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Frequency selective polarization transfer based on multiple chemical shift precession

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Abstract

In this Letter, we have demonstrated a novel strategy for frequency selective polarization transfer in solid-state NMR spectroscopy under magic-angle spinning condition. The polarization transfer during the mixing time is mediated by scalar spin–spin coupling. The frequency selectivity is achieved by inserting free precession periods (windows) in the mixing time, during which the system evolves under the chemical shift difference of the coupled spin pair. Experimental data are obtained for $[U^{13}C, {}^{15}N]$ -alanine and the results can be fully explained by a simple theoretical framework based on the isotropic chemical shifts and the scalar spin–spin coupling. © 2005 Elsevier B.V. All rights reserved.

1. Introduction

Solid-state nuclear magnetic resonance (SSNMR) has proven to be a powerful technique for the structural elucidation of biological solids [1]. The techniques used to restore the anisotropic interactions under the high-resolution condition provided by magic-angle spinning (MAS) are generally known as recoupling [2,3]. There are many frequency-selective techniques available for the recoupling of homonuclear dipolar interactions [4-13]. The feature of frequency selectivity is highly desirable in uniformly labeled systems, which allows the couplings between particular spin pairs to be restored. On the other hand, considerable efforts have also been made to suppress all the internal interactions except the homonuclear scalar spin-spin coupling (J-coupling), so that a scalar zero-quantum Hamiltonian could be obtained for homonuclear polarization transfer [14-21]. J-coupling mediated polarization transfer is inherently selective thanks to its through-bond nature. However, to date it remains difficult to achieve frequency selectivity in this class of SSNMR techniques. One interesting aspect of such development is that one could create a

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pseudo-isolated spin-pair in the context of polarization transfer in a uniformly labeled system. We note in passing that the truncated form of the *J*-coupling Hamiltonian has also been exploited in the context of INADEQUATE experiments [22] and spin-echo measurements [23].

In this work, we propose that multiple chemical shift precession (MCSP) could be employed to achieve frequency selective polarization transfer based on *J*-coupling. Although the MCSP approach will be discussed in the context of *J*-coupling mediated polarization transfer, its utility is quite general and can be readily applied to the regime of dipolar recoupling.

2. Theory

Under the condition of magic angle spinning at frequency $\omega_{\rm R} = 2\pi v_{\rm R}$, the high-field Hamiltonian of a spin-1/2 system takes the following form in the rotating frame:

$$H(t) = H_{\rm rf}(t) + H_{\rm int}(t) \tag{1}$$

$$H_{\rm int}(t) = \sum_{\Lambda m \lambda} \omega_m^{\Lambda} \exp(im\omega_{\rm R} t) T_{\lambda 0}^{\Lambda}, \qquad (2)$$

where Λ represents various internal interactions, ω_m^{Λ} are the orientation-dependent coefficients of the Fourier components of the spatial functions ($-2 \le m \le 2$), and $T_{\lambda 0}^{\Lambda}$ are

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irreducible tensor operators of rank λ . Previously, we have demonstrated that the pulse sequence R-TOBSY [18], which falls within the symmetry class RN_n^{ν} described by Levitt [24,25], can be used to realize homonuclear polarization transfer via spin–spin scalar coupling (*J*-coupling) in biological solids without proton decoupling [21].

2.1. Two-spin system

For simplicity we first consider a two-spin system. The spin dynamics during the polarization transfer and the free evolution periods can be described elegantly based on the single transition operator formalism [26–28]. Accordingly, in the interaction frame defined by rf field of the R-TOBSY sequence, the average Hamiltonian calculated to the lowest order is [18]

$$\bar{H}^* = 2\pi J (\mathbf{I}^{(1,4)} - \mathbf{I}^{(2,3)} + S_x^{(2,3)}),$$
(3)

where $\mathbf{I}^{(i,j)}$ is the identity operator of the subspace (i,j). On the other hand, in the absence of rf irradiation the averaged Hamiltonian in the rotating frame over one rotor period is

$$\bar{H}^{\mathbf{R}} = \omega_{\Sigma} S_{z}^{(1,4)} + \omega_{\Delta} S_{z}^{(2,3)} + 2\pi J (\mathbf{I}^{(1,4)} - \mathbf{I}^{(2,3)}),$$
(4)

where ω_{Σ} and ω_{Δ} denote the sum and difference, respectively, of the isotropic chemical shifts of the two interacting spins in angular frequency unit. For brevity, all the identity operators will be discarded in the subsequent discussion. Referring to the pulse sequence shown in Fig. 1, the shaded part after cross-polarization serves to select the S_1 polarization, which is subsequently identified with the ¹³C polarization of the carbonyl carbon in our experiment. Hence, the initial density matrix operator is written as

$$\sigma^*(0) = S_{1z} = S_z^{(1,4)} + S_z^{(2,3)},$$
(5)

where σ^* denotes the density operator in the interaction frame. Based on the commutation relations of the single transition operators [26,27], Eq. (5) can be calculated as

$$\sigma^*(\tau_1) = S_z^{(1,4)} + S_z^{(2,3)} \cos(2\pi J \tau_1) - S_y^{(2,3)} \sin(2\pi J \tau_1).$$
(6)



Fig. 1. Pulse sequence for the measurements on [U¹³C, ¹⁵N]-alanine. Black rectangular black blocks represent $\pi/2$ pulses. The Gaussian-shaped pulse is a selective $\pi/2$ pulse positioned in the aliphatic region. The shaded part is meant for the preparation of the C' polarization. N denotes the number of R-TOBSY mixing periods. Experimentally, we have $\tau_1 = \tau_3 = \tau$ and the total mixing time $N \times \tau$ is set to the optimum value for the polarization transfer from C' to C_x.

Because the R-TOBSY sequence is cyclic and periodic, the rotating frame and the interaction frame overlap whenever τ_1 equals to an integral multiple, say *m*, of the R-TOBSY cycle time ($\delta \tau_R$). Consequently, for $\tau_1 = m(\delta \tau_R)$ the density matrix operator during the free precession period (τ_2) becomes:

$$\sigma^{R}(\tau_{2}) = S_{z}^{(1,4)} + S_{z}^{(2,3)} \cos(2\pi J \tau_{1}) - S_{y}^{(2,3)} \sin(2\pi J \tau_{1}) \\ \times \cos(\omega_{\Delta} \tau_{2}) + S_{x}^{(2,3)} \sin(2\pi J \tau_{1}) \sin(\omega_{\Delta} \tau_{2}).$$
(7)

Eventually, the evolution of the density matrix operator during the second R-TOBSY mixing period (τ_3) can be calculated as

$$\begin{aligned} \sigma^{*}(\tau_{3}) &= S_{z}^{(1,4)} + S_{z}^{(2,3)} \cos(2\pi J \tau_{1}) \cos(2\pi J \tau_{3}) \\ &- S_{y}^{(2,3)} \cos(2\pi J \tau_{1}) \sin(2\pi J \tau_{3}) \\ &- S_{y}^{(2,3)} \sin(2\pi J \tau_{1}) \cos(\omega_{\Delta} \tau_{2}) \cos(2\pi J \tau_{3}) \\ &- S_{z}^{(2,3)} \sin(2\pi J \tau_{1}) \cos(\omega_{\Delta} \tau_{2}) \sin(2\pi J \tau_{3}) \\ &+ S_{x}^{(2,3)} \sin(2\pi J \tau_{1}) \sin(\omega_{\Delta} \tau_{2}). \end{aligned}$$
(8)

When the duration of the free precession period is chosen as $\tau_2 = 2\pi/\omega_{\Delta}$, we have

$$\sigma^{*}(\tau_{3}) = S_{z}^{(1,4)} + S_{z}^{(2,3)} \cos[2\pi J(\tau_{1} + \tau_{3})] - S_{y}^{(2,3)} \sin[2\pi J(\tau_{1} + \tau_{3})].$$
(9)

The above result is equivalent to Eq. (6), showing that the free precession period practically has no effect on the spin dynamics. That is, for the total mixing time $(\tau_1 + \tau_3)$ equal to 1/2J, the initial polarization on the spin 1 will be completely transferred to the spin 2. On the other hand, when $\tau_2 = \pi/\omega_{\Delta}$, Eq. (8) becomes

$$\sigma^{*}(\tau_{3}) = S_{z}^{(1,4)} + S_{z}^{(2,3)} \cos[2\pi J(\tau_{1} - \tau_{3})] - S_{y}^{(2,3)} \sin[2\pi J(\tau_{1} - \tau_{3})]$$
(10)

When τ_1 is set equal to τ_3 the polarization transfer between the two spins will be quenched. Consequently, our approach has the selection rules $\tau_2 = 2\pi/\omega_{\Delta}$ (transfer) and $\tau_2 = \pi/\omega_{\Delta}$ (no transfer) for frequency selective polarization transfer.

2.2. Three-spin system

For a three-spin system S_1 - S_2 - S_3 , the corresponding average Hamiltonians in different periods are:

$$\bar{H}^* = (2\pi J_{12})S_1S_2 + (2\pi J_{23})S_2S_3 + (2\pi J_{13})S_1S_3, \tag{11}$$

$$\begin{split} \bar{H}^{\kappa} &= \delta_1 S_{1z} + \delta_2 S_{2z} + \delta_3 S_{3z} + (2\pi J_{12}) S_{1z} S_{2z} + (2\pi J_{23}) S_{2z} S_{3z} \\ &+ (2\pi J_{13}) S_{1z} S_{3z}. \end{split}$$
(12)

The evolution of the spin system can be calculated as

$$\sigma^{*}(\tau_{3}) = \exp\left\{-i\bar{H}^{*}\tau_{3}\right\} \exp\left\{-i\bar{H}^{R}\tau_{2}\right\} \exp\left\{-i\bar{H}^{*}\tau_{1}\right\} S_{1z}$$

$$\times \exp\left\{i\bar{H}^{*}\tau_{1}\right\} \exp\left\{i\bar{H}^{R}\tau_{2}\right\} \exp\left\{i\bar{H}^{*}\tau_{3}\right\}.$$
(13)

Since it is not trivial to evaluate Eq. (13) analytically, we have to resort to numerical simulations.

3. Experimental

All NMR experiments were carried out at ¹³C and ¹H frequencies of 75.5 and 300.1 MHz, respectively, on a Bruker DSX300 NMR spectrometer equipped with a commercial 2.5 mm probe. The spectra were measured at room temperature at a spinning frequency of 25 kHz. MAS frequency variation was limited to ± 10 Hz using a commercial pneumatic control unit. The samples were confined in the middle 1/2 of the rotor volume using Teflon spacers. During the cross-polarization contact time (1.5 ms) the ¹H nutation frequency was set to 50 kHz and that of ¹³C was ramped through the Hartmann-Hahn matching. The $\pi/2$ Gaussian selective pulse was set to 475 µs long and positioned at the mid-point between the C_{α} and C_{β} resonances. Recycle delay was set to 4 s. Proton decoupling was set to 100 kHz. For the R-TOBSY pulse block, the ¹³C nutation frequency was set to 125 kHz as required by the pulse symmetry [18]. The overall R-TOBSY mixing time was set to 9.6 ms. A total of eight transients were accumulated for each spectrum based on the CYCLOPS phase cycling scheme. The corresponding pulse sequence is shown in Fig. 1.

We have employed two packages for our numerical simulations, viz. MathNMR [29] and SIMPSON [30]. For our SIMPSON simulation (version 1.1.0.), the maximum time step over which the Hamiltonian is approximated to be time-independent was set to 1.0 µs. Typically, a powder averaging scheme containing 100 REPULSION angles (α and β [31] and 18 γ angles was chosen. Relaxation effects were ignored. There are altogether four spins (C', C_{α} , C_{β} and H_{α}) in the spin cluster. The geometrical and the NMR parameters of the spin system were based on the structural [32] and NMR [33] parameters of alanine. The C'-C_{α} and C_{α}-C_{β} J-coupling constants were set to 50 and 35 Hz, respectively. For simplicity, the orientation of CSA tensors with respect to the dipolar framework was set arbitrarily. Initially the polarizations of C_{α} and C_{β} were nullified. Other simulation parameters were matched to the experimental conditions.

4. Results and discussion

The NMR parameters of the ¹³C species of alanine including the chemical shifts (C', 145 ppm; C_{α} , 31 ppm; C_{β} , 0 ppm) as well as the J couplings (C'- C_{α} , 50 Hz; C_{α} - C_{β} , 35 Hz) are taken to define a three-spin system. To understand the dynamics of the three-spin system described by Eq. (13), we employ the package MathNMR, which is developed for symbolic calculations in NMR [29], to calculate the projection of the density matrix operator onto the operators S_{1z} (C'), S_{2z} (C_{α}) and S_{3z} (C_{β}) at different τ_2 values. Fig. 2 shows the calculated polarizations of the three carbon species as a function of the precession period τ_2 ,

1.0 0.8 olarization 0.6 0.4 0.2 0.0 100 150 200 250 300 350 400 50 $\tau_2^{(us)}$

Fig. 2. Plot of the calculated polarizations of C', C_{α} and C_{β} as a function of the τ_2 precession time. The polarizations are normalized by the initial C' polarization. The calculations were based on Eq. (13), for which we set $\tau_1 = \tau_3 = 5$ ms.

where we have $\tau_1 = \tau_3 = 5$ ms. For $\tau_2 = 0$, the initial polarization of the C' carbon is largely transferred to C_{α} and C_{β} , just as what we expected for a regular TOBSY-like experiment [14]. As the τ_2 value increases to the time point t_a or $t_{\rm c}$, which are close to the no transfer condition between C' and C_{α} , both the C_{α} and C_{β} polarizations become diminished. Indeed, the oscillations of the C' and C_{α} polarizations could be well understood based on the aforementioned selections rules, where we have optimum polarization transfer from C' to C_{α} when τ_2 is equal to 125 μ s (t_b) and 234 μ s (t_d) at 7.05 T. Note that the C_{β} polarization does not follow a simple modulation pattern because its magnitude is affected both by the C_{α} polarization and the small J-coupling between C_{α} and C_{β} . It is interesting to find that the C_{α} polarization shows a maximum at the time point t_d . Because the total polarization is a constant of motion, it is obvious that the gain in C_{α} polarization can be obtained at the expense of the C' and C_{β} polarizations. Although it is impossible to find a particular τ_2 that both C' and C_{β} polarizations are at minimum simultaneously, it remains possible to apply multiple τ_2 free precession periods to achieve the goal. The idea has a close resemblance to the DANTE concept for selective excitation [34].

Fig. 3 shows the calculated polarizations of C_{α} and C_{β} as the number of R-TOBSY mixing periods (*N*) increases, where the τ_2 period and the total mixing time are fixed at 117 µs and 10 ms, respectively. When *N* is equal to unity, the initial polarization of the C' carbon is largely transferred to C_{α} and C_{β} . As expected, the C_{β} polarization diminished monotonically as *N* increases because the τ_2 period differs considerably from the inverse of the chemical shift difference between C_{α} and C_{β} . Since the *J*-coupling between C' and C_{β} is negligible, the loss in the C_{β} polarization will results in an increase of the C_{α} polarization. Our treatment thus far has completely ignored the effects of anisotropic interactions during the τ_2 precession period.



Fig. 3. Plot of the polarizations of C_{α} and C_{β} as the number of R-TOBSY mixing periods increase from 1 to 5. The polarization of C' remains essentially unchanged. The open and filled symbols denote the SIMPSON simulation results and those calculated based on Eq. (13), respectively.

To evaluate the effects of chemical shift anisotropy and the homonuclear dipolar interaction we perform a SIMPSON simulation to verify the results shown in Fig. 3. The open symbols denote the SIMPSON simulation results, which are in good agreement to those calculated based on Eq. (13) (filled symbols).

Experimentally we test our MCSP approach on [U¹³C, ¹⁵N]-alanine based on the pulse sequence shown in Fig. 1. Referring to Fig. 4, the upper trace represents the regular R-TOBSY experiment, i.e. $\tau_2 = 0$, in which a significant portion of the C' polarization has been transferred to C_{α} and C_{β} [21]. As we set τ_2 equal to $1/\Delta$ and increase the N from 1 to 4, a significant increase in the C_{α} polarization is produced at the expense of the C_{β} polarization. This experimental observation is completely in line with our analysis based on Eq. (13). Clearly, the selectivity of the MCSP approach depends on the number of precession



Fig. 4. Experimental results measured for [U ¹³C, ¹⁵N]-alanine based on the pulse sequence shown in Fig. 1. The polarization of C_{α} after the mixing period increases as the number of R-TOBSY mixing periods increases to 4. Accordingly, the C_{β} is nullified eventually.

periods. An optimum value for *N* has to be determined experimentally. To stabilize the performance of our pulse sequence with respect to pulse imperfections the phase inversion supercycles are incorporated as shown in Fig. 4 [35]. A more elaborate theoretical consideration is required to understand whether these supercycles would further enhance the polarization transfer efficiency to C_{α} .

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