Journal of Fluorine Chemistry 140 (2012) 104–106

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

Short communication

Spectral simplification of proton homonuclear correlation experiments utilizing ω1, ω2 fluorine decoupling

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ARTICLE INFO

Article history:
Received 2 December 2011
Received in revised form 28 March 2012
Accepted 3 April 2012
Available online 24 April 2012

Keywords:
Fluorine decoupling
COSY
DQCOSY
Spectral simplification

ABSTRACT

Decoupling ^{19}F during data acquisition is extensively used to simplify proton spectral interpretation of fluorinated compounds. Decoupling applied during the acquisition time (t2) of a 2D experiment, however, only produces partially decoupled spectra as the heteronuclear coupling continues to evolve during t1. The resulting partially decoupled spectra can be difficult to interpret and interferes with cross peak analysis in phase sensitive DQF-COSY. Here we present a procedure for effectively decoupling ^{19}F in both frequency domains, ω1 and ω2. The pulse sequences employed utilize a 180° pulse on ^{19}F placed in the center of the t1 evolution time of the 2D experiment which refocuses the heteronuclear J coupling. Standard broadband decoupling during t2 then produces fully decoupled spectra. This gated decoupling procedure has significant advantages over the alternative of continuous broadband decoupling. This is especially true when the ^{19}F signals are far apart in frequency and power requirements become prohibitive even for continuous adiabatic decoupling.

1. Introduction

Fluorinated compounds are critical components of both agricultural and pharmaceutical chemistry. The complex coupling patterns that often result with partially fluorinated compounds can make simple interpretation of the NMR spectrum by inspection difficult. Acquiring a ^{1}H spectrum with ^{19}F decoupling during acquisition is a common method of spectral simplification. The situation when running two-dimensional (2D) ^{1}H correlation experiments, however, is more problematic. Turning the decoupler on during acquisition only suffices to decouple ω2 leaving ω1 coupled. This results in a homonuclear 2D spectrum where cross peaks are partially decoupled multiplets that are difficult to analyze. The most obvious solution to the problem, continuous broadband decoupling, is not a good option in the case of ^{19}F. The wide chemical shift dispersion of ^{19}F can create prohibitive power demands for continuous decoupling even using adiabatic [1–3] or BIBOP [4] based decoupler schemes.

1.1. ω1 broadband decoupling

The concept of broadband ω1 decoupling in 2D correlation experiments was originally proposed by Bax and Freeman [5] and has found wide use in both protein [6] and small molecule studies [7]. Most ^{1}H homonuclear correlation applications focus on removal of homonuclear coupling using constant time experiments such as CT-COSY [6–8]. In these experiments a 180° refocusing pulse is placed in the center of the evolution period while keeping the time between the radiofrequency pulses constant [5]. Complete removal of heteronuclear coupling from homonuclear correlation experiments is less well documented. Griffey and Redfield [10] explored the use of gated decoupling during t1 or t2 to produce partially decoupled cross peaks as an assignment aid in ^{15}N labeled compounds. Gated decoupling during both t1 and t2 is an obvious extension of their method. However, it is also possible to remove the effect of heteronuclear coupling from spins by placing a 180° pulse on the heteronucleus during t1. This is very commonly used when acquiring NMR data on proteins [9]. The procedure proposed in this study is to merge the concepts of ω1 decoupling using refocusing 180° pulses and gated decoupling. This produces an efficient scheme in terms of power usage and is straightforward to implement.

2. Results and discussion

2.1. Pulse sequence description

The pulse sequences are illustrated in Fig. 1. A basic gradient COSY experiment is shown in Fig. 1A and B shows a phase sensitive gradient DQF COSY experiment which incorporates ^{19}F decoupling in ω1 and ω2. While a simple hard 180° pulse is acceptable if the resonances are close in frequency the bandwidth is often

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http://dx.doi.org/10.1016/j.jfluchem.2012.04.002

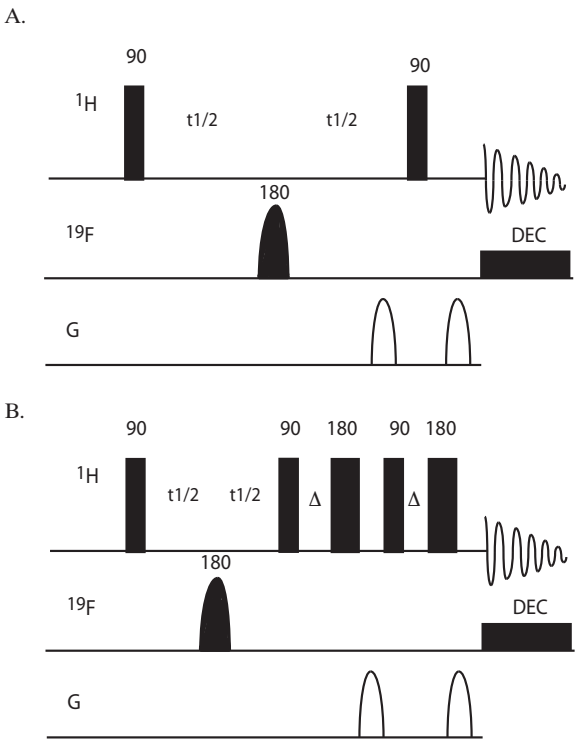

Fig. 1. Pulse sequences for gradient COSY (panel A) and gradient DQF-COSY (panel B) with ω1, ω2 broadband decoupling. Phase cycling of all pulses is identical to the standard sequences. The ^{19}F 180° pulse is a 2 ms composite chirp pulse with 60 kHz bandwidth applied along the *X*-axis.

insufficient for use with ^{19}F. Specifically, the aromatic ^{19}F signals encountered in typical agricultural and pharmaceutical compounds cover a chemical shift range of approximately 60 ppm. For this reason the 180° pulse on ^{19}F needs to be broadbanded. The pulse chosen for these experiments is a refocusing Chirp pulse [11]. The Chirp pulse provides very wide band refocusing of J_{HF} with minimal power. In this case a Chirp with a 60 kHz bandwidth was employed which is sufficient to cover the range of aromatic ^{19}F chemical shifts at frequencies up to 900 MHz. Broadband adiabatic ^{19}F decoupling is then applied during t2 to produce a ω1, ω2 decoupled dataset. It should be noted that the recently introduced constant amplitude broadband refocusing (CAR) pulses would also provide the requisite bandwidth with shorter pulses but with higher power [12]. The use of adiabatic pulses on ^{19}F has another advantage in addition to bandwidth. They are very robust in terms of mis-calibration and are therefore ideal for a routine acquisition environment and automation.

The sequences require a spectrometer equipped with waveform generation capability and the capacity to perform ^{1}H observe with ^{19}F decoupling. Different probe configurations can be used to perform the experiment. Probes that have separate coils tuned to ^{1}H and ^{19}F can be used in addition to probes that have dual tuned ^{1}H, ^{19}F single coils. Probes that have dual tuned coils may require extra cabling and narrow band filters to prevent RF cross talk during ^{19}F decoupling. A probe that has ^{1}H and ^{19}F on separate coils was used for the experiments described in this paper (see Section 4). The separate coil system permits use of these sequences in high throughput systems and in automated structure elucidation environments.

2.2. Evaluation of 2D cross peak complexity

The results of the simplification in cross peak pattern produced by the technique are shown in Fig. 2. A comparison of the gradient COSY of the aromatic region of sample 1 between the fully ^{19}F coupled (Fig. 2A), partially decoupled (Fig. 2B) and fully decoupled spectra (Fig. 2C) are illustrated. The gated decoupled spectra shown in Fig. 2B (broadband decoupling on during t2) have only partial decoupling and cross peaks are elongated in F1. The cross peak shown in Fig. 2C, in contrast, is symmetric with respect to both dimensions indicating complete decoupling in both ω1 and ω2. While in this example there is not direct overlap a significant reduction in spectral complexity is achieved reducing crowding.

Simplification of the cross peak pattern is even more critical in phase sensitive experiments. DQF-COSY and similar experiments can be used to extract homonuclear couplings [13]. Practically this can be a difficult task and the added complexity of additional ^{19}F coupling is highly problematic. More importantly for routine use, even when couplings are not directly extracted the resulting cross peak patterns are often highly diagnostic of specific spin systems [14]. Elimination of the ^{19}F coupling allows determination of the spin pattern. The problem is illustrated in Fig. 3. The cross peak in the fully coupled dataset Fig. 3A shows significant cancellation and is not readily interpretable. Fig. 3B shows the same cross peak after decoupling.

Finally, as previously noted to be generally effective the technique must also work over the entire bandwidth of aromatic ^{19}F signals (approximately 60 ppm). Panels A and B in Fig. 4 illustrate this point. In this case (sample 2) the ^{19}F chemical shifts cover a range of approximately 40 ppm (approximately 15 kHz at

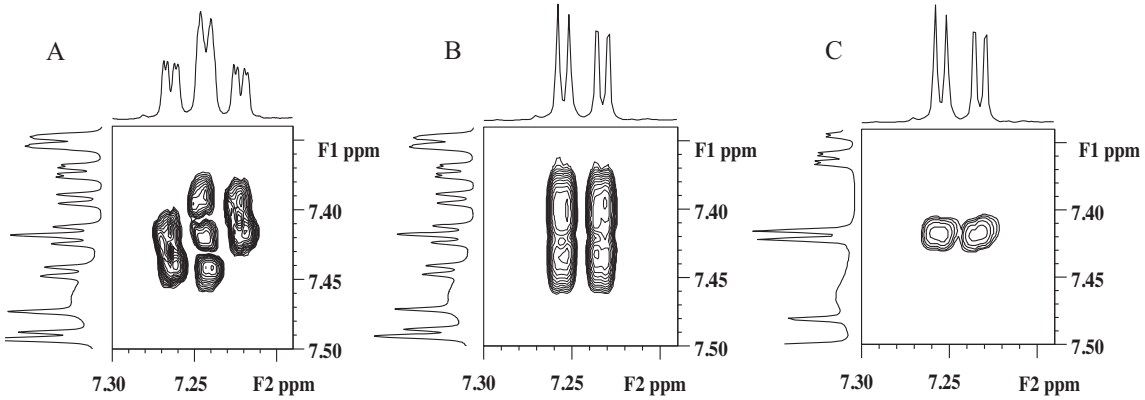

Fig. 2. Demonstration of cross peak simplification in the gradient COSY experiment. Panel A shows a fully coupled cross peak in sample 1. Panel B shows the effect of adiabatic decoupling during t2 only while panel C shows the fully decoupled cross peak. In panels B and C the ^{19}F decoupled proton spectra is plotted on the 2D to show the correspondence with the cross peak.

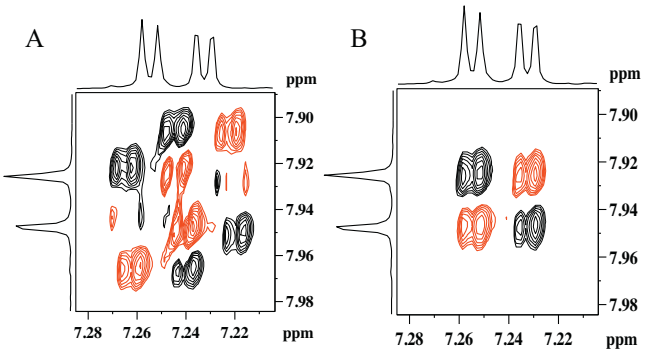

Fig. 3. Cross peak simplification in the gradient DQF-COSY experiment. The complex cross peak in panel A resulting from full ^{19}F coupling into the ^{1}H is very difficult to interpret with significant cancellation. The decoupled cross peak is shown in panel B. This figure demonstrates the simplification achievable in situations where good digital resolution in the ^{1}H dimension can be obtained.

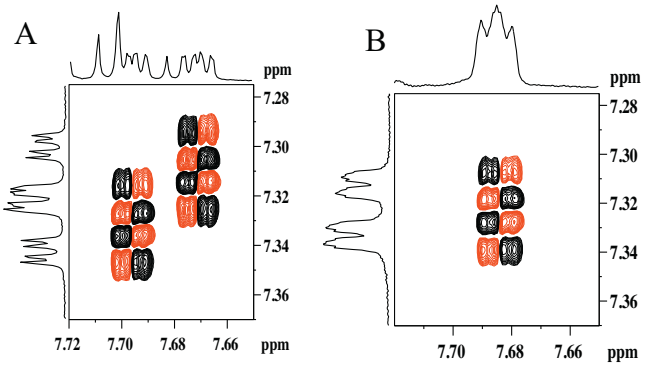

Fig. 4. A representative DQF-COSY cross peak in sample 2 showing the effectiveness of the procedure where the bandwidth of ^{19}F signals covers the range from −110 to −150 ppm. Panel A shows the fully coupled cross peak and panel B the ω1, ω2 decoupled cross peak. The reference 1D spectra plotted on the 2D are coupled and ^{19}F decoupled ^{1}H spectra respectively.

400 MHz) and full decoupling in the 2D experiment is obtained. Panel A is the fully coupled DQF-COSY, panel B is the fully heterodecoupled DQF-COSY. After decoupling, the double doublet structure of the cross peak consisting of two AX type patterns is clearly evident. This data also provides one important caveat to analysis of the cross peaks. While the pattern from the major couplings is clearly visible information on the minor couplings present is lost due to digital resolution limitations imposed by 2D data acquisition.

3. Conclusions

A general procedure for achieving full decoupled ^{1}H homonuclear correlation spectra of partially fluorinated compounds is described. The technique should have wide applicability to both the pharmaceutical and agricultural industries as well as general organofluorine assignment. The sequences are robust and amenable to easy automation making this procedure ideal for high throughput environments in both academia and industry. In addition the simplicity makes the technique readily extensible to other 2D experiments such as NOESY.

4. Experimental

Data were acquired on a Bruker Avance 400 MHz spectrometer utilizing a $^{1}H/^{19}F/^{13}C$ TXO probe. Two demonstration mixtures consisting of 18 mg 3-fluorobenzamide plus 23 mg of 2-acetyl-5-(2,4-difluorophenyl)furan in 0.6 ml deuterated Me_2SO_4 (sample 1) and 4 mg 3-fluorobenzamide plus 8 mg 1-(2,3,5,6-tetrafluorophenyl) imidazole in deuterated Me_2SO_4 (sample 2) were prepared. All materials were purchased from Aldrich Chemical Co. Gradient COSY spectra were acquired with a spectral window of 4 ppm, 4 scans, 256 t1 increments and 2048 K data points in t2. Gradient DQF-COSY spectra were acquired with a spectral window of 4 ppm, 4 scans, 512 t1 increments and 4096 data points in t2. Data were processed using linear prediction to twice the number of increments and the resulting COSY and DQF-COSY data were zero filled to produce 2 K × 2 K and 8 K × 8 K matrices respectively.

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