



## Continuous hyperpolarization with parahydrogen in a membrane reactor

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### ABSTRACT

Hyperpolarization methods entail a high potential to boost the sensitivity of NMR. Even though the “Signal Amplification by Reversible Exchange” (SABRE) approach uses para-enriched hydrogen,  $p$ -H<sub>2</sub>, to repeatedly achieve high polarization levels on target molecules without altering their chemical structure, such studies are often limited to batch experiments in NMR tubes. Alternatively, this work introduces a continuous flow setup including a membrane reactor for the  $p$ -H<sub>2</sub>, supply and consecutive detection in a 1 T NMR spectrometer. Two SABRE substrates pyridine and nicotinamide were hyperpolarized, and more than 1000-fold signal enhancement was found. Our strategy combines low-field NMR spectrometry and a membrane flow reactor. This enables precise control of the experimental conditions such as liquid and gas pressures, and volume flow for ensuring repeatable maximum polarization.

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### 1. Introduction

One approach to improve the sensitivity in NMR is to employ hyperpolarization methods [1] such as dynamic nuclear polarization (DNP) [2], spin exchange optical pumping (SEOP) [3] and methods based on para-enriched hydrogen, i.e.,  $p$ -H<sub>2</sub> [4–7]. The setup for hyperpolarization methods based on  $p$ -H<sub>2</sub> is simple and inexpensive, and it allows to continuously achieve high levels of polarization on target molecules. The polarization transfer in such a setup happens within seconds [8,9], and the spin order from the antisymmetric  $p$ -H<sub>2</sub> singlet can be converted into a detectable magnetization on target molecules by different mechanisms. One straight-forward approach is the hydrogenation of a double bond by chemically incorporating the  $p$ -H<sub>2</sub> into a target molecule, as was demonstrated by Bowers and Weitekamp first in 1986 [4]. The resulting signals in the spectra at high and low fields can be described by two mechanisms called “Adiabatic Longitudinal Transport After Dissociation Endangers Net Alignment (ALTA-DENA) [10] and “Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment” (PASADENA) [5]. A more recent polarization transfer mechanism exploiting the  $p$ -H<sub>2</sub> singlet is “Sig-

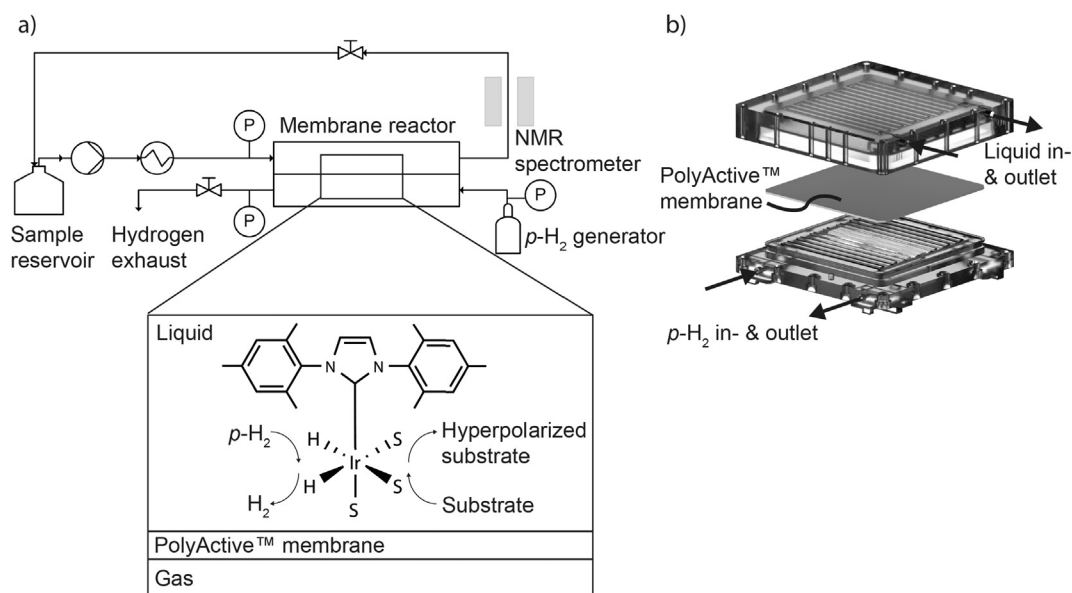
nal Amplification by Reversible Exchange” (SABRE) [6] allowing continuous hyperpolarization by repetitively hyperpolarizing and measuring the same sample [11]. With this mechanism, the polarization is transferred to target nuclei by a temporary  $J$ -coupling network between the coordinated substrate and the classical hydrides stemming from  $p$ -H<sub>2</sub> exchange at the transition metal center of a catalyst (Fig. 1). Very high polarization levels ( $P > 0.1$ ) on different nuclei [12,13] and the hyperpolarization of various chemical compounds [14–19] have been reported using the SABRE approach. Moreover, optimized continuous systems have been reported for hydrogenative “ParaHydrogen Induced Polarization” (PHIP) reactions [20,21].

Up to now, the SABRE experiments, which are performed in the liquid phase, have often been executed in batch experiments using, e.g., Young NMR tubes [6,3,17,18]. The advantage of this approach is that it allows rapid testing of new catalytic systems. In this case also the same sample can be repolarized when supplied with new  $p$ -H<sub>2</sub>. Continuous  $p$ -H<sub>2</sub> supply with repetitive polarization transfer and detection has been demonstrated in several studies with discontinuous flow, e.g. [22–30]. Yet the manual sample preparation and fast NMR detection pose drawbacks like limited reproducibility and insufficient flexibility to study pressure/temperature dependencies. To address these issues, a continuous flow process is highly desirable with a suitable hyperpolarization bubble-free gas/liquid reactor being a prerequisite. We propose to employ a

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**Fig. 1.** Experimental setup for the continuous SABRE reaction. (a) Schematic drawing illustrating the polarization transfer from  $p\text{-H}_2$  to the substrate via a SABRE-active catalyst. (b) Illustration of the 3D-printed membrane reactor highlighting the meandering channel structure and the embedded PolyActive™ membrane to separate the liquid and gas phases.

gas/liquid membrane reactor that combines a chemical reaction task with a membrane process integrated in a single operational device [31]. The membrane itself can be made from porous or dense metallic, ceramic, and polymeric material. In general, membranes are considered to be structures that depending on permeability allow certain molecules or ions to pass while blocking others. Integrated into a reactor, the membrane can (a) selectively remove the product, (b) control the dosing of reactants and (c) enhance the contact between catalyst and reactants. Additionally, membranes are suited to host the catalyst, either on their skin or within their pores, limiting catalyst bleeding and defining the reaction zone well. These features make membrane reactors highly attractive for use in various disciplines such as catalysis [31], biotechnology [32,33] and electrochemistry [34]. In PHIP catalysis, membrane reactors allow controlled dosing of  $p\text{-H}_2$  for well-defined reaction conditions with separated reactive phases enabling systematic studies of the pressure and temperature dependencies of the hyperpolarization effect.

This work reports the first membrane reactor setup to continuously hyperpolarize pyridine and nicotinamide with the SABRE approach. At its core is a 3-D printed membrane reactor which enables the  $p\text{-H}_2$  uptake of a solution and the polarization transfer to the dissolved target molecules. The setup was validated by: (a) conducting single scans of the hyperpolarized substrates, and (b) investigating the effects of changing pressure and volume flow on the signal enhancement. With it highly diluted chemical compounds can be hyperpolarized and monitored over time and multiple samples can consecutively be analyzed after injection.

## 2. Materials and methods

All chemicals were used as received (Sigma Aldrich) without further purification unless otherwise stated except for degassing and drying with a molecular sieve. Methanol was distilled, dried and degassed. All chemical work was conducted under inert gas conditions. Samples were prepared in Schlenk tubes before use. Each sample contained 30 ml methanol as solvent, 7.5 mg [IrCl(COD)IMes] (COD = 1,5-cyclooctadiene, IMes = (1,3-bis(2,4,6-trime-

thylphenyl)-imidazol-2-ylidene) catalyst precursor [35] and 18.5 mg pyridine or 28.7 mg nicotinamide as target substrates. Those two substrates are known to be SABRE-active [6]. [IrCl(COD)IMes] was synthesized from [Ir(COD)(OMe)<sub>2</sub>] and 2 equivalents of IMes in acetone and recrystallized three times in methanol for further purification. For the continuous and homogeneous PHIP catalysis, a microfluidic 'Modular MicroReactor System' setup (Ehrfeld Mikrotechnik) was employed. This commercial setup was furnished with a 3D-printed (micro) membrane reactor which simultaneously enriched the liquid phase with dissolved  $p\text{-H}_2$  gas while the transfer of the  $p\text{-H}_2$  polarization to the substrate took place in the earth's magnetic field (Fig. 1a).

To maximize the polarization transfer, the residence time of the substrate molecules inside the reactor was prolonged by a meandering rectangular channel embedded in the top part of the reactor (Fig. 1b). The liquid and gas phases were separated by a membrane (PolyActive™). This is a composite membrane consisting of a polymeric support and a selective skin made of poly(ethylene oxide)-poly(butylene terephthalate) (PEO-PBT) copolymer. The skin was oriented towards the liquid side. During the experiments, the reactor was kept at a constant temperature of 30 °C via a heat exchanger which was placed in the flow direction upstream of the 3D printed reactor. Since the generated polarization relaxes with time, the tubing length between the membrane reactor and the NMR spectrometer downstream was kept short (less than 15 cm). The integrated back pressure valve (BPV) as well as the various pressure sensors before and after the membrane reactor were used to vary gas and liquid pressures within the reactor. As the membrane separated the gas and liquid phases, it was possible to study the influence of pressure changes on the polarization level in each of the two phases (Fig. 3b). The  $p\text{-H}_2$  gas was supplied by a  $p\text{-H}_2$  converter (Bruker, bphp90). In some rare cases, when the dissolution process is slow at liquid pressures lower than the gas pressure, undesired gas bubbles formed at the membrane surface. This was avoided by choosing the transmembrane pressure as small as possible.

For NMR detection the hyperpolarized substrates were continuously passed through a glass flow cell with an outer diameter of 5 mm and returned to the sample reservoir. The inner diameter

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