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Excitation Sculpting in High-Resolution Nuclear Magnetic Resonance Spectroscopy: Application to Selective NOE Experiments

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Selective pulses are key elements in high-resolution NMR experiments, so great effort has been put into designing pulse shapes with desirable properties.[1−7] In this communication we describe a selective excitation technique which, judged by the usual criteria, outdistances existing methods. Our method gives constant phase and amplitude excitation over an easily adjustable bandwidth, can achieve given selectivity in a shorter time than existing methods, has no out-of-band sidelobes, and in exciting a multiplet, refocuses the evolution of scalar coupling. The method is tolerant of radio-frequency (rf) field inhomogeneity, and altering the net flip angle is easy. The use of pulsed field gradients (PFGs)[8,9] results in these crucial properties being achieved in a single scan, without difference spectroscopy or phase cycling: magnetization from outside the desired bandwidth is destroyed, thus simplifying the subsequent manipulation of the excited magnetization. While PFGs have been used to tailor spectral response using single spin echoes, for example with the WATERGATE sequence,[10] and while selective 180° pulses have been used for selective excitation in conjunction with difference spectroscopy,[11] the approach described here is more general.

The heart of the method is the double PFG spin echo (DPFGSE) sequence ($-G_1-S-G_1-G_2-S-G_2-$), in which S is *any sequence of rf pulses of any kind* and the G_i are PFGs. S induces the unitary transformation $U_S = R_{-z}(\beta)\, R_{-y}(\theta)\, R_x(\alpha)\, R_y(\theta)\, R_z(\beta)$ where, *e.g.*, $R_\epsilon(\gamma)$ represents a rotation through an angle γ about an axis ϵ, and α, β, and θ are arbitrary angles. It can be shown[12] that applying a DPFGSE to isolated spins transforms a magnetization vector $\mathbf{m} = (m_x, m_y, m_z)$ into a vector $\mathbf{M}$ with components

$$M_x = P^2 m_x,\ M_y = P^2 m_y,\ M_z = (1 - 2P)^2 m_z \tag{1}$$

where P, a real number $0 \le P \le 1$, is *the probability that a spin is flipped by the sequence of pulses, S.* P is given by[13]

$$P = (1/2)(1 - \mathrm{Tr}\{I_z U_S I_z U_S{}^{\dagger}\}/\mathrm{Tr}\{I_z{}^2\}) \equiv \cos^2(\theta)\sin^2(\alpha/2) \tag{2}$$

The calculation assumes that G_1 and G_2 are strong and that they do not refocus one another.

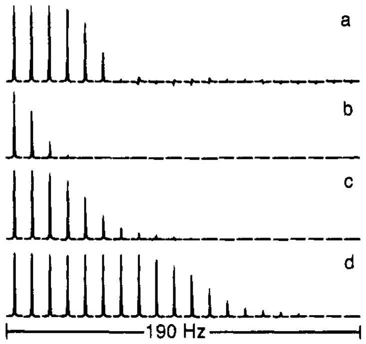

Figure 1. Excitation profiles for various selective pulse methods. Positive resonance offsets are recorded at 10 Hz increments. For each trace, the on-resonance signal was phased to absorption and then the same correction was used for the rest of the spectra. (a) The profile obtained with a 50 ms E-BURP1 selective pulse. (b−d) Profiles obtained with a nonselective 90° pulse followed by a double pulsed field gradient echo, using two 25 ms hyperbolic secant 180° pulses. The time domain envelope is given by the formula $\omega(t) = \omega(0)[\mathrm{sech}(8t/50)]^{(1+i\mu)}$ when t is expressed in milliseconds, $-12.5 \le t \le 12.5$; μ took the values 0, 2.5, and 5.0 in profiles b, c, and d, respectively. The gradients used in the echo sequences were all of duration 1 ms with strengths $G_1 = 0.5$ G cm^{-1} and $G_2 = 1.3$ G cm^{-1}. All spectra were recorded on a 500 MHz Varian UnityPlus spectrometer. The sample was 1% H_2O in D_2O, doped with 0.1 mg/mL $GdCl_3$ to obtain a T_1 of 250 ms.

Three properties follow from eqs 1 and 2. First, independent of both $\mathbf{m}$ and S, transverse magnetization returns to its starting position scaled by a real positive number; the phase is unaffected. Second, magnetization components are not mixed. Third, the excitation profile depends only on the *inversion profile* of S, not its phase properties. Given these properties, the excitation profile can be modified by concatenating several DPFGSEs, each of which may use different rf sequences S; the resulting profile is simply the product of the profiles of each DPFGSE. We note here that a *double* gradient echo is needed to achieve these desirable properties: single echoes create profiles with phase properties that depend on those of the sequence S.[12,14]

The "chipping away" of unwanted magnetization by successive DPFGSEs to reveal the desired excitation profile suggests the name *excitation sculpting* for this technique. Excitation sculpting is a significant advance, as designing specific inversion profiles is far less demanding than controlling both the amplitude and phase of the magnetization. Further, the multiplicative property of the DPFGSE makes it simple to eliminate systematically unwanted excitation sidelobes.

Figure 1 compares four experimental excitation profiles obtained with sequences of identical overall length. Figure 1a shows the profile of a 50 ms E-BURP1 pulse, designed to excite uniformly, and with constant phase, a narrow spectral region.[6] There is only a few degrees variation in phase across the bandwidth, and out-of-band suppression is good, but not excellent; this performance degrades rapidly in both respects if the overall pulse flip angle is miscalibrated (data not shown). Figure 1b−d shows profiles obtained using a hard 90° pulse followed by a DPFGSE in which S is a 25 ms hyperbolic secant (HS) pulse.[3,4] As expected, the phase of all the DPFGSE spectra is constant; out-of-band suppression is far better than with

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(1) Bauer, C.; Freeman, R.; Frenkiel, T.; Keeler, J.; Shaka, A. J. *J. Magn. Reson.* **1984**, *58*, 442.

(2) Gutow, J. H.; McCoy, M.; Spano, F.; Warren, W. S. *Phys. Rev. Lett.* **1985**, *55*, 1090.

(3) Baum, J.; Tycko, R.; Pines, A. *Phys. Rev. A* **1985**, *32*, 3435.

(4) Silver, M. S.; Joseph, R. I.; Hoult, D. I. *Phys. Rev. A* **1985**, *31*, 2753.

(5) Hardy, C. J.; Edelstein, W. A.; Vatis, D. *J. Magn. Reson.* **1986**, *66*, 470.

(6) Geen, H.; Freeman, R. *J. Magn. Reson.* **1991**, *93*, 93.

(7) Emsley, L.; Bodenhausen, G. *J. Magn. Reson.* **1992**, *97*, 135.

(8) Hurd, R. E. *J. Magn. Reson.* **1990**, *87*, 422.

(9) Vuister, G. W.; Bolens, R.; Kaptein, R.; Hurd, R. E.; John, B.; van Zijl, P. C. M. *J. Am. Chem. Soc.* **1991**, *113*, 9688.

(10) Piotto, M.; Saudek, V.; Sklenar, V. *J. Biomol. NMR* **1992**, *2*, 661.

(11) Wu, X. L.; Xu, P.; Freeman, R. *J. Magn. Reson.* **1989**, *83*, 404.

(12) Hwang, T. L; Shaka, A. J. *J. Magn. Reson. A* **1995**, *112*, 275.

(13) Shaka, A. J.; Freeman, R. *J. Magn. Reson.* **1985**, *63*, 596.

(14) Levitt, M. H.; Freeman, R. *J. Magn. Reson.* **1981**, *43*, 65.

0002-7863/95/1517-4199$09.00/0

E-BURP1, and the bandwidth is easily tuned. Furthermore, a modulated HS pulse shows excellent compensation for rf inhomogeneity,[3,4] so pulse miscalibration is relatively unimportant. The transition from 90% to 10% excitation is somewhat less sharp than with E-BURP1.

Excitation sculpting can be used to advantage in the one-dimensional transient NOE experiment. The sequence 90°(x)−DPFGSE−90°(x) inverts a target multiplet, destroying all other magnetization. Cross relaxation occurring during the subsequent mixing time τ_m is then observed by a 90° pulse. A difference method removes unwanted contributions from longitudinal relaxation during τ_m. The unwanted magnetization starts from a null position so that after a short τ_m it is rather small. As the mixing time becomes longer, the magnetization can be kept close to the null position by spacing one or more 180° pulses throughout τ_m. The buildup of the direct NOE enhancements is not affected significantly by these pulses. When a single nulling 180° pulse is incorporated, the timing diagram for the DPFGSE NOE sequence is thus

$$90°(x)-G_1-S-G_1-G_2-S-G_2-90°(x)-\tau_m/2-G_3-180°(x)-\bar{G}_3-\tau_m/2-90°(x)-\text{acquire}$$

where $\bar{G}$ denotes a gradient of opposite polarity.

Figure 2 compares NOE spectra of the organic compound **1** obtained by the conventional steady-state difference method[15] (b) and the DPFGSE NOE method (c). The DPFGSE NOE spectrum approaches the sensitivity of the conventional steady-state spectrum, but has none of the subtraction artifacts evident in the latter. Compared to NOE spectra obtained using the recently published GOESY technique[16] (data not shown) we obtain a theoretical factor of 2 in signal by not discarding one coherence transfer pathway; there is also a large τ_m-dependent gain in sensitivity that we attribute to diffusion losses[17,18] in GOESY, which can be large for long mixing times. As the DPFGSE NOE technique has better sensitivity and the spectra are of the same quality as GOESY spectra, we conclude that the DPFGSE NOE technique is to be preferred.

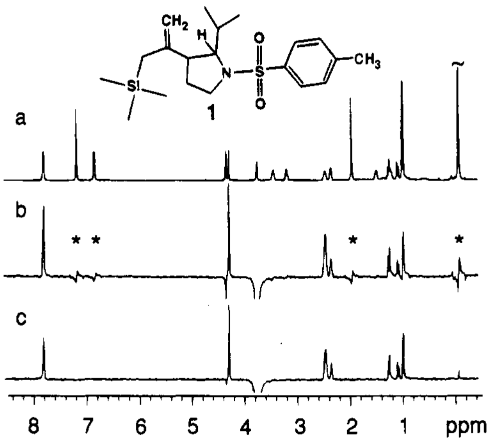

Figure 2. (a) The conventional spectrum of **1**. The target proton is at the 2-positition of the pyrrolidine ring (δ = 3.76). (b) The steady-state NOE experiment (16 scans, 15.0 s saturation, LB = 3 Hz) showing some genuine NOE peaks, some subtraction artifacts (indicated by asterisks), and a small negative indirect NOE (δ = 4.35). (c) The transient DPFGSE NOE experiment (16 scans, τ_m = 2.0 s, LB = 3 Hz). As described in the text, three hard 180° pulses were spaced in the mixing time; the pulses were sandwiched between antiphase gradients, to disperse any transverse magnetization created by an imperfect 180° pulse. Further experiments at different mixing times confirm that the small NOE to the TMS group (δ = −0.1) is genuine. This NOE is undetectable in the conventional steady-state experiment. Spectra b and c are on the same absolute scale. In the DPFGSE NOE experiment the phase of one of the selective pulses was cycled 0°, 90°, 180°, 270° while the receiver followed with 0°, 180°, 0°, 180° to achieve the required subtraction mentioned in the text.

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(15) Sanders, J. K. M.; Mersh, J. D.; *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 353.

(16) Stonehouse, J.; Adell, P.; Keeler, J; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037.

(17) Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *42*, 288.

(18) van Zijl, P. C. M.; Moonen, C. T. W. *J. Magn. Reson.* **1990**, *87*, 18.