Transfer of Parahydrogen-Induced Hyperpolarization to ^{19}F

Lars T. Kuhn,* Ute Bommerich,† and Joachim Bargon*

Institute of Physical & Theoretical Chemistry, University of Bonn, Wegelerstrasse 12, D-53115 Bonn, Germany

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Homogeneous hydrogenations of unsaturated substrates with parahydrogen yield strong NMR signal enhancements of the transferred ^1H nuclei if the symmetry of H_2 is broken in the resulting hydrogenated products. This chemically induced hyperpolarization known as Parahydrogen-induced polarization (PHIP) is also transferred to other protons and heteronuclei (^2H, ^{13}C, ^{29}Si, ^{31}P) when the hydrogenation is initiated at low magnetic fields. Hydrogenating various fluorinated styrenes and phenylacetylenes, we show that PHIP-derived hyperpolarization is transferred to ^{19}F not only in the Earth's magnetic field (ALTADENA condition) but also in a strong magnetic field, e.g., when carrying out the reaction in the NMR spectrometer (PASADENA condition). Upon conducting a systematic analysis of the observed PHIP transfer to ^1H, ^{13}C, and ^{19}F in the hydrogenation products to elucidate the mechanisms that govern this parahydrogen-aided resonance transfer (PART), we conclude that high- and low-field PHIP transfer mechanisms differ in detail depending on either through-bond or through-space interactions. Substrates with high hydrogenation rates and long spin−lattice relaxation times (T_1) yield the highest degree of heteronuclear hyperpolarization. Possible medical applications for hyperpolarized ^{19}F-containing molecules as "active" contrast agents for magnetic resonance imaging (MRI) are outlined.

I. Introduction

A homogeneously catalyzed hydrogenation reaction of unsaturated substrates with H_2 enriched in parahydrogen leads to the observation of strongly enhanced absorptive and emissive signals in the ^1H NMR spectra of the hydrogenation product. This phenomenon, which has been extensively studied ever since its theoretical prediction[1] and experimental verification,[2a−c] has been termed PHIP (parahydrogen-induced polarization) and originates from the breaking of the high symmetry of the parahydrogen molecule during the course of the hydrogenation reaction. The characteristic signal patterns in the resulting NMR spectra are associated with a signal enhancement (SE) of up to 4 orders of magnitude and only occur if the two hydrogen atoms of the parahydrogen molecule are transferred jointly to the unsaturated center of the substrate. This simultaneous transfer is crucial for the observation of PHIP signals because it makes sure that spin correlation between the two hydrogen atoms is maintained during the hydrogenation and also afterward in the hydrogenation products. Moreover, the patterns of the polarization signals depend strongly on the way every individual PHIP experiment is conducted (vide infra).[3a,b]

Ever since the discovery of this parahydrogen-induced hyperpolarization phenomenon, scientists have been interested not only in the generation of polarization of the two protons stemming from the parahydrogen molecule itself but also in transferring the high spin order of the parahydrogen molecule to insensitive heteronuclei of either the dihydride intermediate formed during the catalytic hydrogenation cycle or even to heteronuclei of the reaction product. It could be shown in the past that the polarization originating from the two protons of the parahydrogen molecule can be transferred to heteronuclei of the dihydride intermediate[4] and of the hydrogenation product using specifically designed pulse schemes that include conventional coherence transfer sequences.[5a,b] Furthermore, the *spontaneous* transfer of PHIP to various heteronuclei of the involved species could also be observed when the hydrogenation reaction was carried out in the Earth's magnetic field followed by a subsequent transfer of the sample to the spectrometer and the acquisition of the spectrum (ALTADENA condition). A large number of insensitive heteronuclei (^2H, ^{13}C, ^{29}Si, ^{31}P) are able to benefit from this transfer of the parahydrogen-derived high spin order showing a significant signal enhancement in the resulting NMR spectra of the parahydrogenation products.[6a−d]

Despite of the fact that a large number of heteronuclei have already been reported to exhibit a strong sensitivity enhancement due to PHIP there has been no evidence that this hyperpolarization can also be transferred to ^{19}F nuclei. Due to its unique physical properties, however, ^{19}F has proven to be a very suitable nucleus for the structural analysis of organic compounds using NMR spectroscopy because its relative sensitivity is almost as high as that of ^1H. Furthermore, ^{19}F normally does not occur in organic molecules and this low abundance in naturally occurring molecules makes it a very specific and also sensitive probe for the elucidation of molecular structure when specifically labeled samples are used. The increased chemical shift dispersion of ^{19}F compared to ^1H and the reduced spectral crowding arising from just one or a few strategically placed fluorine probes in a molecule also offers considerable advantages over more conventional NMR methods.

In this contribution we demonstrate that the transfer of PHIP to ^{19}F is feasible using a set of singly fluorinated styrene and phenylacetylene derivatives. Moreover, we take a closer look at the mechanisms responsible for the transfer of PHIP to heteronuclei using ^{19}F as a very sensitive probe of changes in

* To whom correspondence should be addressed. J.B.: address, Institut für Physikalische und Theoretische Chemie, Wegelerstrasse 12, D-53115 Bonn, Germany; tel, +49 228 732261; e-mail, bargon@uni-bonn.de. L.T.K.: new address, Physical & Theoretical Chemistry Laboratory, South Parks Road, Oxford OX1 3QZ, U.K.; tel, +44 1865 275416; e-mail, lars.kuhn@chem.ox.ac.uk.

† New address: Leibniz Institute for Neurobiology, Brenneckestrasse 6, D-39118 Magdeburg, Germany.

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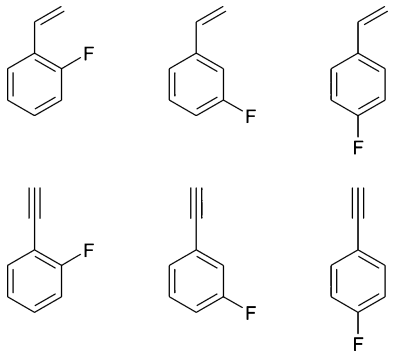


Figure 1. Structures of the parahydrogenation substrates employed in this study. The singly fluorinated styrene and phenylacetylene derivatives were chosen to probe a possible distance dependency of the efficiency of PHIP transfer.

its nearby electronic environment. We then try to show whether a quantitative analysis of our results is capable of either confirming or ruling out a dipolar through-space or a scalar through-bond transfer mechanism.

II. Experimental Procedures

All chemicals used in this study were obtained from Aldrich and used without any further purification. The chemical structure of all parahydrogenation substrates employed in this study is depicted in Figure 1. The fluorinated substrates selected were the three singly fluorinated styrene derivatives 2-fluoro-, 3-fluoro-, and 4-fluorostyrene. These compounds were chosen because the distance between every single fluorine nucleus and the parahydrogenation center is different in every compound, and the analysis of their polarization spectra might thus serve as a "spectroscopic ruler" when probing different transfer mechanisms. Additionally, the three singly fluorinated compounds 2-fluoro-, 3-fluoro-, and 4-fluorophenylacetylene were tested to support the PHIP data taken from the styrene derivatives described above and to probe the effect of different hydrogenation rates on the detection of PHIP transfer to heteronuclei. In all experiments the selected substrates were parahydrogenated using catalytic amounts of the cationic transition metal complex [1,4-bis(diphenylphosphino)butane]-(1,5-cyclooctadiene)rhodium(I) and acetone-d_6 as the solvent.

The individual spectra were acquired using either low-field or high-field hydrogenation conditions. Both experimental setups differ in that the hydrogenation process is initiated outside the strong field of the NMR magnet followed by an immediate transfer of the NMR tube to the spectrometer and the acquisition of the polarization spectrum (ALTADENA spectra). This setup eventually leads to the observation of NMR signals exhibiting net polarization in the resulting spectra showing either enhanced absorption *or* emission. Alternatively, the whole experiment was conducted with the sample being inside the sensitive coil region of the spectrometer throughout the whole experiment (PASADENA spectra) leading to characteristic antiphase patterns of the polarization signals obtained. In both cases experiments were conducted using a Bruker AVANCE 200 MHz NMR spectrometer operating at a field strength of 4.7 T. ^{19}F spin−lattice relaxation times (T_1) of the individual compounds were measured on a Bruker AVANCE DRX 200 MHz NMR spectrometer using a standard inversion recovery pulse sequence. All ALTADENA and PASADENA spectra were acquired using a single 90° radio frequency read pulse.

The ALTADENA experiments carried out in this study involved the use of 5 mm NMR pressure tubes (Wilmad) equipped with a screw closure and a septum. The tubes were charged with the reaction mixture comprising 0.45 M of the fluorinated styrene or 0.46 M of the fluorinated phenylacetylene derivative and 7.36 mM of the Rh(I) catalyst dissolved in 0.75 mL acetone-d_6. Subsequently, the tubes were closed and put under a pressure of 3 bar with H_2 enriched in parahydrogen to about 50%. The enrichment was achieved exploiting the catalytic equilibration of commercially available dihydrogen gas over activated charcoal at 77 K using liquid nitrogen following a procedure first described by Bonhoeffer et al.[7] In the presence of just the Earth's magnetic field (0.5 G), the tubes were then shaken thoroughly and immediately placed in the NMR probe followed by the acquisition of the spectrum.

All PASADENA experiments were conducted similarly using the same amounts and concentrations of all chemicals. To initiate the hydrogenation process inside the NMR probe, the parahydrogen-enriched H_2 gas mixture was introduced into the NMR tube within the magnet using a glass capillary connected to the parahydrogen source with PTFE tubing. The glass capillary itself was immersed into a standard 5 mm NMR tube that contained the reaction mixture. In this case, the parahydrogen enrichment of the H_2 gas was carried out using a cryogenic charcoal cell at a temperature of 35 K, leading to an almost completely para-saturated gas mixture of ca. 96%.

The insertion of the glass capillary into the NMR tube followed by the bubbling of parahydrogen gas through the reaction mixture and the subsequent lifting of the capillary followed by the 90° radio frequency acquisition pulse was controlled and triggered by the pulse program of the NMR spectrometer throughout the whole acquisition procedure. A delay of 2.5 s was placed between the lifting of the glass capillary and the 90° radio frequency pulse to remove all gas bubbles from the sensitive coil region and to let the system reach a "steady-state" under which magnetization transfer could evolve. The acquisition of PASADENA spectra using this setup thus yielded highly reproducible results that were suitable for a quantitative analysis of the obtained polarization signals.

III. Results and Discussions

A. ^{19}F NMR Data. Preliminary experiments were conducted to explore whether the transfer of PHIP to fluorine nuclei of the hydrogenation substrates depicted in Figure 1 is feasible. This feasibility study was necessary because there was no evidence so far that parahydrogen-derived polarization transfer to ^{19}F nuclei actually occurs. Our studies, however, clearly confirm the efficient transfer of PHIP to fluorine nuclei of the selected substrates following their parahydrogenation. Figure 2 shows the ^{19}F ALTADENA spectrum acquired immediately after the parahydrogenation of 2-fluorophenylacetylene yielding hyperpolarized 2-fluorostyrene. As can be seen in the spectrum, the polarization signal representing the single ^{19}F nucleus in the parahydrogenation product shows *net* emission and is characterized by a substantial signal enhancement (SE) of 116 compared to a normal ^{19}F NMR spectrum of the same compound acquired after its hydrogenation using thermally equilibrated dihydrogen gas. Furthermore, PHIP transfer to ^{19}F could also be observed in all other hydrogenation products of the substrates outlined in Figure 1 leading to a large sensitivity enhancement of every individual ^{19}F nucleus. Figure 3 summarizes the extent or efficiency of PHIP transfer to the ^{19}F nuclei in terms of the measured signal enhancement factors (SE) of the obtained polarization signals. As can be seen in this figure, we were able to observe PHIP transfer to ^{19}F not only under low-field conditions using an ALTADENA setup but also under high-field conditions. This observation proves that the transfer of

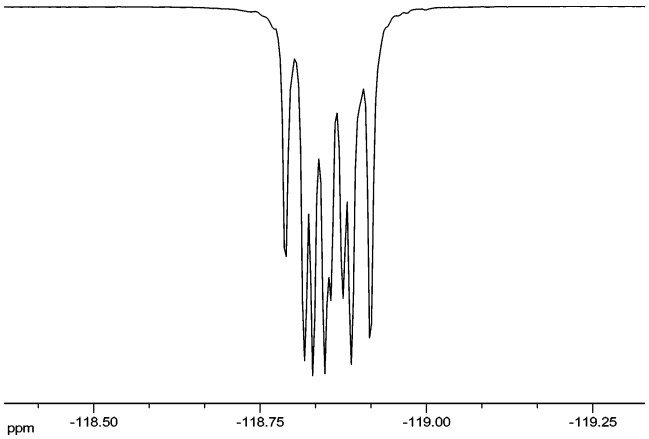


Figure 2. Single scan ^{19}F ALTADENA spectrum acquired immediately after the parahydrogenation of 2-fluorophenylacetylene yielding ^{19}F polarized 2-fluorostyrene. The ^{19}F signal of the reaction product shows net emission and is characterized by a signal enhancement of more than 2 orders of magnitude.

PHIP-derived high spin order to a heteronucleus of the parahydrogenation product is also possible at high magnetic fields using PASADENA conditions that yield weakly coupled spin systems with respect to the transferred protons.

A comparison of all experimentally determined signal enhancement factors attained under ALTADENA conditions shows that PHIP transfer to ^{19}F is very efficient and leads to a substantial enhancement of more than 2 orders of magnitude. However, these ALTADENA results do not suggest a direct distance dependency of the transfer efficiency between the former parahydrogen protons and the fluorine nucleus. Rather, the results for the ALTADENA experiments depicted in Figure 3 show that the highest signal enhancements can be observed for the parahydrogenation product of 3-fluorophenylacetylene and 3-fluorostyrene. In principle, this finding could be a consequence of relaxation processes. A comparison of the measured spin−lattice relaxation times (T_1) of all ^{19}F nuclei in the resulting parahydrogenation products, however, showed that they are virtually identical (Table 1), and thus relaxation alone cannot account for the different amounts of polarization transfer observed for every individual fluorine nucleus. Nonetheless, this observation can still be perfectly explained and understood in terms of different hydrogenation reaction rates for the different isomers. Applying the concept of a linear free energy relation, one can see that the unsaturated bond of the alkene or alkyne portion of these 3-fluoroarene derivatives contains more electron density than that of the 2-fluoro- and 4-fluoroarene derivatives. Therefore, the 3-fluoroarenes will act as much better ligands for the catalyst in the hydrogenation cycle.[8] Accordingly, hydrogenations of these two compounds are postulated to be thermodynamically more favorable than those of the ortho- or para-substituted isomers, and this will thus lead to an increase of the hydrogenation rate constant. Hence, the amount of polarization transferred to the heteronucleus will also be more profound in the hydrogenation products of the 3-fluoroarenes compared to those of all other isomers and hence should result in a higher SE in the resulting NMR spectrum.

Another result of our study is that the parahydrogen-derived polarization transfer to heteronuclei not only occurs under ALTADENA conditions at low fields but is also present when the whole parahydrogenation reaction is carried out in the strong field of the NMR spectrometer. Furthermore, the observation of PHIP transfer to ^{13}C heteronuclei occurring under PASADENA conditions could also be verified for the fluorostyrene and fluorophenylacetylene derivatives used in this study.

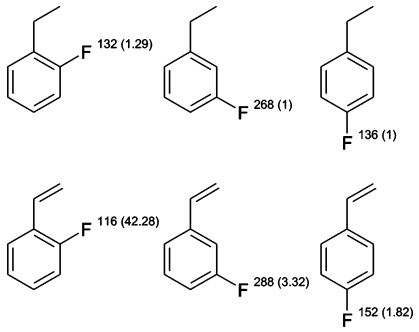
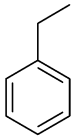
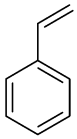


Figure 3. ^{19}F PHIP signal enhancement (SE) factors attained for the singly labeled parahydrogenation products of the fluorostyrene and fluorophenylacetylene derivatives employed in this study using ALTADENA (PASADENA) conditions.

TABLE 1: Measured T_1 Spin−Lattice Relaxation Times (s) for All Individual ^{19}F Nuclei of the Parahydrogenation Products Using a Conventional Inversion Recovery Sequence

	^{19}F Ortho-	^{19}F Meta-	^{19}F Para-
	5.5	5.8	5.7
	5.4	5.7	5.6

A quantitative comparison, however, between the individual ^{19}F polarization signals attained under ALTADENA and PASADENA conditions clearly shows that transfer in the case of our low-field setup is much more efficient. Only for the three phenylacetylene derivatives can a PHIP transfer be observed for all ^{19}F nuclei under low-field conditions. The difference in transfer efficiency between low-field and high-field PHIP can be explained and understood in terms of the concept of "isotropic mixing". According to this concept transfer of PHIP-derived polarization from protons to heteronuclei is considered to be an exchange of energy between nuclear spins having different spin temperatures. To transfer energy between these species efficiently, the resonance condition has to be met. In the strong field of an NMR magnet the precession frequencies of protons differ considerably from those of all heteronuclei; therefore, a polarization transfer from the protons to heteronuclei is less likely to occur. If, however, PHIP experiments are conducted in the presence of low magnetic fields, e.g., in the stray field of an NMR spectrometer or in the Earth's magnetic field, the precession frequencies of all nuclei in a molecule will be rather similar, rendering an efficient energy transfer between them more likely and consequently more efficient. In the complete absence of any magnetic field, a condition we have not been able to satisfy yet experimentally, the concept of individually different precession frequencies of heteronuclei does not apply. In such a case the dominating magnetic coupling between magnetically active nuclei would determine the transfer and the eventual distribution of the resulting hyperpolarization exclusively.

This concept of "isotropic mixing" has been proposed before[6d] and it is suited to explain the observed differences in PHIP

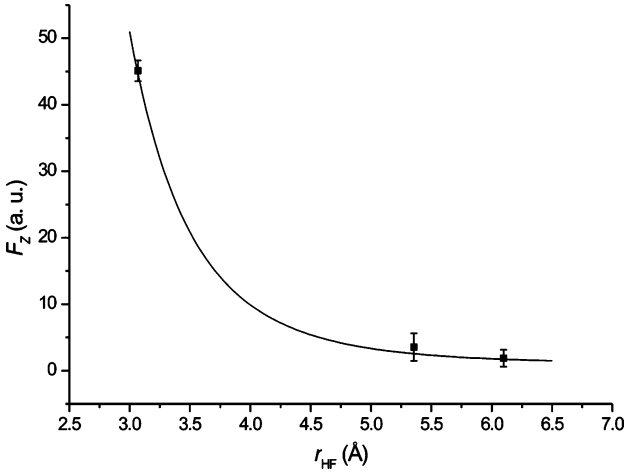


Figure 4. Graph showing the measured longitudinal single-spin order of the ^{19}F nuclei present in the three newly formed styrene derivatives (F_Z) plotted against the mean distance (r_{HF}) between ^{19}F and the two attached parahydrogen protons. A function proportional to the inverse sixth power of r_{HF} could be fitted through the three experimental values using a single parameter.

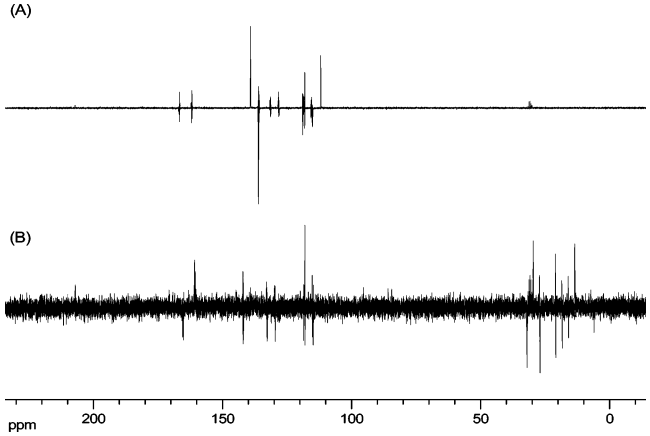


Figure 5. Comparison of the ^{13}C ALTADENA single scan spectra acquired after the parahydrogenation of 4-fluorophenylacetylene (A) and 4-fluorostyrene (B). The large difference in polarization signal intensity can perfectly be explained in terms of different hydrogenation rates for the two compounds, which is modulated by the substitution pattern.

transfer efficiency between the high-field and the low-field results of our study. Nevertheless, PHIP transfer in the spectrometer's high field is not completely impossible, but its observation depends strongly on sufficiently high hydrogenation rates. This observation was supported by the ^{13}C PHIP experiments conducted using the same set of singly fluorinated styrene and phenylacetylene derivatives (vide infra). A quantitative analysis of the attained polarization signals in parahydrogenated phenylacetylene derivatives using highly reproducible PASADENA conditions gives strong evidence for the assumption that PHIP transfer occurring in the spectrometer's high field seems to be mainly governed by a dipolar through-space coupling mechanism because its transfer efficiency seems to correlate with the inverse sixth power of the distance between the hydrogenation center and the receiving heteronucleus (Figure 4). To demonstrate this behavior, the longitudinal single-spin order values F_Z attained for the ^{19}F nuclei of the three newly formed styrene derivatives were plotted against the mean distance r_{HF} between the parahydrogenation center and the heteronucleus. A function proportional to the inverse sixth power of r_{HF} could be fitted through the experimental values using just one parameter. This behavior was expected for a dipolar cross-relaxation interaction being the dominating mechanism responsible for the transfer of initial longitudinal single-spin order of the attached protons (H_Z) to the ^{19}F nucleus (F_Z) according to

$$\sigma_{12} = \frac{\gamma_1^2\gamma_2^2\hbar^2}{10}\left(\frac{\mu_0}{4\pi}\right)^2\frac{\tau_c}{r^6}\left(\frac{6}{1+(\omega_1+\omega_2)^2\tau_c^2} - \frac{1}{1+(\omega_1-\omega_2)^2\tau_c^2}\right) \quad (1.1)$$

In this equation, which represents the general expression of the cross-relaxation rate σ_{12} of a dipolarly coupled spin system comprising two nuclei 1 and 2, τ_c is the rotational correlation time of the individual molecule and ω the angular Larmor frequency of the nuclei observed.[9]

We assume that in the case of our low-field setup all magnetically active nuclei of the parahydrogenation product form a strongly coupled spin system, and PHIP transfer seems to be governed by a superposition of both through-bond *and* through-space interactions making a quantitative analysis and a separation of both effects difficult and hardly feasible. Our observation is in keeping with previous computational studies predicting that a PHIP transfer mediated through scalar through-bond interactions might occur under certain circumstances.[10]

B. ^{13}C NMR Data. In the course of our experiments we also observed PHIP transfer to the aromatic and aliphatic ^{13}C nuclei of the parahydrogenation products of all substrates employed in our study as outlined in Figure 1. Furthermore, as pointed out above, it was shown that the probability of observing this hyperpolarization transfer to heteronuclei crucially depends on the magnitude of the attained hydrogenation rates. A comparison of the ^{13}C PHIP spectra acquired immediately after the parahydrogenation of 4-fluorostyrene and 4-fluorophenylacetylene using a single scan and low-field conditions clearly shows that PHIP transfer occurs in both cases leading to a substantial signal enhancement (Figure 5). The amount of polarization transferred to the individual ^{13}C nuclei of the parahydrogenation products, however, is very different and can be explained in terms of different hydrogenation rates for phenylacetylene and styrene derivates. It is well-known that the gain in free energy is much higher during the hydrogenation of alkynes compared to the hydrogenation of alkenes. Hence, the reaction rate for the hydrogenation of 4-fluorophenylacetylene will be higher than the rate for 4-fluorostyrene. This difference will inevitably cause increased polarization transfer from the two transferred parahydrogen atoms to the individual ^{13}C nuclei of the hydrogenation products of the alkynes compared to the alkenes. Taking the consequences of these observations further into account, it can be said that one crucial condition for the observation of efficient PHIP transfer are sufficiently high hydrogenation rates.

C. ^{1}H NMR Data. To monitor and to possibly measure the efficiency of the catalytic hydrogenation reaction, the acquisition of ^{1}H PHIP spectra was also carried out because the transferred parahydrogen atoms can be observed directly in the ^{1}H NMR spectrum of the corresponding hydrogenation product. Figure 6 shows the ^{1}H PHIP spectrum acquired immediately after the parahydrogenation of 4-fluorostyrene yielding 4-fluoroethylbenzene. The emissive signal at $\delta = 1.19$ ppm can be attributed to the parahydrogen nucleus that is part of the methyl group of the ethyl moiety, and the signal at $\delta = 2.62$ ppm showing enhanced absorption represents the other parahydrogen nucleus of the newly formed ethyl moiety. Furthermore, an additional emissive signal at $\delta = 7.00$ ppm and a signal at $\delta = 7.25$ ppm

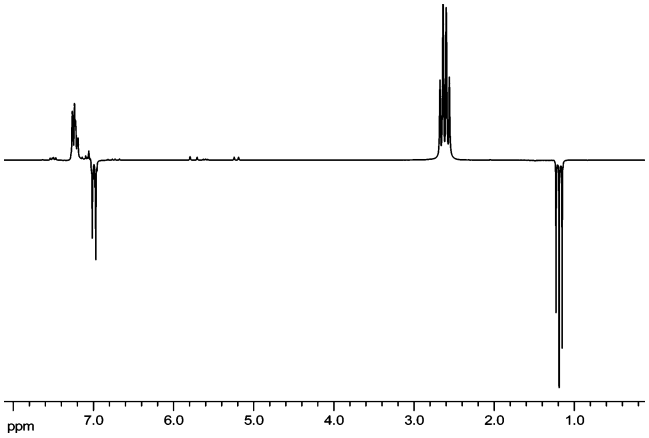


Figure 6. ^{1}H ALTADENA spectrum acquired after the parahydrogenation of 4-fluorostyrene with a single scan.

showing enhanced absorption can also be observed in this spectrum. We attribute these two additional polarization signals to the two groups of chemically equivalent aromatic protons *H*(2,6) at $\delta = 7.00$ ppm and *H*(3,5) at $\delta = 7.25$ ppm, respectively. A thorough analysis of the ^{1}H NMR spectrum of this parahydrogenation product and its comparison with a ^{1}H NMR spectrum of the starting material shows clearly that these signals represent the specified aromatic protons of the parahydrogenated 4-fluorostyrene. The observation of this homonuclear polarization transfer to the aromatic protons of a parahydrogenated styrene derivative, however, appears unprecedented and the presence of ^{19}F in this system seems to facilitate this process substantially.

IV. Concluding Remarks

Exploiting the novel observation of PHIP transfer to ^{19}F nuclei of specifically chosen substrates using both high-field and low-field conditions we have been able to shed some more light on the mechanisms governing the parahydrogen-derived polarization transfer to heteronuclei. We showed that under low-field conditions (ALTADENA) PHIP transfer is mediated by both through-bond and through-space interactions leading to a superposition of both effects. Under high-field conditions, however, the parahydrogen-derived protons and heteronuclei of the parahydrogenation product represent only a weakly coupled spin system, and the transfer of the high spin order stemming from the parahydrogen molecule seems to be mainly governed by a dipolar cross-relaxation mechanism as can be seen from the strongly distance dependent transfer efficiency. The strong differences in transfer efficiency between a high-field and a low-field setup were explained applying the concept of "isotropic mixing", thereby supporting earlier observations made by Aime et al.[6d] Comparing both ^{19}F PHIP and ^{13}C PHIP results acquired in this study, one can clearly see that sufficiently high hydrogenation rates are rather crucial prerequisites for the observation of PHIP-derived transfer of the high spin order to heteronuclei of the hydrogenation product. Furthermore, heteronuclei of interest should have spin−lattice relaxation rates that do not match or exceed the efficiency of polarization buildup associated with the prevailing hydrogenation rates. In this context, the trivial statement can be made that the longer the relaxation times the more likely the observation of PHIP transfer to heteronuclei will be.

The demonstrated feasibility of PHIP transfer to ^{19}F nuclei extends the number of heteronuclei whose sensitivity experiences a significant increase upon the addition of parahydrogen to specifically labeled unsaturated substrates. The amount of polarization transferred to ^{19}F using ALTADENA conditions was found to be substantial and the associated signal enhancement factors exceeded 2 orders of magnitude consistently. This increase in ^{19}F signal intensity opens up a new range of potential applications for hyperpolarized ^{19}F nuclei present in biologically active molecules. Because the development of new drugs very often involves the use of fluorine as a component to modulate biological activity or other physical properties of these compounds, it might be beneficial to exploit this PHIP-derived signal increase for medical imaging techniques as demonstrated by Golman et al. using hyperpolarized ^{13}C nuclei.[11] Specifically chosen molecules might then serve as "active" contrast agents for MRI and MRT experiments following the parahydrogenation of suitable precursor molecules that contain at least one ^{19}F nucleus. Other applications might also involve the use of ^{19}F-hyperpolarized aliphatic blood surrogates in contrast-enhanced magnetic resonance angiography (CE-MRA), as previously shown by Svensson et al. for ^{13}C-hyperpolarized compounds using dynamic nuclear polarization (DNP).[12] However, carefully optimized protocols for the processes yielding ^{19}F-hyperpolarized molecules that are suitable for the injection into living tissue in terms of both biological compatibility and high degrees of hyperpolarization will be necessary to standardize such a procedure. Because our study shows that the most efficient transfer rates can be achieved when working with strongly coupled spin systems that predominate at very low levels of an external magnetic field the construction of a "zero-field" box should assist in obtaining an even more efficient polarization transfer to heteronuclei as achieved using our low-field setup. PHIP transfer experiments involving a similar field-cycling technique were conducted recently by other investigators and have clearly shown the potential applicability and the advantages associated with this method.[13a−c]

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