Supporting Information for

NMR SLIC Sensing of Hydrogenation Reactions Using Parahydrogen in Low Magnetic Fields

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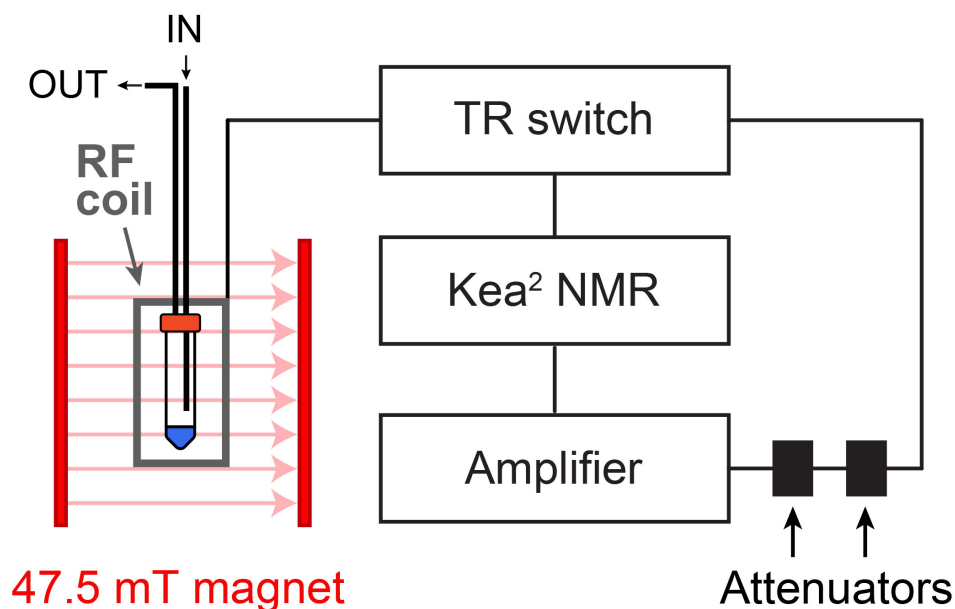# 1. Additional experimental details

Figure S1. Schematic diagram of the arrangement of low-filed NMR detection system. When SLIC pulse was needed, additional attenuators (Bird Technologies, 10 Watt, A Series, Male/Female N Connector, 30 dB and 20 dB) were inserted between the output of the Tomco RF amplifier (P/N BT00250-AlphaS-Dual, Tomco Technologies, Stepney, Australia) and TR switch of the spectrometer.

2. Calculation of signal enhancement and apparent polarization percentage

Apparent polarization percentage (P^{APP}) was calculated for 2-hydroxyethyl propionate (HEP) with the assumption of 100% chemical conversion of 2-hydroxyethyl acrylate. Proton nuclear spin polarization, P^{APP} of HEP produced by hydrogenation with 50% p-H$_2$ was estimated by using the following equation:

$$P^{APP} = \varepsilon P_{therm} = \frac{S_{SLIC}}{S_{therm}} \cdot \frac{4C_{solv}}{2C_{HEP}} \cdot P_{therm} = 22.55 \cdot \frac{4 \cdot 24.7}{2 \cdot 0.08} \cdot P_{therm} = 13{,}940 \cdot 1.6 \cdot 10^{-7} = 0.23\%$$

where ε is enhancement factor, P_{therm} is ^{1}H nuclear spin polarization at 47.5 mT, S_{SLIC} is the signal of HEP after application of a SLIC pulse, S_{therm} is a thermal signal of the solvent (methanol) after application of a $\pi/2$ pulse, C_{solv} and C_{HEP} are concentrations of the solvent and the HEP, respectively.

3. NMR parameters of –CH₂-CH₃ motif for hydrogenation reaction products

Table S1. NMR parameters of –CH$_2$-CH$_3$ motif of studied molecules: 2-hydroxyethyl propionate (**HEP**), ethyl acetate (**EA**), (ethyl)trimethylammonium chloride (**ETMA**), 2-ethylpyridine (**EPy**)

	HEP	EA	ETMA	EPy
^{1}H Chemical shift CH$_2$ (ppm)	2.4	4.1	3.2	2.8
^{1}H Chemical shift CH$_3$ (ppm)	1.1	1.2	1.3	1.1
$^3J_{HH}$-coupling (Hz)	7.6	7.2	7.3	7.6
$x = \delta v / J$ (see Ref. 1)	0.34	0.81	0.52	0.45

4. SLIC signal build-up and decay measurements at 47.5 mT

Varying the reaction time (Fig. 2b), i.e. time spent by reaction mixture in the reactor after injection, allowed calculating NMR signal build-up and decay. If one assumes the following simplified reaction scheme:

$$[CH_2=CH-R] \xrightarrow{k_r} [CH_3-CH_2-R]* \xrightarrow{1/T_S} 0$$

where [CH$_2$=CH-R] and [CH$_3$-CH$_2$-R]* represent thermally polarized and "hyperpolarized reaction species".[2] Solution of these chemical kinetic equations provides the following dependence of the NMR signal (S) vs. time:

$$S = \frac{Ak_r T_S}{1 - k_r T_S} \left(e^{-k_r t} - e^{-t/T_S} \right) \qquad (S1)$$

Plotting the observed SLIC signal dependences vs. reaction time and fitting them with Eq. S1 provides estimates of k_r and T_S for the studied molecules (Table 1, S2).

Table S2. *The same data as in Table 1 of the main text.* Kinetic and relaxation parameters extracted from fitting of the build-up and decay curves for studied substrates.

Methanol	HEP	EA	ETMA	EPy
k_r (s^{-1})	11.8±1.8	11.5±2.3	14.1±2.5	2.8±0.5
T_S (s)	5.5±0.2	7.2±0.5	17.1±1.2	---
Water	HEP	EA	ETMA	EPy
k_r (s^{-1})	12.8±3.9	14.4±5.9	21.9±4.2	---
T_S (s)	8.3±0.8	4.3±0.5	13.2±1.4	---

Note that the values of k_r and the error margins indicated were obtained using the conventional procedures as implemented in the OriginPro's automated fitting routine.

5. Efficiency of the singlet-to-magnetization transformation

We are interested in finding how much singlet spin order originating from parahydrogen can be transferred into $\hat{I}_z$ magnetization.

I) First, let's look at the 2-spin ½ system. The density matrix for an ensemble of hydrogen molecules is

$$\hat{\rho}_{H_2} = x_p |S\rangle\langle S| + \frac{1-x_p}{3}\left(|T_+\rangle\langle T_+| + |T_0\rangle\langle T_0| + |T_-\rangle\langle T_-|\right) = \frac{1}{4}\hat{1} - f \cdot \hat{I}_1\hat{I}_2 \tag{S2}$$

where $f = (4x_p - 1)/3$ and x_p denotes the parahydrogen fraction. From now on, we assume $f = 1$ corresponding to 100% parahydrogen. The density matrix for a thermally polarized ensemble may be written now in the following way:

$$\hat{\rho}_{therm} = \frac{1}{4}\hat{1} + \frac{\mathbb{B}}{4} \cdot \hat{I}_z \tag{S3}$$

where $\mathbb{B} = \frac{\gamma \hbar B}{kT}$ is the Boltzmann factor. We want to achieve the following transformation $\hat{\rho}_{H_2} \Rightarrow \hat{\rho}_z$, where the density matrix is given by the equation

$$\hat{\rho}_z = \frac{1}{4}\hat{1} + \boldsymbol{a} \cdot \hat{I}_z \tag{S4}$$

contains the unknown coefficient $\boldsymbol{a}$. According to the analysis of unitary transformations[3] one may find vectors containing the eigenvalues of corresponding operators, arranged in ascending order:

$$\Lambda_{H_2} \uparrow = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \Lambda_z \uparrow = \begin{pmatrix} 1 \\ 0 \\ 0 \\ -1 \end{pmatrix} \tag{S5}$$

We are interested in finding the coefficient b_{max}[3] only for the singlet-to-magnetization transformation. Hence, we write

$$b_{max} = \frac{1}{(\Lambda_z \uparrow \cdot \Lambda_z \uparrow)} \Lambda_{SO} \uparrow \cdot \Lambda_z \uparrow = \frac{1}{2} \tag{S6}$$

This equation means that

$$\hat{\rho}_{H_2} = \frac{1}{4}\hat{1} - \hat{I}_1\hat{I}_2 \implies \hat{\rho}_z = \frac{1}{4}\hat{1} + \frac{1}{2}\cdot\hat{I}_z \tag{S7}$$

and the unknown coefficient **a** therefore equals ½. The theoretical NMR signal enhancement factor (η) which can be expected in the PHIP experiments with parahydrogen, is given by

$$\eta = \boldsymbol{a}\frac{4}{\mathbb{B}} = \frac{2}{\mathbb{B}} \tag{S8}$$

Usually, thermal polarization is calculated in reference to the single proton, thus, thermal polarization (P_{therm}) equals $\mathbb{B}/2$. It can now be seen that nuclear spin polarization (P) for the spin pair of *parahydrogen*-nascent protons may be converted to

$$P = \eta P_{therm} = \frac{2}{\mathbb{B}}\frac{\mathbb{B}}{2} = 1 \tag{S9}$$

This demonstrates that 100% polarization is achievable in the case of 100% parahydrogen.

II) In the case of the 5-spin system[4]

$$\hat{\rho}_{H_2} = \left(\frac{1}{4}\hat{1} - \hat{I}_1\hat{I}_2\right)\otimes\frac{1}{8}\hat{E} \tag{S10}$$

and the density matrix for a thermally polarized ensemble is written as

$$\hat{\rho}_{therm} = \frac{1}{32}\hat{1} + \frac{\mathbb{B}}{32}\cdot\hat{I}_z \tag{S11}$$

Applying the same theoretical analysis as the one undertaken above for a 2-spin system,[3] we obtain

$$b_{\max} = \frac{1}{(\Lambda_z\uparrow\cdot\Lambda_z\uparrow)}\Lambda_{H_2}\uparrow\cdot\Lambda_z\uparrow= 0.0344 \tag{S12}$$

meaning that the theoretical nuclear spin polarization (P) is

$$P = 0.0344 \frac{32}{\mathbb{B}} \frac{\mathbb{B}}{2} = 0.55 \tag{S13}$$

This demonstrates that ~55% proton polarization is achievable in the case of 100% parahydrogen.

One should note that the theoretical framework described above is elaborated for PASADENA-type experiment, *i.e.*, when hydrogenation reaction is carried out at the same magnetic field where NMR detection is performed. At the same time, experiments were carried out at the magnetic field of the polarizer, and then the reaction products were transferred to the detection chamber located in the magnetic field of the NMR spectrometer (47.5 mT). However, one may show that at such a low magnetic field there is no notable difference between PASADENA and ALTADENA-type experiments (Fig. S2).
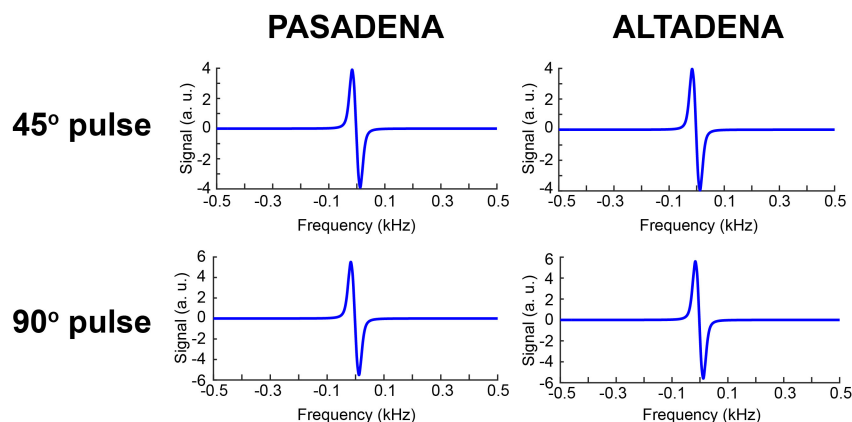

Figure S2. Calculated ^{1}H NMR spectra for 2-hydroxyethyl propionate (HEP) produced by hydrogenation of 2-hydroxyethyl acrylate (HEA) with *p*-H$_2$ at PASADENA and ALTADENA conditions. PASADENA conditions correspond to the situation when hydrogenation and NMR detection are carried out at the same magnetic field (47.5 mT); ALTADENA conditions correspond to the situation when hydrogenation is carried out at the Earth's magnetic field and then the product is transferred to 47.5 mT for NMR detection.

It is seen that there is no detectable difference between PASADENA (*i.e.*, hydrogenation and detection at 47.5 mT) and ALTADENA (*i.e.*, hydrogenation at the Earth's magnetic field) type of spectra for the spin systems under the study. This is, however, not surprising, since at such low static magnetic fields spin systems are already in the strong coupling regime, thus, there are no additional level anti-crossings leading to the disruption of the symmetry of the singlet spin states. Adiabaticity of the polarization transfer does not have the effect on the spin dynamics because of the same reasons."

6. Spin dynamics calculations for *p*-H$_2$-to-magnetization conversion efficiency

Simulations were carried out by numerically treating the Liouville−von Neumann equation for the spin density matrix. The initial density matrix of *p*-H$_2$ was constructed as $\hat{\rho}_{H_2} = \frac{1}{4}\hat{1} - \hat{I}_1\hat{I}_2$. In the case of a 5-spin system, the density matrix of an ethyl moiety was constructed as a direct product between $\hat{\rho}_{H_2}$ and the unit matrix representing the thermally polarized 3-spin system of a vinyl moiety (Eq. S10). In order to account for averaging of coherences arising from the time dispersion of the polarization build-up process, only diagonal elements of the matrix written on the Eigenbasis of the Hamiltonian were kept and all non-diagonal elements were discarded. The matrix obtained was converted back into the Zeeman basis, and exposed to the action of the Hamiltonian representing low-frequency continuous-wave (CW) RF field for a time τ_{SLIC}. Simulation parameters are listed in the Tables S3 and S4 for the 2-spin and 5-spin systems, respectively. Then trace of the product of the operator $\hat{I}_x$ and density matrix of the spin system was taken and plotted vs. B_1 amplitude (Hz) and pulse offset (Hz) for a range of selected values of τ_{SLIC} (Fig. S1 and Fig. S2). GIF files show the full simulation in animation mode. Note that relaxation effects were not included in the simulations.

I)   2-spin system

Table S3. Simulation parameters for 2-spin system simulations. NMR parameters are taken from 2-hydroxyethyl propionate (HEP).

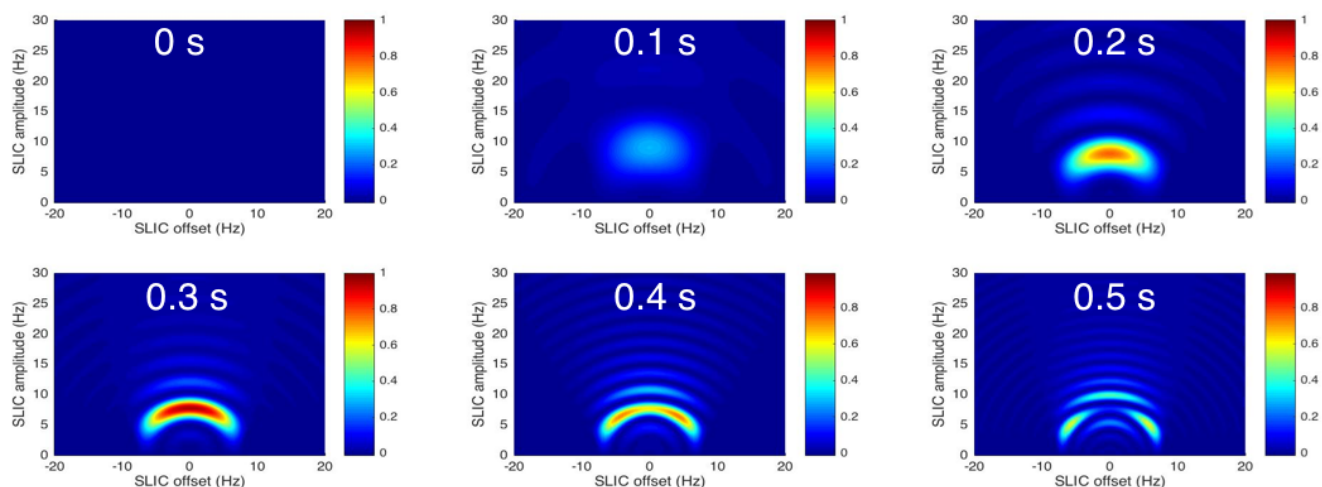| Chemical shift (ppm)	Number of nuclei	J coupling (Hz)	B_1 amplitude (Hz)	Pulse offset (Hz)	SLIC time (s)
1.13	1	7.57	0:0.2:30	-20:0.25:20	0:0.05:1.5
2.37	1				

Figure S3. Simulation of ^{1}H NMR signal dependence in a 2-spin system system on SLIC parameters: B_1 amplitude (Hz), pulse offset (Hz) (position of zero offset corresponds to the center between two resonances) and SLIC pulse time (s).

Figure S1 shows that our simulations match extremely well with the original model of DeVience et al.,[5] i.e. maximum signal is observed for $B_1 = {}^3J_{HH}$, zero pulse offset and

$$\tau_{SLIC} = \frac{1}{\Delta v \sqrt{2}} \tag{S14}$$

which translates to $\tau_{SLIC} \sim 0.28$ sec for the parameters listed in the Table S1. The calculations also show that the maximum value of magnetization for this particular 2-spin system of HEP is $\langle \hat{I}_x \rangle = 0.91$. Given that the theoretical maximum of polarization is 100%, this means that SLIC is able to "extract" ~91% of the theoretically possible polarization from a parahydrogen-derived singlet state for a two spin system with the NMR parameters of HEP.

II)   5-spin system

Table S4. Simulation parameters for 5-spin system simulations. NMR parameters are taken from 2-hydroxyethyl propionate (HEP)

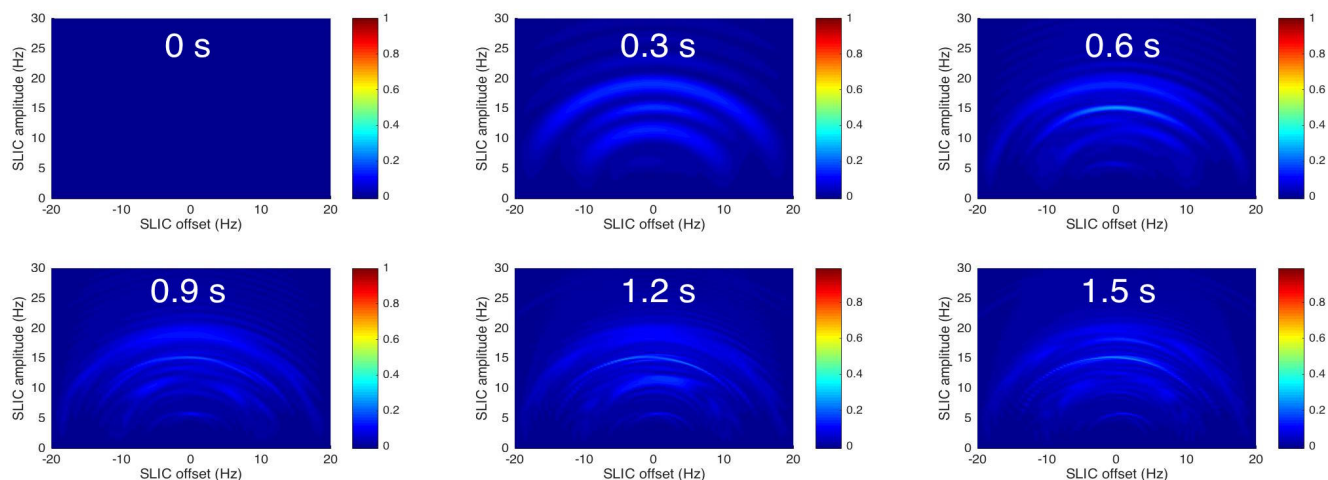| Chemical shift (ppm)	Number of nuclei	$^3J_{HH}$ coupling (Hz)	B_1 amplitude (Hz)	Pulse offset (Hz)	SLIC time (s)
1.13	3	7.57	0:0.2:30	-20:0.25:20	0:0.05:1.5
2.37	2				

Figure S4. *The same data as in Fig. 4 of the main text.* Simulation of ^{1}H NMR signal dependence in a 5-spin system on SLIC parameters: B_1 amplitude (Hz), pulse offset (Hz) (position of zero offset corresponds to the center between two resonances) and SLIC pulse time (s). Note that intensity changes within the interval [0, 1] whereas Fig. 4 from the main text shows evaluations over the interval [0, 0.3].

It is now clear that the simple two-spin model cannot describe the evolution of more complex spin systems. For example, optimal B_1 for the particular 5-spin system (Table S2) was found to be about $2 \cdot {}^3 J_{HH} \sim 15$ Hz and optimal $\tau_{SLIC} \approx 0.6$ s. Calculated results show that the maximum value of magnetization for this particular 5-spin system is $\langle \hat{I}_x \rangle = 0.27$. Given that the theoretical maximum of polarization was found to be 55%, this means that SLIC is able to "extract" ~49% (0.27/0.55) of theoretically possible polarization from a parahydrogen-derived singlet state for a 5-spin system with NMR parameters of HEP. This means that SLIC is not the most optimal method for performing singlet-to-magnetization transformation in multi-spin systems.

7. References Used in Supporting Information

1.   Colell, J.; Turschmann, P.; Gloggler, S.; Schleker, P.; Theis, T.; Ledbetter, M.; Budker, D.; Pines, A.; Blumich, B.; Appelt, S. Fundamental Aspects of Parahydrogen Enhanced Low-Field Nuclear Magnetic Resonance. *Phys. Rev. Lett.* **2013,** *110*.
2.   Barskiy, D.; Pravdivtsev, A.; Ivanov, K.; Kovtunov, K.; Koptyug, I. A Simple Analytical Model for Signal Amplification by Reversible Exchange (SABRE) Process. *Phys. Chem. Chem. Phys.* **2016,** *18*, 89-93.
3.   Levitt, M. Symmetry Constraints on Spin Dynamics: Application to Hyperpolarized NMR. *J. Magn. Reson.* **2016,** *262*, 91-99.
4.   Korchak, S.; Ivanov, K.; Yurkovskaya, A.; Vieth, H. Para-Hydrogen Induced Polarization in Multi-Spin Systems Studied at Variable Magnetic Field. *Phys. Chem. Chem. Phys.* **2009,** *11*, 11146-11156.
5.   DeVience, S.; Walsworth, R.; Rosen, M. Preparation of Nuclear Spin Singlet States Using Spin-Lock Induced Crossing. *Phys. Rev. Lett.* **2013,** *111*, 173002.