

Non-resonant SABRE provides a new and versatile hyperpolarization approach in magnetic resonance

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Abstract: Hyperpolarization approaches in magnetic resonance overcome the sensitivity limitations imposed by thermal magnetization and play an important role in a very wide range of modern applications. One of the newer strategies, variants of what is generically called SABRE, uses para-hydrogen to form hydrides on transition metal catalysts, followed by reversible exchange to polarize target molecules in solution, and has produced large signal enhancements ($\approx 10^4$) on hundreds of different molecules, cheaply and rapidly. Most commonly, the sample is kept in a constant field, matched to make the hydride scalar coupling comparable to the frequency difference between hydride protons and target protons (≈ 6.5 mT) or hydride protons and target heteronuclei (≈ 0.5 μ T). Here we demonstrate a different strategy, applicable to a wide range of target molecules, that produces field-independent spin order in the target molecules that is efficiently converted to magnetization. The observed signal is even independent of field direction, hence significant polarization can be achieved in a sample on a lab bench with no field control at all. We show this signal arises from creation of two-spin order in the target molecules, and discuss multiple ways this strategy should expand SABRE generality and efficiency. We also show that, in many cases, the standard assumption in low-field SABRE of a starting state with only singlet polarization leads to incorrect results.

Introduction

Sensitivity is almost always a limitation in magnetic resonance, because the small energy difference between nuclear spin states (gyromagnetic ratio γ times field B) limits thermal magnetization. For ^1H at 15 Tesla, $\gamma B/k_B T \approx 10^{-4}$; for isotopes with lower γ (^{13}C , ^{15}N) it is much worse. “Hyperpolarization” (HP) methods solve this problem by dramatically increasing the fractional magnetization (and hence the sensitivity), typically by 10^3 - 10^5 . This paper focuses on one of the newer methods, variants of SABRE (signal amplification by reversible exchange) and identifies a significant omission in the general understanding of this method: it neglects creation of two-spin order in target molecules. Correcting this omission should lead to signal enhancements and new experimental strategies.

The obvious hyperpolarization method, drastic cooling (mK-K) in a strong magnetic field¹ is extremely slow². Thus, almost all hyperpolarization technologies get the nuclear spin order from something else, most commonly unpaired electron spins. Examples include optical pumping (nitrogen vacancy centers in diamond,³ electron spins in Rb vapor followed by collisions to polarize noble gases⁴⁻⁹, or triplet states in organic molecules)¹⁰⁻¹⁵. Another strategy is to introduce a paramagnetic species (generally called dynamic nuclear polarization (DNP)),¹⁶⁻²² sometimes by ionizing²³ or UV radiation²⁴, more often by doping the target of interest with a radical²⁵. In the cryogenic case, the sample is then rapidly dissolved in warm solution (dissolution DNP or d-DNP)^{21, 26-34}. The first clinical DNP application³⁵, metabolism of ^{13}C -labeled pyruvate to alanine or lactate, has been validated as a prostate cancer marker and is currently in clinical trials, and other molecules such as HCO_3^- also show promise³⁶⁻³⁸. While all of these methods are being actively improved, none of them approach the level of simplicity, generality and convenience needed to enable (for example) hyperpolarization as a routine improvement in NMR or MRI.

Parahydrogen ($p\text{-H}_2$, the singlet state $S \equiv (|\alpha\beta\rangle - |\beta\alpha\rangle)/\sqrt{2}$ of gaseous H_2) provides a different source of spin order. It is an extraordinary “quantum reagent” in a metastable, pure spin state which can

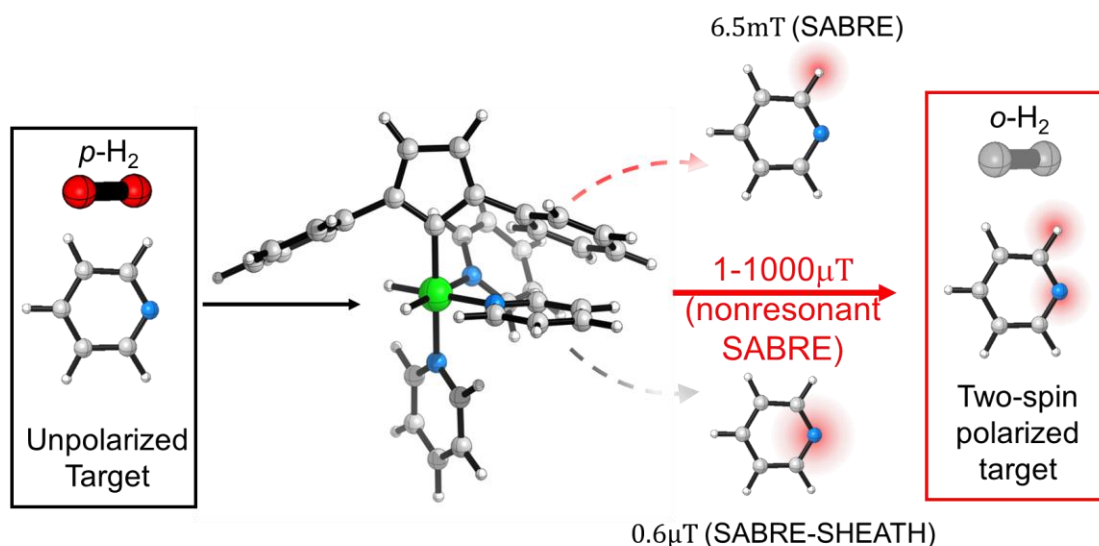


Fig. 1. Comparison of different SABRE variants. In all cases $p\text{-H}_2$ and a target ligand (here pyridine) bind reversibly in the equatorial positions of an Ir complex; typically, one axial position has a large ligand such as iMes illustrated here. In SABRE, four-bond couplings between the hydride and target ^1H atoms create nuclear spin polarization, commonly 1000-10,000 times larger than what is observed at thermal equilibrium in even a large magnet (only one proton is highlighted for simplicity). In X-SABRE methods, the much larger two-bond couplings between the hydride and ^{15}N create polarization. In this paper we demonstrate a third mechanism, nonresonant SABRE, with direct creation of heteronuclear two-spin order in the ligands. This has vastly different properties from the first two approaches.

be made in large quantities at high spin purity and low cost³⁹⁻⁴⁴ and stored stably for weeks.⁴⁵ $p\text{-H}_2$ was initially mostly used in NMR by addition across inequivalent carbon double or triple bonds, then pulse sequences converted singlet order into nuclear polarization⁴⁶⁻⁵¹, but each target molecule requires different optimization (often including a different catalyst) and there is a very limited range of targets. In 2009, Duckett and coworkers introduced SABRE (Fig. 1)⁵²⁻⁵⁶ which works by reversibly binding $p\text{-H}_2$ and target ligands (such as pyridine) to an octahedral transition metal complex, usually iridium-based. Under the right circumstances (see Fig. 1), para order in the hydrides is converted to positive ligand (and negative hydride) magnetization. After both $p\text{-H}_2$ and ligand exchange (typically the ligand exchange is much faster), the Ir atom can catalyze another transfer. SABRE directly polarizes hydrogen on the ligand target; methods for direct heteronuclear polarization such as SABRE-SHEATH⁵⁷ go by the general name X-SABRE (there are now at least a dozen such methods with a wide range of applications).

SABRE and X-SABRE avoid all cooling, can hyperpolarize in seconds, are not as limited in volume as DNP, and have been applied to a wide variety of molecules. Today many groups work on different aspects including methods that use shaped three-dimensional magnetic fields, or work in a high field magnet using rf pulses⁵⁸⁻⁷⁷. However, the “workhorse experiment” since the beginning has used a constant magnetic field and no rf irradiation. There are two basic regimes: the traditional SABRE case, where the field is matched to make the hydride scalar coupling comparable to the frequency difference between hydride protons and target protons (≈ 6.5 mT), and the SABRE-SHEATH case, where the field is matched to the frequency difference between hydride protons and target heteronuclei such as ^{15}N and ^{13}C (≈ 0.5 μT , achieved in a mu-metal shield⁵⁷). In both cases, the matching condition is generally justified as an example of level anticrossings, although this does not quite work in the limit of large couplings as has been detailed elsewhere⁷⁸. Still, as Fig. 2 shows, well-validated simulations^{78, 79} reproduce the experimental field dependence well. Constant-field experiments are constrained by inconvenient field strengths that require a mu-metal shield to achieve, and the high field experiments are very sensitive to experimental complications such as resonance frequency difference between the two hydride spins.

Here we show (to be honest, to our surprise) that this picture is an oversimplification. For a wide range of target ligands which have both protons and heteronuclei (including the most heavily studied molecules in the field), there is a highly efficient path to *two-spin* order in the target which can be quantitatively converted to observable magnetization competitive with SABRE and X-SABRE. Over the field regime between SABRE and X-SABRE, this produces magnetization independent of field strength and direction — in other words, inverting the field has no effect on the magnetization. For this reason, we call this effect nonresonant SABRE. Magnetization can even be produced by bubbling directly on a tabletop with no external magnet or shield. To our knowledge this mechanism has never been considered, and it also opens up many options for SABRE improvement in other regimes.

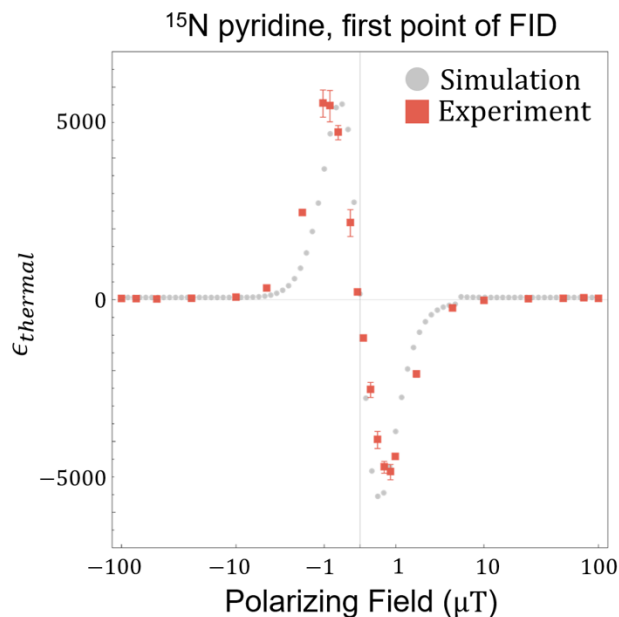


Fig. 2. Signal enhancement ϵ for ^{15}N -pyridine in $\text{Ir}(\text{H})_2(\text{IMes})(\text{pyr})_3$ with continuous application of static polarizing field B . Gray points show theoretical simulation of a $\text{Ir}(\text{H})_2(\text{IMes})(\text{pyr})_3$ system ($k_L = 16$ s^{-1} , $k_H = 2$ s^{-1} , [catalyst]: [ligand] = 1 : 20, and 5-s evolution). Red data points show experimental magnetization enhancement relative to thermal magnetization measured at 1 T (measured as the amplitude of the FID immediately after a 90° pulse).

Results

We start by presenting experimental evidence for nonresonant SABRE. Figure 3 shows hyperpolarized FIDs and spectra for 160 mM ^{15}N -pyridine at two specific fields, one which matches the well-known SABRE-SHEATH condition and one that is about a factor of 100 away. As the field strength increases, the spectrum transitions smoothly from in-phase to antiphase, then remains constant over a wide variety of field strengths. Far from resonance, indeed the FID is zero immediately after a 90 pulse (implying there is no one-spin z magnetization), but the FID grows in at later times. The first maximum occurs at $t = 1/4J_{\text{NH}}$ where J_{NH} is the coupling between the pyridine ^{15}N and the ortho protons (≈ -10 Hz).

Fig. 4 shows this field dependence over about three orders of magnitude. As shown in the SI, detection of ^1H magnetization instead of ^{15}N magnetization reveals signal comparable to the ^{15}N magnetization off resonance, with similar antiphase behavior.

We note several experimental observations which contribute to the analysis below.

1. We stopped the bubbling for a variable period prior to pulsing the sample after moving it from the polarizing field to the 1 T measurement magnet, and saw much faster attenuation of the off-resonance signal ($T_1 = 12.46 \pm 0.26$ s after polarization build-up at 50 μT) than was observed for the conventional SABRE-SHEATH signal ($T_1 = 96.9 \pm 5.9$ s after polarization at 0.5 μT).

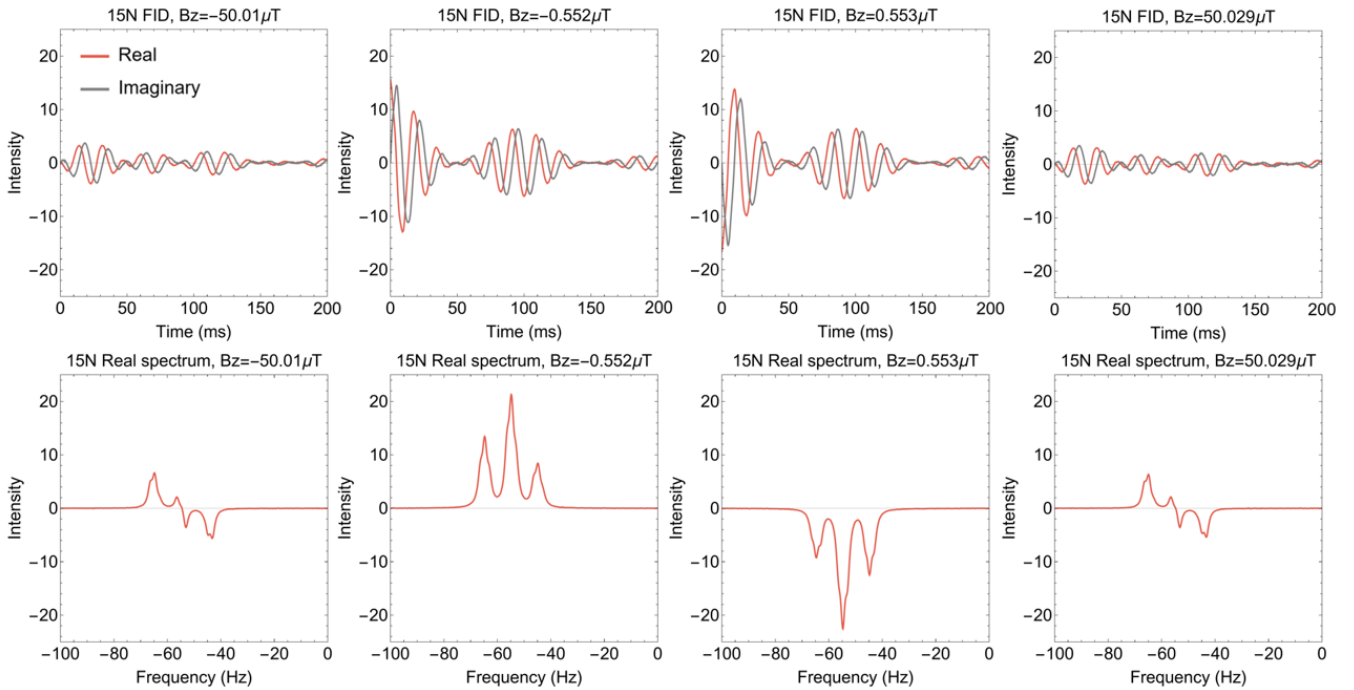


Fig. 3. Experimental one-scan ^{15}N signal from 160 mM ^{15}N -pyridine after excitation at the peak of the SABRE-SHEATH resonance (0.5 μT), and a factor of 100 away from that resonance (50 μT). The off-resonance signal is nearly zero immediately after the pulse, implying that no z -magnetization was directly produced. However, substantial signal grows in at later times. The amplitude and phase of the FID of the off-resonance signal is nearly independent of field over the range 5-500 μT , including inverting the field. ^1H or ^{15}N $\pi/2$ pulses applied after the polarization time produce nearly equal ^1H or ^{15}N fractional magnetization (respectively, see SI).

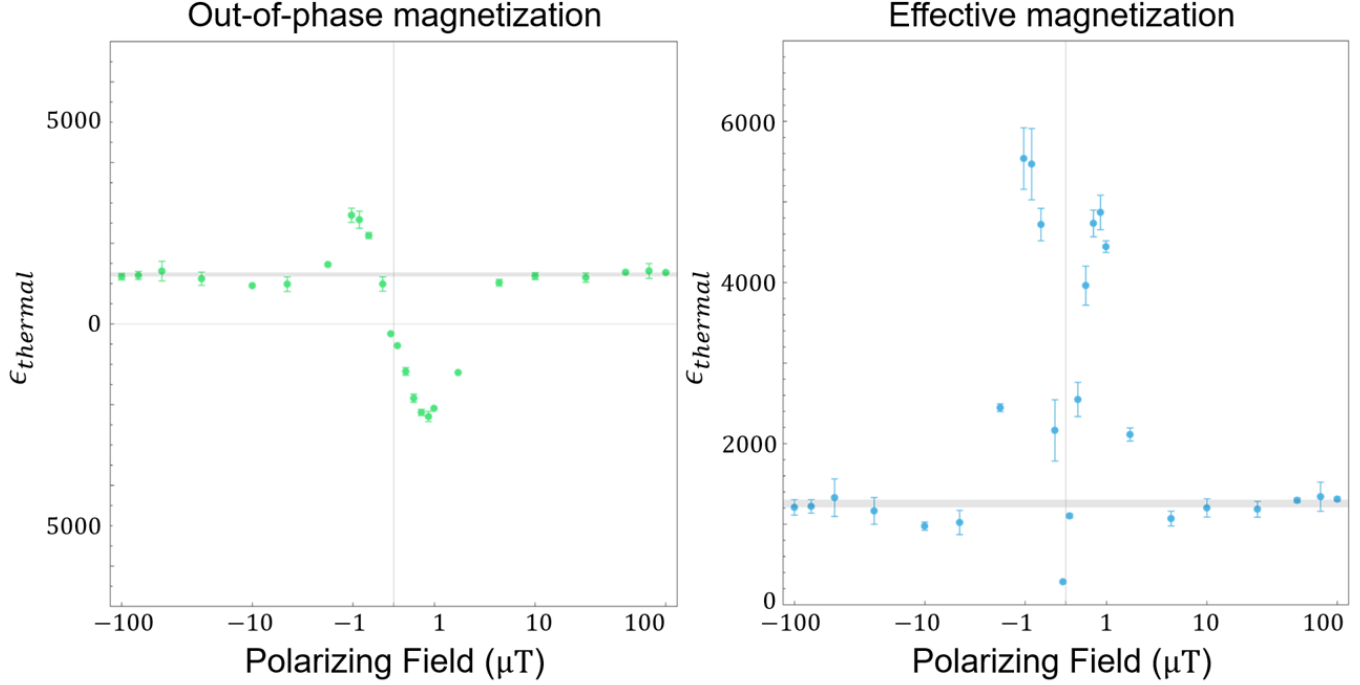


Fig. 4. Experimental ^{15}N SABRE signals as a function of polarizing field. At left, the signal at a time $t = 1/4J_{NH}$ is plotted; this time corresponds to the maximum signal in the off-resonance case. The right plot shows the “effective magnetization”, corresponding to the maximum value of the FID (which would also be the largest z magnetization available after an additional $\pi/2$ pulse). This is mathematically equivalent to acquiring the spectrum, optimizing the zero-and first-order phase, and taking its integral. The gray bars indicate the 95% confidence interval for the mean out-of-phase signal at high ($> 25\mu\text{T}$) fields. Enhancement ε was calculated based on the maximum intensity of a thermally polarized reference sample (see SI).

2. We performed SABRE at three different points in the lab, without a shield, all with roughly $80\mu\text{T}$ field aligned significantly away from the z -axis of the magnet used to detect the magnetization, and all gave comparable antiphase signal.
3. As seen in Figure 4, inverting the direction of the field has no effect on the off-resonance FID.

Theoretical basis for nonresonant SABRE

In this section, we will focus on the simplest spin topology that reveals the nonresonant SABRE effect. This shows that the experiments above provide compelling evidence of a hitherto unappreciated SABRE mechanism which directly and efficiently produces two-spin z order in the target ligand.

We start by summarizing the theoretical approach of ref. [78] for SABRE-SHEATH, as the modifications needed to understand nonresonant SABRE follow directly (Fig. 5). SABRE-SHEATH and SABRE differ only in the assignment of the L nucleus (on the attached ligand) as ^1H or a heteronucleus, typically ^{15}N or ^{13}C . The initial density matrix is assumed to have singlet order between the two hydride protons, derived from binding para-hydrogen from solution, but otherwise is random.

$$\hat{\rho}_0 = \left(\frac{1}{4} \hat{1} - \vec{I}_1 \cdot \vec{I}_2 \right) \otimes \hat{1} \quad [1]$$

The simplest SABRE case is a three-spin system, where the spin operator of the target nucleus is labelled as $\vec{L}$ (which is ^1H for SABRE, and a heteronucleus for SABRE-SHEATH) and the two hydride spins are $\vec{I}_1$ and $\vec{I}_2$. As shown in ref. [78], the three-spin system (which is equivalent to assuming only one of the equatorial positions is occupied by an NMR-active species) gives similar

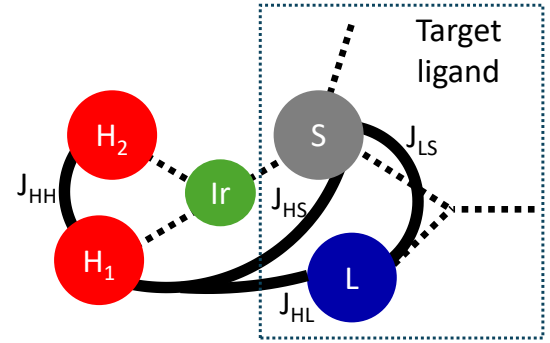
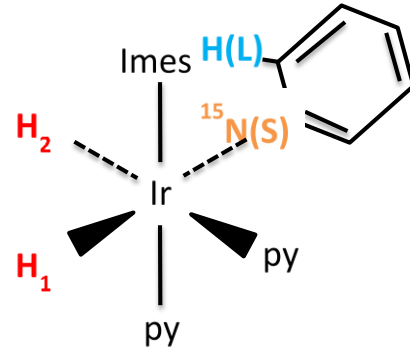


Figure 5. Simplified schematic to explain both resonant and non-resonant SABRE. In the simplest case, para- H_2 and one NMR-active ligand are bound in the equatorial plane of the octahedral Ir complex. The Ir is commonly bound to a lone pair (e.g. ^{15}N or a carbonyl group). In both SABRE and SABRE-SHEATH, this model includes one ligand L that is scalar coupled to hydrogen H_1 . Because of the geometry, only the linear H-Ir-ligand geometry supports a scalar coupling. For nonresonant SABRE, we assume L is ^1H and S is ^{15}N or ^{13}C . The left side illustrates the topology for pyridine, one of the molecules studied extensively in this paper; however, all that matters in our analysis is the coupling network, shown more explicitly at right.

results at this level to the four-spin system (which assumes both positions are occupied) so for simplicity we will stay with this model here.

The nuclear spin Hamiltonian has the form:

$$\hat{\mathcal{H}}(t) = -(B_0)(\gamma_H(\hat{I}_{1z} + \hat{I}_{2z}) + \gamma_L\hat{L}_z) + 2\pi J_{HH}(\vec{I}_1 \cdot \vec{I}_2) + 2\pi J_{HL}(\vec{I}_1 \cdot \vec{L}) \quad [2]$$

here in natural units ($\hbar = 1$). For simplicity, we couple the ligand spin to only one of the hydride spins (spin 1), as this is consistent with experimental observations that only the hydride directly opposite the ligand has an observable coupling. We can rearrange this Hamiltonian as

$$\hat{\mathcal{H}}(t) = -(B_0)\gamma_H(I_{1z} + I_{2z} + L_z) + (\Delta\omega_{HL})L_z + 2\pi J_{HH}(\vec{I}_1 \cdot \vec{I}_2) + 2\pi J_{HL}(\vec{I}_1 \cdot \vec{L}) \quad [3]$$

in which $\Delta\omega_{HL} = B_0(\gamma_H - \gamma_L)$. The first term commutes with the rest of the Hamiltonian (and with the operators we are going to prepare) so we drop it in what follows for simplicity; this is equivalent to viewing the system in the ^1H hydride rotating frame, but without explicit assumptions on the field strength. We will thus use the reduced Hamiltonian

$$\hat{\mathcal{H}}' = (\Delta\omega_{HL})L_z + 2\pi J_{HH}(\vec{I}_1 \cdot \vec{I}_2) + 2\pi J_{HL}(\vec{I}_1 \cdot \vec{L}) \quad [4]$$

The coherence transfer pathway leading from singlet order on the hydrides to magnetization on the target nucleus goes through 4 commutators starting with the initial density matrix in equation [1]. Thus a standard Taylor series expansion for the time evolution of the density matrix at $t = 0$ ($d\hat{\rho}/dt = i[\hat{\rho}_o, \hat{\mathcal{H}}]$; $d\hat{\rho}^n/dt^n = i[d\hat{\rho}^{n-1}/dt^{n-1}, \hat{\mathcal{H}}]$) shows that the first term in the density matrix which has ligand magnetization L_z appears in the fourth derivative. Pathways which produce this term originate from $I_{1z}I_{2z}$ (eq. [5-8]) or from $I_{1x}I_{2x}$ and $I_{1y}I_{2y}$ (eq. [9-12]).

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1y}L_y \xrightarrow{\Delta\omega_{HL}L_z} -iI_{1y}L_x \xrightarrow{J_{HL}(I_{1y}L_y)} L_z \quad [5]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{\Delta\omega_{HL}L_z} I_{1x}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -iI_{1y}L_x \xrightarrow{J_{HL}(I_{1y}L_y)} L_z \quad [6]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1x}L_x \xrightarrow{\Delta\omega_{HL}L_z} iI_{1x}L_y \xrightarrow{J_{HL}(I_{1x}L_x)} L_z \quad [7]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{\Delta\omega_{HL}L_z} I_{1y}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} iI_{1x}L_y \xrightarrow{J_{HL}(I_{1x}L_x)} L_z \quad [8]$$

$$I_{1x}I_{2x} \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1z}I_{2x}L_y \xrightarrow{J_{HH}(I_{1x}I_{2x})} -I_{1y}L_y \xrightarrow{\Delta\omega_{HL}L_z} -iI_{1y}L_x \xrightarrow{J_{HL}(I_{1y}L_y)} L_z \quad [9]$$

$$I_{1x}I_{2x} \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1z}I_{2x}L_y \xrightarrow{\Delta\omega_{HL}L_z} -I_{1z}I_{2x}L_x \xrightarrow{J_{HH}(I_{1x}I_{2x})} -iI_{1y}L_x \xrightarrow{J_{HL}(I_{1y}L_y)} L_z \quad [10]$$

$$I_{1y}I_{2y} \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1z}I_{2y}L_x \xrightarrow{J_{HH}(I_{1y}I_{2y})} -I_{1x}L_x \xrightarrow{\Delta\omega_{HL}L_z} iI_{1x}L_y \xrightarrow{J_{HL}(I_{1x}L_x)} L_z \quad [11]$$

$$I_{1y}I_{2y} \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1z}I_{2y}L_x \xrightarrow{\Delta\omega_{HL}L_z} -I_{1z}I_{2y}L_y \xrightarrow{J_{HH}(I_{1y}I_{2y})} iI_{1x}L_y \xrightarrow{J_{HL}(I_{1x}L_x)} L_z \quad [12]$$

These pathways result in direct magnetization on the target nucleus $\hat{L}_z$ with a t^4 dependence^[78]:

$$\ddot{\ddot{\frac{t^4}{4!}}} = 8\pi^3 J_{HL}^2 \Delta\omega_{HL} J_{HH} \frac{t^4}{4!} (2\hat{L}_z) + \dots \quad [13]$$

This approach shows why a nonzero external magnetic field is necessary. It comes into this derivation in the $\Delta\omega_{HL}$ term by generating a phase shift which is needed to create the final magnetization. Mathematically, this happens because it creates a resonance frequency difference between the hydride and the ligand. Note that in every case in equations [5-12], the “flip-flop” component ($xx+yy$) of the coupling J_{HL} appears as the first and fourth commutator, with the $\Delta\omega_{HL}$ and J_{HH} terms appearing in between (in either order, as they commute with each other).

This approach does not show the optimal field, which was originally found by invoking level anti-crossing arguments. As ref. [78] shows, this prediction generally works when the J_{HH} coupling dominates (as in SABRE) but can be off by as much as an order of magnitude in the SABRE-SHEATH case. However, well-validated numerical calculations starting from the equilibrium density matrix agree with equation [13], and agree with experimental data (Fig. 2).

We now turn to the nonresonant SABRE case. The nucleus L is now assumed to be a proton in the ligand, and we now add one more nucleus S assumed to be a heteronucleus on the ligand. This adds the terms in the bracket below.

$$\begin{aligned} \hat{\mathcal{H}}' = & 2\pi J_{HH} \vec{I}_1 \cdot \vec{I}_2 - \Delta\omega_{HL} L_z + 2\pi J_{HL} (\vec{I}_1 \cdot \vec{L}) \\ & + \{2\pi J_{HS} I_{1z} S_z + 2\pi J_{LS} (S_x L_x + S_y L_y) + 2\pi J_{LS} S_z L_z + 2\pi J_{HS} (I_{1x} S_x + I_{1y} S_y) - \Delta\omega_{HS} S_z\} \end{aligned} \quad [14]$$

For simplicity, we will begin by considering a field regime where the resonance frequency difference between the hydride and ligand protons $\Delta\omega_{HL}$ can be ignored, and the resonance frequency differences between the protons and heteronucleus are large enough to truncate the nonsecular term in those couplings $2\pi J_{HS} (\hat{I}_{1x} \hat{S}_x + \hat{I}_{1y} \hat{S}_y)$ and $2\pi J_{LS} (\hat{S}_x \hat{L}_x + \hat{S}_y \hat{L}_y)$. This would imply fields on the order of 10 μ T-1 mT; in other field regimes there will be additional competing terms. This leaves us with

$$\hat{\mathcal{H}}' = 2\pi J_{HH}\vec{I}_1 \cdot \vec{I}_2 + 2\pi J_{HL}I_{1z}L_z - \Delta\omega_{HS}S_z + 2\pi J_{HL}(I_{1x}S_x + I_{1y}S_y) + 2\pi J_{HS}I_{1z}S_z + 2\pi J_{LS}L_zS_z \quad [15]$$

We now use equation [15] with the initial density matrix [1] and do a Taylor expansion as before for the evolution. Eq.[15-22] illustrate eight of the pathways which lead, in the fourth order, to two-spin order L_zS_z . It is important to note that this order lies *in the ligand itself*, and thus survives dissociation of the ligand from the transition metal complex.

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1x}L_x \xrightarrow{J_{LS}(L_zS_z)} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [16]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1x}L_x \xrightarrow{J_{HS}(I_zS_z)} iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} -L_zS_z \quad [17]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{LS}(L_zS_z)} I_{1y}I_{2z}L_yS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [18]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HS}(I_{1z}S_z)} -I_{1x}I_{2z}L_xS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} -L_zS_z \quad [19]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1y}L_y \xrightarrow{J_{LS}(L_zS_z)} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [20]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1y}L_y \xrightarrow{J_{HS}(I_zS_z)} -iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} -L_zS_z \quad [21]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{LS}(L_zS_z)} I_{1x}I_{2z}L_xS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [22]$$

$$I_{1z}I_{2z} \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HS}(I_{1z}S_z)} -I_{1y}I_{2z}L_yS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} -iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} -L_zS_z \quad [23]$$

As shown explicitly in the Supplementary Information, there are a total of 20 pathways which proceed from $\vec{I}_1 \cdot \vec{I}_2$ (the eight above which proceed from $I_{1z}I_{2z}$, plus six each from $I_{1x}I_{2x}$ and $I_{1y}I_{2y}$). In all of the pathways, the first step is creation of three-spin order with both hydride protons and one of the ligand nuclei. The net effect of the next two steps is to transform this into three-spin order with only the coupled hydride proton and two of the ligand nuclei, with either a two-spin or a four-spin state as the intermediate. The last step strips the hydride term. All of the many terms that can be written out are proportional to $J_{HH}J_{HL}^2$, but there are pathways proportional to either J_{HS} or J_{LS} .

All of these pathways would have been dismissed in past work since they do not result in observable L_z or S_z . However, the critical point we make here is that *two-spin L_zS_z order in the ligand itself* can efficiently create magnetization. After a standard 90 pulse, it becomes antiphase magnetization (L_xS_z or L_zS_x) which converts completely into in-phase magnetization L_y or S_y (respectively) after a time $t = 1/2J_{LS}$.

$$\begin{aligned} L_zS_z &\xrightarrow{90_S, phase x} L_zS_y \xrightarrow{\text{free evolution}} L_zS_y \cos(\pi J_{LS}t) - \frac{1}{2}S_x \sin(\pi J_{LS}t) \\ &\xrightarrow{90_L, phase x} L_yS_z \xrightarrow{\text{free evolution}} L_yS_z \cos(\pi J_{LS}t) - \frac{1}{2}L_x \sin(\pi J_{LS}t) \end{aligned} \quad [24]$$

So, it does not matter at all that it takes a fifth coupling to convert to observable magnetization, as long as J_{LS} is not vanishingly small.

A qualitative way to understand nonresonant SABRE is that the newly-added couplings $2\pi J_{HS}I_{1z}S_z + 2\pi J_{LS}L_zS_z$ act, when spin S is up, to create a resonance frequency difference between spin I_1 and spin L , just as the term $\Delta\omega_{HL}$ did in the original SABRE derivation. Thus, the coupling plays the same role as the magnetic field did in the SABRE case. If $J_{HS}-J_{LS}>0$ and spin S is up, the hydride spin is at the higher frequency; if spin S is up, the hydride spin is at the lower frequency and the produced L magnetization is inverted. This means that the order is two-spin rather than one-spin.

This derivation reproduces the experimental features in Figures 3-4. It is *independent of the applied field magnitude and direction* (subject to the constraint above, that we are only considering the secular part of the J_{LS} coupling). Inverting the field, or pointing it in an arbitrary direction, makes no difference. This mechanism is equally effective at producing L or S magnetization. In the regime where neither SABRE nor SABRE-SHEATH is efficient (e.g. 10 – 1000 μ T), this pathway will dominate; in other regimes it competes. Finally, since it arises from two-spin order, the nonresonant pathway does not share one important advantage SABRE-SHEATH has over SABRE: the ability to store magnetization on a longer-lived spin. In the usual limit, ^1H relaxation is much faster than ^{13}C or ^{15}N relaxation, so in practice the two-spin order decays away with essentially the ^1H relaxation time.

Based on these results, we can also do a more detailed interpretation of the experimental data. For our purposes, it is a good approximation to model ^{15}N pyridine as an AX_2 spin system at high field, here retaining only the two ortho protons and their -10 Hz coupling to the nitrogen. Adding in labels L_1 and L_2 for the two ortho protons, we expect the resonant pathway to create S_z and the nonresonant pathway to create $L_{1z}S_z + L_{2z}S_z$. Giving a 90y pulse to the nitrogen, then calculating evolution under the operators $J_{LS}(L_{1z}S_z + L_{2z}S_z)$ gives the time dependence of these two pathways as:

$$S_z \xrightarrow{90_{S,y} + \text{free evolution}} S_x \cos^2(\pi J_{LS}t) - 2S_y(L_{1z} + L_{2z}) \cos(\pi J_{LS}t) \sin(\pi J_{LS}t) - 4S_x(L_{1z}L_{2z}) \sin^2(\pi J_{LS}t) \quad [25]$$

$$S_z(L_{1z} + L_{2z}) \xrightarrow{90_{S,y} + \text{free evolution}} S_x(L_{1z} + L_{2z}) \cos(2\pi J_{LS}t) + 2S_yL_{1z}L_{2z} \sin(2\pi J_{LS}t) + \frac{1}{2}S_x \sin(2\pi J_{LS}t) \quad [26]$$

Thus, the maximum observable signal for the nonresonant case is around 25ms ($t = 1/4J_{LS}$) as seen experimentally. At that time, the resonant SABRE-SHEATH signal is half of its initial value. This lets us

combine the $t = 0$ and $t = 1/4J_{NH}$ signals to measure the relative size of one-spin and two-spin z order (Fig. 6).

The 20 pathways (in the SI) from $\vec{I}_1 \cdot \vec{I}_2$ to $L_z S_z$ include eight terms of the form $J_{HL}^2 J_{HH} J_{LS}$ (all of which lead to positive $L_z S_z$) and twelve terms of the form $J_{HL}^2 J_{HH} J_{HS}$ (six leading to positive $L_z S_z$, six to negative $L_z S_z$) so the expected functional dependence is $J_{HL}^2 J_{HH} J_{LS}$. However, our *long-time* simulations, which is what are relevant for generating experimental signal, show the functional dependence is $J_{HL}^2 J_{HH} (J_{LS} - J_{HS})$. Figure 7 shows an example of this. Simulations show a broad resonance creating usable magnetization with two gaps: one around $J_{LS} = 0$ (where the antiphase order cannot convert back into magnetization) and one where $J_{HS} = J_{LS}$.

There is a simple explanation for this discrepancy. The eight pathways from $I_{1z} I_{2z}$ to $L_z S_z$ in eq. [15-22] include four terms of the form $J_{HL}^2 J_{HH} J_{LS}$ (all of which lead to positive $L_z S_z$) and four terms of the form $J_{HL}^2 J_{HH} J_{HS}$ (all of which lead to negative $L_z S_z$), which is this exact functional dependence. This strongly suggests that the only term which matters in the initial density matrix for the long-time behavior is the $I_{1z} I_{2z}$ term, which is equivalent to a 50:50 mixture of singlet ($\alpha\beta\text{-}\beta\alpha$) and triplet ($\alpha\beta\text{+}\beta\alpha$). This was verified numerically by replacing the initial condition [1] with

$$\hat{\rho}_0 = \left(\frac{1}{4}\hat{1} - I_{1z} I_{2z}\right) \otimes \hat{1} \quad [25]$$

and replenishing magnetization with the same 50:50 mixture, which as Figure 7 shows has virtually no impact on the predicted signal. This is also true in normal SABRE-SHEATH (data shown in SI).

In effect, what the simulation is showing is that when ligand exchange is much more rapid than hydride exchange, the effect of the $J_{HL} I_{1z} L_z$ and $J_{HS} I_{1z} L_z$ couplings (which commute with $I_{1z} I_{2z}$ but not $I_{1x} I_{2x}$ or $I_{1y} I_{2y}$) is to convert the hydride $I_{1x} I_{2x}$ and $I_{1y} I_{2y}$ order into three-spin terms (e.g. $I_{1y} I_{2x} L_z$) which do not survive ligand dissociation. Thus, in the usual limit where the hydride dissociation is at least an order of magnitude slower than the ligand dissociation, only the $I_{1z} I_{2z}$ term is an effective hyperpolarization source most of the time. This is also a known issue at high fields due to para-ortho interconversion.^{80, 81}

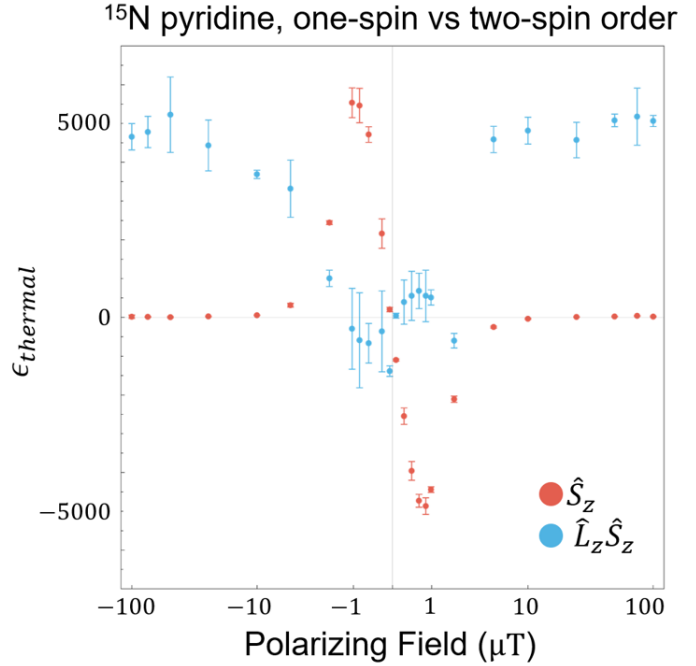


Figure 6. Inferred one-spin and two-spin order from the experimental data in Figures 2 and 3. The one-spin order can be read as the first point in the FID. The two spin order is found by subtracting half of the $t = 0$ signal from the $t = 1/4J_{NH}$ signal, then multiplying by four to account for the two L spins and the factor of $1/2$ in equation [11]

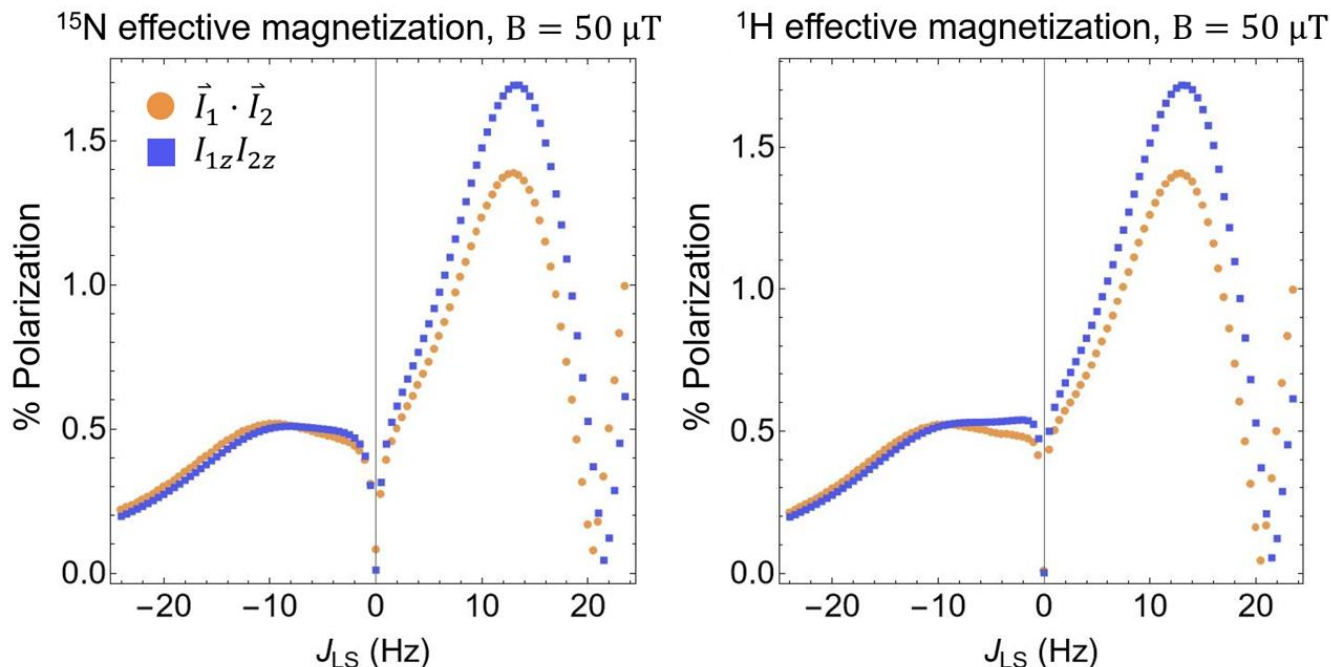


Figure 7. Comparison of the predicted efficiency of generating usable magnetization at 50 μT for a four-spin system modeled on the parameters of pyridine ($J_{HH} = -7$ Hz, $J_{HS} = 19.6$ Hz, $J_{HL} = 1.2$ Hz, $J_{LL} = -0.16$ Hz) as the parameter J_{LS} is varied. The efficiency varies smoothly except around $J_{LS}=0$ (when that coupling is nearly zero, antiphase magnetization cannot convert to single-spin order) and around $J_{LS}=J_{HS}$. This agrees with the predicted $J_{HL}^2 J_{HH} (J_{LS} - J_{HS})$ dependence starting from $I_{1z}I_{2z}$. The orange curves assume the catalyst starts with singlet hydrides and is always replenished with singlet; the blue represents an extreme case where the hydrides and hydrogen in solution have only $I_{1z}I_{2z}$ order. The signals are nearly identical (with a slight shift of the zero, reflecting some action by a mechanism proportional to $J_{HL}^2 J_{HH} J_{LS}$ from the $I_{1y}I_{2y}$ and $I_{1z}I_{2x}$ order). Simulations at the SABRE-SHEATH peak (0.5 μT) also show little effects from $I_{1y}I_{2y}$ and $I_{1x}I_{2x}$ order. This insensitivity comes because, in the usual limit where hydrides exchange far slower than ligands, $I_{1y}I_{2y}$ and $I_{1x}I_{2x}$ order is quenched almost all the time (as discussed in text).

Discussion

Inclusion of the additional pathways that create two-spin magnetization has several practical consequences which have not yet been fully explored but are likely meaningful for SABRE applications.

—The pathways are independent of magnetic field over a broad range, but additional terms come in at frequencies lower than the SABRE-SHEATH or higher than the SABRE condition. This will lead to additional optimal frequencies, particularly in the SABRE case. For example, the C-H coupling in a methyl group $^{13}\text{CH}_3$ is typically about 130 Hz. This implies that if the carbon is spin-down, the methyl protons have an intrinsic 130 Hz difference between spin up and spin down, which is the same as the frequency difference those protons would have from the hydride protons at 120 mT (assuming 25 ppm chemical shift difference). In the normal SABRE condition, the 25 ppm frequency difference between the hydride and methyl protons gives about a 7 Hz frequency difference at 6.5 mT. But this suggests a new resonance would exist offset by this amount from 120 mT, where this field cancels out the J_{CH} coupling. In this case, spin-down ^{13}C nuclei allow polarization of ^1H (because the ligand-hydride resonance frequency difference is matched to the traditional SABRE condition) but spin-up ^{13}C nuclei produce a large frequency difference so they are inactive. Mathematically, this implies normal ^1H and antiphase ^1H - ^{13}C

magnetization are produced in equal quantities. This resonance will move with the chemical shift difference (so it provides some selectivity), and is near the range of commercially available low-field MRI scanners⁷⁴. This effect is also likely responsible for anomalous observations of SABRE resonances near 100 mT in ¹³C labeled pyridines⁶⁶.

—While we have only explicitly considered the case of ¹H plus a heteronucleus, there are likely extensions to two heteronuclei. One example is the ¹⁵N-⁷⁷Se case which has recently been explored experimentally⁸² and to direct pumping of homonuclear singlets such as in diazine^{83, 84}. In the latter case, direct fourth-order pathways from hydride singlet order to ligand singlet order (e.g. $\vec{I}_1 \cdot \vec{I}_2 \xrightarrow{J_{HL}} I_{1z}I_{2y}L_x(cyc) \xrightarrow{J_{HH}} \vec{I}_1 \cdot \vec{L} \xrightarrow{J_{LS}} I_{1x}L_yS_z(cyc) \xrightarrow{J_{HL}} \vec{S} \cdot \vec{L}$) is also field independent.

—Most of the terms in the Hamiltonian in equation [14] are readily controlled, inverted or cancelled by radiofrequency pulses, in the standard ways known in NMR for over half a century. This provides a different strategy for doing high-field SABRE than has been commonly explored. For example, again thinking in terms of field strengths around 100 mT, it would be straightforward to zero out the terms from equation [14] that we omitted in equation [15] using multiple echo sequences on both nuclei, and thus to extend the range of operation of the nonresonant SABRE effect.

—There are likely significant advantages to this strategy for high field SABRE experiments, because most existing methods are highly sensitive to the population difference between hydride singlet ($\alpha\beta\text{-}\beta\alpha$) and the triplet state ($\alpha\beta\text{+}\beta\alpha$). For example, the first such experiment (LIGHT-SABRE)⁸⁵ showed explicitly that polarization is created by weak irradiation at the nitrogen frequency, interchanging states with those two different hydride characters. As noted earlier, the fragility of the $I_{1x}I_{2x}$ and $I_{1y}I_{2y}$ order implies a strong tendency to equalize those populations ($I_{1z}I_{2z}$ has equal population of these two states), which cancels the LIGHT-SABRE effect. Thus, nonresonant SABRE works fine with $I_{1z}I_{2z}$ order, whereas most existing high field SABRE approaches do not. This has been addressed in some recent papers^{81, 86, 87} with relatively complex pulse sequences, but using the nonresonant mechanism will likely improve pulse sequence strategies.

—Finally, extensive optimization of SABRE-SHEATH approaches by computer has led to robust, three-dimensional fields that are accessible in the laboratory⁸⁸. To our knowledge, none of these calculations has ever tried to optimize anything other than magnetization. Feeding two-spin as well as one-spin order into optimization approaches is likely to improve results, as the pathways are largely independent of one another.

Conclusions

We have demonstrated a hitherto unappreciated para-hydrogen based hyperpolarization mechanism which involves direct creation of two-spin zz order in the target ligand. While here we have presented data mostly for pyridine, the mechanism should be accessible for essentially every molecule that has been hyperpolarized by SABRE and has a heteroatom near the hydrogen atoms, and we have found experimental signals in other common molecules such as acetonitrile (see SI). One reason this may have gone undetected until now is relatively simple. In normal hyperpolarization experiments, magnetization is detected by the signal directly after a 90 pulse, so inhomogeneous broadening in the spectrometer is not important. Thus, SABRE testing is often done without removing the bubbling apparatus (which causes susceptibility effects). This is a critical problem for detecting the antiphase

magnetization in nonlinear SABRE, particularly if (unlike the pyridine case) the coupling J_{LS} is small, as the signal disappears before it can refocus. This is of course easily solved in the laboratory — it was just that it was not realized it might be important.

The nonresonant mechanism has multiple desirable features. These include near-independence of external field strength over multiple orders of magnitude (in fact, it can be done quite well in an uncontrolled lab setting in the Earth's field) and low sensitivity to the coupling-induced interconversion between hydride singlet and triplet order. This mechanism likely provides multiple new strategies for SABRE optimization at a wide variety of fields. This amplifies the advantages of SABRE (cheap and simple source of spin order, simple and low-cost apparatus) as the current best candidate for a truly general and versatile hyperpolarization strategy.

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Supplementary Information

A. Materials and methods for experimental demonstration of nonresonant SABRE:

^{15}N -pyridine SABRE samples were prepared with 160 mM ^{15}N -pyridine (Cambridge Isotope Laboratories NLM 305-0.5, CAS 34322-45-7) and 10 mM Ir-Imes catalyst (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, synthesized by collaborator) in methanol- d_4 (Cambridge Isotope Laboratories DLM-24-50, CAS 811-98-3) solvent. For the representative spectra shown in Fig. 3, samples additionally contained 10% v/v methanol (Sigma-Aldrich 34860-4L-R, CAS 67-56-1) so that the measurement magnet could be shimmed on the sample to help reduce inhomogeneity resulting from the presence of the H_2 gas bubbler in the NMR tube. The sample tube was a Wilmad 5mm sapphire NMR tube (WG-507-7) custom-fitted to adapt to the H_2 gas line which was pressurized to 120 PSI.

The Ir-Imes catalyst was activated by bubbling H_2 gas through the sample tube at a rate of 16.15 ccm for 1 hour at 40 °C. For each SABRE experiment, the sample was bubbled with 80-90% $p\text{-H}_2$ gas (produced with a Bruker BPHG 90 generator) at a rate of 43.46 ccm for 5s in the presence of the polarizing field. After this polarization build-up period, bubbling was shut off, and the electromagnet was triggered to output a field with a magnitude of $\approx 50\text{ }\mu\text{T}$ to control the transfer into the lab field. The sample was then transferred into a Magritek Spinsolve benchtop 1 T spectrometer and ^{15}N and ^1H spectra were acquired back-to-back. A repetition time of 200 s was allowed between SABRE experiments to allow for hyperpolarized ^{15}N magnetization to fully relax.

A thermal reference sample containing 2.72 M ^{15}N -pyridine in methanol- d_4 was created and a 250-scan-averaged reference spectrum was recorded using the same NMR tube and measurement magnet as the presented experiments. The signal intensity from the thermal reference was scaled down by a factor of 8.5 (assuming $\frac{1}{2}$ of SABRE sample solvent evaporated during activation to create a final SABRE sample concentration of 320 mM) to control for concentration differences. Enhancement values were obtained by dividing SABRE sample signal by this concentration-scaled thermal value.

B. Simulation methodology:

The simulation framework used here to model SABRE dynamics has been reported in ref. [79]. The ^{15}N -pyridine SABRE complex was modeled as a five-spin system which includes two ^1H (H) from bound $p\text{-H}_2$ as well as one ^{15}N (S) and two ortho ^1H (L) from a bound pyridine. The SABRE complex was treated as a Y system, though it is known that pyridine creates an X geometry in which it binds both available equatorial positions of the SABRE catalyst. Simulations that accounted for the X geometry showed analogous dynamics to the Y geometry (just with twice the efficiency since pyridine is bound to both positions), so Y geometry was preferred for computational efficiency. Unless otherwise specified, this system used the following J-coupling values: $J_{HH} = -7\text{ Hz}$, $J_{HS} = 19.6\text{ Hz}$, $J_{HL} = 1.2\text{ Hz}$, $J_{LS} = -10.06\text{ Hz}$, $J_{LL} = -0.16\text{ Hz}$. Simulations included a 30.75 ppm chemical shift between H and L . The longitudinal relaxation times were assumed to be: $T_{1,H} = 1\text{ s}$, $T_{1,L} = 4\text{ s}$, $T_{1,S} = 40\text{ s}$. As stated in the main text, the simulations accounted for a ligand exchange rate of 16 s^{-1} , a hydride exchange rate of 2 s^{-1} , a 1:20 catalyst to ligand ratio, and assumed that $p\text{-H}_2$ flowed continuously ($[\text{Ir}]/[\text{H}_2]$ is negligible). Unless otherwise specified, SABRE performance was evaluated for a given test condition by allowing the system to evolve in the polarizing field for 5 s before a 90_y pulse was applied to either ^{15}N or ^1H and a simulated FID was acquired by allowing a further 5 s of evolution to proceed at $B = 1\text{ T}$.

C. Extended spin coherence pathways starting from $\vec{I}_1 \bullet \vec{I}_2 \longrightarrow L_z S_z$:

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1z}I_{2x}L_y \xrightarrow{J_{HH}(I_{1x}I_{2x})} -I_{1y}L_y \xrightarrow{J_{LS}(L_zS_z)} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S1]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1z}I_{2x}L_y \xrightarrow{J_{HH}(I_{1x}I_{2x})} -I_{1y}L_y \xrightarrow{J_{HS}(I_{1z}S_z)} -iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} -L_zS_z \quad [S2]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1z}I_{2x}L_y \xrightarrow{J_{LS}(L_zS_z)} -I_{1z}I_{2x}L_xS_z \xrightarrow{J_{HH}(I_{1x}I_{2x})} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S3]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1y}L_y \xrightarrow{J_{LS}(L_zS_z)} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S4]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1y}L_y \xrightarrow{J_{HS}(I_{1z}S_z)} -iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} -L_zS_z \quad [S5]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{LS}(L_zS_z)} I_{1x}I_{2z}L_xS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S6]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1y}L_y)} -iI_{1x}I_{2z}L_y \xrightarrow{J_{HS}(I_{1z}S_z)} -I_{1y}I_{2z}L_yS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} -iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} -L_zS_z \quad [S7]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1z}I_{2y}L_x \xrightarrow{J_{HH}(I_{1y}I_{2y})} -I_{1x}L_x \xrightarrow{J_{LS}(L_zS_z)} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S8]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1z}I_{2y}L_x \xrightarrow{J_{HH}(I_{1y}I_{2y})} -I_{1x}L_x \xrightarrow{J_{HS}(I_{1z}S_z)} iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} -L_zS_z \quad [S9]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1z}I_{2y}L_x \xrightarrow{J_{LS}(L_zS_z)} -I_{1z}I_{2y}L_yS_z \xrightarrow{J_{HH}(I_{1y}I_{2y})} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S10]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1x}L_x \xrightarrow{J_{LS}(L_zS_z)} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S11]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HH}(I_{1z}I_{2z})} -I_{1x}L_x \xrightarrow{J_{HS}(I_{1z}S_z)} iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} -L_zS_z \quad [S12]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{LS}(L_zS_z)} I_{1y}I_{2z}L_yS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S13]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1x}L_x)} iI_{1y}I_{2z}L_x \xrightarrow{J_{HS}(I_{1z}S_z)} -I_{1x}I_{2z}L_xS_z \xrightarrow{J_{HH}(I_{1z}I_{2z})} iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} -L_zS_z \quad [S14]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HL}(I_{1z}L_z)} I_{1x}I_{2y}L_z \longrightarrow \text{no pathways} \quad [S15]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} iI_{1x}I_{2y}S_z \xrightarrow{J_{HH}(I_{y1}I_{y2})} -I_{1z}S_z \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S16]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} -iI_{1y}I_{2x}S_z \xrightarrow{J_{HH}(I_{x1}I_{x2})} -I_{1z}S_z \xrightarrow{J_{HL}(I_{1x}L_x)} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S17]$$

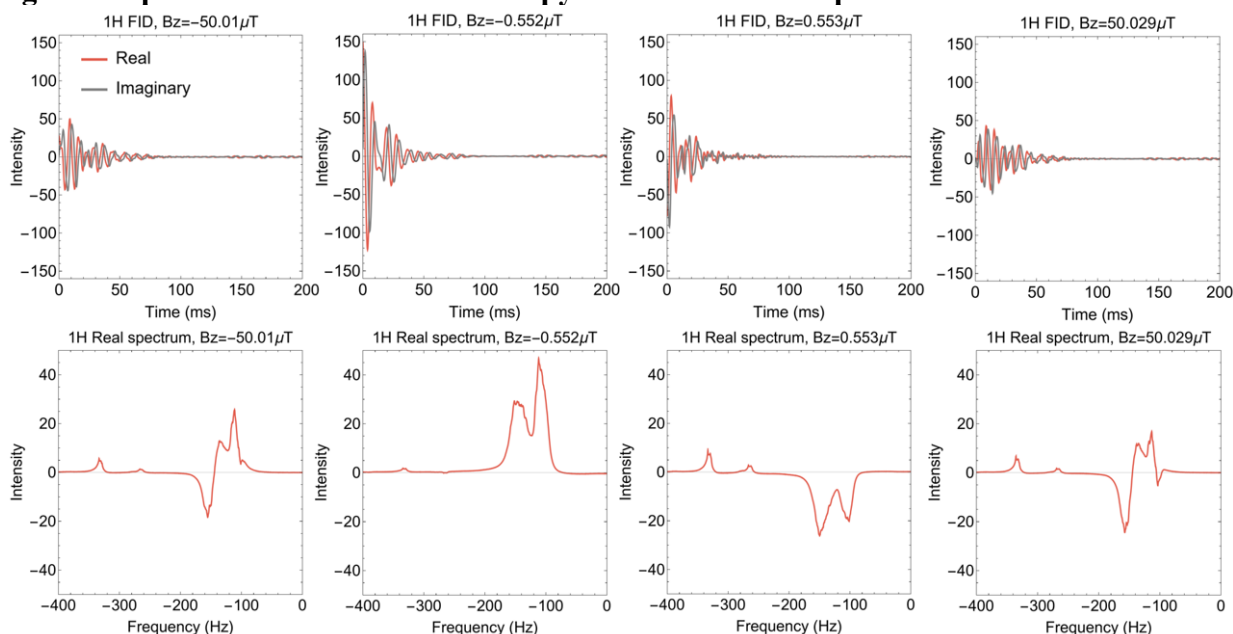
$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} iI_{1x}I_{2y}S_z \xrightarrow{J_{HL}(I_{1y}L_y)} -I_{1z}I_{2y}S_zL_y \xrightarrow{J_{HH}(I_{1y}I_{2y})} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S18]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} -iI_{1y}I_{2x}S_z \xrightarrow{J_{HL}(I_{1x}L_x)} -I_{1z}I_{2x}S_zL_x \xrightarrow{J_{HH}(I_{1x}I_{2x})} -iI_{1y}L_xS_z \xrightarrow{J_{HL}(I_{1y}L_y)} L_zS_z \quad [S19]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} iI_{1x}I_{2y}S_z \xrightarrow{J_{HH}(I_{y1}I_{y2})} -I_{1z}S_z \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S20]$$

$$\vec{I}_1 \bullet \vec{I}_2 \xrightarrow{J_{HS}(I_{1z}S_z)} -iI_{1y}I_{2x}S_z \xrightarrow{J_{HH}(I_{x1}I_{x2})} -I_{1z}S_z \xrightarrow{J_{HL}(I_{1y}L_y)} iI_{1x}L_yS_z \xrightarrow{J_{HL}(I_{1x}L_x)} L_zS_z \quad [S21]$$

Fig. S1. Experimental ^1H data from ^{15}N -pyridine SABRE sample



These
 ^1H

spectra were taken immediately after the ^{15}N spectra shown in main text Fig. 3. The sample composition and experimental procedure for this data set are detailed in supplemental section A above. While the presence of the H_2 bubbler in the NMR tube introduces significant inhomogeneity and reduces resolution, the two peaks at -340 Hz and -260 Hz may be assigned to methanol, while the group centered at -140 Hz may be assigned to the ligand pyridine protons. Similar to what is observed in the ^{15}N signal, ^1H signal far from the SHEATH resonance is antiphase and does not invert when the sign of the field changes. ^1H signal at the SHEATH resonance is predominantly one-spin magnetization which does invert when the sign of the field changes. While the SHEATH condition is far from the ^1H -SABRE resonance (which is maximized at 6.5 mT), polarization may still be transferred to the ligand ^1H from the matched ^{15}N through the J_{LS} coupling during polarization build-up to generate observable ^1H magnetization.

Fig. S2. Magnitude of ^{15}N -pyridine out-of-phase magnetization, simulation and experiment

This plot compares the magnitude of out-of-phase signal (signal at $t = 1/4J_{LS}$) between experimental ^{15}N -pyridine (purple, absolute of the data shown in main text Fig. 3, left) and simulation (gray, same parameters detailed in SI B). Numerical simulations confirm the presence strong effective magnetization far from resonance and predict that the magnitude of out-phase magnetization will be $1/5^{\text{th}}$ the intensity of phase magnetization, which matches experimental observations.

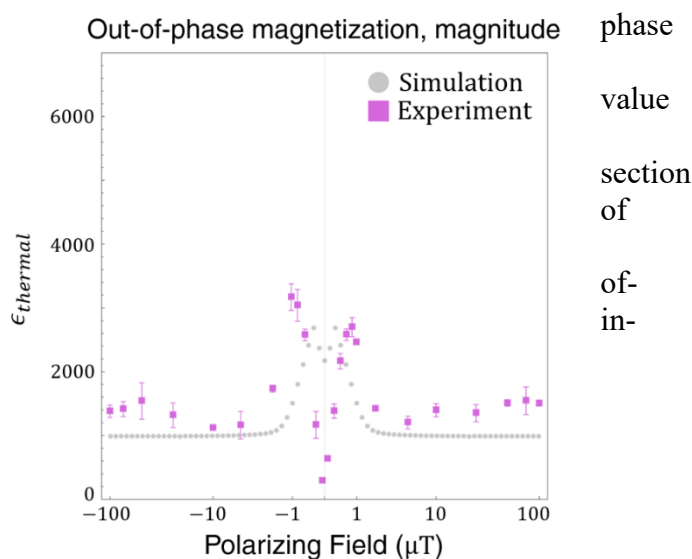


Fig. S3. Effects of supplying $\vec{I}_1 \cdot \vec{I}_2$ vs $I_{1z}I_{2z}$ order in ^1H -SABRE (L only)

These simulations were run according to the methodology outlined in

supplemental section B, except that the system omitted the ^{15}N spin on pyridine and only accounted for couplings to two ortho- ^1H (resulting in a four-spin instead of a five-spin system). The plot records the effective magnetization generated at a certain polarizing field, where effective magnetization is defined as the maximum value of the magnitude of the ^1H FID which was acquired after 5 s of polarization build-up. In the orange curve, the $p\text{-H}_2$ density matrix was defined as $\frac{1}{4}\hat{1} - (\vec{I}_1 \cdot \vec{I}_2)$, which

represents pure singlet order. In the blue curve, $p\text{-H}_2$ is modeled as $\frac{1}{4}\hat{1} - I_{1z}I_{2z}$, representing a mixture of singlet and triplet states. We observe that in the ^1H SABRE regime, for a ligand which does not contain a strongly-coupled

heteroatom, hyperpolarization efficiency decreases by about a factor of 2 in the absence of the $I_{1x}I_{2x}$ and $I_{1y}I_{2y}$ terms.

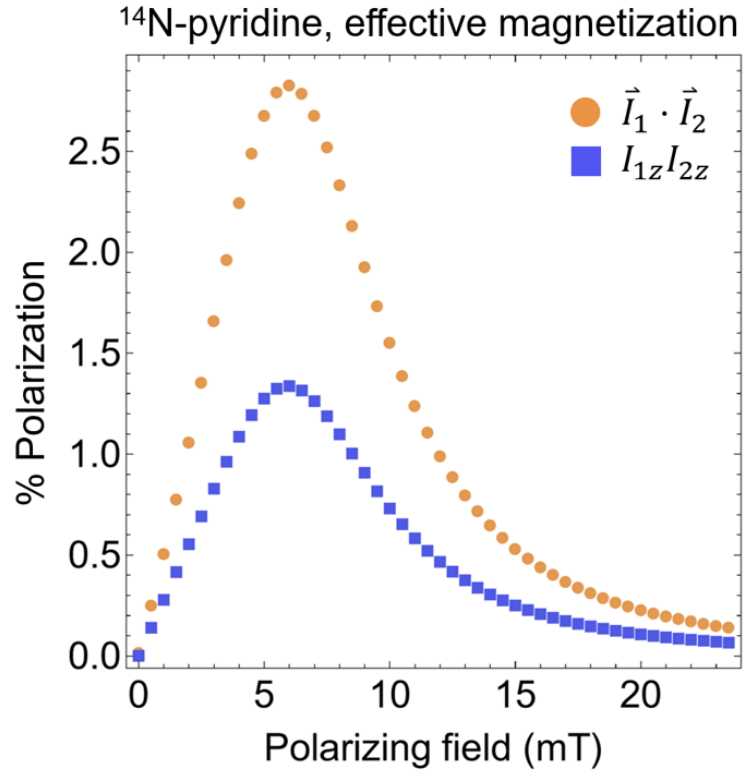
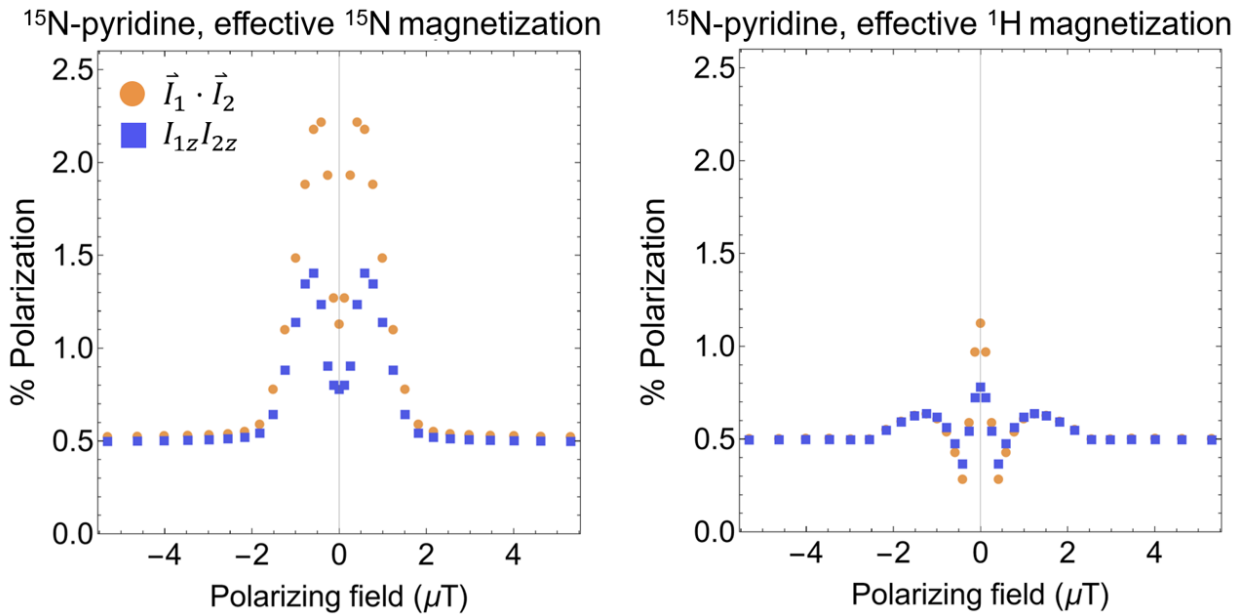


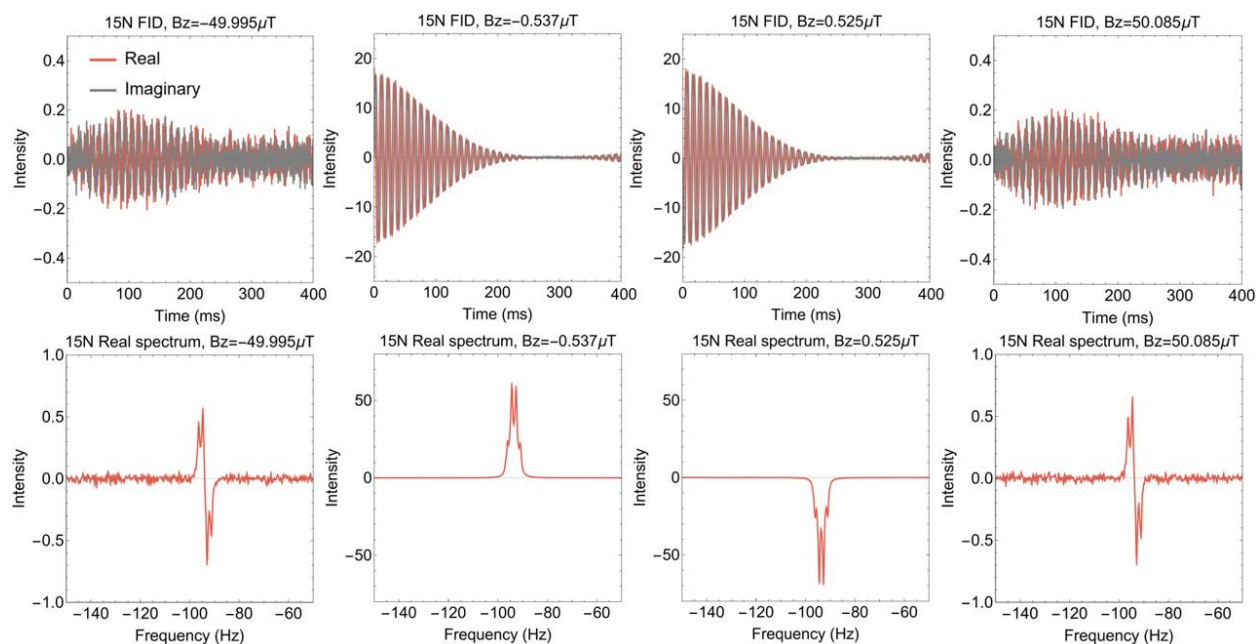
Fig. S4. Effects of supplying $\vec{I}_1 \cdot \vec{I}_2$ vs $I_{1z}I_{2z}$ order in SABRE-SHEATH (L and S)



This figure shows analogous data to Fig. S3, but for the ^{15}N -pyridine system which contains couplings to both L and S (see SI section B for simulation parameters), where the polarizing field sweep is now

centered on the X-SABRE resonance. Similar to what is observed in main text Fig. 7, the effective magnetization resulting from two-spin order is robust to the interconversion of singlet/triplet order on the hydride. Production of one-spin order, which dominates at the SHEATH resonance ($\approx 0.5 \mu\text{T}$), is hindered when the $I_{1x}I_{2x}$ and $I_{1y}I_{2y}$ terms are removed, but to a lesser extent than what is observed in the ^{14}N -pyridine ^1H -SABRE case (Fig. S3).

Fig. S5. Nonresonant SABRE demonstrated using ^{15}N -acetonitrile



A ^{15}N -acetonitrile SABRE sample was prepared with 150 mM ^{15}N -acetonitrile (Cambridge Isotopes Laboratories NLM-175-0.5, CAS 14149-39-4), 50 mM ^{14}N -pyridine as a spin-silent co-ligand (provided by collaborator, CAS 110-86-1), and 6.5 mM Ir-Imes in 250 μL methanol- d_4 . Sample was activated by bubbling H_2 gas through the sample tube at a rate of 16.15 ccm for 30 min at 25 $^\circ\text{C}$. Data acquisition followed the same procedure as described in supplemental section A, with the exception that polarization build-up was allowed to occur for 30 s, as opposed to 5 s. As was observed in the ^{15}N -pyridine experiments, the two-spin magnetization did not invert when the polarizing field was inverted, while the one-spin magnetization did. In acetonitrile, the signal intensity resulting from two-spin order was observed to be about 100 times less intense than the one-spin order. This difference is significantly greater than the roughly ten-fold difference that was observed in pyridine (Fig. 3.). Since the two-spin order has a shorter lifetime than the one-spin order (noted in main text), this difference in signal is likely a result of the longer, 30 s polarization time, as the two-spin order would reach a plateau in polarization build-up faster than the one-spin order.