G_a can therefore be described as the sum of two symmetric signals with respect to $k = 0$. Consequently, two mirror-image echo trains are detected in the ultrafast dimension, for:

$$k = -C\cdot\Omega_1 \quad \text{and} \quad k = C\cdot\Omega_1 \tag{2}$$

Generally, an additional gradient of amplitude G_2 and duration τ_2 is added just before the detection block to control the position of the two mirror-image signals, and their position is therefore given by:

$$k = -C\cdot\Omega_1 - \gamma_a G_2\tau_2 \quad \text{and} \quad k = +C\cdot\Omega_1 - \gamma_a G_2\tau_2 \tag{3}$$

where γ_a is the gyromagnetic ratio of the detected nucleus. The two echo trains are symmetric with respect to $k = -\gamma_a G_2\tau_2$. The parameters of this G_2 gradient are generally set to place the symmetry point on the edge of the detection gradient in order to observe only one of the two mirror-image signals.

However, half of the signal is not observed on the resulting 2D spectrum. The principle of our method is to take advantage of these two symmetric signals to obtain a folded-like spectrum in order to decrease the effective spectral width. For that, an additional gradient (G_1, τ_1) is added just before the mixing period. This gradient is applied to the phase-modulated signal, before the creation of the two symmetric amplitude-modulated signals. Therefore, the effect of this additional gradient is to shift symmetrically the two mirror-image signals, leading to the apparition of echo peaks for:

$$\begin{aligned} &k = -C\cdot\Omega_1 - \gamma_e G_1\tau_1 - \gamma_a G_2\tau_2 \quad \text{and} \\ &k = +C\cdot\Omega_1 + \gamma_e G_1\tau_1 - \gamma_a G_2\tau_2 \end{aligned} \tag{4}$$

where γ_e is the gyromagnetic ratio of the spatially encoded nucleus.

By changing the two gradient parameters (amplitude and/or duration), the two symmetric signals can be partially superimposed and all the relevant signals can be observed in a reduced spectral width. This principle is illustrated in Fig. 2, in the case of the ultrafast DQF–COSY pulse sequence recently proposed by Wu et al. [20] (Fig. 2A). It is applied to ibuprofen, an anti-inflammatory drug whose ^{1}H spectrum is represented in Fig. 2B. ^{1}H resonances are spread over a 8 ppm range. For our hardware (standard commercial spectrometer as described in the experimental part, with a maximum gradient amplitude of 97 G/cm), this value was found too big to obtain a 2D homonuclear correlation in a single scan with a resolution sufficient to separate all resonances while preserving an acceptable Signal-to-Noise Ratio (SNR). Therefore, our gradient-controlled method was applied to shift the aromatic resonances at 7 ppm into the middle of the aliphatic range. Fig. 2C–F show the signal detected during the first acquisition gradient, whose duration was increased for didactic purposes (long acquisition gradients are not suitable for observing a reasonable spectral width in the conventional dimension). In Fig. 2C, G_1 and G_2 were set to observe the two non-overlapping symmetric echo trains. In Fig. 2E, G_2 was modified to observe only one echo train, which corresponds to usual ultrafast detection conditions. Fig. 2D shows how G_1 can be modified to interleave the two signals, by shifting the aromatic resonances from one echo train into the middle of the other *k*-pattern. Finally, suitably modifying G_2 leads to Fig. 2F, where the symmetry point is placed on the edge of the acquisition gradient. As a consequence, the aromatic signals appear folded with respect to the beginning of the detection gradient. All relevant resonances are detected in a shorter time T_a, which makes it possible to decrease the spectral width in the ultrafast dimension SW_1 while increasing it in the conventional dimension ($SW_2 = 1/(2T_a)$).

In Fig. 2, spectra are presented in magnitude mode. Even though it has been highlighted that ultrafast data could be phased when

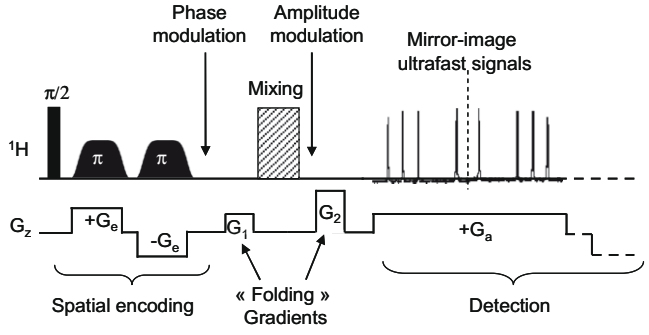

Fig. 1. Generic ultrafast pulse sequence illustrating the principle of gradient-controlled folding. The relative position of the two mirror-image signals can be modified by adjusting G_1, G_2 , τ_1 and τ_2.

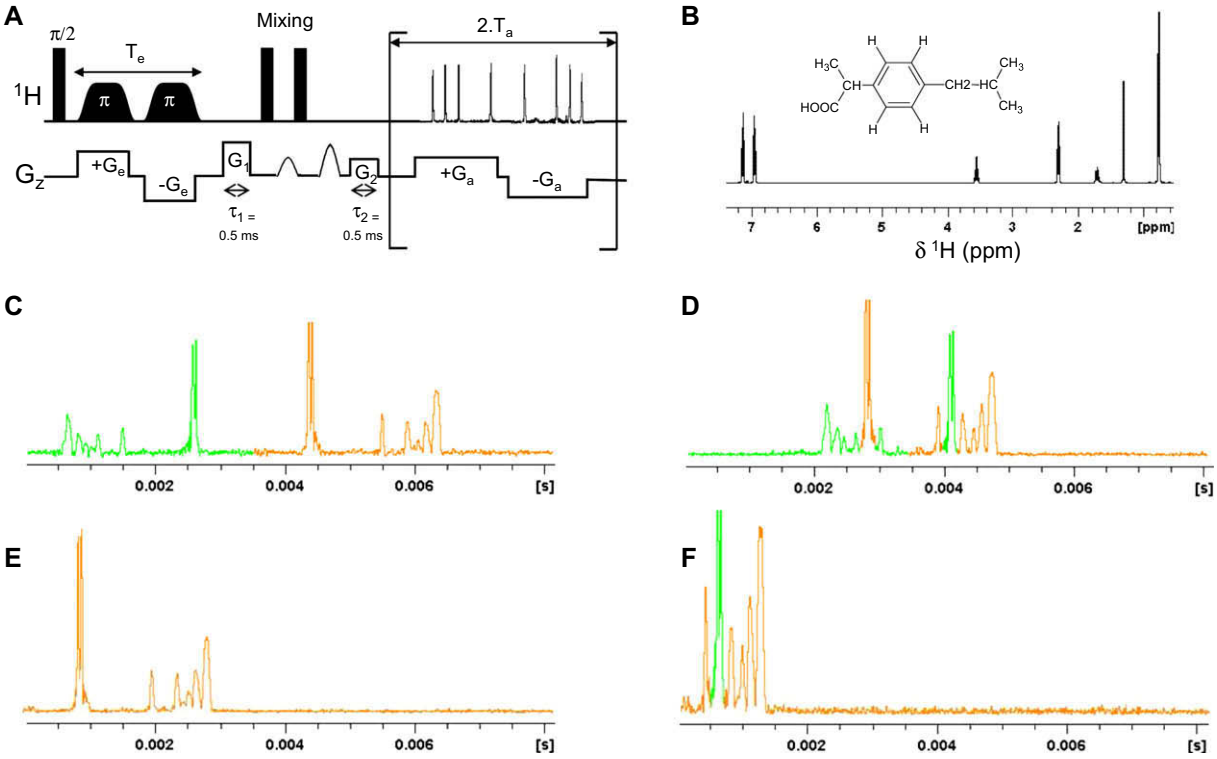

Fig. 2. (A) Ultrafast DQF–COSY pulse sequence including additional G_1 and G_2 gradients. Coherence-selection gradients were also added as indicated with 1:2 amplitude ratios and identical durations. (B) ^{1}H NMR spectrum of ibuprofen. (C–F) Signals acquired for various G_1/G_2 amplitudes during the first acquisition gradient (whose duration was increased on purpose to T_a = 8.2 ms), with G_a = 9.7 G/cm. (C) G_1 = −12.5 G/cm; G_2 = −58.0 G/cm. (D) G_1 = 13 G/cm; G_2 = −58.0 G/cm. (E) G_1 = −12.5 G/cm; G_2 = 0 G/cm. (F) G_1 = 13 G/cm; G_2 = 0 G/cm. The two mirror-image echo trains are represented in green and orange for the sake of clarity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

acquired with the encoding scheme proposed by Pelupessy [14,20], this is unfortunately not the case when our gradient-controlled folding method is employed. Simple calculations show that one of the echo trains experiences an additional dephasing $\Delta\varphi = \Omega_1(\tau_1 + \tau_2)$, whereas its symmetric counterpart is dephased by $\Delta\varphi = \Omega_1(-\tau_1 + \tau_2)$. As a consequence, the folded peaks cannot be phased respectively to the unfolded ones.

As described above, this gradient-controlled folding method allows increasing the spectral width while preserving the resolution of short spectral ranges. Moreover, its technical implementation is relatively straightforward, as no selective pulse is required. The discussion part below presents its application for a variety of pulse sequences.

3. Results and discussion

The additional "folding" gradients were first implemented in the ultrafast DQF–COSY [20] pulse sequence described in Fig. 2A. The conventional and ultrafast 2D DQF–COSY spectra are presented in Fig. 3, with the aromatic resonances circled in blue. The ultrafast spectrum (Fig. 3B) shows that the aromatic signals are folded along the spatially-encoded dimension, thanks to the optimization described in Fig. 2. Their position can be easily modified by adjusting the additional gradient parameters G_1, G_2, τ_1, τ_2. Also noticeable is the well-known regular aliasing that occurs in the conventional dimension. The term "aliasing" is employed for resonances folded with respect to the extremity of the spectral window, whereas "folding" occurs symmetrically with respect to the symmetry point $k = -\gamma_a G_2 \tau_2$, as suggested by Eq. (4). Even if this regular aliasing could be avoided by employing a numeric filter, P. Pelupessy et al. have shown that it can be exploited to enhance the resolution along the conventional dimension [22]. Moreover, aliasing can be optimized with the procedure described by D. Jeannerat [9]. Thanks to this procedure, the full DQF–COSY spectrum of ibuprofen was obtained in 0.2 s and contains the same information as the conventional spectrum recorded in 13 min.

Fig. 3 also raises the question of how folded signals could be distinguished from unfolded ones. A very fast and simple method may be used for differentiating the signals arising from symmetric echo trains. If a second ultrafast acquisition is performed with a slight modification of the difference $\gamma_e G_1 \tau_1 - \gamma_a G_2 \tau_2$, while keeping constant the sum $\gamma_e G_1 \tau_1 + \gamma_a G_2 \tau_2$, one train of echoes will be slightly shifted whereas its symmetric counterpart will remain at its original position. This should help in identifying folded resonances.

In order to illustrate the efficiency of our method on a more complex sample, we applied it to a mixture of two isomers (neral and geranial) which differ only by the configuration of a C=C double bond (Fig. 4A). In order to separate the resonances originating from the two stereoisomers, the mixture was characterized by a zTOCSY pulse sequence [26]. The latter differs from the DQF–COSY pulse sequence by a spin-lock mixing period flanked by two 90° hard pulses. The conventional spectrum (Fig. 4B), obtained in 50 min, exhibits a number of resonances spread over a 10 ppm range. Therefore, the gradient-controlled folding method was necessary to obtain the corresponding ultrafast 2D spectrum in a single scan with a reasonable SNR/resolution compromise. The resulting spectrum is presented in Fig. 4C, showing the same resonances as on the conventional spectrum. Compared to the conventional unfolded spectrum, some peaks were folded along the ultrafast dimension (red[1] dotted line) whereas others were aliased in the conventional dimension (green dotted line). One of the reso-

[1] For interpretation of color in Figs. 2–4, the reader is referred to the web version of this article.

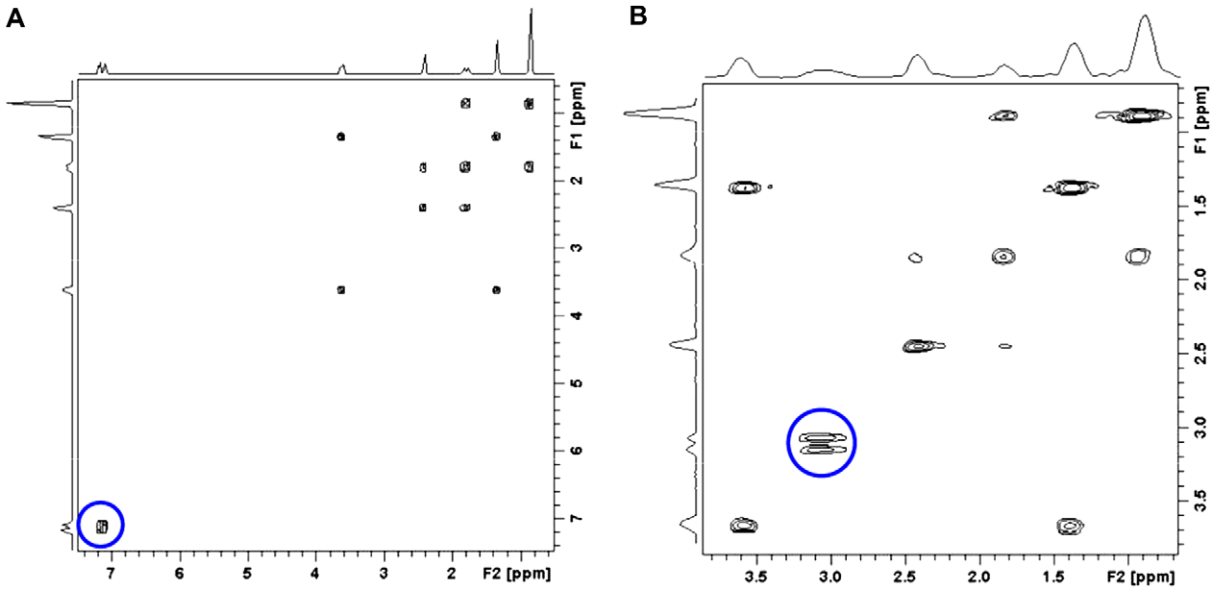

Fig. 3. (A) Conventional DQF–COSY spectrum of a 100 mM ibuprofen sample in DMSO-d_6 recorded in 13 min, and (B) ultrafast DQF–COSY spectrum of the same sample obtained in 0.2 s with the pulse sequence of Fig. 2A and the following "folding" gradient parameters: $G_1 = -15.8$ G/cm; $G_2 = 4.2$ G/cm; $\tau_1 = \tau_2 = 0.5$ ms. Other experimental parameters are indicated in the Section 4. The signals arising from the aromatic protons are circled in blue and appear folded on the ultrafast spectrum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

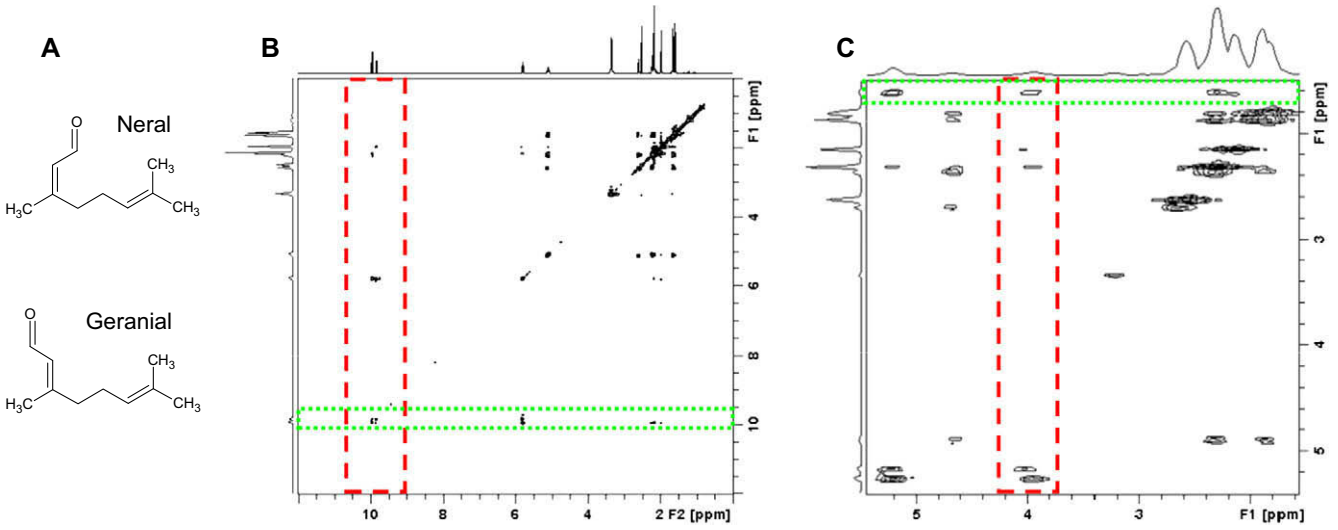

Fig. 4. Isomers of citral (A) and zTOCSY spectra of a 100 mM mixture in DMSO-d_6. (B) Conventional 2D spectrum recorded in 50 min. (C) Ultrafast spectrum recorded in 0.2 s with the parameters indicated in the Section 4 and the following "folding" gradient parameters: $G_1 = -21.3$ G/cm; $G_2 = 0$ G/cm; $\tau_1 = \tau_2 = 0.5$ ms. Other experimental parameters are indicated in the Section 4. On figures (B) and (C), _ _ indicates resonances folded in the ultrafast dimension, whereas ..... represents resonances aliased in the conventional dimension.

nances was folded in both dimensions. A few long-distance correlation peaks that are present on the conventional spectrum are not visible on the ultrafast one, due to the contour level chosen for plotting the ultrafast spectrum. The 1.5–3 ppm region presents a slight overlap due to the inherent lower resolution of ultrafast experiments; however peaks in the rest of the spectrum are clearly defined. Finally, both spectra contain almost the same information, but the ultrafast spectrum was recorded in 0.2 s only.

In the examples presented above, the gradient-controlled folding procedure was applied to homonuclear 2D NMR, resulting in a spectral width approximately divided by two compared to the full ^{1}H spectral width. But the method appears particularly promising for heteronuclear spectroscopy, where the chemical shift range of heteronuclei often exceeds a few tens or hundreds of ppm. This is particularly constraining for ultrafast methods, where the low sensitivity of heteronuclei requires that protons are sampled in the conventional dimension, whereas the long range heteronucleus is detected in the spatially-encoded dimension. Therefore, we evaluated the approach described above in the case of a ^{1}H–^{13}C ultrafast heteronuclear correlation [27]. The studied sample is a mixture of three compounds engaged into a chemical equilibrium: methanol, formic acid and the resulting ester, methyl formate. Their ^{13}C NMR spectrum (Fig. 5A) shows that corresponding resonances cover a 120 ppm range, which is far too big to obtain an ultrafast spectrum in a single scan with the gradient amplitudes available on routine spectrometers. However, by adding suitably chosen gradients on each side of the mixing period (Fig. 5C), an ultrafast 2D HSQC spectrum was obtained in 0.12 s

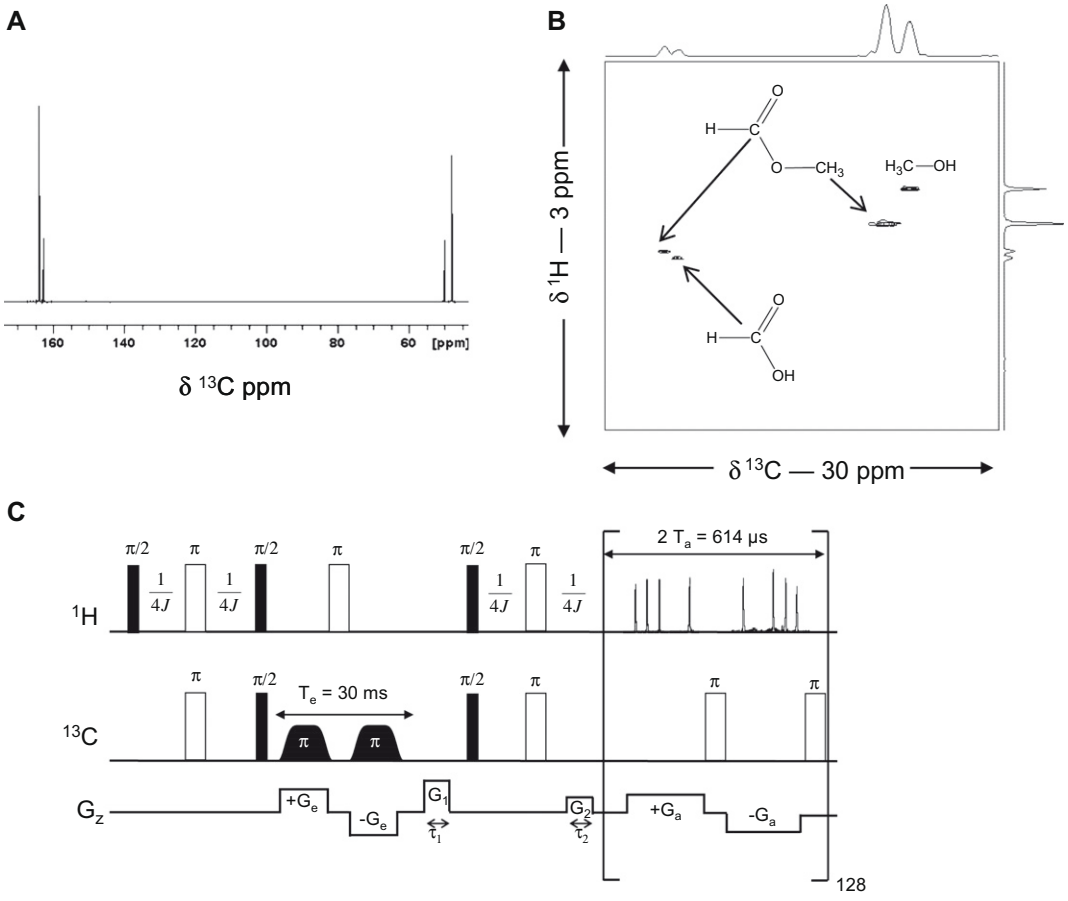

Fig. 5. (A) ^{13}C NMR spectrum of a mixture of methanol, formic acid and methyl formate at natural abundance in D_2O acquired at 298 K. (B) Ultrafast ^{1}H–^{13}C HSQC spectrum of the same sample recorded in 0.12 s with the pulse sequence (C) represented above, and the following parameters $G_1 = -27.1$ G/cm; $G_2 = 87$ G/cm; $\tau_1 = 0.3$ ms; $\tau_2 = 1.0$ ms. Other experimental parameters are indicated in the Section 4.

(Fig. 5B), showing the four expected peaks in a reduced, 30 ppm effective spectral width. Some signals were also folded in the conventional dimension.

The results described above show the efficiency of the gradient-controlled folding procedure in a variety of cases. This procedure is *a priori* applicable to any 2D pulse sequence including a mixing period, provided that it generates an amplitude-modulated signal, which is the case of almost all routine 2D experiments. However, our method is not adapted to mixing periods generating a phase-modulated signal. Therefore, it is not compatible with sensitivity-enhanced methods [28] that have been successfully implemented in ultrafast 2D NMR [14]. Another exception is ultrafast *J*-resolved spectroscopy [29], where the mixingless pulse sequence generates a purely phase-modulated signal. However, in this particular case, the spectral width to be sampled in the conventional dimension is limited to a few tens of Hz and long acquisition gradients can therefore be applied to sample large spectral widths with an excellent resolution [25]. Consequently, folding does not appear to be useful in this case.

Another aspect of the method described in this paper is that its implementation on routine spectrometers is relatively straightforward, as it does not require specific selective pulses. All the spectra presented here were acquired on a commercial 400 MHz spectrometer equipped with standard hardware.

A common feature shared by this method and the selective-pulse based strategies [22–24] is that it requires *a priori* knowledge of the resonances. However, the gradient-based approach is intrinsically robust *vis a vis* chemical shift variations, and an approximative knowledge of the spectral regions to be folded (e.g. aromatic region) should be sufficient in most cases. The main limitation of the method is the possible overlap between folded and non-folded resonances, particularly in the case of complex mixtures. The next step to deal with this drawback would be the adaptation of the algorithm designed by Jeannerat [9] to calculate automatically the gradient parameters minimizing overlap on the resultant spectrum.

The selective-pulse based approaches [22–24] also differ from our gradient-controlled method by their ability to shift more than one region arbitrarily, a feature that is not *a priori* implemented in our new method. The combination of our gradient-controlled approach with a selective-pulse based method could be considered to bypass this limitation and improve further the performances of ultrafast experiments in terms of spectral width.

Finally, in terms of molecular diffusion effects, which particularly affect ultrafast experiments [18,19,30], we observed that the additional gradients did not lead to significant supplementary sensitivity losses compared to basic ultrafast pulse sequences, probably due to their very short duration (less than 1 ms in the examples presented here).

4. Conclusion

This study highlights the potentialities of the gradient-controlled folding method for acquiring ultrafast, "folded-like" spectra in a single scan. It is applicable to almost all ultrafast 2D experiments, and appears to be particularly promising for heteronuclear 2D NMR. This strategy opens new perspectives towards the routine implementation of ultrafast 2D NMR for structural analysis. In order to make its implementation easier, algorithms will have to

be designed: (i) to calculate automatically the gradient parameters form *a priori* information and (ii) to reconstruct the non-folded spectrum from the folded ultrafast data.

5. Experimental

The ibuprofen sample was prepared by dissolving crushed ibuprofen (extracted from a commercial sample) in DMSO-d_6 to obtain a 100 mM final concentration. The citral sample was obtained by dissolving a mixture of geranial and neral (Sigma–Aldrich) in DMSO-d_6 to obtain a 100 mM total concentration. The sample for the ultrafast HSQC experiment was prepared by adding 250 μL of methanol and 250 μL of formic acid (both at natural abundance) with 150 μL D_2O. A spontaneous esterification reaction occurred, leading to the formation of methyl formate. All samples were analyzed in 5 mm tubes.

NMR spectra were recorded at 298 K on a Bruker Avance I 400 spectrometer, at a frequency of 400.13 MHz with a 5 mm dual probe equipped with *z*-axis gradients. Conventional 1D and 2D experiments were recorded with routine pulse sequences available within the commercial software Bruker Topspin 2.1. The conventional DQF–COSY spectrum (Fig. 3A) was recorded with 64 t_1 increments, two scans, a recovery delay of 5 s and an acquisition time of 0.85 s. The conventional zTOCSY spectrum (Fig. 4B) was recorded with 256 t_1 increments, four scans, a recovery delay of 2 s and an acquisition time of 0.8 s.

For all ultrafast experiments, spatial encoding was performed using a constant-time spatial encoding scheme [14] with 15 ms smoothed chirp [31] encoding pulses. The sweep range for the encoding pulses (11 kHz for DQF–COSY and zTOCSY, 57 kHz for HSQC) was set to be significantly larger than the chemical shift range, and the amplitude of the encoding gradients was adapted to obtain a frequency dispersion equivalent to the frequency range of the pulses (G_e = 1.35 G/cm for DQF–COSY and zTOCSY, 27.1 G/cm for HSQC).

Mixing periods were comparable to those employed in conventional 2D experiments. For DQF–COSY, coherence-selection gradients were added as indicated on Fig. 2A. For the zTOCSY experiment (Fig. 4), a 20 ms adiabatic spin-lock period [32] was applied to obtain an optimum efficiency for a minimum mixing duration in order to minimize sensitivity losses due to diffusion effects between encoding and detection. The spin-lock was formed with 500 μs cos/OIA adiabatic pulses with a M4P5 phase cycle scheme [33]. For the ultrafast HSQC pulse sequence (Fig. 5), the INEPT delays were set to 1.38 ms, corresponding to $1/(4\langle J_{CH}\rangle)$.

Acquisition gradient parameters were set as follows: G_a = 46.4 G/cm, T_a = 307 μs for DQF–COSY, G_a = 48.3 G/cm, T_a = 282 μs for zTOCSY and G_a = 87 G/cm, T_a = 269 μs for HSQC. 256 detection gradient pairs were applied for homonuclear ultrafast pulse sequences and 128 pairs for HSQC.

Additional "folding" gradients were set to optimize peak folding along the ultrafast dimension. Corresponding parameters are indicated in the figure legends.

All spectra were acquired and analyzed using the Bruker program Topspin 2.1. The specific processing for ultrafast spectra (as described in Ref. [11]) was performed using our home-written routine in Topspin.

Acknowledgments

The authors would like to thank Michel Giraudeau for linguistic assistance.

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