Microtesla SABRE Enables 10% Nitrogen-15 Nuclear Spin Polarization

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Experimental Details

All discussed SABRE studies were performed by bubbling parahydrogen (≥90% para-) through a methanol-d4 solution at a rate of ~0.7 mL/s under ~6 bars of pressure and room temperature. Pressure and flow rate were chosen to give the highest bubbling rate without displacing the solution out of the medium wall 5 mm OD NMR tube. The solution contained the iridium catalyst [IrCl(COD)(IMes)] (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; COD = cyclooctadiene)2,3 and Py or 15N-Py (Sigma-Aldrich, P/N 486183) as the substrate. The experiments were performed with solutions containing, either, 6.3 mM catalyst and 63 mM Py or 0.24 mM catalyst and 4 mM Py.

SABRE-SHEATH polarization is demonstrated by placing the NMR tube in a 305 mm-long magnetic shield (Lake Shore Cryotronics, P/N 4065) during ~30 s-long of bubbling. No attempt was made to tune the small residual magnetic field to a precise value. After this ~30 s polarization period, para-H2 delivery is stopped, and the NMR tube is quickly transferred (~4 s) to a 9.4 T Bruker Avance III NMR spectrometer to detect the SABRE-SHEATH polarization through conventional 1D-NMR. Both 15N and 1H pulse-acquire NMR experiments are conducted. For comparison, further experiments were conducted. Hyperpolarization was also performed at a low field of 6±4 mT in the mouth of the magnet’s bore (see Fig. 1) followed by transfer to high field for detection. (6-8 mT is ideal for polarization transfer to 1H).2,4-6

Observed 1H enhancements are calculated by comparing the thermal and hyperpolarized signals, which correspond to the hydrogens of the ortho-H-Py. Observed 15N enhancements could not be compared directly to thermal signal in the same solutions because of insufficient signal-to-noise ratio of the thermal signals. Hence, 15N enhancements were calculated by comparison to signal from neat 15N-Py (12.5 M) scaled by the relative concentration, and the ratios of effective liquid
sample cross-section: \( \varepsilon = \left( \frac{S_{\text{HP}}}{S_{\text{REF}}} \right) \left( \frac{A_{\text{REF}}}{A_{\text{HP}}} \right) \left( \frac{[\text{REF}]}{[\text{HP}]} \right) \). For example, the signal from hyperpolarized \(^{15}\text{N}\)-nicotinamide (48 mM concentration corresponding to \(~32\) mM of \(^{15}\text{N}\)-nicotinamide at 66\% \(^{15}\text{N}\) isotopic enrichment) was \(~28\) times greater than the signal from 12.5 M thermally polarized \(^{15}\text{N}\)-Py. Note that the effective cross-section of 5 mm medium-pressure NMR tube was \(~1.85\) times less than that of standard 5 mm NMR tube due to thicker tube walls and the inserted 1/16 in. OD PTFE tubing for \(\text{para-H}_2\) bubbling.\(^7\) Therefore, \(\varepsilon = 28 \times 1.85 \times (12.5/0.032)\) or \(~20,000\) fold. \(^{15}\text{N}\) nuclear spin polarization of hyperpolarized state was calculated by multiplication of \(\varepsilon\) by equilibrium thermal \(^{15}\text{N}\) polarization at 9.4 T of \(3.3 \times 10^{-6}\). For example, \(\varepsilon\) of \(^{15}\text{N}\)-nicotamide was \(P = 20000 \times 3.3 \times 10^{-6} = 0.066\) or \(~7\%\).

**Theory**

This supplement also provides the quantum-mechanical details of our model for the polarization transfer process in the micro-tesla magnetic shield. The model arrives at a very intuitive representation of the polarization transfer process as a simple rotation on a Bloch-sphere.

The polarization is transferred in an AA′BB′ spin system as illustrated in Fig. 1B of the main manuscript. Here in Fig. S1 we simplify the sketch to highlight the important interactions, which are the \(J\)-couplings and the frequency difference, \(\nu_A - \nu_B\), between para-hydrogen derived protons and the pyridine nitrogens.\(^15\)

![Figure S1](image.png)

**Figure S1.** The AA′BB′ spin system and the important interactions. The spins A and A′ are chemically equivalent, i.e. they have the same chemical shift. This also applies for the spins B and B′. However, the magnetic equivalence is broken by the difference in AB \(J\)-couplings: \(\Delta J_{AB} = J_{AB} - J_{AB}' \neq 0\). This term can drive hyperpolarization from the A spins (para-hydrogen) to the B spins (\(^{15}\text{N}\)-pyridine).

The initial state is the para-hydrogen singlet state on the A spins. This state will evolve under the Hamiltonian of the AA′BB′ system. This Hamiltonian contains the magnetic field-dependent frequencies \(\nu_A\) and \(\nu_B\) and the magnetic field-independent \(J\)-couplings. Lastly, we associate the spins A, A′, B and B′ with the spin operators \(I_A, I_A', I_B\) and \(I_B'\).

With this notation the AA′BB′ Hamiltonian is expressed as:
\[ H = v_A (I_{A_z} + I'_{A_z}) + v_B (I_{B_z} + I'_{B_z}) + J_{AA} I_A I'_A + J_{BB} I_B I'_B + J_{AB} (I_A I'_B + I'_A I_B) + J'_{AB} (I'_A I_B + I_A I'_B) \]  
\hspace{1cm} \text{(S1)}

It is now convenient to introduce the sum and the difference of the AB-J-couplings,

\[ \Delta J_{AB} = J_{AB} - J'_{AB} \]
\[ \Sigma J_{AB} = J_{AB} + J'_{AB} \]
\hspace{1cm} \text{(S2)}

and to rewrite Eq. S1 for illustration purposes:

\[ H = v_A (I_{A_z} + I'_{A_z}) + v_B (I_{B_z} + I'_{B_z}) + (J_{AA} I_A I'_A + J_{BB} I_B I'_B) + \frac{\Sigma J_{AB}}{2} (I_A + I'_A) (I_B + I'_B) - \frac{\Delta J_{AB}}{2} (I_A - I'_A) (I_B - I'_B) \]  
\hspace{1cm} \text{(S3)}

Next, with our goal in mind to represent the dynamics in a Bloch sphere, we turn to a specific matrix representation of this Hamiltonian, which will help us identify 2 by 2 blocks isomorphic with the Pauli matrices directly leading us to our goal.

A matrix representation requires a specific basis and the most adequate basis for the problem at hand is the Singlet-Triplet basis for coupled spin pairs:

\[ \begin{align*}
S_0 &= \frac{1}{\sqrt{2}} \begin{pmatrix}
\uparrow \downarrow \\
\downarrow \uparrow
\end{pmatrix} \\
T_+ &= \begin{pmatrix}
\uparrow \uparrow \\
\downarrow \downarrow
\end{pmatrix} & T_0 &= \frac{1}{\sqrt{2}} \begin{pmatrix}
\uparrow \downarrow \\
\downarrow \uparrow
\end{pmatrix} & T_- &= \begin{pmatrix}
\downarrow \downarrow \\
\uparrow \uparrow
\end{pmatrix}
\end{align*} \]  
\hspace{1cm} \text{(S4)}

We use this Singlet-Triplet basis for both the AA' spin pair and the BB' spin pair and then identify all possible combinations resulting in the 16 possible states of an AA'BB' system, sorted by their symmetry:

10 symmetric states with respect to exchange of A with A' and B with B':
\[ \begin{align*}
S_0^A S_0^B, & \ T_0^A T_0^B, \\
T_+^A T_+^B, & T_-^A T_-^B, \\
T_+^A T_-^B, & T_-^A T_+^B \\
T_0^A T_+^B, & T_+^A T_0^B, \\
T_0^A T_-^B, & T_-^A T_0^B
\end{align*} \]  
\hspace{1cm} \text{(S5a)}

6 antisymmetric states with respect to exchange of A with A' and B with B':
\[ \begin{align*}
T_0^A T_0^B, & \ T_-^A T_-^B, \\
T_+^A T_-^B, & T_-^A T_+^B, \\
T_0^A T_-^B, & T_-^A T_0^B
\end{align*} \]  
\hspace{1cm} \text{(S5b)}
\[ S_0^A T_0^B, \quad T_0^A S_0^B, \]
\[ S_0^A T_+^B, \quad T_+^A S_0^B, \]
\[ S_0^A T_-^B, \quad T_-^A S_0^B; \]  
(S5b)

It is valuable to sort these states by symmetry, because states with differing symmetry cannot be connected, hence we will not find off-diagonal elements in the Hamiltonian connecting these two groups.

Once we represent the Hamiltonian of Eq. S3 in the basis introduced in Eqs. S5, we find the following disconnected blocks, all of which are simple 2×2 blocks, except for the first which is a 4×4 block. This exact procedure was also followed by Pople et al.\(^8\) in 1957.

In the symmetric group we obtain the following blocks:

\[
\begin{pmatrix}
S_0^A S_0^B & T_0^A T_0^B & T_+^A T_-^B & T_-^A T_+^B \\
S_0^A S_0^B & -(J_{AA} + J_{BB}) & \Delta J_{AB} / 2 & -\Delta J_{AB} / 2 & -\Delta J_{AB} / 2 \\
T_0^A T_0^B & \Delta J_{AB} / 2 & 0 & \Sigma J_{AB} / 2 & \Sigma J_{AB} / 2 \\
T_+^A T_-^B & -\Delta J_{AB} / 2 & \Sigma J_{AB} / 2 & 0 & -\frac{\Sigma J_{AB}}{2} (v_A - v_B) \\
T_-^A T_+^B & -\Delta J_{AB} / 2 & \Sigma J_{AB} / 2 & 0 & \frac{\Sigma J_{AB}}{2} (v_A - v_B)
\end{pmatrix},
\]
(S6a)

\[
\begin{pmatrix}
T_+^A T_+^B & T_-^A T_-^B \\
T_+^A T_+^B & \frac{\Sigma J_{AB}}{2} + v_A + v_B & 0 \\
T_-^A T_-^B & 0 & \frac{\Sigma J_{AB}}{2} - (v_A + v_B)
\end{pmatrix},
\]
(S6b)

\[
\begin{pmatrix}
T_0^A T_0^B & T_+^A T_0^B & T_-^A T_0^B \\
T_0^A T_0^B & v_B & \Sigma J_{AB} / 2 \\
T_+^A T_0^B & \Sigma J_{AB} / 2 & v_A
\end{pmatrix}
\]
(S6c)

and
\[
\begin{pmatrix}
T_0^{a T_0^B} & T_0^{a T_0^B} \\
T_0^{a T_0^B} & \Sigma J_{AB}/2 - \nu_A
\end{pmatrix}
\] (S6d)

In the antisymmetric group we obtain:

\[
\begin{pmatrix}
S_0^{a T_0^B} & T_0^{a S_0^B} \\
S_0^{a T_0^B} & \Delta J_{AB}/2 - J_{BB} \\
T_0^{a S_0^B} & \Delta J_{AB}/2 - J_{BB}
\end{pmatrix}
\] (S6e)

\[
\begin{pmatrix}
S_0^{a T_0^B} & T_0^{a S_0^B} \\
S_0^{a T_0^B} & \nu_B - J_{AA} - \Delta J_{AB}/2 \\
T_0^{a S_0^B} & \nu_B - J_{BB}
\end{pmatrix}
\] (S6f)

and

\[
\begin{pmatrix}
S_0^{a T_0^B} & T_0^{a S_0^B} \\
S_0^{a T_0^B} & \nu_B - J_{AA} - \Delta J_{AB}/2 \\
T_0^{a S_0^B} & \nu_B - J_{BB}
\end{pmatrix}
\] (S6g)

With this Hamiltonian at hand, an intuitive understanding can be gained about the hyperpolarization dynamics:

The initial state is the parahydrogen derived singlet on the AA' pair and all other states have close to zero population. Hence, our initial state has the following populations:

\[
p(S_0^a S_0^b) = p(S_0^a T_0^B) = p(S_0^a T_0^B) = p(S_0^a T_0^B) = p(S_0^a T_0^B) = 0.25; \\
p(\text{other states}) = 0
\] (S7)

Polarization transfer from this parahydrogen hyperpolarized S_0^a state can now be driven by the Hamiltonian of Eq. S6.

First, it should be stated that under most circumstances the off-diagonal elements \( \Delta J_{AB} \) and \( \Sigma J_{AB} \) are small compared to the on-diagonal elements (\( J_{AA}, J_{BB}, \nu_A, \nu_B \)). This implies that the initial state is locked in place, unless some special compensation of the on-diagonal elements occurs: Only when the difference between on-diagonal elements becomes small compared to the off-diagonal elements, evolution driven by the small off-diagonal elements is possible.
In Eq. S6a, the state $S^A_0 S^B_0$ can be connected to either $T^A_+ T^-_-$ or $T^-_+ T^A_-$ when the corresponding diagonal elements become equal to the $S^A_0 S^B_0$ diagonal element ($= -J_{AA} - J_{BB}$). This can be performed by selecting the adequate magnetic fields. If the magnetic field is chosen such that

$$ (\nu_A - \nu_B) = -J_{AA} - J_{BB} + \frac{\Sigma J_{AB}}{2} \quad (S8) $$

then $S^A_0 S^B_0$ is connected to $T^A_+ T^-_-$ (the diagonal elements become equal).

If the magnetic field is chosen such that

$$ (\nu_A - \nu_B) = J_{AA} + J_{BB} - \frac{\Sigma J_{AB}}{2} \quad (S9) $$

then $S^A_0 S^B_0$ is connected to $T^-_+ T^A_-$ (the diagonal elements become equal).

This establishes the first two resonance conditions:

When the diagonal elements are equal and only off-diagonal elements remain, then the dynamics can be interpreted as simple rotations. The initial state (the source state) is $S^A_0 S^B_0$ initially along the $z$-axis, because it is a population on the diagonal isomorph with the $\sigma_z$ Pauli matrix. The Hamiltonian on the off-diagonal is isomorph with the $\sigma_x$ Pauli matrix, hence aligned with the $x$-axis. The density matrix now simply rotates around the Hamiltonian to produce hyperpolarization as depicted in Fig. S2

![Figure S2](image)

**Figure S2.** Depiction of the dynamics that drive the hyperpolarization as rotations on a Bloch sphere. On the left, the matching condition according to Eq. S8 is depicted. The parahydrogen hyperpolarized $S^A_0 S^B_0$ state is converted to hyperpolarization on hydrogen ($T^A_+$, aligned with the magnetic field) and on the nitrogens ($T^-_+$, anti-aligned with the magnetic field). This process is driven by the on-diagonal elements in the Hamiltonian proportional to $-\Delta J_{AB}$. On the right, the matching condition according to Eq. S9 is depicted. The parahydrogen hyperpolarized $S^A_0 S^B_0$ state is converted to hyperpolarization on hydrogen ($T^-_+$, anti-aligned with the magnetic field) and on the nitrogens ($T^A_+$, aligned with the magnetic field). This process is driven by the on-diagonal elements in the Hamiltonian proportional to $+\Delta J_{AB}$. 
The condition of Eq. S8 transfers hyperpolarization from $S_0^A$ on the hydrides to the $T_-^B$ on the nitrogens, creating magnetization anti-aligned with the magnetic field.

The condition of Eq. S9 transfers hyperpolarization from $S_0^A$ on the hydrides to the $T_+^B$ on the nitrogens, creating magnetization aligned with the magnetic field.

In Eq. S6a, a connection to $T_0^A T_0^B$ cannot be established simply by changing the magnetic field because the diagonal element does not contain frequency dependent terms.

Eqs. S6b-d do not contain the $S_0^A$ state hence that part of the Hamiltonian cannot be involved in creating hyperpolarization. In Eq. S6e the diagonal terms do not depend on the frequencies, hence this part cannot contribute to hyperpolarization transfer either.

Eqs. S6f,g can create hyperpolarization: As above, the magnetic field has to be chosen such that the diagonal elements are equalized.

To equalize the on-diagonal terms in Eq. S6f we obtain

$$\nu_A - \nu_B = J_{BB} - J_{AA} \quad (S10)$$

To equalize the on-diagonal terms in Eq. S6g we obtain.

$$\nu_A - \nu_B = J_{AA} - J_{BB} \quad (S11)$$

Theses matching conditions create evolution driven by the off-diagonal terms proportional to $\Delta J_{AB}$. This evolution can again be depicted as rotations on the Bloch sphere as shown in Fig. S3.

**Figure S3.** Depiction of the dynamics that drive the hyperpolarization as rotations on a Bloch sphere: On the left, the matching condition according to Eq. S10 is depicted. The parahydrogen hyperpolarized $S_0^A T_-^B$ state is converted to hyperpolarization on hydrogen ($T_-^A$ aligned with the magnetic field). On the nitrogens $S_0^B$ is created, which of course does not bear magnetization. However, the state $T_-^B$ is depleted, thus creating magnetization anti-aligned with the field. On the right, the matching condition according to Eq. S11 is depicted. The parahydrogen hyperpolarized $S_0^A T_+^B$ state is converted to hyperpolarization on hydrogen ($T_+^A$ anti-aligned with the magnetic field). On the nitrogens $S_0^B$ is created, which of course does not bear magnetization. However, the state $T_+^B$ is depleted,
thus creating magnetization aligned with the field. The processes are driven by the on diagonal elements in the Hamiltonian proportional to $+\Delta J_{AB}$, depending on which matching condition is fulfilled.

When matching condition S10 is fulfilled, the state $S_0^A T_+^B$ is connected to $T_+^A S_0^B$, since $S_0^B$ on the nitrogens cannot create hyperpolarization (it creates equal amounts of spin up as spin down upon dissociation). The important insight here is that the state $T_+^B$ on the nitrogens is depleted. This depletion of $T_+^B$ creates hyperpolarization anti-aligned with the magnetic field.

When matching condition S11 is fulfilled, the state $S_0^A T_-^B$ is connected to $T_-^A S_0^B$. As above, also here $S_0^B$ on the nitrogens cannot create hyperpolarization, but the state $T_-^B$ on the nitrogens is depleted, creating hyperpolarization anti-aligned with the magnetic field.

Lastly, it is important to realize that $J_{AA}$ (the HH-coupling) typically dominates the $J$-coupling network at hand. In that case, either matching conditions S8 and S10, or S9 and S11 will be fulfilled simultaneously, especially given that the chemical exchange smears out the $J$-couplings and the resonance conditions.

Therefore it is important that the resonance condition described by Eqs. S8 and S10, both produce hyperpolarization on the nitrogens anti-aligned with the magnetic field and hyperpolarization aligned with the magnetic field on the hydrogens. They reinforce each other.

The same is true for resonance conditions described by Eqs. S9 and S11. They reinforce each other by creating hyperpolarization aligned with the magnetic field on the nitrogens and magnetization anti-aligned with the magnetic field on the hydrogens.
Probing proton SABRE and proton SABRE-SHEATH for $^{14}$N-Pyridine and $^{15}$N-Pyridine

Figure S4 contrasts $^1$H hyperpolarization levels observed on $^{15}$N-Py versus those on $^{14}$N-Py. $^1$H-SABRE on $^{15}$N-Py is ~5-10 times less effective than that on $^{14}$N-Py, regardless of whether the experiments are optimized for $^1$H hyperpolarization (SABRE at ~6±4 mT, Figure S4A and B, or optimized for hyperpolarization transfer to $^{15}$N (SABRE in the magnetic shield, Figures S4C and D. These observation imply that polarization transfer strategies, e.g. $^1$H→$^{15}$N via INEPT, are unlikely to be as effective as the direct $^{15}$N-hyperpolarization in the SABRE-SHEATH because only low levels of $^1$H hyperpolarization are available on the $^{15}$N species to be transferred to the $^{15}$N nuclei. Figure S4 also shows that the hydrides give antiphase patterns when the $^{15}$N-Py species are involved, implying antiphase terms that are created during the hyperpolarization process, whereas the hydride signals are purely in-phase, when using $^{14}$N-Py, irrespective of the magnetic field employed during the parahydrogen bubbling period.

Figure S4. $^1$H-NMR spectra obtained via SABRE from $^{14}$N-Py vs. $^{15}$N-Py experiments. SABRE polarization was conducted in both the ~6±4 mT field (A, B) and in the shield (C, D) for $^{14}$N-Py vs. $^{15}$N-Py at 63 mM Py and 6.3 mM catalyst concentrations. $^1$H-SABRE enhancement levels are shown for the ortho-proton of Py (~8.5 ppm) of each spectrum. Additionally, the hydride region (~22.8 ppm) is shown, highlighting the significant difference in line shape between $^{15}$N-Py and $^{14}$N-Py: a sharp singlet of $^{14}$N-Py vs. an anti-phase resonance of $^{15}$N-Py.
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