Frequency-modulated cross-polarization for fast magic angle spinning NMR at high fields: relaxing the Hartmann–Hahn condition

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Abstract

Two novel schemes are described for cross polarization in nuclear magnetic resonance that make it possible to achieve an efficient transfer of polarization from abundant I spins to dilute S spins under high-speed magic angle spinning spectroscopy, which is useful for systems with large chemical shift anisotropies at high fields. The frequency of one of the RF carriers is modulated sinusoidally during spin-locking while the RF amplitude is kept constant. It is shown by experiment that frequency modulation greatly attenuates the critical character of the Hartmann–Hahn matching condition, and allows one to obtain uniform excitation over a wide range of offsets. Signal intensities of $^{13}$C resonances in alanine were obtained as a function of mismatch at spinning speeds of 12 and 15 kHz and a static field strength of 14 T (600 MHz for proton NMR) to illustrate the advantages of these schemes.

1. Introduction

Cross polarization (CP) [1] allows one to enhance the polarization of nuclei S with low gyromagnetic ratios such as $^{13}$C by exploiting the much larger polarization associated with abundant nuclei I with higher gyromagnetic ratios such as $^1$H or $^{19}$F. In static samples, efficient transfer can be achieved by locking both I and S spins with radio frequency (RF) amplitudes that fulfill the Hartmann–Hahn matching condition $\omega_{1I} = \omega_{1S}$ [2], where $\omega_{1I} = \gamma I B_{1I}^I$ and $\omega_{1S} = \gamma S B_{1S}^S$ are the amplitudes of the RF fields applied to the I and S spins. When combined with magic angle spinning (MAS) and high power proton decoupling during signal acquisition, CPMAS [3–5] has become a routine technique in solid state NMR. As long as the spinning speed is much smaller than the homogeneous linewidth of the I spins, spin diffusion among the I spins is efficient, and the Hartmann–Hahn matching condition can be slightly violated without dramatic consequences. However, when the spinning speed is comparable to, or larger than, the linewidth of the I spins, spin diffusion among the I spins is significantly attenuated. As a result, the efficiency of cross-polarization becomes a critical function of the mismatch $\Delta = \omega_{1I} - \omega_{1S}$. The Hartmann–Hahn matching condition is broken up into a series of sidebands at $\Delta = \omega_{1I} - \omega_{1S} = n \omega$, where

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[6,7], where $\omega_s$ is the spinning frequency and $n$ an integer. The width of these sidebands is much narrower than the width of the Hartmann–Hahn condition for a static sample because the dipolar interactions are greatly reduced by spinning at very high speeds. Moreover, cross-polarization is usually fairly ineffective for $n = 0$ and most efficient at the first and second sidebands in the mismatch spectrum, i.e. for $n = \pm 1$ or $\pm 2$. For these sidebands, the matching condition tends to be very sensitive to RF inhomogeneities [8,9], and at high spinning speeds cross-polarization becomes critically dependent on the precise calibration of the RF fields. These problems tend to be exacerbated at high static magnetic fields (e.g. at 14 T or 600 MHz for proton NMR at the National High Magnetic Field Laboratory), in part because the magnitudes of the chemical shift anisotropies make it necessary to use very fast spinning to attenuate spinning sidebands, and in part because the dispersion of the isotropic chemical shifts can be large, so that one must fulfill the matching condition over a wide range of offsets with respect to the RF carrier.

Recently, the difficulties encountered with cross-polarization under fast magic angle spinning have received much attention. Several methods have been developed to enhance the rate of cross polarization and to broaden the width of the Hartmann–Hahn matching condition. Most studies have focused on means to prevent the heteronuclear dipolar interactions from being averaged out completely under fast spinning. Several methods have been suggested to restore the heteronuclear dipolar interaction and to enhance spin diffusion among the protons. Mechanical methods may involve flipping the sample rotation axis away from the magic angle [7,10], slowing or even stopping sample spinning [11,12] during cross-polarization, while acquiring the signal under fast spinning at the magic angle. However, such methods require specific hardware and sacrifice signal intensity because of relaxation during the switching intervals. As alternatives to mechanical methods, a variety of schemes have been proposed which use time-dependent RF fields to recover the heteronuclear dipolar interactions during cross-polarization at high spinning speeds. Barbara and Williams [13] and Wu and Zilm [14] proposed schemes using simultaneous phase-inversion cross-polarization (SPICP) in synchronization with sample spinning. Hediger, Meier and Ernst [8,9] proposed S- and D-AMCP schemes where the RF amplitudes are modulated during spin locking, in synchronization with sample spinning. Zhang [15] and Smith et al. [16–18] described variable-amplitude cross-polarization (VACP) and ramped-amplitude cross polarization schemes where the RF amplitude applied to the I- or S-spin is stepped through a set of discrete values, without requiring rotor synchronization. More recently, an alternative approach was proposed by Kolbert and Bielecki [19] where the RF field applied to the I spins is initially on-resonance but swept adiabatically off-resonance during the contact time, while the RF amplitude is kept constant. This gives rise to an effective precession frequency that starts with $\omega_{1f}$ and gradually increases during cross polarization, while the effects of spin–lattice relaxation in the tilted rotating frame are attenuated.

In this work, we propose alternative schemes where one of the two carrier frequencies $\Delta \omega_i$ or $\Delta \omega_s$ is modulated in a periodic fashion during cross-polarization, oscillating adiabatically back and forth about the respective Larmor frequencies, while the RF amplitudes $\omega_{1f}$ or $\omega_{1s}$ are kept constant on both channels. The modulation period need not be commensurate with the period of sample rotation. The advantages of these schemes will be discussed in the following sections.

2. Theory

For simplicity, we consider an isolated $I$S two-spin system. As in conventional cross-polarization, a 90° pulse is first applied to the $I$ spins along the $+y$ axis, followed by spin-locking pulses along the $+x$ axes of the frames of both $I$ and $S$ spins. The frequencies of the two RF carriers will be modulated during cross polarization:

$$\omega_i(t) = \omega_{0i} + \Delta \omega_{mod}^i(t). \quad (1a)$$

$$\omega_s(t) = \omega_{0s} + \Delta \omega_{mod}^s(t). \quad (1b)$$

Normally, the time-independent terms $\omega_{0i}$ and $\omega_{0s}$ are chosen so that the carriers appear in the middle of the $I$- and $S$-spin spectra if the modulations are
switched off, i.e. if \( \Delta \omega_{\text{mod}}^{l}(t) = \Delta \omega_{\text{mod}}^{S}(t) = 0 \). The Hamiltonian in the laboratory frame is:

\[
H_{RF} = 2 \omega_{1,l} I_{X} \cos \left[ \omega_{0,l} t + \varphi_{l}(t) \right] + 2 \omega_{1,S} S_{X} \cos \left[ \omega_{0,s} t + \varphi_{s}(t) \right],
\]

(2)

where \( \omega_{1,l} \), \( \omega_{1,S} \), \( \varphi_{l}(t) \), and \( \varphi_{s}(t) \) are the constant amplitudes and time-dependent phases of the spin-locking pulses. The latter are defined by integration over the time-dependent parts of the two carrier frequencies of Eqs 1:

\[
\varphi_{l}(t) = \int \Delta \omega_{\text{mod}}^{l}(t) \, dt,
\]

(3a)

\[
\varphi_{s}(t) = \int \Delta \omega_{\text{mod}}^{S}(t) \, dt.
\]

(3b)

In a doubly-rotating interaction frame which tracks the instantaneous carrier frequencies in such a manner that the two RF fields appear stationary, the Hamiltonian of an isolated IS system is:

\[
H = - \Delta \omega_{l} I_{Z} - \Delta \omega_{l}^{l}(t) I_{Z} - \omega_{1,l} I_{X} - \Delta \omega_{s} S_{Z} - \Delta \omega_{s}^{S}(t) S_{Z} - \omega_{1,S} S_{X} + 2 b(\beta, \gamma, t) I_{Z} S_{Z},
\]

(4)

where \( \Delta \omega_{l} \) and \( \Delta \omega_{s} \) are the time-independent isotropic shifts of the \( I \) and \( S \) spins with respect to \( \omega_{0,l} \) and \( \omega_{0,s} \). Because of the high spinning speed, the time dependence due to the modulation of the anisotropic parts of the chemical shifts induced by sample rotation will be omitted from the following discussion. The term \( b(\beta, \gamma, t) \) represents the heteronuclear dipolar coupling for the \( I-S \) pair, which is time-dependent under sample spinning [8,9]:

\[
b(\beta, \gamma, t) = \sum_{k=-2}^{2} b_{k}(\beta, \gamma) \exp(ik\omega_{i} t),
\]

(5)

with the components

\[
b_{0} = 0,
\]

\[
b_{\pm 1}(\beta, \gamma) = - \frac{\gamma_{I} \gamma_{S} h}{4\pi r_{IS}^{3}} \sqrt{2} \sin(2\beta) \exp(\pm i\gamma),
\]

\[
b_{\pm 2}(\beta, \gamma) = - \frac{\gamma_{I} \gamma_{S} h}{4\pi r_{IS}^{3}} \sin^{2}\beta \exp(\pm i2\gamma).
\]

(6)

The angles \( \beta \) and \( \gamma \) define the orientation of the internuclear vector \( r_{IS} \) with respect to the rotor axis, and \( \omega_{i} \) is the spinning frequency. In the doubly-tilted interaction frame, the Hamiltonian of Eq. (4) becomes:

\[
\vec{H} = - \omega_{e,l} I_{Z} - \omega_{e,s} S_{Z} + 2 b_{l,x} S_{X} \sin \theta_{l} \sin \theta_{s} + 2 b_{l,z} S_{Z} \cos \theta_{l} \cos \theta_{s} - 2 b_{s,z} \sin \theta_{l} \cos \theta_{s} - \frac{d\theta_{l}(t)}{dt} I_{Y}
\]

\[
- \frac{d\theta_{s}(t)}{dt} S_{Y},
\]

(7)

with the effective fields

\[
\omega_{e,l,s} = \sqrt{\omega_{e,l,s}^{2} + \left( \Delta \omega_{\text{mod}}^{l,s}(t) + \Delta \omega_{l,s}(t) \right)^{2}}.
\]

(8)

The angles \( \theta_{l}(t) \) and \( \theta_{s}(t) \) are defined by

\[
\tan \theta_{l,s}(t) = \omega_{\text{mod}}^{l,s}(t) + \Delta \omega_{l,s}(t).
\]

(9)

In systems which contain several chemically inequivalent spins \( S \) with distinct isotropic shifts, each site has its own offset \( \Delta \omega_{s} \) and tilt angle \( \theta_{s}(t) \). Even for continuous on-resonance spin-locking, and even for a simple two-spin system, the dynamics of cross polarization under the Hamiltonian of Eq. (7) are difficult to describe analytically [20]. However, if the adiabatic conditions

\[
\frac{d\theta_{l,s}(t)}{dt} \ll \omega_{e,l,s}
\]

(10)

are fulfilled, Eq. (7) can be simplified by dropping the last two time-dependent terms. In Eq. (7), the first two terms represent the effective spin-locking fields of the \( I \) and \( S \) spins, and the next four terms describe the heteronuclear dipolar coupling. Clearly, by modulating the carrier frequencies, i.e. by imposing a suitable time-dependence on the angles \( \theta_{l}(t) \) or \( \theta_{s}(t) \), it is possible to modulate the heteronuclear coupling term.

Fig. 1b and c show two cross-polarization sequences where the carrier frequency of one of the spin-locking pulses applied to either \( I \) (\(^{1}H\)) or \( S \) (\(^{13}C\)) is modulated while the RF amplitudes are kept constant. Of the many possible realizations, we have chosen the simplest scheme where one of the two RF carrier frequencies is modulated sinusoidally,

\[
\Delta \omega_{\text{mod}}^{l,s}(t) = \omega_{d}^{l,s} \sin \omega_{m}^{l,s} t,
\]

(11)

where \( \omega_{d}^{l,s} \) and \( \omega_{m}^{l,s} \) are the amplitudes of the frequency modulations, and \( \omega_{m}^{l} \) and \( \omega_{m}^{s} \) the modula-
2.1. (A) Frequency modulation of the RF field applied to the \( I \) spins

This case is similar to the adiabatic frequency sweep proposed by Kolbert and Bielecki [19]. In their experiments, the carrier frequency was swept away from resonance in such a manner that the amplitude of the effective field increases monotonically, while the modulation is cyclic in our experiments. The adiabatic condition of Eq. (10) can easily be fulfilled throughout the modulation cycle, as can be seen from Eq. (12), so that there are no significant losses of magnetization during spin locking. The effective field is always larger than or equal to the RF amplitude \( \omega_{1I} \), resulting in a slower rotating-frame spin–lattice relaxation rate \( 1/T_{1p}^{I} \) [8,9,19], which is favorable for the outcome of the experiment.

2.2. (B) Frequency modulation of the RF field applied to the \( S \) spins

Again, the adiabatic condition can be fulfilled throughout the modulation cycle, so that there are no significant losses of magnetization during frequency-modulated spin locking. One of the crucial advantages of this scheme is that the efficiency of cross-polarization is less sensitive to time-independent offsets \( \Delta \omega_{2} \) that are due to isotropic shifts of the \( S \) spins, which can be quite significant in high static fields.

In either case (A) or (B), the effect of the Hartmann–Hahn mismatch was evaluated by parametric variation of the amplitude of the RF field that was not subject to frequency modulation.

Simultaneous modulation of the RF fields applied to both \( I \) and \( S \) spins represents a third option which has been explored but was found to be difficult to evaluate with respect to the Hartmann–Hahn mismatch.

3. Experimental

The experiments were performed on a Bruker DMX-600 spectrometer \((B_0 = 14 \text{ T})\) with Larmor frequencies of 150 MHz for \(^{13}\text{C}\) and 600 MHz for \(^{1}\text{H}\), equipped with a Bruker probe with a 4 mm outer
diameter high-speed MAS rotor. The variation of the spinning speed was controlled to within ±3 Hz. A sample of DL-alanine (Aldrich Chemical Co.) was used without further purification. The waveforms of the frequency modulation of the spin-lock pulses were generated by a C program and transferred to the waveform generator. Continuous-wave proton decoupling with an RF amplitude of 70 kHz, which is the maximum power that can safely be used, was applied during the acquisition of the $^{13}\text{C}$ signals. For each experiment, 16 scans were accumulated with a recycle time of 2 s.

4. Results and discussion

Fig. 2 shows so-called 'mismatch profiles', i.e. cross-polarized signal intensities of $^{13}\text{COO}$, $^{13}\text{CH}$ and $^{13}\text{CH}_3$ in a sample of DL-alanine spinning at 12 kHz recorded as a function of the mismatch $\Delta = \omega_{1S} - \omega_1$ from the Hartmann–Hahn condition. The contact time $\tau_{CP}$ for all cross-polarization experiments was 5 ms. The time-independent part of the $^{13}\text{C}$ carrier frequency $\omega_{1S}$, as seen in Eq. (1b), was set to coincide with the $^{13}\text{CH}$ resonance. The offsets $\Delta \omega_{1S}$ (i.e. the distances between the isotropic shifts and $\omega_{1S}$) of the $^{13}\text{COO}$ and $^{13}\text{CH}_3$ resonances were +126.6 and −29.4 ppm respectively (+19.0 and −4.4 kHz at 14 T). When both $^1\text{H}$ and $^{13}\text{C}$ are spin-locked by conventional CW pulses, the mismatch profile recorded while varying the RF amplitude $\omega_{1S}$ breaks up into sidebands (Fig. 2a). Note that the positions of these sidebands vary for the different sites $^{13}\text{COO}$, $^{13}\text{CH}$ and $^{13}\text{CH}_3$, because the effective fields $\omega_{1S}$ depend not only on the RF amplitude $\omega_{1S}$ but also on the resonance offsets $\Delta \omega_{1S}$. When a frequency-modulated RF field with $\omega_1/2\pi = 85$ kHz and $\omega_{10}/2\pi = 1/\tau_{CP} = 200$ Hz is applied to the protons, as shown in Fig. 2b, the Hartmann–Hahn matching condition is significantly broadened. When a similar frequency modulation is applied to $^{13}\text{C}$ rather than to $^1\text{H}$, the Hartmann–Hahn matching condition is again broadened very effectively, as shown in Fig. 2c. As expected, when the $^1\text{H}$ spin locking field is weak (i.e., towards the right-hand side of Fig. 2c), the $^{13}\text{C}$ signals are less intense. It is clear that the intensities of $^{13}\text{CH}_3$ (but not of $^{13}\text{CH}$ and $^{13}\text{COO}$) are significantly enhanced in Fig. 2b, while all three resonances are greatly enhanced in Fig. 2c, because the latter scheme is largely insensitive to the dispersion of the isotropic $^{13}\text{C}$ chemical shifts.

![Fig. 2. Signals recorded as a function of mismatch $\Delta = \omega_{1S} - \omega_1$ with respect to the Hartmann–Hahn condition ('mismatch profiles'). The signal intensities of three $^{13}\text{C}$ resonances of DL-alanine spinning at 12 kHz are recorded with different cross-polarization techniques: $^{13}\text{COO}$ (○), $^{13}\text{CH}$ (+) and $^{13}\text{CH}_3$ (▲). The contact time $\tau_{CP}$ was 5 ms in all cases. (a) Conventional CW spin-locking of both spins, with a fixed amplitude $\omega_1/2\pi = 42$ kHz and parametric variation of the amplitude $\omega_{1S}$ from one experiment to the next. (b) The frequency $\Delta \omega_{10}$ of the $I$ spin–lock pulse, with a fixed amplitude $\omega_{10}/2\pi = 42$ kHz, was modulated with parameters $\omega_1/2\pi = 85$ kHz and $\omega_{10}/2\pi = 1/\tau_{CP} = 200$ Hz. A CW spin-lock pulse was applied to the $S$ spins with parametric variation of the amplitude $\omega_{1S}$. (c) A CW spin–lock pulse was applied to the $I$ spins with parametric variation of the amplitude $\omega_{10}$. The frequency $\Delta \omega_{10}$ of the $S$ spin–lock pulse, with a fixed amplitude $\omega_{10}/2\pi = 42$ kHz, was modulated with parameters $\omega_1/2\pi = 85$ kHz and $\omega_{10}/2\pi = 1/\tau_{CP} = 200$ Hz. All intensities were normalized to the CH signal obtained with $\Delta = 0$ and the conventional scheme (a).]
Fig. 3 shows matching profiles recorded under the same experimental conditions as Fig. 2, except that the spinning frequency was increased to 15 kHz. Again, the matching condition is significantly broadened when frequency modulation is applied to $^1$H (Fig. 3b) or, even more dramatically, when applied to $^{13}$C (Fig. 3c). The signal intensities of the $^{13}$COO site, which has the largest offset $\Delta \omega_s$, are much higher in Fig. 3c than in either Fig. 3a or b, indicating that large offsets can be overcome by frequency modulation on the $S$ channel.

In order to study the ‘build-up’ behavior, we have examined the $^{13}$C signal intensities as a function of the duration of the cross-polarization contact time $0 < \tau_{CP} < 5$ ms, as shown in Fig. 4 for the exact matching condition $\Delta = \omega_{15} - \omega_{11} = 0$ and a spinning speed of 15 kHz. The parameters of the frequency modulation were kept constant in these experiments ($\omega_\Delta / 2\pi = 85$ kHz and $\omega_m / 2\pi = 1 / \tau_{CP}$).

![Fig. 3. Same as Fig. 2 but with a spinning speed of 15 kHz.](image)

![Fig. 4. Build-up curves recorded for $0 < \tau_{CP} < 5$ ms at the Hartmann–Hahn matching condition $\Delta = \omega_{15} - \omega_{11} = 0$ with different cross polarization schemes for $^{13}$COO (O), $^{13}$CH (+) and $^{13}$CH$_3$ (A) in alanine, with $\omega_{11} / 2\pi = \omega_{15} / 2\pi = 42$ kHz and a spinning speed of 15 kHz. (a) Conventional CW spin–locking of both spins. (b) The frequency $\omega_\Delta(t)$ of the $I$ spin–lock pulse was modulated according to Eqs. (1a) and (11) with $\omega_\Delta = 85$ kHz and $\omega_m / 2\pi = 1 / \tau_{CP}^{\text{max}} = 200$ Hz, while a CW spin–lock pulse with $\omega_{15} / 2\pi = 42$ kHz was applied to the $S$ spins. (c) The frequency $\omega_\Delta(t)$ of the $S$ spin–lock pulse was modulated with parameters $\omega_\Delta / 2\pi = 85$ kHz and $\omega_m / 2\pi = 1 / \tau_{CP}^{\text{max}} = 200$ Hz, while a CW spin–lock pulse with $\omega_{11} / 2\pi = 42$ kHz was applied to the proton spin. The oscillatory response and the simulated curves are discussed in the text. In each scheme, all intensities were normalized to the $^{13}$CH signal with $\tau_{CP}^{\text{max}} = 5$ ms.

$= 200$ Hz), so that the contact time $\tau_{CP}$ was not commensurate with the modulation period $2\pi / \omega_m = 5$ ms. As expected for conventional CW cross-polarization (Fig. 4a), the build-up rates are faster for $^{13}$CH$_3$ and $^{13}$CH than for $^{13}$COO, because the carboxylic carbons are weakly coupled to the protons. The decay of the signal amplitudes for larger contact times must be attributed to $T_1^\epsilon$. When frequency modulation is applied to the $^1$H channel (Fig. 4b),
the build-up behavior is significantly improved. On the other hand, when frequency modulation is applied to the $^{13}$C channel (Fig. 4c), an oscillatory behavior is observed. This is due to the fact that the polarized $^{13}$C magnetization is always locked along the effective field that oscillates adiabatically in the $xz$ plane, while only the transverse $S_z$ component is observed, i.e., $S_x = |S|\sin \theta_5(t)$. Of the two continuous curves superimposed in Fig. 4c, the smooth build-up and decay was calculated for the magnitude $|S|$ of the $^{13}$CH$_3$ signal, fitted with only two rates $T_{1S}$ and $T_{1p}$, whereas the oscillating curve incorporates the projection $\sin \theta_5(t)$. The time-dependences of the $^{13}$COO and $^{13}$CH signals can be fitted in similar fashion.

5. Conclusions

We have demonstrated two novel methods for cross polarization that are suitable for high speed magic-angle spinning, when the frequency of one of the spin-locking fields is modulated sinusoidally during the Hartmann–Hahn transfer while the RF amplitudes are kept constant. More general modulation schemes can be defined in terms of appropriate Fourier series. Frequency modulation allows one to introduce a time-dependence to prevent the heteronuclear dipolar interaction from being averaged out by high speed spinning. When frequency modulation is applied to $^{13}$C, cross polarization is effective over a broad range of isotropic chemical shifts, which is a critical advantage at high static fields. Extensions of the principle of frequency modulation to polarization transfer between different dilute spins such as $^{13}$C and $^{15}$N are under investigation. In principle, it should be possible to obtain an accurate measure of heteronuclear distances, in analogy to REDOR [21] and TEDOR [22] where the heteronuclear dipolar terms are partially restored by a series of $\pi$ pulses.

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References