Hyperpolarized Magnetic Resonance of Exchangeable Protons using Parahydrogen and Aminosilane

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ABSTRACT: Efficient, room temperature hyperpolarization of exchangeable solvent protons combining parahydrogen ($p\text{-H}_2$), aminopropyl-diethoxymethylsilane (APDMS) and $\text{IrCl}(\text{COD})(\text{IMes})$ to generate an active aminosilane-iridium complex, broadens the capabilities of SABRE-type hyperpolarization of protons. A primary pool of hyperpolarized exchangeable protons transfers its hyperpolarization to co-solutes with labile protons, partly overcoming the catalytic specificity of SABRE-type spin-transfer catalysis. The silane functionality of APDMS appears to be crucial to the improvement. Its role is unprecedented in $p\text{-H}_2$ -based hyperpolarization of nuclear spins and promises to broaden applicability of ultrasensitive solution-state NMR spectroscopy for the detection and elucidation of molecular behavior, at concentrations undetectable by conventional NMR spectroscopy.

INTRODUCTION

Magnetic fields polarize spin magnetic moments over different spin states, enabling observation using nuclear magnetic resonance spectroscopy (NMR) and imaging (MRI). Sensitivity of MR techniques at thermal equilibrium is limited by the weak partitioning of spin populations among these states: in magnetic fields up to 10 T, the fraction of detectable ^1H nuclei is of the order of 10^{-4} only. Hyperpolarization increases this fraction far beyond the ppm scale of thermal equilibrium, even approaching unity polarization (100% alignment). This can boost NMR and MRI signals by as much as 5 orders of magnitude in ^1H and in many other nuclei (^{13}C , ^{15}N , ^{31}P , etc.).¹⁻³ Thus, interest in hyperpolarization is widespread, examples ranging from analytical chemistry and sub-micromolar trace analysis by NMR⁴, to MRI for metabolic in-vivo imaging of hyperpolarized ^{13}C -labeled metabolites.⁵⁻⁷

Hyperpolarization methods include Dynamic Nuclear Polarization (DNP)⁸, spin-exchange optical pumping (SEOP)⁹, and ParaHydrogen Induced Polarization (PHIP).¹⁰⁻¹³ DNP is applicable to a wide range of molecules, but requires the presence of paramagnetic molecular species, cryogenic sample conditions and other expensive equipment, such as high-power microwave sources. Also, PHIP methods suffer from chemical specificity, limiting its range towards hyperpolarizable molecules, an unfortunate drawback given the cheap and easy availability of parahydrogen ($p\text{-H}_2$), the perfectly ordered singlet-state spin-isomer of hydrogen gas. Specificity in PHIP depends upon the particular method used. ALTADENA^{5,10} and PASADENA^{5,14} operate with a substrate containing a carbon-carbon double or triple bond which can be coherently hydrogenated by $p\text{-H}_2$. This induces quantum symmetry breaking of the singlet spin order on the basis of chemical inequivalence

or even magnetic inequivalence, eventually leading to observable hyperpolarized signals in the hydrogenated product after evolution of the spin system.^{11,12} Despite their substrate specificity and overall depletion of the reagents, PHIP methods that rely on hydrogenation are still unique in demonstrating the feasibility of in-vivo imaging applications based on hyperpolarization with parahydrogen.^{6,7,15,16}

SABRE⁵, another PHIP based hyperpolarization method using $p\text{-H}_2$, requires a nitrogen heterocycle or an amine transiently, but simultaneously bound to a transition metal (typically iridium) together with $p\text{-H}_2$.^{13,17} There, $p\text{-H}_2$ and the N-containing ligand (i.e., the 'substrate') form a multispin system with J-couplings between protons on the substrate and on the hydrides (i.e., the bound $p\text{-H}_2$). In a low 'spin-transfer' field ($B_{\text{transfer}} \sim 5\text{-}10\text{mT}$) chemical-shift differences between these protons are resonant with the J-coupling. Both spins of substrate protons and hydrides are said to be strongly coupled. That effects a spontaneous transfer of spin order from the hydrides to the substrate occurring at a so-called Level Anti

Figure 1. Scheme of polarization transfer through Signal Amplification by Reversible Exchange (SABRE) with parahydrogen.

Crossing (LAC) point.^{13,18–20} The substrate is then released in hyperpolarized form without chemical modification (Figure 1). Upon relaxation, a new catalyst-substrate interaction can be re-established, restoring the previously obtained hyperpolarized state. Figure 1 provides a schematic representation of the SABRE hyperpolarization mechanism. A rigorous chemical and quantum mechanical description of SABRE can be found in the work of Ivanov and co-workers.¹⁸

Here, the scope of p-H₂ methods is broadened by incorporating hydrosilylation chemistry, leveraging the ability of silicon atoms to interact with a range of transition metals including iridium.^{21–24} The rich, but subtle chemistry of silicon holds promise to offer new potential in the field of p-H₂ hyperpolarization. Traditional iridium catalyzed hydrosilylation alcoholysis (Scheme 1) permits the catalytic conversion of silane and hydroxyl residues into hydrogen gas.^{25–27} Reversing the hydrosilylation cycle by introducing excess p-H₂ hydrogen could provide new routes to hyperpolarize silicon²⁸ which is appealing for in-vivo applications due to its long T₁. In addition, this can provide hyperpolarized exchangeable protons of the substrate and peripheral co-solute targets. Interest in transferrable hyperpolarization has grown with recent observations and applications involving small molecules or biomolecules.^{29–32} Additionally, enhancements in target molecules have been obtained by intermolecular Nuclear Overhauser effects (NOEs) or via rapid exchange of hyperpolarized protons with labile protons on various co-solutes.^{33,34} Present results provide new variety among such distributed hyperpolarization schemes.

Experimental

For this work, aminopropyldiethoxymethylsilane (APDMS, Sigma-Aldrich) (Figure 1 and S1) was selected for its combined silicon and primary amine functionality, both exhibiting affinity for the transition metal centre.³⁵ For APDMS-1, 0.5 mmol of aminopropyldiethoxymethylsilane was used to partially dissolve 0.01 mmol of IrCl(COD)(IMes)³⁶ powder. After dissolution of the precursor catalyst in APDMS, 5 ml of deuterated methanol (CD₃OD) was added. This solution was then sealed into a 6 ml brown coloured glass vial with a septum and mounted in a Bruker prototype hyperpolarization setup (Figure 2). The full description and lay-out of the prototype field cycling device can be found in the Supporting Information (Figure S9). During the experiment about 3 ml of the sample solution was transferred to a prototype mixing chamber with low-field ($|B_{\text{transfer}}| \leq 15$ mT) pre-polarising coil mounted in the stray field of a Bruker 800 MHz [Figure 2(a)]. P-H₂ was prepared using a Bruker p-H₂ generator (BPHG-90), yielding a hydrogen flow with 90% p-H₂ by cooling hydrogen gas to 37K in the presence of a metal catalyst. Depending on the experiment, the sample solution was contacted and saturated with p-H₂ in the mixing chamber at B_{transfer} and room temperature for a variable bubbling duration. This provides interaction of p-H₂ with co-ligands (e.g., APDMS) in the regime of strong J-coupling. After activation and sufficient time (120s) at low field with p-H₂ bubbling, the solution was pumped into a high-field 800 MHz spectrometer equipped with a ¹H/¹³C/²⁹Si

Scheme 1. Hydrogen production from alcohol and silane substrates. Introduction of excess p-H₂ can shift the equilibrium leftward, in principle yielding exchangeable proton hyperpolarization on the alcohol (and silane).

Figure 2. Schematic description of a) the mixing chamber where Ir-APDMS catalyst is activated by p-H₂ bubbling at low magnetic field and b) the automated field cycling setup that is used for transferring the catalyst solution from low field to high field (18.8T). 90% p-H₂ is supplied by a p-H₂ generator (Bruker, BPHG-90). A dedicated flow probe with a 200 μ l flow cell allows for measurement of hyperpolarized signals. A full schematic of the Bruker field-cycling prototype can be found in supporting information (Figure S9).

flow probe at room temperature and subsequently returned to the polarizer. A schematic layout of the setup is given in Figure 2(b). The transfer process typically takes about 2 seconds. For APDMS-2, an identical preparation as described for APDMS-1 was followed, only an additional 0.1 mmol of (NH₄)₂CO₃ was added before activating the complex with p-H₂. Later on, experiments were performed with non-exchangeable solvent CD₂Cl₂ instead of CD₃OD. Here the same preparation and concentrations as used in APDMS-1 were employed.

The dependence of the polarisation transfer on the pre-polarization field (B_{transfer}) was evaluated using the polarizer setup shown in Figure 2. Using a constant p-H₂ bubbling time of 10s, B_{transfer} values were varied (using the pre-polarization coil) between -14 mT and 7 mT, followed by an NMR measurement at 18.8T. Information on the lifetime of the proton polarization (exchangeable protons, o-hydrogen (o-H₂) and hydride signals) was estimated by implementation of an additional delay at high field after pre-polarization at low field. Observation was performed following $\pi/2$ excitation. The corresponding hyperpolarized peaks were integrated using the automatized Topspin 'multi_integ' program found in Bruker's standard AU program library. Multiple cycles, each with repeated bubbling, activation, transfer and varied delay time before $\pi/2$ excitation and read-out provides information on hyperpolarization lifetime.

RESULTS AND DISCUSSIONS

Hyperpolarization of Exchangeable Protons. After p-H₂ activation of APDMS-1 in the polarization reactor described in Figure 2(a), hyperpolarized ¹H signals were readily observed by NMR. The solvent hydroxyl peak at 4.9 ppm was inverted relative to all thermal signals in the spectrum. Notably, the hyperpolarized signal consists of exchangeable protons. Non-exchangeable protons of APDMS did not exhibit signal enhancements. Hyperpolarization further increased upon addition of (NH₄)₂CO₃ to the system. (NH₄)₂CO₃ acts both as a pH buffer and as an extra source of exchangeable protons. This

Figure 3. a) Equilibrium ^1H -NMR spectrum (800MHz) of APDMS-2 after $\pi/2$ pulse b) Hyperpolarized ^1H -NMR spectrum (800 MHz) after $\pi/2$ pulse of the APDMS-2 mixture (with ammonium salt) using a p- H_2 contact time of 120s at a polarizer field of 8 mT at 25°C. c) Hyperpolarized ^1H -NMR spectrum (800 MHz) of hydride resonances. The negative peak at 4.9 ppm is the hyperpolarized hydroxyl proton pool in exchange with the protons of the amine functionality and protons of the hydroxyl ethanol fraction. The peak at 4.55 ppm is from hyperpolarized o- H_2 according to multiple previous assignments in literature.³⁸ Full characterization is available in SI, Figure S1.

system (APDMS-2) yielded signal enhancements of 20x, compared to the thermal equilibrium signal recorded at room temperature (Figure 3). Peak assignment of the other resonances between 0-4 ppm are described in Figure S1.

The hydroxyl hyperpolarization results from a new iridium complex with APDMS ligand, representing an extension of the chemical interactions available for SABRE hyperpolarization. The Ir-APDMS interaction is evidenced by the appearance a new ensemble of hydride resonances between -23.4 and -24.2 ppm [Figure 3(c)], only appearing upon introduction of both APDMS and p- H_2 in the catalytic system.^{18,37} Positively phased hyperpolarization of o- H_2 occurs simultaneously with negatively phased hyperpolarization of the exchangeable protons.^{38,39} As APDMS can serve as a grafting agent in high-surface-area materials, the new catalyst could represent a new step towards the production of efficient, heterogeneous p- H_2 polarization transfer catalysts.⁴⁰⁻⁴²

Low-Field Dependency of Hyperpolarization. While full structural elucidation of the new Ir-APDMS complex is difficult due to its low concentration and short-lived nature of the transition states, insight in the mechanism of solvent hyperpolarization is available from the dependence of the signal enhancement on the pre-polarization field. Varying the B_{transfer} field with ± 15 mT, using fixed 10s p- H_2 bubbling, a maximal hyperpolarization was observed at +7.5 and -7.5 mT. Normalized integrals from ^1H signals of hydroxyl, o- H_2 and hydrides are shown in Figure 4(a). The oscillatory dependence of the exchangeable proton signal at 4.9 ppm on the value of B_{transfer} is apparent and consistent with a SABRE-type mechanism.¹⁸ In contrast, hydride and o- H_2 signals do not follow this oscillation.

Figure 4. a) Hyperpolarization levels vs. low-field value (B_{transfer}) in the polarization coil for APDMS-activated solution for (I) hydride (integration from -23.4 to -24.2 ppm), (II) o- H_2 (near 4.3 ppm) and (III) hydroxyl (near 4.9 ppm) resonances. All corresponding spectra were collected with 10s p- H_2 bubbling. Integration values are normalized to the hydroxyl signal. b) Correlation of hyperpolarized signals from solvent hydroxyl and o- H_2 at the different B_{transfer} values, and, c) for hydride and o- H_2 resonances.

Altogether, the field *in*-dependence of the positively phased o- H_2 hyperpolarization, together with the observation of hyperpolarized hydroxyls instead of protons vicinal to the amine function of APDMS, indicates the present mechanism differs from conventional SABRE.^{13,39} Generally, the field dependencies of substrate and hydride/hydrogen are mirrored (like sinusoids shifted 180°) when both species are hyperpolarized in the same spin mixing process.^{39,43} Figures 4(b) and 4(c) plot integrated intensities of the hyperpolarized exchangeable protons (solvent -OH), hyperpolarized o- H_2 and the hydride resonances versus pre-polarization field. In (b), a quasi-independent behaviour of solvent and hydride hyperpolarization is apparent. The Pearson's correlation coefficient (r_{xy}) be-

tween hyperpolarization of solvent and hydride makes $r_{\text{H}_2, \text{solvent}} = -0.39$ indicating a minor inverse correlation. In contrast, positive correlation is very clear between hydrogen and hydride hyperpolarization in Figure. 4c with $r_{\text{H}_2, \text{hydride}} = 0.93$. The latter can be attributed to chemical exchange between free hydrogen and hydrides bound to the Ir-APDMS complex.³⁷ In other words, the strong correlation of Figure. 4(c) suggests hydride and o-H₂ hyperpolarization is of common origin, whereas hyperpolarization of the solvent hydroxyl develops in a different manner.

Hydride Hyperpolarization. A detailed look at the hydride ensemble, as correlated with the hyperpolarization of the exchangeable protons, can further elucidate the relationship of these hyperpolarized signals. The hyperpolarized hydride signals evolve over time, from start (meaning the first activation with p-H₂ at low-field conditions) until 2 hours after the initial activation. Each experiment at the given time point includes 'refreshing' the active complex via low-field p-H₂ bubbling, the transfer to 18.8 T, measurement with $\pi/2$ pulse and a transfer back to low field. Figure 5(a) depicts this process in the hydride spectral region. The left (downfield) hydride resonances decrease in amplitude, while the hydride peak at -24.1 ppm exhibits a continuous growth.

This evolution can be attributed to chemical exchange of protonated ethoxy arms from the APDMS ligand with the deuterated CD₃OD solvent molecules [Figure 5(b)]. The result is an increasing ¹H signal for ethanol hydroxyl in Figure 5(b),⁴⁴ with concurrently decreasing signals from the aliphatic arms of APDMS, measured at thermal equilibrium. The chemical phenomenon of ethanol displacement (from APDMS) depicted in 5(b) is known to be mediated by iridium.²¹ We also separately observed this release by steady state ¹H-DOSY (Diffusion Ordered Spectroscopy, Figure S5). The DOSY spectra further resolved ethanol, methanol and silicon-bounded ethoxy signals by their corresponding rates of molecular diffusion. While such transformations of APDMS could explain concurrent hydride evolution, that situation is even more complicated by simultaneous deuterium scrambling of the amine functionality. Deuterons from the solvent are in chemical exchange with protons attached to the APDMS nitrogen, resulting in different isotopologues of APDMS. Consequentially, changes to the hydride peaks may also occur when different isotopologues of APDMS bind with iridium.

Insights on Proton Exchange using an Aprotic Solvent. To further explore this chemical exchange phenomenon, the Ir-APDMS complex was contacted with p-H₂ in an aprotic solvent: deuterated dichloromethane (DCM-d₂). This prevented proton exchange and simplified the system. In contrast to CD₃OD, operation in DCM-d₂ revealed clear hyperpolarization of the -NH₂ protons of APDMS (Figure S6) without affecting its aliphatic protons. That suggests that previous results in CD₃OD could reflect -OH hyperpolarization derived from traditionally obtained amino hyperpolarization chemically exchanged to the hydroxyls. This is also supported by our observation of SABRE-type oscillations of the exchangeable -OH signal in Figure 4(a).

The concept of the Ir-APDMS yielding spin-transfer reactions from APDMS to a protic solvent is similar to SABRE-RELAY.³⁴⁻⁴⁵ Duckett and co-workers reported NH₃ (and later a range of amines) in the role of a relay agent, initially bound to their Ir complex together with p-H₂, then hyperpolarized and released, finally redistributing spin order via chemical exchange to co-solvated amines, amides, alcohols, etc.^{31,45,46} Notice the difference between spin-(inter)relayed polarization

Figure 5. Spectral evolution of the APDMS-2 mixture for a) hyperpolarization of the hydride resonances, and b) the chemical exchange of solvent CD₃OD molecules for CH₂CH₃OH/D originating from displaced ethoxy groups of APDMS. For APDMS, these were recorded at thermal equilibrium. For the hydride region, each experiment cycle at the given time point includes 'refreshing' the active complex via low-field p-H₂ bubbling, the transfer to 18.8 T, measurement with $\pi/2$ pulse and a transfer back to low field.

due to chemical exchange (between different molecules), as observed here, vs. spin-(intra)relayed polarization (within a molecule). The latter causes typical SABRE enhancements of, e.g. meta- and para-positioned hydrogen atoms in pyridine. Those examples lack a strong active coupling to the hydrides, and are therefore ineffective for direct SABRE. One step further, is the phenomenon of spin-(inter)relayed SABRE involving chemical exchange to transfer hyperpolarization into a non-ligated 'third-party' molecule. Here, with APDMS, inter-relay seems to be the main distributing effect.⁴⁷

Finally, the beneficial role of (NH₄)₂CO₃ to this process can be understood as follows. It acts as an extra source of mobility shuttling protons between solvent and hyperpolarized amines by chemical exchange. Deuterons, in contrast are also exchanged, but those are not hyperpolarized in the current low field optimum of 7–8mT. In addition to its shuttling function, (NH₄)₂CO₃ acts as a buffer. The slightly basic APDMS (pK_b ~ 4 in aqueous conditions) partially exists as its positively charged conjugated acid (APDMS⁺ = APDMS with -NH₃⁺ functionality). This reduces affinity for the Ir complex which in most cases is overall positively charged in its octahedral form. The buffer however will diminish the quantity of APDMS⁺, thus boosting its ligation to iridium.

Figure 6. a) Aliphatic proton resonances H1, H3, H5 and aromatic proton resonances H2, H4, H6, H7 of IMes N-heterocyclic carbene at thermal equilibrium, in blue: IrCl(COD)(IMes) dissolved in CD₃OD, in red: after addition of APDMS and (NH₄)₂CO₃, in green: after p-H₂ bubbling. b) Spectral evolution of IMes aliphatic and aromatic resonances measured at thermal equilibrium matching the indicated time sequence starting after formation of the active Ir-APDMS-2 complex in (a,III). In between these measurements, multiple hyperpolarization experiments were performed, each showing the corresponding black 'hyperpolarized signal'.

Properties of APDMS and IMes, the N-heterocyclic Carbene Ligand. Post-activation evolution of IMes resonances between 2.5–2.1 ppm (aliphatic protons) and 7.5–7 ppm (aromatic protons) offers additional insight in the stereo-conformation of the Ir-APDMS active species. It is known that the stereo-conformation of the IMes ligand, and consequently also its NMR resonances, change during successive steps to activate the IrCl(COD)(IMes) catalyst precursor.^{39,48} For pyridine, this was presented in Pravidtsev et al.³⁹

Figure 6a presents the aromatic and aliphatic features of IMes for the complex containing APDMS, measured at *thermal equilibrium*. Figure 6(a,I) displays the characteristic resonances of IMes in the square-planar 16e[−] precursor IrCl(COD)(IMes) complex dissolved in CD₃OD. From there, IMes resonances evolve on sequential introductions of APDMS and (NH₄)₂CO₃ [Figure. 6(a,II)] and finally with p-H₂ [Figure. 6(a,III)]. Corresponding spectral changes reveal the participation of these additives in the evolving Ir complex. The starting point [Figure. 6(a,I)] exhibits the characteristic IMes resonances of the square planar complex. Addition of APDMS and (NH₄)₂CO₃ [Figure. 6(a,II)] broadens these features as the (Ir(I)(APDMS)(COD)(IMes))⁺Cl[−] complex forms. Note the latter is also 16e[−] and square-planar (See also Figure 8 for structures of these two square-planar complexes). This first evolu-

tion step yields a decreased mobility of the entire trimethylphenyl group of IMes, as well as specific rotational hindrance of the off-axis methyl groups (H1 and H5) due to the influence of APDMS binding with iridium. Consequently, these groups exhibit increased motional correlation times, corresponding to elevated spin relaxation rates (1/T₂) and increased linewidths of the methyl (H1,H5) and aromatic (H2, H4) protons.

Next, after p-H₂ bubbling, IMes resonances [Figure. 6(a, III)] for methyls groups (H1, H5) collapse to a single narrow resonance near 2.25 ppm, while aromatic protons (H2, H4) similarly narrow to a single peak near 7.18 ppm. These observations substantiate the formation of an active APDMS-iridium complex, where rotations of the trimethylphenyl groups are less restricted. This is consistent with formation of the more spacious octahedral 18e[−] (Ir(III)(H)₂(APDMS)₃(IMes))⁺Cl[−] complex formed upon oxidative addition of p-H₂.

Figure 6(b) shows IMes resonances at thermal equilibrium in between multiple p-H₂ hyperpolarization cycles with the Ir-APDMS-2 complex. Thus, the end point from Figure. 6(a) is the starting point to 6(b), where additional evolution of IMes resonances appears. The hyperpolarized spectrum is shown in addition to the time series. There, inverted hyperpolarization is apparent for IMes peaks near 2.2 and 7.1 ppm. In the color-

coded time series of thermal equilibrium spectra, with repeated cycles of low-field $p\text{-H}_2$ bubbling and high-field NMR observation, the IMes spectral complexity increases from 0–120 min. Gradually-rising peaks correspond to the noted inverted hyperpolarized resonances. Both phenomena therefore imply a chemical modification of the IMes molecule over time that induces hyperpolarization only to this modified ligand. This suggests parahydrogenation of IMes that in thermal equilibrium manifests as the gradually-rising peaks in the aliphatic region of Fig. 6(b), while during hyperpolarization conditions this is revealed by inverted hyperpolarization in the same peaks.

An explanation of the hyperpolarized signal appearing in the aromatic region of IMes (Figure 6(b)) is more difficult. Hydrogenation implies that the resulting proton resonances (and thus hyperpolarization) are found upfield. Intra-relayed hyperpolarization from the parahydrogenation to nearby protons or even ^{13}C -carbon nuclei is however a known phenomenon.^{49,50}

It is important to emphasize that these observations of catalytic evolution are likely generalizable to more SABRE catalysts, and not limited only to the Ir-APDMS complexes discussed here. The IMes ligand should be similarly susceptible to chemical modification in traditional SABRE catalysis with N-heterocyclic carbene ligands. The present achievements to observe such effects benefit from experimental advantages of higher resolution due to 800 MHz observation and to the reproducible and stable polarization, transfer and observations steps available from the polarizer and flow control systems we used. Regardless, additional spectroscopic characterization, including multidimensional experiments, may shed further light on the exact nature of chemical and spectral evolution presented in Figure. 6.

Impact of Si from APDMS. In addition to the interaction of the amine functionality of APDMS, the silicon atom offers another site for Ir ligation via its exchangeable ethoxy groups. Indeed, bidentate amine and silicon binding to iridium is known,²⁴ and could contribute to the present potency of APDMS interaction with the Ir-precursor. Stereo-configurations based on electron counting and stereochemistry are reviewed in Figure S7. Such chemical variety may be an additional reason for the distributed pool of hydride signals [Figure 5(a)].

The potential role of the silicon atom was evaluated using methylamine as a simple Si-free substitute for the amino arm of APDMS. Using methylamine at the same molar concentration as APDMS, and in an otherwise identical solution of $\text{IrCl}(\text{COD})(\text{IMes})$ and $(\text{NH}_4)_2\text{CO}_3$ in CD_3OD , $p\text{-H}_2$ was bubbled for 120 s at 7 mT. Following the usual transfer to NMR signals were recorded at 800 MHz. The result was a 256-fold reduction in hyperpolarization of the exchangeable protons situated at 4.9 ppm (Figure S8) as compared to results (Figure 3) with APDMS. This clearly supports the value of complete APDMS inclusion for efficient solvent hyperpolarization, though elucidating a direct role of Si remains beyond current scope. In the future, bidentate ligation of the Ir complex by APDMS might be proven by demonstrating hyperpolarization of ^{29}Si (spin-1/2) in ultralow field (μT) via SABRE-SHEATH⁵¹. That approach to heteronuclear $p\text{-H}_2$ derived hyperpolarization has been successfully employed for a wide range of spin-1/2 targets including ^{15}N .^{52,53} However, SABRE-SHEATH will require substantial experimental modifications and is thus left for follow-up study.

Figure 7. (a) Residual signal intensity after delay implemented at high field for hyperpolarized hydroxyl (solvent), hydrogen ($o\text{-H}_2$) and hydride peaks in APDMS-1 (mixture without $(\text{NH}_4)_2\text{CO}_3$). (b) Equivalent, but for APDMS-2 solution (i.e., with $(\text{NH}_4)_2\text{CO}_3$).

Lifetimes of Hyperpolarization. Additional insights are possible through qualitative observation of the decay of hyperpolarized signals from Ir-APDMS-1 and -2 complexes. Here, relative lifetime are estimated for exchangeable protons ($-\text{OH}$), as well as for $o\text{-H}_2$ and the integrated hydride region. Observation followed a variable delay time implemented at high field after $p\text{-H}_2$ bubbling of the hyperpolarized sample

Figure 7 shows the results. Exponential fits were not reliable, perhaps due to dynamic contributions simultaneous with T_1 relaxation. Nonetheless, a qualitative sense is available by comparing zero-crossings of the integrated intensities. For APDMS-1, hyperpolarization of the 4.9 ppm signal remained negative up to 20s delay at 18.8T [Figure 7(a)]. This is considerably longer than the 5 s value for the hydroxyl pool measured via inversion recovery from thermal equilibrium conditions (Supplemental, Figure S4). For APDMS-2 [Figure. 7(b)], only 12s delay was sufficient to neutralize the negative intensity of the hyperpolarized $-\text{OH}$. This difference is attributable to the impact of ionic strength of $(\text{NH}_4)_2\text{CO}_3$ on longitudinal relaxation. The $o\text{-H}_2$ hyperpolarization also exhibits interesting behaviour with $(\text{NH}_4)_2\text{CO}_3$ (i.e., in APDMS-2, Figure. 7(b)). Although hydrogen itself is known to have a very short $T_1 \sim 1\text{--}2$ s,³⁹ in contrast, the APDMS-2 solution yielded $o\text{-H}_2$ and hydride peaks with slow decaying magnetization, a feature not observed before.

Proposed Mechanism for Exchangeable Proton Hyperpolarization with the Ir-APDMS complex. Based on results presented thus far, Figure 8 proposes a scheme for hyperpolarization of the exchangeable protons. While definite elucidation of the Ir-APDMS complex remains beyond current scope, data is consistent with $-\text{OH}$ hyperpolarization developed by the spin-(inter)relayed mechanism. Indeed, two aspect in the solution facilitate proton exchange: (i) the APDMS

Figure 8. Proposed exchangeable proton hyperpolarization mechanism in case of APDMS. a) Hyperpolarization transfer from $p\text{-H}_2$ to amine protons from APDMS and b) the exchange process for distribution of polarization. More information on other possible stereo-conformations of the Ir-APDMS complex are presented in supporting information (Figure S7).

molecules exist in substantial concentration as APDMS^+ due to its higher basicity than other typical SABRE ligands (e.g., pyridine), and (ii) the chemical displacement of APDMS ethoxy groups by solvent molecules provides additional routes for proton exchange. Nevertheless, as a fundamental step, it is the intrinsic ligation tendency of the APDMS amine towards the iridium precursor that stimulates initial transfer of spin-order from $p\text{-H}_2$ to amine protons [Figure 8(a)].

A last remark covers the polarization distributing proton exchange process itself. It remains open whether this distribution occurs mainly near the organometallic centre or instead in bulk solution. If the free electron pair of nitrogen binds to the iridium, the primary amine group has been assumed to be non-exchangeable.³⁰ Consequently, aminosilane ligands would need to be released from the complex before it can redistribute polarization as depicted in Figure 8(b). However, it is often overlooked that, even in tightly ligated primary amines, N-bound protons can still be labile, similar to the situation in the famous Noyori asymmetric transfer hydrogenation reactions, which contributed to the 2001 Nobel prize in Chemistry.^{54–56} In that case, hyperpolarization and redistribution can happen in a simultaneous (coordinated) manner.

CONCLUSION

In summary, efficient hyperpolarization of exchangeable protons in CD_3OD was accomplished at room temperature by means of an active aminosilane-iridium complex obtained by adding APDMS to the standard SABRE catalytic precursor $\text{IrCl}(\text{COD})(\text{IMes})$. APDMS activates the complex in a previously unobserved fashion, where both nitrogen and silicon-based functionalities appear to play a role in $p\text{-H}_2$ -derived hyperpolarization of exchangeable protons in the system. SABRE-type polarization is supported by the low-field oscillatory dependence of $-\text{OH}$ hyperpolarization. Additional similarity to SABRE-RELAY is apparent by the separate finding that the $-\text{NH}_2$ group of APDMS exhibits hyperpolarization when the same experiment is performed in aprotic solvent. Together these observations point to traditional SABRE polarization of the AMPDS amine with (in the case of a protic solvent) distribution to a larger pool of exchangeable protons.

Moreover, certain effects of Ir complexation by APDMS are revealed by studying the IMes resonances of the organometallic complex after addition of APDMS and $(\text{NH}_4)_2\text{CO}_3$ and finally $p\text{-H}_2$ contact. We expect that present observations of catalytic evolution on the IMes ligand may be generalizable to other implementations of SABRE catalysis (i.e., with or without APDMS). Further study combining high-field observation and operation with the stable and reproducible polarization conditions should further clarify understanding of evolution and durability of the Ir-catalytic complexes utilized in most of the SABRE field.

Finally, in the protic solvent, substitution of an aliphatic amine for APDMS dramatically reduced hydroxyl hyperpolarization, further supporting the importance of the full silane species, which has potential for concurrent silicon and amine coordination to Ir. Further studies are necessary for fuller understanding of silane-enhanced $p\text{-H}_2$ hyperpolarization. Nonetheless, regardless of mechanism, silanes like APDMS also offer excellent opportunity to graft SABRE spin-catalysis onto solid-phase materials. This might lead to heterogeneously catalysed solvent hyperpolarization by $p\text{-H}_2$, with advantages for ready separation of the catalyst from the hyperpolarized molecules that are the targets of chemical and spectroscopic study.^{40–42}

ASSOCIATED CONTENT

Supporting Information. "This material is available free of charge via the Internet at <http://pubs.acs.org>." Experimental procedures, additional NMR data and interpretation.

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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, EB and JMT performed the experimental work. DK and JMT designed and built the pre-polarization reactor (i.e., combined flow system and low-field $p\text{-H}_2$ polarizer).

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Notes

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

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ABBREVIATIONS

§ALTADENA: Adiabatic Longitudinal Transport And Dissociation Engenders Nuclear Alignment

§PASADENA: Parahydrogen And Synthesis Allow Dramatic Enhancement of Nuclear Alignment

§SABRE: Signal Amplification By Reversible Exchange

§COD: cycloocta-1,5-diene

§IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

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TOC Graphic