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Broadband ^{19}F TOCSY using BURBOP-based spin lock

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ABSTRACT

A train of BURBOP universal rotation pulses has been used to generate a spin lock sufficient to observe TOCSY correlations over a 46 kHz ^{19}F spectral window (i.e. 122 ppm on a 9.4 T spectrometer). This spin lock requires lower RF field (γB_1 = 15 kHz), and was employed over a wider spectral window, than previously reported DIPSI-2 spin locks. The BURBOP-based spin lock was effected for 80–160 ms periods with a 2% duty cycle without evidence of harm to the RF coil of the probehead. Spectral separation and full set of correlations were obtained for a mixture of perfluorocarbons.

1. Introduction

The ^{19}F nucleus is in many respects an excellent analogue for ^{1}H in liquid-state NMR experiments on organofluorine compounds. Its high gyromagnetic ratio (0.941 that of ^{1}H) and 100% natural isotopic abundance render its receptivity nearly as great as that of ^{1}H. Perhaps the most salient difference is the large spectral dispersion afforded by ^{19}F, frequently 130 ppm or more in fluorocarbons. Using probes with reasonably strong B_1 fields, it is generally possible to use hard pulses for excitation, broadband inversion (BIP) [1] or adiabatic [2,3] pulses for inversion, and BURBOP [4–6] pulses for refocusing over such a spectral window. Therefore most common ^{1}H-detected multidimensional correlation experiments (COSY [7], NOESY [8], HSQC [9], etc.) can be readily performed as ^{19}F-detected experiments [10,11].

One common component of multidimensional liquids pulse sequences that is challenging to implement for ^{19}F experiments with a wide spectral window is the spin lock [6]. The power requirements for an MLEV [12] or DIPSI [13] type spin lock over 40 kHz or more often cannot be tolerated by the RF coils of a liquids probe without damage. The most successful implementation reported to date on a ^{19}F spectrum was that of Bailey et al. [14], who used a DIPSI-2 spin lock at a γB_1 field of 25 kHz to effect a spin lock over ca. 32 kHz on a 7.0 T system, while reporting some phase distortions at the edges of the spectral window. Such B_1 fields may be barely achievable on singly-tuned inverse probeheads at lower B_0 field strengths; they are typically not achievable on doubly-tuned ^{1}H,^{19}F coils, or on the outer coils of probeheads of a forward design. Other lines of investigation have focused on broadband ^{1}H or ^{13}C spin locks for macromolecules, using adiabatic pulses such as tanh [15], WURST-2 [16], and CHIRP [17], and phase- and amplitude-modulated square pulses [18]. While these reportedly yield clean spectra, the spectral windows of interest do not exceed ca. 20 kHz, even for ^{13}C spin locks at high B_0. Spin locks requiring lower RF power have recently been reported, but with the aim of avoiding sample heating while covering a typical ^{1}H spectral window [19,20]. A generally-applicable ^{19}F TOCSY [12] or ROESY [21] has not been reported over a typical fluorocarbon spectral window.

In recent work exploring the efficacy of such pulses in the ^{19}F-^{13}C HSQC correlation experiment [22], it was noted that the BURBOP functioned effectively as a refocusing pulse that imparted uniform phase on resonances up to 25 kHz away from the transmitter frequency, in contrast to adiabatic pulses such as WURST or CHIRP. This retention of phase uniformity over a large spectral window was noteworthy, and it was therefore of interest to explore whether BURBOP pulses, arranged in sequence, could induce a spin lock superior to DIPSI-2 or adiabatic pulses over a spectral window generally useful for ^{19}F TOCSY experiments. The results of that investigation are reported herein.

2. Experimental

Two simple TOCSY experiments were used to evaluate the effectiveness of BURBOP-induced spin locks, an echo-antiecho 2D sequence and a selective 1D sequence, shown in Fig. 1.

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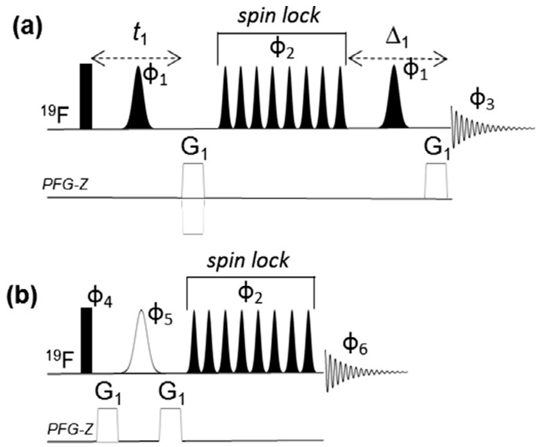
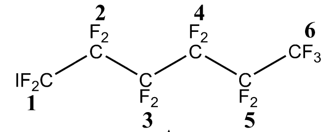


Fig. 1. TOCSY pulse sequences used in this study. Filled rectangles represent hard $\pi/2$ pulses, filled Gaussian shapes represent 50 kHz BURBOP pulses, the unfilled Gaussian shape represents a selective SEDUCE inversion pulse, and the open rectangles on the PFG-Z line represent Z-axis pulsed field gradients for coherence selection. (a) 2D sequence. (b) Selective 1D sequence. Δ_1 = the duration of the 2 ms BURBOP pulse plus twice the duration of the (gradient pulse plus recovery time). Gradient pulses were typically 1 ms in duration and 0.075–0.15 T m^{-1} in intensity. RF pulse phases are +x unless otherwise indicated. ϕ_1 = +x, −x, +x, −x, +y, −y, +y, −y; ϕ_2 = +x, +y; ϕ_3 = +x, −x, −x, +x, +y, −y, −y, +y; ϕ_4 = +x, −x; ϕ_5 = +x, +x, +y, +y, −x, −x, −y, −y; ϕ_6 = +x, −x, −x, +x.



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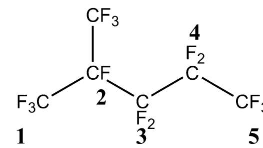

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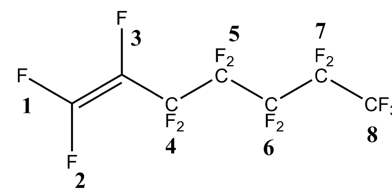

C

All experiments were performed on a Bruker Avance IIIHD spectrometer operating at 9.4 T (Larmor frequency of ^{19}F = 376.3 MHz), equipped with a Prodigy BBFO liquid nitrogen cryoprobe. ^{19}F is detected on the outer coil of this probe, with a typical maximum power of 13 W resulting in a 22.4 kHz γB_1 field. The BURBOP pulses were taken from the Bruker shape library (Topspin v. 3.2), and are optimized for universal π rotation over a 50 kHz spectral window at 15 kHz γB_1 field. The maximum power of the BURBOP pulses applied here was 5.8 W; the mean power during the pulse is 4.1 W. The CHIRP pulse used for comparison was also taken from the standard Bruker shape library, and was nominally optimized for an 80 kHz window. The WURST-2 pulse was translated from the Varian shape library (VNMRJ v. 3.2A), and was nominally optimized for a 60 kHz window.

2D TOCSY experiments were typically performed with a 50 kHz spectral window, 512 uniform increments in the indirect dimension, with 8 scans per increment. A gradient-π/2-gradient element (not pictured in Fig. 1) was added before the recycle delay to null the net magnetization [23]. The recycle delay was set such that the duty cycle of the ^{19}F coil was 2% (e.g. 6.4 s recycle delay with 128 ms spin lock). Typical acquisition time was 83 ms. Simple fast Fourier transforms were performed in each dimension. Spectra were processed with squared sinebell apodization in each dimension. A T_1 noise reduction algorithm (ACD Labs, Toronto) was applied after the transform.

1D selective TOCSY experiments were also acquired with a 2% ^{19}F RF duty cycle. The spectra shown in Fig. 4 were the average of 256 scans, with a 2.1 s acquisition time. Selective refocusing was effected by a SEDUCE pulse shape. Its typical durations were 20–40 ms, requiring 5–20 μW power to refocus a spectral window of 25–50 Hz. Spectra were transformed with exponential or sinebell apodization.

Two samples were prepared for this evaluation. The first was comprised of 20 μL 1-iodoperfluorohexane (**A**, Synquest Labs, >99% purity), 20 μL perfluoro-2-methylpentane (**B**, PCR Labs (defunct), >95% purity), and 660 μL acetone-d_6 (Sigma-Aldrich, 99% isotopic purity). The second was comprised of 20 μL perfluorohept-1-ene (**C**, PCR Labs, >90% purity) and 680 μL acetone-d_6. All spectra were acquired at 298 K.

3. Results

The integrity of the probe coil was of concern at the beginning of this study. The authors utilized a 5 mm liquid nitrogen dual-coil cryoprobe with ^{19}F tuned on the outer coil; this probe generates a ^{19}F γB_1 field of 22,400 Hz (i.e. a hard π/2 pulse width of 11.2 μs) at its ordinary maximum power. It was not certain that the coil would safely support a continuous string of BURBOP pulses at γB_1 up to 15 kHz (the time-averaged γB_1 was 12.6 kHz) for the duration of a useful spin lock. To explore probe safety, dummy versions of the 2D and 1D experiments were run without field gradient pulses, and the level of the ^{2}H field-frequency lock signal was observed. The ^{2}H lock signal was unaffected by the TOCSY experiment, which was taken as evidence that the coil was unaffected. Likewise, no heating was detected by the probe thermocouple near the bottom of the sample tube. At the end of this study, having acquired dozens of TOCSY spectra with BURBOP spin locks, the performance of the probe was unchanged (as determined by both γB_1 fields on both coils, and by lineshape). In all experiments, the duty cycle of the ^{19}F coil was kept at 2% (by extension of the recycle delay), and the spin lock was not extended beyond 160 ms in any experiment.

The benefits of the BURBOP spin lock were readily evident in the first sample (mixture of **A** and **B**). In the ^{19}F spectrum of this mixture, the least shielded multiplet (**A**-**1**) and the most shielded (**B**-**2**) are separated by 121.85 ppm, or 46 kHz on a 9.4 T system. Fig. 2 compares a simple ^{19}F gradient COSY spectrum, a ^{19}F TOCSY acquired with a DIPSI-2 spin lock, a ^{19}F TOCSY with a spin lock effected by concatenated 80 kHz CHIRP pulses, and a ^{19}F spin lock effected by concatenated 50 kHz BURBOP pulses. The duration of the spin lock was 0.128 s in all cases. The spectra acquired with BURBOP and DIPSI-2 spin locks used the same average RF power (12.6 kHz γB_1 field, requiring 4.1 W on the probe used here); the CHIRP required somewhat less power. The COSY spectrum (Fig. 2b) correlates most resonances related by $^4J_{FF}$ scalar coupling, and detects selected $^3J_{FF}$ and $^5J_{FF}$ as well. (In linear perfluoroalkyl chains, $^4J_{FF} > {}^3J_{FF}$, with the latter often near zero. Branching or the presence of atoms other than F disrupts this pattern [24]) The TOCSY with DIPSI-2 spin lock (Fig. 2c) detects the same correlations as the COSY in the CF_2 region near the transmitter frequency in both dimensions, but no additional ones, and detects even fewer correlations when distant from the transmitter. MLEV and