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Evidence for Coherent Transfer of *para*-Hydrogen-Induced Polarization at Low Magnetic Fields

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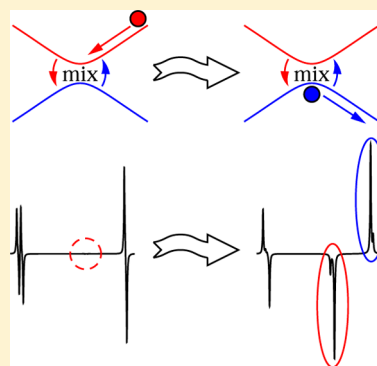
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ABSTRACT: We have investigated the mechanism of *para*-hydrogen-induced polarization (PHIP) transfer from the original strongly aligned protons to other nuclei at low external magnetic fields. Although it is known that PHIP is efficiently transferred at low fields, the nature of the transfer mechanism, that is, coherent spin mixing or cross-relaxation, is not well established. Polarization transfer kinetics for individual protons of styrene was, for the first time, measured and modeled theoretically. Pronounced oscillations were observed indicating a coherent transfer mechanism. Spin coherences were excited by passing through an avoided level crossing of the nuclear spin energy levels. Transfer at avoided level crossings is selective with respect to spin order. Our work provides evidence that the coherent PHIP transfer mechanism is dominant at low magnetic fields.

SECTION: Kinetics and Dynamics



Spin hyperpolarization, that is, strong nonthermal spin polarization, provides a way to increase the otherwise poor sensitivity of NMR methods. By utilizing hyperpolarized spins, new applications of NMR spectroscopy and imaging become feasible.^{1–16} However, it is often desirable to develop methods for hyperpolarization transfer from directly polarized spins to other spins, which are more suitable for NMR observation. This problem is of particular importance for *para*-hydrogen-induced polarization (PHIP),^{17–20} where initially only two spins are hyperpolarized (formed in the singlet state). It is known^{18,21–24} that at low magnetic fields, PHIP can be efficiently redistributed in a molecule. Such polarization transfer is sometimes termed “spontaneous”¹⁸ because it does not require NMR excitation. In principle, PHIP can be transferred either via a coherent mechanism or through cross-relaxation. Coherent transfer mechanisms require strong coupling of spins,^{21,25} which is the case at sufficiently low magnetic fields where the difference, $\delta\nu$, of the Zeeman interactions of spins with the field is smaller than their scalar spin–spin interaction, J . Coherent PHIP transfer effects have been described previously (already in 1997 in the review on PHIP by Natterer and Bargon¹⁷); more recently, a more detailed theory of low-field PHIP has been developed.²¹ It was also possible to realize PHIP transfer among heteronuclei occurring at ultralow fields.²⁶ Furthermore, a recent version of PHIP, the signal amplification by reversible exchange (SABRE) technique,²⁷ has been introduced, which is based on polarization transfer from *para*-H₂ to a substrate in a transient complex. A theory for SABRE based on a coherent

transfer mechanism has been developed.²⁸ However, so far, there were no *direct* observations of the PHIP transfer kinetics and spin coherences mediating the transfer. This is because PHIP requires a catalytic hydrogenation reaction, which typically lasts for a relatively long period of time (tens of seconds) and cannot be stopped instantaneously. The duration of one period of oscillation of spin coherences is roughly $1/J$, which can be less than 0.1 s, being much shorter than the typical PHIP preparation times. As a consequence, spin coherences formed at different instants of time are averaged out and cannot be observed. This is in contrast with the case of chemically induced dynamic nuclear polarization (CIDNP)^{29,30} formed in fast light-induced reactions; in this case, an oscillatory polarization transfer kinetics has been observed,^{31,32} giving clear evidence for the coherent mechanism.

The aim of this work is to study the PHIP transfer kinetics at low magnetic fields in order to establish the nature of the transfer mechanism. To suppress possible effects of averaging of coherences, we will create PHIP at high field (where only the two protons originating from *para*-hydrogen are polarized), then perform a fast field jump to low field where the spins are strongly coupled, and finally, switch the field back to detect NMR signals. This method allows formation of coherences with the same phase and circumvents the problem of destructive

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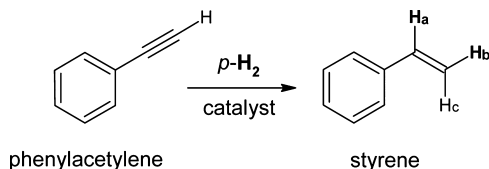
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interference. Direct observation of the PHIP transfer kinetics will allow discrimination between coherent versus incoherent transfer mechanisms.

Experiments were performed for phenylacetylene, which is converted to hyperpolarized styrene (Chart 1) after hydro-

Chart 1. Hydrogenation of Phenylacetylene^a



^aNumbering of the observed styrene protons (H_a , H_b , and H_c) is indicated. H_a and H_b are directly polarized by PHIP.

genation with *para*-hydrogen (the H_2 molecule in its singlet state).²³ At high field, only the H_a and H_b protons originating from *para*- H_2 are hyperpolarized. Polarization of the H_c proton is very weak; the aromatic protons are practically not polarized at high field. The high-field spectrum showing two antiphase doublets corresponds with the PASADENA experiment.^{17,20} This polarization pattern gives the initial condition for our transfer studies. After creating the PASADENA pattern, we performed the following four steps (see Figure 1): (i) field

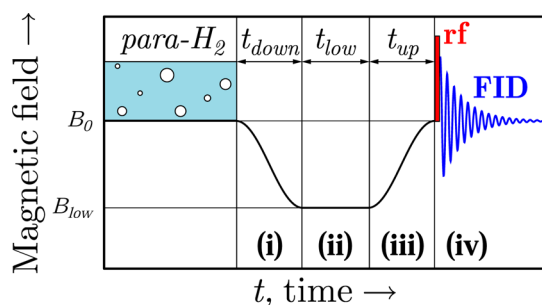


Figure 1. Experimental protocol used to study PHIP transfer effects. After creating PHIP at high magnetic field $B = B_0$, (i) the field is reduced to $B = B_{low}$ during time t_{down} , (ii) spin mixing at $B = B_{low}$ takes place during the time t_{low} , (iii) the field is switched back to $B = B_0$ during the time t_{up} , and (iv) the NMR spectrum is recorded.

reduction during time t_{down} from the NMR observation field ($B_0 = 7$ T) to the variable field, B_{low} ; (ii) spin mixing at $B = B_{low}$ during the time t_{low} ; (iii) going back to $B = B_0$ during the time t_{up} ; (iv) after a short delay (to let field transients settle), detection of the free induction decay in order to obtain the Fourier-transform NMR spectrum of the system. For technical reasons, the time t_{low} was set no shorter than 50 ms. In our experiments changes in the spectrum with respect to the PASADENA pattern reflect polarization transfer effects. We varied both the value of B_{low} in the low-field region and the residence time t_{low} at the mixing field to assess the transfer kinetics. During steps (i)–(iii), the hydrogenation reaction still continues. However, the experimental conditions were such that the amount of polarization created during these steps was negligible as compared to the starting polarization. This enabled the accurate analysis of the low-field PHIP transfer effects. Experimental observations were supported by theoretical calculations based on solving the Liouville–von Neumann equation for the nuclear spin density matrix with a time-

dependent Hamiltonian. In the theory, we considered purely coherent evolution and neglected all relaxation effects because the relaxation times were an order of magnitude longer (proton T_1 -relaxation times measured at high field were 6 s or longer) than the time ($t_{down} + t_{low} + t_{up}$).

The resulting PHIP spectra for different B_{low} fields are shown in Figure 2; each spectrum shows the result of an individual

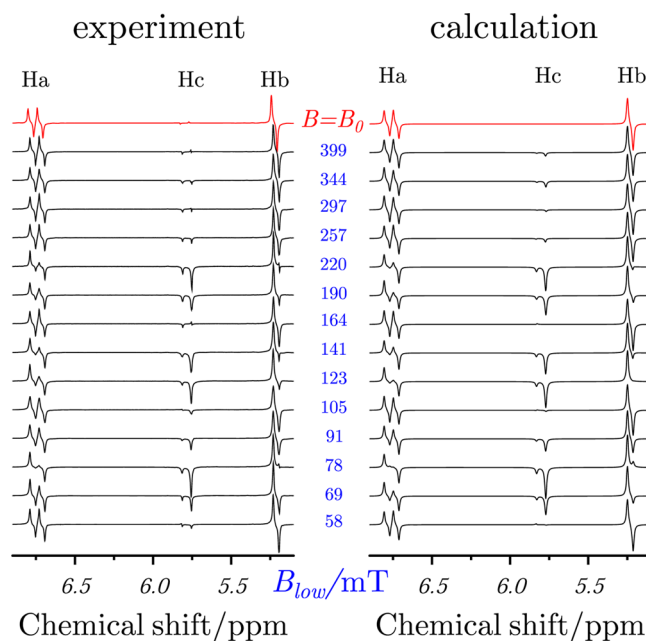


Figure 2. PHIP spectra of styrene obtained for different B_{low} fields: experiment (left) and calculation (right). The uppermost traces (red) show the standard PASADENA spectral pattern taken at $B = B_0 = 7$ T. Spectra were taken with a 45° flip angle, $t_{low} = 50$ ms, and $t_{up} = t_{down} \leq 383$ ms.

experiment, in which hydrogenation was performed at high field. When the mixing field is above 0.4 T, the initial PASADENA-type spectrum (see Figure 2, top line) does not change. However, when the field is low such that all three protons (H_a , H_b , and H_c) are strongly coupled, polarization is transferred to the H_c spin, which acquires both negative net polarization and multiplet alignment (vide infra). In addition, some of the lines in the NMR multiplets of the H_a and H_b protons disappear (see the spectra for $B_{low} = 78$, 123, 141, and 220 mT). These effects are very well reproduced by the calculation. When the net polarization of the H_c proton is plotted as a function of the B_{low} field, one can clearly see an oscillatory component (see Figure 3), which is an indication of quantum mechanical coherent spin mixing. In our case, the oscillations only emerge when spin coherences are excited by fast field jumps. Let us now explain how an oscillatory time dependence can be converted into an oscillatory field dependence.

The experimental results can be explained by spin mixing at low fields where all three spins are coupled strongly; indeed, PHIP transfer only takes place when the B_{low} field is sufficiently low to provide efficient mixing of the coupled spin system. The polarization transfer is coherent and selective. By selective transfer, we mean that only particular spins, H_b and H_c , obtain net polarization; the total net polarization of all three spins stays constant. Only specific lines in the individual NMR multiplets become enhanced or disappear. These effects can be

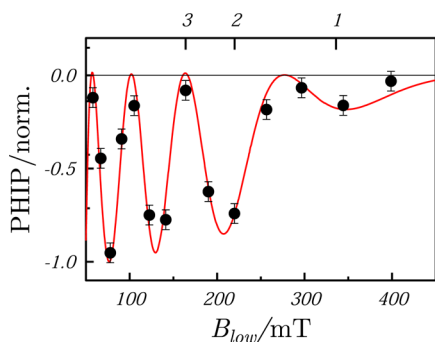


Figure 3. Net polarization of the H_c proton of styrene as function of B_{low} ; the solid line shows the calculation results. Experiments have been repeated three times, and the average value of the polarization was plotted; deviations are shown by error bars; the time t_{low} was 50 ms. Field positions (1, 2, and 3), at which the polarization transfer kinetics was measured, are indicated on the upper scale; the value of the calculated polarization at 77 mT is scaled to -1 .

accounted for by nuclear spin level anticrossing (LAC). A LAC occurs when two energy levels tend to cross, but a coupling matrix element between them then turns the crossing into an avoided crossing or a LAC. In the vicinity of LACs, the eigenstates of the uncoupled system become mixed. This can result in population exchange between them (as predicted, for instance, by the Landau–Zener theory³³) and, additionally, in conversion of state population differences into spin coherences and vice versa. Recently, it has been suggested that LACs play an important role in polarization transfer phenomena.^{25,31,34,35} Analysis of the energy levels of the three-spin system composed of the H_a , H_b , and H_c protons (see Figure 4) shows that within

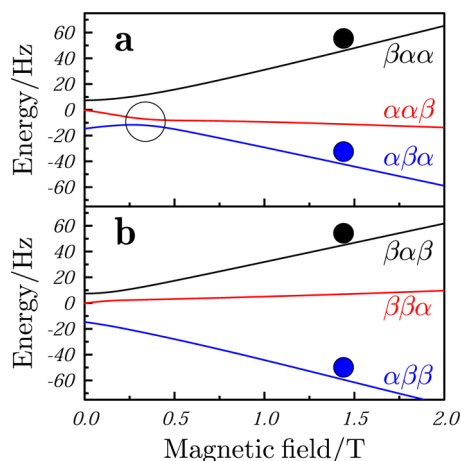


Figure 4. Spin energy levels of the H_a , H_b , and H_c protons of styrene; here, we show two manifolds with $I_z = 1/2$ (a) and $-1/2$ (b). Levels are assigned at high field; the spin states are denoted in the order H_a , H_b , H_c ; initially overpopulated levels are indicated by balls; LAC at $B_{\text{lac}} \approx 0.35$ T is indicated in subplot (a). To show effects on the 100 Hz scale, the large Zeeman energy $E_z = \hbar\gamma B I_z$ is subtracted.

the manifold of states with z -projection of the total spin, $I_z = 1/2$, there is a LAC at a field of $B_{\text{lac}} = 0.35$ T. Passage through this LAC will result in efficient mixing of specific spin orders, in our case, of net and antiphase polarization of spins.

Spin mixing in the vicinity of LACs is coherent.^{31,36} However, to make the coherent mechanism operative, it is necessary that the field switching $B_0 \rightarrow B_{\text{low}}$ be sufficiently fast,

that is, nonadiabatic. In this case, the population difference at B_0 between the crossing levels is converted into spin coherence at $B = B_{\text{low}}$. Subsequent evolution of the coherence (quantum oscillations with the frequency given by the splitting of the crossing levels) mediates polarization transfer. When the delay t_{low} is appropriately set, it is possible to exactly exchange the state populations after going back to the detection field ($B_{\text{low}} \rightarrow B_0$); variation of t_{low} thus enables precise manipulation of the transfer process. In the protocol with two field jumps used here, it is possible to excite the spin coherence after the field variation $B_0 \rightarrow B_{\text{low}}$ such that in all molecules, it has exactly the same phase. Thus, from a population difference, $\delta P_{ij} = P_i - P_j$ of states $|i\rangle$ and $|j\rangle$ at high field, we create a spin coherence, ρ_{ij} . The spin coherence evolves at low field, acquiring a phase φ . When the residence time at low field, t_{low} , is varied, the phase is changed. When the second field variation, $B_{\text{low}} \rightarrow B_0$, is also nonadiabatic, it is possible to convert spin coherences $\rho_{ij} \exp(i\varphi)$ at low B_{low} field into δP_{ij} and thus into NMR observables. The resulting PHIP spectral pattern depends on the phase φ ; by varying the phase, that is, the parameters of the experimental protocol (see Figure 1), one can manipulate the polarization transfer in the system. The phase can be changed by varying the field B_{low} and/or the delay t_{low} ; consequently, the dependence of the PHIP pattern on both quantities exhibits oscillatory components. Thus, the chosen protocol allows one to (i) create spin coherences having the same phase and (ii) measure the coherent PHIP transfer kinetics. Now, let us show how the LAC concept enables interpreting the experimental data.

Let us first explain the changes in the PHIP spectra caused by LACs. Hereafter, we will assume that spin coherences are excited only for a single pair of levels, which has a LAC at $B_{\text{lac}} = 0.35$ T (this assumption has been validated by theoretical calculations). Thus, population exchange is possible only between these levels. The adiabatic energy levels, which cross at $B = B_{\text{lac}}$, correspond to the $\alpha\alpha\beta$ and $\alpha\beta\alpha$ states at high magnetic fields (hereafter, the spin states are denoted in the order H_a , H_b , H_c). During the preparation, the H_a and H_b protons are born in the singlet state, and under PASADENA conditions, the $\alpha\beta\alpha$ state is overpopulated as compared to the $\alpha\alpha\beta$ state. During the spin mixing procedure, the crossing states can exactly exchange their populations with the result that the $\alpha\alpha\beta$ state becomes overpopulated. Thus, after the mixing, the projection of the H_a proton has not changed, while the H_b and H_c protons simultaneously change their projections I_{iz} . The H_c proton changes its positive z -projection to a negative one and thus acquires negative net polarization, while the H_b proton becomes positively polarized. In addition, the multiplet (or antiphase) polarization of the spins changes; the H_a and H_b protons go from the $\alpha\beta$ state to the $\alpha\alpha$ state and change their mutual orientation from an antiparallel to a parallel spin configuration. Simultaneously, the H_a and H_c protons go to the $\alpha\beta$ state, and antiphase polarization is generated between these protons. Because the multiplet polarization for the pairs H_a – H_b and H_a – H_c is almost of the same amplitude but of opposite sign, half of the lines in the spin multiplets cancel each other at $B_{\text{low}} = 78, 123, 141$, and 220 mT (see Figure 2). The passage through the LAC point results in specific spin flips, $\alpha\beta\alpha \rightarrow \alpha\alpha\beta$; in this way, the LAC enables selectivity of the PHIP transfer. Although at low B_{low} fields the spins are almost indistinguishable from the NMR point of view (their Zeeman interactions with the field are nearly the same), selectivity is still possible because at high field, the crossing levels are assigned to

particular Zeeman spin states, thus allowing discrimination of individual spins. It is important to note that in our experiments, there is no noticeable reduction of spin order but only a conversion of the initial singlet alignment of the two *para*-hydrogen spins.

Now, let us discuss the PHIP dependence on the mixing field (see Figure 3). The unusual oscillatory field dependence indeed confirms coherent spin mixing. Spin coherences are excited between the crossing levels when B_{low} is around B_{lac} or below, that is, when the system goes to the LAC (in fact, already slightly above the actual LAC point) or through the LAC. In the latter case, the first field variation creates spin coherence, which oscillates upon going down and going up when $B_{\text{low}} \leq B(t) \leq B_{\text{lac}}$ (and also at $B = B_{\text{low}}$ when $t_{\text{low}} \neq 0$). Because the splitting of the levels is changing during the field variation, the oscillation frequency is not constant, and consequently, the oscillations in the B_{low} dependence are not periodic. However, the type of the PHIP transfer remains the same as that described above, and the presence of the oscillations demonstrates that the transfer is coherent. The oscillations thus reflect the phase φ acquired during the two field jumps as a function of the B_{low} field. The observed B_{low} dependence is in perfect agreement with the simulation, which assumed a purely coherent transfer mechanism.

To address spin coherences directly, we fixed the mixing field B_{low} and varied the mixing period t_{low} (cf. Figure 5). We studied

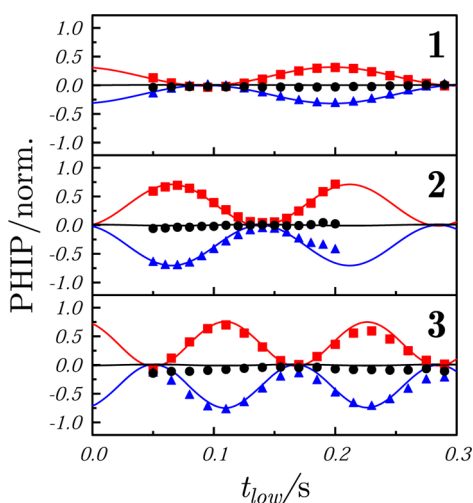


Figure 5. Net polarization of the H_a (black circles), H_b (red squares), and H_c (blue triangles) protons as a function of the mixing time t_{low} for magnetic fields B_{low} of 336 (1), 220 (2), and 164 mT (3). Solid lines show the calculation results. The first experimental point (at $t_{\text{low}} = 50$ ms) is the same as that in Figure 3; scaling is the same as that in Figure 3.

the kinetics at three fields, which are indicated in Figure 3. Two were chosen corresponding to the two extrema of the H_c polarization, to a shallow minimum at 336 mT and to a deep minimum at 220 mT, and the third setting was $B_{\text{low}} = 164$ mT, where no polarization on the H_c proton is seen in Figures 2 and 3. In all of these cases, the time dependences contain pronounced oscillations, each with a single field-dependent frequency. The type of the PHIP transfer (transfer of the initial singlet order into negative polarization of the H_c proton and positive polarization of the H_b proton) is the same as that discussed above because it is due to spin mixing at the same LAC. The frequencies of oscillations are 8.4 Hz for $B_{\text{low}} = 164$

mT, 6.7 Hz for $B_{\text{low}} = 220$ mT, and 4.8 Hz for $B_{\text{low}} = 336$ mT (the frequency grows as $|B_{\text{low}} - B_{\text{lac}}|$ increases), in excellent agreement with the splitting between the crossing levels at these fields. Again, this shows that the PHIP transfer is coherent; due to the specific conditions (presence of a single LAC), only a single coherence is excited, which makes the quantum oscillations well-resolved and enables transfer selectivity. It should be noted that the selectivity is given by the spin system (in our case, only the transition $\alpha\beta\alpha \rightarrow \alpha\alpha\beta$ is operative) and cannot be changed arbitrarily. Nonetheless, selective polarization transfer effects caused by LACs can be of importance for enhancing specific NMR signals.

The results presented in Figure 5 give information not only about the mixing frequency at low field. Also, the initial phase of the coherence and its amplitude characterize the spin mixing during the field switching. One should note that in the experimental data, the points corresponding to $t_{\text{low}} < 50$ ms are missing for technical reasons, while in the calculation, the complete kinetics is shown. The amplitude of the quantum oscillations reflects the efficiency of the forward and backward conversion between the population difference and coherence between the anticrossing levels. It is somewhat lower (see Figure 5, subplot 1) for the LAC field (because the system only goes to the LAC field but not through the LAC field) as compared to the fields below the LAC point (see Figure 5, subplots 2 and 3). As far as the initial phase, φ_0 corresponding to $t_{\text{low}} = 0$, is concerned, it is given by the evolution of the coherence with variable frequency during the passage through the LAC region. Due to this, in fact, $t_{\text{low}} = 0$ does not mean zero transfer time of spin order nor zero phase φ_0 because the transfer is occurring also during the field variation. For example, although in Figure 5, subplot 2, the point at $t_{\text{low}} = 0$ indicates no polarization transfer at $B_{\text{low}} = 220$ mT, the spin coherence is efficiently formed during the field switching time, t_{down} . This can be clearly seen from the subsequent time evolution; it is just a matter of the experimental settings whether transfer of spin order occurs in the system. Likewise, the first measured point, $t_{\text{low}} = 50$ ms, at $B_{\text{low}} = 164$ mT shows no polarization transfer, which happens to be the result of the minimal allowed value of the switching setup. In our simulations, we have taken the evolution of the coherence into account during field variation and the residence time at low field. As a consequence, both the amplitude and the phase are well accounted for by our simulation. In none of the cases are any measurable decoherence effects seen in the kinetics, which clearly shows that the spin dynamics is governed by a coherent process.

Our results give clear evidence that PHIP is efficiently transferred in hyperpolarized molecules at low magnetic fields where the spins are coupled strongly. Moreover, the observed oscillations in the transfer kinetics unambiguously show that the polarization transfer is coherent. We have revealed pronounced LAC effects on PHIP transfer; a LAC makes polarization transfer fast and also selective as the initial singlet two-spin order is converted to a specific polarization pattern. In addition, using fast field variation, one can convert the spin order virtually without losses, giving a tool for efficient manipulation of spin order. Excellent agreement between the experimental results and theoretical calculations, which assumed purely coherent spin evolution, strongly supports our conclusions. We expect that a coherent PHIP transfer mechanism occurs in other cases as well, although direct observation of spin coherences can be more difficult. LAC effects similar to those described above should be ubiqui-

tous^{25,31,34,35} in polarization transfer phenomena. They can be used to manipulate polarization transfer to make it more efficient. It is worth noting that “spontaneous” PHIP transfer takes a certain time, which is required for the evolution of spin coherences. This time is given by half of the inverse splitting of the crossing levels, that is, at the LAC points roughly by 1/2 of the inverse value of the J coupling.

Our observations of an oscillatory time evolution of polarization transfer provide direct evidence for a coherent transfer process. The lack of damping has shown that relaxation effects are negligible. Cross-relaxation effects can be of importance only for nuclei with vanishing J coupling but noticeable dipole–dipole interactions, which determine the cross-relaxation rates.

■ EXPERIMENTAL AND COMPUTATIONAL METHODS

To create PHIP, we used the hydrogenation reaction of phenylacetylene (Sigma-Aldrich, 98%) with dissolved *para*-hydrogen in deuterated acetone in the presence of a rhodium catalyst ([1,4-bis(diphenylphosphino)butane](1,5-cyclo-octadiene)rhodium(I) tetrafluoroborate, Sigma-Aldrich, 98%). Solutions contained 20 μ L of phenylacetylene, 1.5 mg of catalyst, and 700 μ L of acetone- d_6 . Each solution was prepared immediately prior to the experiment because of degradation of the catalyst in solution. Bubbling of the solution with *para*-hydrogen was done in a special NMR sample tube with a porous ceramic insert in the bottom.³⁷

Field variation was performed by using a field-cycling device,³⁸ which moved the whole NMR probe with the sample between two locations having different field strengths, 7 T at the homogeneous spot of the NMR spectrometer cryomagnet versus variable positions in its fringe field and the field from additional coils. The field variation was digitally controlled so that the time profile $B(t)$ was precisely known. Theoretical calculations were performed by numerically solving the Liouville–von Neumann equation for the density matrix, $\hat{\rho}$, of the spin system with a time-dependent Hamiltonian, $\hat{H}(t)$. In \hat{H} , we have taken into account the Zeeman interactions of protons with the variable field and their scalar spin–spin interactions. Thus, the Hamiltonian was completely defined by the chemical shifts, δ_i , of protons and scalar couplings, J_{ij} . For styrene, we have taken the following NMR parameters, $\delta_{\text{Ha}} = 6.764$ ppm, $\delta_{\text{Hb}} = 5.236$ ppm, $\delta_{\text{Hc}} = 5.812$ ppm, $J_{\text{HaHb}} = 10.9$ Hz, $J_{\text{HaHc}} = 17.7$ Hz, and $J_{\text{HbHc}} = 1.05$ Hz. In the initial condition for $\hat{\rho}$, we assume that the two spins, H_a and H_b , were born in their singlet state and neglected the thermal polarization of the third spin, H_c . We also set all spin coherences after the preparation (i.e., before the first field switch) to zero. Spectra of the polarized spin systems were calculated in the same way as before.²¹ Despite the fact that in the calculations we did not use any fitting parameters, the agreement between theory and experiment was very good.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

CIDNP = chemically induced dynamic nuclear polarization; LAC = level anticrossing; NMR = nuclear magnetic resonance; PASADENA = *para*-hydrogen and synthesis allow dramatically enhanced nuclear alignment; PHIP = *para*-hydrogen-induced polarization

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