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Long-term Generation of Longitudinal Spin Order Controlled by Ammonia Ligation Enables Rapid SABRE Hyperpolarized 2D NMR

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Abstract: Symmetry breaking of parahydrogen using iridium catalysts converts singlet spin order into observable hyperpolarization. In this contribution, iridium catalysts are designed to exhibit asymmetry in their hydrides, regulated by *in situ* generation of deuterated ammonia governed by ammonium buffers. The concentrations of ammonia (N) and pyridine (P) provide a handle to generate a variety of stereo-chemically asymmetric N-heterocyclic carbene iridium complexes, ligating either [3xP], [2xP;N], [P;2xN] or [3xN] in an octahedral SABRE type configuration. The non-equivalent hydride positions, in correspondence with the ammonium buffer solutions, enables to extend singlet-triplet or $|S\rangle \rightarrow |T_0\rangle$ mixing at high magnetic field and experimentally induce prolonged generation of non-equilibrium longitudinal two-spin order. This long-lasting magnetization can be exploited in hyperpolarized 2D-OPSY-COSY experiments providing direct structural information on the catalyst using a single contact with parahydrogen. Separately, field cycling revealed hyperpolarization properties in low-field conditions. Controlling catalyst stereochemistry by introducing small and deuterated ligands, such as deuterated ammonia, simplifies the spin-system. This is shown to unify experimental and theoretically derived field-sweep experiments for four-spin systems.

Introduction

Nuclear spin polarization, traditionally limited by Boltzmann statistics, determines sensitivity in nuclear magnetic resonance spectroscopy (NMR) and magnetic resonance imaging (MRI). It can dramatically be enhanced using parahydrogen (p-H₂) to fuel hyperpolarization in target molecules, enabling ultra-sensitive MR diagnostics, highly invited by the chemical and bio-chemical scientific communities.^[1–10] Parahydrogen induced polarization (PHIP) methods transfer the perfectly ordered spin state inherent to p-H₂ into substrate molecules using either an irreversible or reversible chemical reaction.^[11–13] Spin order in p-H₂ is induced due to overpopulation of the symmetric 'singlet' spin state $|S\rangle$, disconnected from the other unpopulated 'triplet' state comprising the $|T_{-1}\rangle$, $|T_0\rangle$, $|T_1\rangle$ manifolds. The different symmetry of singlet

and triplet states uncouples these states, rendering transitions between them forbidden and highly unlikely.^[14] This highlights a first, yet crucial step in all PHIP methods: breaking the singlet symmetry of p-H₂, thereby allowing singlet conversion and enable transfer of high spin order from p-H₂ to targeted substrates.^[8,15] In general, a chemical interaction such as ligation of p-H₂ onto a transition metal complex can initiate this conversion.^[11,13] Using organometallic catalysis, different scenarios are available to induce singlet symmetry breaking. Organometallic complexes can act purely as hydrogenation catalysts. In this process, pairwise incorporation of the two protons of p-H₂ across a double or triple C-C bond yields a new molecule that is hyperpolarized. Here, the singlet $|S\rangle$ state will evolve under the effective Hamiltonian of the product molecule depending on the magnetic field where hydrogenation is conducted.^[9,16,17] This scenario, typically referred to as hydrogenative PHIP, effectively breaks the initial singlet symmetry of p-H₂.

Alternatively, hyperpolarization can also be induced by a temporary symmetry breaking event in which a transient organometallic complex forms with p-H₂ and a substrate molecule as co-ligands. Resulting complexes exhibit a multi-spin network of J-couplings between the bound p-H₂ protons (hydrides) and those on the bound substrate.^[18] This non-hydrogenative PHIP method is referred to as SABRE (signal amplification by reversible exchange) and leaves targets chemically unchanged.^[19] The process can be repeated by chemical exchange of 'fresh' p-H₂ with hydrides, thereby producing additional hyperpolarization until the polarization of the p-H₂ pool is returned to equilibrium.^[13,20]

In low field conditions (between 5-20mT), coherent polarization transfer via SABRE occurs when chemical-shift differences between hydride and substrate protons match differences in the scalar coupling between hydrides.^[21] This strong coupling condition creates a perturbation or level-anti crossing (LAC), enabling coherent transfer of spin order between the coupled eigenstates of the perturbed Hamiltonian^[13]: the hyperpolarization event, generating ¹H polarization levels in the substrate, hydrides and o-H₂, on average up to 3 orders of magnitude larger than the thermal case.^[20] Field cycling to high

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Figure 1. Iridium catalysts are designed via different ammonium buffer solutions NH_4Cl , $(\text{NH}_4)_2\text{CO}_3$ and NH_4OH . This allows for controlling generation of each of the independent catalyst structures represented by I-IV.

field then allows to detect the strongly enhanced resonances with complementary chemical shift resolution.

At high magnetic field, polarization transfer decreases in efficiency since the matching conditions are lifted by the corresponding weak-coupling regime. However, polarization transfer can still rely on a variety of other mechanisms which in itself do not rely on field cycling hardware. Although generally inferior in efficiency, they range from spontaneous cross-relaxation induced polarization^[22] to radiofrequency-driven transfer schemes inducing temporary low field conditions by spin-locking^[23] or low-power continuous wave irradiation^[24]. In particular, for transition metal complexes where hydrides (I_1 and I_2) occupy chemically inequivalent positions, fast coherent singlet-triplet or $|S\rangle \rightarrow |T_0\rangle$ mixing of the hydride nuclear spin states also enables polarization transfer. Non-thermal longitudinal two-spin order $I_{1z}I_{2z}$ is created spontaneously and subsequently can be manipulated using proper NMR pulse sequences.^[5,6,13,25–27]

Traditionally, fast $|S\rangle \rightarrow |T_0\rangle$ mixing results from addition of co-ligands (e.g. 1-methyl-1,2,3-triazole^[5]) with strong affinity for iridium to induce asymmetry in hydrides. Rapid depletion of the singlet pool then leads to only short existence of the triplet state, limiting the period where hyperpolarization can be used for NMR manipulation. Also presence of unwanted trace asymmetric complexes can cause extra singlet-triplet leakage depleting the singlet $p\text{-H}_2$ pool even faster as reported by Knecht *et al.*^[22,28,29] Only administrating ‘fresh’ $p\text{-H}_2$ can replenish the longitudinal two-spin magnetization.^[5,27,29,30]

Inspired by the SABRE-RELAY method,^[31–33] this contribution reports how controlled catalyst design with deuterated ammonia, *in situ* generated at low-field in a protic reaction medium, enables to generate hydride asymmetry with long-lasting observable hyperpolarization at high field. Lifetime analysis shows the presence of long-lasting longitudinal two-spin order in the hydrides (T^* up to 30 s). This feature allowed recording complete hyperpolarized 2D COSY plots at high field with only a single $p\text{-H}_2$ bubbling event at low field since inter-transient recycle delay can be reduced significantly when not dealing with Zeeman magnetization.

In situ generation of ammonia (N) provides rational control over the ligation of the $\text{IrCl}(\text{COD})(\text{IMes})$ and enables to extend singlet-triplet mixing. Controlling the pH in the system by the interplay of pyridine (=P) - the traditional SABRE substrate - with an ammonium buffer, determines the free ammonia concentration. Choosing the right buffer [NH_4Cl (pH=6.43), $(\text{NH}_4)_2\text{CO}_3$ (pH=9.11) and NH_4OH (pH=9.64)] allows to steer the ligation of the metal center in the N-Heterocyclic Carbene (NHC) transition metal

complex $\text{IrCl}(\text{COD})(\text{IMes})$. This enables to *in situ* generate octahedral iridium complexes $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{P}_{\text{ax}})]\text{Cl}^-$ (I), $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{N}_{\text{eq}}\text{P}_{\text{ax}})]\text{Cl}^-$ (II), $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{N}_{\text{eq}}\text{N}_{\text{ax}})]\text{Cl}^-$ (III) and $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{N}_{\text{eq}}\text{N}_{\text{eq}}\text{N}_{\text{ax}})]\text{Cl}^-$ (IV) after $p\text{-H}_2$ bubbling at low-field (≤ 20 mT). Here, dependency of polarization transfer from $p\text{-H}_2$ to pyridine in relation to stereochemistry variations in I-IV was monitored by varying the low-field strength. Introducing small and deuterated ligands, such as deuterated ammonia, seems to simplify the spin-system and unifies experimental and theoretically derived field-sweep experiments for four-spin systems.

Results and Discussion

1. Designing and identifying SABRE-catalysts with ammonium buffer solutions

Four individual iridium SABRE-catalyst mixtures (**M1** to **M4**) were prepared according to the procedure described in Table 1. Rational catalyst design is exerted by controlling the interplay between the traditional, aromatic N-containing pyridine (P) ligand and ammonium (N^+) introduced as part of either of three pH buffering systems: (i) NH_4Cl , (ii) $(\text{NH}_4)_2\text{CO}_3$ and (iii) NH_4OH . Controlling the pH determines the concentration of ammonia (N) in the system (see Table 2 and Figure S1 in SI for speciation modelling via PHREEQC^[34]). This provides fine control over the ligation of Ir, allowing to gradually shift it from pyridine to ammonia. The controlled conversion of the square planar precursor $\text{IrCl}(\text{COD})(\text{IMes})$ into four specific octahedral complexes binding a total of two hydrides [H, H'] and three ligands: $[3\text{xP}]$, $[2\text{xP}; \text{N}]$, $[\text{P}; 2\text{xN}]$ or $[3\text{xN}]$ is graphically presented in Figure 1.

Initial activation of the iridium catalyst mixtures (**M1-4**) for subsequent hyperpolarization experiments was conducted at low-field (6 mT) using a 300 s $p\text{-H}_2$ bubbling step in the automated Bruker polarization reactor described in the experimental section and SI (Figure S2-3). Following initial activation, the mixtures **M1-4** (Table 1) were shuttled towards high field (18.8 T) for detection with a $\pi/4$ pulse.

A distinct hyperpolarized hydride region exhibiting both in-phase and antiphase hydride resonances appeared in the ^1H spectrum, in the chemical shift range from -24 to -22 ppm. As shown in Figure 2a, the hyperpolarized hydride resonances are specific to each mixture. They originate from chemically non-equivalent hydride positions and are generated by conversion of singlet-derived longitudinal two-spin order $I_{1z}I_{2z}$ into observable antiphase transverse $I_{1x}I_{2z} + I_{1z}I_{2x}$ magnetization using a $\pi/4$ pulse.^[5,7] Longitudinal $I_{1z}I_{2z}$ magnetization originates from perturbation of the initial singlet spin order of hydrides. A symmetric singlet $p\text{-H}_2$ molecule is oxidatively added to the Ir complex, forming hydrides which start to evolve under the Hamiltonian of the new spin-system, now characterized by a chemical shift difference ($\delta\nu_{I1-I2}$) due to non-equivalent hydride positions. Oscillation and dephasing of the zero quantum coherence term (part of the initial density operator of the singlet) fuels the central triplet state (T_0) population leading to creation of longitudinal $I_{1z}I_{2z}$ magnetization by $|S\rangle \rightarrow |T_0\rangle$ mixing.^[35,36] Conducting the experiment with $o\text{-H}_2$, no antiphase resonances

Figure 2. a) Hyperpolarized hydride signals (I–IV) observed at 800 MHz after low field (6 mT) $p\text{-H}_2$ activation of **M1–4**, respectively. A $\pi/4$ pulse was used to maximize anti-phase transverse magnetization of the non-equivalent hydrides designed via independent ammonium buffer solution. b) Inter-hydride correlations ($J_{\text{HH}'} \approx 7\text{ Hz}$) observed via a hyperpolarized 2D OPSY-COSY experiment on **M3** via a single $p\text{-H}_2$ activation step at low field. Spontaneous singlet-triplet mixing due to chemical inequivalence of the hydrides in II–IV generate prolonged longitudinal $I_{1z}I_{2z}$ spin order at high field which is used for COSY-type transfer to elucidate each mixture's organometallic complexation behavior. c) Long-range trans connectivity ($J_{\text{HP}} \approx 1\text{ Hz}$) extracted from the same hyperpolarized 2D OPSY-COSY experiment. Ortho protons of ligated pyridine show correlation with trans hydrides and verify stereochemistry for complexes I–IV being the main species in mixtures **M1–4** respectively.

were visible in the hydride region, clearly proving the necessity for singlet magnetization.

Initial lifetime analysis (details in experimental section) indicates the longitudinal spin order in the hydrides, summarized in Figure 4, is long-lasting. Comparing of relaxation rate to the one observed in equilibrium conditions (SI, Figure S6), also the lifetime of free $o\text{-H}_2$ was prolonged by an order of magnitude. The

prolonged generation of longitudinal spin order at high field (infra), enabled the acquisition of a complete and highly resolved 2D Only-Parahydrogen-Spectroscopy (OPSY)-COSY spectrum in under 2.5 min of **M3** (Figure 2b,c). Details about the pulse train can be found in experimental section and SI, Figure S4. In contrast with traditional high field 2D hyperpolarized NMR measurements based on singlet-triplet derived longitudinal magnetization^[5,27], which typically require reactivation with fresh $p\text{-H}_2$ in between every transient, the present system using ammonia as co-ligand only requires a single activation step. The full 2D plot is provided in the supplementary information as Figure S5.

The inter-hydride couplings observed via the cross-peaks in the OPSY-COSY plot of Figure 2b revealed chemically inequivalent hydride couples matching with the antiphase signals displayed in Figure 2a, II and III. This hinted towards the presence of asymmetric, octahedral catalyst complexes, derived from the standard SABRE catalyst $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{P}_{\text{ax}})]\text{Cl}^-$ (**I** in Figure 1) available via **M1**. Replacing one equatorial pyridine ligand with ammonia, and the axial ligand being either pyridine or ammonia, yields the asymmetric complexes $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{N}_{\text{eq}}\text{P}_{\text{ax}})]\text{Cl}^-$ (**II** in Figure 1) and $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{N}_{\text{eq}}\text{N}_{\text{ax}})]\text{Cl}^-$ (**III** in Figure 1). Both complexes contain chemically inequivalent hydrides, for which the chemical shift difference (440 Hz for **II** and 339 Hz for **III**) is dependent on the nature of the axial ligand, controllable via the buffer system used.

With this in mind, it can be derived that the activation of the precursor complex with **M2** (pyridine and NH_4Cl) predominantly yields $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{P}_{\text{eq}}\text{N}_{\text{eq}}\text{P}_{\text{ax}})]\text{Cl}^-$ (**II**). Using **M3**, and thus $(\text{NH}_4)_2\text{CO}_3$ as contributor to the ammonia production, mainly complex **III** was formed. Here the axial ligand position is occupied by ammonia, its concentration in the $(\text{NH}_4)_2\text{CO}_3$ buffer system an order of magnitude higher as compared to the NH_4Cl system (Table 2, experimental section based on PHREEQC simulations). Fully omitting pyridine from the system, the precursor complex was activated with NH_4OH in aqueous medium (**M4**), generating $[\text{Ir}(\text{IMes})(\text{H}_2)(\text{N}_{\text{eq}}\text{N}_{\text{eq}}\text{N}_{\text{ax}})]\text{Cl}^-$ (**IV** in Figure 1). A double anti-phase hydride resonance attributed to this complex occurs around -23.5 ppm (Figure 2a, IV). The same resonance can also be distinguished in Figure 2a, III but with lower relative contribution. Note that activation of the square planar $\text{IrCl}(\text{COD})(\text{IMes})$ precursor with solely NH_4Cl or $(\text{NH}_4)_2\text{CO}_3$ was impossible, most likely due to the weaker alkaline nature of the latter two ammonium buffers.

Interpretation of the hydrides representing **IV** is more complicated. While chemically equivalent hydrides are expected from the stereochemistry in complex **IV**, as is the case for complex **I** (Figure 2a, I), the inter-hydride couplings observed for the resonances at -23.5 ppm (Figure 2b) clearly show a chemical shift difference for both hydrides attached to **IV**. This is attributed to presence of different ammonia isotopologues generated by proton-deuterium exchange between and ammonia (NH_3) and the deuterated methanol (CD_3OD) solvent.^[37] Since the concentration of deuterons (originating from CD_3OD) outnumbers the available protons by two orders of magnitude, ND_3 plays a central role in the chemical inequivalence of the anti-phase hydrides generated in **M2–4**, as can be observed in Figure 2b for **IV**. The slight inequality between abundant ND_3 and minor species NHD_2 gives rise to the asymmetry observed in **IV**. The antiphase character and the small chemical shift difference between both hydrides (38 Hz) are direct consequences. The

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Figure 3. a) Hyperpolarized pyridine signals (I-IV) observed at 800 MHz after low field (6mT) p-H₂ activation of **M1-4**, respectively. A $\pi/4$ pulse was used to measure hyperpolarization levels in appliance to the hydrides shown in Figure 2a. **b)** Field sweep experiments showing the hyperpolarization efficiency vs. low-field value (B_{transfer}) applied through the polarization coil for the ortho-, meta-, para-protons of pyridine in **M1** (I) in **M2** (II) and in **M3** (III) solution. All corresponding spectra used for integration were collected with 15 s p-H₂ bubbling and normalized to the highest polarization level across **M1-3**.

symmetric equivalent of complex **IV**, where both equatorial positions are ligated with ND₃, can also be observed in the hyperpolarized hydride region of both **M3** and **M4**. There, an underlying in-phase resonance from the symmetric equivalent of

complex **IV** creates the irregular line shape observed at -23.5 ppm in Figure 2a, III and IV at -23.5 ppm.

The hyperpolarized OPSY-COSY experiment relying on prolonged generation of longitudinal spin-order, not only enables to obtain inter-hydride couplings, also long-range trans couplings between ortho protons of pyridine ligated to iridium and the up-field hydrides can be observed (Figure 2c). This information independently reveals the ligation of pyridine in **M1-3**, enabling to verify and confirm the assignments derived from the inter-hydride couplings. In Figure 2c, the expanded hyperpolarized external projection of the ortho resonances of ligated pyridine are shown for **M1-4**. The ortho proton at 8.25 ppm exhibits a single long-range correlation to the most up-field hydride partner (H) at -22.7 ppm, which corresponds to complex **II**. The other hydride (H') in **II** lacks any coupling, demonstrating that ammonia occupies the respective trans position. The ortho proton at 8.17 ppm lacks correlation with any hydride, yet it is clearly co-existent with the equatorially bound pyridine in **M2**, as can be observed using the hyperpolarized individual projection in Figure 2c, and disappears in **M3** and **M4**. This allows to assign this resonance to pyridine occupying the axial position in **II**. The middle ortho-proton at 8.29 ppm exclusively correlates to the equatorial hydride of **III** (-23.75 ppm) and consequently it represents pyridine occupying the equatorial position in **III**.

2. Impact of reduced pyridine ligation on low-field analysis of pyridine hyperpolarization

Following their successful assignment, Ir organometallic complexes **I-III** were subjected to a low-field sweep analysis to investigate the impact of on the polarization transfer efficiency resulting from the displacement of pyridine by ND₃. Systematic removal of pyridine from the iridium transition metal exposes trends in hyperpolarization efficiency of pyridine and B_{transfer} field dependence as displayed in Figure 3. It shows the hyperpolarization efficiency of ortho-, meta- and para-protons of free pyridine for complex **I**, **II** and **III** as function of the B_{transfer} field in a range of 0 to 18.5mT. In Figure 3a, the spectral region showing hyperpolarized pyridine signals is presented for each mixture, similar to what is displayed in Figure 2a for the hydride region. In Figure 3b, each data point represents the integrated signal of the hyperpolarized pyridine protons after 15 s p-H₂ bubbling period with variable B_{transfer} field values, normalized across **M1-4** for the largest polarization (see experimental section).

Comparing all three situations, B_{transfer} field resonance conditions are influenced by the gradual removal of pyridine ligands being replaced by deuterated ammonia. In accordance with previous experimental observations, complex **I** with three pyridine ligands, exhibits B_{transfer} field behavior with a single maximum.^[12,18–20,38,39] This maximum reveals the optimal field to induce an avoided energy level crossing (LAC), enabling coherent spin mixing between the initial singlet state of ligated hydrides and the unpolarized spin state of pyridine protons.^[13] Complex **II** (the dominant species in **M2**, with already one equatorial displacement of pyridine with ND₃) exhibits much narrower resonance conditions as compared to **I**. The narrowing is also observed for **III**, the predominant complex in **M3**, in which the axial pyridine ligand is replaced by an additional ND₃. In addition to narrowing the B_{transfer} field resonance, two extra B_{transfer} maxima

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Figure 4. a) Lifetime analysis of hyperpolarization in hydrides (-24 ppm to -22 ppm) and free o-H₂ (4.58 ppm) in **M1-4**. a) Pulse sequence overview of lifetime analysis procedure. A low-field 15 s bubbling step (t_b) at 6 mT is proceeded by field cycling (t_c) to high field at 18.8 T where an adjustable delay (t_d) is implemented before observation with a $\pi/4$ pulse. This field cycling process is repeated until the signal decay can be fitted and lifetime T^* can be extracted accordingly. A full description can be found in the experimental section and SI. b) Schematic representation of field cycling setup used. c-f) Spectral decay observed for hydrides (-24 ppm to -22 ppm) and free o-H₂ (4.58 ppm) when implementing the analysis procedure described.

appear next to fixed LAC at 6mT which retains the highest intensity: 1 mT and 11 mT.

Product operator formalism simulations for coherence transfer in SABRE spin systems, pioneered by Adams *et al.*^[21] predict the existence of multiple maxima in both simple isochronous as well as anisochronous four-spin systems such as [Ir(IMes)(H₂)(P_{eq}P_{ax})Cl]⁻.^[40] However as indicated in Figure 3b, I and all other reports where field-dependent experiments were performed on [Ir(IMes)(H₂)(P_{eq}P_{ax})Cl]⁻, no such behavior could be observed and only the most prominent LAC energy value is present for pyridine.^[12,18–20,38,39] This incongruence between experimental and theoretical experiments has been the topic of a score of hypotheses trying to explain its origins.^[38,40] Hypotheses range from a lack of spins in the simulations (mainly four spins: 2 hydrides and 2 substrate protons of an equatorial bound ligand), a distribution in time of catalyst-ligand interactions, to insufficient resolution in the experimental observations.

Interestingly, the data presented in Figure 3b,III is unique in showing a field-sweep pyridine hyperpolarization curve in agreement with simulations from Hövener *et al.*^[40] and Adams *et al.*^[21] With pyridine ligation reduced to one member on the octahedral complex, while the other equatorial and axial position are occupied by deuterated ammonia, the experimental observation and theoretically derived field-sweep simulation for four-spin systems becomes unified. The importance of this unification has also recently been highlighted by Fekete *et al.*^[41] The experimental realization of highly resolved measurements on this simplified spin system is hypothesized to depend on: (i) controlled formation of [Ir(IMes)(H₂)(P_{eq}N_{eq}N_{ax})Cl]⁻, containing a single pyridine ligand, (ii) using ND₃ instead of NH₃ as the second ligand (deuterons exhibit much lower gyromagnetic ratio) and (iii) highly reproducible, automated data acquisition.

3. Long-term generation of longitudinal two-spin order: lifetime analysis

The importance and influence of $|S\rangle \rightarrow |T_0\rangle$ mixing in asymmetric hydrides on high field hyperpolarization methods has been the topic of many discussions ongoing since the pioneering work by Bargon *et al.*^[35,42] $|S\rangle \rightarrow |T_0\rangle$ mixing produces valuable singlet derived longitudinal $I_{1z}I_{2z}$ spin order that can be manipulated in context of hyperpolarized high field NMR.^[5,26,43,44] However fast singlet-triplet leakage rapidly depletes the singlet pool, which negatively impacts the efficiency of high-field polarization transfer schemes.^[23,29,45]

In Figure 4, lifetime measurements are depicted for the hydride signals (between -24 and -22 ppm) and the absorptive o-H₂ peak (at 4.58 ppm) in **M1-4**. A full experimental description can be found in the experimental section and in SI, Figure S6. Lifetime analysis for the asymmetric complexes (**II-IV**) occurring in **M2-4** (Figure 4c-f) indicates prolonged generation of longitudinal $I_{1z}I_{2z}$ spin order with T^* up to 30 s. In presence of ammonium buffers, fast singlet-triplet leakage seems to be ineffective, thereby enabling to record the hyperpolarized 2D SABRE experiment presented in Figure 2, using a single activation step with p-H₂ at low field preceding the recording of the whole 2D experiment at high field.

While the chemical shift difference $\delta\nu_{1/2}$ between hydrides quantum mechanically allows singlet-triplet mixing to occur, in this case it clearly does not correlate with the lifetime of hydride hyperpolarization. Faster decay of singlet derived longitudinal magnetization is expected when $\delta\nu_{1/2}$ increases^[29], yet here the lifetime is highest in **M3** where **III** with $\delta\nu_{1/2}$ equaling 390 Hz is the major species (Figure 4e). The decreased lifetime in **M4**, where only complex **IV** is formed (Figure 4f with $\delta\nu_{1/2}$ = 38 Hz), proves other factors can influence lifetime here. Additionally, the same complex structure (e.g. complex **II** and **III**) shows different lifetime of longitudinal spin order in different mixtures, exhibiting different chemical environments (**M2** vs **M3**), while within one mixture the different complex structures show similar lifetimes. This can be explained by fast chemical exchange of hydrides between all complex species. While this is of no surprise since exchange between hydrides and free hydrogen is a common process in homogenous catalysis, the long lifetime correlated with prolonged production of longitudinal magnetization has not yet been reported. Also the prolonged lifetime exhibited by free o-H₂ (displayed in Figure 4c-f) is intriguing. When hydrides detach from the complex, the chemical shift difference between the two protons of hydrogen disappears and the populated central triplet state can no longer give rise to observable magnetization ($T_0 \rightarrow T_+$ and $T_0 \rightarrow T_-$ transitions cancel each other out). Although exceptions to this rule exist (partial negative lineshape mechanism^[46]), future research must be conducted to theoretically frame the long lifetime of o-H₂ as well as the understanding the exact nature of the prolonged generation of longitudinal spin order.

Conclusion

Ligand control in organometallic complexation chemistry is essential for the design of iridium catalysts for p-H₂ hyperpolarization transfer. Using ammonium buffers (NH₄Cl,

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(NH₄)₂CO₃ and NH₄OH) provides control over the *in situ* ammonia concentration in protic conditions, thereby enabling to selectively generate multiple mixed-ligand octahedral iridium complexes with pyridine (P) and deuterated ammonia (N) as ligands: [Ir(IMes)(H₂)(P_{eq}P_{eq}P_{ax})]Cl⁻ (**I**), [Ir(IMes)(H₂)(P_{eq}N_{eq}P_{ax})]Cl⁻ (**II**), [Ir(IMes)(H₂)(P_{eq}N_{eq}N_{ax})]Cl⁻ (**III**) and [Ir(IMes)(H₂)(N_{eq}N_{eq}N_{ax})]Cl⁻ (**IV**). Exploiting deuterated ammonia as a ligand provides exciting opportunities, independent of SABRE-RELAY. The presence of ND₃ provides controllable hydride asymmetry accompanied by an experimentally observed prolonged generation of non-equilibrium longitudinal two-spin order. The extended lifetime of hyperpolarized antiphase magnetization produced from the longitudinal two-spin order allowed to record hyperpolarized 2D OPSY-COSY experiments using one single bubbling event at low field, thus enabling efficient structure elucidation of the complexes, while retaining knowledge about low-field spin characteristics. Low-field dependence of pyridine hyperpolarization in relation to the gradual removal of pyridine from the complexes (3xP in **I**, 2xP in **II** and 1xP in **III**) led to experimental demonstration of multiple maxima appearing for pyridine protons, previously predicted on a theoretical basis but hitherto not observed experimentally. While many details of the spin physics in these systems remain uncovered, the ammonium buffer systems provide an experimental tool to advance research in this field. The experimentally observed long-lived nature of the hydride longitudinal magnetization can in addition assist the investigation of high-field SABRE applications such as SLIC-SABRE^[23] and LIGHT-SABRE^[24], or even low-field applications such as SABRE-RELAY^[47]. In addition to the experiments presented here, the use of deuterated ammonia is expected to provide the steric relief necessary to render SABRE compatible with bulkier and bio-derived substrates, an area of research planned as follow-up of the present study.

Experimental Section

Mixture preparation

Samples were prepared according to the specifications displayed in Table 1. Four different mixtures annotated **M1** to **M4** range in added concentration of ammonia based on each ammonium buffer solution used. For all samples, 2mg iridium pre-catalyst IrCl(COD)(IMes) was dissolved in 4mL deuterated methanol (Me-d₄). The pre-catalyst was synthesized in Schlenk conditions in our laboratory following procedures described in literature.^[48] Afterwards, except for **M1**, a varying amount of (i) NH₄Cl, (ii) (NH₄)₂CO₃ and (iii) NH₄OH was added as depicted in Table 1. Values are representing molar concentrations used in millimolar units. Then, excluding **M4**, a constant amount of pyridine (2 μl) finalized the mixture compositions. This resulted in **M1** being the standard SABRE complex with pyridine as ligand, while **M2** and **M3** contained both quantities of ammonia and pyridine. Finally, **M4** is activated by NH₄OH solely. Note that NH₄Cl and (NH₄)₂CO₃ were available in powder form (Sigma Aldrich), while NH₄OH was administrated in 30% aqueous ammonia solution. In the latter, additional contribution of water molecules to the composition must be taken into account. Speciation based on pH contributed generation of NH₃, NH₄⁺, pyridine and pyridinium⁺ were simulated using PHREEQC software and available in Table 2 and Figure S1 in SI.^[34]

Table 1. Catalyst mixture composition of **M1-4** used in the hyperpolarization experiments after activation with p-H₂. Concentrations are in millimolar (mM) units. Note that NH₄OH is dissolved in aqueous solution with 30% diluted concentration. H₂O is included the composition of **M4**.

Composition (mM)	Catalyst Mixture			
	M1	M2	M3	M4
IrCl(COD)(IMes)	0.78	0.78	0.78	0.78
Pyridine	6.21	6.21	6.21	
NH ₄ Cl		104.07		
(NH ₄) ₂ CO ₃			52.03	
NH ₄ OH				50.64
H ₂ O				118.17
Me-d₄	4 mL	4 mL	4 mL	4 mL

Table 2. Theoretical speciation of pyridine, pyridinium, ammonia and ammonium in **M1-4**, calculated using PHREEQC software. Deuteration was not supported by the simulation software, thus values reported are mere guidelines for interpretation of experimental results. Additional theoretical and experimental pH values of the mixtures are included. Concentrations are in millimolar (mM) units.

Composition (mM)	Speciation (PHREEQC)			
	M1	M2	M3	M4
Pyridine	6.2	5.90	6.21	
Pyridinium ⁺	0.003	0.3	0.001	
NH ₃		0.3	45.14	49.73
NH ₄ ⁺		103.8	58.86	0.97
pH (T)	8.511	6.849	9.244	10.968
pH (Exp)	8.53	6.43	9.11	9.64

Field cycling hyperpolarization setup

Parahydrogen activation of **M1-4** was performed in a Bruker field cycling hyperpolarization setup for which a comprehensive description is provided in SI. In a prototype mixing chamber equipped with a low-field ($B_{\text{transfer}} \leq 20$ mT) pre-polarizing coil mounted in the stray field of a 800 MHz Bruker Avance Neo spectrometer, p-H₂ was dispersed in the liquid phase using a glass frit at room temperature. A constant flow of 90% p-H₂ was outputted from a Bruker p-H₂ generator (BPHG-90), cooling hydrogen gas to 37K in the presence of a metal catalyst. After initial activation of 300s, the solution was pneumatically pumped into a high-field 800 MHz spectrometer equipped with a ¹H/¹³C/²⁹Si flow probe, measured at 298K and subsequently returned to the mixing chamber of the polarizer. The transfer process typically takes about 2 seconds. For both regular, lifetime and B_{transfer} field dependence hyperpolarization experiments, a 15s bubbling step after the initial activation of 300s was applied and signal was captured after a $\pi/4$ pulse. Depending on the low-field behaviour, independent B_{transfer} values for each mixtures were used in accordance to maximizing hyperpolarization levels. All processing, automatic integration, phase and baseline corrections are performed using Mestrenova v12 from Mestrelab Research S.L.^[49]

2D Hyperpolarized OPSY-COSY

Catalyst structure elucidation was performed using a 2D OPSY-COSY sequence. Here, a standard COSY pulse train is initiated with only-parahydrogen derived magnetization, generated using an OPSY sequence (see SI, Figure S4 for pulse scheme).^[50] Instead of using a $\pi/4$ pulse to unlock the longitudinal two-spin order $I_{1z}I_{2z}$, the OPSY sequence can produce magnetization starting from the same longitudinal two-spin order $I_{1z}I_{2z}$, transforming it with a $\pi/2$ pulse to the double quantum coherence term $I_{1y}I_{2y}$ and refocussing it after a final $\pi/2$ pulse to antiphase magnetization. Appropriate gradient pulses make sure only p-H₂ derived magnetization is refocused, leaving potential thermal magnetization

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behind. A single parahydrogen activation step of 180 s at 6 mT is sufficient for construction of the hyperpolarized OPSY-COSY plots. Conventional hyperpolarized 2D plots are typically constructed with intermediate p-H₂ bubbling at high-field in between each new transient.^[5,25] A total of 1536 transients in F1 with 15% sparse sampling were recorded with only 500 ms delay between each increment giving a total of 2.5 min experimental time. The 2D data set was processed using a static NUS reconstruction with TRAF apodization of 1 Hz and zero-filled to 4096 (F1) x 8192 (F2) complex points. Hyperpolarized 1D field cycle measurements were used as external projections accordingly.

Lifetime measurements

Lifetime of hyperpolarization was monitored using hyperpolarized signals originating from hydrides and o-hydrogen in **M1-4** (see Figure 4 or S6) after adjustable delays (t_d) at high field (18.8 T). Low-field activation (6 mT) with 15 s p-H₂ bubbling (t_b) is preceded by an adjustable delay (t_d) at high field before observation with a $\pi/4$ pulse (Figure 4a). In each cycle, the delay (additional to the time it takes for the mixture to be sent to high field(t_b)) is varied from 0 to maximum 200 s, depending on each mixture. To enhance reproducibility, 10 dummy experiments with t_d of 0 s were performed before acquiring the full range of delays. Afterwards, remaining signals were integrated (absorption signals) or analysed for intensity (antiphase signals) using Mestrenova and renormalized using the method proposed by Moreno *et al.*^[51] to yield the percentage of the initial hyperpolarization intensity:

$$I(\tau) = [M(\tau) - M(\infty)]/[M(0) - M(\infty)]$$

with $M(\infty)$ being the thermal magnetization, $M(0)$ the hyperpolarized signal without any delay and $M(\tau)$ the corresponding magnetization at delay τ . The exponential decay was then approximated using a single rate constant (T^*) according to: $I(\tau) = M(0)e^{-\tau/T^*}$. The non-linear curve fitting tool in OriginPro 9 was used for extraction of the lifetime rate (T^*) with additional standard deviation errors. Lifetime results are summarized in Figure 4 with additional analysis in SI. Regular longitudinal T_1 lifetime rate was also monitored using the inverse recovery method using thermal magnetization at highfield (800 MHz). This data was fitted using the GNAT Toolbox.^[52]

Low-field sweep hyperpolarization experiments

Dependence of hyperpolarization on the low B_{transfer} field in pyridine (Figure 3) was evaluated using the field cycling setup described in SI. B_{transfer} values were varied (using the pre-polarization coil around the mixing chamber) between 0 mT and 18.5 mT in steps of 0.5 mT followed by an NMR measurement at 18.8 T. The first activation step at 0 mT was repeated 10 times using dummy experiments, before starting the full B_{transfer} field dependency plot. Integration of each resonance was automated using Mestrenova and plotted in Excel.

Author Contributions

JM, FT, JK and EB conceived the project, as part of a co-development effort between Bruker Biospin and KU Leuven, funded by the Flemish Government, department EWI via the Hermes Fund (AH.2016.134). EV and SDR performed the experimental work.

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Notes

The authors declare no competing financial interest. JMT, JGK are employees of Bruker, which sells the para-hydrogen generator used in this work. The combined flow systems and low-field apparatus used here was designed and built at Bruker, but this polarizer system is not a commercial product.

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References

- [1] K. Golman, O. Axelsson, H. Jóhannesson, S. Månsson, C. Olofsson, J. S. Petersson, *Magn. Reson. Med.* **2001**, *46*, 1–5.
- [2] A. M. Coffey, R. V. Shchepin, M. L. Truong, K. Wilkens, W. Pham, E. Y. Chekmenev, *Anal. Chem.* **2016**, *88*, 8279–8288.
- [3] N. M. Zacharias, C. R. McCullough, *J. Mol. Imaging Dyn.* **2016**, *6*, DOI 10.4172/2155-9937.1000123.
- [4] J.-B. Hövener, A. N. Pravdivtsev, B. Kidd, C. R. Bowers, S. Glöggler, K. V. Kovtunov, M. Plaumann, R. Katz-Brull, K. Buckenmaier, A. Jerschow, F. Reineri, T. Theis, R. V. Shchepin, S. Wagner, P. Bhattacharya, N. M. Zacharias, E. Y. Chekmenev, *Angew. Chemie Int. Ed.* **2018**, *57*, 11140–11162.
- [5] N. Eshuis, R. L. E. G. Aspers, B. J. A. Van Weerdenburg, M. C. Feiters, F. P. J. T. Rutjes, S. S. Wijmenga, M. Tessari, *Angew. Chemie - Int. Ed.* **2015**, *54*, 14527–14530.
- [6] N. J. Wood, J. A. Brannigan, S. B. Duckett, S. L. Heath, J. Wagstaff, *J. Am. Chem. Soc.* **2007**, *129*, 11012–11013.
- [7] S. B. Duckett, R. E. Mewis, *Acc. Chem. Res.* **2012**, *45*, 1247–1257.
- [8] C. R. Bowers, D. P. Weitekamp, *Phys. Rev. Lett.* **1986**, *57*, 2645–2648.
- [9] C. R. Bowers, D. P. Weitekamp, *J. Am. Chem. Soc.* **1987**, *109*, 5541–5542.
- [10] S. Glöggler, J. Colell, S. Appelt, *J. Magn. Reson.* **2013**, *235*, 130–142.
- [11] J. Natterer, J. Bargon, *Prog. Nucl. Magn. Reson. Spectrosc.* **1997**, *31*, 293–315.
- [12] A. N. Pravdivtsev, K. L. Ivanov, A. V. Yurkovskaya, P. A. Petrov, H.-H. Limbach, R. Kaptein, H.-M. Vieth, *J. Magn. Reson.* **2015**, *261*, 73–82.
- [13] D. A. Barskiy, S. Knecht, A. V. Yurkovskaya, K. L. Ivanov, *Prog. Nucl. Magn. Reson. Spectrosc.* **2019**, *114–115*, 33–70.
- [14] R. A. Green, R. W. Adams, S. B. Duckett, R. E. Mewis, D. C. Williamson, G. G. R. Green, *Prog. Nucl. Magn. Reson. Spectrosc.* **2012**, *67*, 1–48.
- [15] K. L. Ivanov, A. V. Yurkovskaya, H. M. Vieth, *Zeitschrift für Phys. Chemie* **2012**, *226*, 1315–1342.
- [16] M. G. Pravica, D. P. Weitekamp, *Chem. Phys. Lett.* **1988**, *145*, 255–258.
- [17] R. A. Green, R. W. Adams, S. B. Duckett, R. E. Mewis, D. C. Williamson, G. G. R. Green, *Prog. Nucl. Magn. Reson. Spectrosc.* **2012**, *67*, 1–48.

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- [18] M. J. Cowley, R. W. Adams, K. D. Atkinson, M. C. R. Cockett, S. B. Duckett, G. G. R. Green, J. A. B. Lohman, R. Kerssebaum, D. Kilgour, R. E. Mewis, *J. Am. Chem. Soc.* **2011**, *133*, 6134–6137.
- [19] R. W. Adams, J. A. Aguilar, K. D. Atkinson, M. J. Cowley, P. I. P. Elliott, S. B. Duckett, G. G. R. Green, I. G. Khazal, J. Lopez-Serrano, D. C. Williamson, *Science (80-.)* **2009**, *323*, 1708–1711.
- [20] S. Knecht, A. N. Pravdivtsev, J. B. Hövener, A. V. Yurkovskaya, K. L. Ivanov, *RSC Adv.* **2016**, *6*, 24470–24477.
- [21] R. W. Adams, S. B. Duckett, R. A. Green, D. C. Williamson, G. G. R. Green, *J. Chem. Phys.* **2009**, *131*, 194505.
- [22] S. Knecht, A. S. Kiryutin, A. V. Yurkovskaya, K. L. Ivanov, *J. Magn. Reson.* **2018**, *287*, 74–81.
- [23] S. Knecht, A. S. Kiryutin, A. V. Yurkovskaya, K. L. Ivanov, *Mol. Phys.* **2019**, *117*, 2762–2771.
- [24] T. Theis, M. Truong, A. M. Coffey, E. Y. Chekmenev, W. S. Warren, *J. Magn. Reson.* **2014**, *248*, 23–26.
- [25] N. K. J. Hermkens, R. L. E. G. Aspers, M. C. Feiters, F. P. J. T. Rutjes, M. Tessari, *Magn. Reson. Chem.* **2018**, *56*, 633–640.
- [26] S. B. Duckett, G. K. Barlow, M. G. Partridge, B. A. Messerle, *J. Chem. Soc. Dalton Trans.* **1995**, 3427–3429.
- [27] N. K. J. Hermkens, M. C. Feiters, F. P. J. T. Rutjes, S. S. Wijmenga, M. Tessari, *J. Magn. Reson.* **2017**, *276*, 122–127.
- [28] S. Knecht, K. L. Ivanov, *J. Chem. Phys.* **2019**, *150*, DOI 10.1063/1.5084129.
- [29] S. Knecht, S. Hadjiali, D. A. Barskiy, A. Pines, G. Sauer, A. S. Kiryutin, K. L. Ivanov, A. V. Yurkovskaya, G. Buntkowsky, *J. Phys. Chem. C* **2019**, *123*, 16288–16293.
- [30] D. A. Barskiy, K. V. Kovtunov, I. V. Koptuyug, P. He, K. A. Groome, Q. A. Best, F. Shi, B. M. Goodson, R. V. Shchepin, A. M. Coffey, K. W. Waddell, E. Y. Chekmenev, *J. Am. Chem. Soc.* **2014**, *136*, 3322–3325.
- [31] W. Iali, P. J. Rayner, S. B. Duckett, *Sci. Adv.* **2018**, *4*, eaao6250.
- [32] P. J. Rayner, B. J. Tickner, W. Iali, M. Fekete, A. D. Robinson, S. B. Duckett, *Chem. Sci.* **2019**, *10*, 7709–7717.
- [33] E. Vaneckhaute, J. M. Tyburn, D. Kilgour, J. G. Kempf, F. Taulelle, J. A. Martens, E. Breynaert, *J. Phys. Chem. C* **2020**, *124*, 14541–14549.
- [34] S. R. Charlton, D. L. Parkhurst, *Comput. Geosci.* **2011**, *37*, 1653–1663.
- [35] J. Bargon, J. Kandels, P. Kating, *J. Chem. Phys.* **1993**, *98*, 6150–6153.
- [36] P. Kating, A. Wandelt, R. Selke, J. Bargon, *J. Phys. Chem.* **1993**, *97*, 13313–13317.
- [37] D. A. Barskiy, J. W. Blanchard, M. Reh, T. Sjoelander, A. Pines, D. Budker, *arXiv* **2020**.
- [38] E. B. Dücker, L. T. Kuhn, K. Münnemann, C. Griesinger, *J. Magn. Reson.* **2012**, *214*, 159–165.
- [39] P. TomHon, E. Akeroyd, S. Lehmkuhl, E. Y. Chekmenev, T. Theis, *J. Magn. Reson.* **2020**, *312*, 106700.
- [40] J.-B. Hövener, S. Knecht, N. Schwaderlapp, J. Hennig, D. von Elverfeldt, *ChemPhysChem* **2014**, *15*, 2451–2457.
- [41] M. Fekete, S. S. Roy, S. B. Duckett, *Phys. Chem. Chem. Phys.* **2020**, *22*, 5033–5037.
- [42] M. Haake, J. Barkemeyer, J. Bargon, *J. Phys. Chem.* **1995**, *99*, 17539–17543.
- [43] N. K. J. Hermkens, M. C. Feiters, F. P. J. T. Rutjes, S. S. Wijmenga, M. Tessari, *J. Magn. Reson.* **2017**, *276*, 122–127.
- [44] N. Eshuis, R. L. E. G. Aspers, B. J. A. van Weerdenburg, M. C. Feiters, F. P. J. T. Rutjes, S. S. Wijmenga, M. Tessari, *J. Magn. Reson.* **2016**, *265*, 59–66.
- [45] S. Knecht, A. S. Kiryutin, A. V. Yurkovskaya, K. L. Ivanov, *J. Magn. Reson.* **2018**, *287*, 74–81.
- [46] A. S. Kiryutin, G. Sauer, A. V. Yurkovskaya, H. H. Limbach, K. L. Ivanov, G. Buntkowsky, *J. Phys. Chem. C* **2017**, *121*, 9879–9888.
- [47] S. S. Roy, K. M. Appleby, E. J. Fear, S. B. Duckett, *J. Phys. Chem. Lett.* **2018**, *9*, 1112–1117.
- [48] O. Torres, M. Martín, E. Sola, *Organometallics* **2009**, *28*, 863–870.
- [49] M. R. Willcott, *J. Am. Chem. Soc.* **2009**, *131*, 13180–13180.
- [50] J. A. Aguilar, P. I. P. Elliott, J. López-Serrano, R. W. Adams, S. B. Duckett, *Chem. Commun.* **2007**, 1183–1185.
- [51] K. X. Moreno, K. Nasr, M. Milne, A. D. Sherry, W. J. Goux, *J. Magn. Reson.* **2015**, *257*, 15–23.
- [52] L. Castañar, G. D. Poggetto, A. A. Colbourne, G. A. Morris, M. Nilsson, *Magn. Reson. Chem.* **2018**, *56*, 546–558.

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Entry for the Table of Contents

Hydride asymmetry in SABRE catalysts is controlled via *in-situ* generation of deuterated ammonia using three different ammonium buffers. Extended singlet-triplet mixing at high field provides long-term generation of longitudinal two-spin order in hydrides allowing rapid hyperpolarized 2D NMR.

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