Validation of an efficient and compact para-hydrogen catalytic converter system for PHP studies

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Introduction
The PHP technology for achieving hyperpolarized states of multinuclei has been gaining interest in the biomedical community since its first introduction to in vivo studies1. However, its widespread utilization is still hampered by the lack of an affordable commercial PHP system or laboratory know-how. The purpose of this study was to develop and implement an efficient and compact para-hydrogen catalytic converter system suitable for PHP studies in a hospital environment which is operational near an MRI scanner and designed for the long term goal of studying new hyperpolarized PHP contrast agents in human subjects. To achieve this goal, the catalytic converter system should comply with several requirements such as 1) to locally produce hydrogen in sufficiently small amounts due to a surrounding that is normally not explosion proof; 2) to produce sterile para-hydrogen at ambient pressure; 3) to consist of components that are preferably non-metallic, cost efficient, and disposable; 4) to operate efficiently in terms of heat exchange and catalytic conversion rates. We describe the design, performance, and efficiency of such a system below.

Materials and Methods
Conversion System:
Hydrogen is generated by a chemical reaction of a solid hydrogen source (sodium borohydride) with water. The hydrogen gas is passed through a cold glass-trap containing iron (III) oxide catalyst at ambient pressure (Figure 1). After an hour in liquid nitrogen, the enriched para-hydrogen is collected in a small container and used for PHP studies. 1H-NMR of ortho-para hydrogen gas mixtures were carried out at 500 MHz (Varian). The gas mixture was injected into vacuumed regular NMR tubes via rubber septa (Wilmad, NJ, USA). PHP studies were carried at the same scanner. For both ALTADENA and PASADENA, the hydrogen was injected into the reactant solution (inside the NMR tube) via PEEK tubes (Upchurch Scientific, WA, USA) through the same type of septa.

Results
Measured amounts of sodium borohydride and water allow for strict control over the amount of hydrogen gas produced. The glass trap, with the iron catalyst placed at its bottom, is much more convenient for routine operation in comparison to the metal tube that is mentioned in most of the previous PHP studies2,3 and proved to be highly efficient in terms of heat exchange and conversion rates. The T1 of room temperature hydrogen (25:75 para/ortho) was found to be 3.63 ± 0.91 (n=4) msec. The T2 of the para-enriched mixture (liquid nitrogen temperature) was found to be similar, at 3.81 ± 0.67 (n=6) msec. Fully relaxed 1D NMR spectra of hydrogen mixtures were therefore carried out using a 50 msec repetition time. The content of ortho-hydrogen (the visible spin isomer of hydrogen) was found to be constant for at least 20 minutes, which suggests the same stability for the hydrogen mixture which is brought to reaction during the PHP studies.

PASADENA and ALTADENA PHP experiments3 resulted in the characteristic hyperpolarized signals in the reduction reactions of ethyl propiolate (Scheme 1) and dimethyl acetylenedicarboxylate (Scheme 2) with p-H2, mediated by a rhodium catalyst, as previously described4,5.

Reproducibility tests:
1) 1H-ALTADENA - Upon reaction of 214 mM ethylpropiolate (in 700 µL acetone-d6) with 5 ml of the para-enriched hydrogen (over 5 sec) the product concentration was 0.9 ± 0.4 mM (n=4, 0.42% yield). The hyperpolarized ALTADENA signal resulting from this reaction reached a level equivalent to 1870 ± 420 mM. Therefore, the enhancement factor in these experiments was 2110 ± 420 (n=4).
2) 13C-ALTADENA - Upon reaction of 570 mM dimethyl acetylenedicarboxylate (in 700 µL acetone-d6) with 5 ml of the para-enriched hydrogen (over 5 sec) the product concentration (determined on a 13C spectrum) was 3.85 mM (0.67% yield). The hyperpolarized ALTADENA signal resulting from this reaction reached a level equivalent to 13,600 ± 3730 mM (n=4).

Discussion
It is important to note that the enhancement factors here were calculated with reference to concentration 4,5. The enhancement factor may also be calculated with reference to the noise of the spectrum, in cases where the product signal is not detected after a single hydrogenation step. However, our hands calculation of enhancement factor compared to the noise of the spectrum may result in very different results due to system variations (e.g. different probes and/or magnetic field homogeneity). For example, the same reaction recorded with the same probe in two different days, while resulting in a similar enhancement factor per concentration, showed very different enhancement factors when compared to the noise: 3,400 ± 1530 (n=4) vs. 15,440 ± 7,160 (n=4). Calculation of enhancement factor with reference to concentration is important for validation of hyperpolarization reproducibility. To this end, several repetitions of the reaction may be required for low yield reactions, to achieve reliable product quantification.

Conclusion
Our compact and disposable system proved to be an efficient catalytic converter and an excellent source of para-hydrogen for PHP studies in a hospital/MRI suite environment.

References