Propane-\(d_6\) Heterogeneously Hyperpolarized by Parahydrogen

Kirill V. Kovtunov,*,†,‡, Milton L. Truong,*,§, Danila A. Barskiy,†,‡, Oleg G. Salnikov,†,‡, Valery I. Bukhtiyarov,Ⅲ Aaron M. Coffey,§,‖ Kevin W. Waddell,§,‖ Igor V. Koptyug,§,‡, and Eduard Y. Chekmenev,*,§,‖,∥,◆

1International Tomography Center, 3A Institutskaya St., Novosibirsk 630090, Russia
2Novosibirsk State University, 2 Pirogova St., Novosibirsk, 630090, Russia
3Institute of Imaging Science, Department of Radiology, ⅢDepartment of Biomedical Engineering, †Department of Physics and Astronomy, 4Department of Biochemistry, 5Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, Tennessee 37232-2310, United States
6Boreskov Institute of Catalysis, SB RAS, 5 Acad. Lavrentiev Pr., Novosibirsk 630090, Russia

** Abstract:** Long-lived spin states of hyperpolarized propane-\(d_6\) gas were demonstrated following pairwise addition of parahydrogen gas to propane-\(d_6\) using heterogeneous parahydrogen-induced polarization (HET-PHIP). Hyperpolarized molecules were synthesized using Rh/TiO\(_2\) solid catalyst with 1.6 nm Rh nanoparticles. Hyperpolarized \((P_H \sim 1\%)\) propane-\(d_6\) was detected at high magnetic field (9.4 T) spectroscopically and by high-resolution 3D gradient-echo MRI (4.7 T) as the gas flowed through the radiofrequency coil with a spatial and temporal resolution of 0.5 × 0.5 × 0.5 mm\(^3\) and 17.7 s, respectively. Stopped-flow hyperpolarized propane-\(d_6\) gas was also detected at 0.0475 T with an observed nuclear spin polarization of \(P_H \sim 0.1\%)\ and a relatively long lifetime with \(T_{1_{\text{eff}}} = 6.0 \pm 0.3\) s. Importantly, it was shown that the hyperpolarized protons of the deuterated product obtained via pairwise parahydrogen addition could be detected directly at low magnetic field. Importantly, the relatively low-field \(T_{1_{\text{eff}}}\) of HP propane-\(d_6\) gas is not susceptible to paramagnetic impurities as tested by exposure to ∼0.2 atm oxygen. This long lifetime and nontoxic nature of propane gas could be useful for bioimaging applications including potentially pulmonary low-field MRI. The feasibility of high-resolution low-field 2D gradient-echo MRI was demonstrated with 0.88 × 0.88 mm\(^3\) spatial and ∼0.7 s temporal resolution, respectively, at 0.0475 T.

** Introduction:** While gas imaging is useful in studies of catalysis,\(^1\) reactors,\(^2\) porous media,\(^3,4\) lungs,\(^5\) etc.,\(^6\) it is challenging due to the low molar concentrations of gases at normal pressure. Biomedical applications of gas imaging are of particular importance. For example, there is currently no widespread clinical imaging modality for functional lung imaging because computed tomography (CT), conventional MRI, and X-ray can only provide structural images of dense tissues—for example, tumors or pneumonia—but provide very little or no information about lung ventilation, perfusion, alveoli size, etc. Deadly diseases such as chronic obstructive pulmonary disease (COPD) with over 300 million people affected worldwide and ∼3 million annual deaths do not have any imaging marker as of today.\(^8,9\)

This state of affairs contrasts with cancer imaging, which includes MRI, CT, ultrasound, mammography, positron emission tomography (PET), and others, which enable early detection via population screening and treatment response monitoring. High-sensitivity imaging techniques with low penetration depth such as fluorescence and other optical imaging approaches cannot be directly applied to lung imaging. Conversely, PET and MRI with molecular contrast agents have a relatively high penetration depth of tens of centimeters.

Nuclear medicine approaches require a radioactive exogenous contrast agent such as \(^{133}\)Xe gas or technetium-99m DTPA,\(^7\) which enables lung imaging through visualization of inhaled gas.\(^{133}\)Xe additionally enables brain imaging due to its ability to penetrate the blood-brain barrier. The disadvantages include the requirements for radioactive isotope handling and production and specialized imaging hardware, which result in a relatively high cost.

Conventional MRI unfortunately has a relatively low sensitivity for proton imaging of gases,\(^7\) but two groups of inhalable contrast agents for heteronuclear NMR and MRI have been demonstrated to date. The first group is comprised of fluorinated gases. Perfluorinated carbon (PFC) compounds are used as inhalable contrast agents,\(^10,11\) which, once inhaled, can be imaged via the detection of the relatively NMR-sensitive \(^{19}\)F stable isotope nucleus. Because there is virtually no \(^{19}\)F NMR background signal in vivo, this method offers a very good contrast with the surrounding tissue. The main challenges of this method are (i) the relatively low spatial and especially

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temporal (minutes) resolution, caused by a low NMR signal-to-noise ratio (SNR) for the SOFT of PFC gases compared to tissue 
density, and (ii) the requirement for specialized 
hardware and MRI pulse sequences. The next group of 
methods relies on NMR hyperpolarization, which increases 
nuclear spin polarization by 4–6 orders of magnitude and 
more. The spin exchange optical pumping (SEOP) process hyperpolarizes noble gases including 3He, 129Xe, 
131Xe, and 83Kr. When inhaled, these hyperpolarized (HP) 
gases can be imaged by MRI on a single breath hold providing 
high-resolution 3D maps of lung perfusion, ventilation, 
apparent diffusion coefficient (ADC), and other lung-
function-related metrics. These hyperpolarization methods 
provide a great contrast between the lungs and other tissues 
because of the lack of background signal but require (i) highly 
specialized hyperpolarization equipment to create the hyper-
polarized state and (ii) a multinuclear MRI scanner with a 
second RF detection channel in addition to the conventional proton RF channel. The above requirements limited these 
promising MRI imaging modalities for both PFC and HP noble gas contrast media. Moreover, irrespective of hyperpolarization, low-
sensitivity because low-
significantly reduced static magnetic susceptibility effects 
resulting in the reduced subject-induced B0 inhomogeneities 
and (ii) a significantly reduced specific adsorption rate (SAR). The 
advantages make low-field MRI a more robust, faster, 
and safer procedure in comparison to conventional high-field MRI.

Deuteration results in only a small increase in T1 values of 
the HP product as demonstrated here by high-field NMR and 
MRI and thus provides little benefit in prolonging the 
hyperpolarization lifetime. However, the use of low magnetic fields allows the preparation of hyperpolarized long-lived spin 
states of the nascent pair of hydrogen of parahydrogen (p-H2) after its pairwise addition to propene-d6 and the significantly 
improved hyperpolarization lifetime is potentially suitable for 
biomedical imaging applications.

Propene is a nontoxic asphyxiant, and it has been shown to be 
nontoxic and safe in a long-term (90-day long) occupational 
exposure study at a concentration up to 10 000 ppm, which is 
below its lower explosive limit (LEL) of 2.1%. While 
additional toxicity studies may be required to warrant the 
safety of bolus inhalation of propene gas at significantly greater 
concentrations, the earlier work on long-term systemic exposure clearly advocates for propene being safe and 
nontoxic. Moreover, the potential clinical translation will likely follow in the footsteps of hyperpolarized 129Xe, which is a 
well-known anesthetic, and is now administered as a bolus 
inhalet contrast agent under high concentration of >50%. While 
propene is an explosive gas, it has a very low upper 
explosive level of ~9.5%. Therefore, it can be potentially safely 
administered to humans for lung imaging at gas concentrations 
significantly exceeding its upper explosive limit (UEL) > 9.5%.

EXPERIMENTAL SECTION

Preparation of Gases for Hydrogenation Reactions. Ultrapure (>99.999%) hydrogen gas was used for the preparation of >90% p-H2 using a previously described p-H2 generator. Propene-d6 (99% atom D, Sigma-Aldrich 455687) and propene (Sigma-Aldrich 295663-300G) gases were used as 
supplied by the manufacturer without further purification. Gases were mixed immediately before their use in a custom 
mixing chamber, which represented a previously described high-pressure ~60 mL polysulfone reactor filled with plastic 
balls to yield the effective chamber volume of ~30–60 mL. Propene-d6 gas was filled in the chamber first, and the chamber 
was then filled with p-H2 gas with ~9.5 bar total pressure and a 1:2 ratio of propene-d6:p-H2 gases. Note that when propene gas is 
completely hydrogenated the resulting gas mixture consists of propene-d6:p-H2 in ~1:1 ratio. Rh/TiO2 catalyst (1.6 nm particle size) was described earlier. Approximately 50 mg of this catalyst was packed inside an 1/8 in. OD copper tubing 
representing a variable-temperature (VT) reaction chamber.

9.4 T High-Resolution NMR Spectroscopy. High-resolution high-field NMR spectroscopy was conducted on a 
9.4 T Bruker Avance NMR spectrometer. The experimental setups for ALTADENA34 and PASADENA35 experiments are 
presented in the corresponding figures. For ALTADENA experiments, the hydrogenation reaction was performed in a 
temperature-controlled reaction chamber at Earth magnetic 
field, and the resulting gas was transferred for detection to the 
9.4 T NMR spectrometer via 1/16 in. OD (1/32 in. ID) Teflon 
tubing at a flow rate of 100 mL/min at 1 atm total gas pressure. 
HP gas was delivered to the bottom of a standard 5 mm NMR 
tube via 1/16 in. OD Teflon flexible tubing. The gas exited the 
NMR tube through an additional exhaust line (via 1/16 in. OD 
Teflon tubing) at the top of the NMR tube. For PASADENA experiments, a small quantity (a few milligrams) of Rh/TiO2 
catalyst was placed at the bottom of a standard 5 mm NMR 
tube, and the propene-d6:p-H2 mixture was delivered to the 
catalyst via 1/16 in. OD Teflon tubing. All experiments with
hydrogenation at Earth magnetic field were conducted at a reaction chamber temperature of $\sim 100 \, ^\circ C$. While the gas stream leaves the reactor being very hot, the gas cools down rather rapidly because gases generally have relatively low thermal capacity and because the gas passes through a significant section (>1 m long) of 1/16 in. ID tubing. As a result, when the material is transferred to the 9.4 T magnet, it is already equilibrated to room temperature. This was additionally checked by blowing the stream of produced gases over the hand of the experimenter, and the gas was found to be cooled. The apparent enhancement factor $\varepsilon$ (app,flow) was calculated by comparing the signal intensities of hyperpolarized (flow) and thermally polarized (stopped flow) gas samples using the method described earlier assuming that the HP gas already equilibrated to room temperature after passing through a very long section (>1 m) of tubing. The rapid gas cool-down is a convenient and advantageous feature of this method for potential biophysical translation.

4.7 3D MRI. High-field 3D MRI studies were conducted using a 4.7 T Varian MRI scanner (Varian, Palo Alto, California) and a custom-built 38 mm ID dual-channel MRI coil tuned to $^1$H frequency of 200.25 MHz. A 3D gradient echo sequence was used for MRI with the following parameters: spectral width (SW) = 20 kHz, imaging matrix 64 $\times$ 64 $\times$ 64, field of view (FOV) = 32 $\times$ 32 $\times$ 32 mm$^3$, echo time (TE) = 2.2 ms, repetition time (TR) = 4.3 ms, voxel size 0.5 $\times$ 0.5 $\times$ 0.5 mm$^3$ (125 mL), RF excitation pulse (rectangular shape), $\alpha$ = 15$^\circ$ (500 $\mu$s, Gaussian shape) for HP propane-$d_6$ and $\alpha$ = 2$^\circ$ (500 $\mu$s, Gaussian shape) for the water phantom, total acquisition time of 17.7 s. No compressed sensing or other image acceleration technique was used, and no data manipulation was performed (i.e., zero-filling or smoothing). Percentage polarization of HP propane-$d_6$ gas was calculated as described earlier for HP propane gas and was estimated to be $\sim 1\%$. It should be pointed out that this polarization estimate was done using spectroscopic detection of flowing HP propane with NMR FID of $<100$ ms. This is important because the spectroscopic method provides a more reliable number because imaging of flowing propane gas at 4.7 T may suffer from significant MRI artifacts related to the fast flow and the encoding scheme. A spiral-shaped phantom was prepared using Tygon (3/32 in. ID $\times$ 3/16 in. OD, McMaster Carr, Atlanta, GA, P/N SS52K22) tubing wrapped around a plastic syringe to provide the dimensionality for imaging studies. A constant HP gas flow rate ($\sim 15$ mL/min) was maintained during an entire 3D MRI scan.

0.0475 T NMR Spectroscopy and Nonslice-Selective 2D MRI. All low-field studies were carried out using a Kea2 NMR spectrometer (Magritek, Wellington, New Zealand) with a custom-built frequency optimized dual-channel RF $^1$H-X probe. The flow rate was not controlled in low-field MR experiments due to experimental limitations. Hyperpolarization via hydroenogenation of propane-$d_6$ was conducted at Earth magnetic field, and HP gas was transferred into an $\sim 2$ mL phantom (estimated transfer time $\sim 0.3$ s) placed inside the 0.0475 T NMR magnet (Magritek, Wellington, New Zealand). HP propane-$d_6$ (or propane) gas was allowed to flow for $\sim 1$ s time period, after which the flow was terminated, and the phantom chamber was filled with HP gas mixture (estimated 4.7 bar partial pressure of propane-$d_6$ (or propane) at $\sim 100 \, ^\circ C$—unlike in high-field experiments, the exiting gas was passing through a very short section (<20 cm) of heated tubing) containing $\sim 150$ mM HP propane-$d_6$ (or propane) corresponding to $\sim 300 \, \mu$mol quantity. NMR HP spectroscopic signals of propane-$d_6$ and propane were referenced to the NMR signal from thermally polarized H$_2$O (2.8 g, $\sim 160$ mmol, $55 \, \mathrm{M}$ concentration, containing 5 mM CuSO$_4$). The enhancement factors $\varepsilon$ were calculated by comparing the signal intensities and quantities of HP gas and thermally polarized reference sample of water as follows: $\varepsilon = (S_{\text{HP}} \times X_{\text{HP}})/(S_{\text{H}_2\text{O}} \times X_{\text{H}_2\text{O}}) \sim 6000$, where $S_{\text{HP}}$ and $S_{\text{H}_2\text{O}}$ are the integrals of the NMR signals of HP propane-$d_6$ and water, respectively, and $X_{\text{HP}}$ and $X_{\text{H}_2\text{O}}$ are molar quantities of water and HP propane-$d_6$ respectively. Percentage of proton polarization in HP propane-$d_6$ was computed using thermal equilibrium proton polarization at 0.0475 T of $P_H = 1.6 \times 10^{-7}$ or $1.6 \times 10^{-5}\%$ as follows: $P_H = \varepsilon \times P_{\text{THERMAL}}$, yielding $P_H \sim 0.1\%$ per each (two per molecule) hyperpolarized nascent proton. All NMR spectra were recorded using a 45$^\circ$ excitation rectangular shape RF pulse and one scan. A 2D MRI experiment was conducted using nonslice-selective 2D GRE sequence as supplied by the manufacturer (Magritek, Wellington, New Zealand) using the following pulse sequence parameters: TE/TR = 7.0/20 ms, acquisition time = 6.4 ms, SW = 5.0 kHz, RF excitation pulse (rectangular shape), $\alpha$ = 7$^\circ$ ($6.0 \, \mu$s), FOV = 28 $\times$ 28 mm$^2$ using 32 $\times$ 32 imaging matrix with two dummy scans with the total imaging time of $\sim 0.7$ s. Imaging of HP propane-$d_6$ utilized a single average and was repeated every 3 s, while imaging of water utilized eight averages. All images from propane-$d_6$ utilized one average (NA), while images of water were recorded with NA = 8. All images were interpolated to 1024 $\times$ 1024 pixels via zero-filling the data to enhance visual representation.

Low-Field NMR Spectra Simulation. $^1$H NMR spectra for propane, propane-$d_6$, and [3-13C]propane were calculated based on the conventional spin-density matrix formalism. For propane, the following parameters were used: $\delta$ = 0.899 ppm (methyl, 6H), $\delta$ = 1.336 ppm (methylene, 2H), $J_{HH}$ = 7.4 Hz. For [13C]-labeled propane, $\delta$ [13C] = 16.2 ppm and $J_{CC}$ = 125 Hz were used, with the two H atoms inherited from parahydrogen residing on the two unlabeled (12C) carbons in the propane molecule. For propane-$d_6$, the vicinal couplings were $J_{HH}$ = 7.4 Hz, $J_{HD}$ = 1.12 Hz and $J_{DD}$ = 0.17 Hz, while for the geminal H–D couplings the value $J_{HD}$ = 2 Hz was used.

Evolution of spin density matrix in the external magnetic field was evaluated by diagonalizing the Hamiltonian matrix to find eigenstates and eigenenergies of the spin system. The spin density matrix was then converted to the eigenbasis, and its elements were propagated in time using the respective rotation operators, with only $^1$H nuclei affected by the pulses. Two types of calculations were performed: (1) assuming that both reaction and NMR signal detection took place at the 0.0475 T field and (2) for reaction performed at the Earth’s field followed by adiabatic sample transfer to 0.0475 T for NMR signal detection. The calculation results were found to be almost identical. The field sweep was incorporated, when required, by using a series of short free evolution intervals interleaved with small stepwise increments in the magnetic field. The number of intervals (100–1000) was increased until no further changes in the calculated spectra were observed. The FID was calculated based on the free evolution of the density matrix with periodic calculation of transverse magnetization for $^1$H nuclei, followed by Fourier transform to generate the spectrum. Relaxation effects were not included in the calculations.
RESULTS AND DISCUSSION

The conventional ALTADENA experiment relies on the pairwise addition of \( p \)-H\(_2\) to an unsaturated precursor in a very low magnetic field under conditions of \( \gamma_B B_0 (\delta(H_A) - \delta(H_B))/2\pi \ll J_{HA,1BD} \) which is followed by a rapid yet adiabatic sample transfer to a high-field NMR spectrometer and detection of the dissocitated singlet of nascent parahydrogen protons under conditions of \( \gamma_B B_0 (\delta(H_A) - \delta(H_B))/2\pi \gg J_{HA,1BD} \) where \( \gamma_B B_0 (\delta(H_A) - \delta(H_B))/2\pi \) is the chemical shift difference (in units of Hz) of the two nascent protons H\(_A\) and H\(_B\) (Figure 1b). The resulting ALTADENA spectrum (Figure 1d) of HP propane\(-d_6\) shows the expected two NMR lines corresponding to H\(_A\) and H\(_B\) protons of propane\(-d_6\) gas with the signal enhancement \( \epsilon_{\text{app,flow}} = 100 \pm 5 \) (measured by comparison with the thermal spectrum of stopped gas, Figure 1e; the signal enhancement is similar to that observed for nondeuterated propane under similar experimental conditions).

While deuteration may increase \( T_1 \) this effect was found to be very minor at 9.4 T. For example, \( T_1 \) (CHD\(_2\)) is 684 ± 27 ms vs \( T_1 \) (CH\(_3\)) = 616 ± 16 ms, and \( T_1 \) (CH\(_2\)) is 625 ± 10 ms vs \( T_1 \) (CH\(_2\)) = 532 ± 6 ms, in propane\(-d_6\) and propane, respectively. These relatively low \( T_1 \) values present an experimental challenge for the detection of HP gas because of the relaxation losses during gas transport from the reactor to the NMR detector (Figure 1a). Moreover, short \( T_1 \) is a fundamental barrier for potential biomedical translation of HP propane (and other HP hydrocarbons) as an inhalable HP contrast agent for pulmonary imaging in a manner similar to HP \(^{129}\)Xe and other HP noble gases.

Despite the limitations associated with a relatively short \( T_1 \), HP propane gas can be successfully used for high-resolution hyperpolarized imaging. An example of high-resolution 3D MRI is provided in Figure 2a, where a spiral-shaped phantom was filled with the flowing HP propane\(-d_6\) gas. The MR image with 0.5 × 0.5 × 0.5 mm\(^3\) spatial and 17.7 s temporal resolution is demonstrated using polarization levels of \( P_{fl} \sim 1\% \) for HP propane\(-d_6\) gas. A corresponding image of thermally polarized water is provided in Figure 2b. The SNR of 3D images of HP propane\(-d_6\) gas and water were similar, demonstrating that proton images of hyperpolarized gases can be obtained with a quality similar to that of water. The clear advantages of proton hyperpolarized gas (vs \(^{129}\)Xe\(^{6,7,37}\) or other hyperpolarized noble gases) such as propane\(-d_6\) shown here include the use of widely available proton-detecting imaging hardware and conventional and advanced\(^{38}\) fast 3D proton MRI sequences. For example, the images presented in Figure 2a were acquired using a conventional 3D GRE MRI sequence as supplied by the MRI instrument manufacturer. It should also be noted that the images presented in Figure 2a have an approximately 2-fold better spatial resolution (as measured by the voxel size) compared to 0.625 × 0.625 × 0.625 mm\(^3\) spatial resolution demonstrated earlier with HP nondeuterated propane.\(^{22}\)

Moreover, the fully deuterated unsaturated substrate propane\(-d_6\) enables the studies of the hydrogenation reaction mechanism via the in situ detection of HP products through PASADENA protocol, where heterogeneous hydrogenation is carried out inside a 5 mm NMR tube with the in situ NMR signal detection\(^{9,40}\) (Figure 3a). While the PASADENA spectrum of HP propane\(-d_6\) produced via pairwise addition of \( p \)-H\(_2\) primarily consists of two antiphase NMR lines corresponding to two nascent protons H\(_A\) and H\(_B\) derived from the \( p \)-H\(_2\) molecule (Figure 3b), there are additional enhanced NMR signals, which correspond to HP propane. It should be noted that propane\(-d_6\) (99% labeling with deuterium) carries essentially no protons, while Figure 4b clearly illustrates the enhanced antiphase resonances 3, 4, 5, and 6 of partially deuterated propenes with PASADENA hyperpolarized protons. These observations suggest that these resonances correspond to nascent protons derived from \( p \)-H\(_2\) via (i) pairwise addition to propane\(-d_6\) followed by subsequent dehydrogenation (loss of D\(_2\)) (Figure 4a) or via an alternative pathway of (ii) propane\(-d_6\) dehydrogenation followed by pairwise addition of \( p \)-H\(_2\) to propane\(-d_6\). While both pathways are possible, the second pathway is either nonexistent or has a minor contribution because it cannot produce the HP resonance 4 clearly seen in Figure 4. Note that nonpairwise \( H_2 \) addition is the major reaction mechanism accounting for most (>95%) of the produced propane, and most parahydrogen-derived spin order is lost due to the dominance of the nonpairwise reaction mechanism and relaxation, i.e., only up to 1% is retained on the propane spin ensemble of nascent parahydrogen protons. Nevertheless, the nonpairwise route (i.e., without preservation of \( p \)-H\(_2\) derived hyperpolarization) also involves the H/D exchange process described in Figure 4a on the surface of Rh/
TiO₂ catalyst because the signal ratio of methyl and methylene peaks is far from 1:1 (which would be expected if only one \( p-H_2 \) molecule were incorporated in one propene-\( d_6 \) molecule) as seen in the thermally polarized spectrum (Figure 1e) of hydrogenated gas. This indicates that on average more than two protons are being incorporated in the final hydrogenated product, which strictly speaking should not be referred to as propene-\( d_6 \).

Moreover, these mechanistic studies indicate that enhanced resonances 3, 4, 5, and 6 are derived through \( p-H_2 \) addition and dehydrogenation processes rather than through other mechanisms of polarization transfer from \( p-H_2 \). In contrast, if normal (i.e., nondeuterated) propene was used in the above PASADENA studies, it would be difficult to elucidate the mechanism of formation of HP propene species. Therefore, the deuterated precursor is an important and unique tool for mechanistic studies of hydrogenation processes.

Furthermore, NMR and MRI detection can be performed at low magnetic fields. In addition, the detection efficiency of HP NMR and MRI (defined as SNR) in low magnetic fields.
can in fact significantly exceed that of high-field HP detection.\(^{32,33}\) Low-field NMR can offer the regime of a strongly coupled spin system with \(\gamma_B B_0(\delta(H_A) - \delta(H_B))/2\pi < J_{\text{eff}}\) and therefore the singlet spin state of the nascent protons derived from \(p\)-\(H_2\) may remain partially associated. NMR detection of HP propane-\(d_6\) obtained using the setup shown in Figure 5a enabled NMR detection at 0.0475 T.\(^{32,33}\)

![Figure 5](image_url)

**Figure 5.** Stopped-flow NMR spectroscopy of hyperpolarized propane-\(d_6\) at 0.0475 T. (a) Experimental setup diagram and (b) (left) single-scan NMR spectrum of HP propane-\(d_6\) after pairwise addition of \(p\)-\(H_2\) to propane-\(d_6\) in Earth magnetic field. The inset shows the decay of HP signal measured with a small-angle RF excitation pulse (\(\alpha = 7^\circ\)); (middle) the corresponding spectrum of thermally polarized water, and (right) the corresponding spectrum of HP propane. It should be noted that the effect of \(7^\circ\) RF excitation pulse on magnetization is negligible (>99% of residual polarization is retained after each RF pulse) conveniently allowing in situ direct monitoring of exponential signal decay, i.e., \(T_1\) measurement.\(^{32,37,44}\)

where \(\gamma_B B_0(\delta(H_A) - \delta(H_B))/2\pi \approx 1\) Hz is significantly smaller than \(J_{\text{eff}}\) of \(\sim 7\) Hz. The spectroscopic NMR detection of stopped HP propane-\(d_6\) gas (Figure 5b) revealed a strongly enhanced signal with \(\varepsilon\text{(app,stopped)} \approx 6000\) corresponding to \(P_H \approx 0.1\%\) (per nascent proton) by referencing the NMR signal of thermally polarized water. Experimentations with nondeuterated propane under identical experimental conditions (Figure 5b) revealed a significant collapse of the NMR signal due to a small chemical shift difference between \(H_A\) and \(H_B\).

Theoretical simulations of the experiments intended to verify the observed significant difference in the NMR signals of deuterated and nondeuterated propane were performed (Figure 6). The very large difference between signal enhancements for propane and propane-\(d_6\) can be rationalized as follows. At the magnetic field of 0.0475 T, the methyl and methylene proton spins of propane are strongly coupled and essentially represent a system of eight almost magnetically equivalent spins. In the reaction of propane with \(p\)-\(H_2\), the numerous spin states of propane are populated in such a way that the allowed NMR transitions correspond to very small spin level population differences and thus give very weak signals, whereas significant population differences created by the reaction correspond to transitions which are normally forbidden. In terms of a two-spin system, this would correspond to small population differences within the manifold of the NMR-active triplet spin state and a large population difference between the singlet and triplet manifolds which gives no observable NMR signal. However, because the two chemical shifts are unequal, mixing of the triplet and singlet states makes the nominally forbidden transitions slightly allowed, which, combined with the large population difference between the singlet and triplet manifolds, leads to the observation of a moderate intensity spectrum. We note that for an eight-spin system, this "singlet—triplet" terminology is applicable only in qualitative terms, but it is still quite illustrative. For propane-\(d_6\), the presence of deuterium atoms removes the near-magnetic equivalence of the two \(H\) atoms inherited from \(p\)-\(H_2\), and the corresponding mixing of spin states ensures that large population differences are now associated with fully allowed transitions, leading to much larger signal intensity in the observed NMR spectrum (Figure 6).

The polarization decay time measurements for HP propane-\(d_6\) yielded a value of \(T_{1,\text{eff}} \approx 6.0 \pm 0.3\) s (Figure 5b inset), which is an order of magnitude greater than the high-field \(T_1\) value of \(\sim 0.6\) s. Furthermore, the addition of 0.2 atm of \(O_2\) introduced to HP propane-\(d_6\) did not affect its \(T_{1,\text{eff}}\) of \(\sim 6\) s. The increase in \(T_1\) (and its insensitivity to paramagnetic \(O_2\) impurity) is highly desirable because it renders the opportunity to use HP propane gas for biomedical applications as a potential inhalable proton hyperpolarized contrast agent.

This effect of creation of longer-lived large population differences between the spin states of nascent \(p\)-\(H_2\) proton spins is likely to be universal for PHIP (and potentially other HP methods), and we term it Nuclear Alignment of Spin Hyperpolarization via Interactions in Long-lived Low-field Ensembles (NASHVILLE) to make distinction with PASADE-NA and ALTADENA conditions. A number of perdeuterated PHIP precursors similar to propene-\(d_4\) employed here are already available for efficient, i.e., resulting in near unity, hyperpolarization. These precursors can be used for PHIP of HEP for MRI angiography,\(^{45}\) TFP for coronary plaque imaging,\(^{47,48}\) succinate,\(^{47,48}\) for cancer imaging,\(^{49}\) phospholac-\(13\)\(^{13}\) and propargylocholine.\(^{51}\) It can be speculated that they are good candidates for NASHVILLE experiments to achieve long-lived \(^1\)H spin states in low magnetic field without the requirement for the polarization transfer from nascent protons to \(^{13}\)C or \(^{15}\)N heteronucleus.\(^{52–55}\)
The increase of the lifetime of the HP state of propane-\(d_6\) at low magnetic field through creation of long-lived states is hardly surprising because a significant increase in singlet lifetime vs conventional \(T_1\) was demonstrated in seminal works by Levitt,36,57 Warren,58,59 and others.60 While \(T_1\) of HP propane-\(d_6\) (\(\sim 6\) s) is relatively low, it exceeds that of HP \(\text{\(^{87}Kr}\),61 and it is certainly sufficiently long to enable \textit{in vivo} administration via inhalation.

Low-field MRI has a potential for biomedical application of HP propane-\(d_6\) described above, and the feasibility of subsecond low-field MRI is successfully demonstrated in Figure 7. 2D (without slice selection) GRE MRI images were acquired with submillimeter \((0.88 \times 0.88 \text{ mm}^2\) pixel size) spatial resolution in \(\sim 0.7\) s. The repetition time \((\text{TR} = 20 \text{ ms})\) was limited by the electronics response and can be significantly accelerated in the future similarly to the GRE MRI \((\text{TR} = 4.3 \text{ ms})\) presented in Figure 2a. Furthermore, shorter TR can also potentially enable sufficiently high scan speed required for 3D imaging of HP gas.37,62

The level of signal enhancement \((e \sim 6000)\) enabled higher SNR in the images of HP propane compared to that of thermally polarized water \((\text{Figure } 7)\). This is important because potential \textit{in vivo} direct proton imaging of this HP contrast agent will have to consider the background signal from water in the surrounding tissue.63,64 Moreover, the available \(P_H\) was only 0.1% at 0.0475 T. Further improvements to achieve higher \(P_H\) values are possible for boosting the imaging SNR, which would improve the dominance of the HP propane-\(d_6\) signal over the thermal water background.

A significant discrepancy between the apparent \(P_H\) values for HP propane-\(d_6\) at low and high magnetic fields (\(\sim 1\%\) and 0.1%, respectively) can be explained by (i) the difference in experimental setup (experiments at high field utilized constant gas flow, whereas low-field experiments lacked flow control) and (ii) additional relaxation losses in low-field experiments because HP gas was stopped first, causing an additional time delay (\(\sim 2-3\) s). Moreover, partial collapse of an antiphase NMR peak due to \(B_0\) field inhomogeneities cannot be completely ruled out.65 Furthermore, the possibility of incorporation of more than one pair of \(p\)-\text{H}_2 into the final product via a pairwise route cannot be ruled out (see discussion regarding the mechanism of H/D exchange above), and extra protons may cause collapse of the NMR line similarly to that shown in Figures 5b and 6b for natural abundance propane.

HP propane-\(d_6\) gas was prepared within seconds via heterogeneous catalytic hydrogenation. While a relatively small production quantity (a few milliliters) of HP propane-\(d_6\) was demonstrated, there are no fundamental barriers for scaling it up to a clinically relevant dose of \(\sim 1\) L. Despite a relatively low percentage polarization (0.1–1%) achieved for propane to date,22 it should be pointed out that each HP propane molecule carries a payload of two hyperpolarized protons compared to monatomic hyperpolarized \(\text{\(^{129}Xe}\). Furthermore, protons have a \(3.6\)-fold greater gyromagnetic ratio and a \(4\)-fold greater natural abundance compared to those of \(\text{\(^{129}Xe}\). The combination \((\text{calculated as a product})\) of these factors makes HP propane \(\sim 40\) times more sensitive compared to \(\text{\(^{129}Xe}\) at the same polarization level. Furthermore, the process of SEOP of noble gases is time-consuming, whereas HP propane-\(d_6\) can be prepared on demand, which can additionally enable signal averaging to improve SNR through potentially multiple inhalations of HP propane-\(d_6\). Nevertheless, the recent technological44,66–69 and fundamental14,37 advances in SEOP hyperpolarization of \(\text{\(^{129}Xe}\) enabled \(\text{\(^{129}Xe}\) polarization to approach order unity \((\text{i.e., } \sim 100\%)\). Therefore, despite nominally better detection sensitivity of propane vs \(\text{\(^{129}Xe}\), further improvements in hyperpolarization level of HP propane are required to truly enable better detection sensitivity of HP propane-\(d_6\) vs HP \(\text{\(^{129}Xe}\) in addition to the other two realized benefits of (i) direct proton detection enabling MRI imaging on widely available proton MRI scanners and (ii) the relative ease and cost \((\text{of hyperpolarization equipment})\) of HP propane-\(d_6\) production.

An additional benefit of HP propane is the use of proton NMR detection, which is universally available unlike detection of \(\text{\(^{129}Xe}, \text{\(^{13}C},\) and \(\text{\(^{3}He}\) requiring multinuclear detection capability.71,72 The main limitation of the described use of HP propane-\(d_6\) at 0.0475 T is the prerequisite of low-field MRI scanners, which are less widespread than conventional high-field MRI scanners. However, it should be pointed out that low-field HP MRI62,73,74 can be more sensitive than HP high-field MRI75 making the low-field MRI a very well-suited molecular imaging modality. Moreover, specific adsorption rate (SAR) is negligible at low resonance frequencies,20 which provides fewer limitations \((\text{for example, SAR can limit the speed of MRI scan})\) and an increased patient safety.

**CONCLUSIONS**

Propene-\(d_6\) gas was efficiently hyperpolarized using the HET-PHIP technique and Rh/TiO\(_2\) catalyst allowing for preparation of pure \((\text{from catalyst})\) HP propane-\(d_6\) gas. While deuteriation of the propene precursor was not effective for increasing \(T_1\) at
9.4 T, it nevertheless demonstrates a number of advantages compared to unlabeled propene. PHIP of propane-$d_6$ provides significant advantages for the mechanistic studies of the catalytic hydrogenation reaction, showing in particular that propene gas is hydrogenated to yield propane, which can be subsequently dehydrogenated by the catalyst studied. Propene-$d_6$ can also be useful for high-resolution high-field MRI of flowing HP propane-$d_6$ gas as demonstrated here by 3D MRI with $0.5 \times 0.5 \times 0.5$ mm$^3$ and 17.7 s spatial and temporal resolution.

Low-field NMR at 0.0475 T enabled efficient direct detection of PHIP hyperpolarized propane-$d_6$ in contrast to non-deuterated PHIP polarized propane. The longer-lived low-field ensembles (NASHVILLE effect) additionally allow for a significant (factor of $\sim 10$) increase in hyperpolarization decay time. This new approach can potentially be extended to other perdeuterated precursors suitable for PHIP hyperpolarization. The feasibility of multiscan low-field MRI was demonstrated with the spatial and temporal resolution of $0.88 \times 0.88$ mm$^2$ (pixel size) and $\sim 0.7$ s, respectively. Multiple subsecond MR images were recorded on a single batch of stopped-flow HP propane-$d_6$ gas during an $\sim 15$ s long time window. The feasibility of high-resolution MRI should pave the way to biomedical use of PHIP hyperpolarized propane-$d_6$ as an inhalable contrast agent for pulmonary imaging using proton MRI hardware and pulse sequences.

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