

# Adiabatic $J$ Cross-Polarization in Liquids for Signal Enhancement in NMR

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**Abstract:** In NMR, polarization can be transferred by coherent oscillatory processes or by adiabatic methods. We introduce here the method of adiabatic  $J$  cross-polarization (AJCP), whereby in the liquid state the spin magnetization is transferred from one nuclear species to a second by slowly crossing the rotating frame energy levels. This achieves the expected signal enhancements while obviating the need to match the Hartmann–Hahn condition. Furthermore, AJCP is efficient over an extended chemical-shift range and is relatively insensitive to the magnitude of the  $J$  coupling. The AJCP experiment is demonstrated for the particular case of  $^1\text{H}$ – $^{15}\text{N}$  cross-polarization. The theoretical enhancement factor for an  $\text{AX}_N$  spin system is given.

## Introduction

Liquid-state nuclear magnetic resonance spectroscopy of chemical species of low magnetogyric ratio  $\gamma$  is hampered by the long acquisition times required to achieve usable signal-to-noise ratios. One approach to this problem increases net magnetization by using large-volume sample tubes and high magnetic fields. Additionally, it is often possible to transfer the greater polarization of a higher  $\gamma$  (X) species to the low  $\gamma$  (A) spins of interest, provided that some form of A–X coupling is present. The most common method is nuclear Overhauser enhancement (NOE). Depending on the details of dipolar relaxation processes, signal improvement up to  $1 + \frac{1}{2}(\gamma_X/\gamma_A)$  can be obtained. For systems where  $\gamma_X/\gamma_A$  is negative, application of NOE may actually reduce the polarization.

More recently, other transfer methods have been developed for heteronuclear systems having a resolvable A–X  $J$  coupling.<sup>2–12</sup> These techniques can provide A polarization enhancements essentially equal to  $|\gamma_X/\gamma_A|$ , and provide attractive alternatives to NOE. Their common drawback is that choices of optimal pulse timing and irradiation frequency depend on the value of the  $J$  coupling and the chemical-shift positions of the A and X nuclei. Selective population transfer<sup>5</sup> requires that the frequency of one of the lines of the X multiplet be known to much better than  $J$ , while other laboratory and rotating frame methods,<sup>2,6–10</sup> less sensitive to irradiation frequency, require setting pulse timings in accordance with the  $J$  coupling. When a sample contains spin systems having a range of chemical shifts and  $J$  couplings, or when these values are simply unknown, full enhancement cannot be assured.

Recent improvements to laboratory frame and rotating frame methods are based on refocusing strategies. Morris and Freeman<sup>3</sup> and Müller<sup>4</sup> have devised a laboratory frame method which operates well off resonance. A rotating frame sequence (RJCP<sup>11</sup>) has been presented which maintains high enhancement for moderate deviations from optimal pulse timing as well as rf match.

We demonstrate here a rotating frame cross-polarization strategy which transfers polarization *adiabatically*, rather than relying on coherent oscillations as do previous laboratory<sup>1–5</sup> and rotating frame<sup>6–11</sup> liquid state methods. Unlike these methods, adiabatic  $J$  cross-polarization (AJCP) is both efficient over an extended chemical shift range and relatively insensitive to the strength of the  $J$  coupling. Further, it avoids entirely the problem of matching rf amplitudes.

## Adiabatic $J$ Cross-Polarization

In AJCP, rotating frame Zeeman spin levels are created by simultaneous irradiation of both nuclear species; the levels are made to cross by varying the respective rf amplitudes, resulting

in spin polarization transfer. The process is illustrated in Figure 1 for an AX spin system. We presume that both species are spin  $\frac{1}{2}$  nuclei. The X spins, initially in thermal equilibrium in the laboratory field  $B_0$ , are subjected to an intense  $\frac{1}{2}\pi$  pulse followed by a  $90^\circ$  phase-shifted spin locking pulse of decreasing amplitude  $\omega_{1X}(t)$ . The A spins are simultaneously irradiated by an rf field of increasing amplitude  $\omega_{1A}(t)$ . Here  $\omega_{1A,X} = |\gamma_{A,X}B_{1A,X}|$ , where  $B_{1A,X}$  are the rotating frame rf field strengths. Both fields are turned off after a time  $T$  and the A spin free induction decay is observed (here under X decoupling). At  $t = 0$  the rf amplitudes are set so that the rf mismatch, defined by

$$\Delta\omega_1(t) = \omega_{1X}(t) - \omega_{1A}(t) \quad (1)$$

greatly exceeds  $|J|$  (measured in units of rad/s). The combination of large rf fields and large mismatch averages the  $J$  interaction to zero so that the spins are quantized along the rf fields in their respective rotating frames. As the rf fields approach the Hartmann–Hahn condition<sup>6</sup> ( $\Delta\omega_1 = 0$ ), the inner levels start to cross. The  $J$  coupling, however, connects these states near the crossing, causing them to repel each other as Figure 1 shows. At  $t = T$ , the rf fields satisfy  $-\Delta\omega_1(T) \gg |J|$ , and the Zeeman rf interaction again dominates. Figure 1 shows that the occupation probabilities initially associated with the X levels are transferred adiabatically to the A spin levels.

Similar considerations apply to more general spin systems. In particular, for an  $\text{AX}_N$  system, the generalization must take into account the plurality of values for the total X angular momentum  $I$ , and weight the polarization transfer associated with each  $I$  value according to its associated multiplicity  $g_I$ . For the  $\text{AX}_N$  system, the A spin polarization enhancement  $\epsilon$  for AJCP relative to that produced by an A spin  $\frac{1}{2}\pi$  pulse is given by

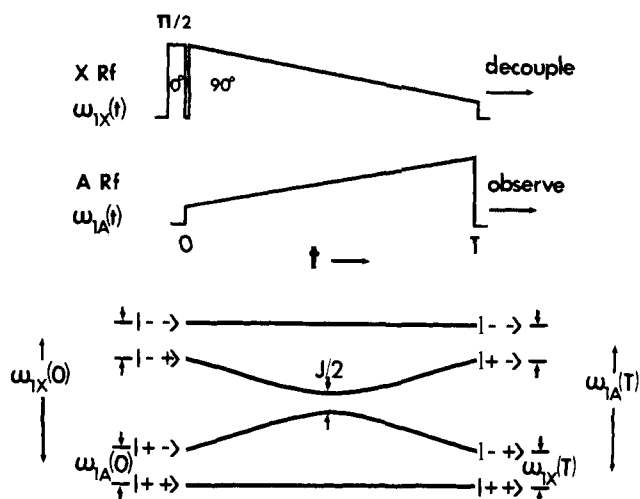
$$\epsilon = 2 \left[ 1 - \frac{(2m)!}{4^m(m!)^2} \right] \frac{|\gamma_X|}{|\gamma_A|} \quad (2)$$

where  $m = \frac{1}{2}N$  for  $N$  even and  $m = \frac{1}{2}(N + 1)$  for  $N$  odd. For realistically small values of  $m$ , the enhancement magnitude is equal to or slightly larger than  $|\gamma_X/\gamma_A|$ .

An important advantage of AJCP over other rotating frame polarization transfer methods is its ability to cross-polarize throughout a wide range of chemical shifts. For off-resonance irradiation, one considers the effective rf amplitude in the tilted rotating frame:

$$\Omega_{1A,X} = [\omega_{1A,X}^2 + \Delta\omega_{0A,X}^2]^{1/2} \quad (3)$$

in place of  $\omega_{1A,X}$ . Here  $\Delta\omega_{0A,X} = \omega_{A,X} - \omega_{0A,X}$  is the difference between irradiation and Larmor frequencies. For coupled spins having chemical shifts which place them off-resonance,



**Figure 1.** Pulse sequence and level diagram for AJCP. The X spins thermally polarize in the static field and are then spin locked by a  $90^\circ$  phase-shifted rf field which is slowly reduced. An A spin rf field is slowly increased until time  $T$  when the A signal is observed (here with X decoupling). The energy diagram is for an AX spin system of spin  $1/2$  nuclei. The rotating frame Zeeman states are labeled according to whether the spin is parallel (+) or antiparallel (−) to the rotating frame rf field; the X spin is indicated first. The crossing at  $\omega_{1X}(t) = \omega_{1A}(t)$  transfers polarization from the X to the A spin system. The polarization enhancement is given by eq 2.

the energy diagram is determined by the values of  $\Omega_{1A,X}$ , so the rotating frame level crossing will occur when  $\Omega_{1X} - \Omega_{1A}$  vanishes, rather than when  $\omega_{1X} - \omega_{1A}$  vanishes. By suitable choice of rf amplitudes, one can ensure that such a crossing will occur somewhere in the interval between 0 and  $T$ . To estimate the chemical-shift coverage of AJCP, we consider the situation at  $t = 0$ . For a crossing to be possible, the effective rf amplitude for the X spins must exceed that of the A species; this occurs if

$$\omega_{1X}^2(0) \geq \omega_{1A}^2(0) + \Delta\omega_0^2 \quad (4)$$

(This stringent criterion assumes resonant X irradiation.) Hence only those A spins in the range

$$|\Delta\omega_{0A}| \leq [\omega_{1X}^2(0) - \omega_{1A}^2(0)]^{1/2} \quad (5)$$

will have initial rf amplitudes smaller than  $\omega_{1X}(0)$ . This shows that the chemical-shift range is determined by the root of the difference between the square of the initial rf amplitudes. Similarly, the X spin chemical shift range is determined by the final rf amplitudes according to

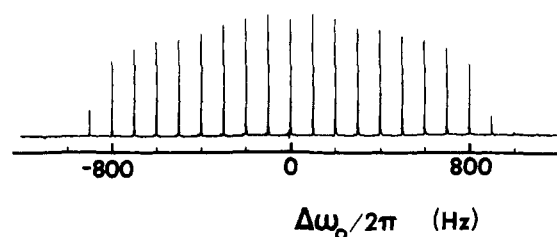
$$|\Delta\omega_{0X}| \leq [\omega_{1A}^2(T) - \omega_{1X}^2(T)]^{1/2} \quad (6)$$

In addition to eq 5 and 6, which guarantee the existence of a level crossing, the passage through the crossing must be adiabatic. This requires the difference in the effective rf fields to change sufficiently slowly that

$$\frac{d}{dt} |\Omega_{1X} - \Omega_{1A}| \ll (1/2J)^2 \left( \frac{\omega_{1A}\omega_{1X}}{\Omega_{1A}\Omega_{1X}} \right)^2 \quad (7)$$

where the right-hand side of the expression represents the square of the effective  $J$  coupling in the tilted doubly rotating frame.<sup>12</sup> If condition (7) is strictly satisfied, then polarization transfer will be *completely independent* of the magnitude of the  $J$  coupling. This differs radically from the situation for oscillatory coherent transfer methods,<sup>2-10</sup> wherein the specific choice of optimal cross-polarization time is required. In contrast, however, the only restriction in AJCP on the cross-polarization time  $T$  is that it be sufficiently long.

In an actual specimen the spin systems are coupled by  $J$  values ranging from  $J_{\min}$  to  $J_{\max}$ . The experimental constraints



**Figure 2.** The  $^{15}\text{N}$  resonance in 95% enriched acetamide using AJCP. The nitrogen transmitter frequency was stepped off resonance in 100-Hz increments to demonstrate the spectral coverage of the sequence. The rapid falloff beyond  $\pm 800$  Hz from resonance occurs where the effective rf fields no longer cause crossings of the rotating frame Zeeman energy levels.

on the spread of  $J$  values which will allow cross-polarization are most easily recognized by using the resonant irradiation case as a guide. The rf fields must begin and end at values well removed from the actual level crossing. Hence

$$|\Delta\omega_1(0)| \gg |1/2J_{\max}| \quad (8a)$$

$$|\Delta\omega_1(T)| \gg |1/2J_{\max}| \quad (8b)$$

(This is equivalent to insisting that a fast passage experiment start and finish away from resonance. Here the Hartmann-Hahn match of the rf fields corresponds to the resonance condition while  $1/2J$  plays the role of the conventional rf field.)

To examine the adiabatic condition, we may assume a linear ramp, though linearity is by no means necessary in these experiments. Then eq 7 becomes, for resonant irradiation:

$$|\Delta\omega_1(0) + \Delta\omega_1(T)|/T \ll (1/2J_{\min})^2 \quad (9)$$

Under the criteria of eq 8 and 9, the most rapid allowable crossing rate is determined by the smallest  $J$ , while the initial and final rf field differences must be much greater than the largest  $J$  interaction. Provided that eq 8 is satisfied, then the adiabatic condition can be rewritten as

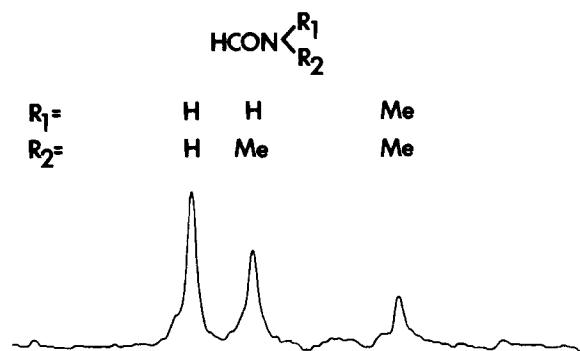
$$T \gg 2|J_{\max}|/J_{\min}^2 \quad (10)$$

Cross-polarizing systems with smaller  $J$  values require a quadratic lengthening of cross-polarization time  $T$ .

## Results and Discussion

Figure 2 demonstrates experimentally the insensitivity of AJCP to resonance offset. To mimic a complex spectrum, we stepped the nitrogen irradiation frequency in 100-Hz increments for the  $^{15}\text{N}$  resonance of 95% enriched acetamide ( $J/2\pi = 89$  Hz). In this AJCP sequence of 100-ms duration, the proton rf field was ramped downward from  $\omega_{1H}/2\pi = 1200$  to 600 Hz with the nitrogen field held at 750 Hz. The nitrogen signal is relatively insensitive to resonance offset and then decreases abruptly beyond  $\pm 800$  Hz, a few  $J$  short of the  $\pm 940$ -Hz crossing limits predicted by eq 5. The smoother decrease just before this drop is a consequence of the tilt of the  $\Omega_{1A}$  axis along which the spin-locked nitrogen polarization develops. With increasing resonance offset, the nitrogen polarization tilts toward the  $B_0$  axis and couples less efficiently to the receiver coil. The profile out to  $\pm 800$  Hz closely follows the expected  $[1 + (\Delta\omega_{0A}/\omega_{1A})^2]^{-1/2}$  contour. While this falloff is slightly faster than that associated with  $1/2\pi$  pulse methods, an advantage is that the phase of the spin-lock polarization remains uniform across the entire spectrum.

The data in Figure 2 were taken with the protons on resonance. Corresponding off-resonance data for both species (not shown) demonstrate that a proton resonance offset of approximately  $\pm 400$  Hz (440 Hz calculated) is covered by this selection of rf field profiles. Hence, even at these very modest rf fields, a reasonable range of chemical shifts is covered: 160 ppm for  $^{15}\text{N}$  and 8 ppm for  $^1\text{H}$  at 2.34 T. Resonance offset



**Figure 3.** AJCP  $^{15}\text{N}$  spectrum of an equimolar mixture of formamide, *N*-methylformamide, and *N,N*-dimethylformamide. Though the values of  $J_{\text{NH}}$  differ (89, 94, and 15 Hz, respectively), AJCP produces the expected signal enhancement for the first two and about 65% for the last. The discrepancy for *N,N*-dimethylformamide is attributed to nonadiabatic conditions in violation of eq 7 (see text).

dependence for coherent cross-polarization using the Hartmann-Hahn sequence is far more severe.<sup>12</sup>

Figure 3 shows the natural abundance  $^{15}\text{N}$  spectrum obtained from an equimolar mixture of formamide, *N*-methylformamide, and *N,N*-dimethylformamide. The dominant  $J_{\text{NH}}$  couplings are 89, 94, and 15 Hz, respectively. The fields were ramped in 400 ms, the proton rf decreasing from 800 to 650 Hz, and the nitrogen rf rising from 650 to 800 Hz. A 5-mm sample tube was used in a static field of 2.34 T, the pulse sequence was repeated at 10-s intervals, and 0.5-Hz line broadening was applied. The dominant peak in Figure 3 shows a 22:1 signal-to-noise ratio after 256 accumulations. The three resonances are observed in the ratios 1.0:0.63:0.33, whereas on the basis of composition the expected ratios are 1.0:0.68:0.51.

We attribute the discrepancy in the *N,N*-dimethylformamide intensity to nonadiabatic conditions in violation of eq 9. The crossing rate is approximately  $2\pi \times 300 \text{ Hz}/400 \text{ ms} = 4.7 \times 10^3 \text{ s}^{-2}$ , whereas  $J^2 = (2\pi \times 15 \text{ Hz})^2 = 8.9 \times 10^3 \text{ s}^{-2}$ .

## Conclusions

Spectrometer requirements for AJCP are rather modest. In principle, separate A and X transmitter coils can be used, whereas rotating frame coherent transfer methods are essentially restricted to probes with common transmitter coils. There is no critical requirement for setting the rf fields. The details of the rf amplitude sweep are constrained only by the adiabatic requirement; in particular, the sweep need not be linear and many rf imperfections are tolerated. The AJCP sequence is relatively insensitive to resonance offset and will work equally well on any coupled spin system having sufficiently long relaxation times to allow the adiabatic transfer. A related adiabatic method<sup>13</sup> transfers polarization through an intermediate state of  $J$  order; in contrast to AJCP, however, this method is particularly sensitive to resonance offset.

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## Ring Inversion in 1,4,7-Cyclononatriene (Trishomobenzene). Force-Field Calculations for Abnormally Large Bond Angles

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**Abstract:** The barrier to ring inversion in 1,4,7-cyclononatriene has been measured by  $^1\text{H}$  dynamic NMR spectroscopy in tetrachloroethylene, 1,1,2,2-tetrachloroethane, and toluene- $d_8$  as solvents. Values of  $\Delta G^\ddagger$  near room temperature vary from  $14.5 \pm 0.1$  to  $14.8 \pm 0.1$  kcal/mol. Values of  $\Delta S^\ddagger$  vary from  $-2.2 \pm 2$  to  $-4.9 \pm 2$  eu, and are not strongly negative ( $-18.2 \pm 0.1$  eu in  $\text{CDCl}_3$ ), as previously reported. Values of  $\Delta H^\ddagger$  vary from  $13.1 \pm 0.5$  to  $14.1 \pm 0.5$  kcal/mol. Calculations with the Boyd force field show that the strain energy of the crown conformation is 4.6 kcal/mol lower than that of the saddle conformation. The barrier for ring inversion is not well reproduced by the calculations, and possible reasons for this are discussed.

*cis,cis,cis*-1,4,7-Cyclononatriene ( $\text{I}$ )<sup>1–7</sup> and related compounds<sup>8–10</sup> show some unusual conformational properties. The ring system can exist in either a crown (I-C) which is rigid and has  $C_{3v}$  symmetry for the parent hydrocarbon or as a saddle conformation (I-S), which is more or less flexible. Both types of conformations have been observed in the cyclotrimeratylene

series,<sup>9</sup> and are separated by relatively high barriers ( $\approx 25$  kcal/mol), thus giving rise to atropisomers. The parent compound, however, exists entirely in the crown conformation and can be considered formally to be a trishomobenzene, although the delocalization energy, as calculated by simple MO methods, is actually negligible.<sup>1,3</sup>