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# Over 12% Polarization and 20 Minute Lifetime of <sup>15</sup>N on Choline Derivative Utilizing Parahydrogen and Rh Nanocatalyst in Water

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Abstract: Hyperpolarization techniques are key to extending the capabilities of MRI for the investigation of structural, functional and metabolic processes in vivo. Recent heterogeneous catalyst development has produced high polarization in water using parahydrogen with biologically relevant contrast agents. Here we introduce a novel heterogeneous ligand-stabilized Rh catalyst capable of achieving <sup>15</sup>N polarization of 12.2 ± 2.7% by hydrogenation of neurine into a choline derivative. This is the highest <sup>15</sup>N polarization of any parahydrogen method in water to date. Notably, this was performed using a deuterated quaternary amine with an exceptionally long spin-lattice relaxation time ( $T_1$ ) of 21.0 ± 0.4 minutes. These results open the door to the possibility of <sup>15</sup>N in vivo imaging using nontoxic similar model systems because of the biocompatibility of the production media and the stability of the heterogeneous catalyst using parahydrogen-induced polarization (PHIP) as the hyperpolarization method.

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The inherently low sensitivity of magnetic resonance methods limits the scope of chemical and biological investigations in clinical contexts. This has motivated recent advancements in hyperpolarization techniques capable of generating several orders of magnitude signal enhancements with contrast agents such as metabolites. Dissolution dynamic nuclear polarization (d-DNP) can generate large polarizations on injectable contrast agents and has shown great promise in medical application<sup>[1-4]</sup>, even though DNP requires high capital equipment investment and requires several hours to produce a polarized sample prohibiting concepts like continuous multiple infusions<sup>[5]</sup>. An alternative approach of hyperpolarization uses the singlet spin state isomer of hydrogen known as parahydrogen (para-H<sub>2</sub>) to generate polarization via PHIP<sup>[6-8]</sup> and Signal Amplification by Reversible Exchange (SABRE)<sup>[9]</sup>. These techniques are significantly more cost-effective as 100% enriched para-H<sub>2</sub> can be easily generated by flowing H<sub>2</sub> gas over a catalyst at low temperatures and stored at room temperature. Additionally, the equipment has a lower base cost since only low magnetic fields are required eliminating the high acquisition cost of a superconducting magnet and maintenance.

The implementation of solution-state PHIP techniques which employs effective homogeneous catalysts in organic solvents and water pose concerns over the bio-toxicity of the hyperpolarized product mixtures<sup>[10]</sup> and has motivated heterogeneous alternatives capable of high aqueous polarization. Though high <sup>13</sup>C polarizations (>3%) have recently been shown by labile transfer of cleavable [1-13C]pyruvate derivatives into pure water using homogeneous catalyst<sup>[11]</sup>, metal degradation was observed in addition to concerns of chemical stability in the presence of unprotected nitrogen groups, necessitating further method optimization. Excellent advances have been made with efficient <sup>15</sup>N polarization using the PHIP variants SABRE and SABRE-SHEATH, however these methods have thus far investigated compounds with subclinical <sup>15</sup>N polarizations<sup>[12]</sup>, optimization in organic solvents<sup>[13,14]</sup>, and limited development of heterogeneous catalysts<sup>[15,16]</sup>. While PHIP has been investigated in vivo<sup>[17-21]</sup>, clinical applications require the production of the nontoxic and preferably pure sterile product; a heterogeneous catalyst can be removed from the mixture after polarization enhancement creating a pure aqueous solution of the hyperpolarized compound of interest<sup>[22]</sup>. Transition metal particles based on Pt, Pd and Rh have been previously reported as capable heterogeneous catalysts for PHIP with a variety of substrate molecules, but none have been used for in vivo imaging because of the reduced polarization values<sup>[23-25]</sup>.

In this work, we introduce an N-acetylcysteine (NAC) stabilize metal using rhodium (Rh) to produce the new heterogeneous nanoparticle, NAC@Rh. This catalyst allows for efficient polarization of quaternary <sup>15</sup>N nuclei with long relaxation times. NAC-stabilized metal nanoparticles have recently been

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demonstrated to generate <sup>1</sup>H polarizations exceeding 1% in water<sup>[26]</sup>, these polarizations are measured values without compensation for signal decay loss from transit to the spectrometer. Since <sup>1</sup>H polarization decays within seconds owing to short longitudinal spin relaxation times *T*<sub>1</sub>, the preservation of polarization via transfer to nearby nuclei such as <sup>13</sup>C, which have a *T*<sub>1</sub> on the order of a minute, or <sup>15</sup>N, which can have *T*<sub>1</sub> on the order of tens of minutes, is essential for clinical utilization<sup>[27]</sup>. Because of the very long relaxation time of <sup>15</sup>N, it could have a distinct advantage over for <sup>13</sup>C for clinical applications. Thus, the hyperpolarization of <sup>15</sup>N nuclei in contrast agents is of high interest. Since the gyromagnetic ratios (γ) of <sup>15</sup>N and <sup>13</sup>C are substantially lower than <sup>1</sup>H, imaging resolution will be inherently lower with comparable gradients, but strategies to overcome this by pulse transfer back to nearby <sup>1</sup>H before acquisition have been shown<sup>[28]</sup>.

While  $^{13}\text{C}$  polarization levels exceeding 50% are readily achieved  $^{[1,29]}$  in various injectable contrast agent systems in d-DNP,  $^{15}\text{N}$  polarization levels obtained by d-DNP remain limited due to the considerably lower gyromagnetic ratio  $\gamma$  of  $^{15}\text{N}$ . Only recently large  $^{15}\text{N}$  polarization were achieved for the partially-deuterated quaternary amine trimethylphenylammonium (TMPA) by cross polarization DNP (CP-DNP)^{[30]}. The use of protonated compounds to achieve high polarization levels in CP-DNP typically results in  $^{15}\text{N}$  relaxation times  $^{[22]}$  shorter than in fully deuterated analogs. While 60-90% starting  $^{1}\text{H}$  polarization was used for polarizing  $^{15}\text{N}$  nuclei via cross polarization, only  $\text{P}_{15\text{N}} \sim 17\%$  was obtained after dissolution  $^{[30]}$ .

To demonstrate the effectiveness of NAC@Rh in aqueous PHIP with respect to prior work, <sup>13</sup>C hyperpolarization in two compounds is investigated: the deuterated angiography contrast agent 1-<sup>13</sup>C-hydroxyethyl propionate- $d_3$  (HEP)<sup>[31]</sup> and the metabolite derivative ethyl acetate (EA) upon hydrogenation of their respective precursors 1-13C-hydroxyethyl acrylate-d<sub>3</sub> (HEA) and vinyl acetate (VA) with natural abundance <sup>13</sup>C. Enhancement of <sup>13</sup>C on HEP is observed upon transfer of nascent proton polarization to carbon via PH-INEPT+, a well-established polarization transfer pulse sequence for PHIP<sup>[32]</sup>. Polarization transfer from <sup>1</sup>H to <sup>13</sup>C after (para)-hydrogenation of VA into EA via field cycling between B0~50  $\mu T$  (Earth magnetic field) and B<sub>0</sub><0.1  $\mu$ T inside a  $\mu$ -metal chamber is also demonstrated. Unsaturated sidearm groups on acetate derivatives can be cleaved following polarization transfer to produce pure acetate<sup>[33]</sup>, a metabolite currently used in metabolic imaging<sup>[34]</sup>. To investigate hyperpolarization of <sup>15</sup>N, a nucleus found in many valuable metabolic probes, the deuterated precursor compound <sup>15</sup>N-neurine-*d*<sub>12</sub> is available, producing d<sub>12</sub>-<sup>15</sup>N-ethyl trimethylammonium (NETMA) upon hydrogenation, a structural analog of choline. Choline has previously been investigated as a metabolic probe by d-DNP<sup>[35]</sup> and positron emission tomography (PET)<sup>[36]</sup> due to its role in cellular phospholipid metabolism and has been used to probe upregulated choline kinase expression in malignant tissues<sup>[37]</sup> and other metabolic information<sup>[38]</sup>. However, production of hyperpolarized choline from the precursor substrate has not been demonstrated, likely because the tautomerization between the keto and enol state prevents adequate hydrogenation.

After significant <sup>1</sup>H polarization was observed following neurine hydrogenation with NAC@Rh ( $5.4 \pm 0.6\%$ ), a recently demonstrated heteronuclear transfer sequence, titled

ESOTHERIC<sup>[39]</sup> was employed for polarization transfer to <sup>15</sup>N. This sequence is well-suited for NETMA as it is able to transfer the nascent para-H<sub>2</sub> longitudinal two-spin order into observable in-phase heteronuclear magnetization in weakly coupled spin systems<sup>[39]</sup>. This is the first reported method for achieving high <sup>15</sup>N hyperpolarization via pulse transfer with aqueous PHIP<sup>[40]</sup>. The relevant precursors and products used in this work as well as the relevant *J*-couplings are shown in Figure 1.

An essential component to advancing PHIP methodologies for in vivo applications is the ability to store nascent polarization as long-lived heteronuclear longitudinal magnetization to allow detection of the enhanced signal after delivery to the target tissues. Unlike previous homogeneous catalysts i.e. Rh[1,4-Bis(diphenylphosphino)butane](norbornadiene)BF4 and its derivatives<sup>[10,33,41,42]</sup>, heterogeneous hydrogenations occurring on a metal surface can lead to randomization of the hydrogen spins. Ligand design not only allows dispersion and particle size control but favors pairwise para-H2 addition via restricting hydride diffusion during hydrogenation, thus preserving the spin order of para-H<sub>2</sub> and hence observable polarization. Cysteine derivatives provide convenient thiol and amine groups which coordinate strongly to transition metals and form stable colloids, as well as suspend in water. Rh has been used in traditionally homogeneous PHIP catalysis and recently in heterogeneous catalysts (HET-PHIP)<sup>[22,23]</sup>, where it has been shown to produce higher polarization than Ir, Pt and Pd systems in similar immobilized materials<sup>[43]</sup>.

PHIP spectra for all compounds investigated are shown in Figure 2 and polarization levels are summarized in Table 1. The polarization method used for each compound was match to the



Figure 1. Reaction mechanisms of HEA, neurine and VA hydrogenation. JAA, JAX and JA'X values are considered in polarization transfer strategy from  $^{1}$ H to  $^{13}$ C and  $^{15}$ N.

methods available to us that has been used in past publications<sup>[26]</sup> and the scalar coupling<sup>[33]</sup> to achieve detectable polarization. Following application of the ESOTHERIC pulse,  $P_{15N}$  of 12.2 ± 2.7% shown in Fig 2c) and 2d) was observed with NETMA, representing a 12.5-fold improvement over the highest previously recorded <sup>15</sup>N PHIP polarization of <sup>15</sup>N-propargylcholine using a homogeneous catalyst<sup>[44]</sup>, and a 186-fold improvement over previous aqueous HET-PHIP values<sup>[22]</sup>. Transfer to <sup>13</sup>C on HEP via PH-INEPT+ and EA via field cycling yielded  $P_{13C}$  of 3.2 ± 0.3% and 1.3 ± 0.3% respectively, representing 2.67-fold and 6.5-fold

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improvements over previous aqueous HET-PHIP investigations<sup>[26]</sup>. Thus the NAC@Rh effectiveness is not exclusive to <sup>15</sup>N and demonstrates a greater overall utility than previous metal nanoparticle catalysts across PHIP polarization methods.

These results also highlight a key advantage for HET-PHIP, which is the stability of metal surfaces used for PHIP of nitrogenous compounds. Because nitrogen groups are excellent electron donors to transition metals, homogeneous catalysts often undergo rapid degradation as alkenes are out-competed by nitrogen groups forming inactive complexes. Upon investigation of NETMA formation using 5 mM homogeneous Rh[1,4-Bis(diphenylphosphino]butane)(cyclooctadiene)BF<sub>4</sub> catalyst, less than 1% <sup>1</sup>H polarization is observed in addition to discolored precipitate forming in reaction tubes. Despite generally higher turnover frequency (TOF), a measurement of hydrogenation rate, homogeneous complexes are unable to polarize <sup>15</sup>N efficiently, as is evidenced by unprecedented <sup>1</sup>H polarization of an unprotected amino acid recently reported with a heterogeneous catalyst<sup>[26]</sup>.



**Figure 2.** Pulse diagram for a) PH-INEPT+ applied to HEP with  $t_1 = 69.8$  ms and  $t_2 = 38.9$  ms in agreement with previous work<sup>[45]</sup> and b) Single <sup>13</sup>C scan of HEP following pulse (red) and single 90° scan of reference 100 mM <sup>13</sup>C pyruvate solution (blue) with vertical scaling. c) ESOTHERIC pulse using timings  $\Delta_A = \Delta_C = 172.4$  ms and  $\Delta_B = 83$  ms corresponding to couplings  $J_{AA}=6.0$  Hz,  $J_{AX}=-0.5$  Hz and  $J_{AX}=2.93$  Hz applied to NETMA following hydrogenation and d) Single <sup>15</sup>N scan of NETMA following application of ESOTHERIC pulse sequence (red) and single reference 90° scan of 2 M <sup>15</sup>N-urea solution (blue) with vertical scaling. e) Schematic of field cycling transport out of zero field over 5 seconds following EA hydrogenation at Earth field consistent with previous reports<sup>[26,33]</sup> before insertion into the magnet and f) Single 90° <sup>13</sup>C scan of EA following transport out of zero field (red) and inlet thermal spectrum after 512 scans (blue) with vertical scaling. Natural abundance vinyl acetate was used (<sup>13</sup>C, 1.1%). All experiments performed with 1 mM precursor concentration.

The <sup>15</sup>N environment of NETMA is particularly well-suited for storing polarization in the form of longitudinal magnetization. The deuteration of the NETMA product contributes to long methyl and methylene <sup>1</sup>H T<sub>1</sub> times (11.7 s and 22.5 s, respectively), shown in Table 1. This allows long <sup>1</sup>H polarization buildup times during para-H<sub>2</sub> bubbling before polarization transfer as well as particularly long <sup>15</sup>N T<sub>1</sub> relaxation times. A previous <sup>15</sup>N PHIP investigation of NETMA assessed the <sup>15</sup>N T<sub>1</sub> at 493 seconds (field strength of 9.4T) by fitting the data to polarization decay without compensation for the 10° sampling pulses<sup>[22]</sup>. Investigation shown in Figure 3 by inversion recovery reveals a  $T_1$  of 1259 ± 22 seconds (21.0 ± 0.4 min) under inert conditions and only a slight drop to 1003 ± 10 seconds (16.7 ± 0.2 min) under air atmosphere at 14T. This allows a system where large <sup>15</sup>N polarization is generated, then separated from the catalyst and injected while still retaining over 50% of its original intensity after 14 minutes, a substantial benefit for medical translation.



**Figure 3.** Inversion recovery plot of NETMA <sup>15</sup>N in D<sub>2</sub>O yielding a)  $21.0 \pm 0.4$  minute and b)  $16.7 \pm 0.2$  minute longitudinal relaxation (*T*<sub>1</sub>) under inert and air atmospheres, respectively.

High polarization levels on <sup>15</sup>N were obtained by using the ESOTHERIC pulse sequence which is suited for transferring the nascent <sup>1</sup>H polarization to a heteronucleus in systems where the added proton pair is a) weakly coupled and b) asymmetrically coupled to the heteronucleus. Since this applies in NETMA, ESOTHERIC can theoretically transfer close to 95% spin order transfer (SOT) from two spin longitudinal order of protons after (para)-hydrogenation to the target nucleus (i.e. <sup>15</sup>N). A more detailed explanation of the polarization transfer mechanism can be found elsewhere<sup>[39]</sup>. In traditional PASADENA experiments at high field, initially a 45° pulse is applied to detect the <sup>1</sup>H signal, achieving a theoretical maximum of 50% SOT, as investigated elsewhere<sup>[45]</sup>. After a 45° pulse was used to detect the <sup>1</sup>H signal,  $P_{1H}$ =5.4 ± 0.6% was observed here in NETMA, this is thus half the spin-order polarization. Application of the ESOTHERIC sequence yields  $P_{15N}$ =12.2 ± 2.7%, showing that within the error, nearly unitary SOT is achievable as observable heteronuclear polarization. To our knowledge, this represents the most efficient <sup>15</sup>N transfer obtained with PHIP at high field.

Table 1 also outlines TOF rates for each contrast agent investigated. Dispersible colloid catalysts tend to suffer activity loss due to surface coverage of ligand in place of potential catalytic sites, typically yielding a much lower TOF than

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heterogeneous catalysts capable of robust polarization. TOF for HEP using NAC@Rh shows 1.67-fold and 3.31-fold improvement over previous NAC@Pd and LCys@Pd catalyst systems respectively under identical experimental conditions. This represents the ability to generate 5.52 mM of HEP in the 15 s required to hydrogenate using a small para-H<sub>2</sub> volume in an NMR tube and apply transfer polarization methodologies. Future work at higher generated product concentrations is still needed.

 Table 1. Product properties and enhancements with NAC@Rh measured at 7 T.

	NETMA	HEP	EA
Method	ESOTHERIC	PH-INEPT+	Zero Field
<sup>1</sup> H <i>T</i> <sub>1</sub> (s)	11.7 ± 1.2, 22.5 ± 2.4	$4.0 \pm 0.5$	5.0 ±0.7
<sup>1</sup> H P%	5.4 ± 0.6	3.2 ± 0.3	2.1 ± 0.3 <sup>[a]</sup>
<sup>13</sup> C <sup>/15</sup> N T <sub>1</sub> (s)	1259 ± 22 <sup>[a]</sup>	55.6 ± 5.6	$65.2 \pm 0.4$
<sup>13</sup> C <sup>/15</sup> N P%	12.2 ± 2.7	3.2 ± 0.2	1.3 ± 0.2 <sup>[a]</sup>
TOF (h <sup>-1</sup> )	44.9	71.8	51.3

[a] measured at 14.1 T

Heterogeneous catalysts in water are highly sought in PHIP experiments because they enable separation of the nascent hyperpolarized products, eliminating toxicity concerns regarding the injection of harmful materials into human patients.<sup>23</sup> Unprecedented <sup>15</sup>N polarization of NETMA in water along with benchmark <sup>13</sup>C enhancements on HEP and EA demonstrates NAC@Rh as a promising catalytic system for aqueous PHIP. This work is the first step in making *in vivo* PHIP<sup>[17–21]</sup> accessible for human use. As surface ligand interactions are better optimized, achievable polarizations of slow-relaxing nuclei such as <sup>13</sup>C and <sup>15</sup>N increase as well. These stabilized metal catalytic systems are conducive to catalyst removal and clean bio-compatible product solutions ready for injection.

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## COMMUNICATION

#### Entry for the Table of Contents (Please choose one layout)

Layout 1:

## COMMUNICATION

#### Text for Table of Contents

**High Polarization in Water**: By using a heterogeneous nanoparticle catalyst and efficient pulse sequence, the observation of <sup>15</sup>N nuclear-spin polarization in excess of 12% in a choline derivative are demonstrated in water by parahydrogen-induced polarization (PHIP). A very long  $T_1$ relaxation of over 20 minutes is also observed, as well as versatility with previous PHIP methods and target nuclei (i.e., <sup>13</sup>C), opening new applications for medical MRI.



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#### Title

Over 12% Polarization and 20 Minute Lifetime of <sup>15</sup>N on Choline Derivative Utilizing Parahydrogen and Rh Nanocatalyst in Water