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Rapid Catalyst Capture Enables Metal-Free *para*-Hydrogen-Based Hyperpolarized Contrast Agents

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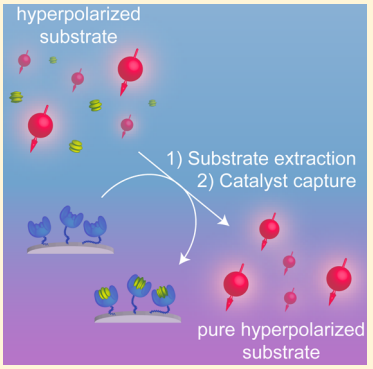
Supporting Information

ABSTRACT: Hyperpolarization techniques based on the use of *para*-hydrogen provide orders of magnitude signal enhancement for magnetic resonance spectroscopy and imaging. The main drawback limiting widespread applicability of *para*-hydrogen-based techniques in biomedicine is the presence of organometallic compounds (the polarization transfer catalysts) in solution with hyperpolarized contrast agents. These catalysts are typically complexes of platinum-group metals, and their administration in vivo should be avoided. Herein, we show how extraction of a hyperpolarized compound from an organic phase to an aqueous phase combined with a rapid (less than 10 s) Ir-based catalyst capture by metal scavenging agents can produce pure *para*-hydrogen-based hyperpolarized contrast agents, as demonstrated by high-resolution nuclear magnetic resonance (NMR) spectroscopy and inductively coupled plasma atomic emission spectroscopy (ICP-AES). The presented methodology enables fast and efficient means of producing pure hyperpolarized aqueous solutions for biomedical and other uses.



Despite being immensely powerful tools for biomedical, chemical, and materials science applications, conventional nuclear magnetic resonance spectroscopy (NMR) and magnetic resonance imaging (MRI) methods are limited by inherently low sensitivity.[1−4] This limitation can be overcome via hyperpolarization techniques, which allow orders of magnitude NMR/MRI signal enhancement. The most widely used hyperpolarization techniques employ polarization transfer from electrons (dynamic nuclear polarization),[5] photons (spin exchange optical pumping),[6] or *para*-hydrogen (*para*-hydrogen-induced polarization, PHIP).[7,8] The latter approach is particularly attractive: PHIP and its recent variant SABRE (signal amplification by reversible exchange)[9,10] allow transfer of the 100% pure singlet spin order of *para*-hydrogen (*para*-H_2) to a variety of nuclei (^{13}C, ^{15}N, ^{19}F, ^{31}P, etc.)[11−14] in a wide range of molecular motifs, including metabolically relevant carboxylic compounds,[15−17] antibiotics,[18] Schiff bases,[19] and bioorthogonal molecular tags.[20] High polarization percentage, short signal build-up times, low cost, and scalability make PHIP and SABRE promising modalities for studying metabolism in vivo by magnetic resonance techniques.[21]

Currently, the main obstacle to *para*-H_2-based polarization techniques in biomedicine is the presence of heavy metal-based complexes (referred to below as catalysts) in solution with hyperpolarized contrast agents. These catalysts are typically Rh-based (PHIP) and Ir-based (SABRE) metal−organic compounds, and they "catalyze" the polarization transfer of spin order from *para*-H_2 to the substrate (Figure 1a). Their presence in solution is necessary to provide polarization transfer from *para*-H_2 to the substrate;[22] however, their administration in vivo should be avoided. Despite efforts to synthesize heterogeneous (HET) PHIP/SABRE catalysts[23−26]—typically in the form of solid particles facilitating hyperpolarization of liquids and gases mixed with *para*-H_2—no discovery has been reported of high (>5%) polarization of biologically relevant molecules, a threshold for biomedical applications.[27]

We demonstrate that a two-step method, involving phase extraction and catalyst capture, can effectively and rapidly separate heavy metal-based polarization transfer catalysts from the biologically relevant hyperpolarized substrates of interest (Figure 1b). This technique, on the time scale of seconds, produces *para*-H_2-based hyperpolarized contrast agents that are effectively isolated from metal complexes (i.e., the metal concentration is less than 1 ppb), as shown by analysis from high-resolution NMR and inductively coupled plasma atomic emission spectroscopy (ICP-AES).

In the present study, we focus on the SABRE hyperpolarization technique and employ the most efficient to date polarization transfer catalyst, [Ir(IMes)H_2S_3]Cl (**1**), obtained via activation of the established Ir catalyst precursor **2** [Ir(COD)(IMes)Cl] (IMes = 1,3-bis(2,4,6-trimethyl- phenyl)-

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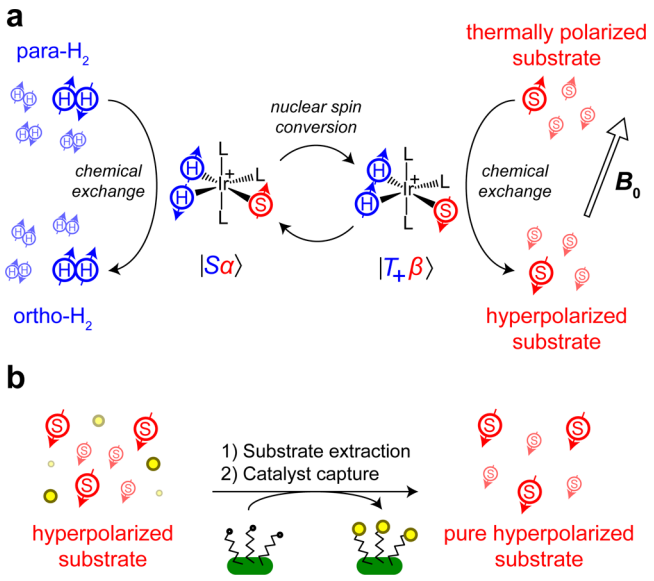

Figure 1. (a) Schematic diagram of the SABRE process. A coherent polarization transfer is carried out between singlet ($|S\rangle$) and triplet ($|T_+\rangle$) spin states of *para*-H_2-derived hydrides and the spin state ($|S\rangle$ or $|T_+\rangle$) of a substrate (S). (b) After polarization buildup in the organic phase, a hyperpolarized contrast agent is extracted to an aqueous medium, and the residual metal complex is rapidly captured by a scavenging agent.

imidazol-2-ylidene; COD = cyclooctadiene).[28] ^{15}N-labeled pyridine (98% ^{15}N, Sigma-Aldrich 486183) was used as a substrate (S). Detailed experimental procedures of the catalyst solution preparation and activation are described in the Supporting Information (SI).

For extraction experiments, the SABRE hyperpolarization technique was used with pyridine, the most studied SABRE substrate.[9] A homemade, automatically controlled polarizer executed the activation and transfer steps of the extraction method (Figure S1). We show that after hyperpolarization buildup via *para*-H_2 bubbling in the organic phase, pyridine can be efficiently transferred to the aqueous phase, while 99.0−99.9% of the catalyst complex **1** remains in the organic phase; these results are verified by ^{1}H NMR and ICP-AES data (Table S2). This observation verifies the recent findings of Iali et al.,[29] indicating that most of the SABRE catalyst tends to remain in the organic phase during the extraction process. However, there is still a measurable amount of catalyst in the aqueous phase solution (1−10 μM), constraining the direct applications of this approach to biomedicine.[30] While iridium complexes are generally considered to be "slightly toxic" (i.e., LD_{50} dosage is 500−5000 ppb),[31] cytotoxicity studies performed with an activated SABRE reaction mixture showed a reduction in cell viability due to the presence of **1**.[32] One should note that the detectable presence of iridium in the aqueous phase after extraction is not surprising because studies of Truong et al. conclusively demonstrated water solubility of **1** after activation in methanol (while **2** is not soluble in water).[33] Therefore, despite the fact that the extraction process allows removal of the main portion of the metal complex, additional filtration steps are necessary to achieve full biocompatibility.

In order to prepare metal-free aqueous solutions containing hyperpolarized tracers, we propose a new catalyst capture technique. This technique involves the use of metal scavenging agents to completely eliminate metal quantities from aqueous solutions. Multiple metal scavenging agents' affinity for **1** were tested (Figure 2a). Remarkably, the commercially available mercaptopropyl silica (QuadraSil MP, Sigma-Aldrich 679526) and 2-mercaptoethyl ethyl sulfide silica (Sigma-Aldrich 745111) were shown to capture **1** most effectively (Figure 2b). The mercaptopropyl silica, however, showed better performance in capturing the Ir complex on a short time scale (under 10 s), shown below. This result is critical because hyperpolarized compounds must be cleared from the polarization transfer

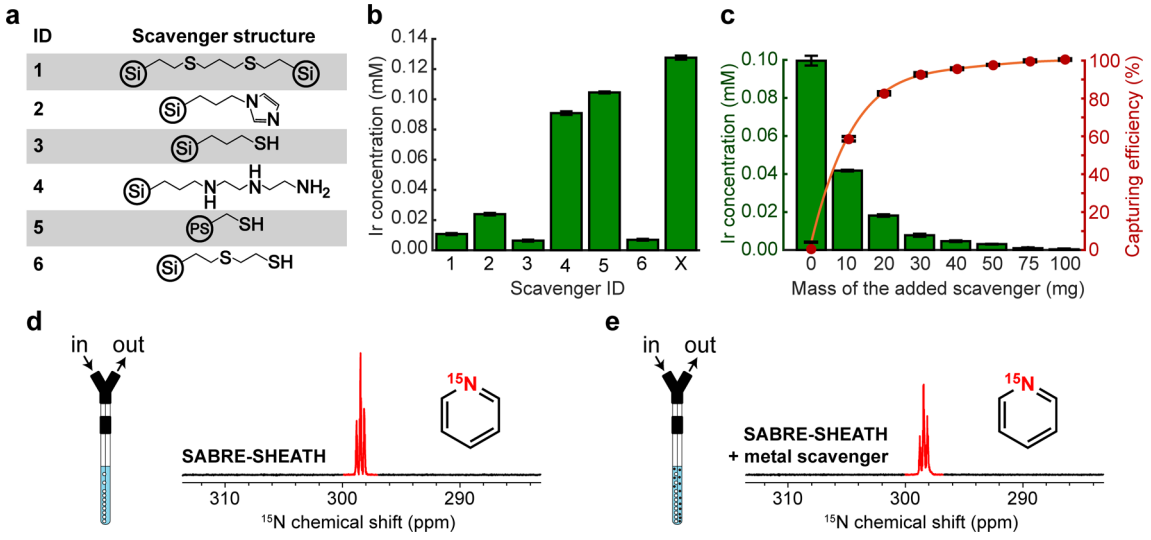

Figure 2. (a) Chemical structures of metal scavengers used in the SABRE catalyst capturing studies. (b) Concentration of Ir detected by ICP-AES after overnight storage of a 0.5 mL aqueous solution of **1** in the presence of different metal scavengers (10 mg). Scavengers' identification (ID) numbers are listed in (a); "X" indicates that no scavenger was added. (c) Concentration of Ir detected by ICP-AES after rapid capture (<10 s) of **1** from the 0.5 mL aqueous solution by different amounts of the added metal scavenger (ID #3). The metal capturing efficiency is shown on the right. (d) ^{15}N NMR spectrum of pyridine-^{15}N hyperpolarized via SABRE-SHEATH[12] (pyridine-^{15}N, 100 mM; Ir catalyst, 7.8 mM; 0.6 mL of CD_3OD). (e) ^{15}N NMR spectrum of pyridine-^{15}N hyperpolarized via SABRE-SHEATH;[12] 21 mg of the metal scavenger #3 is added to the same solution as that in (d).

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catalyst as quickly as possible to preserve high nuclear spin polarization after the capturing process. We note that lifetimes of several tens of minutes for ^{15}N hyperpolarized tracers have been successfully demonstrated.[34]

Interestingly, despite some scavengers having similar functionality (Figure 2a), they perform quite differently (Figure 2b). Nitrogen-containing scavengers (#2 and #4) show generally poorer performance compared to sulfur-containing scavengers (#1, #3, and #6). However, the most striking difference is observed between somewhat similar scavengers #3 and #5. We attribute this difference to the short hydrocarbon chain and different support structure (polystyrene) of #5, which sterically hinder interaction of the bulky complex **1** with −SH groups.

We tested the ability of mercaptopropyl silica (scavenger #3) to rapidly capture the Ir complex from the aqueous solution (Figure 2c). Treating 0.5 mL of the aqueous solution of **1** with only 10 mg of mercaptopropyl silica for less than 10 s reduces the metal amount by approximately 60% (Figure 2c). Increasing the scavenger mass to 100 mg per 0.5 mL of solution allows complete capture of the Ir complex from solution (the measured Ir concentration is 0.3 ± 0.3 ppb, less than the ICP-AES detection sensitivity). This efficient capturing ability is due to the significant concentration of surface thiol groups relative to the concentration of Ir in solution. Indeed, the surface −SH concentration is 1.0−1.5 mmol/g, while the amount of **1** in the studied solutions (0.5 mL) was only 2.0−3.0 μmol. Given the scavenger loading, this corresponds to a two orders of magnitude scavenger excess compared to the metal complex, a prerequisite for efficient and rapid metal capture.

In order to demonstrate that hyperpolarization can survive the catalyst capture process, we performed additional measurements. Unfortunately, due to experimental limitations and the absence of the ^{15}N detection capabilities on the benchtop NMR spectrometer, it was not possible to perform automated catalyst capture using the setup described in Figure S1. However, ^{15}N NMR measurements carried out with 100 mM pyridine-^{15}N solution in methanol-d_4 at 9.4 T with 21 mg of the added mercaptopropyl silica confirmed that the scavenger does not noticeably affect the hyperpolarization level and its lifetime. Indeed, Figure 2d,e shows that the ^{15}N NMR signal of pyridine-^{15}N is only decreased slightly (by ∼20%) due to the presence of the scavenger. We assign this decrease to the catalyst capture process rather than to accelerated ^{15}N relaxation induced by the presence of the scavenger. When the capturing process is complete, attempts to polarize the solution again do not lead to ^{15}N NMR signal observation, additionally confirming the efficacy of the capture process.

Interestingly, we note that the measured T_1 is increased by a factor of ∼10 when the hyperpolarized sample is stored at an elevated field of 0.15 T after production in the μT field compared to storage in the Earth's field (Figure S9). This result is similar to the recent observation of the prolonged ^{15}N lifetime of metronidazole at ∼0.3 T.[35] This result indicates that the final design of the *para*-H_2-based polarizer should include precise control of the magnetic field at the site where catalyst extraction and/or capture are performed.

In conclusion, we demonstrate a new catalyst capture technique that can be used alone or concurrently with phase extraction. When used in conjunction with phase extraction (i.e., when the initial catalyst concentration in water is less than 0.1 mM), one can completely remove the SABRE catalyst from solution in seconds (the Ir concentration is 0.3 ± 0.3 ppb as confirmed by ICP-AES). This result opens the path to produce metal-free aqueous boluses of hyperpolarized contrast agents for in vivo MRI detection. We note that the presented methodology can be further upgraded by using capturing agents that allow recycling of polarization transfer catalysts. Two-step extraction and metal capture approaches can potentially enable higher polarization levels (due to higher solubility of *para*-H_2 in the organic phase), which is synergistically compatible with bioorthogonal ligation strategies and, ultimately, biomedical translations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpclett.8b01007.

Experimental details and additional ICP-AES results (PDF)

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Notes

The authors declare no competing financial interest.

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